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Research Article

A Research on Comparative Study of Floating Tablets of Theophylline Utilizing Different Techniques

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Abstract

The primary intention of the present work is to fabricate the floating tablets of theophylline employing various methodologies of formulation and to execute the comparative study between the formulations developed by different techniques. Theophylline when used in a lower concentration act as an anti-inflammatory drug, when developed as a floating tablet it reduces the frequency of drug administration as it remains buoyant in the gastric contents and release the drug at a pre-determined rate. Different methods are utilized for the formulation of the floating tablets with an intention to prolong gastric residence time and reduction in inconstancy of the drug. Theophylline, a xanthine derivative bronchodilator is used as a model drug and three different techniques were accustomed *viz*, direct compression effervescent technique, non-aqueous wet granulation technique and solvent evaporation technique. Sodium bicarbonate and tartaric acid were used as gas generating agent whereas HPMC 15cps and sodium alginate as polymers. Twelve formulations were fabricated using three techniques, i.e. four formulations of each technique. All the prepared formulations were evaluated as prescribed by the Pharmacopoeial monograph for tablets. The optimized formulation DF2 showed a drug release of 70.225±0.888 at the end of 8 hours with a floating lag time of 08.4 sec and remains buoyant for more than 8 hours. Among the three different techniques, direct compression effervescence technique can be successfully employed for the development of floating tablets of Theophylline. The obtained data were subjected only for descriptive analysis.

Keywords: Theophylline; Direct compression effervescent technique; Non-aqueous wet granulation technique; Solvent evaporation technique

Abbreviations

FDDS – Floating Drug Delivery Systems.
GRDF – Gastroretentive Dosage Form.
COPD – Chronic Obstructive Pulmonary Disease.
GIT – Gastro-intestinal Tract.
HPMC – Hydroxypropyl Methyl Cellulose.
EC – Ethyl Cellulose.
FLT – Floating Lag Time.
TFT – Total Floating Time.
HCl – Hydrochloric Acid.
SR – Sustained Release.
LBD – Loose Bulk Density.
TBD – Tapped Bulk Density.

Introduction

Oral route of drug administration has been the most feasible and preferred route of drug administration. Despite of so much advantageous, researches has been conducted with a purpose to enhance the drug delivery over an extended period of time along with well controlled release profile. Conventional SR dosage forms were unable to extend their duration in stomach which ultimately leads to fluctuations in plasma drug concentration level [1]. To overcome such obstacles it is worth to attain a prolonged gastric residence time by the drug delivery. Gastroretention leads to increment in bioavailability, expansion of the duration of drug release, minimizes drug waste and enhance the drug solubility that are less soluble in a high pH environment. Different methods used with the intention of prolongation of gastric residence time includes floating drug delivery system, swelling and expanding system, polymeric bio-adhesive system, high density system and other delayed gastric emptying system [2].

FDDS is considerably easy and logical approach in the development of GRDF from the formulation and technological point of view. FDDS is the form of gastro-retentive drug delivery system that controls the kinetic release rate of a drug to a specific site for its pharmacological action. FDDS are low density systems thatreleases its component at desired rate when floats over the gastric contents which contribute in increased gastro retention time and reduced fluctuation. After release of drug, the residual system is emptied from the stomach [3, 4]. Theophylline (3, 7-Dihydro-1, 3-dimethylpurine-2, 6(1H)-dione; 1, 3-Dimethylxanthine), a xanthine derivative bronchodilator, is used in treatment of asthmatic attacks as well as in the management of COPD. Theophylline has a short half life and should be administered frequently when is subjected for orally administered dosage forms. But when formulated as GRDF, it provides desirable serum concentrations for prolongedperiods without frequent dosing. Nayak AK et al. (2011) fabricated a HBS single unit capsule for theophylline delivery by physical blending which showed buoyancy in the gastric juice for a longer period of time and concluded that the formulation might improve the oral bioavailability of Theophylline [5].

Therefore, in the present study it was aimed to design gastroretentive floating tablets of Theophylline by using various polymers and different technique as well as to perform a comparative study between the techniques utilized to find out the suitable technique for better FDDS formulation.

Materials and Methods

Materials

The following materials of pharma grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer. Distilled water was used in all the experiments.

Sl. No.	*Materials Used*	*Manufacturers*
1	Theophylline	Yarrow Chem Products
2	Sodium Alginate	Himedia Laboratories Pvt. Ltd.
3	HPMC 15cps	The Himalaya Drug Company
4	Sodium Bicarbonate	Sd Fine Chem. Limited (Mumbai)
5	Tartaric Acid	Thermo Fisher Scientific India Pvt. Ltd.
6	Magnesium Stearate	Signet Chemical Corp. Pvt. Ltd.
7	Lactose	Thermo Fisher Scientific India Pvt. Ltd.
8	Beeswax	Karnataka Fine Chem
9	Acetone	Karnataka Fine Chem
10	Ethyl Cellulose	Indian Fine Chemicals

Table 1: List of Materials and Chemicals used.

Equipment Used

Instruments employed for the preparation of floating tablets of theophylline are listed along with their model/manufacturer in the following table:

Sl. No.	*Equipment*	*Model/Manufacturer*
1	Electronic Analytical Balance	Sartorius
2	Bulk Density Apparatus	Singhla Lab
3	FT-IR Spectrophotometer	Jasco, FT-IR 460 Plus
4	UV-Visible Spectrophotometer	UV-117 / Systronics
5	Single head rotary tablet compression machine	Cadmach
6	Tablet Hardness Tester	Monsanto
7	Vernier Caliper	Mitutoyo, SXR629
8	Roche Friabilator	Electro Lab
9	USP Dissolution Apparatus	DS 8000 / Lab India
10	Stability Chamber	Thermolab

Table 2: List of Equipment.

Methods [6-10]

Direct Compression Technique: (DF1-DF4)

All the ingredients (Table No. 3) used in the formulation are passed through sieve # 40 before mixing. The weighed quantity of Theophylline and other ingredients except magnesium stearate were transferred to a mortar and triturated for thorough mixing. The mixture was passed through sieve #40 and was collected in a plastic bag and mixed for 3 minutes. Magnesium stearate is added to the mixture and mixed for another 2 minutes. Finally, the mixture was compressed into tablets of 350 mg ± 5% each using 10 mm punch in single head rotatory tablet compression machine.

Non-aqueous Wet Granulation Technique: (WF1-WF4)

The required quantity of bees wax was weighed and melted in a large china dish over a water bath. To the molten mass Theophylline was added and mixed properly. In the china dish previously weighed quantities of other ingredients except magnesium stearate was added and mixed well. The china dish was removed from water bath and allowed to cool. Coherent mass thus formed was then scrapped from china dish and passed through sieve #60. Thus, formed granules were lubricated with magnesium stearate and passed through sieve #100 followed by compression of tablets of 350 mg ± 5% each using 10 mm punch.

Solvent Evaporation Technique: (SF1-SF4)

All the required ingredients are weighed individually. Theophylline and polymers are passed through sieve # 40 and placed in a china dish. The required volume of solvent (Acetone) is added to the china dish in such a way that the capacity of the continuous phase is insufficient to dissolve the entire volume of disperse phase solvent. With the help of a glass rod, the components of china dish are stirred continuously. After the evaporation of solvent, the obtained mass is scrapped off from the china dish and passed through sieve # 60. Thus formed granules were lubricated with magnesium stearate and passed through sieve # 100 followed by compression of tablets of 350 mg ± 5% each using 10 mm punch.

Ingredients (mg/ tablet)	*DF1*	*DF2*	*DF3*	*DF4*	*WF1*	*WF2*	*WF3*	*WF4*	*SF1*	*SF2*	*SF3*	*SF4*
Theophylline	100	100	100	100	100	100	100	100	100	100	100	100
HPMC 15cps	100	75	50	25	100	75	50	25	100	75	50	25
Sodium Alginate	15	30	45	60	15	30	45	60	15	30	45	60
Sodium Bicarbonate	40	40	40	40	40	40	40	40	40	40	40	40
Tartaric Acid	15	15	15	15	15	15	15	15	15	15	15	15
Ethyl Cellulose	20	20	20	20	20	20	20	20	20	20	20	20
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Beeswax	-	-	-	-	20	20	20	20	-	-	-	-
Acetone (in ml)	-	-	-	-	-	-	-	-	5	5	5	5
Lactose	56.5	66.5	76.5	86.5	36.5	46.5	56.5	66.5	56.5	66.5	76.5	86.5
Total	350	350	350	350	350	350	350	350	350	350	350	350

Table 3: Formulation codes for floating tablets of Theophylline by various methodologies.

Pre-compression studies [11-14]

Fourier Transform Infrared (FT-IR) studies

FT – IR studies of formulation along with pure drug was carried out at room temperature by FT-IR spectrophotometer using KBr pellet. All the spectra were recorded in the range of 400-4000cm^{-1}.

Bulk Density and Tapped Density

An accurately weighed quantity of powders and/or granules (W) was carefully poured into the graduated cylinder and the volume (V_0) was measured then the graduated cylinder was closed with lid, set into bulk density apparatus which was set for 50 taps. After completion of 50 taps, the volume (V_f) was measured and continued until the two consecutive readings are equal. The bulk density and tapped density was calculated using the following formula:

$$\text{Bulk Density} = W / V_0$$

$$\text{Tapped Density} = W / V_f$$

Where, V_0 = Initial volume

V_f = Final Volume

Compressibility Index and Hausner's Ratio

The compressibility index and Hausner's ratio was calculated using measured values for bulk density (ρ bulk) and tapped density (ρ tapped) as follows:

$$\text{Compressibility index (\%)} = (TBD-LBD)/TBD \times 100\%$$

$$\text{Hausner's ratio} = TBD/LBD$$

Where, TBD = Tapped bulk density

LBD = Loose bulk density

Carr's Index (%)	*Flow character*	*Hausner's ratio*
≤10	Excellent	1.0-1.11
Nov-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

Table 4: Effect of Carr's Index and Hausner's ratio on flow properties.

Angle of Repose

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The angle of repose of blended granule was determined by the funnel method. Accurately weighed granules blend was passed through a funnel that is fixed in such a way that it just touches the apex of the blend. The blend was allowed to flow through the funnel freely on to the surface. The diameter of the granule cone was measured and the angle of repose was calculated using the equation:

$$\theta = \tan\text{-}1\ h/r$$

where,
θ = Angle of repose
h = height of the pile
r = radius of the base of the pile

Angle of Repose (θ)	*Type of flow*
< 20	Excellent
20-30	Good
30-34	Passable
> 35	Very poor

Table 5: Effect of Angle of Repose (θ) on Flow property.

Post -compression studies [15-20]

Shape and Appearance

The formulated tablets were visually observed for its shape and color.

Uniformity of thickness

Thickness and diameter of the tablets were measured using a Vernier Caliper. Three tablets of each formulation were picked randomly and the dimension of each three tablets were measured in mm. This was done in triplicate and standard deviation was calculated. The tablet thickness was controlled within a ± 5% variation of the standard.

Weight Variation Test

The weight variation test was carried out in order to verify the uniformity of the weight of tablets in each formulation. Twenty tablets were selected randomly and weighed individually to check for the weight variation. The following percentage deviation in weight was allowed as shown in the table 6.

Average weight of a tablet	*Percentage deviation (%)*
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

Table 6: Limits for weight variation (U.S.P).

Friability of Tablets

The friability of the tablets was determined for ten tablets taken randomly from each formulation. After weighing, the tablets were placed in the plastic chamber of friability test apparatus. The friability was evaluated by the following formula:

$$F = (W1-W2)/W1 \times 100$$

Where,
W1 = Weight of the tablets before testing.
W2 = Weight of the tablets after testing.
% Friability of the tablets less than 1% is considered acceptable.

Hardness of the Tablets

The crushing strength of prepared tablets of Theophylline was determined using Monsanto tablet hardness tester.

Swelling Index

The swelling index of different formulations was calculated by the following formula:

$$SI = M_t - M_o / M_o \times 100$$

Where SI = swelling index,
M_t = weight of tablet at time 't',
M_o = weight of tablet at time t=0.

Drug content Uniformity

From each batch 10 tablets were taken and finely powdered. A weight equivalent to 100 mg of theophylline was accurately weighed and dissolved in 100 ml of 0.1 N HCl (I). The drug was allowed to dissolve in the solvent, the solution was filtered and 1 ml of the filtrate was suitably diluted to 10 ml with the same buffer (II). Again, from the II stock solution 1 ml was pipetted out and diluted to 10 ml with 0.1 N HCl and analyzed spectrophotometrically at 272 nm. The amount of Theophylline was estimated using standard calibration curve of the drug. The study was carried out in triplicate for each batch of formulation.

Floating tablet of should contain not less than 95.0% and not more than 105.0% of the labeled amount of Theophylline.

In-vitro buoyancy test

The duration for which the formulation floats in the dissolution medium in the upper one-third of dissolution vessel (USP apparatus II, paddle type), was visually observed periodically after 15 min following Fig. a and b shows the effervescence produced on tablet surface as soon as it is placed in dissolution medium. The time between introduction of the dosage form and its buoyancy on the 0.1 N HCl (lag time) and the time during which the dosage form remains buoyant (total buoyancy time) were determined visually. Three replicates of each formula were performed.

In-vitro Drug Release Study

The release characteristics of floating tablets were studied in triplicate using a dissolution apparatus type II, paddle type with a stirring speed of 50 rpm at 37±0.50C in 900ml of simulated gastric fluid (pH 1.2; 0.1N HCl solution) for 8 hrs. Accurately 1ml sample of

dissolution medium was withdrawn from the vessel at 1 hour interval and the withdrawn sample was replaced with equal amount of fresh dissolution medium. The sample was filtered and diluted to a suitable concentration. The concentration of Theophylline released as a function of time was determined at 272 nm with the help of UV spectrophotometer.

Release Kinetics

To analyze the mechanism for the drug release and the release rate kinetics of the dosage form, the data obtained was fitted into Zero order, First order, Higuchi's, and Korsmeyer-Peppas. By comparing the R2 values obtained from this, the best-fit model was selected. The data conversion into descriptive analysis furnishes perceptive information about the obtained data.

Stability Studies

The selected formulation was tested for its stability studies. Short-term stability studies were performed at temperature 40±2°C over a period of 3 months. 5 tablets were packed in amber colored screw capped bottle and kept in stability chamber maintained at 40±2°C. Samples were taken at 1 month interval for their drug content estimation including physical parameters. At the end of 3 months period, dissolution test was performed to determine the drug release profile.

Results and Discussion

Characterization of Drug

The obtained API sample was observed for various organoleptic characters which can be illustrated in the table below along with the inferences.

S. No.	*Parameters*	*Reported*	*Inferences*
1	Nature	Crystalline powder	Crystalline powder
2	Color	White	White
3	Melting point	273.5°C	274°C
4	Odor	Odorless	Odorless
5	Taste	Bitter	Bitter

Table 7: Organoleptic Properties of Theophylline.

Standard calibration plot of Theophylline

The λmax of Theophylline in 0.1 N HCl was found to be 272 nm. The absorbance values are tabulated in the table no. 8. Theophylline obeyed Beer Lamberts law in the concentration range of 0-14 µg/ml with good correlation coefficient 0.9947 indicating good linearity in the concentration range.

Concentration (µg/ml)	*Absorbance*
0	0.00
2	0.145
4	0.210
6	0.298
8	0.395
10	0.527
12	0.619
14	0.696

Table 8: Data for Calibration Curve of Theophylline in 0.1 N HCl at 272 nm.

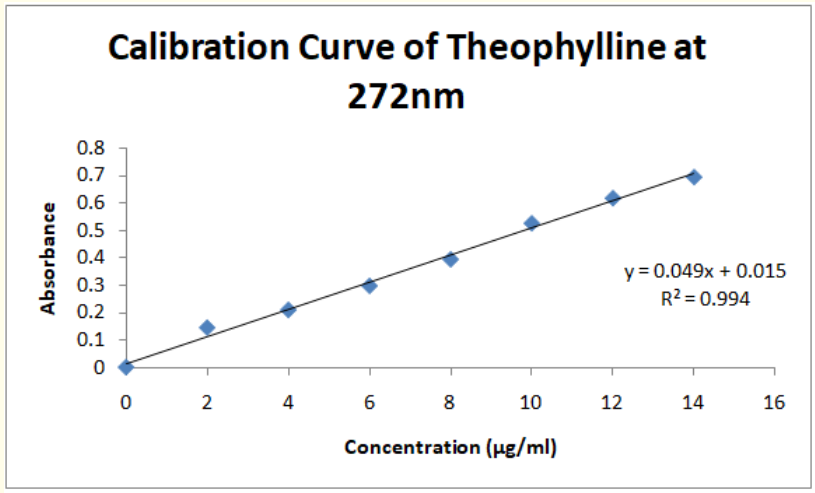


Figure 1: Standard Calibration Curve of Theophylline in 0.1 N HCl at 272 nm.

Pre-compression evaluation

The powder blend of API with the excipients was subjected for various pre-compression parameters like bulk density, tapped density, Carr's index, Hausner's ratio and Angle of repose. The obtained data are shown in table no. 9.

Sl. No.	*Formulation Code*	*Loose Bulk Density (g/ml)*	*Tapped Bulk Density (g/ml)*	*Compressibility Index*	*Hausner's Ratio*	*Angle of Repose(θ)*
1	DF1	0.384 ± 0.12	0.431 ±0.22	10.90 ±0.33	1.12 ±0.08	27.33 ± 0.86
2	DF2	0.416 ±0.08	0.479 ±0.18	13.15 ±0.37	1.15 ±0.06	26.87 ±0.5
3	DF3	0.434 ±0.09	0.489 ±0.15	11.24 ±0.41	1.12 ±0.10	27.84 ±0.74
4	DF4	0.446 ±0.11	0.501 ±0.09	10.97 ±0.35	1.12 ±0.17	27.14 ±0.32
5	WF1	0.377 ±0.18	0.419 ±0.11	10.26 ±0.39	1.11 ±0.11	26.64 ±0.5
6	WF2	0.386 ±0.07	0.442 ±0.20	12.66 ±0.45	1.14 ±0.14	26.38 ±0.98
7	WF3	0.403 ±0.11	0.454 ±0.18	11.23 ±0.47	1.12 ±0.18	27.54 ±1.03
8	WF4	0.429 ±0.15	0.482 ±0.20	10.99 ±0.33	1.12 ±0.18	26.12 ±0.94
9	SF1	0.394 ±0.18	0.438 ±0.12	10.04 ± 0.44	1.11 ±0.12	23.89 ±1.15
10	SF2	0.416 ±0.12	0.466 ±0.20	10.72 ±0.37	1.12 ±0.07	24.49 ±0.45
11	SF3	0.428 ±0.11	0.491 ±0.22	12.83 ±0.49	1.14 ±0.09	24.81 ±0.84
12	SF4	0.437 ±0.08	0.503 ±0.15	13.12 ±0.38	1.15 ±0.19	23.46 ±1.05

Table 9: Data for Pre-compression of powder blend.

As observed LBD ranges from 0.377 ±0.18 to 0.446 ±0.11 and TBD ranges from 0.419 ±0.11 to 0.503 ±0.15; compressibility index ranged from 10.04 ± 0.44 to 13.15 ±0.37 and Hausner's ratio ranged from 1.11 ±0.11 to 1.15 ±0.19. These results are in agreement with the desired value of compressibility index and Hausner's ratio for a formulation. Hence all the formulations studied exhibited good compressibility index.the angle of repose of pre-compressed powders of Theophylline was in the range 23.46 ±1.05 to 27.84 ±0.74, indicating that the studied granules have excellent flow properties because for a formulation to have good flow properties, θ should be ≤ 30°.

Post-compression Evaluation

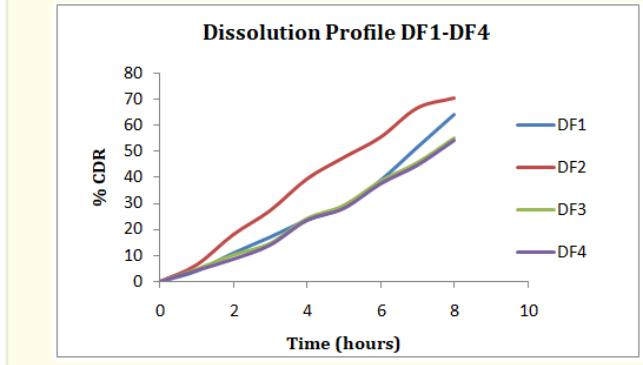
The floating tablets of theophylline were prepared using various techniques. The formulated tablets were evaluated for physical characteristics viz. hardness, friability, weight variation, swelling index, floating properties and these parameters were found to be within ranges as referred by the IP.

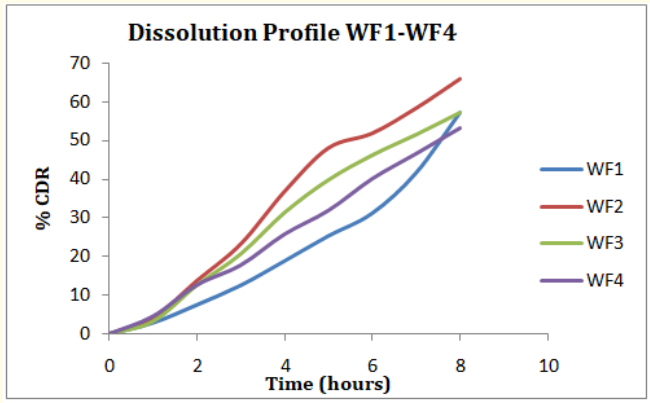
Formulation Code	*Hardness (Kg/ cm²)*	*Friability (%)*	*Weight Variation (mg)*	*Floating Lag Time (sec)*	*Cumulative % drug release*
DF1	3.5	0.13	350.54	17.5	64.002
DF2	4	0.12	348.05	16.4	70.225
DF3	4	0.14	349.87	14.7	55.096
DF4	3.5	0.16	349.59	13.3	54.083
WF1	3.5	0.22	349.98	15.7	57.157
WF2	4	0.24	350.35	21.3	65.804
WF3	4	0.17	349.75	25.2	57.118
WF4	4	0.19	350.15	28.6	53.038
SF1	3.5	0.24	350.02	30.8	54.295
SF2	4	0.20	351.91	32.6	51.379
SF3	4	0.15	349.51	39.4	50.650
SF4	3.5	0.25	349.68	41.7	51.688

Table 10: Post Compression Parameters for formulated tablets.

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. All the tablets passed the weight variation test as the % weight variation was within the Pharmacopoeial limits of ± 5% of the weight. The floating lag time of all the formulations was found to be less than a minute. The measured hardness of tablets of each formulation ranged between 3.5-4 Kg/cm^2.

The data obtained from in-vitro dissolution studies were fitted to mathematical model viz. Zero order, first order and Higuchi model and the coefficients of regression value were compared. It was observed that most of the formulations followed zero order models as the coefficient of regression value was nearer to one. After, the data was subjected to Korsmeyer-Peppas equation for determination of release mechanism the acceptable linearity was observed for all the developed formulation. The release co-efficient "n" varied from 0.771 to 1.457 that indicates both non-fickian and super case – II transport of a drug from polymer i.e., drug release follows both diffusion and relaxation of polymer chain. Figure 2 represents the dissolution profile of various formulations prepared by various technique.





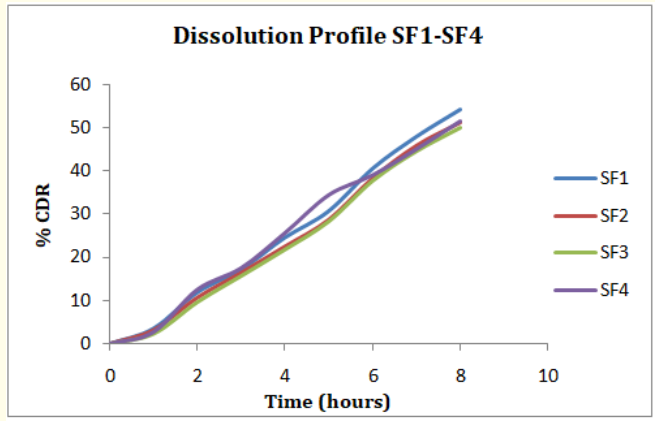


Figure 2: Dissolution Profile of various formulations.

Conclusion

The drugs with narrow absorption window in a unique pharmaceutical dosage form with gastroretentive properties would enable an extended absorption phase of these drugs. After oral administration, such dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract.

Theophylline is incompletely absorbed from GIT with an absorption window confined to upper part of GIT. Therefore, there was a need to develop floating tablets of Theophylline to increase the gastric residence time and hence increase the absorption of drug. Floating tablets of Theophylline were successfully prepared by direct compression, non-aqueous wet granulation and solvent evaporation technique using different concentration of polymers with an approach to increase the gastric residence time and thereby improve drug bioavailability and half-life.

All the formulations were within the standard Pharmacopoeial limits. The optimized formulation was selected DF2 which showed a floating lag time of 8 seconds and remain buoyant for more than 8 hours and showed the best result in friability which concluded that the formulation would be easy to handle and transport. The *in-vitro* drug release of DF2 showed that 70% drug is released at the end of 8 hours which indicate that the frequent dosing would not be required as it remains buoyant in the gastric contents and

release the drug at a pre-determined rate. Dissolution studies were performed in simulated gastric fluid. DF2 showed maximum drug release as compared to the other formulations. The present work can be investigated further to assess the long-term stability study of Theophylline floating tablets, determination of gastric residence time using Gamma scintigraphy, in-vivo evaluation of Theophylline tablets and establishment of in-vitro and in-vivo co-relation. The obtained data were subjected for descriptive analysis only for ease of interpretation and in future can be further studied for statistical significance.

Hence it can be concluded that all the above mentioned three methods can be utilized for the formulation of floating tablets of theophylline. Among the three different technique, Direct compression effervescent technique can be successfully employed for the development of floating tablets of Theophylline.

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