

## FORMULATION AND *IN VITRO* EVALUATION OF COMBINED FLOATING-BIOADHESIVE TABLETS OF IMATINIB MESYLATE

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### ABSTRACT

**Objective:** Gastro retentive drug delivery system (GRDDS) pertaining to its attributes like gastric retention time and the extended drug release profile has significantly improved patient compliance. The objective of the present study was to formulate and evaluate a stomach-specific floating-bioadhesive tablets (FBTs) of imatinib mesylate (IM) for prolonged residence in the stomach in the treatment of gastrointestinal stromal tumours (GIST).

**Methods:** All the FBTs were prepared with hydroxypropyl methyl cellulose (HPMC) K 15M, guar gum, sodium alginate, and carbopol 971P using direct compression technique. Physical characterization, *in vitro* dissolution, swelling characteristics, the mucoadhesive force along with data analysis was done for each FBT.

**Results:** The pre-compression characteristics of powder mixtures found to be satisfactory for all formulation batches. The results of physical evaluation for all batches were complying with pharmacopoeia specification. The swelling index for all formulation batches was approximately 100% after 8 h. The bioadhesive force (mean±SD) reported in a range of 0.05±0.09 to 0.18±0.06 N/m<sup>2</sup>. It was observed that the release rate of FBTs was decreased with an increment of viscosity and concentration of the polymer. Formulation batches IB1, IB2, IB4, IB5, IB6, IB9, IB10, IB11, and IB13 follows Higuchi Matrix model kinetics; whereas IB3, IB7, IB8, and IB12 follows Korsmeyer-Peppas model kinetics.

**Conclusion:** Formulation batch IB9 reported a considerable swelling index, floating behaviour, more bioadhesive strength with uniform drug release pattern. Therefore formulation batch IB9 was selected as optimized batch and kept for further evaluation studies.

**Keywords:** Gastro-retentive, Imatinib mesylate, Swelling index, Bioadhesive strength

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### INTRODUCTION

The most expedient and ideal means of any drug delivery to the systemic circulation is oral administration [1]. Among administration routes utilized for drug delivery systems (DDS), oral DDS has recently been of adding interest in the pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance, and flexibility in formulation [2]. Oral DDS are categorized into immediate release and modified release systems. However, the conventional immediate-release oral dosage form has a problem of a transient overdose followed by a long period of under-dosing, which can be overcome by a designing controlled DDS [2]. The modern development in the technology of oral DDS has outcome numerous novel pharmaceutical products, importantly the controlled release DDS to overcome the mentioned hitches with immediate-release oral dosage forms [3]. Gastro-retentive drug delivery system (GRDDS) pertaining to its attributes like gastric retention time and drug release profile for an extended time has significantly improved patient compliance [4]. Further, certain intrinsic drawbacks of the conventional oral DDS have also kindled the interest to the development of this novel DDS [5]. Various approaches have been proposed to control the gastric residence of the DDSs in the upper part of the gastri intestinal (GIT) tract including floating DDS, high-density DDS, mucoadhesive systems, swelling and expanding DDS, modified shape systems, and other delayed gastric devices [6]. Imatinib mesylate (IM), an anticancer drug with a pKa value of 12.45 in an acidic environment and 8.27 in basic environment shows a discrepancy in its solubility profile [7]. It is reported soluble in acidic condition (pH<5.5) but very slightly soluble to insoluble in neutral and alkaline aqueous buffer solutions [8]. Furthermore, it has high absorption in the upper part of the GIT. In contrast, a conventional tablet of IM pertaining to their rapid and relatively high peak blood levels necessitates

repeated administration to maintain the steady-state plasma drug level. This might produce side effects, decreased effectiveness and poor therapeutic management [9]. Floating dosage forms can provide gastric retention when the stomach is full after a meal. Thus, the buoyancy of a floating DDS in the stomach may be limited to only 3–4 h. Furthermore, floating systems do not always release the drug at the expected site. In addition, during peristalsis, or when the stomach is full, it is quite likely that the tablet becomes dislodged from the stomach mucosa wall in a bioadhesive system [3]. In concern to the mentioned approaches, a combination of the floating-bioadhesive system (FBS) would overcome those drawbacks and would significantly improve the therapeutic efficacy of the involved drug. The objective of the present study was to formulate and evaluate a stomach-specific floating-bioadhesive tablet (FBT) of IM for prolonged residence in the stomach in the treatment of gastrointestinal stromal tumours (GIST).

### MATERIALS AND METHODS

#### Materials

IM was received as a gift sample from Celon lab, Hyderabad. Sodium bicarbonate, citric acid, and carbopol 971P were obtained from Loba chemicals. Guar gum was supplied from Noveon chemicals. Microcrystalline cellulose (MCC), hydroxypropyl methyl cellulose (HPMC) K 15M, and sodium alginate were brought from Sigent chemical corporation, Mumbai. All other reagents are of analytical or pharmaceutical grade and deionized water was obtained by reverse osmosis.

#### Pre-compression characteristics of powder blend

The characteristic parameters of the formulated mixture were evaluated. The flow behavior was determined by the funnel method.

The bulk density, tapped density, and Carr's index were determined and calculated [6].

#### Preparation of FBTs

All the FBTs of IM were prepared by direct compression technique [3]. The ingredients were accurately weighed and blended homogeneously in a mortar according to table 1. The blended mixture was passed through sieve no. 30. Finally, talc, polyethylene

glycol, and magnesium stearate were added to the mixture as a lubricant to promote easy ejection and good anti-sticking property [9]. The homogeneously blended mixture was then compressed on a rotary tablet press (RIMEK, 10 stations, KEL) with 10 mm concaves punch with a compression force of 250 kg/cm<sup>2</sup>.

The tablet hardness was kept in the range 5-6 kg/cm<sup>2</sup> tested on Monsanto tablet hardness tester. At least 30 tablets were prepared for each formulation in a single batch.

Table 1: Formulation of FBTs

Ingredients/Formulation bathes	IM	HPMC K 15M	Guar gum	SA	Carbopol 971P	SB	CA	PVP K30	MCC	Talc andMS
IB1	100	48	12	-	-	40	10	50	30	10
IB2	100	45	15	-	-	40	10	50	30	10
IB3	100	40	20	-	-	40	10	50	30	10
IB4	100	48	-	12	-	40	10	50	30	10
IB5	100	45	-	15	-	40	10	50	30	10
IB6	100	40	-	20	-	40	10	50	30	10
IB7	100	48	-	-	12	40	10	50	30	10
IB8	100	45	-	-	15	40	10	50	30	10
IB9	100	40	-	-	20	40	10	50	30	10
IB10	100	40	10	10	-	40	10	50	30	10
IB11	100	40	10	-	10	40	10	50	30	10
IB12	100	40	-	10	10	40	10	50	30	10
IB13	100	30	10	10	10	40	10	50	30	10

All values specified are in milligram (mg); IM, imatinib mesylate; HPMC, hydroxypropyl methylcellulose; SA, sodium alginate; SB, sodium bicarbonate; CA, citric acid; PVP, polyvinyl pyrrolidone; MCC, microcrystalline cellulose; MS, magnesium stearate

#### Physical characterization and *in vitro* evaluation of the prepared FBTs

The physical characterization and *in vitro* studies were conducted using Indian Pharmacopoeia and USP standard procedures [10, 11].

##### Weight variation

Twenty tablets were randomly selected from each batch and then accurately weighed by using an electronic balance (Shimadzu, AUW-D, Japan).

##### Thickness

Ten tablets were randomly selected and the thickness was measured using a Vernier caliper. Results were expressed as mean±SD.

##### Hardness

The tablet's hardness (n = 5) was investigated using Monsanto hardness tester. The hardness of tablets was expressed as mean±SD.

##### Friability

Ten tablets were randomly selected and the friability was calculated by using Roche friabilator. Results were expressed as mean±SD.

##### Drug content uniformity

For this at least 30 tablets were randomly selected. Out of 30 tablets, 10 tablets were crushed into fine powder and assayed individually. The powder was dissolved in 500 ml of 0.1N HCl, filtered and the specific aliquots were taken and analyzed spectrophotometrically (Shimadzu, SPD-10AVP, Kyoto, Japan) at 237 nm.

##### Floating behaviour

The buoyancy lag time of the tablets (N=10) was studied at 37±0.5 °C, in 100 ml 0.1N HCl. The time required for the tablet to rise to the surface and float and the total floating time (the duration which the tablet remains buoyant) were recorded.

##### Swelling characteristics

The swelling properties of matrices containing IM were determined by placing the tablet in the dissolution test apparatus, in 900 ml 0.1N HCl at 37±0.5 °C. The tablets were removed periodically from the dissolution medium, then free water was sucked with blotting paper

and, after removing free water, the weight gain was measured [3, 4]. The swelling characteristics were expressed in terms of the percentage water uptake.

##### *In vitro* bio-adhesion study

The bioadhesive forces of the FBTs were determined by the physical balance method. The pieces of Sheep fundus tissue were stored and frozen in saline solution and thawed to room temperature immediately before use. At the time of testing a section of tissue was transferred, keeping the mucosal side out, to the upper glass vial using a rubber band and an aluminum cap. The diameter of each exposed mucosal membrane was 1.1 cm. The vials with the Sheep fundus tissue were stored at 37 °C for 10 min. Next, one vial with a section of tissue was connected to the balance and the other vial was fixed on a height-adjustable pan. A tablet was applied to the lower vial with the help of two pieces of adhesive tape.

The height of the vial was adjusted so that the tablet could adhere to the mucosal tissues in the vial. A constant weight (10 g) was placed in the upper vial and applied for 2 min, after which it was removed, and the upper vial was then connected to the balance. Weights were added at a constant rate to the pan on the other side of the modified balance of the device until the two vials were separated. The bioadhesive force, expressed as the detachment stress in N/M<sup>2</sup>, was determined from the minimum weight required to detach the two vials using the following equation [6].

$$\text{Force of adhesion} = \text{Mucoadhesion in gram} \times 0.0981$$

##### *Ex vivo* mucoadhesion time

A modified USP disintegration apparatus was used for determination of the *ex vivo* residence time. The medium was constituted of 900 ml (pH 1.5) of 0.1 N HCl maintained at 37±0.5 °C. The sheep gastric mucosa was tangled to the surface of a glass slab and connected vertically to the disintegration apparatus. The FBTs were hydrated using phosphate buffer (pH 6.8) and the hydrated surface was carried in contact with the mucosal membrane. The glass slide allowed moving up and down and hence that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time taken for complete displacement of the tablet from the mucosal surface was noted [12].

**In vitro dissolution studies**

The release profiles of FBTs were determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1N HCl, at 37±0.5 °C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The absorbance of these samples was measured at 237 nm [6].

**Data analysis**

The data obtained from the dissolution study were fitted into zero order, first order, Higuchi matrix, and Korsmeyer-Peppas model to evaluate the mechanism of drug release and release rate kinetics. Further based on the r value, the best fit model was selected.

**RESULTS AND DISCUSSION**

The FBTs were prepared by direct compression method. HPMC K15M was used as a rate controlling polymer (primary polymer) whereas guar gum, sodium alginate, and carbopol 971P were used as bioadhesive polymers (secondary polymer). Sodium bicarbonate and citric acid were used as gas generating agents. MCC was used as diluent. Tablets of formulation batches IB1 to IB9 contain only single bioadhesive polymer in different concentration, while IB10 to IB13 contains a combination of various bioadhesive polymers (table 1).

**Pre-compression characteristics**

The densities, angle of repose and Carr's compressibility index for all the batches of mixture demonstrates satisfactory flow behaviour. The data has been depicted in table 2.

**Table 2: Pre-compression characteristics of FBTs**

Formulation batches/Characteristics	Bulk density (g/ml)	Tap density (g/ml)	Carr's index (%)	Angle of repose (°)
IB1	0.542±0.07	0.672±0.03	19.34	29±1.7
IB2	0.537±0.03	0.67±0.02	19.85	28±2.0
IB3	0.561±0.08	0.71±0.05	21.12	30±1.8
IB4	0.548±0.01	0.668±0.05	17.96	26±1.5
IB5	0.58±0.09	0.694±0.07	16.42	28±1.2
IB6	0.563±0.04	0.665±0.03	15.33	25±1.3
IB7	0.555±0.02	0.683±0.06	18.74	27±1.7
IB8	0.572±0.03	0.692±0.05	17.34	24±1.3
IB9	0.521±0.04	0.642±0.01	18.84	22±1.5
IB10	0.533±0.05	0.652±0.07	18.25	24±1.5
IB11	0.523±0.08	0.648±0.02	19.29	29±1.8
IB12	0.512±0.02	0.623±0.01	17.81	27±1.2
IB13	0.545±0.07	0.663±0.01	17.79	26±1.1

All values are mean±SD; SD, Standard deviation

**Evaluation of FBTs**

A thickness (mean±SD) in the range of 3.2±0.04 to 3.7±0.08 mm was reported in all formulation batches. Hardness (mean±SD) was found to be 4.8±0.2 to 5.5±0.5. Tablet from all batches passed the weight

variation test as per USP specification. The percentage friability was <0.9%, which stated that all tablets were passed the test. The percentage drug content was up to 99% with some variability observed between formulation batches. The data has been reported in table 3.

**Table 3: Evaluation parameters of FBTs**

Formulation batches/Characteristics	Thickness (mm)*	Hardness (kg/cm <sup>2</sup> )*	Friability (%)	Drug content (%)	Weight variation
IB1	3.4±0.01	5.1±0.6	0.67	99.2	Passes
IB2	3.5±0.03	5.3±0.1	0.57	97.4	Passes
IB3	3.7±0.05	5.2±0.3	0.72	98.2	Passes
IB4	3.5±0.02	5±0.6	0.58	95.1	Passes
IB5	3.6±0.02	5.5±0.5	0.91	91.2	Passes
IB6	3.3±0.07	5.1±0.3	0.8	93.2	Passes
IB7	3.7±0.01	4.8±0.2	0.56	97.1	Passes
IB8	3.5±0.05	4.9±0.3	0.51	99	Passes
IB9	3.2±0.04	5±0.2	0.84	93.5	Passes
IB10	3.3±0.02	5.1±0.7	0.77	94.8	Passes
IB11	3.7±0.08	5.3±0.4	0.67	95.6	Passes
IB12	3.7±0.02	5.4±0.1	0.75	92.9	Passes
IB13	3.5±0.01	5.5±0.2	0.71	93	Passes

\*All values are mean±SD; SD, Standard deviation

**Floating behaviour**

The tablet from all formulation batches reported satisfactory floatation in a range of 18-300 seconds and remained buoyant for more than 8 h in the dissolution medium with rotation. The data has been presented in table 4. The buoyancy lag time varies with the amount of sodium bicarbonate and citric acid concerned

in the CO<sub>2</sub> formation and the concentration of polymers. Furthermore, the ideal matrix or coating material should be highly porous to dissolution media in order to commence rapid generation of CO<sub>2</sub> and allow the release of CO<sub>2</sub> to initiate floating. In addition, higher water content could lead to greater penetration of the gastric fluid into the tablet leading to faster CO<sub>2</sub> generation, thereby reducing the floating lag time.

Table 4: Floating behaviour of FBTs

Formulation batches/Characteristics	Buoyancy lag-time (sec)*	Duration of floating (hr)
IB1	52±0.9	10
IB2	74±0.4	8
IB3	167±0.5	8
IB4	87±0.3	11
IB5	195±0.2	9
IB6	300±0.7	8
IB7	65±0.1	9
IB8	212±0.5	7
IB9	255±0.4	10
IB10	159±0.3	11
IB11	167±0.6	10
IB12	154±0.5	11
IB13	293±0.8	7

\*All values are mean±SD; SD, Standard deviation

### Swelling behaviours

Swelling index of all FBTs was calculated periodically at 1, 2, 4 and 8 h interval. The formulations containing more concentrations of bioadhesive polymer reported additional swelling compared to other formulations. Further, formulation batches with carbopol 971P revealed extraordinary swelling as compared to other two polymers. Furthermore, formulation batch IB9 reported a consistent

and high swelling behaviour as compared to other formulations. The graph has been presented in fig. 1. The swelling index was increased with respect to the increment of the concentration of polymers.

This might be pertaining to the mobility of the polymer chains, which varies dependent on the water content of the system. In the case of high water content, polymer chain relaxation takes place with volume expansion resulting in marked swelling of the system [6].

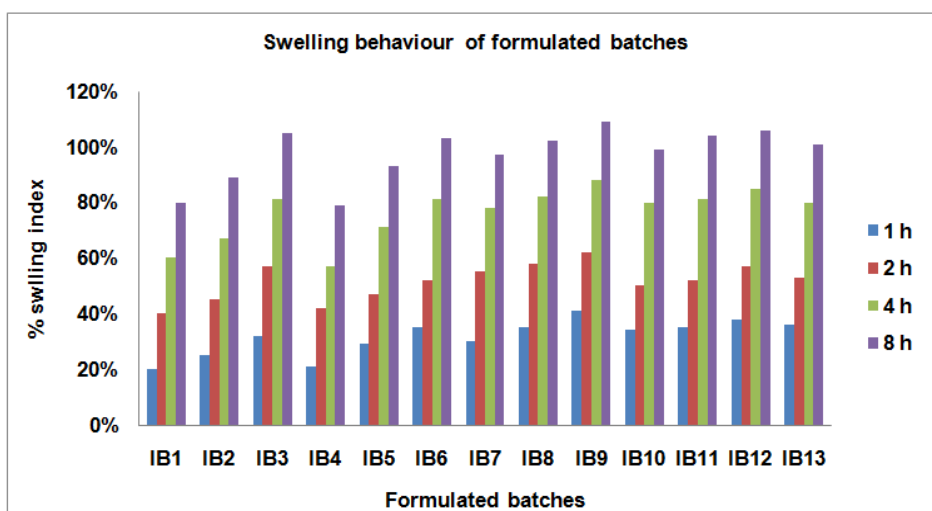


Fig. 1: Swelling behavior of formulated batches

### In vitro bioadhesion strength

The values presented in table 5 indicates that all the tablets had considerable adhesion to the mucosal membrane. The bioadhesive force (mean±SD) reported in a range of 0.05±0.09 to 0.18±0.06 N/m<sup>2</sup>. Formulation batch IB9 reported highest bioadhesion (mean±SD) of 0.18±0.06 N/m<sup>2</sup>. Formulations containing more concentration of bio adhesive polymer pertains increased adhesion in comparison to other formulations.

In addition, a formulation containing carbopol 971P reported extraordinary adhesion than other two polymers. Bioadhesion a surface phenomenon in which a material of natural or synthetic origin adheres or sticks to a biological surface; usually a mucus membrane. Many water-soluble polymers stick to mucosal surfaces as they pull water from the mucus gel layer adhering to the epithelial surface and it has been defined as "adhesion by hydration".

Furthermore various kinds of adhesive force like hydrogen bonding between the adherent polymer and the substrate, which are involved in bioadhesion at the molecular level [6].

### Ex vivo mucoadhesion time

The mucoadhesion residence time was found to be more with batch IB9, IB12 and IB13 (12 h), which contains carbopol 971P, and, a mixture of other three bioadhesive polymers respectively. The data has been represented in table 5.

### In vitro dissolution studies

The release of IM from FBTs varied according to the type and concentration of polymer (fig. 2). Formulation batch IB1, IB2 and IB3 containing HPMC K15M and guar gum in the ratio of 4:1, 3:1, and 2:1 had % cumulative release of 94.12%, 89.78% and 86.45% in 10 h respectively. Similarly formulation batch IB4, IB5 and IB6 containing HPMC K15M and sodium alginate in the ratio of 4:1, 3:1, and 2:1 had % cumulative release of 96.15%, 87.67% and 80.43% in 10 h respectively. Further, formulation batch IB7, IB8 and IB9 containing HPMC K15M and carbopol 971P in the ratio of 4:1, 3:1, and 2:1 had % cumulative release of 98.25%, 92.96% and 89.32% in 10 h respectively. In addition, formulation batches IB10, IB11, IB12, and IB13 containing different ratios of bioadhesive polymers reported a

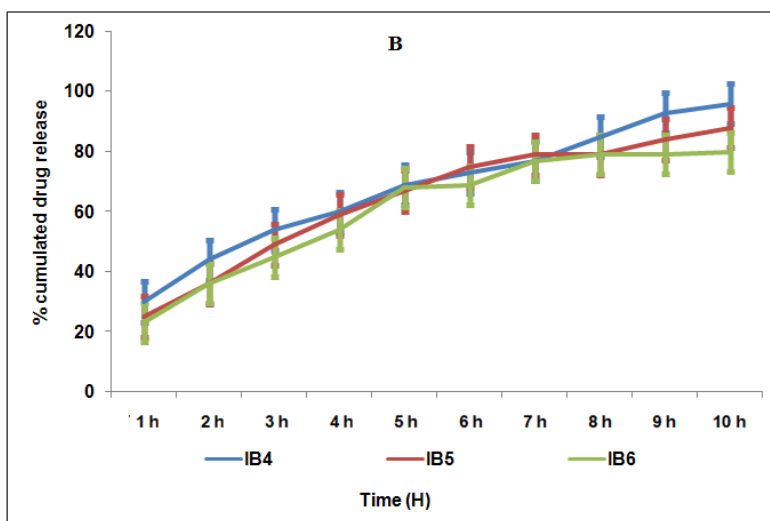
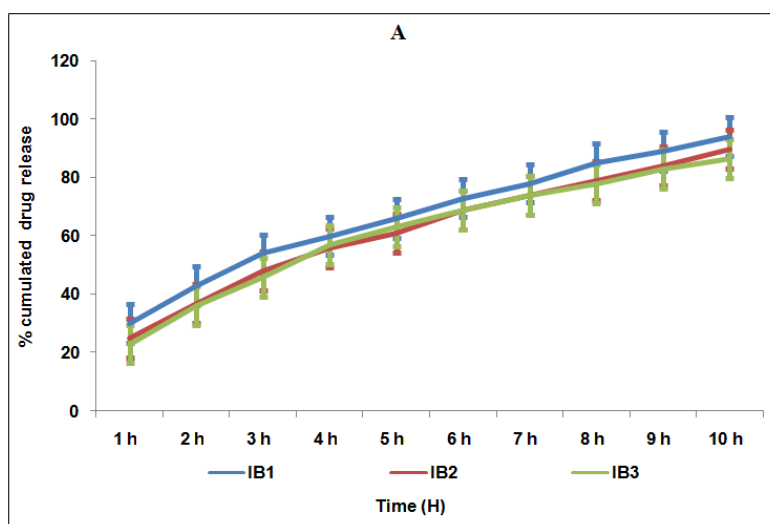
% cumulative release of 94.72%, 96.37%, 97.87% and 98.25% in 10 h respectively. Formulation batches containing carbopol 971P were reported a uniform release pattern. Furthermore, formulation batch IB9, which contained a high concentration of carbopol 971P was helped in abstaining the drug release. The drug is trapped in the glassy core when the table is in the dry state. However, when external surface hydrates, it forms a gelatinous layer like a hydrogel. The hydrogels remain intact and continuously diffuses through the gel layer at a uniform rate. In addition, carbopol 971P is a highly

cross-linked polymer and has a "fuzzball" type of gel structure. It was also observed that the release rate was decreased when the viscosity and concentration of the polymer were increased. The linear relationship was found between the viscosity of the polymer and release rate of the drug from the DDS. Moreover rapid and more swelling of the tablet would lead to an increase in the dimensions of the tablet leading to an increasing in the diffusion pathways and, thus, a reduction in diffusion rate. So, the drug release was found to be high initially and then gradually decreased

Table 5: Adhesion characteristics of FBTs

Formulation batches/Characteristics	<i>In vitro</i> bioadhesion strength (N/m <sup>2</sup> )	<i>Ex vivo</i> mucoadhesion time (hr)
IB1	0.05±0.09	7±0.7
IB2	0.07±0.01	8±0.4
IB3	0.09±0.02	9±0.1
IB4	0.06±0.03	8±0.5
IB5	0.09±0.08	9±0.7
IB6	0.1±0.09	11±0.6
IB7	0.09±0.03	10±0.4
IB8	0.12±0.01	11±0.5
IB9	0.18±0.06	12±0.1
IB10	0.09±0.05	11±0.7
IB11	0.14±0.09	11±0.5
IB12	0.16±0.02	12±0.4
IB13	0.17±0.03	12±0.5

All values are mean±SD; SD, Standard deviation



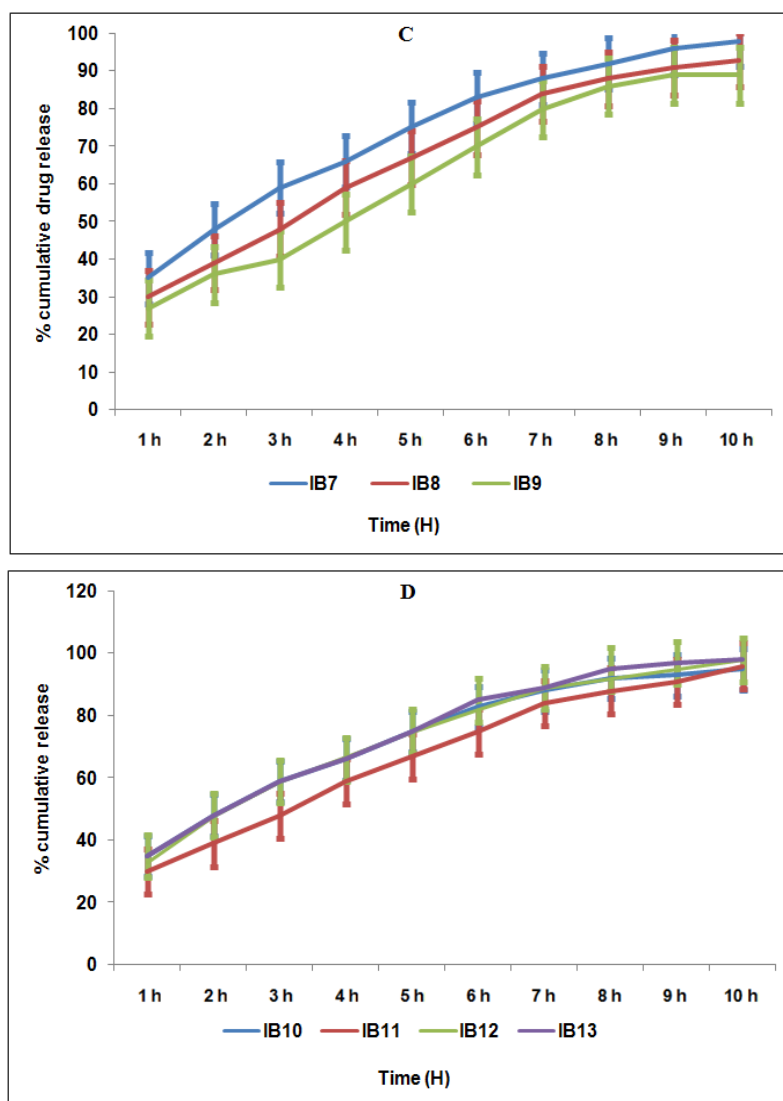


Fig. 2: Dissolution profile of FBTs, (A) formulation batches IB1-IB3, (B) formulation batches IB4-IB6, (C) formulation batches IB7-IB9, (D) formulation batches IB10-IB13

#### Data analysis

The data obtained from *in vitro* dissolution studies were fitted in a different model like zero order, first order, Higuchi and Korsmeyer-Peppas model (table 6). Regression values  $r^2$  were found to be 0.61 to 0.998 for different formulations. Formulation batches IB3, IB7, IB8, and IB12 follows Korsmeyer-Peppas model. This indicates that

the release mechanism is not known or more than one type of release phenomenon could be involved.

However, batch IB1, IB2, IB4, IB5, IB6, IB9, IB10, IB11, and IB13 follows Higuchi Matrix model, which indicates that the drug release is controlled by diffusion of drug through the pores. The mean diffusion exponent value ( $n$ ) was found to be ranged from 0.3076 to 0.6643.

Table 6: Kinetic data of FBTs

Formulation batches	Zero order ( $r^2$ )	First order ( $r^2$ )	Matrix model ( $r^2$ )	Korsmeyer-peppas model ( $r^2$ )
IB1	0.8892	0.9972	0.9994	0.9883
IB2	0.8945	0.9937	0.9988	0.9867
IB3	0.8453	0.9768	0.9876	0.9983
IB4	0.7654	0.9372	0.9965	0.9854
IB5	0.8095	0.9675	0.9982	0.9876
IB6	0.8786	0.9987	0.9983	0.9878
IB7	0.8654	0.9678	0.9884	0.9983
IB8	0.8891	0.9921	0.9882	0.9896
IB9	0.7675	0.8072	0.9982	0.9881
IB10	0.6098	0.9272	0.998	0.9845
IB11	0.8876	0.9923	0.9976	0.9878
IB12	0.8121	0.8978	0.9876	0.9984
IB13	0.8098	0.9976	0.9981	0.9876

**CONCLUSION**

Floating-bioadhesive DDS is an attractive alternative route for administration of drugs that have more bioavailability in upper GIT, or drugs that degraded in intestinal fluids. Tablets from all the formulation batches complied with the specified pharmacopoeia specifications in concern to physical and micromeritics characterization. Formulation batch IB9 reported a considerable swelling index, floating behavior, and more bioadhesive strength with uniform drug release pattern. Furthermore, tablets of formulation batch IB9 follow the Higuchi matrix kinetic model for the pattern of drug release. Therefore formulation batch IB9 was selected as optimized batch and were kept for further evaluation studies.

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**CONFLICT OF INTERESTS**

Declared none

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