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FORMULATION AND EVALUATION OF MATRIX TABLETS OF ALBENDAZOLE FOR COLON TARGETED DRUG DELIVERY

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ABSTRACT

In the present research, an attempt was made to develop an efficient pH sensitive colon targeted drug delivery system of Albendazole for local action in proximal colon against trichuriasis (whip worm infections primarily in cecum and proximal colon). Albendazole matrix tablets containing varying proportions of single blends of three pH sensitive polymers; Eudragit S100, Hydroxy Propyl Methyl Cellulose Phthalate HP 55 (HPMC Phthalate HP55), Ethyl cellulose (Etcell), with different threshold pH 7.0, 6.8, 7.2 respectively were prepared by wet granulation technique involving drug polymer ratio studies in 1:1, 1:1.5, 1:2, 1:2.5 ratios. *In vitro* release profiles of Albendazole was sequentially determined in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) pH 6.8 and simulated colonic fluid (SCF) pH 7.2. The *in vitro* drug release from matrix tablets containing HPMC Phthalate HP55 and EC polymers showed release of 20-47% of Albendazole in SIF, followed by a burst release in SCF. However, matrix tablets containing polymer blends Eudragit S100 showed that no appreciable drug release occurred in SIF (0-20%). Among them, the formulations with drug polymer ratios 1:2 and 1:2.5 showed a minimal release of drug in SIF 1.3% and 0.27%. The formulation with drug polymer ratio 1:2 was selected as optimized formulation because it showed a maximize release in proximal colon i.e. First 2hrs in SCF and the formulation with drug polymer ratio 1:2.5 showed an extended release up to 3hrs in SCF in turn missing the release in the target site i.e. proximal colon. All the systems were found to be stable with respect to drug content as well as physical changes at 40^0C and 75% RH. The results suggest that pH sensitive polymer based matrix tablets containing Eudragit S100 in drug polymer ratios 1:2 are potential means to achieve targeted colon drug delivery for effective therapy of Albendazole.

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INTRODUCTION

From past two decades, considerable amount of research work has been carried out in the area of colon targeting. By considering the advantages of CTDDS like providing friendlier environment for protein and peptide drugs that reducing the adverse effects in the treatment of colonic diseases, site specific release to treat colonic cancer, amoebiasis, and helminthiasis etc, minimizing the extensive first pass metabolism of steroids and produces delay in absorption of drugs to treat rheumatoid arthritis, angina and nocturnal asthma etc., different approaches are designed to develop colonic drug delivery system[1].

Albendazole is a broad spectrum anti helminthic which is used as first line drug for the treatment of trichuriasis which is caused by whipworm primarily in the tissues of cecum and colon. When administered as a conventional formulation it causes abdominal pain, epigastric distress, stomach pain, acute liver failure[3]. To eradicate these side effects, the release of Albendazole in the stomach and intestine must be minimized which in turn can be achieved by targeting Albendazole to its primary site of action i.e. colon. In the present study it has been aimed at developing pHsensitive matrix tablets of Albendazole with a view of minimizing the drug release in the physiological environment of stomach and small intestine and to ensure maximum drug release in the physiological environment of colon with an improved patient compliance, least side effects, better drug therapy and all aspects of an ideal drug delivery system.

MATERIAL AND METHODS

Materials

Albendazole and all polymers were obtained as gift sample from Hetero drugs. Ltd, Hyderabad. other chemicals are obtained from S.D Fine chemicals.

Methods

Formulation of pH sensitive matrix tablets of Albendazole

Wet granulation technique

- The pH sensitive matrix tablets were prepared by wet granulation technique in which the isopropyl alcohol which act as granulating agent.
- Albendazole matrix tablets containing varying proportions of single blends of three pH sensitive polymers; Eudragit S100, Hydroxy Propyl Methyl Cellulose Phthalate HP 55 (HPMC Phthalate HP55), Ethyl cellulose (Etcell), with different threshold pH 7.0, 6.8, 7.2 respectively were prepared by wet granulation technique involving drug polymer ratio studies in 1:1, 1:1.5, 1:2, 1:2.5 ratios.
- Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce granules. First the weighed quantities of Albendazole, diluents and polymer were passed through a sieve of 44 mesh size. Next the mixture was blended to form homogenous mixture. Then Isopropyl alcohol was used as granulating fluid to get the dough mass, which was passed through sieve no 10 to get wet granules. These granules were air dried for 15 minutes and the dried granules are passed through sieve no 18 to get uniform dried granules. Then these granules were lubricated with weighed quantities of magnesium stearate and talc that was previously sieved in sieve no 44.
- The prepared granules are then evaluated for Precompression parameters like angle of repose, bulk density, tapped density, carr's index and hausners ratio.
- Then the granules are compressed to tablets using a tablet compression machine.

Table 1: Composition of Formulation

INGEREDIENTS (mg)	FORMULATIONS											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Albendazole	100	100	100	100	100	100	100	100	100	100	100	100
HPMC Phthalate HP55	100	150	200	250	-	-	-	-	-	-	-	-
Eudragit S100	-	-	-	-	100	150	200	250	-	-	-	-
Ethyl cellulose	-	-	-	-	-	-	-	-	100	150	200	250
Dibasic calcium phosphate	190	140	90	40	190	140	90	40	190	140	90	40
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Total weight of tablet = 400mg. q.s = Quantity sufficient.

POST COMPRESSION EVALUATION TESTS

Weight variation: Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated.

Thickness: Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The thickness of tablet is measured by vernier callipers scale.

Hardness: The strength of tablet is expressed as tensile strength (Kg/cm^2).It was measured using a tablet Monsanto hardness tester.

Friability: Friability of the tablets was determined using Roche Friabilator (Electrolab, India). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula

$$F\ \% = (1 - W_0 / W) \times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test

Content uniformity: 20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 10mg was weighed and dissolved in 100ml of7.2 pH buffer filtered and drug content analyzed spectrophotometrically in U-Vis spectrophotometer at 254 nm.

***In vitro* drug release studies:** *In vitro* drug release of Albendazole pH sensitive matrix tablets of Albendazole was determined using USP Dissolution Apparatus II (Paddle type) (Electrolab TDT-08L). The dissolution test was performed using 900 ml acidic buffer pH 1.2 at $37^0C \pm 0.5^0C$ for 2 hours followed by 3 hours dissolution using phosphate buffer pH6.8 and finally for 3 hours in 7.2 phosphate buffer . The speed of rotation of paddle was set at 100 rpm. 5 ml samples were withdrawn at time points of 2, 5, 5.5, 6, 6.5, 7, 7.5and 8 hours and same volume was replaced with fresh media.

RESULTS AND DISCUSSION

RESULTS

FTIR analysis

Fig. 1: FTIR spectra of albendazole from monograph

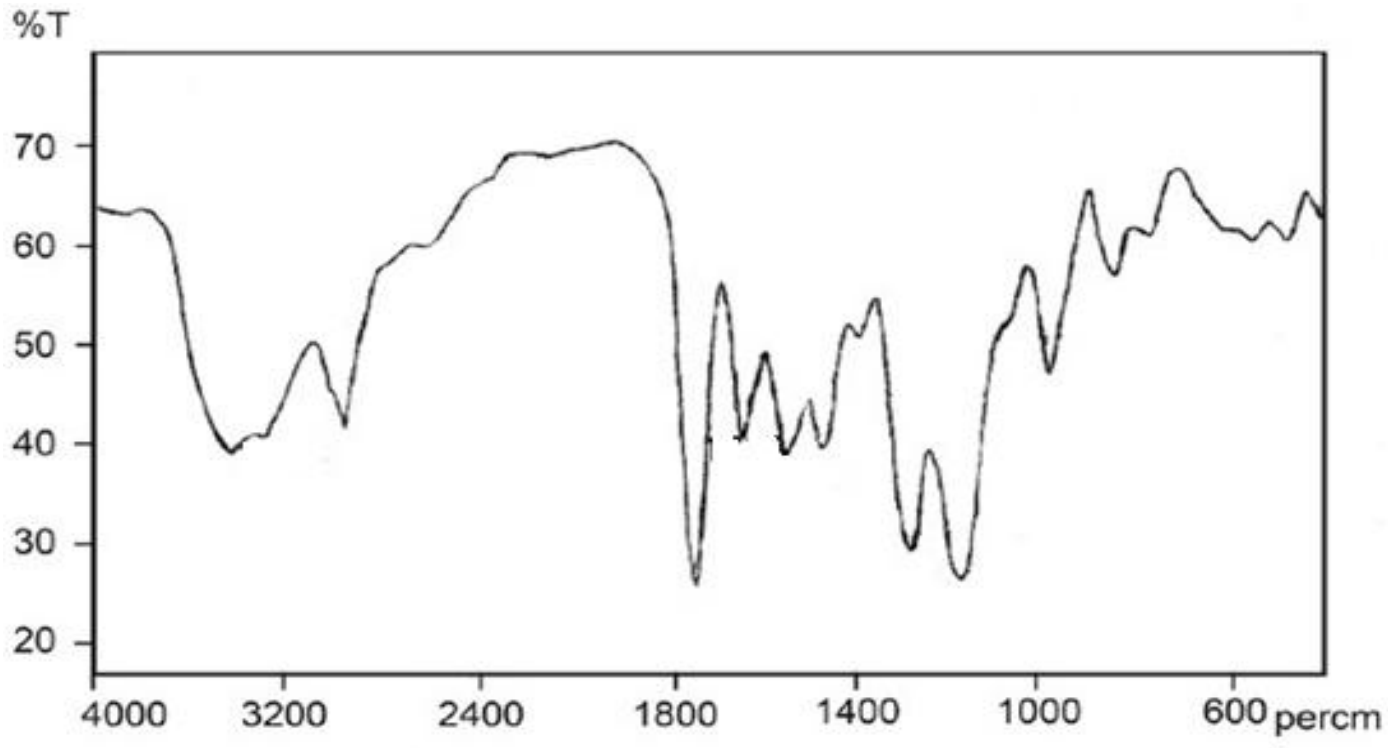
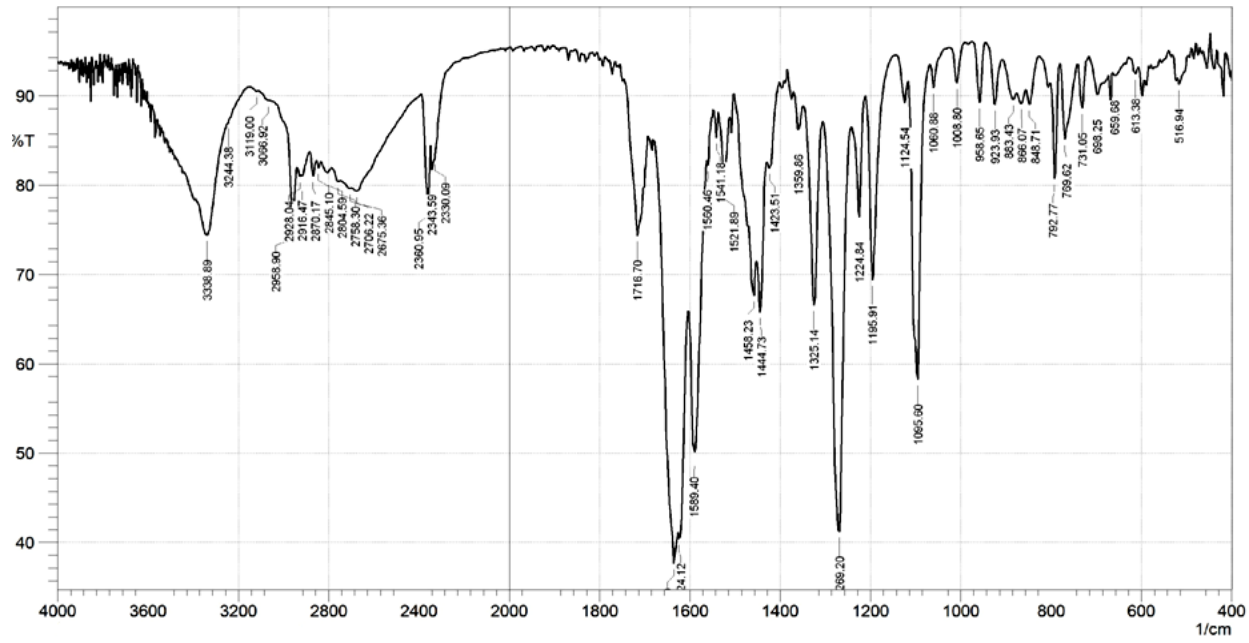


Fig 2: FTIR spectra of albendazole drug sample



POST COMPRESSION EVALUATION TESTS

Physical appearance: tablets were white in color with good texture. Plane on one side and debossed on other side.

Fig 3: FTIR spectra of formulation SF3 (albendazole + Eudragit S100 + DCP)

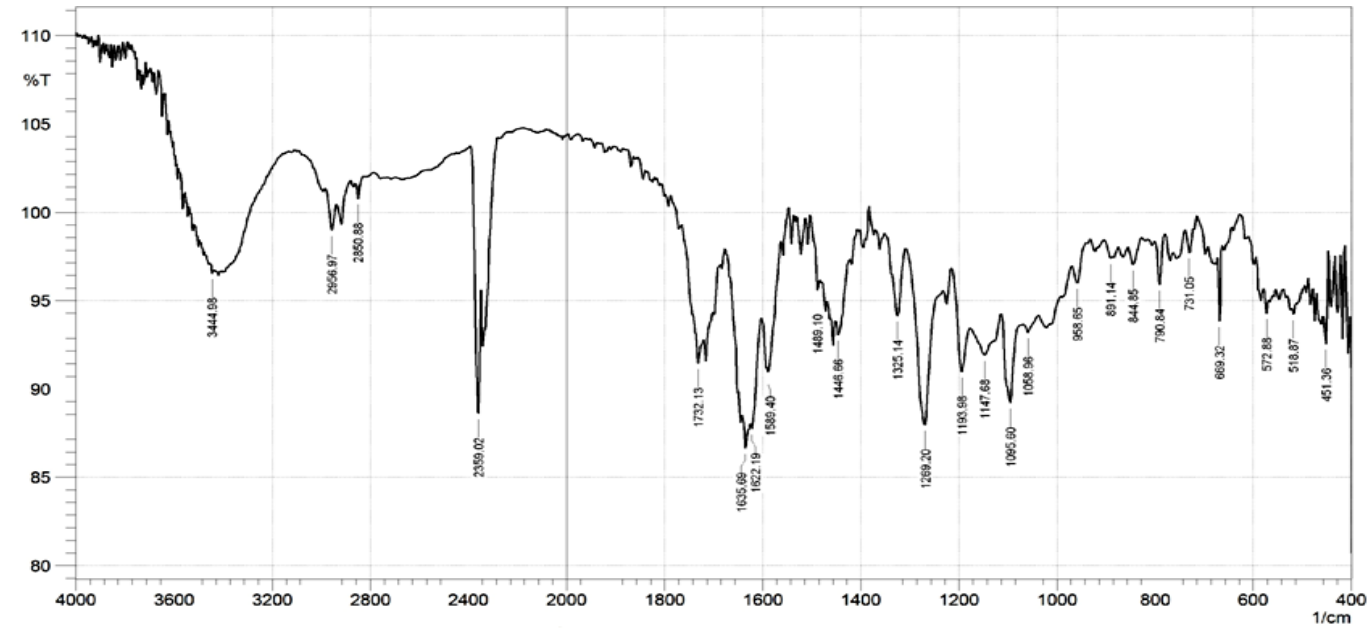
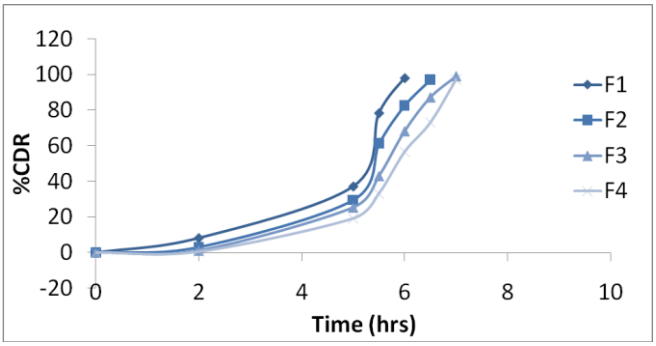
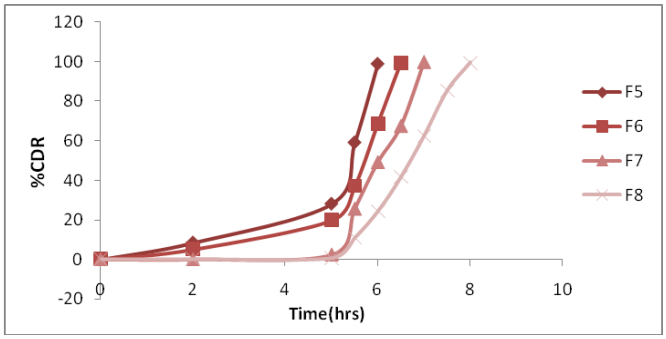
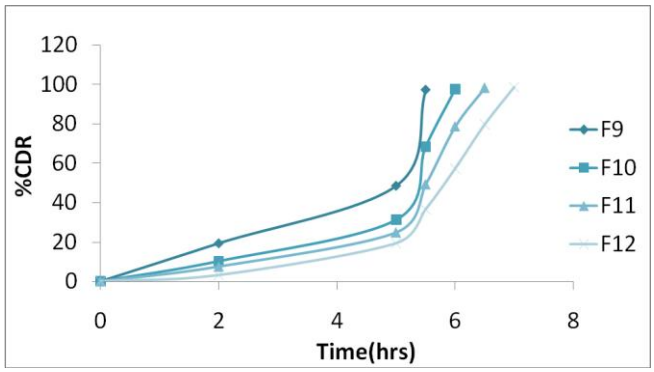


Figure 4-7: Comparison of *in vitro* drug release profile of all the formulations







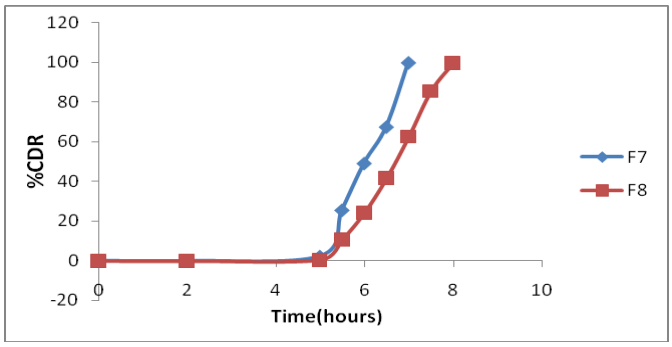
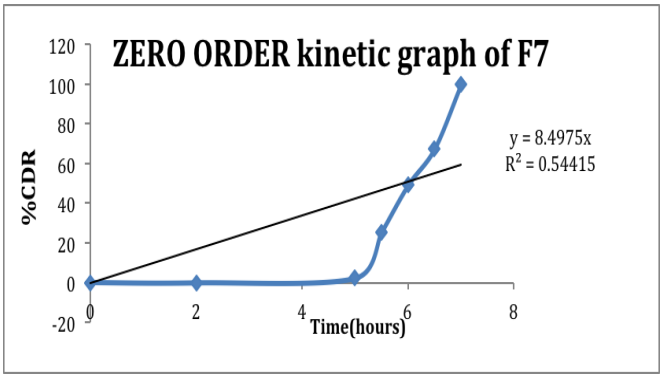
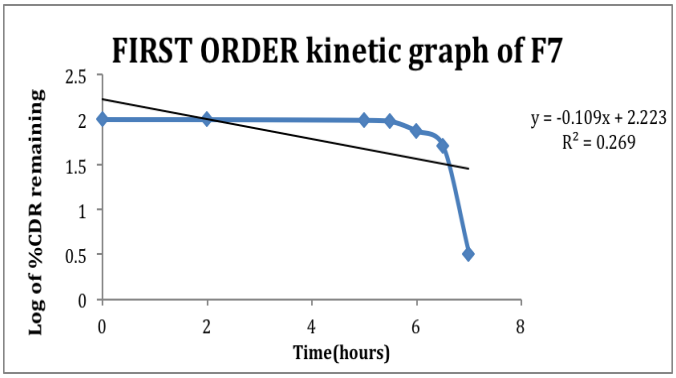
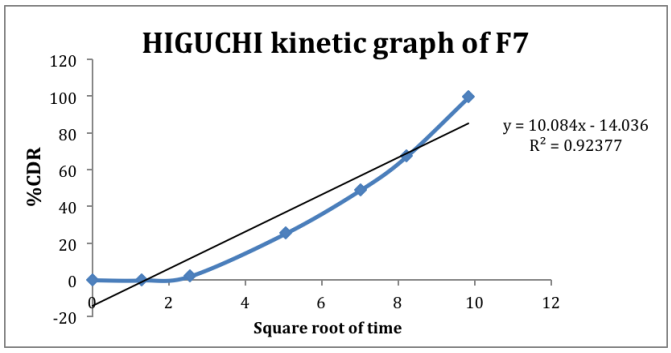


Figure 8-11: Kinetic Data of F7 formulation







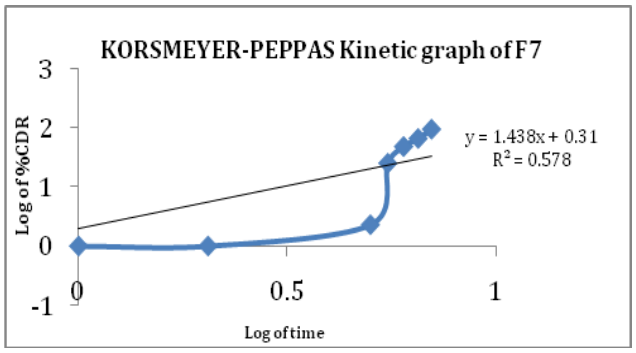


Table 2: Post compression evaluation tests of tablets

Formulation code	Weight Variation Test (mg)	Hardness Test (Kg/cm^2)	Thickness Test (mm)	Friability Test (%)	Content uniformity test (%)
F1	400±1.38	8.7±0.12	4.23±0.24	0.57±0.21	99.25 ±0.31
F2	399±1.25	8.8±0.16	4.21±0.29	0.51±0.19	98.15±0.28
F3	401±0.40	8.6±0.20	4.35±0.18	0.64±0.14	98.53±0.24
F4	398±2.41	8.8±0.17	4.23±0.27	0.52±0.16	98.36±0.23
F5	400±1.42	8.7±0.10	4.21±0.24	0.53±0.13	99.57±0.23
F6	400±0.43	8.7±0.24	4.20±0.29	0.58±0.19	97.37±0.25
F7	399±1.44	8.6±0.21	4.28±0.30	0.59±0.19	99.75±0.22
F8	400±0.45	8.8±0.16	4.22±0.34	0.55±0.18	98.66±0.28
F9	401±0.46	8.7±0.23	4.21±0.22	0.66±0.16	99.33±0.24
F10	398±2.47	8.7±0.14	4.28±0.17	0.58±0.14	99.65±0.22
F11	400±1.48	8.6±0.19	4.21±0.14	0.51±0.15	98.47±0.25
F12	401±0.49	8.8±0.13	4.26±0.25	0.57±0.21	99.63±0.29

All the values are represented as Mean ± SD (n=3)

DISCUSSION

Authentication of drug sample and Drug-excipient interaction study

The drug-polymers interaction was studied by FTIR analysis. From the FTIR studies, the characteristic IR absorption peaks for important functional groups were identified and tabulated as follows.

The spectra of the pure drug were compared with that available in the monograph. Albendazole shows 7 principle peaks at 659.65 cm^{-1} due to –C–S, 2955cm^{-1} due to –C–H (Aromatic), 3338.8 cm^{-1} due to –N–H, 1095 cm^{-1} due to –C–N (Aliphatic), 1624.12cm^{-1} due to –C=N, 1716.70 cm^{-1} due to –C=O and 1195.91 cm^{-1} due to –C–O. The pure drug as that of monograph ensuring its purity showed the same characteristic peaks.(Fig.1and 2)

These peaks of spectrum of pure drug were compared with the peaks of the spectra of physical mixtures of drug and polymers. It was observed that characteristic IR absorption peaks of Albendazole were not altered in physical mixture without any change in their position. This ruled out the drug-polymers interaction indicating the drug is compatible and stable in the formulation.(Fig. 3)

Postcompression evaluation tests

Albendazole granules were compressed into a core tablet. A tablet formulation is primarily evaluated for its weight variation because the pre determined weight should be equally distributed throughout the batch. It is must for the tablet batch to pass this test. The mean weight variation found in the tablet batch consisting of 20 tablets (average weight = 400 mg) was 398±2.41 mg to 401±0.49 mg. The results of the weight variation test (±7.5% of the average weight) indicate that the average weight is equally distributed among the batch of tablets. The hardness of the tablets of Albendazole was found to be 8.6±0.29 kg/cm^2 to 8.8±0.34 kg/cm^2. These results confirm that the tablets are strong enough to resist against the peristaltic movements of stomach and intestine and can reach the colon without any breakage. The tablets were also found to comply with the friability test since the weight loss was found to be 0.51±0.15 % to 0.66±0.16 %. This indicates that tablets can bear any amount of stress and strain brought upon them. The tablets thickness was found to be 4.11±0.29 mm to 4.35±0.18 mm. The mean percent drug content of the tablets was found to be 97.57±0.23 % to 99.66±0.28 % of the labeled amount indicating uniformity of drug content in the formulation **(Table 2)**.

In vitro drug release studies

In vitro release profiles of albendazole was sequentially determined in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) pH 6.8 and simulated colonic fluid (SCF) pH 7.2.

The *in vitro* drug release from matrix tablets containing HPMC Phthalate HP55 (F1, F2, F3 and F4) and Etcell polymers (F9, F10, F11 and F12) showed release of 20-47 % of albendazole in SIF, followed by a burst release in SCF. However, matrix tablets containing polymer blends Eudragit S100 (F5, F6, F7 and F8) showed that no appreciable drug release occurred in SIF (2-25 %). Among them, the formulations with drug polymer ratios 1:2(SF3) and 1:2.5(SF4) showed a minimal release of drug in SIF 1.3% and 0.27% respectively.

The formulation with drug polymer ratio 1:2(F7) was selected as optimized formulation because it showed a maximize release in proximal colon i.e. First 2hrs in SCF and the formulation with drug polymer ratio 1:2.5(F8) showed an extended release up to 3hrs in SCF in turn missing the release in the target site i.e. proximal colon.

Kinetic Data / Model fitting

The *in vitro* drug release data were fit to different equations and kinetic models to explain the drug release profiles. The coefficient of correlation of each of the kinetics was calculated and compared. The *in vitro* drug release profile of the optimized formulation of pH sensitive matrix tablets i.e, F7 did not fit to zero order. They could be best fit to Higuchi model. Higuchi describes

drug release as a diffusion process based in the Fick's law, square root time dependent. The data was further treated as per Korsmeyer's equation. The slope (n) = 1.438 value obtained by this equation indicated that the drug released by super case transport-2. Case-2 relaxation or super case transport-2 refers to the erosion of the polymeric chain.

CONCLUSION

- Among the pH sensitive polymers Eudragit S100 was best suited for colon targeted drug delivery system than HPMC Phthalate HP 55 and Ethyl cellulose because the matrix tablets containing HPMC Phthalate HP55 and Etcell polymers showed release of 20-47% of Albendazole in SIF, followed by a burst release in SCF. However, matrix tablets containing polymer blends Eudragit S100 showed that no appreciable drug release occurred in SIF (0-25%).
- Among the pH sensitive polymers Eudragit S100 was best suited for colon targeted drug delivery system than HPMC Phthalate HP 55 and Ethyl cellulose because the matrix tablets containing HPMC Phthalate HP55 and Etcell polymers showed release of 20-47% of Albendazole in SIF, followed by a burst release in SCF. However, matrix tablets containing polymer blends Eudragit S100 showed that no appreciable drug release occurred in SIF (0-25%).
- The formulation F7 was selected as optimized formulation because it showed minimum release in stomach and small intestine and a maximize release in proximal colon i.e. First 2hrs in SCF and the formulation F8 showed an extended release up to 3hrs in SCF in turn missing the release in the target site i.e. proximal colon.
- The *in vitro* drug release profile of the optimized formulation of pH sensitive matrix tablets i.e, F7 did not fit to zero order. They could be best fit to Higuchi model. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. The data was further treated as per Korsmeyer's equation. The slope (n) = 1.438 value obtained by this equation indicated that the drug released by super case transport-2. Case-2 relaxation or super case transport-2 refers to the erosion of the polymeric chain

  In the present work, it can be concluded that the pH sensitive colon targeted formulation can be an innovative and promising approach for the delivery of Albendazole for the treatment of Trichuriasis.

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