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Research Article

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Fabrication Development and Characterization of Extended Release Film Coated Formulation of Antimuscarinic Agent for the Treatment of Irritable Bowel Syndrome (IBS).

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Abstract The aim of this current study was to develop extended release matrix film coated tablets of mebeverine hydrochloride to augment the therapeutic efficacy, diminish the frequency of administration and get better the patient compliance. The matrix film coated tablets were fabricated by wet granulation method, using different polymers such as Hydroxyl propyl methyl cellulose (HPMC K15M), Eudragit, Microcrystalline cellulose pH 101 (MCC) alone or in combinations and other standard excipients. Drug compatibility with excipients was checked by FTIR studies. 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. Then the tablets were evaluated in terms of their physical parameters (weight variation, hardness, friability and thickness), drug content and *in-vitro* release studies. All the formulations showed compliance with pharmacopoeial standards, Further, tablets were evaluated for *in-vitro* release characteristic for 12 h. Tableting of granules was showed good flow properties and fabricated tablets were exhibited desired compressibility characteristics. Formulation SRTM3 exhibited an *in-vitro* drug release up to of 90 % and the release kinetics of drugs was best explained by First order kinetic model and the mechanism was found to be non-Fickian/anomalous according to Korsmeyer-Peppas equation.

Keywords Antimuscarinic agent, HPMC, Sustained release, Irritable bowel syndrome, Stability studies.

Introduction

Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. 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 [1].

Extended release formulation is an important program for new drug research and development to meet several unmet clinical needs. There are several reasons for attractiveness of these dosage forms viz. provides increase bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug [2-3].

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder of unknown cause. Common symptoms include abdominal cramping or pain, bloating and gassiness, and altered bowel habits. Irritable bowel syndrome has also been called spastic colon, functional bowel disease, and mucous colitis (Chouinard, Jones, Remington 1993). Over the past decade an entirely new technique for the delivery of a drug and other biologically active agents has been developed. This technique for the drug administration is termed as "sustained release or "controlled release" [4-5].
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 2.5 h, plasma protein binding 75 % and rapidly absorbed after oral administration with peak plasma concentration occurring in 1-3 h. A dose of 135 mg Mebeverine appears to provide effective relief from the symptoms of irritable bowel syndrome but higher frequency of administration of drug may lead to high plasma concentration, resulting in to systemic side effects like decreased heart rate and blood pressure. Sustained release oral drug delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects Mebeverine hydrochloride is an antimuscarinic. Mebeverine hydrochloride belongs to a group of compounds called Musculotropic antispasmodics. These compounds act directly on the gut muscles at the Cellular level to relax them. Mebeverine hydrochloride is also an inhibitor of calcium-depot replenishment. Therefore, Mebeverine hydrochloride has dual mode of action which normalizes the small bowel motility [6-8].

Material and Methods

The whole description of material procured and sources are given in Table 1. All other chemicals and solvents were purchased from analytical grade.

Table 1: Description of materials and sources

S. No.	Materials	Company name
01.	Mebeverine HCl	Triveni chemicals, Vapi, Gujarat
02.	HPMCK15M	Colorcon Asia Bio limited. (India).
03.	Eudragit	Colorcon Asia Bio limited. (India).
04.	Micro crystalline cellulose	Colorcon Asia Bio limited. (India).
05.	Magnesium stearate	SD Fine chemicals
06.	Starch	SD Fine chemicals
07.	Talc	SD Fine chemicals

Methods

Compatibility study of Mebervine hydrochloride by FTIR

Compatibility study was carried for pure Mebeverine hydrocloride and combination of Mebeverine hydrocloride with excipients. Fourier transfer infra red (FTIR) spectroscopic (shimadzu, Japan) studies were carried out by approximately diluting the sample with dried potassium bromide and acquiring infrared (IR) spectrum in the range of 400 to 4000 cm^{-1}.

Formulation development

Sustained release tablets containing 135 mg of Mebeverine hydrocloride drug were prepared with a total tablet weight of 300 mg. Considering the preformulation studies and the literature survey conducted the excipients were selected and an attempt to produce Sustained release tablets with basic tablet properties was made [9-10].

Fabrication of sustained release tablets of Mebeverine hydrochloride

Dissimilar tablet formulations were fabricated by the wet granulation technique. Active pharmaceutical ingredient and excipients (HPMC K15M, MCC, Eudragit, Talc, Strach, and Magnesium stearate) were accurately weighed as mentioned in the Table 2. Active pharmaceutical ingredient, Hydroxy propyl methyl cellulose and Micro crystalline cellulose were passed through sieve 40# and mebeverine HCl passed from sieve no 30#. The ingredients were mixed in polylined container, mixed for 5 min to ensure uniform disintegration of drug. Then isopropyl alcohol was added

to water by drop by drop stirred continuously. The binder solution was added slowly to the dry mixed ingredients with constant mixing stirring till to got solid mass to form uniform and optimum granules. The way of determine the optimum granules was to press a portion of the mass in the palm of the hard, the mixture has ready for the next stage in processing which has been wet screened. While drying at different time intervals, samples were removed randomly from the total bulk of the granules, and then checked out the diverse moisture content. After, mass of cohesive material was passed through sieve 22# and 44#. These granules were dried in tray dryer till the preferred limit for loss on drying is achieved. The dried granules were passed through sieve 20# and Magnesium stearate were passed through sieve 60#, and adosbent (colloidal anhydrous silica) homogeneously mixed with the dried granules in the polybag for 5 min get a uniform blend. Then the intermingled product was compressed (10.5mm, diameter, flat punches) using multipunch tablet compression machine (Cadmach, Ahmadabad, India) in such a way that each tablet should contains 200 mg of mebeverine HCl [11].

Table 2: Composition of extended release film coated tablets of mebeverine hydrochloride

Ingredients (mg)	**SRTM1**	**SRTM2**	**SRTM3**	**SRTM4**	**SRTM5**	**SRTM6**
Mebeverine hydrochloride	130	130	130	130	130	130
HPMCK15M	80	100	120	---	---	---
MCC (P^H 101)	25	25	25	25	25	25
Eudragit S-100	---	---	---	80	100	120
Magnesium stearate (2 %)	5	5	5	5	5	5
Talc (3 %)	10	10	10	10	10	10
Starch	50	30	10	50	30	10
Total weight (mg.)	300	300	300	300	300	300
Composition of coating material of extended release tablet of mebeverine hydrochloride						
S. No.	Coating material					
1.	HPMC E5M					
2.	Titanium dioxide					
3.	Ethyl cellulose					
4.	Propyl glycol					
5.	Isopropyl alcohol					
6.	Dichloromethane					

Characterization of sustained release tablets of mebeverine HCl:

Pre-compression studies of sustained release tablets:

Bulk density: It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by: [12]

$$Db = M / Vb$$

Where, M is the mass of powder Vb is the bulk volume of the powder.

Tapped density: It is the ratio of mass the powder taken to the volume occupied after specific tapping. It was determined by USP method II, tablet blend was introduced in the 100 ml graduated cylinder of tap density tester, which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated using the following formula: [12]

$$Dt = M / Vt$$

Where, M is the mass of powder Vt is the tapped volume of the

Angle of repose: It was measured by fixed funnel method. The fixed funnel method employ a funnel that was secured with its tip at a given height 'h', above graph paper that was placed on a flat horizontal surface. Granules

were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel, 'r' being the radius of base of the conical pile. The angle of repose is then calculated as: [13]

$$\mathbf{Tan\ \theta = h/r\ (or)}$$

$$\mathbf{\theta = Tan^{-1}\ h/r}$$

Where θ = angle of repose h = height of the cone r = Radius of the cone base.

Carr's Compressibility Index: The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index: [14]

$$\mathbf{Carr's\ compressibility\ index\ (\%) = [(Dt\text{-}Db)\ X\ 100]\ /\ Dt}$$

Where, Dt is the tapped density Db is the bulk density

Loss on Drying (LOD): The moisture content of the granules was investigated by using Infra Red Moisture Analyzer. 1.0 gm or more quantity of granules was heated at 105 ^{o}C until the change in the weight was no more seen by the instrument. The % loss in weight was recorded. [14]

Hauser's ratio: Hauser's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula: [15]

$$\mathbf{Hausners\ ratio = Dt/Db}$$

Where, Dt is the tapped density, Db is the bulk density.

Post compression studies of sustained release tablets:

The fabricated extended release tablets were charaterized for the following parameters.

Average Weight variation: Weight variation test was done as per USP methods, twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed (Shimadzu, Japan), and Deviation of each tablet from average weight was calculated and percent deviation was computed. The deviation is compared with the Pharmacopoeial limits [16].

Hardness and Thickness: Hardness was measured using Monsanto hardness tester for each batch six tablets were tested. Thickness was done by using Screw-gauge micrometer**.** Twenty tablets from each batch were randomly selected and thickness was measured [17].

Friability: Weigh accurately 20 tablets and situate them in the friability test apparatus. Adjust the timer to 4 min. Maneuver the apparatus at 25 rpm and monitor the tablets while rotating, such that no tablet sticks to the walls of the apparatus. Take the tablets out and scrutinize for possible capping as none of these should be observed for the test to be valid. Weigh the tablets, after dusting excess powder from their surface. Friability in % is calculated using the formula:

$$\mathbf{Friability = (W1\text{-}W2) \times 100/W1}$$

Where **W1** = Initial weight of the tablets taken, **W2** = Final weight of the tablets after testing.

Assay of fabricated tablets:

Twenty tablets from each batch were weighed and powdered. Powder equivalent to the average weight of the tablet was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of buffer pH 6.8. The solution was made up to the mark and mixed well. A portion of the sample was filtered and analyzed by a UV spectrophotometer (Shimadzu UV-150, Japan) at 264 nm [18].

***In-Vitro* dissolution profile of sustained release tablets:**

In vitro drug release was determined by using USP XXIII dissolution apparatus II. The release studies were performed at 100 rpm in 900 ml of using 0.1N HCl for first 2 h and followed by phosphate buffer pH 6.8 up to 12 h. The temperature was maintained at 37 ± 0.5 ^{o}C. Ten milliliters of sample was withdrawn at predetermined time intervals and the volume of the dissolution medium was maintained by adding the same volume of fresh prewarmed buffer every time. The withdrawn sample was filtered through a 0.8 μm filter membrane and the absorbance was measured spectrophotometrically (Shimadzu UV-150, Japan) at 264 nm. [19]

Comparison of dissolution profiles:

The similarity factor (f2) was employed to characterize the release profiles of an assortment of formulations compared with the superlative release profile. Where 'n' is the number of dissolution time points, and R and T are the references and test dissolution values at time t. The similarity factor (f2) is a logarithmic transformation of the sum-squared error of differences between the experimental drug release Tt and the ideal drug release Rt for over all time points 'n'. The similarity factor fit the result between 0 and 100. It is approached 0 as the dissimilarity of the test and the reference profile increased, whereas, it attained 100 when the test and the reference profile were identical Table 3.

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Table 3: Range of similarity factor

S. No.	Similaity factor	Significance
1.	<50	Test and reference profiles are dissimilar
2.	50-100	Test and reference profiles are similar
3.	100	Test and reference profiles are identical
4.	>100	The equation yields a negative value

Kinetics of release of active pharmaceutical ingredient: Release kinetics models are assumed to reflect different release kinetics mechanisms. The zero order rates describe the systems where the drug release rate is independent of its concentration. The first order equation two, describes the release from systems where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion equation [20-21]. The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of tablets or particles:

$$\mathbf{C = k_0 t}$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\mathbf{Log\ C = Log\text{-}C_0\ kt / 2.303}$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$\mathbf{Q = kt^{1/2}}$$

Where, K is the constant reflecting the design variables of the system.

$$\mathbf{Q_0^{1/3} - Qt^{1/3} = KHC\ t}$$

Where, Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson-Crowell rate equation.

The release of drugs from the matrix tablets can be analyzed by release kinetics theories .To describe the kinetics of drug release from matrix tablets, release data was analyzed according to

Korsmeyer- Peppas equation

$$\mathbf{Mt/M\infty = Kt\ n}$$

Where,

Mt/M∞ = fraction solute release, t = release time, K = kinetic constant characteristic of the drug/ polymer system n = exponent that characterizes the mechanism of release of traces

Stability studies: These studies were carried out for the optimized batch for a period of three months at room temperature (25±2 ^{o}C/60±5 % RH) as per ICH guidelines and an accelerated stability conditions (40±2 ^{o}C/75±5 % RH). Then the tablets at specific intervals were evaluated for appearance, average weight, drug content and *In-vitro* release [22-23].

Result and Discussion

Pre-formulation studies: Physical mixture of active pharmaceutical ingredient and polymer was evaluated by FTIR spectral analysis for any physical as well as chemical modification of the drug characteristics. From the outcome, it

was established that there was no intrusion in the functional groups as the principle peaks of the mebeverine HCl, were found to be impervious in the spectra of the drug-polymer physical mixture Figure 1.

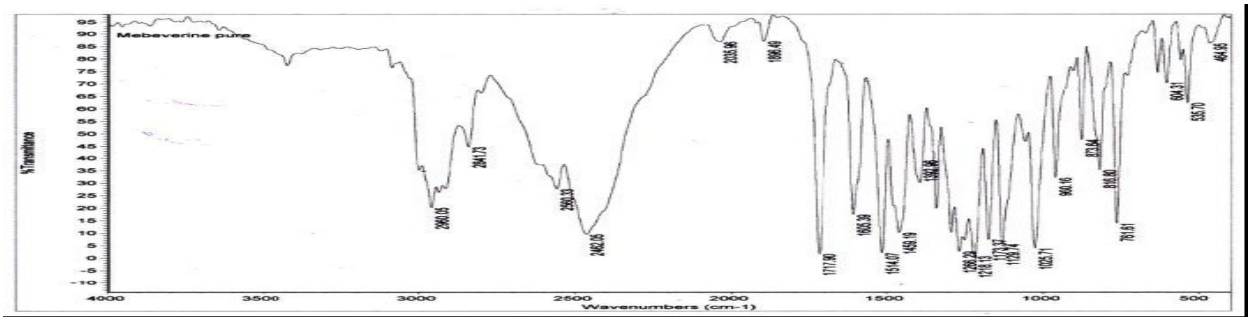

Figure 1: FTIR spectra of active pharmaceutical ingredient (Mebeverine HCl)

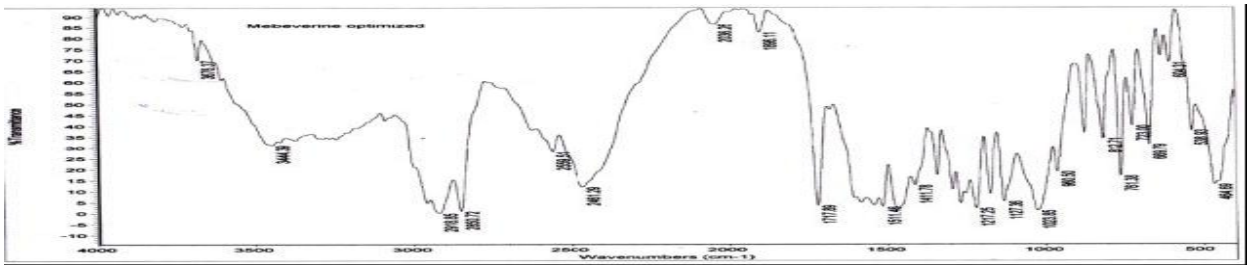

Figure 2: FTIR spectra of optimized formulation SRTM3

Outcome of pre compression of sustained release tablet: All the formulations fabricated by wet granulation method resulted the angle of repose less than 27 ^{o}C, which reveals good flow property Table 4. The loose bulk density and tapped bulk density for the whole formulation blend varied from 0.528 gm/cm^3 to 0.562gm/cm^3 and 0.647 gm/cm^3 to 0.673 gm/cm^3 respectively Table 4. The bulk density depends on particle size, shape and cohesiveness of the particles. The results of compressibility index (%) varied from 14.18 to 20.47. The Hausner's ratio was found from 1.03 ± 0.04 to 1.21 ±0.004, which is well within the possible.

Table 4: Outcome of pre compression of sustained release tablet (SRTM1 to SRTM6)

Evaluation parameters	SRTM1	SRTM2	SRTM3	SRTM4	SRTM5	SRTM6
Angle of repose (Ø)	22.35	23.56	24.54	25.67	25.98	24.78
Bulk density (g/ml)	0.535	0.561	0.546	0.555	0.538	0.542
Tapped density(g/ml)	0.643	0.655	0.650	0.679	0.663	0.659
Compressibility index (%)	16.90	17.34	18.11	16.55	18.98	20.78
Hausenr's ratio	1.23	1.34	1.37	1.28	1.30	1.37
Loss on drying (%)	2.11	1.89	2.34	2.87	1.98	2.77

Outcome of post compression of sustained release tablet: The hardness values ranged from 5 to 9 kg/cm^2 for formulations were almost uniform. Tablet hardness is not as absolute strength. Friability values were found to be within the limit. Thus tablets hold good mechanical strength. All the tablets passed weight variation test as the average percentage weight variation was within the pharmacopoeia limits of 7.5 %. The weight of all the tablets was found to be uniform with low standard deviation. The drug content of the tablets was found to be between 98.2 to 100 %. The outcomes were within the range and that indicated uniformity of mixing. The cumulative percentage drug released by each tablet in the *in vitro* release studies was based on the average drug content present in the tablet. All the figures related to post compression studies are given in Table 5.

Table 5: Outcome of post compression studies of sustained release tablet (SRTM1 to SRTM6)

Evaluation parameters	SRTM1	SRTM2	SRTM3	SRTM4	SRTM5	SRTM6
Average weight (mg)	300	302	300	301	302	301
Thickness	4.2-4.5	4.3-4.7	4.1-4.6	4.34-4.78	4.12-4.66	4.22-4.87
Hardness (kg/cm^2)	6.22	7.16	6.89	6.29	7.23	6.98
Friability (%)	0.245	0.378	0.458	0.222	0.543	0.478
Drug content	98.90	99.23	99.97	98.23	99.34	99.56

***In vitro* release profile of mebeverine sustained release tablets:** The percentage drug release profiles of mebeverine hydrochloride from six formulations were used with dissimilar polymers. It was seen that the polymers sway the drug release pattern. A considerably higher rate and extent of release was observed from batches based on eudragit than those based on hydroxy propyl methyl cellulose. The *in-vitro* drug release characteristics were studied in 900 ml of pH 6.8; using USP XXIII dissolution apparatus type II (paddle) method. Formulation SRTM4 could not able to sustained up to 24 hours , 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. The results of dissolution studies indicates that SRTM6, SRTM5, SRTM1 released 95.67 %, 96.87 % and 85.48 % of mebeverine at the end of 24 h. In case of Formulation SRTM3 drug released up to 24 h with maximum release of 96.77 %, this is due to high consistence of gelatinous layer with help of incorporating high amount of low viscous polymer figure 3.

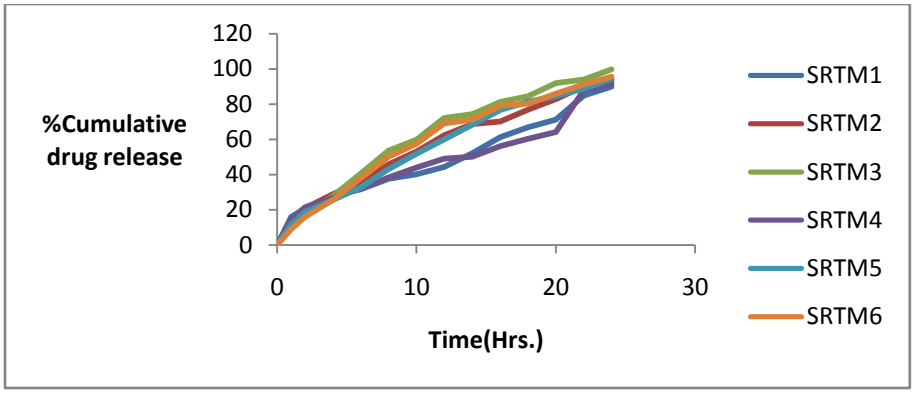

Figure 3: Dissolution release profiles of different sustained release formulations

Kinetics of release of active pharmaceutical ingredient: To depict the drug release kinetics of from matrix tablets, release data was analyzed according to diverse kinetic equations. Such as zero order, first order, Higuchi's model, Korsmeyer-peppas, and Hixson-crowell.The data were analyzed by the regression coefficient method and regression coefficient value (r^2) of all batches are shown in Table 6.

Table 6: Kinetic treatments of dissolution data for optimized formulation SRTM3

S. No.	Formulation code	Correlation coefficients (R^2)				Release exponent (n)
01.	SRTM3	0.9678	0.9885	0.9934	0.9912	0.5389

Table 7: Similarity factor analysis of *In vitro* drug release of SRTM2, SRTM3, SRTM6

Formulation	Similarity factor [F_2]
SRTM2	49.98
SRTM3	82.48
SRTM6	57.34

Table 8: Comparison between optimized SRTM3 and marketed tablet

Time (h)	ColospaTablet (Solvay Pharma)	SRTM3
1	9.12	11.45
2	15.98	17.21
4	25.67	27.87
6	38.01	40.45
8	50.11	53.67
10	57.34	59.81
12	69.12	72.19
14	71.29	74.30
16	78.99	81.27
18	80.24	84.45
20	85.89	91.90
22	91.27	93.88
24	98.45	99.76

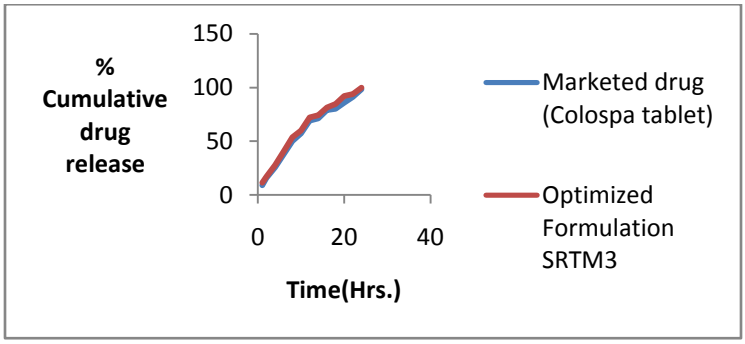

Figure 4: Comparison between optimized formulation SRTM3 and marketed tablet Colospa.

The *in vitro* release profiles of drug from all these formulations could be best expressed by Higuchi's equation as the plots showed highest linearity (r^2=0.975 to 0.982). To authenticate the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation. The formulations showed good linearity (r^2 = 0.971 to 0.990) with slope (n) between 0.465- 0.591, which appears to designate a coupling of diffusion and erosion mechanisms so called anomalous diffusion.

Stability studies:

The optimized formulation was subjected to stability studies as per ICH guidelines at room temperature ($25^oC\pm2^o/60^o\pm5\%RH$) and an accelerated stability conditions ($40^oC\pm2^o$ /75%±5%RH). After the storage period of 1 month and 3 months it was pragmatic that there was no alteration in physical appearance, hardness, drug content and in-vitro dissolution profiles, thus indicating the formulation unwavering. All the characters before and after stability studies and these values were represented in table 9.

Table 9: Stability studies of SRTM3 at room temperature ($25^oC\pm2^o$ /$60^o\pm5\%RH$)*

Evaluation parameter	Initial	After 1 month	After 2 months	After 3 months
Appearance	Satisfactory	Satisfactory	Satisfactory	Satisfactory
Average weight	298±0.12	299±1.23	297±0.09	298±2.51
Hardness (kg/cm^2)	6.56±0.09	6.89±1.13	6.78±2.33	7.12±0.87
Friability (%)	0.456±2.11	0.547±0.98	0.678±2.34	0.445±0.06
In-vitro drug release (%)*	96.31±1.91	97.31±2.91	99.31±1.51	98.16±1.39
Drug content	98.81±0.06	98.22±2.16	99.10±2.10	98.89±1.99

*Data are expressed as mean ±SD, n = 3

Conclusion

Mebeverine HCl film coated tablets were fabriacted for oral extended release delivery. This fabricated tablets showed acceptable parameters like hardness, thickness, friability, percentage weight variation and drug content. The acceptable extended release of the drug was achieved by using different polymers like HPMC, Eudragit, MCC. Batch SRTM3, SRTM5 and SRTM6 formulations were gave better sustained release in comparison to other prepared formulation and these formulations were best fitted to Korsmeyer peppas model. These outcomes suggested that the fabricated extended release have a potential for extended release dosage forms. Similarity factor (f2) which showed that formulation SRTM3 performed similar to marketed product therapeutically.

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