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DRUG RELEASE KINETICS FROM MATRIX COMBINING MIXTURE OF HYDROPHILIC AND HYDROPHOBIC POLYMERS ON MEBEVERINE HCL, ON SITE SPECIFIC DRUG RELEASE TO THE COLON

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ABSTRACT

The investigation of the present work is the modification of the release behavior of matrix tablets of Mebeverine Hydrochloride to reduce the dosing frequency and to improve patient compliance. The matrix tablets were prepared by the combination of hydrophilic and hydrophobic polymers, using HPMC (E5V and 1 LAKH and Eudragit L100). The drug polymer interaction was investigated by FTIR and their results directed further course of formulation. The tablets were prepared by wet granulation technique. Prepared formulations were evaluated for various parameters like weight variation, hardness, friability, % drug content and swelling index. Tablets were subjected to *in vitro* drug release studies. The formulations F_4 containing HPMC (E5V), Eudragit L100 showed good release retardation. The kinetics of the dissolution process was determined by analyzing the dissolution data using various kinetic equations, e.g. Zero-order, First-order, Higuchi and Korsmeyer equations**.** All the prepared formulations showed high regression value for Zero-order release kinetics. The combination of hydrophilic and hydrophobic polymers can effectively control the drug release for freely water-soluble drugs in case of controlled release formulations which are the upcoming dosage forms for patient compliance in all aspects. Kinetic treatment to the in vitro release data revealed that the drug release followed zero order non - fickian diffusion, It means the release of drug from tablet dissolution and diffusion both mechanisms are used.

Keywords: Mebeverine hydrochloride, Hydroxyl propyl methyl cellulose, Eudragit, Evaluation parameters, *in vitro* release, Kinetic treatment.

INTRODUCTION

The oral route of administration is the most common and popular route of drug dosing(Leon shargel *et al.,* 2010). When a new drug is discovered, one of the first questions in pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by the oral route (Leaolachman *et al.,* 2009). Conventional drug products like tablets & capsules are formulated to release the active drug immediately to obtain rapid and complete system absorption of the drug. In recent years various modified drugs have been developed to release the active drug at controlled rate. Controlled release dosage forms cover a wide range of prolonged action formulations which provide continues release of their active ingredient at a predetermined rate and a predetermined time (Javedali *et al.,* 2009).

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Functional Gastrointestinal Disorders are collections of symptoms attributable to the GI tract in the absence of mucosal structural or biochemical disease. Two of the most common disorders, chronic constipation and irritable bowel syndrome (IBS), have common etiopathogenetic feature-notably psychosocial disturbances, dismotility, heightened sensitivity. In some patients with IBS, there is an association with post infective state. In constipation; transit disorders and abnormal evacuation represent disturbances of function that are amenable to therapy (Michael Camilleri *et al.,* 2009).

Mebeverine is an antimuscarinic. Mebeverine belongs to a group of compounds called Musculotropic antispasmodics (Wikipedia). These compounds act directly on the gut muscles at the Cellular level to relax them. Mebeverine is also an inhibitor of calcium-depot replenishment. Therefore, Mebeverine has dual mode of action which normalizes the small bowel motility.

Many polymers have been used in the formulation matrix based CR drug delivery system, reports were found on usage of hydrophilic polymers such as HPMC, Sodium carboxy methyl cellulose (Rangarkv *et al.,* 1988) Carbopols (Parojcicj *et al.,* 2004) and poly vinyl alcohol (Kosenmeyerr *et al.,* 1983) for the purpose of CR formulations of different drugs. The hydrophilic polymers selected for the present study cure HPMC E5V and HPMC 1lakh. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due rapid diffusion of the dissolving the drug through hydrophilic gel network

Hence it is essential to include hydrophobic polymers in matrix systems hence in the present work an attempt has been made to formulate the CR release matrix tablets of Mebeverine using hydrophilic matrix material (HPMC E5V,HPMC 1LAKH) in combination with hydrophobic (EUDRAGIT L-100) polymer .

MATERIALS AND METHOD

MATERIALS

Mebeverine Hydrochloride, HPMC, Eudragit were received as gift samples from Zydus pharmaceuticals, Ahmedabad, India. Lactose anhydride, Magnesium stearate, Poly vinyl pyrrolidine from LobaChem (Mumbai, India). All other chemicals and ingredients were used for study are of Analytical grade.

METHOD

PREPARATION OF MEBEVERINE MATRIX TABLETS

Six different tablet formulations were prepared by wet granulation technique as reported. The composition of 150mg Mebeverine of the drug, polymer (HPMC E5V, 1 LAKH) and Eudragit L100 and filler talc was dry mixed thoroughly and sufficient volume of granulating agent (5%w/v ethonolic solution of PVP-K90). Ethanolic solution of PVP was added slowly. After enough cohesiveness was obtained, the mass was sieved through 20 meshes. The granules were dried at 55ºc for 1 hour. These granule mixtures was blended with magnesium stearate (1.6%w/w) as lubricant, the appropriate and then compressed using a 16 station tablet compression machine round, flat-faced punches of 10-mm diameter and die set. All compressed tablets were stored in air tight container at room temperature for the study.

In-Vitro drug release studies

The release of Mebeverine from the CR tablet was studied up to 2 hours in 900ml of 0.1N HCl and 900ml phosphate buffer up to 20 hours as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37˚± 0.5˚C. An aliquot (1ml) was withdrawn at specific time intervals, filtered and diluted to 10ml with the dissolution medium, and drug content was determined by UV- visible spectrophotometer at 264nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume.

Dissolution studies were performed for a period of 20hrs and the value was taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

Pre-formulation Studies (Compatability Studies)

Compatibility studies were performed by using FT-IR spectrophotometer. The IR spectrum of pure Mebeverine drug was compared with IR spectrum of physical mixture of Mebeverine (HPMC E5V, HPMC 1LAKH and EUDRAGIT -L100).

There is no appearance or disappearance of any characteristic peaks. This shows that there is no chemical interaction between the drug and the polymers. The presence of peaks at the expected range confirms that the materials taken for the study are confirmed.

Evaluation of blend characteristics of controlled-release tablets of mebeverine

The blended granules of different formulation were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index, Hauser's ratio and drug content uniformity. The results of these evaluations are as follows:-

Angle of repose

Angle of repose ranged from 19.29^{O} to 28.25^{O}. The results were found to be below 25^{0} and hence the blend was found to have good flow property.

Bulk density and tapped density

Bulk and tapped densities are used for the

measurement of compressibility index. The LBD and TBD ranged from 0.29 to 0.50 and 0.34 to 0.580 respectively.

Compressibility index (carr's index)

Compressibility index ranged from 12% to 16% the blend was found to have free flowing property as the result were found to be below16 %.

Hauser's ratio

The Hauser ratio ranged from 1.13 to 1.2 the result indicate the free flowing properties of the granules.

Drug content uniformity

Drug content was found to be uniform among the all formulations and ranged from 98.41% to 99.12%.

Evaluation of Oral controlled-release tablets of mebeverine

Mebeverine oral controlled release tablets were evaluated for various physical parameters namely Hardness, Weight variation, Friability, Drug content uniformity test etc.

Hardness test

The hardness of all batches ranged from 4 to 6kg/cm^2 .

Friability test

The percentage friability of all batches ranged from0.066 to 0.232 %.

Weight variation

The percentage weight variations for all formulations are present in (Table: 3). All the formulations passed weight variation test as per the pharmacopoeias limits of 7.5%.

Drug content uniformity

Drug content was found to be uniform among the all formulations and ranged from 98.21 to 99.08 %.

Swelling Index

Swelling study was performed for all batches (F_1 to F_6) for 5 hours. The result is shown in the (Table: 3)

***IN VITRO* DRUG RELEASE**

The in-vitro drug release characteristics were studied in 900 ml of 0.1N HCL for first 2 hours and 900 ml of P^H 6.8 for rest of hours, using USP XXIII dissolution apparatus type II (paddle) method. The results of dissolution studies indicates that F_1, F_2, F_3 released 96.21%, 97%, 94.3% of mebeverine at the end of 8, 12, 10 hours. Low viscosity of HPMC E5V of F_1 formulation extended up to 8 hours, with maximum release of 96.21%. By increasing the viscosity of HPMC 1 LAKH of F_2 formulation goes on increases the duration up to 12 hours with maximum release of 97%. However the equal ratio of F_3 formulation formulated with HPMC (E5V, 1LAKH) release the drug upto 10 hours with maximum of 94.3%, due to equal proportion of low viscosity and high viscosity of Hydrophilic polymers, the time duration declines compared to formulation F_2.

In combination of low viscosity and high viscosity, it proves that low viscosity will not prolong the drug release, desirably due to less consistence of gelatinous layer, where the gel formed presents very low levels, so the drug dissolves rapidly, so is thus not prolong the drug release.

In formulation F_4, F_5, F_6 formulated with combination of both HPMC and Eutragit L 100.In formulation F_4 formulated with HPMC (E5V:15%) and Eutragit (L100:15%) extends the duration up to 20 hours with maximum release of 97.21%.

In formulation F_5 formulated with HPMC (1LAKH: 15%) and Eutragit (L100:15%) extends the duration up to 20 hours with maximum release of 92.34%.

In formulation F_6 formulated with HPMC (E5V: 7.5%), HPMC (1LAKH:7.5%) and Eudragit (L100:15%), it extended the duration of 16 hours with maximum release of 95.6%.

Among them formulation F_4 showed better release retardation (97.3%). When a drug is formulated with gel forming hydrocolloids such as HPMC (E5V) it swells in the gastric fluid. On the other hand Eudragit (L100) is anionic co-polymer of methacrylic acid and methyl methacrylate. The ratio of free carboxyl group to ester is approximately 1:1 it has pH dependent solubility (p^H>6) and is readily soluble in neutral to weakly alkaline condition and forms salts with alkaline.

To know the mechanism of drug release from this formulation the data were treated according to First-order release, Higuchi's and Korsmeyer-equation or peppas's model equation along with Zero-order release pattern. The release kinetic data for all the other equation can be seen in Table .The formulation F_1, F_2, F_3, F_4, F_5, F_6 showed higher R^2 values for zero-order plot indicating that the drug release from this formulation was concentration dependent and followed zero-order kinetics. The in-vitro release profile from all the formulation could be best expressed by Higuchi's equation, as the plots showed high linearity R^2 (0.951 to 0.991). To confirm the diffusion mechanism the data were fit into Korsmayer equation with slope (n) value ranging from (0.587 to 0.817). This indicates that the release of drug follows Non-fickan transport. It means the release of drug from tablet dissolution and diffusion both mechanisms are used.

Table 1. Composition of 300mg Mebeverine hydrochloride tablets

S.No	Ingredients (in mg)	F1	F2	F3	F4	F5	F6
1	Mebeverine hydrochloride	150	150	150	150	150	150
2	HPMC E5V	120	-	60	60	-	30
3	HPMC 1LAKH	-	120	60	-	60	30
4	Eudragit L 100	-	-	-	60	60	60
5	Talc	25	25	25	25	25	25
6	Magnesium stearate	5	5	5	5	5	5

Table 2. Data's for evaluation of properties of the blended granules for CR formulations of the Mebeverine Hcl

S.No	Formulation code	Angle of repose	Loose bulk density	Tapped bulk density	Compressibility index	Hauser's ratio	%Drug content
1	F1	23.80	0.41	0.47	12.0	1.14	98.59
2	F2	23.55	0.29	0.34	14.7	1.17	99.12
3	F3	19.29	0.36	0.41	12.1	1.13	98.41
4	F4	21.54	0.50	0.58	13.7	1.16	98.76
5	F5	28.25	0.45	0.54	16.0	1.2	98.59
6	F6	21.32	0.48	0.56	14.2	1.16	98.41

Table 3. Data's for evaluation of tablets for CR formulations of the Mebeverine Hcl

S.No	Formulation code	Hardness test (kg/cm2)	Friability test (%)	Weight variation	%Drug Content	%Swelling index
1	F1	5.05	0.120	295.5	98.54	75
2	F2	4.81	0.066	292.5	99.08	85
3	F3	4.80	0.133	298.0	98.21	80
4	F4	4.85	0.132	297.0	98.72	65
5	F5	4.68	0.116	292.0	98.56	70
6	F6	5.13	0.232	298.0	98.38	60

Table 4. Data's for kinetic analysis of *in vitro* release rates of controlled release tablets of Mebeverine Hcl

F.code	Zero-order plots		First-order plots		Higuchi's plots	Korsmeyer et al's plots	
	Zero order rate constant R_0	Regression Coefficient (R^2)	First order rate constant K	Regression Coefficient (R^2)	Regression coefficient (R^2)	Slope (n)	Regression coefficient (R^2)
F1	9.107	0.996	-0.106	0.890	0.9740	0.819	0.988
F2	7.432	0.950	-0.101	0.874	0.991	0.587	0.993
F3	9.560	0.980	-0.119	0.957	0.984	0.754	0.988
F4	4.621	0.989	-0.061	0.834	0.955	0.664	0.978
F5	4.889	0.971	-0.055	0.950	0.951	0.775	0.968
F6	5.955	0.987	-0.073	0.902	0.9677	0.7341	0.9839

Fig. 1 Drug, HPMC E5 + EUDRAGIT L-100

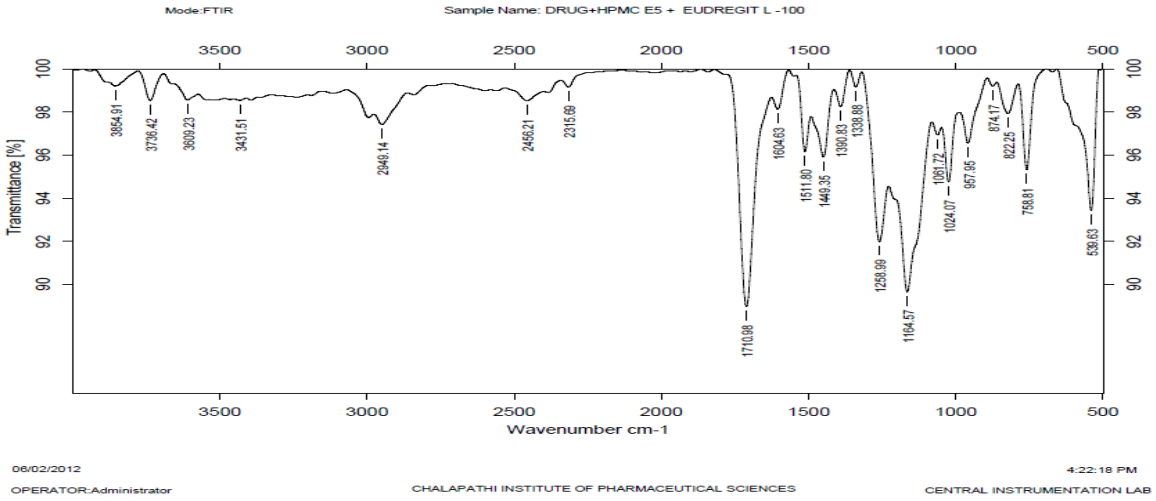
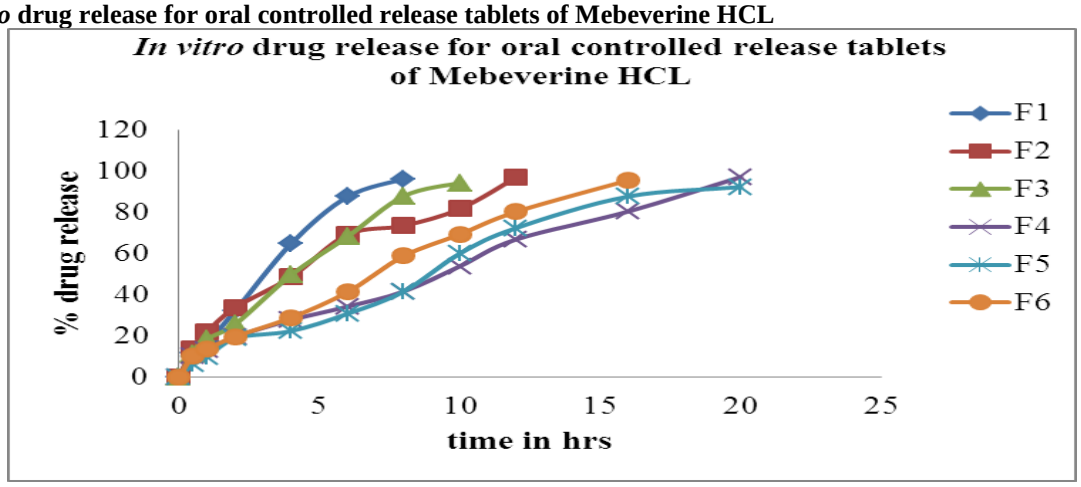


Fig 2. *In vitro* drug release for oral controlled release tablets of Mebeverine HCL



CONCLUSION

The drug release rate was found to be dependent on the release retarding polymer, thus by changing (i.e. hydrophilic or hydrophobic or combination polymer), the required release can be attributed. So this investigation concludes that the matrix tablet containing F_4 formulation formulated with 15% of HPMC (E5M) and 15% of Eudragit (L100) showed that good retardation.

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