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Research

Development And *In Vitro* Evaluation Of Gastroprotective Floating Matrix Tablets Of Cisapride

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Abstract

In the present research work gastro retentive floating matrix formulation of Cisaprideby using various polymers were developed. 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 optimised. Then the formulation was developed by using different concentrations of polymers Amla extract, Ginger extract, Fenugreek extract, Isapgol husk as polymeric substances. 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 Amla extract as polymer were retarded the drug release more than12 hours (F3=98.73%). whereas in low concentrations the polymer was unable to produce the desired action. The optimised formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed peppas release kinetics mechanism of drug release.

Keywords: Cisapride, Amla extract, Ginger extract, Fenugreek extract, Isapgol husk, 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 Css 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]

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of t he therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug deliveysystems[4]. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concent ration in blood with predictable and reproducible release rates for extended time period; enhance ment of activity of duration for short half-life drugs; elimination of side effects; reducingfrequency of dosing and wastage of drugs; optimized ther apy and better patient compliances[5,6].

The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely.

1. The physiochemical characteristics of the drug
2. Anatomy and physiology of GIT and Characteristics of Dosage forms.

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.[7]

Gastrointestinal retention

Gastro retentive systems can remain in the gastric region for several hours and hence significant lyprolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proxima small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and Substantial benefits for patients5. To successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system (FDDS) For maximal gastrointestinal absorption of drugs and site-specific delivery, on needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT. These are outlined and briefly discussed 1.

Stomach anatomy [8,9,10]

The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly. Substantial enzyme tic digestion isinitiated in stomach, particularly of proteins. Vigorous contractions of gastric smooth muscle mix and grind foodstuffs with gastric secretions, resulting in liquefaction of food. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing6.

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions7. It has been reported that the mean value of pH in fasted healthy subjects is 1.1± 0.15. But when food comes into the stomach, the pH may rise to levels in the 3.0 to 4.0 level due to the buffering capacity of proteins. However, in fasted state, basa l gastric secretion in women is slightly lower than that of men8. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further div ided into following 4 phases.

Phase I (Basal phase) lasts from 30 to 60 minutes with rare contractions.

Phase II (Preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) lasts for 10 to 20 minutes. It includesintense and regular contractions for short period. It i s due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

Gastroretentive Drug Delivery Systems

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[11]

Need For Gastroretentive Drug Delivery System

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side

effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3 hours. Gastroretentive systems useful for drugs acting locally in the stomach (Antacids and drugs for H. Pylori viz., Misoprostol), Drugs that are primarily absorbed in the stomach (Amoxicillin), Drugs that is poorly soluble at alkaline pH (Furosemide, Diazepam, Verapamil), Drugs having narrow absorption window (Cyclosporine, Methotrexate, Levodopa), Drugs which are absorbed rapidly from the GI tract (Metonidazole, tetracycline), Drugs that degrade in the colon (Ranitidine, Metformin HCl), Drugs that disturb normal colonic microbes (antibiotics against Helicobacter pylori).[12,13]

Factors Controlling Gastroretention of Dosage Forms

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine, the particle size should be in the range of 1 to 2 mm.[14] The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include : density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metclopramide, cisapride). The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters.[15]

Types of gastroretentive system

High Density System : Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture.[16]

Modified Shape Systems/ Unfolding Systems: These are the dosage forms, which after swallowing, swell to an extent that prevent their exit from the pylorus. As a result, the dosage form is retained for a longer period of time.[17]

Mucoadhesive Systems : Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastricretention.[18] Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

Floating Drug Delivery System: Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time.

Floating drug delivery systems (FDDS) are aimed to retain the drug in thestomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The underlying principle is very simple i.e., to make the dosage form less dense than the gastric fluids so that it can float on them. The density of the system can be reduced by incorporating a number of low density fillers in to the systems such as hydroxyl cellulose lactates or microcrystalline cellulose. However, this system is not ideal because its performance is highly dependent on the presence of food and fluid in the stomach. The basic idea behind the development of such a system was to maintain a constant level of drug in the blood plasma inspire of the fact that the drug dose not undergoes disintegration. The drug usually keeps floating in th gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood [20]. The concept of floating tablets is mainly based on the matrix type drug delivery system such that the drug remains embedded in the matrix which after coming in contact with the gastric fluid swells up and the slow erosion of the drug without disintegration of the tablet takes place. Sometimes for generating a floating system we even need to add some effervescent or gas generating agent which will also ultimately reduce the density of the system and serve the goalof achieving a floating system. These systems have a particular advantage that they can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT.These systems continuously release the drug before it reaches the absorption window, thus ensuring optimalbioavailability. Different approaches are currently used to prolong the gastric retention time, like hydro dynamically balanced systems, swelling and expanding systems, polymeric bio-adhesive systems, modified shape

systems, high density systems and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

MATERIALS

Cisapride-Procured from Himedia, Hyderabad. Provided by SURA LABS ,Dilsukhnagar , Hyderabad, Amla extract-Merck Specialities Pvt Ltd, Mumbai, India, Ginger extract-Merck Specialities Pvt Ltd, Mumbai, India, Fenugreek extract-Merck Specialities Pvt Ltd, Mumbai, India, Isapgol husk-Merck Specialities Pvt Ltd, Mumbai, India, Sodium bicarbonate-CDH (P) Ltd, New Delhi, India, Talc-S.S chemicals, Chennai, India, Magnesium stearate-S.d fine chemicals, Mumbai, MCC-Tablets India Pvt Ltd., Chennai, India.

METHODOLOGY

Analytical method development:

Determination of absorption maxima :

A solution containing theconcentration 10 µg/ mL drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VISspectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve:

10mg Cisapride pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution1 1ml of solution was taken and made up with10ml of 0.1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5, 10, 15, 20 and 25 µg /ml of per ml of solution. The absorbance of the above dilutions was measured at 275 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R2)which determined by least-square linear regression analysis.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by thequality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Table 1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as themass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting.

The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.
The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample
V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk densitythe cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density
M = Weight of sample
V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density
Tap = Tapped Density

Table 2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of floating Tablets

Procedure for direct compression method

1) Drug and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method by using 7 mm punch.

Formulation of tablets

Table 3: Formulation composition for Floating tablets

Ingredients	Formulation chart											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Cisapride	10	10	10	10	10	10	10	10	10	10	10	10
Amla extract	20	30	40	-	-	-	-	-	-	-	-	-
Ginger extract	-	-	-	20	30	40	-	-	-	-	-	-
Fenugreek extract	-	-	-	-	-	-	20	30	40	-	-	-
Isapgol husk	-	-	-	-	-	-	-	-	-	20	30	40
Sodium bicarbonate	10	10	10	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4

MCC	151	141	131	151	141	131	151	141	131	151	141	131
Total tablet weight	200	200	200	200	200	200	200	200	200	200	200	200

All the quantities were in mg

RESULTS AND DISCUSSION

Analytical Method

Determination of absorption maxima

The standard curve is based on the spectrophotometer. The maximum absorption was observed at 275 nm.

Calibration curve

Graphs of Cisapride was taken in 0.1N HCL (pH 1.2)

Table 4: Observations for graph of Cisapride in 0.1N HCL

Conc [µg/mL]	Abs
0	0
5	0.129
10	0.245
15	0.352
20	0.468
25	0.581

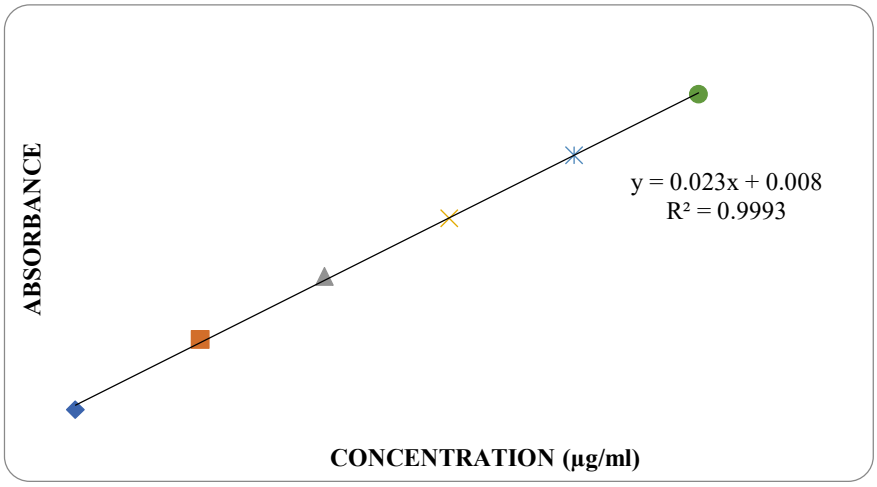

Fig 1: Standard graph of Cisapride in 0.1N HCL

Standard graph ofCisapride was plotted as per the procedure in experimental method and its linearity is shown in Table 8.1 and Fig.8.1 The standard graph of Cisapride showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Preformulation parameters of powder blend

Table 5: 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	34.35±0.39	0.51±0.01	0.64±0.02	20.31±0.02	1.25±0.02
F2	34.49±0.58	0.50±0.01	0.63±0.02	19.04±0.01	1.26±0.01
F3	34.65±0.50	0.49±0.02	0.60±0.01	18.33±0.08	1.22±0.04
F4	33.82±0.53	0.52±0.02	0.63±0.01	17.46±0.01	1.21±0.01
F5	34.45±0.24	0.50±0.01	0.61±0.01	18.03±0.01	1.22±0.02
F6	32.93±0.47	0.53±0.01	0.63±0.02	15.87±0.02	1.18±0.02
F7	33.33±0.21	0.50±0.01	0.62±0.02	19.35±0.01	1.24±0.01

F8	33.60±0.58	0.49±0.01	0.63±0.02	22.22±0.02	1.28±0.01
F9	33.80±0.55	0.51±0.01	0.64±0.01	20.31±0.01	1.25±0.03
F10	34.48±0.56	0.50±0.01	0.65±0.01	23.07±0.01	1.30±0.02
F11	33.93±0.50	0.50±0.02	0.64±0.03	21.87±0.02	1.28±0.02
F12	34.14±0.71	0.49±0.03	0.64±0.04	23.43±0.03	1.30±0.01

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 0.49±0.01 to 0.53±0.01 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.60±0.01to 0.65±0.01showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 23.43 which shows that the powder has good flow properties.All the formulations has shown the hausners ratio ranging between 1.18±0.02to 1.30±0.02indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

Table 6: *In vitro* quality control parameters

Formulation codes	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)	Total Floating Time(Hrs)
F1	198.5	3.6	0.25	3.98	97.69	3.9	6
F2	199.2	3.9	0.61	3.86	98.24	3.8	3
F3	197.8	3.4	0.34	3.19	99.28	2.9	7
F4	198.1	3.1	0.42	3.75	96.19	3.1	5
F5	199.0	3.8	0.19	3.68	95.42	2.6	6
F6	196.4	3.7	0.56	3.49	98.34	3.4	8
F7	200.0	3.4	0.64	3.67	97.42	2.7	5
F8	198.4	3.2	0.72	3.11	100.0	3.4	8
F9	199.7	3.7	0.39	3.29	95.99	2.8	9
F10	197.3	3.8	0.47	3.67	98.19	3.0	6
F11	198.4	3.9	0.58	3.49	96.48	2.9	7
F12	199.9	3.2	0.61	3.42	99.12	2.7	9

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

***In Vitro* Drug Release Studies**

Table 7: Dissolution data of Floating Tablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	7.3	10.38	11.49	12.72	13.34	8.19	11.85	13.83	10.74	21.62	19.41	25.87
1	10.68	14.72	15.85	25.74	18.97	16.75	15.35	18.72	18.42	35.41	23.99	28.19
2	16.24	23.84	24.57	36.22	26.19	22.95	20.84	23.47	24.53	47.44	31.82	34.67
3	21.29	34.12	34.88	48.97	32.99	27.39	26.35	26.81	30.14	56.26	38.06	41.81
4	26.74	45.03	45.80	52.62	38.49	32.98	36.54	31.77	35.44	65.46	46.12	46.37
5	34.95	56.06	56.42	59.78	45.18	39.47	45.35	39.06	46.35	71.19	49.20	52.92
6	41.67	62.17	60.19	63.99	53.75	48.12	50.95	45.53	52.94	79.55	53.81	58.48
7	58.48	69.85	65.96	69.11	58.67	53.62	54.84	49.77	59.47	83.93	62.24	64.72
8	73.75	74.92	71.27	73.15	63.18	57.24	61.56	53.47	64.82	89.72	68.71	67.49
9	79.38	79.56	75.48	78.24	69.87	66.11	66.68	62.18	69.71	93.18	73.82	74.82
10	86.25	83.69	81.15	83.91	74.51	69.44	75.91	68.51	73.28	97.86	79.28	80.97
11	90.11	97.01	86.96	86.11	86.10	73.82	83.19	73.87	77.92		85.31	86.88

12	94.39	98.73	91.42	96.49	80.19	96.87	89.15	81.42	90.87	95.17	

From the dissolution data it was evident that the formulations prepared with Amla extract as polymer were retarded the drug release more than 12 hours. Whereas the formulations prepared with Low concentration of Ginger extract retarded the drug release up to 12 hours in the concentration 30 mg. In higher concentrations the polymer was unable to retard the drug release. Whereas the formulations prepared with low concentration of Fenugreek extract retarded the drug release up to 12 hours in the concentration 20 mg. In higher concentrations the polymer was unable to retard the drug release. Whereas the formulations prepared with higher concentration of Isapgol husk extract retarded the drug release up to 12 hours in the concentration 40 mg. In lower concentrations the polymer was unable to retard the drug release. Hence from the above dissolution data it was concluded that F3 formulation was considered as optimised formulation because good drug release (98.73 %) in 12 hours.

Application of Release Rate Kinetics to Dissolution Data for optimised formulation

Table 8: Application kinetics for optimised formulation

Cumulative (%) Release Q	Time (T)	Root (T)	Log(%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release / T)	1/Cum% Release	Peppas Log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
11.49	0.5	0.707	1.060	-0.301	1.947	22.980	0.0870	-0.940	88.51	4.642	4.457	0.185
15.85	1	1.000	1.200	0.000	1.925	15.850	0.0631	-0.800	84.15	4.642	4.382	0.259
24.57	2	1.414	1.390	0.301	1.878	12.285	0.0407	-0.610	75.43	4.642	4.225	0.416
34.88	3	1.732	1.543	0.477	1.814	11.627	0.0287	-0.457	65.12	4.642	4.023	0.618
45.8	4	2.000	1.661	0.602	1.734	11.450	0.0218	-0.339	54.2	4.642	3.784	0.857
56.42	5	2.236	1.751	0.699	1.639	11.284	0.0177	-0.249	43.58	4.642	3.519	1.123
60.19	6	2.449	1.780	0.778	1.600	10.032	0.0166	-0.220	39.81	4.642	3.415	1.227
65.96	7	2.646	1.819	0.845	1.532	9.423	0.0152	-0.181	34.04	4.642	3.241	1.401
71.27	8	2.828	1.853	0.903	1.458	8.909	0.0140	-0.147	28.73	4.642	3.063	1.579
75.48	9	3.000	1.878	0.954	1.390	8.387	0.0132	-0.122	24.52	4.642	2.905	1.736
81.15	10	3.162	1.909	1.000	1.275	8.115	0.0123	-0.091	18.85	4.642	2.661	1.980
86.96	11	3.317	1.939	1.041	1.115	7.905	0.0115	-0.061	13.04	4.642	2.354	2.288
98.73	12	3.464	1.994	1.079	0.104	8.228	0.0101	-0.006	1.27	4.642	1.083	3.559

Optimised formulation F3 was kept for release kinetic studies. From the above graphs it was evident that the formulation F3 was followed peppas release kinetics.

Drug – Excipient compatability studies
Fourier Transform-Infrared Spectroscopy

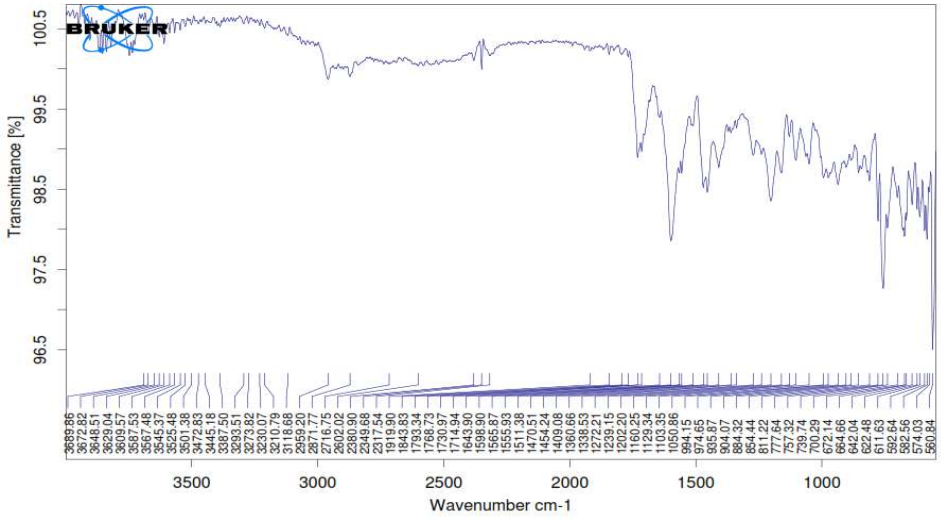

Fig 2: FTIR Spectrum of pure drug

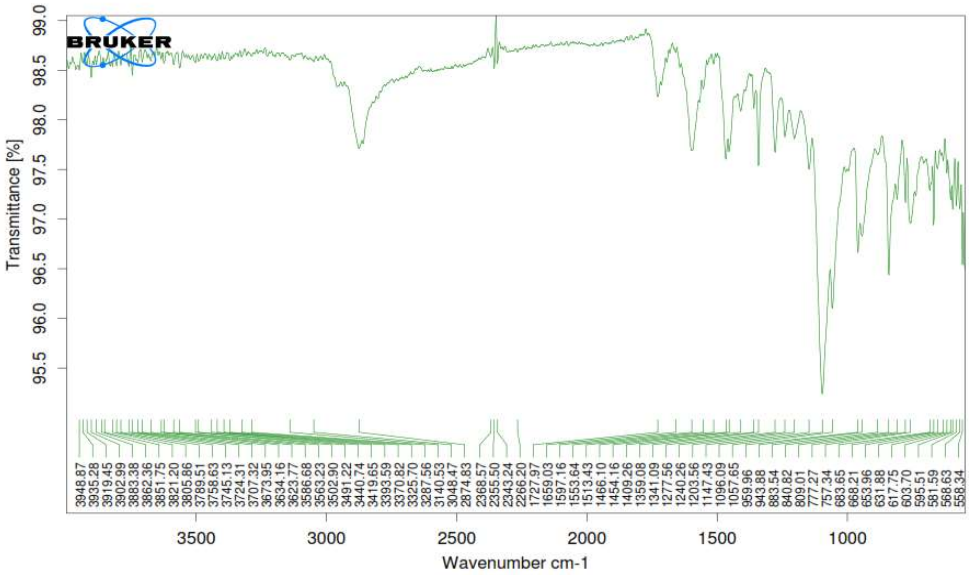

Fig 3: FTIR Spectrum of optimised formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Cisapride are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

CONCLUSION

Development of Gastro retentive floating drug delivery of Cisapride tablets is to provide the drug action up to 12 hours. Gastro retentive floating tablets were prepared by direct compression method.using various polymers like Amla extract, Ginger extract, Fenugreek extract and Isapgol husk. The formulated gastro retentive floating tablets were evaluated for different parameters such as drug excipient compatability studies, weight

variation, thickness, hardness, content uniformity, Floating lag time and *In vitro* drug release studies performed in 0.1N HCL for 12 hrs and the data was subjected to zero order, first order, Higuchi release kinetics and karsmayer peppas graph. The following conclusions could be drawn from the results of various experiments

- ✓ FTIR studies concluded that there was no interaction between drug and excipients.
- ✓ The physico-chemical properties of all the formulations prepared with different polymers Amla extract, Ginger extract, Fenugreek extract, Isapgol husk were shown to be within limits.
- ✓ Quality control parameters for tablets such as weight variation, Hardness, Friability, thickness, drug content were found to be within limits.
- ✓ *In-vitro* drug release studies were carried out for all prepared formulation and from that concluded F3 formulation has shown good results.
- ✓ Finally concluded release kinetics to optimised formulation (F3) has followed peppas release kinetics.
- ✓ Present study concludes that gastro retentive floating system may be a suitable method for Cisapride administration.

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