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Oral Sustained Delivery of Theophylline Floating Matrix Tablets- Formulation and In-vitro Evaluation

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Abstract: The aim of the study was to develop and physicochemicaly characterize single unit controlled delivery system of Theophylline and was formulated as floating matrix tablet by direct compression method using gas generating agent (sodium bicarbonate) and various viscosity grades of hydrophilic polymers (HPMC K15M, K4M; HPC and Carbapol 934P). Formulation was optimized on the basis of buoyancy and in vitro drug release profile. Also tablets were tested for various tests like hardness, thickness, weight variation, friability, swelling index and erosion index. The tablets swelled and eroded upon contact with release medium (0.1 N HCl) at 37 ^{0}C. The release rate could efficiently be modified by varying the matrix forming polymer, the use of polymer blends and the addition of water soluble or water insoluble fillers (such as dicalcium phosphate, lactose or mannitol). Fitting the in-vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

Keywords: Theophylline, Carbapol, HPMC, Floating matrix tablets, swelling index, buoyancy.

1. Introduction

The recent research studies and various literatures reveals that pharmaceutical dosage forms exhibiting good in vitro floating behavior show prolonged gastric residence in vivo.[11] The real issue in the development of oral controlled release dosage form is not just to prolong the delivery of drugs for more than 12 hrs but also to prolong the presence of dosage forms in the stomach or somewhere in the upper small intestine. Dosage forms with prolonged gastric residence time (GRT), i.e. gastro remaining or gastro retentive drug delivery system (GRDDS) will bring about new and important therapeutic options. For instance, these will significantly extend the period of time over which drugs may be released, and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing controlled release dosage forms.[3, 6] Finally, GRDDS will be used as carriers for drugs with so called absorption windows; these substances are taken up only from very specific sites of the gastrointestinal mucosa, often in a proximal region of the small intestine. To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (≈1.004 g/cm^2).However, it has to be pointed out that good in vitro floating behavior alone is not sufficient proof for efficient gastric retention in vivo.[5] The effects of simultaneous presence of food and of the complex motility of the stomach are difficult to estimate.Obiviosly in vivo studies can provide definite proof that prolonged gastric residence is obtained.[9, 17]

Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for drugs (i) that are locally active in the stomach, (ii) that have an absorption window in the stomach or in the upper small intestine,(iii) that are unstable in the intestinal or colonic environment, and/or (iv) have low solubility at high pH values. In addition, as the total gastrointestinal transit time of dosage forms is increased by prolonging the gastric residence time, these systems can also be used as sustained release

devices with a reduced frequency of administration and,therefore,improved patient compliance .Recent approaches to increase the gastric residence time of drug delivery systems include (i) bioadhesive devices (ii) systems that rapidly increase in size upon swallowing and (iii) low density devices that float on the gastric contents.[7,10,16] Thus, Theophylline floating matrix tablets have a relatively short half-life and is more intensely absorbed at the duodenum-jejunum level than in subsequent portions of the gastrointestinal tract. Consequently, for an optimum effect, the administration of Theophylline as conventional tablets (with rapid disintegration and dissolution) must be carried out several times a day.
For these reasons Theophylline is a candidate drug for production of pharmaceutical preparation with controlled release in the proximal upper portions of the gastrointestinal tract (duodenum & jejunum) and hence is good rational for floating drug delivery system.

2. Materials and methods

2.1 Materials:

Theophyline was obtained as a gift sample (Cipla pharmaceutical Ltd., Kurkum MIDC, Pune), Other polymers and chemicals such as HPMC K4M,K15M (Colorcon Asia Ltd.,Goa,India),Carbapol 934P, colloidal silicon dioxide (Aerosil), magnesium stearate, sodium bicarbonate (New Life Pharmaceuticals,Pune,India).Remaining all the materials were obtained commercially and used as such.

2.2Fabrication of floating matrix tablets: [12]

Tablets containing Theophyline as a pure drug were prepared by direct compression method. The respective powders (drug, polymers, and fillers) and optional additives, compositions listed in **Table No.1** were blended thoroughly with a mortar and pestle and finally mixed with magnesium stearate and colloidal silicon dioxide as a lubricant and glidant respectively. Tablets of 402.5mg each were compressed by using multiple-punch tabletting machine (Cadmach,Ahmedabad) with constant weight, thickness, diameter (12mm) and hardness (approximately 5 Kg/cm^2 unless otherwise stated) using beveled flat-faced punches. Hardness was measured by using Monsanto hardness tester and diameter and thickness was measured by digital vernier caliper.

2.3 Characterization of tablets: [12]

The properties of the compressed matrix tablets, such as hardness, friability, weight variation and content uniformity were determined by using reported procedure. Hardness was measured by using Monsanto hardness tester and friability was measured by Roche friability testing apparatus. Weight variation and uniformity of drug content were performed according to I.P.procedures.Content uniformity was determined by weighing 10 tablets individually (Table No.1).

2.4 Floating behavior of the tablets: [1, 2]

In vitro buoyancy study of the tablets (n=3) was determined using USP (type II) dissolution apparatus containing 900 ml of 0.1 N HCl (pH 1.2 at 37 ^{0}C) at 100 rpm. The time (min) taken by the tablet to reach the top from the bottom of the container (floating lag time), and the time for which the tablet constantly floats on the surface of the medium (duration of floating), was measured (Table No.3).

2.5 Determination of swelling and erosion behavior: [4, 14]

The swelling and eroding behavior of matrix tablet was determined, reported by Al-Taani and Tashoush. Matrix tablet was introduced into the dissolution apparatus containing 900 ml of 0.1 N HCl (pH 1.2 at 37 ^{0}C) at 100 rpm. The tablets were removed using a small basket and swollen weight of each tablet was determined. To determine matrix erosion, swollen tablets were placed in a vacuum oven at 40 ^{0}C and after48 hours tablets were removed and weighed. Swelling (%) and erosion (%) was calculated according to the following formula, where S is the weight of the matrix tablet after swelling; R is the weight of the eroded matrix tablet; and T is the initial weight of the matrix tablet:

Swelling Index = $S - T / T$

% Erosion = $(T - R) / T \times 100$.

2.6 Accelerated stability testing: [18]

The stability studies were carried out on optimized formulations. The formulations were stored at 40 ± 2^{0}C/75 ± 5 % RH (% relative humidity) for one month. After interval of 7, 15 and 30 days samples were withdrawn and retested for drug content, floating lag time and drug and hardness.

2.7 In vitro drug release studies:

Dissolution tests were conducted in triplicate for all batches in a USP (type-II) dissolution rate test apparatus (type II) The release studies were performed by using 900 ml of 0.1 N HCl (pH 1.2 at 37 ^{0}C) at 100 rpm. Five milliliters aliquots were withdrawn at specific time intervals and drug content was determined by UV-visible spectrophotometer (simatzu-1650 PC) at 270 nm. The release studies were conducted in triplicate.

2.8 Kinetic analysis of the dissolution data: [14, 15]

In order to study the exact mechanism of drug release from the matrix floating tablets, the release data were fitted to zero-order, first-order and higuichi equation.

These models fail to explain drug release mechanism due to swelling (upon hydration in contact with dissolution medium) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe the drug release behavior from polymeric systems:

$\text{Log } (M_t / M_f) = \text{Log } k + n \text{ Log } t$

Where, M_t is the amount of drug release at time t; M_f is the amount of drug release after infinite time's is a release constant incorporating structural and geometric characteristics of the tablet; and n is the diffusion exponent indicative of the mechanism of the drug release.

In order to make sure the release exponent for different batches of floating matrix tablets, the log value of % drug dissolved was plotted against log time for each batch according to the Equation. Value of n = 0.45 indicates Fickian (Case I) release ;> 0.45 but <0.89 for non-fickian (anomalous) release; and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-fickian) refers to a combination of both diffusion and erosion controlled-drug release. Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel and Lippold):

$MDT = (n / n + 1). k – 1 / n$

Where, n = release exponent and k = release rate constant.

3. Results and Discussion

In the present study, HPMC K4M, K15M, K 100M, HPC & Carbapol 934P which are commonly used in hydrophilic matrix drug delivery systems, have been employed to formulate floating sustained release tablets of theophyline **(Table No.1).**All the physical parameters like hardness, thickness, drug content uniformity and friability etc are evaluated (**Table No 2).** Floating lag time about less than 1 minute to more than 4 minute was observed at different pH shown that **(Table No.3.)** lag time increases with increase in pH value Formulation with Carbapol retards the release of the drug because of its cross-linked polymeric nature with high molecular weight (~2 × 106 Da.) and viscosity and when contacted with water it would swell and hold the water inside its microgel network. Evaluated data demonstrates again that the incorporation of Carbapol 934P has negative effect on the floating behavior of the delivery system .This can be explained by the moisture isotherm of Carbapol 943P which illustrates that Carbapol 934P has a much higher moisture absorption curve compared to cellulose based HPMC and HPC. The moisture gain for Carbapol 943P is significantly higher compared to moisture gain of HPMC (55% weight gain for Carbapol 934P verses ~ 33%for HPMC at RH of 95%).This results in a dramatic increase in the density of the GFDDS which in turn, shows a corresponding decrease in the floating capacity of GFDDS.[17] After accelerated stability testing for one month it was found that irrespective of concentration of polymer, these formulations are able to retain their stability **(Table No.6).**

On exposure of matrices to aqueous fluid, the tablet surface becomes wet and starts to hydrate to form a viscous gel layer. The release of the drug from the matrices can be governed by the diffusion and its subsequent erosion. In order to understand the influence of the polymer system on drug release, swelling and erosion study on matrices containing the polymers only was evaluated. **Fig.No.1** shows the percentage of matrix erosion as well as percentage swelling as a function of pH. It is clear that the matrices underwent both swelling and erosion at the same time as it was placed in the dissolution media.

Since both swelling and erosion occurred simultaneously in the matrix, zero order release can be obtained in such types of matrices. This behavior is responsible for maintaining zero order release in which the increase in diffusion path length due to swelling is balanced with the decrease in the diffusion path length due to matrix erosion. Overall a constant diffusion path length is maintained.

Fitting the in-vitro drug release data **(Table No.5 & Fig.No.2)** to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release with best fitted model. In the present studies of dissolution given in the **Table No.4** formulation of the batches 1,2,3,4 and 5 were shown the release of drug 63.69%, 64.5%, 65.65%, 61.60% and 64.38 at the end of 12 hours and 97.13%, 97.09%, 96.78%, 97.05% and 96.81% of drug at the end of 20 hours, respectively.

Further the result of dissolution studies of formulation batches 4, 6 and 7 composed of HPMC K4M and Carbapol 934P combination with different fillers showing release of drug 51.11%, 53.15%, 49.73% at the end of 12 hours and 91.59%, 93.12%, 93.88% at the end of 20 hours, respectively.

In further dissolution studies of formulations 9, 10 and 11 composed of HPC along with different fillers released the drug 62.43%, 65.55% and 62.45% at the end of 12 hours and 96.42%, 96.52 and 96.09% at the end of 20 hours, respectively.

4. Conclusion

Overall, this study concludes that from all formulations, formulation 1 shown the highest release (best formulation) followed by 2, 3, 4, 5, 9, 10, 11, 6, 7, and 8 at the end of twenty hours. There was not significant difference in all the formulation batches despite different molecular sizes of polymers, the release of the drug was delayed to same extent, except the formulations with Carbapol 934P which was also observed by some other investigators where Carbapol 934P was found to compromise the release and floating property of GFDDS. Also there was no significant difference in the release of the drug with the different types of fillers. Fitting the in-vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

Table No.1: Compositions of floating matrix tablet in mg:

Formulation*	HPMC K4M	HPMC K15M	HPMC K100M	HPC	HPMCK4M + Carbapol 934P**	Lactose	Mannitol	DCP
F-1	242	----	----	----	----	----	----	17.5
F-2	----	242	----	----	----	----	----	17.5
F-3	----	----	242	----	----	----	----	17.5
F-4	242	----	----	----	----	17.5	----	----
F-5	242	----	----	----	----	----	17.5	----
F-6	----	----	----	----	242	----	----	17.5
F-7	----	----	----	----	242	17.5	----	----
F-8	----	----	----	----	242	----	17.5	----
F-9	----	----	----	242	----	----	----	17.5
F-10	----	----	----	242	----	17.5	----	----
F-11	----	----	----	242	----	----	17.5	----

*All batches contained 100mg of drug, 10 %sodium bicarbonate, 1 % magnesium stearate and 1 % Aerosil.

** HPMC K4M and Carbapol 934P blend was taken in 3:1 ratio respectively.

Table No. 2: Properties of the compressed tablets:

Formulation	Thickness *	Drug Content (%)*	Friability (%)	Hardness (kg/cm^2)*
F-1	2.78± 0.025	98.19 ± 1.5	0.34	5.4 ± 0.7
F-2	2.95 ± 0.03	98.21 ± 1.3	0.35	5.5± 0.1
F-3	2.93± 0.01	96.9 ± 1.9	0.39	5.5 ± 0.1
F-4	2.84 ± 0.03	98.3 ± 0 .8	0.43	5.5 ± 0.1
F-5	2.85 ± 0.04	98.4 ± 1.1	0.76	5.5 ± 0.2
F-6	2.90 ±0.0264	97.04 ± 1.2	0.35	5.9 ± 0.3
F-7	2.96 ± 0.025	98.01 ± 1.6	0.27	5.4 ± 0.6
F-8	2.90 ±0.0173	97.03 ± 1.3	0.43	5.5 ± 0.1
F-9	2.92 ±0.0152	98.97 ± 1.3	0.35	5.5 ± 0.3
F-10	2.92 ±0.0264	98.10 ± 1.7	0.35	5.5 ± 0.4
F-11	2.92±.0264	98.33 ± 1.19	0.19	5.6 ± 0.3

- All the values are expressed as mean ± SE, n = 3

Table No. 3: Floating Lag Time:

Formulation	Floating lag time (min)*		
	pH 1.2	pH 2.0	pH 3.0
F-1	<1.0	<4.0	>4.0
F-2	<1.0	<4.0	>4.0
F-3	<1.0	<4.0	>4.0
F-4	<1.0	<4.0	>4.0
F-5	<1.0	<4.0	>4.0
F-6	>1.0	<4.0	>4.0
F-7	>1.0	<4.0	>4.0
F-8	>1.0	<4.0	>4.0
F-9	<1.0	<4.0	>4.0
F-10	<1.0	<4.0	>4.0
F-11	<1.0	<4.0	>4.0

*All the values are expressed as mean ± SE, n = 3

Table No. 4: Percentage drug release data:

Sr. No.	% drug release	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
1	**1 hr**	14.52 ± 0.29	15.52 ± 0.29	14.55 ± 0.27	14.60 ± 0.13	15.11 ± 0.54	12.81 ± 0.29	13.01 ± 0.37	14.28 ± 0.65	13.15 ± 0.47	15.58 ± 0.47	13.88 ± 0.46
2	**2 hrs**	18.13 ± 0.38	19.13 ± 0.38	19.17 ± 0.41	19.13 ± 0.38	19.83 ± 0.51	15.85 ± 0.26	16.01 ± 0.47	19.28 ± 0.85	16.69 ± 0.51	19.87 ± 0.95	17.81 ± 0.35
3	**4 hrs**	30.93 ± 0.34	31.93 ± 0.34	30.95 ± 0.31	30.93 ± 0.34	32.03 ± 0.34	27.28 ± 0.18	26.98 ± 0.57	27.33 ± 0.86	30.15 ± 0.43	31.56 ± 0.66	30.14 ± 0.38
4	**6 hrs**	36.48 ± 0.46	34.33 ± 0.46	37.44 ± 0.48	38.48 ± 0.46	39.00 ± 0.34	34.90 ± 0.46	36.30 ± 0.69	32.46 ± 0.77	36.47 ± 0.61	38.92 ± 0.48	37.10 ± 0.48
5	**8 hrs**	47.29 ± 0.30	48.01 ± 0.30	48.21 ± 0.32	48.29 ± 0.30	49.09 ± 0.72	41.79 ± 0.06	42.07 ± 0.87	39.88 ± 0.48	46.66 ± 0.43	49.29 ± 0.68	46.51 ± 0.43
6	**10 hrs**	54.21 ± 0.27	53.23 ± 0.27	52.24 ± 0.29	54.21 ± 0.27	55.68 ± 0.65	46.41 ± 0.04	45.17 ± 0.48	42.11 ± 0.37	54.16 ± 0.27	55.74 ± 0.57	54.82 ± 0.46
7	**12 hrs**	63.69 ± 0.13	64.50 ± 0.13	65.65 ± 0.17	61.60 ± 0.13	64.38 ± 0.35	51.11 ± 0.89	53.15 ± 0.52	49.73 ± 0.86	62.43 ± 0.44	65.55 ± 1.85	62.45 ± 0.34
8	**14 hrs**	72.43 ± 0.29	73.63 ± 0.29	71.70 ± 0.39	72.73 ± 0.30	73.32 ± 0.30	58.12 ± 0.93	57.23 ± 0.68	59.38 ± 0.75	70.83 ± 0.66	74.00 ± 0.66	72.58 ± 1.00
9	**16 hrs**	82.66 ± 0.15	81.56 ± 0.12	83.64 ± 0.17	82.66 ± 0.15	83.20 ± 0.16	66.98 ± 0.44	69.59 ± 0.59	71.63 ± 0.44	80.19 ± 0.97	83.77 ± 1.00	81.20 ± 0.57
10	**18 hrs**	94.86 ± 0.69	93.76 ± 0.69	94.81 ± 0.71	94.85 ± 0.69	85.92 ± 0.43	79.63 ± 0.49	81.43 ± 0.63	83.25 ± 0.45	85.80 ± 0.23	86.01 ± 0.35	86.06 ± 0.27
11	**20 hrs**	97.13 ± 0.22	97.09 ± 0.49	96.78 ± 0.31	97.05 ± 0.38	96.81 ± 0.32	91.59 ± 0.84	93.12 ± 0.98	93.8 ± 0.69	96.42 ± 0.44	96.52 ± 0.48	96.09 ± 0.20

*Each sample was analyzed in triplicate (n = 3)

Table No. 5: Kinetic treatment to dissolution data for floating matrix tablet formulations:

Formulation	Zero Order Plot	First Order Plot	Korsmeyer-Peppas Plots	Matrix Plots	Hix. Crow. Plots	Best Fit Model
	Regression coefficient (R^2)	Regression coefficient (R^2)	Regression coefficient (R^2)	Regression coefficient (R^2)	Regression coefficient (R^2)	
F-1	0.9817	0.9066	0.9936	0.9711	0.9667	Peppas
F-2	0.9817	0.9066	0.9936	0.9719	0.6971	Peppas
F-3	0.9813	0.9119	0.9936	0.9714	0.9684	Peppas
F-4	0.9720	0.9219	0.9949	0.9807	0.9773	Peppas
F-5	0.9728	0.9149	0.9954	0.9799	0.9749	Peppas
F-6	0.9657	0.9464	0.9944	0.9880	0.9843	Peppas
F-7	0.9681	0.9524	0.9943	0.9822	0.9867	Peppas
F-8	0.9645	0.9649	0.9942	0.9842	0.9904	Peppas
F-9	0.9832	0.9105	0.9949	0.9725	0.9718	Peppas
F-10	0.9722	0.9240	0.9940	0.9799	0.9782	Peppas
F-11	0.9811	0.9220	0.9948	0.9742	0.9765	Peppas

Table No. 6: Parameters evaluated after accelerated stability studies:

Formulation	Floating Lag Time (mins.)*	Drug Content (%)*	Hardness (Kg/cm^2)
F-1	<1	97.9 ± 1.7	5.0
F-2	<1	98.1 ± 1.3	5.1
F-3	<1	97.1 ± 1.6	5.3
F-4	<1	98.1 ± 1.2	5.1
F-5	<1	98.2 ± 1.2	5.3
F-6	>1	96.81 ± 1.3	5.2
F-7	>1	97.01 ± 1.2	5.4
F-8	>1	96.89 ± 1.4	5.6
F-9	<1	98.20 ± 1.3	5.5
F-10	<1	98.0 ± 1.4	5.6
F-11	<1	97.90 ± 1.6	5.7

*Each sample was analyzed in triplicate (n = 3)

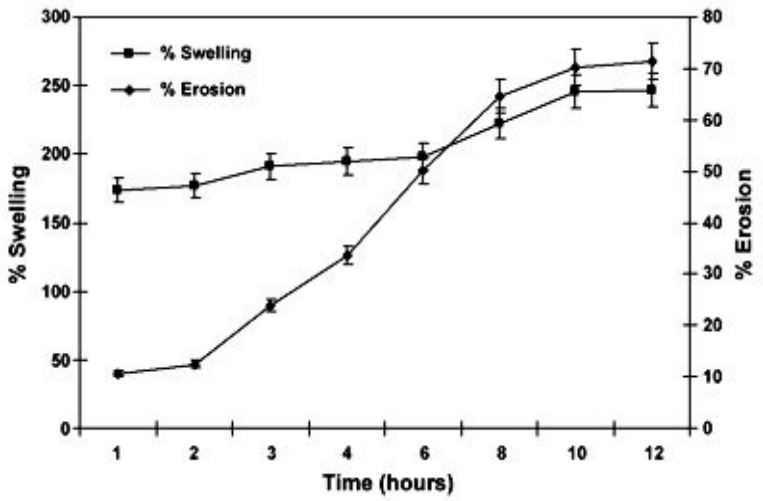
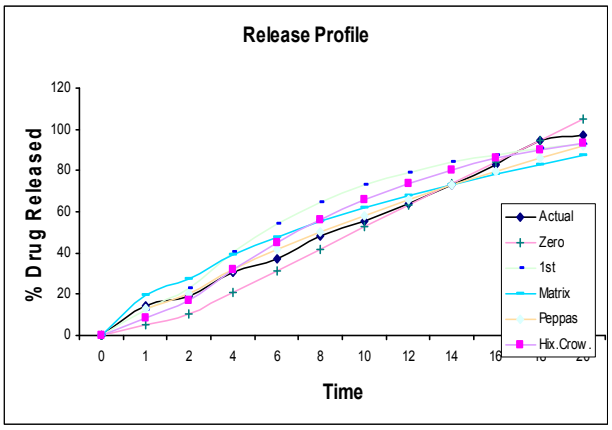


Fig.1: Swelling-eroding behavior of optimized batches of matrix tablet



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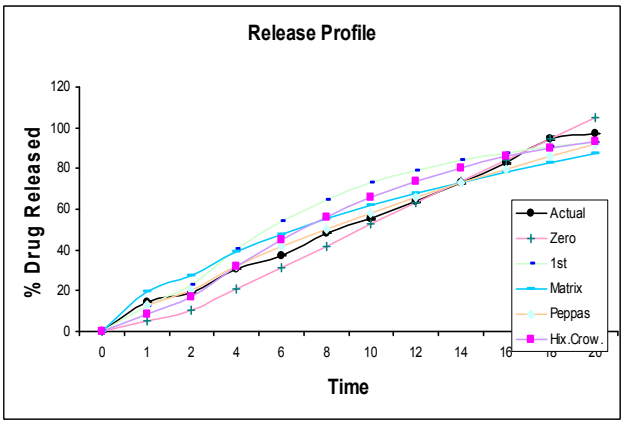

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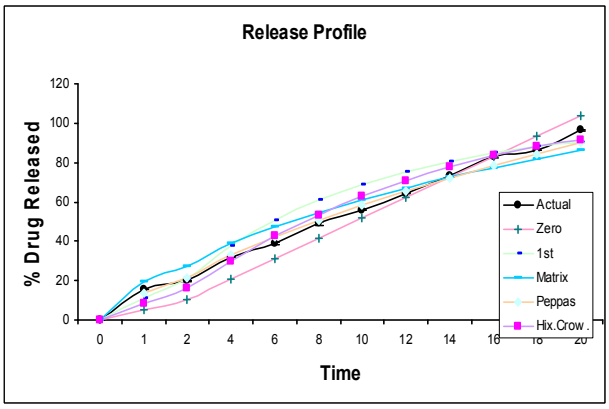

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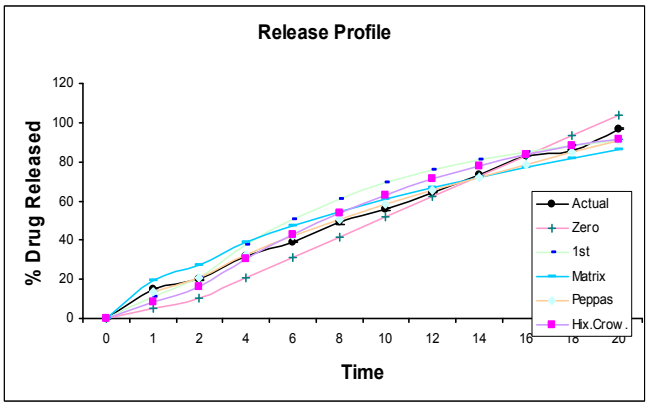

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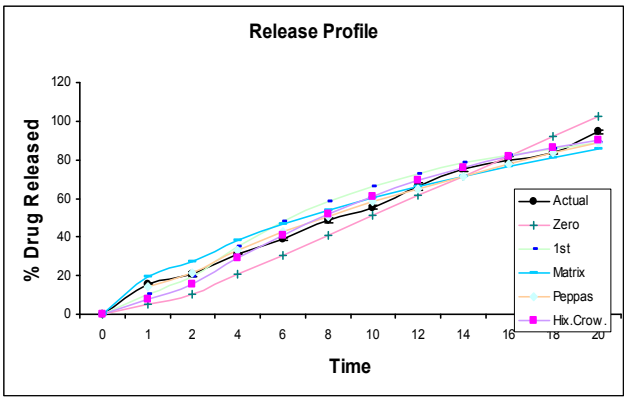

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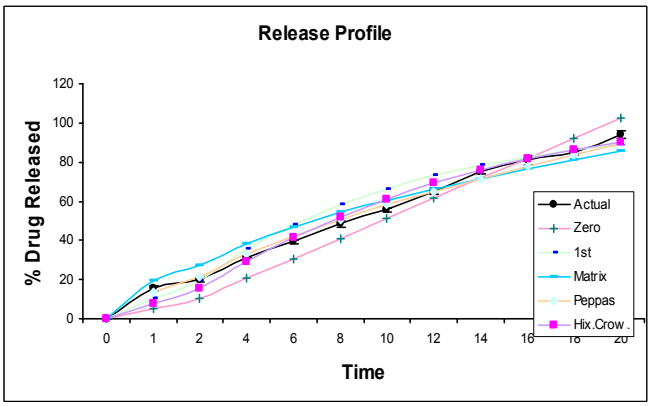

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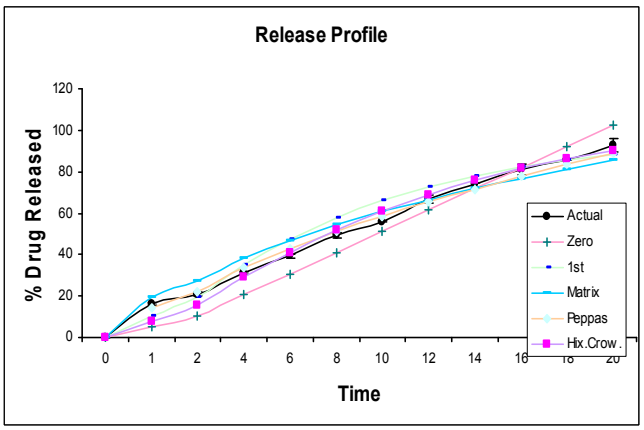

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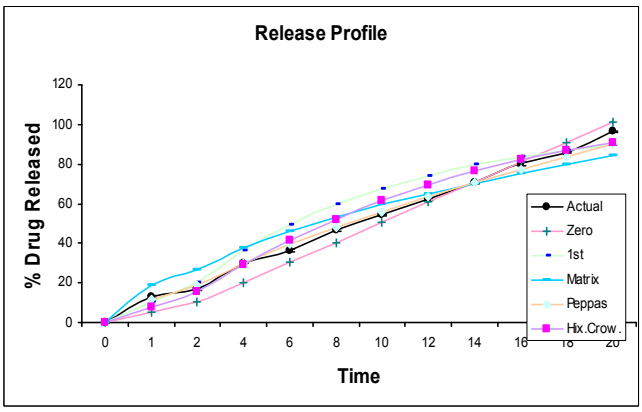

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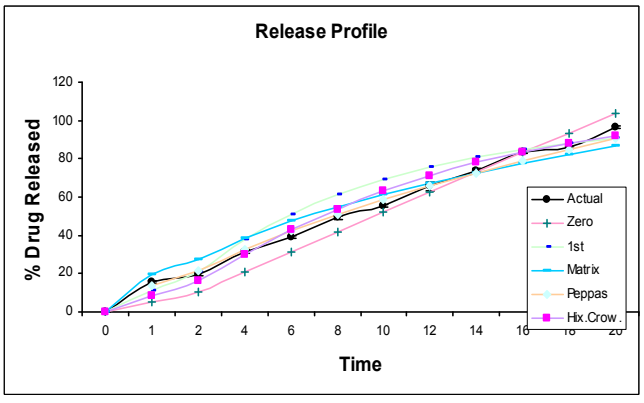

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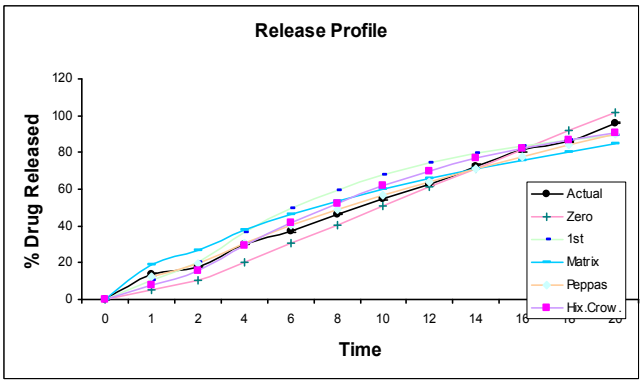

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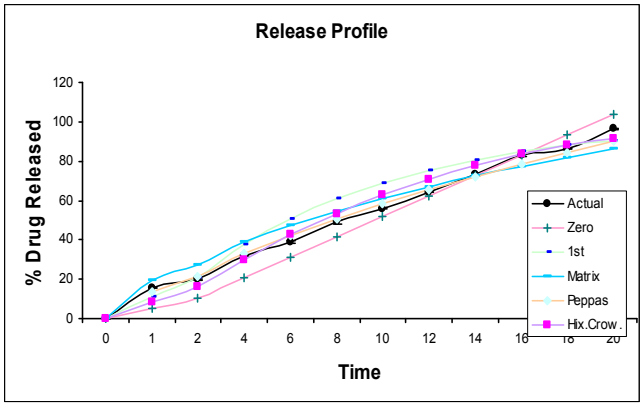

Formulation-11

Fig. No. 2 Kinetic treatment for floating matrix tablet formulations

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