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Research Article

DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF CEFPODOXIME PROXETIL

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ABSTRACT

In this study, we design and evaluated floating matrix tablets of Cefpodoxime Proxetil, to prolong gastric residence time and increase drug absorption further increasing the bioavailability. A simple visible Spectrophotometric method has been employed for the estimation of Cefpodoxime Proxetil at 263 nm and Beer's law is obeyed in the concentration range of 5-40 µg/ml. Preformulation studies were carried out to optimize the required quantity for HPMC (K4M). Sodium CMC, carbopol 934P was used in different concentrations. Total 7 formulations were prepared. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. The tablets were prepared by direct compression technique, using polymer such as hydroxy propyl methyl cellulose (HPMC K4M), sodium CMC and carbopol 934P in different combinations with other standard excipients like sodium bicarbonate, lactose and Magnesium stearate used as gas generating agent, as filler and as lubricant respectively. Tablets were evaluated for physical characterization viz. hardness, friability, swelling index, floating capacity, thickness and weight variation. Further tablets were evaluated *in-vitro* drug release for 12 hr. The effect of polymer concentrations on buoyancy and drug release pattern was also studied. *In-vitro* drug release mechanism was evaluated by PCP V-3 software. All the matrix tablets showed significantly greater swelling index and exhibited controlled and prolonged drug release profiles and some floated over the dissolution medium for more than12 hr. The paddle speed affected the floating lag time and floating duration it had a negative effect on the floating properties. The optimized formulation followed the higuchi release model and showed non-fickian diffusion mechanism. It also showed no significant change in physical appearance, drug content, floatability or *in-vitro* dissolution pattern after storage at 45 ^{o}C at 75 % RH for three months.

Keywords: Cefpodoxime Proxetil, swelling index, floating capacity, HPMC, Sodium CMC,

INTRODUCTION

Oral route is the most convinient and extensively used route for drug administration. This route has high patient acceptability, due to ease of admistration. Over the years the oral dosage forms have become sophisticated with development of controlled release drug delivery system (CRDDS). A number of oral controlled release systems have been developed to improve delivery of drugs to the systemic circulation[1,2].

Cefpodoxime proxetil is a third generation cephalosporin prodrug, having a white to light brownish white powder, odourless, very slightly soluble in water, ether; freely soluble in dehydrated alcohol; soluble in acetonitrile & in

methyl alcohol which is administered orally. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50%. Floating drug delivery is able to prolong the gastric retention of drug and thereby possibly improve oral bioavailability of cefpodoxime proxetil[3]. The half life of cefpodoxime proxetil is 2.2 hours. Cefpodoxime proxetil is a β lactum antibiotic. Its action is by binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall; it inhibits the bacterial cell wall synthesis. It is highly stable in the presence of beta- lactamase enzymes[4].

The gastro-retentive floating matrix tablet of Cefpodoxime proxetil was design by using Cefpodoxime proxetil, Sodium carboxymethylcellulose, carbopol, HPMC, sodium bicarbonate and magnesium stearate.

MATERIALS AND METHODS

Materials

Cefpodoxime proxetil was procured as gift sample from Okasa Pharmaceuticals, Satara. HPMC obtained by Colorcon Asia Ltd, Goa., Sodium CMC was purchased from S.D. fine chemicals Mumbai. All other solvents and reagents were used of analytical grade.

Methods

Formulation of Floating Tablet

Each floating tablets containing 200 mg Cefpodoxime Proxetil were prepared by direct compression method. Cefpodoxime pure drug was mixed with required quantity of HPMC K4M, sodium CMC, carbopol 934P, sodium bicarbonate and lactose by geometric mixing in mortar and pestle for 10 min. The above powder was lubricated with magnesium stearate in mortar and pestle for 2min.The lubricated blend was compressed into tablets using 12 mm flat-face round tooling on CLIT Pilot Press rotary tablet machine[5,6,7]. Compression force was adjusted to obtain tablets of hardness 6-9 kg/cm^2 with 4.0 mm tablet thickness (Table no.1).

Evaluation of Granules

Angle of repose

The angle of repose of Cefpodoxime Proxetil was determined by fixed funnel method[8]. The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using measuring cylinder**.**

Compressibility Index

The Carr's index (%) and the Hausner ratio were calculated using following equations [9].

$$Carr's\ \ Index = \frac{TBD - LBD}{TBD} \times 100$$

$$Hausner\ \ Ratio = \frac{TBD}{LBD} \times 100$$

Evaluation of Tablets

Physical properties like Weight variation, Hardness, Thickness, Friability and Drug content of tablet performed and results shown in Table No.2.

Thickness

Thickness of tablets was determined using Vernier caliper. Three tablets from each batch were used, and average values were calculated[10,11].

Average weight

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method[10].

Drug content

Twenty tablets were crushed and powder equivalent to weight of tablet dissolved in 0.1 N HCl. Then suitable dilutions were made and absorbance at 263 nm wavelength was taken by using a UV spectrophotometer. Drug content was calculated by using absorbance at wavelength 263 nm[10,11].

Hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester[10]. The hardness was measured in terms of kg/cm^2.

Friability

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined[10,11].

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Determination of swelling index

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of distilled water at 37 ± 0.5 ^{0}C paddle rotated at 50 rpm. The tablets were removed periodically from dissolution medium. After draining free from water by blotting paper, these were measured for weight gain.Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation shows relationship between swelling index and time[12,13,14,15].

$$WU\ \% = \frac{\text{Weight of swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

***In Vitro* Release Studies**

The *in vitro* dissolution test was performed using USP type II dissolution test apparatus. The drug release study was carried out in 0.1 N HCl for 12 h in 900 ml of dissolution media, maintained at 37±0.5°C and agitated at 50 rpm. Periodically 5 ml samples were withdrawn and filtered through whatman filter paper and samples were replaced by its equivalent volume of dissolution media. The concentration of Cefpodoxime Proxetil was measured spectrophotometrically at 263 nm.

Buoyancy determination

The buoyancy test of tablet was studied by placing them in 500 ml beaker containing 0.1 N HCl, then tablet from same batches were placed in dissolution test apparatus containing 900 ml 0.1N HCl, maintained at 37±0.5°C and agitated at 50 rpm. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation[16].

RESULT AND DISCUSSION

The reported melting point values for cefpodoxime proxetil was in the range of 160^{0}c.The observed melting point ranged between 155-160^{0}c. The absorption maxima of the standard solution were scanned between 200-400 nm region on shimazdu 1800 spectrophotometer. The absorption maxima were found to be 263 nm.Infrared spectrum shows all prominent peaks of cefpodoxime proxetil. IR spectrum indicated that characteristics peaks belonging to measure functional group such as principle peak at wave number 2937.04,2984.39,3330.81,1618.05 and 1638.19cm^{-1}.The major IR peaks observed cefpodoxime proxetil were 2937.04(C-H), 3330.81(N-H), 1638.19(C=N),1074(C-O), 1761(C=O), 1274(C-N), 1375(C-H) (Fig.1).

The infrared spectrum of physical mixture of polymers (HPMC K4M) and cefpodoxime proxetil was studied and confirmed that there is no interaction with each other. The spectra show all the prominent peaks of drug as well as polymer. IR spectrum indicated characteristics peaks belonging to measure functional group such as principle peaks at wave no. 2941.53, 2984.33, 3332.64, 1623.67 and 1628.19(Fig.2). Hence it can be concluded that there were no any significant changes in the physical mixture of cefpodoxime proxetil and HPMC K4M.

DSC thermogram of cefpodoxime shows endothermic peak at 159^{0}c.where as HPMC K4M shows melting endothermic at 34.40^{0}c.shown in (Fig.3). All formulation from A1 to A7 was evaluated with thickness and diameter of tablets measured by vernier caliper. Thickness and diameter was in range of 3.90 ±0.04 to 4.20±0.04.The hardness was in range of 7.0±0.23 to 9.2±0.40kg/cm^2,which was measured on Monsanto hardness tester. Drug content release was in the range of 96.38±0.12 to 107.73±0.13 shown in (Table 2). The percentage drug release was found 50% after 7 hrs.for all the formulations A1-A7. After12 hrs.it showed 79% drug release shown in Table no.3.

The swelling index was calculated with respect to time. As time increase, the swelling index was

increased because weight gain by tablet was increased proportionally with rate of hydration, later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed as shown in (Fig.4), (Table no.4).

The drug release profile of all 7 formulations from A1 to A7 shown in (Fig.5 & 6).The release rate can be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug. In view of this absorption characteristics, the hypothesis of current investigation is that if the gastric residence time of cepfodoxime proxetil containing formulation is prolonged and allow to float in the stomach for a long period, the oral bioavailability might be increased hence the present research work was to study systematically the effect of formulation variable on the release and floating properties of cepfodoxime proxetil drug delivery system.

For floating drug delivery system,the polymers used must be highly swellable in shortest time. Hence, HPMC was chosen as a main swellable polymeric material. In order to get the longer duration of floating time the high viscosity polymer selected, HPMC K4M was chosen and it was found that, increased viscosity of a polymer prolongs the drug delivery from the dosage form. In order to retain the dosage form in the stomach for a long period of time and to avoid gastric emptying dosage form,carbopol 934P was included.

It was reported earlier that, Carbopol belongs to the class of swellable and adhesive polymers and to utilize this property of carbopol,it was included in the formulation with the intention of adhering the dosage form to the inner wall of the stomach and also possibly to control the release of cepfodoxime proxetil from the dosage form. In the 7 series formulation batch A7 given the highest floating time as compare to A6,A5,A4,A3,A2 and A1 (Table no.5). . Total floating time depends upon the amount of HPMC as the polymer content increased the floating time was increased due to the formation of thick gel which entrapped the gas formed due to $NaHCO_3$ firmly. Due to high viscosity and content of the polymer bursting effect of the tablet was decreased and float for longer duration of time.

From the result of floating lag time it was concluded that, as the concentration of gas generating agent increase the floating lag time get shortens this finding were supported by study of Park et al., reported that as the concentration of gas generating agent ($NaHCO_3$) was increased the floating lag time get shortened and at the same time floating ability get increased.

Carbopol was used as a swelling agent, which also helped in gastric retention due to its adhesive properties. But carbopol affected floating properties.Physicochemical evaluation i.e. the prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. The evaluated parameters were within acceptable range for all the formulations.

Results of Water uptake study showed that the order of swelling in these polymers could indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of polymer was achieved up to 10 hrs and then gradually decreased due to erosion.

CONCLUSION

Formulated matrix Floating tablets of Cefpodoxime proxetil gave satisfactory results for various physicochemical parameters like hardness, friability, thickness, weight variation and content uniformity. Sodium bicarbonate has predominant effect on the buoyancy lag time, while HPMC K4M has predominant effect on total floating time and drug release. Carbopol 934P also shows significant effect on drug release which was given extra adhesion property and helped to maintain the integrity of the tablet. Lactose also shows significant effect on the drug release. Sodium CMC has given extra adhesion property and helped to maintain the integrity of the tablet. From the study it is evident that a promising controlled release floating tablets of Cefpodoxime proxetil can be developed to increase gastric residence time and there by increasing its bioavailability. All the formulations found to be stable over the storage period and conditions tested. Further detailed investigations are required to establish efficacy of these formulations and fix the required dose.

Table 1: Composition of Floating tablets of Cefpodoxime Proxetil

Ingredient (mg)	A1	A2	A3	A4	A5	A6	A7
Cefpodoxime Proxetil	200	200	200	200	200	200	200
HPMC K4M	100	100	100	100	100	100	100
Sodium CMC	30	30	30	-	30	30	30
Guar Gum	-	-	-	-	-	-	-
Carbopol 934P	50	45	40	30	35	25	20
Lactose	109	109	109	144	104	109	109
Sodium bicarbonate	55	60	65	70	75	80	85
Magnesium stearate	6	6	6	6	6	6	6
Total weight of tablets	550	550	550	550	550	550	550

Table 2: Physicochemical properties of Cefpodoxime floating tablets

Batch code	Average wt (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
A1	550	4.15 ± 0.04	12.11 ± 0.05	7.50± 0.02	0.64±0.085	102.08 ± 0.13
A2	545	3.98 ± 0.02	12.07 ± 0.02	8.4± 0.04	0.78±0.041	99.63 ± 0.12
A3	530	4.05 ± 0.07	12.06 ± 0.04	9.0± 0.06	0.77±0.039	104.71 ± 0.22
A4	560	4.18 ± 0.02	12.07 ± 0.07	7.0± 0.03	0.95±0.075	106.91 ± 0.15
A5	550	4.10 ± 0.04	12.06 ± 0.02	7.8± 0.02	0.71±0.044	107.47 ± 0.10
A6	550	4.07 ± 0.02	12.05 ± 0.09	8.8± 0.04	0.66±0.039	108.44 ± 0.12
A7	545	4.20 ± 0.07	12.01 ± 0.05	7.4± 0.03	0.76±0.060	96.38 ± 0.12

All values are expressed as mean ± SD. F= Formulation code

Table 3: Dissolution drug release data of batch A1 to A7

Time (min)	Cumulative % drug release					
	A1	A2	A3	A5	A6	A7
0	0.000	0.000	0.000	0.000	0.000	0.000
30	5.786	10.349	13.543	15.368	19.931	13.543
60	7.917	12.505	17.086	21.659	29.442	17.999
120	11.520	16.134	19.371	26.251	34.076	21.657
180	15.873	20.512	24.497	35.978	40.652	25.883
240	19.337	24.001	28.647	39.278	43.978	32.322
300	22.454	27.144	32.500	41.821	51.109	38.477
360	27.277	31.992	36.692	45.608	54.947	44.072
420	31.624	36.364	39.265	49.141	58.531	51.704
480	34.899	39.665	43.493	52.510	61.585	56.776
540	40.473	45.264	50.025	59.547	64.472	62.332
600	46.031	50.848	52.440	62.012	66.963	68.738
660	49.748	54.590	57.102	66.725	69.877	74.219
720	54.169	59.036	62.930	71.235	72.576	79.409

All values are expressed as mean ± SD, n=3, F=code of formulations

Table 4: swelling index of batch A1 to A7

Time (min)	% Swelling index						
	A1	A2	A3	A4	A5	A6	A7
0	0	0	0	0	0	0	0
15	38	38	39.6	32.14	40.38	37	31.5
30	53.38	51.9	49	35.71	51.92	40	53.7
60	67.73	71.15	64.15	55.35	69.23	68.5	72.2
120	84.61	84.6	84.9	76.8	88.46	85.18	101.85
180	103	101.9	105.66	91.07	119.2	107.4	122.22
240	115.38	119.23	128.3	101.78	123.07	125.9	142.6
300	121.15	126.9	132	108.92	134.61	133.33	157.4
360	134.61	136.53	137.7	116	150	140.74	161.11
420	138.46	142.3	143.39	123.21	153.84	142.6	175.9
480	145.84	146.84	150.05	121.65	160.35	148	178.77
540	153.84	153.84	157.69	115.84	171.15	153.7	181.48
600	151.19	150	150.94	105.65	170	151.85	182.4
660	148	148	150.94	104.77	166	150	185.9
720	136	138	140	102.55	160	140	194.9

Table 5: Floating ability of various Cefpodoxime tablet formulations

Batch Code	Floating Lag time (min)	Floating duration (min)	Integrity
A1	Not float	Not float	Intact
A2	Not float	Not float	Intact
A3	32	20	Intact
A4	28	40	Broken after 6-8Hrs
A5	20	60	Intact
A6	40	>720	Intact
A7	49 sec	>720	Intact

All values are expressed as mean ± SD, n=3, CP= Formulation codes.

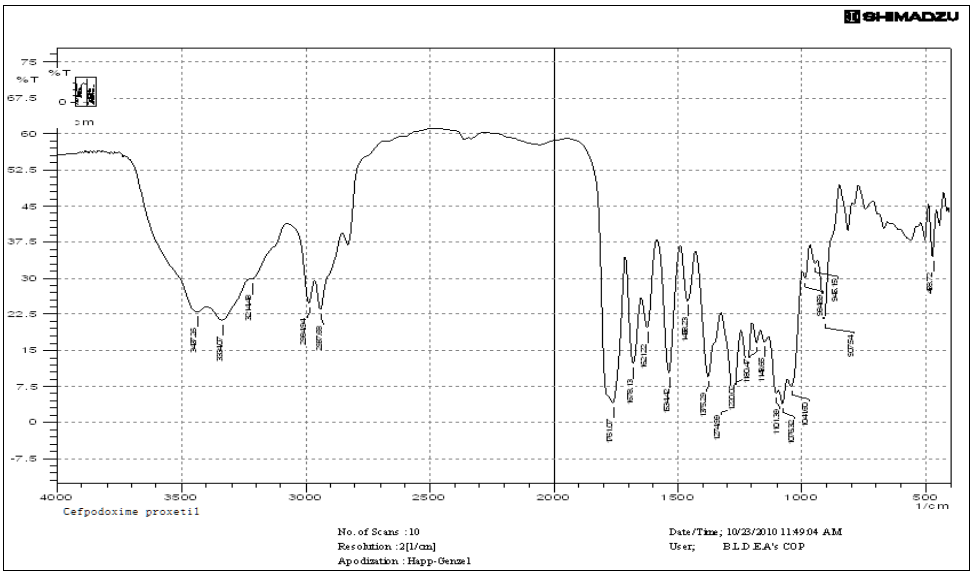

Fig. 1: IR spectrum of cefpodoxime proxetil

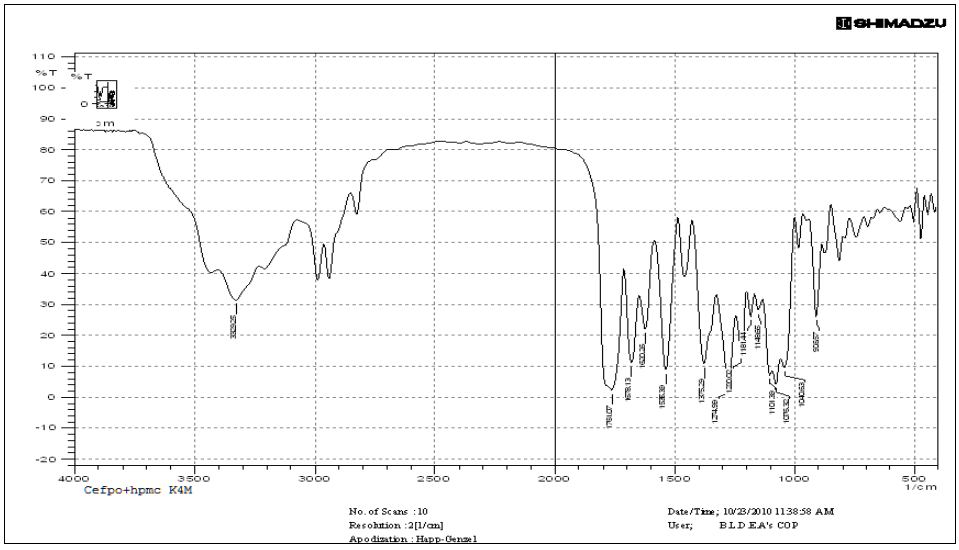

Fig. 2: IR spectra of mixture of Cefpodoxime proxetil + HPMC K4M (2:1)

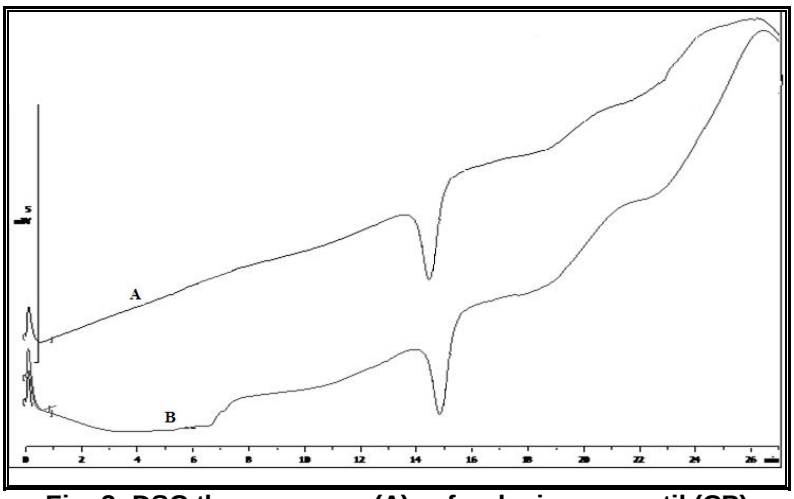

Fig. 3: DSC thermograms (A) cefpodoxime proxetil (CP) (B) CP+HPMC K4M + sodium bicarbonate

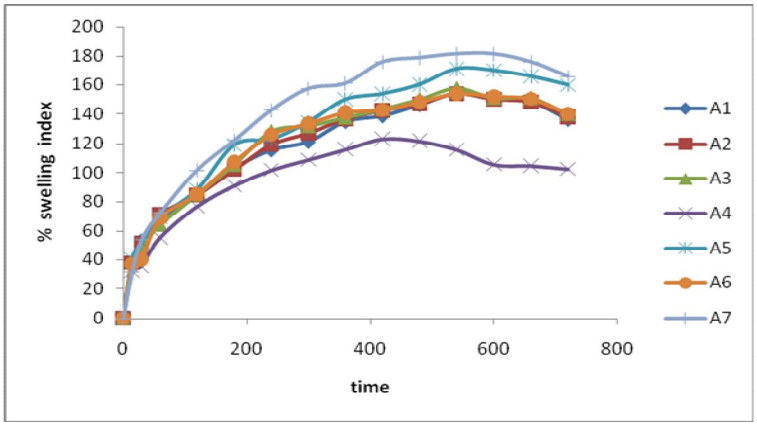

Fig. 4: Relationship between swelling index and time of A1 to A7

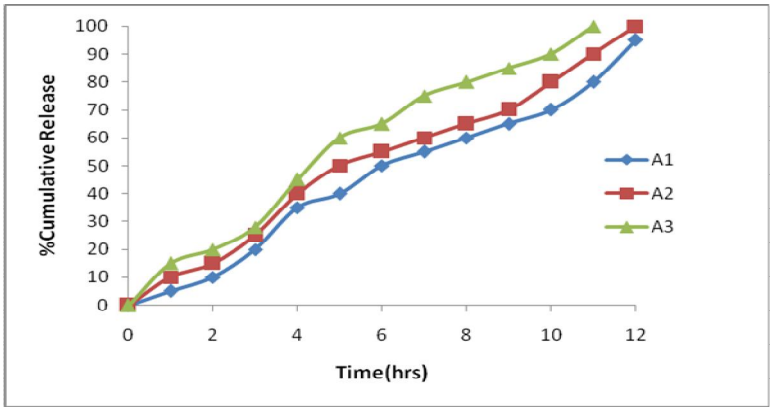

Fig. 5: Drug release Profile of A1, A2, A3

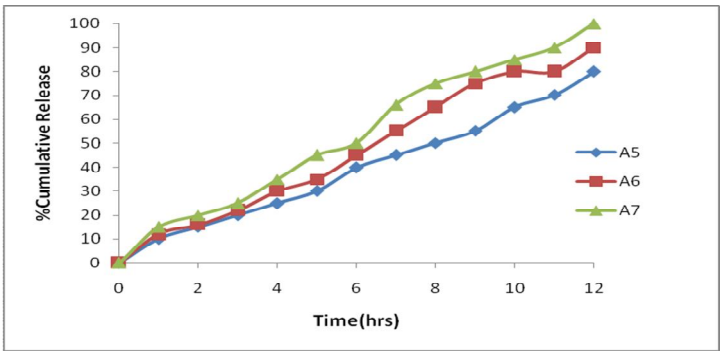

Fig. 6: Drug release Profile of A5, A6, A7

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