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IN-VITRO AND IN-VIVO AVAILABILITY OF MEBEVERINE HYDROCHLORIDE SUPPOSITORIES

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Abstract

Mebeverine hydrochloride suppositories were prepared using Witepsol H15 suppository base. The effect of different concentrations of various enhancers (surfactants, amino acids and osmotic modifiers) on the drug release form the prepared suppositories was studied. The results showed that mebeverine hydrochloride suppositories containing Brij 35 (2%) and urea (10%) were superior to the other formulations containing the tested enhancers. These formulae showed the highest release rates (K = 0.083 ± 0.004 min^{-1} and 0.111 ± 0.005 min^{-1} , respectively) that followed first-order kinetics with $t_{50\%}$ of 8.35 ± 0.45 min and 6.24 ± 0.33 min, respectively. Therefore, these two formulae with the control suppositories were subjected to *in vivo* study in albino rabbits compared to the commercial Duspatalin® tablets and intravenous injection.

Higher C_{max} (1770.26 ± 165.46 $ng.ml^{-1}$) within shorter T_{max} (0.75 ± 0.20 h) was observed after rectal administration of the control suppositories compared to that of commercially available film-coated tablets (Duspatalin® – 135 mg). A significant difference ($p \leq 0.05$) between the absolute bioavailability of Duspatalin® tablets (27.09 ± 3.80%) and control suppositories (46.66 ± 1.72%) was detected. Statistically ($p \leq 0.05$), the mean residence time (MRT) after oral administration of Duspatalin® tablets (3.16 ± 0.30 h) was significantly longer than that after the rectal administration of control suppositories (2.73 ± 0.30 h). suppositories containing 2% Brij 35 showed higher plasma levels of the drug (2766.11± 339.50 $ng.ml^{-1}$) with an

absolute bioavailability of 70.50 ± 10.51% compared to 27.09 ± 3.80% for Duspatalin® tablets.

Keywords

Mebeverine hydrochloride, suppositories, *in vitro* and *in vivo* availability, enhancers, HPLC.

Introduction

Mebeverine is a 3- phenylethylamine derivative of methoxybenzamine [1]. It is the most prescribed product currently available for the treatment of irritable bowel syndrome (IBS). It acts as a musculotropic antispasmodic agent with a direct action on the smooth muscle of the gastrointestinal tract (GIT) especially of the colon [2-4], relieving spasm without affecting normal gut motility, and possessing no atropine-like action [2-4]. Moreover, mebeverine was 2-5 times as potent as papaverin in inhibiting the peristaltic reflex of the guinea-pig ileum and 20-40 times more powerful in inhibiting sphincter of Oddi [4].

Mebeverine HCl is rapidly and completely absorbed after oral administration in the form of tablet or suspension [5]. The spasmolytic activity of this drug was demonstrated 2 hours but not 4 hours after oral administration of formulated mebeverine HCl-polycarbophil loaded tablets indicating rapid absorption and elimination [6]. However, mebeverine was reported to undergo rapid and extensive first-pass metabolism following oral administration [7]. The facile hydrolysis of mebeverine in fresh plasma seems almost attributable to the presence of esterases [8]. The plasma concentrations of the main metabolites: veratric acid [7,9] and mebeverine alcohol [10] were determined in human plasma after oral administration of mebeverine HCl commercial tablets.

On the other hand, mebeverine HCl was formulated as suppositories using different types of bases, and was shown to be well absorbed rectally via ex-vivo studies [11- 14]. Conventional rectal suppositories of mebeverine HCl for the relief of acute gastrointestinal spasm produced satisfactory spasmolytic effects to

spasmogen induced contractions on the isolated guinea pig ileum [11-13]. In addition, a significant extended spasmolytic effect was observed with the development of in situ gelling and mucoadhesive mebeverine HCl rectal solution [14]. The mechanism of drug absorption from the rectum is probably not different than that in the upper part of the GIT [15].

Because of poor bioavailability of oral mebeverine HCl [7], rectal administration of mebeverine to albino rabbits was evaluated. The pharmacokinetics and the extent of systemic bioavailability of mebeverine HCl after oral and rectal administration have not been compared in man or in animals.

In the present study, conventional rectal suppositories of mebeverine HCl were prepared in order to avoid first-pass metabolism in the liver. The influence of different surfactants on the drug release from the prepared suppositories was investigated. The best formulations were subjected to in vivo studies in albino rabbits. Plasma levels and different pharmacokinetic parameters after rectal administration of suppositories were determined and compared with those after intravenous (IV) and oral administrations.

Experimental:

Materials:

Mebeverine HCl powder and Duspatalin® commercial tablet (135 mg) were obtained from scientific office of Duphar B.V.(Weesp, Holland), Witepsol H15 (Novel Dynamite, Witten Werke, Germany), Polysorbate 20, Polysorbate 80 and Triton X-100 (B.P. grade, Atlas Chemical Industries, Wilmington, DE, USA), Brij 35, Sodium lauryl sulfate, L-Lysine hydrochloride and Urea (BDH Ltd., Poole, England), Ibuprofen powder, internal standard, (Boots Company Ltd, Liverpool, England), Acetonitrile HPLC grade (Fischer Scientific International Company, Leicestershire, England), Acetic acid (Koch-Light Laboratories Ltd., Clonbrook Bucks, England), Chloroform HPLC grade (BDH Ltd., Poole, England). All other chemicals were of analytical grade and used as received.

Equipments:

Dissolution Apparatus (Erweka, Type DT-6, Frankfurt, Germany), Centrifuge (Labofuge 200, Heraeus Sepatech GmbH, Germany), Ultrasonic bath XB6 (Grant Instruments Ltd., Cambridge, England), Vortex (Whirlimixer, Fisons Scientific Equipment, Leicestershire, England), Rotary evaporator (Model RE100, Bibby Sterilin Ltd., Stone Staffordshire, England), and A High Performance Liquid Chromatograph (HPLC) system (JASCO Corporation, Tokyo, Japan) which consists of:

- An analytical pump model PU-980,
- A rheodyne injector model IH-980-01/7725I with 20 μl loop,
- C_{18} μ-Bondapak column (Waters Assoc., 30 cm x 3.9 mm I.D., particle size 10 μm) operated with precolumn,
- A fluorescence detector model FP-920, and
- A chromatographic PC based data station.

Methods:

Preparation of Mebeverine HCl Suppositories:

Mebeverine HCl suppositories (200 mg / 1g suppository), either alone or containing different concentrations of selected enhancers (surfactants, amino acids, and urea), were prepared adopting the melting method [16]. Drug or enhancer displacement values in base under test were first determined [16] then the amount of the base required was calculated. The prepared suppositories were kept at 4°C.

Dissolution of Mebeverine HCl Suppositories and commercial tablets (Duspatalin®-135 mg):

Drug release form different suppository formulations was performed using the rotating basket dissolution apparatus. The dissolution medium was 400 ml of phosphate buffer (pH 6.8), kept at 37 ± 0.5°C and stirred at 50 rpm [17]. Samples were collected, filtered, suitably diluted and then assayed for its drug content spectrophotometrically at 263 nm against a blank of a placebo suppository. Six suppositories were used in each run and the results were averaged (±SD).

Drug release from the commercial tablets was performed in 900 ml of 0.1 N HCl at 100 rpm [6]. Samples were treated as for the dissolution test of suppositories and assayed at 264 nm. Six tablets were used and the results were averaged (±SD).

Preparation of intravenous (IV) injection of mebeverine HCl:

Twenty mg of the drug was dissolved in 1 ml buffered normal saline solution (pH 7.2). This solution was sterilized by filtration technique through a 0.22 μm membrane filter under aseptic conditions.

In-vivo study design:

Four male albino rabbits weighing 3.5-4.5 kg were used in this study. The rabbits were fasted (water was allowed ad libitum) for 24 hours prior to initiation of the study. For IV administration, a dose of 20 mg of the drug was injected into the ear vein of the rabbits. For oral administration, a dose of crushed commercial tablet equivalent to 67.5 mg of the drug was administered in a slurry form directly into the stomach by oral intubation. The formulated suppositories were cut longitudinally and rabbits were treated with one half containing 100 mg of the drug. The suppository was inserted into the rectum using a glass injector at about 3 cm depth from the anus. Then the anus was closed with an adhesive tape to prevent leakage. The order of the administration of these dosage forms was designed with Latin square method. At least one week washout period was allowed between the successive dosing.

Blood samples (2 ml) were withdrawn into heparinized vacutainer tubes using an implanted cannula in marginal ear vein prior to and at specified time intervals following drug administration. The blood samples were immediately centrifuged at 3000 rpm for 5 minutes and the plasma was aspirated and extracted immediately for subsequent assay.

Assay method of mebeverine hydrochloride in rabbit plasma:

Plasma samples were analyzed for the drug using a reported HPLC method [18].

Standard curve of mebeverine in rabbit plasma:

Drug-free rabbit plasma (0.5 ml) was spiked with different aliquots of aqueous standard solution of mebeverine HCl in order to obtain mebeverine concentrations in the range between 20 - 400 ng/ml. Then, Ibuprofen solution in methanol was added to each tube as the internal standard. The tubes were treated as reported [18]. The linear regression equation of the calibration curve constructed in the same day was used to calculate the drug concentration in rabbit plasma samples containing unknown concentrations of the drug.

Validation of the assay method:

The assay method utilized was validated for the reproducibility, intra- and interdays accuracy, as well as the percent assay recovery [19].

Pharmacokinetic parameters:

Following IV administration, the plasma level data obtained from four albino rabbits were best fitted to one compartment model using RSTRIP computer program (version 5). The area under the plasma mebeverine HCl concentration – time curve from time 0 to ∞ ($AUC_{0-\infty}$) was calculated from the equation $AUC0_{-\infty} = C_p^o/K_{el}$. All pharmacokinetic prarameters were calculated [20] and expressed as mean ± standard deviation of the means (mean ± SDM) following oral and rectal administrations.

Statistical Analysis:

The difference in the availability of mebeverine HCl from different suppository formulations was evaluated using analysis of variance (ANOVA) test on computer Minitab program (version 10.1). Differences were considered significant at $p \leq 0.05$. Fisher's Least Significant Difference (LSD) was used to reveal any significant difference between two formulations.

Results and discussion:

In-vitro release characteristics of mebeverine HCl from tablets and formulated suppositories:

Kinetic analysis [21] of the release data of mebeverine HCl from both the commercial tablets and formulated Witepsol H15 suppositories (Table 1) revealed that the release of mebeverine HCl from commercial tablets followed zero-order.

Table 1: Kinetic Analysis of the *In-Vitro* Release Data of Mebeverine HCl From the Commercial Duspatalin®Tablets and Formulations of Witepsol H15 Suppositories Containing Different Types And Concentrations of Surfactants.

Formula	Model	Correlation coefficient	Slope	Best-Fitted Release Order	K ± SD*	$t_{50\%}$ ** ± SD
(Duspatalin® Tablets 135 mg)	Zero First Higuchi	0.997 0.947 0.924	1.443 -0.013 10.995	Zero	1.443 [a] ± 0.12	34.65 ± 3.20
Witepsol H15 Suppositories (control)	Zero First Higuchi	0.974 0.988 0.974	1.917 -0.024 14.548	First	0.055[b] ± 0.003	12.6 ± 0.65
Wit. H15 + 0.5%Polysorbate 20 HLB =16.7	Zero First Higuchi	0.947 0.997 0.983	1.633 -0.025 13.792	First	0.057 [b] ± 0.002	12.16 ± 0.63
Wit. H15 + 1% Polysorbate 20	Zero First Higuchi	0.942 0.994 0.987	1.628 -0.026 13.876	First	0.060 [b] ± 0.003	11.55 ± 0.38
Wit. H15 + 2% Polysorbate 20	Zero First Higuchi	0.918 0.990 0.986	1.567 -0.029 13.675	First	0.067 [b] ± 0.003	10.34 ± 0.25
Wit. H15 + 0.5%Polysorbate 80 HLB =15.0	Zero First Higuchi	0.942 0.984 0.976	1.595 -0.025 13.443	First	0.058 [b] ± 0.002	11.95 ± 0.80
Wit. H15 + 1% Polysorbate 80	Zero First Higuchi	0.952 0.994 0.987	1.613 -0.026 13.597	First	0.060 [b] ± 0.003	11.55 ± 0.70
Wit. H15 + 2% Polysorbate 80	Zero First Higuchi	0.924 0.990 0.986	1.568 -0.027 13.616	First	0.062 [b] ± 0.002	11.18 ± 0.45
Wit. H15 + 0.5% Brij 35 HLB =16.9	Zero First Higuchi	0.933 0.993 0.980	1.694 -0.031 14.461	First	0.071 [b] ± 0.004	9.76 ± 0.55
Wit. H15 + 1% Brij 35	Zero First Higuchi	0.970 0.991 0.989	2.361 -0.032 16.047	First	0.074 [b] ± 0.003	9.36 ± 0.51
Wit. H15 + 2% Brij 35	Zero First Higuchi	0.946 0.992 0.990	2.327 -0.036 16.236	First	0.083 [b] ± 0.004	8.35 ± 0.45
Wit. H15 + 0.5% Triton X-100 HLB =19.4	Zero First Higuchi	0.938 0.999 0.975	1.667 -0.024 14.094	First	0.056 [b] ± 0.002	12.38 ± 0.73
Wit. H15 + 1% Triton X-100	Zero First Higuchi	0.938 0.996 0.980	1.663 -0.026 14.137	First	0.060 [b] ± 0.003	11.55 ± 0.53

Wit. H15 +	Zero	0.918	1.680		0.069 [b]	10.04
2% Triton X-100	First	0.996	-0.030	First	±	±
	Higuchi	0.974	14.490		0.004	0.45
Wit. H15 +0.5%	Zero	0.952	1.668		0.056 [b]	12.38
Sod.lauryl sulfate	First	0.992	-0.024	First	±	±
HLB =40	Higuchi	0.982	14.000		0.004	0.78
Wit. H15 +1%	Zero	0.944	1.649		0.058 [b]	11.95
Sod.lauryl sulfate	First	0.993	-0.025	First	±	±
	Higuchi	0.983	13.970		0.002	0.53
Wit. H15 +2%	Zero	0.938	1.653		0.062 [b]	11.18
Sod.lauryl sulfate	First	0.993	-0.027	First	±	±
	Higuchi	0.983	14.090		0.003	0.45

* **SD :** Standard deviation. ****($t_{50\%}$):** Time (min) at which 50% of the drug is released. **[a]:** Zero-order release rate constant ($mg.ml^{-1} . min^{-1}$).

[b] : First-order release rate constant (min^{-1}).

kinetics (r = 0.997), while the release of the drug from the formulated Witepsol H15 suppositories followed first order kinetics (r = 0.988).

The release rate of mebeverine HCl from duspatalin® tablets is significantly ($p \leq 0.05$) lower than that from the formulated suppositories (Table 1), as indicated by their value of the time required for 50% of the drug to be released ($t_{50\%}$). Higher release rate of the drug from Witepsol H15 suppositories could be due to the presence of emulsifying agent (glyceryl monostearate) in this base, which will facilitate the dispersion of the medicament into the surrounding medium. Moreover, mebeverine HCl being a hydrophilic drug has low affinity for the non-polar portion of the fatty base. Drug molecules then were weakly held by the base molecules leading to rapid release of the drug [11].

Effect of the Addition of Different Enhancers:

Surfactants:

The release rate of the drug from all suppository formulations containing surfactants was increased with increasing the concentration of surfactants (Figure 1). This enhancement was observed more clearly during the first 10 minutes of the release time period. However, the enhancing effects of different surfactants were comparable after 30 minutes at all the tested concentrations.

Suppositories containing Brij 35 showed faster release rates of the drug compared to suppositories containing polysorbate 20 or polysorbate 80 (Table 1) . This could be attributed to the chemical composition of the surfactant and the type

of linkage present [22]. In this respect, the ether type surfactant (Brij 35) is better than the ether-ester type surfactants (polysorbates). Also, the nature of the fatty alcohol or fatty acid chain that is present in the surfactant molecule affects drug release [22]. Thus, lauryl alcohol (Brij 35) is better than monolaurate (polysorbate 20) and mono-oleate (polysorbate 80). This effect had been similarly observed for oxyphenbutazone release from Witepsol H15 suppositories [22]. However, Brij 35 had significantly retarded the release of tiaprofenic acid from suppositories [23].

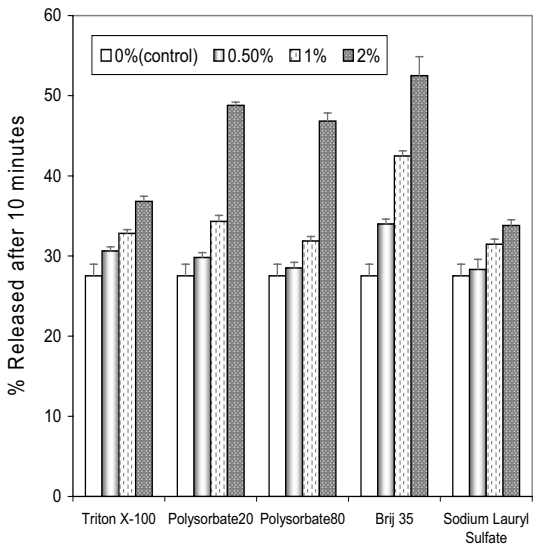

Fig. 1: In-vitro release of mebeverine HCl (after 10 minutes) from Witepsol H 15 suppositories containing different concentrations of surfactants in phosphate buffer (pH 6.8) at 37 ± 0.5 ^{o}C.

The enhancement of the release rate produced by polysorbate 20 was more than that produced by polysorbate 80. This could be explained on the basis of the structure and HLB values, as well as the size and number of micellar aggregates of the surfactant which increase when the length of its lipophilic chain becomes longer [24]. Polysorbate 20 and 80 contain the same hydrophilic chain (20 mol of ethylene

oxide per mol of sorbitol) and the difference between their enhancing activities on the release of mebeverine HCl was due to their lipophilic chain. Polysorbate 80 is an oleic ester (C_{18}), whereas polysorbate 20 is a lauric ester (C_{12}) [24]. Moreover, polysorbate 20 (HLB = 16.7) could enhance the wetting of the base by reducing the interfacial tension between the base and the surrounding fluid more than polysorbate 80 (HLB = 15.0), and therefore helps the flow out of the drug molecules from the interface to the medium [23]. This result is in agreement with that obtained for meclozine HCl release from Witepsol H15 suppositories [25].

Triton X-100 (Octoxynol 9) improved the dissolution rate of mebeverine HCl (Table 1). This could be due to the higher HLB value (19.4) of Triton X-100 which could increase the hydrophilicity of the base and facilitate dispersion of the drug within the surrounding fluids [24]. Similar effect was observed on dissolution of carbamazepine [26].

The addition of sodium lauryl sulfate (ionic surfactant) slightly enhanced the release rate of the drug from suppositories compared to other tested surfactants. Slight effect of sodium lauryl sulfate on the release rate was also observed with indomethacin suppositories [27]. Therefore, it appears that the enhancing properties of the non-ionic surfactants are greater than that produced by the ionic type (Table 1).

A significant difference ($p \leq 0.05$) between different types and/or concentrations of the tested surfactants was revealed by the two-way ANOVA.

Amino Acid (L-Lysine HCl):

The release rate of mebeverine HCl from suppositories was increased by the addition of L-lysine HCl (Figure 2, Table 2). This may be due to reduction of the melting range and disintegration time of Witepsol H15-based suppositories [28] which could reflect better spreading of the suppository base and hence improve the drug release. However, lower release rate constant produced upon the addition of 3% w/w L-lysine HCl (Table 2) compared to 0.75% and 1.5% w/w concentrations, could be attributed to the possible formation of a less soluble mebeverine-lysinate complex [28].

Osmotic Modifier (Urea):

Significant increase ($p \leq 0.05$) in the release rate of mebeverine HCl from suppositories observed by addition of urea (Figure 3, Table 2) may be attributed to the pore – forming ability of urea [29]. Urea was reported to increase the number of "submicron voids", resulting in a more porous, permeable structure from which the drug was released [29]. Also, since urea is a highly soluble substance, thus the

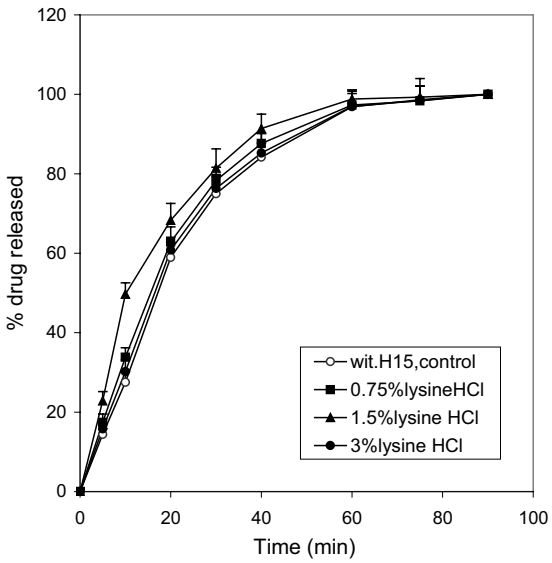

Fig. 2: In-vitro release of mebeverine HCl from Witepsol H15 suppositories containing different concentrations of L-lysine HCl in phosphate buffer (pH 6.8) at 37 ± 0.5 ^{o}C.

Table 2: Kinetic Analysis of the *In-Vitro* Release Data of Mebeverine HCl From Witepsol H15 Suppositories Containing Different Concentrations of L-Lysine HCl and Urea.

Formula	Model	Correlation coefficient	Slope	Best-Fitted Release Order	K† ± SD*	$t_{50\%}$ ** ± SD
Witepsol H15 Suppositories (control)	Zero First Higuchi	0.974 0.988 0.974	1.917 -0.024 14.548	First	0.055 ± 0.003	12.6 ± 0.65
Wit. H15 + 0.75% L-Lysine HCl	Zero First Higuchi	0.938 0.995 0.984	1.638 -0.026 13.973	First	0.060 ± 0.004	11.55 ± 0.58
Wit. H15 + 1.5% L-Lysine HCl	Zero First Higuchi	0.910 0.989 0.984	2.327 -0.031 13.766	First	0.071 ± 0.003	9.76 ± 0.39
Wit. H15 + 3% L-Lysine HCl	Zero First Higuchi	0.946 0.992 0.983	1.646 -0.025 13.914	First	0.058 ± 0.003	11.95 ± 0.60
Wit. H15 + 1% Urea	Zero First Higuchi	0.965 0.985 0.983	2.448 -0.037 16.632	First	0.085 ± 0.003	8.15 ± 0.45
Wit. H15 + 4% Urea	Zero First Higuchi	0.935 0.993 0.989	2.362 -0.045 16.672	First	0.104 ± 0.006	6.66 ± 0.28
Wit. H15 + 10% Urea	Zero First Higuchi	0.907 0.993 0.986	2.283 -0.048 16.542	First	0.111 ± 0.005	6.24 ± 0.33

† **:** First-order release rate constant (min^{-1}). * **SD :** Standard deviation. **$(t_{50\%})$: Time (min) at which 50% of the drug is released.

internal pressure produced by the entry of water could force the drug solution out of the suppository (osmotic effect) [30].

The enhancing effect observed with the addition of 2% urea, besides being compatible with body fluids, warrants *in-vivo* evaluation of this formula. Also, suppositories containing 2% Brij 35 were superior to other formulations containing surfactants or amino acid. Therefore, this formula was also subjected to *in-vivo* evaluation.

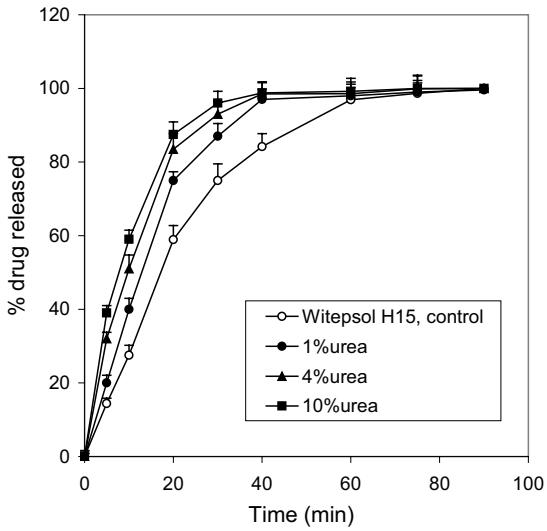

Fig. 3: In-vitro release of mebeverine HCl from Witepsol H15 suppositories containing different concentrations of urea in phosphate buffer (pH 6.8) at 37 ± 0.5 ^{o}C.

In-vivo Evaluation of Different Mebeverine Hydrochloride Preparations:

The assay method used for determination of mebeverine in plasma showed good accuracy with coefficient of variation ranging from 2.51 to 14.5%. The assay recovery data generated over the examined range of mebeverine in plasma were consistent and the coefficients of variation were within 5% on both lower and upper ends of the assay.

The standard calibration curve of mebeverine HCl in rabbit plasma showed a good linearity over the concentration range (20-400 ng/ml).

The decline in plasma concentration following IV administration (Figure 4) was best fitted to a one compartment model using RSTRIP computer program (version 5). The mean pharmacokinetic parameters following IV administration are presented in Table 3.

The rate and extent of absorption of the drug from suppositories were higher than that from the oral slurry (Figure 4). Higher values of C_{max} and shorter T_{max} (Table 3) were observed after rectal administration of control suppositories compared to the oral route. A significant difference ($p \leq 0.05$) between the absolute bioavailabilities of duspatalin® tablet (27.09 ± 3.8%) and control suppositories (46.66 ± 1.72%) was detected. Improved bioavailability following rectal administration of suppositories, compared to oral administrations, was similarly observed with trimethoprim [31] and 6-mercaptopurine [32] suppositories.

The MRT after oral administration (Table 3) was significantly longer ($p \leq 0.05$) than that after rectal administration. The larger values of T_{max} and MRT following oral administration may be due to the delay in gastric emptying of the drug which will slow the rate of drug absorption and thereby delay the onset of the therapeutic effect [33].

Incorporation of 2 % Brij 35 or 10% urea into suppositories resulted in an increase of the C_{max} values and a reduction in T_{max} values (Figure 4, Table 3) compared to the control suppositories.

The enhancing effect of Brij 35 could be attributed to the ability of this non-ionic surfactant to lower the surface tension between the base and the surrounding rectal fluids, thus improving the wetting and contact with the epithelium, as well as distribution of the drug [34]. Also, Brij 35, by its lipid - dissolving action on the rectal membrane [34, 35] may be capable of modifying the properties of biological membrane by solubilizing the membrane components and causing an increase of protein release from the membrane. Moreover, Brij 35 would probably interact with the lipid portions of the membrane thus increase the permeability of rectal membrane [36]. These effects were proposed for the improved bioavailability of cefoxitin [35] from Witepsol H15 suppositories containing Brij 35.

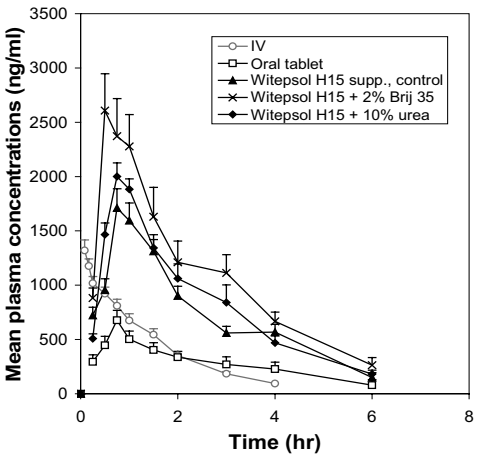

Fig. 4: mean plasma levels of mebeverine HCl in rabbits following intravenous,oral administration of crushed tablets and rectal administration of different suppositories.

The increase in the drug plasma concentration upon the addition of 10% urea (Figure 4, Table 3) to Witepsol H15 suppositories may be due to the effect of urea as a penetration enhancer [37, 38], a keratolytic agent [38] as well as a protein denaturant [39]. Similar results were shown for the enhancement of percutaneous absorption of ketoprofen [38]. The formation of large and extensive hydrophilic diffusion channels within the skin has been also proposed as a possible mechanism [38]. Moreover, hypertonic urea solutions were found to cause a transient opening of the endothelial junctions of the blood brain barrier resulting in an increase of permeability of the barrier [40].

Therefore, the increased systemic availability of mebeverine HCl after rectal administration could be due to partial avoidance of hepatic first-pass metabolism [41]. The fraction of the drug avoided first-pass metabolism after rectal administration (f_{nh}) can be calculated form the equation [42]:

$$f_{nh} = \frac{AUC_{rectal}/Dose_{rectal} - AUC_{oral}/Dose_{oral}}{AUC_{i.v.}/Dose_{i.v.} - AUC_{oral}/Dose_{oral}}$$

The values of f_{nh} for the control Witepsol H15, and suppositories containing 2 % Brij 35 or 10% urea were found to be 26.30 ± 6.64%, 59.72 ± 15.83% and 34.45 ± 6.89%, respectively.

In conclusion, the results of this study have implications for the development of suppositories as a rectal dosage form of mebeverine HCl that is not commercially available. The absolute bioavailability of mebeverine HCl from the control suppositories and those containing 2% Brij 35 and 10% urea were 46.66 ± 1.72 %, 70.50 ± 10.51% and 52.70 ± 4.87%, respectively, and 27.09 ± 3.80% for the drug in film coated tablets in comparison with the I.V. injection.

Table 3: Mean (± SEM) Pharmacokinetic Parameters of Mebeverine HCl in Rabbits Following IV Injection, Oral Administration of Film-Coated Tablets and Control Rectal Suppositories and Those Containing Different Enhancers.

Parameter	IV Injection	Duspatalin® Film-Coated Tablets	Suppositories		
			Witepsol H15 (control)	Wit. H15 + 2% Brij 35	Wit. H15 + 10% Urea
Dose (mg)	20	67.5	100	100	100
C_p^o(ng.ml^{-1})	1312.99 ± 87.82	------	------	------	------
C_{max}(ng.ml^{-1})	------	714.09 ± 59.46	1770.26 ± 165.46	2766.11 ± 339.50	2201.03 ± 215.47
T_{max} (h)	------	0.88 ± 0.14	0.75 ± 0.20	0.56 ± 0.13	0.69 ± 0.24
AUC_{0-t}(ng.h.ml^{-1})	1858.88 ± 188.71	1690.57 ± 196.63	4340.86 ± 153.65	6419.09 ± 973.83	4893.40 ± 453.50
$AUC_{0-\infty}$(ng.h.ml^{-1})	2007.5 ± 234.48	1922.69 ± 298.81	4683.99 ± 172.46	7076.37 ± 1054.85	5289.88 ± 488.45
$AUMC_{0-t}$(ng.h^2.ml^{-1})	2275.88 ± 315.66	4050.42 ± 672.99	9968.32 ± 1306.71	14451.86 ± 1593.27	11071.60± 1911.54
$AUMC_{0-\infty}$(ng.h^2.ml^{-1})	3144.78 ± 653.68	6133.13 ±1544.96	12819.97 ±1681.56	20034.66 ± 2002.87	14318.04 ± 2119.37
MRT (h)	1.55 ± 0.15	3.16 ± 0.30	2.73 ± 0.30	2.85 ± 0.25	2.70 ± 0.29
F_{abs}	------	27.09 ± 3.80%	46.66 ± 1.72%	70.50 ± 10.51%	52.70 ± 4.87%

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