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SUSTAINED RELEASE MATRIX OF MEBEVERINE HYDROCHLORIDE USING POLYACRYLATE RESIN "EUDRAGIT RETARD" KINETIC OF DRUG RELEASE AND EVALUATION OF A KINETIC MODEL

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ABSTRACT

In this study Eudragit RS PM and RL PM were evaluated as carriers for the preparation of prolonged release solid dispersions of mebeverine hydrochloride by solvent and melting methods. The prepared tablets were examined for dissolution at pH 1.2 and 7.4, Eudragit RS PM and RL PM were found satisfactory as potential slow release carriers. The solid dispersion prepared by the solvent method showed a slow release pattern. Drug release appeared to fit both, first order and Higuchi matrix model kinetics. However, on application of the differential rate treatments, the evidence supported the Higuchi matrix model. Effect of temperatures on dissolution rate was studied for thermodynamic consideration.
The drug release was pH - independent until pH 7.4. As the pH increased, the release was significantly reduced due to solubility problem.

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INTRODUCTION

Mebeverine hydrochloride is a musculotropic spasmolytic drug with a strong and selective action on the smooth muscle of the gastrointestinal tract, particularly of the colon. It is given in a dose of 135 mg three times daily.

In the treatment of smooth muscle spasm, sustained blood levels of the drug would be beneficial. In view of the physicochemical and pharmacokinetics properties of mebeverine hydrochloride(1), it seems that it is a good candidate for incorporation in a sustained release formula.

In the present study, sustained release solid dispersions of mebeverine hydrochloride using Eudragit RL PM, RS PM have been prepared and assessed for the purpose of defining conditions for the design of sustained release tablet, and establishing a model of drug kinetic release with thermodynamic information.

Eudragit retard is one of the most widely used polymers for the preparation of sustained release formulations. It is either incorporated as additive(2,3), or used for the preparation and/or coating of microcapsules(4,5). Eudragit is inert to the digestive tract, pH independent, but capable of swelling and release its active ingredients(4). These properties encouraged us to use it as a carrier for the preparation of sustained release solid dispersions of the drug.

The concept of solid dispersions as an approach to increase the dissolution rate of slightly soluble drugs has been the subject of many investigations(5-9). However, their use in providing sustained release drugs have only been tentatively examined(10,11).

EXPERIMENTAL

MATERIALS AND METHODS

MATERIALS

Mebeverine HCl powder (Duphar B.V., Weesp, Holland), Eudragit RL PM and RS PM (Rhom Pharma, GMBH Weiterstadt), chloroform (BDH), 0.1M HCl and Sorenson's buffer were of analytical grades. Infra-red spectrophotometer (783, Perkin Elmer, USA), differential scanning calorimeter (DSC-4, Perkin Elmer, USA)

METHODS

Preparation of solid dispersions: Solid dispersions of various types of Eudragit and drug were prepared by two methods:

1- Solvent method: The calculated amount of the different types of Eudragit and drug were dissolved separately in chloroform with constant stirring and then mixed together. Solvent was allowed to evaporate and the thickened mass was then transfered to a vacuum desiccator for drying. The residue was comminuted and the resulted granules passed through US standard sieves (250 -220 μm). The final product was transfered to a desiccator containing silica gel.

2- Melting method: The required quantity of the different types of Eudragit and drug were mixed in a porcelain dish and heated till fusion and then kept in a vacuum desiccator overnight. The drug mass was then treated as above.

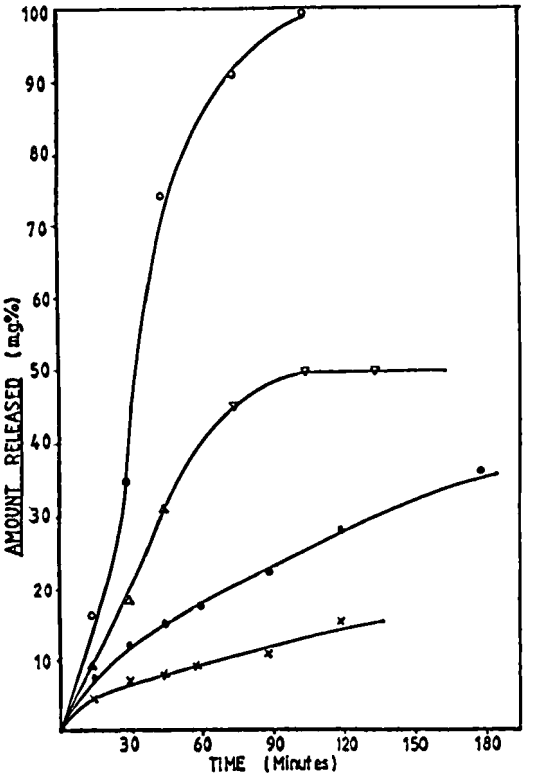

Fig. 1. Release profile of conventional tablet and Eudragit/Mebeverine HCl solid dispersion tablets at two different pHs, 37°C.

o —— o conventional tablet at pH 1.2
Δ —— Δ conventional tablet at pH 7.4
● —— ● Eudragit RS PM(solvent method) at pH 1.1
× —— × Eudragit RS PM(melting method) at pH 7.4

Preparation of tablets: Tablets were prepared using a single-punch tablet press(Erweka-Apparatus GMBH,FRG).A charge of 300 mg of prepared powder contained 100 mg of the drug was placed in a 9.0 mm die,compression was applied,held for 1 min and gradually released over 30 sec.

Dissolution study: In this study,dissolution experiments were performed in 600 ml solution of different pHs(0.1M HCL,Sorenson's buffer pH 7.4,6.9 and 5.0) using the U.S.P. rotating basket apparatus at 100 rpm.Samples were taken at predetermined time intervals, properly diluted and assayed spectrophotometrically for its drug cotent at 263 nm using a Pye Unicam PU 8800 spectrophotometer(Cambridge,U.K.).The experiment was carried in triplicate and the results were averaged.

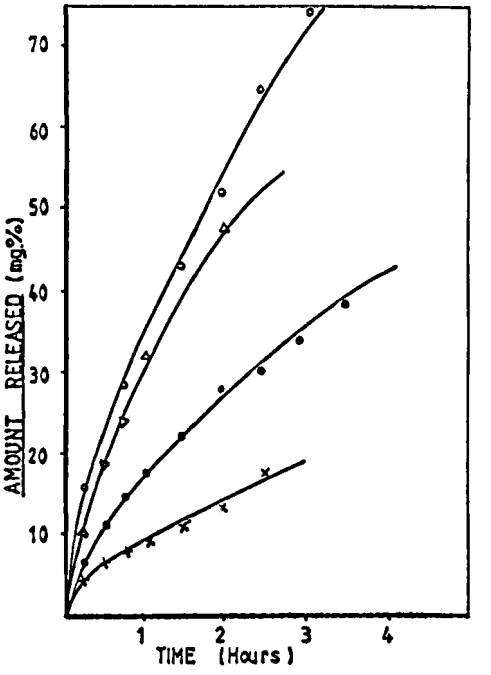

Fig. 2. Release profile of Eudragit/Mebeverine HCl solid dispersion tablet (Solvent method) at pH 1.2 and 7.4. ; effect of type of Eudragit .

o —o Eudragit RL PM/Mebeverine HCl at pH 1.2
Δ —Δ Eudragit RL PM/Mebeverine HCl at pH 7.4
● —● Eudragit RS PM/Mebeverine HCl at pH 1.2
× —× Eudragit RS PM/Mebeverine HCl at pH 7.4

RESULTS AND DISCUSSION

Thin layer chromatography and IR spectra revealed that neither the melting of mebeverine HCl alone, nor its melting with Eudragit modified the product.

It is evident from Fig 1, that Eudragit RS PM and RL PM are satisfactory as potential slow release carriers, moreover, a slower release rate was attained with RS PM(Fig 2), being less hydrophilic than RL PM, due to its lower content in quaternary ammonium functions.

Drug release kinetics: The release of drug from solid dispersion formulated as tablets can be treated using Higuchi equations(12,13)for diffusion controlled transport in a polymer matrix. In a planar homogeneous system, the following relationship helds:

$$Q = [D (2A - Cs) Cs t]^{\frac{1}{2}} \qquad \text{"I"}$$

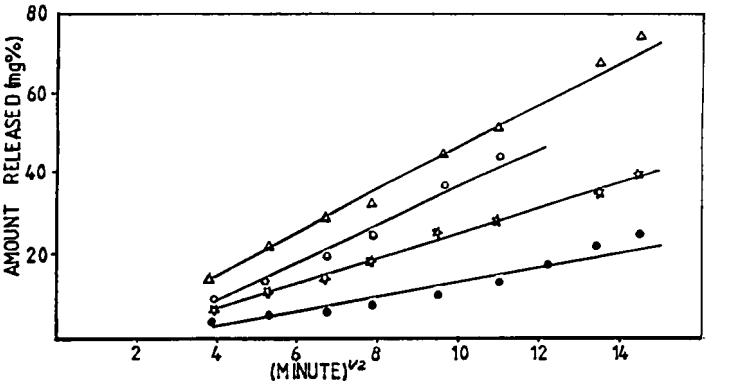

Fig. 3. The release of Mebeverine HCl from Eudragit solid dispersion tablets (solvent method) treated according to the matrix model .

△ — △ Eudragit RL PM at pH 1.2
○ — ○ Eudragit RL PM at pH 7.4
☆ — ☆ Eudragit RS PM at pH 1.2
● — ● Eudragit RS PM at pH 7.4

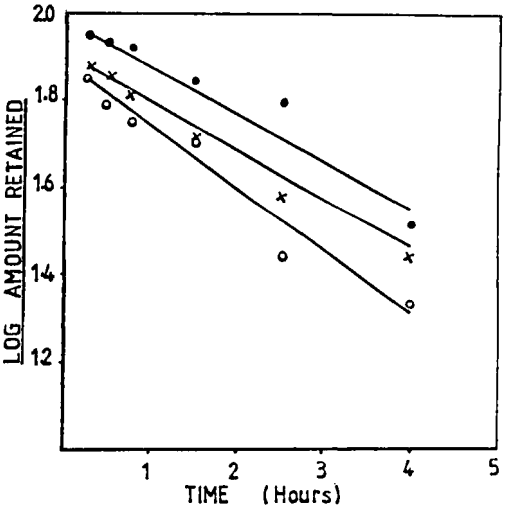

Fig. 4 . The release of Mebeverine HCl from the solid dispersion tablets (melting method) at pH 1.2 and 37°C treated according to the first order model

● —— ● Eudragit RS PM
✶ —— ✶ Eudragit RS/RL PM
○ —— ○ Eudragit RL PM

TABLE 1

Comparison between linearization of Release Rate Data by first order and matrix diffusion treatment for (33.33 % w/w) drug at different pHs and different types of Eudragit at 37°C

Types of Eudragit	pH	First order correlation	Diffusion control correlation	$K(t^{\frac{1}{2}})$
RS PM	1.2	0.974	0.996	3.4
RL PM	1.2	0.972	0.989	4.3
RS PM	7.4	0.890	0.976	0.9
RS PM	6.5	0.972	0.996	3.4
RS PM	5.0	0.955	0.997	3.2

where Q is the amount of drug released per unit area exposed after time t; D,A and Cs are the diffusity,initial concentration,and saturation solubility of the drug in the matrix,respectively. The equation could be reduced to:

$$Q = R\ t^{\frac{1}{2}} \qquad \text{"II"}$$

Treatment of the experimental data obtained in this study on the basis of the diffusion controlled model indicated that the drug concentration increased linearly with the square root of time in all systems,and under all conditions studied (Fig 3).The data also appeared to fit a first order equation (Fig 4),used to describe a release from certain polymer or microcapsules (4).

$$\log C = \log Co - Kt / 2.303 \qquad \text{"III"}$$

Where C is the drug content at time t,Co is the initial drug concentration.

Some typical evaluations of the best statistical lines obtained using the two equations,are listed in Table 1.The diffusion equation gave consistant higher values for the correlation coefficient (0.997 - 0.989),than the first order equation(0.974 - 0.890).

Further evidence bearing upon the relative validity of these two models was obtained by utilizing the differential forms of their rate equations(14,15).For diffusion control,the rate dQ/dt is proportional to the reciprocal 1/Q,where Q is the total drug release at a given time

$$dQ / dt = K^2 / 2Q \qquad \text{"IV"}$$

The rate predicted by the first order kinetics is given by

$$dQ / dt = K_1 Co - K_1 Q \qquad \text{"V"}$$

In the later case,the rate is proportional rather than inver-

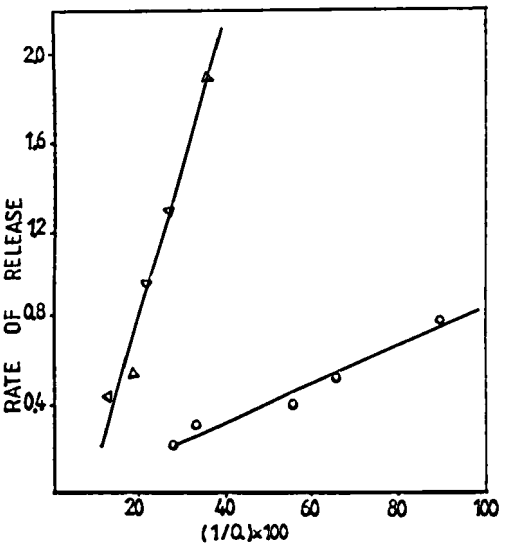

Fig. 5. Release rate (dQ /dt) plotted against the reciprocal of the amount released percent of (1/Q) for release of solid dispersion of Mebeverine HCl/ Eudragit at 37°C and pH 1.2
▽——△ Eudragit RL PM
○——○ Eudragit RS PM

sily proportional to Q .The release rates have to be determined from Q - time curves by measurment on a point to point basis.

The two mechanisms are clearly differentiated by the plots since the rate is linearly related only to 1 / Q (equation IV),indicating that the process follows a matrix release mechanism in these systems (Fig 5 and Table 2).

Controlled drug release thermodynamics:The effect of temperature on the release rate of mebeverine HCl is shown in Fig 6. The temperature dependency of $Q / t^{\frac{1}{2}}$ is defined by the following relationship(16):

$$\log Q / t^{\frac{1}{2}} = \text{constant} - (Ed.m + \Delta H) / 4.606\ R\ .1 / T \quad \text{"VI"}$$

Where Ed.m is the activation energy of drug molecules required to diffuse in polymer matrix,ΔH is the energy required for the solvation of the molecules in the polymer matrix.
As expected from equation VI, a linear relationship of log $Q / t^{\frac{1}{2}}$ versus T^{-1} was followed very well for mebeverine HCl in RL PM and RS PM matrices(Fig 6).As it is evident in Table 3, the calculated(Ed.m + ΔH) value for RS PM is higher than that for the RL PM matrix(6.502 and 5.518 K cal,respectively).This could possibly be attributed to the hydrophilicity and permeability of the RL PM polymer,so less energy was needed for drug diffusion,and this is a further cause for the high release rate of the RL PM over the RS PM polymer.

TABLE 2

Comparison of parameters of linearity obtained from plotting the Release Rate versus the reciprocal amount (1/Q) and the amount of drug released.

Types of Eudragit	Temperature °C	pH	Correlation coefficient	
			1/Q	Q
RS PM	37	1.2	0.979	0.880
RL PM	37	1.2	0.966	0.830
RS PM	37	7.4	0.976	0.935
RL PM	25	1.2	0.980	0.906

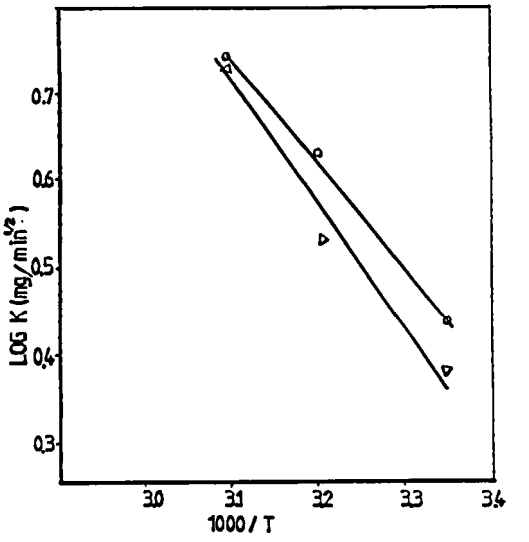

Fig. 6. Arrhenius plot for the release of Mebeverine HCl/ Eudragit solid dispersion (melting method) at pH 1.2
o —— o Eudragit RL PM
Δ —— Δ Eudragit RS PM

TABLE 3

Energy required for the controlled release of mebeverine HCl from Eudragit.

Types of Eudragit	Slope	Correlation coefficient	Em+ΔH K cal	Intercept
RS PM	-1421	0.988	6.502	5.12
RL PM	-1206	0.992	5.518	4.49

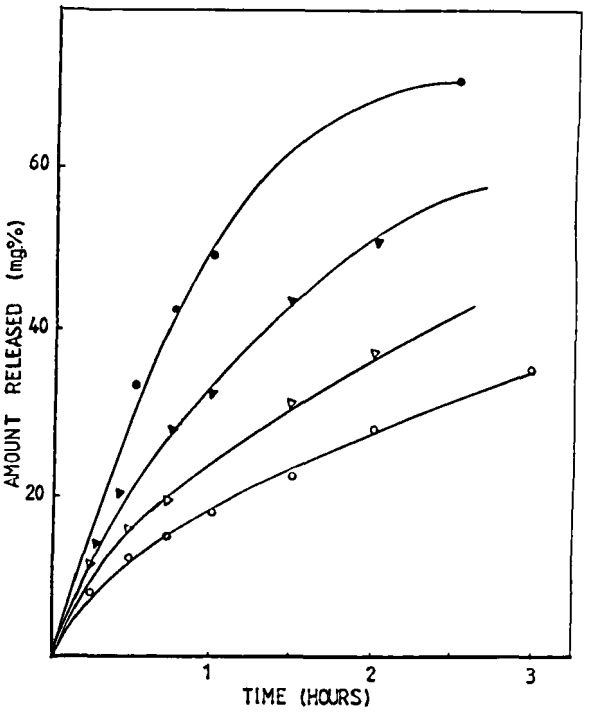

Fig. 7 . Release profile of Eudragit/Mebeverine HCl solid dispersion tablet at 37°C and pH 1.2; effect of methods of preparation .

- ●—● Eudragit RL PM melted method
- ▲—▲ Eudragit RL PM solvent method
- △—△ Eudragit RS PM melted method
- o—o Eudragit RS PM solvent method

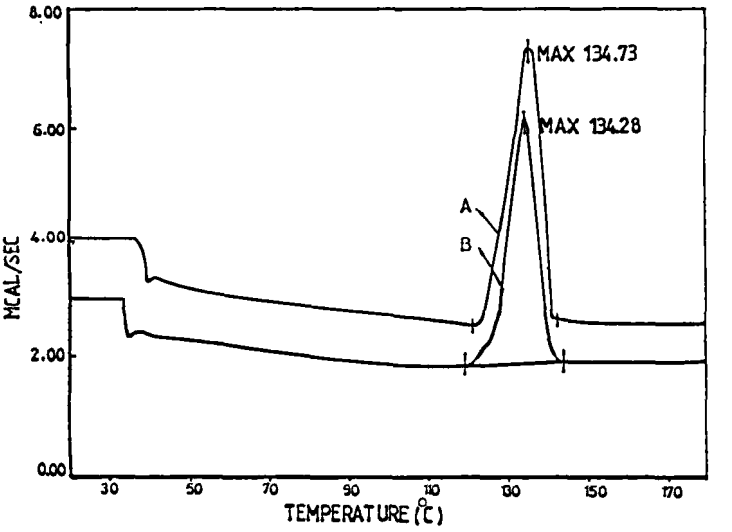

Fig. 8 . DSc diagram for
A - Mebeverine HCl
B - Mebeverine HCl crystallized from chloroform .

The effect of the method of preparation of solid dispersions on the release rate of the drug:Both melting and solvent methods were used for the preparation of mebeverine HCL as solid dispersions in both Eudragit RS PM and RL PM.
It is evident from the results shown in Fig 7,that the tablets prepared by the solvent method showed a slow release rate than that prepared by melting method for both types of Eudragit.

Crystallization of mebeverine HCl from chloroform and characterization of the crystal obtained by the determination of its melting point and by differential scanning calorimeter(DSC), Fig 8, indicated the absence of any polymorphic transformation during solvent preparation.So,the slow rate of drug release could not be attributed to the effect of the solvent on the physical characteristics of the drug.It could be possibly explained on the basis of the effect of the solvent on the Eudragit properties which may decrease its porosity and impede drug diffusion(17).

The effect of pH :The release rate of mebeverine HCl conventional dose tablets and sustained release tablets containing RS PM and RL PM were investigated at different pHs(1.2,5.0, 6.9 and 7.4).It is evident from the results obtained in Fig 1,that the release rate was much reduced at pH 7.4,but it was almost the same at the other pHs studied(1.2, 5.0 and 6.9), Table 1. This could be explained on the fact that the salt form of the drug would predominate in the test buffer as the pKa of the drug is 10.7 The ratio of ionized drug,and hence,

the solubility of the drug in the leaching fluid would be reduced at pH 7.4. So, the solubility and diffusity of the drug in the permeation fluid would determine the release rate.

In conclusion, sustained release forms of mebeverine hydrochloride can be prepared using the melting method or coevaporates with Eudragit RL PM and RS PM. The RL/RS ratio can be optimized to modulate the release profile of the drug. The release rate of the drug from the solid dispersion is not influenced by pH modification up to pH 7.4.

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