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FORMULATION DEVELOPMENT AND EVALUATION OF FLOATING BIOADHESIVE TABLET OF ANTIRETROVIRAL DRUG

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ABSTRACT: Oral route has been commonly adopted and the most convenient route for drug administration. It has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes. Gastroretensive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After the release of a drug, the residual system is emptied from the stomach. The floating bioadhesive tablet was a promising approach. The addition of gel-forming and mucoadhesive polymer like HPMC, xanthan gum, carbopol, and polyethylene oxide and gas generating sodium bicarbonate along with citric acid was essential to achieve in-vitro buoyancy desirable drug release and excellent bioadhesive strength. The formulation retained a longer period of time floated in 0.1N HCl and provided sustained release of the drug. Hence it may increase the therapeutic efficacy of the drug by increasing the bioavailability and patient compliance.

INTRODUCTION:

Gastro Retentive Drug Delivery System: Oral route has been commonly adopted and the most convenient route for drug administration. It has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes.

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In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time. Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fasted state of the stomach.

Normal gastric residence times usually range between 5 min to 2 h. In the fasted state, the electrical activity in the stomach, the inter-digestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and hence, the transit of dosage forms. It is characterized by four phases: Phase I–Period of no contraction (40-60 min), phase II–Period of intermittent contractions (20-40 min), phase III–Period of regular contractions at the maximal frequency that

travel distally also known as housekeeper wave (10-20 min) and phase IV

Period of Transition between Phase III and Phase I (0-5 min): However, this approach is accompanied with several physiological difficulties such as the inability to restrain and locate the controlled drug delivery system within the desired region of the gastro-intestinal tract (GIT) due to variable gastric emptying and motility.

Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, *i.e.*, stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [2]. This has led to the development of oral gastroretensive dosage forms. Gastroretention is essential for drugs that are absorbed from the stomach, drugs that are poorly soluble or degraded by the higher pH of the intestine, and drugs with absorption which can be modified by changes in gastric emptying time [1].

Gastroretensive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bio-availability, reduces drug wastage, and improves solubility for drugs that are less soluble in a high pH environment. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [3].

Various Types of Gastroretentive Dosage Forms:

A. Floating drug delivery systems

a. Non-effervescent systems

i. Colloidal gel barrier system [4]

ii. Microporous compartment system [5]

iii. Alginate beads [6]

iv. Hollow microspheres/ Microballoons [7]

b. (Gas-generating) Effervescent systems [8]

B. Expandable systems

C. Bio/Mucoadhesive systems [9]

D. High-density systems

Mechanism of Floating Systems: Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices, and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

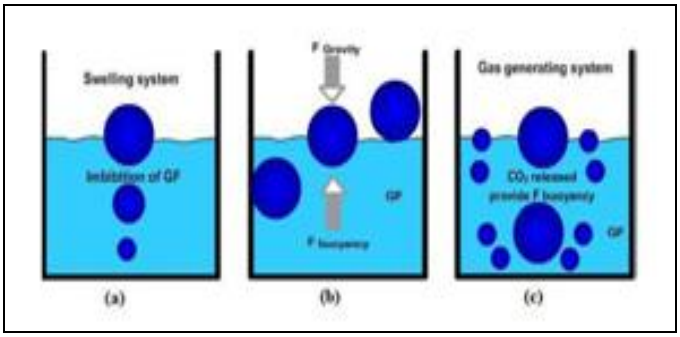

FIG. 1: MECHANISM OF FLOATING SYSTEMS, GF= GASTRIC FLUID

While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After the release of a drug, the residual system is emptied from the stomach. This results in an increased GRT and better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. The apparatus used for the measurement operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to the stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations [10].

$$F = F_{buoyancy} - F_{gravity}$$

$$F= (D_f - D_s)\, g_v \text{--- (1)}$$

Where, F = total vertical force, D_f = fluid density, D_s = object density, v = volume, g = acceleration due to gravity.

Advantages of Floating Drug Delivery System: [11, 12]

- The gastroretensive systems are advantageous for drugs absorbed through the stomach. *e.g.*, Ferrous salts, antacids.
- Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence hydrodynamically balanced system formulation may be useful for the administration of aspirin and other similar drugs.
- Administration of prolonged-release floating dosage forms, tablet or capsules, will result in the dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid and would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- The gastroretensive systems are advantageous for drugs meant for local action in the stomach. *e.g.*, antacids.
- When there is a vigorous intestinal movement, and a short transit time as might occur in a certain type of diarrhoea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in the floating condition in the stomach to get a relatively better response.
- Disadvantages of Floating Drug Delivery Systems
- Floating system is not feasible for those drugs that have solubility or stability problems in G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first-pass metabolism, are only desirable candidates.
- Some drugs present in the floating system causes irritation to gastric mucosa.

Applications of Floating Drug Delivery Systems: Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

These are summarized as follows:

A. Sustained Drug Delivery [13]
B. Site-Specific Drug Delivery [14]
C. Absorption Enhancement [15]

Factors Controlling Gastric Retention of Dosage Forms: The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep, and disease state of the individual (*e.g.*, gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (Cisapride and Metoclopramide).

- Density of dosage form
- Size of dosage form [16]
- Food intake and the nature of food
- Effect of gender, posture and age [17-19]

MATERIALS AND METHODS:

Materials used: API from Desano, Lactose monohydrate (Pharmatose 200M) from DMV Fonterra, Hydroxy Propyl Methyl Cellulose K15M (Methocel) from Dow chemicals, Carbomer 974P NF (Biolpol) from Infinitec, Xanthan gum 180 (Xanthrul) from C P Kelco, Polyethylene oxide N80 (Polyox) from Dow chemicals, Sodium bicarbonate from Merck, Citric acid anhydrous from Merck, Magnesium stearate from Ferro Industries, Aerosil 200 from Evonik.

Pre-formulation Studies: Pre-formulation studies were conducted for the API and other excipients. The API's UV Spectroscopy was obtained using 0.1N HCl, and the solution was scanned over 200-400 nm.

The absorption maxima were obtained from the spectra. Solubility of the API was checked in 4 different media. Solubility of API was determined in 0.1N HCl, water, acetate buffer pH 4.5, and PBS pH 6.8. Compatibility of the drug with different excipients was tested using Infrared Spectroscopy.

The blend was filled in glass vials and closed with grey rubber stoppers and sealed with aluminium, and charged in to stress condition at 25 ºC / 60% RH and 40 ºC / 75% RH. The samples were observed for any physical change in 15 days and 1-month duration.

Powder Flow Properties:

A. Angle of Repose: The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and the horizontal plane.

B. Bulk Density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 20 g of API, previously shaken to break any agglomerates formed, was introduced into 50 ml measuring cylinder.

After that, the initial volume was noted, and the cylinder was kept in tapped density apparatus. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated.

C. Hausner's Ratio: This was calculated as the ratio of tapped density to bulk density of the sample

D. Compressibility Index (CI): The Compressibility Index of the API was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down.

E. Particle Size Distribution (PSD): The particle size distribution was evaluated by sieve analysis, using electromagnetic sieve shaker at power 10 for 10 min.

Standard sieve sizes like #30, #40, #60, #80, #100, were used for the PSD. The fractions were calculated by collecting for each sieve, and percent retained and cumulated percent retained was calculated.

F. Moisture Content: The moisture content of the API was determined in a moisture analyzer using 1.000 g of powder at 100 °C-105 °C for 5 min.

Preparation of Floating Tablets of Model Drug Preparation Using Wet Granulation Method (Effervescent Method): Wet granulation technique was used for the preparation of floating tablets by using different concentrations of HPMC K15M, Carbopol 974PNF, xanthan gum 180, and polyethylene oxide N80 as polymers, lactose monohydrate was used as a diluent, sodium bicarbonate and citric acid were used as gas generating agents, magnesium stearate and aerosil 200 as lubricating agents and water as a binder.

Step 1: Dispensing all ingredients of the required quantity is dispensed.

Step 2: Sifting API, intra-granular chosen Polymers, and diluent were passed through sieve # 40.

Step 3: Mixing the materials obtained after step 2 are mixed geometrically and blended for about 10 to 15 min in a polybag.

Step 4: Granulation process is performed by adding the required amount of purified water to the mixed blend of step 3 and kneaded properly to form granules until the endpoint of granulation.

Step 5: Drying the formed granules by keeping the tray inside a vacuum oven set at 40 °C – 50 °C till the LOD is achieved.

Step 6: Sifting the formed granules are passed through sieve #20.

Step 7: Pre lubrication, then the weighed extra-granular materials are passed through sieve #40 and mixed with intra-granular granules and blended for 10-15 min manually in a polybag.

Step 8: Lubrication then lubricant is blended with aerosil and magnesium stearate for 5 min after passing it through sieve #40 the former and later one through sieve #60. Then pre-compression parameters are examined.

Step 9: Compression, then compress the tablets using a rotary tablet press.

Prototype Formulation by Wet Granulation Process:

TABLE 1: PROTOTYPE FORMULAS FOR TRIAL BATCHES

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Intra-granular (*)										
API(Model drug)	300	300	300	300	300	300	300	300	300	300
HPMC K15M	50	50	50	50	50	50	50	30	25	5
Lactose monohydrate	45	45	48.4	19.8	19.8	16.8	16.8	30.8	35.8	45.8
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Extra granular (*)										
HPMC K15M	-	-	50	100	100	100	100	100	100	110
Xanthan Gum 180	25	25	40	-	-	-	25	25	25	25
Polyethylene oxide N80	-	-	-	100	-	25	25	25	25	25
Carbomer 974P NF	-	-	-	-	100	100	100	100	100	100
Sodium bicarbonate	50	75	60	70	70	120	120	120	120	120
Citric acid Anhydrous	25	35	45.6	53.2	53.2	91.2	91.2	91.2	91.2	91.2
Aerosil 200	-	-	-	-	-	-	-	6	6	6
Magnesium Stearate	5	5	6	7	7	12	12	12	12	12
Total	500	535	600	700	700	815	840	840	840	840

*All amounts were in mg

Optimized Formula for Tablet Preparation

TABLE 2: OPTIMIZED FORMULA FOR TABLET PREPARATION

Ingredients	F10 – A	F10 – B	F10 – C	F10 – D	F10 – E	F10 – F
Intra granular (*)						
API(Model drug)	300	300	300	300	300	300
HPMC K15M	5	5	5	5	5	5
Lactose monohydrate	55.8	35.8	65.8	25.8	55.8	35.8
Purified water	q.s	q.s	q.s	q.s	q.s	q.s
Extra granular (*)						
HPMC K15M	110	110	110	110	110	110
Xanthan Gum 180	15	35	25	25	25	25
Polyethylene oxide N80	25	25	25	25	15	35
Carbomer 974P NF	100	100	80	120	100	100
Sodium bicarbonate	120	120	120	120	120	120
Citric acid Anhydrous	91.2	91.2	91.2	91.2	91.2	91.2
Aerosil 200	6	6	6	6	6	6
Magnesium Stearate	12	12	12	12	12	12
Total	840	840	840	840	840	840

*All amounts were in mg

Post-compression Evaluation of Pre-parted Floating Tablets: [20]

A. Weight Variation Test: Twenty tablets of the formulation were weighed using an electronic balance for the study, and the test was performed according to the compendial method.

B. Content Uniformity: A fine powder of ten tablets which were weighed previously was prepared. An amount of powder equivalent to the average weight of tablets was weighed. 0.1N HCl was used to extract the drug. The content of the drug was determined by measuring the absorbance

at 266 nm after suitable dilution using a Shimadzu UV- Vis double beam spectrophotometer 1700.

C. Hardness: Hardness is used to indicate the ability of a tablet to withstand mechanical shocks while handling. Schleuniger hardness tester was used to assess the hardness of the tablets. Hardness is expressed in Newton. Hardness of the tablets were determined with 3 randomly picked tablets.

D. Thickness: The thickness of five tablets was checked, and average value was calculated. The thickness of the tablets was determined using Vernier callipers.

E. Friability test: Roche Friabilator was used to determine the friability of tablets. Friability is expressed in percentage (%). Ten tablets were transferred to friabilator after weighing. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The weight of the tablets after rotation was noted. The percentage friability was then calculated by equations.

F. *In-vitro* Buoyancy Test: The floating lag time method was used to determine the in vitro buoyancy. The time taken by the tablet to rise up to the surface and float in 0.1 N HCl contained in a 250 ml beaker was determined as floating lag time. The time of introduction of the dosage form and the time taken for the buoyancy of the dosage form in 0.1N HCl, and the duration for which the dosage form remained buoyant were measured. The time required for the dosage form to reach the surface of the medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT), and the total duration for which the dosage form remains buoyant is called Total Floating Time (TFT) [21].

G. *In-vitro* Drug Release Studies:

A. The rate of release of API from floating tablets was determined using dissolution testing apparatus II (paddle method).

B. The test for dissolution was performed in 900 ml of 0.1 N HCl at 37 ± 0.5 °C and 50 rpm. A 10 ml sample of the dissolution solution was withdrawn from the apparatus at intervals 1 h, 2 h, 3h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, and 12 h and the bowl of the dissolution apparatus was replaced with fresh dissolution medium.

C. The samples were diluted to a suitable concentration using 0.1N HCl.

D. Absorbance of these solutions was measured at 266 nm using a Shimadzu UV is double beam spectrophotometer 1700.

E. Percentage of cumulative drug release was obtained using the equation from a standard curve.

H. Release Kinetics: *In-vitro* dissolution is considered as one of the most important elements in drug development. Under certain conditions, *in-vitro* dissolution can be used as a surrogate tool for the assessment of bioequivalence. Several theories/kinetic models have described drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where ft is the function of t (time) related to the amount of drug dissolved from the pharmaceutical dosage system. Model dependent (curve fitting), statistical analysis, and model-independent methods can be used for the comparison of dissolution profiles between two drug products.

I. Swelling Index: The swelling index of tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets were taken at predetermined time intervals. The swelling index was then calculated [22].

J. *Ex-vivo* Bioadhesive Test: Bioadhesive force of the tablets was measured with the help of a modified physical balance. The apparatus for the measurement of bioadhesive force consisted of a modified double beam physical balance.

A lighter pan was used to replace the right pan, and the left pan was replaced using a glass slide (4 cm length and 2.5 cm width). A plastic hang is suspended from the beam using teflon rings and copper wire. The right-hand side of the pan was exactly 5 g lesser in weight compared to the left-hand side. The height of the total assembly was adjusted so as to accommodate a glass beaker of height 6.6 cm. Floating bioadhesive tablets (n=3) were stacked to a glass slide with the help of a knob situated at the base of the physical balance to find the strength of bioadhesion. 5 g weight from the right pan was then removed. This resulted in the lowering of the glass slide along with the tablet

over the membrane with a weight of 5.0 g. The system is kept undisturbed for 5 min. Weight was added in increments of 0.1 g on the right-hand side until the tablet just got separated from the membrane surface. The weight excess on the right pan, *i.e.*, total weight minus 5 g was taken as a measure of the bioadhesive strength. By using the obtained weight, bioadhesive force is calculated.

RESULTS AND DISCUSSION:

Post Compression Evaluation of Floating Tablet:

TABLE 3: PHYSICAL PARAMETERS OF PREPARED FLOATING TABLETS

Batch	Weight variation of Average weight in (mg) ± SD	Hardness (Newton) ±SD	Diameter (mm) ±SD	Thickness (mm) ±SD	Friability (%)±SD	Drug Content Uniformity (%)±SD
F10 –A	840±5	85±1	12.70±0.02	7.12±0.02	0.68±0.02	98.00±0.11
F10 – B	840±5	80±2	12.70±0.01	7.05±0.06	0.54±0.01	99.69±0.02
F10 – C	840±5	90±2	12.68±0.05	6.90±0.04	0.76±0.06	96.98±0.15
F10 – D	840±5	85±1	12.67±0.03	7.10±0.04	0.89±0.02	98.75±0.18
F10 – E	840±5	80±2	12.70±0.02	7.15±0.02	0.50±0.08	97.68±0.02
F10 – F	840±5	85±1	12.69±0.02	7.02±0.04	0.52±0.02	98.20±0.12

All the values are expressed as mean ± S.D (n=3)

Hardness Test: The hardness of tablets of each batch measured ranged between 75 ± 1N to 101 ± 1 N. This ensures good handling characteristics of all batches.

Friability Test: The percentage friability of the tablets was less than 1% in all the formulations ensuring that the tablets were mechanically stable. (Specifications followed as per USP)

Weight Variation Test: All the batches of tablets formulated passed the weight variation test as the percentage of weight variation was within the compendial limits between avg ± 1.32 to avg ± 2.34 of the total weight. The weights of all the tablets were found to be uniform with low standard deviation values. (Specifications followed as per USP)

Drug Content Uniformity: The Percentage of drug content for all the formulations was found to be 97.45 ± 0.05% to 99.79 ± 0.15%; it complies with official specifications. (Specifications followed as per USP)

B. Floating Lag Time and Total Floating Time of Prepared Floating Tablets:

TABLE 4: FLOATING LAG TIME AND TOTAL FLOATING TIME OF OPTIMIZED FORMULATIONS

Batch	Floating Lag time (sec)	Total Floating time (h)
F10 –A	23	>12
F10 – B	22	>12
F10 – C	40	>12
F10 – D	24	>12
F10 – E	245	>12
F10 – F	300	>12

C. *In-vitro* Drug Release of Prepared Floating Tablets:

TABLE 5: *IN-VITRO* DRUG RELEASE DATA OF FLOATING BIOADHESIVE TABLETS OF OPTIMIZED FORMULATIONS

Time (h)	% Cumulative release					
	F10 – A	F10 – B	F10 – C	F10 – D	F10 – E	F10 – F
1	15.01±0.22	13.22±0.32	17.15±0.10	12.56±1.20	14.45±0.83	12.56±0.88
2	24.22±0.96	20.45±0.52	28.02±0.78	21.09±0.83	23.80±1.01	22.92±1.15
3	32.45±0.56	29.21±0.95	36.10±0.02	26.22±1.10	31.82±1.07	30.21±1.68
4	38.25±1.20	37.12±0.78	46.56±1.02	33.01±1.00	35.56±1.30	36.00±0.84
5	43.18±1.02	42.05±0.88	60.12±1.22	39.11±0.70	46.20±0.81	41.82±1.28
6	48.02±1.25	49.05±0.45	69.78±1.54	43.06±1.40	52.86±0.28	46.78±0.86
7	54.15±1.45	52.32±0.83	73.20±0.98	50.81±1.00	63.52±0.12	51.20±1.38
8	65.45±1.82	56.85±0.15	82.78±0.86	55.92±1.30	70.01±0.87	60.96±1.00
9	75.78±0.23	66.12±0.12	88.02±0.45	62.07±0.80	78.99±1.94	72.01±0.48
10	88.20±0.56	70.02±0.88	100.18±0.12	69.11±0.56	86.56±1.74	81.11±0.78
11	92.00±0.45	76.11±0.22	-	72.26±0.75	100.85±1.22	90.01±1.34
12	101.14±0.21	81.12±0.12	-	79.20±1.62	100.96±0.98	98.03±0.21

All the values are expressed as mean ± SD (n=3)

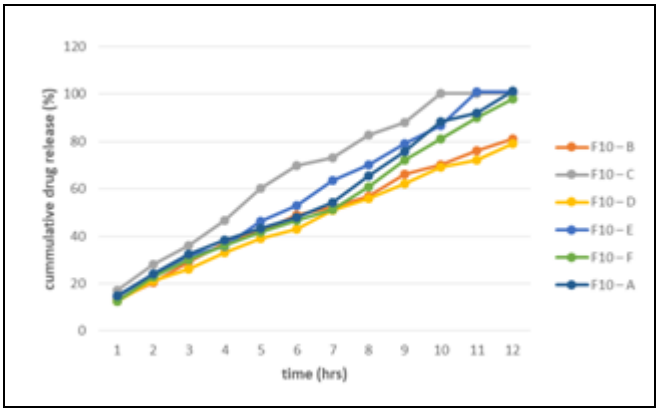

FIG. 2: *IN-VITRO* CUMULATIVE DRUG RELEASE *VS.* TIME PROFILE OF OPTIMIZED FORMULATIONS

Formulation 10A: optimizing the formulation F10 by decreasing the xanthan gum by 10mg cumulative % drug release was found to be 101.14 ± 0.21% at 12 h.

Formulation 10B: optimizing the formulation F10 by increasing the xanthan gum by 10 mg the drug release was retarded more. The cumulative % drug release was found to be 81.12 ± 0.12% at 12 h; this may be due to an increase in xanthan gum.

Formulation 10C: optimizing the formulation F10 by decreasing the carbopol by 20 mg; the drug release was fast.

The cumulative % drug release was found to be 100.18 ± 0.12% at 10 h itself; this is due to a decrease in polymer extra granularly.

Formulation 10D: optimizing the formulation F10 by increasing the carbopol by 20 mg the drug release was retarded more. It shows 79.20 ± 1.62% at 12 h.

Formulation 10E and 10F: optimizing the formulation F10 by decreasing and increasing the polyethylene oxide by 10mg extra granularly showed no much effect on drug release character. The cumulative % drug release was found to be 100.96 ± 0.98% and 98.03 ± 0.21% at 12 h.

Release Kinetics of Floating Bioadhesive Tablet of Formulation F10A-F10F:

TABLE 6: RELEASE KINETICS OF FLOATING BIOADHESIVE TABLET OF FORMULATION

Formulation	Zero order R^2 Value	First order R^2 Value	Higuchi model R^2 value	korsemeyer's peppas model (n value)	korsemeyer's peppas model release exponent (R^2 value)
F10-A	0.9877	0.8714	0.9235	0.7594	0.9809
F10-B	0.9847	0.9859	0.9699	0.7341	0.9975
F10-C	0.9857	0.9522	0.9600	0.7509	0.9928
F10-D	0.9911	0.9833	0.9610	0.7377	0.9965
F10-E	0.9937	0.8804	0.9344	0.8022	0.9897
F10-F	0.9890	0.8832	0.9208	0.7975	0.9862

The data obtained from kinetic drug release studies reveal that the floating bioadhesive tablets follow zero-order drug release, and the R2 value ranges from 0.9617 to 0.9964; these values are higher than the first-order release data. R2 value ranges from 0.7580 to 0.9909. The Higuchi diffusion equation shows R2 value ranges from 0.9186 to 0.9865. *In-vitro* drug release data were fitted to korsemeyer's peppas model equation to confirm the mechanism of drug release. The slope values (n) were in the range of 0.6814 to 0.8979; this shows the floating bioadhesive tablets follow non-fickian and zero-order release.

D. Swelling Index of Prepared Floating Tablets: A swelling study was performed on all the batches for 12 h. Swelling Index was found to be in the range of 73% to 160%. From the results obtained from the study it was concluded that swelling increases with time as the polymer gradually absorbs water due to its hydrophilicity. The hydrophilic polymer in the outermost layer hydrates and swells to form a gel barrier.

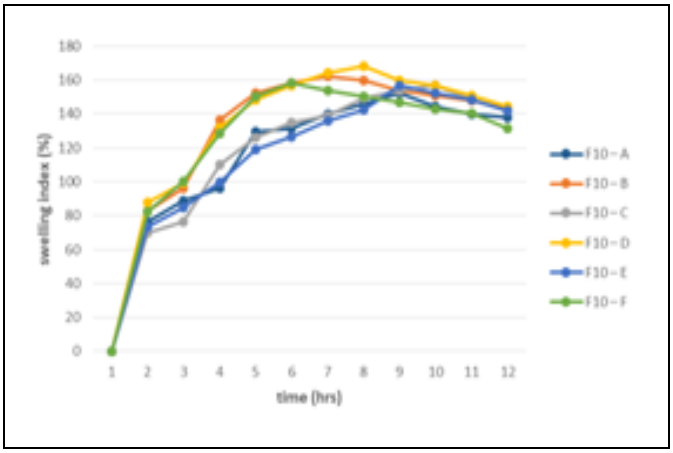

FIG. 3: SWELLING INDEX *VS.* TIME OF OPTIMIZED FORMULATION

A new surface of the gelatinous polymer is exposed each time the existing layer is dissolved and/or is dispersed. The hydration swelling process will continue; this will maintain the integrity of the dosage form.

E. ***Ex-vivo* Bioadhesive Test of Floating Tablets:**

TABLE 7: BIOADHESIVE STRENGTH OF FLOATING BIOADHESIVE TABLET OF OPTIMIZED FORMULATION

S. no.	Batch	Bioadhesive strength(N) ± SD	Bioadhesive strength(g)
1	F10 – A	0.248 ± 0.005	25.288
2	F10 – B	0.292 ± 0.002	29.755
3	F10 – C	0.201 ± 0.001	20.496
4	F10 – D	0.301 ± 0.001	30.693
5	F10 – E	0.266 ± 0.001	27.124
6	F10 – F	0.272 ± 0.002	27.736

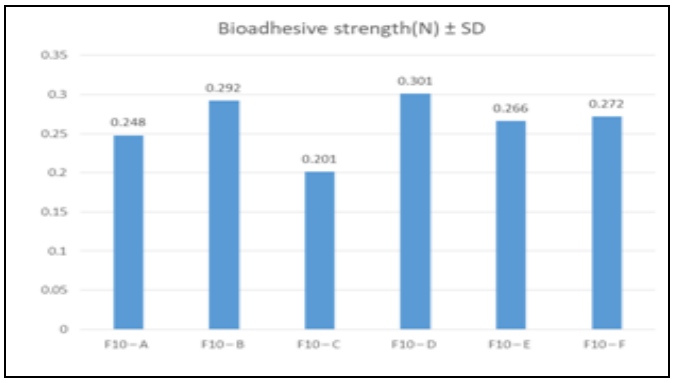

FIG. 4: BIOADHESIVE STRENGTH OF FLOATING BIOADHESIVE TABLET OF OPTIMIZED FORMULATION

Formulation 10A: showed a decrease in bioadhesion strength compared to formulation 10; this may be due to a decrease in the amount of xanthan gum by 10 mg.

Formulation 10B: showed an increase in bioadhesion strength compared to formulation 10; this may be due to an increase in the amount of xanthan gum by 10 mg.

Formulation 10C and 10D: showed a pronounced decrease in bioadhesion strength and vice versa.

Formulation 10E and 10 F: increase and decrease in polyethylene oxide did not show much effect on bioadhesion strength.

Final Formulation: The final best formulation was decided based on floating time, total buoyancy time, % cumulative drug release, bioadhesive strength, and release kinetics it was found to be Formulation 10A.

TABLE 8: FINAL OPTIMIZED FORMULATION

S. no.	Ingredients	Amount (mg)
	Intra granular	
1	API	300
2	HPMC K15M	5
3	Lactose monohydrate (Pharmatose 200)	45.8
4	Distilled water	q.s
	Extra granular	
5	HPMC K15M	110
6	Xanthan Gum 180	25
7	Carbopol 974P NF	100
8	Polyethylene oxide N80	25
9	Sodium bicarbonate	120
10	Citric acid Anhydrous	91.2
11	Aerosil 200	12
12	Magnesium Stearate	6
13	Total	840

TABLE 9: PARAMETERS OF FLOATING BIOADHESIVE TABLETS OF FORMULATION F10-A

S. no.	Parameters	Results
1	Floating lag time	23 seconds
2	Total floating time	>12 hours
3	*Percentage cumulative drug release at 12 hours (%)	101.14 ± 0.21
4	Bioadhesive strength(N)	0.248 ± 0.002
5	Zero order release (R^2)	0.9877
6	First order release (R^2)	0.8714
7	Higuchi equation (R^2)	0.3235
8	korsemeyer's peppas model (n)	0.9809

CONCLUSION: The floating bioadhesive tablet was found to be a promising approach for controlled release.

Gel forming and mucoadhesive polymer like HPMC K15M, Xanthan gum 180, Carbopol 974P NF, and polyethylene oxide N80 and effervescing sodium bicarbonate along with citric acid added to the formulation are essentially required to achieve *in-vitro* buoyancy, desirable drug release, and excellent bioadhesive strength.

The formulation retained a longer period of time floated in 0.1N HCl and provided sustained release of drug from the formulation. Hence it may increase the therapeutic efficacy of the drug by increasing the bioavailability and patient compliance.

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