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EFFECT OF POLYMERIC RATIO AND PORE FORMERS ON SUPER POROUS HYDROGEL OF AMOXYCILLIN TRIHYDRATE

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Keywords:

Super porous hydrogel, Gastro retentive, Zero order, Porosity, Higuchi, Korsmeyer-Peppas, Diffusion

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ABSTRACT: The work aimed to prepare super porous hydrogels (SPHs) of Amoxicillin trihydrate to release the drug in a sustained manner in the gastric environment and study the polymeric ratio and pore effect formers on the physicomechanical properties and drug release kinetics of the formulations. Fourier Transform Infra-Red (FTIR) studies were done to check the compatibility of the drug with the polymers. The super porous hydrogel formulations were prepared in two batches (A and B) using sodium chloride and sodium bicarbonate as pore formers, respectively. Scanning Electron Microscopy observed the structural morphology of hydrogel. The presence of a large number of pores with sizes ranging from 1 to 10 µm was revealed, confirming the formation of a super porous hydrogel. As dictated by *in-vitro* dissolution data, the increases in the polymer concentration of HPMC K4M progressively retards and prolongs the drug release; however, no significant change in the effect was observed among NaCl and $NaHCO_3$ pore formers in the super porous hydrogel. The drug release data were fitted into different kinetic models and were found to be best suited by Higuchi and Korsmeyer-Peppas models. Among the eight batches, drug release from is fully governed by quasi-Fickian diffusion ($n < 0.45$).

INTRODUCTION: Hydrogels are cross-linked hydrophilic polymers consisting of acidic, basic, or neutral monomers forming a network structure, which are able to absorb large amounts of water [1]. The swelling properties of hydrogels are mainly related to the elasticity of the network, the presence of hydrophilic functional groups (such as -OH, -COOH, $-CONH_2$, $-SO_3H$) in the polymer chains, the extent of cross-linking, and porosity of the polymer. A variety of stimuli-sensitive hydrogels have been studied, but slow response to environmental stimuli limited their effective uses in many cases.

There are many situations where a rapidly swelling polymer is more desirable. Super porous hydrogels were introduced a decade ago, and their need was strongly felt in the pharmaceutical area [2]. A three-

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dimensional network of a hydrophilic polymer that can absorb a large amount of water in a very short period due to the presence of interconnected microscopic pores with sizes ranging between 10 nm - 10 µm is known as super porous hydrogels (SPHs) [3]. Due to rapid water uptake by the capillary wetting method through these numerous interconnected open pores, super porous hydrogels swell to equilibrium size within a minute. They swell to large sizes and are intended to have sufficient mechanical strength to withstand the pressure of gastric contraction. SPHs must show acceptable stability at low pH (1.2) to remain in the acidic gastric medium for a prolonged time [4].

This unique swelling property and stability in gastric pH allows them to be used as gastric retention carriers providing sustained drug release through long residence in the stomach [5, 6]. SPHs must have various properties like biocompatibility, biodegradability, high swelling capacity, high mechanical strength, and stability in acidic conditions. SPHs must be non-toxic, non-mutagenic, non-allergenic, and non-irritating. Moreover, an instant swelling of the hydrogel has revealed potential application for peroral intestinal peptide and protein absorption [7, 8,] as a diet aid, super disintegrant [9] in cell scaffolding [10] and essential for tissue engineering [11]. SPHs also can initiate the differentiation of embryonic stein (ES) cells [12].

Controlled drug delivery *via* polymer-based systems has been successful in prevailing both in the present and in the future, as having numerous potential advantages for scientific and economic reasons. The thought behind developing Super porous hydrogel was to deliver Amoxycillin trihydrate in the gastric environment in a continual manner for an extensive period to reduce application frequency and to improve bioavailability, safety than marketed conventional formulation.

MATERIALS AND METHODS:

Materials: The materials required for the present work were acquired from diverse sources. The drug (Amoxicillin trihydrate) was provided as a gift sample by Windlas Biotech LTD, Dehradun, India. The other ingredients used were of analytical grade and were used as required.

Methodology:

Pre-Formulation Study:

Identification of Drug-Polymer Compatibility by FTIR: Fourier Transform Infra-red (FT-IR) is used for solid-state characterization of pharmaceutical solids. The identification of the drug was done by (FT-IR) spectroscopic method using Alpha Bruker FTIR spectrophotometer. The drug was mixed with a suitable amount of KBr and converted into discs using KBr press. The disc thus prepared was placed in a sample compartment and scanned in the region of 4000 to 400 cm^{-1}. The IR spectrum of the drug along with polymers and pore formers thus obtained was compared with standard spectra of the drug.

Formulation of Superporous Hydrogels: The polymers HPMC K4M and Sodium alginate was used in different ratios. HPMC K4M and Sodium alginate were first dispersed in double distilled water along with Carbopol 934 p and croscarmellose. In the meantime, the required amount of drug, Amoxicillin trihydrate, was mixed to it. The mixture was stirred in a magnetic stirrer until it became thick. Then the thick mixture was neutralized by drop-wise addition of 50% (w/w) triethanolamine until a transparent gel appeared. Different pore formers were used for different batches: sodium chloride for batch A and sodium bicarbonate for batch B. The amount of triethanolamine was adjusted to prepare gel with desired pH and viscosity. Gels were stored for 24 h at room temperature in order to stabilize.

Evaluation Parameters of the Prepared Superporous Hydrogel Formulations:

Scanning Electron Microscopy Analysis: Dried SPHCs were cut in such a way as to expose the inner structure to be used for SEM studies. The morphology and porous structures of the SPHCs were examined using ZEISS EVO 18, CARL ZEISS MICROSCOPY (PENTA FET X 3) OXFORD INSTRUMENTS with an operating voltage of 10 kV. Images were captured through the use of a digital capture card.

Measurement of Gelation Kinetics: The gelation time can be defined as a period for gel formation following the addition of triethanolamine and measured by a simple tilting method. It was determined by the duration of time taken by the

reactant mixture to become viscous and the viscous solution no longer flowed in the tilted tube position [13].

Water Retention and Swelling Studies: Water retention - The following equation was used to determine the water retention capacity (WRt) as a function of time of exposure at 37 °C.:

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

Where, Wd was the weight of the dried hydrogel, Ws was the weight of the fully swollen hydrogel and Wp was the weight of the hydrogel at various exposure times like 15, 30, and 60 min. Swelling studies- A completely dry, pre-weighed super porous hydrogel was weighed and then immersed in excess of the swelling medium (HCl-KCl buffer pH 1.2). The hydrogel was removed from the solution at various time intervals and weighed after excessive solution on the surface was blotted.

$$Q = (Ms–Md) / Md$$

Where Q is the swelling ratio, Ms the mass in the swollen state and Md the mass in the dried state [14, 15].

Determination of Porosity and Void Fraction

Porosity: Dried hydrogels were dipped overnight in absolute ethanol and weighed after excess ethanol on the surface was blotted. The porosity was calculated from the following equation:

$$Porosity = (M2 – M1) / \rho V$$

Where, M1 and M2 were the mass of the hydrogel before and after immersion in absolute ethanol, respectively; ρ was the density of absolute ethanol and V was the volume of the hydrogel.

Void Fraction: Dried hydrogels were weighed (H1) . The hydrogel was kept in buffer pH 2.2 HCl-KCl buffer at equilibrium, and final weight was taken (H2).

H2 – H1 is the weight of the pores.

The void fraction was calculated from the following equation:

$$Void\ fraction = H2 / (H2-H1)$$ [16]

Density Measurements: The solvent displacement method was used for density measurement. Dried SPHCs were used for density measurements. This helps in determining the apparent densities of the SPHCs. Pieces of SPHCs were taken and weighed to obtain the mass of each piece. A piece of the polymer was immersed in a predetermined volume of n-hexane in a graduated cylinder, and the increase in the volume of n-hexane was measured as the volume of the polymer. The density was calculated from the following equations [17, 18].

$$Density = MSPHC/VSPHC$$

Where, MSPHC is the mass of the SPHC and VSPHC is the volume of solvent displaced by SPHC.

Water Content and Moisture Uptake: Water content - The SPHs were weighed (W1) and then kept in a desiccator for 3 days along with Calcium chloride. The hydrogel was weighed again (W2).

$$\%\ water\ content = \{(W1-W2)/W1\} \times 100$$

Moisture up takes- The initial weight of the hydrogel was taken (W1). The hydrogels were then kept in a desiccator for 3 days along with sodium chloride. The hydrogels were finally weighed after 3 days, the final weight being (W2).

$$\%\ moisture\ uptake = \{(W2-W1)/W1\} \times 100$$ 19

Mechanical Strength: The technique of ascertaining the mechanical strength of SPH involves placing the SPH material between 2 plates, the top plate having cutting boards attached to the bottom surface, and to add weight on the top surface of the top plate. The point that the structural integrity of the SPH gets broken by the weight put, the same weight is taken as the breaking load for mechanical strength [20].

Drug Content Determination: A weight of super porous hydrogel containing 20 mg of drug in 100 ml volumetric flask was treated with about 10 ml hydrochloric acid solution of pH 1.2 mixed well and made up to volume. The mixture was filtered, and 1ml was taken and diluted to 10 ml, and drug content was determined using a UV-Vis spectrophotometer at 223 nm.

***In-vitro* Release Studies:** *In-vitro* drug release of Amoxicillin trihydrate from the super porous hydrogels was evaluated in triplicates at 37 ± 0.5

°C using a United States Pharmacopoeia (USP) Dissolution Test Apparatus Type 1 (Rotating Basket Apparatus) at a rotation speed of 50 rpm in 900 ml of 0.1 M HCl (pH 1.2) for 6 h. For this study, the capsule filled with hydrogel was kept into the basket, and at regular time intervals, 5 ml of the dissolution medium were withdrawn, replaced with an equivalent volume of fresh dissolution fluid, and analyzed for the drug using a UV-Vis spectrophotometer (UV-1700, Shimadzu, Japan) at 223 nm [21, 22, 23].

Stability Study: Formulations were subjected to stability testing as per ICH norms. The super porous hydrogel was filled in clean, lacquered, collapsible aluminium tubes and was kept at 40 °C and 75% RH in a humidity chamber. The super porous hydrogel was assessed for change in appearance, drug content, and in vitro release profile at an interval of 1, 2, and 3 months [24].

RESULTS AND DISCUSSION: Drug excipient interaction is an important study before the development of any formulations. Among the various methodologies available to study the drug - excipients interaction, common approaches are - FTIR Spectroscopy, DSC and IR Spectra, *etc.* FTIR Spectroscopy shows the interaction between the molecules at the level of functional groups. Here, drug excipients interaction was done using FTIR Spectroscopy **Fig. 1.** It was observed from the FTIR Spectra that there might be some physical interactions due to the generation of weak bonds as no such shifting of the peaks was marked.

The drug (Amoxicillin trihydrate) gives characteristic peaks of IR spectra in the ranges 3400-3500 cm^{-1} (Amine -NH), 3200-3550 cm^{-1} (Phenol -OH), 2850-3000 cm-1(Methyl -CH stretch), 2500-3300 cm^{-1} (Carboxylic acid -OH) and 1720-1740 cm^{-1} (-CO stretch). FTIR study of drug-excipient mixture did not show any major shift of peaks, suggesting no major interaction between drug and excipient. There may be some minor interaction due to the generation of weak hydrogen bonds. The rate of diffusion of drug molecules can be changed by changing entanglement in the polymeric network by using a blend of polymer mixtures. This leads to a change in the diffusion rate of drug molecules by varying the entanglement in the polymeric network, which leads to the change of tortuosity of diffusion pathways [25]. Thus the interaction might be helpful in sustaining the release of drug molecules from the experimental formulations.

The super porous hydrogel of Amoxicillin trihydrate was developed in different ratios of HPMC K4M and sodium alginate along with Carbopol 934p. After the experiments with polymers and observing their consistency, eight polymeric compositions were considered for entire studies which are discussed in **Table 1.** Swelling studies were conducted at pH 1.2 HCl-KCl buffer amongst the batches A (D1, D2, D3, D4) and B (D5, D6, D7, D8) showed comparatively more percentage of weight gain as the ratio of HPMC K4M to sodium alginate is increased. The observations also showed less weight gain in batch B (in which $NaHCO_3$ was used as pore former) as compared to batch A (using NaCl). The hydrophilic polymer like HPMC comes in contact with water; it absorbs water & swells to form a gel layer, making barriers to drug diffusion. The mechanism of drug release from this type of formulation involves solvent penetration, hydration, swelling, and diffusion of the drug.

The super porous hydrogel structure is used as the carrier for the drug; therefore, desirable gastric retention can be achieved only if it possesses adequate strength to resist the forces in the environment. Such forces are being achieved by the addition of Ac- Di- Sol to give a proper structure. Sodium Chloride or Sodium bicarbonate has been used in the formulations as pore-forming agents, which will make it a successful super porous hydrogel form.

Polymer-water interactions are important and serve as the basis for the swelling process in all types of hydrogels. When the SPH is placed in water or other aqueous solutions, the swelling process begins, which continues until each of the functional groups is surrounded by the same amount of water. This process is first dominated by the attractive forces of the hydrophilic and ionic functional groups in the hydrogel structure. As water tries to dilute the polymer chains further, an osmotic effect is created that continues to fill open pores with water until opposed by the contractive forces of the cross-linked hydrogel structure.

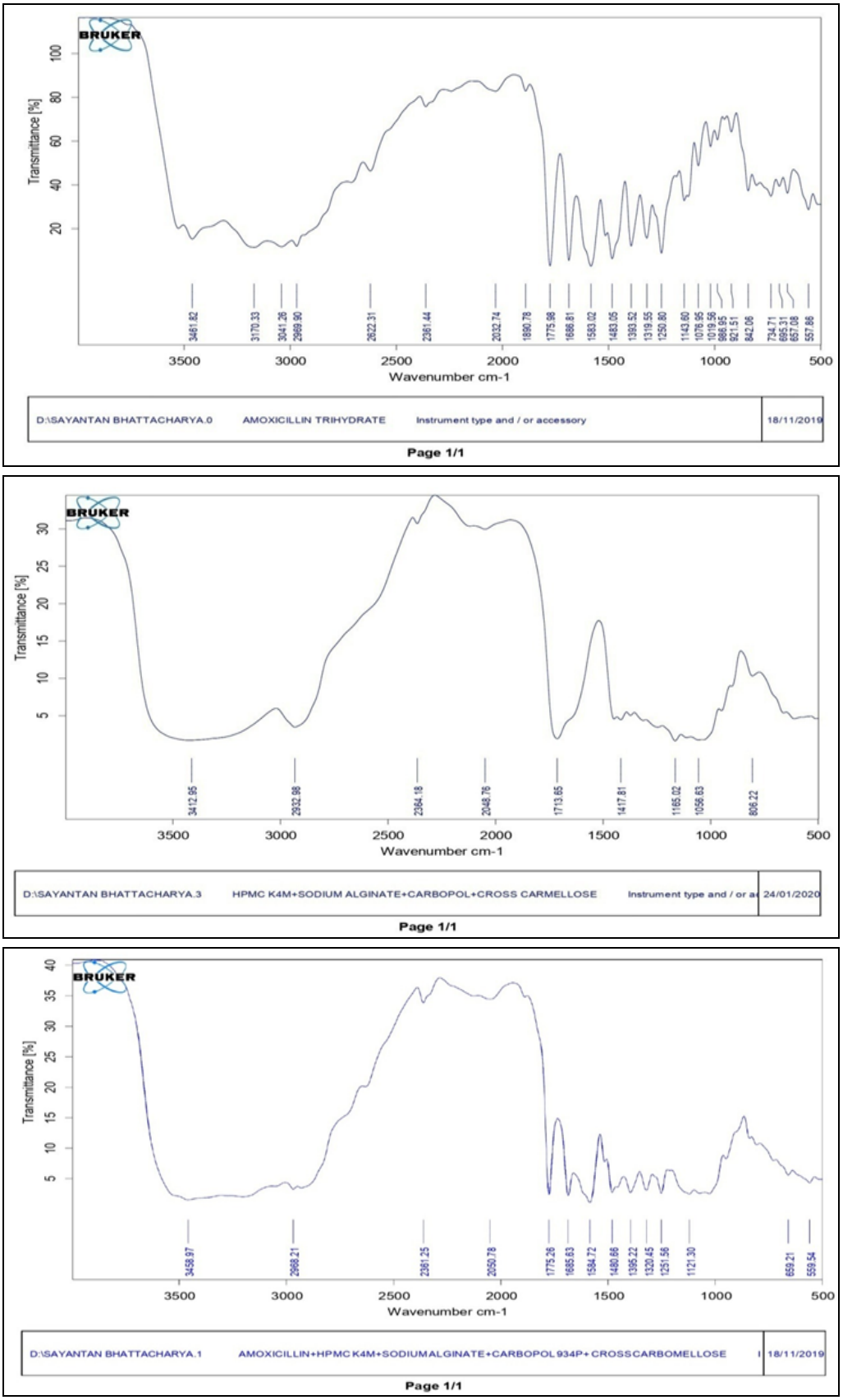

FIG. 1: FTIR OF DRUG, POLYMER MIXTURE, AND DRUG + POLYMER MIXTURE

The structural morphology of hydrogels was investigated by SEM, and some representative SEM micrographs are given in **Fig. 2**. It was found that plenty of pores were formed. The pores are within the size ranges of 1 μm to 10 μm.

TABLE 1: FORMULATION TABLE OF THE SUPER POROUS HYDROGEL

S. no.	Batch	Formulation no.	HPMC K4M :Sodium alginate	Carbopol 934p (mg)	Croscarmellose (mg)	Triethanola mine (ml)	Pore formers
1		D1	2:1	30	20	0.5	
2	A	D2	3:1	30	20	0.5	NaCl
3		D3	4:1	30	20	0.5	(5mg)
4		D4	5:1	30	20	0.5	
5		D5	2:1	30	20	0.5	
6	B	D6	3:1	30	20	0.5	$NaHCO_3$
7		D7	4:1	30	20	0.5	(5mg)
8		D8	5:1	30	20	0.5	

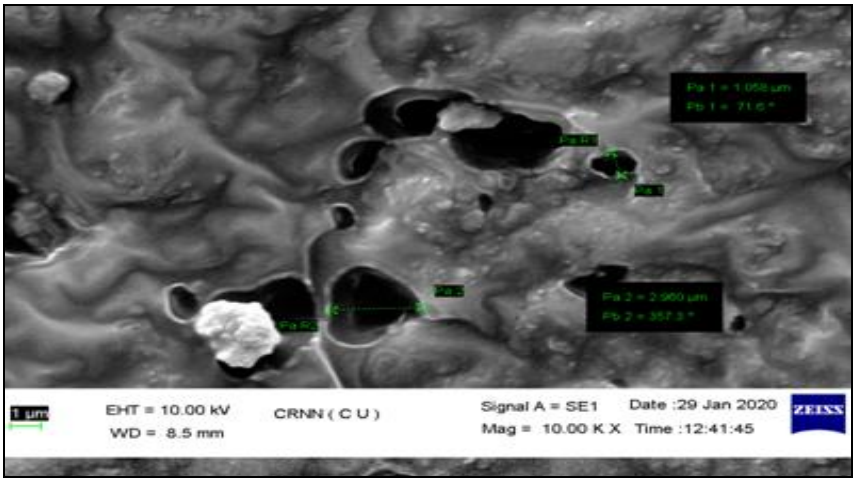

FIG. 2: SCANNING ELECTRON MICROSCOPY PHOTOGRAPH OF SUPER POROUS HYDROGEL AT X 10000 OF FORMULATION D4

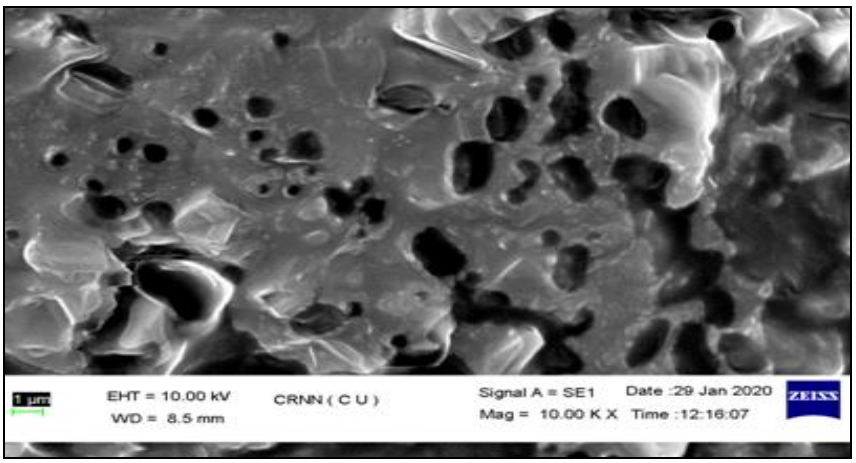

FIG. 3: SCANNING ELECTRON MICROSCOPY PHOTOGRAPH OF SUPER POROUS HYDROGEL AT X 10000 OF FORMULATION D8

Increasing the HPMC K4M and Sodium alginate ratio results in better gelation kinetics and shows satisfactory gelation time and flow time as shown in **Table 2.** The best gelation kinetics is shown by formulation D1 (4:1). However, formulation D4 (5:1) shows unsatisfactory results. In the case of water retention tests, a greater ratio of HPMC and Sodium alginate does not correlate with water retention, with formulation D5 (3:1) showing the best water retention results. For swelling studies it was found that formulation D1 (4:1) shows the best swelling index. The use of sodium chloride as pore former shows a better swelling index than sodium bicarbonate; however, hydrogels with sodium bicarbonate show better water retention properties. Since the SPH possesses lots of pores, their density should be lower compared with conventional hydrogels. As shown in **Table 2**, all of the SPH formulations have a density less than 1 gm/cm^3. The density of the SPH formulations depends on

the ratio of HPMC K4M, and sodium alginate, as higher ratios generally show greater density. Porosity was generally found to be higher in the formulations, where the ratio HPMC K4M and Sodium alginate were higher. The void fraction was found to be independent of the ratio of HPMC K4M and sodium alginate in the formulations. These are presented in **Table 2.** Observations show that the water content of the SPHs is not related to the type of pore former or to the HPMC K4M: Sodium alginate ratio. Moisture uptake is higher amongst batch A formulations in which NaCl was used as pore former **Table 3.** The mechanical strength of the formulations was found to be between 245-320 gm **Table 2.** For a gastric retention device, the swollen SPH should be strong enough to withstand repeated peristaltic contractions. The mechanical load gets shared between Ac-Di-Sol fiber and the polymer structure. So as the polymer ratio of HPMC is increased, the mechanical strength also increases. The drug content of the SPH formulations was found to be within 99.6-99.8%.

TABLE 2: OBSERVATION OF GELATION TIME, FLOW TIME, POROSITY, VOID FRACTION, DENSITY AND MECHANICAL STRENGTH OF THE SPHS

Formulation no	Gelation time (secs)	Flow time (secs)	Porosity	Void fraction	Density (g/cm3)	Mechanical strength (gm)
D1	180	5	0.424	3.31	0.445	255 ± 5
D2	180	6	0.288	3.711	0.525	280 ± 2
D3	240	9	0.364	3.186	0.825	300 ± 2
D4	300	18	0.432	6.593	0.9	310 ± 4
D5	60	3	0.318	4.536	0.465	245 ± 4
D6	180	7	0.251	5	0.66	290 ± 4
D7	300	8	0.409	4.486	0.85	305 ± 2
D8	300	15	0.441	3.869	0.865	320 ± 5

TABLE 3: OBSERVATION OF WATER RETENTION, SWELLING INDEX, % WATER CONTENT AND % MOISTURE UPTAKE OF THE SPHS

Formulation No	Water Retention (N=3) ± Sd	Swelling Index (N=3) ± Sd	% Water Content (N=3) ± Sd	% Moisture Uptake (N=3) ± Sd
D1	0.682 ± 0.03	0.880 ± 0.01	18.27 ± 0.15	45.12 ± 0.3
D2	0.778 ± 0.04	1.14 ± 0.03	17.01 ± 0.1	35.66 ± 0.1
D3	0.667 ± 0.04	1.14 ± 0.01	16.39 ± 0.1	49.89 ± 0.4
D4	0.733 ± 0.05	1.04 ± 0.02	24.49 ± 0.2	50.84 ± 0.3
D5	0.812 ± 0.07	0.52 ± 0.04	13.06 ± 0.2	23.17 ± 0.2
D6	0.852 ± 0.02	0.991 ± 0.04	19.6 ± 0.2	28.74 ± 0.2
D7	0.815 ± 0.04	0.93 ± 0.01	21.01 ± 0.1	40.58 ± 0.1
D8	0.605 ± 0.03	0.997 ± 0.02	8.512 ± 0.2	26.47 ± 0.4

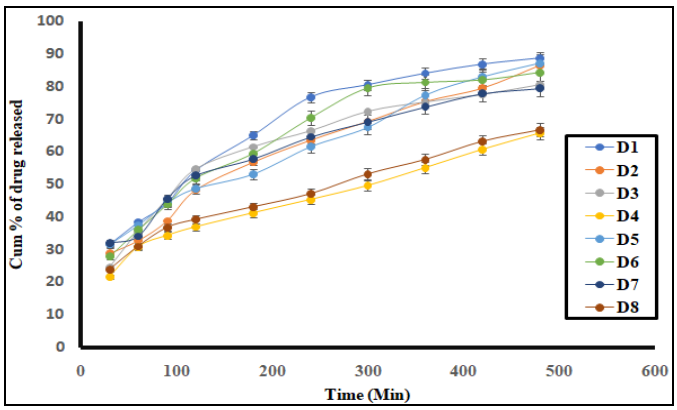

FIG. 4: DRUG RELEASE PROFILE OF THE FORMULATIONS IN BUFFER PH-1.2 (± SD, N=6)

The super porous hydrogel formulations were subjected to drug release studies. As dictated by *in-vitro* dissolution data, the increases in the polymer concentration of HPMC K4M progressively retards and prolong the drug release. Formulation D4 and D8 (HPMC K4M: Sodium alginate = 5:1) shows 65.72% and 78.64% of cumulative drug release respectively after 7 h, which are the slowest drug release amongst the formulations. Meanwhile D2 and D7 (2:1) shows 94.66 and 98.29% of cumulative drug release in 5 h and 6 h respectively, which are the fastest releasing formulations **Fig. 5.** So it can be stated that the ratio of two polymers are responsible for maintain the drug release from the formulations however pore formers NaCl and $NaHCO_3$ are almost same in action here.

To investigate the drug release mechanism, the data were evaluated by kinetic models representing

Zero-order, Higuchi and Korsmeyer-Peppas **Table 4.** The cumulative percent of drug released versus time plot exhibits curvilinear nature. This suggests that drug release is not governed by zero-order kinetics. This observation is confirmed by fitting the dissolution data to a zero-order model where comparatively low values of correlation coefficients (R^2) are obtained. The results of the above-mentioned studies show that drug releases from the super porous hydrogels are much more acquainted with Korsmeyer–Peppas and Higuchi models. The experimental data were fitted to Korsmeyer-Peppas exponential equation $Mt/M\alpha = Ktn$, [$Mt/M\alpha$ = the fractional drug release into the dissolution medium, K = a constant , n = diffusional exponent]. The present study observed (Table 4) that the n varies from 0.2 to 0.4, represents a change in the drug transport mechanism. It is due to the change in the polymeric ratio. Among the eight batches, drug release is fully governed by quasi-Fickian diffusion ($n < 0.45$) [26].

TABLE 4: COMPARISON OF THE R^2 VALUES OF THE VARIOUS RELEASE KINETICS FROM THE DIFFERENT FORMULATIONS

Formulation	Zero order	Higuchi	Korsmeyer Peppas	
	R^2	R^2	R^2	n
D1	0.934	0.944	0.973	0.346
D2	0.973	0.990	0.975	0.382
D3	0.946	0.991	0.984	0.345
D4	0.964	0.983	0.975	0.302
D5	0.913	0.986	0.997	0.279
D6	0.979	0.994	0.981	0.308
D7	0.978	0.997	0.992	0.396
D8	0.880	0.970	0.984	0.343

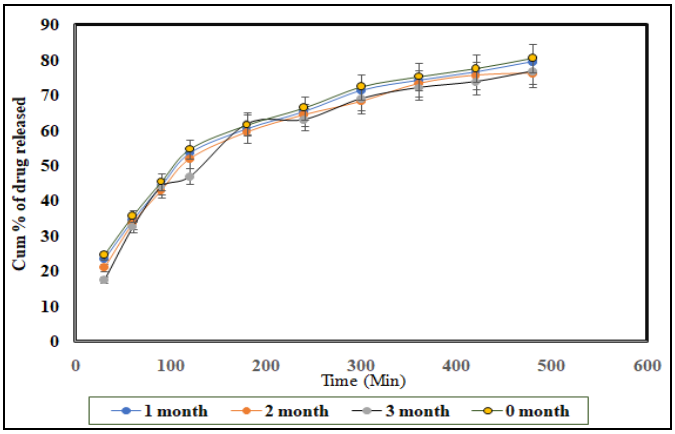

FIG. 5: DRUG RELEASE PROFILE FROM THE FORMULATIONS IN BUFFER PH-1.2 IN RESPECT TO STABILITY STUDY AT 1, 2 AND 3 MONTH INTERVAL

The drug release profile may be easily attributed to the swelling properties of the super porous hydrogels. This study demonstrates that super porous hydrogels of Amoxicillin trihydrate may be suitable for use as a gastro retentive drug delivery system. During stability studies, the formulation appeared to be off-white, hard. It was also noted from the studies that there were no considerable changes in drug content as well as the cumulative percent of drug release. Therefore, no evidence of degradation of the drug was reported. Drug release profiles prior and after 3-month stability study of formulation D3, similarity factor (f2) was calculated **Fig. 5.** The similarity factor was found to be f2 68.09 (>50). As a similarity factor greater than 50 indicates the good stability of the product, in view of this, it can be mentioned that the formulation was stable over the period of 3 months [27].

CONCLUSION: Controlled drug delivery via polymer-based systems achieved profound success for prevailing both in the present and in future work. The thought behind developing Super porous hydrogel was to deliver Amoxycillin trihydrate in the gastric environment in a continual manner for prolonged periods to reduce the frequency of administration. HPMCK100M, HPMC K4M, Carbopol 934p have been employed along with Sodium alginate for the formulations. NaCl and NaHCO3were introduced as pore formers and Ac-DiSol or Croscarmellose to increase the physical cross-linking of polymer chains to fix it. SEM photographs of the formulations clearly indicated the formation of a number of pores confirming it as a super porous hydrogel. A significant variation is observed in the *in-vitro* release pattern of Amoxycillin trihydrate from the SPH in relation to change the ratio of HPMC K4M and Na-alginate. In the present study, it was observed that the n

varies from 0.2 to 0.4 represents a change in the drug transport mechanism. It is due to the change in the polymeric ratio. Among the eight batches, drug release is fully governed by quasi-Fickian diffusion ($n < 0.45$) prospect to get a clear picture of IVIVC.

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