FORMULATION AND EVALUATION OF SUPERPORUS HYDROGEL COMPOSITE AS A GASTRO RETENTIVE DRUG DELIVERY FOR CEFDITOREN PIVOXIL

Abstract

The purpose of this work was to incorporate superporus hydrogels for cefditoren pivoxil by using polymer like poly acrylic acid aqua cc polymer and composite agent like cross linked sodium carboxy methyl cellulose in the presence of N,N-methylene-bis-Acrylamide as crosslinking agent. Pluronic F-127 as a stabilizer and ammonium per sulfate and tetramethylene diamine as a initiator pair. Poly acrylic acid aqua cc polymer-cross linked sodium carboxy methyl cellulose superporus hydrogels of cefditoren pivoxil were incorporate by gas blowing technique. The reaction of pH on the swelling ratio was decisive. Swelling reversibility research was also achieve. Fourier transform infrared spectroscopy analysis and scanning electron microscopy studies were assume to indicate the drug loaded superporous hydrogels, while dissolution studies were achieve to assess release characteristics. Swelling was hugely depending on the term of crosslinking and the quantity of the polymer existing in formulation. The huge amount of cross-linking agent reduced the swelling ratio. The superporous hydrogels were hugely perceptive to pH of swelling medium, and exhibit reversible swelling and de-swelling behavior during still keep their mechanical stability. Apparent density was reliant on the amount of the superporous hydrogels and reduced with developing crosslink density. Degradation kinetics reveals that poly acrylic acid aqua cc polymer superporous hydrogels had good water holding potential. Drug release was similar to quantity of cross-linking agent. The studies report that poly acrylic acid aqua cc polymer superporous hydrogels can be used as a Gastroretentive drug delivery system in view of their swelling characteristics in acidic pH.

Keywords: Gastro retentive drug delivery, superporus hydrogels, swelling ratio, poly acrylic acid aqua cc polymer, cross linked sodium carboxy methyl cellulose, swelling ratio.

Introduction

"The drugs for oral distribution have its own advantage in being simple and profitable management, but the deficiency is the failure of their action due to their brief address time in the shape. About 80% of the orally dispense medicines are expressed to be eliminated without being absorbed"[1]. "Numerous experiment have been recommended to continue the residence space of medicines in the body for entire absorption, but not numerous systems have been strongly practiced"[2].

"Stimuli reactive polymers, which can reversibly swelling in response to outside setting, such as temperature, pH, solvent composition, electrical field and light are of great interest, especially in biomedical and pharmaceutical technique. Among them, pH-sensitive hydrogels

that shift properties by depending upon replace in pH have been extensively considered for the improvement of advanced drug delivery systems" [3]. "These polymers can be arranged by the adding of one or more standard monomers such as poly acrylic acid aqua cc polymer cross linked Na CMC. Basic gels are considered as excellent candidates for gastro retentive drug delivery of medicines that are deterioration in the basic pH. While these type of structure have slow equilibrium degree of buldge in basic medium of intestine, their swelling degree is higher in the stomach and upper area of intestine due to an reduce in pH. Thus, the pH-sensitive drug distribution system save the drug from the base of intestine and discharge the entire medicine in the stomach"[4]

"Hydrogels are cross linked hydrophilic polymers with a network design consisting of acidic, basic, or neutral monomers which are able to ingest high quantity of water"[5]. "Because of the hydrophilic nature of polymer chains, hydrogels swallow water to buldge in the existence of abundant water"[6]. "The swelling things of hydrogels are mainly associated to the flexibility of the network, the existence of hydrophilic functional category (such as -OH, -COOH, -CONH2, -SO3H) in the polymer chains, the extent of crosslinking, and porosity of the polymer"[7]. "A variation of stimuli conscious hydrogels have been studied, but in more cases, modeate response to environment stimulant produce restriction to their effective usage" [8]. "Although such lethargic swelling is useful for many functions, there are more position where a quick bulging of the polymer is more preferable. Therefore, a new genesis of hydrogels, which swell and swallow water very quickly, has been expanded. Examples of this new genesis are superporous hydrogels (SPH) and SPH composites (SPHC), which buldge to equilibrium size in a small period of time"[9].

"A superporous hydrogel (SPH) is a 3-dimensional network of a hydrophilic polymer that swallows a huge volume of water in a very less time due to the existence of interconnected microscopic pores"[10]. "In this research, SPH and SPHC were synthesized in order to prepare these polymers convenient for gastro retentive delivery of drugs. When these polymers are dispatched into the abdomen, they are able to mechanically stick for a definite interval of time at the abdomen wall, sucking up gastric juices and opening the rigid connection before lastly discharging the drug. After having discharged the drug in a time controlled manner, the polymers develop into super hydrated and are readily smashed down by the peristaltic strength of the abdomen and subsequently evacuate as fine pieces"[11].

"In this study, SPHCs of polyacrylic acid aqua cc polymer was prepared employing poly acrylic acid aqua cc polymer, Cross linked sodium carboxy methyl cellulose as a composite agent and N-N methylene-bis-acrylamide as crosslinking agent"[12]. "Cefditoren pivoxil is third generation cephalosporin antibiotic, is highly unstable at basic pH, half-life is 1.6hrs and is extensively absorbed from the stomach and upper part of the GIT. Hence there is a need to develop a gastro retentive system. In this study a superporus hydrogel was developed as a gastro retentive drug delivery system"[13]. Poly acrylic acid is available as acidic and basic polymer, the polyacrylic acid aqua cc polymer is cationic charge containing polymer because it contains more basic groups, it swells more easily in stomach fluids. Cefditoren made into a superporus hydrogel formulation enhanced half-life of drug[14].

EXPERIMENTAL METHOD

Materials: Cefditoren pivoxil was obtained as a gift sample from Hetero laboratories (Hyderabad). polyacrylic acid aqua cc polymer and cross linked sodium carboxy methyl

cellulose, N-N methylene-bis-acrylamide, ammonium per sulfate and tetramethylene diamine were obtained from SD Fine Chem Ltd., pluronic F-127 was obtained from signet chemicals, Mumbai and glacial acetic acid of rankem, Mumbai. Sodium bi carbonate from finar chemicals limited, magnesium stearate from the Loba Chemie,Mumbai, Lactose monohydrate from Merck Specialties private limited, Mumbai were used in this study.

Methods:

Preparation of Superporous Hydrogels and SPHC:

"All ingredients except for sodium bicarbonate were used as solution in distilled water. For the synthesis of superporous hydrogels, the following substances were added subsequently into a test tube at ambient temperature: polyacrylic acid aqua cc polymer (50% v/v), *N*,*N*-methylene bisacrylamide(2.5% w/v), Pluronic-F127 (10% w/v), ammonium per sulphate (20% w/v) and tetramethyl ethylenediamine (20% w/v)"[15]. "The pH was adjusted to 5.0 by adding o.1M acetic acid. Then ,the mixture was vigorously shaken, and sodium bicarbonate was added very quickly to the solution and mixed. For the synthesis of superporous hydrogel composites, the procedure is same as that of superporous hydrogel; however, cross linked sodium carboxy methyl cellulose was added to the mixture after adding ammonium per sulphate (APS) and before adding tetramethylethylenediamine (TMED). Polymerization was allowed to continue for approximately 10 min"[15].

Drug loading:

The drug choosed for the research study was cefditoren pivoxil. The technique of soaking or equilibrium was employed for drug storing. In this technique, the volume of buffer compulsory for thorough buldging of SPHCs was first determined. Thereafter, drug mixture of needed concentration was developed and SPHCs was placed in it and left until all the drug mixture was inhale up. The thoroughly swollen SPHC loaded with the drug was dehydrated at room temperature overnight.

Direct Compression Method:

After complete drying, the SPHC was made into particles. To this SPHC particles add sufficient quantity of lactose and magnesium stearate, directly compress the SPHC particles by using 8mm std concave punch using sixteen station compression equipment[16].

Table 1: Formulations of superporus hydrogel combinations

Constituets	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**
Poly acrylic acid aqua cc polymer	150µl	225µl	300µl	300µl	300µl	450µl	450µl	300µl
Cross linked Na	-	-	-	90µl	180µl	90µl	180µl	180µl

CMC								
N,*N*methylene bisacrylamide	25µl	25µl	25µl	30µl	30µl	40µl	40µl	30µl
Ammonium per sulphate	25µl	25µl	25µl	25µl	25µl	25µl	25µl	25µl
PluronicF-127	20µl	20µl	20µl	20µl	20µl	20µl	20µl	20µl
Tetramethyl ethylenediamine	25µl	25µl	25µl	25µl	25µl	25µl	25µl	25µl
Sodium bicarbonate	100mg	100mg	100mg	100mg	100mg	100mg	100mg	-
Cefditoren pivoxil	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg

Drug excipient compatibility by FTIR Studies:

The IR spectrums of the Cefditoren pivoxil with constituents were taken by developing dispersion in dry potassium bromide under dry condition. Super imposed these spectra. The absorption maxima in the spectra acquire with the specimen corresponded in location and relative dimension to those in the spectrum acquire with the standards.

Weight variation:

Individual weights of 20 tablets were taken and the moderate weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of tablet-Average weight)}}{\text{Average weight of tablets}} \times 100$$

Weight variation should not be more than 7.5%.

Hardness:

Hardness of the tablets was observed by the use of hardness tester. Desired hardness was 6-8Kg/$cm^{2.}$

Thickness:-

Thickness of the tablets was calculated by the use of Digital Vernier calipers. Desired thickness was 2-3mm.

Friability: Friability is determined by the use of roche Friabilator. The percentage friability was must be within the 0.5-1%.

$$\text{Friability} = \left[\frac{(W1-W2)}{W1}\right] \times 100$$

Where W_1 = Initial weight of 20 tablets

W_2 = Weight of the 20 tablets after testing

Drug content:

Take a superporus hydrogel composite tablet and powdered in a motor and pestle, dissolved in suitable solvent. Samples analyzed by UV Spectroscopic method.

Swelling Studies

The dried SPHs and SPHCs were used to decide their bulging ratio in pH 1.2 hydrochloric acid buffers. For calculation of the bulging ratio, the following equation was used:

$$Q = (Ms - Md)/ Md$$

where *Q* is the swelling ratio, Ms the mass in the dilate state and Md the mass in the dried state. At the starting point of each experiment, the dried hydrogel was measured to obtain Md and then it was submerge in a surplus buffer solution for swelling. At different time meanwhile, the hydrogel was detached from the water and measured, when surplus water on the top was blotted, to determine Ms[9]

Density Analysis of the SPHC

The density (d) of the dried hydrogels was determined by the following equation:

$$d = Wd/Vd$$

where Wd is the weight of a dried hydrogel and Vd is the amont of the dried hydrogel. Since SPH and SPHCs invisible their routine structure during the drying progress, straight evaluation of their amounts becomes difficult. Therefore, for evaluation of their volumes, the solvent displacement technique was enforced. Briefly, a dried superporous hydrogel was immersed underneath the surface of hexane in a graduated cylinder and then fastly was detached from the hexane. The amount replace read from the graduated cylinder before and after the elimination was the amount of the dried superporous hydrogel. Hexane was used because it is actual hydrophobic and superporous hydrogels do not swallow it.

Evaluation of gelation kinetics

“As the polymerization response proceeded, the viscosity frequently expanded until the full network system (gel structure) was estabilihed. The gelation time was explained as the extent time for gel formation after inclusion of initiator (APS). It was calculated by a simple tilting technique after alteration of pH to 5.0 with 0.1M Acetic acid. It was evaluated by the duration time until the reactant solution was no longer descending in the tilted tube spot”. [10].

Swelling reversibility studies

" pH-dependent bulging of the superporous hydrogel complex was determined by variation of the swelling median between the 0.1N HCl solution (pH 1.2) and phosphate buffered solution (PBS, pH 7.4). The hydrogels were first swollen in pH 1.2 HCl mixtures for 30 min. The swollen hydrogels in the HCl mixture were measured at each given time and shifted to the phosphate buffered mixture. The same methods were carry out for swelling in PBS before moving the swollen hydrogels back to the HCl mixture. The hydrogels were shifted to the alternating mixtures every 30m" [11].

Evaluation of degradation kinetics

The degradation kinetics of the hydrogels was dete by determined the swelling ratio as a function of water retention. The hydrogels were placed in pH 1.2 (0.1 N HCl) medium at 37˚C for 12h and the samples were regularly weighed at 6 h interval. Water retention capacity (WRt) as a function of time was assessed according to the following equation;

$$WRt = (Wp - Wd) / (Ws - Wd)$$

Where,
Wd is the weight of the dried hydrogel,
Ws the weight of the fully swollen hydrogel,
Wp the weight of the hydrogel at various exposure times.

In vitro drug release studies

"The in vitro release of MT from the superporous hydrogels was carried out at 37 ± 0.5 °C in 900 ml of 0.1N HCl using USP XXIV Type 2 (paddle type). The medium was stirred at 100 rpm and 5 ml aliquots were withdrawal at particular time period; to regularly sink conditions; 5 ml of dissolution medium was instantly added after each sample was detached. Cefditoren was assayed spectrophotometrically" [12].

Release kinetics:

Zero order Kinetics:

The following relation can in a easy way, expressed the Zero order kinetic model:

$$Q_1 = Q_o + K_o t$$

Where Q_1 is the quantity of drug soluble in time t, Q_o is the initial volume of drug in the mixture and K_o is the zero order release rate constant.

Higuchi model:

To study the dissolution from a planar system having a homogeneous matrix, the relation obtained was the following:

$$f_t = K_H t^{1/2}$$

Where f_t = amount of drug released at time t

K_H = the Higuchi release rate.

This is the highest broadly used model to illustrate drug release from pharmaceutical matrices. A linear corrlation of square root of time versus concentration noted that the drug deliver follows Fickian diffusion.

Korsmeyer- Peppas model:

For prediction of mechanism of drug deliver through polymeric system Korsmeyer and Peppas, in 1983 refined a mathematical equation, relating exponentially the drug deliver to the elapsed time. It is a easy semi empirical equation also called as Power law.

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

Where,

M and M_∞ are the absolute cumulative volume of drug delivered at time t and infinite time, k is a consistent integrates structural and geometric characteristics of the device, n is the drug deliver exponent, indicative of the mechanism of drug deliver.

Scanning electron microscopy:

The dried polymers were used for scanning electron microscopy (SEM) studies. SEM was used to evaluate the morphology of the dried samples. A JEOL JSM-840 scanning electron microscope (Jeol USA Inc., Peabody, MA, USA) was used after coating the samples with gold using a method Hummer Sputter Coater. Images were collected using a digital capture card and Digital Scan Generator 1 (Jeol USA Inc., Peabody, MA,USA).

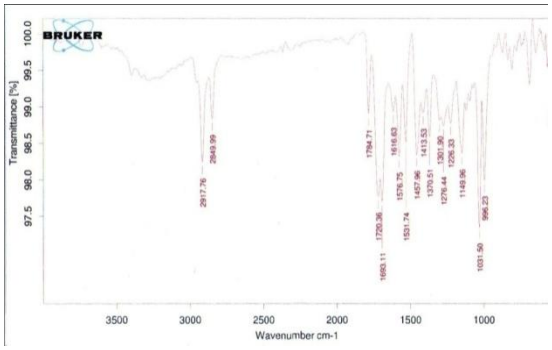
Stability Studies:

The prepared batches were kept in air tight containers and stored in stability chamber (TH-90S, Thermolab, India) at 40 C/75% RH for 3 months. Results of the in vitro drug release studies obtained after three months correlated with the data obtained at the time of preparation. The parallel factor ($f_{2)}$ was applied to study the effect of storage. The similarity factor can be calculated using equation.

$$f_2 = 50 \times \log \{ [1+(1/n)\sum (R_t - T_t)^2]^{-0.5} \times 100 \}$$

Results and discussion

FTIR studies



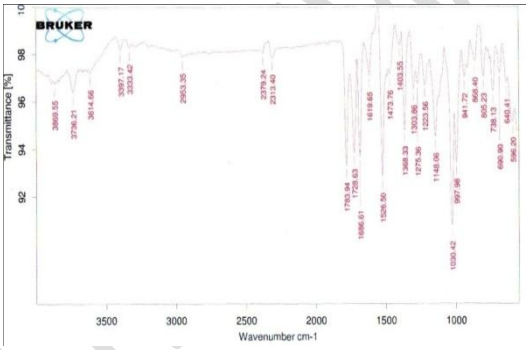


Figure 1: FTIR spectra for drug with excipients **Figure 2: FTIR spectra for pure drug**

Cefditoren pivoxil (pure drug) and hydrogel formulation F_5 were also subjected for FT-IR spectroscopy analysis and it was concluded that the drug in free state and there is no interaction between drug and polymer used.

Chart 1: Post compression parameters:

S.NO	Physical parameter	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
1	Weight variation	499±1.54	501±1.42	498±1.48	505±1.85	494±1.23	506±1.44	498±1.32	500±1.24
2	Hardness(Kg/Square inch	5±0.42	6±0.53	6±0.34	6±0.52	8±0.12	8±0.23	8±0.42	8±0.25
3	Thickness(mm)	3.6±0.02	3.6±0.02	3.6±0.02	3.6±0.02	4±0.05	3.7±0.03	3.6±0.02	3.98±0.04
4	%Friability	0.18±0.02	0.16±0.01	0.32±0.03	0.59±0.03	0.58±0.04	0.65±0.02	0.76±0.02	0.86±0.01

Chart 2 Drug content:

S.NO	Parameter	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
	Assay	99.1% ±0.03	99.3% ±0.02	99.6% ±0.03	102% ±0.06	101% ±0.03	102% ±0.02	99% ±0.02	99.63% ±0.03

Swelling studies:

The swelling ratios of all formulations in 0.1N Hydrochloric acid mixture are represented in Figure three. The Swelling ratio of the processed formulations in Hydrochloric acid mixture was found to rise with time. Bulge was also found to be depending on concentration of polyacrylic acid aqua cc polymer, cross linked sodium carboxy methyl cellulose and sodium bicarbonate. The swelling ratios of superporous hydrogels reduced by increasing the cross-linking density, as much tighter networks were established at greater concentration of cross-linking agents.

Swelling reversibility studies:

This study shows the swelling reversibility of the superporous hydrogel between pH 1.2 and pH 7.4 mixtures. They were able swelling and deswelling the swelling medium fastly upon the pH replace from acidic to basic circumstances fastly and vice versa. The time needed for swelling was more than that for deswelling of the hydrogels.

Gelation kinetics

The gelation kinetics gives valuable instruction to evaluate the extension time of blowing substance (sodium bicarbonate). The foaming response took place only under the acidic condition (pH 5.0-5.5) and therefore the pH was modifying to 5.0. The optimal pH for the gelation was surrounding 7–8, where the polymerization proceeds quickly and the gelling commonly imitated within 0.5-1.0 m. Hence $NaHCO_3$ was added 30s after the modifying of pH to 5.0.

Degradation kinetics

As shown in Figure four, the density fall of aqueous polyacrylic acid hydrogels happened after 36 hours. Reduce the viscosity of the cross-linking substance; the faster was the loss of water from the superporous hydrogel. The superporous hydrogel consisting of large volume of *N*,*N* methylene bisacrylamide had reduced polymer flexibility, thus developing the resiliency of the polymer in reaction to compression and prevention of the water loss effectively. Hence, an rise in the volume of *N*,*N* methylene bisacrylamide reduced the rate of loss of water.

Density of the superporous hydrogels

The apparent thickness of the various superporous hydrogels ranged in the middle of 0.758 and 0.854 g/cm3. Since the hydrogels are heavy porous, the measured thickness related to the porosity of the polymer and can be defined as apparent thickness. The polymer's real thickness is the same, but because it has fewer pores, the engaged quantity is low, resulting in a high

perceived density. As a result, the apparent density increases as the cross linking agent concentration increases.

In-vitro drug release studies from SPHs

The *in-vitro* Cefditoren pivoxil release data from the superporous hydrogels is depicted in Figure five. The data obtained demonstrate that rise in concentration of polyacrylic acid aqua cc polymer and cross linked sodium carboxyl methyl cellulose continue the discharge of the drug. Entire drug release was noticed at 24 hours for formulations F-V, where as the formulation F-I ,F-II,F-III , F-IV and F-VIII completes the release within the 24 hours. Formulation F-VI, F-VII, exhibit sustained release beyond 24 hours. At high crosslink density, the pores of the hydrogel are low in size and number, and hence drug release was less.

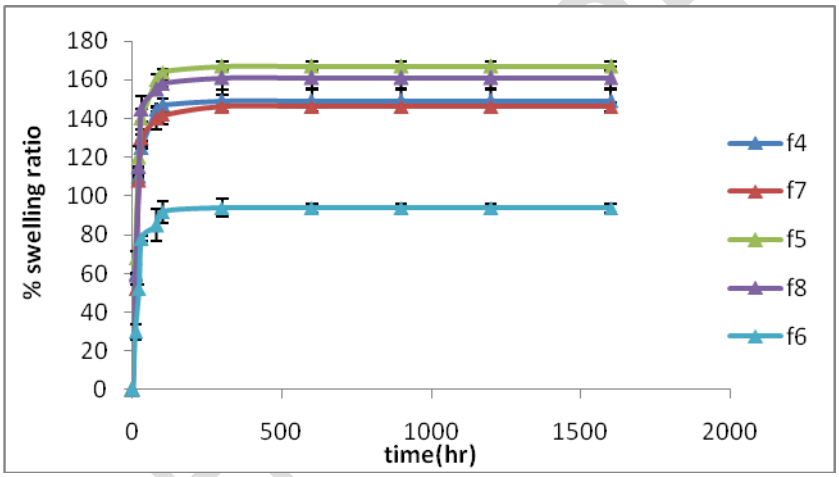


Figure 3: Swelling ratio of superporus hydrogel formulations at pH 0.1N HCL.(n=3,mean±S.D)

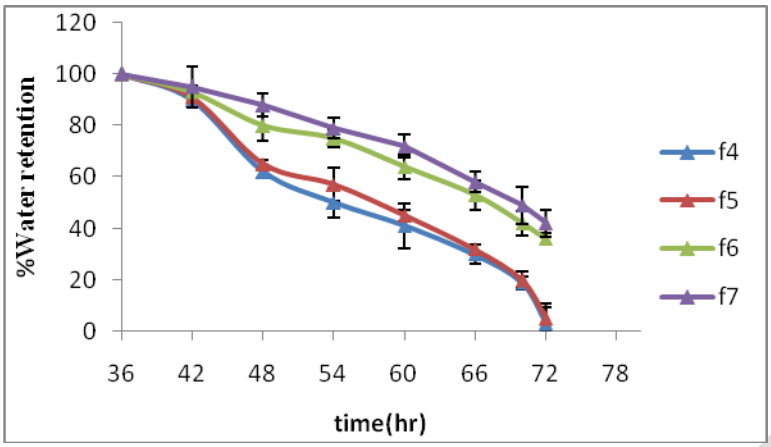


Figure 4 : Degradation of superporus hydrogel tablets. (n=3,mean±S.D)

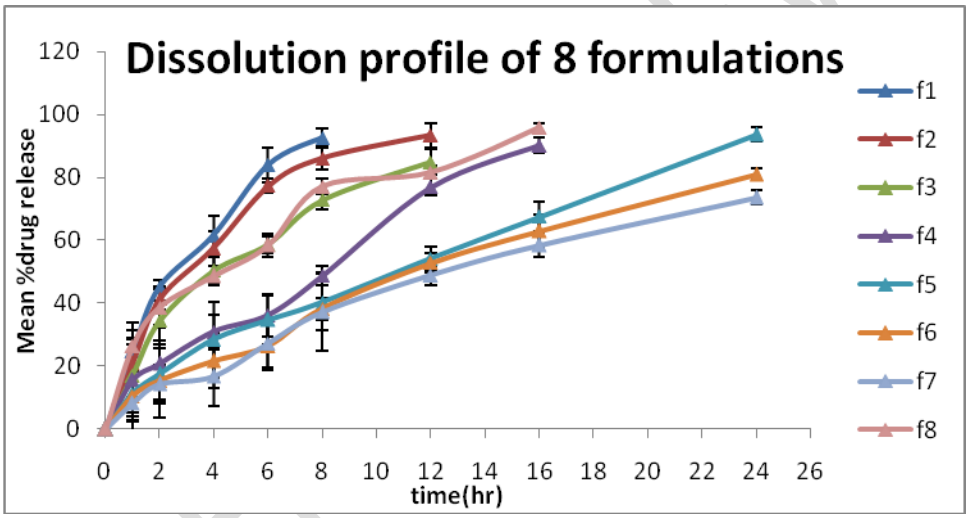
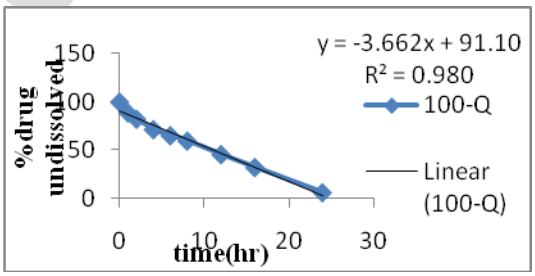


Figure 5: ***In vitro*** **release of prepared Cefditoren pivoxil from superporus hydrogel. (n=3,mean±S.D)**

Release Kinetics:



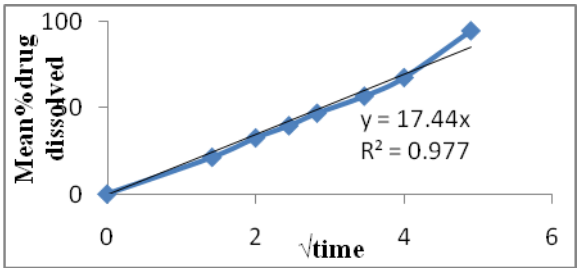


Figure 6:Zero order plot of F_5 **Figure 7:First order plot of F_5**

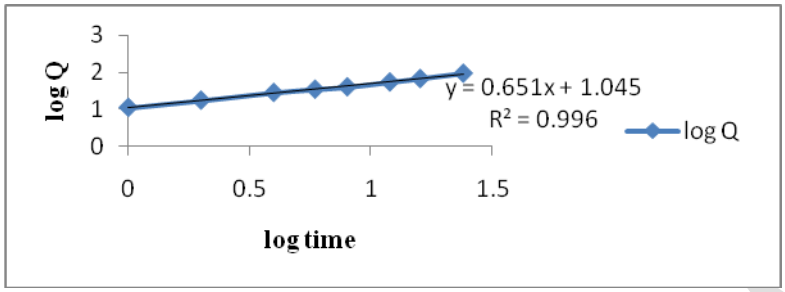


Figure 8:koresmeyer-peppas plot of F_5

Based on these plots due high regression coefficient, superporus hydrogel follows a Zero order, higuchi and Koresmeyer-peppas release. The parameters namely 'n' was caluculated in case of koresmeyer peppas model.The n value was found to be o.65 in drug release profiles,hence the release mechanism is assumed to be anomalous non Fickian diffusion.

Scanning electron microscopy:

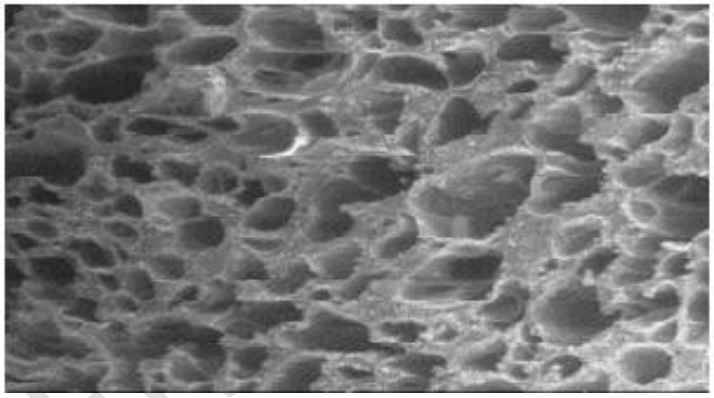


Fig.9.Scanning electron microscopy image of superporus hydrogel containing poly acrylic acid aqua cc polymer and cross linked Na CMC under magnification of 1mm.

Stability Studies:

The objective of stability studies is to predict the shelf life of a product by accelerating the rate of decay, willingly by rising the temperature and relative humidity. The optimized formulations were subjected to stability studies according to International Council for Harmonization guidelines by storing at 40º ± 2º C/75% ±5% RH for three months. These specimens were analyzed and examine for variation in physical presence and drug content at 0, 1, 2 and 3 months. From the obtained report, it is clear that the formulation did not undergo any chemical interaction during the research period.

Conclusion:

In the presented research, Poly acrylic acid aqua cc polymer based superporous hydrogels were developed by gas blowing technique and characterized. From the reports of the swelling studies, it was noticed that with a reduce in pH from 7.4 to 1.2, a considerable rising in swelling was noticed for all the preparations, which may be due to dissociation of the primary groups of aqueous poly acrylic acid, thereby raising the osmotic pressure inside the hydrogels resulting in raised swelling. The detecting noted that the swelling attitude of the SPHs based on the concentration of poly acrylic acid aqua cc polymer, cross linked Na CMC, N-N methylene bisacrylamide and of sodium bicarbonate. From the report of the de-swelling studies, it was noticed that upon replacing from acidic to basic medium, there is a reduce swelling, confirming its pH sensitivity. Generally all preparations explained their applicability *in vitro* as a promising device for pH-dependent gastro retentive delivery of cefditoren pivoxil. Superporous hydrogels can be successfully constructed as a gastro-retentive drug delivery device, according to this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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