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A STUDY ON FORMULATION AND DEVELOPMENT OF GASTRO-RETENTIVE FLOATING DRUG DELIVERY SYSTEM OF CURCUMIN FOR STOMACH TUMORS AND ULCER

Abhishek Kumar[*1, 2] and Brijesh Kr. Tiwari [2]

Mewar University [1], Gangrar - 312901, Rajasthan, India.
NKBR College of Pharmacy and Research Centre [2], Meerut - 250004, Uttar Pradesh, India.

Keywords:

Curcumin, Psyllium husk, *Mangifera indica* gum, Floating lag time, Floating drug delivery system, Gastroretentive dosage form

Correspondence to Author:
Abhishek Kumar

Assistant Professor,
NKBR College of Pharmacy and Research Centre, Meerut - 250004, Uttar Pradesh, India.

E-mail: Pharma.abhishek@yahoo.co.in

ABSTRACT: Purpose: To prepare and evaluate floating tablet of curcumin for prolonged gastric residence time and increased drug bioavailability for the treatment of gastric problem. **Methods:** Floating tablet were prepared by wet granulation method using different ratios of Curcumin, Psyllium husk, HPMC K 15 M, HPMC K 100 M and *Mangifera indica* gum. The respective powders were blended thoroughly and a dump mass was prepared by adding the granulating agent. Dump mass was passed through sieve number 10 and dried in hot air oven at 50 ^{0}C for 30 mins. After drying, granules were further passed through sieve number 22 to attain the uniformity in granules. Finally, optional additives like magnesium stearate and talc were added and finely blended for preparation of floating tablet. **Result:** Floating drug delivery tablets were being formulated and the present study focused on the formulation of FDDS by using different polymes like phyllium husk, HPMC K 100 and HPMC K15 and to evaluate its efficacy in reducing ulcers caused by *H.pylori*. The Floating drug delivery tablets were characterized for their weight variation, hardness, friability, drug content determination, disintegration, *in-vitro* dissolution studies, IR, floating lag time, swelling studies and erosion studies. **Conclusion:** The developed curcumin floating tablet system is a promising floating drug delivery system for oral sustained administration of curcumin.

INTRODUCTION: Effective delivery of the drugs to the stomach, for local action and treatment of gastric disorders such as gastric cancer, gastric ulcers can be treated by floating dosage forms like single and multiple unit gas generating systems, hollow microspheres, hydro-dynamically balanced systems, swelling systems, mucoadhesive systems and other gastro-retentive dosage forms [1].

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Curcumin is a major pigment of the Curcuma species, commonly used as a yellow coloring and flavoring agent in foods particularly in South Asia [2]. The novel trends in medicine have led to extensive investigations to establish the wide spectrum of biological and pharmacological actions of this phyto-chemical. Curcumin has been reported to possess anti-inflammatory, antioxidant, anti-carcinogenic, anticoagulant, anti-arthritic, antibacterial, antifungal, anti-protozoal, antiviral, anti-Alzheimer, anti-psoriatic and neuro-protective activities [4]. The efficacy, pharmacological safety, cost effectiveness of curcumin and no-dose limiting toxicity [4] has also prompted many researchers to further investigate this molecule.

How-ever, it has also been recognized that the therapeutic effectiveness of curcumin is limited due to its poor circulating bioavailability and absorption from the gastrointestinal tract.

Present work was designed to improve the aqueous solubility of curcumin at:

1. Turmeric as a spice in food: The popularity of turmeric has increased worldwide with the Food and Agriculture Organization of the United Nations. [9] Turmeric is obtained from the dried rhizome of the plant *Curcuma longa* widely used as a gold-coloured spice in Indian subcontinent which impart flavour, colour to the food, act as a medicinal herb and used in textile industry as a dye. Curcumin was first isolated almost two centuries ago and its structure was determined in 1910 [10]. Curcumin is the active ingredient of turmeric, which is used daily in Indian and other South Asian cuisines as a spice. The basic pharmacological principles and potential clinical applications of curcumin were reported [11]. Most commercial turmeric preparations consist of ~2-8% active curcumin [9].

2. Photochemistry of the Curcumin: All curcuminoids are often referred to simply as "curcumin [1, 7-bis (4-hydroxy-3 methoxyphenyl)-1, 6-heptadiene-3, 5 -dione, **Fig. 1**]" even though turmeric contains a variety of different curcuminoids [4]. Commercial curcumin contains three major curcuminoids: curcumin (curcumin I), demethoxycurcumin (curcumin II) and bis-demethoxycurcumin (curcumin III). Commercial curcumin contains curcumin I (~77%), curcumin II (~17%) and curcumin III (~3%) as its major components [5].

3. Ethnobotanical uses: In Ayurvedic system of medicine, numerous therapeutic activities have been assigned to turmeric for a wide variety of diseases and conditions, including those of the skin, gastrointestinal systems, aches, pains, wounds, sprains, and liver disorders. Extensive research within the last half century has proven that most of these pharmacological activities associated with turmeric are due to active ingredient curcumin. Ethno-botanically curcumin has been proven as a potent compound which act as an antioxidant and anticancer in both man and animals [7]. It has been reported that these effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes [8]. Curcumin ability to cross the blood brain barrier may afford protection against neurodegenerative problems [9, 10].

4. Pharmacological aspects:

4.3 Anticancer activity: Curcumin act as a potent cancer preventing agent by blocking the nuclear factor-kappa B and also interferes in the production of dangerous glycation end products that trigger inflammation and lead to cancerous mutation in the body [13]. In addition, curcumin mediates anticancer activities by controlling the increasing levels of vitamins C and E, preventing lipid per-oxidation and DNA damage [14].

Curcumin selectivity targeted transformed cells without altering primary astrocytes. Curcumin also showed synergistic effect with the chemotherapeutic cisplatin and doxorubicin drugs to enhance cells death [15]. Results based on solid-state NMR and differential scanning calorimetry showed that curcumin has potent action on cell membrane of the tumor cell [16]. Researcher showed that curcumin effectively inhibited human lens epithelial B3 cell proliferation induced by rhb FGF [17]. Curcumin was found to reduce the spread of breast cancer in mice and prevented numerous forms of cancers very soon,

Childhood leukaemia and in pancreatic cancer [18-19]. Curcumin has been approved to conduct Phase I/ II trial for the treatment of bowel cancer [20]. Curcumin significantly reduced the brain and unwanted cytotoxicity in hippocampal neurons in wistar rats [21]. Curcumin was found to be effective in oral cancer, hepatic cancer and in colon cancer [9]. Curcumin-loaded nanospheres were able to exert a more pronounced effect on the cancer cells as compared to conventional curcumin the potential of nanoparticle-based formulation as an adjuvant therapy for clinical application in prostate cancer [22]. Curcumin lack of systemic toxicity and broad-reaching mechanism of action may make it best suited as an adjuvant therapy for head and neck [23].

Drug Delivery Systems:

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 targeted tissue [24].

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

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

Oral Controlled Drug Delivery Systems: Oral controlled release drug delivery is a drug delivery system that provides the oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic drug action.

Gastro-retentive Dosage Form (GRDF): [25, 26] It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the impotent feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS).

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

Need of gastro-retentive drug delivery system: [27] Some 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 absorb the constituent, 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.[5] In general, appropriate candidates for control release GRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the gastro intestinal tract.

Dosage form with prolonged GRT, i.e. gastro retentive dosage forms (GRDF), will bring about new and important therapeutic options such as:

1. This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, gastro-retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

2. GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the submucosal tissues of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations like calcium carbonate.

3. GRDFs can be used as carriers for drugs with so called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Tetracyclines etc.) are taken up only from very specific sites of the GI mucosa membrane.

Approaches to Gastric Retention [28, 29] Floating Systems: Floating Drug Delivery Systems [30] (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a

prolonged period of time, without affecting the gastric emptying rate.

Types of Floating Drug Delivery Systems (FDDS): [31, 32] Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

A. Effervescent System, and
B. Non- Effervescent System

Advantages of FDDS: [33, 34] Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site-specific drug delivery.

Disadvantages of FDDS:

1. Gastric retention is affected by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diametric size. Therefore patients should not be dosed with floating forms just before going to bed.

MATERIALS AND METHODS:

Materials: Curcumin, HPMC K15M, HPMC K100M, Psyllium husk, *Mangifera indica* gum, Sodium bicarbonate, Citric acid, Magnesium stearate, Talc. The equipments used in this study were Dissolution Apparatus, Disintegration Apparatus, UV Spectrophotometer, Digital Balance, Hardness Tester, Friability Tester, Punching Machine, Venire Calipers and FT-IR.

Methods:

Formulation of Floating Tablets: Different batches of floating matrix tablets were prepared by wet granulation method using different ratios of Curcumin, Psyllium husk, HPMC K 15 M, HPMC K 100 M and *Mangifera indica* gum. The respective powders (drug, polymers & binder) were blended thoroughly and a dump mass was prepared by adding the granulating agent (5 % PVP in isopropyl alcohol). Dump mass was passed through sieve number 10 and dried in hot air oven at 50 ^{0}C for 30mins. After drying, granules were further passed through sieve number 22 to attain the uniformity in granules. Finally, optional additives like magnesium stearate and talc were added and finely blended. The required amount of the blend was weighed and fed manually into the die of single punch tableting machine to produce tablets using concave faced punch of suitable diameter. The tablet hardness was maintained in the range of 4-5 kg/cm^2. The compositions for polymeric solutions were mentioned in **Table 1.**

TABLE 1: COMPOSITIONS FOR DIFFERENT FORMULATIONS

S. no.	Ingredients	Formulations(in mg/tablet)				
		F1	F2	F3	F4	F5
1	Curcumin	100	100	100	100	100
2	HPMC K15M	150	-	-	50	-
3	HPMC K100M	-	150	-	-	50
4	Psyllium husk	-	-	150	100	100
5	*Mangifera indica* gum	50	50	50	50	50
6	Sodium bicarbonate	50	50	50	50	50
7	Citric acid	25	25	25	25	25
8	Magnesium stearate	20	20	20	20	20
9	Talc	5	5	5	5	5

Evaluation of Prepared Tablets: Floating tablets of curcumin extract were evaluated for following physicochemical parameters: Pre-formulation Studies: It is one of the important pre-requisite in development of any drug delivery system. Pre-formulation studies were performed on the drug, which included solubility and compatibility studies.

A. Description: Curcumin was physically examined for colour and odour etc.

B. Solubility: Solubility of curcumin was determined in water, phosphate buffer 7.4, ethanol, DMSO, tetra hydro furan etc.

C. Interaction Studies:

Drug-polymer interaction study: Interaction of drug with polymers was confirmed by IR interaction studies. The pure drug along with polymer was subjected to IR studies. Combinations studied were pure drug, drug with HPMC K15M, drug with HPMC K100M and drug with psyllium husk.

Pre and Post Compression parameters: Primary stock solution: 100 mg of curcumin was accurately weighed and dissolved in 30 ml ethanol and diluted to 100 ml with distilled water.

Secondary stock solution: 1 ml of primary solution was diluted to 100 ml distilled water to get a concentration of 10 µg /ml. From these 1 ml was pipette out diluted to 10 ml to get a concentration of 1 µg/ml. Aliquots of 1 ml, 2 ml, 4 ml, 6 ml, 8 ml, and 10 ml were pipette out and diluted to 10 ml with distilled water to get a 1 µg, 2 µg, 4 µg, 6 µg, 8 µg, and 10µg concentration of curcumin. Standard graph was plotted by keeping the known concentration on X-axis and obtained absorbance on Y-axis. The results are presented in table and represented graphically.

Construction of Standard Plot of Curcumin:

Drug Content Determination (Assay): USP defines content uniformity test for tablets containing100 mg or less of drug substance in case of uncoated tablets and for all sugar coated tablets regardless to the drug content.

Ten tablets are individually assayed for their content (according to the method described in the individual monograph) the requirements for content uniformity are met if the amount of the active ingredient in each tablet lies within the range of 85-115 % of the label claim.

Thickness: [35- 36] The dimensions of the tablet like thickness, diameter were measured using vernier calipers. Ten tablets were selected randomly for this test and the average value was reported.

Size and Shape: [37-38] The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The particle size of the formulations was determined using sieve analysis.

Weight Variation: If the drug forms greater part of the tablet, any variation in the tablet weight obviously indicates a variation in the active ingredient. Weigh 20 tablets individually (i.e. determine the weight of each tablet alone; X1, X2, X3… X20)

The average weight of tablets=Total weight of tablets/ Number of tablets

Average weight of tablets (X) = (X1+X2 +X3+…+X20)/20

Hardness: Tablets require a certain amount of strength, or hardness and resistance to friability, to is withstand mechanical shocks of handling in manufacture, packaging and transportation. Special hardness testers are used for this purpose (manually or motor driven testers). The test measures crushing strength property defined as the compression force applied diametrically to a tablet which just fracture or break it. A force of about 4 Kg is considered the minimum requirement for a satisfactory tablet.

Friability Test: Friability test was done by Roche friabilator. Ten tablets were weighed and were subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Operated for 100 revolutions, the tablets were de dusted and reweighed. The percentage friability was calculated.

Disintegration Test: This test determines whether tablets disintegrate within a prescribed time when placed in a liquid medium under prescribed experimental conditions. The U.S.P. device to test disintegration uses 6 glass tubes that are open at the

top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1L beaker of water. Simulated gastric fluid at 37 °C ± 2 ^{0}C was used. The tablet should remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. The basket containing the tablets was moved up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet.

***In-vitro* Drug Release Studies:** [54-58] The *in-vitro* drug release studies of the 5 batches of curcumin floating drug delivery formulations were performed using USP dissolution rate test apparatus. The dissolution medium was 900 ml 0.1N HCl. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.50C. The tablet was placed into the vessel and a suitable device such as a wire or glass helix was used and the speed of rotation was kept at 50 rpm. At predetermined time intervals 5 ml of samples were withdrawn and replaced by an equal volume of fresh medium to maintain the sink conditions. Samples collected at 0.5,1,2,3,4,5,6,7,8,9,10,12and 24hrs were filtered and analyzed at each interval for curcumin content released at λ_{max} of 420 nm using UV-Visible Spectrophotometer. The results were tabulated in table 9.6 and represented graphically in graph 9.3.

Release Kinetics: The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and it is particularly evident in the case of Floating drug delivery. As a model dependent approach, the dissolution data are fitted to five popular release models such as zero-order, first-order, diffusion, erosion and power law equations, which have been described in the literature. The order of release from matrix systems was described by using zero-order kinetics or first- order kinetics. The mechanism of drug release from floating drug delivery systems was studied by Higuchi equation and erosion equation.

Floating Lag Time: [50- 51] Effect of formulation variables on the floating properties of gastric floating drug delivery system was determined by using continuous floating monitoring system and statistical experimental design. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as floating time. The test for floating time measurement is usually performed in simulated gastric fluid or 0.1M HCl maintained at 370ºC. It is determined by using dissolution apparatus containing 900 ml of 0.1mole/lit as a dissolution medium at 370 ºC. Floating properties of FDDS that enable them to be retained in stomach for prolonged period of time is usually acquired due to low density of the HBS dosage forms.

Swelling Studies: [37-38] Swelling of hydrophilic polymer such as Hydroxy Propyl Methylcellulose greatly depends upon the contents of the stomach and the osmolality of the medium. For each formulation, one tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again up to 8hours. The percentage weight gain by the tablet was calculated by using the formula:

$$\text{Swelling index (S.I)} = \{(Wt-Wo)/Wo\} \times 100$$

Where,
S.I. = swelling index
Wt = Weight of tablet at time t
Wo = Weight of tablet before immersion

Erosion Studies: [54-58] Erosion studies were performed by a method dissolution test apparatus was used for this purpose. The dry matrices were weighed, placed in dissolution basket containing 900 ml of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5 °C, and the basket was rotated at 100 rpm. At regular intervals, the whole basket-matrix assembly was removed from the dissolution vessels and dried to a constant weight in a hot air oven at 50 °C.

$$\text{Matrix erosion (\%)} = Wdt/W0 \times 100$$

W_dt- weights of dried tablet at time t W0 -initial weight of dry tablet

RESULTS AND DISCUSSION: Floating drug delivery tablets were being formulated and the present study focused on the formulation of FDDS by using different polymes like phyllium husk, HPMC K 100 and HPMC K15 and to evaluate its efficacy in reducing ulcers caused by *H.pylori.*

The Floating drug delivery tablets were characterized for their weight variation, hardness, friability, drug content determination, disintegration, *in-vitro* dissolution studies, IR, floating lag time, swelling studies and erosion studies.

Evaluation of Floating Tablets:

Pre-formulation Studies:

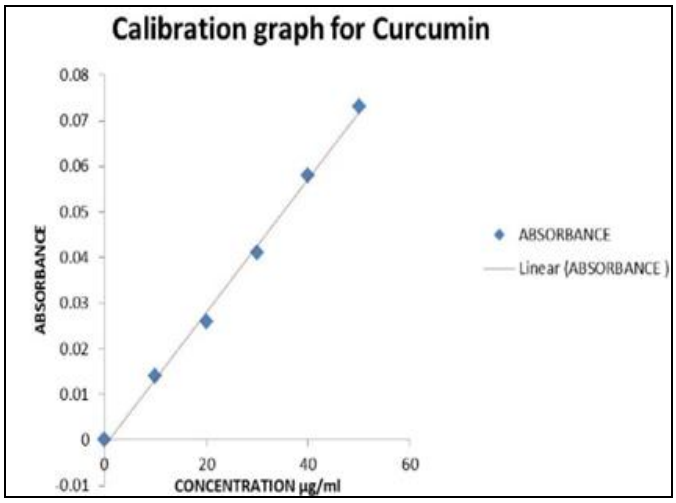
1. Description: Curcumin was physically examined for colour and odour etc. It is an orange yellow powder, with characteristic odour.

2. Solubility: Curcumin was insoluble in water, poorly soluble in buffer solution pH 7.4, and soluble in ethanol, DMSO, and Tetra hydro furan (THF).

Pre and Post Compression Parameters: Calibration Curve for Curcumin: The standard plot as per dilutions 10, 20, 30, 40, and 50 µg/ml mentioned in the experimental procedure for curcumin was done and the results are tabulated in **Table 2** and plotted in **Graph 1**.

TABLE 2: STANDARD VALUES FOR CALIBRATION CURVE OF CURCUMIN

S.no.	Concentration(µg/ml)	Absorbance
1	10	0.014
2	20	0.025
3	30	0.039
4	40	0.058
5	50	0.073



GRAPH 1: CALIBRATION GRAPH FOR CURCUMIN

Drug Content Determination: The assay of the different formulations F_1, F_2, F_3, F_4, F_5 were determined as given in the experimental methods and the results were tabulated in **Table 2**.

TABLE 3: DRUG CONTENT DETERMINATION

S. no.	Formulations	Assay
1	F1	99.6±0.85%
2	F2	98.21±0.41%
3	F3	92.32±0.47%
4	F4	105.15±0.35%
5	F5	100.48±0.72%

The assay or drug content in the formulations ranged between 92-106%. The assay value of F4 was found to be higher compared to the other formulations.

Weight Variation Test: Weight variation test results were plotted in **Table 4**.

TABLE 4: WEIGHT VARIATION

S. no.	Formulations	% Weight
1	F1	100.2 % ± 1.58%
2	F2	99.8 % ± 2.87%
3	F3	101.3 % ± 1.93%
4	F4	103.6 % ± 2.33%
5	F5	98.3 % ± 1.85%

No of tablets taken= 20
Limit of % weight = 90%-110%

Swelling Index: Swelling is a vital factor to ensure floating. To obtain floating, the balance between the swelling and water must be reported. The formulation containing psyllium husk took about 5-8hrs to swell completely as compared to the formulation prepared with HPMC K100M that took 3-5 hrs. To swell completely. In the first hour of study, the swelling index for formulation prepared with psyllium husk alone was 52.2% (batch F3) and 81.73% (batch F2) for the formulation prepared with HPMC K100M.

The swelling index after complete swelling was 302.45% for formulation prepared with psyllium alone (F3) and 291.62% for formulation prepared with HPMC K100M alone (F2). The difference in the swelling index was because, psyllium husk is a natural agent that took more time to hydrate when compared to synthetic polymer HPMC K100M. Addition of HPMC K15M in formulation containing psyllium enhanced the swelling index at initial stage (F4= 61.8%) but swelling index after complete swelling was decreased (F4 = 295.21%). Finally the swelling index optimised formulation after complete swelling was for 295.21% formulation containing psyllium husk in combination with HPMC K15M.

TABLE 5: SWELLING INDEX

Time (hr)	F1	F2	F3	F4	F5
1	82.52	82.53	54.21	65.81	67.23
2	89.33	84.91	76.26	70.84	76.75
3	97.05	92.47	93.74	79.45	82.27
4	108.22	108.33	119.69	87.72	92.23
5	122.86	121.28	125.25	96.09	112.61
6	131.32	129.91	149.18	112.18	134.43
7	143.65	139.19	152.81	132.72	133.13
8	157.32	148.22	178.41	152.61	154.30
9	167.56	169.35	185.22	174.25	168.72
10	181.89	179.86	193.50	182.31	183.53
12	218.76	223.47	217.41	221.42	215.63
18	262.27	263.61	242.52	263.62	259.41
24	293.25	294.61	312.46	296.25	292.45

Floating Capacity: Floating duration & dimensional stability are important in case of once daily formulation to obtain the continuous and constant drug release up to the 24 hrs. If physical integrity of the formulation is not maintained, the tablet could break down in to the small fragments and escape from the upper part of GIT. The floating lag time and duration of floating of formulation F3 containing 200 mg of psyllium husk (drug: polymer ratio of 1:2) was 12 minutes & 8 hrs respectively and the dimensional stability was maintained up to 24 hrs. Incorporation of HPMC K15M enhanced the floating duration (F4= 24 hrs.) This might be due the synthetics nature of HPMC K15M, which hydrated at a faster rate than that of psyllium husk. HPMC K15M also helps to maintain dimensional stability at initial stage. There was no measurable effect of HPMC K15M on FLT. Formulation prepared with HPMC K100M in similar amount as that of psyllium and HPMC K15M combination (F5) showed the floating duration 24 hrs. (**Table 6**)

Erosion Studies: The percentage of matrix eroded was more for the formulations prepared with psyllium husk alone (F3 = 9.35%) than that of HPMC K100M (F2=3.56%) and HPMC K15M (F1=2.32%) after 12 hours study. Addition of HPMC K15M in formulation containing psyllium husk reduced the erosion (F4=5.35 %).

TABLE 6: FLOATING CAPACITY

S. no	F.C	Drug	P	HPMC 15M	HPMC 100M	$NaHCO_3$	FLT (min)	FD (hrs.)	DS (hrs.)	Drug Released(24hrs)
1	F1	100	-	200	-	50	1	24	24	70.58±1.62%
2	F2	100	-	-	200	50	1	24	24	65.57±1.36%
3	F3	100	200	-	-	50	12	8	24	55.63±2.12%
4	F4	100	100	100	-	50	5	24	24	87.82±1.08%
5	F5	100	100	-	100	50	5	24	24	75.15±1.41%

F.C = Formulation Code, P = Psyllium Husk Powder,
$NaHCo_3$ =Sodium Bi Carbonate, FLT = Floating Lag Time,
FD = Floating Duration

***In-vitro* Studies:** The *in-vitro* release studies were performed as mentioned in the experimental methods and the results were tabulated below in the **Table 7** and represented graphically in Graph 9.3. Two different polymers (Psyllium husk and HPMC) were used to prepare the floating tablets. It was observed that type of polymer influences the release pattern. The formulation prepared with psyllium husk alone showed more sustained release (F3 =55.63%) than those prepared with HPMC K100M (F2 =65.57%) and HPMC K15M (F1 =70.58%) after 24hrs study. But formulations prepared with psyllium husk alone were not able to float up to 24 hrs. To enhance floating duration HPMC K15M was added. The formulation containing HPMC K15M and psyllium (F4) was able to float up to 24hrs and release rate was enhanced (F4=87.82%). Finally, the cumulative percent release from optimized formulation prepared with psyllium in combination with HPMC K15M (F4=89.86%) was more than that of formulation prepared with HPMC K100M (F5=75.15%).

Release Kinetics: The *in-vitro* release data of optimized formulations were treated with different kinetics models to explain the release kinetics curcumin from floating matrix tablets. These models were zero order, first order, higuchi model. Higuchi model was considered as the best fitted model.

TABLE 7: *IN-VITRO* RELEASE PROFILES OF THE FORMULATIONS

Time(hrs)	F1	F2	F3	F4	F5
0.5	1.64	1.83	0.85	3.68	2.42
1	5.31	3.67	1.67	9.56	7.79
2	8.26	6.82	3.34	12.47	9.27
3	9.74	7.45	5.68	15.76	11.96
4	11.92	9.51	8.71	18.46	15.76
5	15.61	12.57	10.66	20.72	18.14
6	18.71	16.97	13.76	23.48	22.51
7	22.39	19.28	18.78	30.65	26.78
8	27.48	25.48	21.71	35.39	30.52
9	32.71	29.67	25.27	40.46	36.61
10	38.72	33.73	28.13	45.87	40.41
12	45.85	42.16	37.24	50.75	47.62
18	54.47	51.35	46.89	60.82	57.72
24	70.58	65.57	55.63	87.82	75.15

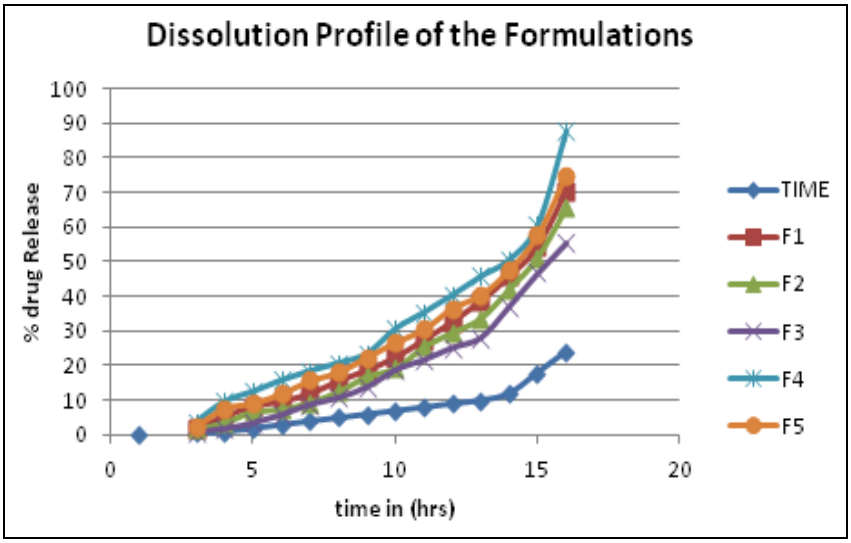


FIG. 1: DISSOLUTION PROFILE OF THE FORMULATIONS

TABLE 8: ZERO-ORDER KINETICS DATA

Time(hrs)	F1	F2	F3	F4	F5
0.5	1.64	1.83	0.85	3.68	2.42
1	5.31	3.67	1.67	9.56	7.79
2	8.26	6.82	3.34	12.47	9.27
3	9.74	7.45	5.68	15.76	11.96
4	11.92	9.51	8.71	18.46	15.76
5	15.61	12.57	10.66	20.72	18.14
6	18.71	16.97	13.76	23.48	22.51
7	22.39	19.28	18.78	30.65	26.78
8	27.48	25.48	21.71	35.39	30.52
9	32.71	29.67	25.27	40.46	36.61
10	38.72	33.73	28.13	45.87	40.41
12	45.85	42.16	37.24	50.75	47.62
18	54.47	51.35	46.89	60.82	57.72
24	70.58	65.57	55.63	87.82	75.15

FIG. 2: ZERO-ORDER PLOT

TABLE 9: FIRST-ORDER KINETICS DATA

Time(hrs)	F1	F2	F3	F4	F5
0	2	2	2	2	2
0.5	1.9928	1.9919	1.9962	1.9837	1.9522
1	1.9776	1.9837	1.9926	1.9562	1.9647
2	1.9625	1.9693	1.9852	1.9421	1.9577
3	1.9554	1.9663	1.9746	1.9255	1.9446
4	1.9448	1.9566	1.9604	1.9113	1.9255
5	1.9262	1.9416	1.9510	1.8991	1.9130
6	1.9133	1.9192	1.9357	1.8837	1.8892
7	1.8899	1.9069	1.9096	1.8410	1.8646
8	1.8604	1.8722	1.8937	1.8102	1.8418
9	1.8279	1.8471	1.8734	1.7748	1.8020
10	1.7873	1.8213	1.8565	1.7334	1.7751
12	1.7335	1.7622	1.7976	1.6924	1.7191
z18	1.6582	1.6870	1.7251	1.5930	1.6261
24	1.4686	1.5369	1.6470	1.0856	1.3952

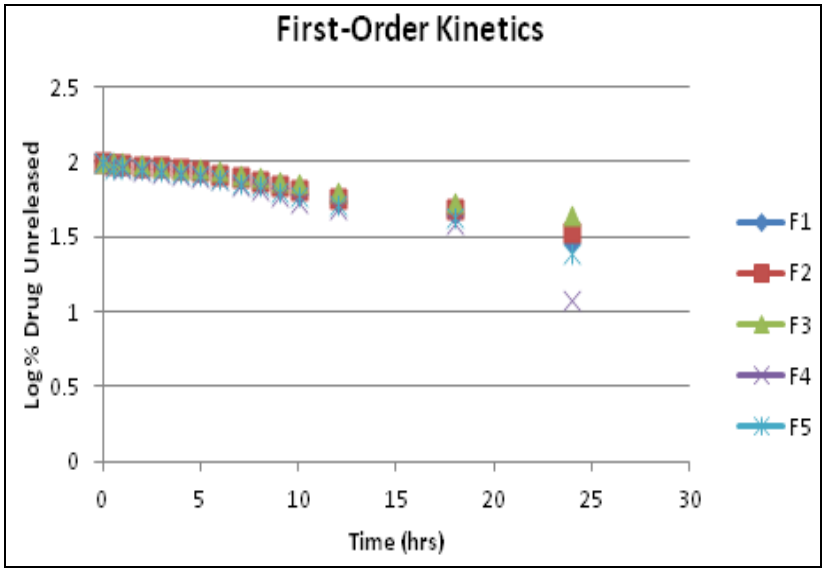


FIG. 3: FIRST-ORDER KINETICS

TABLE 10: HIGUCHI KINETICS DATA

√Time (hrs)	F1	F2	F3	F4	F5
0	1.64	1.83	0.85	3.68	2.42
0.7071h	5.31	3.67	1.67	9.56	7.79
1h	8.26	6.82	3.34	12.47	9.27
1.414h	9.74	7.45	5.68	15.76	11.96
1.732h	11.92	9.51	8.71	18.46	15.76
2h	15.61	12.57	10.66	20.72	18.14
2.2360h	18.71	16.97	13.76	23.48	22.51
2.449h	22.39	19.28	18.78	30.65	26.78
2.6457h	27.48	25.48	21.71	35.39	30.52
2.8284h	32.71	29.67	25.27	40.46	36.61
3h	38.72	33.73	28.13	45.87	40.41
3.1623h	45.85	42.16	37.24	50.75	47.62
3.464h	54.47	51.35	46.89	60.82	57.72
4.243h	70.58	65.57	55.63	87.82	75.15

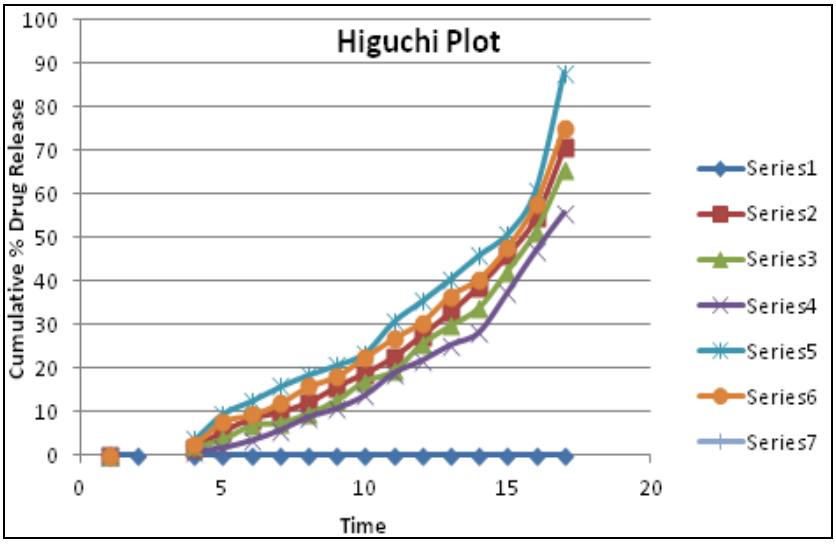


FIG. 4: HIGUCHI PLOT

TABLE 11: PEPPAS KINETICS DATA

Time (hrs)	F1	F2	F3	F4	F5
0.5	0.2148	0.262	-0.070	0.565	0.383
1	0.7250	0.564	0.222	0.980	0.891
2	0.9169	0.8337	0.523	1.095	0.967
3	0.9885	0.872	0.754	1.197	1.077
4	1.076	0.978	0.940	1.266	1.197
5	1.193	1.099	1.027	1.316	1.258
6	1.2720	1.229	1.138	1.370	1.352
7	1.350	1.285	1.273	1.486	1.427
8	1.439	1.406	1.336	1.548	1.484
9	1.514	1.472	1.402	1.607	1.563
10	1.5879	1.528	1.449	1.661	1.606
12	1.661	1.624	1.571	1.705	1.677
18	1.736	1.7105	1.671	1.784	1.761
24	1.848	1.816	1.745	1.943	1.875

Interaction Studies: Drug-polymer interaction study FTIR: Interaction of drug with polymers was confirmed by carrying out IR interactions studies. The IR overlay spectrum of drug alone and drug with polymer were seen. It shows that there are no interactions found between the drug and polymers.

CONCLUSION: From the above work it can be concluded that the objective of the proposed project has been fulfilled any hydrodyanamically balanced systems for curcumin using psyllium husk. HPMC K 15 M, HPMC K 100M and natural binder *Mangifera indica* gum have been successfully

formulated and evaluated. The conclusion of the studies can be summarized as: psyllium husk might be a promising polymer for gastro retentive floating drug delivery system in combination with synthetic polymer like HPMC K15M. Use of HPMCK15 M with Psyllium husk enhanced the floating duration and helped to maintain the dimensional stability at initial stage, which is necessary in case of once daily formulation. The F4 (HPMC K15 M + Psyllium husk) formulation was the optimized formulation for hydro dynamically balanced system from FT-IR studies it was concluded that no interaction exists between drug and polymers. Optimized formulation followed the Higuchi Kinetics while the drug release mechanism was found to be diffusion type through swollen matrix. Gastro-retentive form of curcumin formulation as an effective delivery system to treat stomach cancer and ulcer in human being.

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