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Araştırma

Controlled Release Theophylline Delivery System Based on Bilayer Floating System

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ABSTRACT

INTRODUCTION: Bilayer floating drug delivery system is an approach which helps to overcome the shortcomings of single layered tablets. There is little or no fluctuation of drug in blood stream and tissue, while permitting control over time and site of drug release. In the current study, bilayer theophylline matrix tablets were formulated by double compression and evaluated using granules produced by polymeric granulation and simple coacervation techniques.

METHODS: Bilayer floating theophylline tablets containing an immediate release layer (IRL) and sustained release layer (SRL) were prepared. Granules for the IRL section were produced by wet granulation while that for the SRL section were produced by polymeric granulation and simple coacervation techniques using Eudragit RL100 and Carboxymethylcellulose (CMC) as binder. Resulting granules were characterized for flowability and packing properties. Granules with adequate flow were compressed into flat faced tablets of 12 mm diameter using a single punch tableting machine at arbitrary load of 28 KgF on load scale. Tablets were evaluated for hardness, weight variability, disintegration, friability, swelling index, floating time, and in vitro drug release.

RESULTS: The angle of repose and Hausner ratio were 29.07 ± 0.330 to 40.08 ± 0.660 and 1.07 ± 0.01 to 1.28 ± 0.01 respectively. Tablets hardness values ranged between 4.74 ± 0.36 to 9.84 ± 0.49 KgF, while percentage friability ranged between 0.5 to 1.51%. Floating lag time was between 1 ± 0.41 and 9 ± 0.71 min while the total floating time was between 1 min and 9 h. Over 50 % of drug was released within 7 h.

DISCUSSION AND CONCLUSION: Drug release from the tablets showed prompt release phase and extended release phase. Thus, appropriate combination of Eudragit and CMC and the right reagent can produce well retarded bilayer floating tablets.

Keywords: Eudragit, Carboxymethylcellulose, Bilayer floating tablets, Drug delivery

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INTRODUCTION

Oral route of drug administration is the most versatile, convenient and often employed route. However, fluctuation in drug concentration in the blood stream and tissues with the resulting toxicity are some of the shortcomings associated with conventional oral tablets. Frequent drug administration *vis-à-vis* drug adherence are other problems associated with conventional dosage forms.^{1,2,3} To obviate these shortcomings, controlled release formulations – especially those for oral administration – have been investigated and developed with sole aim of maintaining a constant drug concentration in the blood stream for longer period through slow release of drug into the gastrointestinal tract.⁴ Though the oral route is most preferred for drug administration, studies has demonstrated two physiological influences – short gastric residence time and variable gastric emptying time. Thus, bioavailability and time to achieve maximum plasma concentration cannot be predicted. It must be noted that most drugs are absorbed in the stomach and upper part of the intestine. However, residence time within these regions is short (2 to 3 hours). Hence any methods to prolong the residence time of drugs within these regions will improve bioavailability and therapeutic outcome.^{4,5}

The oral route has received greater attention and successful outcome than any other route in controlled drug delivery system.^{6,7} This is not unconnected with the physiology of the gastrointestinal tract (GIT) which offers better and more flexibility in the design of oral dosage forms compared with other routes.^{8,9,10} The most crucial challenge with oral controlled drug delivery device is not a question of just sustaining the drug release, but also to ensure that the dosage form is sufficiently prolonged within the GIT for complete release from the device. Scientists and the pharmaceutical industries – right from first generation of controlled release (1952 to 1970s) to second generation (1980 to 2010) - have made major break-through in development of oral controlled drug delivery systems by working against the gastrointestinal emptying.¹¹

One of such devices employs the concept of “Gastro Retentive Drug Delivery System (GRDDS)”.^{12,13} Oral dosage forms for GRDDS have received much attention over the years for permitting control over time and site of drug release.^{12,2} Prolongation of gastric retention of drug delivery device has numerous advantages. These include: better absorption, enhanced bioavailability and therapeutic efficacy and possible reduction of dose size.¹⁴

The major principle of GRDDS is prolongation of stay of the dosage form and the release of drug at the absorption site. Many approaches have been adopted, but the most recent is “the floating device”.¹⁵ Floating dosage forms have low bulk density, hence their ability to float in the gastric fluid for a long period of time, thus contributing to improved bioavailability.¹⁶ Floating device can also be improved upon by incorporating a combination of two or more active pharmaceutical ingredients (APIs) in a single dosage form (multi – layered tablets). Multilayer tablets can be used to obviate chemical incompatibilities between APIs through physical separation and also to achieve different drug release profiles - e.g. immediate release and extended release segments.¹⁷ Such approach can be used for formulation of sustained release tablets comprising immediate release outer layer and maintenance inner layer. This has been employed to overcome single layered tablets fluctuation in drug concentration both in the blood stream and site of action.^{18,19} Drugs which are mainly absorbed from the upper part of the gastrointestinal tract such as albuterol, furosemide, theophylline are worthy candidates. Development of these drugs into floating sustained release dosage form help to prolong their limited bioavailability.²⁰

Theophylline has anti-inflammatory property at therapeutic regular dose and as such play an important role in chronic obstructive pulmonary disease, COPD.²¹ Theophylline has narrow therapeutic index (10 – 20 µg/ml), thus the conventional preparations experience fluctuation between maximum and minimum blood concentration resulting in poor therapeutic outcome. On the other hand, patients on regular sustained release preparations may experience delay in onset of drug action since the initial release may not be therapeutics. Thus, in the current study, bilayer theophylline matrix tablets were formulated by double compression using granules produced by polymeric granulation and simple coacervation technique. One layer provides the immediate release component while the second layer provides the sustained release segment.

MATERIALS AND METHODS

Materials: The test drug (theophylline powder) was obtained from Vital Biotic, Nigeria Ltd as free sample.

Excipients and reagents: Absolute ethanol, Citric acid and sodium bicarbonate (Guangdong Guanghua Sci-Tech Co. Ltd, Shantou, Guangdong, China); carboxyl methyl cellulose (CMC) and lactose (Kermel), Normal saline (Unique Pharmaceutical Nigeria Ltd). Acrylic – methacrylic polymer (Eudragit RL100) was received as gift sample from Evonik Industries AG-Werk Röhm, Darmstadt. Amaranth solution (Vinayak Ingredients Pvt Ltd, India); Magnesium stearate, talc and maize starch (Kermel).

Ethical approval: No ethical approval is required in Delta State University for research of this nature since the work does not involve animal studies or clinical trials; however, theophylline is a controlled drug in some countries hence the need for ethical approval. The research work was approved by the Faculty of Basic Medical Sciences Research and Ethics Committee of the Delta State University, Abraka, Nigeria. A scanned copy of the letter is attached and the approval number is REC/FBMS/DELSU/19/45.

Methods: To formulate bilayer floating theophylline tablets, two sets of granules (conventional granules for immediate release segment and a second set of granules for the prolonged release segment) were formulated:

Granules for immediate release layer (IRL): To form the immediate release section, conventional granules were formulated by wet granulation technique (F6, **Table 1.1**). A 1.5 g sample of maize starch powder was weighed and converted to mucilage with boiled water. A sample of theophylline powder (25 g), lactose (18.5 g), maize starch powder (2 g) were weighed and transferred into a clean porcelain mortar. Few drops of amaranth solution (colourant) was added and properly blended. The blend was kneaded with maize starch mucilage to form a damp mass. The wet mass was forced through 1 mm sieve and dried with hot air oven (Lead Engineering, St Helens Merseyside. Model: GP/50/CLAD/100/HYD) at $60 \pm 0.5^\circ\text{C}$ for 24 h. The dried mass was passed through a sieve (710 µm) and characterized by measuring the flow and packing property before storage.

Preparation of granules for sustained release layer (SRL): Granules for SRL were prepared according to the formula in **Table 1.1**. A 5 g sample of Eudragit RL100 (10% w/w) was weighed and dissolved with 30 mL of absolute ethanol. A sample of theophylline powder (20 g) and a 10 g sample of CMC were weighed and transferred to a clean mortar and properly blended. The powder blends were kneaded with the Eudragit – ethanol mixture to form a wet mass. The wet mass was forced through a 1 mm sieve and dried in a hot air oven at $50.0 \pm 1.0^\circ\text{C}$ for 2 h. The dried granules were passed through a 710 µm sieve to form the required granules (batch F1, **Table 1.1**). In other experiments, the quantities of Eudragit and CMC were varied in order to form batches F2, F3 and F5.

Batch F4 was prepared by simple coacervation technique. Here, a 10 g sample (20% w/w) of Eudragit RL100 was weighed and dissolved with 150 mL absolute ethanol. A 20 g sample of theophylline powder was weighed and mixed with the Eudragit– ethanol mixture. Thereafter, 350 ml of normal saline solution (0.9% w/v of sodium chloride) was added, stirred to form coacervates. The coacervates so formed were allowed to settle, filtered and dried in hot air oven at $50.0 \pm 1.0^\circ\text{C}$ for 2 h. The dried mass was passed through a $710\ \mu\text{m}$ sieve to form the required granules. The granules were characterized before storage for further study.

Preformulation studies:

(a) Angle of repose: A 20 g sample of granules was weighed and allowed to flow through a funnel orifice at a height of 7 cm. The height and diameter of cone so formed were measured. The procedure was done in triplicate and the mean value recorded. The angle of repose (θ) was computed from equation (1.1):

$$\tan \theta = \frac{2H}{D} \dots (1.1)$$

Where H and D are height and diameter of powder cone so formed

(b) Densities and compressibility index: A sample of granules (20 g) was weighed and transferred into a 100 ml cylinder of an automated tapped density tester (Model C-TDA2, Campbell Electronics, Mumbai, India). The volumeter was allowed to tap 100 times and the tapped volume recorded. The bulk and tapped densities and the compressibility index computed from equations (1.2), (1.3) and (1.4). The procedure was done in triplicate and the mean values recorded.

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}} \dots (1.2)$$

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Tapped volume of granules}} \dots (1.3)$$

$$\text{Compressibility index (CI)} = \frac{(\text{Tapped} - \text{Bulk})\text{density}}{\text{Tapped density}} * \frac{100}{1} \dots (1.4)$$

(c) Particle size analysis: A sample of granules (50 g) was weighed and transferred into the topmost sieve of a set of sieves arranged in a descending order. The set of sieves was shaken with sieve shaker (Endecott Ltd, UK) for 5 min. The quantity of granules in each sieve was weighed to know the size distribution. The procedure was done in triplicate and mean values recorded.

Compression of granules to tablets: A sample of granules (500 mg) for the sustained release layer was weighed and poured into the die cavity of a single punch tableting machine (Kilian & Co GMBH Kolu-Niel, Type KS 043111-196, Buchschlag-Frank West Germany). A 100 mg sample of granules for the immediate release layer was weighed and transferred to the same die cavity. This was compressed into bilayer tablet at a force of 28 kgF without agitation. The compression force was kept constant and the procedure repeated for all the batches.

Evaluation of tablets:

(i) Percentage weight variability: Twenty (20) were selected at random and the mean weight of each was determined with the aid of analytical balance (Shimadzu Philippines manufacturing Inc.). The percentage weight variability was computed using equation (1.5):

$$Q = \frac{W_m - W_i}{W_m} * \frac{100}{1} \dots (1.5)$$

Where w_m is the mean weight, w_m is the weight of each tablet.

(ii) Tablets tensile strength determination: The diameter (d), thickness (t) and the crushing load (P) of each 10 tablets selected at random were determined using Veeco digital hardness test apparatus. The mean tensile strength of the tablets was determined using equation (1.6)

$$Ts = \frac{2P}{\pi dt} \dots (1.6)$$

(iii) Disintegration test: The method described in the British Pharmacopoeia.²² was employed. Six tablets were selected at random from each batch and a tablet was placed in each of the six baskets of the disintegration apparatus (Manesty Machine, MK4, England). The baskets were immersed in warm distilled water maintained at temperature of $37 \pm 1^\circ\text{C}$. The mean time taken for the tablets to break up and passed completely through the mesh was taken as the disintegration time.

(iv) Tablets friability test: To evaluate the degree of friability of the tablets, ten tablets were picked at random and weighed. The tablets were placed in the drum of a friabilator (Erweka friabilator). The machine was operated at a speed of 25 rpm for 4 min. The tablets were removed from the friabilator, dedusted and reweighed. The difference in the initial and final weights expressed in percentage is taken as the friability.

(v) Dissolution test: This test was carried out using the rotating basket method (USP apparatus one). The dissolution medium is 0.1 N hydrochloric acid (pH 2.3). The apparatus consists of Pyrex glass vessel containing 900 mL of the dissolution medium maintained at $37 \pm 1^\circ\text{C}$ and a cylindrical basket made of stainless-steel wire mesh (aperture size 425 μm). One tablet was placed in the basket which was rotated at a speed of 100 rpm in the dissolution medium. Aliquots (5 mL) were withdrawn at specified time interval and the amount of drug released was determined using UV spectrophotometer (PG Instrument, USA) at a wavelength of 272 nm. Fresh dissolution medium (5 mL) was added each time a sample was withdrawn.

Theophylline analysis (calibration curve): To standardized theophylline release from the various formulations, a standard calibration curve of theophylline was prepared as follows: A sample of theophylline powder (100 mg) was weighed with analytical balanced and dissolved in 100 mL of medium (0.1 N hydrochloric acid) to obtained a solution of 1 mg/mL (i.e. dilution X_1). A 10 mL sample of X_1 was measured and diluted with 0.1 N HCl to 100 mL to obtain a solution of 0.1 mg/mL (X_2). This process of serial dilution continued until solutions of 3, 5, 7, 9, 11, 13, 15 and 17 mcg/mL (or $\mu\text{g/mL}$) were obtained. The absorbances of these standard solutions were measured at a wavelength of 272 nm using UV spectrophotometer. The tests were done in triplicates and mean values recorded. Plots of mean absorbance against concentrations were made and a linear regression coefficient (R^2 values) of 0.9947 obtained. The same procedure was used to compute the amount of theophylline released into the dissolution medium at various time intervals

(vi) Kinetic data analysis: Data obtained from the dissolution study were fitted into three well known release models (equations 1.7, 1.8 and 1.9):

(a) Zero Order: $C = k_0 t \dots (1.7)$

(b) First Order: $\ln C_1 = \ln C_0 + k_1 t \dots (1.8)$

(c) Higuchi Model: $C = k_H t^{1/2} \dots (1.9)$

Where C_0 is the initial amount of drug in the dosage form, C is percentage amount of drug released, and C_1 is percentage of residual drug at time t . K_0 , K_1 , and K_H , are Zero order, First order and Higuchi constants respectively.

(vii) Buoyancy lag time and floating time: A tablet was selected from each batch at random and placed in a 1000 mL beaker containing 900 mL of 0.1 N HCl maintained at $37 \pm 1^\circ\text{C}$. The time required for the tablet to rise to the surface was taken as the buoyancy lag time while the duration of floating on the surface without rupturing was recorded as total floating time determined by visual observation.

(viii) Swelling time: The extent of swelling was measured in terms of percentage weight gained by the tablets. A tablet was selected from each batch, weighed and kept in a beaker containing 900 ml of 0.1 N HCl solution at $37 \pm 1^\circ\text{C}$. The tablet was withdrawn from the beaker at specified time interval (swelling time interval is 2 h); excess HCl was blotted with tissue paper and weighed. Percentage weight gain by the tablet was computed with equation (1.10).

$$Q = \frac{W_s - W_d}{W_d} * \frac{100}{1} \dots (1.10)$$

Where W_s and W_d represent the weight of the swollen tablet and initial weight before swelling respectively.

(ix) Assay procedure (content uniformity): Theophylline assay of the various batches was done according to pharmacopeia method.²³ In this method, 2 tablets from each batch were crushed and 375 mg (equivalent to 240 mg theophylline) was weighed and dissolved in 100 mL of distilled water. A sample (20 mL) of 0.1 M silver nitrate was added and shaken properly for 10 min. The solution so formed was titrated with 0.1 M sodium hydroxide solution using bromothymol blue solution as indicator. Each mL of 0.1 M sodium hydroxide solution is equivalent to 18.02 mg of theophylline.

RESULTS AND DISCUSSION

Packing and flow properties: Results of packing and flow properties such as bulk and tapped densities, Hausner's ratio, Carr's compressibility index (CI), flow rate and angle of repose are shown in **Table 1.2**. The angle of repose for all formulations were within the range of 29.07° to 34.46° except batch F4 (angle of repose is 40.58°) which was prepared by simple coacervation technique. Angle of repose is an indication of powder flowability;²⁴ all formulations except batch F4 had good flow property. Batch F4 exhibited passable (may hang up, flow aid needed) type of flow. Passable flow of batch F4 may be because most of the particles are below $250 \mu\text{m}$ in size (**Figure 1.1**).

"Particles larger than $250 \mu\text{m}$ are usually relatively free flowing but as the size falls below $100 \mu\text{m}$, powders become cohesive and flow problems are likely to occur".²⁵

Compressibility index for all granule formulation varied between 6.33% and 10.45% except for batches F4 and F5. Batch F5 compressibility index value is 12.34% (good flow) while that of batch F4 is 22.15%. These variations could be due to the type and concentrations of binders used. Combination of Eudragit^RRL100 and carboxyl methyl cellulose produced granules with better flow property.

Physicochemical properties of the bilayer floating tablets: The physicochemical properties of the various tablets such as hardness, weight variability, friability and disintegration time are presented in **Table 1.3**. The hardness of the tablets in all batches ranged between 4.74 kgF and 9.84 kgF. The hardness value of the batch which contained only CMC (batch F5) is 6.08 kgF; while batches F1, F2, and F3 has hardness values of 9.84 kgF, 8.04 kgF and 7.14 kgF respectively. The higher the concentration of Eudragit polymer present in these formulations, the greater the hardness. These observations could be due to stronger bonds formed with the hydrophobic polymer (Eudragit). Other researchers reported similar findings when compacts formed with methacrylic polymers (Eudragit L100-55 and Eudragit L100) were compared with

that formed with hydroxyl propyl methyl cellulose, HPMC. Tatavarti *et al*²⁶, 2008 and Naveen *et al*²⁷, 2009 observed weaker compact formation with HPMC than with methacrylic polymers. The friability percentage ranged between 0.5% and 1.04% except batch F5 with friability percentage of 1.51%. Thus, most tablets met pharmacopeia requirement for uncoated tablets. The results showed the ability of tablets to withstand some reasonable levels of abrasion during handling and transportation except batch F5 which contained hydrophilic polymer (CMC) only.

Floating and swelling properties of tablets: The floating lag time and floating time of the various tablets are shown in **Table 1.4**, while swelling indices are shown in **Figure 1.2**. Floating lag time for batches F1 to F5 were within 49 min. Batch F4 prepared by coacervation technique floated within 1 min but disintegrated immediately and lost its integrity. This may be due to insufficient binder (batch F4 has lowest concentration of CMC). Batch F5 which contained only CMC had the lowest floating lag time. The results showed variation in floating lag time with different polymer ratio used. Of all the formulations that contains both Eudragit and CMC, batch F1 which contained Eudragit and CMC in ratio 1:2 has the lowest floating time while batch F3 with Eudragit to CMC ratio of 1:1 has the highest floating lag time. The total floating time for batch F3 was 3 h while batches F1, F2 and F5 floated for more than 8 h.

It was observed from this study that floating lag time and total floating time were function of both hydrophilic (CMC) and hydrophobic (Eudragit) polymers present. The higher the concentration of hydrophilic polymer, the lower the floating lag time (see batch F5). Also, the higher the concentration of hydrophobic polymer, the higher the floating lag time (see batch F3).

Content uniformity: The assay results ranged from 96.82% to 102.12% as shown in **Table 1.3**. Controlled released theophylline bilayer floating tablets contain not less than 90.0 percent and not more than 110.0 per cent of the labeled amount of theophylline²⁸. From the result obtained (96.82 – 102.12 %) as shown on **Table 1.3**, the bilayer floating tablets from all the formulations passed the drug content test. It is important for the tablets to have uniform content of the active ingredients, as this would guarantee the therapeutic effectiveness of all the tablets produced.

In-vitro drug release profiles: **Figure 1.3** showed the dissolution profiles of the various batches. Two distinct phases of release were observed in batches F1, F2, F3 and F4 – one for the immediate release layer and the other for the controlled release layer. All formulated bilayer tablets showed controlled release of drug over 8 h while batch F6 (conventional tablets) released entire drug content within 2 h. Maximum percentage drug release by batches F1, F2, F3 and F5 are 75%, 70%, 80% and 73% respectively. Batch F2 which contain Eudragit and CMC in ratio 1:5 was better prolonged than any other batch (see **Figure 1.3**). **Table 1.5** illustrates the values of the release rate constants (K) and the regression coefficients (R^2) for each model for the six (6) batches of tablets in 0.1 N HCl using basket at 100 rpm. Research has shown that the model that best fit the release data should be the one with highest R^2 values when analyzed for Zero Order, First Order and Higuchi model.²⁹ Higuchi equation was found to have the highest R^2 , thus release of theophylline from the various matrix tablets is by drug diffusion.

CONCLUSION

Bilayer floating tablets of theophylline was the focus of this research. This is an approach to achieve *in vitro* immediate release, buoyancy and prolonged release. The various sets of granules had good flow property; combination of Eudragit RL100 and carboxyl methyl cellulose produced granules with better flow property. The presence of gel forming polymers (CMC and Eudragit RL100) and gas producing agent (sodium bicarbonate) help to achieve prolonged release. Citric acid help to promote buoyancy under elevated pH of the stomach thus enhancing drug release. Prolonged floating time and lesser floating lag time could be achieved by appropriate

combination of CMC and Eudragit. The ratio of Eudragit and CMC affect drug release rate and mechanism of release. The *in vitro* drug release profiles obtained with combination of Eudragit and CMC in ratio 1:2 (F1) produced prolonged floating duration (>8 h) and lesser floating lag time (20 min), an attribute of controlled released product. Thus, appropriate combination of hydrophobic and hydrophilic polymers can produce well retarded bilayer floating tablets.

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3Table 1.1: Composition of sustained release layer of bilayer theophylline floating tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Theophylline	200.0	200.0	200.0	200.0	200.0	200.0
Eudragit RL100	50.0	25.0	75.0	100.0	-	-
Carboxyl methyl cellulose	100.0	125.0	75.0	50.0	150.0	-
Sodium bicarbonate	93.4	93.4	93.4	93.4	93.4	-
Citric acid	46.6	46.6	46.6	46.6	46.6	-
Amaranth solution	-	-	-	-	-	qs
Magnesium stearate	5.0	5.0	5.0	5.0	5.0	5.0
Talc	5.0	5.0	5.0	5.0	5.0	5.0

Maize starch (4%)	-	-	-	-	-	20.0
Maize starch (6%)	-	-	-	-	-	30.0
Lactose	-	-	-	-	-	240.0
Total	500.0	500.0	500.0	500.0	500.0	500.0

Table 1.2: Flow and packing properties of the various granules.

	Flow rate (g/sec)	Bulk den- sity (g/ml)	Tapped den- sity(g/ml)	Hausner's ratio	Compressibi- lity index (%)	Angle of repose (°)
IRL	2.21±0.01	0.57±0.01	0.62±0.01	1.07±0.02	7.59±0.85	32.77±0.13
F1	1.72±0.04	0.55±0.01	0.58±0.01	1.07±0.01	6.33±1.08	30.28±0.13
F2	1.91±0.02	0.46±0.01	0.50±0.01	1.08±0.00	7.26±0.32	29.07±0.33
F3	1.71±0.04	0.51±0.00	0.55±0.01	1.08±0.01	7.42±1.03	34.46±0.28
F4	-	0.41±0.00	0.53±0.00	1.28±0.01	22.15±0.87	40.58±0.66
F5	1.69±0.01	0.52±0.01	0.59±0.01	1.14±0.01	12.34±1.1	29.25±0.50
F6	2.07±0.03	0.51±0.00	0.57±0.00	1.12±0.01	10.5±0.69	33.12±0.37

Table 1.3: Post compression property of various theophylline tablets

Batch Code	Thickness (mm)	Diameter (mm)	Hardness (Kgf)	Weight Var- iation (%)	Friability (%)	Drug Con- tent (%)
F1	3.79 ± 0.09	12.36 ± 0.10	9.84 ± 0.49	0.40 ± 0.95	0.67 ± 0.04	101.00 ± 0.82
F2	3.96 ± 0.18	12.46 ± 0.14	8.04 ± 0.63	0.05 ± 1.18	0.97 ± 0.01	100.13 ± 0.07
F3	4.00 ± 0.05	12.51 ± 0.06	7.14 ± 0.31	0.23 ± 0.93	0.60 ± 0.00	099.44 ± 0.04
F4	4.26 ± 0.07	12.86 ± 0.13	4.74 ± 0.36	0.01 ± 1.01	1.04 ± 0.03	096.82 ± 0.62
F5	4.07 ± 0.11	12.51 ± 0.07	6.08 ± 0.54	0.32 ± 1.11	1.51 ± 0.01	099.03 ± 0.02
F6	3.82 ± 0.10	12.28 ± 0.05	6.89 ± 0.18	0.14 ± 1.03	0.50 ± 0.02	102.12 ± 0.01

Table 1.4: Floating ability of various bilayer tablet formulations

Batches	Floating Lag time Mean ± SD (min)	Total floating time Mean ± SD (h)
F1	20 ± 1.08	>8 ± 0.01
F2	33 ± 1.47	>8 ± 0.07
F3	49 ± 0.71	3 ± 0.01
F4	1 ± 0.41	0.017 ± 0.001
F5	18 ± 1.25	>8 ± 0.06

Table 1.5: Kinetic of theophylline release from the different formulations

Batches	Zero order		First order		Higuchi model	
	R ²	K ₀	R ²	K ₁	R ²	K _H
F1	0.9328	0.1353	0.9214	0.0010	0.9329	3.1328
F2	0.9139	0.1202	0.9180	0.0008	0.9534	2.8445
F3	0.8974	0.1295	0.8406	0.0010	0.9203	3.0366
F5	0.9112	0.1234	0.8977	0.0009	0.9448	2.9102
F6	0.9018	0.8372	0.5342	0.0173	0.8720	8.4363

Figure 1.1: Particle size distribution of various formulations: 500 μm [●], 425 μm [●], 180 μm [●], 150 μm [●], 125 μm [●], <125 μm [●]

Fig 1.2: Swelling index of batches F1 (●), F2 (●), F3 (●) and F5 (●)

Figure 1.3: Dissolution profiles of the various formulations: F1(- - - ■ - - -), F2(—□—), F3 (—▲—), F5 (—x—), F6(—●—)