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Research Article

Formulation and Evaluation of Curcumin Loaded Gastro-Retentive Multi particulate Drug Delivery System

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ABSTRACT

To develop and optimize a multiparticulate gastro-retentive floating dosage form of Curcumin with targeted and sustained release characteristics. Curcumin give protective effect against Inflammation and Cancer but the physicochemical properties of the molecules leads to poor solubility and stability. Aqueous solubility was enhanced by complex formation with Hydroxypropyl β-Cyclodextrin (HP β-CD). This complex with enhanced solubility profile was further used to prepare multiparticulate floating pellets. Floating pellets of Curcumin HP β-CD complex were prepared by Extrusion-Spheronization technique using Hydroxypropyl methylcellulose (HPMC K100 M) as low density controlled release polymer, Ethyl cellulose as a release retardant polymer and Sodium bicarbonate as a gas generating agent. The formulations were evaluated for In vitro Drug release, Buoyancy and Surface morphology study. The investigation revealed that floating pellets of Batch B3 possessed optimum formulation characteristics. The drug release from pellets was Non fickian and sufficiently sustained for 12 hr. This study indicates that multiparticulate gastro-retentive floating dosage form of Curcumin HP β-CD complex with sustained release characteristics can be safely and effectively used to treat Gastric cancer.

Key-words: GRMDDS, floating pellets, Curcumin, HP β-CD, HPMC, Ethyl cellulose.

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Introduction

Curcumin from turmeric (curcuma longa) cultivated in India and used throughout India, China and Indonesia as a spice and medicinal agent. The pharmacological safety and efficacy of Curcumin make it potential compound for the treatment of wide variety of human disease[1]. All the anticancer drug weaken the immune system but Curcumin enhance it and act as an immune restore and does not create any resistance[2]. The efficacy, pharmacological safety and cost effectiveness of Curcumin and having a no dose limiting toxicity[3]. Turmeric is consumption mainly active constituent having an action like Anti-inflammatory, Antioxidant, Angiogenesis, Wound healing, and Anticancer effect. Curcumin having a dose-dependent chemo-prevention effect in several tumors[4]. Gastro-retentive drug delivery system enhances the drug release and prolongs gastric retention time in the stomach. It improves stomach specific absorption and prevents degradation in alkaline environment of intestine[5]. These dosage forms significantly extend the period of time over which the drugs may be released in comparison to other CRDDS[6]. Multiparticulate drug delivery systems are most important widely used dosage forms than the other unit dosage forms for their enhanced bioavailability because of their increased surface area reduction of inter-subject variation, better distribution and transportation and reduction of dose dumping[7]. There are various multiparticulate drug delivery systems such as Pellets, Granules, Minitablets and Beads but one of the most multiparticulate drug delivery system is Pelletization[8]. Pelletization means agglomeration of bulk drug powder or granules in to free flowing or spherical particulate these techniques are called as a Pelletization. Pellets are the small, spherical or semispherical particle with range of 0.5-2 mm[9]. They are used for oral administration. This trend of pellets has increased patient acceptance or patient compliance. It reduces variation in gastric emptying rate and overall transit time. It also provides high degree of flexibility during design and development of oral dosage form[10].

Methods

Preformulation study[11]

1. **UV visible calibration curve of Curcumin[12]:**

   Prepare Stock solution of Curcumin containing 1000 µg/ml were prepared in ethanol and this solution is transferred into 100 ml volumetric flask and their volume was made with the ethanol to prepare different standard dilution varying in between 0 to 50 µg/ml.

   Prepare stock solution of Curcumin containing 1000 µg/ml were prepared in dissolution medium (0.1 N HCl) and this transferred into 100 ml volumetric flask and volume was made with the 0.1 N HCl to prepare different standard dilution varying in between 0 to 60 µg/ml and the absorbance of the above dilution were measured at 416 nm by using UV visible spectrophotometer. Plot a graph between concentrations vs. absorbance which gives straight line.

2. **Drug Excipient compatibility study by FTIR[13]:**

   A complete characterization of physicochemical interactions of an API in the formulation is an integral part of preformulation stage of the new dosage form development as it is most desirable for consistent efficacy, safety and stability of a drug product. In formulation, a drug comes in direct contact with other components of the dosage form that facilitate the administration and release of an active component as well as protect it from the environment. Here check the compatibility of the drug with the polymer which is used to prepare formulation.

   (a). Curcumin

   (b). Curcumin Pellets mixture

Solubility enhancement study

1. **Phase solubility study[14]:**

   Stock solutions of 20 mM concentration of both β-CD and HP β-CD in distilled water (16 mM in case of β-CD as no clear solution was obtained at 20 mM) were prepared and phase solubility studies were done by Higuchi and Conners method. Excess amount of Curcumin was placed in vial bottle containing 20 ml of aqueous solutions of CD and samples were stirred continuously until equilibrium was achieved for 24 hours. Bottles were totally covered with an aluminum foil. Suspensions were filtered using 0.45 micron membrane filter and then analyzed spectrophotometically at a λmax of 416 nm by using aqueous solutions of respective CD as

blanks. Than prepare a graph between concentration of Curcumin vs. Concentration of Both CD individually and select a ratio for the preparation of Inclusion complex.

Preparation of Inclusion complex[15]:

The inclusion complexes of Curcumin with CD were prepared by selecting the ratio after performing phase solubility study.

a. **Grinding method:**
   Here, Curcumin drug was physically mixed with β-CD in mortar-pestle containing molar ratio and it was same for HP β-CD with drug.
b. **Kneading method:**
   Equimolar quantity of Curcumin and CD were blended in clean dry glass mortar pestle then add ethanol to dissolve both the substance or triturated to get a paste like consistency. Trituration was continued until the product started drying on the walls of glass mortar and the products were further dried in the hot air oven at 60 degree C for 20 minutes, powdered, passed through 100-mesh sieve and stored in a dessicator containing Cacl2.
c. **Freeze drying method:**
   Equimolar quantity of Curcumin and CD were dissolved in distilled water with a small amount of ammonia (27%) to aid dissolve Curcumin and sonicated for 15 min in sonicator to get clear solutions. The solutions were frozen in ultra freezer by keeping over night and freeze-dried over 8 hours in a Lyph-lock 6 apparatus. The resulting amorphous products were powdered in glass mortar, passed through 100-mesh sieve and stored in a dessicator containing Cacl2.

2. **Characterization of Aqueous solubility after preparation of Inclusion complex:**
   Excess amount of drug with CD complexes were kept in vial bottles cover with an aluminum foil containing 10 ml of distilled water and stirred on thermo-stated mechanical shaker at room temperature for 24 hours. Suspensions were filtered through 0.45 µ Millipore filter, diluted adequately and analyzed spectrophotometically at 423 nm.

Preparation of Gastro-retentive floating pellets[16]

Gastro-retentive floating pellets containing Curcumin HP β-CD complex were prepared using Extrusion-Spheronization techniques. Equivalent quantity of drug complex was mixed with the different quantities of different polymer like, HPMC K100 M, Ethyl cellulose as a release retardant polymer, and MCC as a Spheronizer enhancer to formulate pellets. All the polymer mixed as per the formula than prepare a dough mass by using Isopropyl alcohol here also mix $NaHCO_3$ as a gas generating agent. Place the dough mass in extruder to obtain extrudates and after 10-15 min place in spheronizer and covert it in to uniform spherical shape pellets.

Figure 5.1: Steps for the preparation of pellets by Extrusion-spheronization process

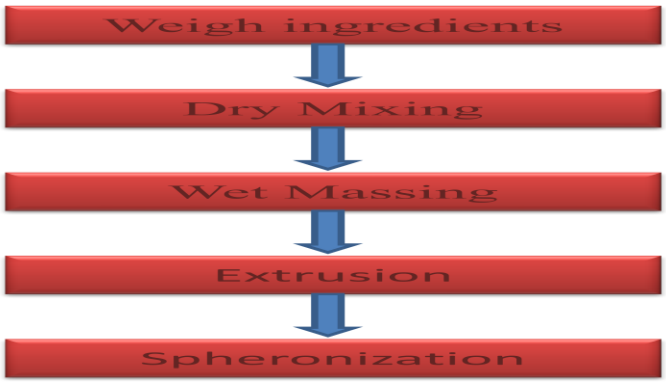


Table 5.1: Batches for the preparation of pellets

Ingredients	A1	A2	A3	B1	B2	B3	C1	C2	C3
Curcumin(mg)	150	150	150	150	150	150	150	150	150
HPMC K100 M (%)	18	20	22	18	20	22	18	20	22
Ethyl cellulose (%)	10	10	10	15	15	15	20	20	20
NaHCO3 (%)	35	35	35	35	35	35	35	35	35
MCC (%)	50	50	50	50	50	50	50	50	50
PVP K30 (%)	2	2	2	2	2	2	2	2	2
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Characterization of Pellets

1. **Drug content Determination:**
   Take a 10 mg of Curcumin accurately and Transfer it in to a 100 ml volumetric flask containing 100 ml 0.1N HCl. Shaken for 30 min. vigorously and then sonicated for 15 min and solution were filtered. Dilutions of filtrate were made with 0.1N HCl and the absorbance of solution was made at 423 nm.
2. **Micromeritic property:**
   Irregular flow property from the hopper produces pellets with uniform weights. As a result, content uniformity and dose precision cannot be achieved in the production of solid form of formulation. A flow property depends on the particle size, shape, porosity, and density of the bulk powder.
3. **Particle size Analysis:**
   The particle size of pellets was measured by using optical microscopic method. It was done by using stage micrometer's slide and calibrated eye piece and final mean size was calculated.
4. ***In vitro* Buoyancy study:**
   Take an equivalent weights of pellets place in 0.1 N HCl as a dissolution medium in vessels containing 900 ml maintain 37 ± 0.5 °C at 50 RPM in USP Type-II paddle apparatus. Note down the floating lag time and Total floating time.
5. ***In vitro* drug release study:**
   In vitro drug release study was carried out by using USP Type-II paddle apparatus at 37 ± 0.5ºc and at 50 RPM using 900 ml of 0.1N HCl as a dissolution medium as a n=3. Weigh accurate amounts of pellets placed in each vessels of dissolution apparatus. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered and diluted suitably and analyzed in UV visible spectrophotometer. After the withdrawal of the sample add equal amount of fresh dissolution medium in a vessel. Calculate % cumulative drug release.
6. **Surface morphology study:**
   Surface morphology study of the pellets was measured by Scanning electron microscope techniques using SEM (Jeol JSM7600F, USA).
7. **Treatment of Dissolution data with different kinetic equation:**
   It was the mathematical method were used to evaluate the kinetic and mechanism of drug release from the pellets. The model that best fits the release data was selected based on the correlation co-efficient (r) value in various kinetic models. There were the various models like Zero order release, first order release, Hixson-crowell release, Higuchi release model and Korsmeyer-peppas release models.

   $$Mt/M\infty = ktn$$

   Where, Mt = amount of drug release at time t,
   M∞ = total amount of drug present in formulation,
   K = release rate constant depend on geometry of dosage form and *n* is diffusion exponent indicating the mechanism of drug release.
8. ***In vivo* X-Ray Study for Buoyancy Ability in Rabbit:**
   To study in vivo buoyancy ability of the optimized batch rabbit was selected. Fasting the rabbit overnight to get the stomach empty. Only more amount of water given to rabbit during the fasting period. Here pellets were

prepared containing 15% barium sulfate as a radio opaque agent. These pellets were feeded by deep feeding tube in rabbit. After the feeding X-ray was taken to check whether the pellets were floated or not. First X-ray was taken at a 0, 6, 12 hr respectively.

The protocol for the above study approved by Institutional Animal Ethical committee (IAEC) at L.J. Institute of Pharmacy.

9. Stability Study of Optimized Formulation:

To determine the any change in drug release profile of the pellets and floating behavior during storage. A temperature sensitivity study of the prepared pellets was performed at 40°C in a stability chamber with 75% relative humidity (RH). Samples were withdrawn after a 1-month interval of time and evaluated for change in *In-vitro* drug release pattern and floating behavior.

Result and Discussion

Preformulation study

UV visible calibration curve of Curcumin:

1. Standard calibration curve of Curcumin in Ethanol:

The standard calibration curve of Curcumin in Ethanol were shown in **Table 6.1** and graph was plotted between concentration vs. absorbance were shown in **Figure 6.1**. The data had co-relation co-efficient value was 0.9773 and equation of regressed line was;

$$y = mx + c$$

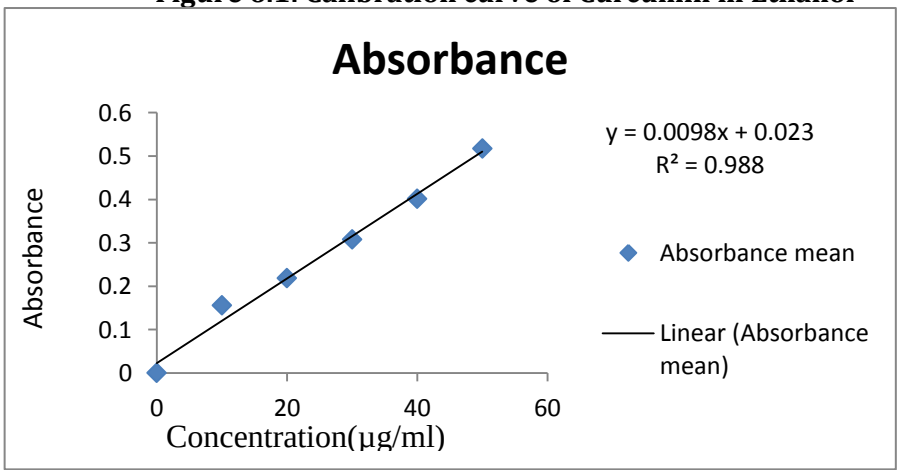
$$y = 0.0095x + 0.0258$$

Table 6.1: Absorbance data of Curcumin in Ethanol

Concentration (µg/ml)	Absorbance at 416 nm ± SD
0	0
10	0.156±0.002
20	0.2183±0.0030
30	0.307±0.0025
40	0.401±0.0035
50	0.517±0.0016

(*Mean±SD, n=3)

Figure 6.1: Calibration curve of Curcumin in Ethanol



2. Standard calibration curve of Curcumin in 0.1 N HCl:

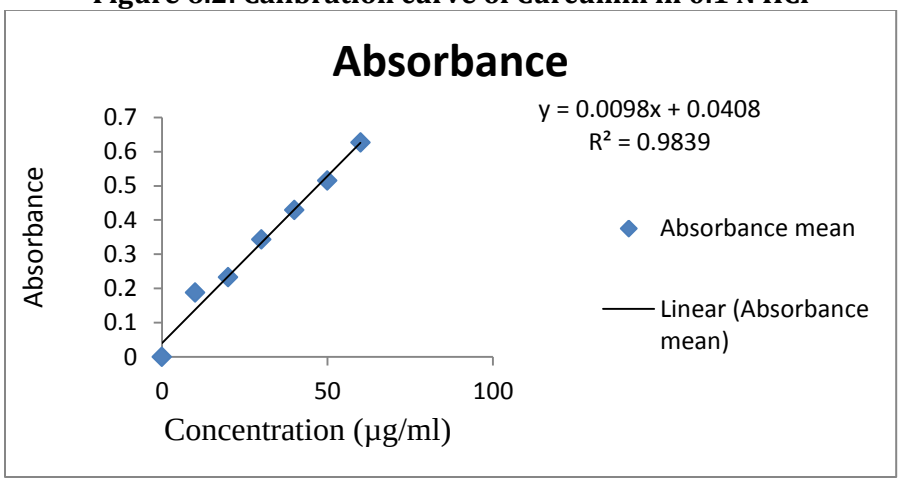
The standard calibration curve of Curcumin in 0.1 N HCl were shown in **Table 6.2** and graph was plotted between concentration vs. absorbance were shown in **Figure 6.2.** The data had co-relation co-efficient value is 0.9839 and equation of regressed line was;

Table 6.2: Absorbance data of Curcumin in 0.1 N HCl

Concentration (µg/ml)	Absorbance at 423 nm ± SD
0	0
10	0.187±0.0030
20	0.233±0.0026
30	0.343±0.002
40	0.429±0.004
50	0.514±0.0012
60	0.627±0.0016

(*Mean±SD, n=3

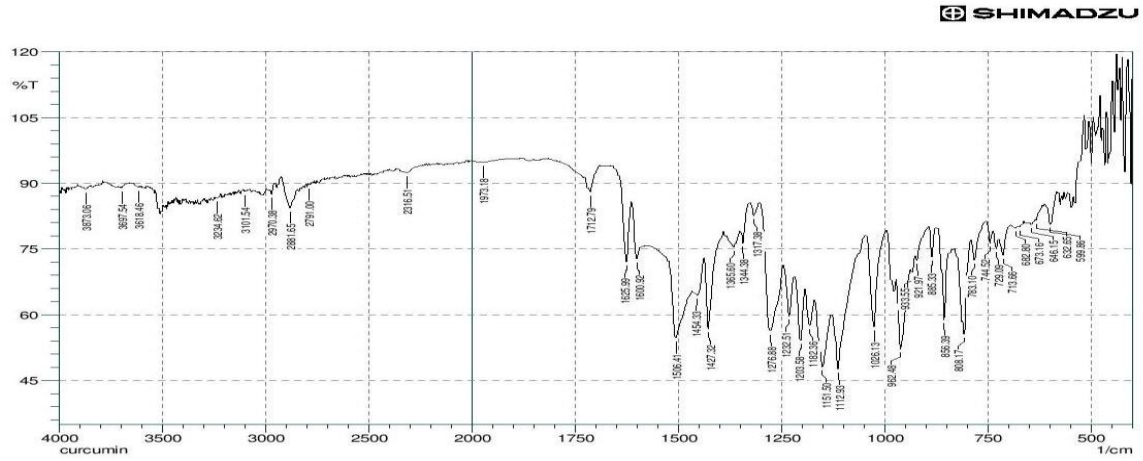
Figure 6.2: Calibration curve of Curcumin in 0.1 N HCl



Drug excipient compatibility study:

1. **Curcumin:**

Figure 6.3: FTIR spectra of Curcumin



2. Curcumin pellets powder:

Figure 6.4: FTIR spectra of Curcumin pellets powder

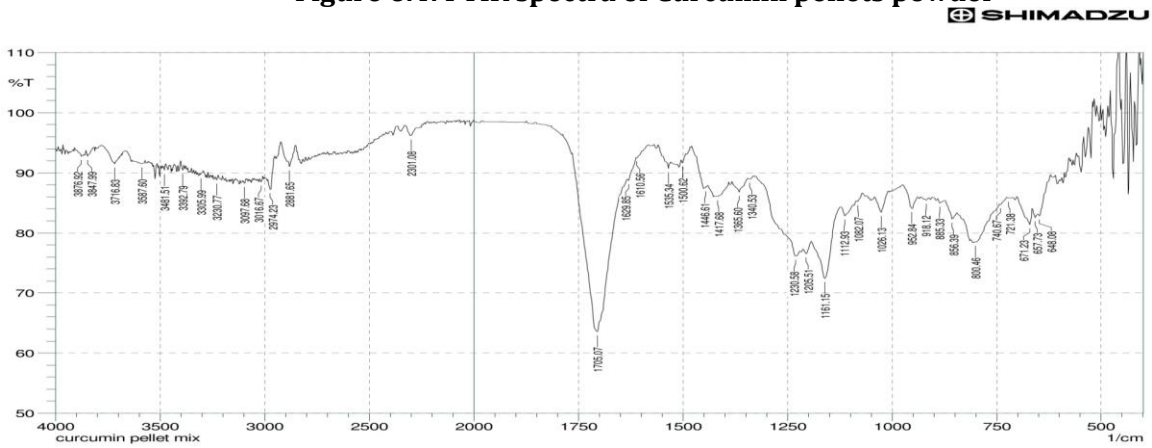


Table 6.3: Interpretation of FTIR data

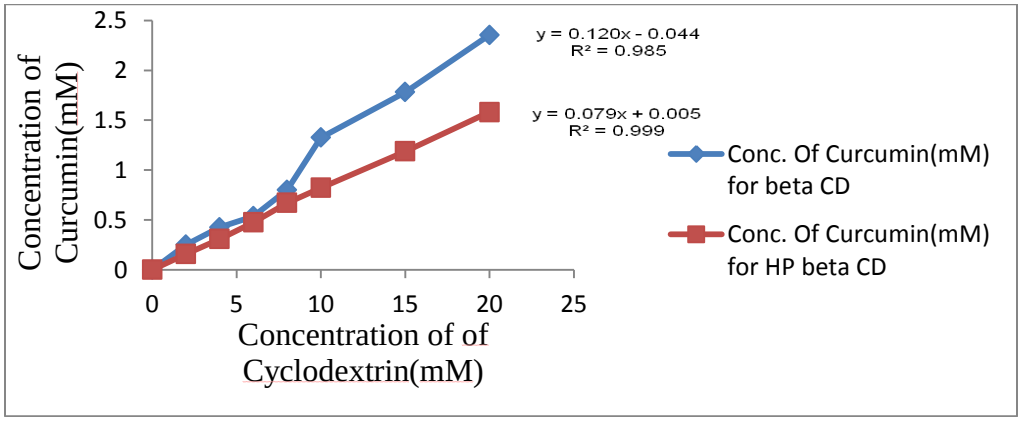
Functional group	Curcumin	Curcumin pellets powder
O-H	3570.24	3481.51
C-H	2970.38	2881.65
C=C	1625.99	1535.34
C=O	1454.33	1446.61

Discussion: It was clear from spectra that as the powder of Curcumin pellet decreased, OH- stretching signal for the Curcumin was superimposed by OH- stretching signal of pellets powder and completely dominated when Curcumin pellets powder was decreased which might be indicate that the insertion of Curcumin in CD complex and with pellets.

Solubility enhancement study

1. Phase solubility study:

Figure 6.5: Phase solubility study of Curcumin with Cyclodextrin



Discussion: According to the data of phase solubility study of both Cyclodextrin. If the curve was not in straight line so select 1:2 ratios and if the curve was in straight line so, select 1:1 ratio.

2. Characterization of Aqueous solubility after Complexation:

Discussion: After phase solubility study data indicate that the ratio of β-CD and HP β-CD selected 1:2 & 1:1 respectively. After the preparation of complex they were characterized shows that the from the all 3 method for the preparation of complex Freeze drying method maximally increase solubility.

Characterization of pellets

Physical evaluation of pellets:

Table 6.4: Observation table of All 9 batches

Parameters	A1	A2	A3	B1	B2	B3	C1	C2	C3
Bulk density (gm/ml)	0.66	0.72	0.66	0.84	0.70	0.76	0.70	0.75	0.81
Tap density (gm/ml)	0.78	0.81	0.84	0.85	0.78	0.93	0.83	0.89	1.02
% friability	0.523	0.469	0.726	0.638	0.608	0.509	0.564	0.453	0.659
Car's index	15.38	11.11	21.42	11.16	10.25	18.27	15.66	15.73	20.58
Hausner's ratio	1.18	1.125	1.273	1.01	1.114	1.223	1.185	1.18	1.25
Angle of repose	26.64	28.57	25.76	29.82	28.67	30.56	28.11	29.8	25.75
Floating lag time (sec)	8	5	7	4	5	5	7	8	6
Total floating time (hrs)	>12	>12	>12	>12	>12	>12	>12	>12	>12
Mean particle size (mm)	1.71	1.77	1.69	1.54	1.78	1.68	1.59	1.72	1.79
Drug content (%)	98.44 ±0.76	99.35 ±0.63	99.26±0. 34	98.56±0. 478	101.97± 0.23	101.38 ±0.54	99.96± 0.25	98.38± 0.25	101.03 ±0.97

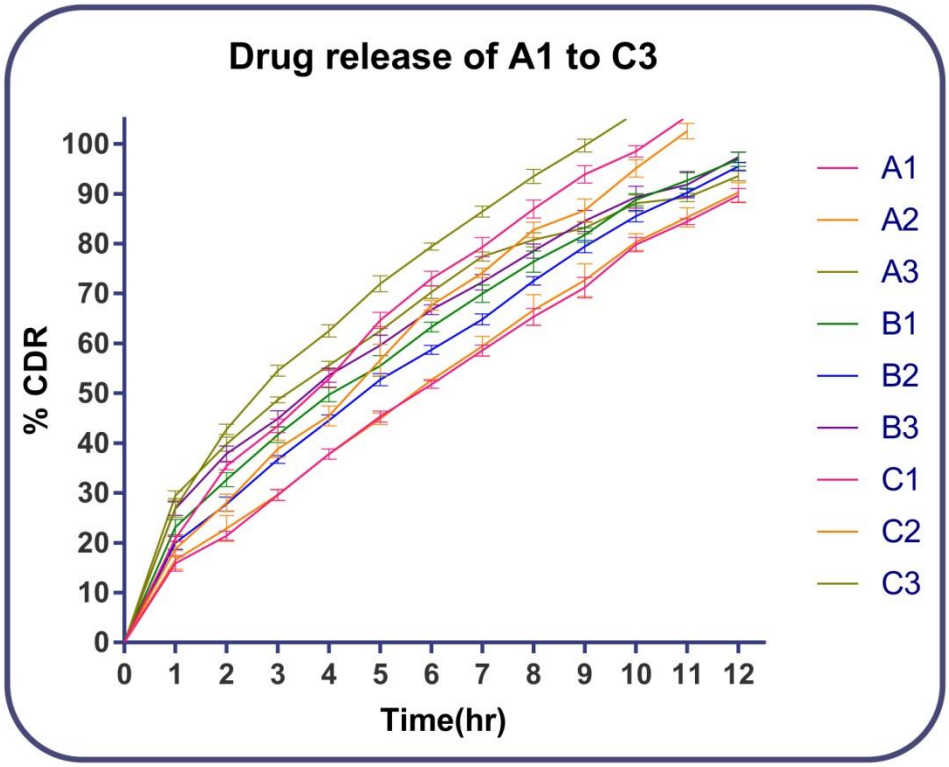
6.3.2 In vitro drug release profile of formulated batches:

Table 6.5: In vitro Drug release profile of Batches of A1 to C3

Time (hr)	A1	A2	A3	B1	B2	B3	C1	C2	C3
0	0	0	0	0	0	0	0	0	0
1	20.84± 0.57	18.75± 1.5	27±1.86	23.12±1.54	19.99±1.32	26.89±1.40	15.85±1.58	16.58±1.86	29.42±0.98
2	35.42± 0.78	28.03± 1.75	42.75±1.0	32.66±1.39	27.73±1.46	37.85±1.54	21.42±0.91	22.85±2.59	39.81±1.40
3	43.46± 1.32	38.81± 1.72	54.52±1.11	41.68±1.55	36.69±0.78	44.88±1.63	29.55±1.11	29.64±1.10	48.69±0.61
4	52.93± 1.66	45.49± 2.0	62.47±1.22	49.73±1.43	44.56±1.08	53.59±1.45	37.79±1.04	37.77±1.05	55.61±0.77
5	64.64± 1.60	56.65± 3.17	71.99±1.63	55.47±2.09	52.74±1.24	59.63±2.11	45.31±1.08	44.90±1.16	62.52±0.89
6	72.96± 1.52	67.64± 0.99	79.41±0.69	63.25±0.96	58.72±0.92	66.73±1.01	51.74±0.82	52.67±0.11	70.28±1.27
7	79.30± 1.55	74.15± 0.95	86.41±1.13	69.99±1.78	64.81±1.08	72.28±1.53	58.58±1.11	59.41±1.99	77.43±0.89
8	86.95± 1.78	82.76± 1.56	93.53±1.46	76.4±2.13	72.51±0.86	78.54±1.43	65.32±1.69	66.66±3.13	80.79±1.44
9	93.92± 1.78	86.68± 2.28	99.67±1.28	81.77±1.50	79.40±1.26	84.55±2.12	71.19±2.03	72.69±3.29	83.19±1.16
10	98.52± 1.75	95.13± 1.75	106.24±1.8 9	88.79±1.26	85.55±1.16	89.35±2.17	79.81±1.44	80.3±1.698	88.10±1.68
11	105.56 ±1.44	102.61 ±1.57	-	92.69±1.54	90.26±0.73	91.83±2.63	84.43±0.58	85.28±1.90	89.26±0.82
12	98.52± 1.75	95.13± 1.75	106.24±1.8 9	96.92±1.40	95.51±0.79	97.39±1.08	89.69±1.43	90.29±1.92	93.60±1.00

(*Mean±SD, n=3)

Figure 6.6: In vitro Drug release profile of Batches A1 to C3



Discussion: By using the HPMC K100 M and Ethyl cellulose in a different concentration it gives release up to 12 hours. In vitro dissolution of batch A1, A2 and A3 indicate that the concentration of HPMC K100 M was increases so release of drug also increases but it gives release in 10-11 hrs not up to 12 hrs. In vitro dissolution of B1, B2 and B3 indicate that the concentration of HPMC K100 M with increase in concentration of Ethyl cellulose so it gives sustained release up to 12 hrs and batch B3 is containing a conc. of HPMC K100 M (22%) and conc. of Ethyl cellulose (15%) it gives highest release of the drug up to 12 hrs. In vitro dissolution of Batch C1. C2 and C3 shows that the increase in conc. of Ethyl cellulose than conc. of HPMC K100 M it decreases the release of the drug. So from the above discussion it can be concluded that the batch B3 was optimized batch.

Treatment of Dissolution data with different kinetic equation:

The result of kinetic treatment applied to dissolution profile of Gastro-retentive floating pellets of optimized batch was shown in **Table 6.5**.

Table 6.6: Kinetic value of the different plot of the optimized formulation

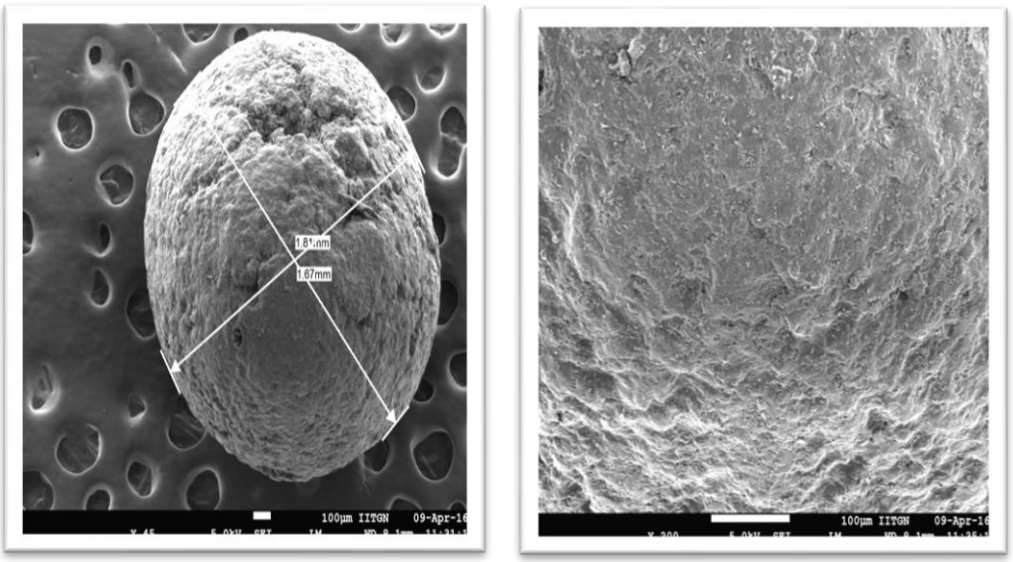
Sr. No.	Variables	Zero order	First order	Higuchi	Korsmeyer-peppas	Hixon-crowell
1	R^2	0.8231	0.7057	0.9387	0.7353	0.9453
2	Slope	0.6111				

Discussion: The optimized batch B3 was treated with different kinetic equations to interpret the order of release of Curcumin and the coefficient of determination (r2) was determined. Results indicates that in the selected B3 formulation, the calculated regression coefficients for Zero order, first order, Higuchi Plot, Korsemeyer and Hixon Crowell models were 0.8231, 0.7057, 0.9387, 0.9453, 0.7353 respectively. Therefore, the release seems to fit in the Higuchi plot and Korse model. The release exponent (n) value for Korsemeyer-peppas is 0.611 so it indicates that the release mechanism follow Non-fickian diffusion.

Surface morphology study:

Surface morphology study of the pellets done by scanning electron microscope. Scanning electron microscopic photograph of optimized batch **B3** shown in **Figure 6.7 (a) & (b).**

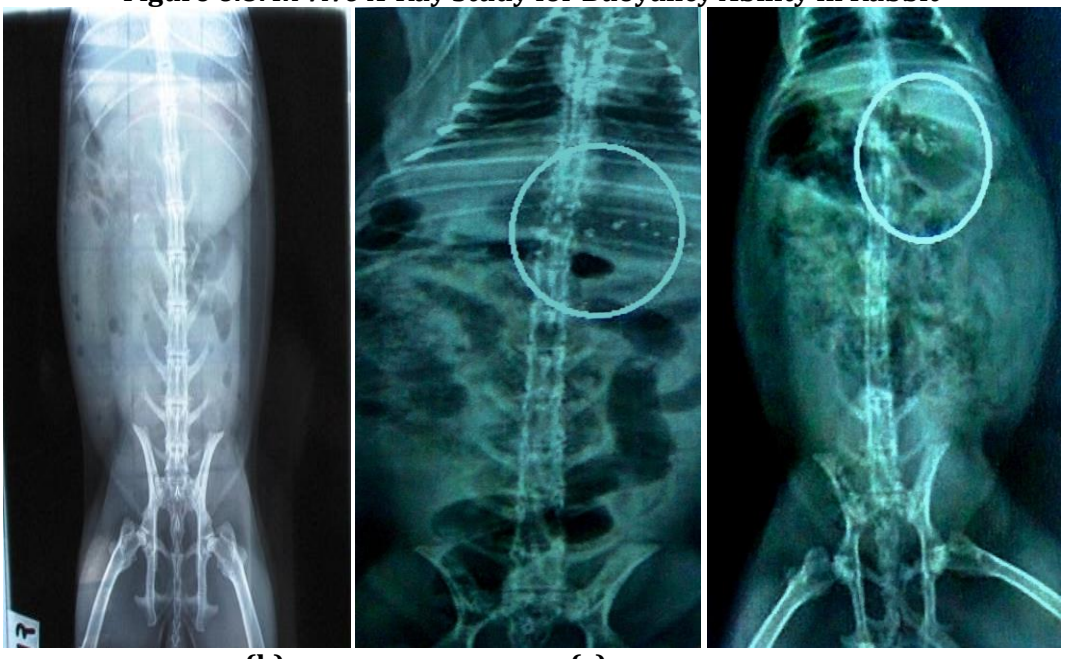
Figure 6.7: Scanning electron microscopic photograph of Gastro-retentive floating pellets of optimized batch B3



(a) **(b)**

6.3.5 *In vivo* X-Ray Study for Buoyancy Ability in Rabbit:

Figure 6.8: *In vivo* X-Ray Study for Buoyancy Ability in Rabbit



(a) **(b)** **(c)**

(a) X-ray without pellets on fasting condition, (b) X-ray at 6 hr after feeding of pellets, (c) X-ray at 12 hr after feeding of pellets

Discussion: The X-ray images confirm that the floating pellets float more than 6 hours in the stomach. So, pellets having a good gastric retention or floating ability in the gastric or stomach region.

Stability study:

The optimized formulation batch B3 maintained at 40 ± 2 °C / 75 ± 5 % RH for one month. Optimized batch are kept in stability chamber for one month mainly for the stability study. The optimized formulations (n = 3) stored at 40 ± 2 °C / 75± 5 % RH were found stable. After the one month, samples were taken out from the stability chamber and analyzed for the drug content, Floating lag time, Total floating time, *In vitro* drug release study were carried out shown in **Table 6.7 and 6.8**. There was not any change in morphological condition during stability study and also not any measurable change in the remaining parameter as shown in **Table 6.8.**

Table 6.7: Comparison of the evaluation data after Stability study

	Floating lag time (sec)	Total floating time (hrs)	Drug content (%)
Initial	5	>12	101.38±0.54
After storage of 1 month	7	>12	99.85±1.189

Table 6.8: Comparison of Drug release profile after Stability study

Time(hr)	% Cumulative drug release (CDR)	
	Initial	After storage of 1 month
0	0	0
1	26.89±1.40	27.74±0.657
2	37.85±1.54	38.423±0.140
3	44.88±1.63	46.50±2.148
4	53.59±1.45	55.03±1.418
5	59.63±2.11	60.99±0.504
6	66.73±1.01	66.86±1.10
7	72.28±1.53	73.66±1.064
8	78.54±1.43	79.22±0.389
9	84.55±2.12	85.31±0.295
10	89.35±2.17	89.77±0.106
11	91.83±2.63	92.73±0.849
12	97.39±1.08	97.78±0.543

(* represents mean ± S.D. n=3)

Conclusion

The concept of formulating Gastro-retentive floating pellets containing Curcumin was a suitable approach to achieve prolongs therapeutic effect by continuously releasing drug over particular period of the time. In present work, Gastro-retentive floating pellets of Curcumin were prepared effectively by extrusion-spheronization method using the different concentration and combination of polymer like HPMC K100 M and Ethyl cellulose. Curcumin was having a low solubility and stability that can be enhanced by preparing complexation with Cyclodextrin. It provides enhanced solubility and effective therapeutic effect. Gastro-retentive multi-particulate drug delivery system of Curcumin with increase gastric residence time can be formulated using HPMC K100 M as a low-density polymer, ethyl cellulose as a release retardant and sodium bicarbonate as a gas generating agent. The formulation batch B3 can provide a delivery of Curcumin for .up to 12 hours. From this investigation it may be concluded that the Curcumin loaded gastro-retentive multiparticulate drug delivery system give better therapeutic effect on the treatment of stomach cancer with enhanced solubility, improve therapeutic efficacy and no side effects.

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