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Research Article

FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING TABLETSCONTAINING CEFPODOXIME PROXETIL SOLID DISPERSIONS

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ABSTRACT

In the present study, an attempt has been made for the formulation of gastro retentive floating tablets of cefpodoxime proxetil (CP) using solid dispersion method, one of the most successful techniques to improve dissolution rate of poorly aqueous soluble drugs. CP is the orally active ester prodrug of third generation cephalosporins and a class IV drug as per BCS is having poor solubility and poor dissolution rate. The main purpose of this investigation was to increase the solubility and dissolution rate of CP by preparing its solid dispersions (SDs) with skimmed milk powder as carrier using solvent dispersion method. Solid dispersions (SDs) and Physical mixtures (PMs) of CP were prepared in various proportions (1:1, 1:2, 1:3 and 1:4). Prepared SDs and PMs were optimized for solubility studies, percent drug content and percent dissolution rate studies. The floating tablets containing SDs of CP were evaluated for uniformity of weight, hardness, friability, drug content, percent swelling index, *in vitro* buoyancy and dissolution studies. The stability studies were conducted as per ICH guidelines. The formulations were found to be stable with insignificant change in the physical properties of tablets and these exhibited satisfactory physico-chemical characteristics. The study revealed that, floating tablets using SDs of CP with skimmed milk powder can enhance its solubility and dissolution rate.

Keywords: Solid Dispersions (SDs), Physical mixtures (PMs), Cefpodoxime Proxetil (CP),Skimmed Milk Powder, Floating Tablets, *In vitro* Dissolution Studies.

INTRODUCTION

Cefpodoxime Proxetil (CP) (1-[(isopropoxycarbonyl) oxy]ethyl ester of (Z)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid) is the orally active ester prodrug of third generation Cephalosporin (**Figure 1**), which is broad-spectrum antibiotic. CP is used orally for the treatment of mild to moderate respiratory tract infections, uncomplicated gonorrhea and urinary tract infections. One of the major problems withthis drug, according to the BCS system (class IV) it has very poor aqueous solubility that results into erratic dissolution in gastric and intestinal fluid and poor bioavailability after oral administration. The efforts to improve the dissolution and solubility of a poorly water-soluble drug remains one of the most challenging tasks in drug development.[1,4]

Solid dispersion (SD) is one of the most successful strategies to improve dissolution rate of poorly aqueous soluble drugs. SDs can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties.[5,7] SDs can be prepared by various methods such as solvent evaporation or melting method. Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug. The mechanism by which the solubility and the dissolution rate of the drug are increased includes: reduction of the particle size of drug to submicron size or to molecular size in the case where solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from amorphous to crystalline form, the high energetic state which is highly soluble; finally, the wettability of the drug particle is improved by the hydrophilic carrier.[8,11]

Oral route is the most convenient and extensively used route for drug administration. Over the years the oral dosage forms have become sophisticated with development of controlled release drug delivery system (CRDDS). CRDDS release drug at predetermined rate, as determined by drug's pharmacokinetics and desired therapeutic concentration. This helps in achieving predictable drug plasma concentration required for therapeutic effect. A number of oral controlled release systems have been developed to improve delivery of drugs to the systemic circulation.[12,13]

One of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT). The gastroretentive drug delivery systems (GRDDS) can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GI tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Various gastro retentive techniques were used, including floating, swelling, high density, and bioadhesivity have been explored to increase the gastro retention of dosage forms.[14,15]

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration and improve oral bioavailability of CP. It is a β lactum antibiotic with half life of 2.2 hours. 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 β- lactamase enzymes.[16,17]

The objective of the present work was to improve the dissolution rate and bioavailability of CP by formulating gastro retentive floating tablets using solid dispersion method in order to control the drug release and provide protection from intestinal milieu.

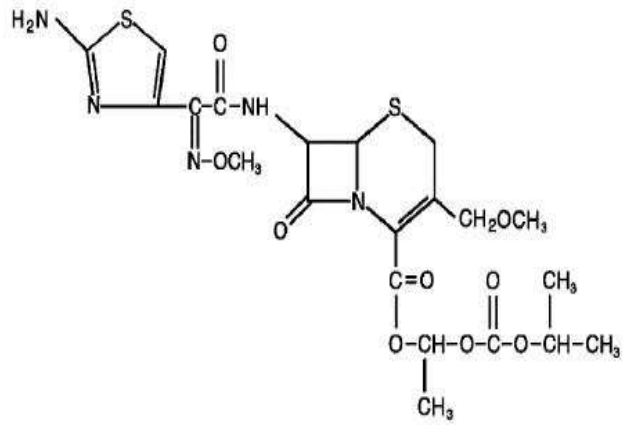

Fig. 1: Chemical Structure of Cefpodoxime Proxetil

MATERIALS AND METHODS

Materials

Cefpodoxime Proxetil was procured as a gift sample from Cadila Pharmaceuticals Pvt. Ltd. (Ahmedabad, India). Skimmed milk powder was kindly provided by Gujarat Co-operative Milk Marketing Federation Anand (India). All other chemicals and reagents were of analytical grade.

Methods

Preparation of Solid Dispersions (SDs) by Solvent Evaporation Method

Solid dispersions of CP were prepared by solvent evaporation method using skimmed milk powder as carrier in the different weight ratios of 1:1, 1:2, 1:3 and 1:4 of drug: carrier polymer. Accurately weighed quantities of carrier (skimmed milk powder) were added to the solutions of CP in ethanol. The solutions were stirred at room temperature and the solvents were allowed to evaporate. Solid dispersions thus formed, were then dried in vacuum oven for 24 hrs at room temperature, pulverized and sieved through sieve no. 60. After the preparation of solid dispersions, the powdered samples were stored in a closed container away from light and humidity until use.

Preparation of Physical Mixtures (PM):

Physical mixtures were prepared by mixing the appropriate amounts of the drug and carrier (skimmed milk) in the different weight ratios of 1:1, 1:2, 1:3 and 1:4 in mortar. The resulting mixtures were sieved through sieve no. 80, collected and stored in closed container away from light and humidity until use.[19,21]

Evaluation of Prepared SDs and PMs

Determination of Saturation Solubility

Saturation solubility was determined by using shake flask method. Excess quantities of pure CP, prepared SDs and PMs were added in 25 ml distilled water in conical flasks which were then put in orbital shaker at 37°C and at 100rpm for 72 hrs. Absorbance of resulting solution was measured on UV/Visible Spectrophotometer (UV-1800Shimadzu, Japan)at 263 nm.

Determination of pH Dependent Solubility

Shake flask method same as that for saturation solubility was used with 0.1N HCl and phosphate buffer saline (pH 7.4) as solvents.

Percent Drug Content

SDs equivalent to 10 mg of CP were weighed accurately and dissolved in 10 ml of ethanol by using mechanical shaker for 30 min. The solutions were filtered using whatman filter paper and drug content was determined by measuring absorbance at263 nm by UV/Visible spectrophotometer.

From above evaluation tests, optimized formulation was confirmed which was then subjected to *in vitro* dissolution studies.

In Vitro Dissolution Studies

In vitro dissolution studies of prepared SDs were carried out in 900 ml of 0.1 N HCl as a medium using USP type 2 test apparatus with three replicates. The paddle rotation speed was 75 rpm, and a temperature of 37 ± 1°C was maintained. In all experiments, 5 ml of dissolution sample was withdrawn at 5 min interval, filtered using a 0.45-mmwhatman filter, and replaced with an equal volume of fresh medium to maintain a constant total volume. Samples were analysedon UV/Visible spectrophotometer at 263nm.[22]

Formulations of Floating Tablets

Each floating tablets containing SDs of CP and carrier complex were prepared by a conventional wet granulation method, employing sodium bicarbonate, citric acid as gas generating agent and water-soluble polymer (HPMCK4M and xanthan gum) as hydrophilic matrix in each formulation. The composition of various formulations isgiven in Table 1. All the ingredients were mixed thoroughly except magnesium stearate and talc. Granules were prepared manually with a solution of the 5% polyvinylpyrrolidone (PVP K30) in sufficient isopropyl alcohol as binder. The wet mass was passed through a 22 mesh sieve no. and the wet granules produced were dried in hot air oven for 30 min at 50°C. The dried granules mixed with magnesium stearate as lubricant, talc as glidant. The granules were then compressed using Lab Press Rotary Tablet Machine using 12mm flat faced punches to obtain the tablets. Prior to compression, granules were evaluated for their flow and compressibility characteristic[23,25]

Table 3: Composition of different floating tablet formulations of SDs of CP

Ingredients (mg)	Formulation Code					
	F1	F2	F3	F4	F5	F6
SDs (CP+ carrier)	100	100	100	100	100	100
HPMC K4M	200	-	100	150	-	100
Xanthan Gum	-	200	100	100	200	100
Sodium bicarbonate	50	60	50	50	50	60
Citric acid	30	30	30	20	20	20
Talc	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10

Evaluation of Granules Properties

Angle of Repose

The angle of repose of was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The Diameter of the powder cone was measured and angle of repose was calculated using the following equation.[26]

$$\theta = \tan^{-1}(h/r)$$

Where, h and r are the height and radius of the powder pile, respectively.

Bulk Density

Both bulk density (BD) and tapped bulk density (TBD) were determined. A quantity of 2g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. BD and TBD were calculated using the following formulas[27].

BD = Weight of the Powder/Volume of the packing.

TBD = Weight of the powder /Tapped volume of the packing.

Compressibility Index/ Carr's Index

The flow property was also determined by measuring the compressibility index. It is an important measure that can be obtained from the BD and TBD. According to the theory, the less compressible materials are more flowable. A material having values of less than 20 to 30% is defined as the free flowing material. Based on the BD and TBD, the percentage compressibility of the bulk drug was determined by using the following formula [28].

Compressibility Index = Tap density – Bulk density/Tap density x 100

Evaluation of Floating Tablets

In vitro Buoyancy determination studies:

In vitro buoyancy studies were performed for all the formulations as per the method described by Rosa *et al.*[29] The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly

remained on the surface of medium was determined as the total floating time (TFT).

Physical properties like General Characteristic, Thickness, Weight variation, Hardness, Friability and Drug Content of tablet performed.[30]

General Characteristic

The formulated tablets were assessed for its general appearance.

Thickness and Diameter

Thickness and diameter of tablets were determined using vernier caliper. Three tablets from each batch were used, and average values were calculated.

Weight Variation

Formulated floating tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is within permissible limits or not.

Friability Test

The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre-weighed tablets were placed in the apparatus, which was given 100 revolutions, after which the tablets were reweighed. The percentage friability was calculated.

$$\% F = 1- (\text{loss in weight/initial weight}) 100$$

Hardness Test

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Percent Drug Content

10 tablets were weighed and powdered. An amount of the powder equivalent to 8mg of CP was dissolved in 100ml of 0.1N HCl, filtered, diluted suitably and analyzed for drug content at 263nm using UV/Visible spectrophotometer.

Determination of Percent swelling index(Percentage Water Uptake)

The swelling properties of floating tablet 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**.**

$$WU\ \% = \frac{\text{Weight of swollen tablet – Initial weight of the tablet}}{\text{Initial weight of the tablet}} X100$$

***In-Vitro* Drug Release Studies**

The *in vitro* dissolution test was performed using USP type 2 test apparatus. The drug release study was carried out for 12 hr in 900 ml of 0.1N HCl 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 absorbance of CP was measured UV/Visible spectrophotometrically at 263 nm.The percentage cumulative drug release was calculated and amount of CP released from tablets was determined.

Dissolution Studies Using USP Type II Apparatus with Wire Sinker

Dissolution test was carried out using USP type II Apparatus with Wire Sinker. The drug release study was carried out for 12 hr in 900 ml of 0.1N HCl 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 absorbance of CP was measured UV/Visible spectrophotometrically at 263 nm.The percentage cumulative drug release was calculated and amount of CP released from tablets was determined. The floating tablet is wound with the helical wire sinker.

Stability Studies

To assess the drug and formulation stability, stability studies were done according to ICH guidelines. The promising formulation F4 was tested for accelerated testing for a period of 2 months at 40°C ± 2°C/ 75% RH ± 5% for their drug content and other parameters.

RESULTS AND DISCUSSIONS

Various SDs of CP were prepared using skimmed milk powder, as carriers by solvent evaporation technique to increase the solubility as well as dissolution of poorly aqueous soluble drug CP. The prepared SDs and PMs of CP were evaluated for saturation solubility, pH dependent solubility, percent drug content, and *in-vitro* dissolution studies.

The saturation solubility and pH dependent solubility of Pure CP, various prepared SDs and PMs of CP in 0.1N HCl & PBS 7.4 were measured (Table1). All PMs showed higher saturation solubility as compared with pure CP. Again, SDs of CP showed higher saturation solubility than their respective PMs of CP and carrier. This might be attributable to an improvement of wetting of drug particles and localized solubilization by the hydrophilic polymeric carriers.

Table 1: Saturation Solubility and pH Dependent solubility Studies of Pure CP, SDs and PMs

Formulation Code	Saturation Solubility in Distilled Water (mg/ml)	pH Dependent Solubility in Distilled Water (mg/ml)	pH Dependent Solubility in PBS 7.4 (mg/ml)
Pure CP	0.3886±0.0044	6.020±0.038	0.3367±0.0027
PM1 (1:1)	0.4481±0.0045	8.328±0.069	0.3265±0.0105
PM2 (1:2)	0.4603±0.0073	9.765±0.0073	0.3981±0.0096
PM3 (1:3)	0.5168±0.0034	10.278±0.086	0.4823±0.0036
PM4 (1:4)	0.5947±0.0046	11.265±0.101	0.5548±0.0174
SD1 (1:1)	1.1802±0.0136	11.984±0.064	0.5107±0.0145
SD2 (1:2)	1.2612±0.0097	12.735±0.028	0.5518±0.0140
SD3 (1:3)	1.4894±0.0036 1.9261±0.0154	13.324±0.071	0.5982±0.0193
SD 4 (1:4)		14.291±0.144	0.6100±0.0248

All values are expressed in Mean ± SD, (n =3)

The low standard deviation values in case of % drug content showed that the drug distribution was uniform in all the SDs and PMsof CP (Table 2).

Table 2: Percentage Drug Content of PMs and SDs

Formula	Percent Drug Content(in 10 mg)
PM1 (1:1)	82.75± 1.54
PM2 (1:2)	86.68± 1.27
PM3 (1:3)	88.01± 0.94
PM4 (1:4)	90.92± 1.44
SD1 (1:1)	93.87± 1.89
SD2 (1:2)	94.50± 2.11
SD 3 (1:3)	95.16± 1.34
SD 4 (1:4)	96.72± 1.53

All values are expressed in Mean ± SD, (n =3)

Based on the saturation solubility and pH dependent solubility in 0.1N HCl & PBS 7.4 and drug content among the 8 formulations, PM4 and SD4 were selected to carry out *in vitro* dissolution study and were compared with that of pure CP.

The in vitro dissolution study of the pure CP, SD4 and PM4 using skimmed milk powder as carrier was carried out in 0.1NHCl at 37±1°C for 60min and it was examined by plotting % drug dissolved against a function of time (Fig 1). SD4 and PM4 showed improved dissolution of CP over that of pure CP. Pure CP alone yields the slowest dissolution with only 30.19% drug and the dissolution of PM4 (78.04%) was found to be significantly faster when compared with pure CP. SD4 showed the fastest dissolution (92.35%) than PM4 and pure CP. This observation indicated that the increased dissolution of CP from SD4 due to presence of drug in amorphous state as compared PM4 and pure CP. As the proportion of skimmed milk powder increased, dissolution rates have alsobeen increased. The improvement of dissolution may be due to its hydrophilic nature of the carrier. Thus it can be concluded that the solubility of the poorly soluble drug, CP can be improved markedly by using solid dispersion technique and the carrier, skimmed milk powder has increased the dissolution of the drug.

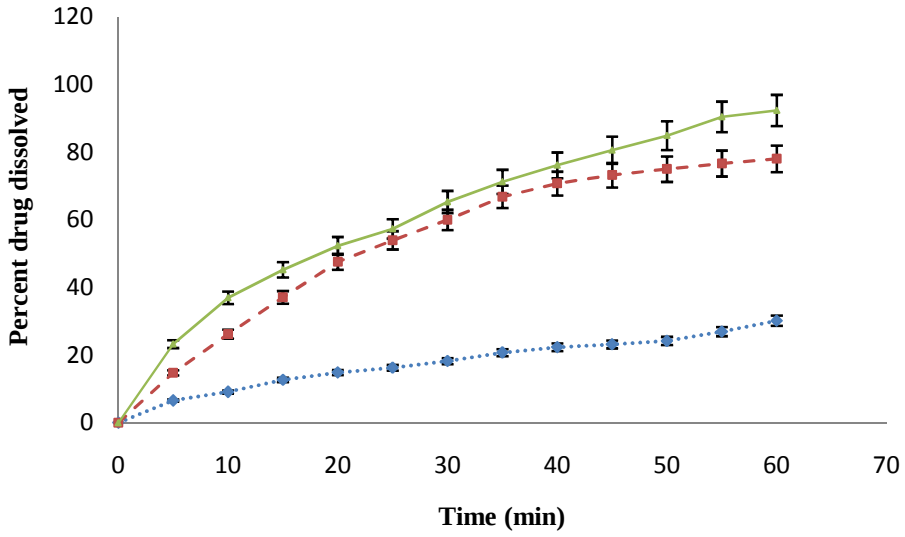

Fig. 2: Percent Drug Dissolution of ---Pure Drug, ---PM 4 and-SD 4

The effervescent floating tablets of SDs of CP were formulated in 6 different batches F1 to F6 by using hydrophilic polymers HPMC K4M and hydrophobic polymer xanthan gum along with effervescing agents, sodium bicarbonate and citric acid (Table 3).

All the formulations were prepared by wet granulation method. 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 gastricemptying dosage form xanthan gum was included, the intention of adhering the dosage form to the inner wall of the stomach and also possibly to control the release of CP from the dosage form.

The pre formulation studies such as angle of repose, bulk density, tapped density, and carr's index evaluated were found to be within prescribed limits and indicated good free flowing property (Table 4).

In vitro Buoyancy of all the prepared tablets formulations were determined using 100 ml beaker containing 0.1NHCl medium shown in (Table 5) and the results can be concluded that the batch F4 containing HPMCK100M and xanthan gum in higher concentration showed good Buoyancy lag time is 4.3 min and total floating time is 15hrs. TFT 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. Among these formulations, the *in vitro* Buoyancy was increased in the following order: F4> F1 > F6 > F3> F5> F2.

Table 4: Pre Compression Parameters of Granules

Parameter	F1	F2	F3	F4	F5	F6
Angle of Repose	22.73^0	22.173^0	22.43^0	22.67^0	22.97^0	22.35^0
Bulk Density	0.963±0.026	0.968 ±0.031	0.972 ± 0.0.098	0.891 ±0.102	0.896 ±0.057	0.901 ±0.083
Tapped Density	1.045±0.011	1.038 ±0.019	1.030±0.026	0.983 ±0.020	0.978 ±0.017	0.971±0.038
Carr's Index	7.84 ±0.94	6.74 ±0.71	5.80 ±0.56	9.35±0.62	8.38 ±0.83	7.20 ±0.49

All values are expressed in Mean ± SD, (n =3)

Table 5: *In vitro* Buoyancy determination

	F1	F2	F3	F4	F5	F6
Floating lag time (FLT) (min)	5.9	9.7	7.1	4.3	9.2	6.5
Total Floating time(TFT) (hr)	13	7	10	15	8	11

The table 5 revealed that FLT maximum for F4 formulation, while its TFT was maximum i.e. 15 hr hence, F4 was selected for further evaluations and *in vitro* drug dissolution studies.

Formulation F4 was evaluated for physical characters like tablet thickness, diameter, hardness, friability, weight variation, percent swelling index, *in-vitro* drug release studies. The Thickness, diameter and hardness of the formulations satisfied the acceptance criteria. The friability and weight variation was found to be within the limits specified in Pharmacopoeia. The drug content was found spectrophotometrically indicating good content uniformity in the prepared formulation results were shown in Table 6.

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. The direct relationship was observed in Table 7.

The floating formulation F4 was subjected for the dissolution studies using USP type II apparatus and USP type II apparatus with wire sinker in 900 ml of 0.1N HCl medium. The results are given in Fig 3. The formulation showed a constant rate of release in a sustained manner similar to zero order kinetics with good buoyancy property.

The formulation F4 was selected for stability studies on the basis of *in vitro* buoyancy and *in vitro* drug dissolution studies. The tablets were evaluated at 40°C ± 2°C/ 75% RH ± 5% for 2 months. At 15 days intervals the tablets were evaluated for all physico-chemical parameter. From the data, the formulation was found to be stable under the conditions mentioned, before since there was no significant change in the percent drug content and other physical parameters (Table 8).

Table 6: General Characteristic of Floating Tablets

Parameter	Formulation F 4
Description	White, circular shape, flat tablets
Thickness	4.21±0.02
Diameter	12.75±0.12
Average weight	793.3±0.04
Hardness (Kg/cm^2)	5.2±0.18
Friability (%)	0.19±0.03
Weight variation	775.8± 2.63
Percent drug content	93.81 ± 0.86

All values are expressed in Mean ± SD, (n =3)

Table7: % Swelling Index (Percentage Water Uptake) of Floating Tablets

% Swelling Index (Percentage Water Uptake)	
Time (hr)	**Formulation F 4**
1.0	23
2.0	39
3.0	51
4.0	66
5.0	75
6.0	87

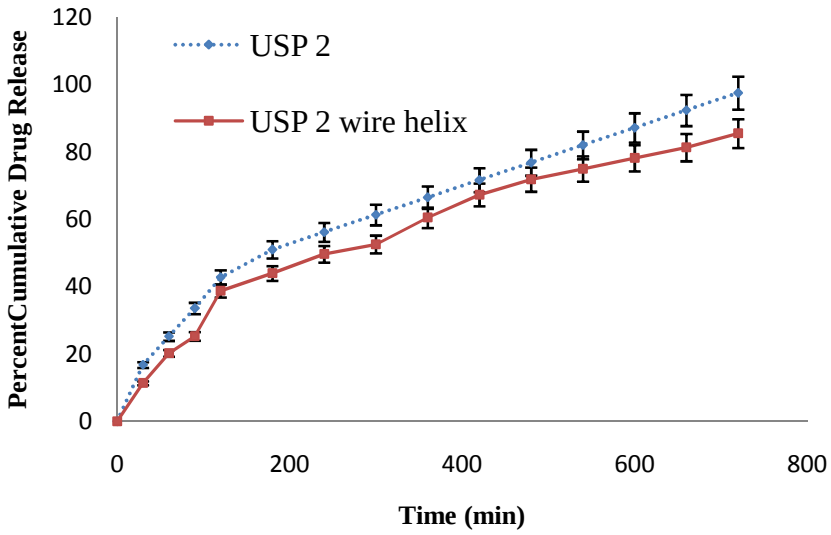

Fig. 3: Percent Cumulative Drug Release by USP 2 and USP 2 Wire Helix Apparatus

Table 8: Stabilities studies of Floating Tablets

Parameter	Formulation F4			
	At 0 day	**At 15 days**	**At 30 days**	**At 60 days**
Physical appearance	White, circular shape, flat tablets	No change	No change	No change
Hardness(Kg/cm2)	5.2	5.2	5.1	5.0
Friability (%)	0.19	0.19	0.20	0.21
Uniformity of Weight(mg)	775-790	770-790	770-790	770-778
Drug content (%)	93.81 ± 0.86	92.68 ± 0.34	92.50 ± 0.58	91.89± 0.12
Thickness (mm)	4.21	4.21	4.2	4.2
Buoyancy Lag Time (min)	4.3	4.2	4.1	3.9
Floating Time (Hrs)	15	14	13.5	11.2

CONCLUSION

According to the results obtained from the experimental work, the SD 4 showed better dissolution when compared with the pure CP and its respective PM which when used to prepare floating tablet which will enhance the solubility, achieve an extended retention in the upper GIT, to protect the prodrug from enzymatic attack which may further enhance the absorption leading to improved bioavailability, reduced dose and minimum side effects.

REFERENCES

1. Todd WM: Cefpodoxime Proxetil: a comprehensive review.Int J Antimicrob Agents.1994; 4: 37-62.
2. Date AA, Nagarsenker MS: Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoximeproxetil.IntJ Pharm. 2007; 329: 166-172.
3. Arora S, Sharma P, Irchhaiya R, Khatkar A, Singh N, Gagoria J: Development, characterization and solubility study ofsolid dispersion of cefpodoximeproxetil by solvent evaporation method. Int JChemTech Res. 2010; 1275-1280.
4. Kakumanu VK, Arora V, Bansal AK: Investigation of factors responsible for low oral bioavailability of Cefpodoxime Proxetil. Int J Pharm. 2006; 12: 155-165.
5. Dhoka M, Joshi P, Gawande V: Preparation and evaluation of solid dispersions of cefpodoximeproxetil. J Pharm Res. 2009; 2(9): 1481-1484.
6. Leuner C, Dressman J: Improving drug solubility for oral solid dispersion.Eur JPharm & Biopharm.2000; 50: 47–60.
7. Vasconcelos T, Sarmento B, Costa P: Solid dispersions as strategy to improve oral bioavailability of poor water solubledrugs. Drug Discov Today. 2007; 12: 1068-1075.
8. Serajuddin ATM: Solid dispersion of poorlywatersoluble drugs: early promises, subsequent problems,and recent breakthroughs. J Pharm Sci. 1999; 88: 1058–1066.
9. Chiou WL, Reigelmann S: Preparation ofdissolution characteristics of several fast release solid dispersions of Griseofulvin. J Pharm Sci.1969; 58: 1505-1509.
10. 10.Friedrich H, Nadal A, Roland B: Solid state and dissolution rate characteristics of co-ground mixture of Nifedipine and hydrophillic carriers. Drug DevInd Pharm. 2005; 31: 719-728.
11. Nakamichi K, Yasuura H, Kukui H, Nakano T, Izumi S and Kawashima Y: New preparation method of soliddispersion by twin screw extruder. Pharm TechnolJpn. 1996; 12: 715-729.
12. Chawla G, Gupta P, Bansal AK:Gastroretentive drug delivery systems. In: JainNK. editor. Progress in controlled and novel drug delivery systems.CBSPublishers and Distributors, New Delhi. 2004:13; 76-97.
13. Kawashima Y,Takeuchi H, Yamamoto H: Gastrointestinal retentive microparticulate system to improve oral drug delivery. In: Wise DL, editor. Handbook of pharmaceutical controlled release technology.:Marcell Dekker Inc.New York.2000; 505-25.
14. Streubel A, Siepmann J, Bodmeier R:Gastroretentive drug delivery system. Expert Opin Drug Deliv. 2006; 3(2): 217-233.
15. Deshpande AA, Rhodes CT, Shah NH, Malick AWC: Controlled release drug delivery system for prolonged gastric residence: An Review. Drug DevInd Pharm.1996; 22:531-539.
16. Singh B, Kim HN: Floating drug delivery system: an approach to oral controlled drug via gastric retention.J Control Rel. 2000; 63: 235-259.
17. Khatri S, Girdhani D, Pahwa R: Recent advances in floating drug delivery system. The Indian Pharmacist.2007; 6: 17–20.
18. Arora S, Ali J, Ahuja A, Khar RK, Baboota S: Floating Drug Delivery Systems: A Review. AAPS PharmSciTech.2005;6(3) :372-390.
19. Franco M, Trapani G, Latrofa A, Tullio C, Provenzano MR, Serra M, Muggironi M, Biggio G, Lisa G: Dissolution properties and anticonvulsant activity of phenytoin-PEG 6000 and PVP K30 solid dispersion. Int J Pharm. 2001; 225:63-73.
20. Venkatesh N , Sangeetha S, Karthick S, Mohammed Fakruddin K, Vivek G, Samanta MK, Sankar S and Elango K: Solid dispersions, a unique technique to improve the aqueous solubility of poorly soluble drugs- A reveiew. Int J Pharm Res. 2008; 1: 5-12.
21. Ahmad M Abdul-Fattah, Bhargva HN: Preparation and in vitro evaluation of solid dispersion of halofantrine. Int J Pharm. 2002; 235:17-33.
22. Chaudhari PD, Kholhe S, Dave K, More DM: Formulation and Evaluation of Fast Dissolving Tablets of Famotidine. Indian Drug. 2005; 44: 641-649.
23. Srivastava AK, Wadhwa S, Ridhurkar D, and Mishra B: Oral sustained delivery of Atenolol from floating Matrix tabletsformulatuion and evaluatuion. Drug Dev & Industrial Pharm. 2005;31:367-374**.**
24. Borkar SN,sureshR, sawantVA, shendeVS, mokaleVJ, damaG: An approach to formulate bilayered gastroretentive floating drug delivery system ofcefpodoximeproxetil. Int J ChemTech Res. 2010;2:1229-1242.
25. Anilkumar JS, Manojkumar SP, HarinathNM: Formulation and evaluation of an oral floating tablet of cephalexin. Int JPharmEdu& Res. 2010;44(3): 243-252.
26. Cooper J, Gunn C: Powder flow and compaction. In: Carter SJ, Eds. Tutorial Pharmacy,CBS Publishers and Distributors,New Delhi.1986; 211-233.
27. Martin A:Micromeritics. In: Martin A, ed. Physical Pharmacy. Baltimore, MD: Lippincott Williams & Wilkins; 2001; 423-454.
28. Shayne Cox Gad Pharmaceutical Manufacturing Handbook: Production and Processes, John Wiley & Sons publications. 2nd edition.881-898.
29. Rosa M, Zia H, Rhodes T: Dosing and testing *in vitro* of a bioadhesive and floating drug delivery system for oral application. Int J Pharm. 1994;105:65-70.
30. Deshpande A.A, Shah N.H, Rhodes C:Development of a novel controlled-release system for gastric retention. Pharm Res. 1997; 14: 815-819.