Development and Evaluation of Interpenetrating Polymer Network Hydrogel for Controlled Release of Cefadroxil

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ABSTRACT

Hydrogels are cross linked, three-dimensional hydrophilic polymers, which swell without dissolving when brought into contact with water or other biological fluids. The water content which makes hydrogel such a special class of materials is also responsible for their biggest disadvantage of the poor mechanical properties. Hydrogel with better mechanical properties could be obtained through the preparation of interpenetrating polymer network. Interpenetrating polymer network hydrogel of cefadroxil (antibiotic) is prepared by chemical cross linking method using chitosan and poly vinyl pyrrolidone polymers and glutaraldehyde as cross linking agent. Then, the interpenetrating polymer network hydrogel was evaluated. From Fourier transfer infrared spectroscopy it was concluded that there is no interaction between exicipients and drug which confirm the stability of the drug in the formulation. *In vitro* drug release studies shows that interpenetrating polymer network hydrogel formulation controlled the drug release up to 36 hours. From swelling studies it is concluded formulation which is formulated can absorb large amount of water and have good swelling property. X-ray diffraction patterns recorded confirm the amorphous nature of the drug after encapsulating in formulation. Scanning electron microscopy shows that the unswollen interpenetrating polymer hydrogel appeared to be in smooth surface and swollen interpenetrating polymer hydrogel showed roughed nature and porous surface. From the *in-vitro* release kinetic study it was observed that data was found to fit best into the zero order release model. Stability studies were also conducted and results were found to be stable for six months at $4°C \pm 2°C$, $25°C\pm2°C/60\%\pm5\%$ RH and $40°C\pm2°C/75\%\pm5\%$ RH. The result showed that interpenetrating polymer network hydrogel release the drug in controlled manner for prolong period of time thus maintain the concentration of Cefadroxil in body.

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Introduction

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered the most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. Conventional drug delivery suffer from certain drawbacks like increased fluctuation in the circulatory drug level, more frequency of dosage administration, increased G.I. irritation and dose related side effects. To overcome these disadvantages, control release oral drug delivery systems were designed[1,2].Controlled release drug delivery system is the one which delivers the drug at a predetermined rate, locally or systemically for a specified period of time[3].Hydrogel are three-dimensional networks composed of hydrophilic polymers cross linked through covalent bonds or held together via physical

intermolecular attractions. Hydrogel can absorb large amounts of water or biological fluids, from 20% up to several thousand percent and swell readily without dissolving. The high hydrophilicity of the hydrogel is mainly due to the presence of a number of hydrophilic moieties such as amino, carboxyl, amide and hydroxyl groups distributed along the backbone of the polymeric strands. In the swollen state the hydrogel are soft and have a rubbery structure, resembling to a great extent to the living tissues.Some hydrogel, such as alginate-based gels, also offer excellent biocompatibility[4,5]. The main objective of the study was to develop Interpenetrating polymer network hydrogel .The hydrogel formulation must give controlled release of drug by which half life of drug increases and it also leads to increase in bioavailability.

In the present research, interpenetrating polymer network hydrogel of cefadroxil was prepared followed by the optimization and the evaluation of the prepared formulation. The ultimate aim was to improve bioavailability of the drug and to improve the market formulation.

Material and Methods
Preparation of Interpenetrating Polymer Network Hydrogel

Interpenetrating polymer network hydrogel was prepared by chemical cross linking method. Chitosan solution (2%, w/v) was prepared in 0.1 M glacial acetic acid. Poly vinyl pyrrolidone solution (4%, w/v) was prepared in double distilled water. Different ratios of these solutions were mixed to form a blend which was given in table no. 1. A specific amount of cefadroxil was added in each formula before cross-linking. Glutaraldehyde solution was used as a cross-linking agent and added at a concentration of 4% (v/v) to the chitosan- Poly vinyl pyrrolidone mixture to form interpenetrating polymer network hydrogel. The solution obtained was poured into Petri dish and kept overnight for cross linking at room temperature. The cross linked hydrogel obtained was then cut into 1×1 cm^2 pieces and dried for 24 h at 40ºC under vacuum. The dried interpenetrating polymer network hydrogel were crushed and passed through sieve No.60/85. The interpenetrating polymer network hydrogel retained on sieve No.85 were taken for further studies**.** We made twelve different formulations by varying the amount of polymer, amount of drug and amount of cross linking agent (glutaraldehyde) and formulae for the preparation of interpenetrating polymer network hydrogel are listed in table no. 1 below[6,7].

Table No. 1: Composition of hydrogels

Formulation Code	Chitosan (1% w/v) ml	Poly Vinyl Pyrrolidone (2% w/v) ml	Drug (mg)	Glutaraldehyde (4% v/v) ml
A- 1	20	70	150	2.5
A-2	40	70	150	2.5
A-3	60	70	150	2.5
A-4	60	60	150	2.5
A-5	60	50	150	2.5
A-6	60	40	150	2.5
A-7	60	40	100	2.5
A-8	60	40	200	2.5
A-9	60	40	250	2.5
A-10	60	40	250	5
A-11	60	40	250	7.5
A-12	60	40	250	9

Evaluation Of Ipn Hydrogel of Cefadroxil
Percentage Yield

The yield was calculated by dividing the weight of collected IPN hydrogel by the weight of non-volatile compound used for the preparation of IPN hydrogel. The percentage yield was then calculated using formula given below[8].

$$\text{Percentage yield} = \frac{Theotrical\ yield}{Practical\ yield} \times 100$$

Drug Entrapment Efficiency (%)

Here an amount of hydrogel containing 100 mg of cefadroxil was placed in 50 ml distilled water for 24 hours. In the distilled water the hydrogel swelled. The swollen hydrogel were crushed in an agate mortar with a pestle and the homogeneous solution formed was sonicated for 2 min at 60 MHz frequency. About 50 ml of water was added to precipitate the blend polymer, which was then removed with water using a high-speed centrifuge for 5

min at the rotation speed of 10,000 rpm after that filter the solution. The amount of cefadroxil was analyzed using UV spectrophotometer at the absorption maxima value of 230 nm. The percentage encapsulation efficiency was calculated using the following equations, respectively[9].

$$\text{Entrapment Efficiency (\%)} = \frac{Total\ amount\ of\ drug\ recovered}{Total\ amount\ of\ drug\ added} \times 100$$

In- Vitro Release Studies

Dissolution experiments were performed at 37ºC using a dissolution tester equipped with six paddles at a paddle speed of 100 rev. /min. A 900 ml solution of phosphate buffer solution (Ph7.4) was used as a dissolution medium in order to simulate the gastrointestinal tract (GIT) conditions. An aliquot (10ml) was withdrawn at specific time intervals and replenished with an equivalent volume of dissolution fluid. Whenever necessary, the samples were diluted before assaying cefadroxil. Drug content was determined by UV-spectroscopy at 230 nm. Percentage drug release was calculated using an equation obtained from calibration curve[10].

Fourier Transform Infra Red Spectroscopy

Fourier Transform Infrared Spectroscopy was used for structure analysis and compatibility study of drug with polymer. The FTIR spectra of pure chitosan, pure PVP, pure drug, and formulation were recorded using FTIR spectrophotometer. The KBr disc technique was employed. Since the KBr has no absorption in the fundamental region of IR spectrum, only the spectrum of sample is obtained. The sample and the dry KBr in ratio 1:100 were taken on a dye set and pressure up to 100Kg/cm2 applied on the dye set with the help of hydraulic press and put it for 5 min, before releasing pressure .The pellet was put in a pellet holder and transferred to FTIR instrument and spectrum of sample was taken at 4000- 400 cm^{-1} [11].

Scanning Electron Microscopy

The formulations were characterized for their shape and surface morphology. Surface morphology of IPN hydrogel in unswollen and swollen (water) state after drying were examined separately. SEM studies were carried out on hydrogel samples. The hydrogel particles (sample) were mounted on metal stubs using double sided tape and these particles were coated with gold to a thickness of about 450 Å using sputted gold coater and visualized under Scanning electron microscope.

X-Ray Diffraction (X-Rd)

X-ray diffraction (XRD) is a tool for determining the molecular structure and crystallinity of a material by obtaining information about lattice parameters. The principle is to bombard the sample with an X-ray beam with different incoming angles generating a diffraction pattern. Constructive interference is observed when Bragg's law (eq.) is fulfilled resulting in peaks in the diffraction pattern.

$$2d\sin\theta = n\lambda$$

(eq.)
Where n is any integer, θ is the scattering angle, λ is the wavelength of the X-rays. The obtained data can be compared with the Joint Committee on Powder Diffraction Standards registry to determine the crystal structure of the material. X-RD was used to determine the crystallinity of Cefadroxil encapsulated in the A-10 hydrogel formulation.

X-RD analysis can provide a clue about crystalline or amorphous nature of the drugs after encapsulation in Interpenetrating polymer network hydrogel. X-RD patterns recorded for plain drug and drug loaded Interpenetrating polymer network hydrogel using X-ray diffractometer (Xpert-Pro). The dried Interpenetrating polymer network hydrogel of uniform size were mounted on a sample holder and X-RD scanning was recorded up to 2θ at 25°C using Copper as radiation source to estimate crystallinity/amorphous nature of the samples[12].

Swelling Studies

Swelling studies of IPN hydrogel were done as dynamic equilibrium study. In dynamic swelling experiment IPN hydrogel were placed in distilled water at 37±2°C. During swelling hydrogel removed from the water bath at regular time intervals and after drying superficially with filter paper, and weighted ,they were return into the same swelling bath the swelling study was done untilled no more swelling (equilibrium swelling). The swelling ratio can be calculated as function of time and it can be calculated from following relationship

$$\text{Percentage Swelling Index} = \frac{W_S - W_D}{W_D} \times 100$$

W_S – Weight of hydrogel in swollen state at a given time
W_D – Weight of hydrogel at dry state[13].

In Vitro Drug Release Kinetics

The mechanism of drug release from the dosage form is an important factor. There are several mechanisms by which drug released from dosage form such as controlled release, delayed release, immediate release and

pulsatile release. For this purpose, the use of mathematical modeling approach to be very useful because this enables the prediction of release kinetics. More often, it allows the measurement of some important physical parameters, such as the drug diffusion coefficient. There are several models which represent the drug dissolution profiles;

- Zero order release kinetics
- First order release kinetics
- Higuchi model
- Korsmeyer- peppas model

Zero order release kinetics

Zero order release kinetic is mainly applicable for the process of constant drug release. The plot was made in between cumulative percent drug release vs. Time (zero order kinetic models). Ideal delivery of drugs would follow zero order kinetics, where in blood levels of drugs would remain constant throughout the delivery period. This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms.

$$Q_t = Q_o K_o t$$

Where , Q_t is the initial amount of drug dissolved at time t; Q_o is the amount of the drug in the solution, most of the times it is equal to zero; K_o is the zero order release rate constant. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as percentage cumulative amount of drug released versus time

First order release kinetics

This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. The data obtained were plotted as log cumulative percentage of drug remaining vs. Time**.** The release of the drug which followed first order kinetics can be expressed by equation:

$$Q_t = Q_o e^{-kt} \text{ or } \ln (Q_T/Q_o) = K_l t$$

Where, Q_t is the initial amount of drug dissolved at time t; Q_o is the amount of drug in the solution; K_l is the first order release rate constant.

Higuchi model

This model is based on the hypotheses that

I. Initial drug concentration in the matrix is much higher than drug solubility.
II. Drug diffusion takes place only in one dimension.

III. Drug particles are much smaller than system thickness.
IV. Matrix swelling and dissolution are negligible.
V. Drug diffusivity is constant.
VI. Perfect sink conditions are always attained in the release environment.

According, model expression is given by the equation:

$$Q_t = Kt$$

Where, Q_t is the initial amount of drug dissolved in the time t; K is Higuchi release constant. The plot was made in between cumulative percentage drug release vs. Square root of time**.**

Korsmeyer-peppas model

Korsmeyer derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-peppas model. The plot made was made log cumulative percentage drug release vs. Log time

$$M_t/M_\infty = Kt^n$$

Where M_t/M_∞ is fraction of drug released at time t; K is the rate constant and n is the release exponent. The plot was made between log of percentage cumulative drug released vs. Log time[14].

Stability Studies

Stability studies represent a vital part of any development program for pharmaceutical products .Stability is defined as the capacity of a drug substance or drug product to remain within the established specification to maintain its identity, strength, quality and purity throughout the retest or expiration dating period. The objective of the stability study is to determine the self life, namely the time period of the storage at a specific condition with in which the drug product still meets its established specification[15].

Stability studies consist of a series of tests in order to obtain an assurance of stability of a drug product, namely maintenance of the drug product packed in it specified packing material and stored in the established storage condition with in the determined time period. Proper design, implementation, monitoring and evaluation of the studies are crucial for obtaining useful and accurate stability data. Stability studies are takes place according to ICH guidelines.

ICH specifies the length of study and storage condition:-

Long term testing 25ºC ± 2ºC/60% RH ± 5% for 12 months

Short term study 40ºC ± 2ºC/75% RH± 5% for 6 months

Method

Stability studies were conducted on optimized formulation of IPN hydrogel at 4ºC± 2ºC, 25ºC ± 2ºC/60%±5% RH and 40ºC ± 2ºC/75% RH ± 5% as per ICH Q1A (R2) regulations for 6 months. Formulation was kept in screw capped amber coloured bottle. During the period of storage after a specific time period (2 month, 4 months and 6 months) the IPN hydrogel were subjected to following test: physical appearance, Drug entrapment efficiency and percentage cumulative drug release. Stability studies of optimized formulation in all three conditions were carried out in triplicate[16,17].

Results and Discussion

Percentage Yield, Drug Entrappment Efficiency And Percentage Cumulative Drug Release

In formulation A-1, A-2 and A-3 when concentration of chitosan was increased increase in drug entrapment efficiency, percentage yield and percentage cumulative drug release is shown. In formulation (A-4, A-5 and A-6) with decrease in PVP concentration the drug entrapment efficiency, percentage yield and percentage cumulative drug release increases. From all the above we conclude that as the concentration of chitosan increase drug entrapment efficiency, percentage yield and percentage cumulative drug release increase but in other hand decrease in concentration of PVP leads to increase in drug entrapment efficiency, percentage yield and percentage cumulative drug release in formulation A-1 to A-6. In another set of formulations, we can see that as the concentration of drug decrease drug entrapment efficiency, percentage yield and percentage cumulative drug release also decreases as shown in formulation A-7 but further increase in drug quantity lead to increase in drug entrapment efficiency, percentage yield and percentage cumulative drug release. From all this we can observe as the concentration of drug increases it leads to increase in drug entrapment efficiency, percentage yield and percentage cumulative drug release. We can conclude that A-9 formulation contains highest drug entrapment efficiency, percentage yield and percentage cumulative drug release so this is optimized amount of drug (250 mg) which we used in preparation of optimized formulation. That as the concentration of cross linking agent increases drug entrapment efficiency increase but in case of percentage yield and percentage cumulative drug release firstly it increases (A-9 to A-10) after that in formulation A-11 and A-12 it decrease. The decrease in percentage cumulative drug release is due to more addition of cross linking agent due to which drug cannot be completely release from the formulation and bind in network of polymers.

Table No. 2: Results of percentage yield, drug entrapment efficiency and percentage cumulative drug release

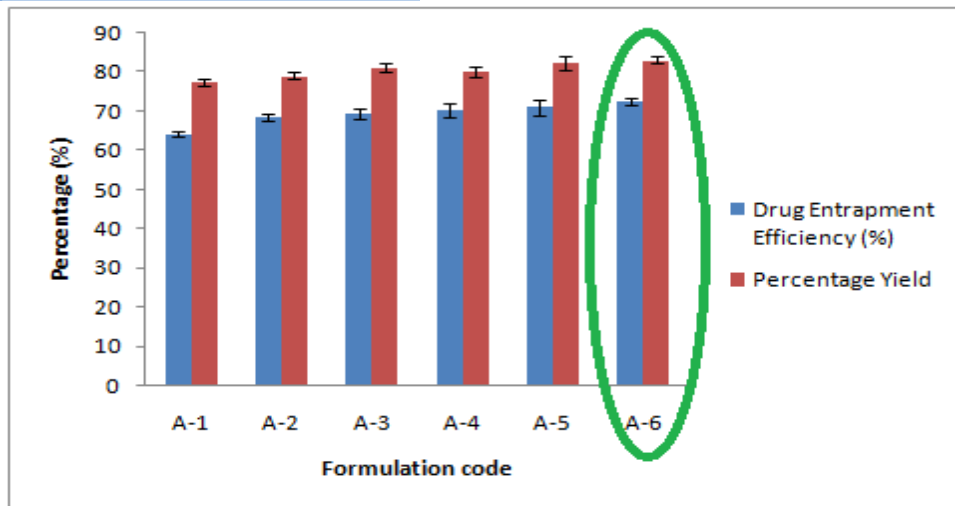| Formulation Code	Drug Entrapment Efficiency (%) (±S.D)	Percentage yield (%) (±S.D)	Percentage Cumulative Drug Release in time (±S.D)
A-1	64.142±0.64	77.276±0.92	94.78±1.96 in 8 hours
A-2	68.527±0.95	79.023±0.85	91.432±1.99 in 12 hours
A-3	69.372±1.43	81.218±0.93	79.107±1.94 in 18 hours
A-4	70.381±1.69	80.012±1.42	83.29±1.88 in 18 hours
A-5	71.050±1.92	82.245±1.66	87.294±1.95 in 18 hours
A-6	72.520±0.91	83.047± 0.90	89.538±1.98 in 24 hours
A-7	66.726±1.42	78.54±1.42	75.542±1.90 in 18 hours
A-8	77.247±1.15	86.528±1.26	90.518± 1.93 in 24 hours
A-9	87.613±0.73	89.013±0.82	93.435±1.94 in 30 hours
A-10	90.710±0.37	96.805±0.36	96.78±1.89 in 36 hours
A-11	91.896±0.48	94.011±0.49	87.238±1.81 in 36 hours
A-12	92.812±0.22	90.054±0.51	84.0424±1.88 in 36 hours

Figure No. 1: Percentage (Drug entrapment efficiency & Percentage Yield) vs. formulation code graph of IPN Hydrogel formulations (A-1 to A-6)
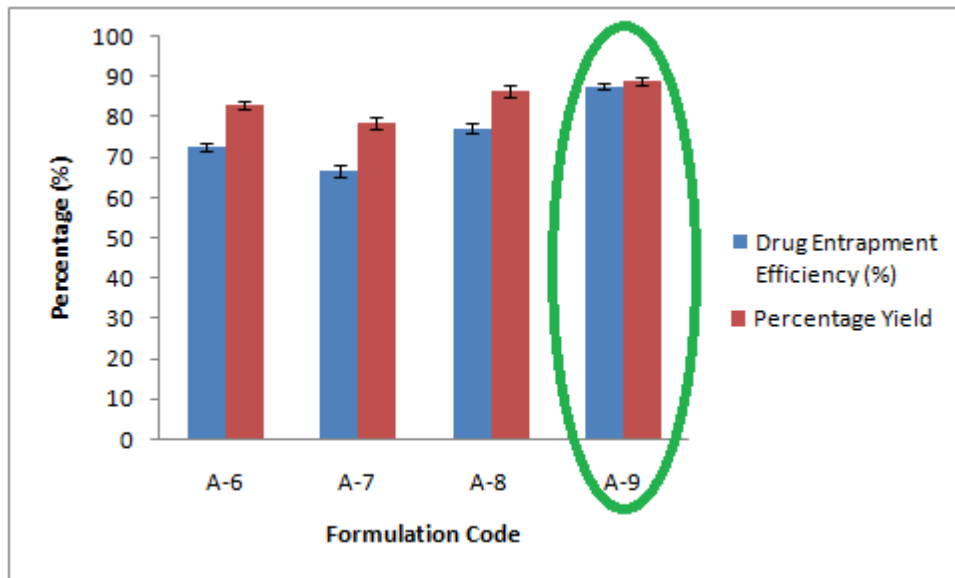

Figure No. 2: Percentage (Drug entrapment efficiency & Percentage Yield) vs. formulation code graph of IPN Hydrogel formulations (A-6 to A-9)
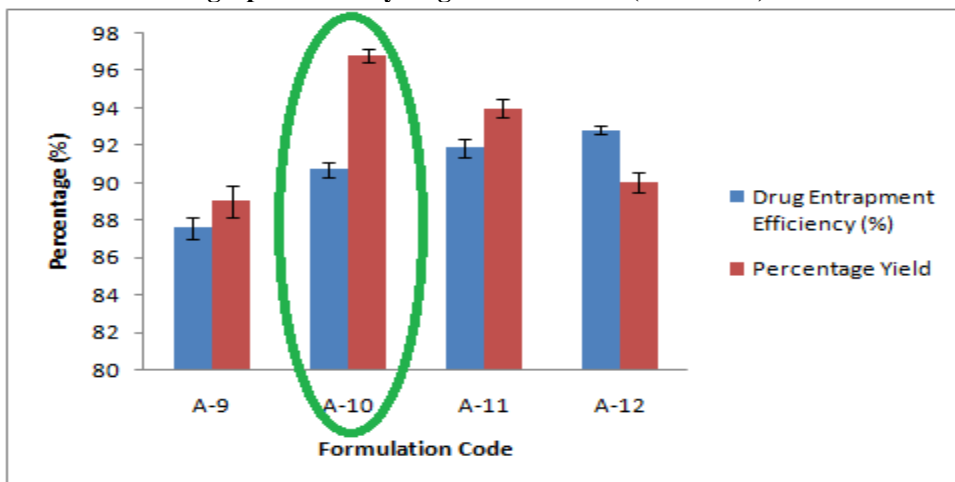

Figure No. 3: Percentage (Drug entrapment efficiency & Percentage Yield) vs. formulation code graph of IPN Hydrogel formulations (A-9 to A-12)

In- Vitro **Drug Release Studies**

In vitro drug release study was carried out for all the formulation in phosphate buffer of pH 7.4 by using dissolution apparatus (paddles type). The obtained result were tabulated in Table no. 3, 4 and graphically represented in Figure no. 4, 5. Out of all the formulation A-10 formulation gives us prolonged drug release (36 hours) with good drug entrapment efficiency (90.710±0.37), percentage yield (96.805±0.36) and percentage cumulative drug release (96.78±1.89). So A-10 is the optimized formulation.

Table No. 3: Percentage cumulative drug release with standard deviation of formulations i.e. A-1, A-2, A- 3, A- 4, A- 5 and A-6

| Time (hrs)	A-1	A-2	A-3	A-4	A-5	A-6
0	0	0	0	0	0	0
1	8.131±2.21	12.033±2.0	7.231±2.23	8.908±0.22	6.567±1.41	5.275±1.62
2	18.01±2.32	24.231±2.83	19.326±2.40	10.991±0.43	13.215±1.54	9.622±1.85
3	28.46±2.42	9.455±2.64	30.338±2.61	15.512±0.61	25.337±1.67	17.535±1.13
4	40.45±2.54	51.64±2.71	45.157±2.83	32.395±1.81	38.981±1.89	30.234±1.56
6	57.07±2.63	62.74±2.97	54.092±2.12	49.523±1.17	49.592±1.74	41.899±1.74
8	94.78±2.71	77.01±2.69	65.725±2.27	60.318±1.29	69.329±2.13	55.414±1.69
12	-	91.43±3.12	71.381±2.34	77.226±1.42	79.784±2.23	68.353±2.32
18	-	-	79.107±2.46	83.29±1.68	87.29±2.42	75.867±2.95
24	-	-	-	-	-	89.538±3.0
30	-	-	-	-	-	-
36	-	-	-	-	-	-
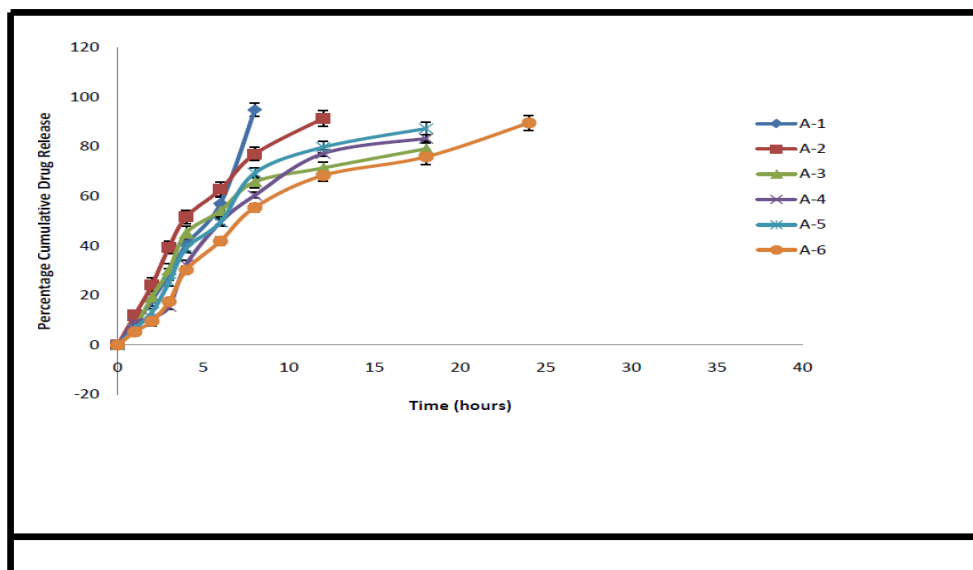
Figure No. 4: Percentage Cumulative release vs. time graph of IPN Hydrogel formulations (A-1 to A-6)

Table No.4 Percentage cumulative drug release with standard deviation of formulations i.e. A-7, A-8, A-9, A-10, A-11 and A-12

Time (hrs)	A-7	A-8	A-9	A-10	A-11	A-12
0	**0**	**0**	**0**	**0**	**0**	**0**
1	10.895 ±0.67	9.254±1.92	6.702±1.23	5.433±0.32	5.212±0.42	3.442±0.22
2	16.134±0.89	11.327±2.12	8.326± 1.42	6.411±0.37	7.931±0.65	5.541±0.35
3	25.265±1.0	19.375±2.31	16.318±1.67	8.788±0.48	13.043±1.23	12.309±0.63
4	30.538±1.54	35.816±2.21	25.591±1.86	10.003±0.56	18.527±1.52	15.371±0.98

6	47.916±1.72	52.518±2.41	34.764±2.14	14.338±0.83	26.395±1.64	21.722±1.29
8	54.724±1.69	69.836±2.52	58.04±2.29	18.521±0.99	32.409±1.69	26.485±1.45
12	65.259±1.32	78.452±2.63	69.889± 2.31	25.348±1.43	49.723±1.32	42.99±1.61
18	75.542±1.95	84.275±2.12	80.387±2.45	41.289±1.65	62.401±1.55	56.326±1.79
24	-	90.518±2.26	86.628±2.52	58.629±1.87	71.192±1.73	62.907±1.96
30	-	-	93.435±2.65	74.325±1.98.	81.281±1.89	78.106±2.06
36	-	-	-	96.78±2.22	87.238±1.92	84.0424±2.24
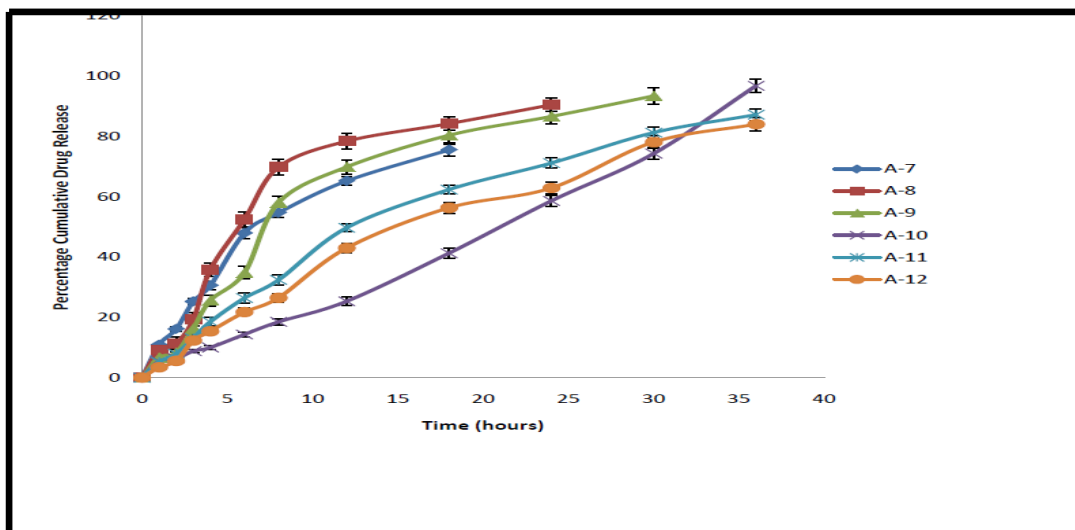
Figure No. 5: Percentage Cumulative release vs. time graph of IPN Hydrogel formulations (A-7 to A-12)

Fourier Transform Infra Red Spectroscopy
Polymers, drug as well as the optimized formulations were characterized by FTIR spectroscopy to know any possible interaction between drug, polymer and the cross linking agent (figure no. 6, 7, 8, 9 and 10). The FTIR spectrum of chitosan showed strong peaks in the range 3700–3500 cm^{-1} peaks corresponding to O-H stretching at 3453.12 cm^{-1} and amine group (NH$_2$) stretching at 2918.54 cm^{-1} respectively. Shown in figure 6, PVP shows the amide carbonyl stretching band at 1462.81 cm^{-1} and C-N stretching at 1170.58 cm^{-1}. The drug cefadroxil showed a broad band at 1756.12 cm^{-1} due to C=O stretching of carboxylic group. The amine group N-H stretching band was observed at 1610.64 cm^{-1} and C-O group stretching at 1270.4 cm^{-1}. For cross-linked chitosan -PVP, an additional peak at 1441.59 cm^{-1} can be observed, which corresponds to stretching vibrations of C=N bond. This strong peak indicates the reaction between carbonyl group of glutaraldehyde and amine group of chitosan and C-N of PVP ensuring the formation of IPN. These all the peaks were maintained in formulation at 3417.95 cm^{-1}, 2954.34 cm^{-1}, 1462.79 cm^{-1}, 1165.2 cm^{-1}, 1758.99 cm^{-1}, 1657.96 cm^{-1}, 1290.76 cm^{-1} and 1441.99 cm^{-1}. This denotes the drug was intact in the formulation and did not react either with the polymers or the cross linking agent.
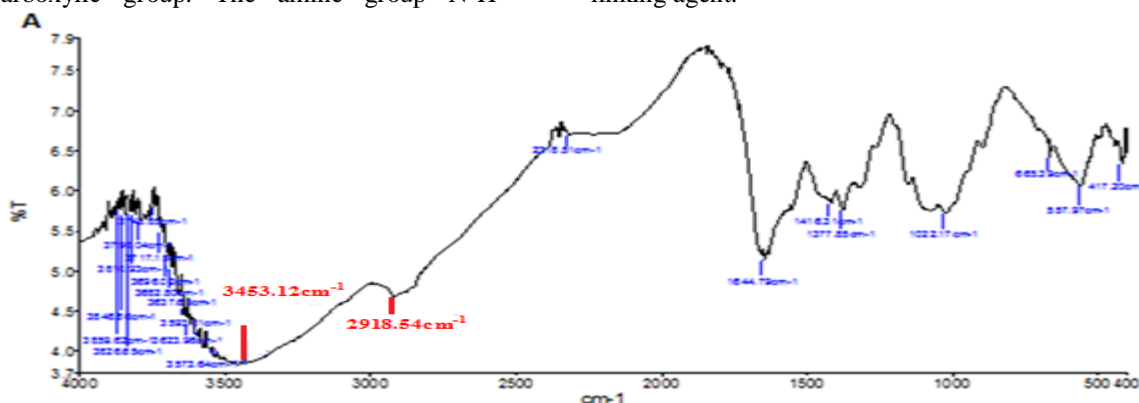

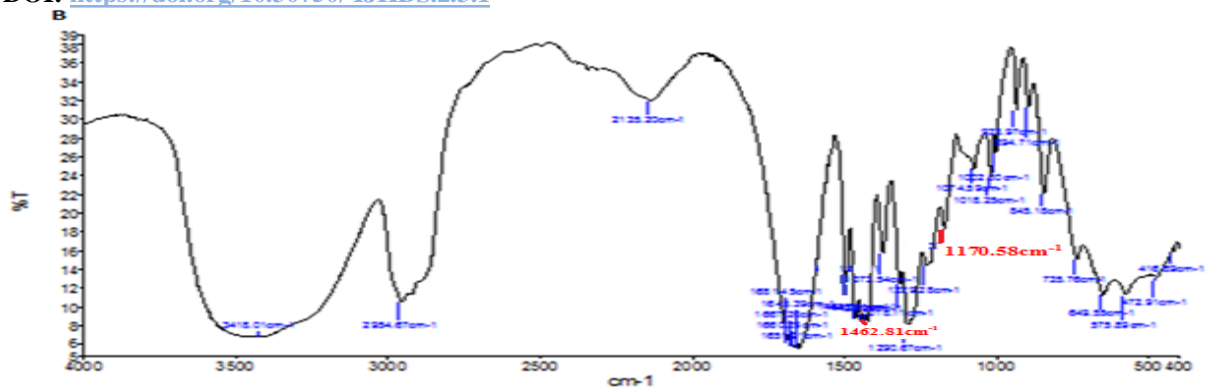**Figure No. 6: Fourier transforms infrared spectrum of chitosan**

Figure No. 7:Fourier transform infrared spectrum of Poly vinyl pyrollidone
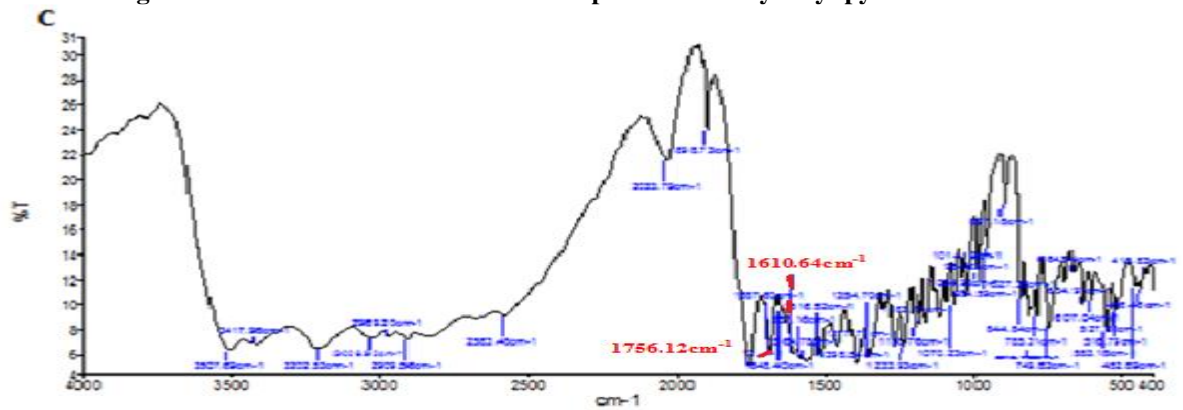
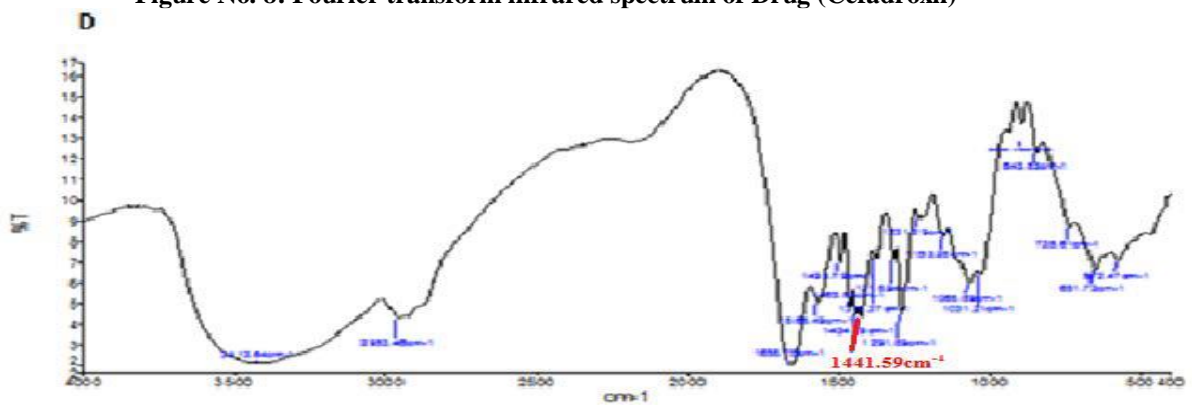**Figure No. 8: Fourier transform infrared spectrum of Drug (Cefadroxil)**

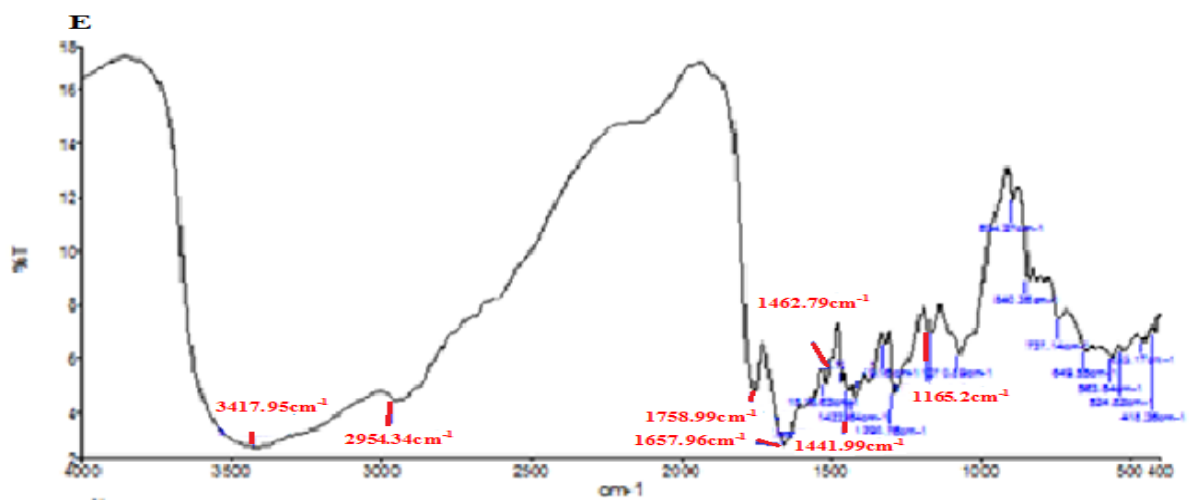**Figure No. 9: Fourier transform infrared spectrum of Blank IPN hydrogel formulation**

Figure No. 10: Fourier transform infrared spectrum of drug loaded IPN hydrogel formulation
Scanning Electron Microscopy

Surface morphology of interpenetrating polymer network hydrogel was examined by Scanning electron microscopy It was observed that hydrogel is irregular in shape and surface of unswollen hydrogel was smooth show no surface pores (photomicrograph 1). The interpenetrating polymer network hydrogel kept in distilled water for swelling. After drying that swollen IPN Hydrogel showed roughed nature and pore on surface of interpenetrating polymer network hydrogel particles showed in Photomicrograph no. 2.
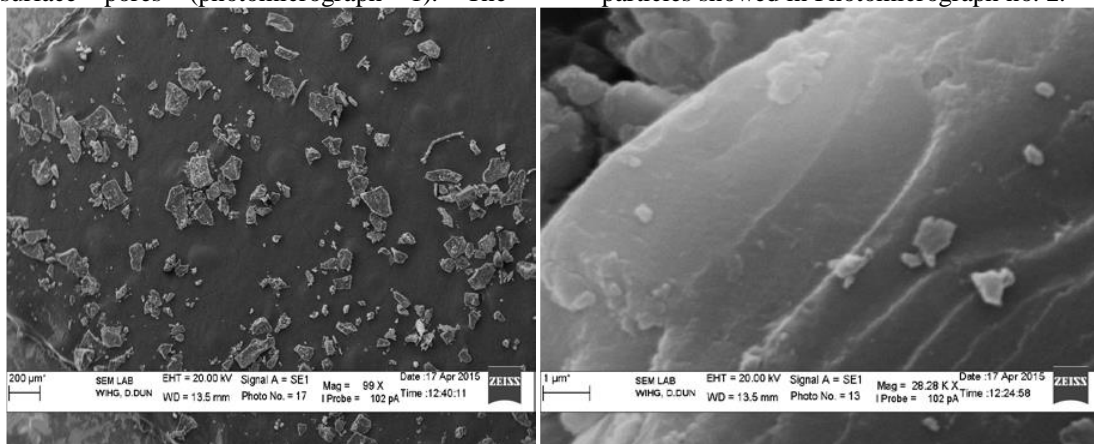
(a)   (b)

Photomicrograph No. 1: SEM images of unswollen IPN hydrogel
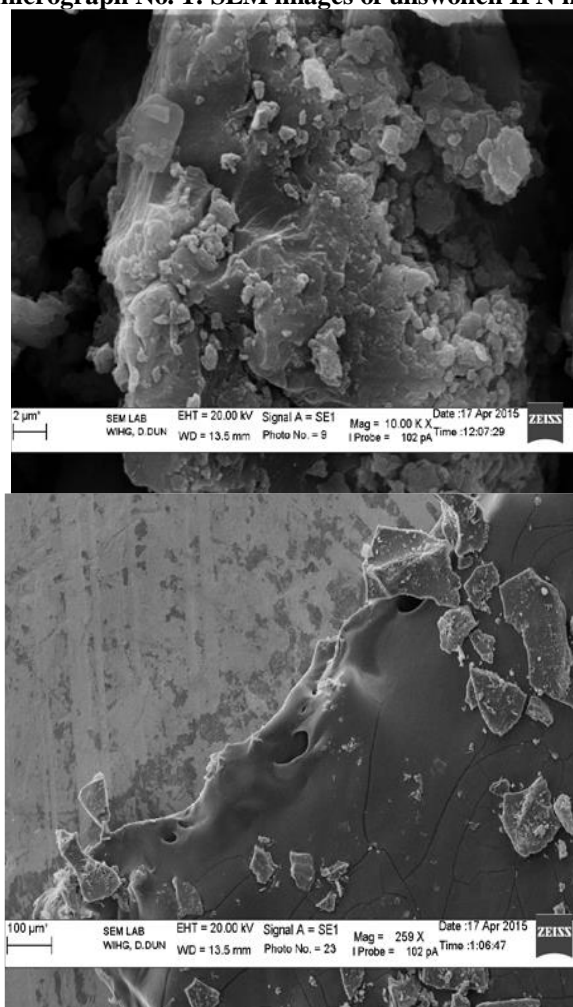
(c)   (d)

Photomicrograph No. 2: SEM images of swollen IPN hydrogel

X- Ray Diffraction

Cefadroxil has shown characteristic intense peaks at 10.06, 12.3379, 18.8377, 19.0066, 21.8152, 23.5173, 25.8244, 26.9169, 32.0170, 34.2332, and 36.4741. These traces reveal the crystallinity of the drug. No peaks were found in the drug loaded interpenetrating polymer network hydrogel because encapsulated drug change from crystalline to amorphous state.

This indicates that most of the drug dispersed at molecular level in the polymer matrices since no indication about the crystalline nature of the drugs was observed in case of drug-loaded interpenetrating polymer network hydrogel.
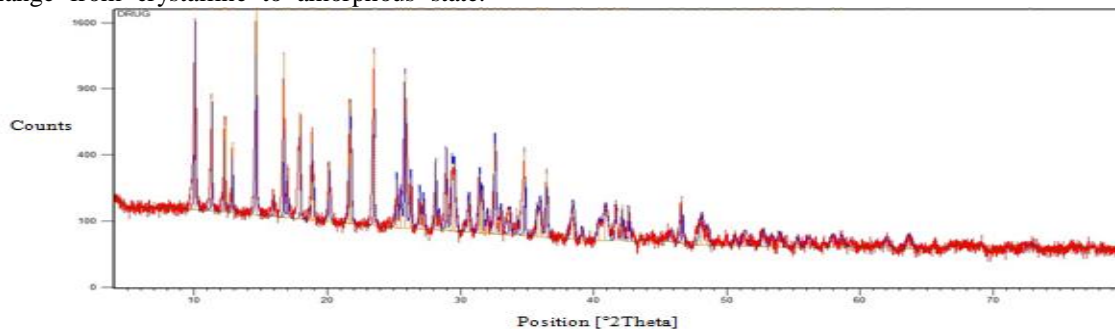

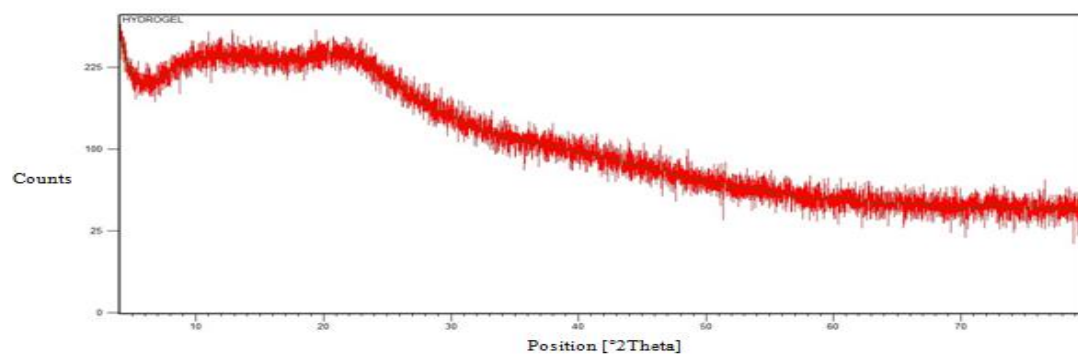**Figure No. 11: X-ray diffraction of Drug (Cefadroxil)**

Figure No. 12: X-ray diffraction of IPN hydrogel formulation (A-10)

Swelling Studies

Swelling studies of IPN hydrogel were done as dynamic equilibrium study. The swelling behaviour of particles was expressed as the ratio of initial weight of particle to the final weight of swollen particles as a function of time (Figure no. 13).The Percentage swelling Index of Optimized formulation of IPN hydrogel was found 650.253±16.60 in 36 hours.

Table No. 5: Percentage swelling Index of Optimized formulation (A-10) of IPN hydrogel

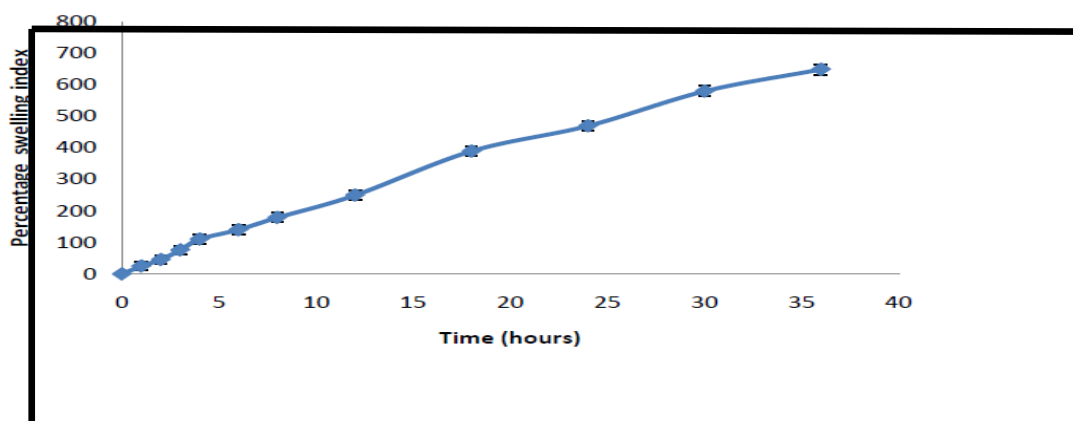| Time (hrs)	A-10 (Percentage swelling Index)
0	0
1	25.224±12.35
2	45.912±12.63
3	76.313± 13.98
6	110.935± 14.29
4	140.715± 13.45
8	179.324±14.61
12	250.336± 14.96
18	390.432±16.06
24	470.691± 15.24
30	580.829±16.41
36	650.253±16.60

Figure No. 13: Percentage swelling Index of Optimized formulation (A-10) of IPN hydrogel

***In- Vitro* Drug Release Kinetics**

To explore and explain the mechanism of drug released from the IPN hydrogel. Formulation (A-10) was subjected to the various release kinetics such as zero order, first order, Higuchi model and Korsmeyer-peppas model shown in Figure 14, 15, 16 and 17 respectively.
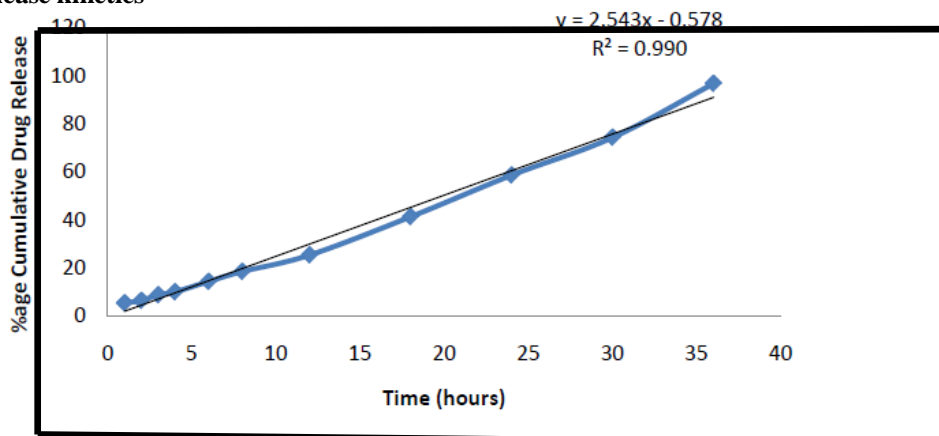
Zero order release kinetics

Figure No. 14: Zero order release kinetics of IPN Hydrogel formulation (A-10)
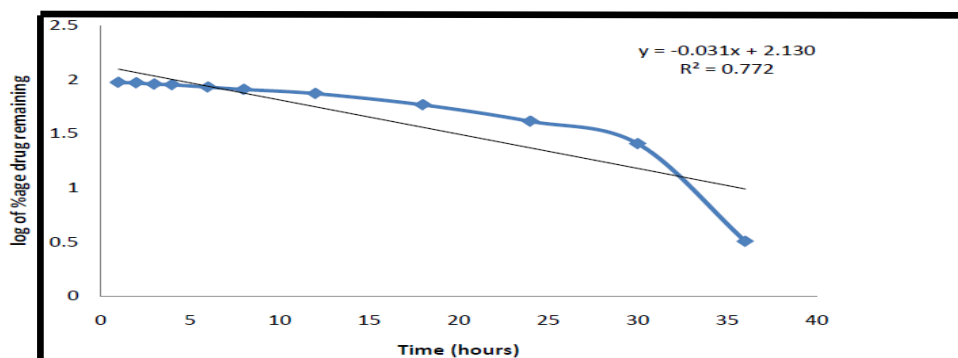
First order release kinetics

Figure No. 15: First order release kinetics of IPN Hydrogel formulation (A-10)
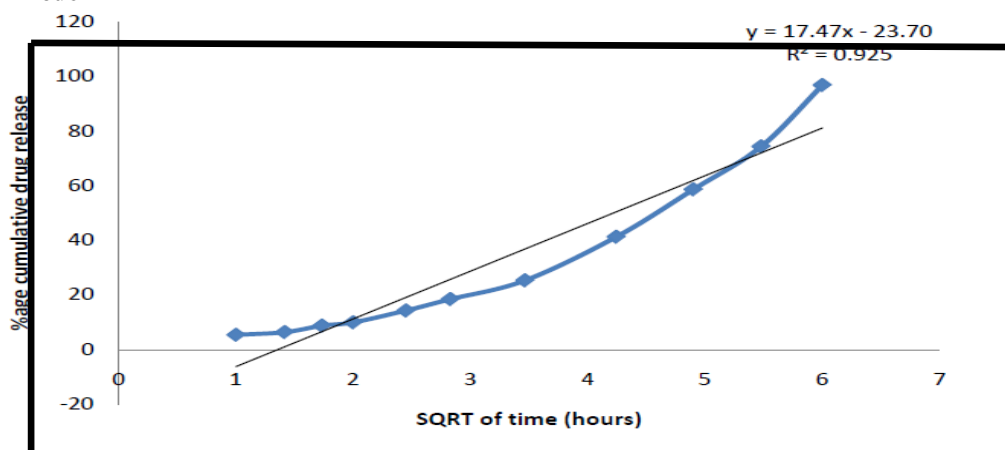
Higuchi model

Figure No. 16: Higuchi model release kinetics of IPN Hydrogel formulation (A-10)

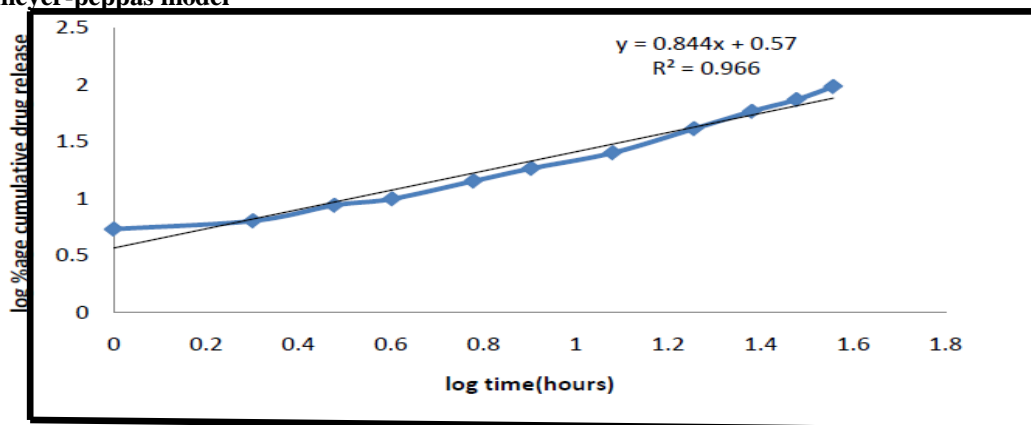**Korsmeyer-peppas model**

Figure No. 17: Korsmeyer-peppas model release kinetics of IPN Hydrogel formulation

Stability Studies

The optimized formulation (A-10) was preceded further for stability studies. Formulation were observed for change in the Physical appearance, Entrapment efficiency and Percentage cumulative drug release studies of IPN hydrogel stored at refrigeration temperature (4°C ± 2°C), 25°C±2°C /60% ±5% RH and 40° C±2°C / 75%±5% RH in humidity chamber.

Table No. 6: Result of IPN hydrogel for stability studies at (4°C ± 2°C) temperature

Test	2 month	4 month	6 month
Physical appearance	no change	no change	no change
Entrapment efficiency (%)	90.121±0.541	89.715±0.989	89.198±0.710

Table No. 7: Result of IPN hydrogel for stability studies at 25°C±2°C/60±5% RH

Test	2 month	4 month	6 month
Physical appearance	no change	no change	no change
Entrapment efficiency (%)	89.906±0.765	88.872±0.994	88.011±0.671

Table No. 8: Result of IPN hydrogel for stability studies at 40° C±2°C / 75%±5% RH

Test	2 month	4 month	6 month
Physical appearance	no change	no change	no change
Entrapment efficiency (%)	88.95±0.217	88.064±0.652	87.832±0.931

Table No. 9: Result of *In Vitro* release studies of IPN hydrogel (A-10) for stability studies at refrigeration temperature (4°C ± 2°C)

Time(hrs)	2 Month	4 month	6 month
0	0	0	0
1	5.030±0.12	4.831±0.21	4.124±0.11
2	6.021±0.18	5.211±0.34	4.9.±0.36
3	8.168±0.56	8.018±0.52	7.219±0.35
4	9.803±0.74	9.091±0.72	8.097±0.51
6	14.123±0.79	14.002±0.72	13.854±0.84
8	18.187±1.32	18.132±1.23	17.087±1.09
12	24.997±1.31	24.01±1.14	23.937±1.81
18	40.289±1.78	40.056±1.00	39.852±1.22
24	58.029±1.71	57.998±1.51	57.476±1.34
30	73.342±1.34.	73.25±1.71	72.860±1.56
36	96.013±1.72	95.43±1.64	95.01±1.28

Table no. 10: Result of *In Vitro* release studies of IPN hydrogel (A-10) for stability studies at 25°C±2°C /60% ± 5% RH

Time(hrs)	2 Month	4 month	6 month
0	0	0	0
1	5.001±0.38	4.236±0.54	3451.±0.12
2	6.098±0.42	5.327±0.76	4.657±0.79
3	8.098±0.23	7.659±0.32	6.538±0.21
4	9.006±0.13	9.675±0.95	8.234±0.86
6	14.021±0.34	13.086±0.83	12.760±0.47
8	18.129±1.03	17.761±1.46	16.645±1.21
12	24.921±1.23	24.661±1.19	23.021±1.05
18	40.761±1.54	39.976±1.61	39.018±1.95
24	58.098±1.23	57.298±1.42	57.01±1.55
30	74.091±1.76.	73.893±1.35	72.067±1.70
36	96.0±1.10	95.870±0.91	94.043±0.72

Table 11: Result of *In Vitro* release studies of IPN hydrogel (A-10) for stability studies at 40° C±2°C 75% ±5 % RH

Time(hrs)	2 Month	4 month	6 month
0	0	0	0
1	4.212±0.98	3.876±0.01	2.553±0.87
2	5.327±0.53	4.567±0.98	3.012±0.19
4	9.091±0.65	8.087±0.56	6.022±0.96
6	13.545±0.76	12.673±1.43	11.432±1.01
8	16.961±1.21	16.094±1.07	15.995±1.05
12	24.980±1.871	24.347±1.77	23.018±1.98
18	40.741±1.21	39.089±1.81	38.261±1.03
24	58.012±1.11	57.342±1.76	56.913±1.41
30	73.098±1.17.	72.665±1.23	71.006±1.19
36	96.001±0.91	95.080±1.27	93.078±0.82

Conclusion

Interpenetrating polymer network hydrogel were prepared by chemical cross linking method. We made twelve different formulations. Out of all the twelve formulation A-10 formulation is optimized and taken for further characterization. Polymers, drug as well as the optimized formulation were characterized by Fourier transfer infrared spectroscopy to know any possible interaction between drug, polymer and the cross linking agent. The peaks were well maintained in formulation which is present in exicipients and drug confirms the stability of the drug in the formulation. The

morphology of cefadroxil loaded IPN Hydrogel formulations were examined by SEM and results shows that the unswollen IPN Hydrogel appeared to be in smooth surface. XRD patterns recorded for plain drug and drug loaded Interpenetrating polymer network hydrogel. From the swelling studies it is concluded that IPN hydrogel which is formulated can absorb large amount of water and have good swelling property. The data obtained from the dissolution profile of IPN hydrogel was fitted into various mathematical models and the data was found to fit best into the zero order release model, which suggests that the mechanism of drug release was constant or independent of concentration. Results of stability studies have shown that all the IPN hydrogel formulations were stable at $4°C \pm 2°C$, $25°C \pm 2°C$ /60% $\pm 5\%$ RH and $40°\,C \pm 2°C$ / 75%$\pm 5\%$ RH but slightly decrease in Entrapment efficiency and Percentage cumulative drug release was observed in this order $4°C \pm 2°C > 25°C \pm 2°C$ /60% $\pm 5\%$ RH $> 40°\,C \pm 2°C$ / 75%$\pm 5\%$ RH. There was no any change in Physical appearance at all three conditions. These result suggest that IPN hydrogel are more stable in $4°C \pm 2°C$ as compare to $25°C \pm 2°C$ /60% $\pm 5\%$ RH and $40°\,C \pm 2°C$ / 75%$\pm 5\%$ RH.

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