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Formulation of mebeverine hydrochloride MR pellets in capsules and comparative characterization against colofac MR capsules

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ABSTRACT

The aim and objective of the present study is to develop Mebeverine Hydrochloride MR pellets in the form of capsule. Pellets with coating for Modified Release have a lower risk of dose dumping than coated tablets. Modified Release capsules of Mebeverine HCl were formulated by using the solid drug layering (SDL) process by dusting the Drug Excipients mixture on inert MCC pellets by using Povidone K-30 + IPA solution as binder. The drug layered pellets were coated by using the Eudragit S-100, PEG 6000 and Talc dispersed in purified water in order to modify the drug release. The coated pellets are filled in capsules and these capsules were evaluated for assay, weight variation, content uniformity, lock length, moisture content and in-vitro dissolution tests and all within the specification limit. There is no physicochemical interaction between drug and excipient which was proven by compatibility study results which was carried out for 4 weeks at Accelerated stability (AS) condition. The optimized batch F7 is kept under AS conditions (40°C/75%RH) and the product is monitored and analyzed for assay, moisture content, content uniformity, in-vitro dissolution study and all the parameters were well within the specification limit. The release rate was compared with the Reference product "Colofac MR" (Abbot Pharmaceuticals Ltd) and F1 & F2 values were within the limit. And it is pharmaceutically equivalent to that of the reference

Keywords: Pellets, MR Capsules, formulation of Mebeverine HCl and Antispasmodic agent.

INTRODUCTION

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased with concomitant recognition of the therapeutic advantages of Sustained drug delivery, greater attention has been focused on development of Modified Release drug delivery systems[1.]

The attractiveness of these dosage forms is due to awareness of toxicity and ineffectiveness of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments etc[2 & 3.] Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. Factors such as repetitive

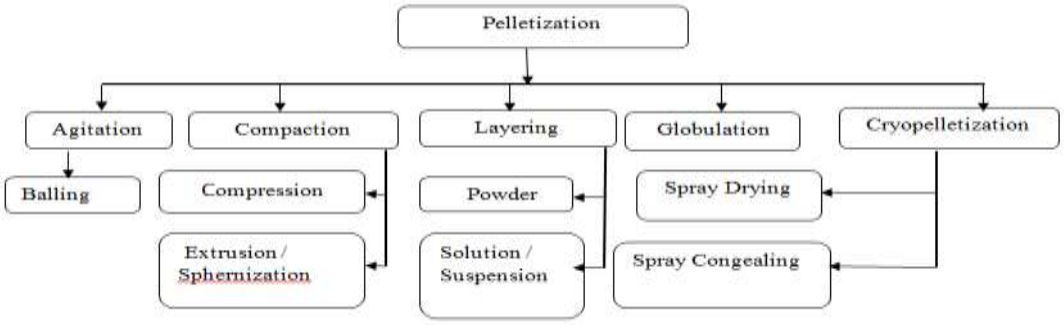
dosing and unpredictable absorption led to the concept of sustained drug delivery system[4]. The goal in designing Sustained Delivery Systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Modified Release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Modified Release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Irritable bowel syndrome (IBS) is a disorder characterized most commonly by cramping, abdominal pain, bloating, constipation, and diarrhoea. 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. An antispasmodic is usually prescribed, which assists to control colon muscle spasms and reduce abdominal pain.[5-10]. Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects. An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Modified Release (MR) delivery system provides an uniform concentration or amount of the drug at the absorption site and thus, after absorption allows maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. MR products are formulations that release active drug compounds into the body gradually and predictably over a 12-24 hr period and that can be taken once or twice a day. Typically these products provide several benefits when compared with immediate release drugs, greater effectiveness in the treatment of chronic conditions, reduced side effects, greater convenience and higher levels of patient compliance due to a simplified dosing schedule[11-14]. Because of the above advantages, such systems form the major segment of the drug delivery market.

A number of techniques are used to achieve Modified Release of drugs via the oral cavity. The majority of the oral MR systems relay on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug to the Gastro intestinal milieu. Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing spherical or semispherical solid units typically from about 0.5 - 1.5mm.

Pellets may be manufactured by using different methods. The methods used for pelletization are essentially the same as the granulation methods.

Fig.1: Different methods of Pelletization



The aim of the present investigation was to formulate and evaluate MR Mebeverine HCl capsules containing coated Mebeverine HCl pellets by eudragit S-100 and the optimized formulation is compared with the reference product "Colofac MR".

MATERIALS AND METHODS

Table2: List of Excipients

Name of ingredients	Grade	Source
Mebeverine HCl	BP	Shasun Pharmaceuticals
Celsphere CP 305	USP/NF/EP	Asahi Kasei – Japan / Signet chemical
Sugar spheres	USP / NF	Signet
Micro crystalline cellulose pH101	USP-NF	FMC Biopolymer
Povidone K 30	USP/BP/EP	ISP corporation
Hypromellose 5cps	BP/EP	Colorcon
Eudragit NE 30 D	USP/NF	Evonik / Degussa
Eudragit L 30 D 55	USP/NF	Evonik / Degussa
Eudragit S 100	Ph.Eur	Evonik / Degussa
Poly ethylene glycol	USP/NF	Vasudha Chemicals
Tri ethyl citrate	USP/EP	Merck Limited
Purified Talc	BP/EP	Luzenac Pharma/Signet
Colloidal silicon dioxide	NF/BP/Ph.Eur	Cabot Sanmar
Magnesium stearate	EP/BP	Ferro Corporation
Isopropyl alcohol	EP/BP/USP	Qualigens
Purified water	USP	Shasun

Table No 3 List of Equipments

S.No	Equipment's	Manufacturer
1.	Electronic Weighing Scale	Sartorius
2.	Mechanical Stirrer	Remi, Mumbai
3.	Electromagnetic Sieve shaker	Electro lab
4.	Multipurpose equipment (Y-Blender) Granulator)	Erweka
5.	Moisture Analyzer	Sartorious
6.	Karl Fischer Volumetric Titrator	Hanna HI 903
7.	Tapped volumeter	Erweka, Germany
8.	Fluidized bed processor (GPCG 1.1)	Palm Glatt
9.	Spheronizer	Umang
10.	Peristaltic Pump	Palm Glatt
11.	pH Meter	Eutech
12.	Capsule filling machine	AF-T Lab
13.	Digital Vernier Caliper	North Lab
14.	Microscope	Nikon
15.	Dissolution apparatus	Electro lab, Mumbai
16.	UV visible spectrophotometer	Shimadzu, Japan
17.	HPLC	Waters, Karnataka
18.	Stability chamber- 40°C/75%RH	Thermolab, Maharashtra

Drug – Excipient compatibility study

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added. Drug: Excipient compatibility studies will be done with the selected excipients.

Sample preparation

Binary mixtures of the drug and excipients are prepared by placing the accurately weighed amount of the drug and excipients in polybag and mixed till homogenous mixture is achieved. Then, these mixtures are filled in vials and closed with bromo butyl rubber stoppers & crimped with tear off clear lacquer aluminum seals. These samples are charged at 40°C/75% RH conditions. The Drug : Excipients ratio was denoted in the table 4.

Table 4 Drug Excipients ratio

Sample ID	Sample Composition	Ratio
Sample 1	Drug	-
Sample 2	Drug + MCC pellets	1:0.5
Sample 3	Drug + MCC pellets	1 :1
Sample 4	Drug + sugar pellets(1:0.5)	1:0.5
Sample 5	Drug + sugar pellets(1:1)	1:1
Sample 6	Drug + Hypromellose 6 cps(1:0.25)	1:0.25
Sample 7	Drug + Hypromellose 6 cps(1:0.75)	1:0.75
Sample 8	Drug + Eudragit NE 30 D(1:0.05)	1:0.05
Sample 9	Drug + Eudragit L 30 D 55(1:0.05)	1:0.05
Sample 10	Drug + Tri ethyl citrate(1:0.025)	1:0.025
Sample 11	Drug + Purified talc(1:0.5)	1:0.5
Sample 12	Drug + Eudragit S 100(1:0.25)	1:0.25
Sample 13	Drug + Eudragit S 100(1:0.75)	1:0.75
Sample 14	Drug + Povidone K30(1:0.5)	1:0.05
Sample 15	Drug + Colloidal silicon dioxide(1:0.5)	1:0.5
Sample 16	Drug + Magnesium stearate(1:0.5)	1:0.5
Sample 17	Drug + MCC pellet + Eudragit NE 30 D + Hypromellose 6 cps + Eudragit L 30 D 55 + Purified Talc + Tri ethyl citrate + Magnesium stearate (in mg)	0.5+0.5+0.375+ 0.375+0.375+.2 5+.375+.25
Sample 18	Drug + Sugar pellet + Eudragit NE 30+eudragit l30 d55 D + Purified Talc + Hypromellose 6 cps + Tri ethyl citrate + Magnesium stearate (in mg)	0.5+0.5+0.375+ 0.375+0.25+0.3 75+0.375+0.25
Sample 19	Drug +Eudragit S 100 + Povidone K30 + + Purified Talc + Hypromellose 6 cps + Magnesium stearate (in mg)	0.5+0.375+0.25 +0.375+0.25+0. 375+0.25
Sample 20	Drug +MCC pellet + Eudragit NE 30 + Hypromellose 6 cps + Eudragit l30 D 55 +Purified Talc + Tri ethyl citrate + Magnesium stearate + colloidal silicon dioxide (in mg)	0.5+0.5+0.375+ 0.375+0.375+0. 25+0.375+0.25+ 0.25
Sample 21	Drug +sugar sphere + Eudragit NE 30 +Eudragit l30 D55 + Purified Talc + Hypromellose 6 cps+ Tri ethyl citrate + Magnesium stearate + colloidal silicon dioxide (in mg)	0.5+0.5+0.375+ 0.375+0.25+0.3 75+0.376+0.25+ 0.25

Sample analysis

All vials were inspected for the appearance, color and odour and recorded. The samples removed from 40°C/75% RH were be analyzed as per the Schedule, in duplicate vials at all conditions were transferred to the refrigerator (2 to 8°C). In the event of out of specification results (significant change in the impurity profile), then the samples which was kept in the refrigerator were taken for analysis

Table No 4 Stability condition and interval

S. No	Parameters	Conditions			
		Initial	40°C/75% RH		
			1M	2M	3M
1	Physical appearance	✓	✓	✓	✓
2.	Related Substance	✓	✓	✓	✓

Selection of Excipient

Formulation studies of Mebeverine hydrochloride Modified Release capsules were formulated based on pre formulation data of various excipients, excipients were selected based on their DEC study results, the results compilation is shown in table no 5

PREPARATION OF DRUG-LOADED PELLETS

Mebeverine Hydrochloride, Micro crystalline cellulose 101, Purified Talc, Colloidal silicon dioxide was pulverized into a fine dusting powder. Binder solution was prepared by adding PVP K-30 in IPA and stirred well to get the clear solution. Umang solid drug layering machine (Spheronizer) was used for preparing drug-layered pellets (Fig: 2) Celsphere CP 305 were loaded into the Spheronizer and the rotor runs at a speed of 120 to 180 RPM, Dusting powder was sprayed from one end of the machine tangentially with and atomizing air pressure 0.2 Kg/cm3, the binding solution was sprayed from the other end as a mist droplets. The drug loaded pellets were unloaded and dried in a room temperature. The dried pellets are sized on a sifter to remove agglomerates, broken pellets and fine powder. The ASTM #16 passed pellets were ready for MR coating. Drug loading trial formula were mentioned in the tablet no 6

PREPARATION OF MODIFIED RELEASE PELLETS

A laboratory scale Fluid bed processor (GPCG 1.1) with bottom spray assembly /Wurster column (Fig:3) was used for coating of pellets. MR Coating solution was prepared by adding Eudragit S-100 in to IPA containing weighed quantity of purified water (3.0%) under continuous stirring untill to form a clear dispersion, Tri Ethyl Citrate added in the clear dispersion under stirring, Purified talc (Sifted through #200 mesh) was added slowly in to the dispersuion, and the stirring was continued for 45 minutes or untill to get a clear dispersion.

Drug loaded pellets were transferred into the FBP and coated with the above prepared coating solution. With the following machine parameters,

Inlet Temp	:	45 – 50º C
Product Temp	:	35 - 40 º C
Atomizing air	:	1.5 – 2 Kg/cm^2
Operating air	:	30 – 40 cfm
Drive speed	:	30 – 40 kg/cm^2
Column length	:	12 – 17 cm
Spray rate	:	1 - 3 gm/min/gun

After complete consumption of MR coating solution, fluidization was reduced for a brief post-drying period. The dried pellets are sized on a sifter to remove agglomerates, broken pellets and fine powder and it is ready for filling in to empty Hard Gelatin Capsules (HGC)

The drug layered pellets of F3 was coated with 4 different trials compositions (F4, F5, F6 & F7) with various polymers composition and the formula denoted in the table 6.

ENCAPSULATION OF MEBEVERINE HYDROCHLORIDE MR PELLETS IN CAPSULES

Mebeverine HCl coated pellets equivalent to 200 mg from the formulation F4-F7 were taken and filled in hard gelatin capsules size 2 with Semi- Automatic capsule filling machine (Rimek formulations).

CHARACTERIZATIONS

Identification of API

Mebeverine HCl was identified by Fourier Transform Infrared Spectroscopy FTIR method. FTIR offers quantitative and qualitative analysis for organic and inorganic samples. FTIR identifies chemical bonds in a molecule by producing an infrared absorption spectrum. The spectra produce a profile of the sample, a distinctive molecular fingerprint that can be used to screen and scan samples for many different components. FTIR is an effective analytical instrument for detecting functional groups and characterizing covalent bonding information.

FTIR spectrum denoted in the Figure 4.

Assay of API

Weigh accurately and transfer about 25 mg of Drug working standards into a 250ml volumetric flask. Add about 100ml of the diluent, sonic ate for about 2 mins to dissolve the content and dilute to volume up to mark with diluent and mix well (Conc: 100ppm). Analyze the sample under HPLC at 362 nm.

The Results were mentioned in the **Table 7.**

Assay of COLOFAC® MR

The drug content in Reference sample was determined by the 50mg of crushed MR layered pellets was weighed and transferred into a 50ml volumetric flash. Add about 50ml of methanol and solicited to dissolve the content, cool the solution to room temperature and made the volume up to the mark with 0.1N HCL and mixed. Diluted 5ml of solution to100ml with mobile phase and mixed (con: 0.05mg/ml). The absorbance of resultant solution was measured spectrophotometrically at 285nm using 0.1N hydrochloric acid as blank. The report will be discussed in result and discussion **Table No: 17**

$$\%ASSAY = \frac{AR\ RP}{AR\ Std} \times \frac{WT\ Std}{DL\ Std} \times \frac{DL\ RP}{WT\ RP} \times \frac{AVG\ Fill\ WT}{LC}$$

Where,

AR RP = Average Area of Drug peak in Reference product.
AR Std = Average Area of Drug peak in standard
WT Std = Weight of Drug in standard
WT RP = Weight of Drug Reference product
DL Std = Standard dilution
DL RP = Reference product dilution
LC = Label claim

The Results were mentioned in the **Table 7**

PARTICLE SIZE DISTRIBUTION (PSD)

PSD was performed by sieve analysis method. The sieves are stacked one over the other in descending order of the mesh size. Weigh the individual empty sieve and place an accurately weighed quantity (about 40g) in the sieve top. Cover the sieve at the top with the lid provided, and place a receiver at the bottom to collect the sample after sieving. Fix and fasten the sieves set up into the sieve shaker and set time at 10min, set the sieving speed rate at power 10 switch on the sieve shaker. After the specified time take the sieves and weigh individual sieve with sample and the sample weight was calculated. The report were discussed in Table 8 in result and discussion part.

WEIGHT VARIATION TEST

Weigh 20 intact capsules individually, and determine the average weight. The requirements are met if each of the individual weights is within limits of 95% and 115% of average weight. If not all of the capsule fall within limits, weigh the 20 capsules individually. Weigh the emptied shells individually and calculate for each capsule the net weight of its contents by subtracting the weight of the shell from the respective gross weight. determine the difference between each individual net content: the requirements are met if (a) not more than 2 of the differences are greater than 10% of average net content and (b) in no case is the difference greater than 25%.If more than 2 but not more than 6 capsules deviate from the average between 10% and 25%, determine the net contents of an additional 40 capsules, and determine the average content of entire 60 capsules. Determine the 60 deviations from the new average: the requirements are met if (a) in not more than 6 of the 60 capsules does the difference exceed 10 % of the average net content and (b) in no case does the difference exceed 25%.
The Results were mentioned in the **Table 7**

Lock length

The lock length of capsules play a major role during blister packing, handling and during in-vitro dissolution, if the lock length is more, there will be a damage during blister packing, if the lock length is lesser than the limit, the capsules will fail in dissolution due to the adherence between pellets into the filled capsules. The length of filled capsules was found to be in the range of 17.4 to 18.2 mm, Results of lock length were denoted in table 7

Microscopic examination of optimized trial (Trial – F7)

The shape of the pellets play a role during functional coating, non-spherical and sharp edged pellets will resulted with opening after functional coating leads to batch to batch variation in dissolution. The Final product was placed under microscope in a slide and examined under 45X to study the surface nature of the pellets. The microscopic examination is denoted in the Fig. 4

DISSOLUTION STUDIES

The following procedure was employed to determine the in-vitro dissolution rate for Reference Product: Dissolution studies of Reference product were carried out employing dissolution apparatus-I (basket) method at 37°C ±0.5°C. Basket rotational speed was held at 100rpm. The dissolution medium was chosen as 900ml of 6.8 phosphate buffer (official medium BP) till 24 h 10 ml samples were taken and diluted to 100ml with pH6.8 phosphate buffer. Subsequently, released amount of antispasmodic agent was determined by HPLC at 263nm. Each measurement was repeated five times for each formulation.

Dissolution medium :
900 ml of 6.8 pH phosphate buffer for 24 h

Temperature : $37^{o}C \pm 0.5^{o}C$

Apparatus : Apparatus I (Basket apparatus),

RPM : 100

Volume withdrawn : 10 ml

The results of dissolution study are mentioned in Table 9, and graphical representation of comparative cumulative drug release is mentioned in Fig. 6

STABILITY STUDIES

The final batches were packed in PVC Alu-blisters and loaded in the stability chambers at accelerated condition (40°C/75% RH) studied for 3 months
The critical attributes like description of pellets, water content, Assay and dissolution of capsules were studied during stability evaluation.
Stability results at accelerated conditions were given in Table 10. Dissolution profile of Optimized formulation F7 during stability study (40°C/75% RH) is recorded in the Table 11 and the Graphical representation cumulative % drug release is shown in Fig. 8. The dissolution curves of optimized batch F7 were completely overlapped with Reference product and there is no significant changes observed on the final trial formulation during stability. Hence the product is considered as stable for 2 years at room temperature (25°C/60% RH)

RESULTS AND DISCUSSION

Table 5: DEC results

Sample ID	Duration	Known Impurities		Unknown Impurities		Total Impurities
		I	II	I	II	
1	Initial	ND*	ND*	0.08	ND*	**0.08**
	3 Month	ND*	ND*	0.072	ND*	**0.07**
2	Initial	ND*	ND*	0.071	ND*	**0.07**
	3 Month	ND*	ND*	0.019	0.052	**0.07**
3	Initial	ND*	ND*	0.08	ND*	**0.08**
	3 Month	ND*	ND*	0.059	ND*	**0.06**
4	Initial	ND*	ND*	0.062	ND*	**0.06**
	3 Month	ND*	ND*	0.045	ND*	**0.05**
5	Initial	ND*	ND*	0.081	ND*	**0.08**
	3 Month	ND*	ND*	0.052	ND*	**0.05**
6	Initial	ND*	ND*	0.063	ND*	**0.06**
	3 Month	ND*	ND*	0.061	0.013	**0.07**
7	Initial	ND*	ND*	0.067	ND*	**0.07**
	3 Month	ND*	ND*	0.029	0.08	**0.14**
8	Initial	ND*	ND*	0.074	ND*	**0.07**
	3 Month	ND*	ND*	0.066	0.033	**0.12**
9	Initial	ND*	ND*	0.068	ND*	**0.07**
	3 Month	ND*	ND*	0.078	0.042	**0.15**
10	Initial	ND*	ND*	0.074	0.058	**0.13**
	3 Month	ND*	ND*	0.078	0.073	**0.15**
11	Initial	ND*	ND*	0.057	ND*	**0.06**
	3 Month	ND*	ND*	0.079	0.051	**0.13**
12	Initial	ND*	ND*	0.052	ND*	**0.05**
	3 Month	ND*	ND*	0.011	0.058	**0.06**
13	Initial	ND*	ND*	0.035	ND*	**0.04**
	3 Month	ND*	ND*	0.04	0.074	**0.13**
14	Initial	ND*	ND*	0.043	ND*	**0.04**
	3 Month	ND*	ND*	0.062	0.018	**0.09**
15	Initial	ND*	ND*	0.052	ND*	**0.05**
	3 Month	ND*	ND*	0.052	0.007	**0.06**
16	Initial	ND*	ND*	0.062	ND*	**0.06**
	3 Month	ND*	ND*	0.047	0.05	**0.05**
17	Initial	ND*	ND*	0.009	ND*	**0.01**
	3 Month	ND*	ND*	0.023	0.028	**0.06**
18	Initial	ND*	ND*	0.02	ND*	**0.02**
	3 Month	ND*	ND*	0.038	0.02	**0.06**
19	Initial	ND*	ND*	0.01	ND*	**0.01**
	3 Month	ND*	ND*	0.012	0.012	**0.02**
20	Initial	ND*	ND*	0.022	ND*	**0.02**
	3 Month	ND*	ND*	0.003	0.016	**0.02**
21	Initial	ND*	ND*	0.2	ND*	**0.02**
	3 Month	ND*	ND*	0.024	0.045	**0.07**

*ND – Not detected

LIMIT: As per ICH Guideline Q3B (R2) Impurities in New Drug Products, the limit for highest unknown impurity is NMT 0.2%

Fig. 2 Preparation of Drug layer

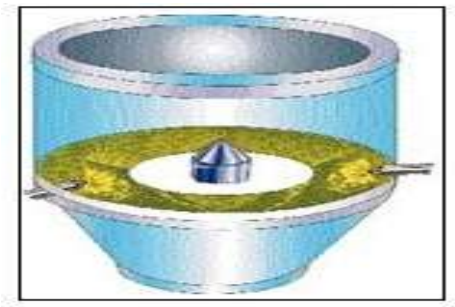


Fig. 3: Preparation of MR layer Pellets

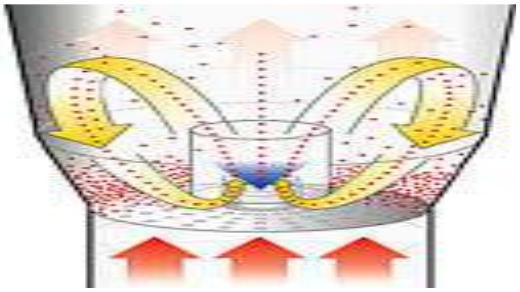
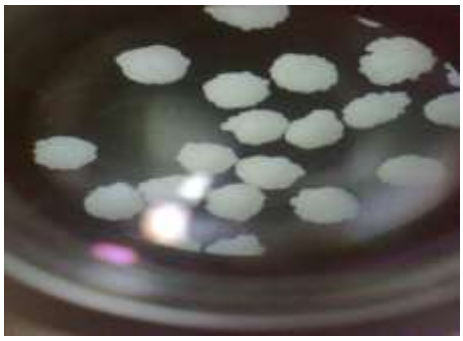
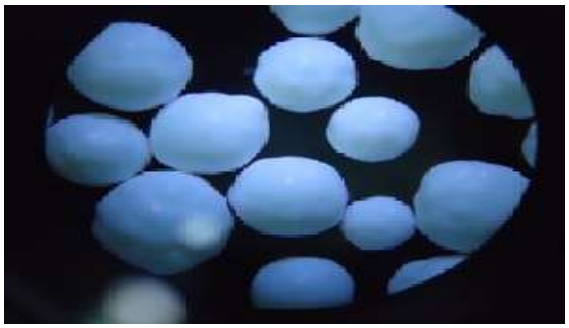


Figure 5. Microscopic examination of pellets



Trial F5 – Poor coating



Trial F7 – Elegant coating.

Table No. 6: formulation trials Drug layering and Modified release coating:

S. No	Ingredients	Percentage quantity						
		T1	T2	T3	F4	F5	F6	F7
DRUG LAYERING OF CORE PELLETS								
1	MCC Pellets	8.16	7.91	7.91	-	-	-	-
2	Mebeverine HCl	81.63	79.13	78.02	-	-	-	-
3	Micro crystalline cellulose 101	8.16	7.91	8.59	-	-	-	-
4	Hypromellose 6 cps	0.82	3.86	-	-	-	-	-
5	Povidone K-30	-	-	4.19	-	-	-	-
6	Purified Talc	0.82	0.79	0.86	-	-	-	-
7	Colloidal silicon dioxide	0.41	0.40	0.43	-	-	-	-
8	Isopropyl alcohol	Q.S	Q.S	Q.S	-	-	-	-
9	Purified water	Q.S	Q.S	Q.S	-	-	-	-
	TOTAL	**100.00**	**100.00**	**100.00**	-	-	-	-

MR COATING OF DRUG LOADED PELLETS								
10	Drug layered pellets	-	-	-	86.57	86.93	85.91	84.63
11	Eudragit L30 D 55	-	-	-	3.53	2.94	---	---
12	Eudragit NE 30 D	-	-	-	5.30	4.66	9.48	---
13	Eudragit S 100	-	-	-	---	---	---	10.58
14	Triethyl citrate	-	-	-	0.88	0.86	0.95	1.06
15	Purified Talc	-	-	-	0.88	1.86	0.95	1.06
16	Isopropyl alcohol	-	-	-	Q.S	Q.S	Q.S	Q.S
17	Purified water	-	-	-	Q.S	Q.S	Q.S	Q.S
LUBRICATION								
18	Colloidal silicon dioxide	-	-	-	0.71	0.69	0.68	0.67
19	Purified Talc	-	-	-	2.12	2.06	2.04	2.01
	TOTAL	-	-	-	**100.0**	**100.0**	**100.0**	**100.0**

Figure 4. IR Spectrum of API

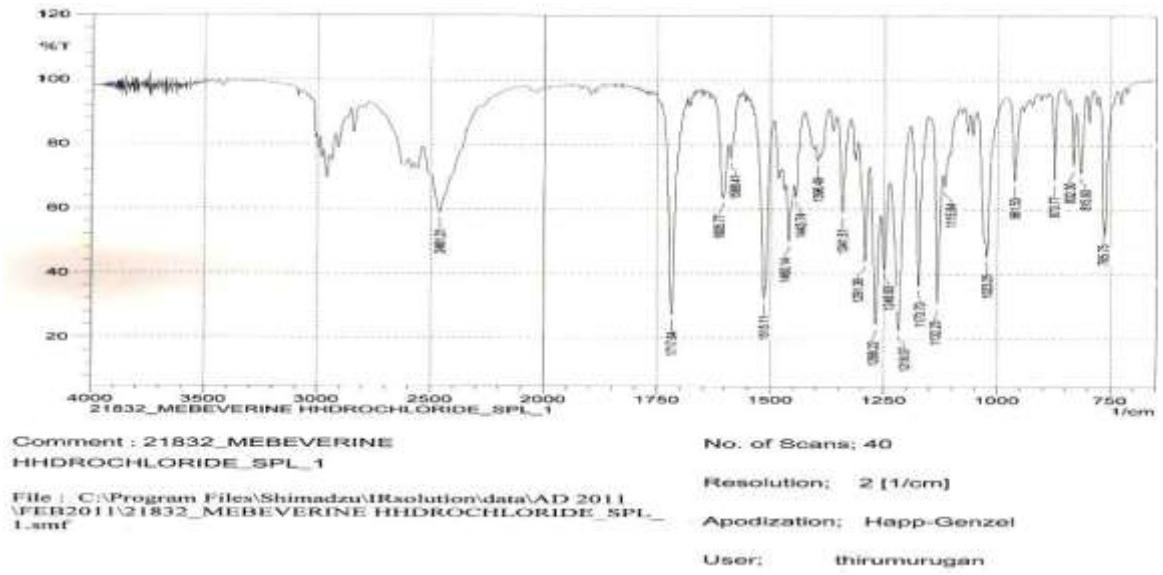


Table 7. Characteristics of "Colofac MR" and Trial batch from F4 to F7

S.No	PARAMETERS	Specification Limits	"Colofac MR"	F4	F5	F6	F7
1.	Bulk density (g/ml)	NA	0.612	0.588	0.597	0.596	0.596
2.	Tapped density (g/ml)	NA	0.652	0.635	0.635	0.643	0.643
3.	Compressibility index (%)	NA	6.13	7.353	5.970	7.353	7.353
4.	Hausner's Ratio	NA	1.07	1.079	1.063	1.079	1.079
5.	Lock length	17.80mm ± 0.40	18.12mm	17.95	17.98	17.99	17.96
6.	Moisture content	NMT 5.0	1.80 %	1.56%	1.67%	1.58%	1.54%
7.	Weight variation	NMT 5.0%	1.12 %	1.82%	1.65%	1.35%	1.16%
8.	Actual Group Weight/Mass of 20 filled capsules	6.56 ±2.0 (6.429 - 6.691 g	± 2.0 %	6.489g	6.514g	6.618g	6.586g
9.	Actual fill Weight/Mass	253mg	250 ± 3.0%	255mg	248mg	255mg	251mg
10	Uniformity of Weight/Mass of filled capsules	± 5.0 %	-1% and +2%	Complies	Complies	Complies	Complies
11	Assay by HPLC	NLT 95 & NMT 105	99.99 %	103	101	103	102

All the product parameters found satisfactory and well within the specification limit

Table 8 : Particle size distribution

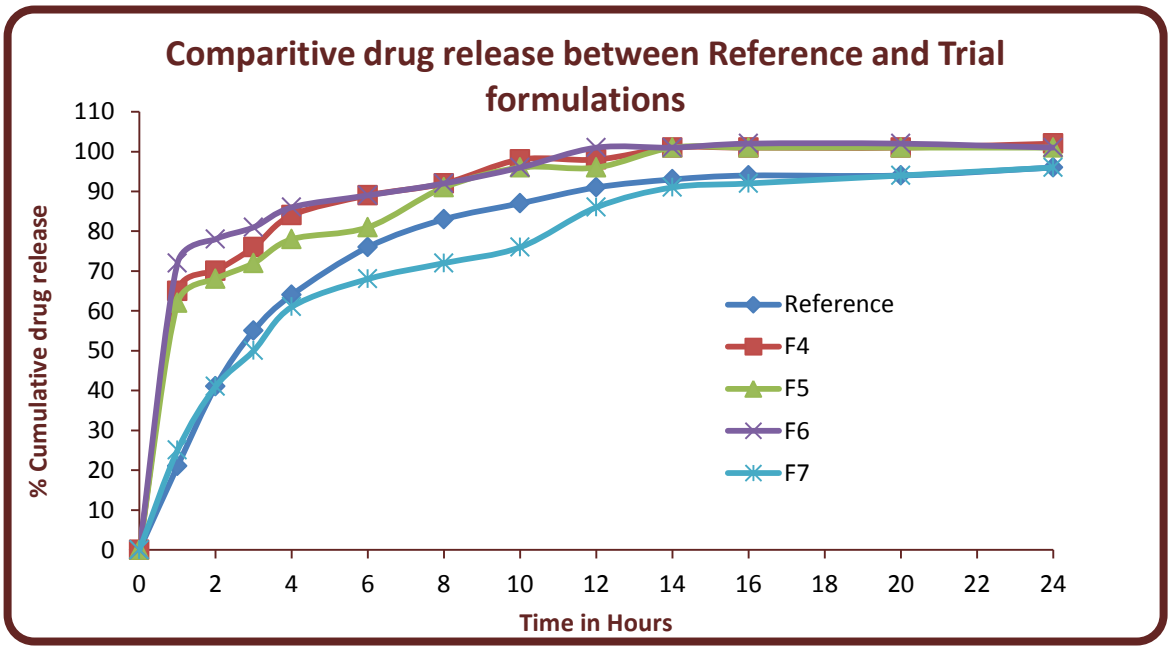
S.No	Sieve No	Cumulative% Retained				
		"Colofac MR"	F1	F2	F3	F4
1	#14	2.09	-	-	-	-
2	#16	22.18	5.86	0.02	0.02	1.22
3	#18	49.37	61.44	7.2	72	91.38
4	# 20	68.2	84.12	93.41	91.61	99.29
5	#25	-	93.45	96.8	95.2	100
6	# 30	89.96	96.38	99.94	98.34	100
7	# 40	99.58	100	100	100	100
8	Pan	100	100	100	100	100

The reference product is manufactured by Extrusion spheronization method, hence the pellets formed is larger and abnormal, Current Wurster coating was produced a uniform and consistent pellets which was proven by the above PSD method.

Table No: 9 *in-vitro* dissolution study of formulations F4 to F7

S. No	TIME (Hours)	"Colofac MR"	F4	F5	F6	F7
1	0	0	0	0	0	0
2	1	21	65	62	72	25
3	2	41	70	68	78	41
4	3	55	76	72	81	50
5	4	64	84	78	86	61
6	6	76	89	81	89	68
7	8	83	92	91	92	72
8	10	87	98	96	96	76
9	12	91	98	96	101	86
10	14	93	101	101	101	91
11	16	94	101	101	102	92
12	20	94	101	101	102	94
13	24	96	102	101	101	96
Dissimilarity factor F1			**34.43**	**28.34**	**39.11**	**9.84**
Similarity factor F2			**31.09**	**33.94**	**27.68**	**57.13**

Fig 6: Comparative dissolution profile of formulations F4-F7 against reference ("Colofac MR").



The dissolution curves of optimized batch F9 were completely overlapped with "Colofac MR".

Table 10: Stability study of optimized formulation:

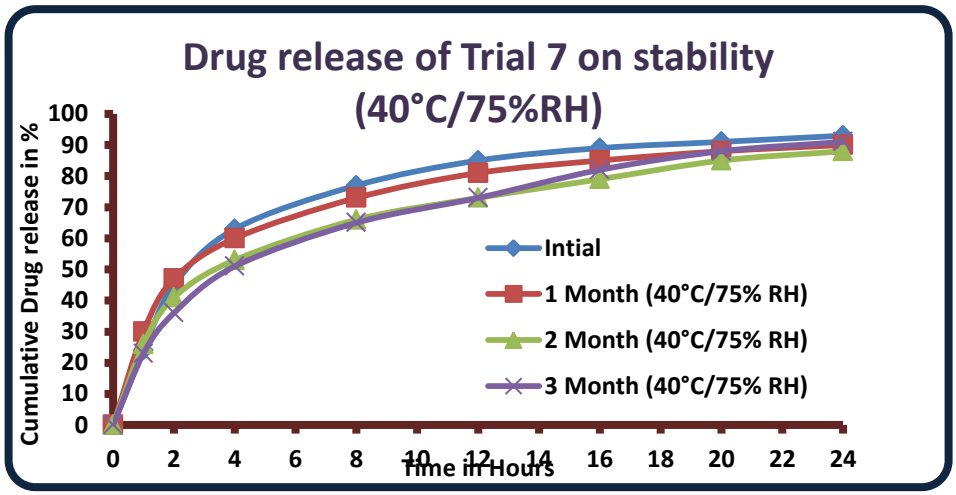
S. No	Test parameter	Specification limit	Initial	1 Month	2 Months	3 Months
1	Description	White to off white Spherical free flowing pellets	Complies	Complies	Complies	Complies
2.	Assay by HPLC %w/w	NLT 90.0 and NMT 110.0	100.8	101.3	100.5	100.7%
3.	Water by KF (% w/w)	NMT 7.0	1.50	1.54	1.96	1.52
4.	**Related substances:**					
	Name of the impurity	**Specification limit**	**Initial**	**40°C/75% RH**		
				1 Month	**2 Months**	**3 Months**
	Known impurity I	NMT 0.20	0.02	0.02	0.01	0.02
	Known impurity II	NMT 0.20	0.01	0.01	0.01	0.01
	unknown impurity	NMT 0.20	0.09	0.09	0.08	0.08
	Total impurities	NMT 1.5	0.17	0.17	0.18	0.18

Table 11: Dissolution study of capsules on stability:

The final batches were packed in PVC Alu-blisters & loaded in the stability chambers at accelerated (40°C/75% RH) up to 3 months and at stress condition

Test Name	TIME POINT	Initial				40°C/75% RH											
						1st month				2nd month				3rd month			
Dissolution by HPLC (%w/w)	**Hours**	**Min**	**Max**	**Avg**	**RSD**	**Min**	**Max**	**Avg**	**RSD**	**Min**	**Max**	**Avg**	**RSD**	**Min**	**Ma**	**Avg**	**RSD**
	1	21	27	**24**	8.4	27	33	**30**	7.9	24	29	**26**	6.7	21	25	**23**	5.8
	2	43	46	**45**	3.1	43	50	**47**	6.6	39	45	**41**	4.8	32	41	**36**	8.8
	4	61	64	**63**	1.7	57	64	**60**	5.0	50	58	**53**	5.7	48	56	**51**	5.3
	8	75	79	**77**	1.8	69	77	**73**	4.5	62	71	**66**	4.5	62	70	**65**	4.1
	12	83	87	**85**	1.8	77	85	**81**	3.9	70	78	**73**	3.7	70	78	**73**	3.8
	16	88	91	**89**	1.7	81	89	**85**	3.7	76	83	**79**	3.2	78	86	**82**	3.5
	20	89	94	**91**	2.1	84	90	**88**	2.6	83	87	**85**	1.8	84	92	**88**	3.1
	24	90	97	**93**	2.7	86	92	**90**	2.9	87	91	**88**	1.7	88	96	**91**	3.4

Fig 8: Drug release on stability



SUMMARY AND CONCLUSION

- The Dissertation work entitled, "**Formulation of Mebeverine Hydrochloride MR Pellets in Capsules and comparative characterization against COLOFAC® MR Capsules**" was carried out for the optimization of the formulation to meet the quality standards with regard to API, excipients, manufacturing process and finished product. Drug-excipient compatibility studies were carried out for 3 months Accelerated condition and the results showed that there was no physical and chemical change in the API.
- This indicated that, the drug was compatible with the formulation components. Hence MCC 101, Povidone K30, Purified Talc, Colloidal silicon dioxide, Eudragit S 100, L100 D55, NE 30 D was selected as inactive excipients for the lab scale development.
- The Prototype formulations were developed (F1 to F7), and the F7 formulation was optimized, the critical product attributes and dissolution profile of the optimized batch F7 was similar to the Reference product, the Mebeverine Hydrochloride Modified Release pellets were filled in size 2 hard gelatin capsules and it is subjected to further studies
- The F7 formulation was taken for stability studies as per the ICH Guidelines, F-7 batch were packed in PVC Blisters charged at 40ºC ± 2 / 75 ± 5 %RH for the period of three months. The results were found satisfactory and complies the specifications.
- The Similarity and Dis-similarity factor (F1& F2 correlation) were calculated for the optimized formulation (F7) and the optimized formulation found that the similarity and dis similarity factors were correlated with the Reference product. So the formulated product was said to be equivalent with "Colofac MR" product.
- While coming to the discussion of dosage form of Modified Release coated pellets in capsule showed better drug release. Modified Release pellets have minimum volume in size, greater surface area, more surface activity and also no need of disintegration time for pellets in capsules. As pellets are small in size they enter into the systemic circulation very fast. Moreover there was no accumulation of drug in the body. Drug release rate was more when compared with the Reference (Colofac MR) sample.
- Finally it concludes that Modified Release pellets in capsule formulation (F7) have relevant drug release rate, stability and bioavailability as that the Reference.

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