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Formulation and Evaluation of Matrix Tablets of Albendazole for Colon Site Specific Drug Delivery

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Research Article

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ABSTRACT

Matrix tablets of albendazole containing various proportions (20%, 25%, 30% and 35%) of guar gum, xanthum gum and dextrin were prepared by direct compression technique using 10 mm concave punch. The prepared tablets were evaluated for hardness, friability, weight variation, drug content uniformity and were subjected to *in vitro* drug release with and without rat caecal content (4% w / v). All formulations (F1 - F12) which shows restricted drug release in stomach and small intestine and which shows more release in colonic environment. The drug release was independent of its concentration and the mechanism of drug release followed by super case-II transport. The accelerated stability studies revealed that there was no significant change in the colour, shape and drug content. The formulation (F9) is most suitable to target colon without being released significantly in the stomach and small intestine, and also it may avoid systemic side effects in the gastrointestinal tract.

INTRODUCTION

The oral route of administration of drugs is considered as the most convenient route. When the conventional dosage form is administered orally, it dissolves in the stomach fluid or intestinal fluid and absorbed from these regions of the gastrointestinal tract (GIT). Further, the absorption depends upon physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT.

Dosage forms that deliver drug into the colon rather than upper GIT has number of advantages. Oral delivery of drugs to the colon is essential in the treatment of diseases of colon (Ulcerative colitis, Crohn's disease, Carcinomas and infections such as helminthiasis) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drug in the upper GIT or unnecessary systemic absorption [1]. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability.

The different approaches for targeting orally administered drugs to the colon include coating with pH-dependent polymers, design of timed-release dosage forms and utilization of carriers that are degraded exclusively by colonic bacteria [2]. As conventional

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tablets are absorbed from the stomach, side effects like nausea, metallic taste, vomiting and head ache are observed. Therefore targeting the drug specifically to the colon is advantageous in treatment of helminthiasis.

Albendazole is a broad-spectrum anthelminthic agent used for the treatment of Neurocysticercosis, Hydatid disease. Albendazole is poorly absorbed from the gastrointestinal tract due to its low aqueous solubility [3, 4]. The conventional albendazole tablets release the drug along the GIT and cause unwanted side effects [5]. The aim of the present study was to develop matrix tablets of albendazole to improve the bioavailability by reducing the dose and side effects.

MATERIALS AND METHODS

Materials

The drug, albendazole was obtained as free gift sample from Microlabs, India. Microcrystalline cellulose was procured from Cosmo Pharma, Chennai, India. Guar gum, xanthum, dextrin was obtained from SD Fine Chemicals, Mumbai, India. Magnesium stearate and talc were procured from Ranbaxy, India. All other chemicals and reagents used are of analytical grade.

Methods

Pre Compression Parameters [6, 7]

Angle of Repose (θ)

Fixed funnel method was used to determine the angle of repose. A funnel was fixed with its tip at a given height 'h' above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using following equation.

$$\theta = \text{Tan}^{-1} (h/r)$$

Where,
θ = Angle of repose
h=Height of pile
r=Radius of the base of the pile

Bulk Density (D_b)

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured, which is the initial bulk volume. Then it is expressed in gm / mL and is given by;

$$D_b = M / V_0$$

Where,
M = mass of powder
V_0 = bulk volume of the powder

Tapped Density (D_t)

Ten gram of powder was introduced into a clean, dry 100 mL measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm / mL and is given by,

$$D_t = M / V_t$$

Where,
M = mass of powder
V_t = tapped volume of the powder.

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Carr's Consolidation Index (I)

Carr's index is an indication of the compressibility of a powder. It is expressed in percentage and is given by

$$I = D_t - D_b / D_t \times 100$$

Where,
Dt =Tapped density
D_b=Bulk density

Formulation of Albendazole Matrix Tablets

The matrix tablets containing 200 mg albendazole were formulated with different proportions of natural polysaccharides such as guar gum, xanthum gum and dextrin (Table 1). Albendazole and all other ingredients were passed through sieve no 60 separately and mixed homogeneously. The powder was lubricated with a mixture of talc and magnesium stearate. Finally the lubricated powders were compressed into tablets containing 200 mg albendazole using 10 mm concave punch.

Table 1: Composition of matrix tablets of albendazole

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
Albendazole	200	200	200	200	200	200	200	200	200	200	200	200
Guar gum	100	125	150	175								
Xanthum gum					100	125	150	175				
Dextrin									100	125	150	160
Microcrystalline cellulose	190	165	140	115	190	165	140	115	190	165	140	115
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
Total weight	500	500	500	500	500	500	500	500	500	500	500	500

Post Compression Parameters

Weight Variation

Randomly selected twenty tablets were weighed individually in a single pan balance. The average weight was noted and repeated thrice.

$$PD= (W_{avg}) - (W_{initial}) / (W_{avg}) \times 100$$

Where,
PD = Percentage deviation,
W_{avg} =Average weight of tablet,
$W_{initial}$ =Individual weight of tablet

Thickness

Control of physical dimensions of the tablet such as thickness is essential for consumer acceptance and tablet uniformity. The thickness of the tablet was measured using digital vernier calipers.

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Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet.

Friability

Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. The percent friability was determined using the following formula.

$$F = (W_{initial}) - (W_{final}) / (W_{initial}) \times 100$$

Drug Content

Five tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar individually and accurately weighed amount of tablet triturate from each blend was taken. Then, samples were transferred to 100 mL volumetric flask, diluted with phosphate buffer (pH 6.8) and agitated for 30 min. Samples (1 mL) was withdrawn and after appropriate dilution assayed by UV Spectrophotometric (Schimadzu-1800, Japan) at 330 nm.

Preparation of Rat Caecal Content Medium

In vitro drug release testing was investigated in presence of rat caecal content medium. The Albino rat weighed in between 150-200 g were kept on a normal diet and administered 1 mL of 1% w/v solution(i.e. guar gum/ xanthum gum / dextrin) with the help of Teflon tubing, directly into stomach region via oral cavity. This process provides the best conditions for in vitro evaluation 30min before the commencement of drug release studies, five rats were killed by spinal traction. The abdomen were opened, the caecal were isolated, ligated at both ends, deselected and immediately transferred into pH 6.8 Phosphate buffer previously bubbled with CO_2 The caecal bags were opened, their contents were individually weighed, pooled and then suspended in PBS, to give a final caecal dilution of 1% w/v. As the caecum is naturally anaerobic, all these operations were carried out under anaerobic condition [8].

***In vitro* Drug Release Study**

In vitro drug release studies of matrix formulation were carried out using USP - 23 Basket type dissolution apparatus. Phosphate buffer (900 mL) was dissolution medium at 100 ± 1 rpm in medium at 37 ± 0.5 °C. Release studies were carried out in dissolution medium with and without rat caecal content (4% w/v). A matrix formulation was transferred to the 900 mL phosphate buffer (pH 1.2, 7.4 and 6.8) as dissolution medium. At predetermined time intervals, the samples were withdrawn from the dissolution medium and after suitable dilution and assayed at 330 nm. For simulating conditions of the GIT, drug release studies were also performed with 0.1 N HCl buffer (pH 1.2) for first 2 h, phosphate buffer (pH 7.4) for next 3 h and 200 mL of phosphate buffer saline 6.8 for further 19 h study with rat caecal content (4% w/v) [9, 10]. To assess the release kinetics, the *in vitro* release data was fitted to the various mathematical models such as Zero order, First order, Higuchi and Korsmeyer-Peppas [11, 12].

Accelerated Stability Studies

The accelerated stability studies were carried out for selected formulation (F9). Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the tablets were kept in an incubator maintained at 40 °C and 75% RH over a period of 3 months [13, 14]. Samples were evaluated at 30th, 60th and 90th days for physical appearance and drug content.

RESULTS AND DISCUSSION

The matrix tablets of albendazole were prepared by direct compression with different proportion of guar gum, xanthum gum and dextrin (20%, 25%, 30% and 35%). The prepared powder blends of the above batches were evaluated for, bulk density (g/ml), tapped density (g / mL), Haussner's ratio, angle of repose (θ) are given in Table 2.

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Table 2: Physical parameters of the powder blend before direction compression

Formulation code	Angle of Repose(°)*	Bulk Density(g/mL)*	Tapped Density(g/mL)*	Carr's Index (%)*	Hausner' Ratio (%)*
F1	31.16±0.76	0.597±0.011	0.676±0.034	11.97±1.96	1.13±0.033
F2	33.45±1.08	0.591±.024	0.677±0.017	12.61±1.66	1.14±0.021
F3	35.02±0.35	0.583±0.012	0.686±0.005	14.75±1.65	1.17±0.023
F4	35.68±0.84	0.600±.012	0.688±0.002	12.76±1.77	1.21±0.021
F5	30.84±0.28	0.614±0.026	0.696±0.020	11.87±1.67	1.13±0.021
F6	34.13±0.51	0.600±0.012	0.678±0.019	11.61±1.89	1.13±0.024
F7	35.26±0.51	0.590±0.017	0.694±0.014	14.91±1.53	1.17±0.021
F8	35.81±0.81	0.584±0.029	0.667±0.029	12.47±1.58	1.14±0.020
F9	30.60±0.61	0.583±0.012	0.667±0.013	12.49±1.87	1.14±0.024
F10	33.68±1.30	0.572±0.016	0.652±0.034	12.26±2.25	1.14±0.028
F11	34.02±1.42	0.585±0.008	0.696±0.017	15.90±1.84	1.18±0.025
F12	35.85±0.39	0.584±0.010	0.695±0.012	15.92±1.87	1.18±0.029

*Mean ± SD, *n* =3

The weight variation of the tablets was found to be in the range of 499.0 ± 3.71 mg to 501.4 ± 3.56 mg. The hardness of the tablets was found to be in the range of 5.96 ± 0.378 Kg/cm² to 6.24 ± 0.219 Kg/cm². These tablets were found to comply with the friability test since the weight loss was found to be less than 1%. The thickness of the tablets was found in the range of 6.21- 6.29 mm. The drug content of the formulations found to be in the range of 96.50 ± 1.04% - 99.68 ± 2.77%. All these results show that the drug was uniformly distributed in all formulation (Table 3).

Table 3: Post compression evaluation of albendazole matrix tablets

Formulation code	Weight Variation (mg)*	Thickness (mm)*	Hardness (Kg/cm²)*	Friability (%)*	Drug content (%)*
F1	500.1±4.30	6.27±0.055	6.10±0.212	0.458 ±0.010	99.047±1.90
F2	501.2±3.41	6.29±0.076	5.96±0.378	0.487±0.009	97.77±1.04
F3	498.8±3.93	6.22±0.050	6.08±0.294	0.638±0.005	96.50±1.04
F4	499.1±4.62	6.22±0.044	6.0±0.339	0.520±0.020	97.14±2.77
F5	499.0±3.71	6.23±0.040	6.02±0.268	0.484±0.015	98.41±2.77
F6	499.7±3.23	6.21±0.028	6.08±0.216	0.579±0.015	97.77±1.04
F7	499.9±3.59	6.23±0.068	6.1±0.254	0.664±0.031	97.50±1.81
F8	499.5±4.03	6.25±0.037	6.14±0.270	0.648±0.043	97.87±1.81
F9	499.7±2.98	6.24±0.039	6.18±0.192	0.524±0.017	99.68±2.77
F10	500.1±4.17	6.25±0.059	6.16±0.178	0.634±0.021	97.14±1.81
F11	501.4±3.56	6.24±0.040	6.22±0.268	0.580±0.007	98.4±1.04
F12	501±4.42	6.23±0.043	6.24±0.219	0.649±0.032	97.70±1.81

*Mean ± SD, *n* = 3

In vitro Drug Release Studies

In vitro release studies of matrix tablets (F1- F12) shows drug release in the first 5 hours (pH 1.2 for first two hours and pH 7.4 for next three hours mimicking stomach and small intestine) was found to be in the range 9.14 ± 0.374% to 6.5 ± 0.35%. The dissolution studies were further carried out in the simulated colonic fluid (phosphate buffer pH-6.8 with and without rat caecal medium) for next 19 h. From the studies it was observed that the formulation of F1, F2, F3, F4 (guar gum 20%, 25%, 30% and 35%) found to release the

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albendazole in the range of 70.05 ± 0.569% to 48.01 ± 0.337% at the end of 24 h in the absence of rat caecal contents. But the same formulation found to release the albendazole in the range of 84.53 ± 0.60% to 62.71 ± 0.336% at the end of 24th h in the presence of rat caecal content Further it was observed that the formulations of F5, F6, F7, F8 (xanthum gum 20%, 25%, 30% and 35%) found to release the albendazole in the range of 57.025 ± 1.43% to 41.66 ± 0.383% at the end of 24th h in the simulated colonic fluid without rat caecal content. But the same formulations found to release the albendazole in the range of 76.16 ± 0.972 to 56.41±1.368 at the end of 24th h in the presence of rat caecal medium. Further it was observed that the formulations of F9, F10, F11, F12 (dextrin 20%, 25%, 30% and 35%) found to release the albendazole in the range of 72.22 ± 0.446 to 44.1 ± 0.333 at the end of 24 h in the simulated colonic fluid without rat caecal content. But the same formulations found to release the albendazole in the range 94.02 ± 0.497% to 64.13 ± 0.86% at the end of 24th h in the presence of rat caecal medium. These results showed that the formulated matrix tablets were able to restrict the release in the stomach and small intestine and able to target the drug release in the colon. From the above results, it was found that the present drug released from albendazole tablets were less in phosphate buffer (pH 1.2 and pH 7.4) than the percentage drug released in phosphate buffer (pH 6.8) containing 4% w/v of rat caecal contents (Figure 1 and Figure 2).

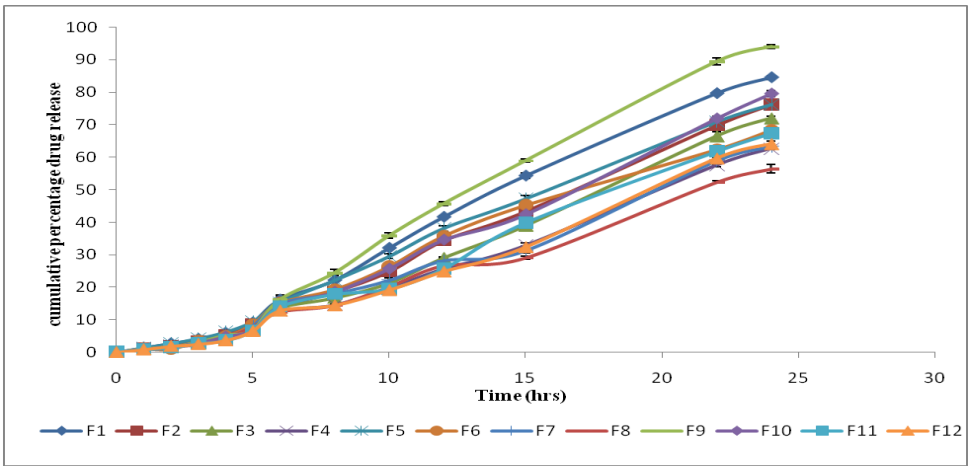

Figure 1: *In vitro* drug release of albendazole matrix tablets with rat caecal content

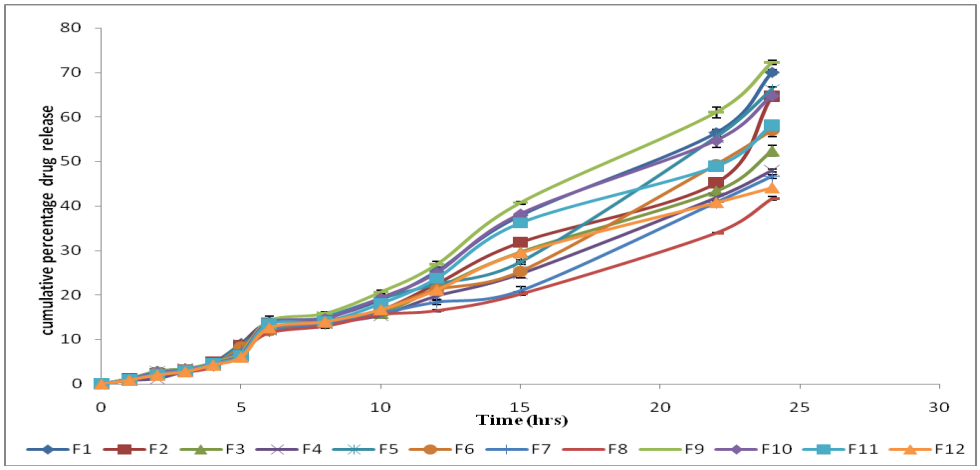

Figure 2: *In vitro* drug release of albendazole matrix tablets without rat caecal content

The r^2, 'k' and 'n' value of the selected formulation (F9) is shown in **Table 4.** According to this, the formulation (F9) with rat caecal medium was best fitted to Korsmeyer-Peppas kinetic equation followed by Zero order kinetics, which can be seen from the highest correlation (r^2) value. It confirms that the drug release was independent of its concentration and the mechanism of drug was Super case-II transport could be due to increased plasticization at the relaxing boundary.

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Table 4: The r^2, 'k' and 'n' value of the selected formulation (F9)

Formulation	Zero Order		First order		Higuchi		Kosmeyer-Peppas	
	r^2	k	r^2	K	r^2	k	r^2	n
F9	0.987	4.280	0.884	0.051	0.863	> 1	0.971	1.560

Accelerated Stability Studies

The accelerated stability studies were carried out by storing the matrix tablets of albendazole at 40 ± 2 °C and 75% ±5 % RH for 3 months. It was found that there was no significant change in color, shape and drug content at the end of storage period **(Table 5).**

Table 5: Accelerated stability studies of selected matrix tablet of albendazole (F9)

Periods (Days)	Physical Appearance	Drug content (%)*
30	No change	99.68 ±1.099
60	No change	98.41 ± 2.909
90	No change	99.04 ± 1.904

*Mean ± SD, *n* = 3

CONCLUSION

The present study was carried out to develop a colon specific drug delivery system for albendazole matrix tablets using guar gum, xanthum gum and dextrin polysaccharides as carriers and subjected to *in vitro* drug release studies with and without rat caecal medium. From the above study it is concluded that, the formulation (F9) are most suitable to target colon without being released significantly in stomach and small intestine and it may not cause the systemic side effects in the GIT.

REFERENCES

1. Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Pharmaceut Sci. 2003; 6(1); 33-66.
2. Naikwade SR, Kulkarni PP, Jathar SR, Bajaj AN. Development of time and pH dependent controlled release colon specific delivery of Tinidazole. Daru. 2008; 16(3); 119-27.
3. Saraswathi R, Simi SP, Sankar C, Krishnan PN, Dilip C, Ameena K. Guar gum based microcapsules for colonic delivery of albendazole: Development and *In vitro* evaluation. Res J Pharm Biol Chem Sci. 2010; 1(4); 373-82.
4. Krishnaiah YS, Seetha DA, Nageswara RL, Bhaskar RPR, Karthikeyan RS, Sathyanarayana V. Guar gum as a carrier for colon specific delivery; Influence of metronidazole and Tinidazole on invitro release of albendazole from guar gum matrix tablets. J Pharm Pharm Sci. 2001; 4(3); 235-43.
5. Joel GH, Lee EL, Alfred GG. The Pharmacological Basis of Therapeutics; 9th ed; Mcgraw-Hill Medical Publisher; Newyork; 1996.
6. The United States Pharmacopoeia 26thand National Formulary 21st ed; Rockville; United States Pharmacopoeial Convention Inc; 1995.
7. Lachman L, Liberman H, Kanig J. The theory and practice of industrial Pharmacy,Varghese Publishing House; 3rd Ed; Varghese Publishing House; Mumbai; 1991.
8. Sinha VR, Mittal BR, Bhutani KK, Kumria R. Colonic drug delivery of 5-fluorouracil: an *in vitro* evaluation. Int J Pharm. 2004; 269(1); 101-08.
9. Yang L. Biorelevant dissolution testing of colon specific delivery system activated by colonic microflora. J Control Rel. 2008; 125(2); 77-86.
10. Yang L, Chu JS, Fix JA. Colon specific drug delivery: new approaches and in vitro/in vivo evaluation. Int J Pharm. 2002; 235(1-2); 1-15.
11. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharm Sci. 1961; 50; 874-75.
12. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983; 15(1); 25-35.
13. Momin M, Pundarikakshudu K. *In vitro* studies on guar gum based formulation for the colon targeted delivery of Sennoside. J Pharm Pharm Sci. 2004; 7(3); 325-31.
14. Krishnaiah YS, Veer RP, Dinesh KB, Bhaskar P, Satyanarayana V. Development of colon targeted drug delivery systems for mebendazole. J Control Rel. 2001; 77(1-2); 87-95.