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Original Research Article

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Formulations and evaluation of Cyclodextrin complexed Ceadroxil loaded nanosponges

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Abstract

Cefadroxil (CFD) is a broad spectrum antibiotic that acts against an extensive variety of bacteria, including Gram-positive and Gram-negative bacteria. The major drawback of orally administered drug like cefadroxil is its shorter half life of 1.2 hrs. The goal of the study is to prolong the drug release, producing a desired blood serum level, reduction in drug toxicity and improving the patient compliance by prolonging the dosing intervals. Cyclodextrin-based nanosponges (NS) are a novel class of cross-linked derivatives of cyclodextrins. They have been used to increase the solubility of poorly soluble actives, to protect the labile groups and control the release. This study aimed at formulating complexes of CFD with three types of β-cyclodextrin NS obtained with different cross-linking ratio (viz. 1:2, 1:4 and 1:8 on molar basis with the cross-linker) to protect the lactone ring from hydrolysis and to prolong the release kinetics of CFD. Crystalline ($F_{1:2}$, $F_{1:4}$ and $F_{1:8}$) and paracrystalline NS formulations were prepared. XRPD, DSC and FTIR studies confirmed the interactions of CFD with NS. XRPD showed that the crystallinity of CFD decreased after loading. CFD was loaded as much as 21%, 37% and 13% w/w in $F_{1:2}$, $F_{1:4}$ and $F_{1:8}$, respectively while the paracrystalline NS formulations gave a loading of about 10% w/w or lower. The particle sizes of the loaded NS formulations were between 450 and 600 nm with low polydispersity indices. The zeta potentials were sufficiently high (-20 to -25 mV) to obtain a stable colloidal nanosuspension. The in vitro studies indicated a slow and prolonged CFD release over a period of 24 h. The NS formulations protected the lactone ring of CFD after their incubation in physiological conditions at 37 C for 24 h with a 80% w/w of intact lactone ring when compared to only around 20% w/w of plain CFD.

Keywords: Cefadroxil; cyclodextrins; nanosponges; paracrystalline.

Introduction

Cyclodextrins are naturally occurring cyclic oligosaccharides generally containing 6, 7 or 8 glucose units, respectively, known as , β and γ cyclodextrins. They are characterized by a typical toroidal cone shape; the atom arrangement is such that the inside cavity is lipophilic, while the outside of the torus is highly hydrophilic. Cyclodextrins are thus able to form stable inclusion complexes with molecules of suitable polarity and size even in aqueous solutions. The complexation mechanism does not involve covalent bonds and the main driving force of complex formation is the release of enthalpy-rich water molecules from the cyclodextrin cavity [1]. Cyclodextrins (CDs) have found numerous applications in many fields due to their ability to complex with a wide range of compounds [2]. To improve the characteristics of native cyclodextrins, many derivatives have been prepared. Cyclodextrin conjugates with biocompatible hydrophilic polymers have been prepared to increase the solubility of β-CD and its complexes in aqueous media [3–6]. In polymeric conjugates, where a number of β-CD units are bound to the same polymer chain, it can happen that cooperation among several β-CD units increases the stability of the drug complex. Moreover, the polymer may cooperate with the β-CD moieties in stabilizing the complexes.

It has recently been reported that, by reacting cyclodextrins with suitable crosslinking agents, a novel nanostructured material consisting of hyper-cross-liked cyclodextrins can be obtained; these are known as nanosponges [7–9]. This composite material shows interesting characteristics; in particular, cyclodextrin-based nanosponges are characterized by their marked capacity to encapsulate a great variety of substances that can be transported through aqueous media or, from the opposite perspective, removed from contaminated water. As a result, they could be a very efficient tool either to remove pollutants from water or to carry substances for biomedical applications. Thanks to their capacity to complex molecules, nanosponges have been proposed as drug delivery systems [10-11].

Cyclodextrin-based nanosponge aregenerally obtained by cross-linking different types of cyclodextrins (CD) with a dicarboxylate or a carbonyl compound as cross-linker. These can be made from many

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different organic or inorganic materials; their structure presents a nanometric dimension or smaller. Well-known examples are titanium or other metal-oxide based nanosponges, silicon nanosponge particles, carbon coated metallic nanosponges, hyper-cross-linked polystyrene nanosponges and also cyclodextrin based nanosponges. The common characteristic of these materials is the presence of nano-scale pores that give them particular properties [12]. In the pharmaceutical field, in particular, they could be employed as solubilizing agents or nanocarriers.

Material and methods

Materials

Cefadroxil (CFD), Diphenyl carbonate, β-cyclodextrin were purchased from Sigma–Aldrich (Milan, Italy). All other chemicals and reagents were of analytical grade. Milli Q water (Millipore) was used throughout the studies.

Synthesis of β-cyclodextrinnanosponges

Nanosponges of β-cyclodextrin were prepared in series of three types using diphenylcarbonate for the cross-linking as described by Trotta, Cavalli et al. (2006). Concisely, diphenylcarbonate melted at 90 C then anhydrous cyclodextrin added and placed for at least 5 h. Then, to remove the organic impurities after cool the mixture, it was ground in mortar and then sohxleted with ethanol for unreacted diphenyl carbonate. The reaction with a cross-linker excess was done with three different molar ratios: 1:2, 1:4, 1:8 (β-cyclodextrin: cross-linker). After purification, nanosponges were stored until further use at 25 C until further use. This reaction was also carried out in the presence of ultrasound, and two different types of NS, namely, crystalline (1:2 NS, 1:4 NS, 1:8 NS) and paracrystalline (1:2, 1:4, or 1:8 NS_{para}), were formed based on the process conditions of the synthesis.

Preparation of Cefadroxil-loaded nanosponges

CFD was dispersed in aqueous suspensions of the various types of nanosponges in a ratio of 1:4 (drug to NS by weight) and was stirred for 24 h in the dark and at acidic pH to avoid the formation of the carboxylate form of Cefadroxil. After 24 h, the suspensions were centrifuged at 2000 rpm for 10 min to separate the uncomplexed drug as a residue below the colloidal supernatant. The colloidal supernatants were freeze-dried to obtain drug-loaded NS formulations, named as $F_{1:2}$, $F_{1:4}$ and $F_{1:8}$ and F_{para}, depending upon the ratio of β-CD:cross-linker. The drug-loaded NS formulations were stored in a covered vacuum desiccator at room temperature until further use.

Preparation of Cefadroxil physical mixtures

Binary physical mixtures of the series of nanosponges with the drug were prepared by mixing appropriate amounts of solid components (4:1 NS:CFD weight ratio) in a glass mortar.

Determination of CFD loading in nanosponges

Weighed amount of loaded nanosponges were dispersed in a methanol:chloroform mixture (1:4 v/v), suitably diluted in methanol and were analyzed by HPLC. Briefly, a Shimadzu instrument model no. LC-9A, equipped with C R5A cromatopac integrator and RF-551 spectrofluorometric detector in isocratic conditions was used. The separation was carried out using an octadecylsilane column with a 5 μm pore size with a mobile phase containing acetonitrile and triethanolamine aqueous solution (1% w/v) in a ratio of 35:65 (v:v) using a fluorescent detector at a λ_{ex} = 360 nm and λ_{ex} = 440 nm. The flow rate was kept at 0.8 ml/min. The peak of CFD (lactone) was obtained at a retention time of about 9 min and that of carboxylate form (if present) was obtained at a retention time of about 3 min. The standard solutions of CFD -lactone and CFD -carboxylate for the calibration curves were made by dilution of the CFD stock solution in dimethylsulfoxide. The analysis of the carboxylate form was carried out 24 h after preparing the solution in NaOH 0.1 N to ensure the complete conversion of the CFD-lactone to the carboxylate forms. The calibration curves were linear in the range 0.1–0.5 ug/ml.

Physicochemical characterization of CFD-loaded nanosponges

Fourier Transform Infrared spectroscopy (FTIR)

It was performed, using a Perkin Elmer system 2000 spectrophotometer, to understand if there exists some interaction between drug and NS. To prepare the pellets, a few milligrams of the sample were ground together in a mortar with about 100 times the quantity of potassium bromide (KBr). The finely ground powder was introduced into a stainless steel die. The powder was then pressed in the die between polished stainless steel anvils at a pressure of about 10000 psi. The spectra were obtained on KBr pellets in the region from 4000 cm^{-1} to 500 cm^{-1}.

Differential scanning calorimetry (DSC)

It was carried out by means of a Perkin Elmer DSC/7 differential scanning calorimeter (Perkin-Elmer, CT-USA) equipped with a TAC 7/DX instrument controller. The instrument was calibrated with indium for melting point and heat of fusion. A heating rate of 10 C/min was employed in the 25–300 C temperature range. Standard aluminum sample pans (Perkin-Elmer) were used; an

empty pan was used as reference standard. Analyses were performed in triplicate on 5 mg samples under nitrogen purge.

Size, polydispersity index and zeta potential values

NS sizes and polydispersity indices were measured by dynamic light scattering using a 90 Plus particle sizer (Brookhaven Instruments Corporation, USA) equipped with MAS OPTION particle sizing software. The measurements were made at a fixed angle of 90 for all samples and 25 C. The samples were suitably diluted with filtered distilled water for every measurement. Zeta potential measurements were also made using an additional electrode in the same instrument. For zeta potential determination, samples of the three formulations were diluted with 0.1 mMKCl and placed in the electrophoretic cell, where an electric field of about 15 V/cm was applied.

Optical microscopy (OM)

The NS suspensions were observed using a Leitz invert microscope after suitable dilution with water and saline solution to evaluate the effect of the dilution on the NS formulations. The OM was also used to investigate the morphology of erythrocytes after the incubation with the NS.

Scanning electron microscopy (SEM)

It was employed to evaluate the structure and surface morphology of the nanosponge A Philips CM 10 Scanning electron microscope was used, and the particle size was measured using the NIH image software. The nanosponge suspensions were sprayed on Formwar-coated copper grid and air-dried before observation.

Fourier transform infrared (FTIR) spectra of different nanosponges

The FTIR spectra of 1:2 , 1:4 , 1:8 nanosponges was done in order to confirm the presence of the carbonate bond in the nanosponges . This shows the occurrence of crosslinking between the cyclodextrin.which has a peak at around 1700—1750 cm^{-1}.

In-vivo studies

In-vivo studies were performed on 2 group of albino rats weighing 250 grams. Dose for albino rat were calculated by using 'Oncology tool: Dose calculator' [27]. Target dose of 7.69 mg/kg/12 hrs of cefadroxil was given to rat. Oral suspension of cefadroxil and cefadroxilnanosponges suspended in saline solution to achieve concentration of 1 mg/ ml of cefadroxil was prepared and is administered by orogastric gavage after anaesthesia. Animal is divided into 2 groups, one rat in Control group and four rat in complex group. Sample were analysed by UV spectroscopy and analysis was done for data studies and pharmacokinetic analysis.

Statistical analysis

Statistical analysis of differences among the formulations was performed using Student's t-test. A 0.05 level of probability was taken as level of significance.

Results and discussion

Cefadroxil was odorless, off white to yellowish, crystalline powder. The physical properties matched with the IP specifications. Identification of drug was confirmed by melting point study, UV spectra and FTIR spectra. Melting point found after triplicate study was 197.33˚C±0.471 and this complies with the pharmacopoeial specification so it was confirmed that sample obtained was cefadroxil (I.P 1996)

FTIR Spectroscopy

The FTIR of sample cefadroxil was taken (fig 1). On interpretation of FTIR spectra of drug it showed characteristic absorbance band at 1354 cm^{-1} and 1759 cm^{-1} of Cefadroxil which were due to stretching vibration of C-N (beta lactam)and C=O (beta lactam) bond respectively. All other indication showed that the drug sample was authentic and pure.

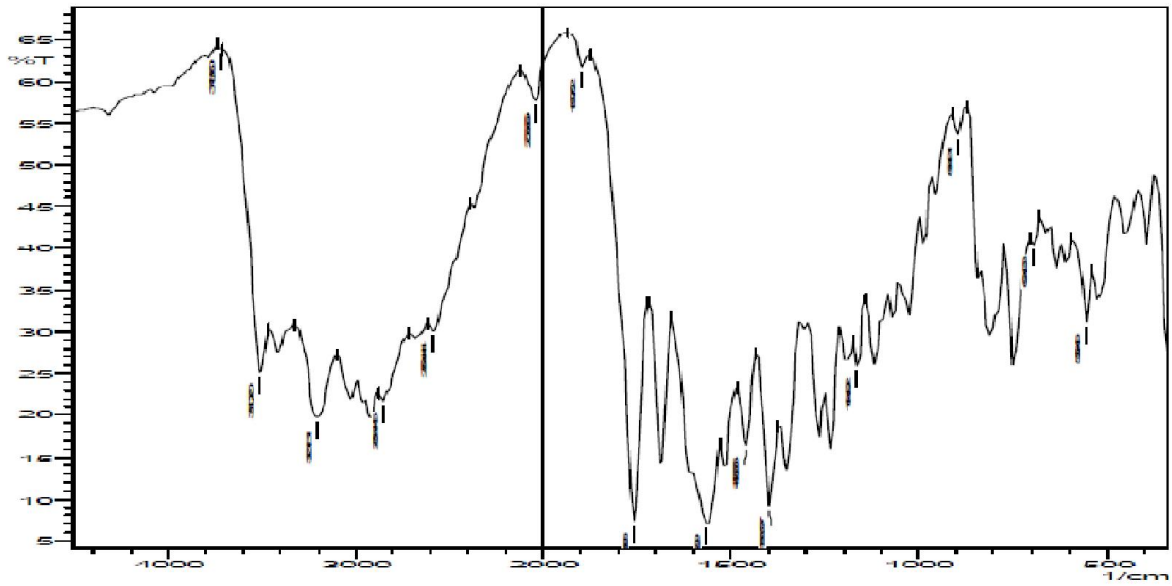


Figure 1: FTIR spectra of cefadroxil (Sample).

Determination of partition coefficient

The partition coefficient (Po/w) was found to be 0.398 using octanol-buffer systems. The Log P value -0.41 indicating hydrophilic nature of the drug and which does not cross biological membrane very easily.

Determination of Absorption maxima (λmax)

The absorption maxima of cefadroxil was determined in phosphate buffer (7.4) (figure 2) in methanol (figure 3).

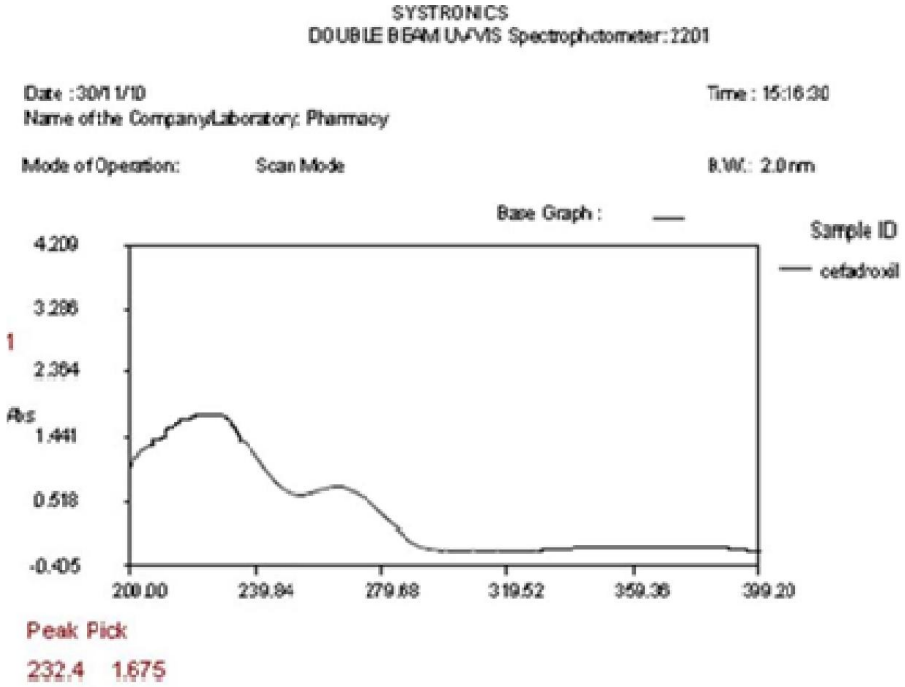


Figure 2: Absorption maximum of cefadroxil in phosphate buffer (pH 7.4)

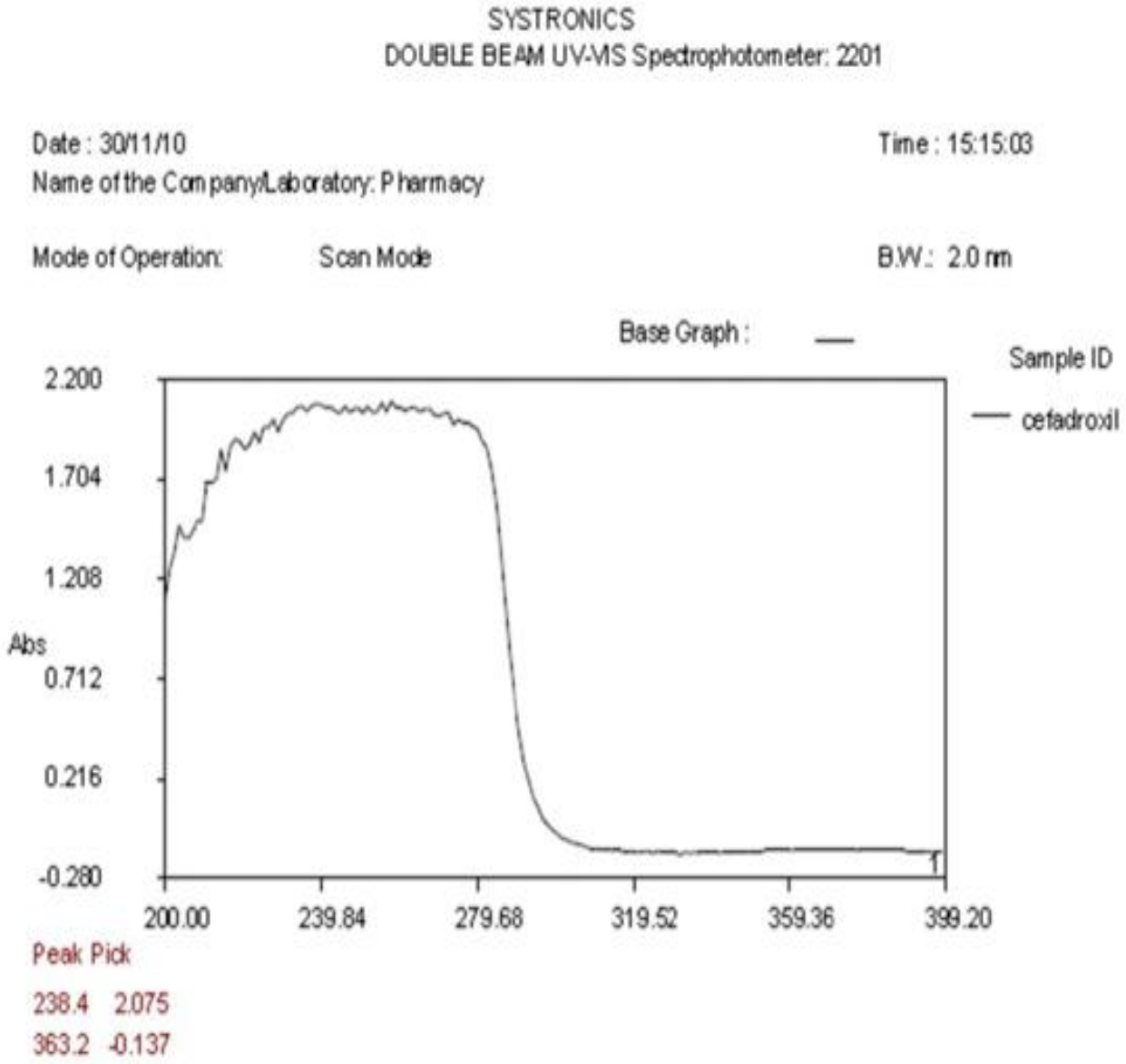


Figure 3: Absorption maxima (λmax) of cefadroxil in methanol

Compatibility studies FTIR spectra of cyclodextrin

Drug polymer interaction study is very important to check the compatibility of drug and polymers.study implies that the stability of drug in presence of excipients.it is done with spectroscopy by Kbr pellet technique using FTIR spectrophotometer (Shumadzu FTIR-8400S). the combination for this are: Drug –cefadroxil
Cyclodextrin
Diphenylcarbonate
Cyclodextrin + cefadroxil
Cyclodextrin + diphenylcarbonate
Cyclodextrin + diphenylcarbonate + cefadroxil

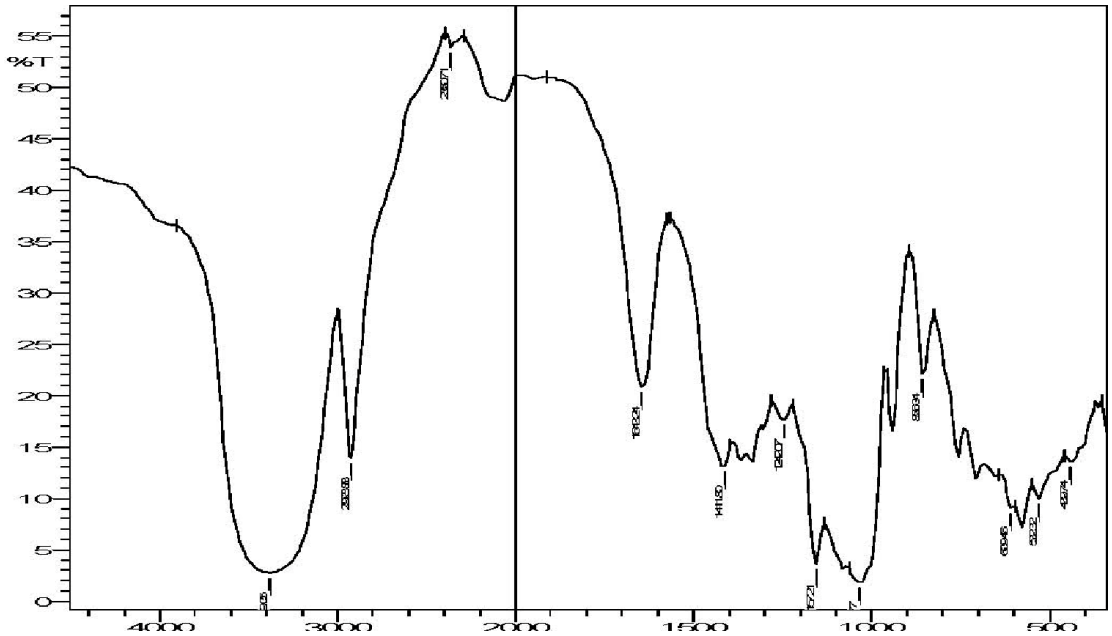


Figure 4: FTIR spectra of cyclodextrin.

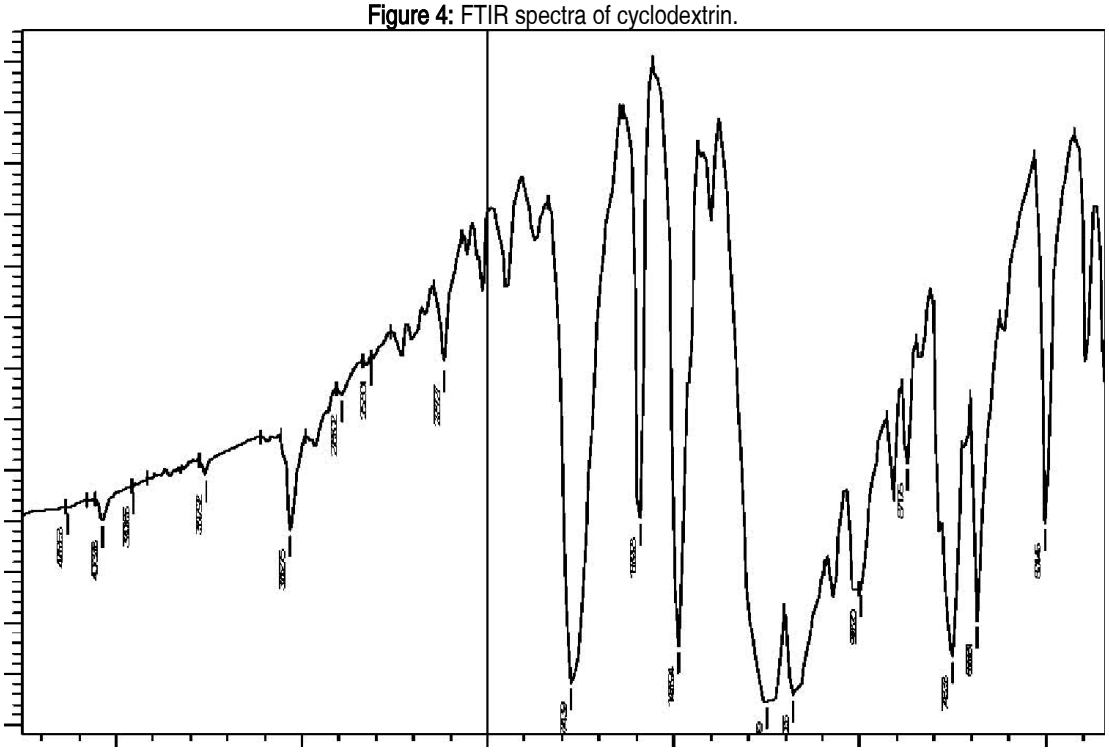


Figure 5 : FTIR spectra of diphenylcarbonate.

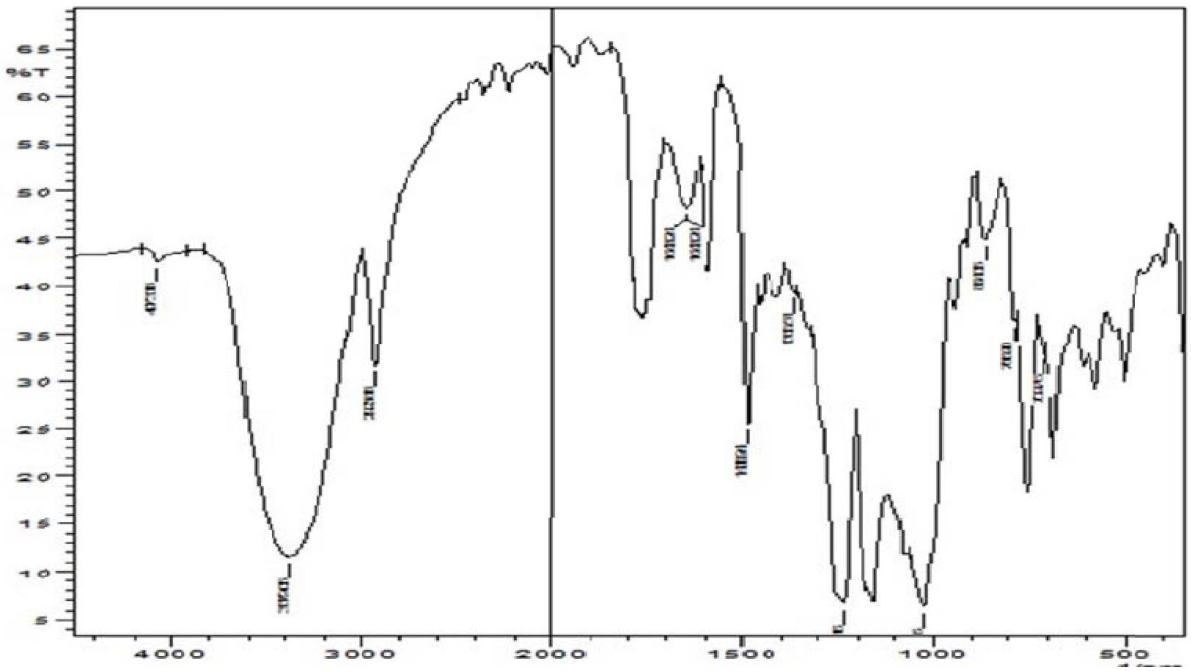


Figure 6: FTIR spectra of cyclodextrin and dpc

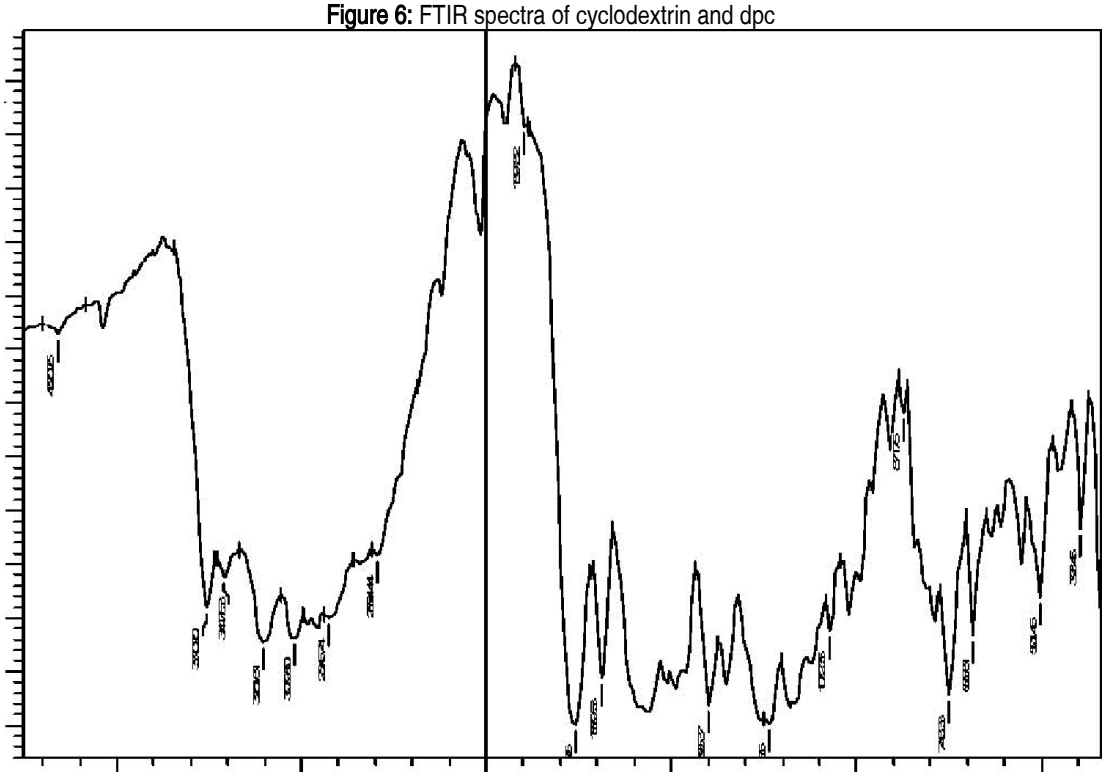


Figure 7: FTIR spectra of cefadroxil andcyclodextrin

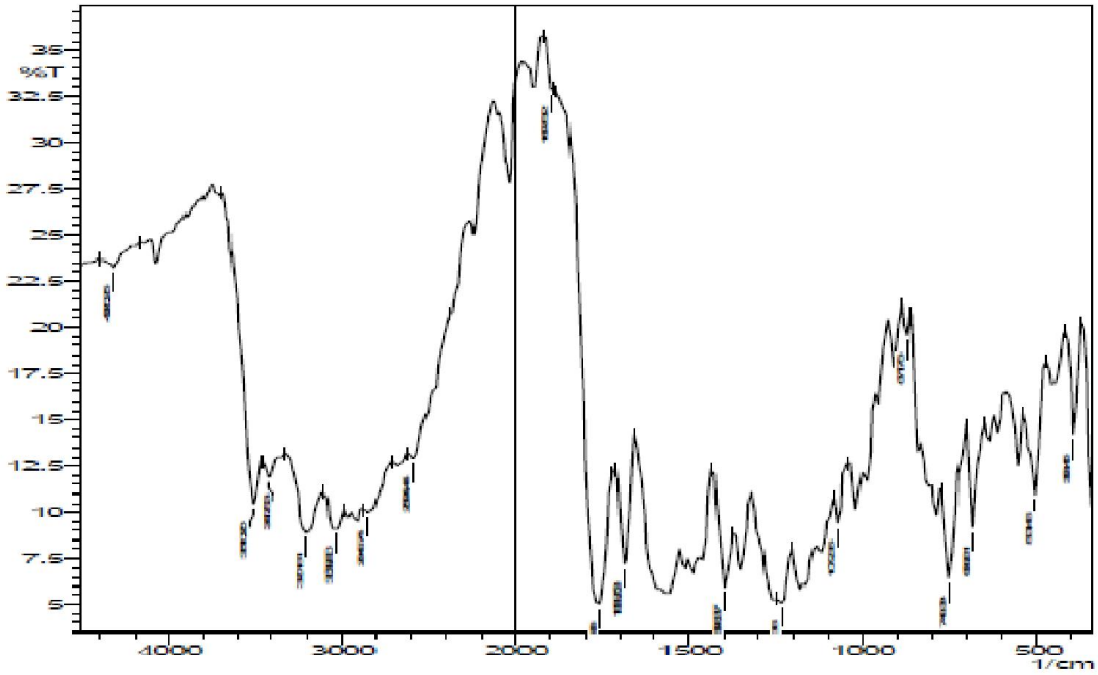


Figure 8: FTIR spectra of cefadroxil anddpc

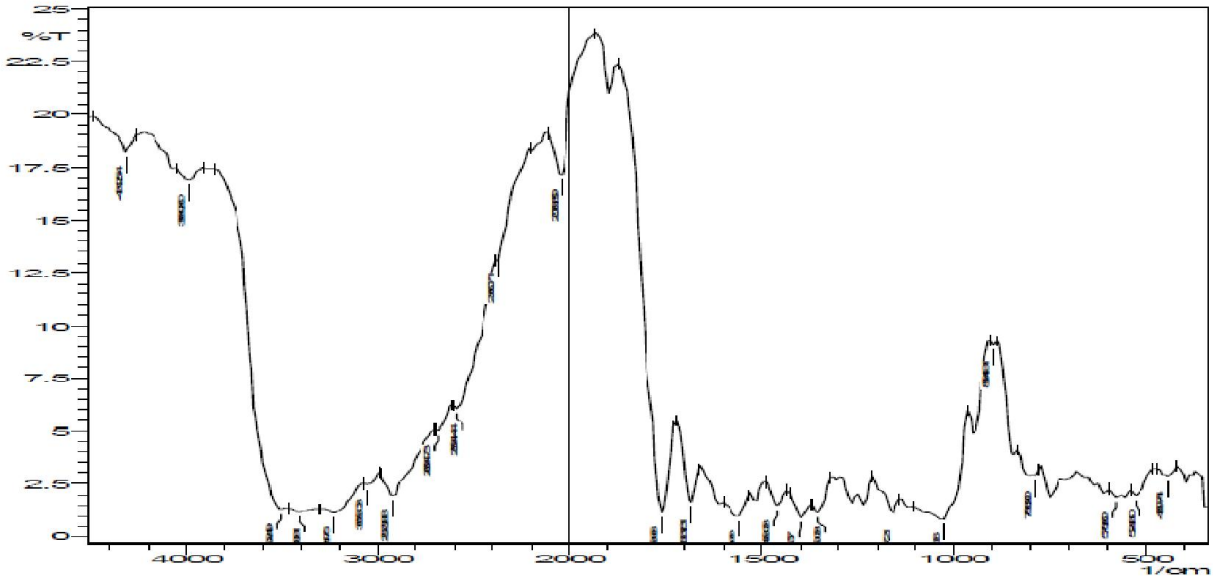


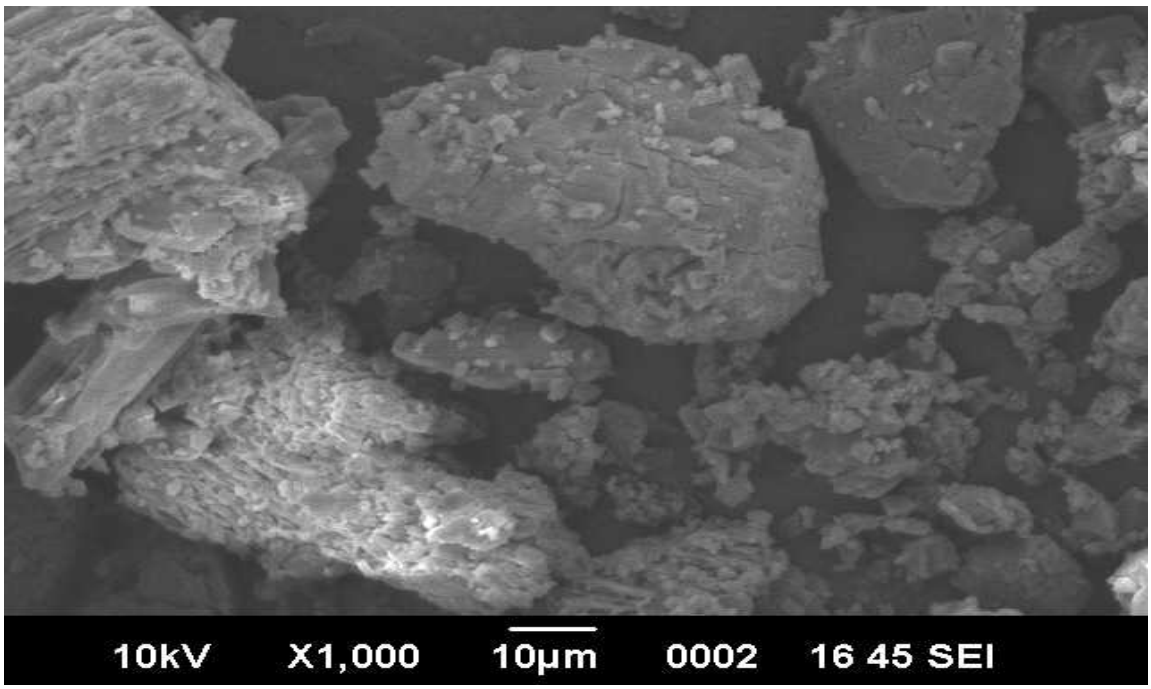
Figure 9: FTIR spectra of cefadroxil and dpc and cyclodextrin

The FTIR study was done for compatibility study with the cefadroxil. FTIR spectra of drug showed charctersitic absorbance band at 1354 cm -1 and 1759 cm -1 of cefadroxil which were due to stretching vibration of C-N (beta lactam) and C=O (beta lactam) bond respectively. The cyclodextrin is characterized by absorbance band at 3300-3600 cm^{-1} for OH group, 1000-1260 cm^{-1} for –CO group and 2800-3300 cm^{-1} for –CH, -CH2 group. The diphenylcarbonatye is characterized by the absorbance band at 1753 cm-1 for carbonate bond. There was no shifting of peaks seen in the IR spectra of cefadroxil with diphenyl carbonate (fig 8). So it was concluded that there was no interaction with the diphenyl carbonate. With cyclodeextrin there is characteristic changes seen in the drug

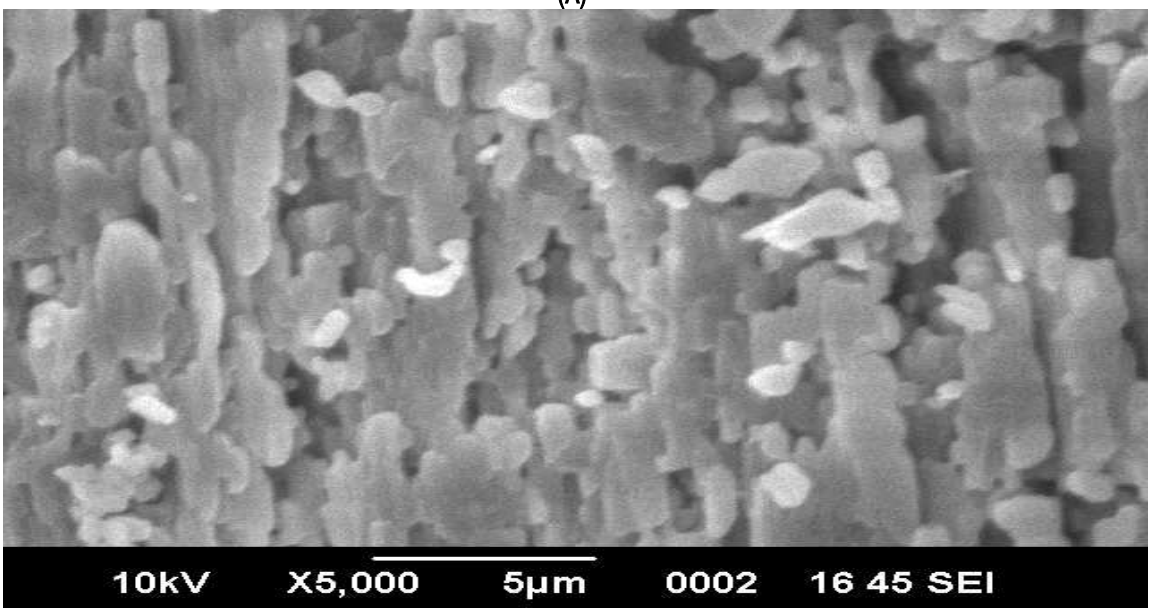
region which can be attributed to the loss of crystallinity of the drug. A similar changes was seen with FTIR of the cefadroxil, cyclodextrin, diphenyl carbonate mixture.

Scanning Electron Microscopy

Scanning electron microscopy of Nanosponges was done to reveal the structure and surface morphology of the nanosponge. Scanning Electron Microscopy of nanosponges illustrated irregular shaped rough surface and porous of the nanosponges. The surface morphology shows a porous structure of nanosponges.



(A)



(B)

Figure 10: (A) SEM of nanosponge (B) SEM indicating Surface morphology of nanosponge.

Fourier transform infrared (FTIR) spectra of different nanosponges

The FTIR spectra of 1:2 , 1:4 , 1:8 nanosponges was done in order to confirm the presence of the carbonate bond in the nanosponges . This shows the occurrence of crosslinking between the cyclodextrin.which has a peak at around 1700—1750 cm-1.

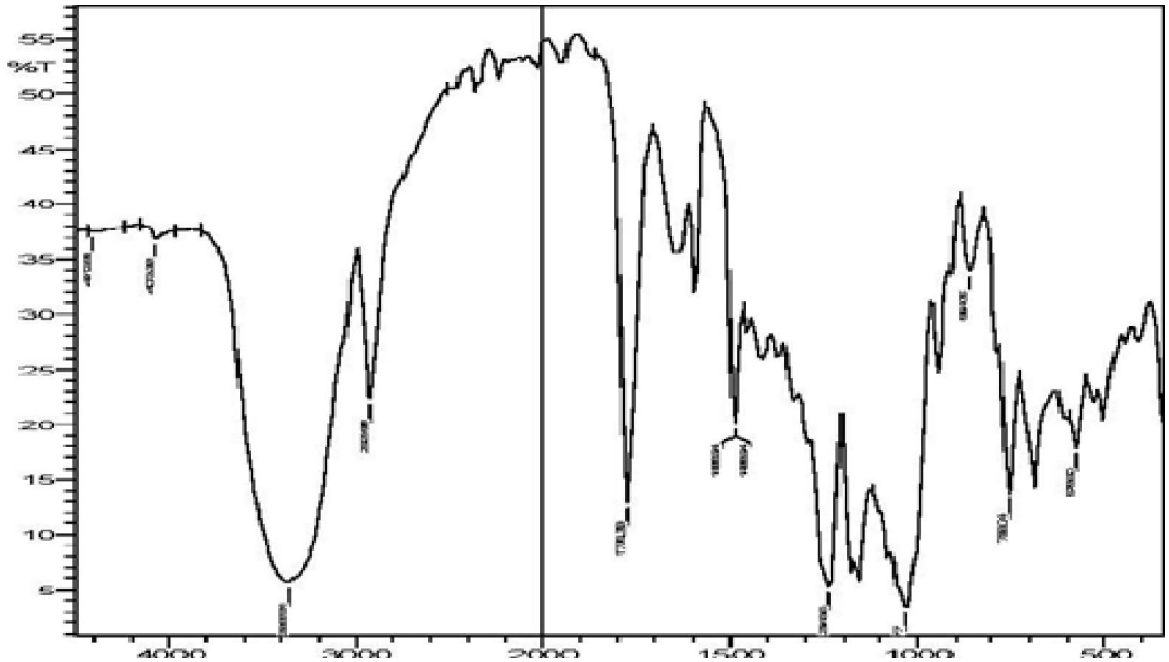


Figure 11 : FTIR spectra of 1:2 nanosponges

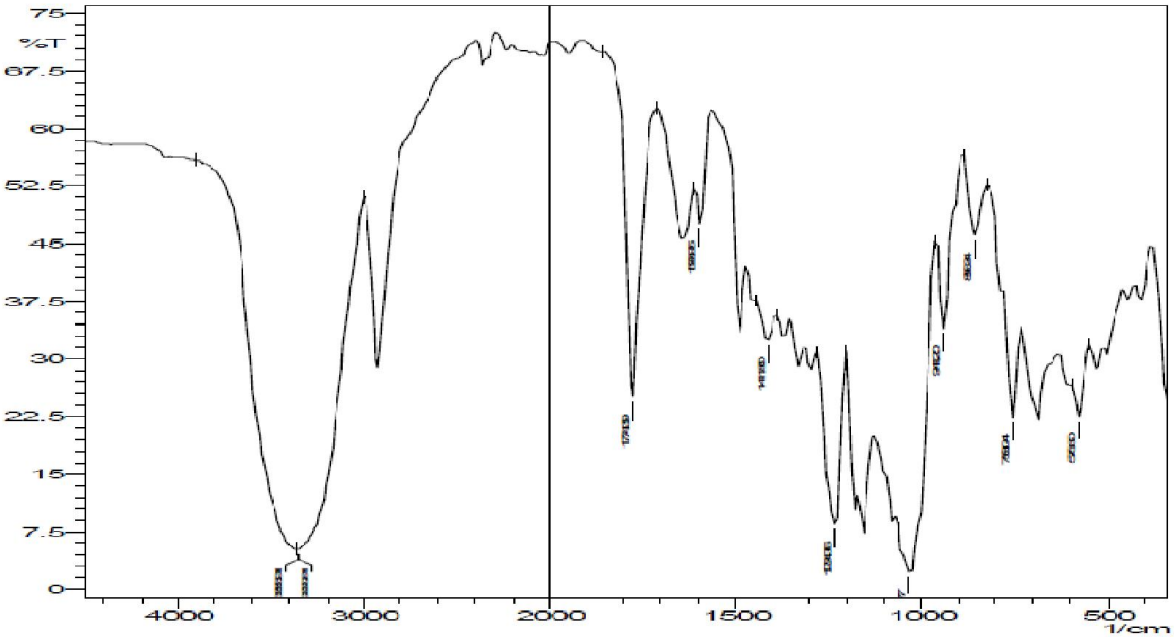


Figure 12: FTIR spectra of 1:4 nanosponges

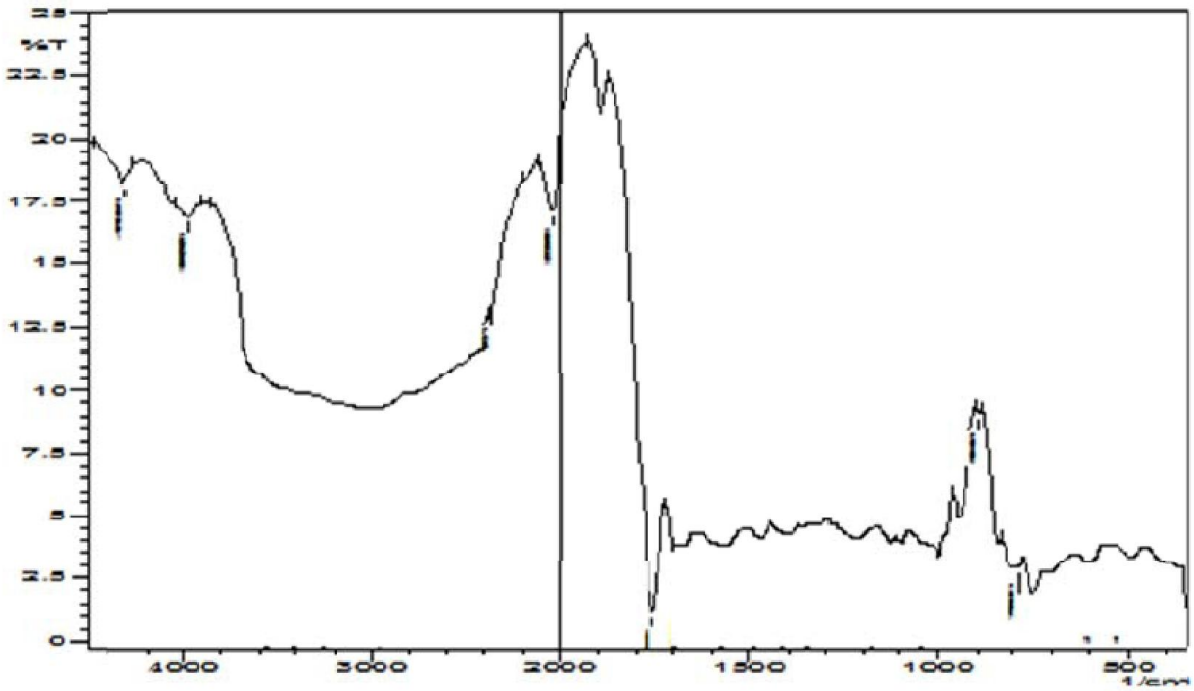


Figure 13: FTIR spectra of 1:8 nanosponges

The FTIR spectra of nanospongesviz 1:2 (fig 11), 1:4 (fig 12), 1:8(fig 13) nanosponges showed the presence of the carbonate bond which has a peak around 1700-1750 cm^{-1} .The presence of carbonate bond sowed that the crosslinking was occurred between the cyclodextrin.

FTIR of drug loaded nanosponges

The FTIR of drug loaded nanosponges was done to determine any changes in the physical form of drug in the nanosponges.

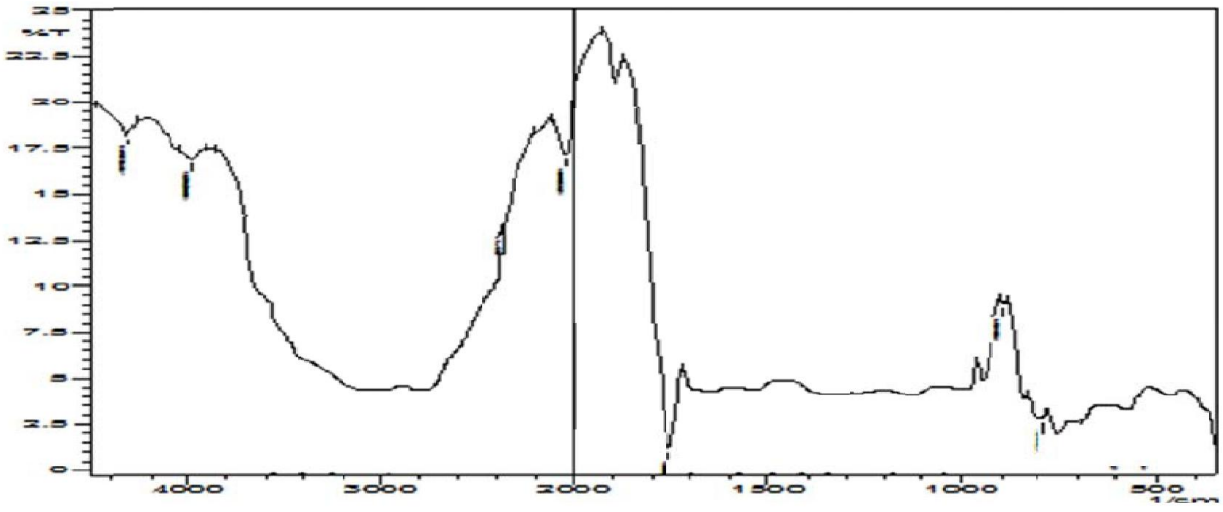


Figure 14: FTIR spectra of drug loaded 1:2 nanosponges

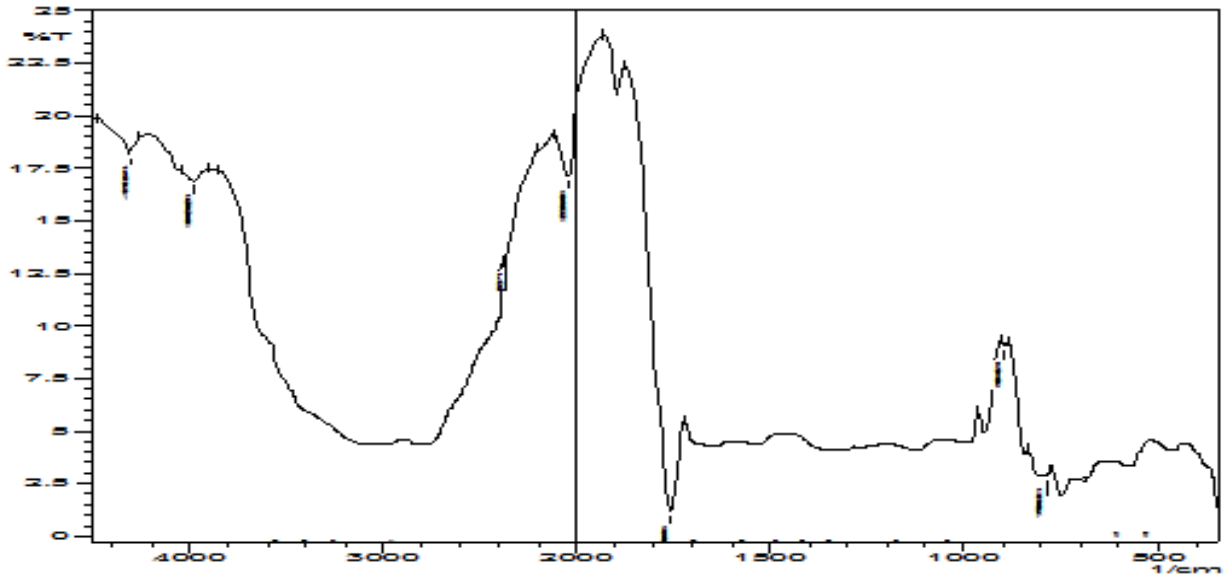


Figure 15: FTIR spectra of drug loaded 1:4 nanosponges

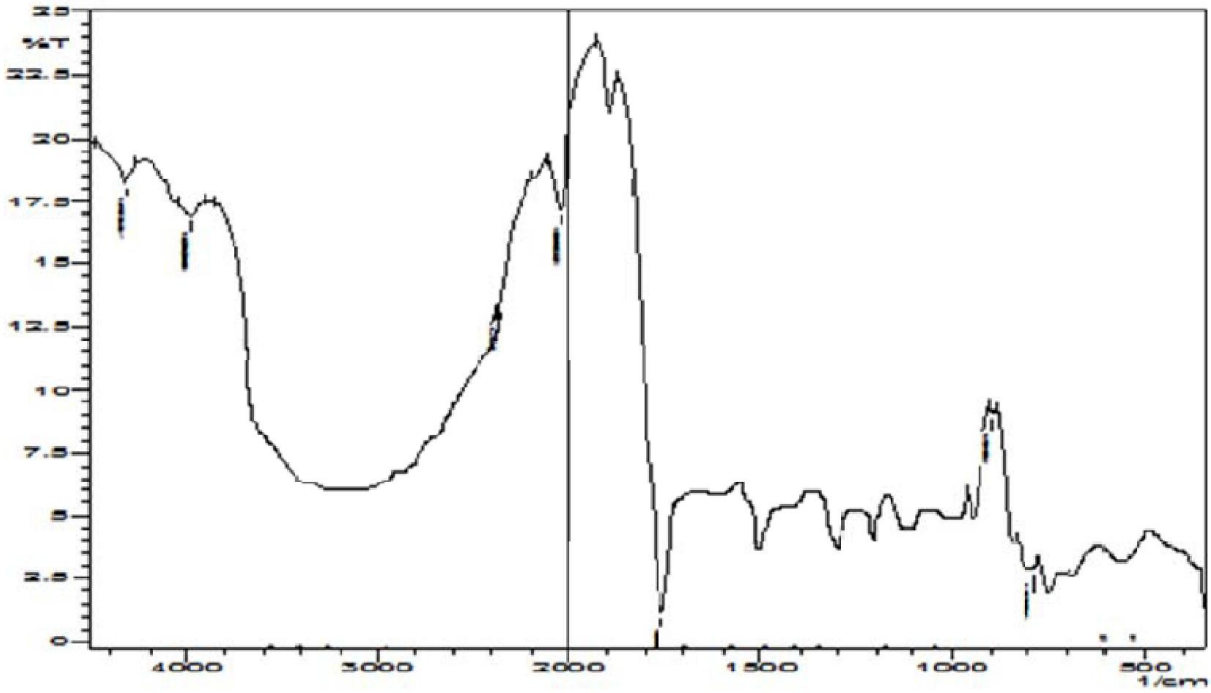


Figure 16: FTIR spectra of drug loaded 1:8 nanosponges

FTIR spectra of drug loaded nanosponges shows broadening of peak in the drug region of 1500 cm-1 to 1700 cm-1 which shows there is significant changes in the drug which may be associated with the loss of crystallinity.

Differential Scanning Calorimetery studies

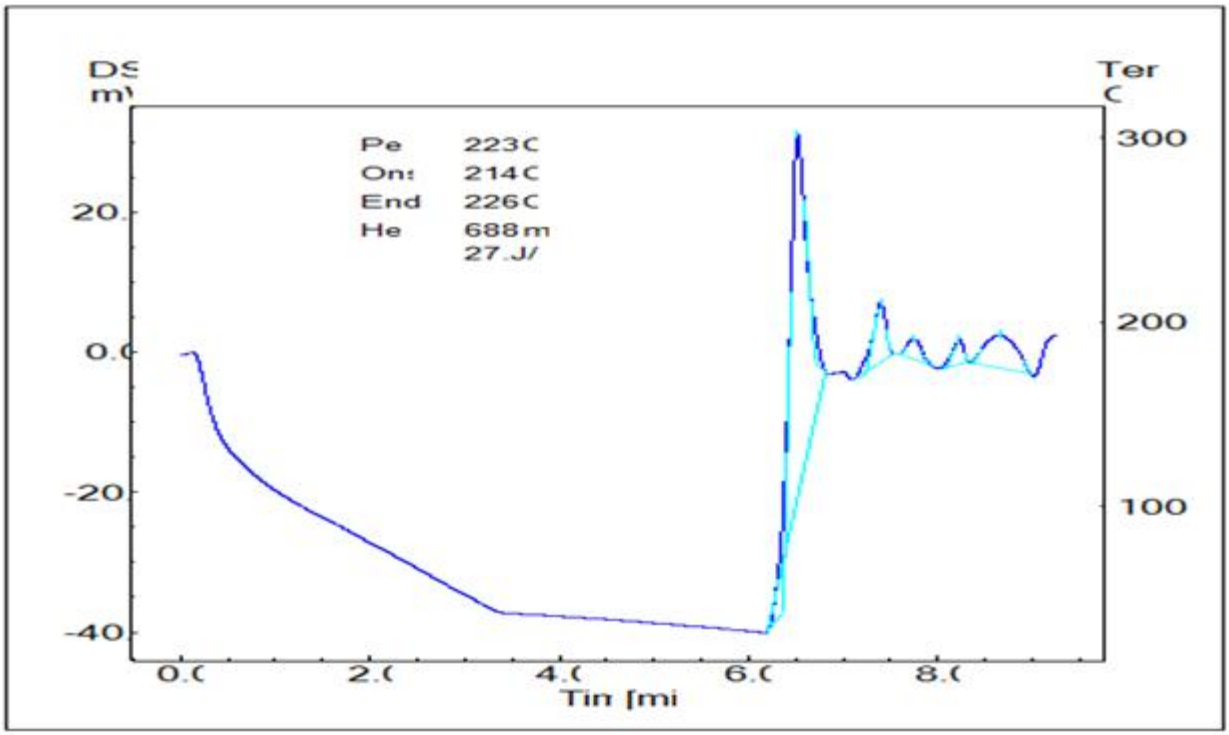


Figure 17: Differential scanning calorimetry of cefadroxil

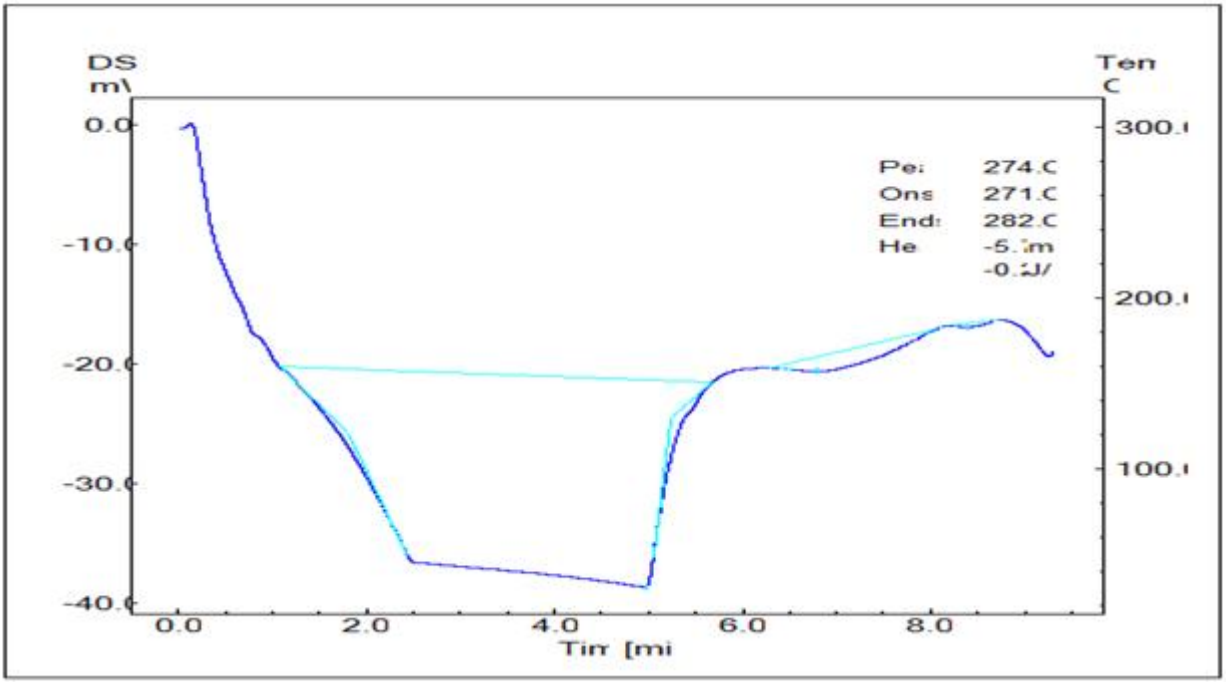


Figure 18: DSC of Nanosponge

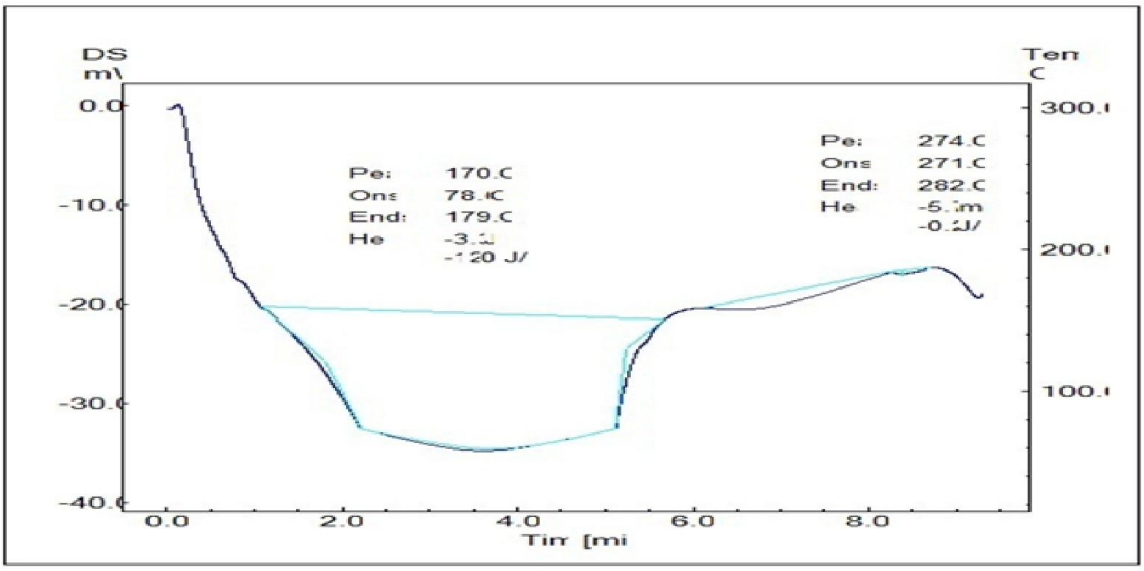


Figure 19: DSC of cefadroxil loaded Nanosponge

The DSC thermograms for drug (cefadroxil) (fig 17) and nanosponge (fig 18) are shown . The DSC thermogram of cefadroxil shows a less intense endothermic peak at 223 C corresponding to its melting point. The onset of melting was observed at 214 C. The DSC thermogram of β-CD nanosponges showed a broad peak at 274 C .The DSC thermogram of cefadroxil with β-CD nanosponges (fig 19) showed a broad peak at 170 C for the cefadroxil and another peak at 274 C for β-CD nanosponges, indicating drug amorphization.

In vivo Studies

Standard curve of cefadroxil in blood serum

The standard curve of cefadroxil in blood serum was scanned at 232.4 nm.

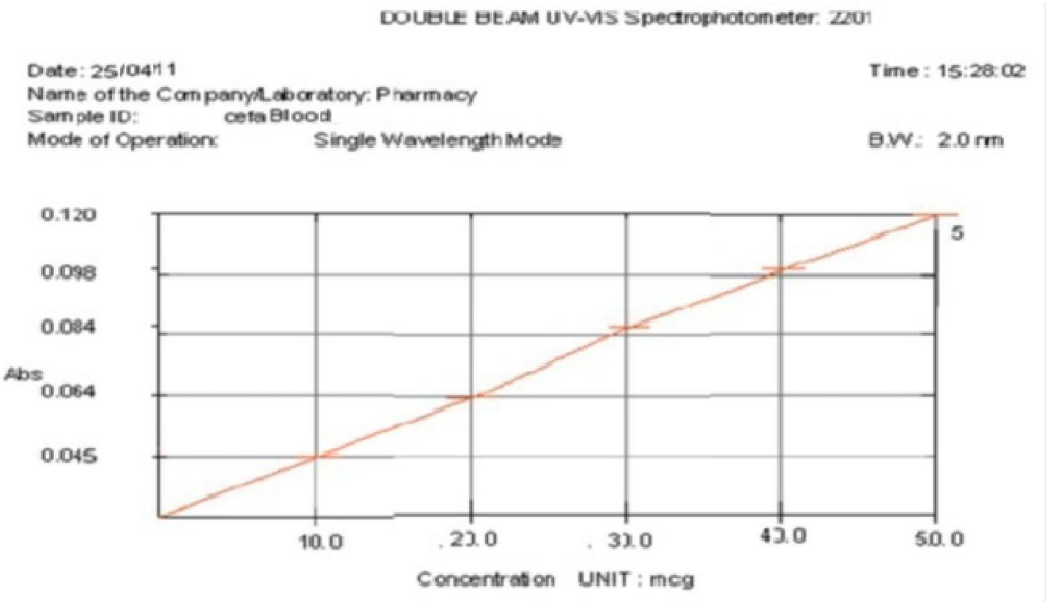


Figure 20 : Standard curve of drug in blood serum

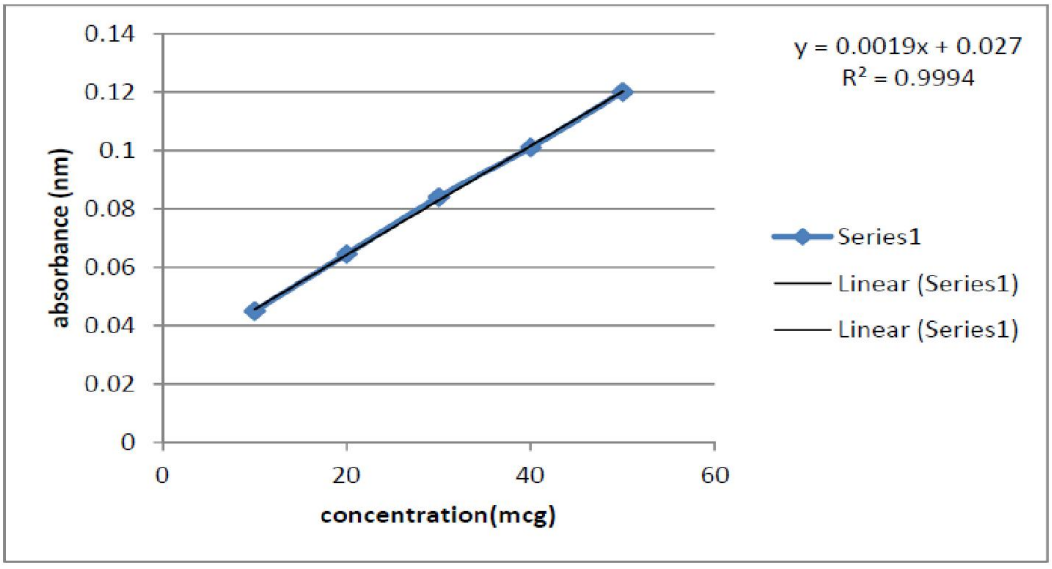


Figure 21: Regression coefficient of cefadroxil in blood serum

Table 1: Time and plasma concentration data of cefadroxil of plain and drug loaded nanosponges

Time (minutes)	Concentration (µg/ml) (Control group)	Concentration (µg/ml) (Complex group)
5	0	0
10	4.7	15.4±0.8
15	6.2	18.1±0.026
30	10.8	23±0.4
60	12.3	26.6±1.2
120	12.1	25.3±0.3

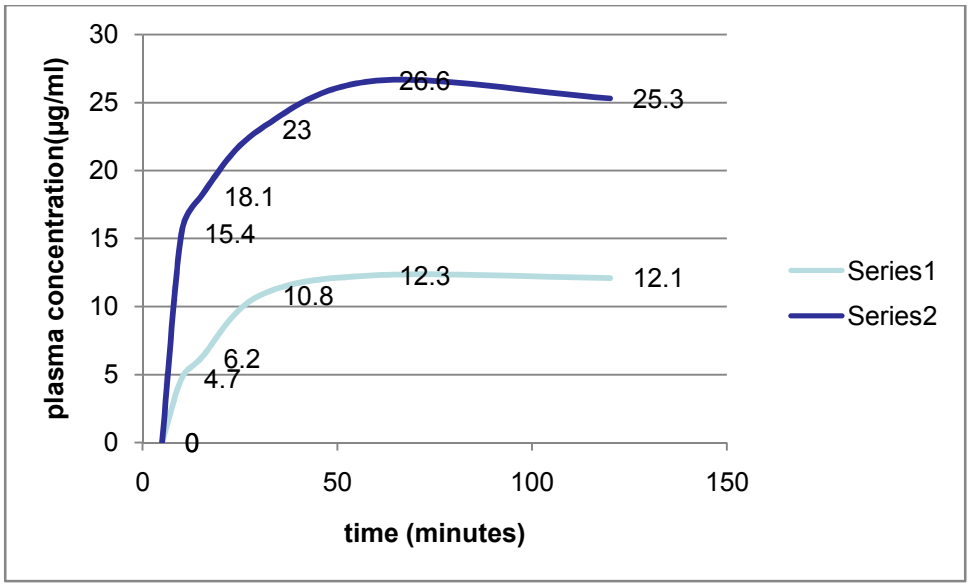


Figure 22: Plot of the plasma time concentration of cefadroxil

The peak plasma concentration of cefadroxil was found to be 12.3 µg/ml after one hour while that for the nanosponges the peak plasma concentration was found to be 26.6 µg/ml after one hour. These study shows that there is an increase in the absorption of the drug.

Summary and Conclusion

In the present study we have selected drug cefadroxil due to poor solubility. It has many side effect such as nausea, vomiting, gastric irritation, darkening of tongue. It has broad spectrum activity against Gm-ve, Gm+ve, aerobic and anaerobic bacteria. Nanosponges as a delivery system has a good capacity to entrap high percentage of drug as well as improved dissolution kinetics. We have prepared three molar ratio of nanosponges by crosslinking β-cyclodextrin with the Diphenyl carbonate. The nanosponge were prepared by ultrasound assisted synthesis and drug loading was done to form solid dispersion. The entrapment efficiency of the N2 is highest (70.57 %). The phase solubility studies shows formulation N2 shows highest solubility of drug in water. The DSC studies shows the shifting of melting peaks from 216 C to 170 C which shows amorphization of drug. The in vivo studies of formulation N2 shows that there is an increase in the absorption of the drug with respect to the pure drug. The FTIR spectra for compatibility study with the cefadroxil shows no significant changes in the drug with diphenylcarbonate. With cyclodextrin there is characteristic changes in the drug region which can be attributed to the loss of crystallinity of the drug. A similar changes was seen in the FTIR of the cefadroxil ,cyclodextrin, diphenylcarbonate mixture. Nanosponges as a delivery system has a good capacity to entrap high percentage of drug as well as improved dissolution kinetics. It can also be administer in the form of solution. Plane nanosponges had particle size approx. 250-310 µm. SEM study shows that the particle are irregular in shape. The surface of the nanosponges is rough and highly porous in nature. On FTIR spectra of different nanospongesviz 1:2, 1:4, 1:8 nanosponges showed the presence of the carbonate bond which has a peak at around 1750 cm^{-1}. The FTIR spectra of drug nanosponge shows no inferring peaks which suggest no interaction between drug and nanosponges.

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