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DEVELOPMENT OF MULTIPARTICULATE SYSTEM OF MEBEVERINE HYDROCHLORIDE FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME

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Abstract:

Pellets were witnessed as one of the promising modified drug delivery systems widely employed now-a-days in the management of various diseases. Mebeverine hydrochloride pellets were coated by suspension layer technique using fluidized bed processor (FBP). This method applied found to be effective to coat the drug uniformly onto the non-pareil (NP) seeds. In this study, three coatings viz., binder (PVP K30), barrier (EC 5 cps) and sustained release (EC 3 cps and HPMC 10 cps) were applied. At each stage of coating, optimized formulation was found out for next subsequent coating and they were F4, B1 and S3. F4 is a formulation with binder solution 2.5% w/v concentration showed 90% coating efficiency with less processing problems and less lump formation. To this formulation barrier coating was given with EC 5 cps. Barrier pellets coated with rate retarding polymers EC 3 cps and HPMC 10 cps. Out of three formulations S3 formulation exhibited 90.39% drug release at 16th hr which matched with the 90.69% release of marketed formulation. Similarity (f_2) and dissimilarity (f_1) factors for S3 were 83.5 and 6.2 respectively. This revealed the S3 is in vitro bioequivalent with marketed formulation. These pellets were evaluated further for micromeritic properties, SEM and dissolution rate test studies. The micrometrics of S3 revealed good flow ability for packing and filling into capsules (Compressibility index, angle of repose and hausner's ratio were 24.29%, 26.04° and 1.009 respectively). The formulation was extended for stability studies at different conditions. The stability data produced evidenced the formulation was intact during storage.

Key words: *pellets, suspension layering technique, rate retarding polymers.*

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INTRODUCTION:

Modified release dosages forms can be defined as one for which the release characteristics of time course and location are chosen to accomplish the therapeutic or convenience objectives, which are not offered by conventional dosage forms. Most modified release products are orally administered tablets and capsules. Several types of modified dosage forms are available [1-3]. The main goal of modified drug delivery systems is to improve the effectiveness of drug therapies [4-8]. Pharmaceutical pellets are agglomerates of fine powder particles or bulk drugs and excipients, small, free flowing, spherical or semi-spherical solid units, size ranges from about 0.5mm to 1.5mm obtained from diverse starting materials utilizing different processing techniques and conditions. The interest in pellets as dosage forms has been increasing continuously, since their multiparticulate nature offers some important pharmacological as well as technological advantages over conventional single-unit dosage forms. Pellets offer a high degree of flexibility in the design and development of oral dosage forms. They can be divided into desired dose strengths without simultaneously and to provide different release profiles at same or different sites in the gastrointestinal tract. In addition, pellets, taken orally, disperse freely in the GI tract; maximize drug absorption [9-15]. Mebeverine is a drug used to alleviate some of the symptoms of irritable bowel syndrome. It works by relaxing the muscles in and around the gut. Mebeverine is an anticholinergic but its mechanism of action is not known; it appears to work directly on smooth muscle within the gastrointestinal tract and may have an anesthetic effect, may affect calcium channels, and may affect muscarinic receptors. The main aim of the present study was to prepare sustained release Mebeverine Hydrochloride pellets of 16hours to reduce the dosing frequency when compared with the marketed product for treating irritable bowel syndrome [16-22].

MATERIALS AND METHODS:

Mebeverine hydrochloride and Isopropyl alcohol from RAChem; Sugar spheres 30#40 from Ocean Pharmacoat; Ethyl cellulose 10 CPs and HPMC 3 CPs from Clariant; Macrogel 8000 from merck and Tween 80 from Degussa. All other reagents are of analytical grades and used without further purification.

Preparation: In the present work, the principle used for the preparation of sustained release pellets was suspension/solution layering technology. Three main steps were involved in the preparation of pellets Drug loading/coating, Barrier coating and Functional coating. The development of present study was mainly based on the process of binding drug to the non-pareil seeds and binding of polymer on to drug coated NPS and to achieve a required release profile. To achieve these different concentrations of binder and polymers were used. The main aim was to compile and match the results of marketed products.

Table 1: Formulation table for sustained release pellets of Mebeverine HCl

Mebeverine hydrochloride 70% w/w					
Batch size		3Kg			
DRUG LOADING					
S.NO.	**INGREDIENTS (g)**	**F1**	**F2**	**F3**	**F4**
	Binder percentage	8	6	4	2.5
1	Sugar spheres	0.300	0.300	0.300	0.300
2	Mebeverine hydrochloride	1.800	1.800	1.800	1.800
3	PVP K30	0.240	0.180	0.120	0.075
4	Tween 80	0.006	0.006	0.006	0.006
5	Iso propyl alcohol	6.000	6.000	6.000	6.000
	TOTAL	**2.346**	**2.286**	**2.226**	**2.181**
BARRIER COATING					
	DRUG PELLETS		**2.181**		
1	EC 5 cps		0.120		
2	Iso propyl alcohol		1.000		
3	Methylene di chloride		1.500		
	TOTAL		**2.290**		
BARRIER COATING					
Barrier pellets			**2.290**		
S.NO.	**INGREDIENTS**	**S1**	**S2**	**S3**	
	SR percentage	2	4	5	
1	Ethyl cellulose 3 cps	0.046	0.092	0.115	
2	HPMC10 cps	0.004	0.007	0.009	
3	Macrogel 8000	0.007	0.015	0.018	
4	Purified water	0.045	0.090	0.112	
5	Isopropyl alcohol	0.469	0.938	1.172	
	TOTAL	**2.347**	**2.404**	**2.432**	
	ASSAY	**76.7%**	**74.0%**	**74.9%**	

Evaluation of Sustained Release Pellets:

Physical evaluation:

Bulk density: A sample powder of Mebeverine hydrochloride (20g) was introduced into 100 ml of graduated cylinder. The volume of material was noted on a graduated cylinder and the bulk density was calculated.

Tapped density:

The sample equivalent to 20g was weighed and filled in 100ml graduated cylinder. The mechanical tapping of the cylinder was carried out using at a normal rate of 300 drops per minute for 500 times initially and tapped volume V_0 was noted. Tapping was proceeding further for an additional tapping 700 times and tapped volume V_b was noted. The difference between the two tapping volume was less than 2%, So V_b was considered as a tapped volume V_f.

Compressibility Index:

Compressibility Index was calculated from bulk density and tap density values.

Hausner's ratio:

The hausner's ratio was calculated from bulk density and tap density values.

Flow Property

The angle of repose of Mebeverine pellets was determined by the funnel method (Reposogram). The accurately weighed quantity of pellets was taken in a funnel. The pellets were allowed to flow through the funnel freely onto the surface. The diameter of the pellet cone was measured and angle of repose was calculated.

Shape and surface roughness:

Shape and morphological features of pellets were observed by scanning electron microscopy (SEM). Surface and shape of the formulated pellets were observed to be varying depending on composition of polymer.

Assay: *In vitro* dissolution

In-vitro drug release profiles of the micropellets were evaluated using USP Apparatus I (Rotating Basket) dissolution apparatus with the basket covered with 40 mesh nylon cloth to prevent escaping of micropellets. Dissollution fluid was 900 ml of pH 6.8 buffer maintained at 35˚C ± 0.5 ^{0}C and the basket was rotated at 100+_ 2 rpm. Pellets equivalent to 200mg of Mebeverine hydrochloride were weighed accurately and transferred into six dissolution jars. Care was taken to avoid air bubbles and apparatus was started immediately. 10ml of sample was collected after each specified time interval from a zone midway between the surface of the medium and top of the rotating basket and not less than 1cm from the vessel wall and filtered through 0.45µ membrane filter. Same amount of sample was replaced into the each vessel. The amount of mebeverine hydrochloride released was assayed spectrophotometrically at 242 nm wavelength. Release kinetic study of all the formulations (functional coating) was studied using zero order, first order, Higuchi, Korsmeyer- peppas mathematical models. The model which best fits the dissolution profile of various formulations was chosen.

RESULTS AND DISCUSSION:

Sustained release pellets were developed for Mebeverine hydrochloride by suspension layering technique with a view to deliver drug in a sustained manner. Preformulation and characterization studies were conducted and their corresponding results were presented in the following sections.

Optimization Studies of Formulation;

Optimization of drug loading:

Drug coating was given to the pellets by suspension layering technology. Four batches were developed with different binder concentrations. (8, 6, 4, 2.5% w/v). Following were the problems I came across while using PVP K30 as a binder at different concentrations. In F1, pellets bed became sticky in 10 minutes. Viscosity of solution also seemed high for coating purpose. All the pellets were sticked on the wall of the chamber and lumps were observed. Fluidization was stopped in 10 minutes and wet pellets were observed during cleaning of machine. In F2, same problem was repeated. Percentage yield obtained was also less. Lumps were observed near spray gun pellets became tacky in no time. In F3, the binder concentration was still reduced to get rid of sticking problem and lump formation. This lot shows the 95% of drug coating efficiency but still there were lumps and process problems. In F4, coating efficiency obtained was 98% and show good percentage yield. Lump formation and processing problems were not observed. From the above trails it was found that 2.5% binder concentration was a suitable concentration for drug loading.

Optimization of barrier coating:

Barrier coat was given to the optimized batch of drug coating i.e., F4. The aim of this coat was to protect the drug coat during functional coating and external environment. It also increases the shelf life of product. EC 5cps 4% was used for this coat and it showed good practical yield and coating efficiency. Hence B1, was concluded as optimized formula.

Optimization of sustained release coating:

Sustained release coat was given using different concentrations of ethyl cellulose 3cps and HPMC 10

cps. Three trails were done using different concentrations of these polymers. S3 showed good percentage yield and its release profile compiles with the marketed product which is the main aim of the present study. S2 also showed good profile but its values were nearer to the upper limit. Hence, S3 was selected as optimized formula among all the formulations meeting necessary release requirements.

Table 2: Table showing optimized formula data

S.No.	Ingredients	Formula
	Drug Coating	**F4**
1.	Sugar Spheres	**0.300**
2.	Mebeverine Hydrochloride	**1.800**
3.	PVP K30 **(2.5%)**	**0.075**
4.	Tween 80	**0.006**
5.	IPA	**6.000**
		2.181
	Barrier Coating	**B1**
6.	EC 5 Cps	**0.120**
7.	IPA	**1.500**
8.	MDC	**1.000**
		2.290
	Sustained Release Coating	**S3 (5%)**
9.	Ec 10 Cps	**0.115**
10.	HPMC 3 Cps	**0.009**
11.	Macrogel 8000	**0.018**
12.	Purified Water	**0.112**
13.	IPA	**1.172**
	Total	**2.432**
	Assay	**74.0%**

***In vitro* dissolution studies**:

Release profile of drug from formulations S1, S2, S3

Conclusion: This formula is finalized for further optimization batch.

were determined and tabulated. *In vitro* dissolution profile of sustained release pellets of Mebeverine hydrochloride was found good and the release mechanism was determined as diffusion. On contact with the buffer, it diffuses into the interior of the particle. There by drug dissolution occurs and the drug solution diffuse across the release coat to the exterior of the ethyl cellulose and hydroxyl propyl methyl cellulose coats. *In vitro* percent drug release for S3 formulation was 90.39% for 16 hrs which complies with the release from marketed product which is 90.69%. From the studies it was observed that release profile extends with the increasing concentration of rate retarding polymers. Observing profiles and comparing regression values it was concluded that optimized formula S3 follows first order kinetics.

Comparative Dissolution Studies of Formulations

By observing the release profile of S1, concentration of the release retarding polymers i.e., hydroxyl propyl cellulose 10cps, ethyl cellulose 3cps should be increased to attain desire release profile and to comply with the marketed product. Based on the observation to get the desired release profile of S2 the concentration of release retarding polymers should be increased. Ideally dissimilarity factor (f1) should be less than 10 and it was found to be 6.2. The similarity factor (f2) should be more than 50 and it was found to be 88.5. Comparative graphs and the f1, f2 details, it was very much clear that the concentration of the release polymers were optimum. The dissolution data were matching with the dissolution data of reference product so the concentrations of the polymers were finalized and the formulation S3 was optimized. Based on the results, the release of the pellets is good and we got reproducible results.

Table 3: *In vitro* dissolution profile of formulations

	Percentage drug release			
Time (hr)	**Marketed**	**S1**	**S2**	**S3**
0	0	0	0	0
2	38.35 ± 0.021	55.82±0.017	47.34 ± 0.009	38.02 ± 0.009
6	67.72 ± 0.019	74.48±0.009	72.27 ± 0.019	68.41 ±0.023
10	77.56 ± 0.028	86.76± 0.014	81.58 ± 0.022	77.6 ±0.017
12	81.35 ± 0.006	92.9± 0.021	84.22 ± 0.008	81.85 ± 0.020
16	90.69 ± 0.012	----	92.66 ± 0.010	90.39 ± 0.18

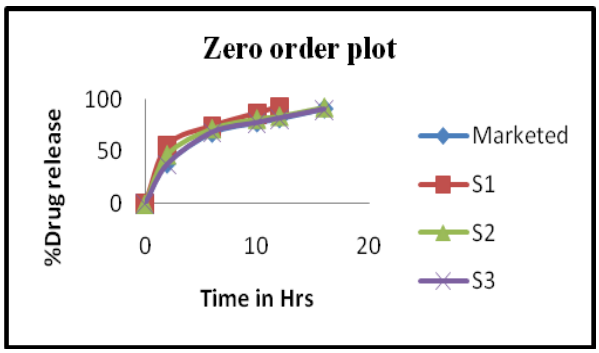

Fig.1: Zero order Comparative Dissolution plot

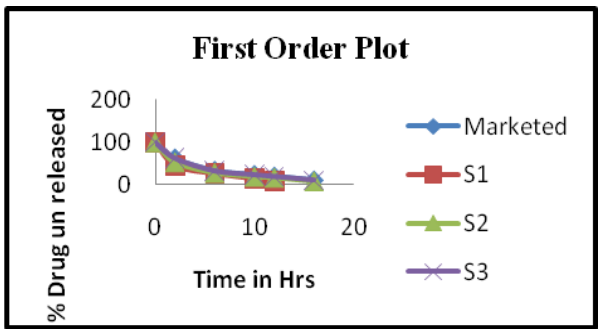

Fig.3: comparative Higuchi plots

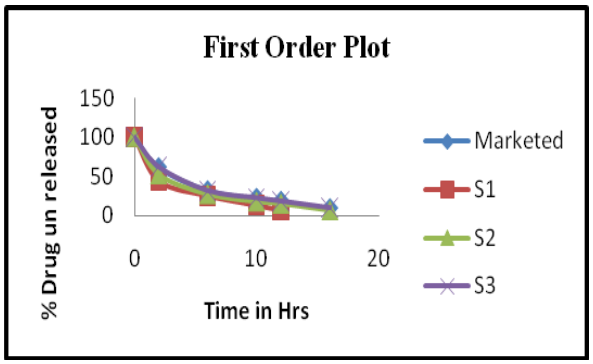

Fig.2: First order comparative dissolution plot

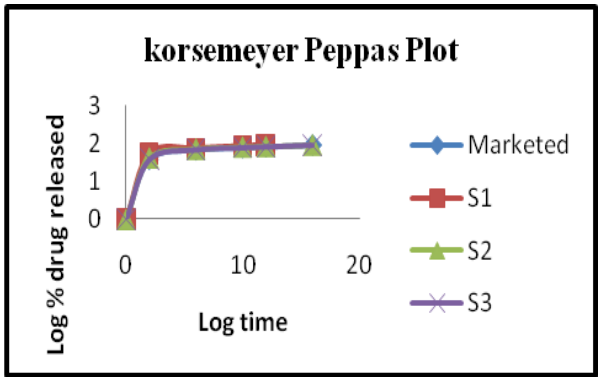

Fig.4: comparative Korsemeyerpeppas plot

Table 4: Physical characteristic evaluation data of trial S3

Core pellets	**Results**
Yield (Limit-NLT 97%)	99.6%
Bulk density	0.648 g/ml
Tapped density	0.658 g/ml
Compressibility index	24.29%
Angle of repose	26.04^0
Hausner's ratio	1.009
Sieve analysis for 100 gm. For uncoated	
# 16 passed	99 g
# 20 retained	99 g
#16 passed and 20 retained	99 g
coated pellets	
Yield (Limit-NLT 96%)	99%
Sieve analysis for 100 gm.	
#16 passed	98 g
#20 retained	98 g
# 16 passed and 20 retained	98 g
Bulk density	0.666 g/ml
Tapped density	0.674g/ml
Compressibility index	1.60
Angle of repose	27.0^0
Hausner's ratio	1.00

Surface Morphology:

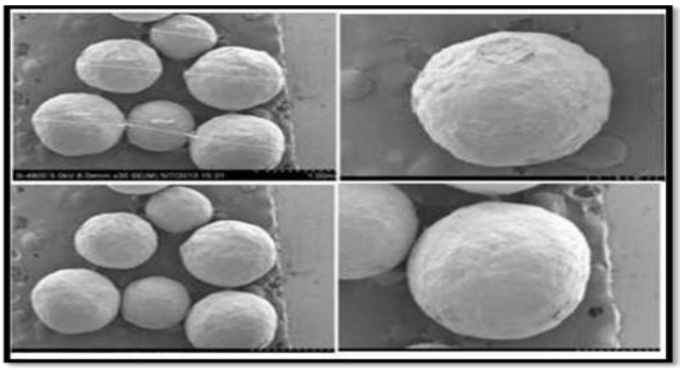

Fig.5: SEM images of mebeverine hydrochloride pellets of S3 formulation

Shape and morphological features of pellets were observed by scanning electron microscopy (SEM). Surface and shape of the formulated pellets were observed to be varying depending on composition of polymer.

Stability studies were done as per ICH guidelines for F3 batch of this product at different storage conditions. Stability data was used for evaluating the formulation and there is no change in the assay, moisture content, content uniformity, dissolution profiles were observed.

Table 5: Evaluation parameter values at different temperature conditions

S.NO	Parameter	stability conditions at		
		25 ^{0}C	30 ^{0}C	40 ^{0}C
1.	Assay	100.13%	100.05%	100.10%

Table 6: In vitro dissolution profile of S3 at 25°/C/60% RH, 30±2°C/65±5% RH and 40±2°C/75±5% RH

Time in Hrs	Percentage of drug release	
	Marketed product	S3
0	0	0
2	38.35±0.021	38.25±0.009
6	67.72±0.019	66.94± 0.023
10	81.35± 0.006	80.97± 0.020
12	90.09±0.012	89.68± 0.18

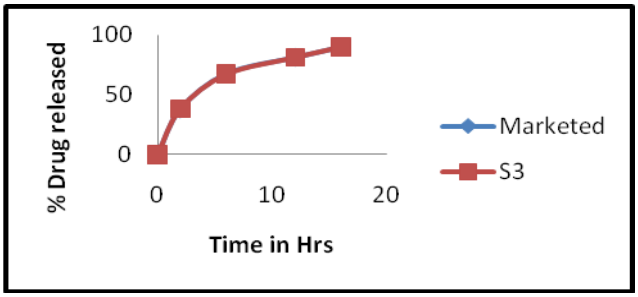

Fig.6: Comparative dissolution profile of formulation S3 at 25 ^{0}C/60% RH, 30±2 °C/65±5% RH and 40±2 °C/75±5% RH

CONCLUSION:

The active pharmaceutical ingredient Mebeverine Hydrochloride was subjected to preformulation study and results obtained with selected excipients showed good compatibility with Mebeverine Hydrochloride. Mebeverine Hydrochloride sustained release (SR) pellets were formulated using commercially available non-pariel seeds and finally three formulations were

formulated with various excipients and concentrations. Optimization procedures were adopted in the stabilization of formula. The products were subjected to analysis tests like bulk density, tapped density, compressibility index, sieve analysis for particle size and SEM analysis for shape determination, assay and *in vitro* dissolution studies. Stability studies were conducted at different storage conditions as per ICH guidelines in HDPE containers. By the stability studies it was proven that formulated pellets were stable throughout the period of storage. The dissolution profile of the formulated Mebeverine Hydrochloride sustained release pellets were compared with that of the marketed product. The release was found to nearer in the case of pellets loaded in formulation S3. The dissolution profile of this formulation was compared with that of marketed product. The release was found similar to that of marketed product. So the prepared product was said to be equivalent with marketed product.

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