Development and *in vitro* characterization of mebendazole delayed release tablet for colonic drug delivery

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Abstract: The main objective behind this study was to formulate delayed release colon targeted tablet of Mebendazole by using different polymers. The precompressional parameters of powder blend were studied. The wet granulation method was used for the preparation of tablets. The tablets of all formulation were subjected for different physicochemical evaluation. The drug-excipient interaction study was carried out by using Fourier transforms Infrared spectroscopy (FTIR). The *in vitro* evaluation was carried out at different pH ranges (0.1M HCl, 6.8 and 7.4 Phosphate buffer) for the prepared tablets. From the stability, Fourier transform infra-red spectroscopy studies Mebendazole tablet does not show any interaction between drug and polymer. The prepared tablets were complied all the physicochemical test as per official limit. The formulated (M3) batch shows better sustained release 99.89% over a period of 12 hours and the data was fitted into Korsemeyer-Peppas kinetic equation. The result indicates that Mebendazole colon targeted matrix tablet remain stable in the stomach and shows better release into the colon with the help of pH dependent synthetic polymers.

Keywords: Mebendazole, Eudragit, PVP K30, colon targeted tablet.

INTRODUCTION

The colonic drug delivery is nothing but the targeted drug delivery of the drug into lower part of the GI tract, which can comes into large intestine (i.e. colon). The targeted delivery of drug to the lower GIT is beneficial into local treatment of colonic disorders (Glibert *et al*., 2002, Abdul *et al.,* 2003, Bajpai *et al.,* 2003). The colonic drug delivery has importance not only for delivering the drugs in the treatment of local disorders, but it can also have effective site for the systemic delivery of proteins and peptide drugs. After the oral administration through this delivery system, the system can allow to release the drug from it once the delivery system reaches into the colon. These types of delayed release mechanism are developed to increase the therapeutic effect of the drug by allowing the drug to release at the targeted site, and also to decrease the side effect and decrease instability of drug in upper parts of GIT (Mathiowitz *et al.,* 2003). Mebendazole is the drug used for the treatment of the helminthiasis caused by bacterial infection like hookworm, whipworm etc. The conventional tablet of Mebendazole gives better release in GIT but also cause unexpected side effects. The targeted delivery of the drug for localised treatment into colon is advantageous to avoid unwanted side effects and to produce effective localized treatment of helminthiasis at lower dose and dosing frequency. The Mebendazole is having half life of approximately 5 hrs and dose of 100 mg once a day (Robert *et al.,* 1992, Philip *et al.,* 2009, Chaurasia *et al.,* 2003, Krishanaiah *et al.,* 2001, Chien *et al* 1992).

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The Mebendazole is having broad-spectrum anthelmintic activity. The mode of action of Mebendazole depends on its inhibitory effect on polymerization of tubulin which produces loss of the cytoplasmic microtubules. Mebendazole produces degenerative modifications into the tegument and intestinal cells of the worm by binding with colchicine sensitive site of tubulin, thus it can inhibit the polymerization into microtubules. The loss of cytoplasmic microtubules can produce impaired uptake of glucose molecule by larval and the adult stages of highly susceptible parasites, and reduces their glycogen storage. Progressive changes into the endoplasmic reticulum, the germinal layer mitochondria, and the successive release of lysosomes give rise to decreased production of adenosine triphosphate (ATP), which is important for the existence of the helminth. Due to the reduced energy production, the parasite is immobilized and finally dies (Rang *et al.,* 1998).

MATERIALS AND METHODS

Materials

Mebendazole was obtained as gift sample from Unichem laboratories, Goa, India. Eudragit L100, S100 was obtained as gift sample from Deggusa India pvt, ltd, Mumbai, India. Guar gum was obtained as a gift sample from Ace gum Industries Ltd Bombay, PVP K-30 was purchased from S.D. fine chemical (India). Microcrystalline cellulose (Avicel pH 102) was obtained as a gift sample from Signet chemical, Mumbai. Talc and Mg. stearate brought from SD fine chemicals, Mumbai, India.

Preformulation Studies

Solubility studies of mebendazole

The solubility studies of mebendazole drug was carried out at different pH range. For the solubility study at pH 1.2, 0.1 N HCl, 6.8 and 7.4 phosphate buffer was used.

Assay of mebendazole

Weighed accurately 0.25 gm of drug then dissolve in 3 ml of anhydrous acetic acid and 30 ml of anhydrous glacial acetic acid and titrate with 0.1 M perchlorric acid. The end point was potentiometrically determined (1ml of 0.1 M perchloric acid = 0.02953 gm of C_{16} H_{13} N_3 O_3) (I.P. 2010).

Fourier transforms infrared spectroscopy (FTIR)

Fourier transform infra-red analysis was carried out for the structural characterization of drug, polymers and their physical mixture. Each sample was mixed with KBr and the analysis of these mixtures was done by FTIR (Shimadzu, IR Affinity-1).

Preparation of granules

The all powdered ingredients were weighed, mixed and granulated with the help of binder solution. This mixture was blended thoroughly and sieve it through aperture size 1 mm. The prepared granules were dried by using tray drier at a temperature range 35-45°C for 5 h. After drying the granules were screen and mixed with lubricants.

Evaluation of granules

Determination of bulk density and tapped density

Weighed amount of powder was transferred into the graduated cylinder and the volume (V_0) was measured. Then the graduated cylinder was packed with the help of lid and cylinder was set into the density determination apparatus. The density was set for 100 tablets and then the volume (V_f) was determined. The operation was continued till the two successive readings are the same. The calculation of bulk density and tapped density was done by using subsequent formulae.

Bulk density (gm/cm^3) = W/V_0 1

Tapped density (gm/cm^3) = W/V_f 2

Where,

W is weight of the powder

V_0 is the initial volume

V_f is the final volume

Hausner's ratio

The Hausner's ratio measured on the basis of the ratio of tapped density to bulk density.

Hausner's ratio was measured by using subsequent formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Carr's index

The compressibility index was measured by using subsequent formula:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Preperation of tablets

The Mebendazole tablets were prepared by wet granulation method using 10% PVP paste as binder. The mixture of magnesium stearate and talc in the ratio of 2:1 was used as lubricant and microcrystalline cellulose were used as diluent. The mebendazole tablets containing Guar gum, Eudragit L100, S100 were prepared. The different composition was used containing 100mg of Mebendazole. Polymers were mixed thoroughly with Mebendazole and MCC. The mixture of powder was blended and granulated with 10% PVP. The wet granules were dried and then dried granules were passed through sieve and lubricated with talc and magnesium stearate. The lubricated granules were passed for compression under 6mm round and concave punches. The compositions of tablet were shown in (table 1).

Evaluation of tablets

The hardness of the tablet was measured with the help of Monsanto hardness tester. The tablet hardness of the randomly selected 10 tablets were measured and described. The tablet friability was measured with the help of Roche friabilator. The randomly selected 20 tablets were weighed and then placed into the friabilator. After 100 revolutions the tablets were removed and dedusted. Reweighed the individual tablet with the help of electronic balance and the difference in weight was

Table 1: Formulation of Mebendazole tablets

Ingredients (mg/tab)	M1	M2	M3	M4	M5	M6
Mebendazole	50	50	50	50	50	50
Eudragit L100	----	50	50	----	----	100
Eudragit S100	50	----	50	----	100	----
Guar Gum	50	50	----	100	----	----
PVP K30	10	10	10	10	10	10
MCC	84	84	84	84	84	84
Magnesium stearate	4	4	4	4	4	4
Talc	8	8	8	8	8	8
Total	256	256	256	256	256	256

calculated as percent loss. The diameter and thickness of the tablets were measured with the help of Vernier caliper, the test was carried out as per the official technique.

Drug content uniformity

The drug content uniformity was measured by crushing and powdering 10 tablets, finally 100 mg of powder was accurately weighed and transfer to 100 ml of volumetric flask. Initially 50 ml of glacial acetic acid was added into the volumetric flask and allowed to stand for 6 hrs with an sporadic sonication for the complete solubility of drug. Make up volume upto 100ml with glacial acetic acid, centrifuge the mixture and 1ml the supernatant liquid was diluted, filtered and analyzed for drug content uniformity by UV spectroscopy method.

In vitro drug release

In vitro drug release study was performed using USP-II dissolution apparatus (Electrolab, 08 TDL) in 900 ml of pH 1.2 buffer for 2 hrs and at pH 4.5 phosphate buffer for 3 hrs. and then in pH 7.4 phosphate buffer for 12 hrs. The temperature of dissolution medium was thermostatically controlled with water bath, at 37±0.5^{0}C. The tablet was then placed into the dissolution flask and the paddle was set at 100 rpm. The 5ml of sample was withdrawn at different time intervals, and analyzed in UV spectrophotometer at 234 nm for the drug release. After each withdrawal, 5 ml of the fresh medium was added to the dissolution flask.

Kinetic modeling

The *in vitro* release data was treated to zero order equation (R=k1t), First order equation (Log UR= k2t/2.303), Higuchi equation (R=k3√t), and Korsmeyer–Peppas equation (Log R= log k4 + n log t) to determine the drug release mechanism of colon targeted tablets.

Accelerated stability studies

The accelerated stability studies were performed on group of tables performed in a batch. The tablets were enclosed into umber coloured glass container at 45°C + 75% RH for the period of 6 months. Samples were withdrawn at the interval of 2, 4 and 6 months and evaluated for physical characteristics, hardness, friability, drug content and *in vitro* drug release.

RESULTS

In the present study mebendazole colon targeted tablets were prepared with the help of natural and synthetic polymers by wet granulation method. After preparation of the tablets evaluation studies of the tablet was carried out by using different parameters and the results was shown below.

Solubility of mebendazole

The solubility of mebendazole was carried out in different pH medium and was given in (table 2).

Table 2: Solubility of Mebendazole

Solubility	Result
Water	0.005738
pH 1.2	0.036570
pH 6.8	0.073625
pH 7.4	0.089567

Assay of mebendazole

The assay of Mebendazole was performed as per the Indian Pharmacopoeia 2010 and the assay value of Mebendazole was found to be in the range of official limit i.e. 98-102%.

Preformulation studies

Micromeritic properties of mebendazole granules

The micromeritic properties such as bulk density, tapped density, hausner's ratio and carr's index of Mebendazole granules for six batches was performed and are shown in (table 3).

FTIR spectroscopy

IR spectra of pure drug, polymer and their physical mixture were carefully studies for the peaks position and their characteristic peak. The different peaks and their position observed in pure drug and polymer were also found in Mebendazole tablet (fig. 1).

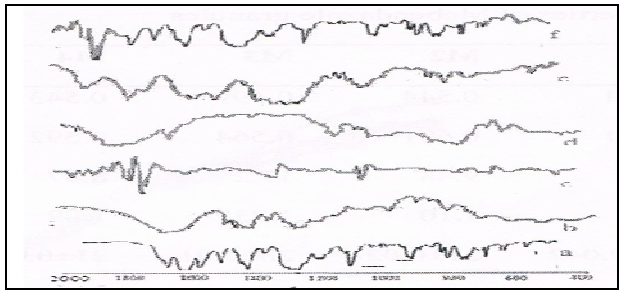

Fig. 1: FT-IR spectrum of drug (a), polymers (b-e) and mixture drug and polymers (f)

Physicochemical properties of tablet

The physicochemical properties of randomly selected tablets from six different batches were performed. The result was shown in (table 4).

In vitro drug release

The results of *in vitro* dissolution studies were performed by using three different pH medium drug release studies of six different batches in pH 1.2 buffer, 6.8 and 7.4 pH phosphate buffer. The % cumulative release of all six batches was shown in (fig. 2).

Kinetic modeling

The kinetic release of the Mebendazole tablets were analyzed by various kinetic models and ranked in order of Higuchi > Korsmeyers –Peppas >Zero order > First order

as shown in (table 5). Korsemeyer-peppas model gave highest squared correlation coefficient (0.989) for mebendazole tablets.

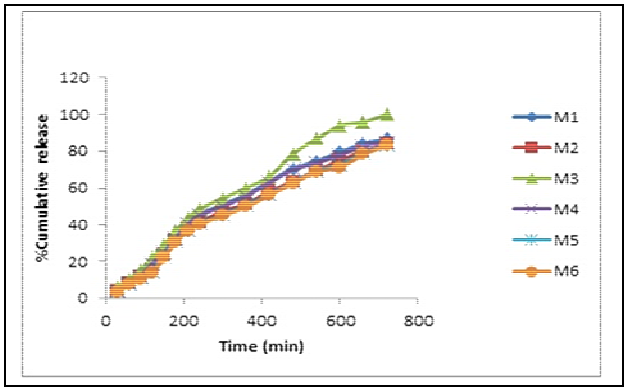

Fig. 2: *In vitro* drug release

F1 –F2 Factor

The value of difference factor (f1) and similar factor (f2) was found to be 6.515 and 89.1 respectively.

Stability study

The stability study was performed at 45°C + 75% RH for the period of 6 months without any significant changes to the physical appearance, hardness, friability and dissolution profiles. The results of stability studies was shown in (table 7)

DISCUSSION

When IR spectra of drug compared with spectra of drug band polymer, it would appear that there was no obvious interaction between drug and the polymers.

The tablet thickness was found in the range of 2.8 to 3.1 mm, hardness of the tablets was found in the range of 4.2 to 5.8 (kg/cm^2), tablet friability and weight variation was found in the range of 0.32 to 0.37% and 250 to 258 mg respectively. And the drug content was uniform and satisfactory (>99%) in all the batches.

All the colon targeted tablet formulation shows less percentage of drug release in first two hours at pH 1.2 buffer and 3-6 hours at pH 6.8 phosphate buffer. At the end of 12 hours all the batches shows less% of drug release but the batch M3 containing polymer Eudragit L100 and S100 in combination shows better release kinetic as compare to other five batches. On the basis of close comparison of the release properties of formulation batch M3 and the reference product and further dissolution studies. The results indicated that there is close similarity between the two products on the basis of low f1 i.e. (<15) and high f2 i.e. (>50). So it was concluded that the tablets of batch M3 (containing 1:1 ratio of Eudragit L100 and S100) was found to be similar to the marketed formulation of Mebendazole (reference) in relation to drug release

Table 3: Micromeritic properties of Mebendazole granules

Test	M1	M2	M3	M4	M5	M6
Bulk density	0.43±0.06	0.53±0.08	0.49±0.03	0.47±0.02	0.52±0.08	0.50±0.07
Tapped density	0.61±0.06	0.60±0.04	0.56±0.08	0.59±0.01	0.60±0.03	0.58±0.06
Carr's index	8.19±0.08	9.48±0.05	17.2±0.04	8.47±0.03	13.1±0.04	13.6±0.05
Hausner's ratio	1.08±0.05	1.10±0.06	1.23±0.03	1.09±0.09	1.15±0.06	1.16±0.08
Angle of repose	24.5±0.042	21.8±0.02	28.2±0.01	21.4±0.02	19.4±0.02	18.9±0.04

Table 4: Physicochemical properties of matrix tablet

Batch	M1	M2	M3	M4	M5	M6
Thickness (mm)	2.9±0.018	2.9±0.025	2.8±0.016	3.1±0.017	3.0±0.022	3.1±0.018
Hardness(kg/cm^2)	5.8±0.26	4.2±0.15	5.8±0.25	5.1±0.23	5.3±0.21	5.5±0.56
Friability (%)	0.32±0.03	0.37±0.02	0.35±0.02	0.39±0.04	0.34±0.02	0.35±0.05
Weight variation	250.5±2.5	256.8±3.1	252.7±1.4	258.1±2.4	254.6±1.8	256.5±2.7

Table 5: Kinetic Release

Formulation Code	Zero order equation	First order equation	Higuchi equation	Korsmeyer-Peppas equation	
	R^2	R^2	R^2	R^2	n
M1	0.889	0.974	0.967	0.958	1.40
M2	0.937	0.976	0.974	0.955	1.22
M3	0.962	0.978	0.912	0.966	1.38
M4	0.925	0.966	0.976	0.989	1.25
M5	0.954	0.970	0.975	0.977	1.37
M6	0.956	0.942	0.961	0.960	1.32

Table 6: Pharmacokinetic studies

Pharmacokinetic Parameter	Sustained Release Marketed Tablet	Colon Targeted Tablet M3	P<
AUC (ng/ml/h)	532.3±86.1	558.0±211.0	NS
Elimination half-life (h)	9.1±2.9	14.1±5.6	NS
Absorption time t_a (h)	5.2±0.9	10.3±1.7	0.05
Absorption rate constant	1.45±0.36	0.7156±0.0089	0.05
T_{max} (h)	8.2±0.9	12.2±1.7	0.001
$C_{max\ (ng/ml)}$	40±6.8	28.7±2.6	0.05

Table 7: Stability of best batch M3 at 45^0 C and 75% RH

Physical Parameters	1 Month	2 Months	4 Months	6 Months
Wt. variation	256	256	256	255
Hardness	5.8	5.8	5.7	5.7
Friability	0.35	0.36	0.36	0.37
Drug Content	0.99	0.99	0.98	0.98

The drug release from the prepared colon targeted tablet is controlled by diffusion and is independent of unreleased drug amount within tablet. The colon targeted Mebendazole tablets follows the Korsemeyer-peppas equation with r^2 value of 0.989. Korsemeyer-peppas model indicated that system majorly depends on diffusion for drug release. This may be due to presence of eudragit which controls drug release through its swelling properties.

In *vivo* pharmacokinetic study in healthy human volunteers shows difference between M3 and marketed formulations was significant for C max, T max, AUC and was found to be comparable indicating that formulation exhibited comparable extended release.

CONCLUSION

From the above study the prepared colon targeted tablets showed excellent physicochemical properties, stability and prolonged drug release. The Mebendazole colon targeted tablets approach with combination of both Eudragit L100 and Eudragit S100 (M3) satisfy all the criteria and show maximum sustained release action as compare to other batches. On the basis of experimental studies we concluded that Mebendazole colon targeted tablet of batch code M3 with the help of pH dependent synthetic polymers (Eudagit L100 and S100) were found significant for the prolong period and prove better delivery of the Mebendazole for colon targeted drug delivery. The formulation method was simple and easily adaptable for commercial purpose.

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