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DEVELOPMENT OF EXTENDED RELEASE DEXTROMETHORPHAN MATRIX TABLETS

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DEVELOPMENT OF EXTENDED RELEASE DEXTROMETHORPHAN MATRIX TABLETS

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By

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Dedication

To my Father, Bakhshish Singh Bharaj and my Mother, Sushil Kaur Bharaj, whose foresight, love and support has and will guide me throughout my life's journey.

Abstract

Dextromethorphan (DM) is a highly potent and commonly used anitussive agent. Dextromethorphan has no narcotic, analgesic or addictive properties and its potency as an antitussive agent is almost equal to that of codeine. At present there are no extended release dextromethorphan matrix tablets available in the USA. An extended release dextromethorphan tablet can lead to the reduction of the number of doses administered, leading to better patient compliance and less of a chance of overdose, in addition to which it can reduce the cost associated with treating cough symptoms.

It was the objective of this dissertation to develop and evaluate extended release dextromethorphan matrix tablets manufactured by the direct compression method.

Formulation and process variables on the effect of hydroxypropylmethylcellulose (HPMC K100LV) in combination with anionic methacrylic acid copolymer (Eudragit L100-55); and polyvinyl acetate/povidone (PVAP) (Kollidon® SR) polymer concentrations in the tablet, filler excipient concentration, compression force, stability storage conditions and variable dissolution agitation rates were evaluated on the produced tablet characteristics. The extended release tablets were then compared to a marketed capsule product by applying the FDA dissolution recommended model independent f2 similarity test. Additionally, bioavailability and bioequivalence studies in healthy adult beagle dogs were performed.

It was found that HPMC (K100LV) at 20% level in combination with methacrylic acid copolymer (Eudragit® L100-55) at 20% level produced extended release

dextromethorphan matrix tablets that are similar to the marketed capsule product according to the model independent FDA guidelines (f2 factor).

Polyvinyl acetate/povidone (PVAP) (Kollidon® SR) at 39.5% in combination with dibasic calcium phosphate also at 39.5% level produced extended release dextromethorphan tablets that are similar to the marketed capsule product according the model independent FDA guidelines (f2 factor).

The extended release dextromethorphan matrix tablets followed square root of time dependent kinetics for drug release indicating a diffusion controlled release mechanism.

Under long term storage conditions at 25°C and 60% RH, physical stability testing performed on the extended release dextromethorphan matrix tablets showed no significant change in the dissolution rates.

The extended release dextromethorphan matrix tablets were not bioequivalent to the marketed capsule product, however, the tablets had higher bioavailability as shown by the $AUC_{(0\text{-}inf)}$. In vitro/invivo correlation between variable dissolution agitation rates and the dextromethorphan released and absorbed was not established for the extended release dextromethorphan matrix tablets.

It was concluded that extended release dextromethorphan tablets were developed using HPMC (K100LV) in combination with methacrylic acid copolymer (Eudragit® L100-55); and PVAP (Kollidon® SR) as the release extending excipients. In vitro testing indicated that the produced tablets had

similar dissolution behavior to the marketed capsule product according to the model independent FDA guideline (f2 factor)

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List of Abbreviations

ANOVA – Analysis of variance

AUC – Area under the curve

Cmax – Maximum plasma concentration

DCP – Dibasic calcium phosphate

DM - Dextromethorphan

DMHBr – Dextromethorphan Hydrobromide

ER – Extended release

FDA – United States Food and Drug Administration

HCl – Hydrochloric acid

HDPE – High density polyethylene

HPLC - High performance liquid chromatography

HPMC – Hydroxypropylmethylcellulose

IR – Immediate release

IV – Intravenous

LC/MS/MS – Liquid chromatography/Mass Spectrophotometry/Mass Spectrophotometry

MCC – Microcrystalline cellulose

Mg Stearate – Magnesium stearate

OTC – Over - the - counter

PVAP – Polyvinyl acetate and povidone

RH – Relative humidity

RSD – Relative standard deviation

Tg – Transition temperature

Tmax – Time to reach maximum plasma concentration

USP – United States Pharmacopoeia

UV - Ultraviolet

1. INTRODUCTION

1.1. Extended release matrix systems

Extended release dosage forms are formulated in such manner as to make the contained drug available over an extended period of time following administration. Expressions such as controlled-release, prolonged-action, repeat action and sustained-release have also been used to describe such dosage forms. A typical controlled release system is designed to provide constant or nearly constant drug levels in plasma with reduced fluctuations via slow release over an extended period of time. In practical terms, an oral controlled release should allow a reduction in dosing frequency as compared to when the same drug is presented as a conventional dosage form (Qiu and Zhang, 2000).

A matrix device consists of drug dispersed homogenously throughout a polymer matrix. Two major types of materials are used in the preparation of matrix devices(Venkatraman et al., 2000):

Hydrophobic carriers:

- Digestible base (fatty compounds) – glycerides - glyceryltristearate, fatty alcohols, fatty acids, waxes - carnauba wax (Chiao and Robinson, 1995);
- Nondigestible base (insoluble plastics) - methylacrylate - methylmethacrylate, polyvinyl chloride, polyethylene, ethyl cellulose;

Hydrophilic polymers – methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, xanthan gum, polyethylene oxide and carbopols.

Matrix systems offer several advantages relative to other extended release dose forms:

- easy to manufacture
- versatile, effective, low cost
- can be made to release high molecular weight compounds
- since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release.

Disadvantages of the matrix systems:

- the remaining matrix must be removed after the drug has been released
- the drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front (Qiu and Zhang, 2000). However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order (Jantzen and Robinson, 1996).

1.2. Mechanisms of drug release from matrix systems

The release of drug from controlled devices is via dissolution of the matrix or diffusion of drug through the matrix or a combination of the two mechanisms.

1.2.1. Dissolution controlled systems

A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs that are highly water-soluble. This can be done by:

- preparing an appropriate salt or derivative
- coating the drug with a slowly dissolving material – encapsulation dissolution control
- incorporating the drug into a tablet with a slowly dissolving carrier – matrix dissolution control (a major disadvantage is that the drug release rate continuously decreases with time) (Jantzen and Robinson, 1996).

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. The dissolution process at steady-state is described by the Noyes-Whitney equation:

$$\frac{dC}{dt} = k_d \cdot A \cdot (C_s - C) = \frac{D}{h} \cdot A \cdot (C_s - C) \qquad \text{Equation 1.}$$

where:

$\frac{dC}{dt}$ - dissolution rate

k_d - the dissolution rate constant (equivalent to the diffusion coefficient divided by the thickness of the diffusion layer D/h)

D - diffusion coefficient

C_s - saturation solubility of the solid

C - concentration of solute in the bulk solution

Equation 1. predicts that the rate of release can be constant only if the following parameters are held constant: surface area, diffusion coefficient, diffusion layer thickness and concentration difference.

However, under normal conditions, it is unlikely that these parameters will remain constant, especially surface area, and this is the case for combination diffusion and dissolution systems (Jantzen and Robinson, 1996).

1.2.2. Diffusion controlled systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier, which is usually a water-insoluble polymer.

In general, two types or subclasses of diffusional systems are recognized: reservoir devices and matrix devices (Jantzen and Robinson, 1996).

1.2.2.1.Reservoir devices

Are ER formulations where film coating constitutes the main factor in controlling drug release. Examples of materials used to control drug release include hardened gelatin, methyl or ethyl cellulose, polyhydroxymethacrylate, methacrylate ester copolymers, and various waxes. Ethyl cellulose and methacrylate ester copolymers are the most commonly used systems in the pharmaceutical industry. (Venkatraman et al, 2000).

1.2.2.2. Matrix extended release systems

In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix (Jantzen and Robinson, 1995).

Derivation of the mathematical model to describe this system involves the following assumptions:

a) a pseudo-steady state is maintained during drug release;
b) the diameter of the drug particles is less than the average distance of drug diffusion through the matrix;
c) the diffusion coefficient of drug in the matrix remains constant (no change occurs in the characteristics of the polymer matrix (Jantzen and Robinson,1995);
d) the bathing solution provides sink conditions at all times;
e) no interaction occurs between the drug and the matrix;
f) the total amount of drug present per unit volume in the matrix is substantially greater than the saturation solubility of the drug per unit volume in the matrix (excess solute is present) (Chiao and Robinson, 1995);
g) only the diffusion process occurs (Qiu and Zhang, 2000).

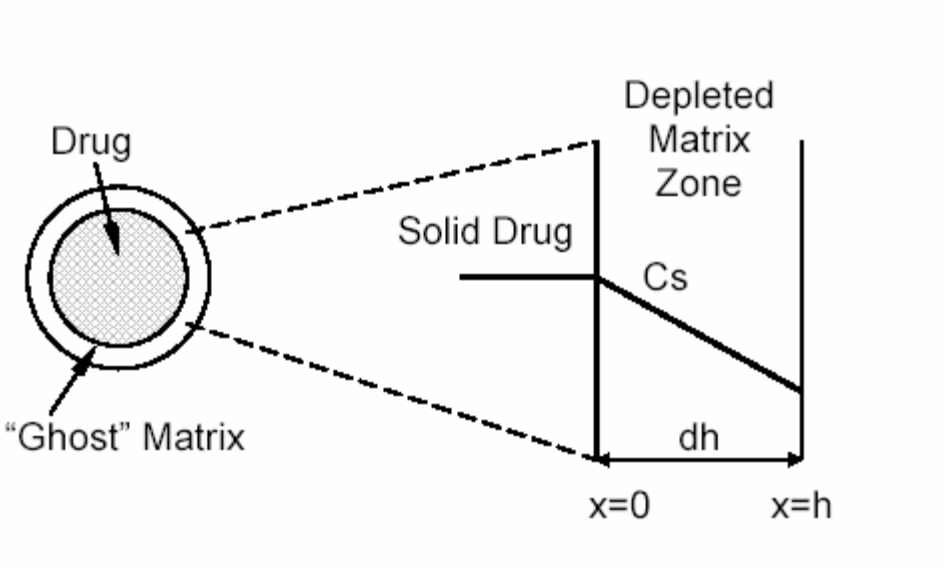


Figure 1. Schematic representation of a matrix release system

Release from a monolithic matrix system can be graphically depicted as in shown in Figure 1 – page 18.

The release behavior for the system can be mathematically described by the following equation:

$$\frac{dM}{dh} = C_o \cdot dh - \frac{C_s}{2}$$ Equation 2.

where

dM - change in the amount of drug released per unit area

dh - change in the thickness of the zone of matrix that has been depleted of drug

C_o - total amount of drug in a unit volume of matrix

C_s - saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

$$dM = \frac{D_m \cdot C_s}{h} \cdot dt \qquad \text{Equation 3}$$

where:

D_m - is the diffusion coefficient in the matrix.

h - thickness of the drug-depleted matrix

dt - change in time

By combining equation 2 and equation 3 and integrating:

$$M = [C_s \cdot D_m \cdot (2C_o - C_s) \cdot t]^{1/2} \qquad \text{Equation 4}$$

When the amount of drug is in excess of the saturation concentration, then:

$$M = [2C_s \cdot D_m \cdot C_o \cdot t]^{1/2} \qquad \text{Equation 5}$$

Equation 4 and equation 5 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion-controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line.

Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

$$M = [D_s \cdot C_a \cdot \frac{p}{T} \cdot (2C_o - p \cdot C_a) \cdot t]^{1/2}$$ Equation 6

where:

p - porosity of the matrix

t - tortuosity

C_a - solubility of the drug in the release medium

D_s - diffusion coefficient in the release medium.

T – diffusional pathlength

For pseudo steady state, the equation can be written as:

$$M = [2D \cdot C_a \cdot C_o \cdot \frac{p}{T} \cdot t]^{1/2}$$ Equation 7

The total porosity of the matrix can be calculated with the following equation:

$$p = p_a + \frac{C_o}{\rho} + \frac{C_{ex}}{\rho_{ex}}$$ Equation 8

Where:

p – porosity

ρ – drug density

p_a – porosity due to air pockets in the matrix

ρ_{ex} – density of the water soluble excipients

C_{ex} – concentration of water soluble excipients

For the purpose of data treatment, equation 6 can be reduced to:

$$M = k \cdot t^{1/2}$$ Equation 9

where k is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled.

If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

- initial concentration of drug in the matrix
- porosity
- tortuosity
- polymer system forming the matrix
- solubility of the drug (Jantzen and Robinson, 1996, Chiao and Robinson,1995).

1.2.3. Bimodal release

In certain systems there is a bimodal or anomalous release of the active ingredient. In these systems there is diffusion as described previously; additionally, the extended release polymer may become hydrated and begin to dissolve leading to release upon erosion. These systems are complex and difficult to mathematically model since the diffusional path length undergoes change due to the polymer dissolution.

A series of transport phenomena are involved in the release of a drug from a swellable, diffusion/erodable matrix:

a.) Initially, there are steep water concentration gradients at the polymer/water interface, resulting in absorption of water into the matrix. A

description of this process requires the consideration of device geometry, axial and radial direction of mass transport, and the significant dependence of the water diffusion, coefficient on the matrix swelling ratio.

b.) Due to the absorption of water, the polymer swells, resulting in dramatic changes of drug and polymer concentration, increasing the dimensions of the system and increasing macromolecular mobility.

c.) Upon contact with water the drug dissolves and diffuses out of the device.

d.) With increasing water content, the diffusion coefficient of the drug increase substantially.

e.) In the case of a poorly water soluble drug, dissolved and non-dissolved drug coexist within the polymer-matrix

f.) In the case of high initial drug loading, the inner structure of the matrix changes significantly during drug release, becoming more porous and less restrictive to diffusion.

g.) Finally, the polymer itself dissolves (Siepmann and Peppas, 2000)

These systems are described in terms of fronts. The following fronts have been defined, with regard to anomalous release systems:

- the “swelling front”, the erosion front, and the diffusion front (Figure 2 – page 23). The swelling front separates the rubbery region (swelling polymer area) which has enough water absorbed within the polymer to lower the Tg of the polymer below the respective environmental temperature allowing for macromolecular mobility and swelling, from the non-swelling polymer region (where the polymer exhibits a Tg that is above the respective environmental temperature).
- the “erosion front” separates the matrix from the bulk solution and is the interface between the unstirred layer with polymer

concentration gradient and the well stirred medium (Siepmann et. al. 1999).

- the “diffusion front” is between the swelling and erosion front and separated the areas of non dissolved drug from the area of dissolved drug.

With regard to swelling matrix systems, alternate models have been proposed to describe the diffusion, swelling, and dissolution processes occurring with into the system and these phenomena lead to drug release. (Siepmann and Kranz, 2000, Siepmann et. al. 1999a, 1999b, 1999c and Peppas and Colombo, 1997)

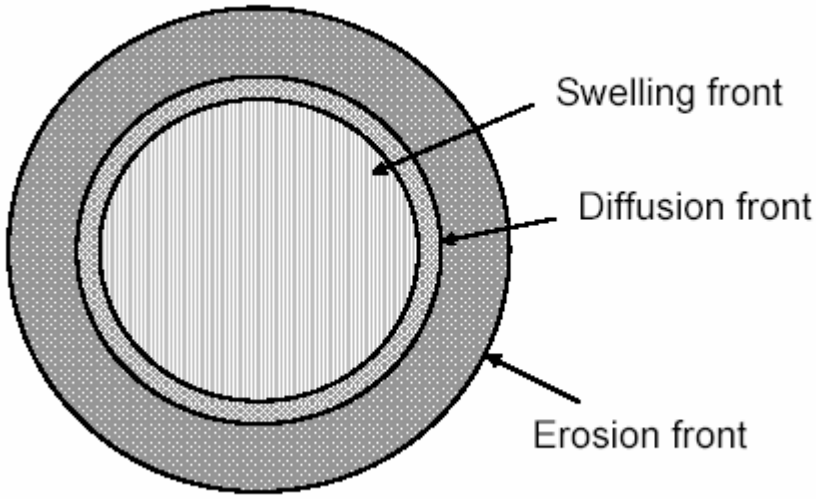


Figure 2. Fronts in bimodal release system

The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethylcellulose, hydroxypropylcellulose or tragacanth gum do not

form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices (Colombo et al., 2000, Colombo et al., 1999 and Colombo et. al 1996).

In 1985 Peppas introduced a semi-empirical equation describing the drug release behavior from anomalous-release, hydrophilic matrix systems:

$$Q = k \cdot t^n \qquad \text{Equation 10}$$

where:
Q – fraction of drug release in time (t)
t – time
k – rate constant (incorporates characteristics of polymer system and drug)
n – diffusional exponent

The value of n is indicative of the drug release mechanism. For n=0.5, drug release follows a Fickian diffusion mechanism that is driven by a chemical potential gradient. For n=1 drug release occurs via the relaxational transport that is associated with stresses and phase transition in hydrated polymers. For 0.5<n<1 non-Fickian diffusion is often observed as a result of the contributions from diffusion and polymer erosion (Qiu and Zhang, 2000).

In order to describe relaxational transport, Peppas and Sahlin (1989) then modified equation 10 in order to account for relaxational transport:

$$Q = k_1 \cdot t^n + k_2 \cdot t^{2n} \qquad \text{Equation 11}$$

where:

k_1 – fickian diffusion constant

k_2 – relaxational mechanism constant

If the surface area of the system is fixed, which is unlikely, the value of n should be 0.5 and equation 11 is transformed to:

$$Q = k_1 \cdot t^{0.5} + k_2 \cdot t \qquad \text{Equation 12}$$

The first term of this equation above accounts for diffusional phenomena, while the second term of this equation accounts for polymer erosion (Qiu and Zhang, 2000).

Drug release is controlled by the interaction between water, polymer and drug. The delivery kinetics depends on the drug gradient in the gel layer. Therefore, drug concentration and thickness of the gel layer governs the drug flux. Drug concentration in the gel depends on drug loading and solubility. Gel-layer thickness depends on the relative contributions of solvent penetration, chain disentanglement and mass (polymer and drug) transfer in the solvent. Initially solvent penetration is more rapid than chain disentanglement, and a rapid build up of gel-layer thickness occurs. However, when the solvent penetrates slowly, owing to an increase in the diffusional distance, little change in gel thickness is observed since penetration and disentanglement rates are similar. Thus gel-layer thickness dynamics in swellable matrix tablets exhibit three distinct patterns. The thickness increases when solvent penetration is the fastest mechanism, and it remains constant when the disentanglement and water penetration occur at a similar rate. Finally, the gel-layer thickness decreases when the entire polymer has undergone the glassy–rubbery

transition. In conclusion, the central element of the release mechanism is a gel-layer forming around the matrix in response to water penetration. Phenomena that govern gel-layer formation, and consequently drug-release rate, are water penetration, polymer swelling, drug dissolution and diffusion, and matrix erosion. Drug release is controlled by drug diffusion through the gel layer, which can dissolve and/or erode.

1.3. Impact of the formulation and process variables on the drug release from extended release matrix systems

1.3.1. Formulation variables

The physicochemical characteristics of the drug, in particular its aqueous solubility, should be considered in the formulation of a matrix system. Other drug properties affecting system design include drug stability in the system and at the site of absorption, pH-dependent solubility, particle size and specific surface area.

1.3.1.1. Drug particle size

Effect of drug particle size on release is important in the case of moderately soluble drugs. Hogan, (1989), showed that in the case of water-soluble aminophylline or propranolol HPMC-based tablets an increase in drug particle size did not significantly alter the release rate of the drug. A noticeable effect was seen only at a low drug:HPMC ratio and at a large drug particle size (above 250μm), in this case, rapid dissolution of the water soluble drug would leave a matrix with low tortuosity and high porosity.

Velasco et al.,1999, showed that for a given effective surface area, diclofenac particle size influenced the release rate from HPMC tablets. The smallest particle size of drug dissolved more easily when dissolution medium penetrated through the matrix resulting in a greater role for diffusion. The larger particle size dissolved less readily and therefore was more prone to erosion at the matrix surface. A similar dependence was shown for a less soluble drug, indomethacin by Ford et al., (1995).

1.3.1.2. Drug: polymer ratio

For diclofenac tablets formulated with HPMC, Velasco et al. (1999) showed that an increase in polymer:drug ratio reduced the release rate. This was because an increase in polymer concentration caused an increase in the viscosity of the gel (by making it more resistant to drug diffusion and erosion) as well as the formation of a gel layer with a longer diffusional path.

Reportings by Rekhi et al. (1999) also confirmed this. Diffusional release of the water soluble drug metoprolol decreased with increasing HPMC incorporation. By varying the polymer level (Methocel® K4M 10-40%), Nellore et al. (1998) achieved different metoprolol in vitro release profiles.

Sung et al. (1996) demonstrated that changes in HPMC: lactose ratio can be used to produce a wide range of drug release rates.

1.3.1.3. Polymer type

Various grades of commercially available HPMC differ in the relative proportion of the hydroxypropyl and methoxyl substitutions; increasing the amount of hydrophilic hydroxypropyl groups leads to a faster hydration: Methocel®K >Methocel®E > Methocel®F. Generally rapid hydrating Methocel®K grade is preferred, especially for highly soluble drugs where a rapid rate of hydration is necessary. It is important to note that an inadequate polymer hydration rate may lead to dose dumping, due to quick penetration of gastric fluids into the tablet core (Dow Pharmaceutical Excipients, 1996).

In each grade, for a fixed polymer level, the viscosity of the selected polymer affects the diffusional and mechanical characteristics of the

matrix. By comparing different Methocel®K viscosity grades, Nellore et. al. (1998) found that the higher viscosity gel layers provided a more tortuous and resistant barrier to diffusion, which resulted in slower release of the drug (metoprolol HCl).

Sung et al. (1996) compared different viscosity grades of HPMC (Methocel®K100LV, K4M, K15M, K100M). The fastest release of adinazolam mesilate was achieved for the K100LV formulation. The K4M formulation exhibited a slightly greater drug release than K15M and K100M. Due to the lack of a significant difference in the release profiles between K15M and K100M, the authors suggested a limiting HPMC viscosity of 15000cP, above which, if viscosity increased, the release rate would no longer decrease.

In the case of ethyl cellulose, the findings are completely different. The lower viscosity grades of ethylcellulose are more compressible than the higher viscosity grades, resulting in harder tablets and slower release (Upadrashta et. al., 1993).

1.3.1.4. Fillers

Nellore et al. (1998) studied the effect of filler (57% of the tablet weight) on a metoprolol formulation at 20% Methocel® K4M level. They concluded that filler solubility had a limited effect on release rate. The release profiles showed a decrease of about 5-7% after 6h, as the filler was changed from lactose to lactose – microcrystalline cellulose then to dicalcium phosphate dihydrate -microcrystalline cellulose. Addition of soluble fillers enhanced the dissolution of soluble drugs by decreasing the tortuosity of the diffusion path of the drug, while insoluble fillers like dicalcium phosphate dihydrate got entrapped in the matrix. Also, it was

assumed that the presence of a swelling insoluble filler like microcrystalline cellulose changed the release profile to a small extent due to a change in swelling at the tablet surface.

Changing the filler from 100% dicalcium phosphate dihydrate to 100% lactose resulted in an increase in metoprolol release from Methocel® K100LV tablets at 4, 6 and 12h (Rekhi et al., 1999). This was explained by dissolution of lactose and the consequent reduction in the tortuosity and or gel strength of the polymer. Similar dissolution profiles were obtained for filler concentration up to 48%. No dose dumping due to stress cracks (Dow Pharmaceutical Excipients, 1996) during gelling were observed in the case of insoluble fillers.

1.3.1.5. Polymeric excipients

Freely and Davis (1988) reported that non-ionic polymers did not alter drug release significantly from HPMC matrices; however, ionic polymers were capable of retarding the release of oppositely charged molecules. They studied the effect of polymeric additives (non-ionic polyethylene glycol 6000 or ethyl cellulose, cationic diethylaminoethyl dextran, anionic sodium carboxymethyl cellulose Na-CMC) on drug release (chlorpheniramine maleate, sodium salicylate and potassiumfenoxymethylpenicillin) from HPMC matrix (85%). Non-ionic polymers (15% of tablet weight) did not significantly alter the release rates. Na-CMC (50% replacement of HPMC) reduced the chlorpheniramine maleate release in pH 7 buffer (near zero order release), but not in an acidic medium. There was a complexation of the drug with the anionic polymer; which was not possible below pH 3, when Na-CMC was in its un-ionized insoluble form. As a result of the complexation, the gel erosion became the prominent release mechanism instead of diffusion. No

interaction occurred between sodium salicylate and Na-CMC (both anionic).

In the presence of diethylaminoethyl dextran, sodium salicylate release was slower at pH 7, but not altered at pH 1 (when the drug was present in its unionized form). Overall, the effect of ionic polymers incorporated into HPMC matrices on the release of oppositely charged drugs was small.

Takka et. al. (2003) used the drug-polymer ionic complexation approach in designing oral dosage formulation for controlled release of buspirone. Anionic exchange polymers sodium carboxymethyl cellulose and methacrylic acid /ethylacrylate copolymer were recommended based on the complexation affinity and dispersability in the aqueous environment of the gastrointestinal tract. The weight ratio of buspirone to anionic exchange polymer varied between 4:1 and 1:6, preferably between 2:1 and 1:4. In addition to facilitating the controlled release of buspirone, the formulations increased the bioavailability and reduced the inter-individual variability. Therefore, the buspirone-ion exchange polymer HPMC tablets permitted enhanced targeting of therapeutic amounts and effects of the drug.

Takka et al. (2001) studied the effect of the addition of anionic polymers (Eudragit® S, Eudragit® L 100-55, and Na-CMC) on the release of weakly basic propranolol hydrochloride from HPMC matrices. The interaction between propranolol hydrochloride and anionic polymers influenced the drug release. The HPMC: anionic polymer ratio also affected the drug release. The matrix containing HPMC: Eudragit® L 100-55 (1:1) produced pH-independent extended release tablets.

Bonferoni et al. (1998) used an optimization procedure to determine the HPMC:λ-carrageenan ratio (34:30) required for a pH-independent release of chlorpheniramine maleate. λ-Carrageenan was added to overcome the increase in diffusion path length and decrease in the release rate associated with HPMC systems. λ-carrageenan was subjected to erosion, which was higher at acidic pH.

1.3.2. Process variables

1.3.2.1. Compression force

Velasco et al., (1999) reported that for HPMC tablets, although the compression force had a significant effect on tablet hardness, its effect on drug release from HPMC tablets was minimal. It could be assumed that the variation in compression force should be closely related to a change in the porosity of the tablets. However, as the porosity of the hydrated matrix is independent of the initial porosity, the compression force seems to have little influence on drug release.

Rekhi et al. (1999) reported that changes in compression force or crushing strength had minimal effect on drug release from HPMC matrix tablets once critical hardness was reached. Increased dissolution rates were observed when the tablets were found to be extremely soft, and this phenomena was attributed to a lack of powder compaction, as tablet hardness was only 3 kp.

1.3.2.2. Tablet shape

Rekhi et al. (1999) showed that the size and shape of the tablet for the matrix system undergoing diffusion and erosion might impact the drug dissolution rate. Modification of the surface area for metoprolol tartrate

tablets formulated with Methocel® K100LV from the standard concave shape (0.568 sq. in.) to caplet shape (0.747 sq. in.) showed an approximately 20-30% increase in dissolution at each time point. Based upon these results, the researchers concluded that for maximum uniformity of extended release characteristics, tablet matrices should be manufactured to be as spherical as possible, in order to produce the minimum release rate, with regard to tablet shape.

Siepman et al. (1999b) showed that varying the aspect ratio (radius/height) of the HPMC tablets is a very easy and effective tool to modify the release rate of the matrix system. Release rate for tablets with the same volume was higher for flat shape (ratio = 20) than regular cylinders (ratio 2) and almost rod-shaped cylinders (ratio 0.2). The results were attributed to difference in tablet surface area. A mathematical model was proposed that could employed in order to calculate the optimal aspect ratio and size of a cylindrical tablet required to achieve a specific release profile. The model takes into account Fickian diffusion of water in and drug out of the tablets and swelling; it does not take into account dissolution and it cannot be applied for water insoluble drugs, which are released by dissolution process.

The mathematical model proposed above was then used to predict the dissolution rates of propranolol hydrochloride and chlorphenramine maleate (water soluble drugs) by Siepmann et. al., in 2000.

1.3.2.3. Tablet size

For tablets having the same aspect ratio and drug concentration, Siepman et al. (1999b) found that the tablet size had a very strong influence on the release rate; within 24 hours, 99.8% was released from the small tablets,

83.1% from the medium size and 50.9% from the large tablets. It was hypothesized that the smaller tablets released drug more rapidly due to an increased surface area per volume. Additionally, it was concluded that larger diffusion pathways existed in the larger tablet leading to a decrease in drug release.

1.4. Hydroxypropylmethylcellulose (HPMC)

HPMC is a methylcellulose modified with a small amount of propylene glycol ether groups attached to the anhydroglucose of the cellulose. HPMC HPMC is available in 4 different chemistries (E, F, J, and K series) based on the varying degrees of hydroxypropyl and methyl substitutions. The K series is premium series meaning it has the fastest hydration rate. The K100LV polymer thus has fast hydration, has a viscosity of 100cps and is termed low viscosity as per the "LV" designation. HPMC K100LV is a hypermellose 2208 which meets the requirements of the USP and European Pharmacopoiea and has been certified kosher.

1.4.1. Physiochemical Properties

Description: White to slightly off white powder, fibrous or granular powder
Particle size: Minimum 99% through a #40 US standard sieve
Methoxyl content: 19-24%
Hydroxypropoxl content: 7-12%
Bulk density: 0.5 g/cm^3
Solubility: HPMC K100LV is a low viscosity polymer which is soluble in water.
pH (1% content): 5.5-8

Nonionic cellulose ethers, like HPMC have been very widely studied for their applications in oral extended release systems.(Rajabi-Siahboomi et.

al. 2000). It is very commonly used to formulate extended release hydrophilic matrix tablets due to it's water solubility. HPMC has broad FDA clearance as a direct food additive. Additionally, HPMC is a very widely studied polymer and most data on it's method of action has been studied and published as is clearly evident with the number of literature citations seen the tablet process and formulation variables sections above.

1.5. Eudragit L 100-55

Eudragit L is an anionic polymer synthesized from methacrylic acid and acrylic acid ethyl esters. It is insoluble in acids and pure water. It becomes soluble in a neutral to weakly alkaline milieu by forming salts with alkalis. The polymer corresponds to USP, Methacrylic Acid Copolymer, Type C.

1.5.1. Physiochemical Properties

Description: white, moderately fine free-flowing powder
Particle size: Minimum 95% less than 0.5 mm
Solubility: In soluble in water. Soluble in isopropyl alcohol.

Eudragit L 100-55 is an FDA approved coating polymer that is widely used in pharmaceutical industry. In this instance however, the use will be in direct compression tablets. The Eudragit is used in granulation for isolation of incompatible ingredients and to improve the long term keeping properties.(Data sheet, Rohm Pharma, Germany).

1.5.2. Previous studies with Eudragit

Acrylic resins have also been used as the basis for compressed matrices. Cameron and McGinity (1987) have reported that the combination of cationic and anionic resins as a retardant matrix in a tablet formulation

was demonstrated to have good potential in a controlled release dosage form. Vela et al. (1995) reported that a direct compression technique gave erodible matrix tablets of paracetamol using Eudragit L and S. Eudragit S is also an anionic polymer synthesized from methacrylic acid and acrylic acid ethyl esters, however has only 30% free carboxyl groups compared to 50% in Eudragit L. A greater delay in the dissolution process was created by increasing the amount of Eudragit without producing any change in the indicated release mechanism.

Admixing another polymer to the hydrophilic matrix may bring about different effects according to the type and strength of the interactions between the polymers forming the matrix and also between polymer and drug. The use of mixtures of polymers represents a potential way of achieving required release properties as per Dabbagh et. al (1999). Takka et. al (2001) evaluated the effect of different anionic polymers (Eudragit L 100-55, Eudragit S and NaCMC) on pH dependent drug release from HPMC matrices. They found that the blends of HPMC and Eudragit L 100-55 in 1:1 ratio succeeded in producing pH – independent extended release propranolol hydrochloride matrix tablets. The possibility of the use of Eudragit RS (water-insoluble, swellable film formers based on neutral methacrylic acid esters with a small proportion of trimethylammonioethyl methacrylate chloride) as a sustained release matrix agent for the incorporation of water-soluble active compound has been investigated by Plazier et. al. (1997). It was concluded that Eudragit RS has a much smaller influence as a sustained release agent, however, the combination of polyvinylpyrrolidone/Eudragit RS decreased the release rate at the highest and lowest level.

1.6. Kollidon® SR (PVAP)

Polyvinylacetate/Povidone (PVAP) based polymer (Kollidon® SR) is a relatively new extended release matrix excipient. It consists of 80% Polyvinylacetate and 19% Povidone in a physical mixture, stabilized with 0.8% sodium lauryl sulfate and 0.2% colloidal silica.

Polyvinylacetate – homopolymer of vinyl acetate. It is obtained by emulsion polymerization. Description: water white, clear solid resin, soluble in benzene and acetone, insoluble in water (Ash and Ash, 1995). Polyvinylacetate is a very plastic material that produces a coherent matrix even under low compression forces.

Regulatory status: diluent in color additive mixtures for food use exempt from certification, food additive (21CFR73).

Povidone (polyvinylpyrrolidone) – white amorphous hygroscopic powder, soluble in water (Ash and Ash, 1995). It has good binding properties both under dry or wet conditions. Due to its hygroscopicity, povidone promotes water uptake and facilitates diffusion and drug release (Shivanand and Sprockel, 1998).

1.6.1. Physicochemical properties

Description: white or slightly yellowish, free flowing powder;
Particle size distribution: average particle size of about 100μm;
Molecular weight of polyvinyl acetate 450 000;
Bulk density: within the range of 0.30-0.45g/ml; 0.37g/ml (Ruchatz et al., 1999);
Tap density: 0.44g/ml (Ruchatz et al., 1999);
Flowability: good flow properties with a response angle below 30° (BASF, 1999).

Solubility: Polyvinylacetate is insoluble in water. Povidone gradually dissolves in water; in tablets it acts as a pore-former.
pH: 3.5-5.5.

1.6.2. Previous studies with PVAP

BASF generally claims PVAP to be good at compressibility and drug release independent of the dissolution medium (pH and salt/ion content) and rotation speed. The pH-independent release was also tested for caffeine (BASF, 1999).

Pathan and Jalil (2000) evaluated Kollidon® SR as matrix excipient for Theophylline tablets. Tablets containing 20-70% theophylline showed Higuchian release kinetics; the release rates increased exponentially with the drug loading. The increase in compressional force from 20kN to 60kN caused a slight linear decrease in the release rate. Annealing of the tablets for 24 hours at temperatures of 45 and 55°C showed a slight decrease in the release rate compared to the room temperature.

Shao et al. (2001) reported the effect of accelerated stability conditions on diphenhydramine HCl tablets prepared with Kollidon® SR. A decrease in dissolution rate along with an increase in tablet hardness was noticed for tablets with high level of Kollidon® SR (>37%) prepared without diluents or with 15% diluent (lactose, Emcompress®). At 25% Emcompress®, no changes occurred. Such changes were not observed for tablets stored at 25°C/ 60%RH or cured at 60°C for at least one hour.

Rock et al. (2000) evaluated different additives: diacetyl-tartaric acid diglyceride ester, pectin, stearic acid and methyl hydroxyethylcellulose for optimization of caffeine release from Kollidon® SR -based matrix tablets.

Stearic acid retarded the initial drug release in acidic medium due to its hydrophobic character, but failed to accelerate it in neutral medium. Diacetyl-tartaric acid diglyceride ester, methyl hydroxyethyl cellulose and pectin reduced the initial drug release and intensified the dissolution after the pH change.

Flick et al. (2000) showed the applicability of Kollidon® SR in hot melt technology using acetaminophen.

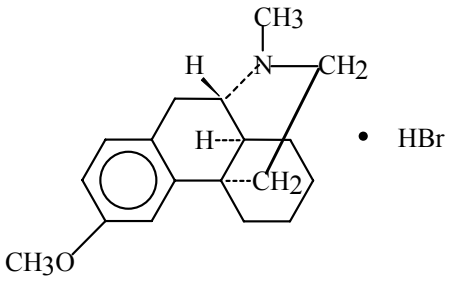
Draganiou et. al. 2001 evaluated PVAP in both wet and direct compression extended release tablets using propranolol HCl as the drug of choice. They found that reproducible and pH independent sustained release rates could be achieved successfully by incorporating the PVAP in matrix tablet dosage forms.

Tillotson et. al 2004 showed the applicability of PVAP in the development and evaluation of an extended release bumetanide matrix tablets.

1.7. Dextromethorphan

Dextromethorphan was first reported in 1953 as an effective treatment of cough without the undesirable side effects of codeine, i.e., drowsiness, nausea, and constipation (Cass and Frederick, 1953). Since that time, dextromethorphan has become the active ingredient in many over – the - - counter (OTC) products for treatment of cough due to upper respiratory infection, i.e., the common cold. Dextromethorphan is a safe and effective antitussive agent.

1.7.1 Physiochemical properties of dextromethorphan



dextromethorphan hydrobromide (anhydrous)

Synonyms: Dextromethorphani hydrobromidum

Chemical Name: Dextromethorphan hydrobromide

Molecular Formula: C(18)H(25)NO,HBr,H(2)0

Molecular Weight: 370.3

CAS Registry: 125-69-9 (anhydrous dextromethorphan hydrobromide); 6700-34-1 (Dextromethorphan hydrobromide monohydrate)

Pharmacopoeias: In Belg., Br., Braz., Eur., Fr., Gr., Int., It., Jpn., Mex., Neth., Port., Swiss., and US

A white or almost white crystalline powder, with a faint odor.

Soluble in 60 (BP) or 65 (USP) parts water and 1 in 10 parts alcohol; freely soluble in chloroform with the separation of water; practically insoluble in ether. A 1% solution in water has a pH of 5.2 to 6.5. Store in airtight containers.

1.7.2. In vivo studies of dextromethorphan

Dextromethorphan has been extensively investigated in animals for study of toxicity and pharmacology. Effective antitussive activity has been repeatedly demonstrated in experimental cough in several species

(guinea-pigs, rabbits, cats, and dogs). Therapeutic doses have not been shown to cause respiratory depression, inhibition of ciliary activity, ataxia, lethargy, or sleep (Huni, 1978).

Toxicity is rare at therapeutic doses with signs of adverse effects (mild sedation/ataxia) appearing with doses of 20 mg/kg providing a large safety factor. Subchronic evaluation of high doses over a 6-month period was without significant adverse effects. (Orzecowski, 1971)

1.7.3. Pharmacology of dextromethorphan

Dextromethorphan is the dextro-isomer of levorphanol, a non-narcotic codeine analog with little analgesic or addictive properties. It is thought to act on the cough center in the medulla oblongata by direct suppression of the cough reflex. Dextromethorphan is also thought to bind to two sites in the brain, high and low affinity sites which are distinct from opioid and other neurotransmitter binding sites (Grattan et al., 1995). A steric hindrance mechanism may exist where the (O) methylated (+) form of racemorphan (dextromethorphan) prevents binding to the analgesic/addictive receptors in the medulla to abate the narcotic side effects (Delgado et al., 1991).

The pKa of dextromethorphan has been reported to be 9.12 by Gilligan and Po, (1991).

Table 1. Pharmacokinetic parameters of dextromethorphan

Elimination half life ($t_{1/2}$) (hr)	2.7
Terminal disposition rate constant (k_{el}) (h^{-1})	0.2566
Apparent volume of distribution (V_d) (l/kg)	1.1
Fraction of Unchanged Drug Excreted in Urine (f_{el})	0.2
Fraction of drug absorbed or Absolute bioavailbility (f)	0.75
Ionization Constant (pK_a)	9.12
Therapeutic range or Minimum effective concentration (ug/ml)	0.2-0.35
Dose size (mg)	30
Dosing interval (hr)	6-8
Time to reach peak (t_{max}) (hr)	2

After oral administration, dextromethorphan is rapidly absorbed from the gastrointestinal tract where onset of pharmacologic activity is between 15–30 minutes and peak serum levels are achieved within 2.5 hours (Pender & Parks, 1991). A controlled-release suspension containing 60 mg dextromethorphan given twice daily was bioequivalent to an immediate-release solution containing 30 mg dextromethorphan given four times daily in slow and intermediate dextromethorphan metabolizers (Woodworth et al., 1987).

Dextromethorphan undergoes first-pass metabolism to O- and N-demethylated metabolites including dextrorphan, the O-demethylated metabolite with antitussive activity (Ramachander, 1977, Cleveland, 1990). Another metabolite is 3-methoxymorphinan. Metabolism of dextromethorphan involves the oxidative enzyme cytochrome P4502D6 (or CYP2D6), for which activity is genetically determined and has polymorphic distribution in most populations studied. It has been estimated that approximately 10% of Caucasians in North America, Europe, and Australia are poor dextromethorphan metabolizers in which DM persists in the plasma and is relatively slowly metabolized to DT (Guttendorf et al., 1988; Chen et al., 1990). The dextromethorphan metabolic polymorphism is determined by the molar ratio of dextromethorphan to dextrorphan in the urine after a single dose administration of dextromethorphan, i.e., urine molar dextromethorphan to dextrorophan ratio > 0.3 and ≤ 0.3 are indicative of slow and fast dextromethorphan metabolizers, respectively (Guttendorf et al., 1988). Elimination half-life of dextromethorphan is 2 to 4 hours in the majority of individuals but may be as long as 28-74 hours in slow metabolizers. No

difference between fast and slow dextromethorphan metabolizers was reported for capsaicin-induced cough frequency (Capon et al., 1996). In contrast, slow dextromethorphan metabolizers had twice the citric acid administered(CAA) induced cough threshold observed in fast dextromethorphan metabolizers (Chen et al., 1990). To date, no published reports of increased incidence or severity of adverse events in slow metabolizers relative to fast metabolizers have been found (Ramachander et al., 1977; Hou et al., 1991; Bem et al., 1992). The effects of liver disease on dextromethorphan oxidation was studied in 107 subjects and found that liver disease did impair dextromethorphan O-demethylation, but to a much less extent than that observed in slow dextromethorphan metabolizers (Larrey et al., 1989).

1.7.4. Safety and dosage

Dextromethorphan is dosed orally to adults at 10 to 20 mg every 4 hours, or 30 mg every 6–8 hours, to a maximum of 120 mg in 24 hours (PDR, 2005). Children aged 6–12 years may be given 5–15 mg every 4–8 hours to a maximum of 60 mg in 24 hours, and children aged 2 to 6 years 2.5–5 mg every 4 hours, or 7.5 mg every 6 to 8 hours, to a maximum of 30 mg in 24 hours. Dextromethorphan polistirex (Delsym®) (a dextromethorphan and sulphonated diethenylbenzene copolymer complex) is used in controlled-release preparations (Woodworth et al., 1987).

Animal toxicity and clinical efficacy studies with dextromethorphan indicate that single doses of up to 120 mg/day produce few adverse effects which are usually minor and reversible. Ingestion of less than 10 mg/kg is unlikely to produce toxicity in a child. Long-acting preparations may have

greater potential for toxicity in children. A study evaluating repeated dosing of dextromethorphan with 75 mg/day for 32 days was fairly well tolerated by subjects, with only 3 of 20 subjects reporting nausea, vomiting, and dizziness (Ralph et al., 1954).

2. Objective, hypothesis and specific aims

2.1. Objective

The objective of this dissertation was to develop extended release dextromethorphan matrix tablets.

2.2. Hypothesis

Hydroxypropylmethylcellulose (K100LV) in combination with anionic methacrylic acid copolymer (Eudragit L100-55); and polyvinyl acetate/povidone (PVAP) (Kollidon® SR) will produce extended release dextromethorphan tablets.

2.3. Specific aims

2.3.1. Specific aim 1

Study the effects of the following variables on the characteristics of dextromethorphan extended release matrix tablets:

- Filler excipient concentration
- Extended release polymer concentration
- Compression force
- Formula reproduction
- Variable dissolution agitation rates

2.3.2. Specific aim 2

Compare the in vitro release profiles of the extended release tablets with the only internationally marketed capsule product, tuss hustenstiller retardkapseln.

2.3.3. Specific aim 3

Evaluate the bioavailability and bioequivalence of selected extended release tablets to the marketed capsule product.

3. Experimental

3.1. Materials and supplies

Name	Manufacturer	Location of Manufacturer
Dextromethorphan Hydrobromide	Roche	Roche Vitamins Inc, Parsippany, NJ, USA
Hydroxypropylmethylcellulose (HPMC, K100LV)	Dow Chemical	Midland MI, USA
Methacrylic acid copolymer (Eudragit® L100-55)	Rohm	Damstadt, Germany
Avicel® PH102	FMC Biopolymer	Philadelphia, PA, USA
Lactose N.F.	Quest International	Hoffman Estates, IL USA
Magnesium Stearate	Mallinckrodt Chemical Inc.,	St. Louis, MO, USA
Polyvinylacetate and povidone polymer (PVAP) (Kollidon® SR)	BASF	Ludwigshafen/Rh. Germany
Microcrystalline Cellulose (Emcocel® 90M)	Penwest	Cedar Rapids, IA, USA
Dibasic calcium phosphate dihydrate (Emcompress®)	Penwest	Cedar Rapids, IA, USA
Colloidal Silicon dioxide (Aerosil® 200)	Degussa	Parsippany, NJ, USA

Name	Manufacturer	Location of Manufacturer
Hydrochloric Acid	EM Science	Gibbstown, NJ, USA
Sodium phosphate, tribasic	Mallinckrodt Chemical Inc.,	St. Louis, MO, USA
Sodium hydroxide	Mallinckrodt Chemical Inc.,	St. Louis, MO, USA
Glacial acetic acid	J. T. Baker	Phillipsburg, NJ, USA
Methanol HPLC grade	J.T. Baker	Phillipsburg, NJ, USA
Marketed ER capsules (Tuss Hustenstiller retardkapslen)	Dr. Rentschler Arzneimittel GmbH and Co.	Germany
Dextromethorphan hydrobromide standard	USP Convention	Rockville, MD, USA
Stable isotope internal standards for dextromethorphan and dextrorphan	Procter & Gamble, Health Care Facility	Mason, OH, USA
Beta-glucuronidase type HP-25	Sigma Chemicals	St. Louis, MO, USA
Ammonium acetate	J. T. Baker	Phillipsburg, NJ, USA
Formic acid	J. T. Baker	Phillipsburg, NJ, USA

3.2. Equipment

Equipment	Model	Manufacturer	Manufacturer Location
Analytical balance	1702	Sartorius Corporation	West Bury, NY
pH meter	pH 702	Fisher Scientific	Pittsburgh, PA, USA
Turbula Mixer T2G	T2C	WAB Maschinenfabrik	Basel ,Switzerland
Manesty rotary tablet press	Manesty D3B	Manesty	Liverpool, UK
Hand held Sieve	#25 Mesh	VWR Scientific	West Chester, PA, USA
Friability tester	Friabilator 45-2000	Vankel Technology Group	Cary, NC, USA
Hardness tester	HT-500II	Key International, Inc.	Englishtown, NJ, USA
Portable Dial Hand Micrometer	EDP 56130	L.S. Starlett Co	Athol, MA, USA
Disintegration Tester	ZT 3-4E	Erweka Instrument Corporation	Huesenstamm, Germany
Dissolution (USP 24) Tester	VK 7010	Vankel Technology Group	Cary, NC, USA

Automated sample collector	VK 8000	Vankel Technology Group	Cary, NC, USA
High performance liquid chromatography (HPLC)	HP-1100	Hewlett-Packard, Analytical Group	Novi, MI, USA
HPLC Column	Xterra Rp 18	Waters Corporation	Milford, MA, USA
HPLC	308/305	Gilson	Middletown, WI, USA
LC-MS/MS Mass Spec.	AP III-Plus	PE-Sciex	Thornhill, Ontario, Canada
Autosampler	234	Gilson	Middeltown, WI, USA
C_8 column	(2.1 X 50 mm, 3.5 um)	Waters	Milford, MA, USA
Gelatin capsules "00"	"00"	Capsugel	Greenwood, C, USA
I.V. Catheters	Abbocath-T^R 20gx1-1/4" with Terumo^R Surflo 0.2ml injection caps.	Abbot Labs Terumo Medical	Abbot Park, IL, USA Somerset, NJ, USA
Plastic Mouthpiece	Webster 27400	VWR	Indianapolis, IN, USA

3/8” canine feeding tube 0	Webster #43045	VWR	Indianapolis, IN, USA
Saf-T shield collars	Ejay International #418 or 424	VWR	Indianapolis, IN, USA
5 ml sodium heparinized blood tubes	VT-6481	VWR	Indianapolis, IN, USA
Centrifuge	BD Dynac model 420101	Becton Dickinson	Franklin Lakes, NJ, USA
2 ml Cryovials	VWR 66008-284	VWR	Indianapolis, IN, USA
Capsule filler	Profill	Capsugel	Greenwood, SC, USA

3.3. Software

Name	Manufacturer	Location of Manufacturer
Beam Spider	Hottinger Baldwin Messtechnik	Darmstadt, germany
Design Expert Software	Stat-Ease	Minneapolis, MN, USA
SAS Windows Release 8.02	SAS Institute Inc.	Cary NC, USA
PK Solutions 2.0^{TM}	Summit Research Services.	Montrose, CA

3.4. Tablet manufacture

Tablets manufactured by direct compression were:

1. HPMC alone
2. Eudragit alone
3. HPMC/Eudragit combination
4. PVAP

The process flow diagrams are presented in Figure 3 – page 55 and Figure 4 – page 57. The tablets were then stored in airtight high density polyethylene (HDPE) bottles until further testing.

HPMC/Eudragit – Manufacture Process Flow

The corresponding amounts of DMHBr, HPMC, Eudragit, microcrystalline cellulose and lactose were accurately weighed.

The powders were sieved using screen #25.

The screened powders were then transferred into the turbula mixer jar and mixed for 10 minutes.

Magnesium stearate was accurately weighed, sieved through screen #25 and added to the turbula jar and mixed for an additional 2 minutes.

The powder mix was then compressed into tablets using the instrumented tablet press, using a 7 mm round punch.

Tablets were collected during compression for in-process testing (weight and hardness)

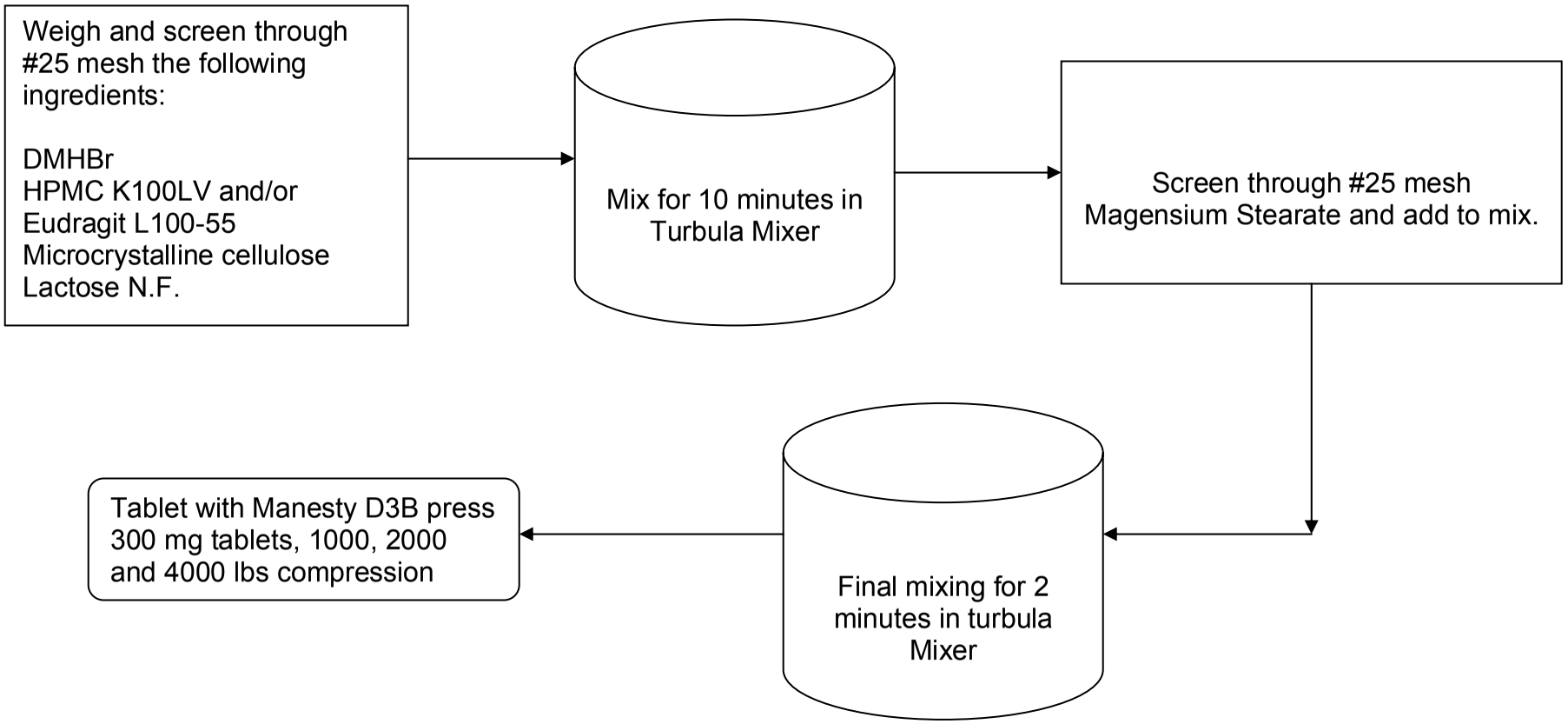


Figure 3: Process flow chart for HPMC/Eudragit tablets manufactured by direct compression.

PVAP – Manufacture Process Flow

The corresponding amounts of DMHBr, PVAP, microcrystalline cellulose, dibasic calcium phosphate dehydrate and colloidal silicon dioxide were accurately weighed.

The powders were sieved using screen #25.

The screened powders were then transferred into the turbula mixer jar and mixed for 15 minutes.

Magnesium stearate was accurately weighed, sieved through screen #25 and added to the turbula jar and mixed for an additional 3 minutes.

The powder was then compressed into tablets using the instrumented tablet press, using a 7 mm round punch.

Tablets were collected during compression for in-process testing (weight and hardness)

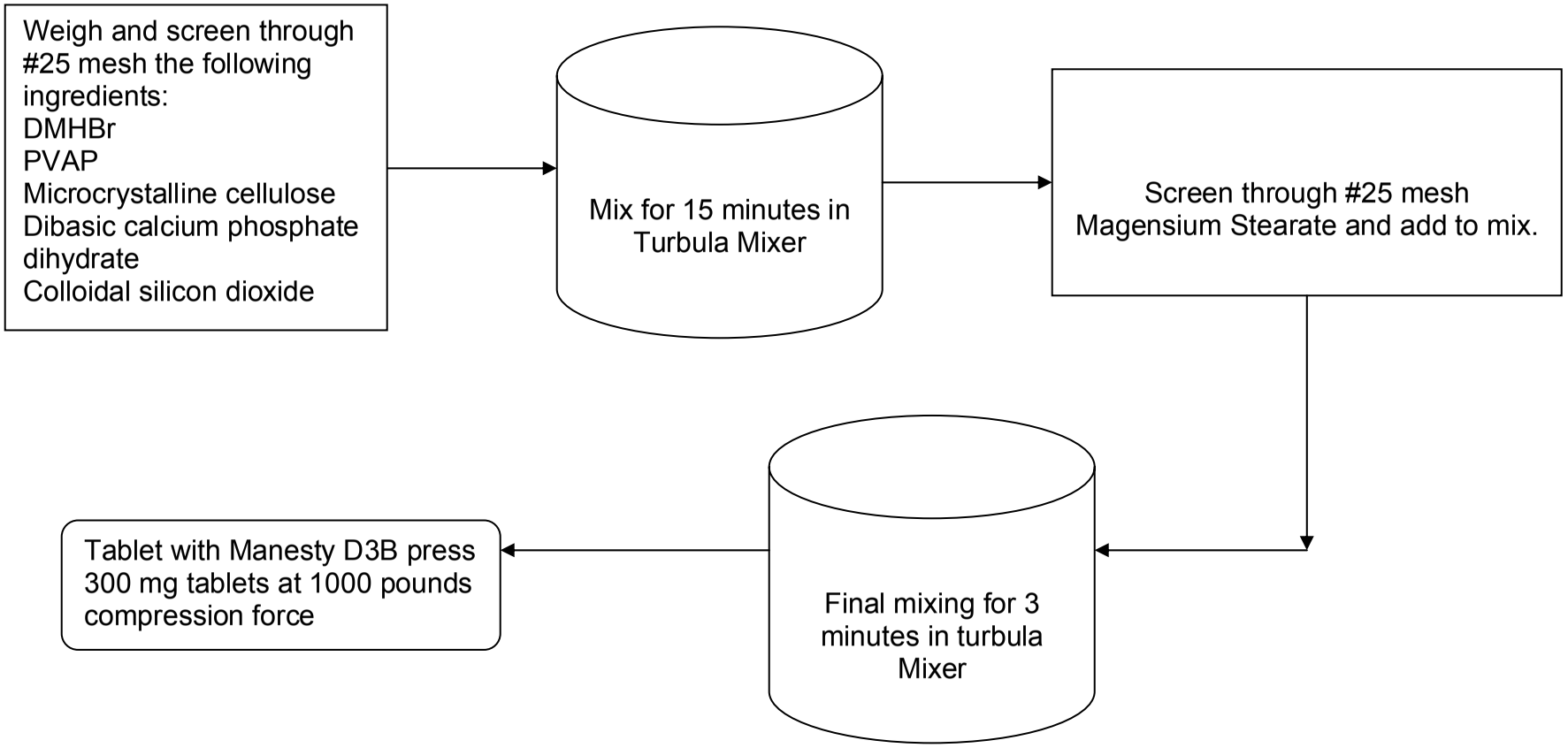


Figure 4. Process flow chart for PVAP tablets manufactured by direct compression.

3.5. Tablet testing

3.5.1. Weight variation

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight, standard deviation and relative standard variation were reported.

3.5.2. Tablet thickness

The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets by using a starrett portable dial hand micrometer. The average weight, standard deviation and relative standard variation were reported.

3.5.3. Tablet hardness

Tablet hardness was measured using a Key hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kiloponds (kp) and the average hardness, standard deviations, and relative standard variation were reported.

3.5.4. Uniformity of dosage units

This was assessed according to the USP requirements <905> for content uniformity. The batch meets the USP requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the label claim and the RSD is less than or equal to 6%. According to the USP criteria, if one of these conditions is not met, an additional 20 tablets need to be tested. Not more that 1 unit of the 30 tested should be

outside the range of 85% and 115% of the label claim and no unit outside the range of 75% to 125% of label claim. For all RSD should not exceed 7.8%.

3.5.5. Friability

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets were rotated at 25 rpm for 4 minutes (100 rotations) in the VanKel tablet friabilitor. The tablets were then will dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

3.5.6. In vitro drug release

In vitro drug release was performed for the manufactured tablets according to the USP 26 “Dissolution procedure” <711>, over a 12-hour period, using an automated Van Kel paddle dissolution system. A minimum of 6 tablets per batch were tested. The dissolution of dextromethorphan from the extended release tablets was monitored using an automated VK 7010 dissolution tester coupled to an automated VK 8000 sample collector. The USP 24 (apparatus 2) paddle method was used at 100 rpm. The media used was 0.1N HCl at a pH 2.0 and a volume of 750 ml for the first 2 hours after which 250 ml of 0.2 M sodium phosphate, tribasic, was added to give a final pH of 6.8 and maintained at $37 \pm 0.5^{o}C$.

Dextromethorphan release from each tablet (in the dissolution samples) was determined by high performance liquid chromatography (HPLC). The HPLC equipment was the Hewlett-Packard series 1100 equipped with a built in degasser, an autosampler and a variable wavelength UV-VIS detector. The

column used was an XTerra Rp18, 5μm particle, 15 cm X 4.6 mm id equipped with a 4.6 mm X 2 cm guard column.

The HPLC conditions were as follows:

Mobile Phase:	65% 0.1 N Acetic Acid : 35% Methanol
Flow Rate:	1.0 ml/min
Detection:	λ = 280 nm
Injection Volume:	20 ul

Dextromethorphan is normally analyzed by reversed-phase high performance liquid chromatography (HPLC) with ultraviolet (UV) detection. The amine functional group in the compound produces tailing peaks on many silica-based stationary phases unless ion pairing agents are added. This method employs a specially deactivated stationary phase to minimize tailing effects and eliminates the need for modifiers in the mobile phase. The method employs the same detection wavelength, 280 nm, as the USP assay method for dextromethorphan hydrobromide.

Different dissolution profiles were compared to establish the effect of formulation or process variables on the drug release as well comparison of the test formulations to the marketed product. The dissolution similarity was assessed using the FDA recommended approach (f2 similarity factor) (Food and Drug Administration 1997b). The similarity factor is a logarithmic, reciprocal square root transformation of the sum of squared errors, and it serves as a measure of the similarity of two respective dissolution profiles:

$$f2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} x100\right\} \qquad \text{Equation 13}$$

where:

n = number of sample points

R_t = percent of marketed product release profile

T_t = percent of test formulations release observed

FDA has set a public standard of f2 value between 50-100 to indicate similarity between two dissolution profiles. To use mean data, for extended release products, the coefficients of variation for mean dissolution profile of a single batch should be less than 10% (FDA, 1997b). The average difference at any dissolution sampling point should not be greater that 15% between the tested and the reference products, marketed product in this case, (FDA, 1997a).

The dissolution profiles were fitted using the Higuchi model of linear regression, plotted against square root of time and the r^2 was reported. For the dissolution profiles, which confirmed the diffusion control release mechanism, the slopes of the curves were used to compare the release rates.

3.6. Experimental design and methodology

3.6.1. Manufacture of the HPMC and Eudragit matrix tablets

A constrained mixture design (Myers et. al. 1995) using 4 different concentrations of HPMC K100LV and Eudragit L100-55, individually and in

combination were manufactured by direct compression methods mentioned above. (Section 3.4 – Page 54).

The experimental design studied the HPMC and Eudragit polymers alone with a range of 10-60% of the final tablet weight. When combining HPMC and Eudragit, the levels of the polymers were in the range from 5-30% of the final tablet weight.

The other excipients in the tablets, i.e. microcrystalline cellulose and lactose in a 1:1 ratio varied accordingly with the percent of the polymers in the tablet. The drug, dextromethorphan, at a 20% level (w/w) and the lubricant, magnesium stearate, at a 1% level (w/w) were kept constant. The range of the different ingredients in the formula was based on the results of a previous studies performed by Takka et. al. 2001.

All ingredients in their specified ratios as mentioned in Table 2 – page 63 were blended in a Turbula mixer T2G and tablets manufactured by direct compression method on a Manesty D3B rotary tablet press at compression pressures of 1000, 2000 and 4000 lbs using 7 mm round punches (process flow chart – Figure 3, page 55) to a target weight of 300 mg/tablet.

Table 2. Composition of dextromethorphan matrix tablets using HPMC and Eudragit

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
DMHBr	20	20	20	20	20	20	20	20	20	20	20	20
HPMC K100LV	10	20	40	60	-	-	-	-	5	10	20	30
Eudragit L100-55	-	-	-	-	10	20	40	60	5	10	20	30
Microcrystalline cellulose	34.5	29.5	19.5	9.5	34.5	29.5	19.5	9.5	34.5	29.5	19.5	9.5
Lactose	34.5	29.5	19.5	9.5	34.5	29.5	19.5	9.5	34.5	29.5	19.5	9.5
Mg stearate	1	1	1	1	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100	100	100	100	100

(% w/w of the tablet weight)

3.6.1.1. Testing of the HPMC and Eudragit matrix tablets

Tablets were tested for physical properties and in vitro drug release according to the USP 26 (apparatus 2) paddle method at 100 rpm as per Section 3.5 – page 58.

The applicability of the diffusional release mechanism (Higuchi time square model) was assessed.

3.6.1.2. Study the reproducibility of dextromethorphan release from HPMC tablet batches.

In order to test reproducibility and robustness of technology, three batches of HPMC ER matrix tablets at 40% polymer level were manufactured. These three batches were then tested for dextromethorphan release dissolution. Profiles were compared by f2 similarity factor.

3.6.2. Manufacture of the PVAP matrix tablets

The experimental design was a mixture study based on a three component system made out of the rate controlling PVAP polymer, microcrystalline cellulose and dibasic calcium phosphate dehydrate with a range of 0-79% of the final tablet weight for each of these components.

The other components in the test formulations were kept constant: 20% (w/w) DMHBr, 0.5% magnesium stearate and, 0.5% colloidal silica. The range of the different ingredients in the formula was based on the results of a previous studies performed by Draganoiu et. al. 2001.

In a mixture experiment, the independent factors are proportions of different components of a blend. The fact that the proportions of the different factors must sum to 100% complicates the design as well as the analysis of mixture experiments. When the mixture components are subject to the constraint that they must sum to one, then standard mixture designs for fitting standard models, such as simplex-lattice designs are used (Myers et. al 1995). Tillotson et. al (2004) employed a simplex mixture experiment to study and predict the release of fluoride from an extended- release matrix system. They concluded that the mixture design and response surface methodology provides a reliable manner of mathematically mapping and understanding multi-polymer systems, allowing for the targeting of specific release profiles based on multiple point optimization with a minimum of experiments.

Matrix systems can be viewed as mixtures of different ingredients, the change in the percentage of the rate controlling polymer implies a change in the percentage of the other excipients as well. Thus, the change in the drug release rate coming out as a result is due to the effect of many excipients rather then the rate controlling polymer alone. As such, the simplex-lattice design was used to evaluate and model the effects of different excipients commonly used in matrix systems on the release from PVAP based tablets using mixture designs and response surface methodology.

A 10 point simplex-lattice design with center repetitions was used to evaluate the experimental factors. The experimental runs in the design are presented in table 5, page 69.

All ingredients in their specified ratios as mentioned in Table 5 – page 69 were blended in a Turbula mixer T2G and tablets manufactured by direct compression method on a Manesty D3B rotary tablet press at compression pressures of 1000 lbs using 7 mm round punches (process flow chart – Figure 4, page 57) to a target weight of 300 mg/tablet.

Table 3. Experimental design for dextromethorphan formulation using PVAP (Coded form)

Formulation	PVAP Coded Form	Microcrystalline Cellulose Coded Form	Dibasic calcium phosphate dihydrate Coded Form
KSR01	1	0	0
KSR02	0	1	0
KSR03	0	0	1
KSR04	0.5	0.5	0
KSR05	0.5	0	0.5
KSR06	0	0.5	0.5
KSR07	0.66667	0.16667	0.16667
KSR08	0.16667	0.66667	0.16667
KSR09	0.16667	0.16667	0.6666
KSR10	0.33333	0.33333	0.33333
KSR11	0.33333	0.33333	0.33333
KSR12	0.33333	0.33333	0.33333

Table 4. Experimental design for dextromethorphan formulation using PVAP (% tablet weight)

Formulation	PVAP % tablet weight	Microcrystalline Cellulose % tablet weight	Dibasic calcium phosphate dihydrate % tablet weight
KSR01	79%	0	0
KSR02	0	79%	0
KSR03	0	0	79%
KSR04	39.5%	39.5%	0
KSR05	39.5%	0	39.5%
KSR06	0	39.5%	39.5%
KSR07	52.67%	13.17%	13.17%
KSR08	13.17%	52.67%	13.17%
KSR09	13.17%	13.67%	52.67%
KSR10	26.33%	26.33%	26.33%
KSR11	26.33%	26.33%	26.33%
KSR12	26.33%	26.33%	26.33%

(%w/w table weight)

Table 5. Composition of dextromethorphan matrix tablets using PVAP

Ingredients	KSR01	KSR02	KSR03	KSR04	KSR05	KSR06	KSR07	KSR08	KR09	KSR10	KSR11	KSR12
DMHBr	20	20	20	20	20	20	20	20	20	20	20	20
PVAP	79	0	0	39.5	39.5	0	52.67	13.17	13.17	26.33	26.33	26.33
Microcrystalline cellulose	0	79	0	39.5	0	39.5	13.17	52.67	13.67	26.33	26.33	26.33
Dibasic calcium phosphate dihydrate	0	0	79	0	39.5	39.5	13.17	13.17	52.67	26.33	26.33	26.33
Colloidal silicon dioxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mg stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100	100	100	100	100	100	100	100	100	100	100	100

(% w/w of tablet weight)

3.6.2.1. Testing of the PVAP Matrix tablets

Tablets were tested for physical properties and in vitro drug release according to the USP 26 (apparatus 2) paddle method at 100 rpm as per Section 3.5 – page 58.

The applicability of the diffusional release mechanism (Higuchi time square model) was assessed.

3.6.3. Manufacture of the IR dextromethorphan capsules

For the IR capsule, gelatin capsules “00” and Profill capsule filling machine were used purchased from Capsugel (Capsugel, Greenwood, SC). To each IR capsule was added 30 mg of DMHBr.

3.6.3.1. Testing of the IR dextromethorphan capsules

Cumulative drug release testing by dissolution was performed using USP 26, apparatus II, paddle stirrer, at 100 rpm in 0.1N HCl for 1 hour (750 ml) and then pH 6.7 phosphate buffer for 1 hour (total 1000 ml). Data was reported on a mean of 8 replicates

3.6.4. Testing of marketed capsule product, tuss hustenstiller retardkapseln.

The marketed capsules were tested for in vitro dextromethorphan release as per methodology outlined in Section 3.4 - page 58. This was done because the marketed capsule served as a comparison for the developed matrix tablet formulations.

3.6.5. Selection of developed extended release dextromethorphan matrix tablets for in vivo dog bioavailability and bioequivalence study

The in vitro release profiles of the developed matrix tablet formulations were compared to the marketed product using the model independent approach using the similarity factor f2.

3.6.6. Effect of storage on tablet physical properties and drug release

The selected developed matrix tablet formulations were stored in HDPE bottles and tested for stability under the long-term conditions. Accelerated conditions were not studied.

Long term stability study (FDA, 2001 ICH Q1A, FDA, 1997 ICH Q1C):

Storage: 25 $\pm$ 2^{o}C / 60 $\pm$ 5% Relative humidity

Frequency of testing: 0,1,3,6, and 9 months

Tests performed: Appearance, weight, thickness, hardness, drug release

3.6.7. In vivo dog bioavailability and bioequivalence study

3.6.7.1. Design

The relative bioavailabilities of the selected HPMC/Eudragit dextromethorphan and PVAP dextromethorphan extended release matrix tablets and the marketed, tuss hustenstiller retardkapseln, product were evaluated in a dog bioavailability and bioequivalence study. An immediate release dextromethorphan capsule was also manufactured to serve as the control. The study was conducted in a 4 x 8 randomized crossover design (Latin Square), using eight (8) adult male beagle dogs. Animals were dosed once (ER) or twice (IR) daily, then serial blood samples were collected from intravenous catheters or venipuncture. The dogs received a minimum 6-day wash-out and rest period between treatments to provide for drug clearance, blood volume recovery, and intravenous catheter site healing.

This in vivo study was conducted in a federally regulated animal species (beagle dog), and thus the protocol was submitted for full Institutional Animal Care and Use Committee review and approval at The P&G Co.

This was a non-clinical laboratory efficacy study and as such GLP quality and accordance was maintained as closely as possible.

3.6.7.2. Treatments

Table 6 – page 74 shows the description of treatments for the in vivo dog study.

Randomization schedule of the in vivo dog study is shown in table 7 – page 75.

Table 6. Description of the treatments for the in vivo dog study.

Treatment	Description
A	Commercial Extended Release (ER) Capsule – (tuss hustenstiller retardkapslen; Dr. Rentschler Arzneimittel GmbH and Co.) Dose = 1 capsule containing 60 mg DMHBr, dosed 1X.
B	PVAP polymer ER matrix tablet. Dose = 1 tablet containing 60 mg DMHBr, dosed 1X.
C	HPMC K100LV/Eudragit L100-55 combination ER matrix tablet – Dose = 1 tablet containing 60 mg DMHBr, dosed 1X.
D*	Control Treatment - Immediate Release (IR) dextromethorphan gelatin capsule Dose = 2 capsules each containing 30 mg DMHBr given in 2 separate doses six hours apart.

(*) - For the control treatment, it was decided to use an immediate release dextromethorphan capsule instead of a solution as this dose form was similar to the extended release solid dose forms, thus reducing the variability that a solution dose form would have contributed to the study

Table 7. Randomization schedule of the bioequivalence dog in vivo study

LEG 1/ Dog #	DOSE
028001	D
028002	A
028003	B
028004	B
028005	D
028006	C
028007	C
028008	A
LEG 2/ Dog #	**DOSE**
028001	A
028002	B
028003	C
028004	C
028005	A
028006	D
028007	D
028008	B
LEG 3 / Dog #	**DOSE**
028001	C
028002	D
028003	A
028004	A
028005	C
028006	B
028007	B
028008	D
LEG 4 / Dog #	**DOSE**
028001	B
028002	C
028003	D
028004	D
028005	B
028006	A
028007	A
028008	C

3.6.7.3. Methodology

Over-night food-fasted animals were weighed and moved into holding cages at approximately 6:30 a.m. The forelegs of the dogs were clipped and surgically scrubbed with Xenodyne^{R} solution, then intravenous catheters were placed in the cephalic veins (Abbocath-T^{R} 20gx1-1/4" with Terumo^{R} Surflo 0.2ml injection caps). Dogs were manually restrained for intravenous catheter placement, product dosing, and blood collection. The dogs were fitted with 18" or 24"safety collars throughout the study to prevent chewing on the catheters (Saf-T shield collars).

Baseline blood samples were collected; the dogs then received a 5 ml oral dose of water to ease capsule/tablet dosing. The dogs were dosed once at 8:00 a.m. with one capsule or tablet of product, followed by a second 5 ml oral dose of water to ease capsule/tablet swallowing. Once capsule/tablet swallowing was confirmed, the dog received a 150 ml dose of high quality water via oral gavage (plastic mouthpiece - Webster# 274000 and 3/8" canine feeding tube 0 Webster# 43045). The purpose of the water dose is to help with product dissolution/absorption in the stomach, and to simulate human dosing practices. For the IR product a second dose of was given six (6) hours later using the same methods described above. Room lights were turned out after the 8:00 p.m. blood sample, turned on for approximately 45 minutes during the 2 a.m. blood samples, and then turned off again until the 8:00 a.m. blood sample. Animals receiving 1x daily doses were fed their normal daily food ration 8 hours after the morning dose. Animals receiving 2x daily doses were fed their normal daily food ration 4 hours after the second dose (10 hours after the morning dose). Animals had access to water *ad libitum* during the study.

3.6.7.4. Blood sampling

Blood collection time points for the IR control formulation were 0, 1, 2, 4, 6 (second dose administration), 7, 8, 10, 12, 18 and 24 hours.

Blood collection time points for the ER formulations were 0, 1, 2, 4, 6, 8, 10, 12, and 24 hours.

All blood samples consisted of 3 mls blood collected into 5 ml sodium heparinized blood tubes (VWR# VT-6481). Catheters were flushed with 1 ml sterile injectable saline after blood collection to prevent clotting. The first 1 ml of blood collected at the next blood sample was discarded prior to actual blood collection to remove saline from the catheter. After blood collection, all blood samples were placed on an automatic blood rocker at room temperature until centrifugation. Blood samples were then centrifuged for fifteen (15) minutes (BD Dynac model 420101, setting 90), then the plasma drawn off, transferred into 2ml cryovials (VWR# 66008-284), and stored frozen at –70^{o}C until analysis.

The catheters were removed after 12 hours at which time the subsequent blood collection was done by venipuncture.

3.6.7.5. Analysis of dextrorphan in plasma

Dextromethorphan undergoes rapid first-pass metabolism in vivo to produce the primary metabolite dextrorphan (Ramachander et. al., 1977, Cleveland et. al., 1990). As such analytical methods for in vivo plasma levels were designed to evaluate the primary metabolite dextrorphan.

Dextrorphan was analyzed in plasma by LC/MS/MS method, developed based on published data by Eichhold et. al. 1997.

3.6.7.5.1. Preparation of plasma control samples

A series of control plasma samples were prepared by spiking blank plasma with an appropriate aliquot of a combined dextromethorphan and dextrorphan stock standard solution to yield final plasma calibration standards of 0.1, 0.2, 1.0, 2.0, and 10 ng/mL. These samples were then prepared for analysis using the sample preparation as described below.

3.6.7.5.2. Sample preparations

Unknown, control samples and calibration standards were prepared for analysis as follows. To the 200 ul of the plasma samples, 4000 units of beta-glucuronidase in 200 ul (pH 5.0 acetate buffer) was added. This was mixed well on a vortex and incubated at 37^{o}C for 24 hours. After 24 hours, the internal standards of dextromethorphan and dextrorphan (50 ul of stock 100 ug/ml) were added to the samples. 500 ul of methanol was then added. The sample was mixed on a vortex for 30 seconds and then centrifuged for 10 minutes at 2500 rpm (20^{o}C). The supernatant was then collected in a clean injection vial, capped tightly and refrigerated at 4^{o}C

3.6.7.5.3. LC/MS/MS conditions

A Gilson (Middletown, WI, USA) model 308/305 HPLC system, a PE-Sciex (Thornhill, Ontario, Canada) API III-Plus triple-quadruple, mass spectrometer and a Gilson model 234 autosampler were used with a Waters Symmetry C_8 column (2.1 X 50 mm, 3.5 um) for LC/MS/MS analysis. The mobile phases were water-methanol-formic acid (67:33:0.1, v/v/v). The flow rate and injection volume were 0.5 ml/min and 20 ul, respectively.

The mass spectrometer was operated in the Turbo-Ionspray configuration. The turboprobe temperature and nitrogen gas flow were 450^{o}C and 8 l/min respectively. The nebulizer gas pressure was 52 psi (Nitrogen). Protonated analyte ions were generated using the ESI and orifice potentials of 4000 and 70 V, respectively. Collisionally activate dissociation (CAD) was achieved using argon as the collision gas, at a thickness of 300 X 10^{13} molecules/cm^{2} . The SRM transitions m/z 272 to 147 and m/z 275 to 150 were sequentially monitored for the detection of dextromethorphan and dextrorphan. The dwell time for each transition was 200 ms. Peak area ratios for the chromatographic peaks were determined using the PE-Sciex software package MacQuan.

3.6.7.6. Pharmacokinetic analysis

The plasma concentration values obtained were naturally log-transformed and the pharmacokinetic (pK) parameters C_{max}, T_{max} and $AUC_{(0-\infty)}$ were calculated using model independent methodology. An Excel based program, PK Solutions 2.0™ (Summit Research Services, Montrose CA) was used to calculate the above pK parameters. The pK parameters were calculated from the dog study which was a 4 x 8 randomized crossover design (Latin Square), using eight (8) adult male beagle dogs.

Bioequivalence testing was done be applying the FDA (2001), guidance approach. The conditions for this statistical analysis was two one sided tests procedure for the parameters of interest, and for the bioequivalence study it is the AUC and the C_{max}. Using log transformed data, ANOVA was run modeling the period, sequence, subject and treatments. Using 90% confidence intervals (CI) bioequivalence is concluded if the confidence

intervals about the ratio of AUC and Cmax both fall within the range of 80-125%. This means that the lower bounds of the confidence intervals must be greater then or equal to 80% (0.8) and the upper bounds of the confidence intervals must be less than or equal to 125% (1.25)

3.6.7.7. Statistical analysis

Two way ANOVA was performed with the SAS General Linear Models procedure at a significance level of 0.05. The HPMC/Eudragit and PVAP and the marketed capsule product treatments were compared with respect to the pK parameters C_{max}, T_{max} and $AUC_{(0-\infty)}$ using analysis of variance with subject, treatment and period effects of the raw data. Means and standard deviations for the pK parameters were calculated. (Geng-Chang et. al. 2003)

3.6.8. In vitro/in vivo investigation at variable dissolution agitation rates

The data generated from the in vitro and the in vivo study was used to investigate if a IVIVC correlation could be established. The percent drug dissolved was determined by using the dissolution testing by calculating the cumulative release of the drug.

The measured dextrorphan plasma concentration was used to calculate the area under the plasma concentration-time profile from time zero to the last concentration time point (AUC_{0-t}). The AUC_{0-t} was determined by the trapezoidal method. $AUC_{(0-\infty)}$ was determined by the following equation:

$$AUC_{(0-\infty)} = AUC_{(0-t)} + \frac{C_{(t)}}{K_e} \qquad \text{Equation 14}$$

K_e was estimated by fitting the logarithm of the concentrations versus time to a straight line over the observed exponential decline. The Wagner – Nelson method was used to calculate the percentage of the dextrorphan dose absorbed (Wagner, 1971):

$$F_{(t)}=C_{(t)} + K_e * AUC_{(0-t)} \qquad \text{Equation 15}$$

Where $F_{(t)}$ is the amount absorbed. The percent absorbed is determined by dividing the amount absorbed at any time by the plateau value, $K*AUC_{(0-\infty)}$ and multiplying this ratio by 100.

$$\textit{\% dose absorbed} = \left(\frac{C_{(t)} + K_e * AUC_{(0-t)}}{K * AUC_{(0-\infty)}} \right) * 100 \qquad \text{Equation 16}$$

Linear regression analysis was used to examine the relationship between the percent of drug dissolved and the percent of drug absorbed. The dissolution rate constants were determined from percent released vs. the square root of time. Linear regression analysis was applied to the *in vitro* – in vivo correlation plots and r^2, slope and intercept values were calculated (Takka, et. al. 2003). In addition to the in vitro dissolution testing done at 100 rpm, in vitro dextromethorphan release was also tested at variable dissolution agitation rates of 10, 25 and 50 rpms. The selected ER matrix tablets were tested for in vitro drug release as per methodology outlined in Section 3.5, page 58. This was done as it has been shown by Eddington et. al. (1998) that agitation rates in the biological species can be varied.

4. Results and Discussions

4.1. Development of HPLC method for the detection of dextromethorphan from the dissolution media.

Dextromethorphan calibration curves was constructed in phosphate buffer, pH 6.8.

4.1.1. Accuracy

The recovered dextromethorphan concentrations calculated using the developed calibration equations were ± 5 % of theoretical concentration for individual dextromethorphan solutions tested.

4.1.2. Precision

The estimated relative standard deviations for the three different dextromethorphan concentrations each measured three times were less than 1%.

4.1.3. Linearity and range

The linearity ranges of the dextromethorphan calibration curves were checked by calculating the regression coefficients over the concentration range used (10 – 60 ug/ml). The regression coefficients estimated were above 0.99 for all calculated calibration equations.

4.2. Testing of marketed capsule product, tuss hustenstiller retardkapseln.

The marketed capsules were tested for in vitro dextromethorphan release as per methodology outlined in Section 3.5, page 58. Figure 5 – page 84 shows the dextromethorphan release from the marketed capsules.

Regression parameters

Slope (n) = 24.384, Intercept (I) = 10.521 and r^2 = 0.915

The regression parameters of the drug release curve showed a correlation coefficient of 0.91. This data suggests that the marketed capsules, which consist of coated beads (reservoir systems) fit the Higuchi model, however, with the low r^2 also show that drug release is not limited to only diffusion drug release mechanism but to dissolution drug release as well as has been discussed in the introduction above. (Jantzen and Robinson, 1996).

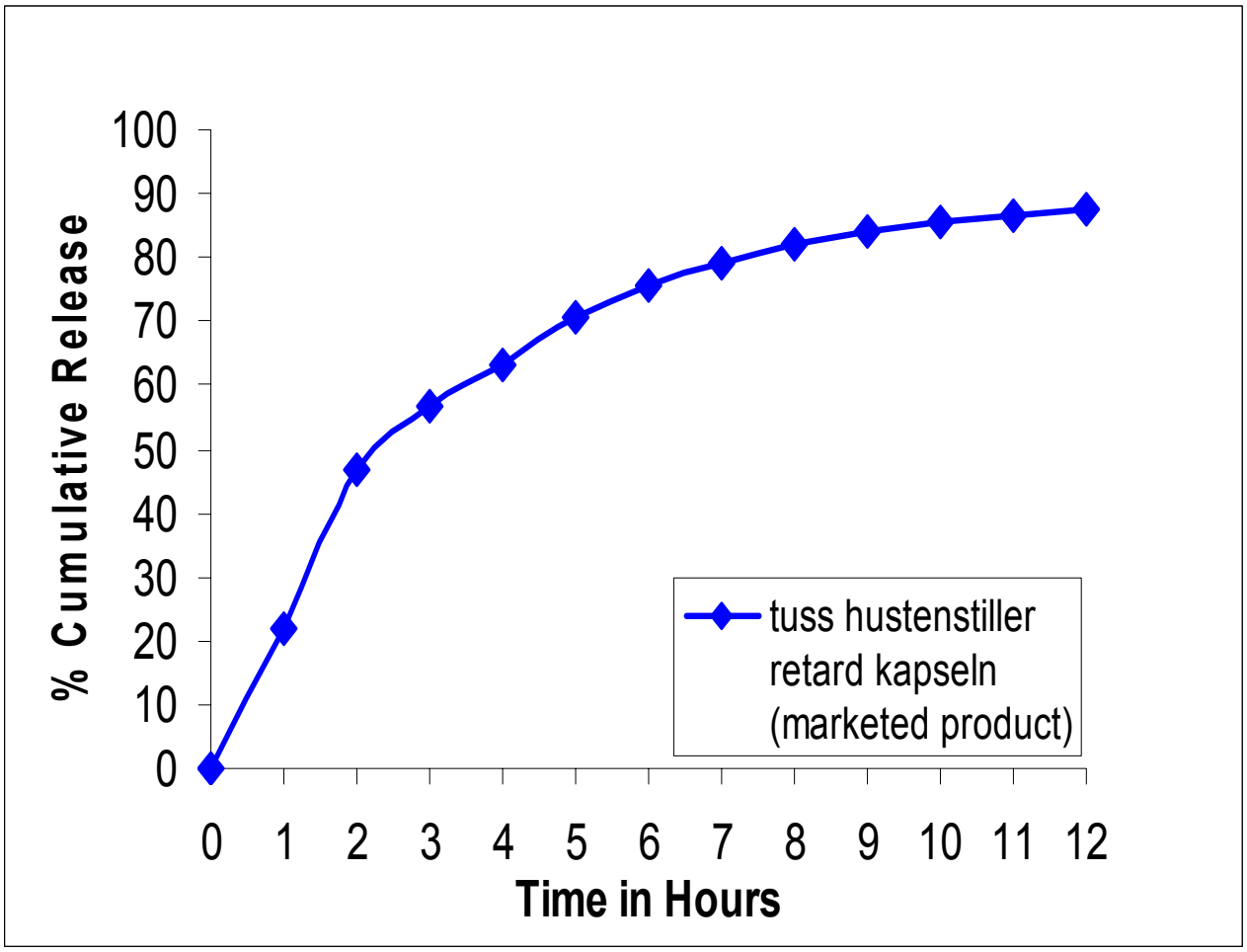


Figure 5. Dextromethorphan release profile of marketed capsule product, tuss hustenstiller retard kapseln. (plotted values are average values, n=8, RSD<3%)

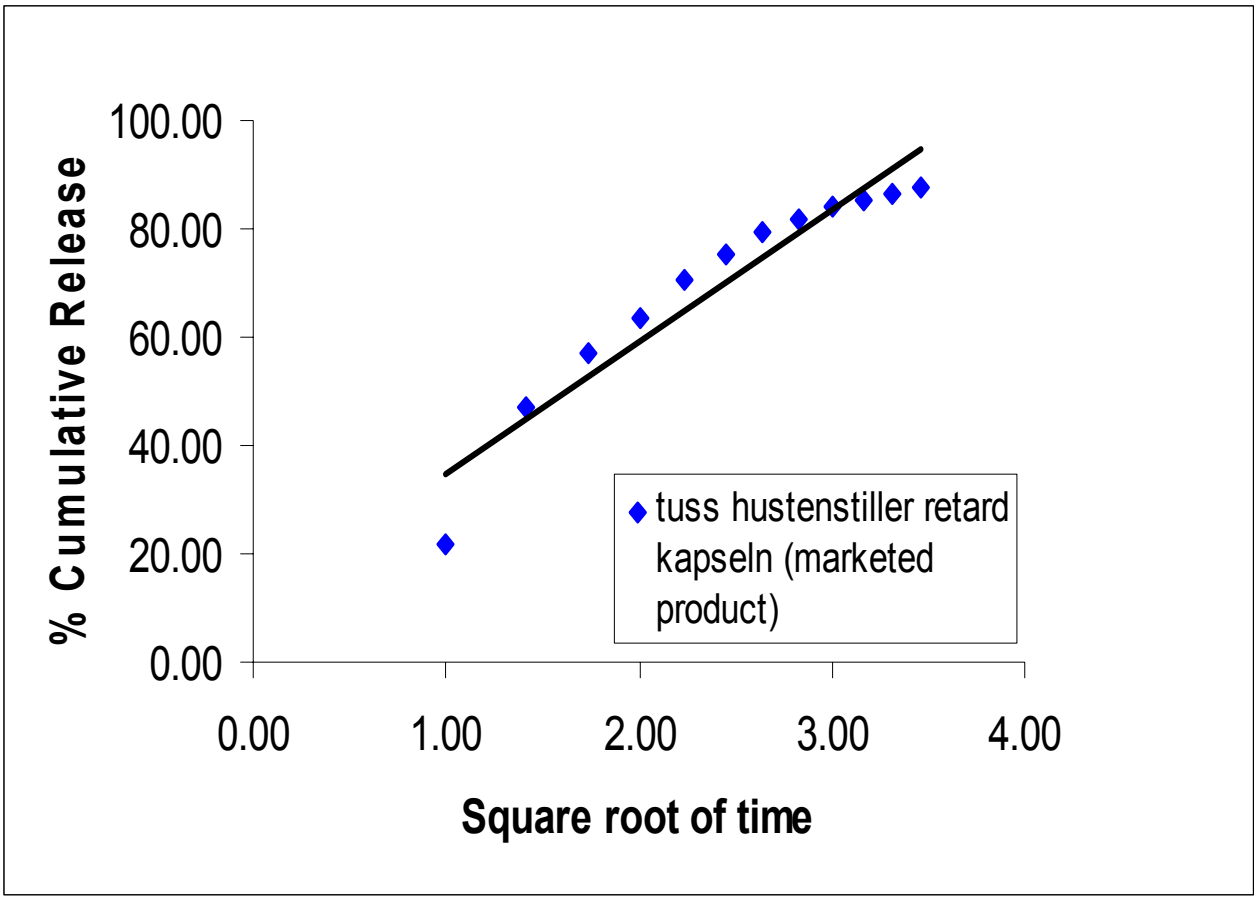


Figure 6. Higuchi plot for marketed capsule product, tuss hustenstiller retard kapseln.

4.3. HPMC/Eudragit ER matrix tablets

4.3.1. Effect of HPMC/Eudragit on dextromethorphan release from ER matrix tablets.

Dextromethorphan ER matrix tablets were manufactured with different concentrations of HPMC and Eudragit, either alone and in combination. The results of weight and thickness parameters are expressed as mean ± standard deviation. For all the compression forces used the weight variation was under 3.5%. The tablet weight variation was found minimum for all the formulations. It was also observed that the variation of thickness was minimal as can be seen in Tables 8, 9 and 10 – pages 87, 88, and 89. The standard deviation of tablet thickness in all the formulations was also quite uniform, ranging from 0.01% to 0.12%. As expected, a decrease in thickness was found with an increase in the compression force from 1000 to 2000 to 4000 lbs. No significant differences on weight uniformity and thickness values were observed between the different formulations.

Table 8. Effect of HPMC on physical properties of dextromethorphan ER matrix tablets (Mean ± Standard deviation)

Formulation	Compression force (lbs)	Weight (mg)	Thickness (mm)	Hardness (Kp)	Friability (%)
HPMC 10%	1000	304 ± 2.35	5.17 ± 0.01	3.69 ± 0.47	0.126
	2000	305 ± 2.04	4.53 ± 0.02	11.2 ± 1.77	0.013
	4000	304 ± 2.03	4.49 ± 0.03	9.20 ± 0.49	0.005
HPMC 20%	1000	303 ± 2.36	5.18 ± 0.01	5.37 ± 0.38	5.1
	2000	302 ± 2.08	4.62 ± 0.03	9.24 ± 0.42	0.025
	4000	303 ± 2.06	4.56 ± 0.04	11.0 ± 0.84	0.095
HPMC 40%	1000	304 ± 2.47	5.39 ± 0.02	6.09 ± 0.43	0.681
	2000	306 ± 2.77	4.94 ± 0.02	10.5 ± 0.75	0.043
	4000	301 ± 2.15	4.75 ± 0.06	11.3 ± 0.46	1 tb capped
HPMC 60%	1000	302 ± .003	5.33 ± 0.01	6.61 ± 0.87	0.182
	2000	303 ± .003	4.86 ± 0.04	13.3 ± 0.99	0.024
	4000	298 ± 0.02	4.79 ± 0.09	12.8 ±1.72	0.013

Table 9. Effect of Eudragit on physical properties of dextromethorphan ER matrix tablets (Mean ± Standard deviation)

Formulation	Compression force (lbs)	Weight (mg)	Thickness (mm)	Hardness (Kp)	Friability (%)
Eudragit 10%	1000	303 ± 2.35	5.17 ± 0.01	3.20 ± 0.28	0.126
	2000	304 ± 2.03	4.51 ± 0.02	10.10 ± 1.03	1 tb capped
	4000	303 ± 2.02	4.47 ± 0.03	9.09 ± 0.76	0.044
Eudragit 20%	1000	304 ± 3.19	5.91 ± 0.02	0.87 ± 0.22	50.2
	2000	305 ± 2.23	4.79 ± 0.04	8.21 ± 1.04	0.047
	4000	302 ± 2.08	4.61 ± 0.03	7.68 ± 0.49	0.129
Eudragit 40%	1000	306 ± 2.44	5.36 ± 0.03	2.48 ± 0.48	0.315
	2000	304 ± 2.21	4.93 ± 0.04	8.61 ± 0.74	12 tb capped
	4000	304 ± 2.20	4.89 ± 0.04	7.93 ± 1.32	0.192
Eudragit 60%	1000	308 ± 0.002	5.63 ± 0.02	4.39 ± 0.92	4 tb capped
	2000	301 ± 0.003	5.29 ± 0.12	7.08 ± 1.48	10 tb capped
	4000	301 ± 0.001	5.11 ± 0.05	8.33 ± 0.51	10 tb capped

Table 10. Effect of HPMC/Eudragit combination on physical properties of dextromethorphan ER matrix tablets (Mean ± Standard deviation)

Formulation	Compression force (lbs)	Weight (mg)	Thickness (mm)	Hardness (Kp)	Friability (%)
HPMC 5%/	1000	308 ± 2.35	5.18 ± 0.01	5.3 ± 0.35	0.040
Eudragit 5%	2000	307 ± 2.17	4.79 ± 0.03	9.69 ± 0.80	0.020
	4000	306 ± 2.01	4.46 ± 0.02	14.6 ± 0.90	0.020
HPMC 10%/	1000	300 ± 2.36	5.28 ± 0.01	2.7 ± 0.41	0.511
Eudragit 10%	2000	302 ± 2.25	4.61 ± 0.02	10.3 ± 0.52	0.025
	4000	310 ± 2.17	4.66 ± 0.02	11.6 ± 0.98	0.016
HPMC 20%/	1000	303 ± 2.47	5.42 ± 0.01	3.54 ± 0.16	0.270
Eudragit 20%	2000	308 ± 2.25	4.95 ± 0.02	9.24 ± 0.70	0.013
	4000	311 ± 2.19	4.85 ± 0.03	13.8 ± 1.86	0.007
HPMC 30%/	1000	302 ± 0.002	5.48 ± 0.05	5.43 ± 1.67	0.262
Eudragit 30%	2000	305 ± 0.002	5.12 ± 0.02	8.81 ± 0.77	0.061
	4000	304 ± 0.002	5.04 ± 0.10	9.63 ± 1.59	5 tb capped

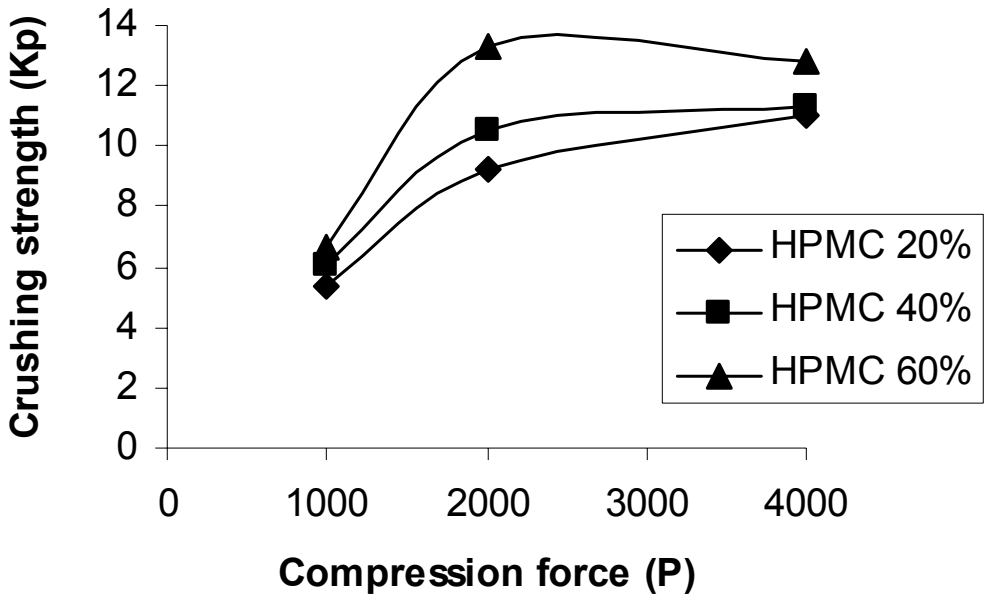


Figure 7. Effect of compression force on the hardness (crushing strength) of HPMC tablets

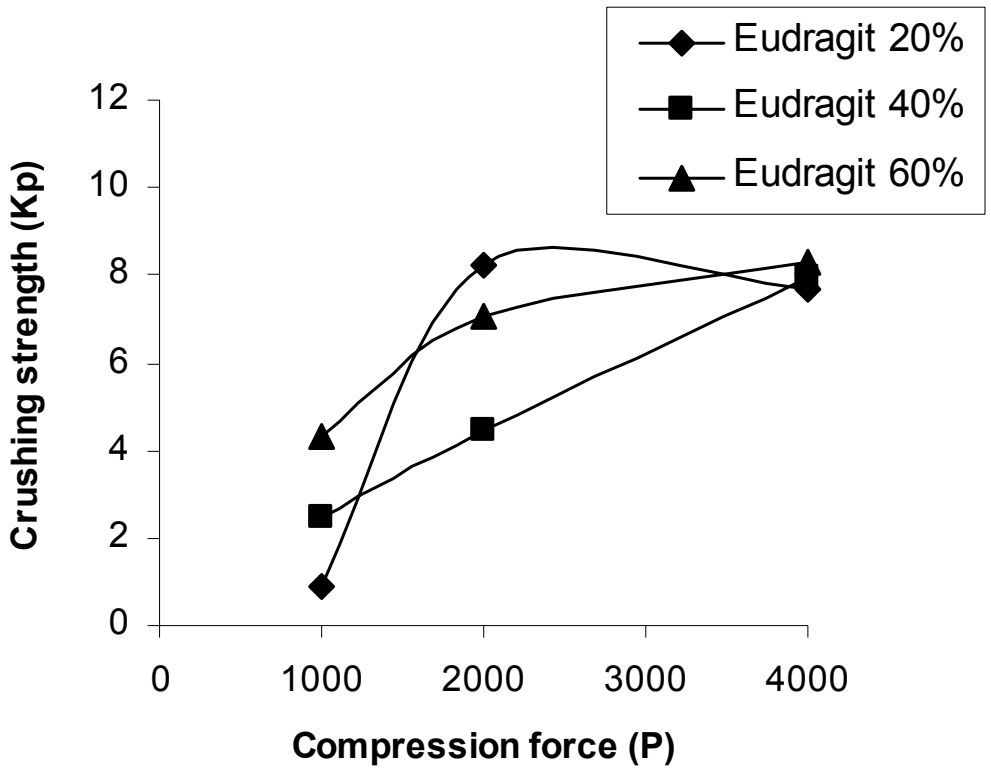


Figure 8. Effect of compression force on the hardness (crushing strength) of Eudragit tablets

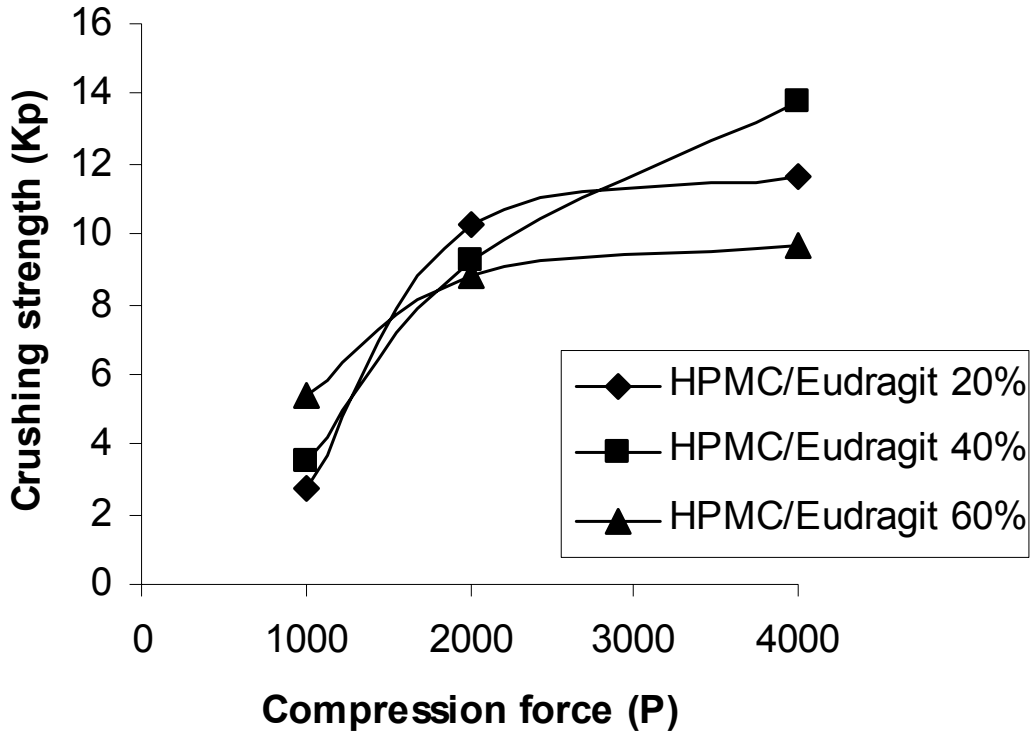


Figure 9. Effect of compression force on the hardness (crushing strength) of HPMC/Eudragit tablets

The hardness values of dextromethorphan tablets compressed at three different compression forces are given in Tables 8, 9 and 10 – pages 87, 88, and 89. Hardness of tablets clearly describes a certain mechanic property of a whole tablet. The hardness of the tablets increased with increasing compression force. At lower compression force, this increase was exponential but reached a constant level at a compression force of 4000 lbs. A plateau was observed for all the formulations. This suggests that a maximum hardness had been reached for tablets made from these polymers, and that further increases in compaction load would not result in harder tablets. Increasing the amount of Eudragit or the combination blend of HPMC/Eudragit increased tablet hardness at 1000 lbs compression force. The formulation containing only Eudragit had low tablet hardness values of ranging from 0.87±0.22 Kp with 20% level to 4.39±0.92 Kp with 60% Eudragit level. The tablet hardness remained almost similar at 2000 and 4000 lbs compression forces when the polymer level increased. The formulations containing only HPMC at 20, 40 and 60% levels generated tablets with hardness values of 9.24±0.42, 10.5±0.75, and 13.3±0.99 Kp, respectively at 2000 lbs compression force. It was observed that tablet hardness was strongly influenced by the type of polymer. The hardness of tablets containing only HPMC was higher than that of tablets containing only Eudragit. The major reason for this may be that Eudragit has a rigid structure but HPMC exhibits plastic deformation properties (Cameron et. al. 1987). The higher hardness of HPMC K 100LV is the result of relatively low methoxy and the high hydroxylpropyl group content and also the high moisture content which may contribute to the development of relatively strong hydrogen bonds within the tablets.

As expected, the friability decreased with increasing upper punch force as shown in Tables 8, 9 and 10 – pages 87, 88, and 89. A limiting value of 1% for friability tests of tablets has been suggested by the USP and European Pharmacopeas. At compression forces of 2000 lbs, tablets provided a friability of <0.5%. Extended release tablets based on Eudragit only were liable to capping in the friability test. Capping was particularly observed in the formulations containing Eudragit at 60% level under three applied compression forces.

Results from the physical properties show that the tablets manufactured at 2000 lbs compression pressure were ideal. Consequently, further testing of the HPMC/Eudragit ER dextromethorphan matrix tablets was carried out on tablets manufactured at a compression force of 2000 lbs.

Content uniformity for all the batches manufactured was tested. Results showed that the percent of the dextromethorphan in the compressed tablets was within in the 85%-115% of the theoretical label claim (60 mg/tablet) with a relative standard deviation of less than 4%.

The effect of the amount of HPMC 10%, 20%, 40% and 60 % on the dextromethorphan release is shown in Figure 10 – page 98. The dextromethorphan release decreased as the percent amount of HPMC level in the tablet increased. Drug release is controlled by the hydration of HPMC, which forms a gelatinous barrier layer at the surface of the matrix. In addition, the resistance of such a gel layer to erosion is controlled by the viscosity grade of the HPMC. HPMC K100LV is a low viscosity

polymer (100 cps), therefore, 10% and 20% polymer level showed a fast drug release from the matrix. It was observed that for the 10% HPMC level, within 1 hour, 100% of the dextromethorphan was released while for the 20% HPMC level after 3 hours, 85.4% of the dextromethorphan was released in the dissolution media. An increase in polymer amount causes an increase in the viscosity of the gel as well as the formation of a gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate. The results from the HPMC polymer show this predictable behavior. The dextromethorphan release from the formulations containing 40% and 60% HPMC was found to be 88% and 85%, respectively at 12 hours. Release rate data from table 11 – page 97 show a very high r^2 for the HPMC 40 and 60% formulations suggesting diffusion release kinetics. Figure 11 – page 99 shows the Higuchi graph. The gel thickness might have prolonged the drug release from the formulations. Table 11 – page 97 shows the release rate data. Release rate data for 10% HPMC level was not calculated due to fast release of the drug.

Dissolution profiles of the HPMC alone ER matrix tablets showed that at levels of 40% and 60%, the profiles were close to the profile obtained by the marketed capsule product. Figure 12 – page 100 shows the comparison profiles.

The FDA recommended f2 similarity test was then applied to compare the HPMC at 40% and 60% levels to the marketed product as shown below.

a.) HPMC 40%, f2 value of 61

b.) HPMC 60%, f2 value of 45

The f2 values show that the HPMC ER matrix tablet with a level of 40% was similar to the marketed product.

Table 11. Release rates and correlation coefficients according to Higuchi equation

Formulation	Release rate ($\%h^{-1/2}$)	Correlation Coefficient (r^2)
HPMC 10%	-	-
HPMC 20%	42.5	0.966
HPMC 40%	34.6	0.999
HPMC 60%	29.2	0.999
Eudragit 10%	-	-
Eudragit 20%	-	-
Eudragit 40%	-	-
Eudragit 60%	18.3	0.888
HPMC 5% / Eudragit 5%	-	-
HPMC 10% / Eudragit 10%	-	-
HPMC 20% / Eudragit 20%	26.5	0.995
HPMC 30% / Eudragit 30%	29.0	0.995
tuss hustenstiller retardkapseln, marketed product	***24.38***	***0.915***

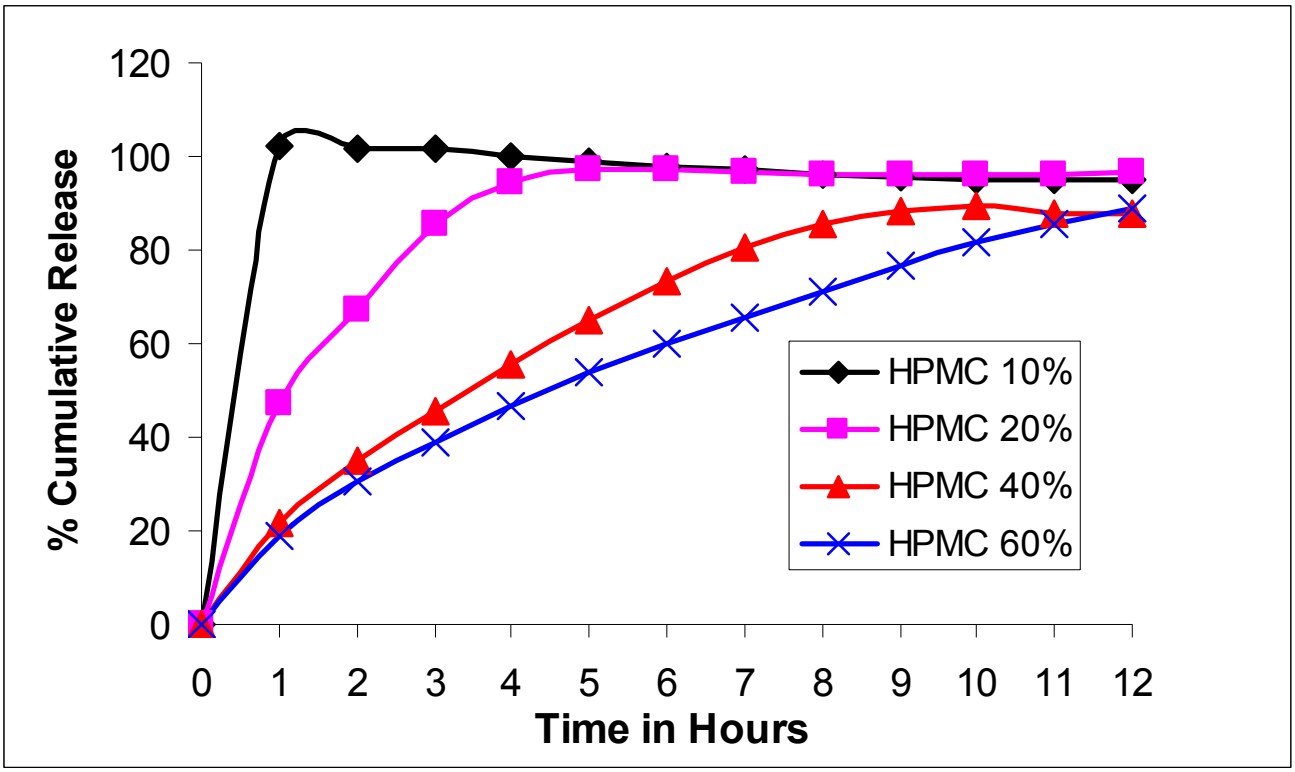


Figure 10. Effect of HPMC on dextromethorphan release from ER matrix tablets. (plotted values are average values, n=8, RSD<3%)

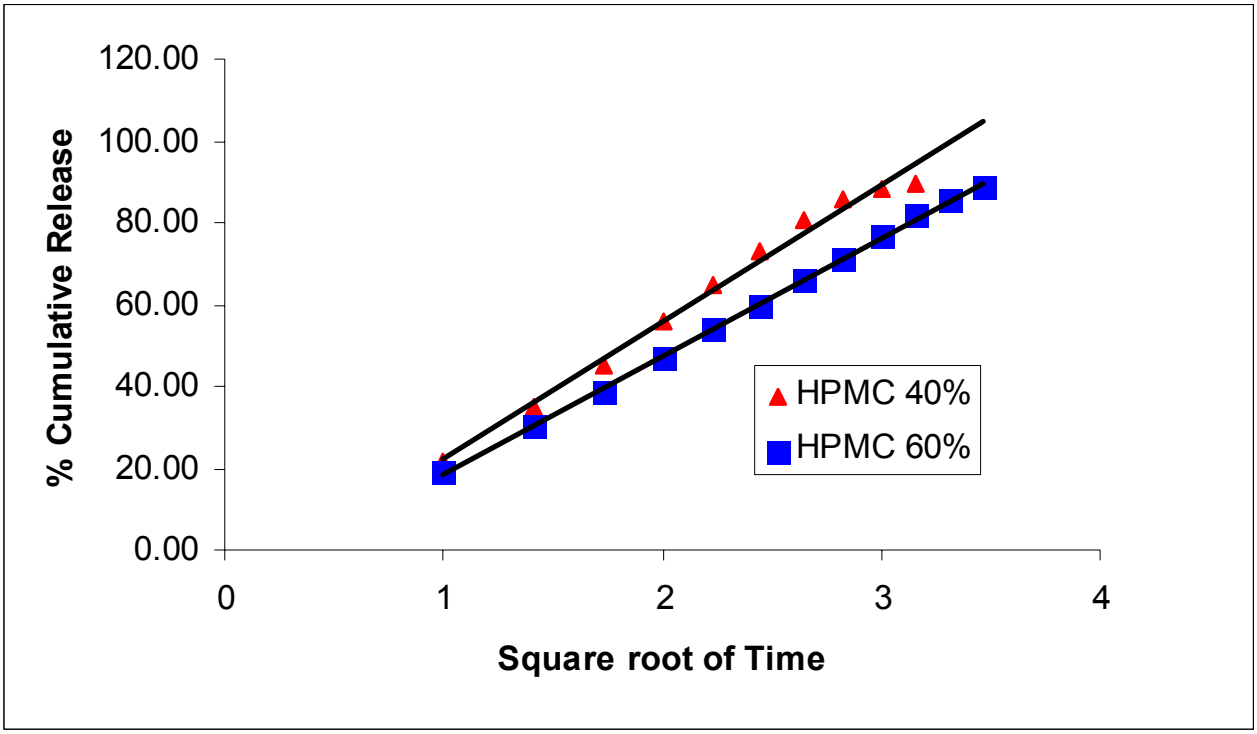


Figure 11. Effect of HPMC on diffusion controlled dextromethorphan release from ER matrix tablets

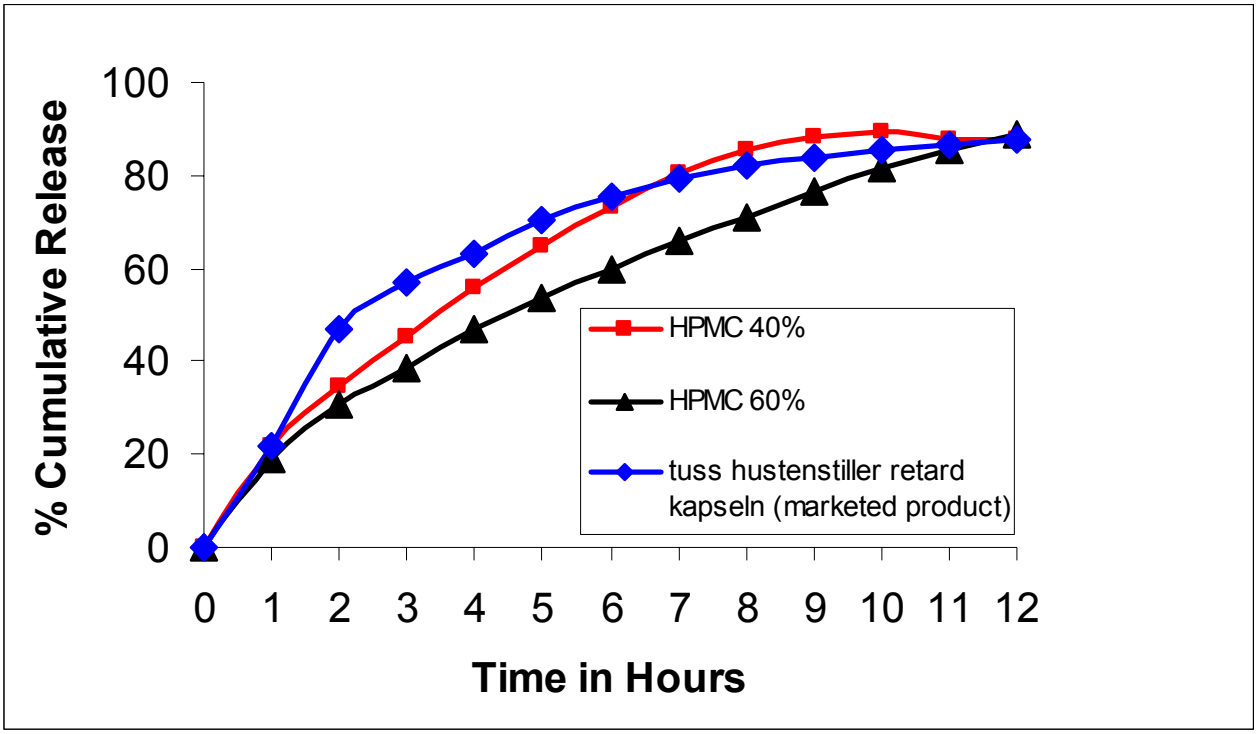


Figure 12. Dextromethorphan release dissolution profile comparison of HPMC ER matrix tablets and the marketed capsule product. (plotted values are average values, n=8, RSD<3%)

Matrix tablets containing 20%, 40% and 60 % Eudragit showed fast release of dextromethorphan because of disintegration (Figure 13 – page 102). The release rate data from these matrices were not calculated because of the fast release of the drug (table 11, page 97). For the ER tablet containing 60% Eudragit, 82.1% of the dextromethorphan was released within 2 hours. The data thus suggests that for the different levels of Eudragit L 100-55 alone in the tablets does not promote extended release of the dextromethorphan.

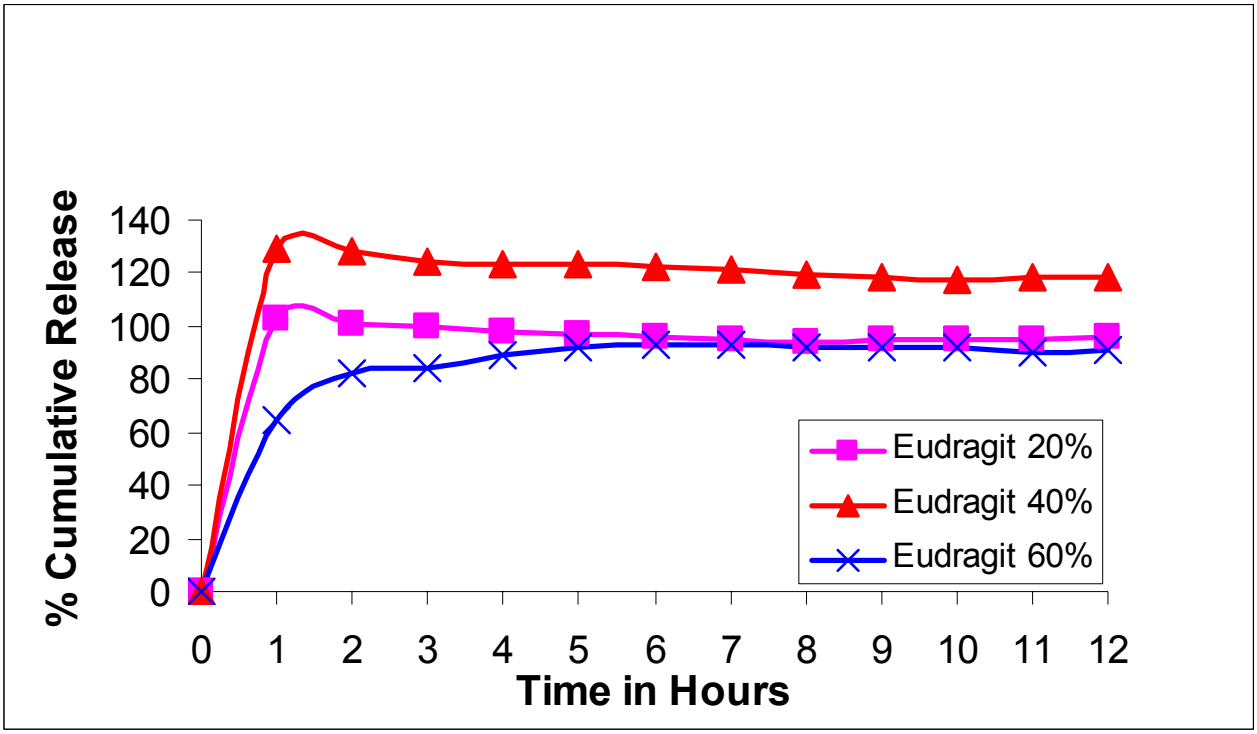


Figure 13. Effect of Eudragit on dextromethorphan release from ER matrix tablets. (plotted values are average values, n=8, RSD<3%)

It was observed that the combination of HPMC at 5% and 10% and Eudragit at 5% and 10% polymer levels did not retard the drug release. The low HPMC level probably played an important role for the faster release of dextromethorphan. The combination of HPMC at 20% and 30% and Eudragit at 20% and 30% level showed a slow release of drug comparable to the formulations containing only HPMC at 40% and 60% level. The release rates were found to be 26.5 and 29.0 % $h^{-1/2}$ for the blends of HPMC/Eudragit at 20% and 30% levels each respectively (table 11 – page 97). Figure 15 – page 106. shows the Higuchi graph for HPMC/Eudragit combination at 20 and 30% individual polymer levels. The release rate results for the HPMC/Eudragit blend at 20% levels each respectively is in agreement to data in literature as reported by Takka et. al (2003), where the release rate of a ER tablet manufactured by direct compression using HPMC – Eudragit polymer combination at a 1:1 ratio was 24.4 $h^{-1/2}$. Propranolol hydrochloride was used as the model drug in that study. Polymer dissolution plays a large role in regulating drug release for low-viscosity grades of HPMC, a point that is in agreement data reported in literature by Pham et. al. (1994).

In a study by Campos-Aldrete and Villafuerte-Robles (1997), for low HPMC concentration (10%) formulations, the lag time was found to be dependent on the viscosity grade. The increasing burst effect produced by higher viscosity grades was attributed to slower swelling with increasing polymer viscosity, allowing greater time for the dissolution of the drug (metronidazole) before the gel barrier was established. For HPMC concentration of 20% or more, the porosity was a less important factor in the drug release and the effect of viscosity grade was minimized.

Dissolution profiles of the HPMC and Eudragit combination blends at 20% and 30% individual level ER matrix tablets were comparable to the profile obtained by the marketed product. Figure 16 – page 107 shows the comparison profiles.

The FDA recommended f2 similarity test was then applied to compare the HPMC and Eudragit combination blends at 20% and 30% individual level ER matrix tablets to the marketed product as shown below.

a.) HPMC 20% / Eudragit 20%, f2 value of 58
b.) HPMC 30% / Eudragit 30%, f2 value of 57

The f2 values show both formulations of the HPMC and Eudragit combination blends at 20% and 30% individual level ER matrix tablets to be similar to the marketed product.

The findings from the above study have been published in Die Pharmazie, Takka et. al. 2003.

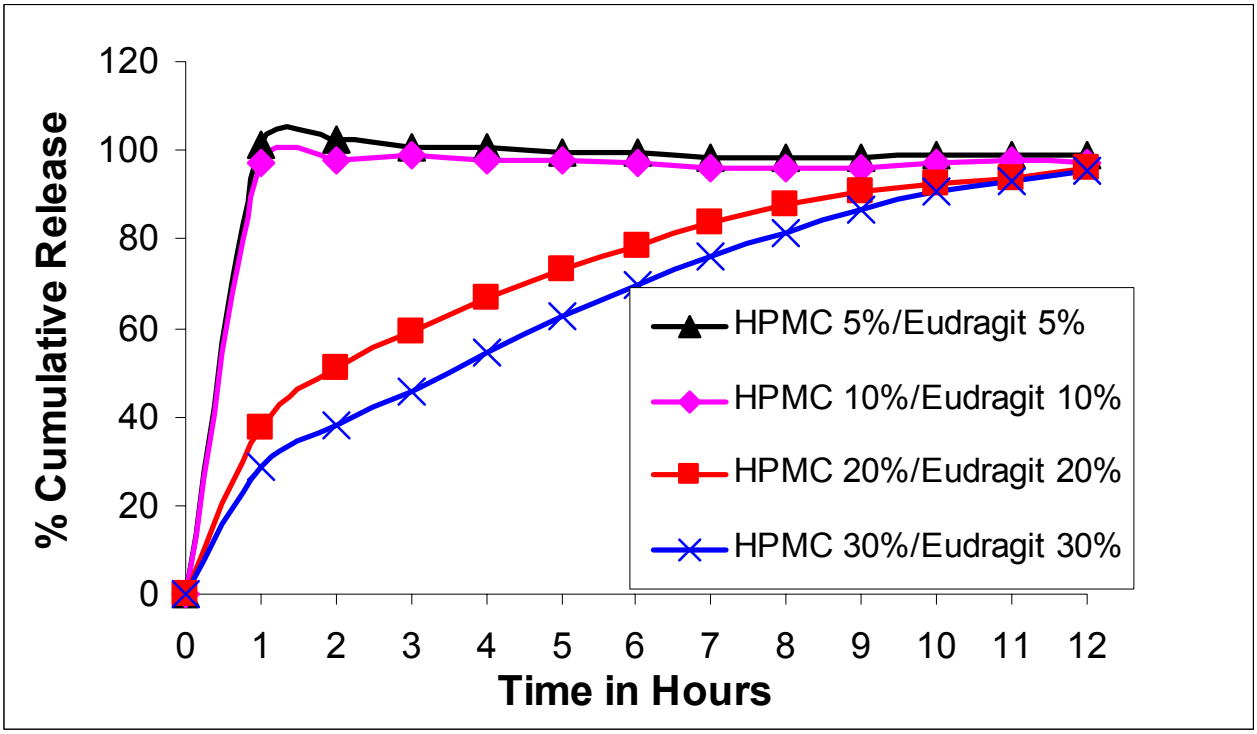


Figure 14. Effect of HPMC/Eudragit combination blends on dextromethorphan release from ER matrix tablets. (plotted values are average values, n=8, RSD<3%)

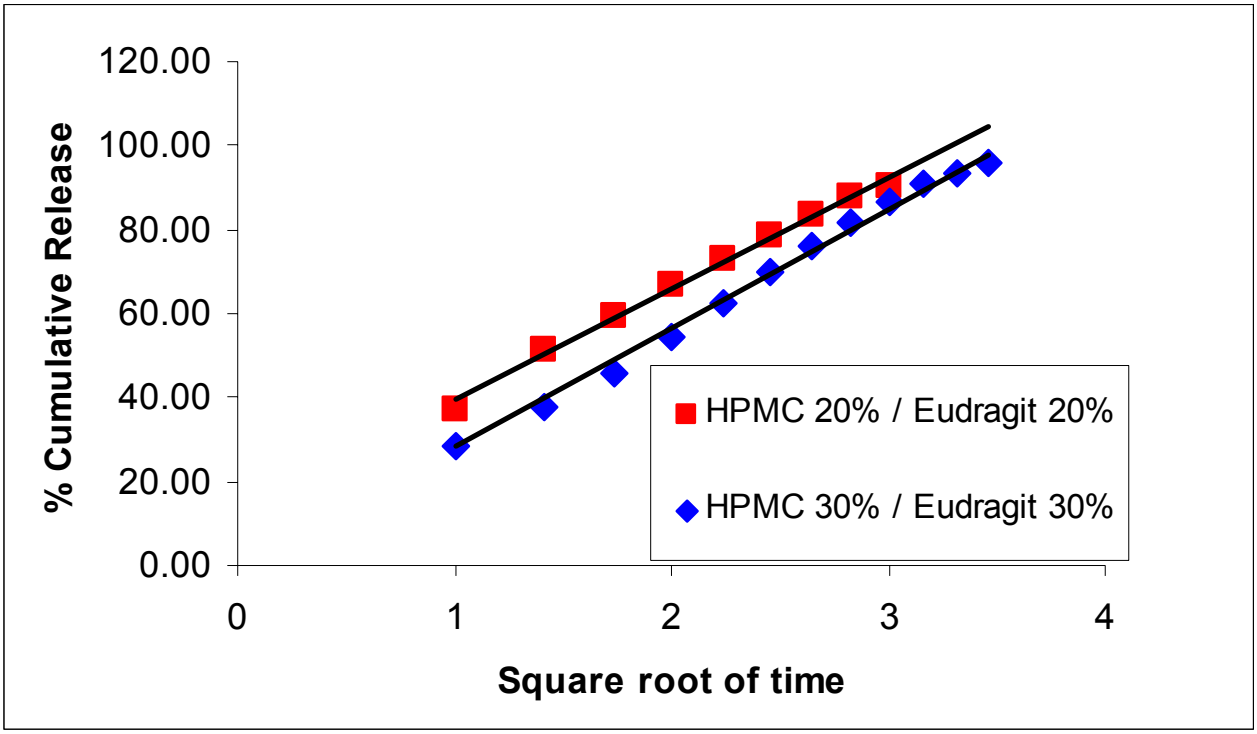


Figure 15. Effect of HPMC/Eudragit combination blends on diffusion controlled dextromethorphan release from ER matrix tablets

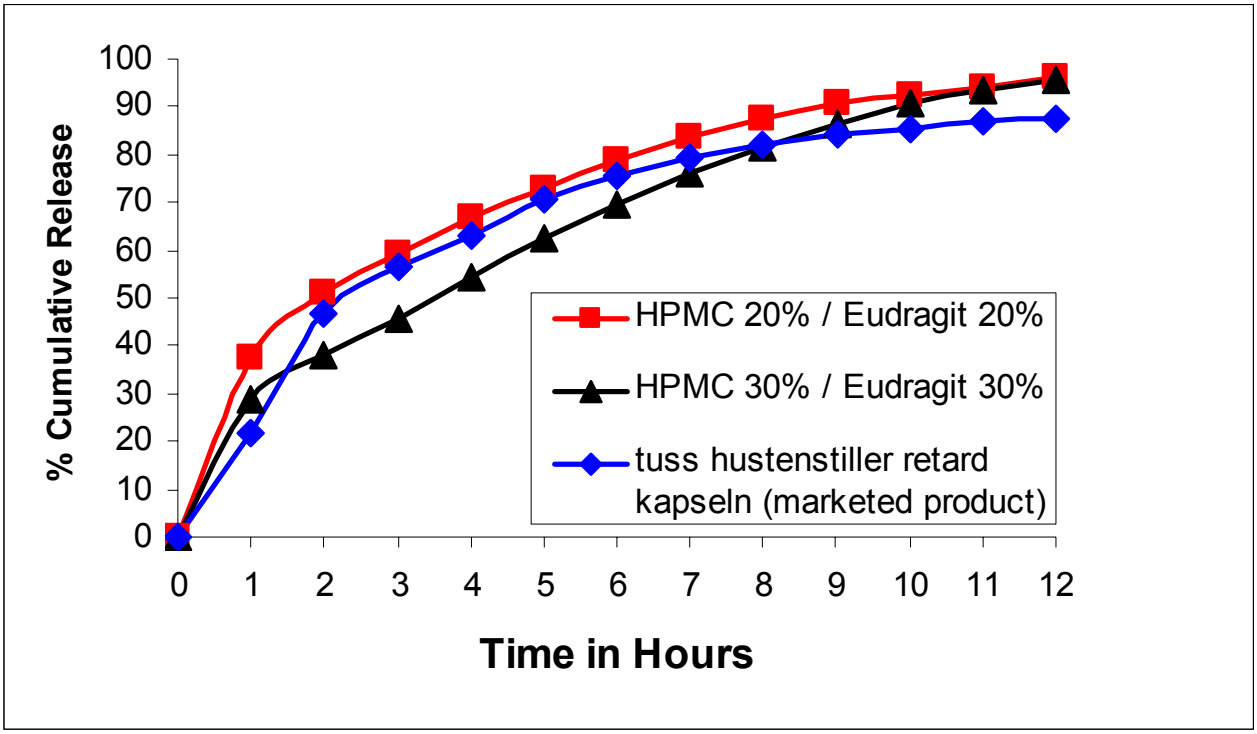


Figure 16. Dextromethorphan release dissolution profile comparison of HPMC/Eudragit combination ER matrix tablets and the marketed capsule product. (plotted values are average values, n=8, RSD<3%)

4.3.2. Reproducibility of HPMC ER matrix tablet batch

Reproducibility of batches was done to confirm batch reproducibility and robustness of technology. The HPMC 40% was selected for this study. The powder mix was compressed at 2000 lbs compression force.

Physical properties evaluation showed tablet weight variation to be minimum as observed in the original batches. It is also observed that the variation of thickness was minimal. Tablet hardness was also similar to the original batch.

In vitro dextromethorphan release was evaluated by the model independent FDA recommended f2 similarity factor. An f2 value of 71 (repeat batch 1), 73 (repeat batch 2) and 68 (repeat batch 3) was obtained suggesting that the original batch and the repeated batches were similar in in vitro dextromethorphan release. Figure 17 – page 109 shows the in vitro drug release profiles.

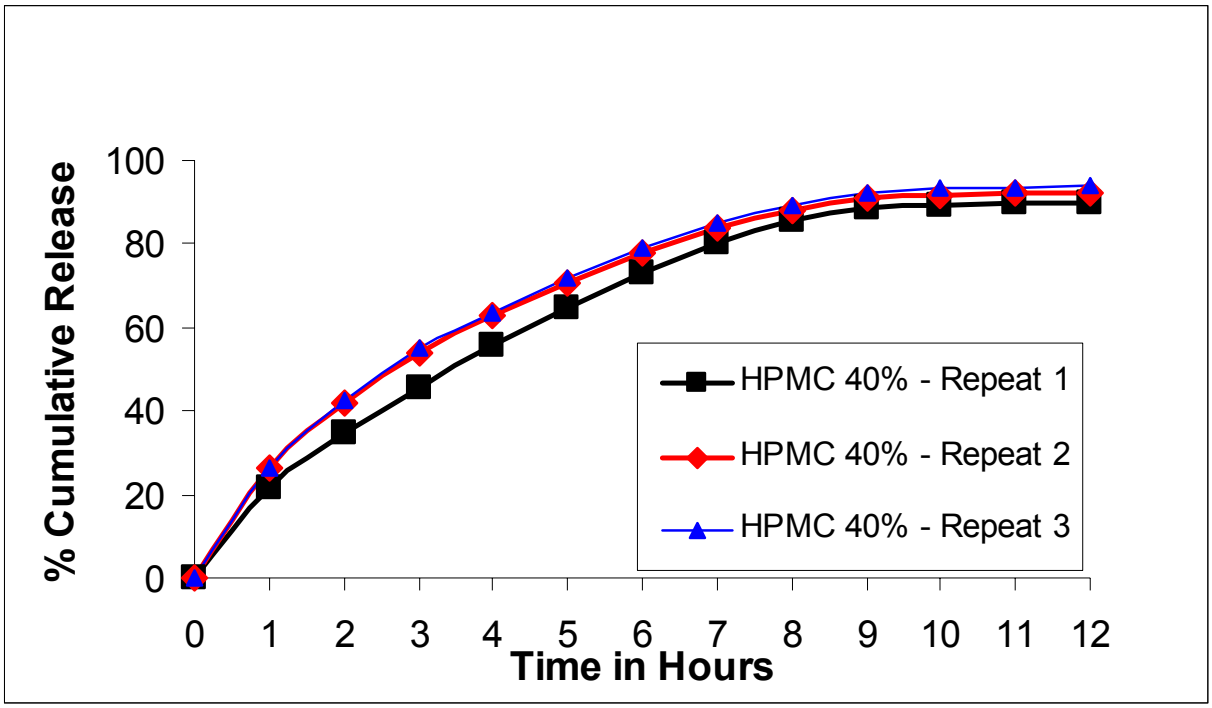


Figure 17. Reproducibility of HPMC batches on dextromethorphan release from ER matrix tablets. (plotted values are average values, n=8, RSD<3%)

4.4. PVAP ER matrix tablets

4.4.1. Effect of PVAP on dextromethorphan release from ER matrix tablets

Dextromethorphan ER matrix tablets were manufactured with different concentrations of PVAP (Section 3.6.2 - page 64). The results of weight and thickness parameters are expressed as mean ± standard deviation. The results (table 12 – page 112) show very low weight variations for all the 12 formulations manufactured. Tablet thickness also showed little variation between the 12 formulations manufactured.

Tablet hardness values showed a high degree of variability between the 12 formulations. The matrix tablet formulation with high levels, i.e. greater than 50%, of PVAP polymer, i.e. formulation variable KSR01 and KSR07, showed high tablet hardness 27 ± 1.44 kp and 25.4 ± 2.7 kp respectively. The matrix tablet formulation with high levels, greater than 50%, of microcrystalline cellulose, formulation variable KSR02 and KSR08, also showed high tablet hardness 26.2 ± 1.1 kp and 20.9 ± 1.2 kp respectively. The high tablet hardness using high levels of microcrystalline cellulose did not necessary translate into slow drug release. The matrix tablet formulation with high levels, greater than 50%, of dibasic calcium phosphate dehydrate, formulation variable KSR03 and KSR09, showed low tablet hardness 1.7 ± 0.6 kp and 5.9 ± 0.7 kp respectively. The formulation KSR03 showed capping of the tablets. These results show that dibasic calcium phosphate dihydrate alone at high percentages, in

this case greater than 50%, is not ideal in the manufacture of an extended release matrix tablet with PVAP, since the result is a soft tablet.

Table 12. Effect of PVAP on physical properties of dextromethorphan ER matrix tablets (Mean ± Standard deviation)

Formulation	Weight Variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%)
KSR01	299± 1	4.96± 0.94	27.0± 1.44	0.06
KSR02	303± 1	4.43± 0.03	26.2± 1.1	0.02
KSR03	290± 8.3	3.74± 0.03	1.7± 0.6	All Capped
KSR04	300± 2.0	4.79± 0.01	28.8± 1.2	0
KSR05	298± 1.7	4.37± 0.02	11.1± 0.9	0.02
KSR06	302± 1.8	4.16± 0.01	8.6± 0.8	0.17
KSR07	301± 2.0	4.74± 0.03	25.4± 2.7	0.03
KSR08	297± 6.9	4.39± 0.01	20.9± 1.2	0.02
KSR09	300± 1.6	4.17± 0.01	5.9± 0.7	0.27
KSR10	300± 2.2	4.42± 0.02	14.4± 0.6	0.06
KSR11	300± 1.3	4.41± 0.01	15.2± 0.8	0.03
KSR12	300± 1.5	4.41± 0.01	14.1± 0.8	0.03

Content uniformity for all the batches manufactured was tested. Results showed that the percent of the dextromethorphan in the compressed tablets was within in the 85%-115% of the theoretical label claim (60 mg/tablet) with a relative standard deviation of less than 4 %.

The matrix tablet formulation with high levels, greater than 50% of polyvinyl acetate/povidone polymer, formulation variable KSR01 and KSR07, showed a low drug release (Figure 18 – page 115). This confirms the findings by Draganoiu et. al. (2001) where it was found that the higher the percent polymer level in the tablet matrix, the slower the drug release rate. This slowed drug diffusion can be explained by the reduction in the porosity and higher tortuosity of matrix. Thus PVAP, which is a very plastic material, produces a coherent matrix, sustaining the drug release from the matrix tablet. Similarly, Ruchatz et. al. (1999) reported the caffeine was released from PVAP matrix tablets by diffusion for more than 16 hours. The matrix remained intact during the dissolution test due to the water-insoluble polyvinyl acetate. The f2 similarity number when compared to the marketed product for KSR01 was 29 and for KSR07 was also 29. So, while KSR01 and KSR07 do show an extended release in vitro of the dextromethorphan from the matrix tablets, the similarity factor tells us that these two formulations are not similar to the marketed product.

The matrix tablet formulation with high levels, greater than 50%, of microcrystalline cellulose, formulation variable KSR02 and KSR08, showed high drug release rate (Figure 19 – page 116) as the level of PVAP polymer in KSR02 was 0% while in KSR08, it was 13.1%.

Microcrystalline cellulose allows water to enter the tablet matrix by means of capillary pores, resulting in a disruption of the hydrogen bonding between adjacent bundles of the cellulose microcrystals (Peck et, al., 1989). Therefore, at a higher rate of incorporation, 79% for KSR02 and 52.67% for KSR08, microcrystalline cellulose acted as a disintegrant, destroying matrix cohesion, and in essence, producing an immediate release tablet. This is not surprising as Peck et. al., 1989 have shown microcrystalline cellulose in levels as low as 10% tablet weight to act as a disintegrant. Draganoiu et. al. 2001, also showed PVAP to have minimum drug retarding properties unless it is in levels of greater than 40% in a tablet matrix.

The matrix tablet formulation with high levels, greater than 50%, of dibasic calcium phosphate, formulation variable KSR03 and KSR09, showed high drug release rate (Figure 20 – page 117). This can be explained by the fact that dibasic calcium phosphate on it's own at high levels of 79% w/w of tablet does not compress well**,** as was the case for KR03, and produced a tablet whose hardness was only 1.7kp and which when tested by the friability test failed miserably as all tablets capped. KSR09 also showed a very fast in vitro drug release.

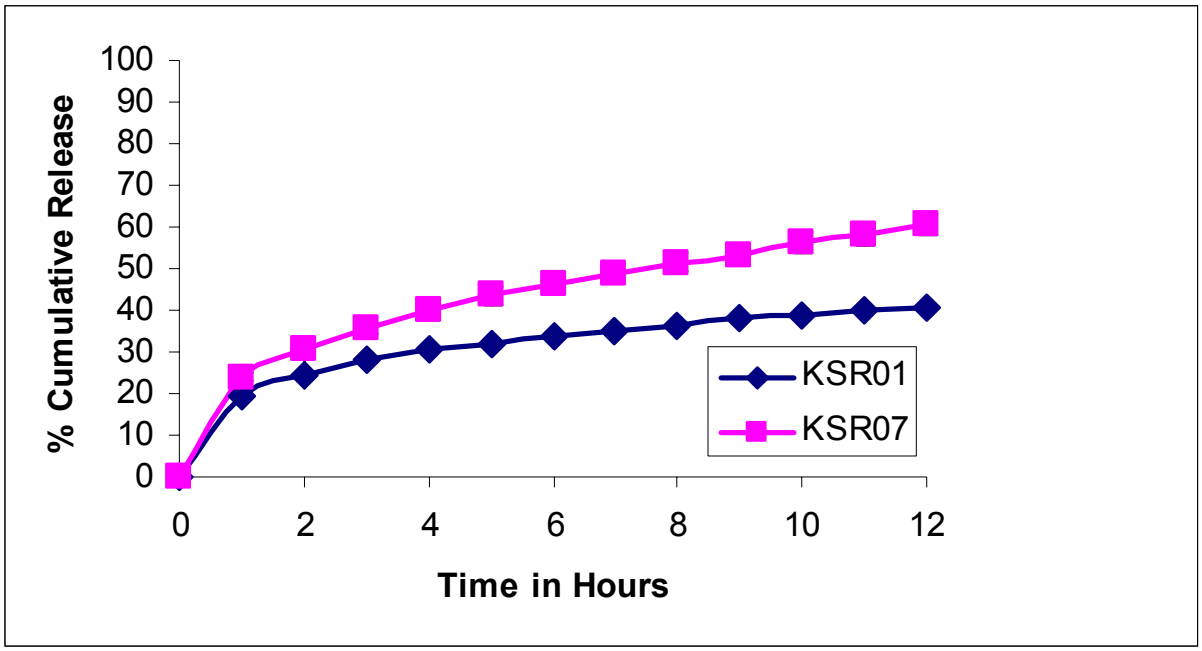


Figure 18. Effect of high levels, >50%, of PVAP polymer on dextromethorphan release from ER matrix tablets. (plotted values are average values, n=8, RSD<4%)

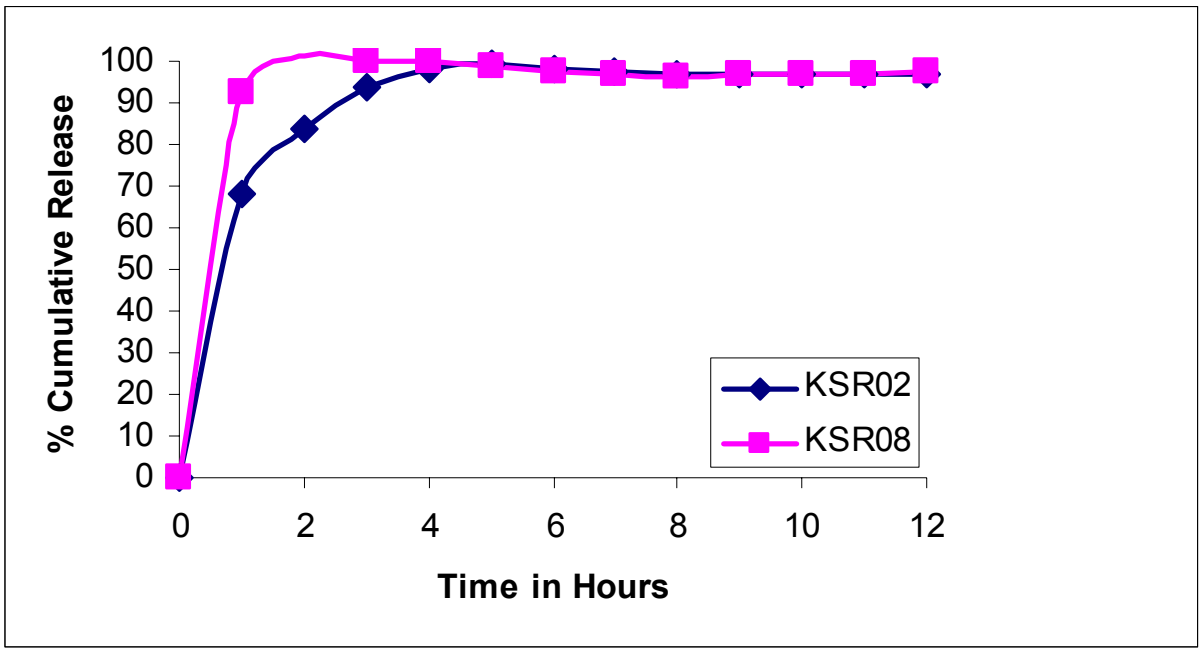


Figure 19. Effect of high levels, >50%, of microcrystalline cellulose excipient on dextromethorphan release from ER matrix tablets. (plotted values are average values, n=8, RSD<4%)

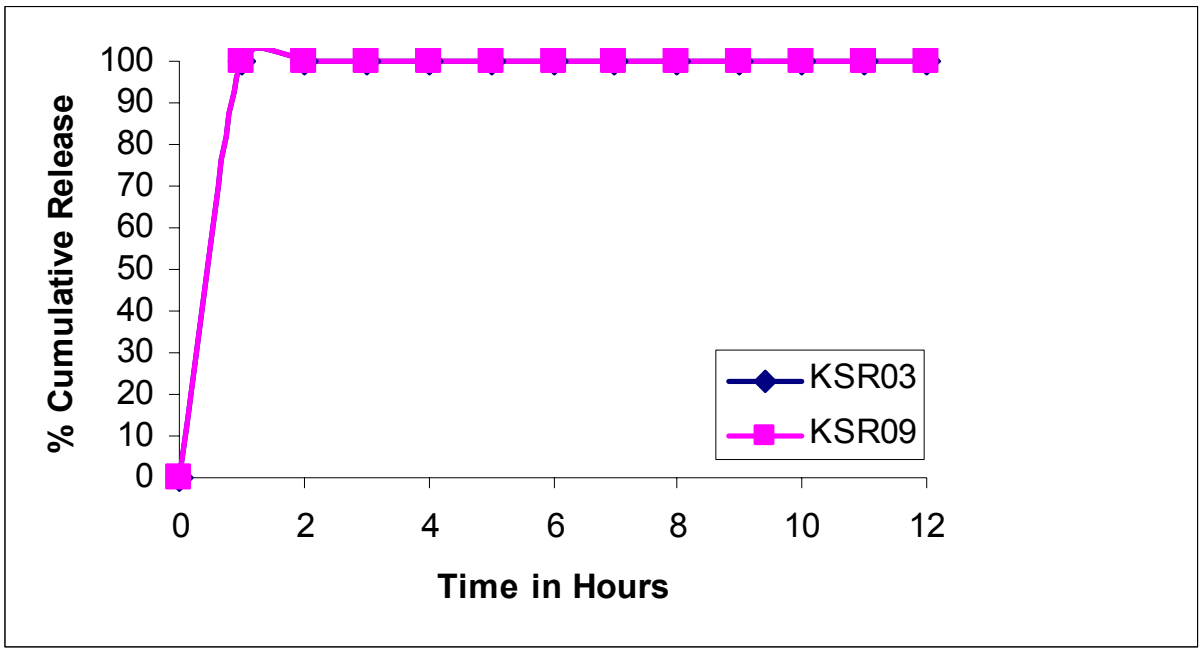


Figure 20. Effect of high levels, >50%, of dicalcium phosphate excipient on dextromethorphan release from ER matrix tablets. (plotted values are average values, n=8, RSD<4%)

Figure 21, 22 – page 119, 120 shows the drug release profiles of the formulation variables, KSR04 and KSR05 and comparison to the marketed product. KSR04 and KSR05 both have a high level (39.5%) of PVAP in their formulations and as such exhibit low dextromethorphan release in vitro. KSR04 has high level of microcrystalline cellulose which as we have seen can act as a disintegrant. In this instance however, the level of PVAP overrides this property, hence the extended release of the dextromethorphan in vitro. KSR05 has a high level of dibasic calcium phosphate which combines well with the PVAP to give an extended release of dextromethorphan in vitro. The f2 value for KSR04 is 43 when calculated in comparison to the marketed product while the f2 value for KSR05 is 53 thus suggesting that KSR05 is similar to the marketed product in dextromethorphan release over 12 hours.

Figure 23 – page 121 shows the drug release profiles of the formulation variables, KSR06, KSR10, KSR11 and KSR12. KSR06 has no PVAP polymer incorporated into the formulation and the in vitro drug release results show a tablet the behaved like an immediate release.

KSR10, KSR11 and KSR12 had PVAP levels of 26.3% and as has been reported by Draganoiu et. al. 2001, PVAP has minimum drug retarding properties unless it is in levels of greater than 40% in a tablet matrix.

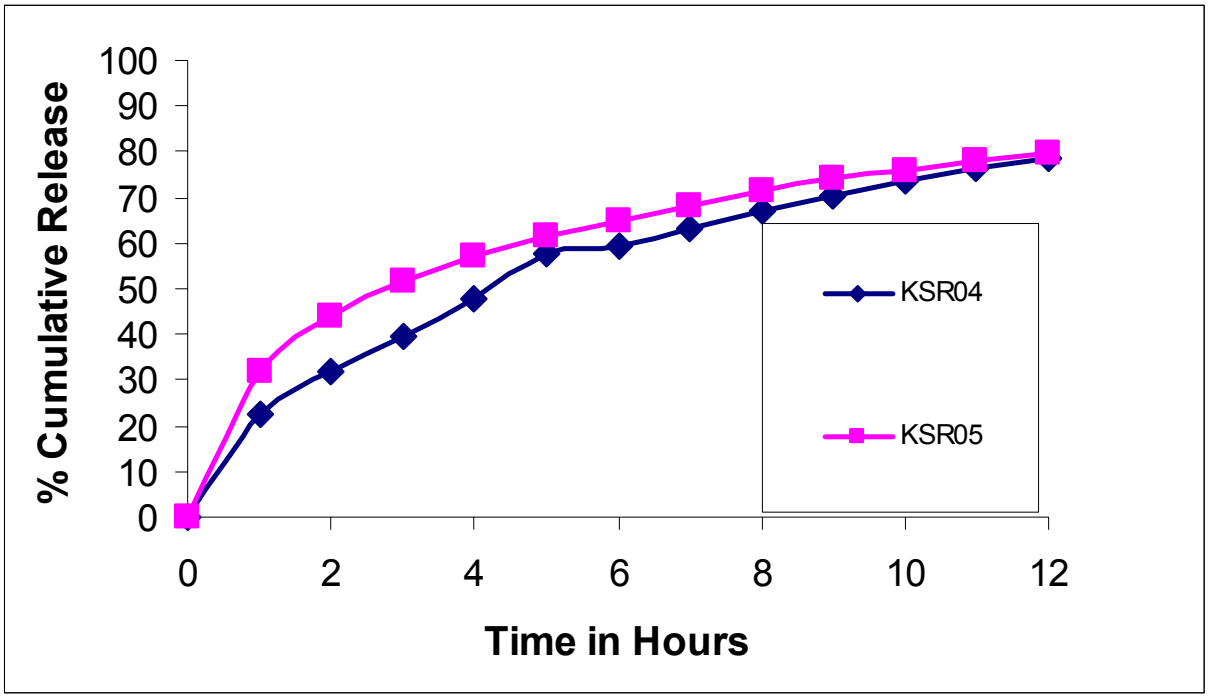


Figure 21. Effect of PVAP on dextromethorphan release from ER matrix tablets. (plotted values are average values, n=8, RSD<4%)

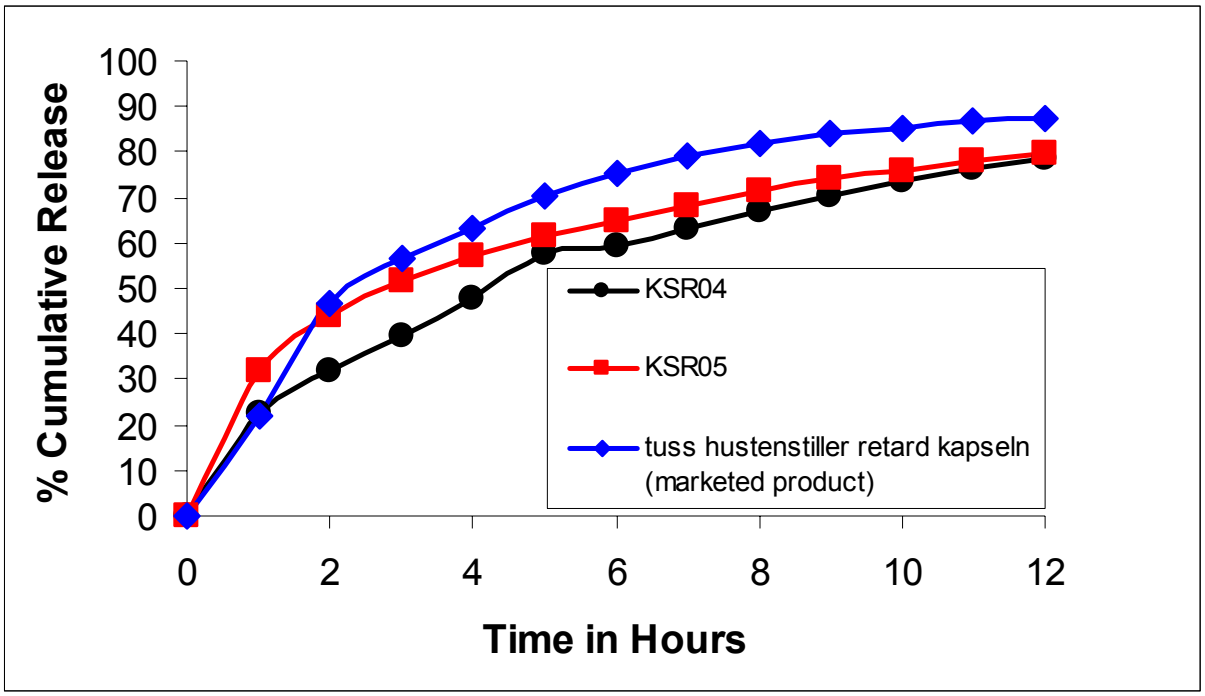


Figure 22. Dextromethorphan release dissolution profile comparison of KSR04 and KSR05 ER tablets and the marketed capsule product. (plotted values are average values, n=8, RSD<4%)

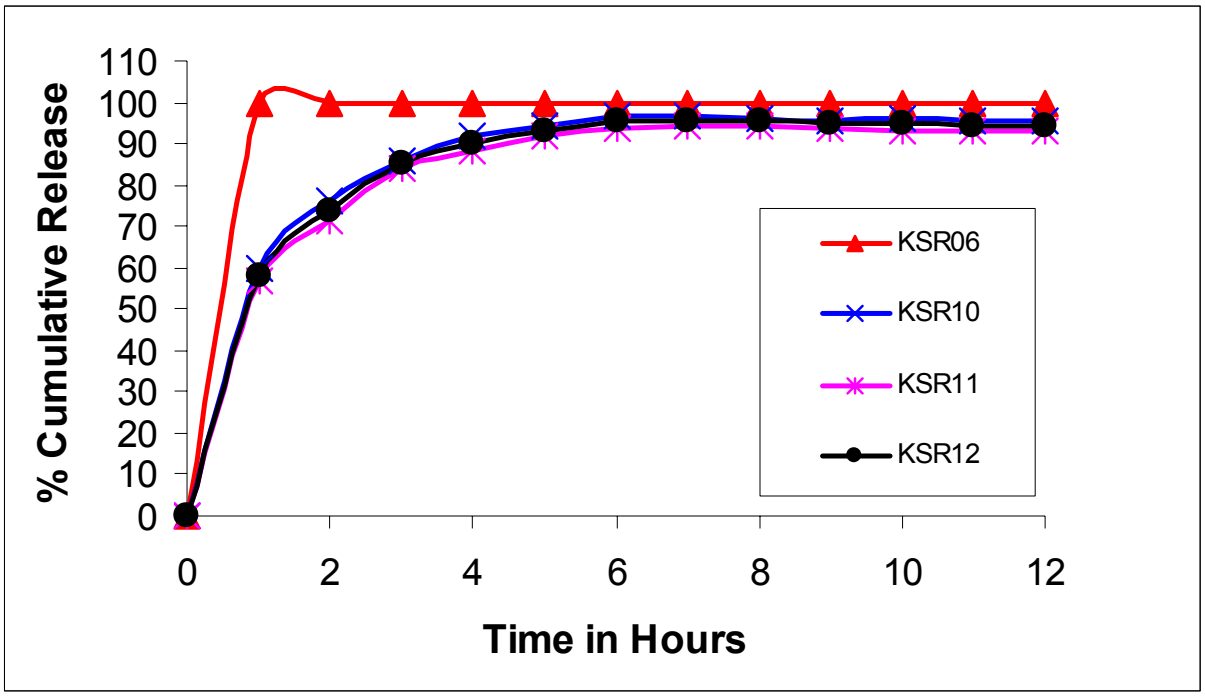


Figure 23. Effect of PVAP on dextromethorphan release from ER matrix tablets. (plotted values are average values, n=8, RSD<4%)

The plot for percent drug released versus square root of time as per Higuchi's equation, is shown in Figure 24, page 123. Looking at the slopes from the regression parameters, it can be interpreted that the drug release rate from slow to faster is in the order of KSR01, KSR07, KSR05 and KSR04.

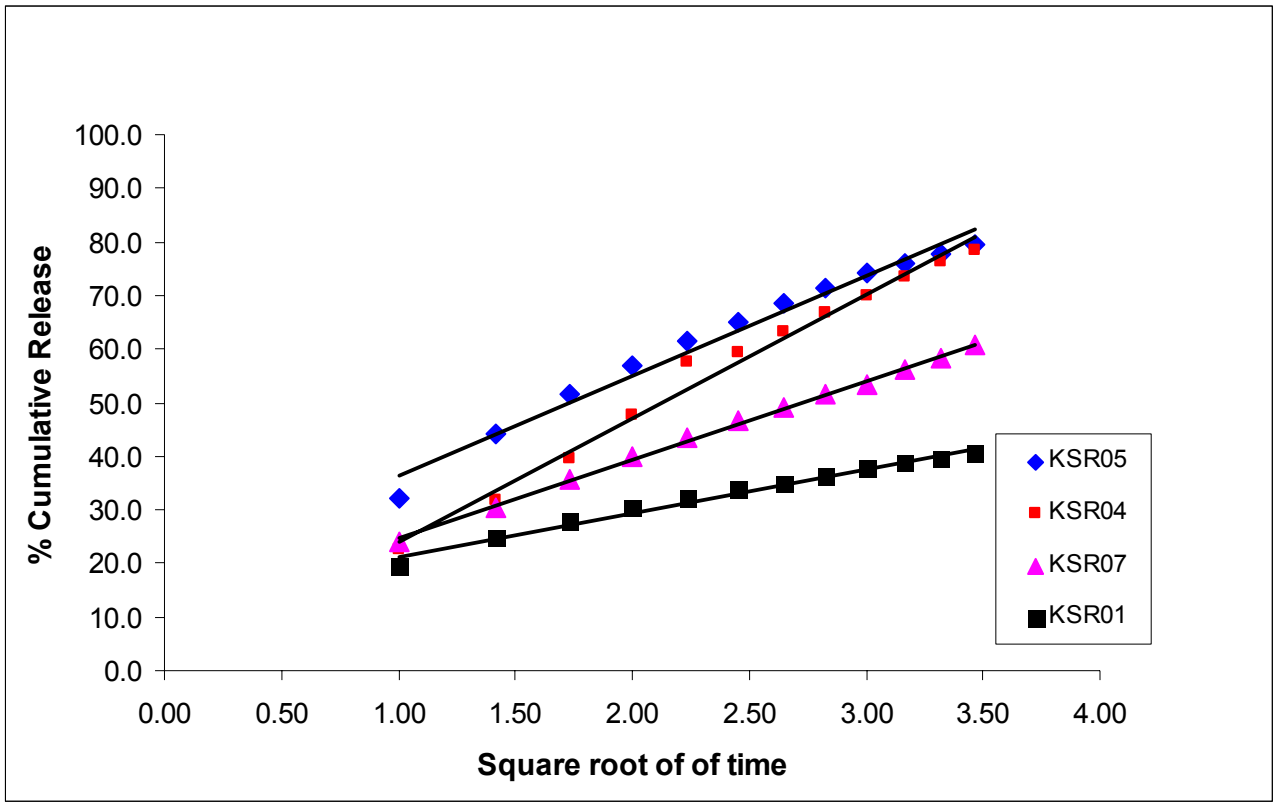


Figure 24. Effect of HPMC/Eudragit combination blends on diffusion controlled dextromethorphan release from ER matrix tablets

4.4.2. Effect of filler excipients and PVAP concentration on the release of dextromethorphan release from ER matrix tablets

The multiple linear regression rates of the dextromethorphan release are shown in table 13 – page 124.

A positive sign in front of the coefficient indicates that the parameter promotes the release of dextromethorphan, while a negative sign in front of the coefficient indicates that the parameter retards the release of dextromethorphan from the tablets. The data shows as expected that the PVAP alone exerts a retarding effect on the release of dextromethorphan. Microcrystalline cellulose and dibasic calcium phosphate alone promote the release of dextromethorphan. PVAP in combination with microcrystalline cellulose and dibasic calcium phosphate, shows an even higher retardation of dextromethorphan than with PVAP alone, however, the data is not significant as the p-values are greater the 0.05. Microcrystalline cellulose in combination with dibasic calcium is a big promoter of release of dextromethorphan from the developed ERx tablets.

These results show that the fillers microcrystalline cellulose and dibasic calcium phosphate do not significantly affect the release of dextromethorphan when combined with PVAP. This reason for this is that with increasing PVAP concentration, the magnitude of the filler excipient affect decreases. These findings confirm what Tillotson, 2004, reported in his findings when using the same fillers with bumetanide as the drug of choice.

Table 13. Multiple linear regression rates

Variable	Coefficient	p-value
PVAP	-64.5	0.0094
Microcrystalline cellulose	82.34	0.0031
Dibasic calcium phosphate	101.34	0.0011
PVAP*Microcrystalline cellulose	-157.82	0.0857
PVAP*Dibasic calcium phosphate	-142.28	0.1134
MCC*Dibasic calcium phosphate	1118.05	0.1752

4.5. Dextromethorphan IR capsules

4.5.1. In vitro dextromethorphan release

Figure 25 – page 127 shows the in vitro release of dextromethorphan from the gelatin capsules. Testing was performed as per the methodology detailed in Section 3.5 – page 58. Results show an immediate release, within 15 minutes. The study was terminated at the 2 hour time point as the capsule had completely disintegrated and all DMHBr was completely dissolved in the dissolution media.

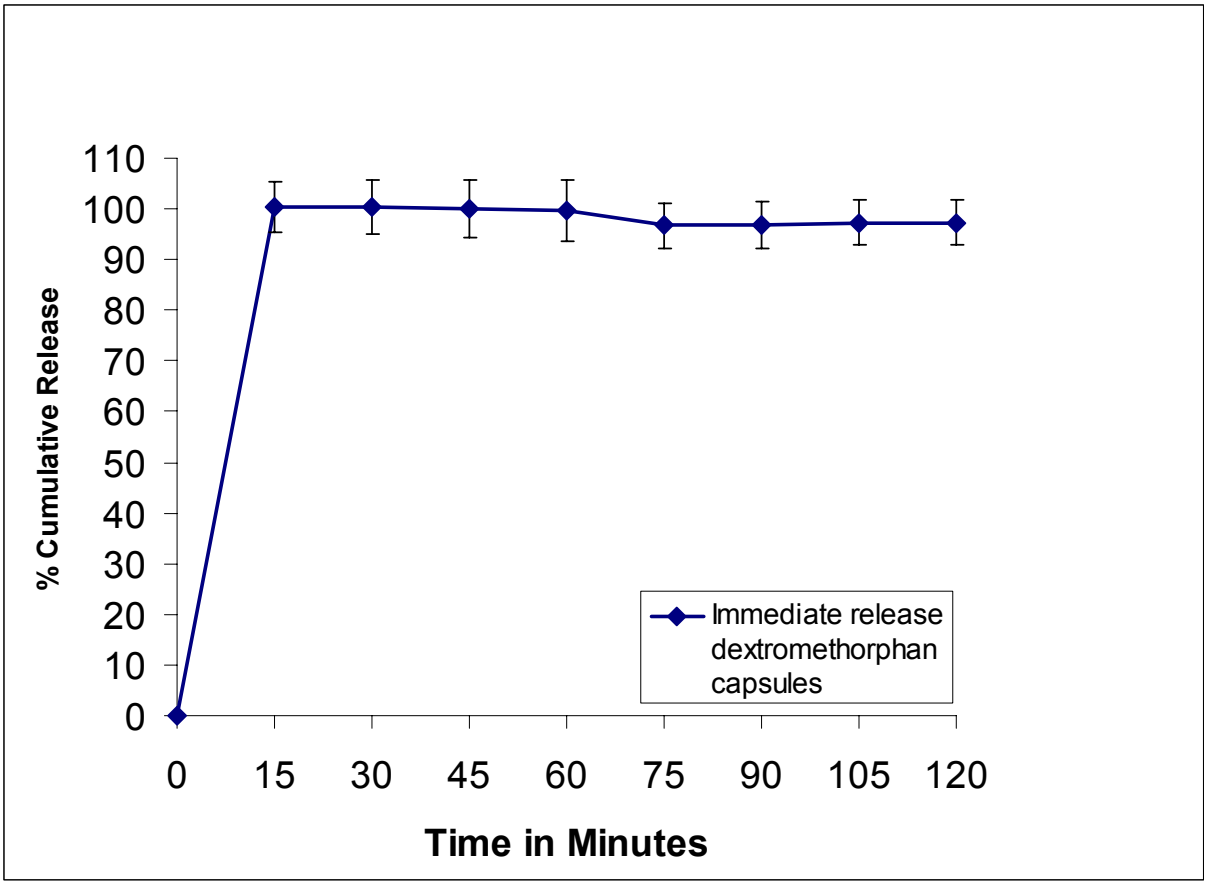


Figure 25. In vitro dextromethorphan release from immediate release gelatin capsules.(plotted values are average values, n=8)

4.6. Selection of developed extended release tablets for in vivo dog bioavailability and bioequivalence study.

Selection of the developed extended release tablets for further testing in the in vivo model was based on the following criteria:

1. Model independent FDA recommended f2 similarity factor comparing the marketed product and the developed extended release tablets and

2. Drug release rate constant as calculated using Higuchi's equation.

A summary of the data that has been presented above for the HPMC/Eudragit and PVAP extended release dextromethorphan tablets is shown in table 14 – page 129.

Table 14. Summary of f2 factor and in vitro drug release constant data for selection of developed ER tablets.

Product	f2 factor	In vitro drug release constant
HPMC 40%	61	34.6
HPMC 20% / Eudragit 20%	58	26.5
HPMC 30% / Eudragit 30%	57	29.0
PVAP (KSR04)	43	23.15
PVAP (KSR05)	53	18.58
Tuss hustenstiller retardkapseln, marketed capsule product		***24.38***

From table 14 – page 129 of the developed extended release tablets, it was decided to select HPMC 20% / Eudragit 20% and PVAP (KSR05) ER matrix tablets for use in the in vivo bioavailability and bioequivalence study. The reasoning behind this choice was based on the in vitro drug release constant. It was seen that while HPMC 20% / Eudragit 20% and HPMC 30% / Eudragit 30% ER matrix tablets both showed f2 similarities to the marketed capsule product, however, the in vitro drug release rate for HPMC 20% / Eudragit 20% ER matrix tablet was closer to the marketed capsule product and as such was selected for use in the in vivo bioavailability and bioequivalence study.

For the PVAP ER matrix tablet, while the KSR04 formula was closer to the marketed capsule product in vitro drug release constant, the KSR04 formula was not similar as per the f2 similarity factor. As such for the PVAP ER matrix tablets, the KSR05 formula was selected for use in the in vivo bioavailability and bioequivalence study.

Figure 26 – page 131 shows the dextromethorphan in vitro drug release profiles for the products to be tested.

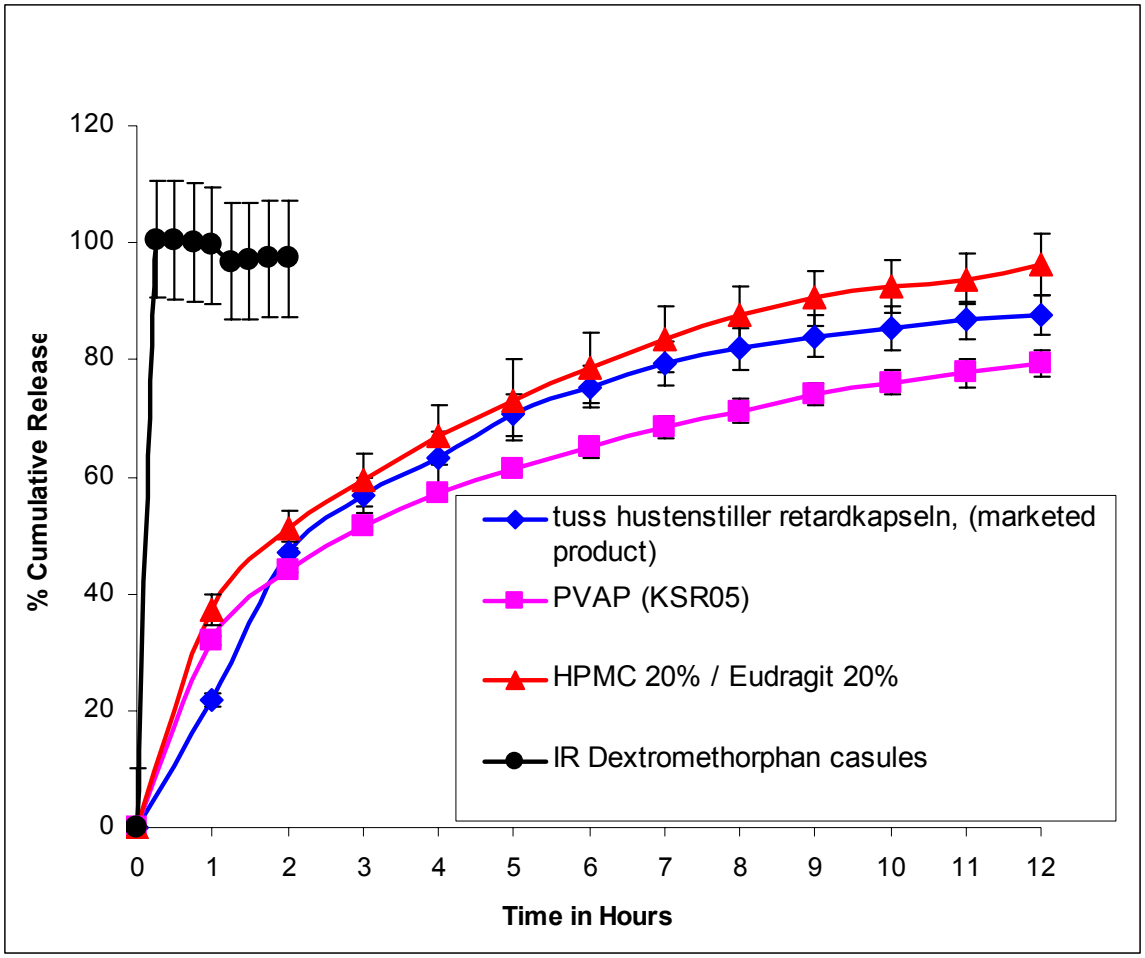


Figure 26. In vitro dissolution profiles of the 3 ER and the IR treatments (Mean of 8 replicates. Error bars ± Standard Deviation)

4.7. Effect of stability conditions on physical characteristics and release of dextromethorphan from selected tablets.

Results of physical properties of the HPMC/Eudragit and PVAP matrix tablets are shown in Tables 15, 16– pages 133, 135, the conditions for the long term storage were based off of the ICH guidelines:

Long term stability study (FDA, 2001 ICH Q1A, FDA, 1997 ICH Q1C):

Storage: 25 $\pm$ 2^{o}C / 60 $\pm$ 5% Relative humidity

Frequency of testing: 0,1,3,6, and 9 months

Tests performed: Appearance, weight, thickness, hardness, drug release

4.7.1. HPMC 20% / Eudragit 20% stability data

Table 15- -page 133 shows the effect of long term stability storage on the physical properties of HPMC/Eudragit.

Results show no change in the dissolution profile for tablets stored under long term stability conditions for upto 9 months. (Figure 27 – page 134)

Table 15. Effect of long term stability storage on the physical properties of HPMC/Eudragit tablets

Physical property	Initial	1 month	3 months	6 months	9 months
Weight (mg)	308±2.25	307.3±1.1	308±1.12	309±1.2	309±1.18
Thickness (mm)	4.95±0.02	4.94±0.01	4.95±0.01	4.96±0.02	4.97±0.02
Hardness (kp)	9.2±0.7	9.2±0.5	9.25±0.5	9.4±0.8	9.5±0.6

(*) significantly different from initial at 0.05 level

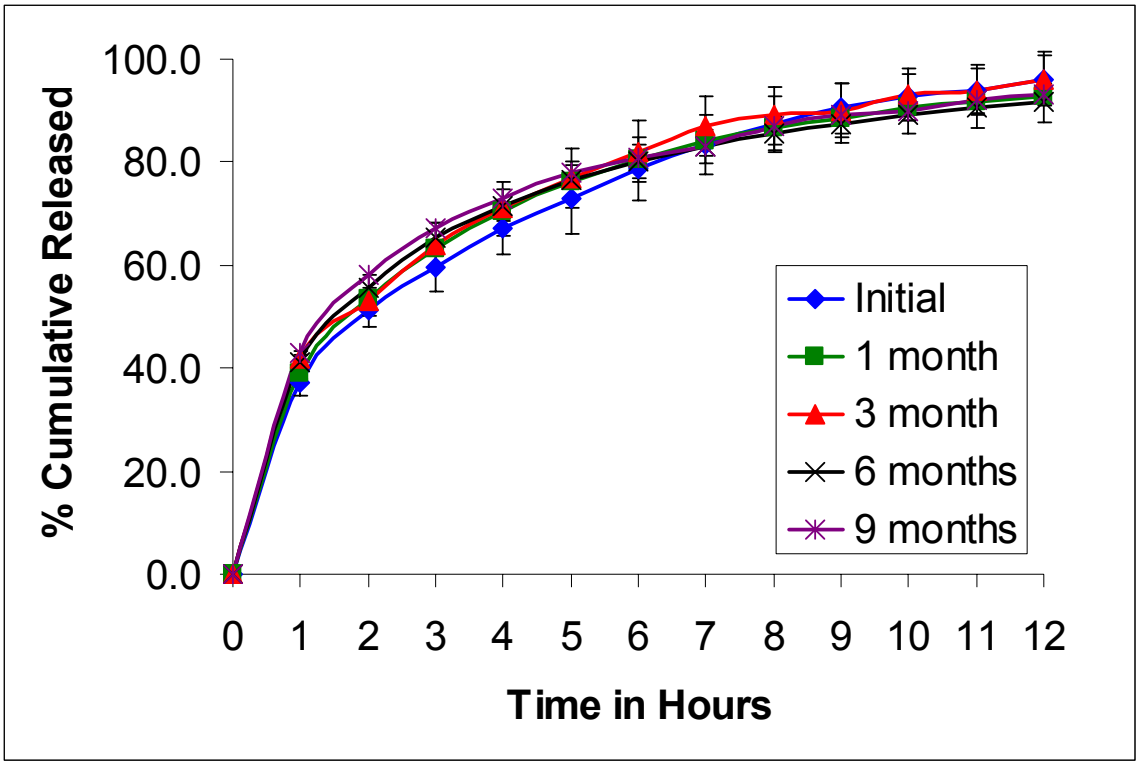


Figure 27. Effect of storage on dextromethorphan release from HPMC/Eudragit matrix tablets under long term stability conditions (plotted values are average values, n=8)

4.7.2. PVAP (KSR05) stability data

Table 16 – page 135 shows the effect of long term stability storage on the physical properties of PVAP tablets.

Results show a significant change in hardness at the 3 month, 6 month and 9 month period. However, there was no significant change in the dissolution profile (Figure 28 – page 137) for tablets stored under long term stability conditions for upto 9 months. This is similar to results reported by Shao et. al. (2001), Draganoiu (2003) and Tillotson (2004).

Table 16. Effect of long term stability storage on the physical properties of PVAP tablets

Physical property	Initial	1 month	3 months	6 months	9 months
Weight (mg)	299±0.00	298±2.1	299±1.1	301±1.3	300±1
Thickness (mm)	4.37±0.02	4.40±0.01	4.41±0.01*	4.42±0.02*	4.5±0.04*
Hardness (kp)	11.1±0.7	12.0±0.5	13.2±0.5*	14.2±0.6*	15.2±0.8*

(*) significantly different from initial at 0.05 level

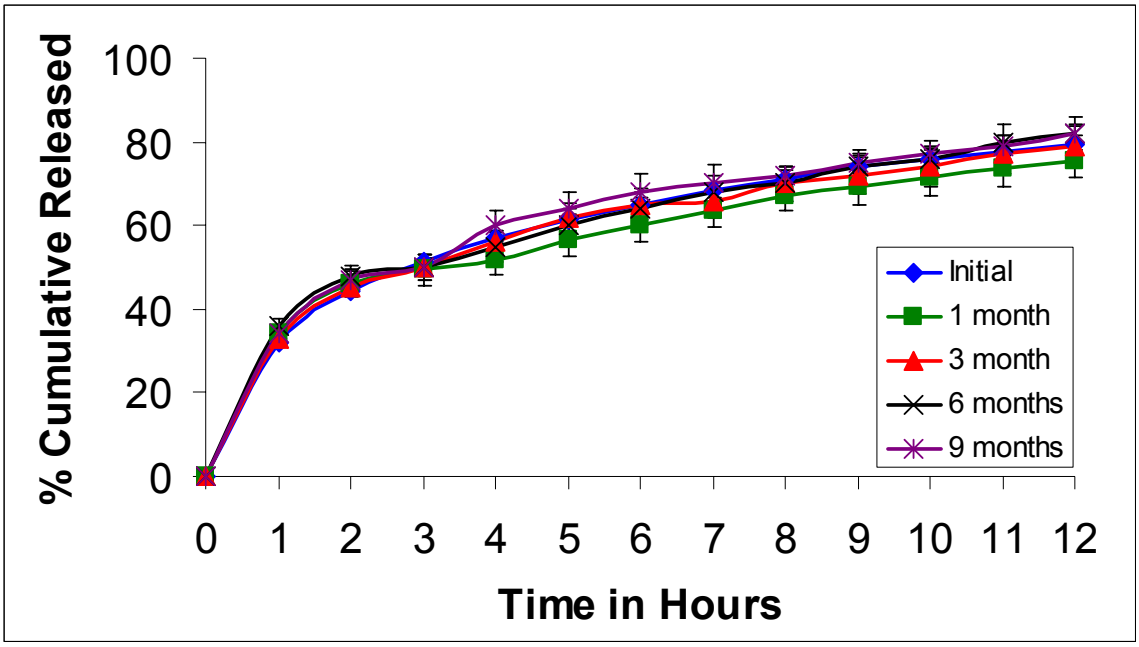


Figure 28. Effect of storage on dextromethorphan release from PVAP matrix tablets under long term stability conditions (plotted values are average values, n=8)

4.8. Evaluation of bioavailability and bioequivalence of selected extended release tablets to the marketed capsule product.

Dextromethorphan undergoes rapid first-pass metabolism in vivo to produce the primary metabolite dextrorphan (Ramachander et. al., 1977, Cleveland et. al., 1990). As such analytical methods for in vivo plasma levels was designed to evaluate the primary metabolite dextrorphan.

4.8.1. Analysis of dextrorphan in plasma

4.8.1.1. Accuracy, linearity and range

The calibration curves generated by combining dextromethorphan and dextrorphan stock standard solution to yield final calibration standards of 0.1, 0.2, 1.0, 2.0, and 10 ng/ml were linear over the whole range.(r^2>0.99)

4.8.1.2. Precision

The estimated relative standard deviations for the 5 different dextrorphan concentrations each measured three times were less than 1%.

The dextromethorphan plasma values are not presented here as the values are too low, i.e. >0.5 ng/ml, nearly equivalent to background noise.

Silvasti et. al. (1987) reported that due to the rapid first pass metabolism of the dextromethorphan, the levels of the unmetabolized drug found in the body (humans) are very low while that of the metabolite dextrorphan are about 60-170 times higher.

4.8.2. Dextrorphan plasma concentrations after treatment dose administration.

Total dextrorphan (free and conjugated) plasma concentrations obtained after administration of the developed extended release dextromethorphan matrix tablets and the marketed capsule for each dog are graphically displayed in Figure 29 – Figure 36, pages 140 – 147. Mean results comparing the marketed product and the PVAP tablet are shown in Figure 37 – page 148. Mean results comparing the marketed product and the HPMC/Eudragit tablet are shown in Figure 38 – page 149. The summary mean results showing the 4 treatment groups are shown in Figure 39 – page 150.

The calculated AUC 0-24hr, AUC 0-∞, and C_{max} for each dog are presented in table 17 – page 151.

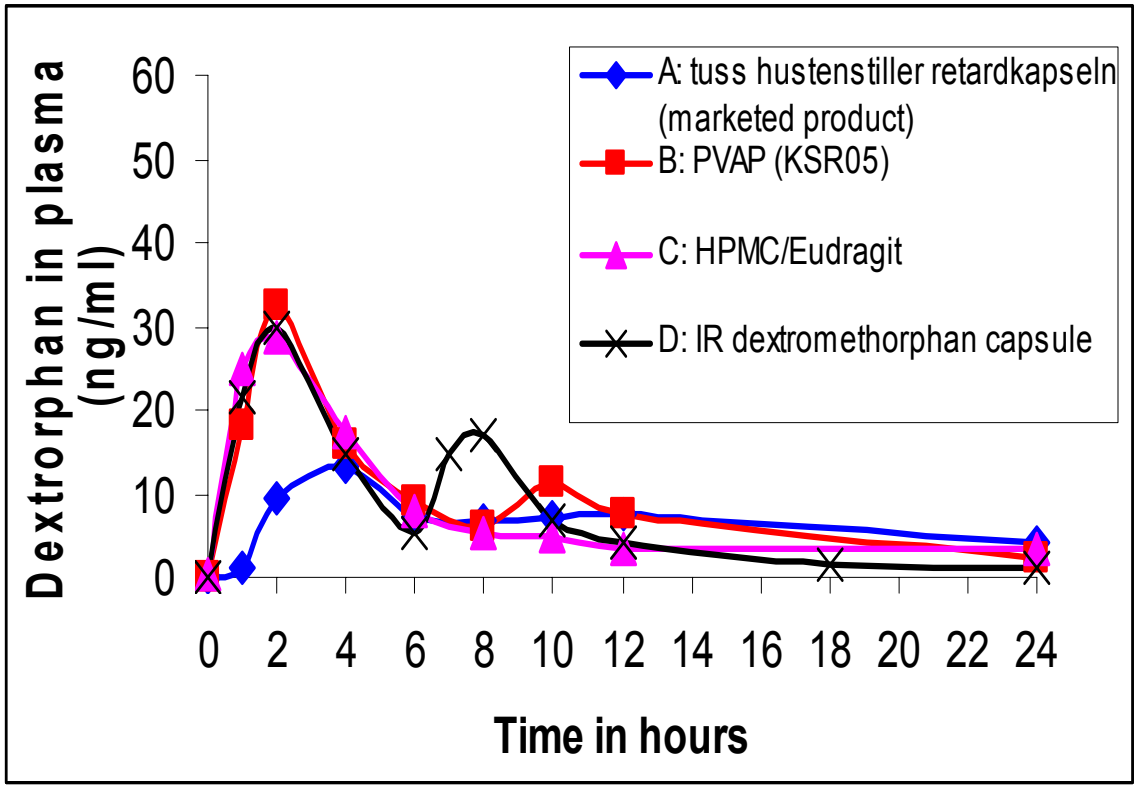


Figure 29. Plasma levels of dextrorphan following administration – Dog 28001

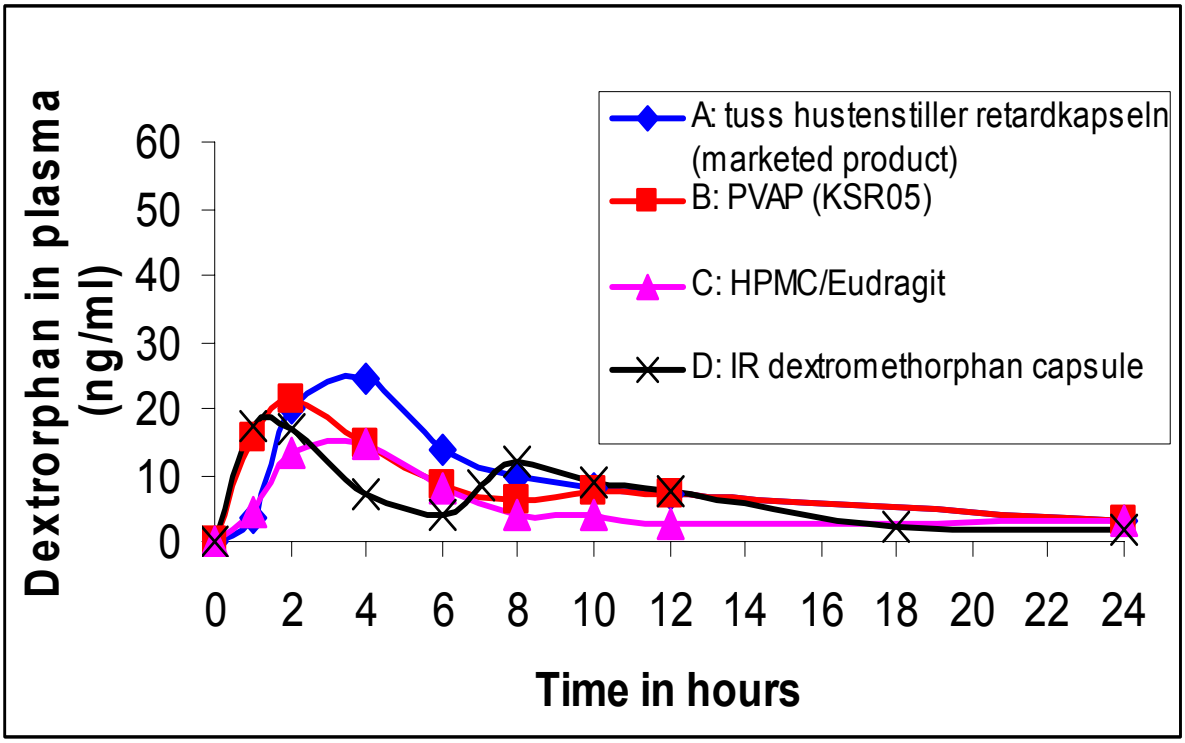


Figure 30. Plasma levels of dextrorphan following administration – Dog 28002

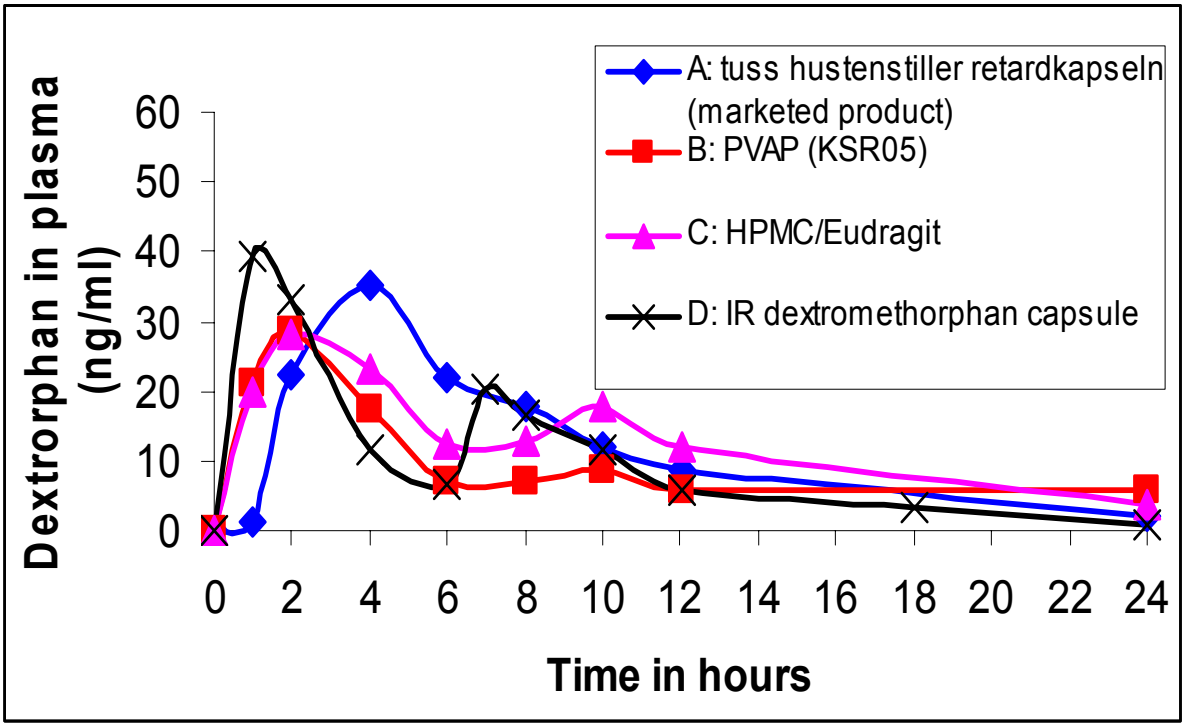


Figure 31. Plasma levels of dextrorphan following administration – Dog 28003

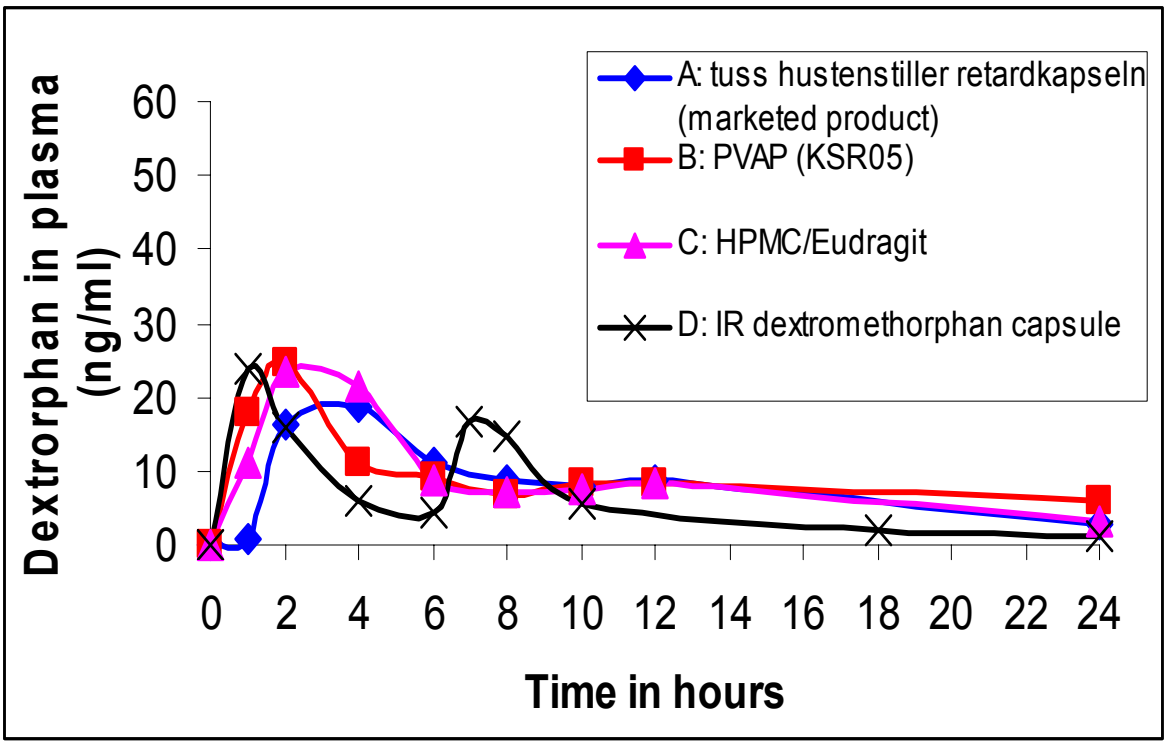


Figure 32. Plasma levels of dextrorphan following administration – Dog 28004

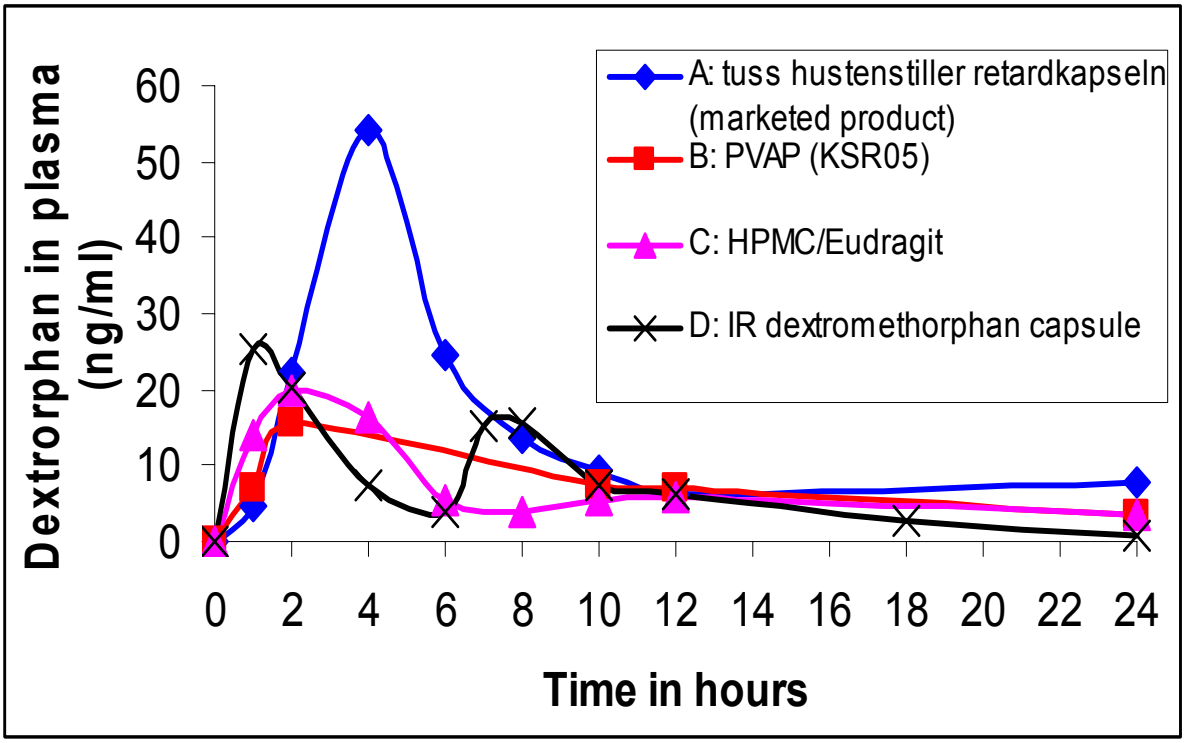


Figure 33. Plasma levels of dextrorphan following administration – Dog 28005

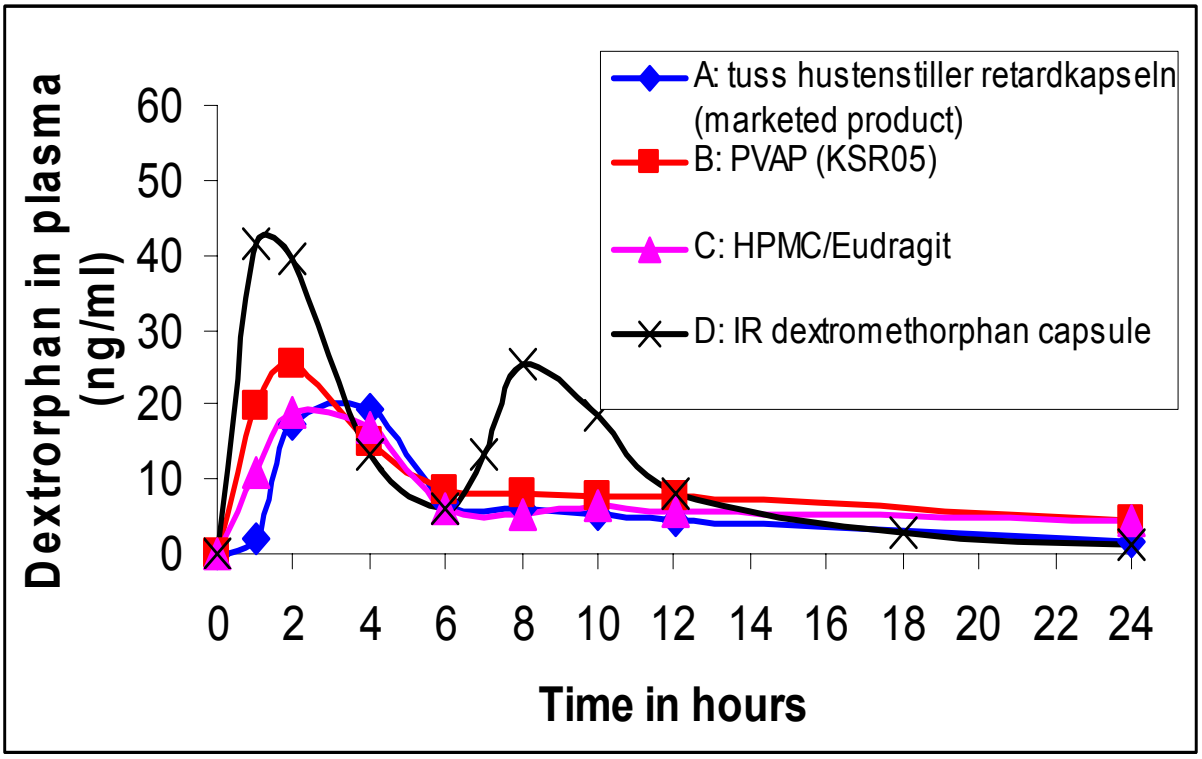


Figure 34. Plasma levels of dextrorphan following administration – Dog 28006

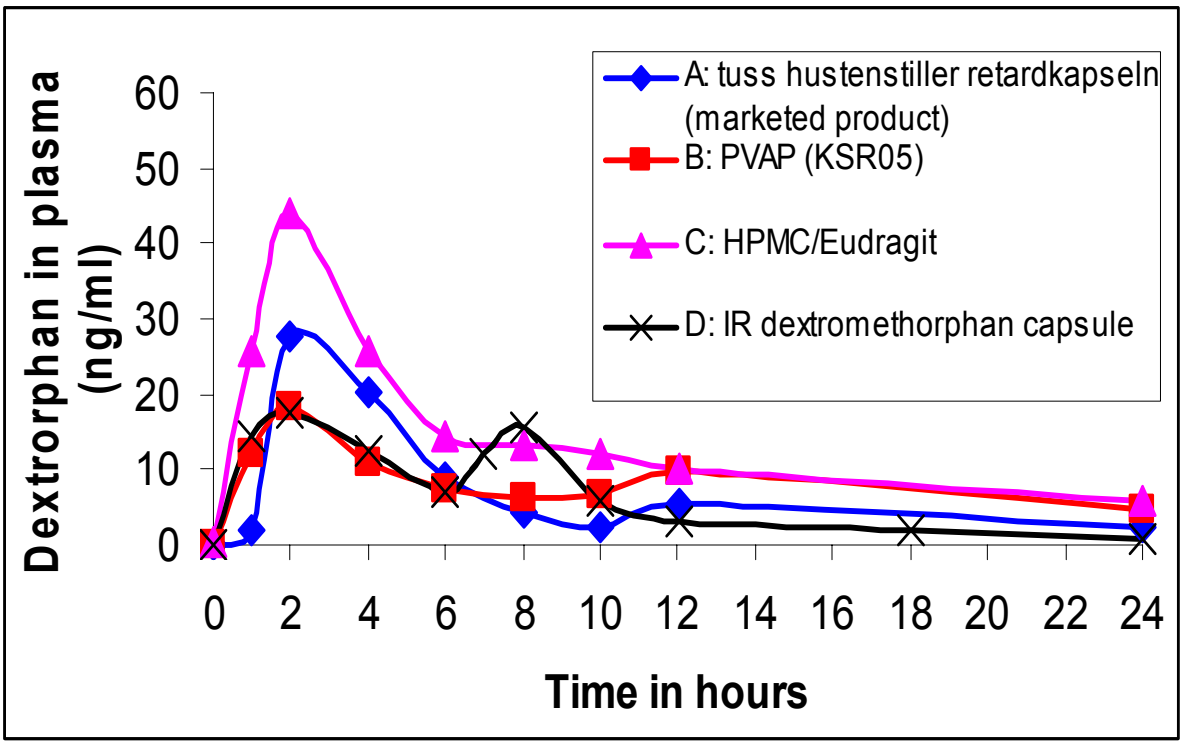


Figure 35. Plasma levels of dextrorphan following administration – Dog 28007

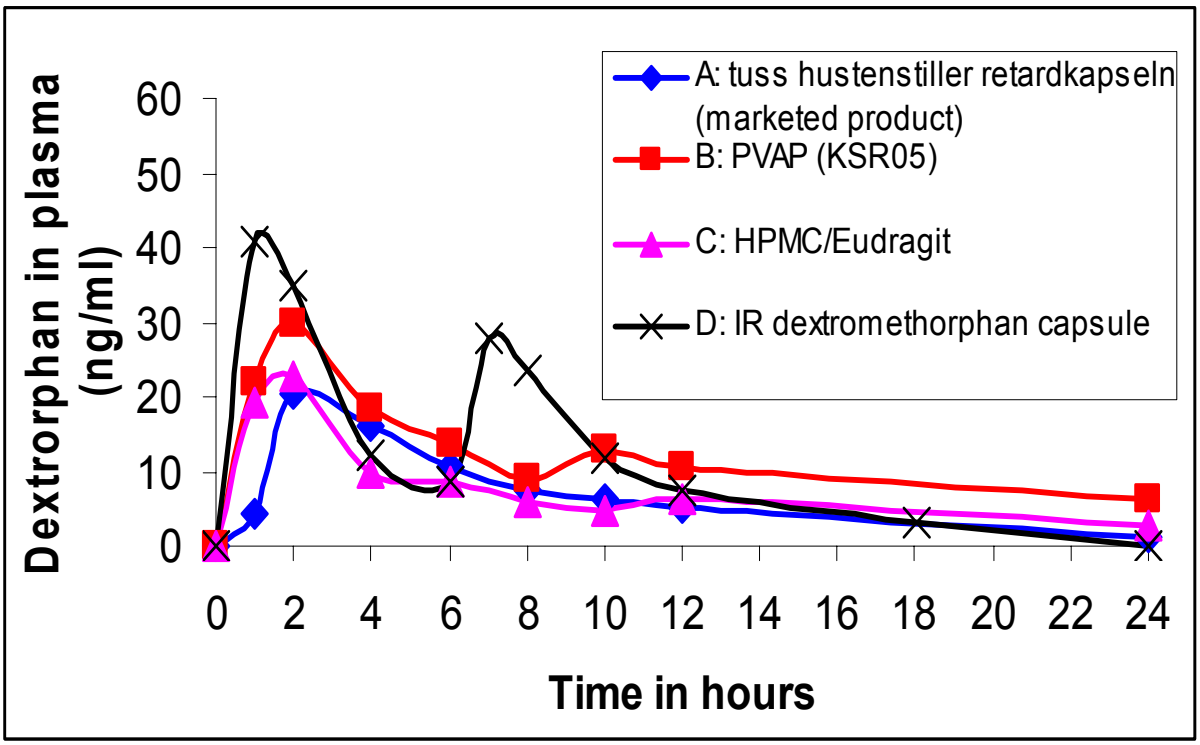


Figure 36. Plasma levels of dextrorphan following administration – Dog 28008

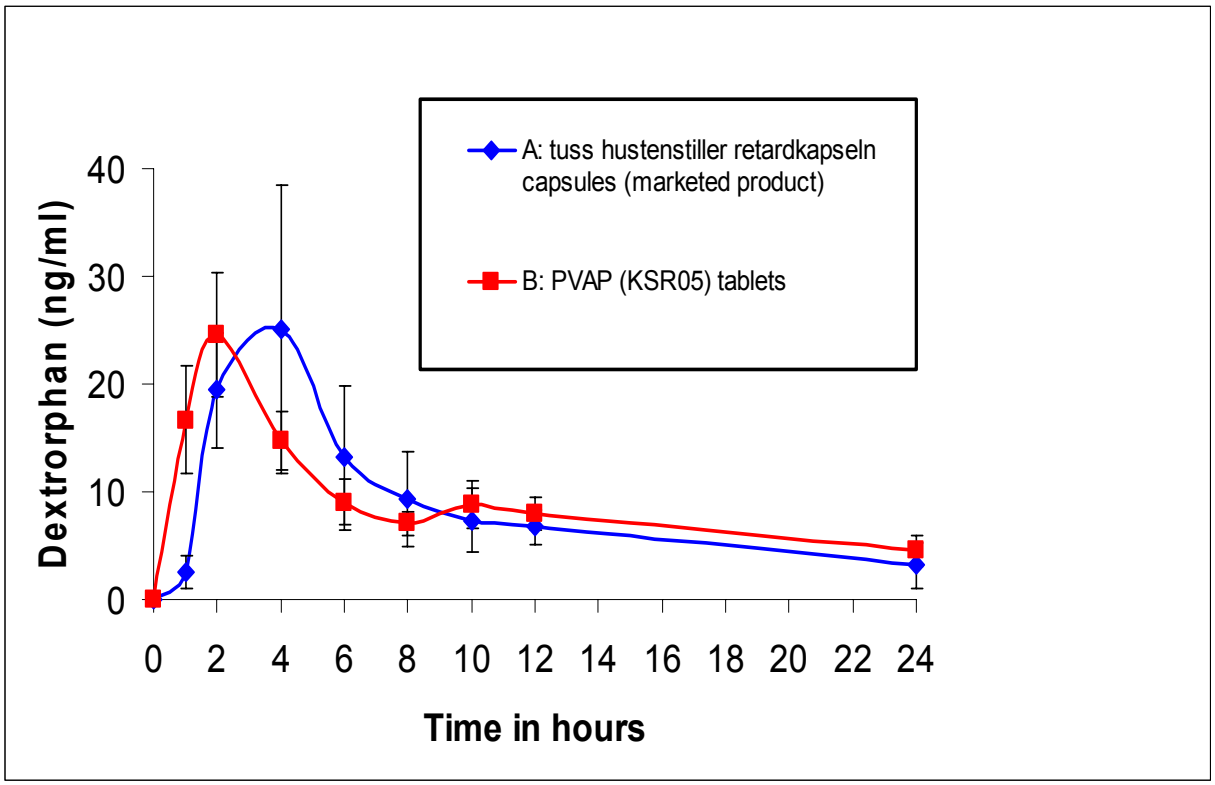


Figure 37. Plasma levels of dextrorphan following administration of marketed capsule product and PVAP (KSR05) ER matrix tablets. (mean ± Standard Deviation)

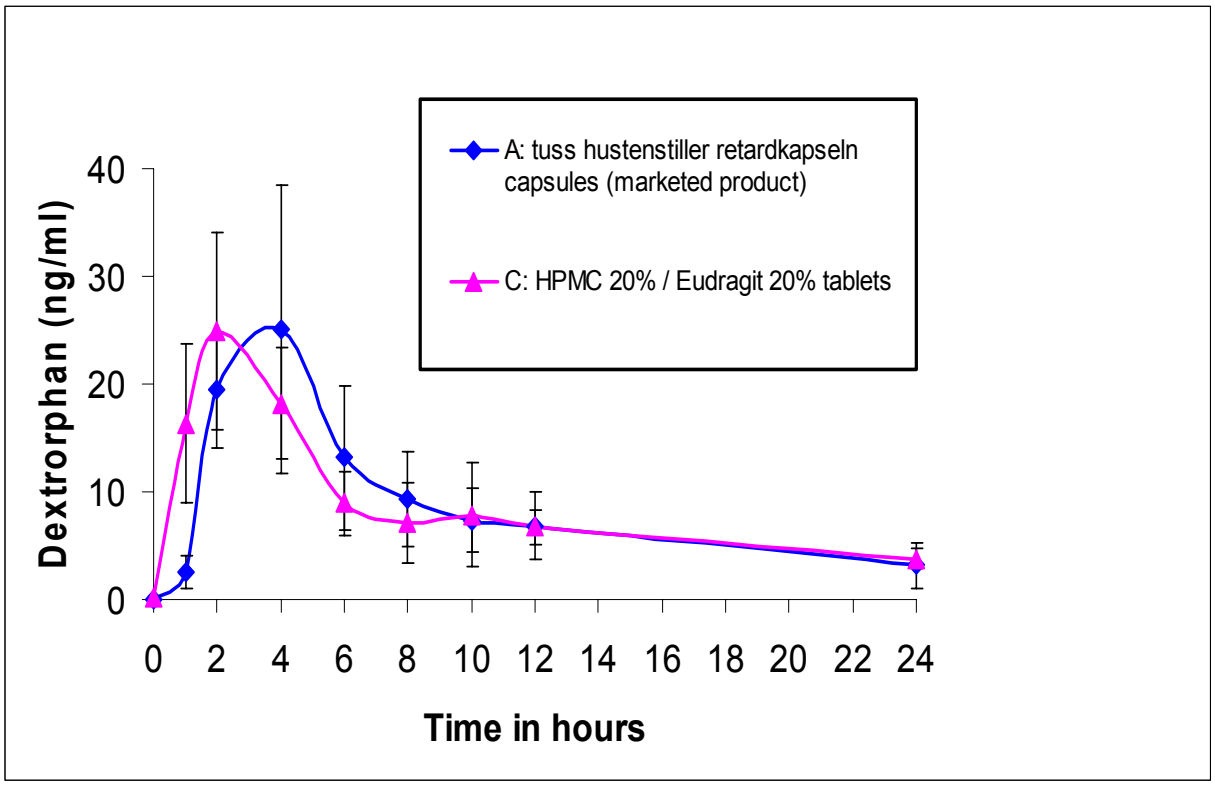


Figure 38. Plasma levels of dextrorphan following administration of marketed capsule product and HPMC/Eudragit ER matrix tablet. (mean ± Standard Deviation)

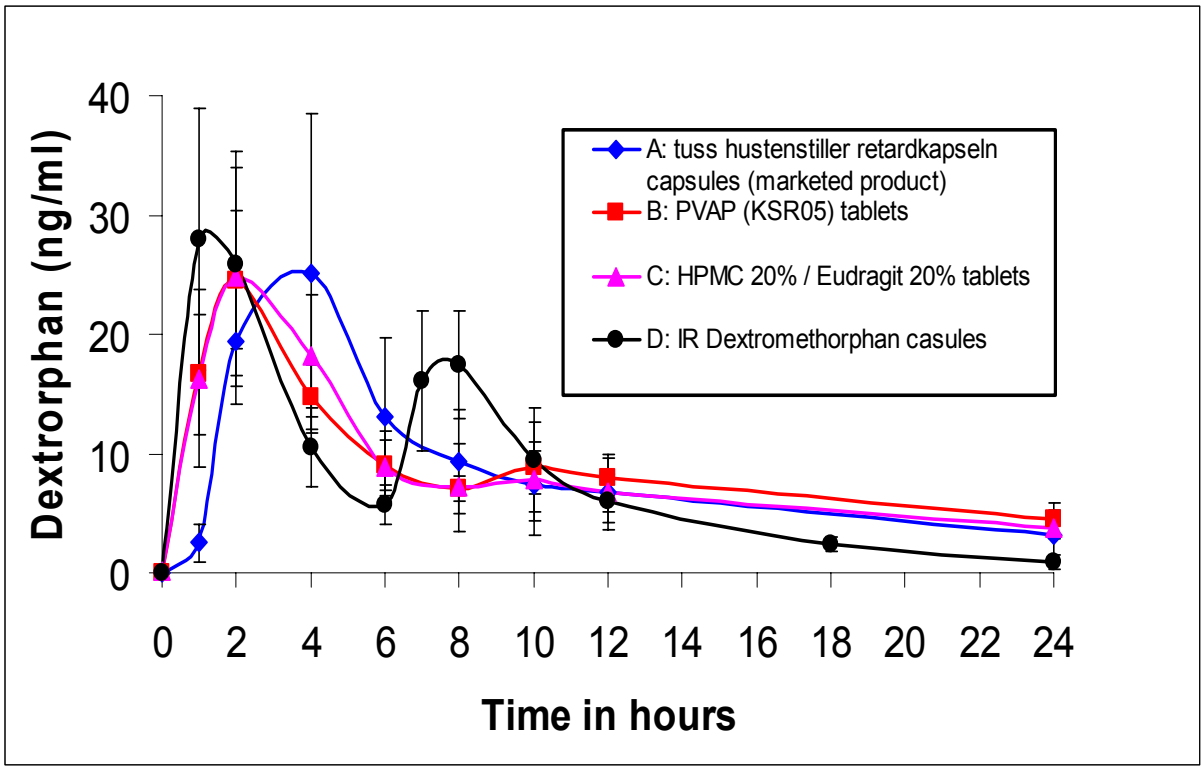


Figure 39. Plasma levels of dextrorphan following administration of marketed capsule product and developed selected PVAP and HPMC/Eudragit ER matrix tablets.(mean ± Standard Deviation)

Table 17. Pharmacokinetic parameters from in vivo dog study.

Dog #	A: tuss hustenstiller retardkapseln capsules, (marketed product)			B: PVAP (KSR05) tablets			C: HPMC 20% / Eudragit 20% tablets			D: IR dextromethorphan capsules		
	AUC 0-24h	AUC 0-∞	C_{max}	AUC 0-24h	AUC 0-∞	C_{max}	AUC 0-24h	AUC 0-∞	C_{max}	AUC 0-24h	AUC 0-∞	C_{max}
28001	163.00	242.00	13.30	189.30	236.00	21.50	175.00	373.00	19.00	166.88	197.47	17.20
28002	213.70	261.00	24.50	221.00	379.00	28.70	124.00	159.00	14.70	247.76	254.56	39.30
28003	283.00	302.00	35.10	218.00	240.00	32.30	300.00	338.00	28.10	288.36	301.04	41.30
28004	196.00	229.00	18.50	No data			213.00	256.00	23.60	156.72	163.57	17.70
28005	334.00	376.00	54.00	286.00	415.00	30.00	329.00	445.00	44.00	275.02	275.02	40.90
28006	145.00	167.00	19.40	215.00	310.00	25.20	183.90	221.00	28.50	194.39	218.28	30.00
28007	168.00	197.00	27.50	199.40	273.00	18.30	167.00	260.00	19.90	182.99	189.23	25.30
28008	158.90	171.00	20.30	220.00	441.00	24.60	173.00	214.00	22.60	140.92	172.71	23.90

The plasma dextrorphan release profiles patterns from the 4 treatments closely mimic those observed by Lilienfield et. al, 1983 where for the ER treatments there is a gradual increase in the drug level which is sustained and then gradually falls off and for the IR treatments, there is a sharp increase in drug level which falls off just as fast and the second dose of the IR treatment does not show the levels of drug attained as attained from the first dose.

Statistical analysis by ANOVA on the data in table 17 – page 151 was performed.

Table 18 – page 153 shows the mean $AUC_{(0-\infty)}$, C_{max} and T_{max} values from the study.

Table 18. $AUC_{(0-\infty)}$, C_{max} and T_{max} calculated pK parameters.

Treatment	$AUC_{(0-\infty)}$ (Std. Dev.)	C_{max} (Std. Dev.)	T_{max} (Std. Dev.)
A: tuss hustenstiller retardkapseln capsules, (marketed capsule product)	243.1 (70.5)	26.6 (12.9)	3.5* (0.93)
B: PVAP (KSR05) tablets	327.7* (84.2)	25.8 (4.9)	2.0* (<0.00)
C: HPMC 20% / Eudragit 20% tablets	283.3 (94.6)	25.1 (8.9)	2.25* (0.71)
D: IR dextromethorphan capsules	221.5 (50.2)	29.5 (10.0)	1.25* (0.46)

*Statistically Significant in Comparison to Marketed Capsule Product

It was found that the $AUC_{(0-\infty)}$ of the marketed product capsule (243 ± 70.5 ng/ml/hr) was not statistically different from the HPMC/Eudragit tablets (283 ± 94.6 ng/ml/hr) and the IR dextromethorphan capsule (221 ± 50.2 ng/ml/hr). However, the $AUC_{(0-\infty)}$ of the marketed product capsule (243 ± 70.5 ng/ml/hr) was statistically different from the PVAP tablets (327 ± 84.2 ng/ml/hr). The PVAP tablets shows a higher $AUC_{(0-\infty)}$ which is consistent with what Shao et. al, 2001 found whereby higher levels of insoluble dibasic calcium phosphate (Emcompress®) in combination with PVAP polymer enhanced drug release. This may explain why the $AUC_{(0-\infty)}$ for the PVAP tablets is higher then that of the marketed product capsules, the HPMC/Eudragit tablets or the IR dextromethorphan capsules.

The peak concentration levels of dextrorphan in plasma were achieved at 3.5 hours with the marketed product capsule (26.6 ± 12.9 ng/ml), at 2.0 hour with the PVAP tablets (25.8 ± 4.9 ng/ml), and at 2.25 hour with the HPMC/Eudragit tablet (25.1 ± 8.9 ng/ml). The C_{max} data showed that there was no statistical significance difference among the 4 treatments, although the immediate release capsule control trended higher then the other 3 treatments indicating more dextromethorphan was released in comparison to the ER treatments. However, comparison of the T_{max} by ANOVA revealed statistically significant differences between the PVAP and HPMC/Eudragit tablets when compared to the marketed product capsules.

The observed statistical difference between the treatments may be the result of a slower dissolution process in vivo for the marketed product capsules which consists of coated particles. The short T_{max} of the PVAP

and HPMC/Eudragit matrix tablets can be attributed to an initial burst effect. This difference was detected in the in vitro dissolution testing where, as has been reported earlier in table 14 – page 129, the release rate of the marketed product capsules was lower than that of the HPMC/Eudragit tablets.

Table 19. Results of bioequivalence testing

	PVAP ER matrix tablets		**HPMC/Eudragit ER matrix tablets**	
	AUC	**C_{max}**	**AUC**	**C_{max}**
Lower bounds >0.8	1.0529	1.0407	0.9459	0.9852
Upper bounds <1.25	1.7058	1.6861	1.5324	1.5961

According to the FDA, the PVAP and the HPMC/Eudragit in comparison to the marketed capsule product are considered bioequivalent if the 90% confidence interval for the ratio of the averages (population geometric means) of the measures for the test (PVAP & HPMC/Eudragit) and reference (marketed capsule product) falls within a bioequivalent limits usually 80-125% for the ration of the product averages. (FDA 2001, FDA 2002). By applying this criterion, the two test tablets (PVAP & HPMC/Eudragit ER matrix tablets) were not bioequivalent with regards to AUC (table 19 - page 155). The tablets produced a higher AUC than the marketed capsule product.

4.8.3. Effect of variable dissolution rates on in vitro/in vivo correlation.

Eddington et. al. (1998), reported that it is imperative to utilize a dissolution methodology that discriminates between formulations and mimics the in vivo release profile. Since the composition of the dissolution medium was adjusted to simulate in vivo conditions, it was possible to selectively study the effect of hydrodynamics on the dissolution process in vitro and to compare the results directly with the in vivo data. Thus an in vitro/in vivo correlation was investigated using the percent dissolved versus the percent absorbed data at different agitation rates of 10, 25, 50 and 100 rpms.

Figure 40, 41 and 42 – pages 157, 158 and 159 show the summary graphs of in vitro dextromethorphan release at variable agitation rates.

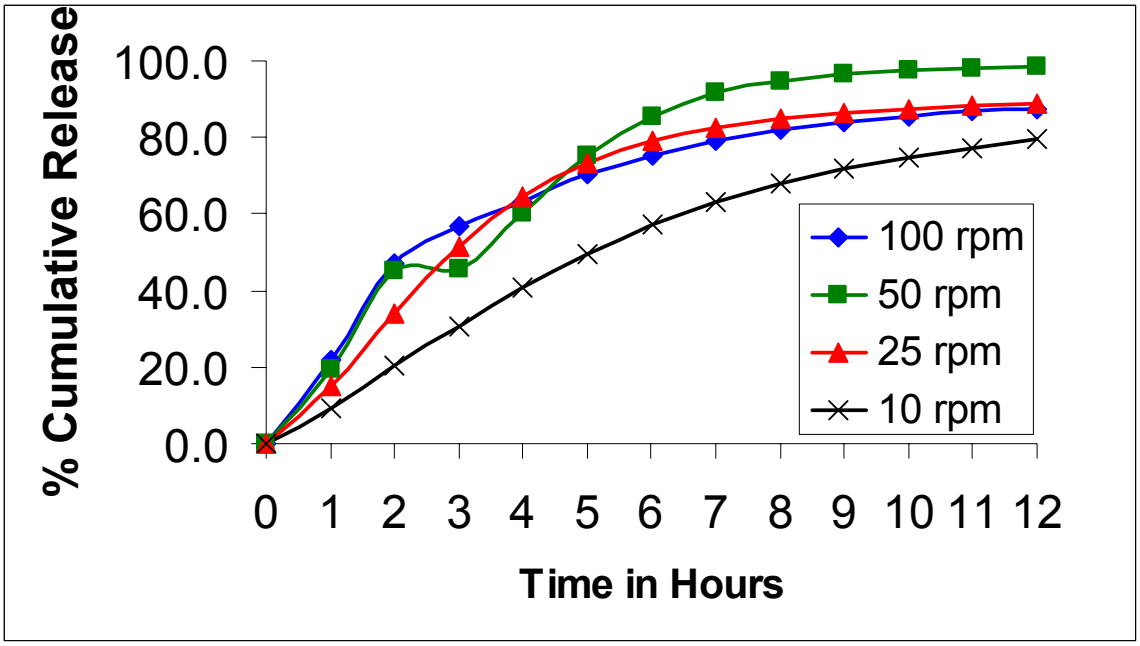


Figure 40. In vitro dissolution profiles of marketed capsule product at variable dissolution agitation rates. (plotted values are average values, n=8, RSD<3%)

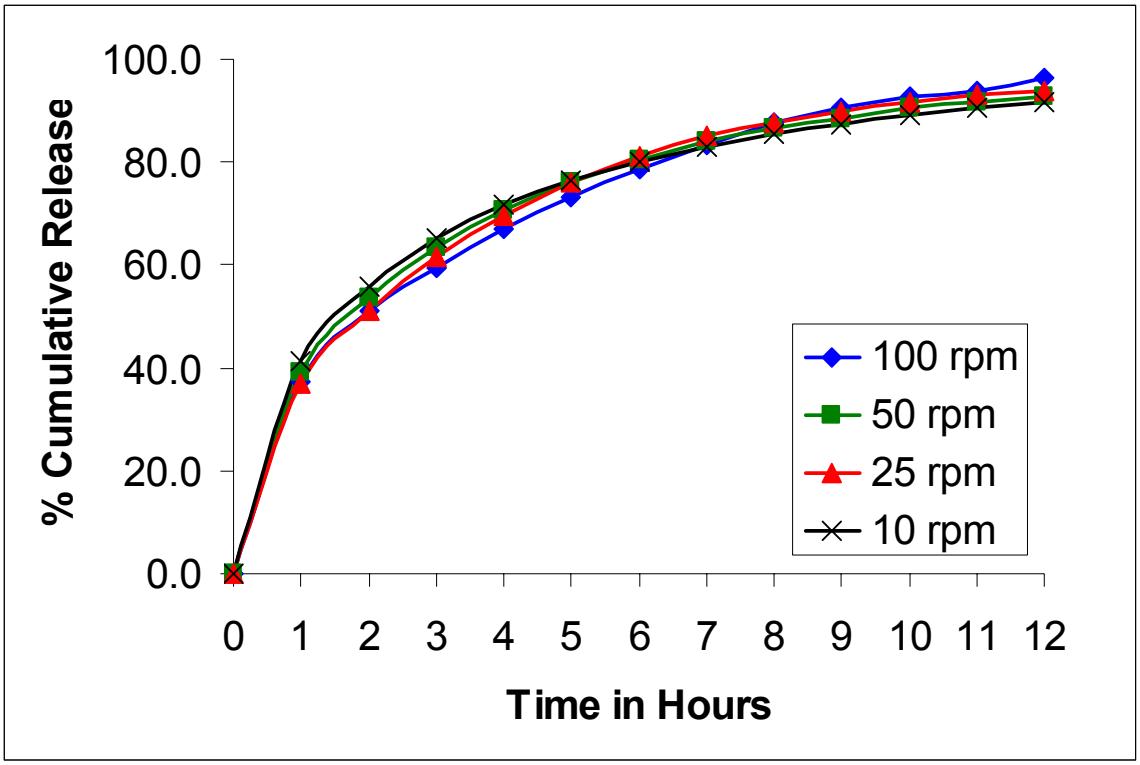


Figure 41. In vitro dissolution profiles of HPMC/Eudragit ER matrix tablets at variable dissolution agitation rates. (plotted values are average values, n=8, RSD<3%)

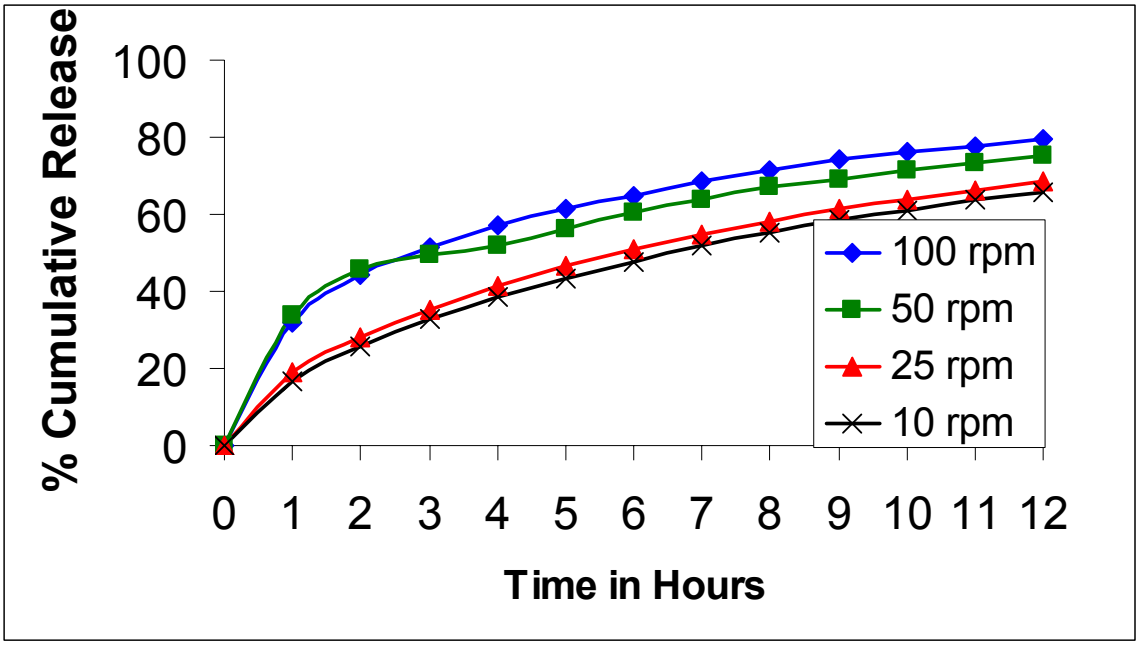


Figure 42. In vitro dissolution profiles of PVAP ER matrix tablets at variable dissolution agitation rates. (plotted values are average values, n=8, RSD<3%)

Results show that the marketed product capsules, despite consisting of coated pellets of drug (reservoir system), showed a sensitivity to the agitation rate as did the PVAP ER matrix tablets. The HPMC/Eudragit tablets on the other hand showed no little or no sensitivity to the different dissolution agitation rate.

Correlation at variable dissolution agitation rates of percent dissolved dextromethorphan in vitro to percent absorbed in vivo is shown in table 20- page 161.

Results show that the best in vitro-in vivo correlation was observed at 100 and 50 rpm with the marketed product capsule and the PVAP and HPMC/Eudragit tablets respectively. However, due to the low correlation (r^2), an in vitro/in vivo correlation was not established. While matrix tablets has a much faster release in the stomach, followed by a relatively slower release in the intestine region. This release characteristic might contribute further to the failure to establish a correlation. The above in vivo study has been accepted for publication as 2 parts in Pharm. Ind. (Bharaj et. al. 2005)

Table 20. Correlation (r^2) at variable agitation rates (rpms) of percent dissolved in vitro to percent absorbed in vivo.

Treatment	10 rpm	25 rpm	50 rpm	100 rpm
A: tuss hustenstiller retardkapseln capsules, (marketed capsule product)	0.68	0.82	0.77	0.84
B: PVAP (KSR05) tablets	0.63	0.65	0.79	0.76
C: HPMC 20% / Eudragit 20% tablets	0.79	0.74	0.76	0.73

5. Conclusions

Hydroxypropylmethylcellulose (K100LV) at 20% and 30% level in combination with methacrylic acid copolymer (Eudragit® L100-55) at 20% and 30% level produced extended release dextromethorphan matrix tablets that are similar to the marketed capsule product in vitro according to the model independent FDA guidelines (f2 factor).

Polyvinyl acetate/povidone (PVAP) (Kollidon® SR) at 39.5% in combination with dibasic calcium phosphate also at 39.5% level produced extended release dextromethorphan tablets that are similar to the marketed capsule product in vitro according the model independent FDA guidelines (f2 factor).

Both selected extended release dextromethorphan matrix tablets followed square root of time dependent kinetics for drug release indicating a diffusion controlled release mechanism.

Under long term storage conditions at 25°C and 60% RH, stability testing performed on the selected HPMC/Eudragit and PVAP tablets showed no significant change in the dissolution rates. Based on this finding, the recommended storage conditions are 25°C and 60% RH.

The selected extended release HPMC/Eudragit and PVAP dextromethorphan tablets were not bioequivalent to the marketed capsule product, tuss hustenstiller retardkapslen, however, the tablets had higher bioavailability as shown by the $AUC_{(0-\infty)}$. In vitro/in vivo correlation between variable dissolution agitation rates and the dextromethorphan released and absorbed was not established for the extended release dextromethorphan matrix tablets. Although similar in vitro dissolution profiles can be obtained using completely different controlled release

technologies, their in vivo behavior can differ significantly due to different release mechanisms in vivo and physiological factors, such as GI transit time, pH gradient and hydrodynamics.

Based on the above, it is concluded that extended release dextromethorphan matrix tablets were developed using HPMC/Eudragit combination and PVAP as the release extending excipients. In vitro testing indicated that extended release dextromethorphan matrix tablets had similar dissolution behavior to the marketed capsule product according to the model independent FDA guideline (f2 factor).

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