STUDY OF DRUG RELEASE FROM AN ELEMENTARY OSMOTIC PUMP TABLET BY NMR IMAGING

by

ALAIN MUSENDE

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Department of **Pharmaceutical Sciences**

The University of British Columbia
Vancouver, Canada

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ABSTRACT

BACKGROUND: Osmotic pump tablets offer highly predictable and programmable delivery of drugs into solution, ready for absorption. The design and formulation of an osmotic pump tablet determines the release rate of the drug and are based on exhaustive and expensive physico-chemical testing of the system's characteristics. The results of these tests are approximations of the real system with considerable limitations and non-negligible uncertainties. They do not provide an understanding of the dynamics and interactions of water within the tablet core and their influence on the drug release.

OBJECTIVES: The overall objectives of this research were first to develop a system of measuring the percent core tablet eroded in an elementary osmotic pump tablet and to correlate it with the percent drug released, during a 24 hour-dissolution process, using NMR Imaging techniques which have been successfully used in the analysis of the release dynamics inside hydrogels. Second, to propose a mechanism of drug release based on the ingredients-water dynamics inside the tablet. The system developed constitutes a direct, qualitative and quantitative method of analysis of an osmotic pump tablet, in a non-invasive, non-destructive and non-interruptive way.

METHODS: First, the aqueous solubility of the model drug, triflupromazine HCl, was determined at 37 ± 0.5 °C. Second, reference mixtures of the lactose, stearic acid and triflupromazine HCl blend with water were prepared, at concentrations from 2 % to 22 % by weight, for future water proton relaxation times (T2) measurements. Then three sets of elementary osmotic pump tablets were formulated with different membrane thicknesses. One set of control tablets, without a drilled hole was also formulated. The percent drug released during a 24-hour dissolution at 37 ± 0.5 °C was measured for these tablets. Gray-scale NMR images and T2 value maps of the osmotic pump tablets, were obtained every 3 hours, during a 24-hour dissolution and the total volume of core tablet eroded at each time-point calculated and correlated with the percent drug released.
RESULTS AND DISCUSSION: The average tablet weight, thickness and hardness were within our target specifications and thus provided batch to batch tablet uniformity in weight, hardness and thickness. The NMR gray-scale images of the tablets during dissolution confirm the strength and flexibility of the membrane and the unimpeded flow of water into the core tablet, as expected. Higher percent core tablet erosion was obtained from the tablets with the thinner membrane (73 μm) compared to the thicker one (121 μm). This follows Fick’s law as core tablet erosion is proportional to the flux of water molecules into the tablet. The results suggest that during dissolution, water permeates through the semi-permeable membrane, moves between lactose particles, allowed by the tablet porosity, and dissolves the extremely water-soluble triflupromazine HCl independently of dissolving lactose. As dissolution progresses, more and more triflupromazine HCl molecules and a relatively smaller percent of lactose molecules are dissolved.

CONCLUSION: Qualitative and quantitative analysis of osmotic pump tablets during 24-hour dissolution testing were performed without interrupting the process or destroying the samples. NMR axial and sagittal slices of the osmotic pump tablets were taken thus allowing for a complete and more accurate study of the system then previously possible. The percent drug released, the water distribution inside the tablet and the rate of core tablet erosion were determined quantitatively, while the membrane strength and permeability were evaluated qualitatively. A tentative explanation of the drug release mechanism inside the tablet is proposed for the first time.
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<table>
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<tbody>
<tr>
<td>%</td>
<td>Percent</td>
</tr>
<tr>
<td>μm</td>
<td>Micrometer</td>
</tr>
<tr>
<td>π</td>
<td>Pi (3.14)</td>
</tr>
<tr>
<td>ΔC</td>
<td>Difference in concentration between the solutions on either side of the membrane</td>
</tr>
<tr>
<td>ΔE</td>
<td>Energy difference between two energy states</td>
</tr>
<tr>
<td>ΔP_{max}</td>
<td>Maximum tolerated hydrostatic pressure difference between the inside and outside of the tablet.</td>
</tr>
<tr>
<td>ε</td>
<td>Porosity term reflecting the fractional volume of the membrane pores</td>
</tr>
<tr>
<td>τ</td>
<td>Tortuosity factor</td>
</tr>
<tr>
<td>μl</td>
<td>Microliter</td>
</tr>
<tr>
<td>ºC</td>
<td>Degree Celsius</td>
</tr>
<tr>
<td>(\frac{dv}{dt})</td>
<td>Volume flux through the drilled orifice</td>
</tr>
<tr>
<td>ν</td>
<td>Viscosity of the dispensed solution</td>
</tr>
<tr>
<td>(\frac{dm}{dt})</td>
<td>Solute delivery rate</td>
</tr>
<tr>
<td>ν₀</td>
<td>Frequency of precession</td>
</tr>
<tr>
<td>γ</td>
<td>Nuclear gyromagnetic constant of the nucleus</td>
</tr>
<tr>
<td>μₙ</td>
<td>Magnetic moment of the particle</td>
</tr>
<tr>
<td>μs</td>
<td>Microsecond</td>
</tr>
<tr>
<td>τ</td>
<td>Time value</td>
</tr>
<tr>
<td>φ</td>
<td>Phase angle acquired at a given position in a sample</td>
</tr>
<tr>
<td>ρ(x, y)</td>
<td>Concentration of spins</td>
</tr>
<tr>
<td>Δ</td>
<td>The delay between gradients</td>
</tr>
<tr>
<td>A_{max}</td>
<td>Maximum drilled orifice size</td>
</tr>
<tr>
<td>A_{min}</td>
<td>Minimum drilled orifice size</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>a.u.</td>
<td>Arbitrary units</td>
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<td>B₀</td>
<td>External magnetic field</td>
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</table>
c: Concentration
C*: Concentration of water dissolved in the polymer membrane
\(^{12}\text{C} \): Carbon
\(^{14}\text{C} \): Carbon 14. Carbon isotope with 6 protons and 8 neutrons.
CA-398: Cellulose acetate with 39.8 % acetyl content
cm: Centimeter
2D: Two dimensional
3D: Three dimensional
D: Diffusion coefficient
D': Diffusion coefficient in the liquid phase
DS: Degree of substitution
Ed: Energy of activation of diffusion
Er: Energy of intermolecular repulsion
Eb: Energy of intramolecular bending
F: Dimensionless factor expressing the diffusional contribution to the release
f2: The similarity factor
\(^{19}\text{F} \): Fluorine
FOV: Field of view
Fr: Frequency encoding gradient
FT: Fourier transformation
FID: Free induction decay
g: Gram
G: Gauss
g_\text{s}: Nuclear magneton
G_x: Physical gradient along the x-axis
G_y: Physical gradient along the y-axis
\text{h}: Hour
\text{h}: Planck’s constant (6.6262 \times 10^{-27} \text{ erg.s})
\text{H}: Hydrogen proton
HCl: Hydrochloric acid
\text{He}: Helium
HPMC: Hydroxypropylmethylcellulose

xxx
HPMCP: Hydroxypropylmethylcellulose phthalate
HP-β-CD: Hydroxypropyl-β-cyclodextrin

\( I \): The average % drug released for sample I at time \( t \).
\( II \): The average % drug released for sample II at time \( t \).
\( I \): The spin quantum number
\( I(t) \): Signal intensity
\( \text{in} \): Inch
\( J \): Permeant flux
\( k \): Boltzmann constant \((1.38 \times 10^{-16} \text{ erg/Kelvin})\)
\( K \): Distribution coefficient of permeant
\( K' \): Permeant distribution between the surrounding fluid and the fluid in the membrane pores
\( \text{KCl} \): Potassium chloride
\( kp \): Kilopond
\( l \): Length of the drilled orifice
\( M \): Molar
\( \text{MDM} \): Magnetic dipole moment
\( \text{MFG} \): Magnetic field gradient
\( mg \): Milligram
\( \text{MHz} \): Megahertz
\( mI \): Energy level of the nucleus
\( ml \): Milliliter
\( mm \): Millimeter
\( M_0 \): Net magnetization vector
\( \text{MR} \): Magnetic resonance
\( \text{MRI} \): Magnetic Resonance Imaging
\( M_z \): Net magnetization vector along the z axis
\( n \): The total number of samples
\( N \): Total number of spins
\( N_1 \): Number of protons in the higher energy state
\( N_2 \): Number of protons in the lower energy state
\( \text{NF} \): National Formulary
nm: Nanometer
NMR: Nuclear Magnetic Resonance
$N_{0,\text{SLICE}}$: The initial total number of black pixels in the tablet slice at 0.5 hour.
$N_{t,\text{SLICE}}$: The total number of black pixels in the tablet slice at time $t$.
p: $p$-value: the probability of observing a difference as large as that obtained given the Null hypothesis is true.
P: Angular momentum
PDL: Prednisolone
PEG: Polyethylene glycol
PGSE: Pulsed-Gradient-Spin-Echo
pH: Hydrogen ion potential
Ph: Phase encoding gradient
rf: Radio frequency
RPM: Rotation per minute
s: Second
S: Solubility of the drug in water
$^{32}\text{S}$: Sulfur
(SBE)$_{7\text{m}}$: Sulfobutyl ether-$\beta$-cyclodextrin
S.D.: Standard deviation
SI: Slice selection gradient
SP: Single punch
$S(x, y)$: Signal intensity
T: Tesla
t: Duration of the gradient
$T_1$: Spin-lattice relaxation (longitudinal relaxation)
$T_2$: Spin-spin relaxation (transverse relaxation)
$T_E$: The time-to echo in a spin-echo pulse sequence, the time from the middle of the 90° pulse to the maximum amplitude of the echo.
Tg: Glass transition temperature
$T_R$: The repetition time, the delay between repeats of an NMR experiment.
USP: United States Pharmacopeia
U.V.: U.V. spectrophotometry
$V_{O\text{-SLICE}}$: The initial volume of the tablet slice occupied by the black pixels (100% lactose) at 0.5 hour.

$V_{O\text{-TABLET}}$: The initial volume of the whole tablet occupied by the black pixels (100% lactose) at 0.5 hour.

$V_{I\text{-SLICE}}$: The volume of the tablet slice occupied by the black pixels at time $t$.

$V_{I\text{-TABLET}}$: The volume of the whole tablet occupied by the black pixels at time $t$.

wt %: Weight percent

$w_i$: The weighing factor

$X_i$: The measurement of sample $i$

$y$: Position within the $y$-gradient
ACKNOWLEDGEMENT

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Finally, warmest thank you to my Wife, my Children, my Brother and my Mom for their sacrifices, unconditional love and invaluable support throughout my Master’s program.
Dedicated to the memory of Musende Mujigulu Wa Gahasa Nu Nganda
INTRODUCTION

The elementary osmotic pump tablet (Figure 1) constitutes a type of solvent-controlled drug delivery system that offers several specific advantages: delivery of the drug in solution and ready for absorption; predictable, programmable delivery rates, and delivery that is primarily independent of the biological environment influences such as motility of the gastrointestinal tract, pH or enzymatic activity (Baker, 1979):

In an aqueous environment, water diffuses through the semi-permeable membrane and micro-porous membranes into the core tablet, drawn by the osmotic pressure of the ingredient(s) therein. Water dissolves the core tablet, forming a saturated aqueous solution inside the tablet. Because the membrane is non-extensible, the increase in volume caused by the imbibition of water raises the hydrostatic pressure inside the tablet. The hydrostatic pressure is then relieved by pumping the saturated solution out of the tablet, through the drilled orifice.

![Diagram of an elementary osmotic pump tablet](image)

Figure 1: A schematic of the cross-sectional view of an elementary osmotic pump

The drug release rate of an osmotic pump is predetermined by the design and formulation of the tablet. The release characteristics are dependent on membrane properties such as its tolerable hydrostatic pressure, and permeability. Despite the need to be able to predict and control the drug release rate of osmotic pump tablets, the dynamics of drug release and the mechanism involved remains poorly understood. Attempts to acquire this information require conducting a dissolution experiment, extracting wet samples under study, drying and dissecting for analyses.
This method, widely used in the study of hydrogels, (Colombo et al., 1997; Peppas et al., 1997) is labour intensive and highly variable.

Shapiro et al. (1995) and Fahie et al. (1998) used NMR Imaging in the study of osmotic pump tablets. Shapiro et al. (1995) examined the causes of variable release rates from a batch of osmotic pump tablets. NMR Imaging was used to examine the degree of water penetration through the tablet membrane and it was found that the slow release tablets had a thicker membrane compared to faster release tablets, and that the membrane was asymmetrically coated: thinner on the sides of the tablets. This study was strictly qualitative. No quantitative measurements were obtained. The rate of erosion of the core tablet and the dynamics and interactions of water within the tablet core and their influence on the drug release were not investigated. Fahie et al. (1998) compared two formulations of ranitidine hydrochloride tablets coated using two different polymeric solutions. NMR Imaging showed that the tablet formulation with a faster drug release allowed water permeation through the coat at an early stage, prior to the release of all the drug. The formulation with a slower release rate showed that the water did not fully penetrate the outer coat until all the drug had been released.

$^1$H NMR Imaging is a technique sensitive to mobile protons and provides pictographic and quantitative data. In this technique, the relaxation times ($T_1$ and $T_2$) of protons are measured and they determine the motions of the water protons. The spatial distributions of $T_1$ and $T_2$ indicate the influence of the environment on the mobility of water. During a dissolution process, axial and sagittal slices (Figure 2) of the tablet under study can be selected, providing gray-scale images. Regions of black colour signals the absence of water, while bright regions indicate the presence of water. The depth of brightness is an indication of the extent of water absorption through the sample.

In this research, a $^1$H NMR Imaging method was designed to provide the ability to perform a direct, qualitative and quantitative analysis of an osmotic pump tablet during dissolution, without interrupting the process or destroying the sample. The osmotic pump tablet is "sliced" (Figure 2) in a non-invasive way during operation, thus allowing for a complete and reproducible analysis of the system and its parameters both inside and outside the tablet. These parameters include drug release, membrane strength and permeability, rate of core tablet erosion, drug and water
distribution inside the tablet, drug-water and drug-excipient concentration ratios in the saturated mixture exiting the tablet.

To our knowledge, little is known about the interactions of water within the tablet core, core erosion and factors influencing drug release.

In this work, osmotic pump tablets were formulated using lactose, stearic acid and the model drug, triflupromazine hydrochloride as core tablet ingredients. Cellulose acetates 398 and 320 mixed with polyethylene glycol constituted the semi-permeable membrane ingredients, and hydroxypropylmethylcellulose was added for the micro-porous membrane. The purpose of the research was firstly, to correlate the percent drug released with the percent core tablet eroded during a 24 hour dissolution in water, for three formulations: the 73 μm membrane thickness-with hole, the 121 μm membrane thickness-with hole and the 73 μm membrane thickness-without hole, as a control and, secondly, to explain the mechanism of core tablet erosion.

Figure 2: NMR Imaging slice selection of a tablet.
(a) 1 mm sagital slice. (b) 1 mm axial slice. FOV: Field of view
(Adapted from Wong, 2001)
BACKGROUND

1. CONTROLLED RELEASE ORAL DRUG DELIVERY SYSTEMS

The controlled release of drugs involves designing drug delivery systems which release a pharmacologically active agent over a prolonged period of time with a predictable or controlled release profile. In the conventional dosage form, the release of drugs is rapid and uncontrolled. Controlled release offers many advantages compared to conventional drug formulations: extension of the time the effective therapeutic dose is present at the site of action from a single administration, promotion of patient compliance, and reduction of the risks of drug concentration exceeding therapeutic requirements thus reducing dose-related side effects (Figure 3).

![Drug Concentration in Blood vs. Time](image)

Figure 3: Theoretical plasma concentration after administration of various dosage forms: (a) Standard oral dose, (b) Oral overdose, (c) Intravenous injection, (d) Controlled release system. (Adapted from Sinko and Kohn, 1992).

Early attempts at controlling the release of drugs were mostly using sustained or prolonged release oral medications. The most notable example is enteric-coated tablets incorporating pH-sensitive drugs. Other types of formulations include: encapsulated pellets or beads and insoluble tablets containing dispersed drug.
Controlled release drug delivery systems can be classified according to the type of release mechanism (Sinko and Kohn, 1992):

Solvent controlled: the rate of drug release is predominantly controlled by interaction with water. Two categories are included in this group: polymer swelling controlled systems and osmotic systems. An example of swelling systems are hydrogels, a polymer which forms a gel and swells when in contact with water. Hydrogels remain water-insoluble while retaining a significant amount of water. The diffusion rate of a drug depends on the chemical nature and the physical structure of the hydrogel polymer network. Diffusion occurs mostly through the pores when the polymer reaches a high level of hydration. Some polymers are rendered insoluble by cross-linking between the chains which diminishes the diffusion rate of the drug (Martin, 1993). The rate of drug release from the hydrophilic matrix is a function of water absorption, polymer hydration and drug diffusion through the swollen polymer gel (Blazek, 1998).

Diffusion controlled: the rate is controlled by the diffusion of drug molecules through a matrix or membrane.

Chemically controlled: the rate is controlled by a chemical process such as polymer degradation.

Controlled release drug delivery systems can also be categorized according to the design features, as given below (Baker, 1987):

1.1 **Membrane-controlled reservoir systems:**

In this case a rate controlling membrane encloses the drug (Figure 4). They are also described as “depot” devices. In this system, a suspension of the drug contained in the reservoir will provide constant zero-order release rates across the membrane as long as there is excess drug in the reservoir. When the drug is totally dissolved in the reservoir fluid, the release rate will resemble a first order process.
Membrane

Reservoir

Figure 4: Membrane-controlled reservoir system in operation: drug molecules (black dots) from the reservoir diffusing across the membrane. $l$: membrane thickness. (Adapted from Paul, 1976).

1.2 **Diffusion-controlled monolithic systems:**

In these systems, there is no membrane. The drug is homogeneously dispersed throughout the carrier material, usually a polymer (Figure 5). The rate of release of the drug is independent of the rate of solid dissolution but dependent on the rate of drug diffusion. Factors such as the geometry of the device, the nature of the carrier and the loading of the drug influence the release pattern.

![Drug in Polymer Matrix](image)

Figure 5: Diffusion-controlled monolithic system. (Adapted from Martin, 1993)

1.3 **Degradation-controlled systems:**

In this system the drug is also dispersed in the carrier material, usually a polymer, but the release rate of drug is controlled by biodegradation of the polymeric carrier (Figure 6).
Osmosis is the phenomenon involving the passage of a pure solvent into a solution separated from it by a semi-permeable membrane. The membrane is permeable to the solvent but not to the solute of the solution. The phenomenon of osmosis is based on the fact that the chemical potential of solvent molecules in solution is less than in the pure solvent. In order to equalize the chemical potential of the solvent molecules on both sides of the membrane i.e. the pure solvent and the solution, the pure solvent will spontaneously pass into the solution until the chemical potential of both the pure solvent and the solution are equal. Equilibrium of the system is then reached. In practice terms, osmosis can be conceived as an attempt to equalize the solute concentration on both sides of the membrane. The dilution of the solute as a result of solvent passage into solution raises the vapor pressure of the solution’s solvent back to that of the pure solvent. The osmotic pressure, $\pi$, is a measure of the pressure which must be applied to the solution to prevent any net movement of solvent molecules into the solution (Martin, 1993).

The common underlying principle of all osmotic pumps is that because of the difference in osmotic pressure across the semi-permeable membrane, water or an aqueous solution such as the patient’s stomach fluid is drawn into the osmotic pressure generating material, a salt, a drug or a combination of the two. The rate of water permeation across the semi-permeable membrane will remain constant as long as sufficient solid drug or salt is present to maintain a constant osmotic pressure driving force.
In the case of non-tablet osmotic pumps (see section 3), the increase in volume of the osmotic pressure generating compartment is the driving force that affects the flexible membrane or elastic diaphragm which thus forces the drug out through the orifice at a controlled release rate. In the case of tablet osmotic pumps (see section 3), the hydrostatic pressure built-up within the core, caused by the increase in volume and the membrane being non-extensible will force or pump the drug solution out through a hole or holes at a controlled rate.

Beside the general advantages of controlled release systems, osmotic systems present the following benefits (Baker, 1979): the drug is delivered in solution, ready for absorption, higher delivery rates are possible compared to diffusion-controlled systems (Theeuwes, 1975), delivery rates are predictable and programmable, and within specified limits, the delivery rates in vitro and in vivo are equal. In this systems, the delivery rates are also independent of biological environmental influences such as motility of the gastrointestinal tract, pH or enzymatic activity. In fact, Theeuwes (1975), using phenobarbital sodium osmotic pump tablets in artificial gastric fluid (pH = 2) and intestinal fluid (pH = 7.5, without enzyme), found that the release rates were similar and independent of the pH of the environment. Cellulosic polymers were used as semi-permeable membranes. It should be pointed out that this pH independence is greatly affected by the chemical properties of the polymer used as membrane.

2. MEMBRANE DIFFUSION

Diffusion describes a process of mass transfer of individual molecules of a substance, due to random molecular motion and is associated with a concentration gradient (Martin, 1993). A membrane is an inter-phase or film separating two phases and restricting the transport of various species between the phases. Material passes across a membrane actively, passively or by facilitated transport. Membranes are therefore involved in the rate-controlling step (Baker, 1987).

Most controlled release delivery systems including the elementary oral osmotic pump require a membrane or film to contain the active agents. Membranes used in oral osmotic systems can be categorized in two groups: homogeneous and micro-porous membranes. Homogeneous membranes are polymer films that are homogeneous, dense, isotropic, simple to prepare and are
the most commonly used. In this case, the permeant diffuses by random molecular motion through the free volume between the polymer chains. In the case of micro-porous membranes, the presence of pores allows the permeant to diffuse through liquid-filled pores within the membrane (Baker, 1987). The diffusion permeant flux is calculated differently for the two types of membranes:

Fick’s law of diffusion states the following:

\[
J = \frac{D K \Delta C}{l}
\]  
(Equation 1)

Where \( J \) is the permeant flux (rate of diffusion per unit area), in \( \text{g/cm}^2 \cdot \text{s} \); \( D \) is the diffusion coefficient (the measure of the mobility of the individual permeant molecules in the membrane), in \( \text{cm}^2 / \text{s} \); \( K \) is the distribution coefficient (analogous to liquid-liquid partition coefficient) of permeant between the solutions on either side of the membrane; \( \Delta C \) is the difference in concentration between the solutions on either side of the membrane, in \( \text{g/cm}^3 \), and \( l \) is the thickness of the membrane, in cm.

Fick’s law of diffusion assumes a perfectly uniform and homogeneous membrane without differences in structures or properties at the microscopic level. Equation 1 will thus be used for homogeneous membranes, while modifications will be needed for its use with micro-porous membranes since diffusion takes place through the membrane pores. Accordingly Equation 1 becomes:

\[
J = \frac{D' K' \varepsilon \Delta C}{\tau l}
\]  
(Equation 2)

Where \( D' \) is the diffusion coefficient in the liquid phase filling the membrane pores, \( K' \) is the permeant distribution between the surrounding fluid and the fluid in the membrane pores (\( K' \) is usually 1 because the fluids are the same), \( \varepsilon \) is the porosity term reflecting the fractional volume of the membrane pores and \( \tau \) is the tortuosity factor (it reflects the geometrically longer average path over which a molecule must diffuse).
3. OSMOTIC PUMPS

3.1 Evolution and classification

The Rose-Nelson pump (Figure 7): In 1955, Rose and Nelson produced the first application of osmotic pressure to drug delivery, and this pump is considered as the forerunner of modern osmotic devices. It consists of an orifice and three chambers: a water chamber, a salt chamber containing excess solid salt and a drug chamber. A semi-permeable membrane separates the water chamber from the salt chamber while an elastic diaphragm, separates the salt chamber from the drug chamber. Water enters the salt chamber, creates an increase in the salt chamber’s volume leading to a distention of the elastic diaphragm thereby pumping drug through the orifice. Since the osmotic pressure of the salt is the driving force for pumping the drug out, the rate of water permeation through the membrane will remain constant as long as there is a saturated solution of the salt present in the salt chamber (Baker, 1987).

The Higuchi-Leeper osmotic pump: In 1973, Higuchi and Leeper generated a new variation of the Rose-Nelson osmotic pump. The main difference from the Rose-Nelson pump is that there is no water chamber as imbibition of water is from the surrounding environment. The version still has a salt chamber and a drug chamber but a membrane constitutes one side of the pump.
Figure 7: The Rose-Nelson osmotic pump principle. (1): before operation, the three chambers are full. (2): water from the water chamber increases the volume of the salt chamber as it moves into it. This volume increase distends the elastic diaphragm separating the salt and drug chambers, thereby pumping the drug out. (3) same as in (2), with more volume increase of the salt chamber and more drug is pumped out. (4) All the water has moved into the salt chamber, maximum volume increase of the salt chamber, the drug is completely pumped out. (Adapted from Baker, 1987).

The miniature osmotic pump (Figure 8): In 1973, Theeuwes produced another version of the Rose–Nelson osmotic pump (Baker, 1987). It is more sophisticated and different from the Higuchi-Leeper version as the semi-permeable membrane covers the pump entirely. Like the Higuchi-Leeper pump, the Theeuwes osmotic pump has no water chamber as imbibition of water is from the surrounding environment.
Figure 8: The miniature osmotic pump. (a): before use. (b): in operation, in an aqueous environment. Water from the environment diffuses across the rigid semi-permeable membrane, reaching the osmotic agent layer and causing it to swelling. This swelling in turn squeezes the drug solution which will then be pumped out through the delivery port. (Adapted from Baker, 1987).

In this system, the salt chamber and the drug chamber are still present. The outermost component is a rigid semi-permeable membrane, usually a cellulosic polymer. The innermost component is an impermeable, flexible drug reservoir. The dry energy source is contained between the two compartments. In order to provide a leak proof seal between the drug reservoir and the semi-permeable membrane, a rigid polymeric plug is used. A stainless steel cap and tube are used as a flow modulator. This pump comes unfilled and is filled with a syringe. It is sold under the trade name Alzet® (from Alza Corporation) and is mostly used in research as an implantable drug delivery system. A pump of this type has a volume of approximately 170 µl and a delivery rate of 1 µl/h.

The elementary osmotic pump (Figure 9): Theeuwes designed a further variation of the miniature osmotic pump (Baker, 1987). This pump has no salt chamber and is simply a compacted core tablet coated with a polymeric semi-permeable membrane. An orifice is drilled through the membrane. Water from the surrounding environment will access and dissolve the drug core tablet through the semi-permeable membrane. Since the membrane is non-extensible, an increase of the hydrostatic pressure will occur which will be relieved by the pumping of a
saturated solution of the drug through the drilled orifice at a controlled rate. Theeuwes (1975), developed potassium chloride and phenobarbital osmotic pumps, and established that the drug is delivered at a constant zero-order delivery rate as long as excess solid is present in the core tablet. When all the solid in the core is dissolved, the delivery rate declines and becomes non zero-order (Figure 10). Drug release is almost exclusively osmotically driven. Several other variations of the elementary osmotic pump have been developed to overcome specific problems such as insolubility or partial solubility of the drug (Baker, 1987).

Figure 9: Elementary osmotic pump. (a): before use. (b): in operation, in an aqueous environment. Water moves into the drug reservoir by osmosis. The hydrostatic pressure builds up inside the reservoir and pumps the drug out through the portal. (Adapted from Martin, 1993).
Figure 10: Theoretical drug release profile from an elementary osmotic pump. Zero-order release: from 0 to 17.8 hours. Parabolic decrease in release rate: from 18 to 22 hours. $c = 206.3 \text{ mg/cm}^3$: sub-saturation concentration. (Adapted from Martin, 1993).

The porosity controlled osmotic pump: Zentner et al. (1985) produced the porosity controlled osmotic pump (Figure 11). The key difference emerging from the elementary osmotic pump is that there is more than one orifice and leachable materials are used as pore formers creating pores once in contact with water. Therefore this system consists of a core tablet and a semi-permeable polymer film containing a pore former. Drug release from this dosage form is driven by both osmosis and diffusion.

For the porosity-controlled osmotic pumps, Zentner et al. (1985), used potassium chloride tablets as the core, cellulose acetates as the water permeable polymer, diethylphthalate as the plasticizer, sorbitol and polyethylene glycol as the leachable materials, and demonstrated that active agents could be released according to a zero-order release profile.
Figure 11: Porosity controlled osmotic pump in operation in an aqueous environment: water dissolves the water soluble part of the membrane, leaving pores in the membrane, then reaches the core tablet, by osmosis. The hydrostatic pressure build up inside the tablet pumps the drug out through the various membrane pores created. (Adapted from Lee and Robinson, 1978).

3.2 Factors affecting drug release from osmotic devices

3.2.1 Materials used as film formers

Polymers are widely used in controlled release drug delivery systems: as membranes, through which a solvent or an active agent should pass; as matrices, in which an active agent is dispersed; or as a drug carrier, attached to active agents (Sinko and Kohn, 1992).

In an elementary osmotic pump, it is required that the membrane used be water-insoluble and selectively water-permeable. Other desired properties of the membrane are (Jerzewski and Chien, 1992): sufficient wet strength as to retain its dimensional integrity during the use of the device, biocompatibility and drug compatibility, flexibility and elasticity in order to function successfully under different osmotic pressures, and sufficient water permeability, so as to provide the desired water flux rate. “Water vapor transmission rate” is used to evaluate the flux rate. Permeability is the product of diffusivity and partition coefficient.
3.2.1.1 Cellulose acetate membrane

Cellulosic polymers constitute one of the most important and most extensively used membranes. Cellulose, the structure-forming element of plant cells, is one of the most abundant of all organic polymers and is a polysaccharide with glucose repeat units (Figure 12(a)). Despite the presence of free hydroxyl groups, pure cellulose is insoluble in water because of its high crystallinity. Cellulose acetates used in elementary osmotic pumps are film-forming polymers. In addition to the favourable properties of cellulose acetate films, their use in these dosage forms was desirable since they could be applied to tablets using the same solvents and equipment that are used for conventional solvent-based coatings of other water-insoluble polymers such as ethylcellulose.

Acetylation of cellulose involves the substitution of the hydroxyl groups with acetyl groups and can be accomplished by a reaction with acetic anhydride, using glacial acetic acid as solvent and sulfuric acid as catalyst, to produce cellulose acetate sulfate triester. The removal of the sulfates leads to cellulose acetate (Figure 12(b)). Acetylation is expressed as weight percent of acetyl group or degree of substitution (DS). DS = 3 means that all three hydroxyl groups are substituted by acetyl groups. The cellulose chain length and the number of acetyl groups attached to the chain affect the physical properties of cellulose acetates.

Figure 12: The chemical structures of (a): cellulose and (b): cellulose acetate.
Increased acetylation leads to decreased interchain hydrogen bonding, decreased regularity of the polymer chains and reduced crystallinity. The melting point increases (the triacetate has a melting point of approximately 230 °C with an acetyl content of 38.0 – 39.0 and a melting point of approximately 306 °C at an acetyl content of 43.0 – 44.8), the moisture sensitivity and vapor permeability rate decrease and the thermoplastic characteristics are highly improved with increasing acetylation (Bogan and Brewer, 1985).

Acetyl groups on cellulose acetates reduce the polymer's solubility in water while hydroxyl groups promote it by establishing hydrogen bonds with water molecules. At 13 weight % acetyl content, the polymer becomes water-soluble. More acetylation will make the cellulose acetate more hydrophobic, becoming water-insoluble at approximately 19 weight % acetyl content.

Cellulosic polymers are of great interest also because of their generally high water permeability and low salt permeability. Data on the effect of acetyl content on diffusion of water and the permeability of cellulose acetate membranes are difficult to gather because different techniques of membrane preparation have been used. Table 1 provides a summary of potentially useful data (Baker, 1987). Diffusivity of water molecules is higher in polymers containing flexible chains, without double bonds and/or ring structures along the polymer backbone, as diffusivity depends on the mobility of segments of the polymer chains (Sinko and Kohn, 1992). Diffusivity also decreases as density increases because of the reduced amount of free volume. The density increases as the distance between polymer chains decreases and the effect of tacticity increases. Diffusivity is higher in amorphous polymers compared to semi-crystalline polymers because of their higher free volumes. Weaker polymer interchain forces (such as Van der Waals forces) promote diffusivity while stronger interchain forces (such as hydrogen bonds) reduce diffusivity. An increase in crosslinking decreases diffusivity and diffusivity is higher above Tg and lower below Tg.
Table 1: Effect of acetyl content on the sorption and diffusion of water, sodium chloride and sodium sulfate in cellulose acetate membranes (Baker, 1987)

<table>
<thead>
<tr>
<th>Acetyl content (%)</th>
<th>33.6%</th>
<th>37.6%</th>
<th>38.3%</th>
<th>39.5%</th>
<th>39.8%</th>
<th>41.0%</th>
<th>43.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D (cm²/s)</td>
<td>5.7x10⁻⁶</td>
<td>2.9x10⁻⁶</td>
<td></td>
<td>1.5x10⁻⁶</td>
<td>1.6x10⁻⁶</td>
<td></td>
<td>1.3x10⁻⁶</td>
</tr>
<tr>
<td>C (g/cm³)</td>
<td>0.29</td>
<td>0.20</td>
<td>≈ 0.19</td>
<td>0.17</td>
<td>0.16</td>
<td>0.15</td>
<td>0.12</td>
</tr>
<tr>
<td>DK (cm²/s)</td>
<td>16x10⁻⁷</td>
<td>5.7x10⁻⁷</td>
<td></td>
<td>2.6x10⁻⁷</td>
<td>2.6x10⁻⁷</td>
<td></td>
<td>1.5x10⁻⁷</td>
</tr>
<tr>
<td><strong>NaCl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D (cm²/s)</td>
<td>2.9x10⁻⁸</td>
<td>4.3x10⁻⁹</td>
<td></td>
<td>9.4x10⁻¹⁰</td>
<td></td>
<td></td>
<td>3.9x10⁻¹¹</td>
</tr>
<tr>
<td>K</td>
<td>0.17</td>
<td>0.062</td>
<td></td>
<td></td>
<td>0.035</td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>DK (cm²/s)</td>
<td>4.9x10⁻⁹</td>
<td>2.7x10⁻¹⁰</td>
<td></td>
<td>3.3x10⁻¹¹</td>
<td></td>
<td></td>
<td>5.8x10⁻¹¹</td>
</tr>
<tr>
<td><strong>Na₂SO₄</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D (cm²/s)</td>
<td>1.01x10⁻⁸</td>
<td></td>
<td>1.03x10⁻⁹</td>
<td></td>
<td>7.2x10⁻¹⁰</td>
<td>3.4x10⁻¹⁰</td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>0.039</td>
<td></td>
<td>0.027</td>
<td></td>
<td>0.0013</td>
<td>0.00031</td>
<td></td>
</tr>
<tr>
<td>DK (cm²/s)</td>
<td>4.0x10⁻¹⁰</td>
<td></td>
<td>2.8x10⁻¹²</td>
<td></td>
<td>9.3x10⁻¹³</td>
<td>1.03x10⁻¹³</td>
<td></td>
</tr>
</tbody>
</table>

Where, D is the diffusion coefficient, K is the distribution coefficient and C is the concentration of water dissolved in the polymer membrane.

The activation energy for diffusion decreases above Tg. If the activated diffusion process is considered to involve only two neighboring polymer chains which have moved apart in order to accommodate the passage of a permeant molecule (Figure 12), there are three types of molecular motions that cause the active state. Firstly, there is intermolecular repulsion between the
molecular chains (accommodating the diffusant) and their neighbors. Secondly, the partial rotation of chain units out of their equilibrium positions against a hindering potential of internal rotation since the intramolecular resistance (i.e. bond distances and bond angles) is difficult to change. A torsional strain, evenly distributed over the entire segment will be generated. Thirdly, the number of degrees of freedom in a segment of the polymer chain which is proportional to the segment length.

![Diagram of polymer chains and diffusant molecule](image)

Figure 13: Diffusion of a molecule in polymer structure. Two polymer chains moved apart in order to accommodate the passage of a permeant molecule. (Adapted from Lee and Robinson, 1978).

The energy of activation of diffusion for a polymer with $x$ degrees of freedom is:

$$ Ed = Er + Eb $$

(Equation 3)

Where $Ed$ is the energy of activation of diffusion, $Er$ is the energy of intermolecular repulsion, and $Eb$ is the energy of intramolecular bending.

Cellulose acetate polymer chains do not offer much flexibility because of the presence of rings. The use of plasticizer will lower the polymer’s $T_g$ and also increase diffusivity. The polymer is treated to provide the same amount of free volume as at its $T_g$ while being held below $T_g$. This can be achieved by increasing the temperature and bringing the polymer above its $T_g$, then subjecting it to very rapid cooling.
Table 2: Factors affecting the diffusivity of a polymer (Lee and Robinson, 1978)

<table>
<thead>
<tr>
<th>Increases in factor listed below</th>
<th>Effect on diffusivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-chain forces</td>
<td>Decrease</td>
</tr>
<tr>
<td>Segmental mobility</td>
<td>Increase</td>
</tr>
<tr>
<td>Permeant molecular weight</td>
<td>Decrease</td>
</tr>
<tr>
<td>Polymer crystallinity</td>
<td>Decrease</td>
</tr>
<tr>
<td>Plasticizer</td>
<td>Increase</td>
</tr>
<tr>
<td>Temperature</td>
<td>Increase</td>
</tr>
<tr>
<td>Glass transition</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

Acetylated celluloses are also referred to as cellulose esters and are generally classified in two groups: enteric and non-enteric. Enteric esters are soluble in mildly acidic to slightly alkaline solutions. Non-enteric esters mostly do not show pH-dependent solubility characteristics and are insoluble in water. The three commercially available enteric cellulose esters are cellulose acetate phthalate, cellulose acetate trimellitate and hydroxypropylmethylcellulose phthalate (HPMCP). They display pH-dependent solubility characteristics and are soluble in mildly acidic to slightly alkaline solutions. Three of the most investigated and commercially available non-enteric cellulose esters are cellulose acetate, cellulose acetate butyrate and cellulose acetate propionate. They do not have pH-dependent solubility. They are for the most part insoluble in water, with one exception: cellulose acetates with low acetyl content (Eastman, 1997).
Table 3: Water vapor transmission rates of membranes (Jerzewski and Chien, 1992).

<table>
<thead>
<tr>
<th>Polymer membrane</th>
<th>Water vapor transmission rate (g/100 in²/24 h/mm thick)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinyl alcohol</td>
<td>100.0</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>30.0 – 150.0</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>70.0</td>
</tr>
<tr>
<td><strong>Cellulose acetate</strong></td>
<td><strong>40.0 – 75.0</strong></td>
</tr>
<tr>
<td>Ethylcellulose</td>
<td>75.0</td>
</tr>
<tr>
<td>Cellulose acetate butyrate</td>
<td>50.0</td>
</tr>
<tr>
<td>Polyvinylchloride – cast</td>
<td>10.0 – 20.0</td>
</tr>
<tr>
<td>Polyvinylchloride – extruded</td>
<td>6.0 – 15.0</td>
</tr>
<tr>
<td>Polycarbonate</td>
<td>8.0</td>
</tr>
<tr>
<td>Polyvinylfluoride</td>
<td>3.0</td>
</tr>
<tr>
<td>Ethylene-vinyl acetate</td>
<td>1.0 – 3.0</td>
</tr>
<tr>
<td>Polysterse</td>
<td>2.0</td>
</tr>
<tr>
<td>Cellophane, polyethylene coated</td>
<td>&gt; 1.2</td>
</tr>
<tr>
<td>Polyvinylidene fluoride</td>
<td>1.0</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>0.5 – 1.2</td>
</tr>
<tr>
<td>Ethylene propylene copolymer</td>
<td>0.8</td>
</tr>
<tr>
<td>Polypropylene</td>
<td>0.7</td>
</tr>
<tr>
<td>Polyvinyl chloride, rigid</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Quantity of water permeating the membrane per 100 in², per 24 h, per mm thickness

In controlled release applications, the permeability of the membrane to be used is of the utmost importance. Patel et al. (1964) investigated some cellulose acetates such as cellulose acetate butyrate, cellulose acetate phthalate, and cellulose acetate stearate and concluded that water permeability decreased with increasing length of the acid chain moiety. It was also found that water permeability of cellulose acetate stearate was relatively independent of temperature. Amann et al. (1974) studied the water vapor permeation through a cellulose acetate film applied to the surface of solid systems that have an affinity for water. Cellulose acetate phthalate was
used and it was concluded that the method of film application influenced the rate of water penetration as well as physical properties of the material being coated.

3.2.1.2 Membrane thickness

Zentner et al. (1985), using KCl compressed core tablets coated with cellulose acetate mixed with sorbitol as a leaching agent for a porosity controlled osmotic pump, showed that as coating thickness increased from 0.12 mm to 0.46 mm, KCl release rate decreased from 0.29 g/h to 0.090 g/h. Mohammadi et al. (2000) also investigated the effect of membrane thickness on release rate. Propranolol hydrochloride core tablets were coated with cellulose acetate and it was shown that an increase in coating thickness resulted in a decreased release rate of propranolol hydrochloride. Murthy et al. (1988) have noted the required minimum coating thicknesses of some polymers (applied from organic solvent) for suitable gastric fluid resistance (Table 4).

Table 4: Minimal coating thickness required for suitable gastric fluid resistance (Eastman, 1991)

<table>
<thead>
<tr>
<th>Polymer film applied from organic solvent</th>
<th>Minimum coating thickness (mg/cm²)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate phthalate</td>
<td>2.1</td>
</tr>
<tr>
<td>Poly(vinyl acetate phthalate)</td>
<td>4.9</td>
</tr>
<tr>
<td>Acrylic copolymer (Eudragit L-100)</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*Average thickness of the polymer film per cm².

3.2.1.3 Polymer molecular weight

Eastman (1997) studied osmotic pump tablets of theophylline core tablet, coated with cellulose acetate of various molecular weights, from 30,000 to 50,000. The coated tablets had the same film thickness and it was concluded that the increase of the molecular weight of the polymer used as membrane had no effect on the release profile of the osmotic pumps.
3.2.2 Tablet core

Many studies of osmotic systems, both elementary osmotic pumps and porosity controlled pumps have used potassium chloride (KCl) as the compacted core tablet. The solubility is measured by electrical conductance measurements, and in those studies, the solubility of KCl varied from 330 mg/ml to 343 mg/ml (Theeuwes, 1975; Zentner, 1985). Several other water-soluble (high to low solubility) drugs have been used in porosity controlled osmotic pumps: cyclobenzaprine HCl (25 mg of cyclobenzaprine HCl mixed with 500 mg of α-D-glucose), trimazosin (40 wt % trimazosin, 58 wt % microcrystalline cellulose and 2 wt % magnesium stearate) (Zentner, 1985). The osmotic pressure is first measured with a commercially available osmometer that measures the vapor pressure difference between the solution under study and pure water. Then, thermodynamic principles can then be applied in order to convert the vapor pressure difference into osmotic pressure. Table 5 lists osmotic pressures of saturated solutions of some compounds and mixtures of compounds at 37 °C, in water.

When using poorly water-soluble active agents, the addition of solubilizers or an osmotic agent in the formulation of the core tablet or other techniques can improve the dissolution of the agent. Okimoto et al. (1998) used prednisolone (PDL), a poorly water-soluble drug, for a controlled-porosity osmotic pump. The aqueous solubility of prednisolone at 37 °C is 0.2 mg/ml, compared to 300 – 343 mg/ml for KCl. Sulfobutyl ether-β-cyclodextrin ((SBE)$_7$-β-CD), was used as a solubilizer and an osmotic agent, at 1:1 and 2:1 molar ratios of PDL. This combination was compared with three other combinations: PDL:lactose-fructose sugar mixture, PDL:Hydroxypropyl-β-cyclodextrin (HP-β-CD) at 1:1 molar ratio and PDL:HP-β-CD at 1:2 molar ratio. The core tablets were coated with a suspension of micronized lactose/cellulose acetate (CA-398-10)/triethyl citrate in a weight ratio of 2/2/1 in ethanol/dichloromethane in a weight ratio of 10.5/31.5. The in-vitro release rate of PDL from both the core and coated tablets showed the following order: PDL: (SBE)$_7$-β-CD at 1:2 > PDL:HP-β-CD at 1:2 > PDL: (SBE)$_7$-β-CD at 1:1 > PDL: Sugar mixture. PDL: (SBE)$_7$-β-CD at 1:2 provided the only complete release with 90% of PDL released at zero-order. These results are consistent with the fact that compared to HP-β-CD and the sugar mixture, (SBE)$_7$-β-CD has a greater ability to solubilize PDL and produces higher osmotic pressures. This also illustrates that an appropriate amount of solubilizer is required in order to achieve complete release of the agent.
Theeuwes (1978) suggested two modifications of the elementary osmotic pump, for delivering insoluble drugs from osmotic pump tablets. In the first, the osmotic agent particles would be initially coated with an elastic semi-permeable film then mixed with the low-solubility drug, the mixture compressed into a core tablet and subsequently coated with a rigid semi-permeable membrane. In the aqueous environment, water would first enter the core tablets through the rigid semi-permeable membrane then reach the osmotic agent through the elastic semi-permeable membrane. The elastic membrane would swell thus creating a hydrostatic pressure build-up inside the core tablet which would force the poorly water-soluble drug through the drilled orifice (Figure 14). The second approach is commonly referred to as the “Push-pull” osmotic pump. In this system, the drug and the osmotic agent are separated in the tablet by an elastic diaphragm and the tablet coated with a semi-permeable membrane with the drilled hole on the side of the poorly soluble drug. Water will enter the tablet through the membrane, the hole-free side, the osmotic agent will swell and push the diaphragm into the upper chamber resulting in the drug being pushed through the drilled orifice (Figure 15) (Baker, 1987).

Bittner et al. (2000) introduced a different approach to dealing with non water-soluble compounds. Using the Alzet osmotic pumps and $^{14}$C-mannitol as the drug under study, they compared three water-miscible co-solvents with the potential for increasing the solubility of poorly water-soluble compounds in pure water: polyethylene glycol 400, N-methyl-2-pyrrolidone and N, N-dimethylacetamide. They concluded that different ratios of these co-solvents with water were compatible with the interior of the Alzet. The release rates of these mixtures were similar to that of pure water.
Figure 14: Delivery method for insoluble drugs proposed by Theeuwes. The drug is between the small spheres of elastic semi-permeable membranes which contain salt. (a): before operation. (b): in operation, in an aqueous environment. Water diffuses first across the rigid semi-permeable membrane of the tablet then across the elastic semi-permeable membrane enclosing the osmotic agent salt, by osmosis. The elastic membranes will swell thus creating a hydrostatic pressure build-up inside the core tablet which will force the poorly water-soluble drug through the drilled orifice. (Adapted from Baker, 1987).

Figure 15: The “Push-pull” osmotic pump proposed by Theeuwes. (a): before operation, the drug and salt (osmotic attractant) chambers are full. (b): in operation, in an aqueous environment. Water increases the volume of the salt chamber as it moves into it. This volume increase distends the elastic diaphragm separating the salt and drug chambers, thereby pumping the drug out. (c): same as in (b), with further increase in the volume of the salt chamber and more drugs pumped out. (Adapted from Baker, 1987).
Table 5: Osmotic pressures of various compounds and mixtures at 37°C, in water
(Theeuwes, 1976)

<table>
<thead>
<tr>
<th>Saturated solutions of compound / mixture</th>
<th>Osmotic pressure (atmosphere)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose – Fructose</td>
<td>500</td>
</tr>
<tr>
<td>Dextrose – Fructose</td>
<td>450</td>
</tr>
<tr>
<td>Sucrose – Fructose</td>
<td>430</td>
</tr>
<tr>
<td>Mannitol – Fructose</td>
<td>415</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>356</td>
</tr>
<tr>
<td>Fructose</td>
<td>355</td>
</tr>
<tr>
<td>Lactose – Sucrose</td>
<td>250</td>
</tr>
<tr>
<td>Potassium Chloride</td>
<td>245</td>
</tr>
<tr>
<td>Lactose – Dextrose</td>
<td>225</td>
</tr>
<tr>
<td>Mannitol – Dextrose</td>
<td>225</td>
</tr>
<tr>
<td>Dextrose – Sucrose</td>
<td>190</td>
</tr>
<tr>
<td>Mannitol – Sucrose</td>
<td>170</td>
</tr>
<tr>
<td>Sucrose</td>
<td>150</td>
</tr>
<tr>
<td>Mannitol – Lactose</td>
<td>130</td>
</tr>
<tr>
<td>Dextrose</td>
<td>82</td>
</tr>
<tr>
<td>Potassium sulfate</td>
<td>39</td>
</tr>
<tr>
<td>Mannitol</td>
<td>38</td>
</tr>
<tr>
<td>Sodium phosphate tribasic. 12 H₂O</td>
<td>36</td>
</tr>
<tr>
<td>Sodium phosphate dibasic. 7H₂O</td>
<td>31</td>
</tr>
<tr>
<td>Sodium phosphate dibasic. 12 H₂O</td>
<td>31</td>
</tr>
<tr>
<td>Sodium phosphate dibasic anhydrous</td>
<td>29</td>
</tr>
<tr>
<td>Sodium phosphate monobasic H₂O</td>
<td>28</td>
</tr>
</tbody>
</table>
3.2.3 Drilled hole

Using KCl osmotic pumps, Theeuwes (1975) established that the size of the drilled hole must be between a maximum size $A_{\text{max}}$ and a minimum size $A_{\text{min}}$. A hole size greater than $A_{\text{max}}$ allows for the contribution of solute diffusion through the hole to the overall delivery rate. A hole size smaller than $A_{\text{min}}$ enhances the hydrostatic pressure inside the tablet, affecting the zero-order release rate. The hydrostatic pressure not only decreases the osmotic influx but also increases the volume of the system which decreases delivery, caused by an in-flow larger than the out-flow. The minimum and maximum hole sizes expressed as cross-sectional areas are:

$$A_{\text{min}} = 5 \sqrt{\frac{l \frac{dv}{dt}}{\Delta P_{\text{max}}}}$$  \hspace{1cm} \text{(Equation 4)}

Where $l$ is the length of the drilled orifice, $\frac{dv}{dt}$ is the volume flux through the orifice, $\nu$ is the viscosity of the dispensed solution, $\Delta P_{\text{max}}$ is the maximum tolerated hydrostatic pressure difference between the inside and outside of the tablet.

$$A_{\text{max}} = \frac{l}{F} \left( \frac{dm}{dt} \right)_z \frac{1}{S}$$  \hspace{1cm} \text{(Equation 5)}

Where $F$ is a dimensionless factor expressing the diffusional contribution to the release rate (it specifies how many times greater is the zero-order pumping rate than the free diffusion rate.

Perfect membrane-controlled osmotic delivery has been obtained when $F \geq 40)$, $\frac{dm}{dt}$ is the solute delivery rate and $S$ is the solubility of the drug in water.
4. NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY

4.1 Nuclear Magnetic Resonance physics

4.1.1 Nucleus of the atom

The chemical properties of an atom are determined mostly by its electron structure while its physical properties are primarily dependent on the atom’s nucleus. The NMR signal arises from the atom’s nucleus, which accounts for almost all of the atom’s mass. The nucleus of the atom is composed of two types of particles or nucleons: protons and neutrons. The hydrogen nucleus contains no neutrons and only one proton. The number of protons and orbiting electrons are usually the same in order to maintain electrical neutrality of the atom. In contrast, the number of protons and neutrons are often unequal (Lufkin, 1990).

Nuclei with an odd number of protons, neutrons or protons plus neutrons (unpaired protons or neutrons or both) spin about their axes and thus have a nuclear spin with an associated angular momentum (P). The angular momentum is zero when there are no unpaired nucleons. Although a neutron is electrically neutral, its component charges are not uniformly distributed and thus may have net spin if not balanced with a partner. The angular momentum describes the rotational motion of a body and must be non-zero in order for the NMR phenomenon to occur. The angular momentum means a nucleus will precess when placed in a magnetic field and thus generate resonance and an NMR signal (Bloch et al., 1946; Purcell et al., 1946).

NMR is most easily observed for the hydrogen nucleus for many reasons: it is the simplest atom with a nuclear spin (it has only one nucleon, a proton), it is very abundant in organic molecules and, importantly for biological systems, in water. It has a high magnetogyrlic ratio which yields a high magnetic resonance sensitivity, it is widely used in Magnetic Resonance Imaging (MRI) of human tissues and organs as it constitutes approximately two thirds of all atoms in human beings (in water molecules) (Gunter, 1995).
4.1.2 Magnetic properties of the nucleus

A magnetic field is induced when there is a moving electrical charge. Atoms and molecules are composed of moving electrical charges: positively charged spinning nuclei and negatively charged spinning electrons. Each of the NMR active nuclei induces a minute magnetic field termed magnetic dipole moment (MDM) and thus behaves like a magnet, with north and south poles (Figure 16). In the presence of a strong external magnetic field $B_0$, the MDMs of these nuclei (mathematically represented by vectors) must align themselves in parallel or anti-parallel orientations with respect to the external magnetic field and precess around it, yielding a resultant vector of all MDMs, $M_0$ also referred to as the net magnetization field vector (Figure 17) (Horowitz, 1989). The nuclei oriented parallel to the external magnetic field are in the ground state (lower energy) while the ones anti-parallel to the external field are in the excited state (higher energy). The difference in the populations of the two states depends on the strength of the applied magnetic field, the magnetogyric ratio and the temperature (Lufkin, 1990).

![Figure 16](image_url)

Figure 16: A: magnetic dipole moment of a proton spinning about its axis (represented by the oblique arrow) with a north and south pole. B: magnetic fields produced by a bar magnet (represented by curved lines to the left and right of the bar magnet). N: north, S: south. (Adapted from Lufkin, 1990).
4.2 Principles of NMR spectroscopy

Since the nuclei rotate about an axis, they have the property of spin. The angular momentum associated with the spin of a particle is an integral or half integral of $\frac{h}{2\pi}$, with $h$ being the Planck constant. Odd integral values are also possible e.g. 3/2. The spin quantum number $I$ is the maximum spin component for a particular nucleus. It is a fixed number, assigned to a nucleus in its stable ground state. It is proportional to the angular momentum of the particle and characterizes its ability to undergo NMR. Nuclei with even mass and atomic numbers (even number of protons and neutrons), such as $^4\text{He}$, $^{12}\text{C}$, $^{32}\text{S}$, have $I = 0$. They do not possess a net angular momentum and thus cannot experience NMR under any circumstances. A nucleus has $2I + 1$ discrete states. The angular momentum component for these discrete states in any direction have values of $I, I-1, I-2, \ldots, -I$. In the absence of an external magnetic field, these discrete states have identical energies. For the proton, the spin number $I = 1/2$, corresponds to two spin states: $I = +1/2$ and $I = -1/2$. The spin of a nucleus generates a magnetic field because of the charge it contains. The corresponding magnetic dipole $\mu$ (in the magnetic dipole concept, local magnetic fields from subatomic particles, ions and small molecules are considered to emanate from a tiny bar magnet with north and south poles at the center of the particle) is oriented along the axis of spin and is characteristic of each nucleus. The magnetic quantum
states m correlate the particle spin quantum number and the magnetic dipole moment: m = I, I-1, I-2, ..., -1

In the presence of the external magnetic field, each MDM vector is precessing around the magnetic field axis. The nucleus is spinning and the MDM is precessing about the axis of the applied magnetic field $B_0$ (Figure 18). The frequency of precession is called the resonance or Larmor frequency, after the British physicist Sir Joseph Larmor (Gunter, 1995) and is given in the following equation:

$$v_0 = \frac{\gamma}{2\pi} B_0$$

(Equation 6)

Where $v_0$ is the frequency of precession (in Hertz), $\gamma$ is the nuclear gyromagnetic constant of the nucleus, and $B_0$ is the external magnetic field. The frequency is proportional to the strength of the applied magnetic field and the nucleus.

Thus a particle possessing a magnetic dipole moment will display certain properties: it will orient its magnetic dipole, thus its spin axis parallel to the external field (against or with the external magnetic field) and a nuclear energy level diagram will be generated, because the magnetic energy of the nucleus is restricted to certain discrete values. The energy of the nucleus can assume only $2I + 1$ discrete values corresponding to $2I + 1$ positions. Transitions between energy levels of the diagram can be stimulated through a radio frequency (rf) transmitter. The absorption of energy (transition from a lower energy level to a higher energy level) can be detected, amplified and recorded as a spectral line: the resonance signal (Figure 19). In other words, a spectrum can only be generated for atoms whose nuclei have non-zero magnetic moment such as $^1H$ and $^{19}F$ (Gunter, 1995).
Figure 18: (a) Nuclear spins represented as vectors (shorter arrows), precessing around the axis of the external magnetic field $B_0$. Spins with $m_I = +1/2$: lower energy (more populated). Spins with $m_I = -1/2$: higher energy (less populated).

(b) The external magnetic field $B_0$ and the net magnetization vector $M_0$. (Adapted from Blazek, 1998).

Figure 19: Formation of an NMR signal. $E$: energy level, $h$: the Planck constant, $v_0$: frequency, $g_N$: nuclear magneton, $\mu_N$: magnetic moment of the particle, $\gamma$: nuclear gyromagnetic constant of the nucleus, $B_0$: magnetic field. (Adapted from Gunter, 1995).
4.3 Pulse NMR spectroscopy

Pulse/Fourier transform NMR is the most common modern NMR technique. In this technique, the sample is irradiated periodically with a brief, very strong rf radiation (0.01 – 0.4 Tesla). Following irradiation, the free induction decay signal, a radio frequency emission signal is recorded as a function of time (Elster, 1994). Usually, pulses of 1 to 10 µs are employed and the delay time between pulses is chosen around 1 s, for complete recovery of $M_0$. For quantitative measurements, a delay time of approximately 5x$T_1$ must be used before repeating the experiment in order for the spin magnetization to recover to equilibrium (Elster, 1994).

NMR experiments used to be done by continuous wave method where a sample was in a fixed magnetic field and the rf field was scanned through a range of values (or vice-versa). After the resonance for each type of nucleus in the sample had been matched, an absorption peak was observed in the NMR spectrum. In the current Pulse FT-NMR experiments, the applied rf pulses have a broad excitation range and simultaneously satisfy the resonance condition for all the different nuclei in the sample within that range. In this method, as the perturbed systems relax toward equilibrium, the NMR spectrum is obtained by detecting the decay of the net magnetization in the x,y plane (free induction decay or FID) as a function of time. The NMR spectrum is obtained by Fourier transformation of the FID which gives a signal intensity as a function of frequency i.e. the NMR spectrum (Blazek, 1998).

4.4 Relaxation processes

4.4.1 $T_1$: Spin – lattice relaxation (longitudinal relaxation)

In NMR, the term lattice refers to the assemblage of atoms constituting the sample, including when the sample is a liquid or a gas. The spin – lattice relaxation is a first order process defined by the time $T_1$ and involves a net transfer of energy from the nuclear spin system to its environment. Since all NMR energy exchanges must be stimulated, $T_1$ relaxation can occur only when a proton encounters another magnetic field fluctuating near the Larmor frequency. The properties of the spin – lattice relaxation are (Skoog, 1985):
• T₁ is the reciprocal of the first order rate constant for the recovery of the Boltzmann distribution between energy levels after a perturbation.

• T₁ is affected greatly by the mobility of the lattice and the nuclei being observed.

• T₁ is long for low mobility lattices i.e. in rigid crystalline solids and viscous liquids.

• T₁ is short for high mobility lattices because of the increase in vibrational and rotational frequencies which enhance the probability of a magnetic fluctuation of the proper frequency for a relaxation transition.

• T₁ is also long for very high mobility lattices since the fluctuation frequencies are further increased and spread over such a broad range that the probability of a suitable frequency for a spin – lattice transition decreases again.

• T₁ is very short in the presence of an unpaired electron. This is due to the fact that the unpaired electron’s spin creates strong fluctuating magnetic fields.

When a molecule moves or tumbles too quickly, as in the case of free water (small molecular size), T₁ is long (approximately 2 to 3 seconds for free water). When a water molecule moves too slowly, as in ice (crystalline state), T₁ is also very long. The same principle applies to hydrogens on large macromolecules as they, too, move or tumble very slowly. T₁ values are shorter for water bonded to other molecules such as macromolecules and proteins as their motion is that of the large, slow moving macromolecule (Elster, 1994).

The T₁ values of nuclei are very important as they provide information about the dynamic properties of molecules (Gunter, 1995). Knowledge of the T₁ values also helps in obtaining quantitative signals since the delay between successive rf pulse irradiations should be five times T₁ for a complete recovery to the Boltzmann equilibrium (Equation 7 & 8). The experiment conducted to measure T₁ is the inversion recovery experiment (Figure 20) (Vold et al., 1968). In this experiment, an 180° rf pulse is applied at the beginning of the experiment which results in shifting the vector M₀, the macroscopic magnetization (resultant of individual magnetic moments of the nuclei constituting the excess population of the ground state) into the negative z direction (Figure 20(b)). Spin – lattice relaxation will take place during the time τ and the value of M₀ will change until the Boltzmann equilibrium is reached. An 90° rf pulse is then applied at a series of time values τ, shifting the vector M₀ in the x,y-plane in order for the sign and magnitude
of the magnetization to be detected from the observed signal obtained from Fourier transformation of the FID.

The Boltzmann equation is given by:

\[
\frac{N_1}{N_2} = e^{\frac{-\Delta E}{kT}} \tag{Equation 7}
\]

Where \(N_1\) is the number of protons in the higher energy state, \(N_2\) is the number of protons in the lower energy state, \(k\) is the Boltzmann constant \((1.38 \times 10^{-16} \text{ erg/Kelvin})\) and \(\Delta E\) is the energy difference between the two energy states.

The magnitude of the total magnetization can be expressed by:

\[
M_0 = N \left( \frac{\gamma}{2 \pi} \right)^2 \frac{B_0}{2kT} \tag{Equation 8}
\]

Where \(N\) is the total number of spins.

Figure 20 (c) and Equation 9 show the relationship between the intensity of the signal \(I(t)\) and \(\tau\):

\[
I(t) = I_0 + Ae^{\frac{-\tau}{T_1}} \tag{Equation 9}
\]
Figure 20: (a) The inversion recovery sequence. A 180° rf pulse (represented by a rectangle) is applied along the x-axis, at the beginning of the experiment. Spin – lattice relaxation will take place during a time $\tau$. After the time $\tau$, a 90° rf pulse (represented by a rectangle) is applied, then the signal, FID (Free Induction Decay), is detected. $T_R$: repetition time (time between two sequences), $\tau$: delay time between two rf pulses.

(b) Vector description of the net magnetization as a consequence of the inversion recovery. The application of the 180° pulse results in shifting the vector $M_0$, the macroscopic magnetization (resultant of individual magnetic moments of the nuclei constituting the excess population of the ground state) into the negative z direction. After the time $\tau$, a 90° rf pulse is applied, the vector $M_0$ is shifted in the x,y-plane in order for the sign and magnitude of the magnetization to be detected from the observed signal obtained from Fourier transformation of the FID.

(c) Effect of delay time $\tau$ on the signal intensity. (Adapted from Blazek, 1998).
$T_1$ can also be measured by saturation recovery. The main advantage of this sequence is the ability to measure $T_1$ more quickly than an inversion recovery pulse sequence. In the saturation recovery sequence, an initial 90° rf pulse tilts the magnetization of the spin system into the $x,y$-plane perpendicular to the main magnetic field. This initial 90° rf pulse and a group of spoiler pulses effectively destroy the residual recovered longitudinal magnetization. The longitudinal magnetization developed after a time $T_R$ is rotated into the $x,y$-plane by another 90° rf pulse. A gradient echo is acquired immediately after this.

Figure 21: A schematic of the saturation recovery sequence: A 90° rf pulse (represented by a rectangle) is applied. After a time $T_R$, another 90° rf pulse is applied and then the signal is acquired.

4.4.2 $T_2$: Spin–spin relaxation (transverse relaxation)

It is defined by the parameter $T_2$, which is the reciprocal of the first order rate constant for the dephasing of the spins in the $x,y$ plane. It occurs with or without energy transfer, unlike $T_1$, and is caused by any intrinsic process leading to a loss of phase coherence. Some properties of $T_2$ are given as follows (Elster, 1994):

- Anything that causes $T_1$ relaxation can also cause $T_2$ relaxation.
- $T_2$ relaxation can occur without $T_1$ relaxation.
- $T_2$ is always less than or equal to $T_1$.
- $T_2$ is mostly caused by static or slowly fluctuating local magnetic field variations within the sample.
• $T_2$ arises also when two neighboring nuclei of the same kind have identical precession rates, but are in different quantum states, the magnetic fields of each can interact to cause an interchange of states. Thus the nuclei in the excited state would relax to a lower state and the nuclei at the lower spin state would be excited to a higher quantum state. No net change in the relative spin state population will occur.

• $T_2$ is short in slow or quasi-static molecular motions.

• $T_2$ is very short in very slow molecular motions i.e. in rigid molecules such as membrane phospholipids.

• $T_2$ is long in rapidly moving molecules and is approximately equal to $T_1$.

$T_2$ relaxation cannot be measured directly from the FID (free induction delay), although it contributes to the FID because additional factors like magnetic field inhomogeneities enhance the rate of the decay and thus the true $T_2$ value cannot be measured. $T_2$ relaxation is measured by the spin – echo experiment (Hahn, 1950) (Figure 22) or by multi-echo pulse experiment (Carr and Purcell, 1954) (Figure 23). In the spin-echo experiment, an 90° rf pulse is applied in the x-direction, on the sample and it shifts the z-magnetization into the x,y-plane (Figure 22(b)). Because the inhomogeneity of the applied magnetic field causes a range of Larmor precessional frequencies, the individual nuclear spins begin to fan out and the magnitude of the transverse magnetization decreases (there is also additional decay due to real $T_2$ processes). There is a delay of magnitude $\tau$. An 180° rf pulse is then applied so that all vectors are turned around into the negative y-direction. The faster vectors now lag behind the slower ones. Another delay $\tau$ is implemented. After this last delay, the vectors refocus, because of the different precession frequencies. The refocused vector though has a reduced magnitude as a result of true $T_2$ dephasing. The resultant transverse magnetization can now be detected in the receiver coil as a signal: the spin – echo.

It can be concluded that the intensity of the spin echo would depend only on the transverse (spin – spin) relaxation rate, the irreversible loss of transverse magnetization during the period 2$\tau$, because the contributions of the field inhomogeneity to the fanning out process for the elementary spins have been eliminated by the refocusing process. Measurements of this echo intensity as a function of $\tau$ yield the true $T_2$ value.
Figure 22: The spin-echo experiment:

(a) Spin-echo pulse sequence: A 90° rf pulse (represented by a rectangle) is applied in the x-direction, on the sample. After a delay of magnitude $\tau$, a 180° rf pulse (represented by a rectangle) is applied. Another delay $\tau$ is implemented. After this last delay, the signal, the spin-echo is detected.

(b) Vector description of the effect of the spin-echo pulse sequence on the net magnetization vector in the x,y-plane. A 90° rf pulse is applied in the x-direction, on the sample and it shifts the z-magnetization into the x,y-plane. After a delay of magnitude $\tau$, a 180° rf pulse is then applied so that all vectors are turned around into the negative y-direction. The faster vectors now lag behind the slower ones. Another delay $\tau$ is implemented. After this last delay, the vectors refocus, because of the different precession frequencies. The refocused vector though has a reduced magnitude as a result of true $T_2$ dephasing. The resultant transverse magnetization can now be detected in the receiver coil as a signal: the spin-echo. F: fast precessing vector, S: slow precessing vector (not exactly on resonance).

(c) Effect of $T_E$ on the signal intensity. (Adapted from Blazek, 1998).
The multi-echo pulse sequence offers a faster $T_2$ determination and ultimately a more efficient experiment, compared to the spin-echo, as multiple data points at $n \times 2\tau$ that are acquired from a single excitation pulse consists of an echo train, contrary to the spin-echo pulse sequence which consists of a single incremented $T_E$. The drawback of the multi-echo pulse sequence is that the $T_2$ values obtained are not true $T_2$ because of the presence of stimulated echoes. However, this disadvantage does not affect the correlation between the $T_2$ and concentration values as long as $T_2$ is reproducible since this correlation is only empirical (Wong, 2001).

In the multi-echo experiment (Figure 23), after a recycle delay $T_R$, a 90° pulse is applied tipping the net magnetization to the $x,y$ plane. After a time $\tau$, the spins begin to dephase and a 180° pulse is applied. This last pulse rotates the spins around the $x,y$-axes. After $2\tau$, the spins are refocused and the signal is detected. After $3\tau$, a second 180° pulse rotates the spins around the $x,y$-axes again. After $4\tau$, the spins are refocused and are detected. Each echo that is collected has a decreased signal intensity from the previous echo as the $T_E$ is increased along the train. The presence of stimulated echoes with slightly increased intensity in the multi-pulse sequence are due to the fact that any two pulses create an echo. After the 90°-180° pulse pair, an echo is created and after the 180°-180° pulse pair, a second echo is created. However, any three pulses create a stimulated echo. This translates to $T_2$ values different by as much as a factor of two, between the two pulse sequences (Carr and Purcell, 1954).

Figure 22 (c) and Equation 10 show the relationship between the intensity of the signal $I(t)$ and $T_E$:

$$I(t) = Ae^{\frac{T_E}{T_2}}$$  \hspace{1cm} (Equation 10)
number of echoes

Figure 23: Multi-echo pulse sequence for measuring T₂: a 90° pulse (represented by a rectangle) is applied along the x-axis. After a time τ, a 180° pulse (represented by a rectangle) is applied. After a time 2τ, the signal is detected. After 3τ, a second 180° is applied (not shown here). After a time 4τ (not shown here), the signal is detected again and the sequence repeated n times. (Adapted from Wong, 2001).

In a pulse FT-NMR experiment, the rf pulse disturbs the population balance in the spin states and a temporary phase-coherence in the spins is generated. The system population returns to the Boltzmann equilibrium population after the pulse. The Bloch equation for Boltzmann relaxation expresses this relaxation process (Bloch et al., 1946):

\[
\frac{\partial M_z}{\partial t} = - \frac{(M_z - M_0)}{T_1}
\]

(Equation 11)

Where T₁ is the spin-lattice (longitudinal) relaxation time. In the T₂ relaxation process, the decay of the FID is caused by the spin-spin (transverse) relaxation. The nuclear spins, phase-coherent during the rf pulse, start to dephase again, a decrease from the maximum intensity:

\[
\frac{\partial M_a}{\partial t} = - \frac{M_a}{T_2}
\]

(Equation 12)

Where a = x, y. Thus, the T₁ and T₂ relaxation times are characteristic of a nuclear spin species in a particular local environment. T₁ allows quantitative signals to be obtained by setting the delay
(T_R) between successive repetitions of pulse sequence at five times T_1 to permit complete recovery to Boltzmann equilibrium. During inversion-recovery sequence (Figure 20), the magnetization changes from -M_0 to +M_0 are described by:

\[
M_Z = M_0(1 - 2e^{-\frac{T_R}{T_1}}) \quad \text{(Equation 13)}
\]

Where T_R is the incremented delay. As mentioned earlier, the true T_2 values are not directly measurable from the FID envelope because although T_2 relaxations are responsible for the FID decay, other factors such as the magnetic field inhomogeneities, increase the rate of the decay. The spin-echo is a method which eliminates these spurious contributions (Figure 22) (Hahn, 1950):

\[
M_Z = M_0e^{\frac{T_E}{T_1}} \quad \text{(Equation 14)}
\]

Where T_E is the time-to-echo = 2\tau and \tau is the incremented delay.
5. **NMR IMAGING**

5.1 **Magnetic Resonance image formation**

NMR Imaging offers a nondestructive, noninvasive tool of measurement (Lauterbur, 1973). Currently, the most widely used NMR image formation technique is the sequential plane (2D-FT: two dimensional-Fourier Transformation) imaging. This technique allows for fast and efficient image acquisition (Lufkin, 1990).

![Image matrix, voxel & pixel. (Adapted from Lufkin, 1990).](image1)

Figure 24: Image matrix, voxel & pixel. (Adapted from Lufkin, 1990).

![Three intersecting perpendicular planes. (Adapted from Young, 1984).](image2)

Figure 25: Three intersecting perpendicular planes. (Adapted from Young, 1984).
A magnetic resonance imaging acquisition consists of a set of planar images through some sample volume. Signals are the NMR signals of nuclei in the sample (most often $^1$H in water). The sample volume is known as a volume element or voxel. An array of voxels constitutes the image slice. The slice thickness corresponds to the voxel thickness. One surface of the voxel is called the picture element or pixel (Figure 24). Each pixel has its own signal strength. The entire voxel volume determines the NMR signal and appears on the image as an intensity value for that pixel (Lufkin, 1990). An NMR image is obtained by determining the signal strength for each individual pixel. Each plane contains a two dimensional image which is composed of intensities located on this plane with the use of two coordinates. Two coordinate axes would be required to portray the image on each plane and three coordinate axes are required for images in all three major orthogonal planes in space (Figure 25). Thus NMR imaging acquisition is a three dimensional experiment requiring three coordinate axes (Horowitz, 1989). NMR images are created by first exciting selectively a slice of an object being imaged then signals arising from each part of the object are spatially encoded by differences in frequency and phase (Elster, 1994). This is accomplished with Magnetic Field Gradients (the external magnetic field magnitude is varied linearly from one point in space to another. Since three coordinates are required to localize a point in space, three magnetic field gradients oriented along the three major orthogonal axes in space will also be required: the slice select gradient, the phase encoding gradient and the frequency encoding gradient. The gradient is generally achieved by adding a set of coils which will produce a linearly varying field whose (small) effect is superimposed on the (large) homogeneous external magnetic field (Horowitz, 1989).

5.1.1 Slice select gradient

The slice select gradient imposes a linear change in the magnitude of the external magnetic field in one axis direction perpendicular to the plane of the desired slice such as the x-axis (Figure 26). According to the Larmor equation (Equation 6), the precession frequency of the Magnetic Dipole Moment (MDM) vectors is directly proportional to the external magnetic field magnitude (strength). Thus, the MDM vectors will precess at different frequencies from one end of the slice to the other. A frequency selective $90^\circ$ rf pulse is concomitantly applied with the gradient, allowing only MDM vectors whose precession frequency equals the frequency of the $90^\circ$ rf pulse to be “flipped” (resonance). Thus a plane in which the MDM vectors are to be “flipped” could
be selected by selecting a certain 90° rf pulse frequency (only the MDM vectors within that plane will be “flipped”. That rf pulse affects no other vectors). This rf and plane selection process constitutes the selection of an image plane (Figure 27) (Horowitz, 1989).

![Figure 26](image_url)

**Figure 26:** Linear magnetic field gradient: the height of the arrows is proportional to the field strength. The magnetic field varies linearly with distance along the gradient direction (x). $G_x$: physical gradient along the x-axis. (Adapted from Lufkin, 1990).

A range of rf frequency of the 90° pulses whose center frequency matches the Larmor frequency is selected instead of a single one, which would otherwise yield an infinitesimally thin cut. This range of frequencies is called a bandwidth. The thickness of the image slice can be modified by either changing the range of frequencies of the rf or by changing the slope of the slice select gradient (gradient amplitude). The slice select gradient is “turned on” only during the application of the rf pulse (Horowitz, 1989).

![Figure 27](image_url)

**Figure 27:** Slice selections: selective stimulation of a plane of protons. (a): axial slices, (b): sagital slices. (Adapted from Lufkin, 1990).
5.1.2 Phase encoding gradient

The slice select gradient allows for the selection of a slice. Now other gradients are required to encode the remaining two spatial dimensions and to generate an image. The phase-encoding gradient encodes spatial information in the phase of the detected signal while the frequency-encoding gradient encodes spatial information in the frequencies of the detected signal. These two processes are illustrated in Figure 28, which shows how the combined phase and frequency encoding uniquely characterize a specific region of the sample.

In this figure, a sample slice is divided in 16 squares each corresponding to a voxel. The straight arrows inside the voxels represent nuclear spins. Applying a gradient in one axis direction (x or y-axis) will change the external magnetic field's strength along that axis which in turn will change the Larmor frequencies of the nuclear spins according to their position along this gradient. In (a), all nuclear spins have the same phase and frequency i.e. all straight arrows are pointing in the same direction. This is because they are all experiencing the same external magnetic field. In (b), the differential precession of the spins during the application of the phase-encoding gradient is illustrated. A magnetic field gradient is applied in the y-axis direction that is the external magnetic field strength is varied along the y-axis. The Larmor frequencies of the nuclear spins along the y-axis are indicative of their locations. Because the nuclear spins have different Larmor frequencies according to their locations along the y-axis, they will no longer stay in phase: each group of nuclear spins situated at the same magnetic field strength will have the same Larmor frequency thus will have the same phase angle. The higher the magnetic field strength, the higher the phase angle (Figure 28 (c)). The gradient is then turned off.
Figure 28: Phase and frequency encoding processes. Each of the 4 big squares represent a sample slice and is divided in 16 small squares each corresponding to a voxel. The straight arrows inside the voxels represent nuclear spins.

(a) all nuclear spins have the same phase and frequency i.e. all straight arrows are pointing in the same direction. This is because they are all experiencing the same external magnetic field strength.

(b) A magnetic field gradient (MFG, represented by a triangle) is applied in the y-axis direction, that is the external magnetic field strength is varied along the y-axis. The nuclear spins are now rotating (circular arrows).

(c) Each group of nuclear spins situated at the same magnetic field strength will have the same Larmor frequency thus will have the same phase angle (angle of rotation from their initial position in (a)). The higher the magnetic field strength, the higher the phase angle. No change in the phase angle indicates that the nuclear spin is located in the bottom row of voxels. A 270° phase angle corresponds to the top row of voxels.

(d) At this stage, all protons have the same frequency but have different phase angles depending on their locations on the y-axis. The frequency encoding gradient is then applied along the x-axis direction, the external magnetic field strength is changed along the gradient and the frequencies of the nuclear spins will now change according to their spatial location. (Adapted from Blazek, 1998).
The spatial locations of the spins along the y-axis gradient has been encoded with phase. Although all nuclear spins are once again experiencing the same external magnetic strength, their phase angles remain different according to their location along the y-axis. No change in the phase angle indicates that the nuclear spin is located in the bottom row of voxels. A 270° phase angle corresponds to the top row of voxels. Unlike the slice select gradient which must be activated during the 90° rf pulse, the phase encoding gradient is turned on and off in the absence of any rf stimulation (Lufkin, 1990).

5.1.3 Frequency encoding gradient

The application of the frequency-encoding of the spins is displayed in (Figure 28 (d)). At this stage, all protons have the same frequency but have different phase angles depending on their locations on the y-axis. When the frequency encoding gradient is applied along the x-axis direction, the external magnetic field strength is changed along the gradient and the frequencies of the nuclear spins will now change according to their spatial location. The frequency encoding gradient is “turned on” during the echo collection i.e. it is applied only when the signal is measured (Horowitz, 1989).

The frequency encoded spatial information is detected in the rf output of the echo. The frequency encoding gradient creates a one-to-one correspondence between the frequency of the returned signal and the position of the nuclear spin which generated it, along the x-axis. The location of the proton along the frequency encoded axis (x-axis) can be specified exactly, from the strength of the readout gradient and the difference between the return signal frequency and resonant frequency of the background field.

In order to produce a signal, a proton must be located in the selected slice (from the slice selection step) and its location along the phase axis i.e. y-axis will be proportional to its phase angle (from the phase encoding step). The location of the proton along the frequency axis i.e. x-axis will be proportional to its frequency (from the frequency encoding step). At this time the machine receives a signal but cannot provide the sum of the signal strengths for each pixel grid (Horowitz, 1989).
A Fourier Transform (FT) is a mathematical technique that allows a Magnetic Resonance (MR) time-domain signal to be decomposed into a sum of sine waves of different frequencies, phases, and amplitudes. As discussed above, signals arising from each part of an imaged object are spatially encoded by differences in frequency and phase. Thus phase encoding and frequency encoding make the MR signal naturally amenable to analysis by FT. FT is always executed in order to acquire an NMR spectrum. The spectrum in imaging is usually a single line (from H₂O). The brightness of a pixel is just the magnitude of this signal from the pixel.

5.2 Two-dimensional imaging

The standard NMR experiment is conducted with a homogeneous magnetic field, yielding an NMR spectrum containing a single peak at the resonance frequency of the studied compound. In one-dimensional imaging experiment, a controlled magnetic field inhomogeneity is introduced with the application of a linear magnetic field gradient. In this experiment, the gradient is called frequency-encoding gradient because the gradient encodes spatial information in the frequencies of the detected signal. In the 2D-FT-NMR, a second magnetic field gradient is directly included in the pulse sequence in order to spatially resolve the NMR signal in a second dimension. This second gradient is termed the phase-encoding gradient (Figure 28). In both the one and two-dimensional imaging, there is a division of the entire sample into voxels.

Figure 29 shows the two-dimensional multi-echo sequence. The slice selection allows for the "selection" of a plane of the sample from which the NMR signal is detected. This is achieved by combining a selective pulse along with a linear magnetic field gradient. The latter generates a range of resonance frequencies over the sample. The combination of selective pulse and the linear magnetic field gradient results in the excitation of nuclei within a small cross-section or slice through the sample. The magnetization of the slice is then refocused by immediately applying a small negative gradient after the slice selection. The thickness of the slice is varied by controlling the gradient strength and the frequency distribution of the selective pulse. The orientation of the excited region can be varied by the application of gradients along either the x,y and z directions. Only nuclei within the selected slice are detected and their T₂ relaxation times determined.
As described in 4.4.2, the 90° selective pulse is applied, followed by a delay \( \tau \). The 180° selective pulse is then applied, which rotates all the spins inside the selected plane around the \( x,y \)-axes. After a delay \( 2\tau (T_E) \), the spins are refocused and detected. After a delay \( 3\tau \), a second 180° selective pulse is applied which rotates all the spins inside the selected plane around the \( x,y \)-axes. After a \( 4\tau (2 \times T_E) \), the signal is detected.

In the 2D-FT-NMR, the phase angle acquired at a given position in the sample is calculated by (Blazek, 1998):

\[
\phi = (v_0 + \gamma G_y y) t_1
\]

(Equation 15)

Where \( v_0 \) is the frequency of precession, \( G_y \) is the strength of the \( y \)-gradient, \( y \) is the position within the \( y \)-gradient, and \( t_1 \) is the duration of the gradient. The phase-encoding gradient is obtained by modulating the phase angle in the experiment. This can be accomplished by executing four operations (Blazek, 1998). First the \( t_1 \) time in successive experiments is increased. The drawback of this method is the increase of the \( T_2 \) relaxation effect on the signal with increasing \( t_1 \). Second, the spin-warp modification: varying \( G_y \) while maintaining \( t_1 \) constant. This will prevent \( T_2 \) effects on the signal (Ernst, 1987). Third, the spin-echo: to separate data acquisition from the pulses and to enhance the signal-to-noise ratio by \( \sqrt{2} \) by acquiring two equivalent FID’s from the two halves of the echo. Fourth, a Fourier transformation of the frequency and phase domains of the two-dimensional data set in order to obtain the final two-dimensional image.

The signal intensity of each voxel is related to the concentration of spins, and the effects of \( T_1 \) and \( T_2 \) relaxation processes:

\[
S(x, y) = C\rho(x, y)[1 - 2e^{-\left(\frac{T_R}{2T_2}(x, y)\right)} + e^{-\left(\frac{T_R}{T_1}(x, y)\right)}]e^{-\left(\frac{T_R}{T_1}(x, y)\right)}
\]

(Equation 16)

Where \( S(x, y) \) is the signal intensity and \( \rho(x, y) \) is the concentration of spins.

A quantitative signal is obtained when \( T_R \gg T_1 (x, y) \), \( T_E \ll T_2 (x, y) \) and, \( T_E \gg T_1(x, y) \).
Figure 29: The multi-echo pulse sequence for the two-dimensional imaging experiment used in all our imaging experiments: A 90° selective pulse is applied, followed by a delay \( \tau \). Then a 180° selective pulse is applied. After a delay \( 2\tau \) (\( T_E \)), a signal is detected. After a delay \( 3\tau \) (not shown here), a second 180° selective pulse is applied and after a \( 4\tau \) (2 x \( T_E \), not shown here), a signal is detected. The slice selection gradient (SI) is applied during the 90° and the 180° pulses. The phase encoding gradient (Ph) is applied after the 180° pulse. The frequency encoding gradient (Fr) is applied during the echo collection. Co: corrector gradients. (Adapted from Wong, 2001).
6. DRUG RELEASE FROM OSMOTIC PUMP DELIVERY SYSTEMS

6.1 Analytical methods for determining release rates

The most common analytical technique used for measuring drug release profiles is the dissolution method outlined in the US Pharmacopeia (US Pharmacopeial Convention Inc., 2000). Tablets are placed inside a vessel containing a dissolution medium maintained at 37 ± 0.5 °C. The amount of drug released after a specified length of time is determined using spectrophotometry, chromatography or other suitable methods.

However, in order to obtain information on the concentration and distribution of water or drug within an osmotic pump tablet, a wet tablet must be withdrawn from the vessel at each time point and dissected into sections of known dimensions. The tablet slices will be dried to a constant weight to allow for water determination. A suitable assay would then be conducted on the slices for drug concentration determination. This process is widely used in the investigation of hydrogels. Peppas and Colombo (1997), used tablets coated with a water impermeable membrane, on one concave side, both concave sides, or the cylindrical area of the tablet, to study the tablet swelling process during dissolution in water. At each specific time-point, a wet tablet was removed and sliced. Microphotographs of the slices were then taken and allowed for the measurement of the thickness and diameter, and the calculation of the total surface area and volume of the swelling tablet.

This method is destructive, labour intensive, requires the use of multiple samples, and is irreproducible because of the handling of wet tablets.

6.2 NMR spectroscopy and NMR Imaging in the study of drug release from osmotic pumps

NMR spectroscopy and NMR Imaging have been extensively used in the investigation of swelling hydrophilic matrix systems. The degree of tablet swelling, the gel layer thickness, and the diffusivity of water in the polymer at different time-points during the swelling of the polymer have been studied. Quantitative concentration distributions of the drug, water and the polymer
within the swollen polymer tablets have been determined and the use of other NMR active nuclei such as $^{19}$F, allowing for the independent monitoring of the drug species in an aqueous environment have also been reported (Fyfe and Blazek, 1997; Blazek, 1998; Fyfe and Blazek-Welsh, 2000). The earliest study using NMR Imaging as a research tool in drug delivery systems in general was by Carpenter et al. (1989). The release of a paramagnetic contrast agent, gadolinium diethylene triamine penta acetic acid, from an Alzet 2ML1 osmotic pump was studied. This research highlighted the non-invasive nature of NMR Imaging in controlled drug release investigations and its potential to observe drug delivery systems in-vivo.

Shapiro et al. (1995) examined the causes of variable release rates from the same batch of osmotic pump tablets. Since NMR allows for the discrimination of different water nuclei based on their environment, concentrations and behavior, the permeability of the coated membrane to water was studied. Since NMR Imaging is sensitive to mobile protons, spin-lattice and spin-spin relaxation times determine the motions of the water protons and the spatial distributions of $T_1$ and $T_2$ indicate the influence of the environment on the mobility of water (behavior). The regions of the membrane and the tablet were ranked in terms of water absorption, according to the gray scale, from “black”: where there is no water, to “very bright”: presence of large amount of water. Thus as water molecules entered the tablet membrane (change in the environment), they were detected experimentally through a change in the proton signal intensity which was translated in the image as an increase in brightness inside the tablet. The depth of the brightness was an indication of the extent of absorption through the membrane (concentration). Eight transverse slices of 1 mm thickness each were selected per tablet. Shapiro et al. (1995) found that the slow release tablets had thicker membranes compared to faster release tablets and that the membrane was asymmetrically coated: thinner on the sides of the tablets. It was reported a face/side membrane thickness average of 120/90 µm for slow tablets and 75/55 µm for fast tablets.

Fahie et al. (1998) studied two formulations of coated tablets coated on both concave sides, using two different polymeric solutions and, the core tablet was exposed in the cylindrical area. Tablets were placed in NMR tubes containing simulated gastric fluid USP without enzyme. The coat was formulated to allow absorption of water to weaken its structure and effect its disintegration at some time point after all of the drug was released. Based on the sensitivity of
NMR Imaging to mobile protons during the diffusion of water into polymeric systems, a series of images of the two formulations taken at specific time intervals were taken and examined (also using the gray scale). They found that the tablet formulation with a faster drug release allowed water permeation through the coat at an early stage, prior to the release of all the drug as predicted. In the other formulation, the water did not fully penetrate the outer coat until all the drug had been released. This observation through NMR Imaging demonstrated the porosity of the coat.

Fyfe et al. (2000) also investigated osmotic pumps in a flow-through USP dissolution apparatus by NMR Imaging. Images of the physical changes occurring in the osmotic pump during dissolution were obtained. In order to gain a better understanding of the processes involved in the drug release, simultaneous cumulative drug release measurements were also performed. Coated tablets of the following core formulation: salbutamol sulphate, sodium chloride and magnesium stearate were used in the study. Based on NMR Imaging principles and the gray scale, the images taken showed the osmotic pressure build up at the initial stage of dissolution and the progressive hydration of the inner core.

Fyfe and Blazek (1997) and Fyfe and Blazek-Welsh (2000) designed NMR Imaging techniques to conduct quantitative studies on hydrogels formed from HPMC tablets. $^1$H NMR or $^{19}$F NMR measurements of $T_1$ and $T_2$ were carried out on equilibrium mixtures of the drug, HPMC and water (or just HPMC and water when no drug was involved), using a series of HPMC/water or HPMC/drug/water weight percent ratios. This provided an insight into the polymer-drug interactions and helped determine the effect of the drug and the polymer concentrations on the water relaxation times and the drug's self-diffusion in the polymer. Using the Mathematica computer program, mathematical equations relating weight percent ratios with $T_1$ and $T_2$ (or $T_2$ only) were obtained from non-linear least squares fits of the data. From NMR images and mathematical equations, the image intensity, HPMC concentration, the density of the nuclear spins and thus the concentration of the nuclei under study such as $^1$H or $^{19}$F were obtained.
6.3 Osmotic pump tablet formulation design and materials

6.3.1 Core tablet ingredients

6.3.1.1 Triflupromazine hydrochloride:

The chemical structure of triflupromazine HCl is shown in Figure 30. Triflupromazine hydrochloride is a white powder with a yellow cast, used therapeutically as a tranquilizer and an anti-psychotic agent. It is light sensitive, its molecular weight is 388.8 g/mol, it is soluble in water (>1 g/ml) (Klaus, 1973), ethanol, and acetone (Budavari, 1996). Its pKa is 9.45 (Klaus, 1973).

Since the initial objectives of this research included the use of \( ^{19}F \) NMR Imaging, a model drug with \( ^{19}F \) nuclei was required. Triflupromazine HCl was selected for this work since numerous NMR Imaging parameters have been previously established by Fyfe and Blazek (1997). It is less toxic than the other fluorinated drugs previously studied by Fyfe and coworkers and is thus easier to handle, without special precautionary measures.

![Figure 30: The chemical structure of triflupromazine hydrochloride](image)

6.3.1.2 Lactose monohydrate NF:

The chemical structure of lactose is shown in Figure 31. Lactose is a suitable ingredient for the core tablet formulation. Fast-flowing, spray dried powder was chosen instead of the standard lactose powder, to allow for easy, direct tablet compression.
6.3.1.3 Stearic acid:

Stearic acid is a commonly used lubricant that fulfills efficiently the following three functions: the lubrication of the individual particles to aid in the release of the tablet from the die wall, anti-adhesive properties which facilitate the release of the tablet material from the faces of the lower and upper punches, and glidant properties to improve material flow from the powder hopper onto the machine table and into the dies. Stearic acid was also chosen because no other ingredient in the tablet is an alkaline salt of organic compounds. Stearic acid used with alkaline salts causes excessive sticking (Lieberman and Lachman, 1980).

The tablet target specifications were chosen based on experience, in order to obtain elegant, physically stable tablets with optimum hardness, without applying excessive compression force, and assuring reasonable drug dissolution. The tablets were sufficiently strong so that they did not break, cap, laminate, crack or chip during handling, especially during coating.

6.3.2 Coating solution ingredients

6.3.2.1 Cellulose acetates:

Cellulose acetate membranes are one of the most studied and commonly used polymer membranes for osmotic pump systems similar to the one designed in this research (Theeuwes, 1976). Cellulose acetates 320 and 398 were mixed in solution, to impart
the mechanical strength of cellulose acetate 398 and the flexibility and malleability of cellulose acetate 320, to the coated membrane.

6.3.2.2 Other ingredients:

Polyethylene glycol – 400 is used as a plasticizer to impart malleability and smoothness to the coated tablet membrane, especially around the edges. HPMC was used as a pore-former. It dissolves in water, leaving holes in the membranes. Methylene chloride and methanol were used as co-solvents to solubilize the two cellulose acetates as either solvent used separately was ineffective.

6.3.3 Overall osmotic pump tablet design

Two polymer membranes were coated on the tablet. The inner membrane, micro-porous, served as a supporting structure and added strength to the membrane system without impeding the diffusion of water. The outer membrane served as the rate-controlling membrane. This double membrane system prevented membrane failure which may cause a large amount of drug to be released at once (dose dumping).
7. **SIGNIFICANCE OF PROPOSED RESEARCH**

The system developed constitutes a direct, qualitative and quantitative method of analysis of an osmotic pump tablet, in a non-invasive, non-destructive and non-interruptive way. This approach is an attractive alternative to current exhaustive and expensive techniques that achieve more modest goals. The method developed here enables the "slicing" of the tablet in operation and a complete analysis of a single system, avoiding the sample to sample variation affecting other techniques thus allowing for a more accurate quantitative determination of the percent core tablet eroded and the drug distribution inside the tablet and qualitative evaluation of the membrane strength during dissolution: details not obtainable using other techniques.

Information from NMR Imaging is of critical importance in the research and development of the pharmaceutical industry. The development time for a controlled release formulation such as an osmotic pump is longer than that for a conventional one like an immediate-release system because in the first case, great effort and significant changes are required in order to achieve the desired release rate or profile. Changes and modifications on these formulations are mostly deduced from their drug release profiles, visual examination and knowledge of the ingredients properties. Unfortunately, these data provide little information about the changes to the intrinsic characteristics of the formulation during drug release and the effect these changes have on the rate and mechanism of drug release. Pilot batch testing by NMR Imaging provides accurate data on the coated membrane's water diffusion and strength, on the core tablet's ability to generate osmotic pressure and on the drug release rate. These data allow for better, accurately designed adjustments, improvements and predictability of drug release profile. Quality control testing by NMR Imaging pin-points with images, coating defects, inadequate water permeation and other causes of unexpected release rates, thus saving considerable time and money that would have been otherwise invested in other analytical investigation techniques leading to approximations and informed guesses.
8. SPECIFIC OBJECTIVES

In this work, it was hypothesized that the drug release profile of an elementary osmotic pump is influenced by the core tablet erosion profile. The objective of this research was to develop a system of measuring the percent core tablet eroded in an elementary osmotic pump and to correlate it with the percent drug released, during a 24 hour-dissolution process, using NMR Imaging techniques.

The specific aims designed to achieve the above mentioned objective of the research were to:

1) Determine the aqueous solubility of the model drug, triflupromazine HCl, at 37 ± 0.5 °C.

2) Formulate osmotic pump tablets: compound the blend of triflupromazine HCl, lactose, and stearic acid; compress the core tablets, coat the core tablets with cellulose acetate membranes, measure the coated membrane thickness, and drill the orifice.

3) Measure the percent drug released from the osmotic pump tablets, during a 24-hour dissolution in water, at 37 ± 0.5 °C.

4) Prepare a series of mixtures of the blend in water and measure the T$_2$ relaxation times of the water protons in these mixtures. Plot and fit the data and generate a mathematical equation relating lactose concentration to T$_2$.

5) Acquire gray-scale images and T$_2$ values maps of the osmotic pump tablets, every 3 hours, during a 24-hour dissolution in water, at 37 ± 0.5 °C.

6) Determine the total volume of core tablet eroded every 3 hours and correlate these with the measured percent drug released.

7) Explain the mechanism of drug release as influenced by the core tablet erosion.
EXPERIMENTAL

1. MATERIALS

1.1 Drug

Triflupromazine hydrochloride: Powder, Lot # 59H0786
Sigma Chemical CO (St Louis, MO)

1.2 Excipients

Lactose monohydrate NF: Fast-flowing, spray dried powder # 316,
Lot # 8500011461
Charles Tenant & Co. (Vancouver, B.C.)

Stearic acid NF: Powder, Lot # L (1T0759)
Witco Corporation (Willowdale, Ont.)

1.3 Coating materials

Cellulose acetate 320 S (CA-320 S): Pellets, Lot # 26520
Eastman Chemical Company (Kingsport, TN)

Cellulose acetate 398 (CA-398-10NF): Powder, Lot # CA-0099 NF
Eastman Chemical Company (Kingsport, TN)
See Figure 12 (b)

Hydroxypropylmethylcellulose (HPMC), USP: Powder, E-15 LV Premium
Dow Chemical Company (Midland, MI)

Polyethylene glycol (PEG)-400, NF: Liquid, Carbowax 400
Dow Chemical Company (Midland, MI)
Methylene chloride: Liquid, certified A.C.S.
Fisher Scientific (Fair Lawn, NJ)

Methanol: Liquid, HPLC grade
Fisher Scientific (Fair Lawn, NJ)

2. EQUIPMENT

2.1 Balances

Low masses: Mettler AE 163 (Hightstown, NJ)

Top-loading: Sartorius models: BP 6100, B310P and H120 (Mississauga, Ont.)

2.2 Oven

Oven: Set at approximately 37 ± 0.5 °C
Chicago Surgical & Electrical CO
A division of Lab-Line Instruments Inc. (Melrose Park, Ill)

2.3 UV Spectrophotometer systems

HP System: Hewlett Packard 8452A diode array spectrophotometer
(equipped with a deuterium lamp) (Mississauga, Ont.)
HP89532A UV-vis software (rev. A.00.00)

2.4 Blender

Cube blender: Erweka AR 400 (Milford, CT)
2.5 Compression equipment

Tablet Press: Manesty SP single punch
Manesty Machines Ltd. (Liverpool, England)

Punch tooling: 10/32" round standard concave

Scientific caliper: Code 500-133, model CD-6B
Mitutoyo Canada Inc. (Vancouver, B.C.)

Hardness tester: CT40, Engineering Systems (Nottingham, UK)
2.6 **Coating equipment**

Fluid bed column: Aeromatic AG Strea-1 coating column  
Niro Inc. (Columbia, MD)

Pump: H.R. Flow Inducer  
Watson-Marlow Ltd. (Cornwall, England)

Mixer: Dyna-Mix  
Fisher Scientific Canada (Toronto, Ont.)

![Figure 34](image)

**Figure 34:** (a): An Aeromatic AG Strea-1 fluid bed coater. (b) its principle of operation.

Figure 34 shows a Strea-1 fluid bed coater. In this experiment, a cylindrical glass column was fabricated and used instead of the plastic column. The glass column is inert to the solvents used (methanol and methylene chloride).
2.7 **Film thickness measurement equipment**

Light microscopy: Wild M5 Stereoscope with an Empix Spot Digital Camera
Leica Microsystems (Heerbrugg) GMBH
(Heerbrugg, Switzerland)

2.8 **Tablet orifice-drilling**

Computer controlled milling machine: Hermle UWF 721 H
Berthold Hermle AG (Gosheim, Germany)

2.9 **Dissolution equipment**

Dissolution: Vanderkamp 600 six-spindle dissolution tester
Autosampler: Vanderkamp model 10 fraction collector
Vanderkamp 10400 motorised drive bar
Vanderkamp VK JPS 12 pump
Vanderkamp EDS-10 programmable sequencer
Van-Kel Industries Inc. (Edison, NJ)

2.10 **NMR spectroscopy and NMR Imaging**

NMR Spectrometer: Bruker Avance DRX 360 mhz (8.46 T) with a gradient coil system permanently mounted to the room temperature shim set inside the bore of the magnet.

Micro-imaging probe: Bruker micro-imaging probe consisting of a body with a 30 mm diameter rf coil in the probe-head, tuned to $^1$H.

Temperature control unit: Bruker variable temperature unit
Bruker Medical GMBH (Rheinstetten, Germany)
Dissolution unit: Sotax flow-through dissolution unit (USP apparatus 4)
Made by the Chemistry department's mechanical shop, UBC.

Pump: Gilson Minipuls 3
Mandel Scientific CO. Ltd. (Villiers Le bel, France)

Heating water bath: Blue M
Blue M electric company (Blue Island, Ill)

4 ml glass vials: Fisher brand
Fisher Scientific Ltd. (Nepean, Ont.)

Figure 35: (a): A Sotax flow-through dissolution unit (USP apparatus 4). (b): The dissolution unit in a beaker (i), beside the 30 mm rf coil (ii).
Figure 36: Sotax flow-through dissolution unit (USP apparatus 4) in a beaker (i), the 30 mm rf coil (ii), and the probe-head (iii). (a): separately. (b): mounted.

Figure 37: (a): The Sotax flow-through dissolution unit (USP apparatus 4) and the 30 mm rf coil mounted on the probe-head (i), the Gilson Minipuls 3 pump (ii), and the Blue M Heating water bath (iii). (b): The 360 MHz superconducting magnet (marked “Magnet”).
Figure 38: The Bruker Avance DRX 360 mhz (8.46 T) system.
3 METHODS

3.1 Aqueous solubility of triflupromazine HCL at 37 ± 0.5 °C

Since triflupromazine HCl is light sensitive, every flask was wrapped with aluminum foil. Distilled water was the solvent used in all dilutions and the solutions were filtered through a 0.45 μm Millipore filter.

3.1.1 Calibration curve – preparation of standard solutions

Solutions of triflupromazine HCl in water were prepared between $1.03 \times 10^{-3}$ M and $2.06 \times 10^{-5}$ M. The maximum absorbance at a wavelength of 256 nm was recorded for all samples by U.V. spectrophotometry. As water was chosen as the dissolution fluid, distilled water served as the blank. The measured absorbances varied from 0.3142 to 0.6110. A calibration curve of absorbance versus concentration and a linear relationship were obtained.

3.1.2 Preparation of saturated solutions

Saturated solutions of triflupromazine HCl were prepared by incubating an excess of the drug in 3 ml of water in stoppered test tubes. The test tubes were stirred and placed in a 37 ± 0.5 °C oven for 48 hours with periodic stirring. The contents of each test tube were first filtered, then 1 ml was diluted to 100 ml. One ml of the diluted solution was diluted to 1000 ml; then 15 ml of this last solution was diluted to 25 ml.

The amount of drug in the diluted solutions was quantified by U.V. spectrophotometry. The maximum absorbance at a wavelength of 256 nm was recorded for all samples and distilled water served as the blank. Using the calibration curve’s linear equation and solutions dilution factors, the concentration and amount of triflupromazine HCl dissolved in the saturated solutions were then determined.
3.2 Formulation and design of osmotic pumps

3.2.1 Blending of drug and excipients

The composition of the powder blend for the triflupromazine HCl core tablets is given in Table 6.

Table 6: Blending formulation for a batch of 2000 triflupromazine HCl tablets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Use</th>
<th>Quantity (g)</th>
<th>Weight % (w/w)</th>
<th>Quantity per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose Monohydrate NF-316</td>
<td>Agent under study</td>
<td>533.2</td>
<td>95.2</td>
<td>266.6</td>
</tr>
<tr>
<td>Code #: W70-015-23 Lot #: 8500011461</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triflupromazine HCl</td>
<td>Agent under study</td>
<td>10.0</td>
<td>1.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Code #: T2896 Lot #: 59H0786</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stearic acid Powder</td>
<td>Lubricant</td>
<td>16.8</td>
<td>3.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Code #: RM 494 Lot #: L (IT0759)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>560.0</td>
<td>100.0</td>
<td>280.0</td>
</tr>
</tbody>
</table>

Triflupromazine HCl was blended with the excipients as follows: first, the triflupromazine HCl was blended with 60.0 g lactose monohydrate in a mortar, then passed through a #25 mesh (707 micron) screen. Second, the stearic acid was blended with 60.0 g lactose monohydrate in a mortar, then passed through a #25 mesh screen. Third, the remainder of the lactose monohydrate was passed through the #25 mesh screen, then loaded into the cube blender. Fourth, the premixes from the first and second steps were loaded into the cube blender and all ingredients were blended for 5 minutes with the blender rotating at 40 RPM. Fifth, the mixture was removed from the blender and stored in a sealed polyethylene bag.
3.2.2 Compression of core tablets

Core tablets were compressed using a Manesty SP single station tablet press fitted with 10/32 in. (0.3125 mm) round standard concave tooling. Tablet weight, thickness and hardness were measured every 5 minutes initially then every 10 minutes and finally every 15 minutes throughout the compression process to ensure that the target specifications were met. Tablets were compressed to the following specifications:

Table 7: Core tablet compression specifications

<table>
<thead>
<tr>
<th>Weight (mg)</th>
<th>Thickness (mm)</th>
<th>Hardness (Kp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>277.0 - 282.0</td>
<td>5.25 - 5.35</td>
<td>8.0 - 12.0</td>
</tr>
</tbody>
</table>

Samples of 10 tablets were collected in a plastic weighing-dish and weighed using a top-loading balance. The same 10 tablets were measured for thickness, from one concave side of the tablet to another, using digital calipers. Tablet hardness was then measured using the CT40 hardness tester. Tablets were broken radially during this process. Average weight, thickness and hardness were recorded.

3.2.3 Preparation of the coating solutions

The formula for the micro-porous membrane is given in Table 8.
Table 8: Micro-porous membrane formulation for a batch of 1000 tablets
Average membrane thickness: 33.52 ± 0.51 μm

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Use</th>
<th>Quantity (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate 320 S</td>
<td>Film formation</td>
<td>2.50</td>
</tr>
<tr>
<td>Eastman Lot #: 26520</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulose acetate 398 (CA-398-10NF)</td>
<td>Film formation</td>
<td>2.50</td>
</tr>
<tr>
<td>Eastman Lot #: CA-0099 NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMC (E 15 LV PREM)</td>
<td>Pore-former</td>
<td>2.50</td>
</tr>
<tr>
<td>Lot #: KL 13012 N21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol – 400</td>
<td>Plasticizer</td>
<td>0.61</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>Solvent</td>
<td>233.0</td>
</tr>
<tr>
<td>Methanol</td>
<td>Solvent</td>
<td>58.3</td>
</tr>
</tbody>
</table>

This solution was prepared as follows: methylene chloride and methanol were placed in a large beaker, covered to minimize evaporation, and stirred with a mixer-propeller set at 4 RPM. After 15 minutes of stirring, cellulose acetate 320 S was added. Twenty five minutes after the addition of cellulose acetate 320 S, cellulose acetate 398 was added. Five minutes after the addition of cellulose acetate 398, HPMC was added. Ten minutes after the addition of HPMC, PEG-400 was added. The mixture was mixed for further 15 minutes and prior to use.

Three different total amounts of the rate-controlling coating were used. All three were geometric scale-ups. Formulas for the three coating solutions are given in Tables 9, 10 and 11.
Table 9: Rate-controlling membrane formulation for a batch of 1000 tablets
Average membrane thickness: 73.12 ± 0.09 μm

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Use</th>
<th>Quantity (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate 320 S</td>
<td>Film formation</td>
<td>1.75</td>
</tr>
<tr>
<td>Eastman Lot #: 26520</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulose acetate 398 (CA-398-10NF)</td>
<td>Film formation</td>
<td>1.75</td>
</tr>
<tr>
<td>Eastman Lot #: CA-0099 NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol – 400</td>
<td>Plasticizer</td>
<td>0.55</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>Solvent</td>
<td>116.5</td>
</tr>
<tr>
<td>Methanol</td>
<td>Solvent</td>
<td>29.15</td>
</tr>
</tbody>
</table>

Table 10: Rate-controlling membrane formulation for a batch of 1000 tablets
Average membrane thickness: 85.06 ± 0.64 μm

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Use</th>
<th>Quantity (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate 320 S</td>
<td>Film formation</td>
<td>3.5</td>
</tr>
<tr>
<td>Eastman Lot #: 26520</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulose acetate 398 (CA-398-10NF)</td>
<td>Film formation</td>
<td>3.5</td>
</tr>
<tr>
<td>Eastman Lot #: CA-0099 NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol – 400</td>
<td>Plasticizer</td>
<td>1.1</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>Solvent</td>
<td>233.0</td>
</tr>
<tr>
<td>Methanol</td>
<td>Solvent</td>
<td>58.3</td>
</tr>
</tbody>
</table>
Table 11: Rate-controlling membrane formulation for a batch of 1000 tablets
Average membrane thickness: 121.32 ± 2.24 μm

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Use</th>
<th>Quantity (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate 320 S Eastman Lot #: 26520</td>
<td>Film formation</td>
<td>8.29</td>
</tr>
<tr>
<td>Cellulose acetate 398 (CA-398-10NF) Eastman Lot #: CA-0099 NF</td>
<td>Film formation</td>
<td>8.29</td>
</tr>
<tr>
<td>Polyethylene glycol – 400</td>
<td>Plasticizer</td>
<td>1.33</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>Solvent</td>
<td>515.5</td>
</tr>
<tr>
<td>Methanol</td>
<td>Solvent</td>
<td>129.04</td>
</tr>
</tbody>
</table>

Solutions were prepared using the same process used for the micro-porous coating solution except for the addition of HPMC.

3.2.4 Coating

The coating solution was placed on a top-loading balance. A peristaltic pump was in-line between the coating reservoir and the liquid port of the spray nozzle. Pump rotation speed was adjusted to vary the spray rate and spray rate was determined by loss in weight of the coating reservoir. Prior to coating, the spray nozzle was inserted into the centre of the air distribution plate at the base of the column and fixed in position.

A batch size of 300 g of core tablets was placed inside the column and the fan and heater were turned on. During the spraying process, the change in weight of the spray solution was recorded every 15 minutes initially then every 30 minutes in order to determine the spray rate. The coating parameters are presented in Table 12.
Table 12: Coating parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inlet air temperature</td>
<td>40 °C</td>
</tr>
<tr>
<td>Atomizer</td>
<td>0.8 bar</td>
</tr>
<tr>
<td>Spray-rate range</td>
<td>3-5 g/min</td>
</tr>
</tbody>
</table>

At the end of the coating process, the freshly coated tablets were collected on a 9” diameter screen and placed in an oven set at 40 °C, for 24 hours to allow for residual solvent evaporation. The tubing and spray nozzle were flushed first with a mixture of 50 ml of methylene chloride and 50 ml of methanol, then with 50 ml of methanol and finally with 200 ml of water. After 24 hours, 50 tablets were weighed and the average weight of a coated tablet calculated.

3.2.4.1 Coated membrane weight and tablet weight gain

Average weight of a core tablet:

\[
\frac{\text{Weight of 50 core tablets}}{50} = a
\]

Average weight of a coated tablet:

\[
\frac{\text{Weight of 50 coated tablets}}{50} = b
\]

Membrane (coated film) weight:

\[b - a = f\]

Tablet weight gain:

\[
\frac{f \times 100}{a}
\]
3.2.4.2 Theoretical membrane weight and tablet weight gain

Total theoretical weight of coating material: \( x \) g

Theoretical membrane weight: \( x \) g / 1000 tablets = \( y \) g

Theoretical tablet weight gain (%): \( \frac{yg \times 100}{\text{theoretical tablet weight}} = z \) %

3.2.5 Drilling of the orifice

The orifice was drilled on the top convex side of the tablet with a Hermle UWF 721 H computer controlled milling machine. Orifice diameter was 0.26 mm and depth was 1 mm. The tablet was placed in a sample holder and the bit gradually drilled the coated tablet in a up and down motion for 1 minute, to produce a 0.26 mm diameter orifice with a depth of 1 mm. The depth of 1 mm was arbitrarily chosen to ensure that the drilled orifice reached the core tablet, to allow for the saturated solution to exit the tablet.

3.3 Membrane thickness measurements

The micro-porous and the rate-controlling membranes thicknesses were measured by light microscopy, using a Wild M5 Stereoscope with an Empix Spot Digital Camera. Three tablets were randomly picked per 1000 tablet batch. Each tablet was sliced in half through the concave side, generating 6 half tablet pieces. The film thickness of each half-tablet piece was photographed and measured at 4 different locations and the average thickness calculated.

3.4 Dissolution testing

The dissolution testing was conducted using a Vanderkamp 600 six-spindle dissolution tester. Following USP protocol (US Pharmacopeial Convention Inc, 2000), six coated tablets per 1000 tablet batch were randomly chosen, for each of the 4 different tablet types (73 \( \mu \)m membrane –
with hole, 73 μm membrane – without hole, 85 μm membrane – with hole and 121 μm membrane – with hole), for a 24 hour dissolution test. The test station was fitted with Apparatus 1 baskets and operated at 100 RPM with water at 37 ± 0.5 °C, as the test medium. The sampling probes were fitted with in-line, 35 μm Van-Kel full flow filters. Solvent replacement after sampling was not done as the automated system was not equipped to do this. Losses due to sample removal were accounted for in the calculation of total drug released for the dissolution profiles and the amount of drug released was quantified by U.V. spectrophotometry. The maximum absorbance at a wavelength of 256 nm was recorded for all samples and distilled water served as the blank. The amounts of triflupromazine HCl released were then calculated using the linear equation of the calibration curve of standard solutions. The dissolution parameters used are listed in Table 13.

Table 13: Dissolution parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paddle speed</td>
<td>100 RPM</td>
</tr>
<tr>
<td>Temperature</td>
<td>37 ± 0.5 °C</td>
</tr>
<tr>
<td>Medium</td>
<td>distilled water</td>
</tr>
<tr>
<td>Initial volume</td>
<td>900 ml</td>
</tr>
<tr>
<td>Sampling time (hour)</td>
<td>0.5, 1, 2, 6, 10, 14, 18, 22, 24</td>
</tr>
<tr>
<td>Sample volume</td>
<td>10 ml</td>
</tr>
</tbody>
</table>
3.5 Dependence of $T_1$, $T_2$ and the diffusion coefficient ($D$) of water on the concentration of lactose in a water-lactose mixture.

The mixtures are solutions of lactose in water.

3.5.1 Mixture preparation

Although the concentration of lactose in the tablet at various dissolution times cannot be determined directly by NMR measurements, in principle it could be inferred indirectly through its effects on NMR parameters such as the water $^1$H relaxation times and diffusion coefficients. For quantitative analysis of lactose tablets by NMR, these parameters must be measured and correlated to known lactose concentrations. In this study, the blend of lactose, stearic acid and triflupromazine HCl compounded in section 3.2.1 was used in mixtures prepared to serve as the basis of the correlation, by weighing out the appropriate amount of the blend, at concentrations from 2% to 22% by weight, using a Mettler AE 163 balance (Hightstown, NJ) and mixing it with the appropriate amount of water in a 4 ml Fisher brand glass vial, to a total mixture weight of 4 g. The vial was capped, its content shaken and parafilm used to seal it. The sealed vials were placed in a water bath.

3.5.2 $T_1$, $T_2$ and $D$ measurements

The water spin-lattice relaxation times ($T_1$), spin-spin relaxation times ($T_2$) and the diffusion coefficients ($D$) were measured for these mixtures. All experiments were carried out using a Bruker Avance DRX 360 MHz and its accessories. Before the experiments, the vials were placed in a water bath for 1 hour, to allow the temperature of the mixture to reach $37 \pm 0.5 \, ^\circ C$. They were then placed inside a 20 mm rf coil attached to the probehead. The probe was inserted inside the 360 MHz magnet and a heating coil coupled with a dewar inserted into the probe. The $37 \pm 0.5 \, ^\circ C$ temperature was kept constant by a Bruker variable temperature unit. A compressed air line was connected to the dewar and together with the heating coil and BVT unit provided a constant air flow temperature of $37 \pm 0.5 \, ^\circ C$. 

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3.5.2.1 \textbf{T}_1 \text{ measurements}

\( T_1 \) measurements were conducted using the inversion recovery and saturation recovery sequences shown in Figures 20 and 21. In the inversion recovery sequence, after a recycle delay time \( T_R \) of 30 sec, which was selected to be 5 times \( T_1 \), the 180° pulse tipped the net magnetization to the \( z \)-axis. After a time \( \tau \), a 90° pulse tipped the net magnetization from the \( z \)-axis to the \( x,y \) plane where it is detected. The intensity of the signal \( I(t) \) was a function of \( \tau \) and the determination of \( T_1 \) involved a two parameter non-linear fit to Equation 9 using the XWIN-NMR 2.6 program. In the saturation recovery sequence, a chain of 90° pulse with a \( T_R \) of 3 sec was applied. An initial 90° rf pulse tilted the magnetization of the spin system into the \( x,y \)-plane perpendicular to the main magnetic field. This initial 90° rf pulse and a group of spoiler pulses effectively destroyed the residual recovered longitudinal magnetization. After a time \( T_R \), the longitudinal magnetization developed was rotated into the \( x,y \)-plane by another 90° rf pulse. A gradient echo was acquired immediately after this.

3.5.2.2 \textbf{Diffusion coefficient (D) measurements}

The diffusion coefficients of water in lactose were measured by the Pulsed-Gradient-Spin-Echo (PGSE) method. The maximum gradient strength was 95 G/cm, the delay between gradients \( \Delta \) was 14 ms and a \( T_R \) of 25 s. The diffusion coefficient values were then plotted versus lactose concentrations of the mixtures.

3.5.2.3 \textbf{T}_2 \text{ measurements}

\( T_2 \) measurements were carried out using the multi-echo pulse sequence shown in Figure 29. After a recycle delay \( T_R \), a 90° pulse was applied tipping the net magnetization to the \( x,y \) plane. After a time \( \tau \), the spins began to dephase and a 180° pulse was applied. This pulse rotated the spins around the \( x \)-axis. After \( 2\tau \), the spins were refocused and the signal was detected. After \( 3\tau \), a second 180° pulse rotated the spins around the \( x \)-axis again. After \( 4\tau \), the spins were refocused and were detected. This train of echoes continued and the imaging software stored every echo separately into memory. \( T_2 \) relaxation times were determined for three different echo times \( (T_E) \). The \( T_2 \) relaxation times were obtained by fitting the acquired \(^1\text{H} \) signal intensity \( I(t) \)
in each pixel to corresponding $T_2$ values from Equation 10 using the Bruker imaging software, Para Vision 2.1 BII, supplied by Bruker. The protocol at 10 ms with 100 echoes was used for the experiments as it offered a more efficient experimental time (10 ms x 100 echoes = 1000 s). The protocol at 10 ms with 100 echoes was repeated 5 times and the average $T_2$ values were fitted using the Mathematica program, using a non-linear least squares fitting and correlating the lactose concentration to the $T_2$ dependence of the water in the reference samples, generating Equation 19. This equation was plotted using the Excel program, as the calculated values of best fit and compared to the experimental (observed) values.

Table 14: Parameters for $T_2$ measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Protocol 1</th>
<th>Protocol 2</th>
<th>Protocol 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_E$ (ms)</td>
<td>7.5</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Number of echoes</td>
<td>50</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>$T_R$ (s)</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

3.6 NMR Imaging experiments

All experiments were carried out using a Bruker Avance DRX 360 MHz and its accessories. The tablet was placed in a modified Sotax flow-through dissolution unit (USP apparatus 4) with distilled water initially heated to $37 \pm 0.5 \, ^\circ \text{C}$ as the dissolution medium. The Sotax flow-through dissolution unit was connected to a distilled water reservoir through two hoses, one from the top and another one from the bottom, passing through a calibrated Gilson Minipuls 3 pump (Mandel Scientific CO. Ltd.). Water coming from the reservoir entered the dissolution unit from the bottom and exited through the top. The water reservoir was immersed in a Blue M heating bath unit (Blue M electric company), allowing the reservoir water to be maintained at $37 \pm 0.5 \, ^\circ \text{C}$. The dissolution unit was then placed inside a 30 mm rf coil attached to the probe-head. The probe was inserted inside the 360 MHz magnet and a heating coil coupled with a dewar inserted into the probe. The $37 \pm 0.5 \, ^\circ \text{C}$ temperature was kept constant by a Bruker variable temperature unit. A compressed air line was connected to the dewar and together with the heating coil and
BVT unit provided a constant air flow for a $37 \pm 0.5$ °C temperature. The determination of $T_2$ was done using the protocol and parameters listed in Table 15.

Table 15: NMR-imaging: parameters for $T_2$ imaging measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_E$ (ms)</td>
<td>10</td>
</tr>
<tr>
<td>Number of echoes</td>
<td>100</td>
</tr>
<tr>
<td>$T_R$ (s)</td>
<td>30</td>
</tr>
<tr>
<td>Image size (pixels)</td>
<td>128 x 128</td>
</tr>
<tr>
<td>FOV</td>
<td>30.0 mm</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Slice selection gradient</td>
<td>$G_x$ and $G_z$</td>
</tr>
<tr>
<td>Experiment time</td>
<td>32 minutes</td>
</tr>
<tr>
<td>Pump speed</td>
<td>16 ml/min</td>
</tr>
</tbody>
</table>

A macro program was written for data collection every 3 hours over a 25.5 hours period of:

- An axial $T_2$ image of individual $T_2$ values for all the voxels
- A sagital $T_2$ image of individual $T_2$ values for all the voxels
- An axial gray scale image with water signal intensity for all the voxels
- A sagital gray scale image with water signal intensity for all the voxels

The $T_2$ images were exported as ASCII files where they were processed using the Matlab 5.2.0.3084 program, using Equation 19 while the gray scale images did not require any further processing and could be printed directly.

The Matlab program provided a graph of the signal intensity of the axial slice's center row showing change in the tablet's cross-sectional length width, a two-dimensional axial $T_2$ images showing the change in the core tablet due to the water erosion, and a three-dimensional plot comparing the axial slice's volume occupied by dry lactose at different time-points.
The total volume of the slice occupied by dry lactose at each time-point was calculated as follows:

1. Since we observed and obtained only 0 % and 100 % lactose from the T2 values of the tablet slice, Equation 19 was not used to correlate % lactose with T2 values but rather the total number of pixels in the tablet slice (100 % lactose) was counted.

2. At the beginning of the dissolution, all pixels inside the tablet slice were black, which corresponded to the initial total number of pixels in the tablet slice at 0.5 hour.

3. At each time point (every three hours), the total number of black pixels in the tablet slice was divided by the initial total number of black pixels in the tablet slice at 0.5 hour, yielding the ratio:

\[
\frac{N_{t-\text{SLICE}}}{N_{0-\text{SLICE}}} = \frac{1}{k}
\]

Where \(N_{0-\text{SLICE}}\) is the initial total number of black pixels in the tablet slice at 0.5 hour, \(N_{t-\text{SLICE}}\) is the total number of black pixels in the tablet slice at time t, and \(\frac{1}{k}\) is the ratio.

4. Two assumptions were made:

Assumption I:

\[
\frac{V_{t-\text{SLICE}}}{V_{0-\text{SLICE}}} = \frac{N_{t-\text{SLICE}}}{N_{0-\text{SLICE}}} = \frac{1}{k}
\]

Where \(V_{0-\text{SLICE}}\) is the initial volume of the tablet slice occupied by the black pixels (100 % lactose) at 0.5 hour, and \(V_{t-\text{SLICE}}\) is the volume of the tablet slice occupied by the black pixels at time t.

Assumption II:

The ratios of the change in volume occupied by the black pixels (100 % lactose) in the tablet slice and in the whole tablet were equal:
\[
\frac{V_{t\text{-SLICE}}}{V_{0\text{-SLICE}}} = \frac{V_{t\text{-TABLET}}}{V_{0\text{-TABLET}}} = \frac{1}{k}
\]

Where \( V_{0\text{-TABLET}} \) is the initial volume of the whole tablet occupied by the black pixels (100% lactose) at 0.5 hour, and \( V_{t\text{-TABLET}} \) is the volume of the whole tablet occupied by the black pixels at time \( t \).

5. Since \( V_{0\text{-TABLET}} \) = total volume of the tablet (calculated from the tablet dimensions, appendix I)

\[= 241 \text{ mm}^3\]

The volume of the tablet occupied by the total dry lactose concentration at time \( t \) (every 3 hours) was obtained by:

\[V_{t\text{-TABLET}} = \frac{241 \text{ mm}^3}{k}\]

The percent core tablet eroded was calculated for each time-point and correlated to the percent release of triflupromazine HCl.

\[
\% \text{ core tablet eroded} = \left(\frac{241 \text{ mm}^3 - V_{t\text{-TABLET}}}{241 \text{ mm}^3}\right) \times 100
\]
3.7 **Statistical treatment of data**

3.7.1 **Standard deviation**

The standard deviations of samples were calculated as follows (Zar, 1999):

\[
S.D. = \sqrt{\frac{\sum X_i^2 - \frac{(\sum X_i)^2}{n}}{n-1}}
\]

(Equation 17)

Where S.D. is the standard deviation of samples, \(X_i\) is the measurement of sample \(i\), and \(n\) is the total number of samples.

3.7.2 **ANOVA and Tukey-Kramer tests**

When measurements of a variable are obtained for two samples only, the Two-samples t test is most appropriate for the comparison of the samples, to infer whether differences exist between the two populations sampled. However, the use of the Two-samples t test to test hypotheses of more than two samples is invalid. This is accomplished with the use of Analysis Of Variance (ANOVA) (Zar, 1999).

The underlying assumptions of ANOVA are that the samples to be tested are from a normal population and of equal variances. However, the ANOVA test is still robust when operating under considerable deviations from these assumptions, especially when the sample sizes are small and as nearly equal as possible (which is the case in this work).

ANOVA allows the investigator to test whether or not all of the tested population means are equal. To conclude between which means the equalities or inequalities lie, we must use the Tukey-Kramer test (Zar, 1999), a multiple means comparison procedure. Pairs of means are compared to determine which ones are significantly different.
One-way Anova was performed for the following:

1. To test the Null hypothesis $H_0$, that "the mean % triflupromazine HCl released from the 73 \mu m membrane-with hole, the 73 \mu m membrane-without hole, the 85 \mu m membrane-with hole, and the 121 \mu m-with hole were all equal at 1.0 hour of dissolution".

2. To test the Null hypothesis $H_0$, that "the mean % triflupromazine HCl released from the 73 \mu m membrane-with hole, the 73 \mu m membrane-without hole, the 85 \mu m membrane-with hole, and the 121 \mu m-with hole were all equal at 24.0 hours of dissolution".

In both cases, the single factor was "tablet type" (73 \mu m membrane-with hole, the 73 \mu m membrane-without hole, the 85 \mu m membrane-with hole, and the 121 \mu m-with hole) and the variable was "% triflupromazine HCl released". The experimental design was balanced (all the means have the same number of observations: 6). The significance level (probability used as the criterion for rejection) was 0.05 (5 %).

3. To test the Null hypothesis $H_0$, that "the mean % core tablet eroded for the 73 \mu m membrane-with hole, the 73 \mu m membrane-without hole, and the 121 \mu m-with hole were all equal at 25.5 hours of dissolution".

The single factor here was "tablet type" (73 \mu m membrane-with hole, the 73 \mu m membrane-without hole, and the 121 \mu m-with hole) and the variable was "% core tablet eroded". The experimental design was balanced (all the means have the same number of observations: 3). The significance level (probability used as the criterion for rejection) was 0.05 (5 %).

In all of the above three cases, the Tukey-Kramer test, a multiple means comparison procedure was used to conclude among which means the equalities or inequalities lied.
A two-sample t-test was performed to for the two-tailed Null hypothesis $H_0$, that "the mean % triflupromazine HCl released from the 73 μm membrane-with hole and the 73 μm membrane-without hole were equal at 25.5 hours. The significance level (probability used as the criterion for rejection) was 0.05 (5 %).

### 3.7.3 Similarity factor ($f_2$)

The similarity factor $f_2$ is used to compare dissolution profiles of percent drug released. $f_2$ allows comments on the extend of similarity of two curves that may graphically appear to be the same (Moore, 1996). An acceptance limit of $f_2 = 50$ or greater between two dissolution profiles corresponds to 10 % or less difference and is sufficient to declare the two profiles similar (US Department of Health and Human Services, August 1997)(US Dept. of Health and Human Services, 1997). The similarity factor is calculated as follows:

$$f_2 = 50 \times \log \left( \frac{100}{\sqrt{1 + \frac{1}{n} \sum_{t=1}^{n} w_t (I_t - II_t)}} \right)$$  \hspace{1cm} \text{(Equation 18)}

Where $f_2$ is the similarity factor, $n$ is the number of sampling points, $w_t$ is the weighing factor ($w_t = 1$, since no particular part of the curves are of greater interest), $I_t$ is the average % drug released for sample I at time $t$, and $II_t$ is the average % drug released for sample II at time $t$. 

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RESULTS

1. OSMOTIC PUMP TABLET FORMULATIONS

1.1 Aqueous solubility of triflupromazine HCl at 37 ± 0.5 °C

Figure 39 represents the absorbance versus concentration plot of the six triflupromazine HCl standard solutions. The average solubility value of 0.9 g/ml was obtained (Table 16). The value reported in the literature is given as > 1 g/ml.

![Figure 39: Triflupromazine HCl standard solutions calibration curve](image)

Table 16: Triflupromazine HCl saturated solutions

<table>
<thead>
<tr>
<th>Saturated solution I</th>
<th>Saturated solution II</th>
<th>Saturated solution III</th>
<th>Average ± S.D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility (g/mL)</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9 ± 0.0</td>
</tr>
</tbody>
</table>

*S.D.: Standard deviation
1.2  *Formulation and design of osmotic pump tablets*

1.2.1  **Core tablet properties**

During the compression run, a sample of 10 tablets was collected every 15 minutes and the average tablet weight, thickness of each tablet and hardness of each tablet determined. After 5 sample collections of 10 tablets each (total of 50 tablets), the total average tablet weight, thickness and hardness were calculated and are presented in Table 17. The average tablet weights, thicknesses and hardnesses all fell within target specifications ranges of 277.0 mg – 282.0 mg for the weight, 5.25 mm – 5.35 mm for the thickness and 8.0 kp – 12.0 kp for hardness.

<table>
<thead>
<tr>
<th>Batch number</th>
<th>Average weight ± S.D.* (mg)</th>
<th>Average Thickness ± S.D* (mm)</th>
<th>Average Hardness ± S.D* (Kp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T92-0802-B5</td>
<td>282.5 ± 0.0007</td>
<td>5.28 ± 0.02</td>
<td>9.73 ± 0.76</td>
</tr>
<tr>
<td>T93-0802-B8</td>
<td>279.5 ± 0.0035</td>
<td>5.29 ± 0.06</td>
<td>8.86 ± 0.85</td>
</tr>
</tbody>
</table>

* Value is an average of 5 sample collections of 10 tablets each.

1.2.2  **Membrane thickness measurements**

Figure 40 shows a light microscopy image of the 121 µm membrane thickness. Table 18 presents the membrane thickness measurements data. The average micro-porous membrane thickness was 34 µm. An additional coating film with a 1.4 % tablet weight gain of the rate-controlling membrane, on top of the micro-porous membrane yielded a total membrane thickness (micro-porous and rate-controlling) of 85 µm, while an additional coating film with a 6.2 % tablet weight gain of the rate-controlling membrane yielded a total membrane thickness of 121 µm.
Figure 40: Light microscopy image showing the 121 μm membrane thickness as indicated.
Table 18: Membrane thickness measurements by light microscopy

<table>
<thead>
<tr>
<th>Membrane type</th>
<th>Formulation type</th>
<th>Theoretical tablet weight gain (%)</th>
<th>Theore. Membrane weight (g)</th>
<th>Membrane thickness** (µm)</th>
<th>Ave. thickness (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-porous</td>
<td>T92-0802-B5-C7</td>
<td>2.9</td>
<td>0.008 g</td>
<td>32.30 34.92 34.25</td>
<td>33.82 ± 1.36</td>
</tr>
<tr>
<td>Micro-porous</td>
<td>T93-0802-B8-C9</td>
<td>2.9</td>
<td>0.008 g</td>
<td>33.35 33.12 34.10</td>
<td>33.52 ± 0.51</td>
</tr>
<tr>
<td>Micro-porous</td>
<td>T93-0802-B8/1-C10</td>
<td>2.9</td>
<td>0.008 g</td>
<td>35.23 32.60 34.75</td>
<td>34.20 ± 1.40</td>
</tr>
<tr>
<td>Rate-controlling</td>
<td>T92-0802-B5-C7/R</td>
<td>6.2</td>
<td>0.020 g</td>
<td>118.82 121.99 123.14</td>
<td>121.32 ± 2.24*</td>
</tr>
<tr>
<td>Rate-controlling</td>
<td>T93-0802-B8-C9/R</td>
<td>1.4</td>
<td>0.004 g</td>
<td>73.20 73.02 73.15</td>
<td>73.12 ± 0.09*</td>
</tr>
<tr>
<td>Rate-controlling</td>
<td>T93-0802-B8/1-C10/R</td>
<td>2.8</td>
<td>0.008 g</td>
<td>85.61 84.35 85.21</td>
<td>85.06 ± 0.64*</td>
</tr>
</tbody>
</table>

*Total average membrane thickness: micro-porous plus rate-controlling.

**Average of 4 measurements.
Figure 41 shows the release profiles of triflupromazine HCl released during a 24 hour dissolution test for the 73 μm membrane – with hole, the 73 μm membrane – without hole (control), the 85 μm membrane – with hole, and the 121 μm membrane – with hole. The 73 μm – with hole tablet had a burst of triflupromazine HCl release, to nearly 8 % release at 0.5 hour. The 85 μm – with hole tablet also showed a burst although of smaller magnitude, from 0 to an average of 6 % release at 0.5 hour. The 73 μm – without hole curve showed a lag-time of more than 1.0 hour with no triflupromazine HCl released. The 73 μm – with hole and the 85 μm – with hole reached their plateau first, at around 7.5 hours and 10 hours respectively, the 73 μm – without hole at around 14 hours, and the 121 μm – with hole at around 18 hours.

At 1.0 hour of dissolution, the 73 μm membrane – with hole had the highest mean percent triflupromazine HCl released (15.20 %), followed by the 85 μm membrane – with hole (9.00 %), the 121 μm membrane – with hole (3.14 %) and finally the 73 μm membrane – without hole with no drug released. Using one-way ANOVA, a statistically significant difference (p < 0.0001) was found among the four means (Figure 41). The Tukey-Kramer test compared pairs of means and it was concluded that after 1.0 hour of dissolution, significant differences in percent triflupromazine HCl release among pairs of means were: the 73 μm membrane-with hole compared to the 73 μm membrane-without hole, the 73 μm membrane-with hole compared to the 121 μm membrane-with hole, and the 85 μm membrane-with hole compared to the 73 μm membrane-without hole.

After 24 hours of dissolution, the 73 μm membrane – with hole still had the highest mean percent triflupromazine HCl released (76.70 %), followed by the 85 μm membrane – with hole (72.04 %), the 121 μm membrane – with hole (71.32 %) and finally the 73 μm membrane – without hole with 54.70 % of the drug released. Using one-way ANOVA, a statistically significant difference (p < 0.0001) was also found among the four means (Figure 41). The Tukey-Kramer test compared pairs of means and it was concluded that after 24.0 hours of dissolution, the most significant differences in % triflupromazine HCl release between pairs of means are: the 73 μm membrane-with hole compared to the 73 μm membrane-without hole, the 85 μm membrane-with hole compared to the 73 μm membrane-without hole, and the 121 μm membrane-with hole compared to the 73 μm membrane-without hole.
A two-sample t-test was performed to test the effect of the presence of a drilled orifice and a statistically significant difference in percent triflupromazine HCl released ($p < 0.0001$) was found between the $73 \mu m$ membrane-with hole and the $73 \mu m$ membrane-without hole means.

A similarity factor of 50 was obtained when comparing the release profiles of the $85 \mu m$ membrane – with hole and the $121 \mu m$ membrane – with hole; and a similarity factor of 57 when the release profiles of the $73 \mu m$ membrane – with hole with the $85 \mu m$ membrane – with hole were compared. Triflupromazine HCl release profiles of the $85 \mu m$ membrane – with hole and the $121 \mu m$ membrane – with hole were stated to be similar while the $73 \mu m$ membrane – with hole and the $85 \mu m$ membrane – with hole were also similar since both similarity factors are $\geq 50$.

![Figure 41: Total percent release of triflupromazine HCl during 24 hour dissolution studies of the $73 \mu m$ membrane – with hole, the $73 \mu m$ membrane – without hole (control), the $85 \mu m$ membrane – with hole, and the $121 \mu m$ membrane – with hole osmotic pump tablets versus time (dissolution medium: H$_2$O, temperature: $37 \pm 0.5$ °C). Using one-way ANOVA, a statistically significant difference in percent release of triflupromazine HCl ($p < 0.0001$) was found among the four means at 1.0 hour ($\uparrow$) and 24 hours ($\downarrow$) of dissolution. Values are averages of 6 tablets $\pm$ S.D.](image-url)
2. $^1$H NMR EXPERIMENTS

2.1. **The dependence of $T_1$, $T_2$ and the self-diffusion coefficient of water on the concentration of lactose in water/lactose mixtures.**

$T_1$ and $T_2$ decreased as the weight-percent of lactose increased (Figures 42 through 46). Figures 42 and 43 show only a weak dependence of water $^1$H $T_1$ values on lactose concentration. Measurements of the diffusion coefficient also did not show any strong dependence on the lactose concentration (data not presented). However, the $T_2$ plots of the three different protocols ($T_E = 7.5$ ms with 50 echoes, 40 ms with 80 echoes and 10 ms with 100 echoes) showed a clear and strong dependence of water $^1$H $T_2$ values as a function of lactose concentration, with a greater dependence at the lower concentrations up to approximately 6 % lactose (Figures 44 through 46).

![Graph](image)

**Figure 42:** Dependence of water $^1$H $T_1$ values on the % lactose in water/lactose mixtures, 37 ± 0.5 °C. Inversion recovery sequence.
Figure 43: Dependence of water $^1$H $T_1$ values on the % lactose in water/lactose mixtures, 37 ± 0.5 °C. Saturation recovery sequence.

Figure 44: Dependence of water $^1$H $T_2$ values on the % lactose in water/lactose mixtures, 37 ± 0.5 °C. $T_E$-7.5 ms and 50 echoes. $T_R$ was 30 s.
Figure 45: Dependence of water $^1$H T$_2$ values on the % lactose in water/lactose mixtures, 37 ± 0.5 °C. T$_E$-40 ms and 80 echoes. T$_R$ was 30 s.

Figure 46: Dependence of water $^1$H T$_2$ values on the % lactose in water/lactose mixtures, 37 ± 0.5 °C. T$_E$-10 ms and 100 echoes. T$_R$ was 30 s.
Equation 19, relating lactose weight-percent and $T_2$ values, was obtained from nonlinear least squares fits of the data using Mathematica. Equation 19 was plotted and overlaid with the observed data, using the Excel program in Figure 47. Figure 47 demonstrates that the experimental $T_2$ values (averages of 5 measurements) could be smoothly described by this equation, especially in the region of interest and depended on % lactose change (approximately up to 6 %). $T_2$ values on this graph deviated from the fitted curve at around 20 % lactose.

$$[\text{lactose}] = 49.71851 \cdot e^{-0.013255T_2} + 9.422154 \cdot e^{-0.001935T_2} \quad \text{(Equation 19)}$$

* Observed (Experimental) data are averages of 5 measurements ± S.D.

Figure 47: Dependence of water $^1$H $T_2$ values on the % lactose in water/lactose mixtures, 37 ± 0.5 °C. $T_E$-10 ms and 100 echoes.
2.2 NMR Imaging gray – scale images and water signal intensities

2.2.1 NMR Imaging gray – scale images

Figures 48 through 52 and 53 through 57 are gray-scale images of axial and sagittal scans respectively, taken every 3 hours, during 24 hour dissolution studies, illustrating the permeation of water into the osmotic pump tablets. Each image is the first image of a set of 100 and is that which captures the widest range of water environments. "White" represents the highest concentration of water as in the water outside the tablet. “Black” represents the absence of water, as inside the tablet, at 0.5 hour. TR was 15 seconds and the experiment time was 32 minutes for the collection of a set of 100 axial and sagittal images.

These images share some common features: as more water penetrates the core tablet, from 0.5 hour to 25.5 hours, the intensity of the blackness of the tablet, strongest at 0.5 hour, decreased every 3 hours, tending progressively toward gray. At 0.5 hour, all three tablet types (the 73 μm membrane – with hole, the 73 μm membrane – without hole (control), and the 121 μm membrane – with hole) displayed a completely black inner core, indicating the absence of water. As dissolution progressed, at 4.5 hours, changes were noticeable on the 73 μm membrane – with hole and the 73 μm membrane – without hole (control): the outer area of the tablet, at the interface with water, began to erode. This outer area’s colour was changing from black to gray, then to white, illustrating the gradual permeation of water into the osmotic pump tablets. The thicker membrane, the 121 μm membrane – with hole displayed no change in the inner core tablet. At 10.5 hours, water had permeated the core tablet of the 73 μm membranes substantially and clearly separated the remaining core from the membrane. The colour of 121 μm membrane – with hole’s inner core was becoming slightly gray but there was no noticeable erosion. At 25.5 hours, the core tablets of the 73 μm membrane – with hole, the 73 μm membrane – without hole were completely eroded while the 121 μm membrane – with hole core’s outer area began to erode noticeably.
Figure 48: 24 hour dissolution studies of osmotic pump tablets at 37 °C (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Gray-scale images: 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – axial slices. First echoes – maximum signal intensity. Tₑ-10 and 100 echoes. 0.5 and 1.5 hours (respectively). White: presence of water, Black: absence of water.
Figure 49: 24 hour dissolution studies of osmotic pump tablets at 37 °C (dissolution medium: H₂O, temperature: 37 ± 0.5 °C ). Gray-scale images: 73 µm membrane – with hole, 73 µm membrane – without hole and 121 µm membrane – with hole – axial slices. First echoes – maximum signal intensity. Tₑ-10 and 100 echoes. 4.5 and 7.5 hours (respectively). White: presence of water, Black: absence of water.
Figure 50: 24 hour dissolution studies of osmotic pump tablets at 37 °C (dissolution medium: H2O, temperature: 37 ± 0.5 °C). Gray-scale images: 73 µm membrane – with hole, 73 µm membrane – without hole and 121 µm membrane – with hole – axial slices. First echoes – maximum signal intensity. T_E-10 and 100 echoes. 10.5 and 13.5 hours (respectively). White: presence of water, Black: absence of water.
Figure 51: 24 hour dissolution studies of osmotic pump tablets at 37 °C (dissolution medium: H₂O, temperature: 37 ± 0.5 °C ). Gray-scale images: 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – axial slices. First echoes – maximum signal intensity. Tₑ-10 and 100 echoes. 16.5 and 19.5 hours (respectively). White: presence of water, Black: absence of water.
Figure 52: 24 hour dissolution studies of osmotic pump tablets at 37 °C (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Gray-scale images: 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – axial slices. First echoes – maximum signal intensity. Tₑ-10 and 100 echoes. 22.5 and 25.5 hours (respectively). White: presence of water, Black: absence of water.
Figure 53: 24 hour dissolution studies of osmotic pump tablets at 37 °C (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Gray-scale images: 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – sagital slices. First echoes – maximum signal intensity. Tₑ-10 and 100 echoes. 0.5 and 1.5 hours (respectively). White: presence of water, Black: absence of water.
Figure 54: 24 hour dissolution studies of osmotic pump tablets at 37 °C (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Gray-scale images: 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – sagital slices. First echoes – maximum signal intensity. T_E-10 and 100 echoes. 4.5 and 7.5 hours (respectively). White: presence of water, Black: absence of water.
Figure 55: 24 hour dissolution studies of osmotic pump tablets at 37 °C (dissolution medium: H₂O, temperature: 37 ± 0.5 °C ). Gray-scale images: 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – sagital slices. First echoes – maximum signal intensity. Tₑ-10 and 100 echoes. 10.5 and 13.5 hours (respectively). White: presence of water, Black: absence of water.
Figure 56: 24 hour dissolution studies of osmotic pump tablets at 37 °C (dissolution medium: H2O, temperature: 37 ± 0.5 °C). Gray-scale images: 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – sagital slices. First echoes – maximum signal intensity. TE-10 and 100 echoes. 16.5 and 19.5 hours (respectively). White: presence of water, Black: absence of water.
Figure 57: 24 hour dissolution studies of osmotic pump tablets at 37 °C (dissolution medium: H₂O, temperature: 37 ± 0.5 °C ). Gray-scale images: 73 µm membrane – with hole, 73 µm membrane – without hole and 121 µm membrane – with hole – sagital slices. First echoes – maximum signal intensity. Tₑ-10 and 100 echoes. 22.5 and 25.5 hours (respectively). White: presence of water, Black: absence of water.
2.2.2 Water signal intensities

Figures 58 through 62 were obtained from intensity values of the tablet center row of the axial slices during a 24 hour dissolution study. The region between approximately 40 a.u. to 75 a.u. of the field of view distance corresponds to the diameter of the center of the tablet and expresses the change in water signal intensity in the center of the tablet. This region was initially a depression at 0.5 hour and was progressively filled as the dissolution progressed. From 0.5 hour to 25.5 hours, there was a consistent and faster water signal intensity increase for the two 73 μm membrane thickness tablets, going from < 20 to 90. The water signal intensity for the 121 μm membrane thickness tablet remained under 20 over a 25.5 hour period.
Figure 58: 24 hour dissolution studies of osmotic pump tablets (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Water signal intensity graphs of the tablet center row. From 40 a.u. (arbitrary units) to 70 a.u.: diameter of the tablet. 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – axial slices. First echoes – maximum signal intensity. Tₑ=10 and 100 echoes. 0.5 and 1.5 hours (respectively). Water signal intensity outside the tablet adjusted to 100 %.
Figure 59: 24 hour dissolution studies of osmotic pump tablets (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Water signal intensity graphs of the tablet center row. From 40 a.u. (arbitrary units) to 70 a.u.: diameter of the tablet. 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – axial slices. First echoes – maximum signal intensity. Tₑ-10 and 100 echoes. 4.5 and 7.5 hours (respectively). Water signal intensity outside the tablet adjusted to 100%.
Figure 60: 24 hour dissolution studies of osmotic pump tablets (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Water signal intensity graphs of the tablet center row. From 40 a.u. (arbitrary units) to 70 a.u.: diameter of the tablet. 73 µm membrane – with hole, 73 µm membrane – without hole and 121 µm membrane – with hole – axial slices. First echoes – maximum signal intensity. T_E-10 and 100 echoes. 10.5 and 13.5 hours (respectively). Water signal intensity outside the tablet adjusted to 100%.
Figure 61: 24 hour dissolution studies of osmotic pump tablets (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Water signal intensity graphs of the tablet center row. From 40 a.u. (arbitrary units) to 70 a.u.: diameter of the tablet. 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – axial slices. First echoes – maximum signal intensity. T₁₀ and 100 echoes. 16.5 and 19.5 hours (respectively). Water signal intensity outside the tablet adjusted to 100%.
Figure 62: 24 hour dissolution studies of osmotic pump tablets (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Water signal intensity graphs of the tablet center row. From 40 a.u. (arbitrary units) to 70 a.u.: diameter of the tablet. 73 μm membrane – with hole, 73 μm membrane – without hole and 121 μm membrane – with hole – axial slices. First echoes – maximum signal intensity. T₁=10 and 100 echoes. 22.5 and 25.5 hours (respectively). Water signal intensity outside the tablet adjusted to 100 %. 
2.3 Core tablet volume and percent eroded

Figures 63 through 72 illustrate the changes occurring in the axial slice of the 73 μm membrane – with hole during a 24 hour dissolution study. They were obtained from the $T_2$ values of water correlated to the corresponding lactose concentrations from the reference solutions (Equation 19), using the Matlab program.

For each Figure, (a) represents the change in width of the core tablet (dry lactose) in the axial slice’s center row (tablet’s cross-sectional length). The tablet width is 8 mm and corresponds to the original slice width, represented here with dotted lines. The new slice width, every three hours, is represented with solid lines. At 0.5 hour and 1.5 hours, there is no dotted line, only the solid line, indicating that changes in the width of the core tablet are not apparent. At 4.5 hours, the dotted line appears. The core tablet is eroding from the outer area, at the interface with water, thus the tablet width is reduced. At 10.5 hours, the core tablet’s width is further decreased as the area within the solid line has decreased and the gap between the dotted line and the solid line has increased. At 16.5 hours, the width of the core tablet has decreased by nearly half. At 25.5 hours, there is no more solid line, only the dotted line, indicating that the core tablet has eroded completely.

For each Figure, (b) represents the corresponding $T_2$ images of Figures 48 through 52. In this set, the top image illustrates the core tablet at 0.5 hour and the lower image represents the core tablet at specific time-points $t$, every 3 hours. The changes occurring in the tablet are observed on the image at time $t$. As dissolution progresses, at 4.5 hours, although both core tablets still appear completely black, the size of the core tablet at 4.5 hours has started to shrink, as it is eroding. At 13.5 hours, the size of the core tablet is further reduced and the membrane appear clearly detached from the remaining core. At 25.5 hours, the core tablet is no longer black. The core tablet is completely eroded, replaced by water.

For each Figure, (c) provides a 3 dimensional comparison of the volume of the core tablet in the slice: at the beginning of the dissolution (at 0.5 hour) and at specific time-points $t$, every 3 hours. The changes occurring in the tablet are observed on the image at time $t$. As dissolution progresses, at 4.5 hours, the volume of the core tablet is slightly reduced, compared to the
volume at 0.5 hour. The volume reduction is more advanced at 16.5 hours. At 25.5 hours, the core tablet is no longer present as it has eroded completely.
0.5 hour

(a) Plot illustrating tablet width change during dissolution. Dotted line shows original tablet dimension.

(b) Tablet images based on T2 and lactose concentration

(c) 3D Plot of the tablet’s axial slice comparing volumes of core tablets

Figure 63: 24 hour dissolution studies (dissolution medium: H2O, temperature: 37 ± 0.5 °C). Tablet center row: 73 μm membrane – with hole osmotic pump tablet – axial slice – at 0.5 hour.
1.5 hours

(a) Plot illustrating tablet width change during dissolution. Dotted line shows original tablet dimension.

(b) Tablet images based on T<sub>2</sub> and lactose concentration

(c) 3D Plot of the tablet's axial slice comparing volumes of core tablets

Figure 64: 24 hour dissolution studies (dissolution medium: H<sub>2</sub>O, temperature: 37 ± 0.5 °C). Tablet center row: 73 μm membrane – with hole osmotic pump tablet – axial slice – at 1.5 hours.
4.5 hours

(a) Plot illustrating tablet width change during dissolution. Dotted line shows original tablet dimension.

(b) Tablet images based on T$_2$ and lactose concentration

(c) 3D Plot of the tablet’s axial slice comparing volumes of core tablets

Figure 65: 24 hour dissolution studies (dissolution medium: H$_2$O, temperature: 37 ± 0.5 °C). Tablet center row: 73 μm membrane – with hole osmotic pump tablet – axial slice – at 4.5 hours.
7.5 hours  

(a) Plot illustrating tablet width change during dissolution. Dotted line shows original tablet dimension.

(b) Tablet images based on T<sub>2</sub> and lactose concentration  

(c) 3D Plot of the tablet's axial slice comparing volumes of core tablets

Figure 66: 24 hour dissolution studies (dissolution medium: H<sub>2</sub>O, temperature: 37 ± 0.5 °C). Tablet center row: 73 μm membrane – with hole osmotic pump tablet – axial slice – at 7.5 hours.
10.5 hours

(a) Plot illustrating tablet width change during dissolution. Dotted line shows original tablet dimension.

(b) Tablet images based on $T_2$ and lactose concentration

(c) 3D Plot of the tablet’s axial slice comparing volumes of core tablets

Figure 67: 24 hour dissolution studies (dissolution medium: $H_2O$, temperature: $37 \pm 0.5 ^\circ C$). Tablet center row: 73 $\mu m$ membrane – with hole osmotic pump tablet – axial slice – at 10.5 hours.
13.5 hours

(a) Plot illustrating tablet width change during dissolution. Dotted line shows original tablet dimension.

(b) Tablet images based on T2 and lactose concentration

(c) 3D Plot of the tablet's axial slice comparing volumes of core tablets

Figure 68: 24 hour dissolution studies (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Tablet center row: 73 μm membrane – with hole osmotic pump tablet – axial slice – at 13.5 hours.
16.5 hours

(a) Plot illustrating tablet width change during dissolution. Dotted line shows original tablet dimension.

(b) Tablet images based on T₂ and lactose concentration

(c) 3D Plot of the tablet’s axial slice comparing volumes of core tablets

Figure 69: 24 hour dissolution studies (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Tablet center row: 73 μm membrane – with hole osmotic pump tablet – axial slice – at 16.5 hours.
19.5 hours

(a) Plot illustrating tablet width change during dissolution. Dotted line shows original tablet dimension.

(b) Tablet images based on T2 and lactose concentration

(c) 3D Plot of the tablet's axial slice comparing volumes of core tablets

Figure 70: 24 hour dissolution studies (dissolution medium: H2O, temperature: 37 ± 0.5 °C). Tablet center row: 73 μm membrane – with hole osmotic pump tablet – axial slice – at 19.5 hours.
(a) Plot illustrating tablet width change during dissolution. Dotted line shows original tablet dimension.

(b) Tablet images based on T$_2$ and lactose concentration

(c) 3D Plot of the tablet's axial slice comparing volumes of core tablets

Figure 71: 24 hour dissolution studies (dissolution medium: H$_2$O, temperature: 37 ± 0.5 °C). Tablet center row: 73 µm membrane – with hole osmotic pump tablet – axial slice – at 22.5 hours.
25.5 hours  

(a) Plot illustrating tablet width change during dissolution. Dotted line shows original tablet dimension.

(b) Tablet images based on $T_2$ and lactose concentration  
(c) 3D Plot of the tablet’s axial slice comparing volumes of core tablets

Figure 72: 24 hour dissolution studies (dissolution medium: H$_2$O, temperature: 37 ± 0.5°C). Tablet center row: 73 μm membrane – with hole osmotic pump tablet – axial slice – at 25.5 hours.
Figure 73 illustrates a case of heterogeneous core tablet dissolution where cracks filled with water appear in the core tablet. The cracks appear at the 16.5 hours of dissolution image. Table 19 compares the percent core tablet eroded of the three 73 μm membrane – with hole tablets (I, II and III) before and after the appearance of cracks on the tablet core. From 0.5 to 10.5 hours, before the appearance of the cracks, tablets I and III have higher percent core tablet eroded per hour, 3.33 % and 6.19 % respectively, compared to 1.24 % for sample II, where the cracks appeared later. From 16.5 hours (onset of the cracks) to 25.5 hours, the trend is reversed as tablets I and III have 5.11 % and 2.33 % percent core tablet eroded per hour compared to 7.44 % for tablet II. Images of tablets I and III do not show any noticeable cracks in the core tablets (Appendix VII-1 to VII-3).

Table 19: 24 hour dissolution studies (dissolution medium: H₂O, temperature: 37 ± 0.5 °C).
Average percent core tablet eroded per hour before and after the onset of cracks on the tablet (at 16.5 hours) for the 73 μm membrane – with hole tablets (I, II and III).

<table>
<thead>
<tr>
<th>Period (hour)</th>
<th>Tablet I (% eroded/h)</th>
<th>Tablet II (% eroded/h)</th>
<th>Tablet III (% eroded/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>From 0.5 – 10.5</td>
<td>3.33</td>
<td>1.24</td>
<td>6.19</td>
</tr>
<tr>
<td>From 16.5 – 25.5</td>
<td>5.11</td>
<td>7.44</td>
<td>2.33</td>
</tr>
</tbody>
</table>

The tablet used in this experiment has two concave parts, at the top and bottom, and a cylindrical section in the middle (Appendix I). Figure 74 illustrates another case of heterogeneous core tablet dissolution: preferential erosion, as the top area of the core tablet still retained most of its concave shape while the bottom area has become completely flat.
Figure 73: Axial slice of the 73 μm membrane – with hole after 16.5 hours of dissolution (dissolution medium: H₂O, temperature: 37± 0.5 °C). Showing heterogeneous core tablet dissolution: presence of cracks in the core tablet.
Figure 74: Sagital slice of the 73 μm membrane – with hole after 16.5 hours of dissolution (dissolution medium: H₂O, temperature: 37± 0.5 °C). Showing heterogeneous core tablet dissolution: preferential core tablet erosion.
Figures 75 through 78 compare the average percent core tablet eroded with the average percent triflupromazine HCl released of the 73 µm membrane – with hole, the 73 µm membrane – without hole, and the 121 µm membrane – with hole. After 25.5 hours of dissolution, the percent erosion for the 73 µm membrane – with hole and the 73 µm membrane – without hole, was 100 % of average core tablet eroded, compared to the 121 µm membrane – with hole, which showed 7.41 % average core tablet erosion only. It was interesting to note that the 121 µm membrane – with hole, had an extremely low total percent core tablet erosion of 7.41 %, but a high total percent drug released (71.32 %), whereas the 73 µm membrane – without hole, showed a 100 % total core tablet eroded, with a lower total triflupromazine HCl released (54.70 %).

After 25.5 hours of dissolution, the 73 µm membrane – with hole and the 73 µm membrane – without hole both showed 100 % core tablet eroded compared to 7.41 % for the 121 µm membrane – with hole. Using a single factor ANOVA, a statistically significant difference (p < 0.0001) was found between the 73 µm membranes and the 121 µm membrane – with hole (Figure 78). The Tukey-Kramer test compared pairs of means and it was concluded that after 25.5 hours of dissolution, significant differences in percent core tablet eroded between pairs of means are: the 73 µm membrane-with hole compared to the 121 µm membrane-with hole, and the 73 µm membrane-without hole compared to the 121 µm membrane-with hole.
Figure 75: Total percent release of triflupromazine HCl and percent core tablet eroded versus time during 25.5 hour-dissolution studies for 73 μm membrane – with hole osmotic pump tablet (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Values are averages of 6 tablets ± S.D. for percent release and 3 tablets ± S.D. for percent eroded.

Figure 76: Total percent release of triflupromazine HCl and percent core tablet eroded versus time during 25.5 hour-dissolution studies for 121 μm membrane – with hole osmotic pump tablet (dissolution medium: H₂O, temperature: 37 ± 0.5 °C). Values are averages of 6 tablets ± S.D. for percent release and 3 tablets ± S.D. for percent eroded.
Figure 77: Total percent release of triflupromazine HCl and percent core tablet eroded versus time during 25.5 hour-dissolution studies for 73 µm membrane — without hole osmotic pump tablet (dissolution medium: H2O, temperature: 37 ± 0.5 °C). Values are averages of 6 tablets ± S.D. for percent release and 3 tablets ± S.D. for percent eroded.

Figure 78: Total percent core tablet eroded versus time during 25.5 hour-dissolution studies for the 73 µm membrane — with hole, 73 µm membrane — without hole & 121 µm membrane — with hole osmotic pump tablets (dissolution medium: H2O, temperature: 37 ± 0.5 °C). Using one-way ANOVA, a statistically significant difference in percent core tablet eroded (p < 0.0001) was found among the four means at 25.5 hours of dissolution. Values are averages of 3 tablets ± S.D.
DISCUSSION

1. FORMULATION AND DESIGN OF OSMOTIC PUMP TABLETS

The NMR Gray-scale images demonstrated that the flow of water into the core tablet was not impeded by the presence of a second membrane (micro-porous), as had been expected (Figures 48 through 57). In the micro-porous membrane, HPMC, a water soluble polymer was used as a pore former. In an aqueous environment, HPMC was expected to dissolve and leave large pores to allow for the unimpeded flow of water into the core tablet. There was also no evidence of membrane defects or failure as the membrane appeared to be strong and slightly flexible, under hydrostatic pressure. This is due to the use of two cellulose acetates with two levels of acetylation: cellulose acetate (CA) 320 and (CA) 398 (level of acetylation: 32.0 % and 39.8 % respectively). An increase in percent acetyl content is known to cause an increase in inter-chain hydrogen bonding and Tg, leading to an overall stronger film. Tg also increases while vapor-permeability (a measure of diffusivity) decreases. Variation in the polymer ratio results in greater film strength as the proportion of CA 398 increases while film flexibility and diffusivity increases as the proportion of CA 320 increases. In both the micro-porous and rate-controlling membranes, polyethylene glycol was used as a plasticizer, to provide flexibility and maleability to the films. This resulted in elegant coated tablets with smooth edges, without cracking or peeling. Polyethylene glycol allowed the membrane to expand with the increase in volume of water inside the tablet but the overall tablet swelling was minimal, even for the thinner 73 μm thickness membrane. In addition, at steady state, the amount of water entering the tablet will be balanced by the amount of water leaving the tablet thus keeping the overall volume of the pump constant.

One of the limitations of these studies was the inability to determine the permeation rates of water through the rate-controlling membrane. This could have been accomplished by first measuring directly the amount of drug released at each time-point. Then, assuming that the solution exiting the pump was saturated, the total volume of water at that point could be determined, using the solubility of triflupromazine HCl at 37± 0.5 °C. This volume would be equivalent to the amount of water that permeated the membrane during that time. The volume divided by the duration of permeation would then yield the permeation rate. Unfortunately,
because the amount of triflupromazine HCl in the tablet was very small, the solution exiting the pump was probably saturated with lactose (5 mg of triflupromazine HCl, compared to 266.6 mg of lactose in a 280 mg tablet), and thus the solubility of triflupromazine HCl could not be used. In order to determine the water permeation rates, a tablet with triflupromazine HCl as the major component would have to be used.

The drilled orifice was of a cylindrical shape, with 1 mm depth and 260 μm in diameter. A computer controlled milling machine operated by the same operator, contributed to the accuracy, precision and reproducibility of the hole diameters, from tablet to tablet. This orifice diameter of 260 μm allowed for complete membrane-controlled delivery, where the drug delivery rate was predominantly controlled by the diffusion of water through the rate-controlling membrane and the release of the drug through the drilled orifice, by hydrostatic pressure. There are few literature reports which discuss the influence of orifice size on drug release. Theeuwes (1975), using osmotic pumps of KCl with cylindrical hole diameters of 75 μm, 128 μm, 190 μm, 274 μm, 368 μm and 435 μm demonstrated that complete membrane-controlled delivery was observed for hole diameters 75 μm to 274 μm. For hole diameters 368 μm and greater, this control was lost as more drugs was diffusing through the hole and through the membrane instead of being pumped through the hole. This is also supported in this research, in terms of membrane diffusion, by the much higher percent triflupromazine HCl released from the 73 μm membrane – with hole, 77 %, compared to 55 % for the 73 μm membrane – without hole. With the presence of an orifice, the percent drug diffusing through the membrane should be less than 55 %. This is because in the absence of an orifice, the drug was also forced through the membrane by the build up of hydrostatic pressure. This resulted in a percent drug release higher than that obtained in the presence of an orifice because the hydrostatic pressure would be relieved through the orifice.

Another limitation of this experiment was the inability to perform an independent monitoring of the drug concentration distribution inside and outside the tablet, which would have allowed for the distinction between drug released through the drilled-hole and drug released through the membrane. This would have required the use of 19F NMR Imaging techniques. Investigating the same osmotic pump systems by 19F NMR, an ideal nucleus for NMR studies, second only to protons in sensitivity, would allow for the observation of the model drugs independently without interference from the abundant water signal.
2. DISSOLUTION TESTING

A burst phase of triflupromazine HCl release was observed for the 73 μm membrane – with hole and the 85 μm membrane – with hole tablets and not for the 121 μm membrane – with hole (Figure 41). For the 73 μm membrane – with hole and the 85 μm membrane – with hole, water molecules would cross the semi-permeable membrane more rapidly than for the 121 μm membrane – with hole. From Fick’s law, a higher water permeation rate would be expected from the 73 μm membrane and the 85 μm membrane thickness tablets compared to the thicker membrane. It is likely that this early phase of drug release (released within 0.5 hour of the dissolution) was probably not attributable to osmotic or hydrostatic pressure but rather to drug diffusion through the orifice. After the hydrostatic pressure builds-up, the drug would be pumped through the drilled orifice which presents itself as the path of least resistance. Fick’s first law of diffusion also explains why at every time-point, there was more water present inside the 73 μm membranes compared to the 121 μm membrane (Figures 58 through 62), and the average percent triflupromazine HCl followed the trend expressed in Figure 41.

The 73 μm membrane – without hole curve showed a lag-time of more than 1.0 hour, with no triflupromazine HCl released (Figure 41). The 73 μm membrane thickness allowed for a significant amount of water to quickly diffuse through the semi-permeable membrane, reach the core tablet and dissolve triflupromazine HCl, as displayed by Figures 48 through 52, Figures 53 through 57 and supported by Figures 58 through 62. The lag-time was caused by the absence of a drilled hole. Assuming that the semi-permeable membrane had no defects or pores, triflupromazine HCl release measured at 2 hours occurred by diffusion through the semi-permeable polymer membrane's free volume, between the polymer chains (Baker, 1987). The lag-time is a combination of the time required for sufficient hydrostatic pressure built-up and the low drug diffusivity.

The four tablet types could be categorized in three groups, based on their triflupromazine HCl release profiles and processes: the 73 μm membrane – with hole and the 85 μm – with hole pumps in one group as they shared many similarities, the 73 μm membrane – without hole in the second group, and the 121 μm membrane – with hole in the third group. In order to study and investigate significantly different osmotic pumps in terms of their release process and profiles by
NMR Imaging, it was considered appropriate to select the 73 μm membrane – with hole, the 73 μm membrane – without hole as a control and the 121 μm membrane – with hole. Further discussion of these tablet types in terms of the release mechanism is presented in the next section.

3. \(^1\)H NMR EXPERIMENTS

As expected, both \(T_1\) and \(T_2\) decreased as the weight-percent of lactose increased, due to a decrease in the tumbling frequency of the water in the mixtures (Figures 42 through 46). Since only the \(T_2\) values showed a clear and strong dependence as a function of lactose concentration suggests that processes that do affect \(T_2\) more than \(T_1\) are occurring. An increase in lactose concentration may result in an increase in slowly fluctuating internal magnetic fields that cause local magnetic field inhomogeneity and force the spin-spin exchange thus causing dephasing and significant decrease in \(T_2\) (Stark, 1988).

The experimental \(T_2\) values deviated from the fitted curve at around 20% lactose (Figure 47) because \(T_2\) measurements of lactose concentration \(\geq 20\%\) were not reliable as the mixture became heterogeneous and undissolved lactose was in equilibrium with the solution.

The short echo time, \(T_E = 7.5\) ms was considered best for the determination of the \(T_2\) values of the high percent lactose (> 10%) while the long echo time, \(T_E = 40\) ms was more appropriate for the \(T_2\) determination at lower % lactose (< 10%) (Wong, 2001). The protocol at 10 ms with 100 echoes was used for subsequent experiments in this work as it offered an overall more efficient experiment: a relatively short \(T_E\) of 10 ms (first echo collected at 10 ms. Each subsequent echo had a decreased signal intensity from the previous echo as the \(T_E\) is increased along the echo train) allowed for an enhanced signal intensity, compared to a \(T_E\) of 40 ms. 100 echoes, although large, allowed for increased accuracy in determining shorter and longer \(T_2\) values as more data were collected, compared to 50 echoes. The overall experimental time of 1000 ms (10 ms x 100 echoes) was also more practical compared to 3200 s (40 ms x 80 echoes).
4. NMR IMAGING GRAY - SCALE IMAGES AND WATER SIGNAL INTENSITIES

Tablets with thinner membrane showed a faster core tablet erosion compared to the thicker membrane tablets (Figures 48 through 57). The key difference between these two groups of tablets is their different membrane thicknesses. Since the same core tablet formulation was used in all cases, the core tablet erosion rate would be determined mostly by the flux of water through the membrane, according to Fick's law of diffusion (Equation 1). A higher water permeation rate and a subsequently higher percent core tablet erosion would be expected from the two 73 μm membrane thickness tablets compared to the 121 μm membrane thickness tablet. The relative similarity in core tablet erosion between the two 73 μm membrane thickness tablets suggests that the presence or absence of the drilled hole was not critical to the rate of core tablet erosion. The water permeation trends expressed in these gray-scale images and discussed above were also demonstrated in the water signal intensity graphs (Figures 58 through 62). There was no evidence for substantial lactose concentrations in the water between the outer membrane and the tablet core. The rate of dissolution of the lactose was slow and the diffusion of the water through the membrane and then out of the tablet should be fast enough that there was no building up of the lactose in solution. This was evident in Figures 63 (a) through 72 (a) where the lactose concentrations in the region between the dotted line (coated membrane) and the solid line (core tablet) were at the same level as the lactose concentration in the region between the dotted line and the y-axis, representing water outside the osmotic pump tablet. In this latter region, lactose concentration was predicted to be negligible given that there was 266.6 mg of lactose in a tablet, dissolved in a total of 900 ml of water. In the region within the solid line, lactose concentration was 100%.

5. DETERMINATION OF THE PERCENT CORE TABLET ERODED

Figures (c) of Figures 63 through 72 provided a ratio of the total number of black pixels (absence of water, 100 % dry lactose) in the tablet slice at each time point (every three hours) divided by the initial total number of black pixels in the tablet slice at 0.5 hour. Assuming that the ratio of the change in volume occupied by the black pixels in the tablet slice and in the whole tablet are equal, the ratio obtained times the initial tablet volume (241 mm$^3$) yielded the volume of the
tablet occupied by the total dry lactose concentration at time t (every 3 hours). The difference in volume of core dry lactose between 0.5 hour and time t, expressed in percentage, corresponds to the percent core tablet eroded.

The percent core erosion was higher in the 73 μm membrane tablets compared to the 121 μm membrane tablet (Figures 78). This was expected since the erosion was related to the flux of water into the tablet. The thinner membranes, with a shorter diffusion path length provided a higher water diffusion flux thus a faster erosion compared to the thicker membrane. There was a clear dependence of percent drug release and percent erosion on membrane thickness. The thinner the membrane thickness, the higher the core tablet erosion and drug release (Figures 75 and 76).

The degree of intactness and thickness homogeneity of the membrane are important formulation parameters since they influence the rate of core tablet erosion. The large error bars in the average core tablet erosion for 3 tablets of the same type (Figures 75 and 77) were probably due to membrane inhomogeneity and/or imperfection.

Instances of heterogeneous core tablet dissolution also occurred. In a case where cracks filled with water appeared in the core tablet (Figure 73), it could be anticipated that the presence of cracks would substantially accelerate the erosion or dissolution of the affected core tablet. This likely explains why the average percent core tablet eroded per hour for tablet II is lowest in the period prior to the cracks, from 0.5 to 10.5, and highest from 16.5 hours (onset of the cracks) to 25.5 hours (Table 19).

Another example of heterogeneous core tablet dissolution was the preferential erosion (Figure 74). Shapiro et al. (1995), in order to investigate why the same batch of manufactured osmotic pumps displayed different release rates, used and ranked the gray-scale images according to their blackness intensity. They found that the slow release tablets had thicker membranes compared to faster release tablets and that the membrane was asymmetrically coated: thinner on the sides of the tablets. Fahie et al. (1998) along with Fyfe’s research team also studied coated tablets with faster than predicted drug release and they too found that coating non-uniformity caused the substantially different drug release rates. In the present research, non-uniform coating of the
two convex sections of the tablet was felt to be highly unlikely because of the very efficient controlled particle flow system of the Aeromatic AG Strea-1 coating column; and because there was no evidence of membrane defects in the tablet convex areas. The reasons for this preferential erosion is unknown.

It was expected that the drug release curve of the 121 µm membrane – with hole would reach its plateau before the one of the 73 µm membrane – without hole (Figure 41). This was expected because drug started being released earlier in the 121 µm membrane – with hole, and the 73 µm membrane – without hole had a much longer lag time with no drug released, but the opposite occurred. This is because the core tablet where lactose and triflupromazine HCl are mixed, approximates an insoluble granular matrix (Martin, 1993), where the drug, triflupromazine HCl is dispersed in the lactose matrix. With different water solubilities between lactose (1g/5 ml) and triflupromazine HCl (0.9 g/ml to > 1 g/ml), water permeates through the semi-permeable membrane, moves between lactose particles, allowed by the tablet porosity, and dissolves the extremely water-soluble triflupromazine HCl independently of dissolving lactose, as illustrated in Figure 79 below. As dissolution progresses, more and more triflupromazine HCl molecules and a relatively smaller percent of lactose molecules are dissolved. The liquid filled voids left behind will be inter-connecting, thus creating water-filled network channels that will allow for more and faster drug release. This may ultimately lead to visible cracks as in Figure 73. A high percent core tablet erosion will evidently contribute to drug release as triflupromazine HCl will be dissolved faster and in greater amounts.

This type of drug release mechanism follows the release from granular matrices (porous, non-homogeneous matrices), where the release of a drug involves the simultaneous penetration of the surrounding liquid, dissolution of drug, and leaching out of the drug through interstitial channels or pores (Martin, 1993). In the case of a strict non soluble granular matrix, a shell of the matrix is left behind after most of the drug has been leached-out. In this research, since lactose is reasonably soluble in water, both lactose and triflupromazine HCl leave the core tablet, though at different rates and in different amounts, through the drilled hole or/and the membrane. This release mechanism explains the higher triflupromazine HCl release profile for the 121 µm membrane – with hole compared to the 73 µm membrane – without hole (Figure 76 and 77).
From the drug release profile of Figure 77, it can be concluded that triflupromazine HCl is preferentially released through the drilled hole. In the absence of a drilled hole, the drug, and the eroded lactose will be released through the semi-permeable membrane. This would be affected by two parameters: sufficient hydrostatic pressure build-up inside the pump (Theeuwes, 1975), capable of pumping them out of the pump, and their diffusivities through the polymer membrane.
Figure 79: Schematic of the dissolution of triflupromazine HCl independently of lactose particles. *Empty circles: lactose particles. Hatched squares: triflupromazine HCl particles. Undulating arrows: water movement.* (a): water permeates through the semi-permeable membrane, moves between lactose particles, allowed by the tablet porosity. (b): triflupromazine HCl and lactose dissolved in water exist the tablet through the semi-permeable membrane.
The diffusivity of a permeant is a measure of its mobility in the membrane. As stated earlier, the diffusivity is dependent on the size and the nature of the permeant and the media through which it is diffusing (Baker, 1987). Since diffusion usually involves two neighboring polymer chains moving apart to accommodate the passage of a diffusant molecule, the flexibility of the polymer must be considered. The polymer membrane, in this case cellulose acetate (Figure 13), is insoluble in water and does not offer a lot of flexibility because of the presence of rings. Polyethylene glycol used in the membrane formulation as a plasticizer contributes to increasing this flexibility by reducing the bonding between polymer chains.

In an osmotic pump tablet without hole (Figure 77), the improved flexibility combined with a considerable hydrostatic pressure inside the osmotic pump allowed lactose molecules to diffuse more readily through the membrane despite the presence of rings in the lactose molecules. The strong chemical similarities of lactose and cellulose acetate also contributed to the diffusion of lactose. On the other hand, the presence of three benzene rings and a long side chain on triflupromazine HCl do not provide flexibility and constitutes a major hinderance to its diffusivity through the cellulose acetate membrane. Also, triflupromazine HCl is positively charged thus its interaction with the relatively neutral cellulose acetate should negatively affect its diffusion. In fact, Fyfe and Blazek-Welsh (2000), in a study of the release behavior of triflupromazine HCl and 5-fluorouracil from swelling hydroxypropylmethylcellulose (HPMC) tablets, determined that triflupromazine HCl was only released at the eroding edge of the tablet where the HPMC concentration dropped below 10 %, while the much smaller 5-fluorouracil molecule was released much more rapidly from the tablet and could diffuse from regions of as high as 30 % HPMC. This is because the self-diffusion of triflupromazine HCl was estimated at approximately 3 x 10^{-6} \text{cm}^2 \text{s}^{-1} while for 5-fluorouracil was much higher than this value until the HPMC concentration reached about 30 %. This explains why a high percent core tablet erosion does not necessarily lead to a high percent drug release as shown in Figure 77, where the 73 \text{\mu m} membrane – without hole, showed maximum core tablet erosion, with the lowest total triflupromazine HCl released.
SUMMARY AND CONCLUSIONS

The compressed core tablets were elegant and physically stable as they showed no obvious signs of breakage, cracking or chipping during handling and coating. This indicates that the compression specifications chosen were adequate.

The use of a porous membrane provided the required strength to the osmotic system. No membrane rupture or failure of any kind were noticed in all the batches. The gray-scale images demonstrated that the flow of water in the core tablet was not impeded. The 260 μm drilled-hole diameter and selected membrane thicknesses allowed for an acceptable drug release, predominantly pumped through the drilled orifice as demonstrated by the dissolution results. The general features of drug release profiles are typical of osmotic pump tablets: with a lag-time due to the time required for sufficient hydrostatic pressure built-up, a burst and leveling after few hours.

Higher values of total percent triflupromazine HCl released were obtained from tablets with holes (76.70 % for the 73 μm, 72.04 % for the 85 μm, and 71.32 % for the 121 μm) compared to the tablet without a drilled orifice (54.70 %).

Higher values of percent core tablet erosion were obtained from tablet with thinner membranes since core tablet erosion was proportional to the flux of water molecules into the tablet.

Qualitative and quantitative analysis of osmotic pump tablets in operation during 24-hour dissolution testing was performed without interrupting the process or destroying the sample. "Slices" of the osmotic pump tablets were selected axially and sagitally thus allowing for a complete and more accurate study of the system: besides the percent drug released, the rate of core tablet erosion was determined for the first time and correlated to the percent drug released. The water distribution inside the tablet was also determined quantitatively, while the membrane strength and permeability were evaluated qualitatively.

An explanation of the drug release mechanism inside the tablet has been proposed. The type of drug release mechanism approximates the release from granular matrices. Water permeates
through the semi-permeable membrane, moves between lactose particles, allowed by the tablet porosity, and dissolves the extremely water-soluble triflupromazine HCl independently of dissolving lactose. As dissolution progresses, more and more triflupromazine HCl molecules and a relatively smaller percent of lactose molecules are dissolved.
FUTURE WORK

It would be interesting to combine the NMR Imaging experiment with a U.V. Spectrophotometer to allow for direct measurements of the amount of drug released. This would then be used for the determination of the membrane water permeation rates as described in section 1 of the discussion (FORMULATION & DESIGN OF OSMOTIC PUMPS). Since at steady state, the volume of saturated solution delivered is equal to the volume of water that permeated through the semi-permeable membrane in any time interval, knowledge of the membrane water permeation rate would allow for accurate prediction of drug release rates under the same conditions, once the drug solubility in water is known.

The use of 5-fluorouracil as the model drug in $^{19}$F NMR Imaging would be of great benefit in the study of its distribution inside and outside the tablet because its smaller and less bulky size will offer easier diffusion through the polymer membrane, compared to triflupromazine HCl. During dissolution, at each time-point, the concentration of the drug in the aqueous region between the remaining core tablet and the detached coated membrane; and in the aqueous solution outside the tablet could be determined, which could not be done in the present studies as we were analyzing water protons. As dissolution progresses, a map of the drug distribution inside the tablet would show directly the changes in drug concentration, and thus allow for a better understanding of drug dissolution with respect to water progression inside the core tablet, rather than lactose dissolution as in the current study.
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APPENDIX I: OSMOTIC PUMP TABLET VOLUME CALCULATION

The shape of the tablet is a Cylinder with two spherical sectors: one on the top and one on the bottom.

\[ D = \frac{d^2}{4h} + h \]

\[ D = \frac{(7.94 \text{ mm})^2}{4 (0.864 \text{ mm})} + 0.864 \text{ mm} = 19.1 \text{ mm} \]
I. THE CYLINDRICAL SECTION

Volume of the Cylinder:

\[ V = \pi \left( \frac{d}{2} \right)^2 H \]

II. CONCAVITY-THE SPHERICAL SECTIONS

Volume of one spherical section:

\[ \frac{d}{2} = \sqrt{h(D-h)} \]

\[ V = \frac{\pi}{3} h^2 \left( \frac{3D}{2} - h \right) \]

III. TOTAL VOLUME OF THE TABLET

\[ V = \pi \left( \frac{d}{2} \right)^2 H + 2 \left[ \frac{\pi}{3} h^2 \left( \frac{3D}{2} - h \right) \right] \]

\[ V = [3.14 \times (3.97 \, mm)^2 \times 4 \, mm] + 2 \left[ \frac{3.14}{3} \times (0.864 \, mm)^2 \times \left( 3 \times \frac{19.1 \, mm}{2} - 0.864 \, mm \right) \right] \]

\[ V = 198 \, mm^3 + 2 \times [0.781 \, mm^2 \times 28.0 \, mm] \]

\[ V = 241 \, mm^3 \]
**APPENDIX II-1:** Total amount of triflupromazine HCl released from osmotic pump tablets – 73 µm membrane – with hole

24 hour dissolution (*dissolution medium: H₂O, T°: 37±0.5 °C – absorbance: @ 256 nm*)

<table>
<thead>
<tr>
<th>Tablet duration in water (hour)</th>
<th>Tablet # 1 (mg)</th>
<th>Tablet # 2 (mg)</th>
<th>Tablet # 3 (mg)</th>
<th>Tablet # 4 (mg)</th>
<th>Tablet # 5 (mg)</th>
<th>Tablet # 6 (mg)</th>
<th>Average ± S.D. (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.243</td>
<td>0.603</td>
<td>0.471</td>
<td>0.351</td>
<td>0.339</td>
<td>0.387</td>
<td>0.399 ± 0.12</td>
</tr>
<tr>
<td>1.0</td>
<td>0.722</td>
<td>0.827</td>
<td>0.597</td>
<td>0.743</td>
<td>0.780</td>
<td>0.881</td>
<td>0.758 ± 0.10</td>
</tr>
<tr>
<td>2.0</td>
<td>1.893</td>
<td>1.423</td>
<td>1.343</td>
<td>1.262</td>
<td>1.476</td>
<td>1.457</td>
<td>1.476 ± 0.22</td>
</tr>
<tr>
<td>10.0</td>
<td>3.549</td>
<td>3.552</td>
<td>3.537</td>
<td>3.476</td>
<td>3.456</td>
<td>3.740</td>
<td>3.552 ± 0.10</td>
</tr>
<tr>
<td>14.0</td>
<td>3.761</td>
<td>3.725</td>
<td>3.532</td>
<td>3.640</td>
<td>3.733</td>
<td>3.651</td>
<td>3.674 ± 0.08</td>
</tr>
<tr>
<td>18.0</td>
<td>3.774</td>
<td>3.412</td>
<td>3.752</td>
<td>3.595</td>
<td>3.843</td>
<td>3.919</td>
<td>3.716 ± 0.18</td>
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<tr>
<td>22.0</td>
<td>3.966</td>
<td>3.717</td>
<td>3.700</td>
<td>3.632</td>
<td>3.800</td>
<td>3.745</td>
<td>3.760 ± 0.11</td>
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<tr>
<td>24.0</td>
<td>3.981</td>
<td>3.853</td>
<td>3.852</td>
<td>3.707</td>
<td>3.800</td>
<td>3.803</td>
<td>3.833 ± 0.09</td>
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</tbody>
</table>
APPENDIX II-2: Total percent release of triflupromazine HCl from osmotic pump tablets – 73 μm membrane – with hole
24 hour dissolution (dissolution medium: H₂O, – T°: 37±0.5 °C – absorbance: @ 256 nm)

<table>
<thead>
<tr>
<th>Tablet duration in water (hour)</th>
<th>Tablet # 1 (%)</th>
<th>Tablet # 2 (%)</th>
<th>Tablet # 3 (%)</th>
<th>Tablet # 4 (%)</th>
<th>Tablet # 5 (%)</th>
<th>Tablet # 6 (%)</th>
<th>Average ± S.D. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>4.86</td>
<td>12.06</td>
<td>9.42</td>
<td>7.02</td>
<td>6.78</td>
<td>7.74</td>
<td>7.98 ± 2.50</td>
</tr>
<tr>
<td>1.0</td>
<td>14.44</td>
<td>16.54</td>
<td>11.94</td>
<td>14.86</td>
<td>15.60</td>
<td>17.62</td>
<td>15.20 ± 1.95</td>
</tr>
<tr>
<td>6.0</td>
<td>62.76</td>
<td>66.62</td>
<td>63.98</td>
<td>61.12</td>
<td>67.34</td>
<td>64.74</td>
<td>64.43 ± 2.34</td>
</tr>
<tr>
<td>10.0</td>
<td>70.98</td>
<td>71.04</td>
<td>70.74</td>
<td>69.52</td>
<td>69.12</td>
<td>74.80</td>
<td>71.03 ± 2.01</td>
</tr>
<tr>
<td>14.0</td>
<td>75.22</td>
<td>74.5</td>
<td>70.64</td>
<td>72.80</td>
<td>74.66</td>
<td>73.02</td>
<td>73.47 ± 1.70</td>
</tr>
<tr>
<td>18.0</td>
<td>75.48</td>
<td>68.24</td>
<td>75.04</td>
<td>71.90</td>
<td>76.86</td>
<td>78.38</td>
<td>74.32 ± 3.70</td>
</tr>
<tr>
<td>22.0</td>
<td>79.32</td>
<td>74.34</td>
<td>74.00</td>
<td>72.64</td>
<td>76.00</td>
<td>74.90</td>
<td>75.20 ± 2.30</td>
</tr>
<tr>
<td>24.0</td>
<td>79.62</td>
<td>77.06</td>
<td>77.04</td>
<td>74.14</td>
<td>76.00</td>
<td>76.06</td>
<td>76.70 ± 1.80</td>
</tr>
</tbody>
</table>
APPENDIX II-3: Total amount of triflupromazine HCl released from osmotic pump tablets – 73 μm membrane – without hole

24 hour dissolution (dissolution medium: H₂O, T°: 37±0.5 °C – absorbance: @ 256 nm)

<table>
<thead>
<tr>
<th>Tablet duration in water (hour)</th>
<th>Tablet # 1 (mg)</th>
<th>Tablet # 2 (mg)</th>
<th>Tablet # 3 (mg)</th>
<th>Tablet # 4 (mg)</th>
<th>Tablet # 5 (mg)</th>
<th>Tablet # 6 (mg)</th>
<th>Average ± S.D. (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>1.0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>2.0</td>
<td>0.114</td>
<td>2.77 x 10⁻²</td>
<td>0.00</td>
<td>2.21 x 10⁻²</td>
<td>0.00</td>
<td>7.34 x 10⁻³</td>
<td>0.029 ± 0.04</td>
</tr>
<tr>
<td>6.0</td>
<td>1.636</td>
<td>1.177</td>
<td>0.972</td>
<td>0.912</td>
<td>1.124</td>
<td>0.862</td>
<td>1.114 ± 0.28</td>
</tr>
<tr>
<td>10.0</td>
<td>2.307</td>
<td>1.962</td>
<td>1.941</td>
<td>1.697</td>
<td>1.731</td>
<td>1.750</td>
<td>1.898 ± 0.23</td>
</tr>
<tr>
<td>14.0</td>
<td>2.676</td>
<td>2.207</td>
<td>2.418</td>
<td>1.916</td>
<td>2.072</td>
<td>2.006</td>
<td>2.216 ± 0.29</td>
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<tr>
<td>18.0</td>
<td>2.896</td>
<td>2.322</td>
<td>2.542</td>
<td>2.255</td>
<td>2.279</td>
<td>2.369</td>
<td>2.444 ± 0.24</td>
</tr>
<tr>
<td>22.0</td>
<td>2.963</td>
<td>2.540</td>
<td>2.626</td>
<td>2.379</td>
<td>2.265</td>
<td>2.413</td>
<td>2.531 ± 0.25</td>
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<td>3.177</td>
<td>2.729</td>
<td>2.905</td>
<td>2.533</td>
<td>2.335</td>
<td>2.732</td>
<td>2.735 ± 0.29</td>
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</tbody>
</table>
APPENDIX II-4: Total percent release of triflupromazine HCl from osmotic pump tablets – 73 μm membrane – without hole

24 hour dissolution (dissolution medium: H₂O, T°: 37±0.5 °C – absorbance: @ 256 nm)

<table>
<thead>
<tr>
<th>Tablet duration in water (hour)</th>
<th>Tablet # 1 (%)</th>
<th>Tablet # 2 (%)</th>
<th>Tablet # 3 (%)</th>
<th>Tablet # 4 (%)</th>
<th>Tablet # 5 (%)</th>
<th>Tablet # 6 (%)</th>
<th>Average ± S.D. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.0</td>
<td>2.28</td>
<td>0.554</td>
<td>0</td>
<td>0.442</td>
<td>0</td>
<td>0.1468</td>
<td>0.57 ± 0.87</td>
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<tr>
<td>6.0</td>
<td>32.72</td>
<td>23.54</td>
<td>19.44</td>
<td>18.24</td>
<td>22.48</td>
<td>17.24</td>
<td>22.27 ± 5.66</td>
</tr>
<tr>
<td>10.0</td>
<td>46.14</td>
<td>39.24</td>
<td>38.82</td>
<td>33.94</td>
<td>34.62</td>
<td>35</td>
<td>37.96 ± 4.59</td>
</tr>
<tr>
<td>14.0</td>
<td>53.52</td>
<td>44.14</td>
<td>48.36</td>
<td>38.32</td>
<td>41.44</td>
<td>40.12</td>
<td>44.32 ± 5.71</td>
</tr>
<tr>
<td>18.0</td>
<td>57.92</td>
<td>46.44</td>
<td>50.84</td>
<td>45.10</td>
<td>45.58</td>
<td>47.38</td>
<td>48.90 ± 4.90</td>
</tr>
<tr>
<td>22.0</td>
<td>59.26</td>
<td>50.8</td>
<td>52.52</td>
<td>47.58</td>
<td>45.30</td>
<td>48.26</td>
<td>50.62 ± 4.93</td>
</tr>
<tr>
<td>24.0</td>
<td>63.54</td>
<td>54.58</td>
<td>58.10</td>
<td>50.66</td>
<td>46.70</td>
<td>54.64</td>
<td>54.70 ± 5.83</td>
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</tbody>
</table>
APPENDIX II-5: Total amount of triflupromazine HCl released from osmotic pump tablets – 85 μm membrane – with hole
24 hour dissolution (dissolution medium: H2O, T°: 37±0.5 °C – absorbance: @ 256 nm)

<table>
<thead>
<tr>
<th>Tablet duration in water (hour)</th>
<th>Tablet # 1 (mg)</th>
<th>Tablet # 2 (mg)</th>
<th>Tablet # 3 (mg)</th>
<th>Tablet # 4 (mg)</th>
<th>Tablet # 5 (mg)</th>
<th>Tablet # 6 (mg)</th>
<th>Average ± S.D. (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.232</td>
<td>0.300</td>
<td>0.280</td>
<td>0.308</td>
<td>0.312</td>
<td>0.251</td>
<td>0.281 ± 0.03</td>
</tr>
<tr>
<td>1.0</td>
<td>0.440</td>
<td>0.451</td>
<td>0.468</td>
<td>0.443</td>
<td>0.424</td>
<td>0.471</td>
<td>0.450 ± 0.02</td>
</tr>
<tr>
<td>2.0</td>
<td>1.053</td>
<td>1.045</td>
<td>0.863</td>
<td>0.994</td>
<td>0.945</td>
<td>0.994</td>
<td>0.982 ± 0.07</td>
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<tr>
<td>6.0</td>
<td>2.743</td>
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<td>2.291</td>
<td>2.523</td>
<td>2.527 ± 0.19</td>
</tr>
<tr>
<td>10.0</td>
<td>3.504</td>
<td>3.360</td>
<td>3.154</td>
<td>3.261</td>
<td>3.062</td>
<td>3.178</td>
<td>3.253 ± 0.16</td>
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<tr>
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<td>3.557</td>
<td>3.287</td>
<td>3.508</td>
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<td>3.338</td>
<td>3.385 ± 0.20</td>
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<td>3.433</td>
<td>3.563</td>
<td>3.366</td>
<td>3.312</td>
<td>3.550</td>
<td>3.477 ± 0.13</td>
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<td>3.406</td>
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<td>3.511 ± 0.10</td>
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<td>24.0</td>
<td>3.701</td>
<td>3.502</td>
<td>3.753</td>
<td>3.539</td>
<td>3.531</td>
<td>3.587</td>
<td>3.602 ± 0.10</td>
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</table>
APPENDIX II-6: Total percent release of triflupromazine HCl from osmotic pump tablets – 85 μm membrane – with hole

24 hour dissolution (dissolution medium: H₂O, T°: 37±0.5 °C – absorbance: @ 256 nm)

<table>
<thead>
<tr>
<th>Tablet duration in water (hour)</th>
<th>Tablet # 1 (%)</th>
<th>Tablet # 2 (%)</th>
<th>Tablet # 3 (%)</th>
<th>Tablet # 4 (%)</th>
<th>Tablet # 5 (%)</th>
<th>Tablet # 6 (%)</th>
<th>Average ± S.D. (%)</th>
</tr>
</thead>
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<tr>
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<td>5.6</td>
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<td>6.24</td>
<td>5.02</td>
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<td>9.02</td>
<td>9.36</td>
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<td>8.48</td>
<td>9.42</td>
<td>9.00 ± 0.36</td>
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<tr>
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<td>20.90</td>
<td>17.26</td>
<td>19.88</td>
<td>18.90</td>
<td>19.88</td>
<td>19.64 ± 1.41</td>
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<tr>
<td>6.0</td>
<td>54.86</td>
<td>54.28</td>
<td>46.24</td>
<td>51.58</td>
<td>45.82</td>
<td>50.46</td>
<td>50.54 ± 3.86</td>
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<tr>
<td>10.0</td>
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<td>63.08</td>
<td>65.22</td>
<td>61.24</td>
<td>63.56</td>
<td>65.06 ± 3.18</td>
</tr>
<tr>
<td>14.0</td>
<td>71.26</td>
<td>71.14</td>
<td>65.74</td>
<td>70.16</td>
<td>61.14</td>
<td>66.76</td>
<td>67.70 ± 4.00</td>
</tr>
<tr>
<td>18.0</td>
<td>72.72</td>
<td>68.66</td>
<td>71.26</td>
<td>67.32</td>
<td>66.24</td>
<td>71.00</td>
<td>69.54 ± 2.04</td>
</tr>
<tr>
<td>22.0</td>
<td>73.42</td>
<td>69.08</td>
<td>71.72</td>
<td>68.94</td>
<td>68.12</td>
<td>70.00</td>
<td>70.22 ± 2.00</td>
</tr>
<tr>
<td>24.0</td>
<td>74.02</td>
<td>70.04</td>
<td>75.06</td>
<td>70.78</td>
<td>70.62</td>
<td>71.74</td>
<td>72.04 ± 2.52</td>
</tr>
</tbody>
</table>
APPENDIX II-7:  Total amount of triflupromazine HCl released from osmotic pump tablets – 121 μm membrane – with hole

24 hour dissolution (dissolution medium: H₂O, T°: 37±0.5 °C – absorbance: @ 256 nm)

<table>
<thead>
<tr>
<th>Tablet duration in water (hour)</th>
<th>Tablet # 1 (mg)</th>
<th>Tablet # 2 (mg)</th>
<th>Tablet # 3 (mg)</th>
<th>Tablet # 4 (mg)</th>
<th>Tablet # 5 (mg)</th>
<th>Tablet # 6 (mg)</th>
<th>Average ± S.D. (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.154</td>
<td>0.147</td>
<td>0.165</td>
<td>0.127</td>
<td>0.147</td>
<td>0.066</td>
<td>0.134 ± 0.04</td>
</tr>
<tr>
<td>1.0</td>
<td>0.153</td>
<td>0.153</td>
<td>0.165</td>
<td>0.138</td>
<td>0.186</td>
<td>0.144</td>
<td>0.157 ± 0.02</td>
</tr>
<tr>
<td>2.0</td>
<td>0.318</td>
<td>0.308</td>
<td>0.356</td>
<td>0.300</td>
<td>0.336</td>
<td>0.373</td>
<td>0.332 ± 0.03</td>
</tr>
<tr>
<td>6.0</td>
<td>1.618</td>
<td>1.616</td>
<td>1.536</td>
<td>1.419</td>
<td>1.467</td>
<td>1.691</td>
<td>1.558 ± 0.10</td>
</tr>
<tr>
<td>10.0</td>
<td>2.541</td>
<td>2.584</td>
<td>2.431</td>
<td>2.252</td>
<td>2.405</td>
<td>2.586</td>
<td>2.467 ± 0.13</td>
</tr>
<tr>
<td>14.0</td>
<td>3.124</td>
<td>3.090</td>
<td>2.962</td>
<td>2.732</td>
<td>2.920</td>
<td>3.143</td>
<td>2.995 ± 0.16</td>
</tr>
<tr>
<td>18.0</td>
<td>3.400</td>
<td>3.366</td>
<td>3.360</td>
<td>3.051</td>
<td>3.220</td>
<td>3.414</td>
<td>3.302 ± 0.14</td>
</tr>
<tr>
<td>22.0</td>
<td>3.661</td>
<td>3.540</td>
<td>3.510</td>
<td>3.170</td>
<td>3.481</td>
<td>3.621</td>
<td>3.497 ± 0.17</td>
</tr>
</tbody>
</table>
APPENDIX II-8: Total percent release of triflupromazine HCl from osmotic pump tablets – 121 μm membrane – with hole
24 hour dissolution (dissolution medium: H₂O, T°: 37±0.5 °C – absorbance: @ 256 nm)

<table>
<thead>
<tr>
<th>Tablet duration in water (hour)</th>
<th>Tablet # 1 (%)</th>
<th>Tablet # 2 (%)</th>
<th>Tablet # 3 (%)</th>
<th>Tablet # 4 (%)</th>
<th>Tablet # 5 (%)</th>
<th>Tablet # 6 (%)</th>
<th>Average ± S.D. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>3.08</td>
<td>2.94</td>
<td>3.30</td>
<td>2.54</td>
<td>2.94</td>
<td>1.32</td>
<td>2.68 ± 0.71</td>
</tr>
<tr>
<td>1.0</td>
<td>3.06</td>
<td>3.06</td>
<td>3.30</td>
<td>2.76</td>
<td>3.72</td>
<td>2.88</td>
<td>3.14 ± 0.34</td>
</tr>
<tr>
<td>2.0</td>
<td>6.36</td>
<td>6.16</td>
<td>7.12</td>
<td>6.00</td>
<td>6.72</td>
<td>7.46</td>
<td>6.64 ± 0.57</td>
</tr>
<tr>
<td>6.0</td>
<td>32.36</td>
<td>32.32</td>
<td>30.72</td>
<td>28.38</td>
<td>29.34</td>
<td>33.82</td>
<td>31.16 ± 2.05</td>
</tr>
<tr>
<td>10.0</td>
<td>50.82</td>
<td>51.68</td>
<td>48.62</td>
<td>45.04</td>
<td>48.10</td>
<td>51.72</td>
<td>49.34 ± 2.60</td>
</tr>
<tr>
<td>14.0</td>
<td>62.48</td>
<td>61.80</td>
<td>59.24</td>
<td>54.64</td>
<td>58.40</td>
<td>62.86</td>
<td>59.90 ± 3.14</td>
</tr>
<tr>
<td>18.0</td>
<td>68.00</td>
<td>67.32</td>
<td>67.20</td>
<td>61.02</td>
<td>64.40</td>
<td>68.28</td>
<td>66.04 ± 2.82</td>
</tr>
<tr>
<td>22.0</td>
<td>73.22</td>
<td>70.80</td>
<td>70.20</td>
<td>63.40</td>
<td>69.62</td>
<td>72.42</td>
<td>69.94 ± 3.48</td>
</tr>
<tr>
<td>24.0</td>
<td>73.42</td>
<td>72.46</td>
<td>71.80</td>
<td>66.62</td>
<td>70.60</td>
<td>73.00</td>
<td>71.32 ± 2.50</td>
</tr>
</tbody>
</table>
APPENDIX II-9: Average percent release of triflupromazine HCl from osmotic pump tablets – 24 hour dissolution (dissolution medium: H$_2$O, T$^\circ$: 37±0.5 °C – absorbance: @ 256 nm)

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>73 μm with hole</th>
<th>73 μm without hole</th>
<th>85 μm with hole</th>
<th>121 μm with hole</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>7.98 ± 2.50</td>
<td>0</td>
<td>5.62 ± 0.65</td>
<td>2.68 ± 0.71</td>
</tr>
<tr>
<td>1.0</td>
<td>15.20 ± 1.95</td>
<td>0</td>
<td>9.00 ± 0.36</td>
<td>3.14 ± 0.34</td>
</tr>
<tr>
<td>2.0</td>
<td>29.51 ± 4.39</td>
<td>0.57 ± 0.87</td>
<td>19.64 ± 1.41</td>
<td>6.64 ± 0.57</td>
</tr>
<tr>
<td>6.0</td>
<td>64.43 ± 2.34</td>
<td>22.27 ± 5.66</td>
<td>50.54 ± 3.86</td>
<td>31.16 ± 2.05</td>
</tr>
<tr>
<td>10.0</td>
<td>71.03 ± 2.01</td>
<td>37.96 ± 4.59</td>
<td>65.06 ± 3.18</td>
<td>49.34 ± 2.60</td>
</tr>
<tr>
<td>14.0</td>
<td>73.47 ± 1.70</td>
<td>44.32 ± 5.71</td>
<td>67.70 ± 4.00</td>
<td>59.90 ± 3.14</td>
</tr>
<tr>
<td>18.0</td>
<td>74.32 ± 3.70</td>
<td>48.90 ± 4.90</td>
<td>69.54 ± 2.04</td>
<td>66.04 ± 2.82</td>
</tr>
<tr>
<td>22.0</td>
<td>75.20 ± 2.30</td>
<td>50.62 ± 4.93</td>
<td>70.22 ± 2.00</td>
<td>69.94 ± 3.48</td>
</tr>
<tr>
<td>24.0</td>
<td>76.70 ± 1.80</td>
<td>54.70 ± 5.83</td>
<td>72.04 ± 2.52</td>
<td>71.32 ± 2.50</td>
</tr>
</tbody>
</table>
APPENDIX III-1: Estimated similarity factors for average percent triflupromazine HCl released from osmotic pump tablets. 24 hour dissolution (dissolution medium: \( H_2O \), \( T^\circ: 37\pm0.5 \) °C – absorbance: @ 256 nm).

<table>
<thead>
<tr>
<th>Dissolution drug released profiles compared</th>
<th>Similarity factors ((f^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>73 μm membrane with hole &amp; 73 μm membrane without hole</td>
<td>28</td>
</tr>
<tr>
<td>73 μm membrane with hole &amp; 85 μm membrane with hole</td>
<td>57</td>
</tr>
<tr>
<td>73 μm membrane with hole &amp; 121 μm membrane with hole</td>
<td>39</td>
</tr>
<tr>
<td>85 μm membrane with hole &amp; 73 μm membrane without hole</td>
<td>35</td>
</tr>
<tr>
<td>85 μm membrane with hole &amp; 121 μm membrane with hole</td>
<td>50</td>
</tr>
<tr>
<td>121 μm membrane with hole &amp; 73 μm membrane without hole</td>
<td>45</td>
</tr>
</tbody>
</table>
APPENDIX IV-1: Dependence of water $^1H$ $T_1$, $T_2$ ($T_R = 30$ sec) and $D$ values on weight-percent lactose in water/lactose mixtures at $37 \, ^\circ C$

<table>
<thead>
<tr>
<th>Percent lactose (%)</th>
<th>$T_1$</th>
<th>$T_1$</th>
<th>$T_2$</th>
<th>$T_2$</th>
<th>$T_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inv. reco. (sec.)</td>
<td>Sat. rec. (sec)</td>
<td>($m^2/sec) \times 10^{-9}$</td>
<td>TE-7.5 (msec)</td>
<td>TE-40 (msec)</td>
</tr>
<tr>
<td>0</td>
<td>3.734</td>
<td>3.586</td>
<td>4.586</td>
<td>1.81 x $10^3$</td>
<td>1.64 x $10^3$</td>
</tr>
<tr>
<td>2</td>
<td>3.873</td>
<td>3.530</td>
<td>4.019</td>
<td>919</td>
<td>829</td>
</tr>
<tr>
<td>4</td>
<td>3.639</td>
<td>3.862</td>
<td>3.868</td>
<td>411</td>
<td>396</td>
</tr>
<tr>
<td>6</td>
<td>3.458</td>
<td>3.455</td>
<td>3.859</td>
<td>273</td>
<td>268</td>
</tr>
<tr>
<td>8</td>
<td>3.395</td>
<td>3.430</td>
<td>4.417</td>
<td>191</td>
<td>190</td>
</tr>
<tr>
<td>10</td>
<td>3.377</td>
<td>3.291</td>
<td>3.932</td>
<td>177</td>
<td>172</td>
</tr>
<tr>
<td>12</td>
<td>3.150</td>
<td>3.114</td>
<td>3.632</td>
<td>117</td>
<td>117</td>
</tr>
<tr>
<td>14</td>
<td>3.095</td>
<td>3.176</td>
<td>3.844</td>
<td>107</td>
<td>107</td>
</tr>
<tr>
<td>16</td>
<td>3.015</td>
<td>3.020</td>
<td>1.577</td>
<td>85.7</td>
<td>88.8</td>
</tr>
<tr>
<td>18</td>
<td>2.861</td>
<td>2.844</td>
<td>1.493</td>
<td>80.4</td>
<td>83.6</td>
</tr>
<tr>
<td>20</td>
<td>2.706</td>
<td>2.679</td>
<td>2.272</td>
<td>64.2</td>
<td>65.0</td>
</tr>
<tr>
<td>22</td>
<td>2.503</td>
<td>2.435</td>
<td>1.795</td>
<td>56.4</td>
<td>56.2</td>
</tr>
</tbody>
</table>
**APPENDIX IV-2:** Dependence of water $^1$H $T_2$ values on the weight-percent lactose in water/lactose mixtures at 37 °C. 

$T_2$ – Measurements – $T_E = 10$ msec - # Echo images = 100 – $T_R = 30$ sec

<table>
<thead>
<tr>
<th>% lactose</th>
<th>Meas. 1 (msec)</th>
<th>Meas. 2 (msec)</th>
<th>Meas. 3 (msec)</th>
<th>Meas. 4 (msec)</th>
<th>Meas. 5 (msec)</th>
<th>Average (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$1.60 \times 10^3$</td>
<td>$1.76 \times 10^3$</td>
<td>$1.78 \times 10^3$</td>
<td>$1.97 \times 10^3$</td>
<td>$1.42 \times 10^3$</td>
<td>$1706 \pm 207$</td>
</tr>
<tr>
<td>2</td>
<td>819</td>
<td>876</td>
<td>823</td>
<td>910</td>
<td>852</td>
<td>$856 \pm 38.1$</td>
</tr>
<tr>
<td>4</td>
<td>414</td>
<td>457</td>
<td>436</td>
<td>513</td>
<td>503</td>
<td>$464.6 \pm 42.6$</td>
</tr>
<tr>
<td>6</td>
<td>266</td>
<td>264</td>
<td>276</td>
<td>328</td>
<td>328</td>
<td>$292.4 \pm 33.0$</td>
</tr>
<tr>
<td>8</td>
<td>186</td>
<td>225</td>
<td>226</td>
<td>278</td>
<td>278</td>
<td>$238.6 \pm 39.4$</td>
</tr>
<tr>
<td>10</td>
<td>172</td>
<td>198</td>
<td>203</td>
<td>232</td>
<td>238</td>
<td>$208.6 \pm 27.0$</td>
</tr>
<tr>
<td>12</td>
<td>117</td>
<td>163</td>
<td>157</td>
<td>203</td>
<td>204</td>
<td>$168.8 \pm 36.3$</td>
</tr>
<tr>
<td>14</td>
<td>106</td>
<td>141</td>
<td>141</td>
<td>171</td>
<td>177</td>
<td>$147.2 \pm 28.4$</td>
</tr>
<tr>
<td>16</td>
<td>86.9</td>
<td>121</td>
<td>124</td>
<td>153</td>
<td>156</td>
<td>$128.2 \pm 28.1$</td>
</tr>
<tr>
<td>18</td>
<td>79.8</td>
<td>97.9</td>
<td>99.2</td>
<td>117</td>
<td>114</td>
<td>$101.6 \pm 15.0$</td>
</tr>
<tr>
<td>20</td>
<td>64.5</td>
<td>44.9</td>
<td>43.5</td>
<td>58.9</td>
<td>60.0</td>
<td>$54.36 \pm 9.5$</td>
</tr>
<tr>
<td>22</td>
<td>55.6</td>
<td>41.2</td>
<td>41.9</td>
<td>50.9</td>
<td>49.8</td>
<td>$47.88 \pm 6.2$</td>
</tr>
</tbody>
</table>
APPENDIX V-1: 24 hour-dissolution studies (dissolution medium: H₂O – T°: 37±0.5 °C). Percent triflupromazine HCl core tablet eroded volume determination. 73 μm membrane thickness-with hole – sample I

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Core tablet volume ratio*</th>
<th>Core tablet volume (mm³)</th>
<th>Core tablet eroded volume (mm³)</th>
<th>Percent eroded volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1</td>
<td>241</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4.5</td>
<td>0.81</td>
<td>195.21</td>
<td>45.79</td>
<td>19</td>
</tr>
<tr>
<td>7.5</td>
<td>0.74</td>
<td>178.34</td>
<td>62.66</td>
<td>26</td>
</tr>
<tr>
<td>10.5</td>
<td>0.65</td>
<td>156.65</td>
<td>84.35</td>
<td>35</td>
</tr>
<tr>
<td>13.5</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>16.5</td>
<td>0.46</td>
<td>110.86</td>
<td>130.14</td>
<td>54</td>
</tr>
<tr>
<td>19.5</td>
<td>0.35</td>
<td>84.35</td>
<td>156.65</td>
<td>65</td>
</tr>
<tr>
<td>22.5</td>
<td>0.27</td>
<td>65.07</td>
<td>175.93</td>
<td>73</td>
</tr>
<tr>
<td>25.5</td>
<td>0</td>
<td>0</td>
<td>241</td>
<td>100</td>
</tr>
</tbody>
</table>

* Initial volume: @ 0.5 hour
APPENDIX V-2: 24 hour-dissolution studies *(dissolution medium: H₂O – T°: 37±0.5 °C). Percent triflupromazine HCl core tablet eroded volume determination. 73 μm membrane thickness-with hole – sample II

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Core tablet volume ratio*</th>
<th>Core tablet volume (mm³)</th>
<th>Core tablet eroded volume (mm³)</th>
<th>Percent eroded volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1</td>
<td>220.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1.5</td>
<td>0.98</td>
<td>215.6</td>
<td>4.4</td>
<td>2.0</td>
</tr>
<tr>
<td>4.5</td>
<td>0.96</td>
<td>211.2</td>
<td>8.8</td>
<td>4.0</td>
</tr>
<tr>
<td>7.5</td>
<td>0.92</td>
<td>202.4</td>
<td>17.6</td>
<td>8.0</td>
</tr>
<tr>
<td>10.5</td>
<td>0.87</td>
<td>191.4</td>
<td>28.6</td>
<td>13.0</td>
</tr>
<tr>
<td>13.5</td>
<td>0.81</td>
<td>178.2</td>
<td>41.8</td>
<td>19.0</td>
</tr>
<tr>
<td>16.5</td>
<td>0.67</td>
<td>147.4</td>
<td>72.6</td>
<td>33</td>
</tr>
<tr>
<td>19.5</td>
<td>0.54</td>
<td>118.8</td>
<td>101.2</td>
<td>46</td>
</tr>
<tr>
<td>22.5</td>
<td>0.21</td>
<td>46.2</td>
<td>173.8</td>
<td>79</td>
</tr>
<tr>
<td>25.5</td>
<td>0.00</td>
<td>0.0</td>
<td>220.0</td>
<td>100</td>
</tr>
</tbody>
</table>

* Initial volume: @ 0.5 hour
APPENDIX V-3: 24 hour-dissolution studies (dissolution medium: H₂O – T°: 37±0.5 °C). Percent triflupromazine HCl core tablet eroded volume determination. 73 μm membrane thickness-with hole – sample III

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Core tablet volume ratio*</th>
<th>Core tablet volume (mm³)</th>
<th>Core tablet eroded volume (mm³)</th>
<th>Percent eroded volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1</td>
<td>220</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>0.82</td>
<td>180.4</td>
<td>39.6</td>
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</tr>
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<td>99</td>
<td>45</td>
</tr>
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<td>7.5</td>
<td>0.44</td>
<td>96.8</td>
<td>123.2</td>
<td>56</td>
</tr>
<tr>
<td>10.5</td>
<td>0.35</td>
<td>77</td>
<td>143</td>
<td>65</td>
</tr>
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<td>50.6</td>
<td>169.4</td>
<td>77</td>
</tr>
<tr>
<td>16.5</td>
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<td>173.8</td>
<td>79</td>
</tr>
<tr>
<td>19.5</td>
<td>0.21</td>
<td>46.2</td>
<td>173.8</td>
<td>79</td>
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<td>100</td>
</tr>
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<td>25.5</td>
<td>0</td>
<td>0</td>
<td>220</td>
<td>100</td>
</tr>
</tbody>
</table>

* Initial volume: @ 0.5 hour
APPENDIX V-4: 24 hour-dissolution studies (*dissolution medium: H₂O – T°: 37±0.5 °C). Percent triflupromazine HCl core tablet eroded volume determination. 73 μm membrane thickness-without hole – sample I.

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Core tablet volume ratio*</th>
<th>Core tablet volume (mm³)</th>
<th>Core tablet eroded volume (mm³)</th>
<th>Percent eroded volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
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<tr>
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<td>11.616</td>
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</tr>
<tr>
<td>4.5</td>
<td>0.8278</td>
<td>182.116</td>
<td>37.884</td>
<td>17.22</td>
</tr>
<tr>
<td>7.5</td>
<td>0.7592</td>
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<td>52.976</td>
<td>24.08</td>
</tr>
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<td>145.618</td>
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<td>125.994</td>
<td>94.006</td>
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</tr>
<tr>
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<td>0.4898</td>
<td>107.756</td>
<td>112.244</td>
<td>51.02</td>
</tr>
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<td>0.2039</td>
<td>44.858</td>
<td>175.142</td>
<td>79.61</td>
</tr>
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<td>100</td>
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<td>25.5</td>
<td>0</td>
<td>0</td>
<td>220</td>
<td>100</td>
</tr>
</tbody>
</table>

* Initial volume: @ 0.5 hour
**APPENDIX V-5:** 24 hour-dissolution studies (*dissolution medium: H₂O – T*: 37±0.5 °C). Percent triflupromazine HCl core tablet eroded volume determination. 73 μm membrane thickness-without hole – sample II

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Core tablet volume ratio*</th>
<th>Core tablet volume (mm³)</th>
<th>Core tablet eroded volume (mm³)</th>
<th>Percent eroded volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>220</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>0.98</td>
<td>215.6</td>
<td>4.40</td>
<td>1.99</td>
</tr>
<tr>
<td>4.5</td>
<td>0.89</td>
<td>196.3</td>
<td>23.70</td>
<td>10.77</td>
</tr>
<tr>
<td>7.5</td>
<td>0.85</td>
<td>187.6</td>
<td>32.41</td>
<td>14.73</td>
</tr>
<tr>
<td>10.5</td>
<td>0.81</td>
<td>179.0</td>
<td>41.14</td>
<td>18.7</td>
</tr>
<tr>
<td>13.5</td>
<td>0.69</td>
<td>152.3</td>
<td>67.70</td>
<td>30.76</td>
</tr>
<tr>
<td>16.5</td>
<td>0.52</td>
<td>115.2</td>
<td>104.80</td>
<td>47.63</td>
</tr>
<tr>
<td>19.5</td>
<td>0.44</td>
<td>95.7</td>
<td>124.30</td>
<td>56.48</td>
</tr>
<tr>
<td>22.5</td>
<td>0.32</td>
<td>71.2</td>
<td>148.81</td>
<td>67.64</td>
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<tr>
<td>25.5</td>
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<td>0</td>
<td>220.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

* Initial volume: @ 0.5 hour
APPENDIX V-6: 24 hour-dissolution studies (dissolution medium: \( H_2O \) – \( T^\circ \): 37±0.5 \(^\circ\)C). Percent triflupromazine HCl core tablet eroded volume determination. 73 μm membrane thickness-without hole – sample III

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Core tablet volume ratio*</th>
<th>Core tablet volume (mm(^3))</th>
<th>Core tablet eroded volume (mm(^3))</th>
<th>Percent eroded volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1</td>
<td>220</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>0.97</td>
<td>212.48</td>
<td>7.52</td>
<td>3.42</td>
</tr>
<tr>
<td>4.5</td>
<td>0.74</td>
<td>162.69</td>
<td>57.31</td>
<td>26.05</td>
</tr>
<tr>
<td>7.5</td>
<td>0.69</td>
<td>150.99</td>
<td>69.01</td>
<td>31.37</td>
</tr>
<tr>
<td>10.5</td>
<td>0.61</td>
<td>134.09</td>
<td>85.91</td>
<td>39.05</td>
</tr>
<tr>
<td>13.5</td>
<td>0.56</td>
<td>122.43</td>
<td>97.57</td>
<td>44.35</td>
</tr>
<tr>
<td>16.5</td>
<td>0.47</td>
<td>103.22</td>
<td>116.80</td>
<td>53.08</td>
</tr>
<tr>
<td>19.5</td>
<td>0.47</td>
<td>102.60</td>
<td>117.41</td>
<td>53.37</td>
</tr>
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<td>22.5</td>
<td>0.40</td>
<td>87.43</td>
<td>132.57</td>
<td>60.26</td>
</tr>
<tr>
<td>25.5</td>
<td>0.33</td>
<td>73.35</td>
<td>N/A</td>
<td>N/A</td>
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</tbody>
</table>
APPENDIX V-7: 24 hour-dissolution studies *(dissolution medium: H₂O – T°: 37±0.5 °C).* Percent triflupromazine HCl core tablet eroded volume determination. 121 μm membrane thickness-with hole – sample I

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Core tablet volume ratio*</th>
<th>Core tablet volume (mm³)</th>
<th>Core tablet eroded volume (mm³)</th>
<th>Percent eroded volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1</td>
<td>220</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>1</td>
<td>220</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4.5</td>
<td>0.99</td>
<td>217.8</td>
<td>2.2</td>
<td>1</td>
</tr>
<tr>
<td>7.5</td>
<td>0.98</td>
<td>215.6</td>
<td>4.4</td>
<td>1.55</td>
</tr>
<tr>
<td>10.5</td>
<td>0.98</td>
<td>215.6</td>
<td>4.4</td>
<td>1.65</td>
</tr>
<tr>
<td>13.5</td>
<td>0.98</td>
<td>215.6</td>
<td>4.4</td>
<td>1.84</td>
</tr>
<tr>
<td>16.5</td>
<td>0.98</td>
<td>215.6</td>
<td>4.4</td>
<td>2.02</td>
</tr>
<tr>
<td>19.5</td>
<td>0.97</td>
<td>213.4</td>
<td>6.6</td>
<td>2.80</td>
</tr>
<tr>
<td>22.5</td>
<td>0.95</td>
<td>209.0</td>
<td>11.0</td>
<td>4.60</td>
</tr>
<tr>
<td>25.5</td>
<td>0.93</td>
<td>204.6</td>
<td>15.4</td>
<td>7.23</td>
</tr>
</tbody>
</table>

* Initial volume: @ 0.5 hour
APPENDIX V-8: 24 hour-dissolution studies (dissolution medium: \(H_2O\) – \(T^\circ\): 37±0.5 °C). Percent triflupromazine HCl core tablet eroded volume determination. 121 μm membrane thickness-with hole – sample II

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Core tablet volume ratio*</th>
<th>Core tablet volume (mm(^3))</th>
<th>Core tablet eroded volume (mm(^3))</th>
<th>Percent eroded volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1</td>
<td>220</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>0.9995</td>
<td>219.89</td>
<td>0.11</td>
<td>0.045</td>
</tr>
<tr>
<td>4.5</td>
<td>0.9995</td>
<td>219.89</td>
<td>0.11</td>
<td>0.045</td>
</tr>
<tr>
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<td>0.998</td>
<td>219.56</td>
<td>0.44</td>
<td>0.20</td>
</tr>
<tr>
<td>10.5</td>
<td>0.9967</td>
<td>219.27</td>
<td>0.73</td>
<td>0.33</td>
</tr>
<tr>
<td>13.5</td>
<td>0.9923</td>
<td>218.31</td>
<td>1.70</td>
<td>0.77</td>
</tr>
<tr>
<td>16.5</td>
<td>0.9923</td>
<td>218.31</td>
<td>1.70</td>
<td>0.77</td>
</tr>
<tr>
<td>19.5</td>
<td>0.9914</td>
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<td>1.90</td>
<td>0.86</td>
</tr>
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<td>5.32</td>
<td>2.42</td>
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<td>206.00</td>
<td>14.12</td>
<td>6.42</td>
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* Initial volume: @ 0.5 hour
APPENDIX V-9: 24 hour-dissolution studies (dissolution medium: H₂O – T°: 37±0.5 °C). Percent triflupromazine HCl core tablet eroded volume determination. 121 μm membrane thickness-with hole – sample III

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Core tablet volume ratio*</th>
<th>Core tablet volume (mm³)</th>
<th>Core tablet eroded volume (mm³)</th>
<th>Percent eroded volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
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<td>220</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>1</td>
<td>220</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>0.9526</td>
<td>209.57</td>
<td>10.43</td>
<td>4.74</td>
</tr>
<tr>
<td>7.5</td>
<td>0.9315</td>
<td>204.93</td>
<td>15.07</td>
<td>6.85</td>
</tr>
<tr>
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<td>0.9301</td>
<td>204.62</td>
<td>15.38</td>
<td>6.99</td>
</tr>
<tr>
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<td>0.9294</td>
<td>204.50</td>
<td>15.53</td>
<td>7.06</td>
</tr>
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<td>17.80</td>
<td>8.10</td>
</tr>
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<td>0.9141</td>
<td>201.10</td>
<td>18.90</td>
<td>8.60</td>
</tr>
<tr>
<td>22.5</td>
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<td>201.10</td>
<td>18.90</td>
<td>8.60</td>
</tr>
<tr>
<td>25.5</td>
<td>0.9141</td>
<td>201.10</td>
<td>18.90</td>
<td>8.60</td>
</tr>
</tbody>
</table>

* Initial volume: @ 0.5 hour
APPENDIX VI-1: 24 hour-dissolution studies (*dissolution medium: H₂O – T°: 37±0.5 °C*).

Average* % core tablet eroded: 73 μm membrane – with hole.

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Sample #1 (%)</th>
<th>Sample #2 (%)</th>
<th>Sample #3 (%)</th>
<th>Average (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>N/A</td>
<td>2</td>
<td>18</td>
<td>10 ± 11.31</td>
</tr>
<tr>
<td>4.5</td>
<td>19</td>
<td>4</td>
<td>45</td>
<td>23 ± 20.74</td>
</tr>
<tr>
<td>7.5</td>
<td>26</td>
<td>8</td>
<td>56</td>
<td>30 ± 24.25</td>
</tr>
<tr>
<td>10.5</td>
<td>35</td>
<td>13</td>
<td>65</td>
<td>51 ± 15.10</td>
</tr>
<tr>
<td>13.5</td>
<td>N/A</td>
<td>19</td>
<td>77</td>
<td>48 ± 40.01</td>
</tr>
<tr>
<td>16.5</td>
<td>54</td>
<td>33</td>
<td>79</td>
<td>55 ± 23.03</td>
</tr>
<tr>
<td>19.5</td>
<td>65</td>
<td>46</td>
<td>79</td>
<td>63 ± 16.56</td>
</tr>
<tr>
<td>22.5</td>
<td>73</td>
<td>79</td>
<td>100</td>
<td>84 ± 14.20</td>
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<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*Average of 3 samples


APPENDIX VI-2: 24 hour-dissolution studies (*dissolution medium: H₂O – T°: 37±0.5 °C). Average* % core tablet eroded: 73 μm membrane – without hole

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Sample #1 (%)</th>
<th>Sample #2 (%)</th>
<th>Sample #3 (%)</th>
<th>Average (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>5.28</td>
<td>1.99</td>
<td>3.42</td>
<td>3.56 ± 1.65</td>
</tr>
<tr>
<td>4.5</td>
<td>17.22</td>
<td>10.77</td>
<td>26.05</td>
<td>18.01 ± 7.67</td>
</tr>
<tr>
<td>7.5</td>
<td>24.08</td>
<td>14.73</td>
<td>31.37</td>
<td>23.40 ± 8.34</td>
</tr>
<tr>
<td>10.5</td>
<td>33.81</td>
<td>18.7</td>
<td>39.05</td>
<td>30.52 ± 10.56</td>
</tr>
<tr>
<td>13.5</td>
<td>42.73</td>
<td>30.76</td>
<td>44.35</td>
<td>39.28 ± 7.42</td>
</tr>
<tr>
<td>16.5</td>
<td>51.02</td>
<td>47.63</td>
<td>53.08</td>
<td>50.60 ± 2.75</td>
</tr>
<tr>
<td>19.5</td>
<td>79.61</td>
<td>56.48</td>
<td>53.37</td>
<td>63.15 ± 14.34</td>
</tr>
<tr>
<td>22.5</td>
<td>100</td>
<td>67.64</td>
<td>60.26</td>
<td>76.00 ± 21.14</td>
</tr>
<tr>
<td>25.5</td>
<td>100</td>
<td>100.00</td>
<td>N/A</td>
<td>100.00</td>
</tr>
</tbody>
</table>

*Average of 3 samples
APPENDIX VI-3: 24 hour-dissolution studies (dissolution medium: H₂O – T°: 37±0.5 °C). Average* % core tablet eroded: 121 μm membrane – with hole.

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Sample #1 (%)</th>
<th>Sample #2 (%)</th>
<th>Sample #3 (%)</th>
<th>Average (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>0</td>
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<td>0</td>
<td>0.015 ± 0.03</td>
</tr>
<tr>
<td>4.5</td>
<td>1</td>
<td>0.045</td>
<td>4.74</td>
<td>1.93 ± 2.50</td>
</tr>
<tr>
<td>7.5</td>
<td>1.55</td>
<td>0.20</td>
<td>6.85</td>
<td>2.87 ± 3.52</td>
</tr>
<tr>
<td>10.5</td>
<td>1.65</td>
<td>0.33</td>
<td>6.99</td>
<td>3.00 ± 3.52</td>
</tr>
<tr>
<td>13.5</td>
<td>1.84</td>
<td>0.77</td>
<td>7.06</td>
<td>3.22 ± 3.36</td>
</tr>
<tr>
<td>16.5</td>
<td>2.02</td>
<td>0.77</td>
<td>8.10</td>
<td>3.63 ± 3.92</td>
</tr>
<tr>
<td>19.5</td>
<td>2.80</td>
<td>0.86</td>
<td>8.60</td>
<td>4.07 ± 4.03</td>
</tr>
<tr>
<td>22.5</td>
<td>4.60</td>
<td>2.42</td>
<td>8.60</td>
<td>5.20 ± 3.13</td>
</tr>
<tr>
<td>25.5</td>
<td>7.23</td>
<td>6.42</td>
<td>8.60</td>
<td>7.41 ± 1.10</td>
</tr>
</tbody>
</table>

*Average of 3 samples
APPENDIX VI-4: Comparison of the average* % core tablet eroded: 73 μm membrane – with hole, 73 μm membrane – without hole, and 121 μm membrane – with hole. 24 hour-dissolution studies (dissolution medium: H₂O – T°: 37±0.5 °C).

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>73 μm – with hole (%)</th>
<th>73 μm – without hole (%)</th>
<th>121 μm – with hole (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>10 ± 11.31</td>
<td>3.56 ± 1.65</td>
<td>0.015 ± 0.03</td>
</tr>
<tr>
<td>4.5</td>
<td>23 ± 20.74</td>
<td>18.01 ± 7.67</td>
<td>1.93 ± 2.50</td>
</tr>
<tr>
<td>7.5</td>
<td>30 ± 24.25</td>
<td>23.40 ± 8.34</td>
<td>2.87 ± 3.52</td>
</tr>
<tr>
<td>10.5</td>
<td>51 ± 15.10</td>
<td>30.52 ± 10.56</td>
<td>3.00 ± 3.52</td>
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<tr>
<td>13.5</td>
<td>48 ± 40.01</td>
<td>39.28 ± 7.42</td>
<td>3.22 ± 3.36</td>
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<tr>
<td>16.5</td>
<td>55 ± 23.03</td>
<td>50.60 ± 2.75</td>
<td>3.63 ± 3.92</td>
</tr>
<tr>
<td>19.5</td>
<td>63 ± 16.56</td>
<td>63.15 ± 14.34</td>
<td>4.07 ± 4.03</td>
</tr>
<tr>
<td>22.5</td>
<td>84 ± 14.20</td>
<td>76.00 ± 21.14</td>
<td>5.20 ± 3.13</td>
</tr>
<tr>
<td>25.5</td>
<td>100</td>
<td>100.00</td>
<td>7.41 ± 1.10</td>
</tr>
</tbody>
</table>

*Average of 3 samples
APPENDIX VII-1: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (dissolution medium: \( H_2O \); \( T^\circ \): 37±0.5 °C). Gray-scale images: 73 μm membrane – with hole I – Axial (first and second rows) & Sagital (third and fourth rows) slices. First echoes – maximum signal intensity. TE-10 & 100 echoes. From left to right (top to bottom): Axial & Sagital: 0.5, 4.5, 7.5, 10.5, 16.5, 19.5, and 22.5 hours.
APPENDIX VII-2: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (dissolution medium: H$_2$O; T°: 37±0.5 °C). Gray-scale images: 73 μm membrane – with hole III – Axial slices. First echoes – maximum signal intensity. \( T_E \) – 10 & 100 echoes. From left to right (top to bottom): 0.5, 1.5, 4.5, 7.5, 10.5, 13.5, 16.5, 19.5, 22.5 and 25.5 hours.
APPENDIX VII-3: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (dissolution medium: $H_2O$; $T^\circ$: 37±0.5 °C). Gray-scale images: 73 μm membrane – with hole III – Sagital slices. First echoes – maximum signal intensity. $T_E$-10 & 100 echoes. From left to right (top to bottom): 0.5, 1.5, 4.5, 7.5, 10.5, 13.5, 16.5, 19.5, 22.5 and 25.5 hours.
APPENDIX VII-4: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (*dissolution medium: H₂O; T°: 37±0.5 °C*). Gray-scale images: 73 μm membrane – without hole I – Axial slices. First echoes – maximum signal intensity. Tₑ-10 & 100 echoes. *From left to right (top to bottom): 0.5, 1.5, 4.5, 7.5, 10.5, 13.5, 16.5, 19.5, 22.5 and 25.5 hours.*
APPENDIX VII-5: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (dissolution medium: H₂O; T°: 37±0.5 °C). Gray-scale images: 73 μm membrane—without hole I—Sagital slices. First echoes – maximum signal intensity. Tₑ-10 & 100 echoes. From left to right (top to bottom): 0.5, 1.5, 4.5, 7.5, 10.5, 13.5, 16.5, 19.5, 22.5, 25.5 and 28.5 hours.
APPENDIX VII-6: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (dissolution medium: H$_2$O; $T$: 37±0.5 °C). Gray-scale images: 73 μm membrane– without hole III– Axial slices. First echoes – maximum signal intensity. $T_E$-10 & 100 echoes. From left to right (top to bottom): 0.5, 1.5, 4.5, 7.5, 10.5, 13.5, 16.5, 19.5, and 22.5 hours.
APPENDIX VII-7: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (*dissolution medium: H₂O; T°: 37±0.5 °C*). Gray-scale images: 73 um membrane—with hole III—Sagital slices. First echoes—maximum signal intensity. *Tₑ=10 & 100 echoes.* *From left to right (top to bottom): 0.5, 1.5, 4.5, 7.5, 10.5, 13.5, 16.5, 19.5 and 22.5 hours.*
APPENDIX VII-8: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (dissolution medium: H$_2$O; $T^\circ$: 37±0.5 °C). Gray-scale images: 121 µm – with hole I– Axial slices. First echoes – maximum signal intensity. $T_E$-10 & 100 echoes. From left to right (top to bottom): 0.5, 1.5, 4.5, 7.5, 10.5, 13.5, 16.5, 19.5, 22.5 and 25.5 hours.
APPENDIX VII-9: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (dissolution medium: \( H_2O; T^\circ: 37\pm0.5^\circ C \)). Gray-scale images: 121 \( \mu \)m membrane – with hole I- Sagital slices. First echoes – maximum signal intensity. \( T_E-10 \& 100 \) echoes. From left to right (top to bottom): 0.5, 1.5, 4.5, 7.5, 10.5, 13.5, 16.5, 19.5, 22.5 and 25.5 hours.
APPENDIX VII-10: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (*dissolution medium: H₂O; T*: 37±0.5 °C). Gray-scale images: 121 μm membrane – with hole III– Axial slices. First echoes – maximum signal intensity. Tₑ-10 & 100 echoes. From left to right (top to bottom): 0.5, 1.5, 4.5, 7.5, 10.5, 13.5, 16.5, 19.5 and 22.5 hours.
APPENDIX VII-11: 24-hour dissolution studies of triflupromazine HCl osmotic pump tablets (dissolution medium: H₂O; T°: 37±0.5 °C). Gray-scale images: 121 μm membrane – with hole III– Sagital slices. First echoes – maximum signal intensity. TE-10 & 100 echoes. From left to right (top to bottom): 0.5, 1.5, 4.5, 7.5, 10.5, 13.5, 16.5, 19.5 and 22.5 hours.