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

Abstract

The aim of this work was to synthesize 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 synthesized by gas blowing method. The effect of pH on the swelling ratio was determined. Swelling reversibility studies were also carried out. Fourier transform infrared spectroscopy analysis and scanning electron microscopy studies were undertaken to characterize the drug loaded superporous hydrogels, while dissolution studies were carried out to assess release characteristics. Swelling was highly dependent on the extent of crosslinking and the amount of the polymer present in formulation. The higher the amount of cross-linking agent, lower was the swelling ratio. The superporous hydrogels were highly sensitive to pH of swelling medium, and showed reversible swelling and de-swelling behavior while still retaining their mechanical stability. Apparent density was dependent on the volume of the superporous hydrogels and decreased with increasing crosslink density. Degradation kinetics showed that poly acrylic acid aqua cc polymer superporous hydrogels had good water retention capability. Drug release was related to amount of cross-linking agent. The studies revealed 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 delivery have its own convenience in being easy and economic administration, but the weakness is the loss of their functions due to their short residence time in the body. About 80% of the orally administrated drugs are reported to be excreted without being absorbed[1]. Many attempts have been proposed to prolong the residence time of drugs in the body for complete absorption, but not many systems have been successfully applied in practice[2].

Stimuli responsive polymers, which can reversibly swell or shrink in response to external conditions, such as temperature, pH, solvent composition, electrical field and light are of great interest, especially in biomedical and pharmaceutical technology. Among them, pH-sensitive

hydrogels that change properties by depending upon changes in pH have been extensively investigated for the development of new drug delivery systems[3]. These polymers can be prepared by the incorporation of one or more basic monomers such as poly acrylic acid aqua cc polymer, cross linked Na CMC. Basic gels are considered as good candidates for gastro retentive drug delivery of drugs that are degradation in the basic pH. While these kinds of systems have slow equilibrium degree of swelling in basic medium of intestine, their swelling degree is more in the stomach and upper part of intestine due to an decrease in pH. Thus, the pH-sensitive drug delivery system protects the drug from the base of intestine and releases the entire drug in the stomach[4]

Hydrogels are cross linked hydrophilic polymers with a network structure consisting of acidic, basic, or neutral monomers which are able to imbibe large amounts of water. Because of the hydrophilic nature of polymer chains, hydrogels absorb water to swell in the presence of abundant water. The swelling properties of hydrogels are mainly related to the elasticity of the network, the presence of hydrophilic functional groups (such as -OH, -COOH, -CONH2, -SO3H) in the polymer chains, the extent of crosslinking, and porosity of the polymer. A variety of stimuli sensitive hydrogels have been studied, but in many cases, slow response to environmental stimuli caused limitation to their effective use[5]. Although such slow swelling is beneficial for many applications, there are many situations where a fast swelling of the polymer is more desirable. Therefore, a new generation of hydrogels, which swell and absorb water very rapidly, has been developed. Examples of this new generation are superporous hydrogels (SPH) and SPH composites (SPHC), which swell to equilibrium size in a short period of time[6].

A superporous hydrogel (SPH) is a three-dimensional network of a hydrophilic polymer that absorbs a large amount of water in a very short period of time due to the presence of interconnected microscopic pores. In this study, SPH and SPHC were synthesized in order to make these polymers appropriate for gastro retentive delivery of drugs. When these polymers are delivered into the stomach, they are able to mechanically stick for a certain period of time at the stomach wall, sucking up gastric fluids and opening the tight junctions before finally releasing the drug. After having released the drug in a time controlled manner, the polymers become super hydrated and are easily broken down by the peristaltic force of the stomach and subsequently excreted as fine particles[7].

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. 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. 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.

EXPERIMENTAL

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). The pH was adjusted to 5.0 by adding o.1M acetic acid. 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.

Drug loading:

The drug selected for the study was cefditoren pivoxil. The method of soaking or equilibrium was employed for drug loading. In this method, the amount of buffer necessary for complete swelling of SPHCs was first determined. Thereafter, drug solution of required concentration was prepared and SPHCs was placed in it and left until all the drug solution was sucked up. The completely swollen SPHC loaded with the drug was dried 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 16 station compression machines.

Table 1: Formulations of superporus hydrogel composites

Ingredients	**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 CMC	-	-	-	90µl	180µl	90µl	180µl	180µl
N,*N*methylene	25µl	25µl	25µl	30µl	30µl	40µl	40µl	30µl

bisacrylamide								
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 excipients were taken by preparing dispersion in dry potassium bromide under dry condition. Super imposed these spectra. The transmission minima (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the standards.

Weight variation:

Individual weights of 20 tablets were taken and the average 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 determine their swelling ratio in pH 1.2 hydrochloric acid buffer. For calculation of the swelling ratio, the following equation was used:

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

where *Q* is the swelling ratio, Ms the mass in the swollen state and Md the mass in the dried state. At the beginning of each experiment, the dried hydrogel was weighed to obtain Md and then it was immersed in an excess buffer solution for swelling. At various time intervals, the hydrogel was removed from the water and weighed, when excessive water on the surface was blotted, to determine Ms[9]

Density measurement of the SPHC

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

$$d = Wd/Vd$$

where Wd is the weight of a dried hydrogel and Vd is the volume of the dried hydrogel. Since SPH and SPHCs lost their regular shapes during the drying process, direct measurement of their volumes becomes difficult. Therefore, for measurement of their volumes, the solvent displace ment method was applied. Briefly, a dried superporous hydrogel was submerged underneath the surface of hexane in a graduated cylinder and then quickly was removed from the hexane. The volume change read from the graduated cylinder before and after the removal was the volume of the dried superporous hydrogel. Hexane was used because it is very hydrophobic and superporous hydrogels do not absorb it.

Measurement of gelation kinetics

As the polymerization reaction proceeded, the viscosity continuously increased until the full network structure (gel structure) was formed. The gelation time was defined as the duration time for gel formation after addition of initiator (APS). It was measured by a simple tilting method after adjustment of pH to 5.0 with o.1M Acetic acid. It was determined by the duration time until the reactant mixture was no longer descending in the tilted tube position[10].

Swelling reversibility studies

pH-dependent swelling of the superporous hydrogel composite was evaluated by alternation of the swelling medium 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 solutions for 30 min. The swollen hydrogels in the HCl solution were weighed at each given time and transferred to the phosphate

buffered solution. The same procedures were performed for swelling in PBS before transferring the swollen hydrogels back to the HCl solution. The hydrogels were transferred to the alternating solutions every 30m[11].

Evaluation of degradation kinetics

The degradation kinetics of the hydrogels was examined by measuring 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 periodically 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 withdrawn at specified time intervals; to maintain sink conditions; 5 ml of dissolution medium was immediately added after each sample was removed. Cefditoren was assayed spectrophotometrically[12].

Release kinetics:

Zero order Kinetics:

The following relation can in a simple way, express the Zero order kinetic model:

$$Q_1 = Q_o + K_o t$$

Where Q_1 is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution 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 most widely used model to describe drug release from pharmaceutical matrices. A linear relationship of square root of time versus concentration indicates that the drug release follows Fickian diffusion.

Korsmeyer- Peppas model:

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

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

Where,

M and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, k is a constant incorporating structural and geometric characteristics of the device, n is the drug release exponent, indicative of the mechanism of drug release.

Scanning electron microscopy:

The dried polymers were used for scanning electron microscopy (SEM) studies. Scanning electron microscopy was used to determine 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 Technics Hummer Sputter Coater.Images were captured using a digital capture card and Digital Scan Generator 1 (Jeol USA Inc., Peabody, MA,USA).

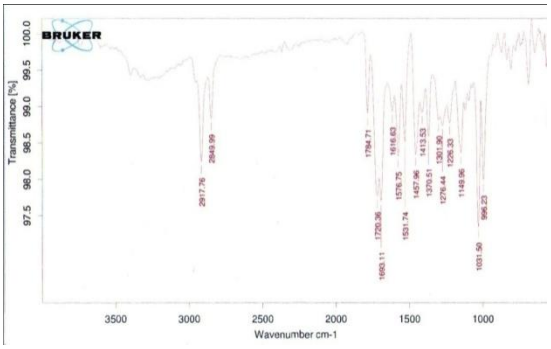
Stability Studies:

The prepared batches were kept in air tight containers and stored in stability chamber (TH-90S, Thermolab, India) at 40 C/75% RH for three months. Results of the in vitro drug release studies obtained after three months compared with the data obtained at the time of preparation. The similarity 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



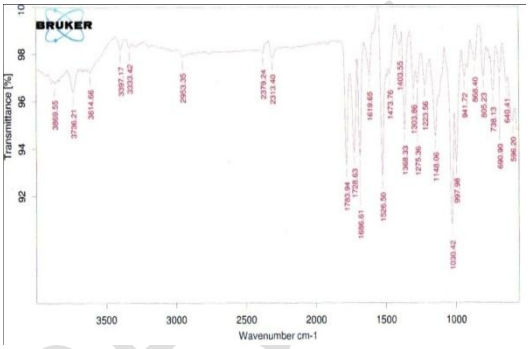


Figure 1: FTIR spectra for drug with excipients **Figure 2: FTIR spectra for pure drug**

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 HCl solution are represented in Fig 3. The Swelling ratio of the prepared formulations in HCl solution was found to increase with time. Swelling was also found to be dependent on concentration of polyacrylic acid aqua cc polymer, cross linked Na CMC and sodium bicarbonate. The swelling ratios of superporous hydrogels decreased by increasing the cross-linking density, as much tighter networks were formed at higher concentration of cross-linking agents.

Swelling reversibility studies:

These studies show the swelling reversibility of the superporous hydrogel between pH 1.2 and pH 7.4 solutions. They were able absorb and deabsorb the swelling medium quickly upon the pH change from acidic to basic conditions quickly and vice versa. The time required for swelling was longer than that for deswelling of the hydrogels.

Gelation kinetics

The gelation kinetics give good information to determine the addition time of blowing agent (sodium bicarbonate). The foaming reaction took place only under the acidic condition (pH 5.0-5.5) and therefore the pH was adjusted to 5.0. The optimal pH for the gelation was around 7–8, where the polymerization proceeds rapidly and the gelling usually started within 0.5-1.0 m. Hence sodium bicarbonate was added 30s after the adjustment of pH to 5.0.

Degradation kinetics

As shown in Fig. 4, the weight loss of aqueous polyacrylic acid hydrogels occurred after 36h. Lower the concentration of the cross-linking agent, the faster was the loss of water from the superporous hydrogel. The superporous hydrogel consisting of higher amount of *N*,*N* methylene bisacrylamide had decreased polymer rigidity, thus improving the resiliency of the polymer in response to compression and prevention of the water loss efficiently. Hence, an increase in the amount of *N*,*N* methylene bisacrylamide decreased the rate of loss of water.

Density of the superporous hydrogels

The apparent densities of the various superporous hydrogels ranged between 0.758 and 0.854 g/cm3. Since the hydrogels are very porous, the measured density is related to the porosity of the polymer and can be defined as apparent density. The actual density of the polymer is the same but when the polymer has fewer pores, the occupied volume will be less, thus resulting in high apparent density. Therefore, higher the concentration of the cross linking agent, the greater is the apparent density.

***In-vitro* drug release studies from SPHs**

The *in-vitro* Cefditoren pivoxil release data from the superporous hydrogels is depicted in Fig 5. The data obtained showed that increase in concentration of polyacrylic acid aqua cc polymer and cross linked Na CMC prolong the release of the drug. Complete drug release was observed at 24 hrs 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 h. Formulation F-VI, F-VII, showed sustained release beyond 24 h. At high crosslink density, the openings (pores) of the hydrogel are less in size and number, and hence drug release was lower.

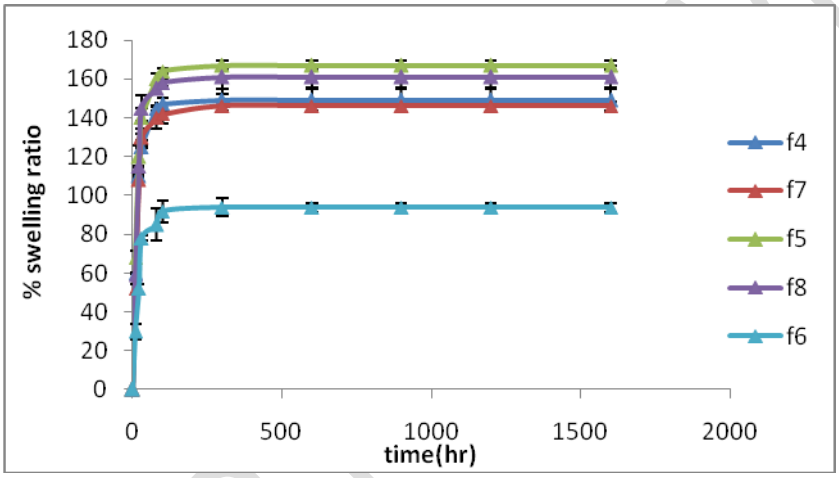


Figure 3: Swelling ratio of superporus hydrogel formulations at pH 0.1N HCL.(n=3,mean±S.D)

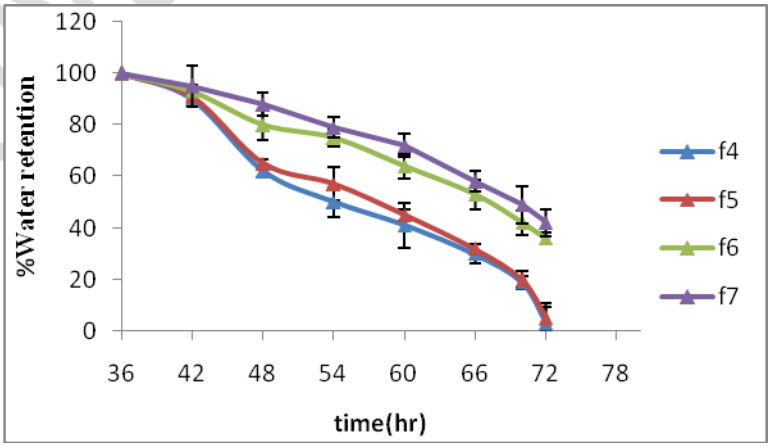


Figure 4 : Degradation of superporus hydrogel tablets. (n=3,mean±S.D)

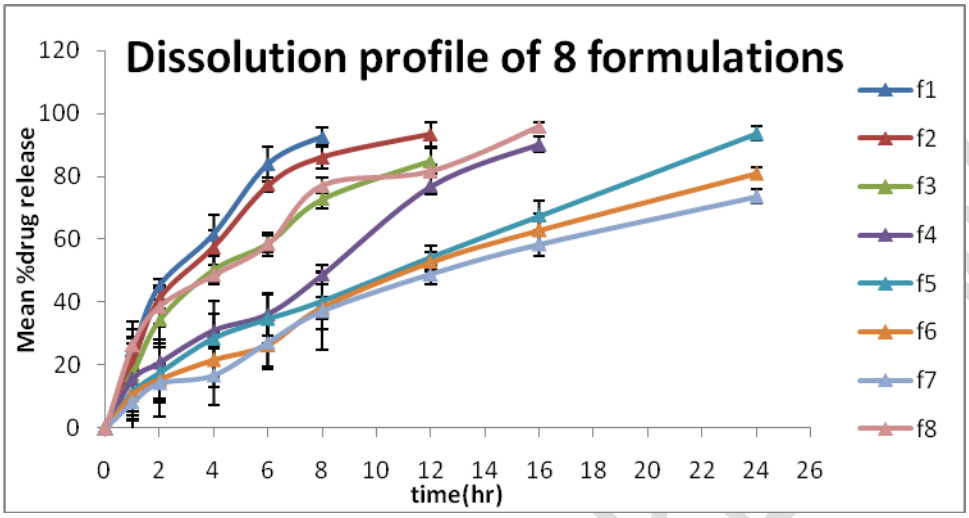


Figure 5: *In vitro* release of prepared Cefditoren pivoxil from superporus hydrogel. (n=3,mean±S.D)

Release Kinetics:

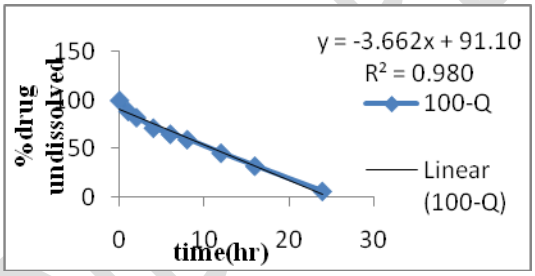


Figure 6:Zero order plot of F_5

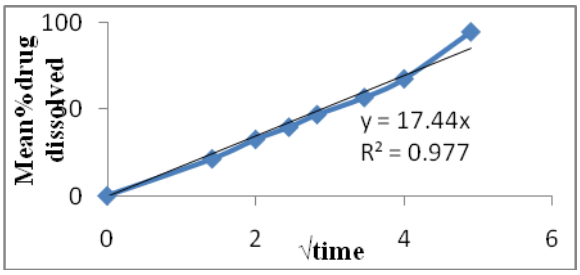


Figure 7:First order plot of F_5

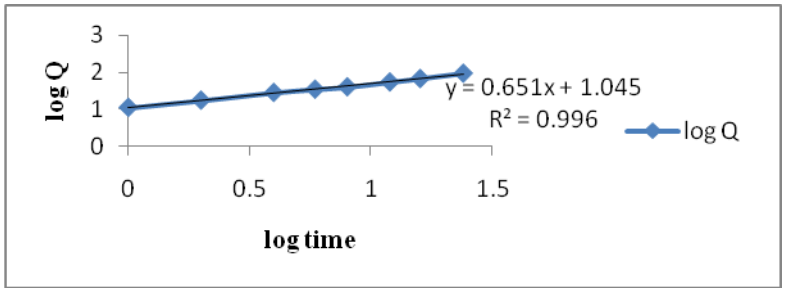


Figure 8:koresmeyer-peppas plot of F_5

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:

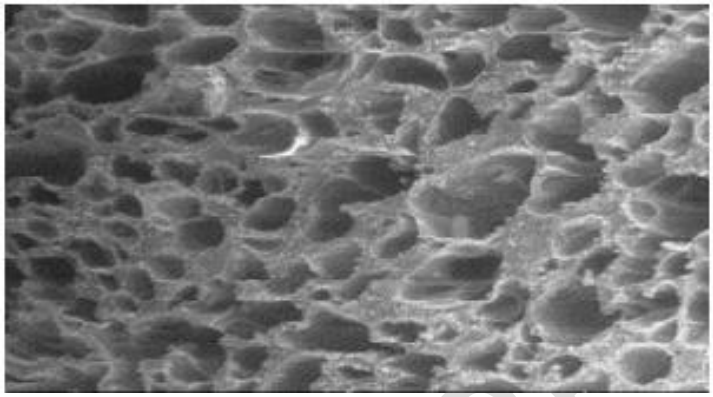


Fig.9.Scanning electron microscopy image of superporus hydrogel containing poly acrylic acid aqua cc polymer and cross linked Na CMC under magnification of 1mm.

Stability Studies:

The objective of stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature and relative humidity. The optimized formulations were subjected to stability studies according to ICH guidelines by storing at 40º ± 2º C/75% ±5% RH for 3 months. These samples were analyzed and checked for changes in physical appearance and drug content at 0, 1, 2 and 3 months. From the obtained data, it is clear that the formulation did not undergo any chemical changes/interaction during the study period.

Conclusion:

In the presented study, Poly acrylic acid aqua cc polymer based superporous hydrogels were formulated by gas blowing method and characterized. From the results of the swelling studies, it was observed that with a decrease in pH from 7.4 to 1.2, a considerable increase in swelling was observed for all the formulations, which may be due to dissociation of the basic groups of aqueous poly acrylic acid, there by increasing the osmotic pressure inside the hydrogels resulting in increased swelling. The findings indicated that the swelling behavior of the SPHs depends on the concentration of poly acrylic acid aqua cc polymer, cross linked Na CMC, N-N methylene bisacrylamide and of sodium bicarbonate. From the results of the de-swelling studies, it was observed that upon changing from acidic to basic medium, there is a decrease in swelling, confirming its pH sensitivity. Generally all formulations demonstrated their applicability *in vitro* as a promising device for pH-dependent gastro retentive delivery of cefditoren pivoxil. This study indicated that superporous hydrogels can be successfully formulated as a gastro-retentive drug delivery device.

CONSENT

As per international standard or university standard, Participants' written consent has been collected and preserved by the author(s)

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References:

1. Chen, J., Blevins, W.E., Park, H., and Park, K. Gastric retention properties of superporous hydrogel composites. J. Control. Release. 2000; 64: 39-51.
2. Qiu, Y., and Park, K.Environment-sensitive hydrogels for drug delivery. Adv. Drug Del. Rev.2001; 53: 321-339.
3. Peppas, N.A., Buresa, P., Leobandunga, W., and Ichikawa, H. Hydrogels in pharmaceutical formulations. Eur. J. Pharm.Biopharm.2000; 50: 27-46.
4. Kost, J., and Langer, R. Responsive polymeric Delivery systems. Adv. Drug Del. Rev.2000; 46: 125-148.
5. Allan, S.H. Hydrogels for biomedical applications. Adv. Drug Deliver. Rev.2000; 43:3-12.
6. Chen, J., Park, H., and Park, K. Synthesis of superporous hydrogels: Hydrogels with fast swelling and superabsorbent properties. J. Biomed. Mater. Res. A.1999; 44: 53–62.
7. Chavada.HV,Patel.CN. Preparation and evaluation of a stomach specific drug delivery system based on superporus hydrogel composite.Indian J.of pharm.Sci.2011; 73:
8. Tang, C., Chunhua Y., Yuanying P., Min Z., and Lifang W. New superporous hydrogels composites based on aqueous Carbopol solution (SPHCcs): synthesis, characterization and in vitro bioadhesive force studies. Eur. Polym. J.2005; 41: 557–562.
9. Assadang, P., Verhoef, J.C., Borchard, G., Sarisuta, N., and Hans, E.J.In vitro evaluation of intestinal absorption of desmopressin using drug-delivery systems based on superporous hydrogels. Int. J. Pharm. 2004; 269: 303-310.
10. Park, H., Park, K., and Kim, D. Preparation and swelling behavior of chitosan-based superporous hydrogels for gastric retention application. J. Biomed. Mater. Res. A.2006; 76: 144-150.
11. Gupta NV, Shivakumar HG. Development of a Gastroretentive Drug Delivery System based on Superporous Hydrogel. Trop. J.Pharm. Res. 2010; 9(3): 257-264.
12.Kumar A, Pandey M, Koshy MK, Saraf S A.Synthesis of fast swelling superporous hydrogel: effect of concentration of crosslinker and Ac-Di-Sol on swelling ratio and mechanical strength. Int. J. Drug. Del. 2010; 2:135-140.