Formulation and Evaluation of Mebeverine Hydrochloride Sustained Release Capsules

Manasa.P[1], Suresh Kumar.P[2], Jagannath Patro.V[3], Sunitha.CH[4]
[1,2,3,4]*Department of Pharmaceutics, Browns College of Pharmacy, Khammam, Telangana, India*

Abstract **- The objective of present investigation is to develop and evaluate development and evaluation of sustained release matrix tablets of Mebeverine hydrochloride to achieve sustained drug release with reduced frequency of drug administration, reduced side effects and patient compliance and to prolong the drug release in GIT and consequently into the plasma. Sustained release matrix tablets of Mebeverine hydrochloride were prepared by using polymers like hpmc E5, ethyl cellulose, micro crystalline cellulose, talc, magnesium stearate, and mannitol. Mebeverine is an antispasmodic agent which exerts direct action on the GIT smooth muscle. Rapidly absorbed from the GI tract (oral); peak plasma concentrations within 1-3 hr. Mebeverine hydrochloride sustained release matrix tablets were prepared by direct compression method. The powder blend was subjected for pre-compressional parameters such as bulk density and tapped density, angle of repose, compressibility index and Hausner's ratio. The prepared tablets are evaluated to post-compressional parameters such as hardness, friability, average weight, uniformity of weight and invitro dissolution studies. Drug compatibility with excipients was checked by FTIR studies. The values of precompressional parameters evaluated were within prescribed limits and indicated good free flowing property. The values of post-compressional parameters evaluated were within acceptable limits. The dissolution profiles of all the formulations were evaluated. Amongst all the formulations, the release profile of formula f12 gave optimum results. It was concluded that Mebeverine hydrochloride sustained release matrix tablets; f12 is successful formulation and can be manufactured with reproducible characteristics from batch to batch. The optimized formulation (F12) was compared to the marketed product and hence found to be superior over the marketed product.**

Index Terms **- Sustained release tablets, Matrix tablets, Mebeverine Hydrochloride, Ethyl cellulose, Micro Crystalline Cellulose, Hydroxy propyl methyl cellulose.**

INTRODUCTION

Sustained release tablet allowing a twofold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form. It is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug. It enhances patient compliance and convenience by Reduction in dosing frequency[1]. Product lifetime is increased in sustained release formulations. Particles of drug are coated with matrix or entire product is matrix coated which along with its main function of sustained action, avoid exposure of unstable drug to the environment and render it stable[2]. Mebeverine Hcl is a musculotropic antispasmodic drug without atropic side effect, whose major therapeutic role is in the treatment of irritable bowel syndrome. Mebeverine Hcl directly act on the gut muscles at the cellular level to relax them. It is having a short biological half-life of 2.5hrs, plasma protein binding 75% and rapidly absorbed after oral administration with peak plasma concentration occurring in 1-3hrs. However, Mebeverine Hcl suffers from extensive first pass metabolism in the gut wall and liver[3,4]. High plasma concentration of veratric acid (one of the main inactive metabolites of Mebeverine Hcl) in addition to negligible amounts of the parent drug was observed in plasma 20- 30 minutes after oral administration[5,6]. Hence, Mebeverine Hcl has been selected as a model drug as it fulfills the required pharmacokinetic and physicochemical properties for the controlled delivery. Irritable bowel syndrome (IBS) is a disorder characterized most commonly by cramping, abdominal pain, bloating, constipation and diarrhea. IBS causes a great deal of discomfort and distress, but it does not permanently harm the intestines and does not lead to a serious disease, such as cancer[7,8].

MATERIALS AND METHOD

Mebeverine hydrochloride, HPMC K 100, Ethyl cellulose, Micro Crystalline Cellulose, Talc, Magnesium stearate, Starch and Guar gum are obtained as a gift sample from Darwin formulations, Vijayawada. All other chemicals and solvents were purchased from analytical grade[9,10,11].

Preparation of tablets by direct compression method:
The matrix tablets of mebeverine Hcl were prepared by employing various polymers like HPMC K 100, Ethyl cellulose, Micro Crystalline Cellulose, Starch, Guar gum by direct compression method using Cadmach-single punch tablet machine. For the preparation of matrix tablets, the active ingredient was thoroughly mixed with polymer(s) using a mortar and pistle for 10min. Magnesium stearate was added to the above blend as flow promoter. In all the formulations the amount of mebeverine Hcl was kept constant at 135mg and the polymers like HPMC K100, Ethyl cellulose, Guar Gum were used in different ratios with respect to drug[12,13,14].

Table.1: Composition of mebeverine hcl capsules F1 to F12

S. No.	Ingredients	mg/cap											
		F 1	F 2	F 3	F 4	F 5	F 6	F 7	F8	F 9	F 10	F 11	F 12
1.	mebeverine hcl	60	60	60	60	60	60	60	60	60	60	60	60
2.	Sugar spheres(20#25)	20	20	20	20	20	20	20	20	20	20	20	20
3.	Mannitol	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
4.	Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
5.	Pvpk-30	4.0	–	–	4.0	–	–	4.0	–	–	4.0	–	–
6.	Hpc	–	4.0	–	–	4.0	–	–	4.0	–	–	4.0	–
7.	HPMCE5	–	–	4.0	–	–	4.0	–	–	4.0	–	–	4.0
8.	Mdc	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20.0 ml
9.	IPA	80ml	80ml	80ml	80ml	80ml	80ml	80 ml	80 ml	80 ml	80 ml	80 ml	80 ml
BARRIER COATING													
10.	HPMCE5	9.3	9.3	9.3	14	14	14	18.6	18.6	18.6	23.25	23.25	23.25
11.	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
SUSTAIN RELEASE COATING													
12.	Ethylcellulose (10 cps)	5.2	5.2	5.2	10.7	10.7	10.7	–	–	–	–	–	–
13.	Ethylcellulose (7 cps)	–	–	–	–	–	–	5.6	5.6	5.6	11.6	11.6	11.6
14.	DEP	3	3	3	3	3	3	3 ml	3 ml	3 ml	3 ml	3 ml	3 ml
15.	IPA	12	12	12	260	260	260	130	130	130	280	280	280
16.	MDC	18.2	18.2	18.2	37.45	37.45	37.45	19.6	19.6	19.6	40	40	40

RESULTS AND DISCUSSION

The present study was undertaken to formulate capsules. The study involves mebeverine hcl sustained release preformulation studies of drug and excipients, formulation and processing development along with evaluation of capsules made with the optimized formulation. Finally, mebeverine hcl sustained release capsules were evaluated by in vitro methods.
Results and discussion of the above studies are presented below:

Preformulation studies

Table 2: Preformulation studies of all formulations

Parameters	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Compressibility index (%)
F1	24.45^0	1.03	1.4	1.05	7.2
F2	25.42^0	1.02	1.2	1.07	6.9
F3	25.46^0	1.04	1.3	1.05	7.7
F4	25.32^0	1.03	1.3	1.08	8.9
F5	25.38^0	1.03	1.4	1.03	7.5
F6	24.62^0	1.04	1.2	1.05	7.3
F7	25.39^0	1.03	1.2	1.06	6.5
F8	25.64^0	1.02	1.3	1.05	6.8
F9	25.42^0	1.02	1.1	1.07	8.8
F10	24.62^0	1.02	1.3	1.05	7.5
F11	25.43^0	1.04	1.2	1.05	8.2
F12	26.42^0	1.03	1.2	1.08	7.5

Drug – Excipients compatibility studies

TABLE 3: Drug – Excipients compatibility studies:

S no	Drug and excipient	ratio	Initial physical description	25°c/60% RH, 40°c/75%RH		
				1 month	2 months	3 months
1	Mebeverine HCl		White cristalline powder	*	*	*
2	Mebeverine HCl + sugar spheres	1:1	Off white powder contains spherical pellets	*	*	*
3	Mebeverine HCl+pvp k30	1:1	Off white powder	*	*	*
4	Mebeverine HCl+HPC	1:1	Off white powder	*	*	*
5	Mebeverine HCl+HPMC E5	1:1	Off white powder	*	*	*
6	Mebeverine HCl+ ethyl cellulose	1:1	Off white powder	*	*	*
7	Mebeverine HCl+IPA	1:1	Off white thick paste	*	*	*
8	Mebeverine HCl+mannitol	1:1	white powder	*	*	*
9	Mebeverine HCl+DEP	1:1	Off white thick paste	*	*	*
10	Mebeverine HCl+talc	1:1	Off white powder	*	*	*
11	Mebeverine HCl+MDC	1:1	Off white thick paste	*	*	*

NOTE: star mark (*) indicates that there is no interaction between drug and excipients at 25°C/60% RH, 40°C/75%RH

Physical Evaluation

Table 4: Physical Evaluation

S. No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
1	Weight variation (±10%)	5.66	5.57	6.42	5.57	4.16	5.35	6.44	6.25	4.46	5.54	6.63	5.37
2	Disintegrat-ion time(min)	4.30	4.20	4.50	4.40	4.25	5.50	4.55	4.60	4.40	4.30	4.20	4.25

Chemical Evaluation

Table: 5 Chemical Evaluation

S. No	Parameters	F 1	F 2	F 3	F 4	F 5	F 6	F7	F8	F9	F10	F11	F 12
1	Assay (90-110%)	94	95.6	96.8	97	98	98.5	97.8	96.4	96.8	97.9	98.5	99.8
2	Dissolution study	98.2	69.3	93.5	95.2	93.2	90.7	92.3	91.4	89.5	90.4	89.4	86.4

Stability studies

Table:6 Stability Data for F 12

Batch number and stability condition	Assay (%)	Drug release in pH 6.8 buffer
Room temperature (Initial)	99.82%	86.21%
40° C / 75% RH (1month)	99.33%	85.22%
40° C / 75% RH (2month)	99.29%	83.14%
40° C / 75% RH (3month)	99.22%	82.16%
25° C/60% RH (1month)	99.42%	85.78%
25° C/60% RH (2month)	99.38%	84.89%
25° C/60% RH (3month)	99.25 %	82.45%

ASSAY

Assay is an indicative of the amount of the drug present in the dosage form. Here it gives the insight information about the substances of the process and about effect of changes.

In Formulation 12 the assay of the capsules was found to be 99.82%% initially, after 1 month it was decreased to 99.33% and 99.42%%, later it was found to be 99.29% and 99.38% after 2months and after 3months it was found to be 99.22% and 99.25% at 40^0 C/75% RH and 25^0 C/60% RH respectively.

DISSOLUTION STUDIES

The dissolution was carried out for different experimental trials and also for the innovator. The various results that are obtained are tabulated below. Dissolution studies are carried out in the following media.

Table 7: Dissolution Profile of MEBEVERINE HCL (innovator):

Time(hrs)	Cumulative% drug dissolved
1	28.45±0.65
2	35.75±0.98
4	49.62±0.85
6	56.93±0.56
8	68.37±0.90
10	74.81±0.99
12	87.37±0.52

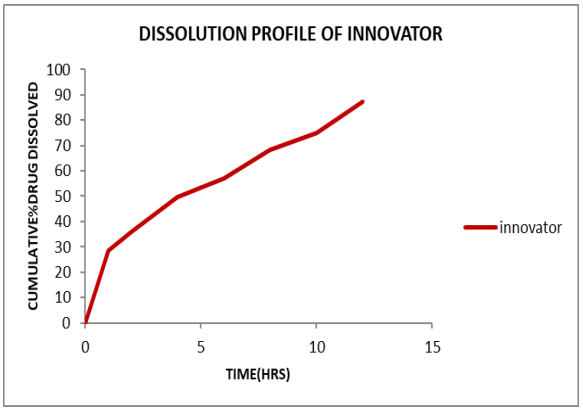

Fig 1:Dissolution plot for innovator

Table 8: Dissolution Profile of F12:

TIME (HRS)	Sample1	Sample2	Sample3	Sample4	Sample5	Sample6	Mean ±SD
1	26.2	26.4	26.5	26.3	26.3	26.3	26.3± 0.48
2	33.7	33.7	33.6	33.8	33.9	33.7	33.7± 0.59
4	47.5	47.6	47.6	47.7	47.8	47.6	47.6± 0.65
6	54.3	54.3	54.2	54.4	54.5	54.3	54.3± 0.62
8	68	67	66	69	68	68	68±0. 86
10	72.7	72.6	72.8	72.7	72.9	72.7	72.7± 0.64
12	86.4	86.3	86.4	86.4	86.5	86.6	86.44 ±0.74

Table 9 :comparision of Dissolution Profile of F12 with innovator:

Time(hrs)	Cumulative% drug dissolved	innovator
0	0	0
1	26.3±0.48	28.45±0.65
2	33.7±0.59	35.75±0.98
4	47.6±0.65	49.62±0.85
6	54.3±0.62	56.93±0.56
8	68±0.86	68.37±0.90
10	72.7±0.64	74.81±0.99
12	86.44±0.74	87.37±0.52

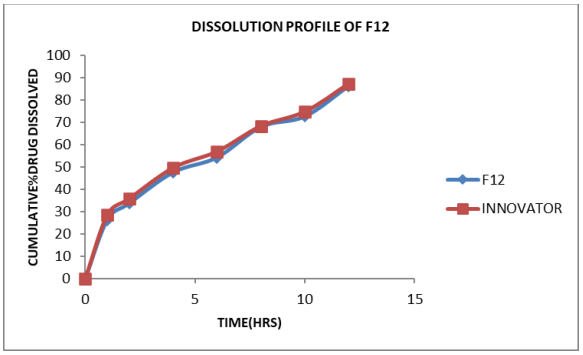

Fig 2: Dissolution plot for F12

CONCLUSION

The mebeverine hydrochloride is a anti spasmodic drug which is used in the treatment of IBS. In this study mebeverine hydrochloride sustained release capsules were prepared by using ethyl cellulose as sustained release coating polymer. Twelve formulations of sustain release capsules of mebeverine hydrochloride were developed by preparing capsules using PVP, hpc, hpmcE5 as binders in different proportions and varying the compositions of barrier coating and sustain coating using different viscosity grades of ethyl cellulose (7 cps&10 cps).

The formulation 12 was found to be the best of all the formulations showing drug release matching the innovator product. The formulation F12 was evaluated for all the quality control tests. The release mechanism was found to be “Anomalous transport” based on n value obtained 0.472 which is between >0.45 and < 0.89 hence it follows non fickian release. showing Anomalous transport. Stability study was carried out for 3 months at 25° C/60% RH: and 40° C/75%RH, according to ICH guidelines. The capsules were tested for drug release during the stability period and confirmed that the results were found within the limits.

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