WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.647
Volume 6, Issue 6, 830-841 Research Article ISSN 2278 – 4357

FORMULATION, DEVELOPMENT AND EVALUATION OF 'PENTOXIFYLLINE, FLOATING TABLET

Pradip S. Patil* S.A. Tadavi, V.H. Jain and Dr. S.P. Pawar

Department of Pharmaceutics, P.S.G.V.P. Mandal's College of Pharmacy, Shahada, Dist. Nandurbar (425409) Maharashtra, India.

Article Received on
22 March 2017,

Revised on 13 April 2017,
Accepted on 03 May 2017

DOI: 10.20959/wjpps20176-9206

***Corresponding Author'**
Pradip S. Patil
Department of Pharmaceutics, P.S.G.V.P. Mandal's College of Pharmacy, Shahada, Dist. Nandurbar (425409) Maharashtra, India.,

ABSTRACT

Gastric emptying is a complex process and makes in-vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the gastric retention time of the drug-delivery systems for more than 12 hours. Floating drug delivery systems release gas (CO_2), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate so it can be used to prolong the gastric residence time in order to improve the bioavailability of drug. The recent developments of FDDS including the physiological and Formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail.

KEYWORDS: FDDS, prolonged period, Bioavailability, gastric retention time etc.

INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems. Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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 release of drug, the residual system is emptied from the stomach. Floating systems are low density systems that have sufficient buoyancy to float over the gastric

contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation. This results in an increased GRT and a 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. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

Pentoxifylline is widely used as vasodilator in peripheral and cerebral vascular disorder to inhibit the production of cytokines tumors necrosis alpha factor thus, used in metastasis. Pentoxifylline is a PDE4 inhibitor increasing intracellular cAMP. It also acts as inhibitor of tumors necrosis factor-alpha. It is a drug of choice for vasodilation and metastasis. But it has several drawbacks such as narrow therapeutic index, short biological half-life. These factors necessitated liposomal formulation for pentoxifylline. As this dosage form would reduce the dosing frequency hence better patient compliance. Phospholipids such as phosphatidylcholine and cholesterol were selected for the formation of liposomes into which the drug was incorporated. Cholesterol incorporated into phospholipids membranes in very high concentration up to 1:1 or 2:1 molar ratio. Cholesterol acts as a 'fluidity buffer' since below the phase transition it tends to make membrane less ordered while above transition it tends to make membrane more ordered thus suppressing the tilts and shifts in membrane structure specifically at phase transition. The present study is aimed with the formulation of liposomes of pentoxifylline followed by the evaluating parameters such as encapsulation efficiency, particle size, phase transition study and *in vitro* drug release.

EXPERIMENTAL

Pentoxifylline is a gift sample of Sanofiindia Ltd .Ankleshwar. and HPMC E15 is also gift sample of Sanofi India Ltd. Ankleshwar, Gujarat. Sodium bicarbonates is S. D. Fine chemicals, Mumbai, Citric acid and Talc were obtained from Loba chemicals, Mumbai, Maharashtra.

METHOD

Preparation of Pentoxifylline Floating Tablets: Floating tablets of pentoxifylline were prepared by direct compression technique using polymers like HPMC E15 and different effervescent agent like sodium bicarbonate and in the combination with citric acid as gas

generating agent. The different formulation F1 to F12 were prepared, the composition of each formulation is given in formulation Table No.1. Magnesium stearate used as a lubricant. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in mortar, After sufficient mixing of drug as well as other components, Magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation.

Table .no. 1 composition of all the formulation (F1 to F12).

Formulation	Drug (pentoxifylline)	HPMC E 15	Sodium Bicarbonate	Citric acid	Talc	Magnesium Stearate
F1	300	200	90	-	6	4
F2	300	225	65	-	6	4
F3	300	250	40	-	6	4
F4	300	275	10	5	6	4
F5	300	200	60	30	6	4
F6	300	200	-	90	6	4
F7	300	225	-	65	6	4
F8	300	250	-	40	6	4
F9	300	200	70	20	6	4
F10	300	225	55	10	6	4
F11	300	250	20	20	6	4
F12	300	240	40	10	6	4

- **PRE-COMPRSSION PARAMETER**
- **Bulk Density**

Bulk density of the powder was determined by pouring gently 2gm of sample through a glass funnel into a 10ml graduated cylinder. The volume is occupied by the sample was recorded. The bulk density was calculated by following formula:

Bulk density = weight of powder (gm)/ volume of powder in measuring cylinder.

- **Tap density**

The 2gms of powder was introduced into a 10 ml of measuring cylinder. After firstly note down the initial volume, then tapping was continue until no further change in volume was noted.

Tap density = weight of powder (gm) / volume of powder in measuring cylinder.

- **Angle of Repose**

The angle of repose was determined by using fix funnel method. The accurately weighted powder were allowed to flow through the funnel. The funnel is adjusted to a stand at definite height. The diameter of powder cone was measured. The angle of repose was then calculated by following formula:

Tan θ = h /r

Where,

h = height of the heap

r = radius of the heap

- **Compressibility Index**

The flow ability of powder can be determine by comparing the bulk density and tapped density of powder. Carr's index was calculated by =

Carr's index **=** (tap density – bulk density) ×100 / tap density.

- **Hausner ratio**

Hausner ratio is related to inter particle friction and as such used to predict powder flow property. Hausner ratio calculated by using following formula.

Formula= tapped density / bulk density.

- **POST-COMPRESSION PARAMETER**
- **Tablet thickness and diameter**

Thickness and diameter were measured using a calibrated Vanier caliper. Twenty tablets of each formulation were picked and measure the thickness and diameter was individual.

g) Hardness

The hardness of the tablets was determined using Monsanto hardness tester. Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness was expressed in kg/cm2.

h) Friability test

The friability of tablets was determined by using Roche Friabilator. Twenty tablets were initially weighed and transferred into friabilator. Which was given 100 revolutions at 25rpm for 4 minutes. It was expressed in percentage (%). The tablets were reweighed. The % friability was then calculated by.

%Friability = (W_0 –W / W_0) 100.

Where,

W_0 = initial weight

W = final weight

% Friability of tablets less than 1% was considered acceptable.

i) Weight Variation Test

Twenty tablets were selected and weighted collectively and individually. From the collective weight, average weight was calculated. Each weight of tablet was compared with average weight to ascertain whether it was within permissible limit or not. The percentage deviation was calculated by following formula.

% deviation = individual weight – average weight / average weight × 100

j) Buoyancy / Floating Test

The tablet was introduce in to beaker containing 100ml of 0.1 N HCL. The time is taken by the tablet to come up to surface and floated was taken as the buoyancy time. The time taken for dosage form to emerge on surface of medium called Floating Lag Time and total duration of by which dosage form remain buoyant is called Total Floating Time.

k) Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain as given by the equation.

$$WU = \frac{(W_1 - W_0) \times 100}{W_0}$$

Where

W_1= Weight of dosage form at time t.

W_0 = Initial weight of dosage form.

l) Buoyancy time

A tablet was introduce into a beaker containing 100ml of 0.1 N HCL. The time is required for tablet get floated was taken as the buoyancy time.

m) Determination of In – Vitro Dissolution Study

Dissolution study is carried out in USP dissolution testing apparatus II (basket type). Dissolution study was performed using 900ml 0.1(N) HCL, at 50 rpm. A 5ml of sample was withdrawn from the dissolution apparatus at a predetermined interval and the sink condition is maintain by adding same volume of dissolution medium. The sample diluted to a suitable concentration with 0.1 N HCL. The absorption of withdrawn sample was measured Spectrophotometric, and the corresponding concentration was determined from the respective calibration curve.

RESULT AND DISCCUSION

Pentoxifylline is a vasodilator widely used in the treatment of the peripheral& cerebral vascular diseases mainly atherosclerosis obliterans , Raynaud s phenomenon & diseases its short biological half-life 0.4-0.8hrs The chief objective of controlled release matrix tablets is to increase the efficacy as well as bioavailability& to prevents its first pass metabolism It also leads to reduction in frequency of dosing &drug toxicity which in turn improve patient compliance. One method of fabricating controlled release dosage forms is by incorporating the drug in a matrix containing ahydrophilic, rate controlling polymer. The most commonly used polymer are cellulose ether derivatives which include HPMC Drug release from these types of systems is controlled by the hydration of HPMC which forms a gelatinous barrier layer at the surface of matrix through which the included drug diffuses water soluble drug are released primarily by diffusion of dissolved drug molecules across the gel layer, while poorly water soluble drugs are released predominantly by erosion mechanisms

The effervescent floating tablet of pentoxifylline were formulated in 12 different batches F1 to F12 by using hydrophilic polymers HPMC E 15 with effervescing agent sodium bicarbonate, &citric acid All the formulation were prepared by direct compression technique.

Characterization of drug Pentoxifylline

Determination of melting point

Melting point of Pentoxifylline was found in the range of 102-105^{o}C which is in the reported range that is 102-104^{o}C indicated absolute purity of drug sample.

Determination of λ max

The wavelength of maximum absorbance (λ_{max}) for the solution of pentoxifylline prepared in 0.1 N HCL was found to be 271 nm.

Preparation of calibration curve for Pentoxifylline in 0.1N HCL

0.1N HCL Pentoxifylline 100 mg was dissolved in 0.1N HCL and volume was made up to 100 ml in 100 ml volumetric flask i e. 1000ug/ml. this stock solution was diluted with 0.1N HCL to make the conc. of 0.5,1,1.5,2 and 2.5 ug/ml. Absorbance of each solution was measured at 271 nm using shimadzu UV/ Visible double beam Spectrophotometer by using 0.1 N HCL as a reference std.

Table 6.1 Calibration curve of Pentoxifylline in 0.1N HCL.

Sr.No.	Concentration (ug/ml)	Absorbance
1	0.5	0.203
2	1.0	0.330
3	1.5	0.466
4	2.0	0.667
5	2.5	0.851

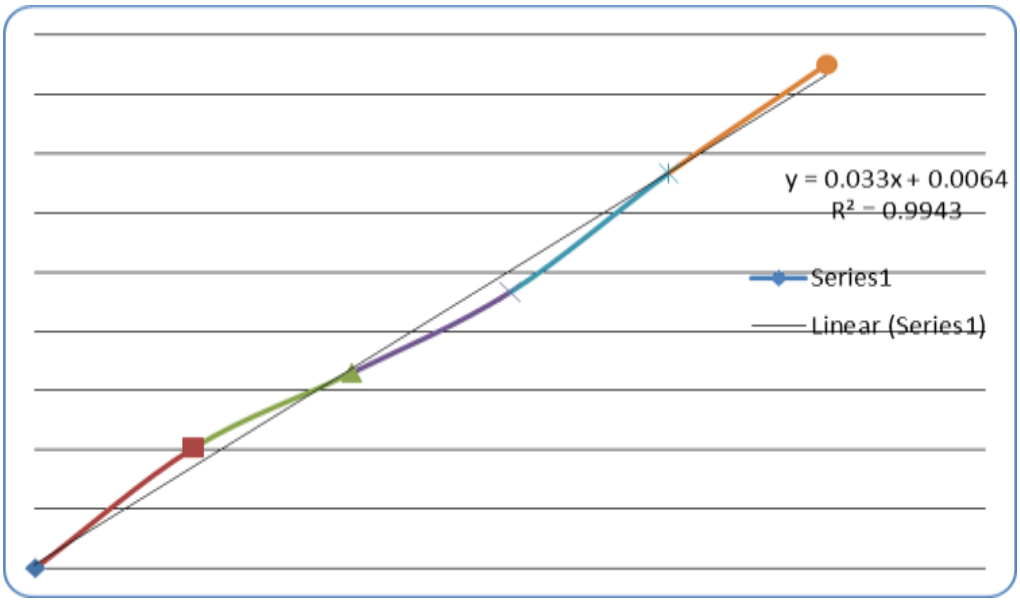

Fig 1: Calibration curve of Pentoxifylline in 0.1N HCL.

Evaluation of powder

The flow property and mechanical properties of all the formulation were evaluated like bulk density, tap density, angle of repose, hausner's ratio, and Carr's index were shown in table no 6.3.

Table 6.3 Result of evaluation of tablet blend

Formulation	Angle of repose	Bulk density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner Ratio
F1	34	0.41	0.48	14.58	1.17

F2	31	0.40	0.46	13.04	1.15
F3	32	0.36	0.41	12.19	1.13
F4	35	0.42	0.50	16	1.19
F5	29	0.35	0.40	12.05	1.05
F6	31	0.41	0.49	16.32	1.19
F7	33	0.36	0.42	14.28	1.16
F8	32	0.40	0.47	14.89	1.17
F9	35	0.35	0.43	18.60	1.22
F10	30	0.38	0.46	17.39	1.21
F11	31	0.41	0.48	14.58	1.16
F12	32	0.42	0.49	14.28	1.17

Evaluation of floatin tablet (batches f1-f12)

The Hardness, Thickness, Friability. Weight variation and drug content of all the formulation were determined and the result obtained are mentioned in the table 6.4.

The tablet evaluated for the variation showed with in limit and thus passed the test. The friability if the tablet was found to be less than 1% which was considered with in the limit. The drug content of the optimized formulation was found to be with in the limit (98-102%)

Table 6.4 Result of characterization of formulation.

Formulation	Weight Variation (%)	Thickness (cm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	4.8	5	4.9	0.44	98.3
F2	4.6	5	5	0.46	97.2
F3	4.9	5	4.8	0.55	95.1
F4	4.8	5	4.9	0.45	97.3
F5	**4.5**	**5**	**4.8**	**0.40**	**99.5**
F6	4.8	5	5	0.45	93.1
F7	4.7	5	5.1	0.38	94.2
F8	4.9	5	5.3	0.51	97.4
F9	4.6	5	5	0.39	96.4
F10	5	5	4.7	0.43	92.1
F11	4.9	5	4.6	0.44	98.2
F12	4.7	5	4.5	0.46	98.6

Floating lag time and floating time

The floating lag time is determined by the prepared tablet was kept in 100ml of 0.1 N HCL and time taken to reach the surface of solution was recorded. The result of all formulations showed in.

Table no. 5 the floating lag time and floating time formulation.

Formulation	Floating lag time(S)	Floating time (Hrs.)
F1	45.1	>12
F2	42.3	>12
F3	43.6	>12
F4	44.6	>13
F5	40.0	>12
F6	38.9	>12
F7	42.5	>12
F8	32.2	>12
F9	37.3	>12
F10	45.6	>12
F11	43.2	>13
F12	42.8	>12

Formulation f1 to f12 shows the floating lag time ranges from 32.2 to 45.6 sec the floating time of formulation f4 and f11 shows up to 13 hrs.

In vitro dissolution studies

In order to investigate the effect of effervescent agents such as sodium bicarbonate and on effervescent floating tablet of pentoxifylline, there are formulation were prepared F1-F12 as generated from experimental design. Formulation F1-F12 was subjected to dissolution studies as shown in table no. 6, and figure no. 2 & 3.

Table no.6 Dissolution profile of Pentoxifylline floating tablet.

Hrs.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	**0**	0	0	0	0	0	0	0
1	12.85	13.48	10.37	9.92	**14.75**	12.94	11.64	12.67	14.20	11.10	12.27	8.98
2	15.00	17.29	16.37	18.63	**19.05**	18.20	17.38	18.20	19.41	17.73	20.30	15.25
3	26.97	28.82	19.66	27.42	**30.65**	28.83	24.59	25.63	27.45	26.79	27.72	21.94
4	34.17	36.73	29.36	36.71	**38.60**	39.48	34.53	32.61	34.66	32.61	37.67	30.27
5	39.73	46.47	37.31	46.54	**48.41**	50.68	42.38	43.59	42.97	40.57	49.49	37.31
6	50.84	55.47	46.17	55.45	**56.00**	56.90	53.14	50.59	50.44	47.64	55.80	46.17
7	56.15	63.92	56.04	65.38	**60.71**	68.64	65.77	59.19	61.48	59.24	63.76	56.05
8	66.96	68.94	64.37	73.48	**70.78**	74.50	76.17	72.48	70.81	68.13	68.97	64.37
9	74.53	74.80	71.78	81.21	**75.87**	81.03	82.71	80.36	81.78	75.56	78.12	71.78
10	83.17	82.96	79.47	89.86	**83.91**	91.33	91.57	90.60	92.45	82.82	87.11	79.47
11	90.01	95.29	84.93	93.09	**96.25**	95.48	94.45	95.28	96.24	90.11	94.45	84.94
12	94.72	97.64	94.53	93.95	**99.55**	96.89	95.86	97.63	98.59	93.61	97.71	94.54

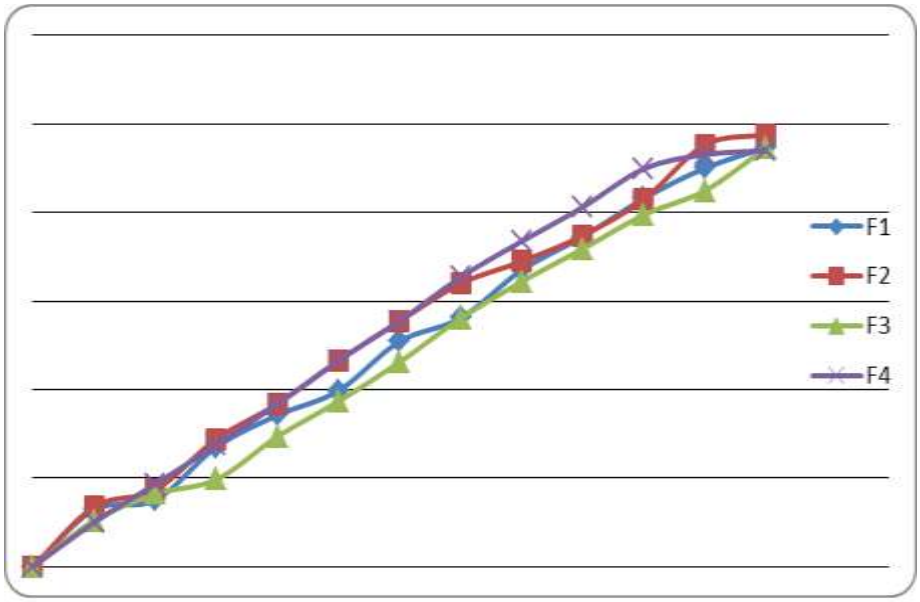

Figure no.2 Dissolution profile of formulation F1-F4.

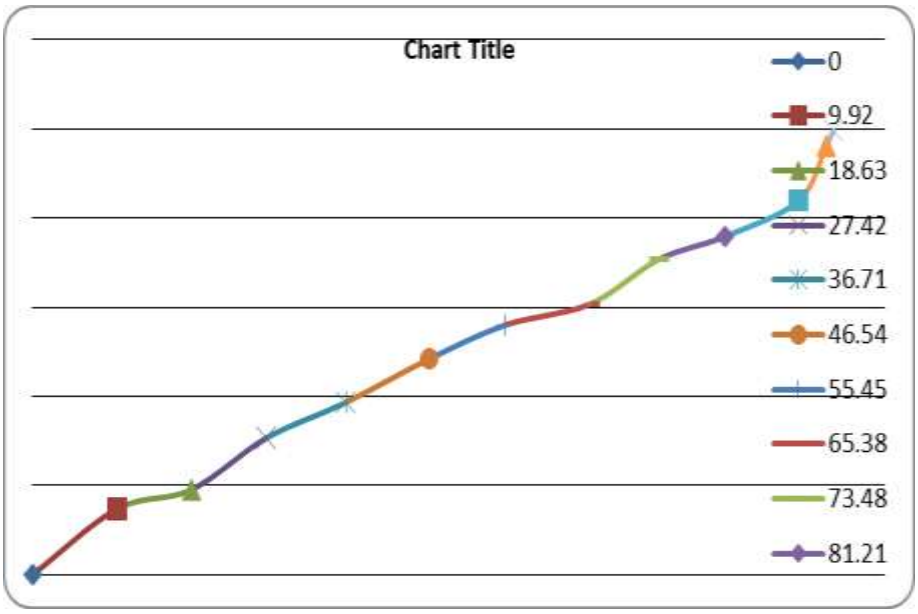

Figure no.3 Dissolution profile of formulation F5.

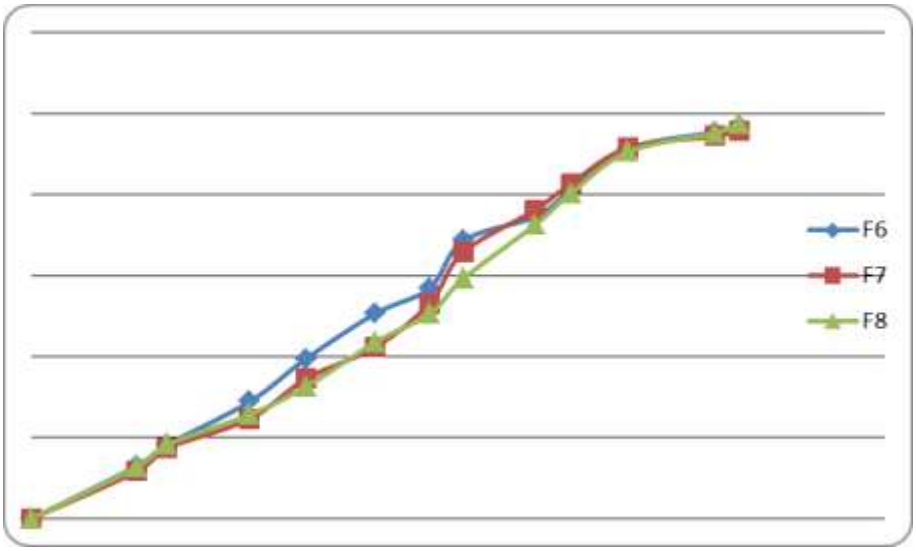

Figure no.4 Dissolution profile of formulation F6-F8.

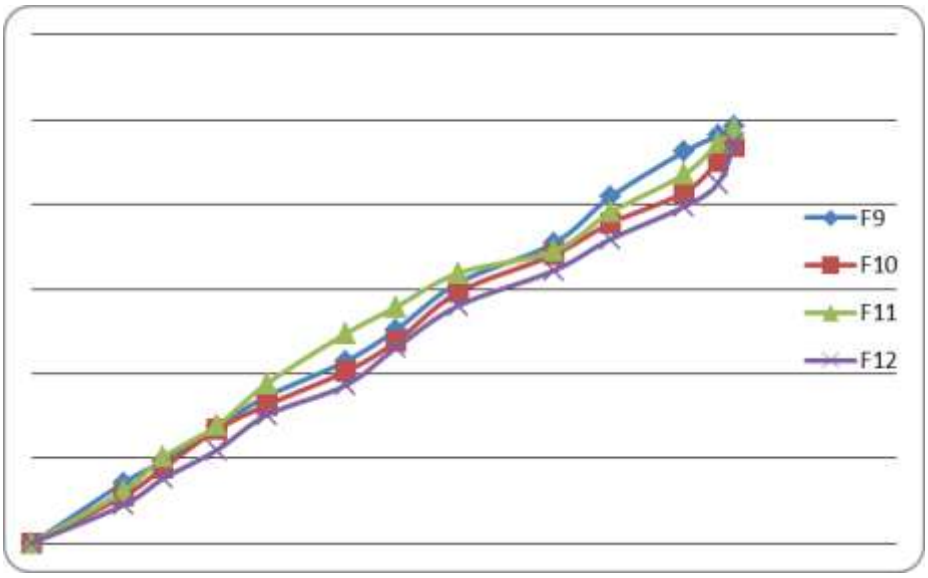

Figure no. 5 Dissolution profile of formulation f9 to f12.

CONCLUSION

In present study, the new effervescent floating system of pentoxifylline was formulated and evaluated, by using synthetic polymer like and HPMC E 15 with combination of sodium bicarbonate and citric acid as an effervescent agent. The formulations f5 containing HPMC E15 with combination of sodium bicarbonate, citric acidhave shown better floating properties, in-vitro release properties and the buoyancy studied showed that tablet remain float for more than 12 hrs.It can be conclude that effervescent floating tablet of pentoxifylline may be increase the retention time and absorption by using the formula f4 and f11.

REFERENCES

1. Arora S; Ali, A; Ahuja, A; Khar, RK and Baboota, S "Floating drug delivery systems: A review", *AAPS Pharm. SciTech*, 2005; 6(3): 72-90.
2. Yie, W. Chein, "*Novel Drug Delivery System*", Marcel jekker Inc., New York, 1992; 2: 1-3.
3. K. D. Tripathi, Essentials of medical pharmacology, 6th Edn. Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, 2004; 536: 568.
4. G. Gregoriadis, Liposome technology: Liposome preparation and related techniques, 3rd Edn.Vol. l, Informa Health care, New York, 2007; 21.
5. R. K. Chang and J. R. Robinson. Sustained drug release from tablets and particles through coating. In: H. A. Lieberman, L. Lachman and J. B. Schwartz (eds.), *Pharmceutical Dosage form: Tablets* Vol III., Marcel Dekker, New York, 2005; 199-202.
6. Kumar S., Jamil F., Rajput M. and Sharma S., Gastro retentive drug delivery system: features and facts. Int J Res Pharm Biomed Sci, 2012; 125-136.
7. British Pharmacopoeia, 2009; 2: 4597-4598.
8. Thube W. M., Formulation and evaluation of extended release tablet of Pentoxifylline. Int J of Pharm Res and Development, 2008; 2(4): 1-11.
9. R. K. Chang and J. R. Robinson. Sustained drug release from tablets and particles through coating. In: H. A. Lieberman, L. Lachman and J. B. Schwartz (eds.), *Pharmceutical Dosage form: Tablets* Vol III., Marcel Dekker, New York, 2005; 411.
10. Indian Pharmacopoeia 1996. Vol. 2. The Indian Pharmacopoeia Commission, Ghaziabad, 734.
11. Indian Pharmacopoeia. The Indian Pharmacopoeia Commission, Ghaziabad, 2007; 2: 134- 135.