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Der Pharmacia Lettre, 2014, 6 (1):16-29
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Monolithic osmotic tablets for controlled and enhanced delivery of cefixime

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ABSTRACT

An oral monolithic osmotically controlled delivery system for Cefixime using controlled porosity membrane technology was developed and evaluated. Unlike conventional osmotic systems, which require laser drilling, this system releases the drug in a controlled manner from asymmetric membrane coated core tablets. Asymmetric membrane is formed by solvent evaporation process with co solvency technology process using cellulose acetate as the coating material. Higher water influx of this membrane aids in delivery of Cefixime, which is highly water insoluble. The porous structure of the membrane was confirmed by scanning electron microscopy. Influence of different osmotic agents (NaCl & Mannitol) on drug release was evaluated. In vitro release studies showed that as concentration of osmotic agents was increased, the drug release was also enhanced. Drug release from the developed monolithic system was independent of external agitation and pH of dissolution media. Comparative in vitro release data was obtained using different levels and concentrations of coating membranes in controlled porosity membrane, different level of osmogen and with water soluble cellulose acetate phthalate in controlled porosity coating membrane. The optimized formulation follows zero order release mechanism. The FTIR and DSC studies revealed that no physicochemical interaction between excipient and drug. The influence of pH and agitation intensity on the release of drug was studied and the release mechanism was through osmosis. Stability studies revealed that optimized formulation was stable. The osmotic pressure developed was found to be linearly proportional to time and concentration of osmotic agent. The solubility and availability of water insoluble drug (Cefixime) was enhanced by use of solubilizing agent SLS (3.63 %).

Keywords: controlled porosity semi permeable membrane, zero order, cellulose acetate, osmotic delivery, Cefixime, osmotic pressure gradient, in vitro, water influx, pore former.

INTRODUCTION

Osmotic systems for controlled drug delivery employs osmotic pressure gradient as the driving force allowing maintenance of plasma concentration within the therapeutic range. Because pharmaceutical agents can be delivered in a controlled (zero order) manner over a long period by osmotic pressure, there has been increasing interest in the development of osmotic devices in past few decades and various types of osmotic pumps were developed. The elementary osmotic pump (EOP) was introduced by Theeuwes. The EOP consists of an osmotic core, with the drug surrounded by a semi permeable membrane (SPM) with a delivery orifice. In operation, the osmotic core acts by imbibing water from the surrounding medium via the SPM. Subsequently, drug solution is generated within the device and delivered out of the device via the orifice at an approximate zero-order rate. However, the generic EOP is only suitable for the delivery of water-soluble drugs, to overcome the limitation of EOP, two-compartment, two-layer push-pull, monolithic osmotic system and sandwiched osmotic delivery system (three-layer osmotic system) were developed[1].

However, all such osmotic tablet systems have a common disadvantage; a sophisticated laser drilling technique is needed, to make the delivery orifice. Various attempts to increase the permeability of the coating have been reported, including addition of plasticizers in the coating. Here controlled porosity semi permeable membrane

coated osmotic tablets using conventional spray-coating technique have been developed. The dry process involves use of a solvent system for both the polymer and pore former. During membrane formation, the solvents evaporate more rapidly than pore former to create the asymmetric membrane. This controlled porosity membrane coating offers several significant advantages over conventional osmotic tablets. High water fluxes can be achieved using asymmetric coatings, facilitating osmotic delivery of drugs with low solubilities and enabling higher release rates [1]. The permeability of the coating to water can be adjusted by controlling coating thickness. By using oral controlled drug delivery system, continuous delivery of drugs at predictable and reproducible kinetics throughout the GI transit can be provided. To maintain drug concentration within the therapeutic window the drug dose and dosing interval are optimized, thus ensuring efficacy while minimizing toxic effects. Oral CPOP provides greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule. Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Drug delivery from this system (CPOP) is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. The oral osmotic pump tablets have many advantages, such as, reducing risk of adverse reactions, zero order delivery rate, a high degree of in vitro in vivo correlation and improving patient compliance.

Cefixime, a widely used antibiotic was chosen as the model drug. Cefixime is 3rd generation cephalosporin water insoluble antibiotics, which resembles in structure and activity to beta lactam antibiotics. It is used in several chronic and acute prophylaxes both orally and parenterally. It is highly water insoluble with a solubility of $\leq 10 \mu\text{g/ml}$. Cefixime has short elimination half life of 3-4 hours and 45% oral bioavailability, the recommended dose is $8 \mu\text{g/kg}$ body weight daily hence twice or thrice daily dose of 200mg tablet is required to achieve an MEC of $3 \mu\text{g/ml}$ of plasma within 4-5 hours after oral administration. The objective of the study was to develop once-a-day osmotically controlled asymmetric membrane coated tablets of Cefixime. In vitro release rates of Cefixime were studied using different osmogens like sodium chloride and mannitol. The tablets were coated with cellulose acetate as the semi permeable membrane containing nonvolatile pore former poly ethylene glycol -400(50%) and D-sorbitol (25%).

MATERIALS AND METHODS

CHEMICALS REQUIRED:-

The chemicals used in this experiment were of following specifications. The ingredients that is the Lactose(LR), Sodium chloride(LR), D Sorbitol(LR), Poly Vinyl pyrrolidone K 30(LR), Poly ethylene Glycol 400(LR), Cellulose Acetate(39.26% acetylation) were procured from Merck, India. The chemicals namely Mannitol(LR), Sodium lauryl sulphate(LR), Methanol(AR), Ethanol(AR), Dichloro methane(AR) and Iso Propyl alcohol(AR) were procured from Qualigens, Mumbai.

Cefixime was obtained as a gift sample from Concept Pharmaceuticals Pvt. Ltd., Aurangabad, India. It is a white, crystalline powder with melting point in the range of 222°C - 224°C . The percent purity of the drug sample was found to be $99.56 \pm 0.5\%$ on dry basis. Sodium lauryl sulphate was used as solubilizing and wicking agent and various osmogens like sodium chloride and mannitol used for osmotic delivery of cefixime were obtained from Merck India Ltd. Cellulose Acetate (39% acetylation) Merck India Ltd. was used to form a semipermeable membrane.

CHARACTERISATION OF DRUG:-

The characterization of drug, polymer and excipients is carried out by conducting the physical tests such as melting point, IR and DSC studies.

The melting point of Cefixime was determined by open capillary method using the melting point apparatus (Veego, Model - VMP-D, India). Physical mixtures of were used for Fourier Transform Infrared Spectroscopy (FTIR) to study the compatibility and identity of drug.

DSC studies were carried out for the pure drug, and physical mixtures of drug with excipients of the porous osmotic pump tablets to study the compatibility. The analysis were performed under nitrogen (nitrogen flow rate 50 ml/min) in order to eliminate oxidative and pyrolytic effects at a standard heating rate of $10^\circ\text{C}/\text{min}$ over a temperature range of 50°C – 400°C using a Universal V4 5A TA instruments.

PREPARATION OF POROUS OSMOTIC PUMP TABLET

Preparation of core tablets

Core tablets of CPOP were prepared by wet granulation method. All the ingredients (Table no. 2) except povidone K30, magnesium stearate, aerosil and talc were accurately weighted and sieved through 85# sieve, then mixed in mortar with a pestle for 10 minutes to get the uniform mix. The dry blend was granulated with sufficient quantity of

PVP K30 which was dissolved in isopropyl alcohol . The dried granules were mixed with magnesium stearate ,aerosil and talc for 3 min .The tablets were prepared using osmogents like sodium chloride and mannitol in varying ratios . The tablets were evaluated for the different physicochemical parameters, viz . appearance, weight variation, thickness, hardness, friability, drug content, and in vitro release .These granules were compressed on tablet compression machine (Labpress,8 station single rotary machine) . These core tablets were coated by semipermeable coating membrane in coating pan (Dolphin, Mumbai) .

API Calculations:

Strength of tablet is 200 mg . The assay submitted by Concept pharma claimed 99 .56 %w/w of purity, hence

$$\text{Compensation} = \frac{\text{Labeled claim} \times 100 \times 100 \times \text{Molecular weight of Cefixime}}{\text{Assay on dried basis} \times (100 - \% \text{ water content}) \times \text{Molecular weight of cefixime}}$$

Various formulations were designed using different osmogents in core tablet, different concentrations of osmogents in core tablet and different coating compositions .

FORMULATION OF CORE TABLETS BY USING DIFFERENT OSMOGENS IN DRUG LAYER:

Formulations were designed by using different osmogents and different concentrations of osmogents in core along with drug . To study the effect of osmogents in core tablet on drug release (F1,F2,F5 and F6) ,effect of various osmogents(F3 and F4)was studied and the level of solubility modulator and pore former and polymer composition was kept same for all formulations (F1 – F6) **Table no .1** .

Table No .1 Formulation of core tablets by using different osmogents in core tablet

Formulation	F1	F2	F3	F4	F5	F6
D:Osmogent	1:0 .5	1:1 .5	1:0 .5	1:0 .5	1:0 .5	1:1 .5
Lactose	204	04	204	204	204	04
Drug	200	200	200	200	200	200
NaCl	100	300	50	33 .33	-	-
Mannitol	-	-	50	66 .66	100	300
SLS	20	20	20	20	20	20
PVP(K30)	20	20	20	20	20	20
IPA	Qs	Qs	Qs	Qs	Qs	Qs
Mg .Stearate	3	3	3	3	3	3
Aerosil	3	3	3	3	3	3
Total	550	550	550	550	550	550

All quantities are in mg per tablet

Quantities of powder for formulation were calculated to yield 100 tablets of every formulation .

PREPARATION OF GRANULES OF DRUG LAYER:

Cefixime, osmogents, diluents and solublizing agent were sifted through # 85 A .S .T .M mesh . Iron oxide red was sifted through # 60 A .S .T .M mesh . Magnesium stearate, aerosil and PVP K 30 were sifted through # 85 A .S .T .M mesh .PVP K 30 was shifted separately and solution of PVP K30 was prepared in sufficient quantity of isopropyl alcohol . Mix all sifted material other than lubricants and PVP K 30 thoroughly and then it was granulated with povidone K30 solution to get thick dough mass . The thick dough mass of so prepared was passed through # 8 A .S .T .M mesh to get granules . These granules were dried at 50° C in tray dryer till loss on drying is not more than 2 % w/w (10 minutes were required to dry the bulk of 55 gm of granules) . Dried granules were passed through #12 A .S .T .M . mesh . Sifted granules of above step were lubricated with magnesium stearate and aerosil and mixed properly for 5 minutes .

EVALUATION OF LUBRICATED BLEND OF GRANULES[1]:

Lubricated blend of granules was evaluated for angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio .

1) Angle of repose: The angle of repose for the blend was determined by fixed funnel method . Angle of repose was calculated using equation:

$$\tan \theta = \frac{h}{r} \quad \text{Equation 1}$$

Where, θ = angle of repose, h = height of powder heap in cm, r = radius of powder heap in cm

2) Bulk density (BD) and tapped density (TD):

Tapped density was measured by tapped density tester for 100 taps . Bulk density and tapped density were calculated using following formulae;

$$\text{Bulk density (D}_b\text{)} = \text{Mass (g)/ Bulk volume (v}_0\text{)} \quad \text{Equation 2}$$

$$\text{Tapped density (D}_t\text{)} = \text{Mass (g)/Tapped volume (v}_t\text{)} \quad \text{Equation 3}$$

3) Carr's Compressibility Index (CI) :

The compressibility index of the powder blend was determined using Carr's Compressibility Index:

$$\text{(CI)} = [\text{D}_t - \text{D}_b / \text{D}_b] \times 100 \quad \text{Equation 4}$$

4) Hausner's ratio:

Hausner's ratio was determined for characterization of flow of powder blend . A Hausner's ratio greater than 1 .25 is considered to be an indication of poor flow ability . Formula used was as follows:

$$= \text{D}_t / \text{D}_b \quad \text{Equation 5}$$

EVALUATION OF CORE TABLETS:

The core tablets were evaluated for dimensions in which the diameter and thickness of 20 tablets from each batch was determined using a digital micrometer screw gauge (Alex instruments) .The Weight variation test was carried on twenty tablets . Mean and SD was calculated to access the variation . The hardness test was carried out on three tablets from each batch and hardness was checked using Monsanto Hardness Tester . The permissible hardness for oral gastric dissolving tablet is 6-7 kg /cm² and the requisite for osmotic tablet is 5-8 kg/cm² as to withhold the forces of coating in pan .

All formulations were subjected to friability and were assayed for uniformity of drug content and disintegration test of uncoated tablets was conducted test in the Veego-Digital-tab disintegration test apparatus with distilled water as media, the standard limit for disintegration of uncoated tablets for oral use as per USP is not more than 15 minutes .

PREPARATION OF COATING SOLUTION[2][3]:

Cellulose acetate with acetyl content 39 .56% (CA- 398-10NF) was dissolved in methanol and DCM solution by stirring at moderate to high speed accordingly to get clear solution . To this solution, appropriate amount of plasticizer was added under stirring . The coating solution consisted of cellulose acetate (1% w/v) with a water-soluble pore-forming agent like polyethylene Glycol 400 (PEG 400; 50% w/w) and Sorbitol (25 % w/w) in Methanol and Dichloromethane combination in 1:4 ratio .

The coating solution is prepared by dissolving the polymer in the co solvent system prepared first with 1:4 proportions of methanol and DCM at room temperature using mechanical stirrer at low RPM for 30 minutes

Coating Process:

Coating of core tablet is carried out in Dolphin conventional coating pan (12" dia) . The core tablets were coated in a coating machine (Dolphin coater) by spray coating process . The coating process parameters were optimized with respect to pan speed, inlet air temperature and spray rate . Coating process was started once the required bed temperature was attained . Coating process parameters were set as coating pan speed -12-16 rpm , inlet air temperature -45-50°C (inlet), exhaust air temperature -35°C (outlet) and spray gun speed -3 ml/min .

Coating trials[4]:

Following coating composition was used for coating of core tablets . Different combinations containing different composition and concentrations of polymers and hydrophobic or hydrophilic plasticizers in constant amounts .The coating solution CI contained following ingredients Cellulose Acetate as polymer 3gm , D-Sorbitol (25 %) as pore former 0 .75gm, PEG 400(50 %) as pore former 1 .5 ml , DCM as solvent 240 ml, Methanol as solvent 60 ml and Iron Oxide as colorant in quantity sufficient.

The tablets were coated to get different weight gain (3% or 5% or 7% or 9%) . After completion of coating, tablets were allowed to dry (curing) at 45-50 °C in the coating pan itself for 10 min .The viscosity of optimized coating solution was screened for viscosity, with the help of BROOKFIELD viscometer . The 63 number spindle was used for this purpose, the rotation speed was adjusted from 100 to 300 .

EVALUATION OF COATED TABLETS[5]:**Weight gain:**

Uncoated tablets taken for coating were accurately weighed before initiating of the coating process . The coated tablets after coating and drying were again weighed and the difference in the two weights indicated weight gain .

Coating Thickness:

The thickness of coated tablets was measured using micrometer screw gauge and after coating the thickness of coated tablet was measured .The difference obtained is the thickness of coat on both sides of tablet, hence dividing by two the thickness of coat on each side of tablet is obtained in mm .

Assay of tablets:

Ten tablets were accurately weighed and finely powdered . Quantity equivalent to 10 .00mg of Cefixime was dissolved in 100 ml methanol and sonicated for 15 min drug content was measured spectrophotometrically at 289 nm and compared with the absorbance of the standard to get the % drug content of the tablet .

IN VITRO DRUG RELEASE STUDIES:-**Drug release study:**

Drug release test was carried out in two medias namely (SIF) phosphate buffer p^H 7 .4 and (SGF) acidic buffer p^H 1 .2 . The coated tablets were subjected to dissolution study to check the drug release profile and dissolution kinetics . The in vitro dissolution of Cefixime from controlled porosity osmotic drug delivery system was under following conditions using USP Type II dissolution apparatus with 900 ml volume of dissolution medium, the Speed of paddle rotation was adjusted between 50 rpm and 75 rpm . Temperature of $37 \pm 0 .5^\circ C$ was maintained and dissolution medium used was SIF and SGF (without enzyme) .

Confirmation of drug release mechanism of batch no .F2 (optimized batch):

To confirm drug release mechanism, coated tablets of optimized formulation (batch no .F2) were subjected for drug release study under similar dissolution conditions however the dissolution media is made hyper osmotic by adding 2 gm of NaCl in the media, so that the milliosmolality of 114 is exceeded . The drug release is studied and the deformation of coated tablet is observed in this hyper tonic solution .

Influence of formulation variables on the release rate from controlled porosity osmotic pump tablets[5]:

Batch no . F2 was selected as optimized formulation and further study of effect of formulation variables was carried out on the same formulation .

Effect of osmogen concentration in the core:**Batch no . F1, F2, F5 and F6 (Table no . 1)**

This formula was designed by using NaCl (100 and 300 mg/tab F1, F2) in core tablet as well as Mannitol (100 and 300 mg/tab F5, F6) in core tablet . Coating compositions CI were used for coating, weight gain up to 3% . Dissolution profile of batches was studied .

Effect of type of osmogen in core:**Batch number F3 and F4 (Table no .1):**

To study the effect of change in type of osmogen, tablets of batch F3 and F4 with minimum drug to osmogen ratio (1:0 .5) with different type of osmogen(NaCl+ Mannitol), were coated with coating solution CI for weight gain up to 3% .

Effect of weight gain:**Batch number F1 and F2 (Table no .1):**

To study the effect of weight gain during coating, tablets of optimized core were coated for weight gain up to 3% (batch no .F1 andF2) and 7 % (batch no .F1 and F2) . Coating composition C I was used for coating .

Effect of pH of dissolution medium:

In order to study the effect of pH and to assure a reliable performance of the optimized formulation (F2), independent of pH, release studies of the optimized formulation was conducted in media of different pH (Acidic buffer1 .2pH and Phosphate buffer pH 7 .4) .

Effect of different agitation speed on drug release:

To study the effect of different agitation speed on drug release from coated tablet ,all formulation were subjected to dissolution in both (SIF and SGF) media with similar operating conditions, only the rpm of dissolution machine was operated at 75 and 50 rpm and the drug release kinetics was studied .

Scanning Electron Microscopy:

The shell (semipermeable membranes) of optimized formulation (F2) was subjected to SEM before and after dissolution studies, to confirm the formation of sufficient pores and suitable pore size development in the coating membrane, after leaching of water soluble pore former from semipermeable membrane .

Stability studies:

Stability studies on the optimized formulation (F2) was carried out to determine the effect formulation additives on the stability of the drug and also to determine the physical and chemical stability of the formulation under accelerated storage conditions . The tablets were stored in 40 cc HDPE bottles with 2gm silica bags and subjected to following conditions in a programmable environmental test chamber as per ICH guidelines. The temperature is maintained at $40 \pm 2^\circ\text{C}$,relative humidity of $65 \pm 5\%$ RH and duration of study was 3 months . Initial samples (t=0 M) and stability samples (t= 1 M ,t=2M and t=3M) were evaluated for:

1)Description :-Stability samples were evaluated physically for colour and appearance of tablets .

2) In-vitro drug release :-Accelerated stability sample was studied for in vitro drug release profile . Dissolution conditions were kept constant for control sample and accelerated stability sample for batch no . F2 of stability sample (t=1M,2M and 3M) against initial sample (t= 0M) was calculated .

3) Drug content:- Tablets of initial sample and stability samples were analyzed for Cefixime content by UV method as stated above .

Procedure for assay[6]:

Standard and Test solution was filtered through 0.45 μ filter . Absorbances of all dilutions were reported and the percentage of drug content in stability sample tablet and controlled tablets was estimated .

Formula for determination of cefixime contents:

The linearity equation calculated is:

$$Y = 0.0588X - 0.102 \dots\dots\dots 7$$

Therefore

$$X = \frac{y + 0.102}{0.0588} \dots\dots\dots 8$$

After substituting the value of y (absorbance) for particular dilution, it gives concentration ppm . The formula to calculate the content of drug in this 10 ppm dilution in that tablet is

$$\text{mg/tablet} = X \times 100/10 \dots\dots\dots 9$$

The percentage drug released can be calculated using formula;

$$\text{Percentage of drug released} = \frac{X \times 10 \times 0.5 \times 900 \times 100}{200 \times 5 \times 100} \dots\dots\dots 10$$

RESULTS AND DISCUSSION**PREFORMULATION STUDIES****Characterization of Cefixime:**

The characterization of drug was carried out by conducting various physicochemical tests including melting point determination, spectral analysis such as UV spectrum and IR Spectrum for pure Cefixime .It was found that cefixime is heavy crystalline in nature with very good flow property . The appearance of cefixime is white to off white crystalline powder with water content of 0.34 % .The Bulk density and Tapped density of cefixime was found to be 1.0 and 1.45 gm/ml respectively . The melting point was found to be 222°C – 224°C as compared to 224°C which is reported value in literature . FTIR spectrum of Cefixime shown in **Figure no .1** .

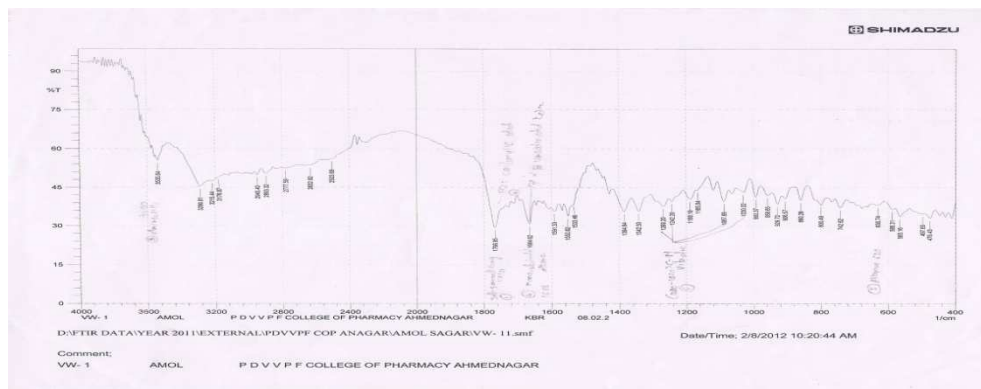


Figure no .1 FTIR spectrum of Cefixime

Functional groups of cefixime were present in the FTIR spectrum . This confirms the purity of substance .

Compatibility Study⁷:

Compatibility study for cefixime was carried out with potential formulation excipients to determine possibility of any drug-excipient interaction/incompatibility . The observations revealed that the assay of drug with all excipients separately was between 98 .63 to 100 .1 % after 30 days of accelerated studies . Compatibility studies at elevated temperature conditions showed that drug itself was stable at higher temperature as well as compatible with all probable excipients selected for proposed research work . Also Differential Scanning Calorimetry was carried out to estimate the possibility of chemical interaction of drugs and polymer with other excipient .The drug does not interact with the excipient and not trans stable product is formed, the result of DSC thermo gram is shown in fig .no .2

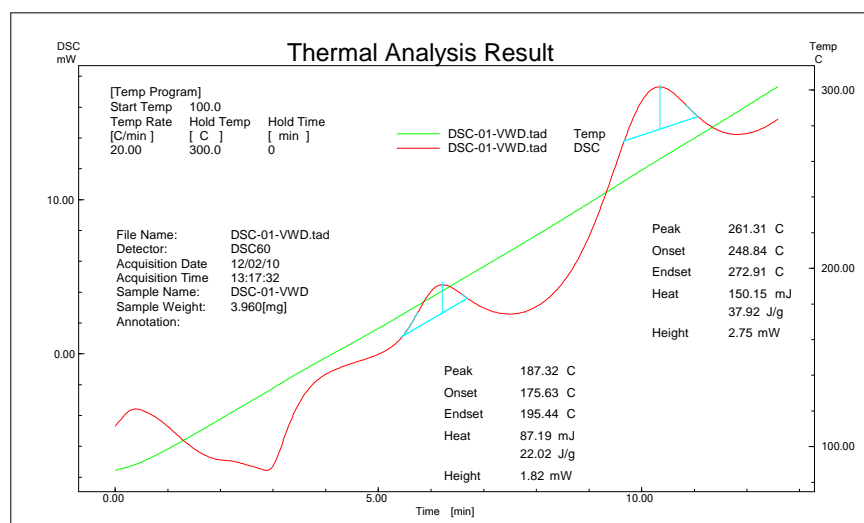


Fig .no .2(A) DSC Thermo graph of individual drug cefixime

Evaluation of Lubricated blends^[8]:

All the parameters namely Angle of Repose in $^{\circ}$ for all formulations ranges from 26 .321⁰ to 30⁰ with standard deviation of ± 0 .0036, Bulk Density ranging from 0 .3524 to 0 .4705 gm/ml with SD of ± 0 .0042, the Hausner's ratio was found to be 1 .132 to 1 .114 with SD of ± 0 .150 and Carr's Index was ranging from 9 .875 to 12 .58 with a SD ± 0 .2861, all this values suggests that powder blend has good flow properties and compressibility .

Unilayer core tablets consisting of drug, osmogent and solubility enhancer were prepared using 10 mm standard punch . An 8 station single rotary tablet compression machine (Labpress, India) was used for compression . All product and process variables like hardness, friability, thickness were kept constant and within permissible limits . The machine was set to yield tablets with mean weight of 550 mg, hardness of 6 kg/cm², thickness of 5 .450 mm and diameter of 9 mm .

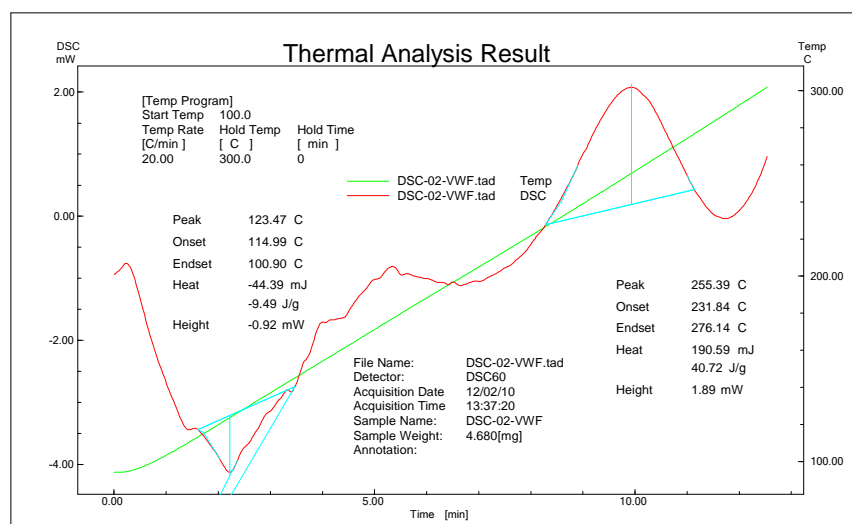


Fig.no .2(B) DSC Thermo graph of drug cefixime with excipients

Evaluation of Cefixime core tablets[9-10]:

The core tablets were evaluated for weight variation, hardness, tablet thickness, % friability and percentage drug content. The hardness was kept in range of 6 to 7 kg/cm². The % friability was found to be within limits. Table no. 6 shows various physical parameters of core tablets. The weight variation accepted as per USP is +/- 2%, all formulations were within limit and standard deviations of all parameters were calculated.

IPQC of Uncoated Tablets:

- Size -5 .510 mm thickness and 9 .00 mm in diameter
- Shape -round
- Color -white
- Odour -odourless
- Surface Texture -smooth
- Marking -scored
- Mottling -absent

The formulations from F1 to F6 were evaluated for all Pharmacopoeial standards and showed following observations; in each test 20 tablets were sampled and tested. The Weight variation test demonstrated an weight from 549 to 552 .3 mg with SD of ± 2 .158, the thickness of tablet ranged from 5 .507 to 5 .512 and SD of ± 0 .002, tablets have the friability of 0 .4545 to 0 .562 %. The disintegration time was from 12 to 15 minutes and the percentage of drug content was found to be 99 .5 t 100 .1 percent, all these demonstrates that the tablet compression parameters are valid and the core tablets are within Pharmacopoeial limits.

The core tablets were subjected to disintegration in (Veego-Digital-tab disintegration test apparatus) disintegration machine to understand the drug release without coating, this test is as per USP guideline for Cefixime uncoated tablet. The results of the dissolution of uncoated tablet illustrated that the drug release from various formulations in 60 minutes was for **F1** (100 .9%), **F2**(100 .5%), **F3**(96 .25 %), **F4**(98 .65 5), **F5**(96 .36 %) and **F6**(98 .99 %).

Determination of Cefixime content[11]:

Cefixime content of coated tablets was determined and found to be within limits. The drug content of each formulation was found to be F1-96 .30 %,F2-100 .00 %,F3-99 .75 %,F4-98 .55 %,F5-99 .12 %,F6-99 .95 %. The other parameters for evaluation of coating process were found to satisfactory and were as follows. The weight variation for all formulations was within 563 .95-568 .88 mg and a standard deviation of ± 0 .74 to ± 1 .56, the weight gain was from 3 .00 to 3 .21 % and membrane thickness attained was 0 .102 to 0 .106 mm after coating.

In vitro Dissolution study[12]:

Coated tablets were evaluated for drug release profiles. Conditions for dissolution were kept similar for all batches as mentioned earlier.

In controlled porosity osmotic pump tablets the drug release rate depends on the concentration of the osmotic agent and the pore former used. The osmotic agent concentration increases then the osmotic pressure created inside the tablet also increases, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug so the release of the drug also will increase.

The pore former concentration increases then the number of pore formed or the pore size also increases it will cause easy leaching out of the drug from the formulation. Results are shown in Fig. 8.

Tablets were coated up to 3% weight gain and dissolution profiles of all formulation were studied. During dissolution studies, it was found that tablets coated up to 3% weight gain did not bust up till 16 hours. of dissolution and drug release was very less. Dissolution of F1 to F6 in various media and the values of R (coefficient of correlation) and K (rate constant) of release models of F1 is as shown in table no. 8

Formulation F1:

This formula was designed by using sodium chloride alone (100 mg/tab) as an osmogen and the proportion of drug to sodium chloride was 1:0.5, this was chosen as minimum base for osmotic activity, Coating composition C 1 was used for coating of the tablets[13]

Formulation F2:-

This formula was designed by using sodium chloride (300 mg/tab) as an osmogen and the ratio of drug to osmogen was 1:1.5 in the core of tablet. Coating composition C 1 was used for coating of the tablets and dissolution profiles of formulation F2 were studied. During dissolution studies, it was found that tablets coated up to 3% weight gain (F2) released 100 % of drug in 12 hours and the drug release profile was constant; neither did the tablet busted during entire period. Drug release up to 5 hours was excellent (up to 40 %) in batch F2 than F1, indicating that increase in concentration of sodium chloride leads to increase in drug release. Tablets after dissolution study were subjected to SEM study to ascertain the density and size of pores formed during dissolution of optimized formulation. Dissolution of F2 in various medias in. **Table no. 2** shows percentage cumulative drug release of F2 in SIF & SGF.

Table no. 2 Percentage cumulative drug release of F2 in SIF & SGF

Time in min.	Cumulative drug release in SIF %		Cumulative drug release in SGF %	
	75 rpm	50 rpm	75 rpm	50 rpm
0	0.000	0.000	0.000	0.000
15	11.580	11.346	11.040	11.116
30	11.134	11.054	11.230	11.069
45	12.278	11.725	11.676	11.524
60	13.167	12.289	12.495	11.945
120	14.041	13.212	13.480	13.294
180	19.872	15.296	16.274	15.510
240	21.380	16.526	16.970	16.274
300	29.242	19.628	18.927	18.124
360	32.847	24.015	23.114	20.371
420	46.122	38.393	34.590	32.677
480	54.446	53.794	49.576	47.938
540	71.167	68.165	66.152	64.994
600	82.193	75.969	79.881	78.623
660	99.627	85.167	90.891	85.845
720	99.056	98.914	97.364	95.820
780		98.205		97.094

Formulation F3 :-

This formula was designed by using sodium chloride (50 mg/tab) and mannitol (50mg/tablet) as an osmogen and the ratio of drug to osmogen was 1:0.5. within themselves the ratio of osmogen as 1:1 with respect to one another. Coating composition C 1 was used for coating of the tablets. Tablets of F3 did not bust till 16 hours. But the drug release was decreased to a minimum level and efficiency of synergism of osmogen was not as effective as sodium chloride alone. Hence further batch was planned using varying proportion of NaCl and mannitol to give more osmotic pressure than F3 so as to achieve higher drug release.

Formulation F4 :-

This formula was designed by placing mannitol as major component of osmogen mixture and sodium chloride as minor (3:2), while the drug to osmogen ratio is kept constant 1:0.5. Coating composition C 1 was used for coating of the tablets. Percentage drug release was less in batch F4 than batch F3. As mannitol and sodium chloride was used in 2:3 ratio, less osmotic pressure was generated inside core tablet which leads to less uptake of dissolution

medium inside the tablet which was further responsible for less drug release than earlier batches. Still drug release was 100% within 16 hours, so further batch was planned with increased amount of mannitol and itself alone as osmogen and to study the resulting drug release.

Formulation F5 and F6[14] :-

Formulation number F5 and F6 was designed by increasing amount of mannitol in core tablet to increase rate of pushing process by faster hydration of polymer. Amount of mannitol was increased from 100 mg/tab to 300 mg/tab in core tablet. Coating composition C1 was used for coating of the tablets.

Drug release was not satisfactory i.e. still 100% release was observed in 24 h from batch number F5 and F6. This indicates that change in osmogen has severe effect on drug release rate in this osmotic drug delivery system. This is augmented to the osmotic pressure generated by the respective osmogen in similar concentration, as osmotic pressure is colligative property it will differ according to the molecular weight of osmogen and not according to metric weight. With change in osmogen if equi molal concentration are prepared then the type of osmogen used is immaterial.

CONFIRMATION OF DRUG RELEASE MECHANISM:

To confirm drug release mechanism, coated tablets of optimized formulation (F2) were subjected for drug release study under similar dissolution conditions as that of optimized formulation (F2) but in media of different osmotic pressure. To increase the osmotic pressure of the release media, NaCl was added to water in the concentration of 2 M. These tablets did not burst up to 6 hours of dissolution study. Only 5% drug release was observed for these tablets up to 6 hours. This indicates that drug is released only through pores and not because of diffusion of drug through semi permeable coating. Pressure gradient was reduced due to use of 0.2 M NaCl solution, which was responsible decrease in rate of drug release. This confirms that osmotic pressure is the primary mechanism of drug release.

Influence of formulation variables on the release rate from controlled porosity osmotic pump tablets:

Formulation F2 was selected as optimized formulation and further study of effect of formulation variables was carried out on the same formulation.

Effect of polymer concentration in coating solution layer:

F2 was coated with CI, CII, CIII, out of which the formulation CI with 1% w/v polymer as compared to the volume of coating solution was seen to give 100% drug release within 12 hours, and there of with CII and CIII the drug release after 12 hours was 48% and 36% respectively.

Effect of pH of dissolution medium:

In order to study the effect of pH and to assure a reliable performance of the optimized formulation (F2) is independent of pH, release study of the optimized formulation was conducted in media of different pH (Acidic buffer pH 1.2, phosphate buffer pH 7.4). Dissolution apparatus used was rotating paddle type (USP type II) at 75 rpm and 50 rpm. Aliquots of 2 ml were withdrawn after 15, 30, 45, 60 min and 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16 hours and samples were analyzed spectrophotometrically. Also all formulation were subjected to dissolution in SGF and SIF to assure that entire formulations are showing drug release independent of pH and hence independent of location in GIT. Comparative dissolution profiles show that drug release through osmotic drug delivery system is pH independent release system as shown in **table no.4**.

Effect of varying agitation on drug release:

To study the effect of varying agitation, simulated to changing motility in GIT due to physiological and pathological change, an drug release is carried out by subjecting the optimized formulation to dissolution in both media (SIF & SGF) at two different rpm that is 75 rpm and 50 rpm. The F2 formulation was subjected to dissolution and drug release was studied in SIF and SGF at 75 and 50 rpm as in table no. 4 and figure no. 3. Dissolution conditions were kept similar for all three trials.

Drug release kinetics and optimization[14]. (Curve fitting analysis)

The in vitro release data was fitted to various kinetic models like Higuchi, First order, Zero order and Peppas. Results are given in the table no. 4 and fig. no. 4. The percentages of drug release from all formulations were studied and the best model fitting for drug release profile is selected for all formulations. In controlled porosity osmotic pump tablets all formulations (F1-F6) follows zero order kinetics, out of which formulation F2 shows maximum values of R^2 and K_0 , indicating its perfect suitability for zero order release. Then the optimized formulation F2 giving required and predictable drug release of 100% drug release within 12 hours is studied for drug release

pattern and the best fitting model is decided by comparing the coefficient of correlation (R) and the release rate constant for all models. The model with maximum value of R & K is selected as best fit model.

Figure no .3 Comparison of dissolution profiles at 75 & 50 rpm

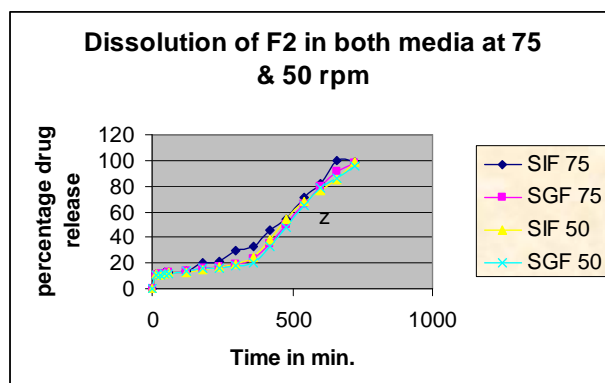
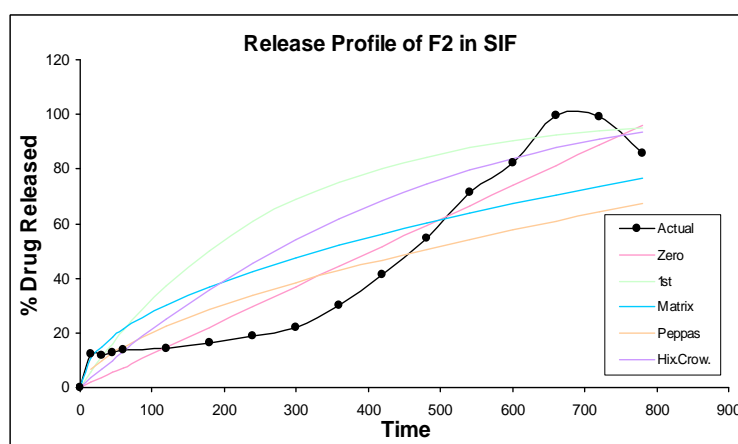


Figure no .4 Release profile of F2 in SIF



Dissolution of F5 & F6 in various media as in fig . no . 5 and the values of R (coefficient of correlation) and K (rate constant) of release models of F5 & F6 is as shown in table no .3.

In vitro drug release study at 12 hour (h) and Comparative evaluation

The drug release percentage of all formulations was studied under identical dissolution conditions preferably in SIF, and the percentage drug release at 720 minutes is calculated so as to evaluate which formulation gives 100 % or near drug release at that time. The formulation (F2) causing maximum (100%) drug release at that time is more suitable to be used for achieving the best predictable and controlled drug release with no fluctuations in plasma drug concentration. The drug release at 720 min from all formulations was respectively as follows F1(82 .28 %), F2(99 .05 %), F3(62 .32 %), F4(64 .31 %), F5(64 .05 %) and F6(54 .04%) .

Table no .3 Rate constants of drug release model for all formulations

Formulation	Constants	Zero order	I st order	Matrix	Peppas	Hix .Crow
F1	R	0 .9612	0 .8719	0 .9100	0 .9342	0 .9333
	K	0 .1023	-0 .0024	2 .555	0 .783	0 .0006
F2	R	0 .9874	0 .7355	0 .8914	0 .9148	0 .8613
	K	0 .1253	-0 .0035	2 .307	1 .2157	-0 .0008
F3	R	0 .9286	0 .7142	0 .8175	0 .8686	0 .8198
	K	0 .0879	-0 .0022	2 .0767	1 .1810	-0 .0005
F4	R	0 .9083	0 .7357	0 .7923	0 .8429	0 .8110
	K	0 .0889	0 .0023	2 .089	1 .2429	-0 .0055
F5	R	0 .9441	0 .6726	0 .8292	0 .8460	0 .8289
	K	0 .0853	-0 .0022	2 .0753	1 .0157	-0 .0005
F6	R	0 .9000	0 .6272	0 .7840	0 .8318	0 .7710
	K	0 .0838	-0 .0029	1 .9697	1 .3401	-0 .0004

From comparative study within the (F1,F2,F3,F4,F5 and F6)formulations the F2 is the batch with 100 %drug release within the expected time and also follows the perfect zero order drug release which is desired .The F2 drug release is also confirmed by plotting the graph of cumulative drug release against time in minutes which is a straight line in indicating the constant zero order drug release . Every formulation obeys the basic equation of zero order release that can be represented by the equation:

$$Q_0 - Q_t = K_0t \quad (1)$$

Rearrangement of equation (1) yields:

$$Q_t = Q_0 + K_0t \quad (2)$$

where

Q_t is the amount of drug dissolved in time t ,

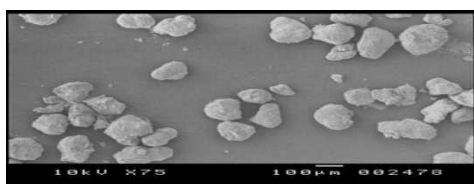
Q_0 is the initial amount of drug in the solution .

K_0 is the zero order release constant expressed in units of concentration/time .

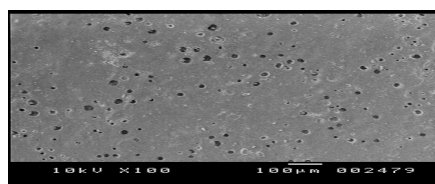
Membrane morphology and Pore size analysis shell of porous osmotic pump tablets:-

To get a perfect idea of the pore size formed by the dissolution of water soluble pore formers (PEG 400 and D sorbitol) contained in the coating semipermeable membrane, the SEM is performed . Membranes obtained before dissolution clearly showed non porous region (Fig . 7) . After 12 h dissolution, clearly showed pores formed in range of 1 to 50 μm owing to dissolution of PEG 400 (Fig . 5) . The leaching of PEG 400 from the membrane leads to formation of pores, and thus the release of drug takes place . In formulation F2 contains 50% PEG which produces sufficient pores .

Figure no .5 SEM studies which showed the pore size analysis (a)before dissolution and (b) before dissolution.



(a)before dissolution



(b) before dissolution

Stability studies:

Stability studies on the optimized formulation (F2) were carried out to determine the effect of presence of formulation additives on the stability of the drug and also to determine the physical and chemical stability of the formulation under accelerated storage conditions . The tablets were stored in 40 cc HDPE bottles with 2gm silica bags and subjected to following conditions in a programmable environmental test chamber (CHS 6 REMI, India) as per ICH guidelines . The temperature is maintained at $40 \pm 2^\circ\text{C}$,relative humidity of $65 \pm 5\%$ RH and duration of study was 3 months . Initial samples ($t = 0\text{M}$) and stability samples ($t = 1\text{M}, 2\text{M}$ and 3M) were evaluated for:

Description:

Tablets of stability sample ($t = 1\text{M}, 2\text{M}$ and 3M) were observed for physical change . There was no change in color and appearance of tablets after stability studies . The parameters evaluated after accelerated stability studies were weight variation, thickness, hardness, disintegration time and percentage content . All tests were employed with $n=20$ for better statics and all parameters were within limits of agreement .

In vitro drug release profile:

Accelerated stability sample ($t = 1\text{M}, 2\text{M}$ and 3M) was studied for in vitro drug release profile. Dissolution conditions were kept constant for initial sample ($t = 0\text{M}$) and accelerated stability sample. After $t=3\text{M}$ the optimized formulation F2 showed 100 % drug release within 12 hours.

No changes in drug release were seen after 3 months of storage under 40°C , 65% relative humidity, this indicates that no untoward reaction or degradation of drug in formulation has occurred during accelerated storage conditions that will effect drug release profile of formulation F2 .

Active drug content (assay by UV)

Initial samples ($t = 0$ M) and accelerated stability samples ($t = 1$ M, 2M and 3 M) were analyzed for cefixime content by using UV system. Freshly prepared standard solution was used and the results of drug content was in range of 99.63 to 100.0%.

CONCLUSION

The aim of present investigation was to develop once a day CPOP for Cefixime with controlled porosity osmotic unilamellar tablet and cellulose acetate as coating polymer. The developed osmotic drug delivery system would deliver Cefixime at zero order mechanism. At the same time systemic drug levels will be above minimum effective concentration, constant without fluctuations and thus may reduce adverse effects and improve the efficacy.

From preformulation studies of Cefixime (M.P, Solubility, UV identification, density, IR spectroscopy and DSC thermo gram), it is confirmed that the sample is pure and authentic as the observation coincides with standards of Cefixime. Similarly the preformulation of polymers and excipient was carried out, which assured the purity and identity of all polymers and excipient. The DSC of drug along with polymer and excipient establishes the compatibility of drug with all excipient. The shift in the position of exothermic peak corresponding to the melting point of drug in the formulation thermo gram is prominent and broad (100-124 C) and not transient, so no unstable by product of drug is formed in the formulation. A number of formulation batches were tried with various osmogent (NaCl and D sorbitol) alone and their combinations, with varying concentrations of cellulose acetate (39.65% acetylation) polymers and with varying proportion of pore former (PEG 400), in the coating semipermeable membrane.

The compressed core tablets produced showed the evaluation parameters, mean thickness (5.540-5.550 mm), weight variation (545- 555 mg), mean hardness (5-7 kg/cm²), friability less than 0.6% and drug content between 96.00 to 100.36%, which are excellent for coating into an osmotic tablet. After the coating of core tablets in conventional coating pan the evaluation of coating is established by the calculation of parameters like weight gain, which was found to be not more than 3%, the thickness of coat was found to be 102 to 105 μm and is as planned to achieve the predictable drug release.

More than 70% drug was released in 12 hours from all formulations and 100% drug released from optimized formulation (F2). Increase in concentration of osmotic agents lead to increase in release rate of Cefixime (F1 to F2 and F5 to F6), due to increase in osmotic pressure gradient between the core compartment and external environment. Its release was not only affected by osmogent and its concentration in core tablet but also by the size and density of pores formed in semipermeable membrane. Increase in coating thickness leads to decrease in its release rate. Increase in polymer concentration in the coating layer leads to decrease in its release rate.

Optimized formulation's tablets busted within 8 hours of dissolution study in hyper osmotic 2M of NaCl mixed in phosphate buffer pH 7.4, which indicates that drug is released through orifice only by osmosis and not by diffusion through membrane.

Cefixime release from developed osmotic system was not affected by the pH of dissolution media. Optimized formulation batch (F2) with 1:1.5 cefixime to sodium chloride was subjected for dissolution in SGF and SIF at 50 and 75 rpm to prove the independence of drug release from pH and agitation speed, this confers the release of Cefixime from F2 was unaffected by the physiological changes and pathological conditions which causes change in pH and gastric motility. Cefixime content and drug release along with hardness and weight variation were found to be within limits after accelerated stability studies. Thus optimized formulation (F2) was found to be stable under accelerated stability conditions.

From release profile it can be seen that dissolution of Cefixime in CPOP increase with increase in osmogent and in formulation F2 the drug release is 100% at 12 hours (1:1.5 ratio of drug: osmogent) as in table no. 4.

It was found that the drug release from CPOP was also directly proportional to thickness of coating, weight gain in coating and level of pore former in proportion to polymer in coating solution. (Wt. Gain -3%, PEG 400-50%).

The SEM revealed that sufficient density and suitable size (50-100 μ) of pores were responsible for drug release and generation of suitable saturated osmotic pressure inside compartment.

From the above study it is concluded that the dissolution and invitro drug release of Cefixime, a drug with low solubility, can be increased by use of SLS as solubilizing agent (3.36%).

Also the controlled drug release can be achieved by formulating the Cefixime in formulation F2 to give a zero order drug release for 12 hours and thereby decreasing the dose of drug to 200 mg daily without fluctuations in plasma drug concentration .

The results suggest that drug release takes place via the in situ formed micro porous structure . Developed osmotically controlled oral delivery system can be used as once-a-day controlled-release formulation, thus increasing patient compliance . This system is cost effective and simple to prepare as no drilling is required and can be used for controlled delivery of water-insoluble drugs .

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