FLOATING BILAYER TABLET FOR DRUG DELIVERY SYSTEM CONTAINING CEFPODOXIME PROXETIL FOR PROLONGED GASTRIC RESIDENCE

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ABSTRACT

In the present study, formulation of bilayer floating tablet containing cefpodoxime proxetil is developed and evaluated for prolongation of gastric residence time. Bilayered floating tablets of cefpodoxime proxetil were prepared by direct compression technique, with ion exchange resin to achieve the deliver of drug at sustained/ controlled manner in gastrointestinal tract and consequently into systemic circulation. In order to validate the technological design of this system, two different batches were prepared and in both cases, the time necessary for the tablets to begin to float was less than 30 min. Twelve formulations were prepared, A1 - A6 formulations which showed drug release between 95.29-79.87 % respectively. In the B1 to B6 formulations first three formulations have given the 100% drug release within 9 hrs and remaining formulations showed controlled drug release up to 12 hour. Scanning electron microscopy was done to find the swelling and the porosity of the tablet.

Key words - Cefpodoxime proxetil, bilayered floating tablets, floatation, controlled release, buoyancy.

1. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form (Chein YW, 1992). Despite several advantages associated with controlled drug delivery system, there are number of disadvantages present with this type of drug delivery system such as over-dose, less flexibility in dose adjustments, side effects, accidental poisoning and cost of production. To overcome these problems and improve the efficacy of oral administration, some recent studies have reported that controlled oral drug delivery system with prolonged gastric residence time, such as floating dosage system have following advantages for the specific drugs (Robinson JR, 1987). Drugs that act locally in the stomach e.g., antacids, antibiotics for bacterially based ulcers etc. Drugs that are absorbed primarily in the stomach e.g. albutamol. Drugs that are poorly soluble in alkaline pH. Drugs that have a narrow window for absorption i.e. Drugs that are absorbed mainly from the proximal part of small intestine. e.g. riboflavin, levodopa, p-amino benzoic acid. Drugs that are absorbed rapidly from the GI tract. e.g. amoxicillin. Drugs that degrade in the colon. e.g. Captopril, metoprolol. However, each system may also have its own problems such as high variability in gastric emptying time due to variations in emptying process. Drugs that cause irritation and lesions to gastric mucosa and unstable in gastric fluid cannot be formulated as Floating drug delivery system (FDDS). Unpredictable bioavailability, and in most cases the minimum effective concentration is achieved slowly. Gastric retention is influenced by many factors such as gastric motility, pH, and presence of food. These factors are never constant and hence the buoyancy cannot be predicated.

In this investigation, studies were carried out to design a drug delivery system for water insoluble third generation cephalosporin drug, cefpodoxime proxetil, as a model drug to improve the bioavailability of the drug, using FDA approved cellulosic polymers while utilizing the technological concepts of swelling and flotation in order to obtain a unique drug delivery system which could solve the above problems and remain in a stomach for a much longer period of time. In vitro tests

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for release of drug, floating and swelling of the tablets were performed.

2. MATERIALS AND METHODS

Cefpodoxime proxetil, HPMC K100M, HPC-HF, carbopol 934, sodium starch glycolate and sunset yellow (FD&C grade) were procured from Karnataka antibiotics, Bangalore. Tulsion T-339 was procured from Thermax Ltd., Pune. Glycine, sodium bicarbonate, lactose, talc, magnesium stearate, sodium chloride and hydrochloric acid were procured from S.D. Fine Chem. Ltd., Mumbai.

Preparation of bilayer floating controlled release matrix tablets with fast release layer:

Floating bilayer tablet controlled release matrix tablet consisting of two layers i.e. fast release & controlled matrix layer. Fast release layer consisting drug & excipients as mentioned in Table 1 mixed thoroughly in mortar. The second layer is matrix layer consisting of drug, polymer & excipients including gas-generating agents were mixed thoroughly as mentioned in different proportions as mentioned in Table 2. Bilayer tablets were prepared by punching by using Ellite punching machine with a die & punch of 14 mm diameter. First the matrix controlled release layer was compressed followed by fast release layer.

Evaluation of Bilayer tablets:

The prepared floating bilayered tablets were evaluated for hardness, weight variation ,friability (Banker GS, 1990). Friability test was conducted for ten tablets using a Roche friabilitor (electrolab) and the percentage weight loss was calculated. Crushing strength of the tablets was measured by using a Monsanto hardness tester. Weight variation test, the mean weight of 20 tablets of each batch was determined using an electronic balance (Satorium UK) in order to verify the uniformity and conformity of tablets within the each batch (U.S. pharmacopoeia) the mean weight is expressed in milligram.

Drug content:

The assay of the drug content was carried by weighing ten tablets and calculated the average weight. The tablets were triturated to a fine power. The powder was weighed accurately about 650 mg of the power (Equivalent to 350 mg of cefpodoxime proxetil) was taken in a beaker and 50 ml of glycine dissolution media was added, and stirred for 2 h. The solution is filtered through Whatman filter paper in to 100 ml volumetric flask. The volume was made with dissolution media. From the above solution 0.5 ml and 1.0 ml aliquots were pipetted into two separate 50 ml volumetric flask and the volume is made with dissolution media and the absorbance was measured at 259nm.

Floating property study:

One tablet from each formulation batch was placed in 1000 ml beaker containing glycine dissolution medium maintained at $37^0 \pm 2^0$ C. The floating time by which the tablet constantly remains on surface of medium was noted (USP, 2005; IP, 1996).

Swelling characteristics:

Swelling of tablet excipients involves the absorption of a liquid resulting in an increase in weight and volume. The liquid enters the tablets through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling was measured in terms of % weight gain by the tablet.

Dissolution study:

Dissolution study for each batch was carried out using USP type II apparatus using paddle. The 900 ml of glycine dissolution media at the temperature of $37^0 \pm 2^0$ was set. One tablet was placed in each dissolution vessel and the rotational speed of paddle was set at 75 rpm. The 5.0 ml of sample was withdrawn at predetermined time interval for 12 h & same volume of fresh medium was replaced. The samples were analyzed for drug content at 259 nm using double beam UV visible spectrophotometer (USP, 2005).

Data analysis:

The matrix systems were reported to follow the zero order release rate and the diffusion mechanism for the release of the drug. To analyse the mechanism for the release and release rate kinetics, regression coefficient values for *In vitro* drug release kinetics calculated using zero order, first order, Higuchi matrix, Peppas and Hixson Crowell model (. Paulo C, 2005).

Scanning electron microscopy:

SEM has been used to determine particle size distribution, surface topography, and texture and also to examine the morphology of fractured or sectioned surface. The SEM analysis was conducted using a JOEL, JSM- T330A Scanning microscope for the optimized formulations (Jacob S, 1999).

3. RESULTS AND DISCUSSION

Evaluation of physical parameters for tablets done and results are shown in Table 3. Hardness of all tablets was observed in the range of 5.75 to 8.45 Kg/ cm^2 Results of friability tests all formulations were found in the range of 0.24 to 0.45 %, which was found to be within the limits. The drug content was done as per USP specifications, which was found in the range of 96.16 to 102.83 %. Results of floating properties study reveals that all tablets had good floating properties. This might be due to the presence of gas generating agent i.e., $NaHCO_3$, HPMC and HPC content. These finding were supported by study of (Baumgartner et al., 2000) who reported that incorporation of sodium bicarbonate helps to improve floating properties by reacting with gastric fluid when dosage form comes in contact and produce carbon dioxide gas which entrapped inside the hydrophilic matrices leads to increase in volume of dosage form resulting in lowering of density and dosage form starts to float.

Scanning electron microscopy of the formulation was mainly carried out to examine the surface of polymeric drug delivery system which provide important information about the porosity and microstructure of the device. From the scanning it was observed that as the time increases the swelling and the porosity of the tablet was increased which was mainly helps to drug release shown in Fig 1.

In the A series formulations, batch A6 given the highest floating time as compared to A5, A3, A1, A4 and A2 respectively. The total floating time mainly depend upon the amount of HPMC and HPC content, as the polymer content increased the floating time was increased due to formation of the thick gel which entrapped the gas formed due to $NaHCO_3$ firmly and float longer duration of time. Due to high viscosity and content of the polymer bursting effect of the tablet was decreased and float for longer duration of time.

In the B series formulations, batch B6 given the highest floating time as compared to B5, B4, B2, B5 and B1 formulations respectively. The floating time of this series formulations was less as compared to the A series formulations, mainly due to less polymer content. It was observed from the floating results, hardness of the tablet was not much affecting the floating time of the tablet as compare to the polymer and lactose content as shown in the Table 3 and Fig 2.

In the A series formulations, A1 batch given the maximum swelling due to high viscosity HPMC and the swelling decreased as the amount of HPC is increased in the formulation. In the B series formulations B1 batch showed the maximum swelling as compared to remaining formulations. So it was concluded that HPC polymer has a negative impact on the swelling. In the formulation of B series B1, B2 and B3 showed the swelling within the 6-8 h, after this swelling index was decreased due to erosion rapidly which leads to maximum drug release in short period. From the results it was concluded that formulation A1, A2, B4, B5 and B6 showed the good swelling index as compared to the remaining formulations which leads to the maximum drug release with required period of time as shown in the fig 3.

From the results of *in vitro* release study shown in the Fig 4 it was observed that the tablet of batch A1 and A2 gave highest % cumulative drug release which might be due to the presence of low level of HPC-HF than that in A3, A4, A5 and A6. These batches gave the drug release of 95.29%, 93.11%, and 89.81%, 87.11%, 82.65% and 79.87 % respectively. In these formulations the amount of HPMC-K100M is constant and the amount of HPC-HF was in increasing order from batch A1 to batch A2. From this study it was evaluated that, as the content of HPC-HF increased the drug release was less. In the second group of formulation, it was observed that the tablet of batch B1, B2 and B3 gave maximum % cumulative drug release with in 9 hours only as compared to remaining batches B4, B5 and B6. These remaining batches gave the drug release of 98.86%, 96.26% and 93.47% respectively. In these formulations the amount of HPMC-K100M was less as compared to the first group of formulations. The hardness of these formulations was less as compared to the above formulations.

The curve fitting results of the release rate profile of the designed formulations gave an idea on the release rate profile and the mechanism of the drug release (Higuchi T, 1963; Peppas NA, 1985). Fitting of the release rate data to the various models revealed that most of the formulations such as A2, A3, A5, A6, B1, B4 and B5 follow Higuchis Model. Formulations A1 and A4 follows Peppas model and remaining B2, B3 and B6 followed first order release rate kinetics as shown in the Table 5.

4. CONCLUSION

- All the formulations A group and B group showed good floating property and a controlled drug release.
- It was revealed that polymer content, lactose content and hardness had significant influence on drug release (floating lag time increased in case of elevated hardness).
- The stability study revealed that there was not significant change in dissolution profile for a period of 1 month. From FTIR spectral analysis, it was concluded that there was no interference in the functional group as the principle peaks of the drug were found to be unaltered in the drug polymer physical mixture.
- It was observed that tablets of batch A1, B5 and B6 given maximum drug release up to 12 hours and followed zero order drug release profile. Model fitting of the release profile of all formulations using five different models viz. Zero order, First order, Higuchi matrix, Peppas model and Hixson-Crowell equation. Most of the formulations followed Higuchi model and remaining followed Peppas and first order release kinetics.
- The hydrophilic matrix of HPMC, HPC and Tulsion T-399 helps in the floating of drug thereby prolonging the gastric residence time. Further exploration of floating drug delivery systems for drugs having site-specific absorption in upper part of gastrointestinal tract.

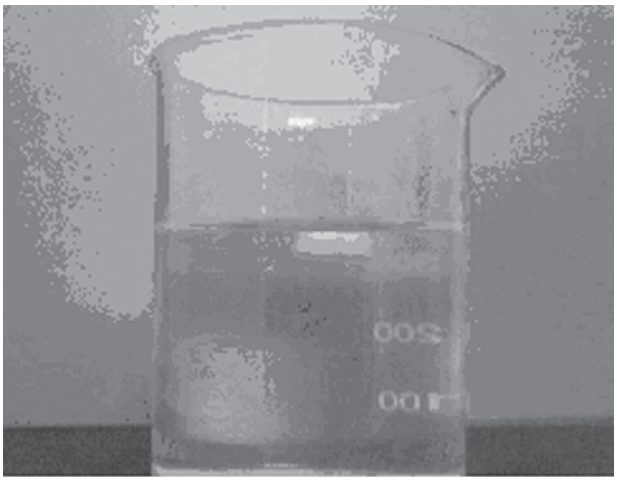

Fig 2: Bilayer floating tablet floats in dissolution media

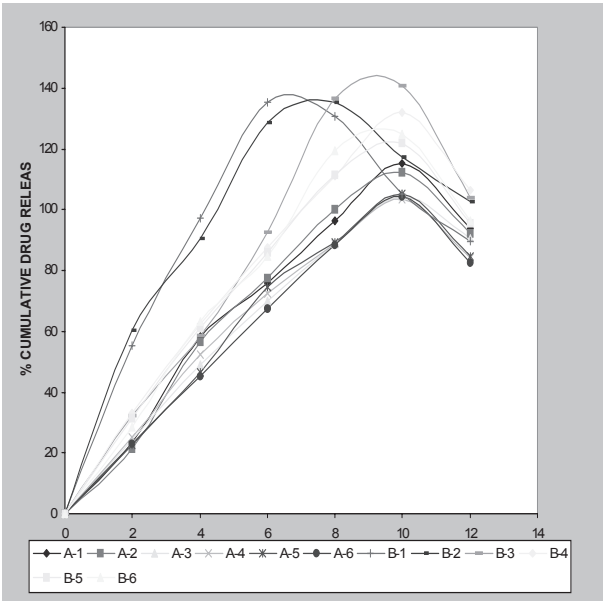

Fig 3: Swelling index of formulations

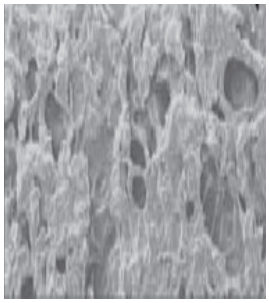

Fig 1c) SEM for A1 after 8 hrs swelling at X500 magnification

Fig 1d) SEM for A1 after 12 hrs swelling at X500 magnification

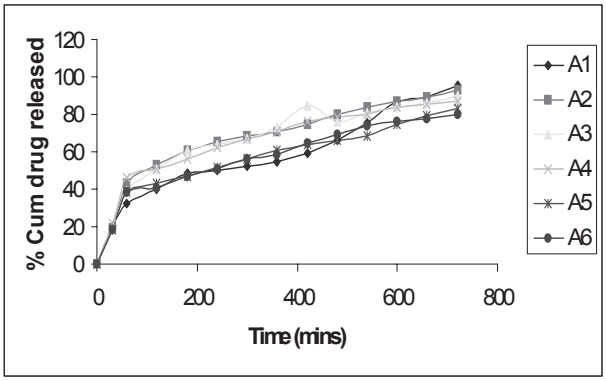

Figure 4a) *In-vitro* release of formulation A1 to A6

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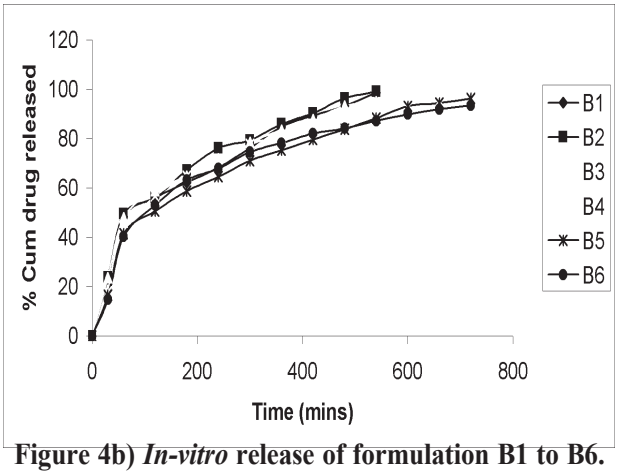

Figure 4b) *In-vitro* release of formulation B1 to B6.

Table 1: Formulation of fast release layer

Ingredients	FR1 (mg)	FR2 (mg)	FR3 (mg)	FR4 (mg)	FR5 (mg)	FR6 (mg)
Cefpodoxime proxetil	100	100	100	100	100	100
SSG	4 (2%)	6 (3%)	8 (4%)	12 (6%)	14 (7%)	16 (8%)
Sunset yellow	3	3	3	3	3	3
Talc	8	8	8	8	8	8
Lactose	85	73	81	67	75	63
Magnesium stearate	--	10	--	10	--	10

Table 2: Formulation of controlled release layer

Ingredients mg / tab	Formulation code											
	A1	A2	A3	A4	A5	A6	B1	B2	B3	B4	B5	B6
Cefpodoxime proxetil	250	250	250	250	250	250	250	250	250	250	250	250
Tulsion T- 399	15	15	15	15	15	15	15	15	15	15	15	15
HPMC	60	60	60	60	60	60	50	50	50	50	50	50
HPC	40	50	60	70	80	90	40	50	60	70	80	90
Carbopol	05	05	05	05	05	05	05	05	05	05	05	05
Sodium bicarbonate	30	30	30	20	30	10	30	30	30	20	30	10
Lactose	50	40	30	30	10	20	60	50	40	40	20	30

Table 3: Evaluation Parameters of Floating Bilayer Tablet of Cefpodoxime Proxetil

Batch	Thickness mm ± S.D	Hardness Kg/cm^2 ± S.D	%Friability ± S.D	Weight Variation %	Drug Content (%)	Floating lag time (min)	Total floating time (hour)
A1	3.77±0.5	8±0.5	0.245±0.1	0.648±1.15	99.12	15±1	16:35
A2	3.76±0.2	7.85±0.1	0.354±0.13	0.647±0.97	99.1	16±0.5	16.2
A3	3.75±0.1	8.15±0.14	0.456±0.11	0.648±1.98	99.37	18±0.5	16:40
A4	3.77±0.5	8.22±0.17	0.348±0.14	0.651±0.50	99.45	25±2	16:22
A5	3.80±0.4	7.90±0.11	0.423±0.24	0.653±1.37	99.68	16±0.1	18:00
A6	3.71±0.2	8.45±0.25	0.4530±0.10	0.648±1.45	100.32	28±0.2	19:10
B1	4.45±0.2	6.14±0.17	0.241±0.09	0.651±1.55	99.55	13±0.1	16:00
B2	4.40±0.5	5.85±0.32	0.323±0.14	0.652±0.55	99.42	14±0.4	16:15
B3	4.44±0.1	5.96±0.09	0.422±0.12	0.647±0.75	99.84	14± 0.2	16:35
B4	4.38±0.3	6.16±0.02	0.399±0.23	0.647±0.76	100.1	20±0.1	16:20
B5	4.42±0.4	6.50±0.08	0.413±0.14	0.648±1.22	100.19	16±0.4	16:05
B6	4.48±0.1	5.75±0.34	0.443±0.23	0.652±0.98	100.1	23±0.4	17:30

Table 4: Model Fitting of the Release Profiles Using Different Models (R Values)

Formulation code	Mathematical Models (Kinetics) r values					Best fit model
	Zero order	First order	Higuchi matrix	Peppas	Hixson Crowell	
A1	0.803	0.924	0.975	0.979	0.922	Peppas
A2	0.625	0.945	0.96	0.953	0.88	Higuchi
A3	0.649	0.941	0.966	0.964	0.877	Higuchi
A4	0.591	0.93	0.955	0.958	0.658	Peppas
A5	0.646	0.905	0.964	0.968	0.844	Higuchi
A6	0.717	0.942	0.974	0.966	0.893	Higuchi
B1	0.761	0.974	0.979	0.962	0.94	Higuchi
B2	0.745	0.879	0.978	0.964	0.936	First order
B3	0.696	0.184	0.974	0.969	0.957	First order
B4	0.688	0.815	0.876	0.845	0.826	Higuchi
B5	0.768	0.978	0.982	0.959	0.958	Higuchi
B6	0.708	0.976	0.971	0.947	0.928	First order

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