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FORMULATION AND IN VITRO EVALUATION OF EFFERVESCENT FLOATING TABLETS OF MEBENDAZOLE

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ABSTARCT
In the present research work the gastro retentive floating matrix formulation of Mebendazole by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Sodium CMC were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with Chitosan retarded the drug release up to 12 hours in the concentration of 200 mg (F6).The formulations prepared with Guar gum were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

KEYWORDS: Mebendazole, Guar gum, Sodium CMC, Chitosan, Floating tablets.

INTRODUCTION

Oral delivery of drugs is the most preferable route of drug delivery. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient compliance and flexibility in formulation and cost effective manufacturing process.[1] Many of the drug delivery systems, available in the market are oral drug delivery type systems Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as.

1. Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.
2. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.
3. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{ss} values fall or rise beyond the therapeutic range.
4. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.[2]

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[3]

Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.[4]

Controlled drug delivery or modified drug delivery systems are divided into four categories.

1. Delayed release.
2. Sustained release.
3. Site-specific targeting.
4. Receptor targeting.

More precisely, controlled delivery can be defined as

1. Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2. Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.

3. Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4. Provide physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.[5]

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug (Figure 1).[6] Controlled drug deliveries usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

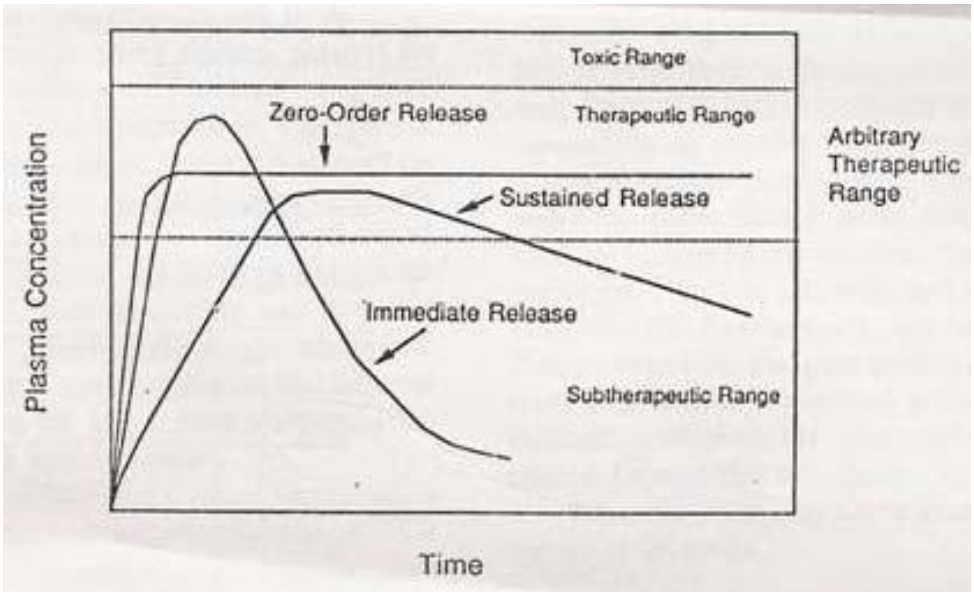

Figure 1: Drug level verses time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet.

Oral drug delivery systems have progressed from immediate release to site-specific delivery over a period of time. Every patient would always like to have a ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action.[7]

Thus the objective of the pharmacist is to develop systems that can be as ideal system as possible. Attempts to develop a single- dose therapy for the whole duration of treatment have focused attention on controlled or sustained release drug delivery systems. Attention has been focused particularly on orally administered sustained drug delivery systems because of the ease of the administration via the oral route as well as the ease and economy of manufacture of oral dosage forms. Sustained release describes the delivery of drug from the dosage forms over an extended period of time. It also implies delayed therapeutic action and sustained duration of therapeutic effect. Sustained release means not only prolonged duration of drug delivery and prolonged release, but also implies predictability and reproducibility of drug release kinetics. A number of different oral sustained drug delivery systems are based on different modes of operation and have been variously named, for example, as dissolution controlled systems, diffusion controlled systems, ion-exchange resins, osomotically controlled systems, erodible matrix systems, pH- independent formulations, swelling controlled systems, and the like.

An orally administered controlled drug delivery system encounters a wide range of highly variable conditions, such as pH, agitation intensity and composition of the gastrointestinal fluids as it passes down the G.I tract. Considerable efforts have been made to design oral controlled drug delivery systems that produce more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, like inability to retain and localize the drug delivery system within desired regions of the G.I tract and highly variable nature of the gastric emptying process. An important factor, which may adversely affect the performance of an oral controlled drug delivery system, is the G.I transit time. The time for absorption in the G.I transit in humans, estimated to be 8-10 hr from mouth to colon, is relatively brief with considerable fluctuation. G.I transit times vary widely between individuals, and depend up on the physical properties of the object ingested and the physiological conditions of the gut. This variability may lead to predictable bioavaialability and times to achieve peak plasma levels. One of the important determinants of G.I transit is the residence time in the stomach.

Majority of the drugs are well absorbed from all the regions of the G.I tract while some are absorbed only from specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, as well as to the degradation of the drug by the microorganisms present in the colon. Therefore, in instances where the drug is not absorbed uniformly over the G.I tract, the rate of drug absorption may not be constant in spite of the drug delivery system delivering the drugs at a constant rate into the G.I fluids. More particularly, in instances where a drug has a clear cut absorption window, i.e., the drug is absorbed only from specific regions of the stomach or upper parts of the small intestine; it may not be completely absorbed when administered in the form of a typical oral controlled drug delivery system. It is due to the relatively brief gastric emptying in humans, which normally averages 2-3 hrs through the major absorption zone. It may cause incomplete drug release from the dosage form at absorption sites leading to diminished efficacy of the administered dose. It is apparent that for a drug having such an absorption window, an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a long period of time. For this drug, increased or more predictable availability would result if controlled release systems could be retained in the stomach for extended periods of time.

It is suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of these drugs. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage form for these drugs.

Incorporation of the drug in a controlled release gastroretentive dosage form (CRGRDF) can yield significant therapeutic advantages due to a variety of pharmacokinetic and pharmacodynamic factors.

Controlled release or Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for drugs.[8] which are.

1. Administered two or more time a day.
2. Only absorbed in the upper GI regions.
3. Insoluble in water.
4. Targeted at sites in the upper GI tract.
5. Bioavailable through active transport mechanisms.
6. Irritating to the mucosa.
7. Misbalancing, irritating, or unsafe in the lower GI region.
8. More effective when plasma levels are more constant.
9. That is locally active in the stomach.
10. That has an absorption window in the stomach or in the upper small intestine.
11. That is unstable in the intestinal or colonic environment or degrades in colon.
12. Have low solubility at high pH values.

Biological aspects of gastric retention dosage forms

To comprehend the considerations taken in the design of gastric retention dosage forms and to evaluate their performance the relevant anatomy and physiology of the G.I tract must be fully understood. The extent of drug absorption in a segment of the G.I. tract depends generally on the rate of absorption as well as on the exposed surface area and time available for drug absorption. The G.I. Transit times of dosage forms in the various segments of the G.I. tract are listed in Table 1. The other factors influencing drug absorption are surface area, absorption mechanisms, pH values, enzymes and number of microorganisms.

Table 1: The Transit time of Different Dosage Forms across the Segments of GI Tract.

Dosage form	Transit time (h)		
	Gastric	Small intestine	Total
Tablets	2.7±1.5	3.1±0.4	5.8
Pellets	1.2±1.3	3.4±1.0	4.6
Capsules	0.8±1.2	3.2±0.8	4.0
Oral solution	0.3±0.07	4.1±0.5	4.4

It is well recognized that the stomach may be used as a depot for controlled release dosage forms. The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. The stomach is composed of the following parts.[9,10]

- Fundus
- Body
- Antrum

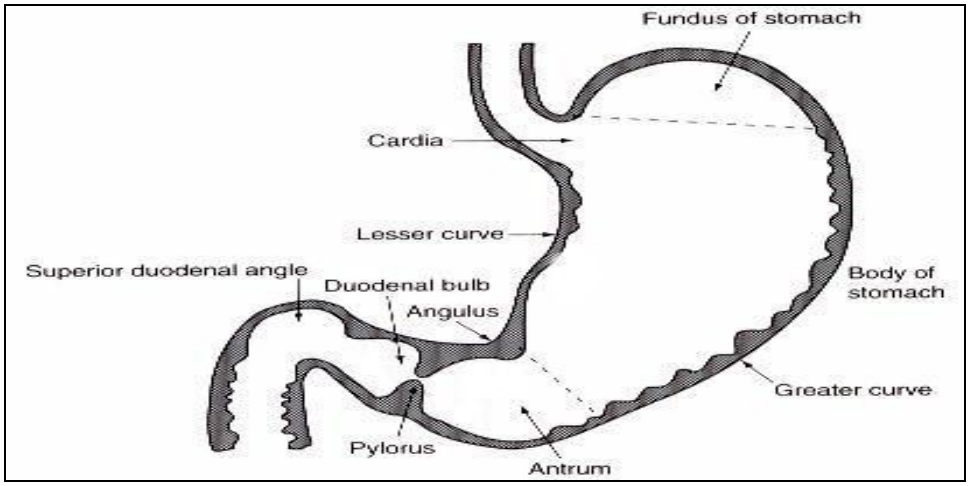

Figure 2: Anatomy of stomach.

The proximal stomach made up of the fundus and body regions, Serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying. The pylorus is an anatomical sphincter situated between the most terminal antrum and the duodenum.

Gastric emptying[11, 12, 13, 14]

The process of gastric emptying occurs in two states:

- Fasting as well as
- Fed states.

The pattern of motility is distinct in both states.

In fasting state: An interdigestive series of electrical events occurs in a cyclic manner both through stomach and small intestine every 2 to 3 hours.[15] This activity is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 consecutive phases as.[16]

- *Phase I (basal phase:* It is a period with rare contractions lasting from 40 to 60 minutes.
- *Phase II (preburst phase):* It is period of similar duration lasting for 40 to 60 minutes consisting of intermittent action potentials and contractions that gradually increase in intensity and frequency as the phase progresses.
- *Phase III (burst phase):* It is a short period of intense, large regular contractions lasting for 4 to 6 minutes. It is this phase, which gives the cycle the term housekeeping wave, since it serves to sweep undigested materials out of the stomach and down the small intestine.
- *Phase IV:* It is a brief transitional phase that occurs between phase III and phase I of their two consecutive cycles.

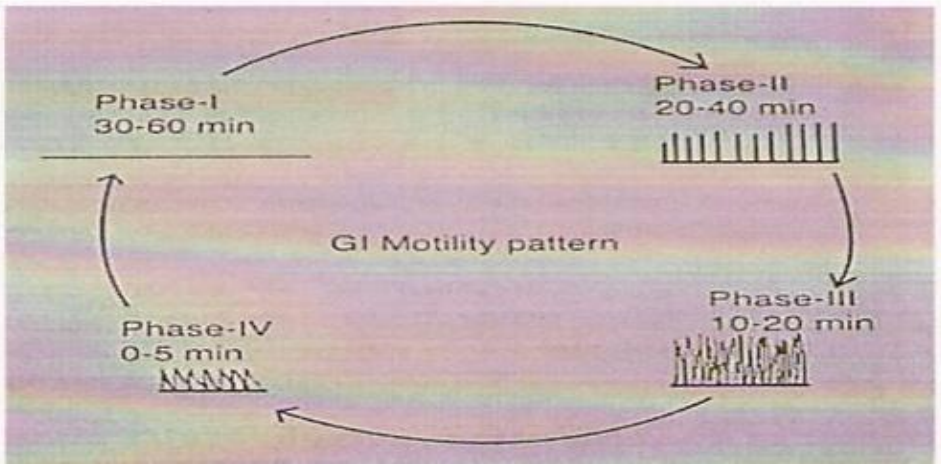

Figure 3: Gastrointestinal motility pattern.

In fed state: The motor activity in the fed state is induced 5-10 min after ingestion of a meal and persists as long as food remains in the stomach. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state These contractions are not as severe as those in the third phase of the fasted motility pattern.. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is

delayed resulting in slowdown of gastric emptying rate.[17]

Orally administered controlled release dosage forms are subjected to basically 2 complications that of short gastric residence time and unpredictable gastric emptying rate. These can be overwhelmed by altering the gastric emptying, which is affected by age, sex and health condition of a subject. So with extended gastro intestinal residence time, controlled release dosage forms are formulated.

Factors Affecting Gastric Retention[18]

Density: GRT is a function of dosage form buoyancy that is dependent on the density of a dosage form which affects the gastric emptying rate. A buoyant dosage form should have a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.[19]

Size: Dosage form units having a diameter of more than 7.5 mm are reported to have an increased gastric residence time compared with those having a diameter of 9.9 mm. Gastric retention time of an dosage form in the fed state can also be influenced by its size. Small tablets are emptied from the stomach during the digestive phase while large size units are expelled during the house keeping waves.[20]

Table 2: Effect of tablet size on Gastric Emptying time

Tablet size	Gastric emptying time
13 mm	171 ± 13 min
11 mm	128 ± 17 min
7 mm	116 ± 19 min

Shape of dosage form: The six shapes tested (ring, tetrahedron, cloverleaf, disk, string and pellet) displayed different gastric retention times, due to their size and geometry of the systems. The tetrahedron resided in the stomach for longer periods than other devices of a similar size; likewise extended gastric retention was observed with rigid rings. Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) have a better gastric residence time as compared with other shapes and had been reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

AIM AND OBJECTIVE

Aim of the Work Aim of the study is to formulate and evaluate Mebendazole floating tablets using different polymers Guar gum, Sodium CMC, Chitosan, and Sod. Bicarbonate, Mag. stearate, Talc in different ratios.

In order to optimize the therapy research efforts have been focused on the development of oral sustained release (SR) preparations as well as controlled release gastro retentive dosage forms.

The above drawbacks provide a rationale for developing Mebendazole as a gastro retentive dosage form, which is retained in the stomach and produces a constant input of drug to the absorption site. This improves the bioavailability of the drug, reduces frequency of dosing, thus minimizes side effects and enhances patient compliance. The present study was a systematic approach for the development of Intragastric Buoyant Tablets of Mebendazole with a view to enhance its oral bioavailability and efficacy.

Objective of the Study

1. To formulate and perform the various invitro evaluation test parameters for Mebendazole Gastro retentive floating tablets.
2. To optimize the concentration of gas generating agent sodium bicarbonate.
3. To optimize the concentration of various hydrophilic polymers.
4. To interpret the invitro dissolution data.

PLAN OF WORK

1. Preparation of powders
2. Evaluation of powders
   - Angle of repose
   - Bulk density
   - Tapped density
   - Powder flow Properties
   - Solubility
3. Compression of powders into tablets
4. Tablet evaluation
   - Thickness
   - Hardness
   - Friability
   - Uniformity of weight
   - Drug content
   - In vitro dissolution
   - In vitro buoyancy studies
5. IR absorption spectroscopy

RESULTS AND DISCUSSION

Analytical Method

Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 266 nm.

Calibration Curve

Graph of Mebendazole was taken in Simulated Gastric fluid (pH 1.2).

Table 3: Observations for graph of Mebendazole

Conc [µg/ml]	Abs
1	0.131
2	0.232
3	0.347
4	0.459
5	0.629

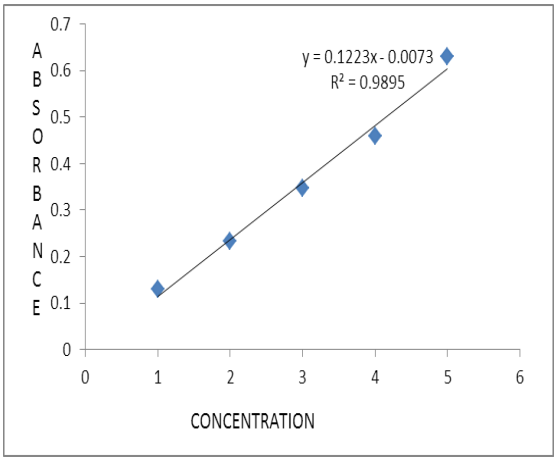

Figure 4: Standard graph of Mebendazole in 0.1N HCl.

Standard graph of Mebendazole was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Mebendazole showed good linearity with R^2 of 0.989, which indicates that it obeys "Beer- Lamberts" law.

Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy

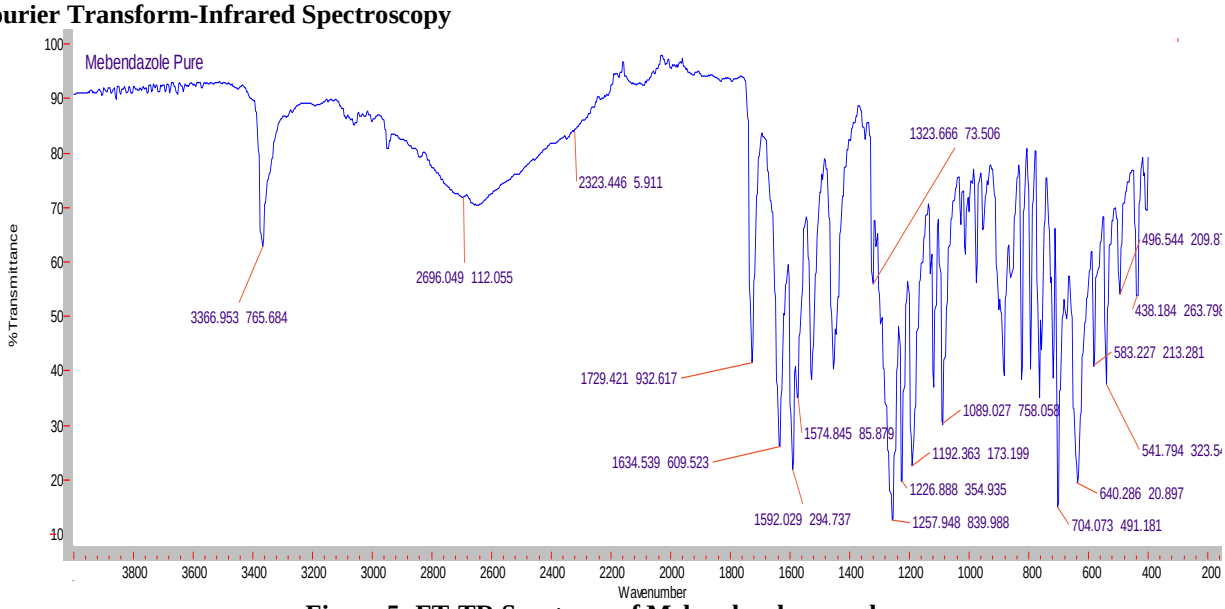

Figure 5: FT-TR Spectrum of Mebendazole pure drug.

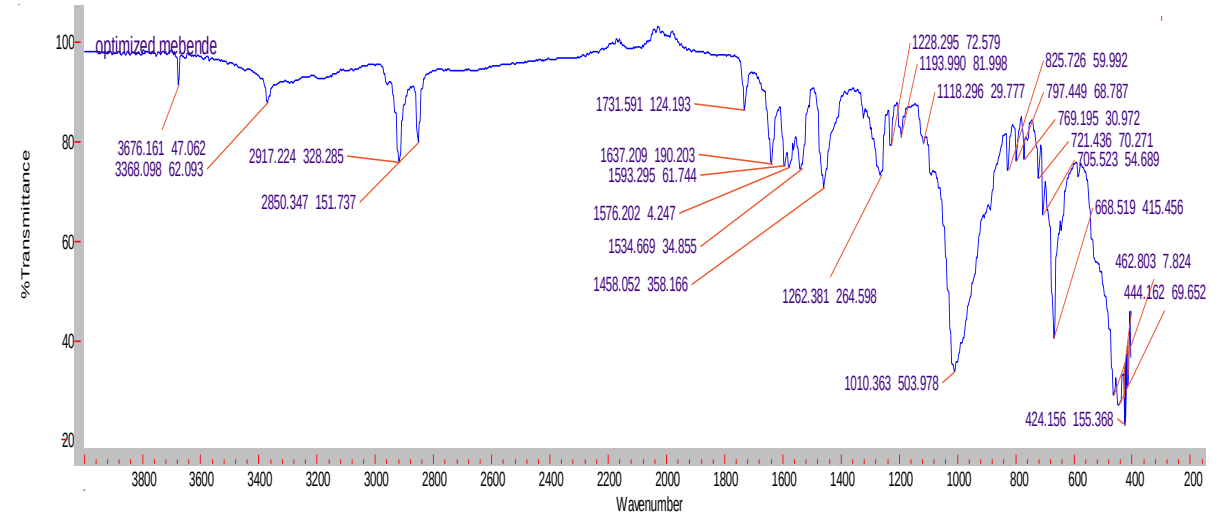

Figure 6: FT-IR Spectrum of Optimised Formulation.

From the results of FTIR studies it was evident that the drug and excipients does not have any interactions.

Preformulation parameters of powder blend.

Table 4: Pre-formulation parameters of blend.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	1.16±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	1.07±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	1.30±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.18±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.17±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	1.18±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.18±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Optimization of sodium bicarbonate concentration

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 75mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness and drug release studies in different media were performed on the tablets.

Table 5: Invitro quality control parameters for tablets.

Formulation code	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)
F1	512.5	4.5	0.52	4.8	99.76	4.0
F2	505.4	4.2	0.54	4.9	99.45	4.2
F3	498.6	4.4	0.51	4.9	99.34	4.5
F4	510.6	4.5	0.55	4.9	99.87	4.1
F5	509.4	4.4	0.56	4.7	99.14	4.0
F6	510.7	4.2	0.45	4.5	98.56	4.4
F7	502.3	4.1	0.51	4.4	98.42	4.5
F8	501.2	4.3	0.49	4.7	99.65	4.6
F9	498.3	4.5	0.55	4.6	99.12	4.7

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies**

Table 6: Dissolution Data of Mebendazole Tablets Prepared With SODIUM CMC In Different Concentrations.

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F1	F2	F3
0.5	21.73	18.52	19.53
1	59.23	37.47	28.97
2	84.9	59.93	35.89
3	94.873	65.85	45.7
4	94.873	77.54	54.38
5		89.55	61.2
6		96.6	67.06
7			72.52
8			77.88
9			86.6
10			89.09
11			94.52

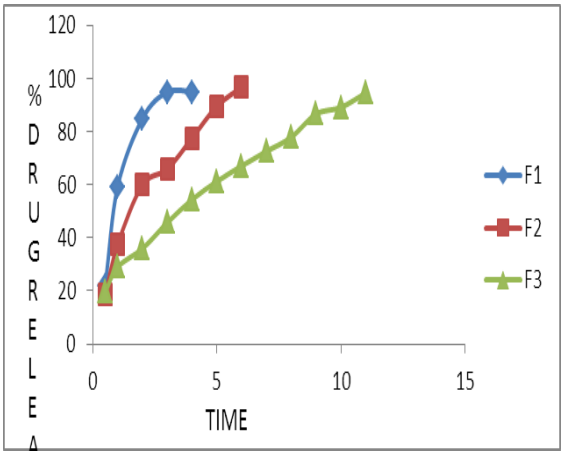

Fig 7: Dissolution profile of Mebendazole floating tablets (F1, F2, F3 formulations).

Table 7: Dissolution Data of Mebendazole Tablets Prepared With Chitosan In Different Concentrations.

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F4	F5	F6
0.5	18.45	18.42	19.62
1	36.26	27.73	27.86
2	52.16	35.63	36.35
3	70.01	42.04	41.45
4	87.26	57.25	47.80
5	93.10	64.33	55.25
6		75.41	60.24
7		83.84	66.73
8		92.80	71.34
9			78.52
10			80.17
11			88.75
12			96.33

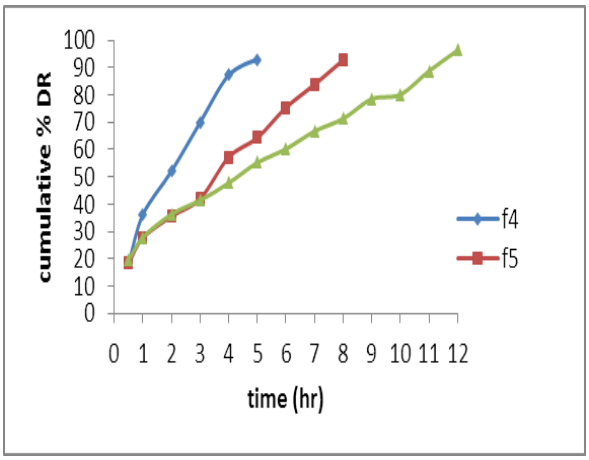

Fig 8: Dissolution profile of Mebendazole floating tablets (F4, F5, F6 formulations).

Table 8: Dissolution Data of Mebendazole Tablets Prepared With Guar Gum In Different Concentrations.

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F7	F8	F9
0.5	18.81	19.89	14.21
1	29.02	28.04	18.87
2	35.70	35.43	27.19
3	43.32	41.65	35.66
4	49.25	47.18	43.32
5	55.28	53.81	51.06
6	60.92	58.89	57.13
7	66.08	64.53	63.63
8	70.44	69.43	69.71
9	77.22	72.83	73.34
10	80.90	79.98	79.27
11	87.83	83.52	82.86
12	91.90	88.65	85.97

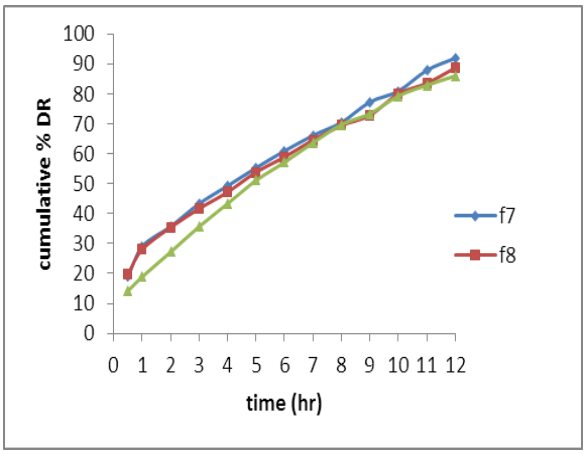

Fig 9: Dissolution profile of Mebendazole floating tablets (F7, F8, F9 formulations).

From the dissolution data it was evident that the formulations prepared with Sodium CMC as polymer were unable to retard the drug release up to desired time period i.e., 12 hours.

Whereas the formulations prepared with Chitosan retarded the drug release in the concentration of 200 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.33% in 12 hours (Formulation F6) with good floating lag time and floating buoyancy time.

The formulations prepared with Guar gum showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into.

Table 9: Release kinetics data for optimised formulation (F6) zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

CUMULATIVE (%) RELEASE Q	TIME (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining
0	0			2.000				100
19.62	0.5	1.293	-0.301	1.905	39.240	0.0510	-0.707	80.38
27.86	1	1.445	0.000	1.858	27.860	0.0359	-0.555	72.14
36.35	2	1.561	0.301	1.804	18.175	0.0275	-0.439	63.65
41.45	3	1.618	0.477	1.768	13.817	0.0241	-0.382	58.55
47.8	4	1.679	0.602	1.718	11.950	0.0209	-0.321	52.2
55.25	5	1.742	0.699	1.651	11.050	0.0181	-0.258	44.75
60.24	6	1.780	0.778	1.599	10.040	0.0166	-0.220	39.76
66.73	7	1.824	0.845	1.522	9.533	0.0150	-0.176	33.27
71.34	8	1.853	0.903	1.457	8.918	0.0140	-0.147	28.66
78.52	9	1.895	0.954	1.332	8.724	0.0127	-0.105	21.48
80.17	10	1.904	1.000	1.297	8.017	0.0125	-0.096	19.83
88.75	11	1.948	1.041	1.051	8.068	0.0113	-0.052	11.25
96.33	12	1.984	1.079	0.565	8.028	0.0104	-0.016	3.67

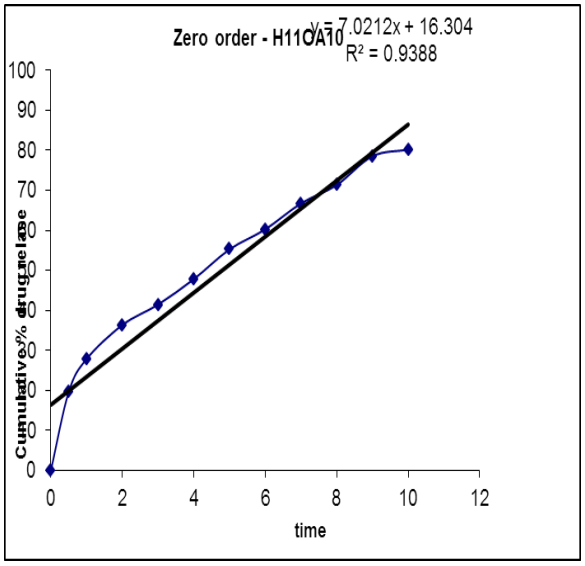

Fig 10: Zero order release kinetics graph.

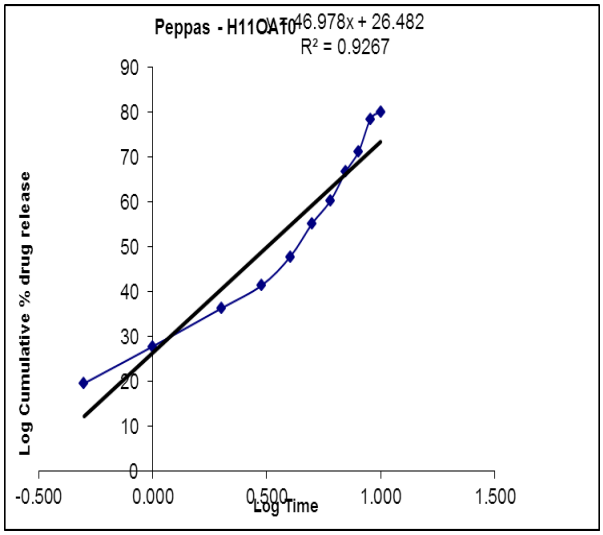

Fig 12: Kars mayer peppas graph.

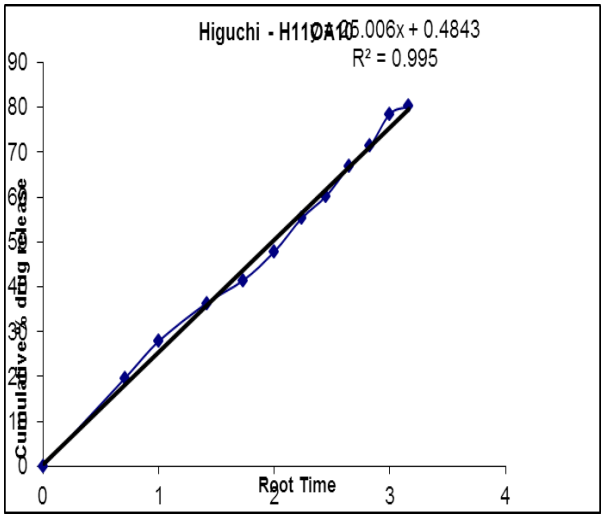

Fig 11: Higuchi release kinetics graph.

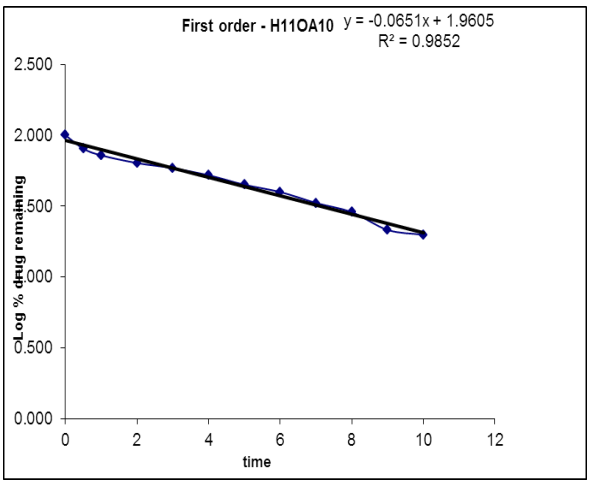

Fig 13: First order release kinetics graph.

From the above graphs it was evident that the formulation F6 was followed Higuchi mechanism.

CONCLUSION

In the present research work gastro retentive floating matrix formulation of Mebendazole by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Sodium CMC were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with Guar gum were also retarded the drug release for more than 12 hours. Hence they were not considered. The formulations prepared with Chitosan retarded the drug release up to 12 hours in the concentration of 200 mg (F6). The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

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