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**FORMULATION AND EVALUATION OF SINTERED FLOATING TABLETS OF  
CEFPODOXIME PROXETIL**

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## **ABSTRACT**

### **Objective**

Aim of the study is to develop sintered floating tablets of Cefpodoxime proxetil using locust bean gum as release controlling material. Cefpodoxime proxetil [CP] is an orally administered, extended spectrum, semi-synthetic antibiotic of cephalosporin class.

### **Materials and methods**

CP has short elimination half-life, possesses high solubility, chemical, enzymatic stability and absorption profiles in acidic pH, makes it suitable candidate for formulating it as gastro retentive dosage form for improved bioavailability. Camphor was used to get the desired floating properties. The prepared Cefpodoxime proxetil floating tablets were subjected to sintering technique, where the cross linkage within the polymeric structure was increased by exposing tablets to acetone vapors. Advantage with sintering is that prolong drug release can be attained at low hardness and low concentrations of polymers.

### **Results**

The prepared tablets were evaluated and found to have acceptable physicochemical properties. Formulation S2 containing locust bean gum: drug [0.3:1.0] and camphor [10% w/w], which was exposed to acetone vapors for a period of 6 hrs has shown optimum floating properties and better dissolution profile i.e. 97.3% in 12 hrs. Hence, S2 formulation was considered as optimized formulation. The *in vitro* release data of optimized formulation was treated with mathematical equations and was concluded that drug release followed zero order kinetics [0.9599] with anomalous transport mechanism [0.5331].

### **Conclusion**

Based on the results, it can be concluded that sintered floating matrix tablets of Cefpodoxime proxetil containing locust bean provides a better choice for controlled release.

### **Key Words:**

Cefpodoxime proxetil, Controlled material, Gastro retentive floating tablets and Sintering technique

## INTRODUCTION

Gastro retentive systems swell and are retained in the stomach for a number of hours, while it continuously releases the drug at a controlled rate leading to higher bioavailability, therapeutic efficacy, reduced time intervals for drug administration and thus improved patient compliance. Hence these GRDDS are advantageous for the drugs absorbed mainly from the upper part of GIT having narrow absorption window and are unstable in the medium of distal intestinal regions [1]. They are even beneficial in the local therapy of the stomach. Compounding drugs having narrow absorption window in a GRDDS would enable an extended absorption phase of these drugs [2]. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa.

**Sintering techniques:** Sintering is defined as “the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat or by exposing to solvents”. The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release.

Sintering means fusion of particles or formulations of welded bonds between particles of polymer. In other words sintering technique increases the cross linking between particles in the polymer. Sintering can be done by physical (thermal) [3] and chemical (solvent casting) [4, 5] methods.

**Physical method:** It includes exposing dosage form to different temperatures, then polymer molecules rearrange at high temperature and result in increased cross linking in the dosage forms.

**Thermal sintering:** Sustained Release (SR) oral dosage forms exposed to temperature above the glass transition ( $T_g$ ) point of the polymer. Hence minute amounts of polymer on surface melt or deform. These molecules move on the polymer or move into the cross linked structure of the polymer and get entangled in the three dimensional structure of the polymer thereby increasing the complexity resulting in decreased drug release by increased retardation hardness of the dosage forms.

**Chemical method:** It includes exposing dosage form to solvent for different time points. In this method polymer molecules undergo partial solubilization in given

solvent and then reoriented to give denser forms with new cross linking by forming bonds between the polymer molecules. Generally cross linking solvents used are acetone, glutaraldehyde, formaldehyde etc.

**Solvent casting method:** In this method the prepared tablets are exposed to acetone vapors as cross linking agent. Cefpodoxime proxetil is available for oral dosing as an ester-prodrug which keeps it stable and increases the oral absorption and is less likely to produce G.I upset, palatability problems and changes in intestinal flora prior to absorption. In present study, Cefpodoxime proxetil floating drug delivery system with locust bean gum as rate retarding material. The prepared tablets are subjected to sintering technique using acetone as cross linking agent.

## **MATERIALS & EXPERIMENTAL WORK**

### **Materials**

Cefpodoxime proxetil gift sample from Micro labs Pvt. Ltd., Bangalore. PVP K30 obtained from Burgoyne Burbidges & Co., Mumbai. Magnesium stearate purchased from SD fine chemicals, Mumbai. Locust bean gum purchased from Himedia laboratories Pvt. Ltd., which contains galactomannans are plant reserve carbohydrates present in large quantities in the endosperm of the seeds of many leguminosae such as Ceratonia siliqua. Chemically, they consist of a (1-4)-linked  $\beta$ -D-mannose backbone with (1-6)-linked side chains of  $\alpha$ -D-galactose [6, 7] being thus neutral polymers [8] Citric acid anhydrous purchased from Universal Laboratories, Mumbai. Camphor purchased from Sigma-Aldrich Chemicals Pvt. Ltd., Mumbai and all other chemicals, reagents and solvents used are of analytical grade.

### **Experimental work**

Cefpodoxime proxetil have good stability, solubility in acidic pH. Tablets were prepared by wet granulation method using locust bean gum as retardant material.

### **Preformulation studies**

Preformulation studies are for testing of physical and chemical properties of a drug substance alone and in combination with excipients.

### **Precompression parameters of powder blends and granules**

Required quantities of all the ingredients were subjected to grinding then passed through sieve no. #60. The granules were prepared by blending powder with PVP K 30 in Iso Propyl Alcohol (IPA) solution as granulating agent and the wet mass was screened using sieve no. #44, then dried at 40 °C in hot air oven. The powder blend

and dried granules are tested for flow properties by angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio [9].

### ***Angle of repose***

Angle of repose is the angle between the surface pile of granules and horizontal plane. Fixed amount of blend was taken and carefully poured through the funnel whose tip was fixed at a height of 2.5 cm above the graph paper which is placed on a horizontal surface. The blend of the powder was poured till the apex of the conical pile just touches the tip of the funnel. Angle of repose is calculated by the following formula.

$$\theta = \text{Tan}^{-1}(h/r) \quad (1)$$

Where,  $\theta$  = angle of repose,  $r$  = radius of the pile,  $h$  = height of the pile

### ***Bulk density***

Bulk density is defined as the ratio mass of an untapped powder divided by the bulk volume including the inter particulate void spaces. Apparent bulk density (BD) was determined by pouring the blend into a graduated cylinder. The bulk volume (V) and weight of the powder (M) was determined. The bulk density was calculated using the formula.

$$\text{BD} = M/V \quad (2)$$

### ***Tapped density***

The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 100). The minimum volume ( $V_t$ ) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (TD) was calculated using the formula.

$$\text{TD} = M / (V_t) \quad (3)$$

### ***Carr's index***

Compressibility index is an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of powder. The correlation between compressibility index and powder flow properties is given in the formula.

$$\text{CI}(\%) = \frac{\text{Tapped Density(TD)} - \text{Bulk Density (BD)}}{\text{Tapped Density(TD)}} \times 100 \quad (4)$$

### ***Hausner's ratio***

Is an indirect index of ease of powder flow and is measured by the ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (5)$$

## **Drug-Excipient compatibility studies**

### **Fourier Transform Infrared (FTIR)**

The spectrum analysis of pure drug and physical mixture of drug and different excipients which are used for preparation of tablets was studied by FTIR. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a Shimadzu Corporation (Koyto, Japan). KBr disks were prepared by mixing few mg of sample with potassium bromide and compressed at 10 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the spectrum was recorded from 4000  $\text{cm}^{-1}$  to 500  $\text{cm}^{-1}$ . The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in the compound.

### **Formulation of Cefpodoxime proxetil floating tablets**

#### **Dose calculation**

Cefpodoxime is available in proxetil salt form. Dose is calculated based on its  $t_{1/2}$  and  $V_d$ .

$$K^0 r = \text{Rate in} = \text{Rate out} = K_e \cdot C_d \cdot V \quad (6)$$

Where  $K^0 r$  is the zero-order rate constant for drug release (amount/time),  $K_e$  is the first-order rate constant of overall drug elimination ( $\text{hr}^{-1}$ ),  $C_d$  is the desired drug level in the body (amount/volume), and  $V_d$  is the volume in which the drug is distributed.

$$K_e = 0.693 / t^{1/2} \quad (7)$$

$t^{1/2}$  (elimination half-life) of Cefpodoxime proxetil is 2.4 hours then  $K_e = 0.693/2.4 = 0.288 \text{ Hr}^{-1}$

$C_d$  is 1.4 mg/L, and  $V_d$  is 32.3 L, then  $K^0 r = K_e C_d V_d = 0.288 * 1.4 * 32.3 = 13.05 \text{ mg/h}$ .

$K^0 r$  calculated was 13.05 mg/h, so the drug release constant should also have been equal to the elimination constant, to maintain the steady-state condition.

Cefpodoxime having only 50% of oral absorption in fasting conditions, whereas along with food, to ~75%.

$$K^0 r = 13.05 * 125 / 100 = 16.32 \text{ mg/h}$$

$$DL = D_i - K^0 r T_p \quad (8)$$

Time to reach the peak drug level ( $T_p$ ) is 2.5 hours.

$$D_m = K^0 r T_d \quad (9)$$

$$\text{Total dose} = \text{Loading dose (DL)} + \text{Maintenance Dose (Dm)} \quad (10)$$

Where  $T_d$  is the total time desired for sustained release from 1 dose (i.e., 12 hours).

Hence, Total dose =  $(100 - 16.32 \times 2.5) + 16.32 \times 12 = (100 - 40.8) + 195.28 = 255.04$

Since 130 mg of Cefpodoxime proxetil is equivalent to 100 mg of Cefpodoxime.

$= 255.04 \times 1.3 = 331.55$  mg. Hence the dose used was 330 mg/tablet.

#### **Preparation of tablets by wet granulation method using sublimating agent**

Tablets are prepared by wet granulation method using sublimating agent. All the ingredients locust bean gum and drug were passed through the sieve no. # 60. Granules were prepared using 5% PVP in IPA as binder solution and passed through sieve no. #44. Granules were dried at 40°C for 2 hrs and passed through sieve no. # 30. Camphor was added according to respective formula and lubricated with magnesium stearate. Formulations were prepared as given in the **Table no. 1** and final blend was compressed into tablets on a 10 station rotary tablet machine using 11.9 punches. Prepared tablets were sublimated in hot air oven at 60°C for 3 days. Tablets with final weight equal to theoretical weight after complete sublimation were selected for further experiment. (See Fig. no. 1)

#### **Evaluation of Cefpodoxime proxetil floating tablets**

The prepared bilayer tablets are evaluated for varied parameters like weight variation, thickness, density, hardness, friability [9], drug content, content uniformity and *in vitro* dissolution studies [10,11,12].

##### **Tablet thickness**

The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets by using vernier calipers. The average thickness and standard deviation were reported.

##### **Density of tablets**

The density of the sublimated tablets ( $\text{g}/\text{cm}^3$ ) was calculated both before and after sublimation from the tablet height, diameter, and mass using the following:

$$D = W / [(M/2)^2 \times \pi \times h] \quad (11)$$

Where W is the mass of a tablet, M is the tablet diameter,  $\pi$  is the circular constant, and h is the tablet height.

##### **Tablet hardness**

Tablet hardness was measured using Monsanto hardness tester. The average crushing strength of the 5 tablets with known weight and thickness of each was reported.

### ***Friability Test***

Ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator), rotated at 25 rpm for 4 minutes. The tablets were taken, dedusted and reweighed. The friability was calculated as the percentage weight loss using equation 12. Friability values below 1% are generally acceptable.

$$\% \text{ Friability} = (W_1 - W_2) \times 100 / W_1 \quad (12)$$

Where,  $W_1$  = Initial weight of the tablets,  $W_2$  = Final weight of the tablets

### ***Weight Variation Test***

To study weight variation individual weights ( $W_i$ ) of 20 tablets from each formulation were noted down using electronic balance. Their average weight ( $W_A$ ), percentage weight variation was calculated using equation 13.

$$\% \text{ Weight variation} = (W_A - W_i) \times 100 / W_A \quad (13)$$

### ***Drug Content***

Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to 100 mg of Cefpodoxime proxetil was transferred to a 100 ml volumetric flask containing methanol. It was shaken mechanically for 1hr, then filtered using whatman filter paper [10]. From this filtrate 1 ml was taken, diluted to 10 ml with 0.1N HCl and absorbance was measured against blank at 264.2 nm using UV-Spectrophotometer. The drug content of the floating tablets meets the requirements if the tablet amount lies within the range of 90% to 110%.

### ***Buoyancy / Floating test***

The tablet is introduced into a 100 ml beaker containing 0.1N HCl and the time gap between the introduction and tablet to emerge onto surface of medium is called "floating lag time". The total duration of time by which dosage form remain buoyant is called "Total floating time (TFT)".

### ***In vitro dissolution studies [10, 12]***

The tablet was placed in a dissolution test apparatus USP II, containing 900 ml of 0.1N HCl at speed of 50 rpm. 5ml of aliquot was withdrawn for every 1 hr up to 12 hrs and replaced with 5ml of fresh dissolution medium. Each sample was analyzed at 264.2 nm using double beam UV spectrophotometer against reagent blank.

### ***Sintering***

According to the compositions given in **Table no. 1**, tablets were prepared and subjected for sublimation, then these tablets are subjected to lower as well as higher

polymeric concentrations were prepared using low hardness and subjected to sintering process.

*Procedure:*

The lower chamber of the dessicator was filled with acetone, closed and kept aside for saturation. After saturation of chamber, the compressed tablets were placed over a wire-mesh which is kept above the lower chamber of the dessicator containing acetone. The dessicator is made airtight by closing the lid with the help of vacuum grease. Tablets of each formulation described in **Table no. 2** were exposed to different durations of sintering (1.5, 3.0, 4.5, 6, 7.5, 9 and 10.5 hrs). At last, the tablets were dried in an oven at 36 °C temperature for 24 hours and then stored in a vacuum desiccators fused with calcium chloride until further use.

***Evaluation of sintered tablets***

Sintered tablets were subjected to various evaluation tests including hardness, friability, buoyancy studies and *in vitro* dissolution studies. Buoyancy and dissolution studies were carried out in 0.1N HCl.

***Kinetic analysis of dissolution data (Model dependent method)***

The dissolution profiles of optimized formula in 0.1 N HCl were fitted to zero-order, first order, Higuchi and Korsmeyer-Peppas kinetic models. The model with the highest correlation coefficient was considered to be the best fitting one. By these studies the release mechanisms were determined.

***Determination of surface morphology of prepared tablets by Scanning Electron Microscopy (SEM)***

The effect of the sublimation material (camphor) on the morphology of the prepared tablets was examined using SEM. The main objective of the study is to examine the surface of prepared tablets during sublimation before and after sintering.

***FTIR studies of sintered matrix tablets***

FTIR studies were performed for the powdered tablets after sintering. The spectrum obtained was observed for the presence of characteristic peaks and compared with pure drug.

***Determination of residual acetone by GC (Gas Chromatography)***

***Analytical instrument settings***

The Gas Chromatography technique was employed for the determination of acetone in the tablet. The GC used was Make - Aligent, Model – 7890, GC equipped with a FID (Flame ionization detector). The analysis was performed under the following

chromatographic conditions: Column - WCOT Fused Silica, 30x0.32x1.8  $\mu\text{m}$ . The temperature of the FID was 220°C, and the injector temperature was 220°C. The oven temperature was programmed to 40°C (for 2 min), followed by an increase of 5°C/min until 200°C. The carrier gas was nitrogen with a flow of 1.5 mL/min. The injection of test and standard was performed by means of a 10  $\mu\text{L}$  hamilton syringe. Optimized sintered tablet was crushed and taken in 1000 ml volumetric flask and made up the volume with deionized water. The flask was shaken and kept aside to get clear supernatant. A fixed volume of supernatant (0.5  $\mu\text{L}$ ) was injected into the chromatographic system and amount of acetone in tablet was calculated.

#### ***Determination of Gastric Retention Period by X-ray imaging studies***

Evaluation of gastric retention of Cefpodoxime proxetil sintered floating tablet was performed on rabbit by using radio opaque marker barium sulfate. X-Ray imaging studies are non-invasive method provides identification or monitoring of total GI residence time without affecting normal gastro intestinal motility.

Dose translation was based on Body Surface Area (BSA). The animal dose should not be extrapolated to a human equivalent dose (HED) based on body weight by simple conversion. The use of body surface area (BSA) normalization method is suggested for more appropriate conversion of doses from human beings to animals or vice versa. BSA correlates well with most of the mammalian species by several parameters of biology, including oxygen utilization, caloric expenditure, basal metabolism, blood volume, circulating plasma proteins, and renal function.

The rabbit dose was calculated according to following equation

**Animal dose (mg/kg) = Human equivalent dose X Human Km value/ Animal Km value (14)**

To convert dose in mg/kg = dose in mg/m<sup>2</sup> X Km value.

Human (Human Adult of weight 60 Kg) Km value 37, Animal (Rabbit weighing 1.8 Kg) Km value 12.

Values based on data from FDA Draft Guidelines.

Animal dose (mg/kg) = 5.5 x 37/ 12 = 5.5 x 3.08 = 16.94 mg / kg.

Rabbit under studies was weighing 1.9 kg. So, 16.94 X 1.9 = 32.1 mg.

Hence the dose for *in vivo* studies taken was 32.1 mg. 25% of drug was replaced with barium sulfate i.e., so 8.025 mg per each tablet. The formulas for *in vivo* gastro retentive tablets are given in **Table no.3**.

The tablet was prepared on 10 station rotary tablet machine using 4 mm punches. Prepared tablets were sublimated at 60 °C in hot air oven for 3 days. The sublimated tablet was exposed to acetone for 6 hours for sintering. Then the tablets were dried in hot air oven at 36 °C temperature for 24 hours and then stored in vacuum desiccators.

Healthy rabbit of  $2.0 \pm 0.2$  kg was fasted over night and on the next day morning, tablet formulation S2 which was adjusted to rabbit dose with tracing radio opaque agent was administered through plastic tubing followed by flushing of 25–30 ml of water. During the entire study, the rabbits had free access to water alone. At different time intervals of 0, 1, 2, 4, 6 and 8 hours, rabbit GI tract was X-Ray photographed in supine position and observed for the nature and position of the Cefpodoxime proxetil floating tablet.

#### ***Determination of stability of tablets after sublimation by Thin layer Chromatography (TLC)***

Stability of Cefpodoxime proxetil, which can be determined by exposed to acetone vapors in dessicator for 9 hours, was evaluated using TLC method.

*Procedure:*

*Preparation of standard solution:* An accurately weighed quantity of 10 mg of Cefpodoxime proxetil was transferred to a 10 ml of volumetric flask and dissolved in methanol. Volume was made up with the same solvent to obtain a concentration 1 mg/ml.

Mobile phase: Water; Methanol 50:50 v/v composition.

#### ***Antimicrobial studies for sintered GR tablets:***

The microbial assay is based upon a comparison of the inhibition of growth of bacteria by measured concentrations of the compound to be examined with that produced by known concentrations of standard preparation of the antibiotic having known activity.

The microbial assay may be carried out by two methods. Method A: Cylinder or cup-plate diffusion method and Method B: Turbidimetric or Tube assay method.

In the present investigation cylinder or cup-plate technique was employed.

The following strains of bacteria have been used for the study.

1. Gram positive bacteria - Bacillus subtilus
2. Gram negative bacteria – Escherichia coli

### ***Preparation of standard antibiotic solution:***

The stock solution (1 mg/ml) of antibiotics was prepared by dissolving 10 mg of Cefpodoxime proxetil in volumetric flask 10 ml Di Methyl Sulfoxide (DMSO). From Stock solution 2 ml was taken and further diluted to 10 ml with DMSO to get 10 µg/ 50 µl.

### ***Preparation of test solutions:***

The formulation was crushed into powder. Powder weight equivalent to 10 mg of drug was dissolved in 10 ml of DMSO. (Drug assay was performed for tablets and equivalent to 10 mg was taken). From this solution, further dilutions were made using DMSO to get concentrations of 10 µg/ 50 µl, 5 µg/ 50 µl, 2.5 µg/ 50 µl and 1.25 µg/ 50 µl.

### ***Accelerated stability studies***

Optimized formulation F2 was subjected to stability studies at 40 °C ± 2 °C/ 75% ± 5% RH and room temperature analyzed for its physical characteristics, drug content and dissolution studies for period of one month.

## **RESULTS & DISCUSSION**

### ***Preformulation studies***

#### ***Drug-excipients compatibility study by FTIR***

Cefpodoxime proxetil compatibility with excipient was studied by FTIR and shown in **Fig. no. 2** and **Table no. 4**. FTIR results shown that the characteristic functional groups matches with the literature reported [13].

It was found that the drug and the other powder blends do not possess the required flow characteristics for direct compression as the values of angle of repose, Hausner's ratio, Carr's compressibility index were not found to be within flow property limits as shown in **Table no. 5**. Hence tablets were prepared by wet granulation method.

Flow property values of the granules of all the formulations were found to possess good flow properties and were within the compendial limits of Indian Pharmacopoeia [12] the values as shown in **Table no. 6**.

### ***Evaluation of Cefpodoxime Proxetil floating tablets***

Prepared floating tablets were evaluated for physicochemical properties.

The physicochemical evaluation of tablets such as weight variation test, friability, hardness, content uniformity of all the formulations were within compendial standards. The values are as shown in **Table no. 7**.

#### ***Effect of sublimation of camphor on tablet properties:***

The floating properties of the GR tablets and effects of sublimation on thickness, density and crushing strength (hardness) of the tablets are summarized in **Table no. 8**.

The crushing strength of the tablets decreased after sublimation. As camphor content in the tablet increased from 5% to 15% w/w, the crushing strength of the GR tablet decreased, as well as the densities of tablets decreased [14]. When more than 40 mg of camphor was added to the GR tablet formulations, the density of the tablets was less than 1.00 g/cm<sup>3</sup>. In all formulations, the thickness and porosity of tablets were slightly increased after sublimation, which finally resulted in the tablets having density less than 1 gm/cm<sup>3</sup>. So the tablets prepared float on dissolution media due to air in the porous tablets without any lag time [15].

#### ***Buoyancy /Floating test:***

In sublimation method camphor was used at different concentrations and floating properties were studied (**Table no. 9**).

Camphor upon sublimation resulted in slight increase in thickness and also increases porosity which finally resulted in the tablets having density less than 1 gm/cm<sup>3</sup>. Tablets so formed float on dissolution media without any lag time.

Formulations containing 15 % of camphor has shown floating property without lag time but after certain time (between 9 to 10 hours) cracks developed in the tablets, as a result chipping was observed on tablet surface. Hence formulations F2 and F5 were found to have optimum floating property (**Fig. no. 3**).

The formulations showing lag time of less than 30 minutes and total floating time of greater 12 hours were selected and subjected to dissolution studies for optimization of floating tablets.

#### ***In vitro drug dissolution testing of floating tablets***

Hence based on results of floating studies, the formulations F2 and F5 were selected and subjected for dissolution studies for further optimization.

Among different formulations which were subjected for dissolution studies the formulation F2 containing 0.35 ratio of locust bean gum with respect to drug and camphor 10% has shown comparatively better dissolution profile of 95.8 % for 12 hours (**Fig. no. 4**). Hence based on results of floating studies (no lag time) and dissolution studies F2 formulation was selected and further subjected for sintering technique [16].

#### ***Effect of camphor concentration on in vitro release of Cefpodoxime proxetil***

Different formulations from F1 to F6 were studied with increased amount of camphor, leads to the decreased density of resultant GR tablets after sublimation.

#### ***Drug release kinetics- Model dependent Method***

Release kinetics for different formulations was calculated using Microsoft Office Excel 2007 version. The release data was analyzed by fitting the drug release profiles of all the formulations into zero order release, first order release, Higuchi and Korsmeyer-Peppas models.

From the results of model dependent kinetic analysis of dissolution profiles of the different formulations F2 and F5, it was found that the release of the drug from these formulations followed zero order kinetics and mechanism of release was found to be anomalous transport from  $n^2$  and  $n$  values as shown in **Table no. 10**.

#### ***Sintering technique***

The prepared floating tablets were exposed to acetone vapors for sintering. Based on results on floating test and *in vitro* dissolution studies F2 formulation (0.35 ratio polymer to drug) was found to be better when compared to other formulation. Hence 0.35 ratio was selected.

The effect of sintering (exposure to acetone vapors) on the formulation S1 was found that the release of the drug retardation was increased on long exposure times to acetone vapours. This may be due to cross linking of polymer as well as the process of sintering was initiated. Further exposure to acetone i.e., for 9 hours and 10.5 hours there was no significant difference for the drug release due to saturation of cross linking on surface of tablet.

From the dissolution studies of the formulations S1 to S3 it can be concluded that S2 on exposure of 6 hours to acetone has better sustained drug release (97.3%, in 12 hours). Hence it was selected as optimized formulation. The Optimized S2 formulation physically evaluated for hardness and friability before and after sintering (**Table no.12**).

### **Scanning Electron Microscopy (SEM)**

**Fig. no. 8 a, b** shows the morphology of S2 before sublimation and after sublimation respectively as viewed by SEM [13], **Fig. no. 8c** shows the morphology of S2 after sintering.

The morphology of the tablet composites after sublimation is highly porous which affects the density and floating property of the tablets. It was observed that the pore cavity on the tablets and also porosity (to some extent) was reduced after sintering. The reason attributed for decrease in porosity was due to redistribution of polymer during sintering process. Polymer undergoes partial solubility in acetone vapors and results in redistribution of polymer molecules on the surface of tablets and also into the pores so formed due to sublimation.

### **FTIR studies**

Prepared tablets both after sublimation and after sintering were subjected for FTIR studies to conform the drug stability in final formulation shown in **Fig. no. 9**.

From the results of FTIR, it was found that the functional peaks of the drug were retained after being subjected to the processes like sublimation and sintering. This implies that the drug was stable and also compatible with other excipients throughout the process.

### **Determination of residual camphor and acetone by GC (Gas Chromatography)**

Gas chromatography was employed to estimate the amount of residual acetone in the optimized tablets. The retention time of acetone was found to be 9 minutes and 30 seconds. The regression equation for standard curve so constructed by taking known concentrations ( $\mu\text{g/ml}$ ) of acetone was found to be  $y=1605x-177$ .

The chromatograms of acetone (known concentration i.e  $10 \mu\text{g/ml}$ ) shown in **Fig. no. 10**, unsintered tablets (not exposed to acetone vapors) **Fig. no. 11** and optimized tablet (tablet exposed to 6 hours of acetone) **Fig. no.12**.

Based on results of GC, the residual concentration of acetone in optimized tablet was found to be within the limits of GRAS (**Table no. 13**). Hence it can be concluded that the tablets prepared by chemical sintering using acetone are safe and this method can be used as alternate technique in preparation of matrix tablets.

#### ***In vivo Buoyancy Study***

*In vivo* buoyancy study was performed on healthy rabbit. The animal dose was calculated using dose translation based on Body Surface Area (BSA). **Fig. no. 13** depicts the position and nature of the tablets at different time intervals after oral administration.

From the obtained results it was observed that the floating tablets formulated with Cefpodoxime proxetil and locust bean gum remained in the gastric region even after 8 hours of administration indicating good retention of the tablets in the stomach region [17,18].

#### ***Thin layer Chromatography (TLC)***

TLC was performed to check the stability of Cefpodoxime proxetil when exposed to acetone vapors, by comparing the  $R_f$  values of test with pure or standard Cefpodoxime proxetil.

From TLC, no colored spot other than the principal spot of Cefpodoxime proxetil was observed in the chromatogram with test sample, which also showed similar  $R_f$  value as that of the standard (0.67) (**Fig. no. 14**). This indicated that Cefpodoxime proxetil did not degrade even after exposed to acetone vapors.

#### ***Anti microbial studies***

As the drug used was anti bacterial, hence anti microbial activity was performed using final formulation. Zone of inhibition studies were performed by using test drug solution and standard (pure) antibiotic solution. **Fig. no.15** shows the zone of inhibition of test and standard solutions and diameter of zones were obtained. The values of diameter were reported in **Table no. 14**.

From the microbiological studies, similar zones of inhibition were shown for both pure drug as well as sintered matrix tablets. Hence it can be concluded that Cefpodoxime proxetil in the formulation has retained its antibacterial activity in the final formulation.

#### **STABILITY STUDIES**

Optimized formulation was subjected for stability studies and results are given in **Table no. 15** and shown in **Fig. no. 16**.

During the accelerated stability studies, optimized tablets were stable with insignificant change in the floating lag time, floating time, drug content and *in vitro* drug release characteristics.

## CONCLUSION

In conclusion, S2 formulation prepared using locust bean gum as rate control polymer at the ratio of 0.3:1.0 (locust bean gum: drug), shown better floating properties <14 min. and dissolution profile with 95.0% for 12 hrs. Hence, S2 can be concluded as final optimized formulation for sintered floating gastro retentive matrix tablet of Cefpodoxime proxetil as to increase gastric residence time and thereby improving its bioavailability.

## REFERENCES

- 1) Chavanpatil M , Jain P, Chaudhari S, Shear R, Vavia P. Development of sustained release gastroretentive drug delivery system for ofloxacin: In vitro and in vivo evaluation. *Int. J. Pharm.* 2005;304:178–184.
- 2) Uhumwhangho MU, Ramana Murty KV. Release characteristics of diltiazem hydrochloride wax-matrix granules- Thermal sintering effect. *J. App. Sci. Environ. Manage.* 2011;15(2):365-370.
- 3) Sameer shafi, Chowdary KA, Nagoba S, Sachin A. Formulation and evaluation of sintered matrix tablets of diltiazem hydrochloride. *Int. J. App. Sci.* 2011;3(3):16-19.
- 4) Srinivas Rao B, Prasanna Raju Y, Srinivas L, Seshasayana A. Design and evaluation of Eudragit RL100 sintered matrix tablets. *Indian J. Pharm. Sci.* 2012;66(2):202-207.
- 5) Laurienzo. P, Marine polysaccharides in pharmaceutical applications: An overview. *Mar Drugs.*,8:2435–65(2010).
- 6) Rinaudo. M, Main properties and current applications of some polysaccharides as biomaterials. *Polym Int.*, 57:397–430(2008).
- 7) Beneke. C, Viljoen. A, Hamman.J. Polymeric plant-derived excipients in drug delivery. *Molecules.*,14:2602–20(2009).

- 8) Indian Pharmacopeia (2010), published by Indian Pharmacopeia Commission, Ghaziabad Volume II, 751- 754.
- 9) Siddalinga Swamy M.S, et al. UV-visible spectrophotometric methods for the estimation of cefpodoxime proxetil in bulk drug and pharmaceutical dosage form. International Journal of PharmTech Research. 2012;4(2):750-756.
- 10) Sreenivasa Rao K, *et al* Gastro-Retentive Floating Matrix Tablets of Cefpodoxime Proxetil. J. App. Pharm. Sci. 2011;1(10):190-194
- 11) United States Pharmacopeia 24 and National Formulary 19 - 2000 by United States Pharmacopoeial convention, INC, 1941-43.
- 12) Alonso-Sande M, Teijeiro-Osorio D, Remuñán-López C, Alonso MJ. Glucomannan, a promising polysaccharide for biopharmaceutical purposes. Eur J Pharm Biopharm. 2009; 72:453–62.
- 13) Fahim Khan, Rajesh Kataram Suman Ramteke Enhancement of Bioavailability of Cefpodoxime Proxetil Using Different Polymeric Microparticles; AAPS PharmSciTech. 2010 Sep; 11(3): 1368–1375. doi: 10.1208/s12249-010-9505-x
- 14) Rania A. H. Ishak Buoyancy-Generating Agents for Stomach-Specific Drug Delivery: An Overview with Special Emphasis on Floating Behavior J Pharm Pharm Sci (www.cspsCanada.org) 18(1) 77 - 100, 2015.
- 15) Oh TO, Kim JY, Ha JM, Chi SC, Rhee YS, Park CW. Preparation of highly porous gastroretentive metformin tablets using a sublimation method. Eur J Pharm Biopharm. 2013; 83(3):460-467. DOI:10.1016/j.ejpb.2012.11.009
- 16) Rao B.S., Seshasayana A., Himasankar K., Raju Y.P., Murthy K.R.: Design and evaluation of ethylene vinyl acetate sintered matrix tablets. Ind. J. Pharm. Sci. 2003, 65(5), 496–502.
- 17) Satish H Patil, Gokul S Talele, Formulation development and in vitro and in vivo evaluation of gastroretentive floating drug delivery system of Lafutidine; Asian Journal of Pharmaceutics, April-June 2013, 68-74. DOI: 10.4103/0973-8398.115969
- 18) K.Gnanaprakash , K.B.Chandhra Shekhar, C.Madhu Sudhana Chetty, Floating tablets of Ranitidine HCl with natural polymer: An approach for gastric treatment; Int.J.Pharm.& Health Sci. Vol. 1 (2), 2010, 109-115.

**Table no. 1: Formulation of floating tablets**

Formulation code	Cefpodoxime proxetil (mg)	Locust bean gum (mg)	Camphor (mg)	Magnesium stearate(mg)	PVP (mg)
F1	330	115.5	22.27	5	23.6
F2	330	115.5	44.55	5	24.7
F3	330	115.5	66.82	5	25.8
F4	330	100	21.5	5	22.8
F5	330	100	43	5	25.6
F6	330	100	64.5	5	26.8

**Table no. 2: Formulation of sintered tablets containing camphor**

Formulation code	Cefpodoxime proxetil (mg)	Locust bean gum (mg)	Camphor (mg)	Magnesium stearate(mg)	PVP (mg)
S1	330	82.5	41.2	5	22.9
S2	330	100	43	5	23.9
S3	330	115.5	44.5	5	24.75
S4	330	132	46.2	5	25.6

**Table no. 3: Formula according to animal dose**

S.No	Ingredient	Quantity taken (mg)
1	Cefpodoxime proxetil	24
2	Barium sulfate	8
3	Locust bean gum	7.2
4	Camphor	4
5	Magnesium stearate	0.5
6	PVP K 30	2.18

**Table no. 4: Interpretation of Cefpodoxime proxetil FTIR scan**

S. No	Region in $\text{cm}^{-1}$	Type of vibration	Functional group Present
1	3396.41, 3230.54	N-H stretching	Primary amine
2	1676	N-H bending	Aromatic Primary Amine
3	1274	C-N	Amine
4	3066.61	Aromatic C-H stretch	Aromatic
5	1638	C=N	--
6	809	C-S-C stretching	--
7	1753	C=O	Lactam

**Table no. 5: Precompression parameters of the powder blends**

Ingredients	Angle of repose ( $\theta$ )	Hausner's ratio*	Carr's Index (%)
Drug	53.3 $\pm$ 0.54	1.40 $\pm$ 0.09	29.67 $\pm$ 0.2
Drug+ locust bean gum	44.92 $\pm$ 0.13	1.32 $\pm$ 0.04	22.46 $\pm$ 0.15
Drug + LG + camphor	50 $\pm$ 0.49	1.46 $\pm$ 0.02	24.1 $\pm$ 0.17

Values are expressed as Mean  $\pm$ SD, \*n = 3

**Table no.6: Precompression parameters of the granules**

Formulation code	Angle of repose( $\theta$ )*	Bulk density ( $\text{gm}/\text{cm}^3$ )*	Tapped density ( $\text{gm}/\text{cm}^3$ )*	Hausner's ratio *	Carr's Index (%)*
F1	26.76 $\pm$ 0.76	0.310 $\pm$ 0.013	0.392 $\pm$ 0.01	1.23 $\pm$ 0.09	16.84 $\pm$ 0.14
F2	26.26 $\pm$ 1.0	0.344 $\pm$ 0.01	0.432 $\pm$ 0.013	1.137 $\pm$ 0.011	17.06 $\pm$ 0.84
F3	26.34 $\pm$ 0.82	0.361 $\pm$ 0.01	0.346 $\pm$ 0.012	1.228 $\pm$ 0.010	19.39 $\pm$ 0.78
F4	26.26 $\pm$ 0.69	0.368 $\pm$ 0.01	0.458 $\pm$ 0.016	1.234 $\pm$ 0.00	17.87 $\pm$ 0.82
F5	27.54 $\pm$ 0.81	0.346 $\pm$ 0.01	0.428 $\pm$ 0.00	1.226 $\pm$ 0.04	20.19 $\pm$ 0.34
F6	22.47 $\pm$ 0.84	0.322 $\pm$ 0.00	0.421 $\pm$ 0.00	1.395 $\pm$ 0.06	21.72 $\pm$ 0.52

Values are expressed as Mean  $\pm$ SD, \*n = 3

**Table no. 7: Physiochemical evaluations of tablets containing camphor.**

Formulation code	Drug content (%) <sup>a</sup>	Weight variation (%) <sup>b</sup>	Friability <sup>a</sup>
F1	96.4±0.20	3.03±0.30	0.62±0.01
F2	97.1±0.23	4.02±0.60	0.55±0.06
F3	96.8±0.64	4.1±0.30	0.71±0.01
F4	99.4±0.77	3.9±0.50	0.77±0.01
F5	95.3±0.40	3.7±0.22	0.71±0.04
F6	97.6±0.96	2.8±0.70	0.69±0.02

Values are expressed as Mean ±SD, a: n = 10; b: n=20

**Table no. 8: Comparison of physical parameters before and after sublimation**

Formulation code	Before sublimation			After sublimation		
	Thickness (mm) <sup>a</sup>	Density (gm/Cm <sup>3</sup> ) <sup>a</sup>	Hardness (Kg/Cm <sup>2</sup> ) <sup>a</sup>	Thickness (mm) <sup>a</sup>	Density (gm/Cm <sup>3</sup> ) <sup>a</sup>	Hardness (Kg/Cm <sup>2</sup> ) <sup>a</sup>
F1	4.6 ±0.01	1.10±0.00	7.1±0.01	4.8±0.00	1.02±0.01	6.2±0.01
F2	4.8±0.00	1.03±0.01	6.9±0.35	5.1±0.67	0.873±0.00	6.1±0.00
F3	5.0±0.08	1.08±0.01	7.3±0.28	5.3±0.00	0.84±0.06	5.8±0.30
F4	4.5±0.12	1.12±0.03	7.1±0.01	4.7±0.01	1.01±0.21	6.0±0.30
F5	4.7±0.80	1.03±0.22	7.0±0.00	5.1±0.16	0.84±0.01	6.1±0.01
F6	4.9±0.07	1.05±0.21	7.2±0.01	5.3±0.18	0.82±0.09	5.7±0.45

Values are expressed as Mean ±SD, a: n = 5

**Table no. 9: Floating lag time and Floating time of formulation containing camphor**

Formulation code	Floating lag time	Floating time (hrs)
F1	Not floating	-
F2	Floating with no lag time	>12
F3	Floating with no lag time	< 10
F4	Not floating	-
F5	Floating with no lag time	>12
F6	Floating with no lag time	< 10

**Table no. 10: Model dependent kinetic analysis for the dissolution profile of different formulation**

Formulation	Zero order	First order	Higuchi	Korsmeyer-Peppas		Release Mechanism
	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	n	
F2	0.9842	0.8396	0.9628	0.9748	0.6348	Anomalous transport
F5	0.9691	0.8766	0.9783	0.9744	0.5549	Anomalous transport

**Table no. 11: Comparison of different physical parameters before and after sublimation**

Formulation	Drug content <sup>a</sup>	Before Sintering			After Sintering		
		Thickness (mm) <sup>a</sup>	Density (gm/Cm <sup>3</sup> ) <sup>a</sup>	Hardness (Kg/Cm <sup>2</sup> ) <sup>a</sup>	Thickness (mm) <sup>a</sup>	Density (gm/Cm <sup>3</sup> ) <sup>a</sup>	Hardness (Kg/Cm <sup>2</sup> ) <sup>a</sup>
S1	97.2±0.7	4.6±0.01	1.02±0.01	5.7±0.01	4.9±0.46	0.85±0.01	4.9±0.07
S2	96.4±0.6	4.7±0.00	1.03±0.66	5.7±0.00	5.1±0.01	0.83±0.01	5.0±0.50
S3	97.1±0.6	4.8±0.24	1.03±0.07	5.8±0.58	5.1±0.09	0.84±0.05	5.1±0.11

Values are expressed as Mean ±SD, a: n = 5

**Table no. 12: Comparative physical evaluation of optimized formulation S2 both before and after sintering**

Parameters	Before sintering	After sintering
Hardness Kg/cm <sup>2</sup> <sup>a</sup>	5.0±0.02	6.4±0.23
Friability <sup>a</sup>	0.7%±0.01	0.5%±0.22

Values are expressed as Mean ±SD, a: n = 5

**Table no. 13: Different concentrations of acetone with its corresponding peak area**

Preparations	Peak area	Concentration (µg/ml)
Standard acetone solution	157416	10
Optimized formulation	15746	0.9

**Table no. 14: Comparison of zones of inhibition between test and standard antibiotic solutions**

Antibiotic solution	<i>Escherichia coli</i>	<i>Bacillus subtilis</i>
Standard antibiotic solution (10µg/ 50 µl)	16	17
Test antibiotic solutions (10µg/ 50 µl)	15	18
Test antibiotic solutions (5µg/ 50 µl)	10	11

**Note:** Values of zone of inhibition in mm, Diameter of bore: 8mm, Zone of inhibition is average of duplicate.

**Table no. 15: Physico chemical properties of optimized formulation during stability studies**

Parameters	Time in weeks			
	0 (Initial)	1 <sup>st</sup> week	2 <sup>nd</sup> week	1 <sup>st</sup> month
Floating lag time	No lag time	No lag time	No lag time	No lag time
Floating time	> 12 hours	> 12 hours	> 12 hours	> 12 hours
Drug content <sup>a</sup> (%)	98.3±0.38	97.6±0.69	96.5±1.06	97.5±0.73
Thickness (mm) <sup>a</sup>	5.1±0.01	5.1±0.01	5.0±0.01	5.1±0.01
Density (gm/Cm <sup>3</sup> ) <sup>a</sup>	0.83±0.01	0.829±0.01	0.83±0.01	0.83±0.01
Hardness (Kg/Cm <sup>2</sup> ) <sup>a</sup>	5.0±0.50	5.1±0.50	5.0±0.50	5.0±0.50

Values are expressed as Mean ±SD, a: n = 5

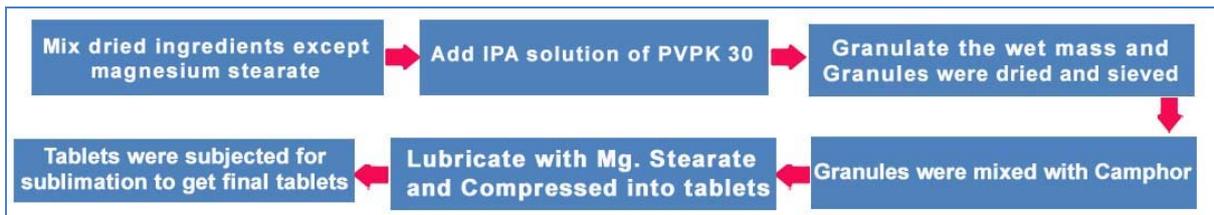


Fig. no.1: Preparation of Cefpodoxime proxetil floating tablets by wet granulation using sublimating agent.

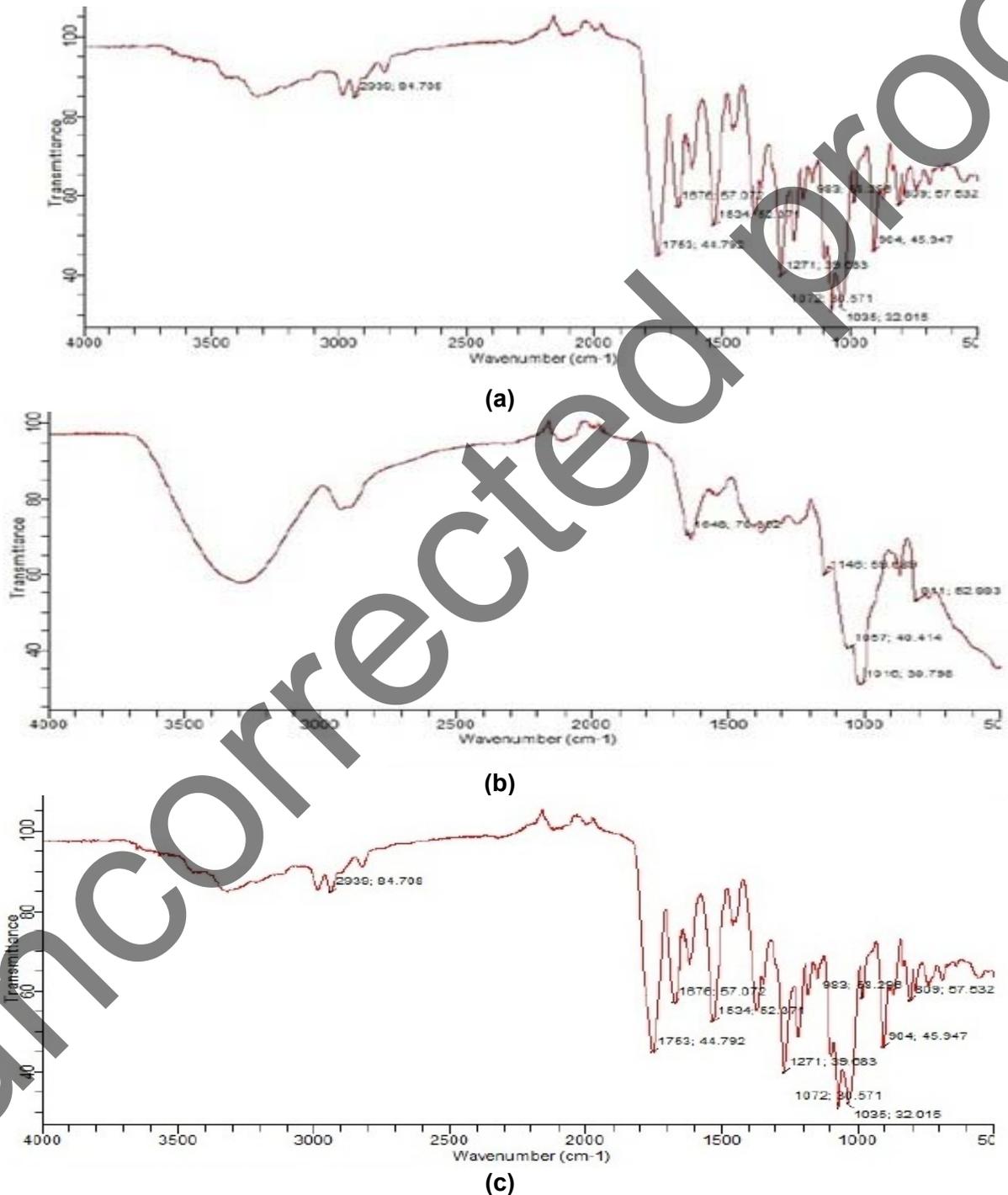


Fig. no. 2: FTIR spectra of (a) Cefpodoxime proxetil (b) locust bean gum and (c) physical mixture of Cefpodoxime and locust bean gum.

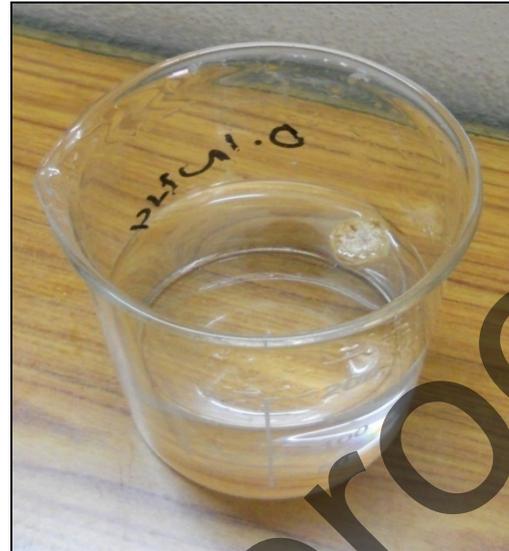
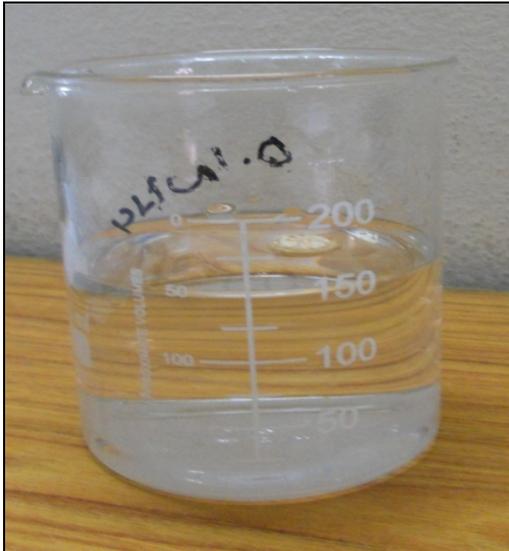


Fig. no. 3: Floating ability (without lag time) of Cefpodoxime proxetil tablets containing camphor

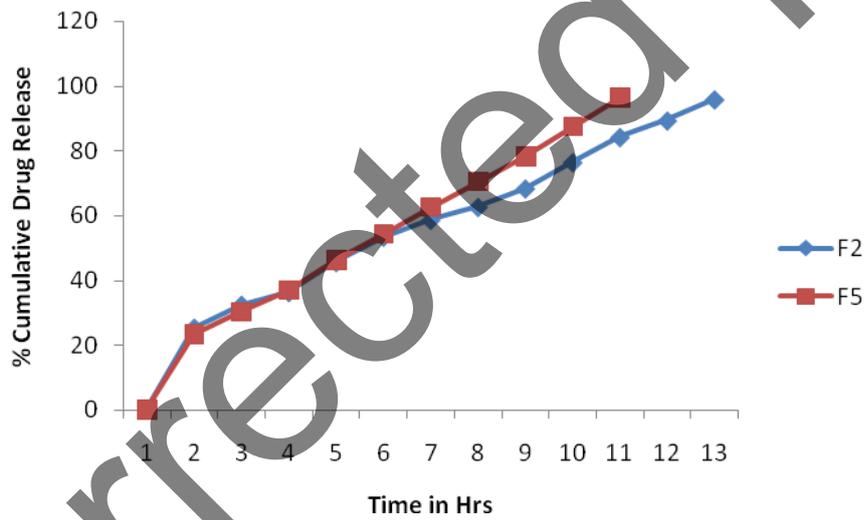
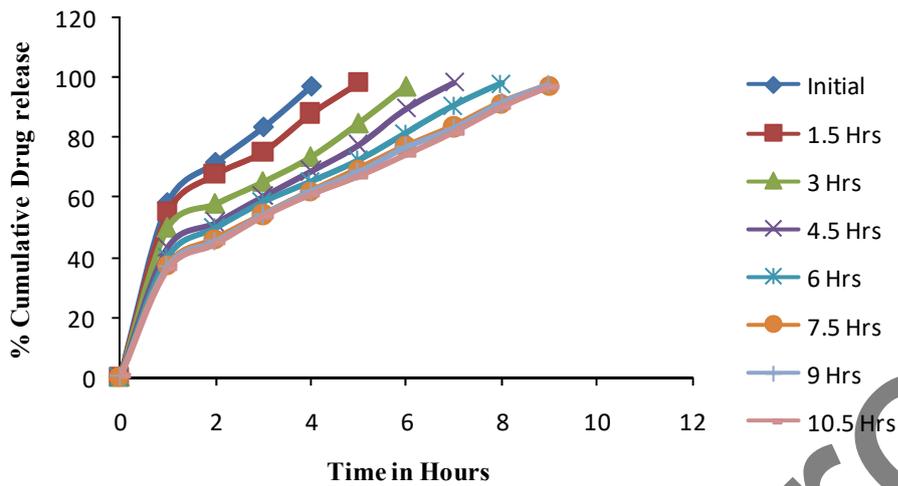
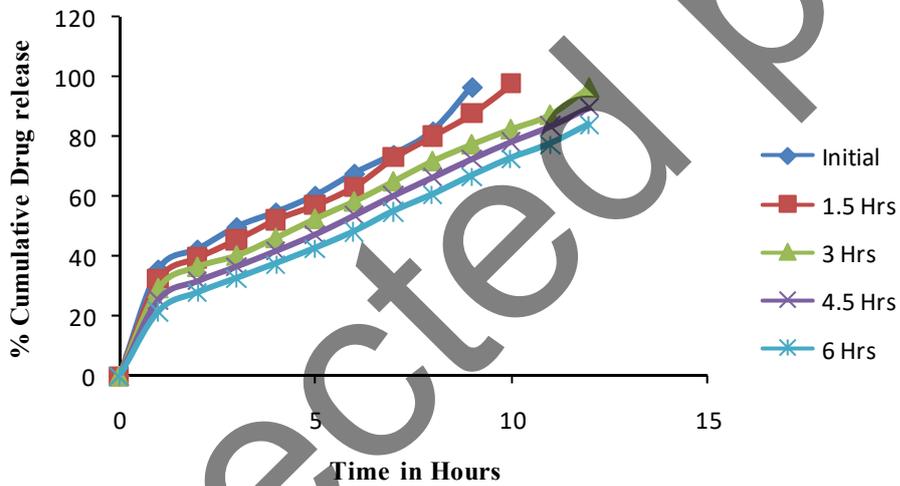


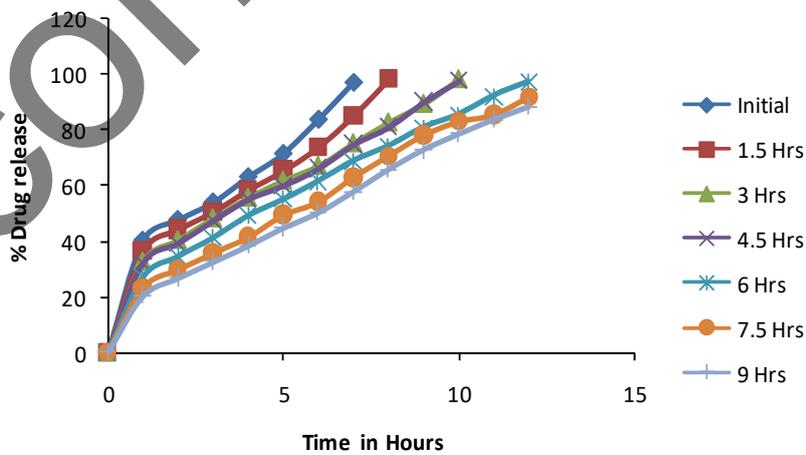
Fig. no.4: Dissolution profiles of F2 and F5 formulations.



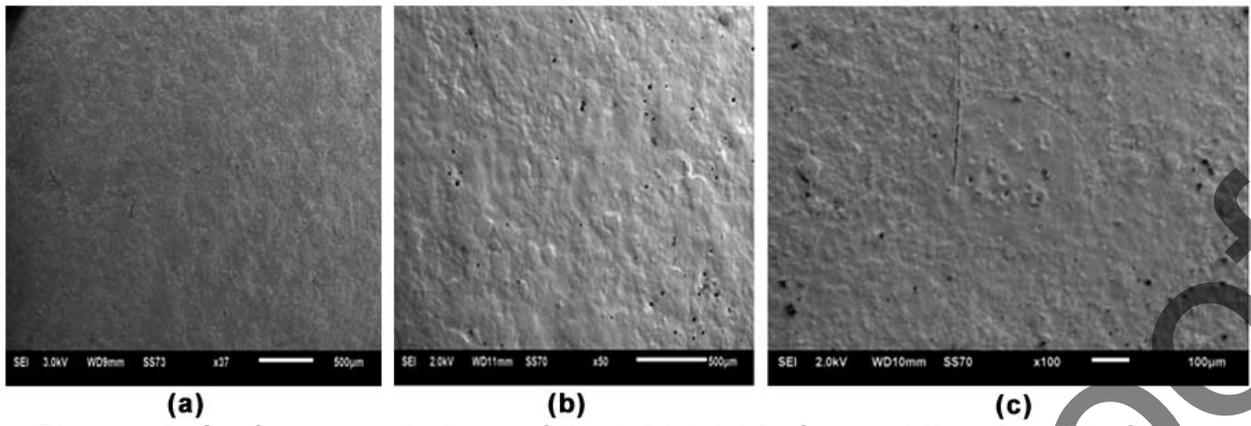
**Fig. no.5: Dissolution profiles of S1 formulation**



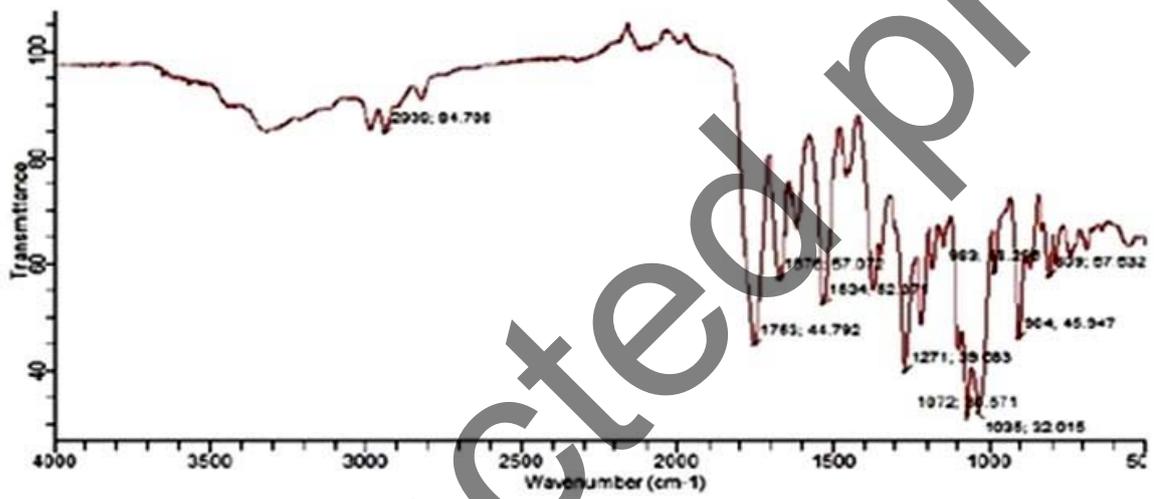
**Fig. no. 6: Dissolution profiles of S2 formulation**



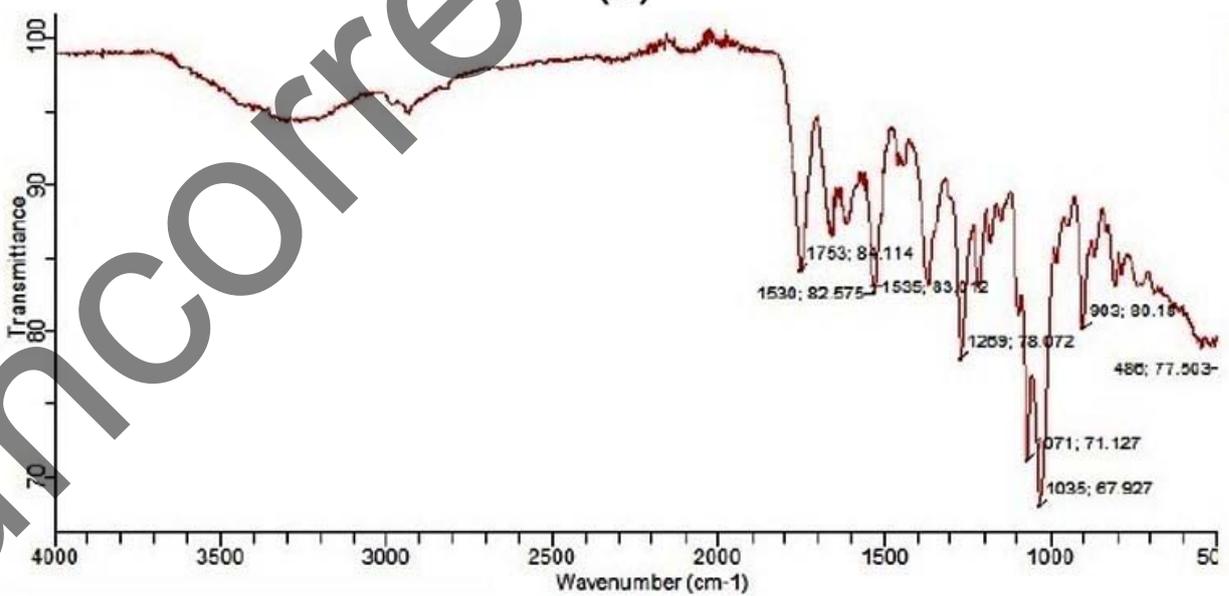
**Fig. no. 7: The dissolution profiles of S3 formulation**



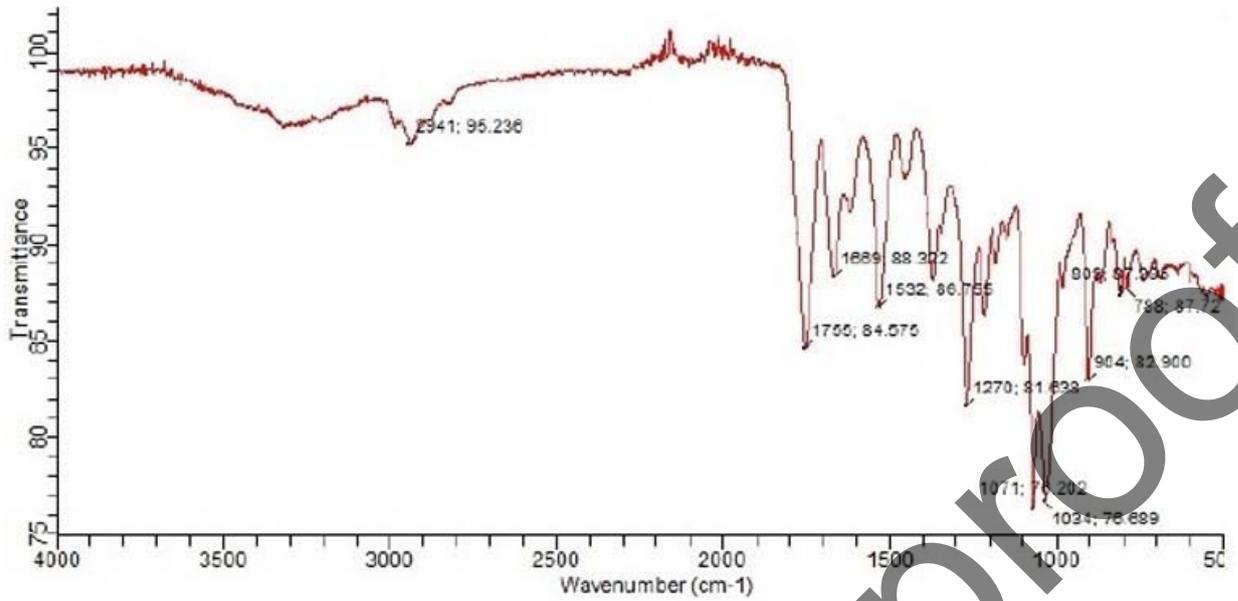
(a) (b) (c)  
**Fig. no. 8: Surface morphology of the tablet (a) before sublimation (b) after sublimation (c) after sintering**



(a)



(b)



(c)

Fig. no. 9: FTIR spectra of (a) pure Cefpodoxime proxetil (b) after sublimation (c) after sintering

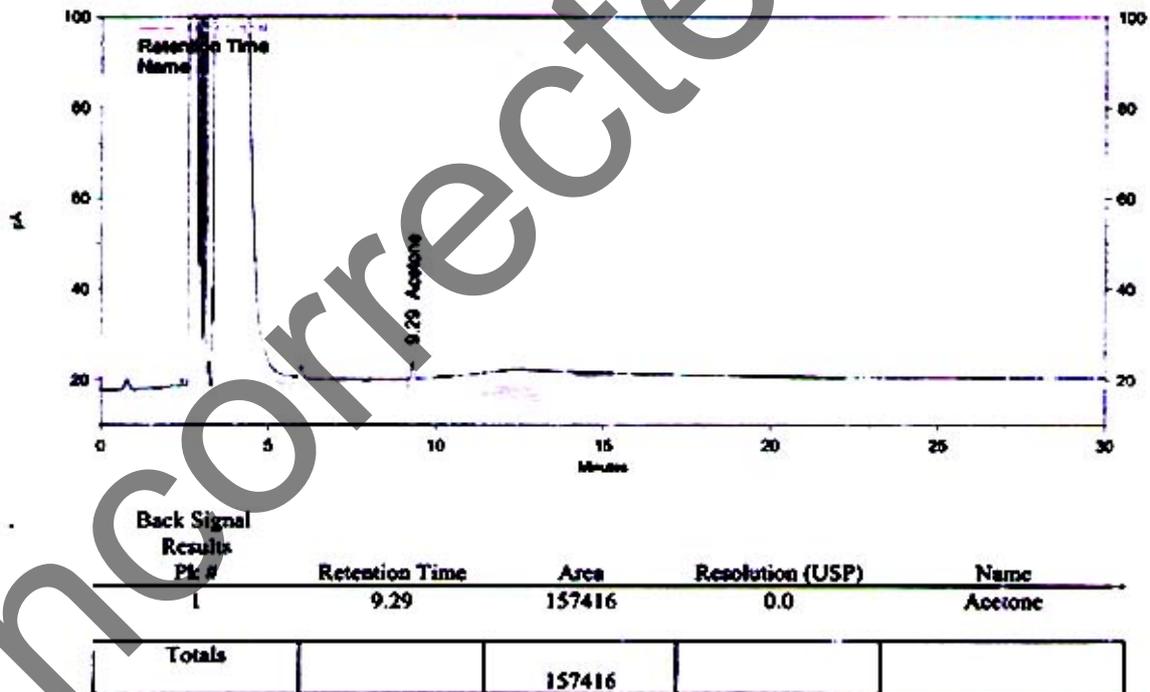


Fig. no. 10: Chromatogram showing peak area for standard acetone concentration (10 µg/ml)

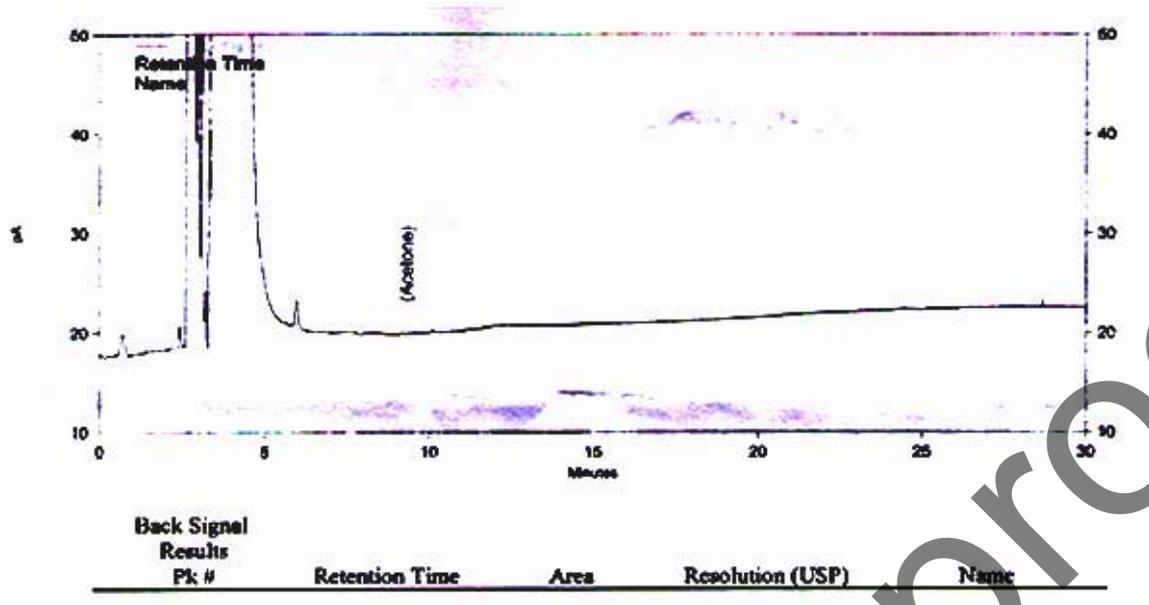


Fig. no. 11: Chromatogram of unsintered tablets

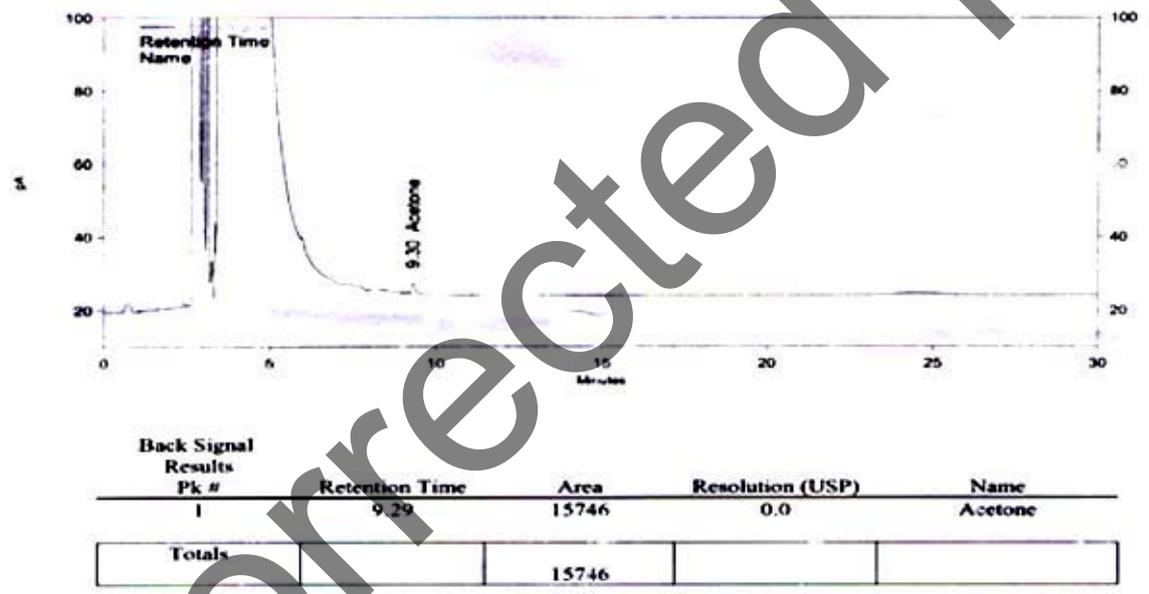
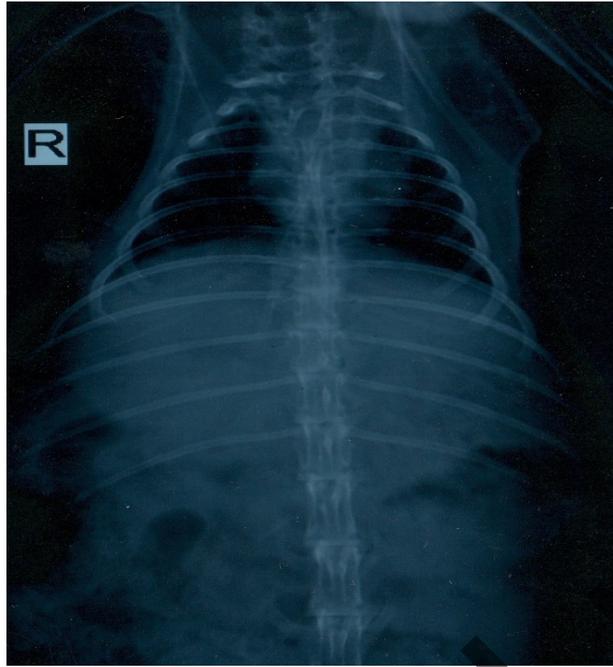


Fig. no. 12: Chromatogram of sintered tablets i.e. exposed for 6 hours to acetone vapors



(A) Before administration



*Immediately After Administration*

*After 1 hr Administration*

*After 2 hrs of Administration*

(B) Immediately after administration, After 1 hr, 2 hrs administration



*After 4 hrs Administration*



*After 6 hrs Administration*



*After 8 hrs Administration*

(C) After 4 hrs, After 6 hrs and 8 hrs Administration

Fig. no. 13 X-ray photographs of GIT of rabbit at different time intervals after administration of floating tablet a) Before administration b) Immediately after administration, After 1 hr, After 2 hrs Administration c) After 4 hrs, After 6 hrs and 8 hrs Administration



Fig. no. 14: Chromatogram showing pure drug spot and test drug spot

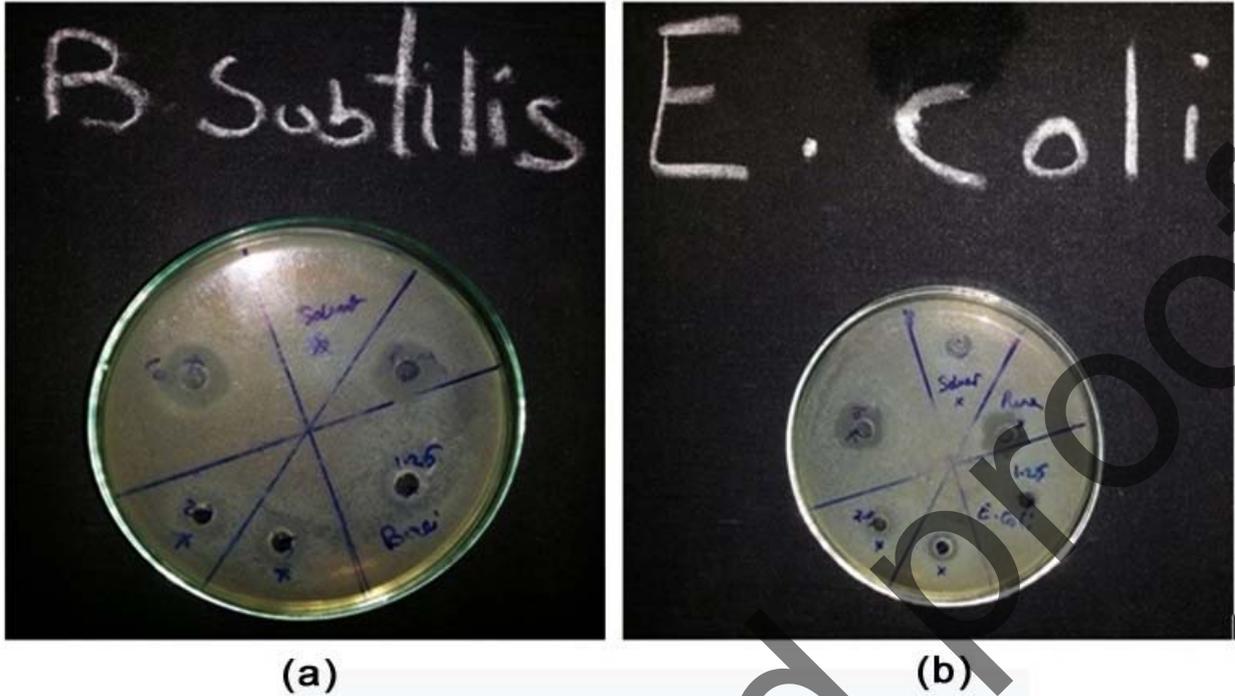


Fig. no. 15: Composition of zone of inhibition between test and standard antibiotic solutions on (a) *Bacillus subtilis* (b) *Escherichia coli*

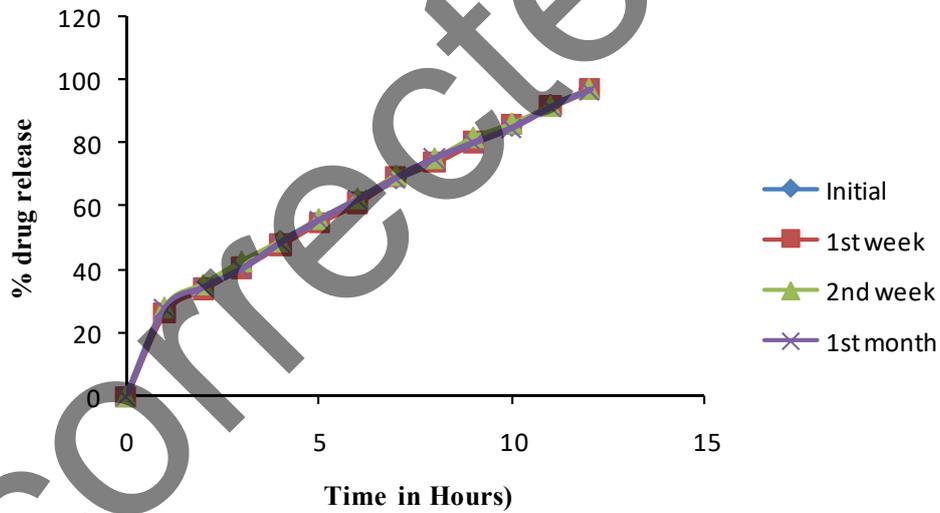


Fig. no. 16: Percentage drug release of optimized formulation during accelerated stability studies