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Research Article

FORMULATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM FOR HYDRODYANAMICALLY BALANCED SYSTEMS OF CURCUMIN TABLET TO TREAT STOMACH ULCER

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ABSTRACT

The present work focuses on formulation and evaluation of floating drug delivery system for hydrodyanamically balanced systems of curcumin tablet to treat stomach ulcer. Floating drug delivery tablets were designed and the present study focused on the manufacture of FDS using various polymers such as HPC and HPMC K15 and H. Its efficacy in reducing ulcers due to pylori was evaluated. Floating drug delivery tablets were characterized for their weight variation, stiffness, stability, drug content determination, dissolution, *in-vitro* dissolution studies, IR, floating interval time, inflammation studies, and erosion studies. The developed curcumin floating tablet system is a promising floating drug delivery system for oral continuous administration of curcumin.

Keywords: Curcumin, Floating lag time, Floating drug delivery system, Gastro-preventive dose form.

1. INTRODUCTION

For the local action and treatment of gastric disorders such as gastric cancer, effective delivery of drugs into the stomach can be treated by temporary dosage forms such as single and multiple unit gas forming systems, hollow microcephases, hydro-dynamic balanced systems, swelling systems, mucoadhesive systems and other gastro-retentive dosage forms [1,2]. Curcumin is a major pigment of the Curcuma species, commonly used as a yellow pigment and flavor-enhancing agent in foods in South Asia [3]. The novel trend in medicine has led to widespread investigations to establish the broad spectrum of biological and pharmacological functions of this phytochemical. Curcumin is reported to possess anti-inflammatory, antioxidant, anti-carcinogenic, anti-coagulant, anti-arthritic, antibacterial, antifungal, anti-protozoal, antiviral, anti-Alzheimer's, anti-psoriatic and neuro-protective activities [4-6]. The efficacy, pharma-cological safety, cost-effectiveness of curcumin and no-dose limited toxicity have also prompted many researchers to investigate this molecule. However, the therapeutic effectiveness of curcumin has been limited due to poorly disseminated bioavailability and absorption from the gastrointestinal tract. Turmeric has gained worldwide popularity with the Food and Agriculture Organization of the United Nations [7]. Turmeric is obtained from the dried rhizome of the plant *Curcuma longa* which is widely used in the Indian subcontinent as a gold-colored spice that gives flavor, food coloring, and serves as a medicinal herb and used as a dye in the textile industry. Curcumin was first separated two centuries ago and its composition was determined in 1910. Curcumin is the active ingredient of turmeric, used daily as a spice in Indian and other South Asian cuisines. Basic pharma-cological principles and potential clinical applications of curcumin were reported [8]. Most commercial turmeric preparations contain ~ 2-8% of activated curcumin [9]. Curcumin selectivity targeted transformed cells without altering primary astrocytes. Curcumin showed synergistic effects with chemotherapistic cisplatin and doxorubicin drugs to increase cell death [10]. Results based on solid state NMR and differential scanning chlorometry showed that curcumin exerted a strong action in the cytoplasm of tumor cell [11]. The researcher showed that curcumin effectively inhibited Human lens epithelial B3 cell proliferation induced by rhb FGF [12]. Curcumin was found to reduce the spread of breast cancer in mice and many forms of cancer were prevented very soon in childhood leukemia and pancreatic cancer [13-15]. Curcumin has been approved to undergo phase I / II tests for the treatment of bowel cancer. Curcumin in hippocampal neurons in Wip mice reduced brain and avascular cytotoxicity [16-18]. Curcumin was found to be effective in oral cancer, liver

cancer, and colon cancer [19, 20]. Curcumin-loaded nanosurfs were able to exert a more pronounced effect on cancer cells, as the ability of nanocortical-based formulations as an adjuvant therapy for clinical application in the prostate gland was comparable to conventional curcumin. The efficacy, pharmacological safety, economic effectiveness of curcumin and no-dose limiting toxicity has also motivated numerous researchers to further explore this chemical. [21-23].

2. MATERIAL AND METHODS

2.1. Ingredients

Curcumin, HPMC K15M (AR Grade), HPMC K100M (AR Grade), sodium bicarbonate (LR Grade), citric acid (LR Grade), magnesium stearate, talc. The devices used in this study were Disposal Appliances, Disassembly Appliances, UV Spectrophotometer (Shimadzu uv-1900), Digital Balance, Hardness Tester (Rockwell) (P,-friability Tester (Systonic S-938), Punching Machine, Forestry Calipers and FT-IR (Shimadzu 8400S).

2.2. Preparation of floating tablets

Curcumin floating tablets were prepared using wet granulated method. The formulation structure of different batches is shown in table 1. All the powders were passed through a 40mesh sieve. The required amount of curcumin, various polymers and filler were well mixed. A 10% polyvinyl-pyrrolidone solution in isopropyl-alcohol was prepared for preparing the wet mass granules that passed with 18 mesh size. After drying, the grains kept in a tread dryer for 1 hour, the grains were passed through a 16mesh size strainer. Magnesium stearate and talc were added as lubricants and guides, respectively. The grains were directly compressed (8 mm diameter, spherical flat punches) on a rotary pellet punching machine. Each tablet contained 60 mg of curcumin. All the tablets were stored in airtight containers for further study.

Table 1: Composition of different batches of floating matrix tablets of Curcumin (%w/w)

S. No	Drug	HPMC K15M	HPC	$NaHCO_3$	Citric acid	MCC	Lactose	Mag.st.	Talc
1	20	10	5	10	5	37	10	02	01
2	20	15	5	10	5	32	10	02	01
3	20	20	5	10	5	27	10	02	01

2.3. Evaluation of prepared tablets

The floating tablets of curcumin extract were evaluated to follow physicochemical parameters: Pre-formulation studies: This is one of the important pre-requisites in the development of any drug delivery system. Prior formulation studies were performed on the drug, including solubility and compatibility studies.

2.3.1. Description

Curcumin was physically tested for color and odor etc.

2.3.2. Solubility

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

2.3.3. Participatory Studies

2.3.3.1. Drug-polymer interaction studies

Drug interactions with polymers were confirmed by IR interaction studies. The drug purified with the polymer was subject to IR study. The combinations studied were pure drug, drug with HPMC K15M, drug with HPC and medicine with all ingredients.

2.3.3.2. Pre and post compression parameters

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

2.3.3.3. Secondary stock solution

One ml of primary solution was diluted in 100 ml of distilled water to obtain a concentration of 10 µg/ml. These were diluted to 10 ml to obtain a concentration of 1 µg/ml from 1 ml. 1 ml, 2 ml, 4 ml, 6 ml, 6 ml, 8 ml and 10 ml. Aliquots were pipetted and diluted to 10 ml with distilled water to obtain 1 µg, 2 µg, 4 µg, 6 µg, 8gg and so on. 10µg concentration of curcumin. The standard graph was plotted by taking into account the known concentration on the x-axis and obtaining the absorbance on the y-axis.

2.4. Determination of drug content (assay)

The USP defines a content homogeneity test for tablets of substance of 100 mg or less in the case of all tablets and all sugar-coated tablets, regardless of the drug. Ten tablets were used individually for their content (according to the method described in the individual

monographs), meeting the requirements for uniformity of the material if the amount of active ingredient in each tablet is 85-115% of the label claim.

2.4.1. Thickness

The dimensions of tablets such as thickness, diameter were measured using Vernier calipers. Ten tablets were randomly selected for this test and the average value was stated.

2.4.2. Size and shape

Particle size and shape play a major role in determining the solubility rate of drugs and thus possibly its bioavailability. The particle size of the aggregates was determined using strainer analysis.

2.4.3. Weight variation

If the drug forms a greater part of the tablet, any change in the tablet's weight clearly indicates a difference in the active ingredient. 20 pills were weighed individually (i.e. determination of the weight of each tablet alone; X1, X2, X3… X20)

Average weight of pills = total weight of pills / number of pills

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

2.4.4. Hardness

The tablet requires a certain amount of strength or hardness and resistivity to withstand mechanical shocks in manufacture, packaging, and transport. Special hardness testers are used for this purpose (manually or motorized tester). The test measures the crushing properties of power that is defined as the compressive force applied practically to a pellet that just fractures or breaks it.

2.4.5. Friability test

Friability test was done by Roche Friabilator. 20 tablets were weighed and were subjected to a combined effect of attraction and trauma, using a plastic chamber rotating at 25 rpm dropping the bullets at a distance of 6 inches with each revolution. Powered for 100 revolutions, the tablet was washed with dust and reattached. The percentage constant was calculated.

2.4.6. Dissolution test

This test determines whether the tablets decompose within the prescribed time when placed in a liquid medium under prescribed experimental conditions. The device uses 6 glass tubes that open at the top and 10 mesh screens at the lower end to test the dissolution. To test the dissolution time, a tablet was placed in each tube and the basket rack was placed in a 1L beaker of water. Simulated gastric fluid was used at 37°C + 2°C. Tablets should be 2.5 cm below the surface of the liquid in their upward movement and their downward movement should not be closer than 2.5 cm below the bottom of the beaker. The basket containing the bullets was moved up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. The floating of tablets can be prevented by placing perforated plastic discs on each tablet.

2.5. *In-vitro* Drug Release Study

Curcumin floating drug delivery formulations were used in 5 batches of *in-vitro* drug release studies using the USP dissolution rate test mechanism. The dissolution medium was 900 ml 0.1N HCl. The dissolution medium was placed in a thermostatically controlled water bath, which was kept at 37°C ±0.5°C. The tablet was placed in the vessel and a suitable device such as a wire or glass helix was used and the rotation speed was kept at 50 rpm. To maintain the sink condition at predetermined time intervals, 5 mL samples were withdrawn and replaced with equal amounts of fresh medium. Samples collected at 0.5,1,2,3,5,5,6,7,8,9,10,12 and 24hrs at each interval for curcumin content released in λmax of 420 nm using UV-Visible spectrophotometer was analyzed.

2.6. Release Kinetics

Analysis of drug release mechanisms in drug dosage form is an important but complex process and 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 the matrix system was described using zero-order kinetics or first-order kinetics. The mechanism of dropping the drug from the floating drug delivery system was studied by the Higuchi equation and the decay equation.

2.7. Floating lag time

The effect of the formulation variable on the temporal properties of a gastric floating drug delivery system was determined using a continuous floating monitoring system and statistical experimental design. The time

taken by the dosage form to float is called floating lag time and the time for which the dose form is floated is called floating time. The test for floating time measurement is usually performed in simulated gastric fluid or 370M HCl maintained at 37°C + 0.1°C. This is determined using a dissolution mechanism with 900 ml of 900 ml/liter of 37°C as the dissolution medium. The floating properties of FDDS that enable them to remain in the stomach for a longer period of time are usually acquired due to the low density of HBS dosage forms.

2.8. Inflammation studies

Inflammation of hydrophilic polymers such as hydroxy propyl methylcellulose depends on the contents of the stomach and the osmosis of the medium. For each formulation, a tablet was weighed and placed in a beaker with 200 ml of distilled water. After every hour the tablet was removed from the beaker and weighed again for 8hours. The percent weight gain by the tablet was calculated using the formula:

Swelling index (S.I) = {(Wt-Wo)/Wo} x 100

where,

SI = inflammation index

Tt = weight at time t

Vis = weight of pellet before immersion

2.9. Erosion studies

Erosion studies were done by a method dissolution test mechanism for this purpose. The dry matrices were weighed, placed in a dissolution basket containing 900 ml 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 entire basket-matrix assembly was removed from the dissolution vessels and dried to a constant weight in a hot air oven at 50°C.

Matrix degradation (%) = Wdt / W0 × 100

Wdt-weight of dry tablet on time t W0-weight of dry tablet

3. RESULTS AND DISCUSSION

Floating drug delivery pills were prepared and the present study focused on the manufacture of FDS using various polymers such as HPC and HPMC K15 and H. Its efficacy in reducing ulcers caused by pylori was evaluated. Floating drug delivery tablets were characterized for their weight variation, stiffness, stability, drug content determination, dissolution, *in-vitro* dissolution studies, IR, floating lag time, inflammation studies.

3.1. Evaluation of floating tablet

3.1.1. Pre formulation study

3.1.1.1. Description

Curcumin was physically tested for color and odor etc. It is an orange yellow powder, which has a special smell.

3.1.1.2. Solubility

Curcumin was insoluble in water, soluble in buffer solution pH 7.4, and soluble in ethanol, DMSO, and tetra hydro ferron (THF).

3.1.1.3. Pre and Post Compression Parameters

Calibration curve for curcumin. The standard plot mentioned in the experimental procedure for curcumin according to standard 10, 20, 30, 40 and 50 µg / ml was done and the results are tabulated in table 2 and plotted. The graphs are represented in fig. 1.

Table 2: standard values for calibration curve of curcumin

S. No.	Concentration (µg/ml)	Absorbance in 0.1N HCL(at291$_{nm}$)
1.	0	0
2.	1	0.123
3.	2	0.203
4.	4	0.311
5.	6	0.448
6.	8	0.587
7.	10	0.701
8.	12	0.821
9.	14	0.978
10.	16	1.086
11.	18	1.208
12.	20	1.336
13.	R^2	0.998
14.	Intercept	0.049
15.	Slope	0.064

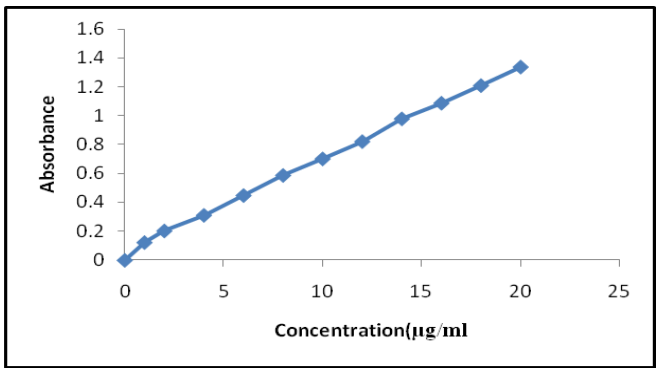

Fig. 1: Calibration curve for curcumin

3.2. Drug Content Determination

The assay of the different formulations F_1, F_2, F_3 were determined as given in the experimental methods and the results were tabulated in table 3.

The assay or drug content in the formulations ranged between 95-98 %. The assay value of F1 was found to be higher compared to the other formulations.

Table 3: Drug content determination

S. No.	Formulation	Assay
1	F1	98.6±0.82%
2	F2	97.31±0.50%
3	F3	95.29±0.51%

3.3. Weight Variation Test

Weight variation test results were done and it was between 301.29 to 301.34 mg and results are represented in 4.

3.4. Post Compression evaluation of Curcumin floating tablets

Post compression parameters of curcumin floating tablets are shown in table 4. The tablets prepared from all formulations were evaluated for quality control parameters i.e. Weight variation, Hardness, Friability, Drug content uniformity and thickness. All the formulations have average tablet weight in the range of 298.24mg to 301.34mg.

Table 4: Post compression parameter of telmisartan floating tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm)	Friability (%)	Thickness (mm)	Drug content (%)
F1	301.29±0.7	4.5±0.71	0.15±0.17	3.32±0.22	98.14±0.79
F2	300.56±1.6	4.3±0.70	0.19±0.12	3.31±0.17	98.89±0.67
F3	301.34±1.4	4.8±0.72	0.17±0.07	3.30±0.24	97.17±0.93

No of tablets taken= 20

Limit of % weight = 90%-110%

3.5. *In-Vitro* Buoyancy Test

A tablet was placed in a 100ml beaker containing 0.1N HCl solution at 37°C +0.5°C, the tablet floated and remained without dissolution. Other polymer-containing formulations F1, F2 and F3 have shown higher temporal lag times and a total floating time of more than 12 hours.

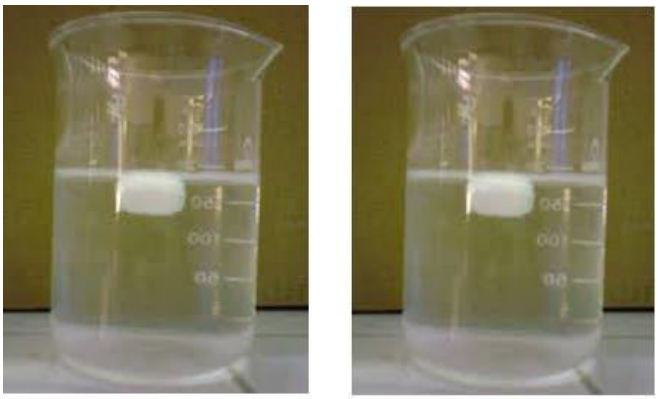

Fig. 2: Floating of Tablet in 0.1N HCl Initial (A) after 10 min (B)

3.6. Swelling index

The amount of swelling was measured in terms of % weight gain by the tablet. The inflammatory behavior of all formulations was studied. One tablet from each formulation was placed in a petridish containing 2.5 pH 0.1N HCl. At the end of 1 hour, the tablet was withdrawn, soaked with tissue paper and weighed. The tablets were then noted for each 1hr weight and the process was continued until the end of 7hrs. The equation index was expressed in terms of percent over water (WU%) according to the equation showing the relationship between swelling idex and time. The swelling index of F1 to F9 was not satisfactory, as their aggregates were decomposed before 7 hrs and the tablets did not absorb HCl properly and did not increase weight because the reason for this is that very small amounts of HPMC exist and some formulas are not HPMC.

WU% = (weight of swollen tablet - initial weight of tablet) / (initial weight of tablet) × 100

Table 5: Results of floating lag time and total floating time

Formulation code	Floating lag time (sec.)	Total floating time(hrs)
F1	26±0.57	8
F2	27±0.55	7
F3	22±0.58	10

Table 6: Swelling index (%) of different formulation

Time(hr)	F1	F2	F3
0	0	0	0
1	44.903	47.432	46.431
2	82.352	96.210	83.475
3	106.571	112.892	102.671

3.7. *In-Vitro* drug release

The *in-vitro* release of the different formulations is shown in table 7.The formulations were carried out for the release studies for 9 hrs. F1, F2 and F3 formulation contained 10%, 15% and 20% HPMC K 15M and each contained 5% HPC respectively. Each formulation release nearly 75% of drug in 9 hrs. Therefore, these findings clearly suggest that therelease rate according to polymer concentration. Among all the formulation has better sustain release in 9 hrs. The release rate obtained from the formulation (F1 to F3) represented in table 7 and log % drug retained of F1to F3 represented in table 8.

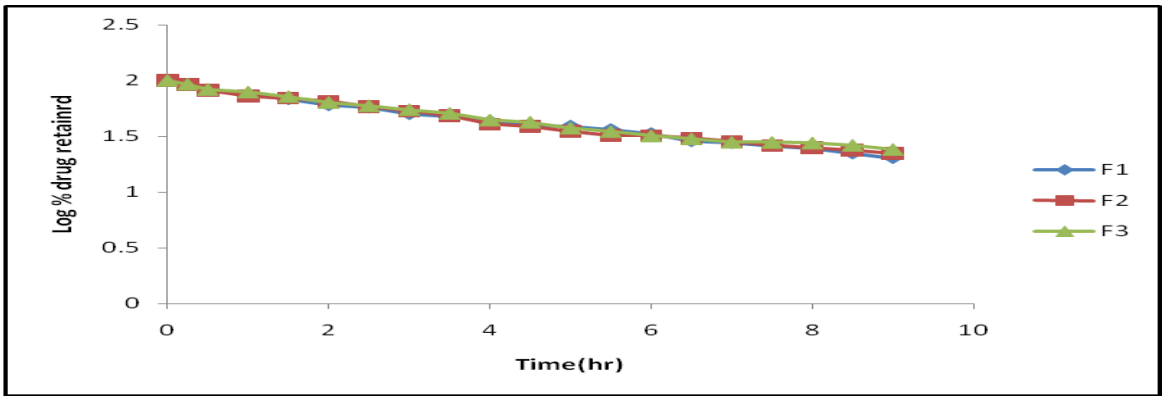

Fig. 3: Log Percent (%) Drug Retained of F1to F3

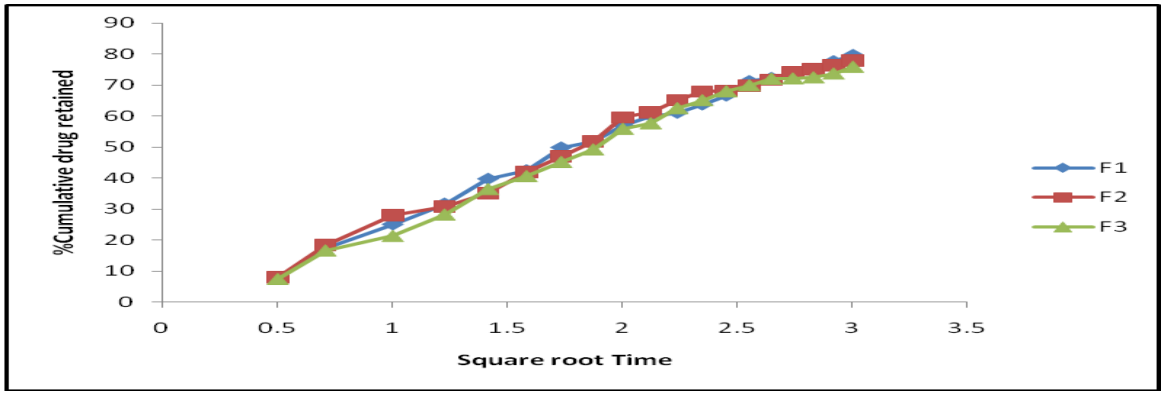

Fig. 4: Percent Cumulative Drug Release Vs Time (F1to F3)

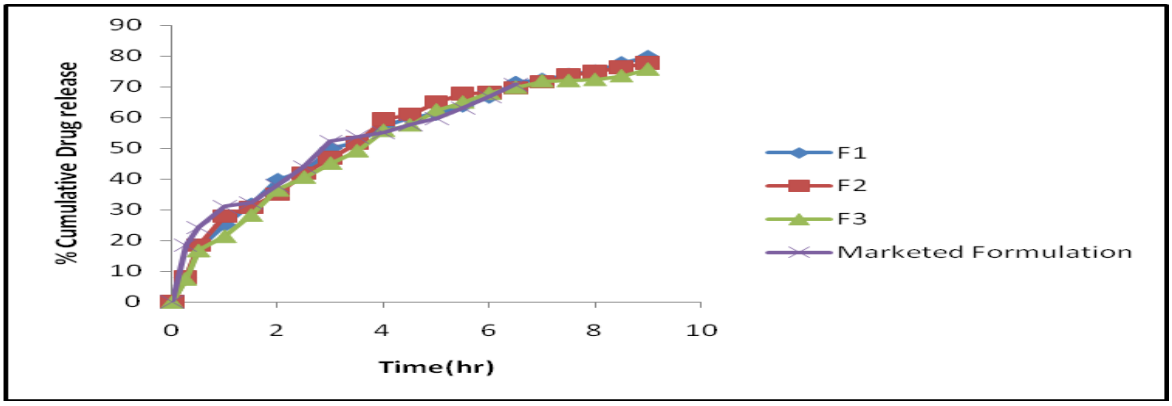

Fig. 5: Zero Order Kinetics of Marketed Formulation and Best Formulation F1 to F3

Table 7: Cumulative Drug release (%) of F1 to F3

Time(hr)	Cumulative Drug release (%) of F1 to F3		
	F1	F2	F3
0	0	0	0
0.25	7.913	7.994	7.567
0.5	17.789	18.456	16.782
1	25.056	27.987	21.430
1.5	31.778	30.789	28.309
2	39.407	34.098	36.502
2.5	42.521	41.933	40.643
3	47.846	46.015	45.232
3.5	49.347	51.231	49.378
4	50.765	57.274	55.276
4.5	51.956	59.241	57.672
5	57.081	61.048	62.532
5.5	60.098	65.057	65.098
6	61.067	67.897	67.348
6.5	63.468	68.023	69.902
7	66.462	69.416	71.923
7.5	68.774	71.563	72.095
8	71.324	72.987	73.642
8.5	72.091	73.112	74.987
9	73.482	73.459	75.384

Table 8: Log Percent (%) Drug Retained of F1to F3

Time(hr)	Log Percent (%) Drug retained of F1 to F3		
	F1	F2	F3
0	2	2	2
0.25	1.964	1.945	1.965
0.5	1.916	1.911	1.920
1	1.874	1.857	1.895
1.5	1.833	1.840	1.855
2	1.779	1.812	1.802
2.5	1.759	1.763	1.77
3	1.682	1.724	1.738
3.5	1.681	1.683	1.705
4	1.632	1.606	1.644
4.5	1.600	1.589	1.626
5	1.589	1.542	1.573
5.5	1.559	1.506	1.542
6	1.523	1.503	1.505
6.5	1.457	1.481	1.478
7	1.441	1.452	1.442
7.5	1.415	1.414	1.445
8	1.396	1.398	1.440
8.5	1.347	1.373	1.420
9	1.306	1.344	1.382

Table 9: Percent Cumulative Drug Release Vs Square root of Time (F1to F3)

Square Root of Time	Percent(%)cumulative drug release Vs square root of time of F1 to F3		
	F1	F2	F3
0	0	0	0
0.5	7.913	7.999	7.567
0.707	17.789	18.456	16.782
1	25.056	27.987	21.430
1.224	31.778	30.789	28.309
1.414	39.407	34.098	36.502
1.581	42.521	41.933	40.643
1.732	47.846	46.015	45.232
1.870	49.347	51.231	49.378
2	50.765	57.274	55.276
2.121	51.956	59.241	57.672
2.236	57.081	61.048	62.532
2.345	60.098	65.057	65.098
2.449	61.067	67.897	67.348
2.549	63.468	68.023	69.902
2.645	66.462	69.416	71.923
2.738	68.774	71.563	72.095
2.828	71.324	72.987	73.642
2.915	72.091	73.112	74.987
3.000	73.482	73.459	75.384

3.8. Drug Release Kinetics

The data was plotted for kinetics of drug release according to zero-order, first order, Higuchi model, and Corsmeyer-Papas patterns. The regression equation of the optimized formulation F3 was found according to zero order 0.989, first order equation 0.254, and Higuchi Model 0.952 respectively. These results clearly suggest that zero order kinetics is the best fit for the F3 formulation. The result indicated that the zero-order kinetics was followed by all aggregates because the graph showed the highest R2 value. The 'n' value of all preparation found between 0.5- 1, indicating the drug release to be non-fickian diffusion-controlled.

The dissolution data were also plotted for the well-known exponential equation (Corsmeyer Poppus EMA), often described for drug release behavior from the polymer system. According to this model, a value of $n < 0.45$ indicates Fickian release, $n > 0.45$ but $n < 0.89$ for non-Fickian (discrepancy) releases and $n > 0.89$ indicates super case 2 type releases. Phase 2 generally refers to erosion control of polymeric chains and anomaly transport (non-Fickian). Both proliferation and erosion control drug release.

Table 10: Comparison between Drug Release study of Optimized Best formulation F1 to F3 and Marketed Formulation

Drug Release Study of Marketed Tablet of Telmisartan					
Zero Order Kinetics (Percent Cumulative Drug Release)		**First Order Kinetics (Log Percent Drug Retained Vs Time)**		**Higuchi Kinetics (Percent Cumulative Drug Release Vs SQRRT)**	
Time(hr)	% CDR	Time(hr)	Log % Drug Retained	SQRT	% CDR
0	0	0	2	0	0
0.25	18.530	0.25	1.910	0.5	18.530
0.5	24.186	0.5	1.879	0.707	24.186
1	30.978	1	1.838	1	30.978
1.5	32.282	1.5	1.830	1.224	32.282
2	37.857	2	1.793	1.414	37.857
2.5	44.005	2.5	1.748	1.581	44.005
3	52.300	3	1.678	1.732	52.300
3.5	53.752	3.5	1.674	1.870	53.752
4	55.114	4	1.652	2	55.114
4.5	57.706	4.5	1.626	2.121	57.706
5	59.731	5	1.615	2.236	59.731
5.5	63.127	5.5	1.566	2.345	63.127
6	66.736	6	1.534	2.449	66.736
6.5	70.810	6.5	1.479	2.549	70.810

Table 11: Result of release kinetics of all formulation

Formulation	Zero order		First order		Higuchi		Korsemeyer papas	
	R^2	K_0(-)(1/s)	R^2	K_1(-)M/L.S	R^2	K_H	R^2	N
F1	0.934	7.917	0.990	0.166581	0.991	28.09	0.977	0.593
F2	0.925	7.878	0.979	0.1635	0.982	27.97	0.971	0.585
F3	0.910	7.877	0.978	0.1566	0.984	28.15	0.981	0.613

4. CONCLUSION

This floating delivery system was successfully formulated for delivery of curcumin using various concentrations of HPMC, Carbopol 974, 15 M of HPMC. Compatibility studies were performed before the system was prepared using differential scanning calorimetry (DSC) and infrared spectroscopy (IR) and the system was found to be compatible. The finished system was characterized by pre compression parameters and post compression parameters, stiffness, weight variation. Thickness, stability of drug content, *in-vitro* buoyancy studies, *in-vitro* drug release studies were suitably performed. The tablet's stability was the best. Floating drug delivery was a promising approach to achieve prolonged gastric residence time of the drug. The gas-producing agent sodium bicarbonate was used to improve the floating capacity of tablets and citric acid used as floating enhancers. Finally, the customized formulation shows the desired drug release profile over 9 hr. Thus, it can be concluded that the developed formulation may be a possible alternative to the traditional dosage form by providing sustained release and improving patient compliance The results indicate a promising potential of curcumin floating tablets as an alternative to the conventional dosage form to treat stomach ulcer.

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Conflict of Interest

We declare that we have no conflicting interests in this research.

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