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An Approch to Formulate Bilayered Gastro Retentive Floating Drug Delivery System of Cefpodoxime Proxetil

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Abstract: Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic antibiotic of cephalosporin class. Cefpodoxime proxetil is prodrug; its active metabolite is cefpodoxime. The present investigations involve formulation and evaluation of bilayered floating tablets with cefpodoxime proxetil as model drug for prolongation of gastric residence time. An attempt was made to prepare bilayered floating tablets of cefpodoxime proxetil by direct compression technique, with a view to deliver the drug at sustained or controlled manner in gastrointestinal tract and consequently in to systemic circulation. The prepared bilayered floating tablets were evaluated for compatibility study, buoyancy lag time, total floating time, in-vitro dissolution and stability studies. Twelve formulations were prepared, A1 - A6 formulations had shown 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 given controlled drug release up to 12 hour. Bilayered floating tablets have shown drug content between 98 to 102 %. Fourier transform Infrared spectroscopy confirmed the absence of any drug-polymer interaction. The stability of the drug loaded bilayered floating tablet showed that the drug was stable at storage condition of room temperature. *In-vitro* release studies were carried out in glycine dissolution medium and the formulations A1, A2, B4, B5 and B6 have shown good results. The study also indicated that the amount of drug released decreases with an increase in the polymer concentration

Key words: Cefpodoxime proxetil, Bilayered-floating tablets, Flotation, Controlled release, Buoyancy lag time, Total floating time.

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[1].

Now days most of the pharmaceutical scientists are involved in developing an ideal Drug delivery system. This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site. Scientists have succeeded to develop a system that can be as near to an ideal system and it encourages the scientists to develop controlled release system. The design of oral controlled drug delivery systems should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose[2].

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 advantages.

A gastrointestinal drug delivery system can be made to float in the stomach by a gelling process of hydrocolloid materials or by incorporating a floatation chamber, vacuum or gas filled. In this way bulk density less than that of gastric fluid is produced. However, most of the devices generating gas or gelling need time to be floated and this parameter must be checked carefully in order to prevent the dosage form from transiting in to the small intestine together with food before floating in stomach. Among the floating system, multiple unit formulation shows several advantages over monolithic ones; more predictable drug release kinetics, less chances of localized mucosal damage, insignificant impairing of performance due to failure of a few units, co administration of units with different release profile or obtaining incompatible substances, larger margin of safety against dosage form failure [1,3].

These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs. The gastric emptying time mainly depend upon on the design of the dosage form and physiological state of the subject, which last from a few minutes to 12hrs. The relatively brief gastric emptying time in human is 2-3hrs through major absorption zone (stomach and upper part of the intestine), which leads to incomplete drug release from the Drug delivery system leading to diminished efficacy of the administered dose. So, for the drugs, which have stability problem, this Drug delivery system plays an important role. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities [4].

Gastroretentive floating drug delivery system (GRFDDS) will also greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time.

Finally, GRFDDS 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. Need of gastro retention arises because of two reasons, viz [5]

- To improve bioavailability of drugs such as cyclosporin, ciprofloxacin, ranitidine, metoprolol tartarate, cefuroxime axetil etc. which are mainly absorbed from upper part of GIT or get degraded in basic $P^{H.}$
- For local action in case of pathologies of stomach.

The time required for the content of the stomach to enter small intestine is denoted by gastric retention time (GRT). This retention time is almost similar for particular species. In case of human beings, it is 3 to 4 hours short transit time of many conventional dosage forms in stomach, limits complete utilization of active agents. Extended GRT is required, if either drug action is required locally i.e., in stomach or if drug is not absorbed through small intestine. For this several methods are reported which can be employed to increase gastric emptying time. Hydrodynamically balanced drug delivery system is most widely used. Multilayered tablet concept has long been utilized to develop controlled release formulations. Such tablets have fast release rate and may contain one (bi-layered) or two (triple) layers to sustain drug release so as to maintain therapeutic concentration.[6]

The gastroretentive dosage form will release the drug over an extended period in stomach and upper GI tract thus enhancing opportunity for absorption.

Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic antibiotic of cephalosporin class. Cefpodoxime proxetil is prodrug; its active metabolite is cefpodoxime. After oral administration cefpodoxime proxetil is absorbed from the gastrointestinal tract and de-esterifies to active metabolite cefpodoxime. Over the recommended dosing range (100 to 400 mg) only the 50% of administered cefpodoxime dose was absorbed systemically. Also the drug has only 2 to 3 hours half-life.

In the present investigation it is intended to formulate and evaluate the floating bilayered drug delivery system for increasing the bioavailability of cefpodoxime proxetil. Formulation of Floating tablet containing cefpodoxime proxetil as a drug candidate which would remain in stomach and/or upper part of GIT for prolonged period of time thereby maximizing the drug release at desired site within the time before GRFDDS left the stomach and /or upper part of GIT.

Cefpodoxime proxetil floating delivery was prepared by incorporating the drug and polymer in one layer, and the gas generating agent and polymer in another layer, then compressing both into a single unit[7].

Materials and methods

The active drug Cefpodoxime proxetil obtained from Lupin pharmaceutical Pune, and other ingredients such as HPMC K100M, Carbopol 934p, $NaHC0_3$, Lactose, and HPC-HF

obtained from Lupin pharmaceutical Pune, and S.D. Fine Chemicals Ltd., Mumbai. Tulsion T-339 was obtained from Thermax Ltd, pune.

Drug Excipients Interaction Study

Infra red spectrometry is a useful analytical technique utilized to check the chemical interaction between the drug and the other excipients used in the formulations. The samples were powdered and intimately mixed with dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler and the spectra recorded by scanning in the wavelength region of 2.5 to 25 μ in a FTIR spectrophotometer (Thermo Nicolet, Japan). The IR spectrum of drug was compare with that of the physical mixture to check for any possible drug-excipents interaction[8].

Formulation Design

Preparation of fast release layer

The fast release layer contained uniform mixture of drug, and excipients. The tablets were prepared by using direct compression technique. Weighed quantities of drug and excipients as shown in **(Table 1)** were mixed properly in a mortar. The well-mixed powder was compressed using a multi station punching machine with a die and punch of 14 mm diameter. The hardness is adjusted for the 8 kg/cm^2.

Preparation of matrix layer for controlled release

The matrix layer contains uniform mixture of drug, polymer and excipients including gas-generating agent. The tablets were prepared by using direct compression technique. Weighed quantities of drug equivalent to 200 mg cefpodoxime proxetil, was mixed properly in a mortar with weighed amount of polymer and excipients as shown in

(Table 2) The well-mixed powder was compressed using a multi station punching machine with a die and punch of 14 mm diameter. The hardness is adjusted for the 8 kg/cm^2.

Preparation of bilayer tablets[6]:

Matrix tablet is prepared as mentioned above in the procedure of preparation of matrix layer controlled release. After the compression upper punch was lifted and the blend of powder for immediate release layer was poured in the die, containing initially compressed matrix tablet and compressed for the hardness of 8 kg/cm^2.

Effect of polymer content, hardness and lactose on floating lag time and drug release study [9, 10]

The effect of different formulations and process parameters such as polymer content, hardness and lactose concentration on the drug release and floating time of the tablet was carried out. In this case the amount of HPMC polymer and lactose was decreased. The hardness of the tablet is decreased from 8 kg/cm^2 to 6kg/cm^2. The same procedure was used for the preparation of the bilayer-floating tablets.

Evaluation of Prepared Floating Tablets

These tablets were evaluated for thickness, hardness, friability, drug content, floating lag time, total floating time (TFT), swelling index. **(Table-3, 4 and 5).**

Dissolution study [11]

Dissolution of the tablet of each batch was carried out using USP type II apparatus using paddle. Nine hundred ml of glycine dissolution media was filled in a dissolution vessel and the temperature of the medium were set at $37^0 + 2^0$ C. One tablet was placed in each dissolution vessel and the rotational speed of paddle was set at 75 rpm. The 5 ml of sample was withdrawn at predetermined time interval for 12 hours and same volume of fresh medium was replaced. The samples were analyzed for drug content against glycine dissolution media as a blank at 259.0 nm using double beam UV visible spectrophotometer. The content of drug was calculated using the equation generated from standard curve. The % cumulative drug release was calculated.

Scanning electron microscopy (SEM):

The SEM analysis was conducted using Jeol, Japan (Model - JSM 5610LV) scanning electron microscope for the optimized formulation in the following states,

- Dry tablet surface and
- Tablets after swelling of 4, 8 and 12hrs.

As with SEM high vacuum is required for image formation and samples must be thoroughly desiccated before entering the vacuum chamber, therefore samples were thoroughly dried after swelling for analysis. The dried samples were mounted on sample holder using double sided adhesive carbon tape. The SEM was operated at 15 KV. The condenser lens position was maintained at a constant level[12].

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 of the dosage form, the data obtained was fitted in to, Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected[12].

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a varity of environmental factors such as tempreture, humidity and light, and enables recommended storage conditions, re-test periods and shelf –lives to be established.

ICH specifies the length of study and storage conditions:

Long term testing 25^0c ± 2^0c /60 % RH±5% for 12 months.

Accelerated testing 40^0c ±2^0c / 75% RH ±5% for 6 months[7].

In the present study, stability studies were carried out at for a specific time period up to the 30 days for selected formulations. The selected formulations were analyzed for the following parameters Appearance, Hardness and Drug content.

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	Formulation code											
	A1 (mg)	A2 (mg)	A3 (mg)	A4 (mg)	A5 (mg)	A6 (mg)	B1 (mg)	B2 (mg)	B3 (mg)	B4 (mg)	B5 (mg)	B6 (mg)
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 934P	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 tablets of each batch

Formulation code	Evaluation parameters				
	Thickness± S.D. (mm)	Hardness ± S.D. (Kg/cm^2)	Friability ± S.D. (%)	Average weight Variation (%)	Drug Content (%)
A1	3.77±0.5	8±0.5	0.245±0.1	0.648±1.15	99.12
A2	3.76±0.2	7.85±0.1	0.354±0.13	0.647±0.97	99.1
A3	3.75±0.1	8.15±0.14	0.456±0.11	0.648±1.98	99.37
A4	3.77±0.5	8.22±0.17	0.348±0.14	0.651±0.50	99.45
A5	3.80±0.4	7.90±0.11	0.423±0.24	0.653±1.37	99.68
A6	3.71±0.2	8.45±0.25	0.4530±0.10	0.648±1.45	100.32
B1	4.45±0.2	6.14±0.17	0.241±0.09	0.651±1.55	99.55
B2	4.40±0.5	5.85±0.32	0.323±0.14	0.652±0.55	99.42
B3	4.44±0.1	5.96±0.09	0.422±0.12	0.647±0.75	99.84
B4	4.38±0.3	6.16±0.02	0.399±0.23	0.647±0.76	100.1
B5	4.42±0.4	6.50±0.08	0.413±0.14	0.648±1.22	100.19
B6	4.48±0.1	5.75±0.34	0.443±0.23	0.652±0.98	100.1

Table 4. Results of floating property of the bilayered floating formulations

Formulation code	Floating lag time (min)	Total floating time (hr)
A1	15±1	16:35
A2	16±0.5	16.20
A3	18±0.5	16:40
A4	25±2	16:22
A5	16±0.1	18:00
A6	28±0.2	19:10
B1	13±0.1	16:00
B2	14±0.4	16:15
B3	14± 0.2	16:35
B4	20±0.1	16:20
B5	16±0.4	16:05
B6	23±0.4	17:30

Table 5. Results of swelling studies of Bilayered floating Formulations

Formulation code	Percentage swelling in hour						
	0	**2**	**4**	**6**	**8**	**10**	**12**
A1	0	23.44	58.32	75.93	96.25	115.35	94.25
A2	0	21.22	56.45	77.45	100.17	112.37	92.41
A3	0	24.45	48.90	69.87	88.49	104.37	90
A4	0	25.30	52.45	72.65	88.45	103.31	84.21
A5	0	22.42	46.67	74.57	89.15	105.32	84.00
A6	0	22.92	45.07	67.75	88.57	104.93	82.16
B1	0	55.27	97.02	135.67	130.67	104.93	89.00
B2	0	60.52	90.64	128.48	135.24	117.45	102.44
B3	0	32.45	58.45	92.42	131.56	140.87	104.05
B4	0	33.20	62.20	87.67	110.81	132.05	106.45
B5	0	31.45	61.25	85.66	111.45	121.84	95.67
B6	0	28.45	63.45	84.67	109.58	124.90	96.45

Table 6. Model Fitting of the Release Profiles Using Five 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

Table 7. Selected formulations stored at 25^0C / 60% RH

Formulation code	Tested after time (In -days)	Hardness (Kg /cm^2)	Drug content uniformity (%)	CDR (%)
A1	10	7.95±0.12	99.45	96.26
	20	7.87±0.41	99.23	95.45
	30	7.80±0.32	99.16	95.26
A2	10	7.85± 0.24	99.15	94.12
	20	7.54±0.32	99.18	93.27
	30	7.21±0.45	99.09	93.12
B4	10	6.15±012	100.25	97.57
	20	6.05±0.23	100.30	97.52
	30	5.97±0.15	100.18	97.46
B5	10	6.50±0.45	100.18	96.51
	20	6.39±0.23	100.16	96.24
	30	6.26±0.10	100.15	96.35
B6	10	5.75±0.14	100.13	93.32
	20	5.70±0.21	100.14	93.36
	30	5.66±0.11	100.06	93.29

Table 8. Selected formulations stored at 40^0C / 75% RH

Formulation code	Tested after time (In -days)	Hardness (Kg /cm^2)	Drug content uniformity (%)	CDR (%)
A1	10	7.92±0.14	99.46	96.75
	20	7.91±0.22	99.42	96.42
	30	7.87±0.23	99.45	99.32
A2	10	7.85±0.24	99.18	94.56
	20	7.82±0.12	99.22	94.43
	30	7.80±0.41	99.14	94.33
B4	10	6.12±0.24	99.16	97.54
	20	6.23±0.26	99.21	97.64
	30	6.12±0.36	99.12	97.26
B5	10	6.50±0.23	99.22	96.54
	20	6.49±0.24	99.16	96.35
	30	6.48±0.21	99.15	96.45
B6	10	5.74±0.23	99.30	93.65
	20	5.72±0.21	99.14	93.78
	30	5.70±0.31	99.26	93.44

Result and discussion

Oral drug delivery system represents one of the frontier areas of controlled drug delivery system. Such a dosage forms are having a major advantage of patient compliance. Floating drug delivery system belongs to oral controlled drug delivery system group that are capable of floating in the stomach by bypassing the gastric transit. These dosage forms are also defined as Gastro Retentive drug delivery system or hydrodynamically balanced dosage form or gastric floating drug delivery system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged period. The release rate will 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 characteristic, the hypothesis of current investigation is that if the gastric residence time of

cefpodoxime proxetil containing formulation is prolonged and allowed 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 variables on the release and floating properties of cefpodoxime proxetil floating drug delivery system.

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From results, it was concluded that there was no interference in the functional group as the principle peaks of the cefpodoxime were found to be unaltered in the drug polymer physical mixture. The physical parameters of drug as well as excipients concluded that these were considerably good to formulate the tablet using direct compression technique. Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics **(Figure 1a, b).**

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-K100M 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 of dosage form, carbopol 934-P 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 cefpodoxime proxetil from the dosage form. The HPC- HF is also mainly used for the controlled release of the drug. It was reported that it helps to maintain the integrity of the tablet and carried out prolonged drug release in the desired concentration. Tulsion T-339 is used as a disintegrant. Tulsion T-339 swells up at a very fast rate upon contact with water or gastrointestinal fluid and acts as a tablet effective disintegrant. The rate of swelling of polymer depends upon the amount of water taken up by the polymer. Hence, sodium bicarbonate ($NaHCO_3$) is added in the formulation which upon contact with HCl liberates carbon dioxide (CO_2) and expels from the dosage form creating pores through which the water can penetrate into the dosage form and the rate of wetting of polymer increases and the time required for drug release decreases. Lactose a hydrophilic agent, with assumption that capillary action of lactose may facilitate higher drug release without affecting the matrix (there by floating ability) is used. The incorporation of lactose showed appropriate release and floating time. The immediate release layer was formed by using SSG as a disintegrant that was widely used due to its effectiveness in standard concentration range of 2 to 8%. SSG gives the maximum disintegration at the 4%. In the prepared formulations FR5 had given less disintegration time as compared to the FR4 formulation. From this it was concluded that magnesium stearate has a gelation property and it retards the disintegration time of formulation. Lactose was used due to its capillary action. In these formulations FR5 gives the best result as compared to FR4, FR3, FR6, FR2 and FR1.

From the results of the in vitro release study of the tablets with different hardness between the A type and B type formulations, it was observed **(Figure 2 to 7)** that there was a drastic drug release from the tablet at less hardness i.e., 8 kg/cm^2 to 6 kg/cm^2. Lactose also played the important role in drug release, as it is hydrophilic polymer. Due to its capillary action there was more amount of drug release by the diffusion process. The in-vitro release study of all formulations showed a retarded release with increased percentage of both HPMC and HPC polymer. The hardness of the tablet and the amount of filler such as lactose also plays an important role for retardation of the drug.

On the basis of release data and graphical analysis formulations A1, A2, B4, B5 and B6 showed good controlled release profile with maximum drug release following zero-order kinetics and floating time more than 12 hours.

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.[13] 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. 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 less polymer content. It was observed from the floating results that, hardness of the tablet was not much affect the floating time of the tablet as compare to the polymer and lactose content.

From the results of floating lag time it was concluded that as the concentration of gas generating agent increases the floating lag time get shortens. These findings were supported by study of Park et al [14] who 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.

Another aspect of result of these studies clears that the level as well as viscosity of the polymer had a great impact over the floating lag time and total floating time, as the level and viscosity of the polymer was reduced the floating lag time get shorten. It was also observed that total floating time was greater when the viscosity of the polymer used was greater, which was supported by Li and co-workers[15] who reported that higher viscosity grade generally exhibited greater floating capability.

Buoyancy of the tablet was governed by both the swelling of the hydrocolloid particle on surface when it contacts the gastric fluids, which in turn results in an increase in the bulk volume and the presence of internal void space in the dry center of the tablet (porosity). On decreasing the hardness of tablets of A series to B series from 8 kg/cm3 to 6 kg/cm^2, resulting in drastically decreased in lag time which might be due to less compression resulting in increase of porosity of the tablets and moreover, the compacted surface hydrocolloid particles on the surface of the tablet can hydrate rapidly when the tablets contacts the gastric fluids and as a results of this, the capability of the tablet to float is significantly increased[11].

Results of water uptake (swelling) study cleared that order of swelling observed in these polymers (HPMC) could indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of polymer was achieved after 6-8 hrs and then gradually decreased due to erosion. 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 hours, 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 A1, A2, B4, B5 and B6 given the good swelling index as compared to the remaining formulations which leads to the maximum drug release with required period of time.

From the results of in vitro release study, **(figure 2 and figure 3)** 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.

To overcome an initial burst effect, the high viscosity HPMC polymer used. HPMC-K100M gives prolonged floating and drug release as compare to the low viscosity polymers. According to free volume of theory of diffusion, the probability for a diffusing molecule to jump from one cavity into other decreases due to high viscosity and more concentration of polymer. This leads to decreased drug diffusion co-efficient and decreased release rates with increasing polymer content or viscosity of the polymer. These findings were supported by Xu and Sunada[16] who reported that HPMC content was the predominant controlling factor, as the content of HPMC increased, drug release rare decreased and vice versa.

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. 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 6).**

Scanning electron microscopy of the formulation was mainly carried out. This was mainly used for

examination of 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 **(Fig 8 a, b, c, d).**

Stability study that was carried out concluded that there was no much more effect of the tempreture and moisture on the hardness, drug content and drug release of the tablet as shown in the **(Table 7 and 8).**

Fig 1a IR spectra of pure drug Cefpodoxime proxetil

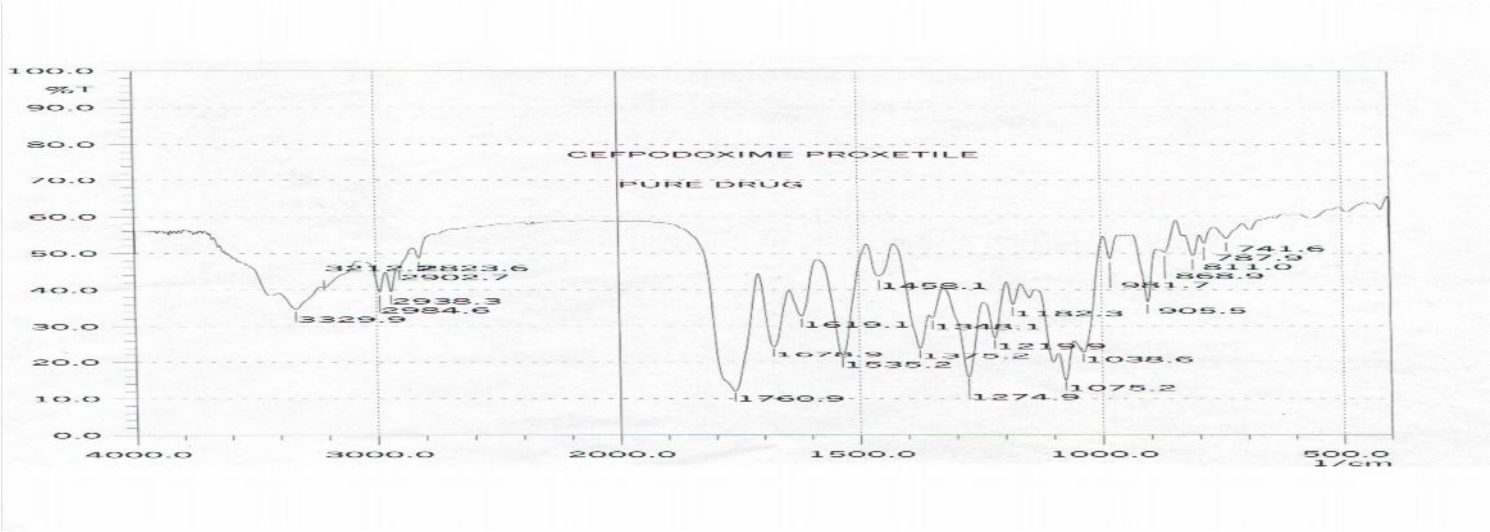

Fig 1b. IR spectra of pure drug along with excipients and polymers

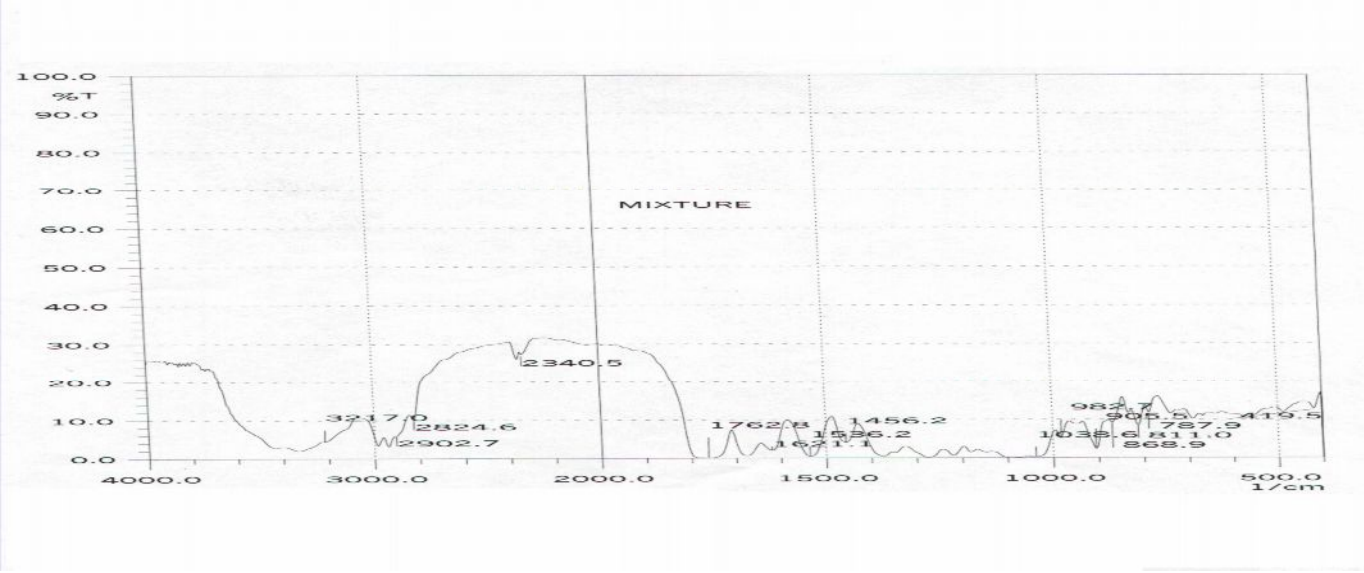

Figure 2: In-vitro release profile of formulation A1 and B1

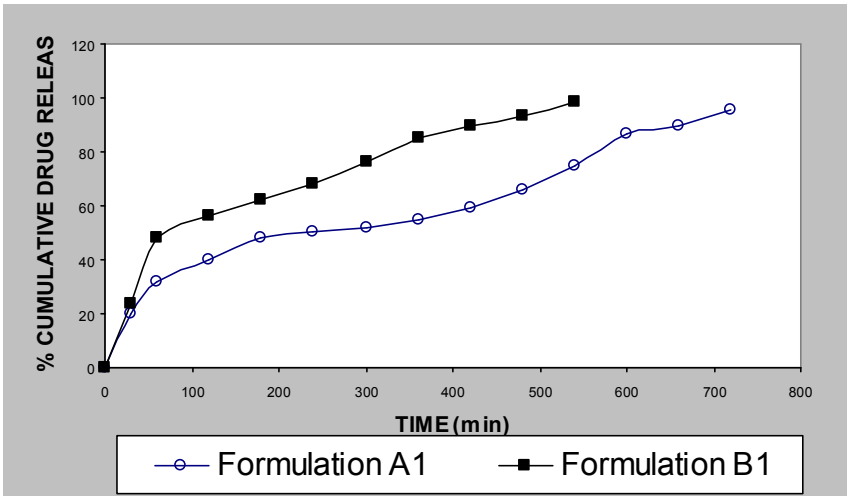

Figure 3: In-vitro release profile of formulation A2 and B2

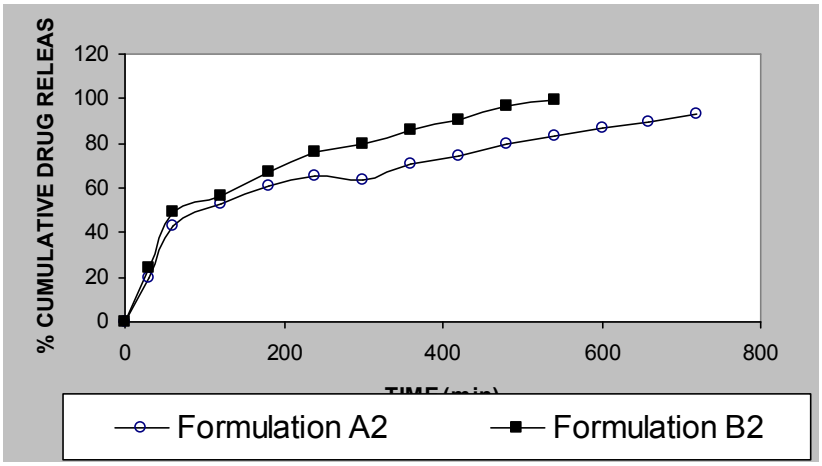

Figure 4: In-vitro release profile of formulation A3 and B3

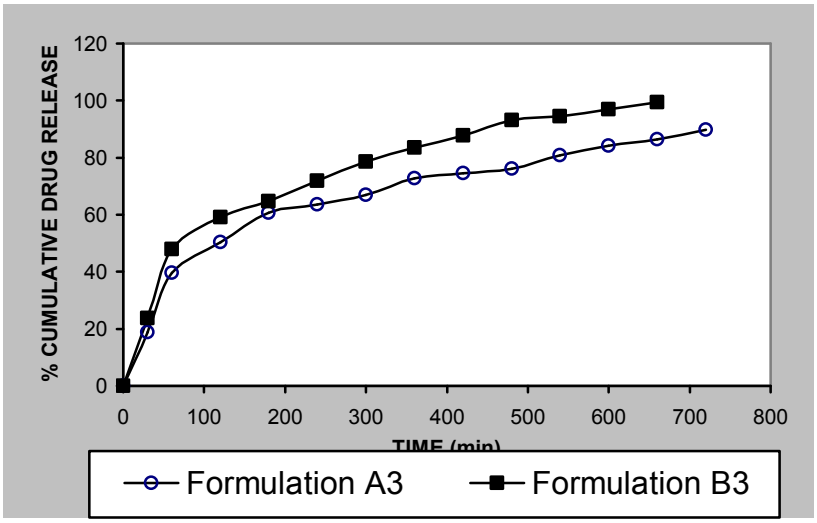

Figure 5: In-vitro release profile of formulation A4 and B4

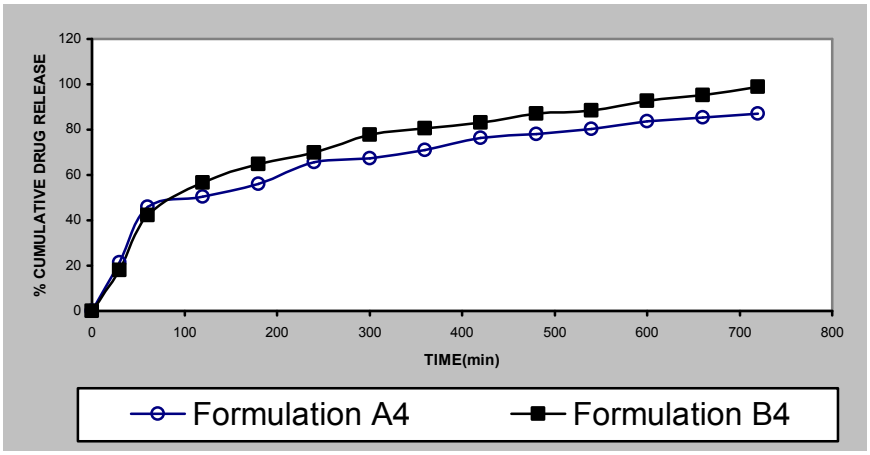

Figure 6: In-vitro release profile of formulation A5 and B5

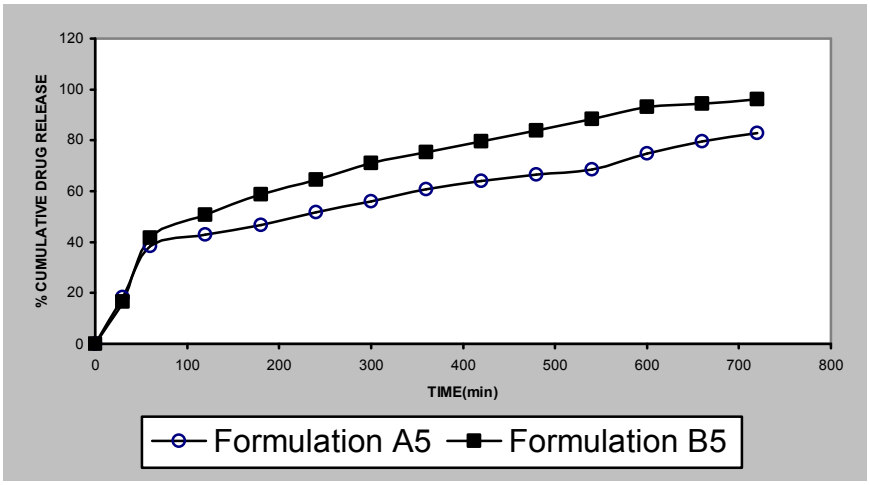

Figure 7: In-vitro release profile of formulation A6 and B6

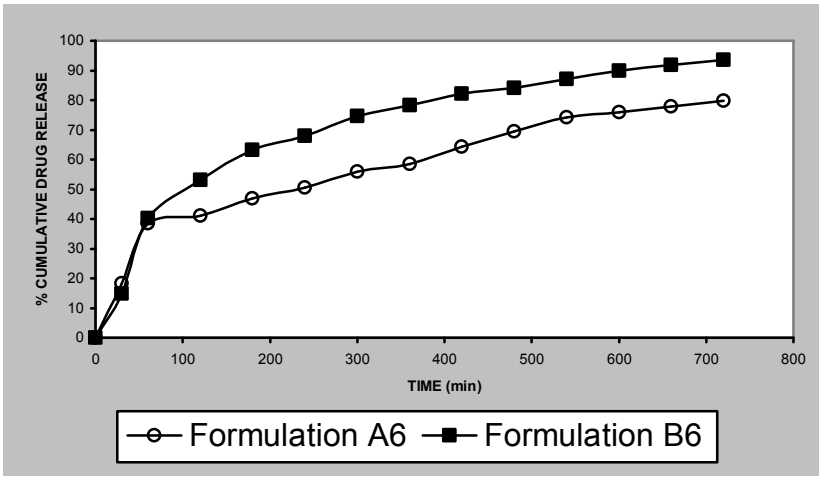

Fig 8. SEM of formulation (A1) at various time intervals

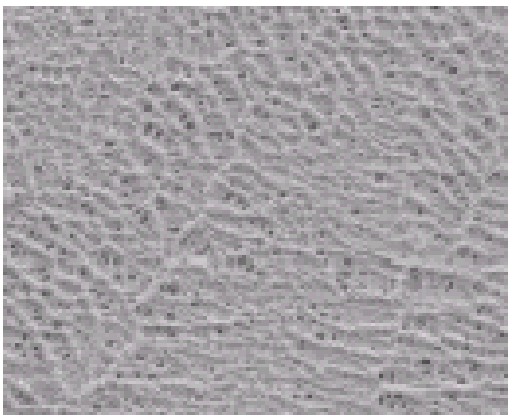

Fig 8a: dry surface at X500

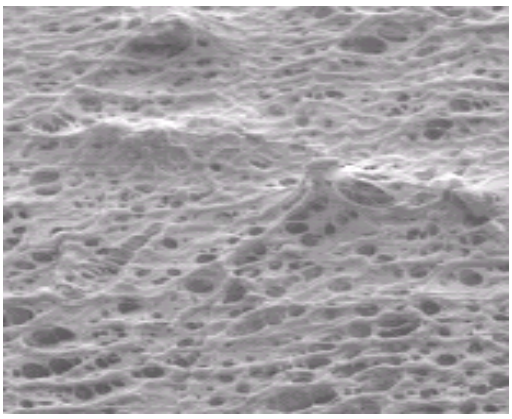

Fig 8b: after 4 hrs at X500

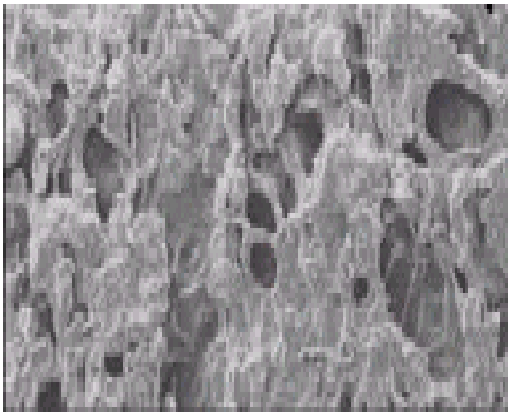

Fig 8c: after 8 hrs at X 500

Fig 8d: after 12 hrs at X500

Conclusion

Sodium bicarbonate has predominant effect on the buoyancy lag time, while HPMC K100M and HPC-HF has predominant effect on total floating time and drug release. Lactose also shows significant effect on drug release. Carbopol P934 has given extra adhesion property and helped to maintain the integrity of the tablet. Bilayered floating matrix tablet with immediate release layer give good floating and a controlled release pattern after initial immediate release. Hardness of bilayered floating tablets show significant effect on the drug release. In-vitro release rate studies showed that the maximum drug release was carried out in the A1, A2, B4, B5 and B6 in the required period of time. All the formulations found to be stable over the storage period and conditions tested. From the study it is evident that a promising controlled release by bilayer floating tablets of cefpodoxime proxetil can be developed.

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