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Research Article

Formulation Development and Evaluation of Effervescent Floating Matrix Tablet As Gastroretentive Drug Delivery System

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ABSTRACT:

The present work was aim to formulate effervescent floating matrix tablets of Pentoxifylline as gastro retentive drug delivery system. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. Pentoxifylline is the hemorrheologic agent, lowering blood viscosity and improving erythrocyte flexibility. It is having half-life 0.4 - 0.8 h (1-1.6 h for active metabolite) with the usual oral dose is 400 mg three times daily. The tablets were prepared by direct compression technique, using polymers such as hydrophilic polymer HPMC K15M and hydrophobic polymer MCC (Avicel PH101). Sodium bicarbonate and citric acid used as a gas generating agent. The prepared tablets were evaluated for their physicochemical properties as well as drug release profile. The effect of effervescent agents and polymeric substance were also investigated for floating properties and drug release characteristics. Drug release pattern of all formulations followed non-fickian diffusion or anomalous diffusion. Thus, a combination of HPMC K15M and MCC PH101 extends the release for a period of 12 h

Keywords: Floating drug delivery system, Pentoxifylline, gastric residence time and effervescent agent.

INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredient by the product and the subsequent transport of the active ingredients across the biological membranes to the site of action.[1]

Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).[2]

MATERIALS AND METHODS

Pentoxifylline was received as a gift sample from Sun Pharma, Mumbai. HPMC K15M was received as a gift samples from Colorcon Asia Pvt. Ltd., Goa, India. Micro crystalline cellulose (MCC), polyvinyl pyrrolidone K-30 (PVP K-30), Sodium bicarbonate and citric acid anhydrous were obtained from Loba Chemical, Mumbai, India. Magnesium stearate and talc were procured from S. D. Fine Chem. Ltd. Mumbai, India. All other chemicals and reagents used were of analytical grade.

Preformulation studies:

Melting Point:

The melting point Pentoxifylline was determined by capillary method and was found to be 103 ^{0}C to 107 ^{0}C which complies with the melting point reported in BP.

Ultra-violet scanning:

The scanning of Pentoxifylline was performed in simulated gastric fluid and λ_{max} was found to be 254 nm which compiles with the λ_{max} reported in B.P.[3]

Formulation of effervescent floating matrix tablet

of Pentoxifylline:

An effervescent floating matrix tablet of Pentoxifylline with hydroxyl propyl methyl cellulose (HPMC) was prepared by wet granulation method. Microcrystalline cellulose was used as diluent along with sodium bicarbonate and citric acid as an effervescent agent (gas generating agent). Poly vinyl pyrollidine K30 (PVP K30) dissolved in sufficient isopropyl alcohol as a granulating agent; magnesium stearate as a lubricant and talc as a glidant.

All the ingredients were accurately weighed and sieved through sieve No. 60. In order to mix the ingredients thoroughly, drug and all the excipients (shown in Table I) except the lubricant (magnesium stearate and talc) were blended geometrically in mortar and pestle for 15 min and granulated using PVP K30 dissolved in sufficient isopropyl alcohol by passing through sieve No. 12. Granules were dried at 60°C for 4 h. The dried granules were sized through sieve No. 18 and lubricated by adding magnesium stearate and talc. Tablets were compressed on a single punch tablet machine (Rimek Minipress II, Mehsana) using flat surfaced, round shaped punches of 16 mm diameter.[4]

Table I: Composition of floating matrix tablet

Ingredients (mg)	Formulation code								
Pentoxifylline	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
HPMC K15M	400	400	400	400	400	400	400	400	400
Micro crystalline cellulose	100	100	100	150	150	150	200	200	200
PVP K30	30	35	40	30	35	40	30	35	40
Sodium bicarbonate	24	24	24	24	24	24	24	24	24
Anhydrous citric acid	142	142	142	142	142	142	142	142	142
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Magnesium stearate	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5

Evaluation of effervescent floating matrix tablets:

Tablets were evaluated for both its precompression parameters like bulk density, tapped density, carr's index, hausner ratio, angle of repose as well as their post compression parameters tablet thickness, hardness, friability, uniformity of weight, content uniformity of drug and all other specific evaluation tests for floating drug delivery system like floating lag time, total floating time and release rate of drug.

Precompression Parameters:

Bulk density and Tapped density:

Both bulk density (BD) and tapped density (TD) was determined. A quantity of 2 g of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced into 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. BD and TD were calculated using the following equations.[5]

The results of bulk density and tapped density were reported in Table II.

Bulk density = W/V_0

Tapped density = W/V_f

Where, W - weight of powder, V_0 - initial volume, V_f - final volume

Compressibility index and Hausner ratio:

The compressibility index and hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the hausner ratio.[5] The compressibility index and hausner ratio were calculated by using measured values for bulk density (D_b) and tapped density (D_t) and results are shown in Table II.

Compressibility index = $D_t - D_b/D_t$ X 100

Hausner ratio = D_t / D_b

Where, D_b- Bulk density, D_t - Tapped density.

Angle of repose:
The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface.[5] The diameter of the powder cone was measured and angle of repose was calculated.

$$\text{Tan } \theta = h/r \quad \text{or} \quad \theta = \tan^{-1}(h/r)$$

Where, h = height of pile, r = radius of the base of the pile, θ = angle of repose

Table II: Precompression parameters for formulations F1- F9

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner ratio	Angle repose (º)
F1	0.509	0.555	8.22	0.92	24.56 ± 0.21
F2	0.517	0.564	8.33	0.92	23.62 ± 1.12
F3	0.510	0.555	8.17	0.92	23.89 ± 0.26
F4	0.513	0.575	10.68	0.89	22.84 ± 0.62
F5	0.521	0.564	7.52	0.92	25.64 ± 0.21
F6	0.517	0.556	7.05	0.93	24.80 ± 0.45
F7	0.515	0.573	10.22	0.90	22.15 ± 0.21
F8	0.515	0.566	9.04	0.91	26.48 ± 0.12
F9	0.516	0.567	8.89	0.91	25.26 ± 1.20

* All values are expressed as mean ± SD (n=5)

Post- compression parameters:

Tablet Hardness:
The crushing strength of prepared tablets was determined for tablets of each batch by using Monsanto hardness tester.[5]

Tablet Thickness:
The thickness of the tablets was determined by using vernier caliper. Five tablets were used and average values were calculated.[5]

Weight variation test:
Twenty tablets were selected randomly from each batch and weighed individually. The average weight of each batch of tablet was calculated. Individual weight of the tablets was compared with the average weight. Since the tablets weighed over 250 mg, Indian Pharmacopoeia specifies that the tablets pass the test if not more than two of the individual weights deviate from the average weight by more than 5 %.[5]
The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions.[5] The tablets were weighed again (W_f) and friability was calculated. (Table III)

$$\% \text{ Friability} = (1-W_f / W_0) \times 100$$

Where, W_0 -Weight of tablet before test, W_f -Weight of tablet after test

Drug content uniformity:
The tablets were weighed and taken in a mortar and crushed to powder. A quantity of powder equivalent to 400 mg of Pentoxifylline was taken in a 100 ml volumetric flask and 0.1 N HCl was added. It was then heated at 60°C for 30 ml. The solution was filtered using Whatman filter paper and then its absorbance was measured at 254 nm. The amount of drug was calculated using standard calibration curve. The result of drug content uniformity was reported in Table III.[6]

Table III: Postcompression parameters for formulations F1 – F9

Formulation code	Hardness ^ (kg/cm^2)	Thickness ^ (mm)	Weight variation * (mg)	Friability # (%)	Content uniformity ^ (%)
F1	4.5 ± 0.04472	2.3 ± 0.0194	705 ± 1.6050	0.45 ± 0.0621	98.3 ± 0.0134
F2	5.0 ± 0.04472	3.0 ± 0.0311	712 ± 1.8467	0.55 ± 0.0616	97.8 ± 0.0345
F3	5.0 ± 0.05477	3.3 ± 0.0311	715 ± 1.7770	0.46 ± 0.0153	98.6 ± 0.0532
F4	4.5 ± 0.05477	2.4 ± 0.0320	756 ± 1.0954	0.28 ± 0.0185	97.9 ± 0.0709
F5	5.0 ± 0.05477	3.0 ± 0.0421	760 ± 1.2258	0.40 ± 0.0377	98.6 ± 0.0219
F6	5.0 ± 0.04472	3.1 ± 0.0709	768 ± 1.1697	0.45 ± 0.0190	99.1 ± 0.0326
F7	5.0 ± 0.07071	3.5 ± 0.021	805 ± 2.4767	0.38 ± 0.0157	99.8 ± 0.0324
F8	4.5 ± 0.04472	2.4 ± 0.0365	810 ± 2.3004	0.43 ± 0.0268	98.8 ± 0.0435
F9	5.0 ± 0.08944	3.0 ± 0.0270	815 ± 2.1343	0.51 ± 0.0355	98.6 ± 0.0532

* All values are expressed as mean ± SD (n=20); ^ All values are expressed as mean ± SD (n=5)
# All values are expressed as mean ± SD (n=10)

Swelling study (Water uptake study):

Swelling of tablet excipients particles involves the absorption of a liquid, resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by tablet.[7]

The swelling capacity study of the tablet was done using USP XXII type I dissolution apparatus. The medium used was 0.1 N HCl (900 ml) and rotated at 100 rpm. The medium used was maintained at 37 ± 0.5°C throughout the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed.[8] Swelling characteristics of the tablets were expressed in terms of swelling index (%). (Table IV)

$$\text{Swelling index (\%)} = W_f - W_i / W_i \times 100$$

Where, W_f - Weight of swollen tablet, W_i - Initial weight of tablet

Table IV: Results of swelling study of formulations F1 – F9

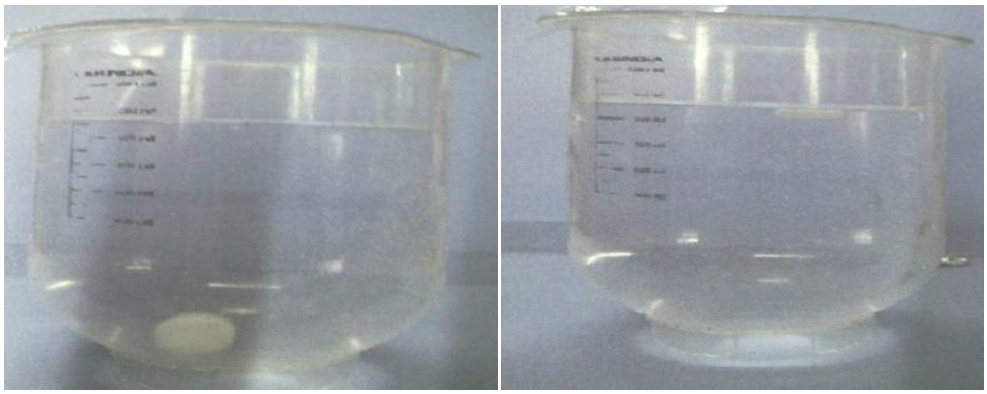
Sr. No.	Formulation Code	Swelling index (%)
1.	F1	85.06 ± 1.12
2.	F2	92.65 ± 4.12
3.	F3	91.96 ± 3.12
4.	F4	85.22 ± 4.59
5.	F5	93.57 ± 6.45
6.	F6	95.41 ± 3.21
7.	F7	99.58 ± 2.87
8.	F8	97.36 ± 1.56
9.	F9	98.28 ± 1.37

All values are expressed as mean± SD (N=5)

***In vitro* buoyancy study:**

The time, tablets took to emerge on the water surface i.e. floating lag time (FLT) and the time, tablets constantly float on the water surface i.e. total floating time (TFT) were evaluated. The buoyancy of the tablets were studied in

USP XXII type II dissolution apparatus at 37± 0.5°C with paddle rotation at 100 rpm in 900 ml of stimulated gastric fluid at pH 1.2. The measurements were carried out for each formulation of tablets. The time of duration of floatation was observed visually and reported in Table V and Figure I.[9]



[a] [b]

Figure I: *In-vitro* buoyancy study [a] Before floating [b] After floating

Table V: *In vitro* buoyancy data of floating tablets

Formulating Code	Floating lag time (s)	Total floating time (h)	Matrix integrity
F1	45.1 ± 1.2	>12	+
F2	42.3 ± 2.6	>12	+
F3	43.6 ± 3.1	>12	+
F4	39.7 ± 4.4	>12	+
F5	41.2 ± 3.3	>12	+
F6	36.9 ± 5.8	>12	+
F7	32.3 ± 2.7	>12	+
F8	37.3 ± 6.1	>12	+
F9	41.6 ± 3.2	>12	+

***In vitro* drug release studies**

The Pentoxifylline released from different floating tablet formulation was determined by using a USP XXII paddle apparatus under sink condition (Lab India Disso 2000). The dissolution medium was 900 ml simulated gastric fluid (pH-1.2, no enzyme) at 37 ± 0.5ºC; paddle speed 100 rpm, to stimulate *in vivo* condition. The prepared formulation was subjected to dissolution tests for 12 h. At every 1 h interval, a sample was withdrawn, filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium. Drug content in the dissolution sample was determined at 254 nm by UV spectrophotometer (UV- 1700). Cumulative percent drug released was found at each time interval and graph was plotted between cumulative % drug released and time in h.[7] The results of *in vitro* drug release was shown in Table VI.

Table VI: *In vitro* drug release data of formulation F1 TO F9

Time (h)	% Cumulative drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00
1	23.11 ± 0.13	21.39 ± 0.34	16.26 ± 0.05	24.15 ± 0.14	18.36 ± 0.06	19.95 ± 0.10	24.52 ± 0.11	20.94 ± 0.15	25.29 ± 0.06
2	30.89 ± 0.12	30.63 ± 0.19	22.76 ± 0.06	29.26 ± 0.07	25.14 ± 0.12	26.19 ± 0.07	32.49 ± 0.11	27.59 ± 0.07	32.48 ± 0.07
3	37.19 ± 0.14	38.24 ± 0.09	31.58 ± 0.01	36.14 ± 0.10	31.51 ± 0.08	33.82 ± 0.07	43.16 ± 0.09	34.17 ± 0.13	39.71 ± 0.06
4	43.15 ± 0.12	42.26 ± 0.24	39.65 ± 0.08	42.49 ± 0.05	41.58 ± 0.11	41.35 ± 0.07	49.79 ± 0.03	41.34 ± 0.09	46.35 ± 0.11
5	51.26 ± 0.09	45.23 ± 0.14	46.15 ± 0.08	51.27 ± 0.09	49.26 ± 0.06	48.15 ± 0.08	56.76 ± 0.10	49.64 ± 0.08	52.45 ± 0.05
6	56.18 ± 0.06	51.62 ± 0.16	51.25 ± 0.06	59.65 ± 0.67	56.21 ± 0.05	55.72 ± 0.06	63.18 ± 0.08	54.76 ± 0.12	56.75 ± 0.14
7	63.84 ± 0.12	56.41 ± 0.10	58.19 ± 0.09	65.16 ± 0.05	62.79 ± 0.05	63.17 ± 0.09	71.26 ± 0.07	62.25 ± 0.07	61.28 ± 0.07
8	69.17 ± 0.08	62.58 ± 0.33	64.16 ± 0.07	72.85 ± 0.05	70.61 ± 0.09	71.95 ± 0.09	76.48 ± 0.05	71.49 ± 0.05	68.19 ± 0.07
9	75.26 ± 0.05	69.56 ± 0.32	72.76 ± 0.06	79.24 ± 0.18	78.26 ± 0.07	80.62 ± 0.07	81.26 ± 0.09	79.62 ± 0.02	73.82 ± 0.12
10	81.36 ± 0.06	76.45 ± 0.18	80.54 ± 0.08	83.49 ± 0.39	81.56 ± 0.05	88.48 ± 0.07	88.19 ± 0.08	83.99 ± 0.15	80.59 ± 0.12
11	87.45 ± 0.04	84.56 ± 0.38	89.14 ± 0.19	89.19 ± 0.56	86.95 ± 0.13	94.16 ± 0.10	93.84 ±0.09	91.47 ± 0.03	88.96 ± 0.10
12	93.26 ± 0.09	93.66 ± 0.14	95.08 ± 0.07	96.25 ± 0.58	95.28 ± 0.04	96.35 ± 0.12	99.70 ± 0.13	97.25 ± 0.07	96.47 ± 0.18

*All values are expressed as mean ± SD (n=5)

Treatment of drug release data with different kinetic equations

Different mathematical model may be applied for describing the kinetics of the drug release process from matrix tablets, the most suited being the one which best fits the experimental results. The kinetics of Pentoxifylline was determined by finding the best fit of the dissolution data to distinct models- Zero order, First order, Higuchi and Korsmeyer Peppas.[10]

Zero order kinetics: A zero-order release would be predicted by the following equation.

$A_t = A_0 - K_0 t$

Where, A_t - Drug release at time't'

A_0 - Initial drug concentration

K_0 - Zero-order rate constant

First order kinetics: A first-order release would be predicted by the following equation.

$\text{Log } C = \text{Log } C_0 - 303.2\ K_f\ t$

Where, C - Amount of drug remained at time't'

C_0 - Initial amount of drug

K_f - First-order rate constant

Higuchi's model: Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$Q = K_h t^{½}$

Where, Q - Percentage of drug released at time't'

K_h- Higuchi's drug release rate constant

Korsmeyer peppas model: The release rates from controlled release polymeric matrices can be described by the equation proposed by Korsmeyer Peppas *et al*.

$Q = K_m t^n$

Where, Q - Percentage of drug released at time't'

K_m - Kinetic constant incorporating structural and geometric characteristics of the tablets

n - Diffusional exponent indicative of the release mechanism

The results of *in vitro* drug release profile obtained for all the floating tablet formulations were plotted in modes of data treatment as follows:

i. Cumulative percent drug released versus time (zero-order kinetic model)
ii. Log cumulative percent drug remaining versus time (First-order kinetic model)
iii. Cumulative percent drug released versus square root of time (Higuchi's model)
iv. Log cumulative percent drug released versus log time (Korsmeyer Peppas equation).[10]

Table VII: Kinetic treatment of drug release data of various formulations F1 to F9

Formulation code	Zero order	First order	Higuchi's matrix	Korsmeyer Peppas model	**Diffusion co-efficient (n)**
			R^2		
F1	0.97	0.943	0.983	0.993	0.67
F2	0.969	0.871	0.964	0.992	0.68
F3	0.992	0.932	0.951	0.997	0.68
F4	0.973	0.960	0.978	0.993	0.68
F5	0.981	0.960	0.972	0.998	0.68
F6	0.990	0.826	0.957	0.996	0.69
F7	0.961	0.817	0.991	0.994	0.68
F8	0.982	0.975	0.969	0.996	0.68
F9	0.963	0.923	0.979	0.989	0.67

Stability studies:

Stability studies were carried out for optimized batch (F7) of effervescent floating matrix tablets of Pentoxifylline. The tablets were packed in aluminium foil placed in airlight container and kept at 4°C in refrigerator, 40°C / 75 % RH and 60°C for 60 d. At the interval of 15 d, the tablets were withdrawn and evaluated for physical properties and *in vitro* drug release. The results of stability studies are shown in following tables. (Table VIII-XIII)

Table VIII: Effects on visual appearance of tablets after subjecting to stability studies

Sampling intervals (d)	4 ± 0.5°C	40 ± 0.5°C / 75 %RH	60 ± 0.5°C
0	-	-	-
15	-	-	-
30	-	-	-
45	-	-	+
60	-	+	++

-No change, + Dull white colour, + + Light yellow colour

Table IX: Effects on hardness of tablets after subjecting to stability studies

Sampling intervals (d)	4 ± 0.5°C	40 ± 0.5°C / 75 %RH	60 ± 0.5°C
0	5.5	5.2	5.2
15	5.5	5.2	5.2
30	5.6	5.2	5.1
45	5.7	5.2	4.8
60	5.7	5.1	4.8

Table X: Effects on weight variation of tablets after subjecting to stability studies

Sampling intervals (d)	4 ± 0.5°C	40 ± 0.5°C / 75 %RH	60 ± 0.5°C
0	-	-	-
15	-	-	-
30	-	-	-
45	-	+ 1.30	-
60	-	+ 1.01	-

Table XI: Effects on friability of tablets after subjecting to stability studies

Sampling intervals (d)	4 ± 0.5°C	40 ± 0.5°C / 75 %RH	60 ± 0.5°C
0	0.28	0.28	0.28
15	0.28	0.32	0.36
30	0.29	0.39	0.42
45	0.31	0.43	0.49
60	0.31	0.51	0.57

Table XII: Effects on % drug content of tablets after subjecting to stability studies

Sampling intervals (d)	4 ± 0.5°C	40 ± 0.5°C / 75 %RH	60 ± 0.5°C
0	98.80	98.80	98.80
15	98.62	98.43	98.13
30	98.54	98.28	97.32
45	98.37	97.91	97.16
60	97.97	97.23	96.98

Table XIII: Effects on % drug released of tablets after subjecting to stability studies

Sampling intervals (d)	4 ± 0.5°C	40 ± 0.5°C / 75 %RH	60 ± 0.5°C
0	99.70	99.70	99.70
15	99.57	99.63	99.54
30	99.31	99.35	99.37
45	99.17	98.89	98.91
60	98.96	98.78	98.87

DISCUSSION AND CONCLUSION

The approach of present study was to develop effervescent floating matrix tablet of Pentoxifylline and hence evaluated the release profile of these formulations. The prepared tablets showed excellent *in vitro* effervescent floating properties. For effervescent, sodium bicarbonate and citric acid are added resulted in the reduction of floating lag time.

All the effervescent floating matrix tablets have showed a floating time of 12 h. The floating lag time is depended upon the concentration of gas generating agent i.e. an optimum concentration of sodium bicarbonate (142 mg per tablet) and citric acid (3.5 mg per tablet) were found to be essential to achieve an optimum *in vitro* floating. Floatability can be achieved by generation of gas bubbles. The *in vitro* dissolution profile of all the prepared effervescent floating matrix tablets of Pentoxifylline were found to control the drug release over a period of 12 h and drug release decreased with increased in polymer concentration as well as viscosity of polymer.

Release of Pentoxifylline from most of the formulation was found to follow zero order kinetics (0.96 to 0.99) and derived correlation coefficient 'R^2'(0.99) indicated good fit of Higuchi model suggesting that diffusion is the predominant mechanism controlling the drug release. When drug release data fitted to Korsmeyer Peppas equation, the values of slope 'n' (0.65 to 0.69) indicated that the drug release was by Non-Fickian mechanism.

Among the various effervescent floating matrix tablet formulation studied, formulation F7 containing drug polymer ratio (4:2) prepared with HPMC K15M showed promising results releasing 99.70 % of the drug in 12 h with a floating lag time of 32.3 s and floating time of 12 h has been considered as an ideal formulation.

Optimized batch of floating tablet of Pentoxifylline (F7) was further subjected for short term stability studies and found to be stable for 60 d. Formulation F7 appears suitable for further pharmacodynamic and pharmacokinetic studies to evaluated clinical safety of these floating tablets in suitable animal and human models.

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