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PREPARATION AND CHARACTERIZATION OF SUPERPOROUS HYDROGELS AS GASTRORETENTIVE DRUG DELIVERY SYSTEM FOR ATENOLOL

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ABSTRACT: Gastro-retentive drug delivery system can retain the drug in the gastric region for several hours which enhances drug release and improves bioavailability. Atenolol, an antihypertensive drug has a short half-life, limited bioavailability, highly unstable at basic pH and is extensively absorbed from the stomach. These features triggered the need for developing the gastro-retentive system. In the present study, a superporous hydrogel was developed as a gastro-retentive drug delivery system. Chitosan/poly (vinyl alcohol) interpenetrating polymer network (IPN) type superporous hydrogels were prepared using a gas foaming method employing glyoxal as the cross-linking agent. Sodium bicarbonate was used as a foaming agent to introduce the porous structure. Swelling behaviors of the superporous hydrogel in acidic solution were studied to investigate their applications for gastric retention device. The optimum preparation condition of superporous hydrogels was obtained from the gelation kinetics. SPH tablets of atenolol were prepared by direct compression incorporating microcrystalline cellulose, magnesium stearate, talc and sodium bicarbonate, *etc*. and evaluated. The super porous hydrogels were highly sensitive to pH of swelling media and showed fast swelling and good porosity. SPH tablets of atenolol showed good pre-compressional and post-compressional properties. Formulation IV containing chitosan (160 mg), glyoxal (400 mg) and polyvinyl alcohol (400 mg) exhibited good swelling ratio and sustained release of drug throughout 12 h through gastro-retention. Compatibility studies proved the integrity of the developed tablets. Stability studies indicated that optimized formulation is stable. Thus the superporous hydrogel tablets of atenolol have been successfully prepared with prolonged drug release to enhance bioavailability of the drug.

INTRODUCTION: Oral controlled drug delivery systems release drug from the systems predictably and reproducibly and achieve better bioavailability of basic drugs that have poor solubility at higher pH as well as drugs that have short elimination half-lives [1].

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A major problem encountered with oral formulations is the inability to increase their retention time in the stomach and proximal part of small intestine [2].

About 80% of administered drugs are excreted without being absorbed [3]. Under these conditions, it becomes necessary to prolong the residence time of drug in the stomach and upper part of the small intestine which prolongs overall gastrointestinal (GI) transit time of drug [4]. There are several approaches have been reported for prolonging the residence time of drug delivery system in a

particular region of the gastrointestinal tract, such as floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, swelling and expanding systems, modified shape systems, high-density systems, and other delayed gastric emptying devices [5]. Superporous hydrogels are one of the promising approaches for gastro-retention.

Hydrogels are cross-linked hydrophilic polymers with a network structure consisting of acidic, basic, or neutral monomers which can absorb large amounts of 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, $-CONH_2$, $-SO_3H$) 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 limited their effective uses [6]. Although such slow swelling is beneficial for many applications, there are many situations where a fast swelling 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), which swell to an equilibrium size in a short period [7].

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 due to the presence of interconnected microscopic pores. When applied as drug carriers, these highly swollen hydrogels remain in the stomach for a long time, releasing almost all loaded drugs since their volumes are too big to transport through the pylorus and their sheer bulk hinder their transport to the next organ via the narrow pylorus. This unique swelling property allows them to be used as gastric retention carriers providing a sustained release through long residence in the stomach. To be used as an effective gastric retention device, the hydrogels are required to possess not only fast swelling but also following properties such as biocompatibility, biodegradability, high swelling capacity, and stability in acidic condition [8].

Chitosan, a natural polysaccharide, is a biocompatible, biodegradable, and non-toxic material. Because chitosan has abundant amine groups within the polymer chain, it dissolves in an acidic solution and forms a gel with dialdehydes such as glutaraldehyde and glyoxal. Thus, in the low pH solution, chitosan hydrogels swell due to the presence of the positive charges in the network [9]. Poly (vinyl alcohol) (PVA) is a well known hydrophilic, biocompatible, and commercially available polymer.

Atenolol is a beta-adrenoreceptor antagonist or more commonly known as a beta-blocker used in the treatment of hypertension and angina pectoris. The human jejunal permeability and the extent of absorption is low thus It has an oral bioavailability of only 50%, while the remaining is excreted unchanged in feces. It undergoes little, or no hepatic first-pass metabolism and its short elimination half-life are 3 to 4 h favors development of a gastro-retentive superporous hydrogel tablets to improving its oral bioavailability [10].

The interpenetrating polymer network (IPN) of chitosan superporous hydrogel was strengthened by polyvinyl alcohol (PVA) and prepared using a freeze-drying/gas blowing technique and glyoxal as a crosslinking agent [11]. The applications of the superporous hydrogels prepared in gastric retention devices were investigated by measurement of their swelling properties. Emphasis was made upon the high swelling capacities with a focus on stimuli-sensitive swelling and water-retention capacities which were highly demanded when the polymers are developed as a potential drug delivery system.

MATERIALS AND METHODS:

Materials: Atenolol was obtained as a gift sample from Zydus Cadila, Mumbai. Chitosan was purchased from Molychem, Mumbai. Sodium bicarbonate (Poona chemical laboratory, Pune), Glyoxal (10% water solution, Aldrich, Steinheim, Germany) and PVA (Molychem, Mumbai) were used in this study. All other reagents were of analytical grade.

Methods:

Synthesis of Superporous Hydrogels: A 2% w/w stock solution was prepared by dissolving chitosan in 0.1M acetic acid. A 10% w/w aqueous PVA solution was also prepared. The chitosan and PVA

solutions were mixed in the way that to have different compositions. Each chitosan / PVA mixture was placed in a test tube, and its pH value was adjusted to 5.0 by addition of acetic acid. A glyoxal aqueous solution, 10% w/w, was added to each chitosan / PVA mixture. To the stock solution, was added 80 mg of sodium bicarbonate powder and the mixture was stirred vigorously to induce the gelation and foaming reactions, simultaneously. The foamed hydrogels were left to stand overnight at room temperature. The hydrogels were frozen in a deep freeze-drier at -60 °C for 12 h. After freeze-drying, the samples were removed from the freeze-drier and thawed at room temperature for 4 hrs. Ten formulations were prepared by changing the amount of the ingredients as shown in **Table 1**.

TABLE 1: FORMULATION OF SUPERPOROUS HYDROGEL

Ingredients (mg)	Formulation									
	I	II	III	IV	V	VI	VII	VIII	IX	X
Chitosan (2% w/v)	40	80	120	160	80	80	80	80	80	80
Polyvinyl alcohol (10% w/v)	400	400	400	400	200	600	800	400	400	400
Glyoxal (10% v/v)	400	400	400	400	400	400	400	200	600	800
Sodium bicarbonate	80	80	80	80	80	80	80	80	80	80
Atenolol	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500

SPH BEFORE FREEZE DRYING **SPH AFTER FREEZE DRYING**

FIG. 1: PREPARATION OF SUPERPOROUS HYDROGEL

Formulation of SPH Tablets: Tablets were formulated by using the amount of SPH equivalent to 100 mg of atenolol, microcrystalline cellulose, sodium bicarbonate, magnesium stearate, talc, *etc*. All ingredients were triturated one by one in mortar and pestle for uniform mixing of all ingredients. The blend obtained was then directly compressed to form uniform tablets.

TABLE 2: FORMULATION OF SPH TABLETS OF ATENOLOL

Ingredients (mg)	I	II	III	IV	V	VI	VII	VIII	IX	X
Atenolol*	116.68	105.17	96.25	91.28	128.61	125.73	108.41	128.41	119.5	112.83
Microcrystalline cellulose	61.32	72.83	81.75	86.72	49.39	52.27	69.59	49.59	58.5	65.17
Sodium bicarbonate	16	16	16	16	16	16	16	16	16	16
Magnesium stearate	4	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200	200	200

*indicates the amount of SPH equivalent to 100 mg of atenolol

Characterization of Superporous Hydrogel: Superporous hydrogel can be characterized by the following parameters:

Physical Appearance: The prepared hydrogels were inspected visually for clarity, color, and presence of any particles.

Percent Yield of SPH: Percent yield describes how much of material was obtained after freeze-drying of SPH compared to how much was kept for freeze drying. It can be calculated by the formula,

$$\text{Percentage yield} = \frac{\text{Weight of sample after drying}}{\text{Weight of sample before drying}} \times 100$$

Drug Content of SPH: Drug content of Superporous hydrogel was measured to know how much amount of drug is present in a particular amount of Superporous hydrogel.

Superporous hydrogel required amount was taken in 100 ml volumetric flask. About 10 ml of buffer is added, mixed well and made up to volume. This mixture was filtered, and drug content was measured using UV visible spectrophotometer at the appropriate wavelength.

Gelation Kinetics: As polymerization reaction proceeds, viscosity continuously increases until full 0network gel structure is formed. Gelation time gives information about the introduction time of blowing into the formulation. Gelation time was measured by simple tilting method after adjustment of pH to 5.0 with acetic acid. It is determined by the duration of time taken reactant mixture to become viscous and henceforth viscous solution no longer falls in tilted tube position [12].

Swelling Studies: Superporous hydrogels characterized by swelling properties. Swelling studies included swelling time and swelling ratio.

Swelling Time: Swelling time is time taken by the hydrogel to attain its equilibrium swelling point where swelling is stopped. Swelling is mostly measured gravimetrically and volumetrically; a texture analyzer is used to measure swelling time. Dried SPH was allowed to hydrate more than swelling medium (25 ml) at room temperature. At various time intervals, the hydrogel was removed from the solution and weighed after excess solution on the surface was blotted.

Swelling Ratio: The dried SPH was allowed to hydrate more than deionized distilled water at room temperature. The weight of the hydrating sample was measured at time intervals after excess water was removed by gentle blotting. The formula calculated the swelling ratio,

$$Q_s = W_s - W_d \times 100 / W_d$$

Where Q_s is swelling ratio; W_s is the weight of swelled hydrogel and W_d is the weight of dried hydrogel [13].

Density Measurement: The solvent displacement method was used. Dried SPH was used for density measurement which shows the apparent density of SPHC. A piece of SPH was taken and weighed to determine the mass of piece. A piece of the polymer was immersed in a predetermined volume of hexane in a graduated cylinder, and the increase in the hexane volume was measured as the volume of the polymer. The density was calculated as,

$$\text{Density} = M/V$$

Where M is a mass of SPHC and Vis volume of solvent displaced by SPHC [14].

Porosity Measurement: Solvent replacement method is used. Dried SPHC was immersed overnight in absolute ethanol. It absorbed ethanol, and swollen, which then weighed after excess ethanol on the surface was blotted. The porosity was calculated from the formula,

$$\text{Porosity} = M2 - M1 / \rho V$$

Where M1 and M2 are mass of hydrogel before and after immersion in absolute ethanol and V is the volume of the hydrogel, ρ is the density of absolute ethanol. The total volume of SPHC can be measured from its dimensions, as it is cylindrical [15].

Measurement of Void Fraction: Void fraction was measured by immersing hydrogels in hydrochloric acid buffer (pH-1.2). Dimensions of swollen hydrogels were measured and by using these data, sample volumes were determined as dimensional volume. In the meantime, amount of absorbed buffer into hydrogel was determined by subtracting the weight of dried hydrogel from the weight of swollen hydrogel, and resulting values were assigned as the total volume of pores in hydrogels**.** Void fraction calculated by formula [16].

$$\text{Void fraction} = \frac{\text{Dimentional volume of SPHC}}{\text{The total volume of pores}}$$

Water Retention: The following formula was used to determine the water retention capacity (W_{rt}) as a function of time at 37 ºC,

$$Wrt = \frac{W_p - W_d}{W_s - W_d} \times 100$$

Where W_d is the weight of dried hydrogel; W_s is the weight of fully swollen hydrogel and W_p is weights of the hydrogel at various exposure times [15].

Morphological Analysis: SEM was performed to identify the morphology of a dried superporous hydrogel. The samples were coated with gold using Hummer sputter coater (Techniques, Ltd.), then

carried using a Jeol JSM-840 scanning electron microscope (Jeol USA, Inc., Peabody, MA), and captured the images using a digital capture card and Digital Scan Generator 1 (Jeol).

Characterization of Tablets: The formulated tablets were evaluated for parameters like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, tablet dimensions, hardness, friability, weight variation, uniformity of content, in vitro drug release profiles were determined as per following procedure.

Pre Compressional Parameter:

Angle of Repose: Angle of repose depends upon interparticulate friction and cohesion. It helps to evaluate powder flowability by assessing interparticulate friction. In general, the higher is the angle of repose poor is the flowability of the powder. The angle of repose of the granules was determined using the funnel method suggested by Neumann. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured, and the angle of repose was calculated by using formula,

$$\theta = \tan^{-1} h/r$$

Where *h* is height and *r* is the radius of a pile of powder.

Bulk Density: Bulk density is the ratio of mass and bulk volume. It may influence compressibility, tablet porosity, dissolution, and other properties and is dependent on particle size, shape and tendency of particles to adhere together. It helps to decide appropriate packing of the dosage form. Accurately weighed 20 g granules were allowed to flow in a fine stream into a graduated cylinder and final volume was noted.

$$\text{Bulk density} = \frac{\text{Bulk mass}}{\text{Bulk volume}}$$

Tapped Density: 20 gm blend was allowed to flow in a fine stream into a graduated cylinder of a mechanical tapping device. The measuring cylinder was tapped for 100 times, and final tapped volume was noted. The tapped density was obtained by dividing the weight of the sample in grams by final tapped volume in $cm^{3,}$ and it was calculated by using formula,

$$\text{Tapped density} = \frac{\text{Bulk mass}}{\text{Tapped volume}}$$

Carr's Index: Carr's index evaluates interparticulate cohesive properties with the angle of repose measurements and studies the effects of packing geometry of solids with bulk and tapped density. Carr has developed an indirect method of measuring powder flow from bulk densities. The percentage compressibility of powder was a direct measure of the potential powder arch or bridge strength and stability. The formula calculated Carr's index of each formulation,

$$\text{Carr's} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio: It is essential to determine the compressibility strength of powder. Hausner's ratio is a simple method to evaluate the stability of the powder column and to estimate flow properties. Hausner's ratio was calculated using formula [17],

$$\text{Housner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \times 100$$

Post Compressional Parameter:

Tablet Dimensions: Thickness and diameter of tablets were important for uniformity of tablet size. If the tablet has no much variation in thickness in each formulation, is indicate that powder blends are consistent in particle size and uniform behavior during the compression process. Thickness and diameter were measured using Vernier caliper. Average values of tablet thickness and diameter are reported.

Hardness: Tablet hardness was measured regarding kg/cm^2. The resistance of tablets to shipping or breakage under conditions of storage, transportation, and handling before usage depends on its hardness. For each formulation, the hardness of five tablets was checked using the Monsanto hardness tester. The tester consists of a barrel containing compressible spring held between two plungers. The lower plungers placed in contact with the tablet, and a zero reading was taken. The upper plunger was then forced against spring by turning a

threaded bolt until the tablet fractured. As the spring was compressed, a pointer ride along a gauge in the barrel indicates the force. Force of fractured was recorded, and the zero force reading was deducted from it. Average values of hardness are reported.

Friability: Friability is the measure of tablet strength. Roche friabilator was used for testing the friability 20 tablets were weighed separately and placed in the drum that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min the tablets were weighed, and the percentage loss in tablet weight was calculated using formula,

$$\% \text{ Loss} = \frac{W_o - W_f}{W_f} \times 100$$

Where W_0 is the initial weight of tablets and W_f is finals weight of tablets.

Uniformity of Weight: Uniformity of weight helps to ensure uniformity of dosage forms. It is the simplest way to assess variation in drug dose and helps in quality control procedure during tablet production. The test was performed on 20 tablets. Each tablet was weighed individually using an electronic balance. The average weight was calculated, and individual tablet weight was compared with the average value, and the deviation was recorded.

Uniformity of Content: Drug content is determined to check dose uniformity in the formulation. Total 20 tablets were weighed and powdered. The stock solution was prepared by dissolving drug powder equivalent to 10 mg in 10 mL water. The stock solution was shaken for 20 min on a Sonicator.

This resulting solution was further diluted with water to achieve concentration up to 10µg/mL, and the absorbencies were measured at the 222 nm [18].

***In-vitro* Dissolution Study:** The *in-vitro* dissolution study was carried out using USP apparatus type II at 50 rpm. The dissolution medium was 900 ml hydrochloric acid buffer (pH-1.2) maintained at 37 ± 0.5 ºC. Aliquots of dissolution medium were withdrawn at predetermined intervals and content of atenolol was determined at 222 nm spectrophotometrically. The dissolution experiments were conducted in triplicate [19].

Stability Studies: FDA and ICH specify the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. Stability studies on promising formulation were carried out by storing the tablets at 40 ºC / 75% relative humidity throughout three months according to ICH guidelines.

The sample was withdrawn at predetermined time intervals of 0 (initial), 30, 60 and 90 days. At the end of three months, the time interval the tablets were examined for any physical changes, changes in drug content, hardness, and *in-vitro* dissolution studies.

Compatibility Studies:

Fourier Transform Infrared (FT-IR) Spectroscopic Studies: FTIR studies were done to assess whether any possible interaction among drug, the polymer is done by FTIR spectrophotometer (Jasco-4100). Infrared spectrums of pure drug, a physical mixture of ingredients of the formulation were recorded. From the overlay spectrum analysis, the compatibility of ingredients in the formulations was found out. Pure, completely dried KBr is used as blank and before every running of a sample, it was mixed thoroughly with KBr at a ratio of sample to KBr 100:1 and then the spectrum was scanned over a wave number range from 4000 - 400 cm^{-1}.

Differential Scanning Calorimetry Studies (DSC): DSC of Atenolol, freeze-dried optimized hydrogel batch were obtained using DSC (DSC 60 Schimadzu) equipped with an intercooler. A platinum crucible used with alpha alumina powder as a reference to calibrate the DSC temperature and enthalpy scale. The powder samples were hermetically kept in the aluminum pan and heated at a constant rate of 10 °C per min, over a temperature range of 35 °C to 200 °C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 150 ml/min.

Powder X-ray Diffraction Studies (PXRD): The powder X-ray diffraction patterns were recorded using an X-ray Diffractometer (PW1729. Philips, Netherland) with Cu as an anode material and

crystal graphite on ochromator operated at a voltage of 30 kV and a current of 30 mA. The samples were analyzed in the 2θ angle range of 2 to 50º. The range and the chart speed were 5×10^3 CPS and 10 m/2θ, respectively.

Stability Studies: Stability studies of optimized Batch-IV were carried out as per ICH guidelines at specific conditions of temperature (40 ºC) and relative humidity (75%) for three months. The sample was withdrawn 30 days and evaluated for drug content, percent drug release, Differential scanning calorimetry analysis and Powder X-ray diffraction analysis.

RESULTS AND DISCUSSIONS:

Characterization of Superporous Hydrogel: Superporous hydrogel was characterized for its various physical properties as follows:

Physical Appearance: The prepared SPH observed white, opaque with the absence of particulate matter. There were no visible particles present in SPH indicating that drug was not precipitated.

TABLE 3: CHARACTERIZATION OF SUPERPOROUS HYDROGEL

Batch code	Parameters							
	Percent yield (%)	Drug content (%)	Gelation time (sec)	Swelling time (min)	Swelling ratio	Density (g/cc)	Porosity (%)	Void fraction (%)
I	21.55±0.14	85.70±0.00	30.33±0.57	5.03±0.05	103.33±5.20	0.51±0.02	3.97±0.23	5.81±1.99
II	17.77±0.19	94.74±0.57	35.00±1.00	5.00±0.00	124.33±3.21	0.51±0.02	4.25±0.17	4.04±0.41
III	14.70±0.47	103.89±0.01	30.00±0.00	5.00±0.00	143.33±2.88	0.24±0.00	8.50±0.34	3.88±0.66
IV	11.49±0.24	109.55±0.00	15.33±0.57	5.00±0.00	184.00±8.71	0.27±0.00	10.35±0.17	3.75±0.23
V	21.41±0.25	77.75±0.27	23.00±1.00	5.00±0.00	116.66±5.85	0.48±0.02	17.32±7.35	3.58±0.40
VI	15.25±0.17	79.53±0.26	19.66±1.52	4.96±0.05	108.66±1.52	0.36±0.01	29.51±5.03	2.70±0.26
VII	13.30±0.47	92.23±0.01	15.66±1.52	5.00±0.00	58.33±5.204	0.31±0.00	31.59±0.08	1.91±0.30
VIII	9.34±0.38	77.87±0.01	80.66±1.15	4.66±0.20	84.66±5.033	0.28±0.00	25.35±0.04	2.64±0.13
IX	16.71±0.79	83.67±0.02	90.00±0.00	5.10±0.17	26.66±2.30	0.31±0.01	35.92±5.44	1.67±0.03
X	24.87±0.37	88.61±0.01	193.33±2.88	5.00±0.00	24.00±5.29	0.35±0.00	42.32±0.21	1.57±0.13

Standard deviation (n=3)

Percent Yield of SPH: Percent yield of every batch of SPH was calculated. The percent yield of all formulations was found to be in the range of 9.34 ± 0.3896 to 24.87 ± 0.3789. Batch-X had the highest percent yield while batch VIII had given least percent yield after freeze drying. The values of the percent yield of all batches of SPH are given in **Table 3**.

Drug Content: The percent drug contents of all the formulations were determined with the help of UV spectrophotometer. The percent drug content of all batches of SPH varied from 77.75 ± 0.2730 to 109.55 ± 0.0051. Batch-IV showed highest drug content whereas Batch-V showed least drug content. The values of the drug content of all batches are given in following **Table 3**.

Gelation Time: Gelation kinetics gives good information that aids in determining the most suitable time to introduce the blowing agent (Sodium bicarbonate). Gelation times of all batches of SPH were determined. The gelation time of all batches of SPH was found to be in the range of 15.33 ± 0.5773 to 193.33 ± 2.8867. Batch IV shows least gelation time while batch X shows highest gelation time. Gelation times of all batches are given in **Table 3**.

The most salient property of superporous hydrogel is its fast swelling ability, because of the presence of large and uniform pores within the polymer structure which are produced due to the formation of foam at the time of polymerization. To produce large and uniform pores, the blowing agent must be introduced when the reactants have appropriate viscosity. Bubbles cannot maintain their shape for a long time if a gas blowing agent is added too early, or if gelation time is relatively longer.

On the other hand, bubbles cannot even be formed if porogen is introduced too late or the gelation time is extremely short because the reaction system becomes viscous at such a short period that the added porogen cannot produce bubbles. The gelation time should be very short otherwise bubbles would collapse leading to the formation of non-porous hydrogels. 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 min. Hence, sodium bicarbonate was introduced 30 sec after the addition of glyoxal.

Density Measurement of SPH: Densities of all batches of SPH were determined. Results of Density measurement indicated that the density of SPH increases with increase in the concentration of the cross-linking agent. As the concentration of cross-linking agent (Glyoxal) increases it forms much tighter networks. Polymer chains were attached more strongly, and the size of pores during foam formation was smaller thus it increases the density of SPH. Values of density measurement of SPH are given in **Table 3**.

Measurement of Porosity: Porosity of all batches of SPH was determined. Results of porosity measurement indicated that porosity of SPH increases with increase in the concentration of monomer (chitosan). It also indicated that an increase in the concentration of cross-linking agent increases the porosity of SPH. This is due to the incorporation of higher crosslink density within the polymer structure leading to a decrease in the occupied volume. Results of porosity measurement of all batches of SPH are given in **Table 3** below. Batch-X showed the highest porosity while Batch-I showed the least porosity

Measurement of Void Fraction: Void fractions of all batches of SPH were measured. Void fraction of all batches of SPH is given in **Table 3**. Results of a Void fraction of SPH indicated that as the concentration of monomer (chitosan) increases the void fraction of SPH decreases. It also indicated that an increase in the concentration of cross-linking agent (glyoxal) decreases the void fraction of SPH. This is due to an increase in porosities of SPH with increased concentrations of both chitosan and glyoxal. The decrease in void volume led to a decrease in the amount of uptake of water into the structure resulting in a decrease in the swelling ratio.

Swelling Studies: Swelling studies includes swelling time and swelling ratio of SPH. Swelling time and swelling ratio of SPH in hydrochloric acid buffer (pH-1.2) were determined as given in **Table 3**.

Effect of Monomer (Chitosan) on Swelling Capacity of SPH: In acidic environment, chitosan superporous hydrogels showed higher swelling ratio compared to the basic environment since the amine groups in the chitosan molecules are ionized to ammonium ion (NH^{3+}) in acidic aqueous media and these cationic charges in gel phase act as cationic repulsive forces between polymer molecules. Moreover, the ionization also caused an increase in ion osmotic pressure. The capillary wetting of interconnected open pores of superporous hydrogel also thus responsible for a higher degree of swelling in the acidic pH (9). As the concentration of chitosan increased swelling ratio of SPH also increased. Values of swelling ratio of SPH are given in **Table 3**.

Effect of Cross-Linking Agent (Glyoxal) on Swelling Capacity: The swelling ratio of SPH was found to be decreased with increase in the cross-linking density. Cross-linking densities of SPH increases with increase in the concentration of the crosslinking agent. This is because as the concentration of cross-linking agent (Glyoxal) increases much tighter networks were formed. Polymer chains were attached more strongly, and the size of pores during foam formation was smaller, thus decrease in the chain flexibility reduced the swelling capacity of SPH.

Measurement of Water Retention: Water retention of all batches of SPH was measured. From the results of water retention studies of SPH, it was concluded that the weight loss of chitosan hydrogels occurred after 12 h. Value of water retention after 12 h is given below.

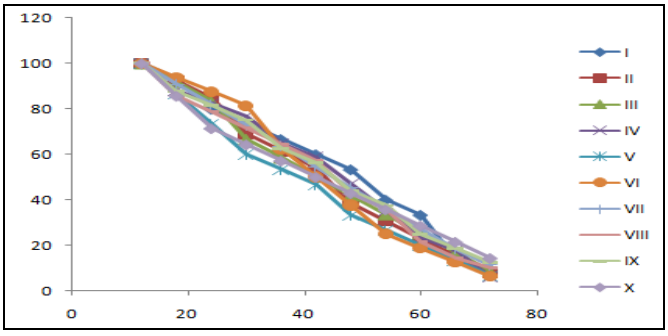

FIG. 2: LOSS OF WATER FROM SUPERPOROUS HYDROGEL AFTER 12 h

Fig. 2 showed the loss of water from SPH after 12 h. Lower the concentration of cross-linking agent, the faster was the loss of water from superporous

hydrogel. This is because, in an acidic environment, superporous hydrogels kept equilibrium swelling ratios for a certain period, being protonated as ammonium ions. D-glucosidic linkages in chitosan were slowly cleaved by acid hydrolysis. As amine groups stabilize D-glucosidic linkage's cleavage by acids, a part of chitosan oligomers, especially not highly crosslinked, was slowly dissolved in the swelling media, inducing the weight loss of samples. The interconnected pores allowed the polymer to hold more water by capillary force.

The superporous hydrogel consisting of the higher amount of glyoxal 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 glyoxal decreased the rate of loss of water.

Morphological Studies: Scanning electron microscopic photographs of SPH are given in below.

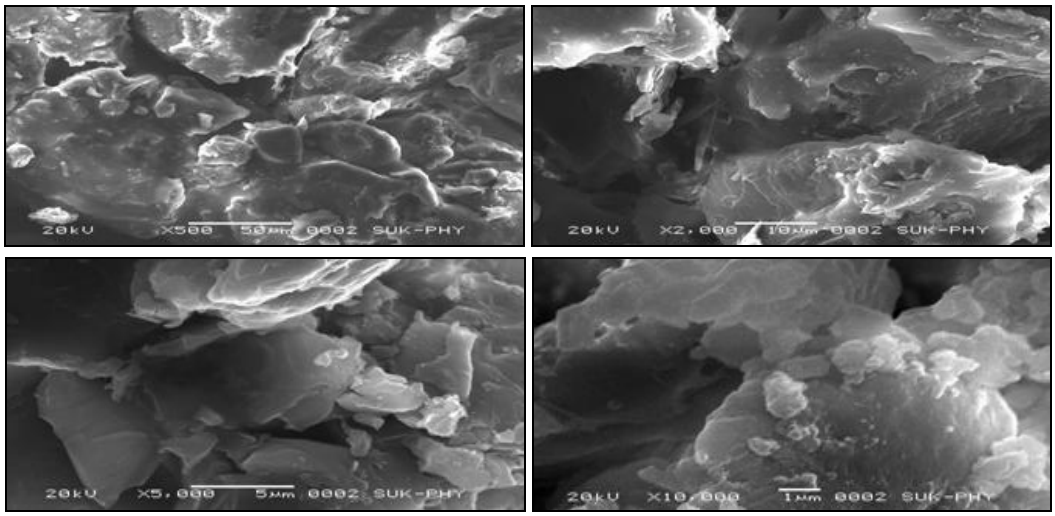

FIG. 3: SEM IMAGES OF SPH SHOWING POROSITY

Above **Fig. 3** showed optical Scanning electron microscopic photographs of optimized Batch-IV respectively. This photograph gives an idea about surface morphology of SPHs

Characterization of SPH Tablets:

A. Precompression Parameters: Amount of SPH equivalent to 100 mg of atenolol, microcrystalline cellulose, sodium bicarbonate, magnesium stearate, talc, *etc*. were used for the preparation of superporous hydrogel tablets. All the ingredients were triturated one by one in mortar and pestle for uniform mixing of all ingredients.

The resultant blend was then evaluated for precompression parameters like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. Values of all precompression parameters are given in **Table 4**.

TABLE 4: PRECOMPRESSIONAL PARAMETERS OF SPH TABLETS

Batch	Precompressional parameters				
	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (^{o})
I	0.24±0.0069	0.27±0.0084	9.84±0.2655	1.10±0.0031	22.39±1.77
II	0.28±0.0094	0.31±0.0000	7.63±3.0299	1.08±0.0362	26.96±5.83
III	0.26±0.0084	0.30±0.0106	10.64±5.1165	1.12±0.0644	30.24±1.24
IV	0.19±0.0044	0.23±0.0062	16.84±2.0649	1.19±0.0400	28.30±1.61
V	0.60±0.0404	0.88±0.0964	31.94±6.3905	1.47±0.1350	16.97±3.17
VI	0.48±0.0262	0.60±0.0404	19.06±8.7280	1.24±0.1326	24.11±2.45
VII	0.42±0.0218	0.51±0.0288	16.90±0.3925	1.20±0.0057	21.96±2.49
VIII	0.40±0.0184	0.48±0.0262	16.03±7.3964	1.19±0.1045	19.00±2.11
IX	0.15±0.0027	0.17±0.0035	11.33±1.6909	1.12±0.0212	32.82±10.9
X	0.31±0.0000	0.36±0.0158	14.57±3.6087	1.17±0.0508	18.79±1.53

(Standard deviation n=3)

Bulk densities and tapped densities of blends were found to be in the range of 0.15 ± 0.0027 to 0.60 ± 0.0404 and 0.17 ± 0.0035 to 0.88 ± 0.0964 respectively. Carr's index of all batches was found to be in the range of 7.63 ± 3.0299 to 19.06 ± 8.7280 which indicated that all batches possessed good flow properties. Hausner's ratio of all batches varied between 1.08 ± 0.0362 and 1.47 ± 0.1350 which indicated better flow properties of all batches.

The angle of repose of all batches was calculated by the funnel method. The values of angle of repose of all batches were found to be in the range of 16.97 ± 3.17 to 32.82 ± 10.9 which indicated good flow properties of all batches.

B. Postcompressional Parameters: Superporous hydrogel tablets of atenolol were prepared using dried SPH, microcrystalline cellulose, sodium bicarbonate, magnesium stearate, talc, *etc*. by direct compression. These prepared tablets were evaluated for postcompressional parameters like weight variation, dimensions, hardness, friability, disintegration time, content uniformity and in-vitro drug release studies. Results of all evaluation parameters except *in-vitro* drug release studies are given in **Table 5**.

TABLE 5: POSTCOMPRESSIONAL PARAMETERS OF SPH TABLETS

Batch	Postcompressional parameters						
	Weight variation (%)	Diameter (mm)	Thickness (mm)	Hardness (g/cm^2)	Friability (%)	Disintegration time (min)	Content uniformity (%)
I	0.25±0.2564	8.04±0.005	2.72±0.000	5.56±0.057	0.225	28.66 ±1.52	98.98±0.88
II	0.20±0.2513	8.05±0.000	2.71±0.010	5.53±0.057	0.125	29.33± 1.52	99.43±0.58
III	0.18±0.2000	8.05±0.000	2.71±0.005	5.50±0.100	0.200	36.00± 1.00	99.71±0.87
IV	0.17±0.2384	8.04±0.005	2.71±0.005	5.53±0.115	0.225	43.00± 2.00	99.99±0.83
V	0.18±0.2261	8.05±0.000	2.71±0.000	5.46±0.057	0.250	27.66 ±0.57	100.1±0.74
VI	0.30±0.2449	8.04±0.005	2.71±0.005	5.53±0.115	0.200	29.66 ±1.52	99.90±0.50
VII	0.27±0.2552	8.05±0.000	2.71±0.005	5.53±0.057	0.100	30.33± 0.57	99.98±0.85
VIII	0.33±0.2231	8.04±0.005	2.71±0.005	5.50±0.000	0.150	30.00± 1.00	99.97±0.84
IX	0.18±0.2311	8.05±0.000	2.71±0.010	5.53±0.057	0.200	31.33± 1.52	99.98±0.77
X	0.27±0.2680	8.05±0.000	2.71±0.011	5.56±0.057	0.277	35.33± 0.57	100.1±0.64

(Standard deviation n=3)

The percent weight variations of all batches were varied from 0.17 ± 0.2384% to 0.33 ± 0.2231%. It complied with USP monographs of weight variation which is 7.5% for tablets having weights in between 130-324 mg. Tablet dimensions were measured in the form of diameter and thickness. The values of tablet diameter and thickness were found to be in the range of 8.04 ± 0.005 mm to 8.05 ± 0.000 mm and 2.71 ± 0.000 mm to 2.72 ± 0.000 mm respectively. The hardness of all batches was measured using Monsanto hardness tester. The hardness of all batches was found to be in the range of 5.46 ± 0.057 g/cm^2 to 5.56 ± 0.057 g/cm^2 which complied with Indian pharmacopoeial specifications.

Friability of all batches was evaluated using Roche Friabilator. The percent friability of all batches was found to be in the range of 0.100% to 0.277% which complied with Indian pharmacopoeial specifications, *i.e.* 0.8%. The disintegration time of all batches was evaluated using the disintegration test apparatus. The disintegration time of all batches was found to be in the range of 27.66 ± 0.57 min. to 43.00 ± 2.00 min which complied with Indian pharmacopoeial monographs of disintegration time for sustained release formulations. The content uniformity of all batches was determined with the help of UV spectrophotometer. The values of all batches were found to be in the range of 98.98 ± 0.88% to 100.1 ± 0.74% which complied with Indian pharmacopoeial monographs

C. Dissolution Studies: Dissolution studies of superporous hydrogel tablets were carried out using Dissolution test apparatus USP type-II in 900 ml hydrochloric acid buffer (pH-1.2) at 50 rpm for 12 h. Aliquots of 5 ml were withdrawn after 30 min intervals and evaluated using UV Spectro-photometer to obtain percent drug release. The percent drug release data of all batches of Superporous hydrogel tablets were given in below.

Fig. 4 showed dissolution profiles of all batches of superporous hydrogel tablets. All batches released the drug in a sustained manner throughout minimum 10 h. As the concentration of chitosan

increased, there is the prolonged release of the drug was observed through gastroprotection. This is due to the high swelling ratio of SPH due to increased concentration of chitosan. Batch-IV showed the prolonged release of drug throughout 12 h with zero order kinetics. This indicated that superporous hydrogel releases the drug in controlled manner by retaining in the stomach for a prolonged period. This will results in enhanced bioavailability of the drug through gastroretention.

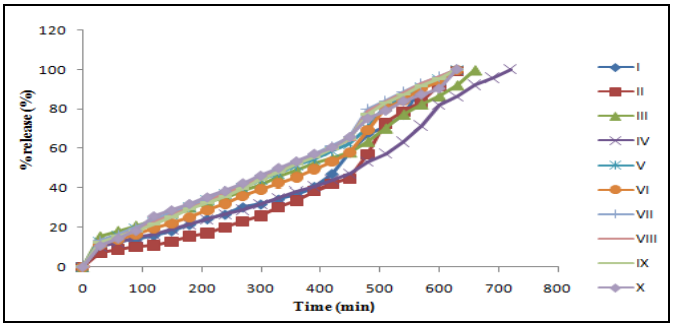

FIG. 4: GRAPH SHOWING DISSOLUTION PROFILE OF SPH

Compatibility Studies:

Fourier Transforms Infrared Spectroscopy Studies: FTIR studies were done to assess whether any possible interaction among drug, the polymer is done by FTIR spectrophotometer (Jasco-4100). Infrared spectrums of pure drug, excipient and physical mixture of ingredients of the formulation were recorded. From the overlay spectrum analysis, the compatibility of ingredients in the formulations was found out. Pure, completely dried KBr is used as blank and before every running of a sample, it was mixed thoroughly with KBr at a ratio of sample to KBr 100:1 and then the spectrum was scanned over a wave number range from 4000 - 400 cm^{-1}. **Fig. 5** showed overlain of FT-IR spectrums of pure atenolol, pure chitosan and Batch-IV.

TABLE 6: INTERPRETATION OF IR SPECTRA

Functional group	Characteristic frequency (cm^{-1})	Observed frequency (cm^{-1})
O-H stretching	3500-3400	3295.22
C-H stretching	2936-2916	2930.10
C=C aromatic	1680-1620	1637.20
N=O stretching	1460-1430	1458.17

Characteristics peaks of FT-IR spectra of Batch- IV gave in **Table 6**. Results of FT-IR studies indicated that there were no any physical as well as chemical interactions between drug and excipients as FT-IR spectra of formulation showed characteristics peaks of both drug and excipient. Thus we concluded that drug and excipients are compatible with each other.

Differential Scanning Calorimetry Studies: DSC technique helps to detect crystallization, degradation, and phase transformation in solid sample. Overlain DSC thermograms of pure drug and its formulation are given in **Fig. 6**.

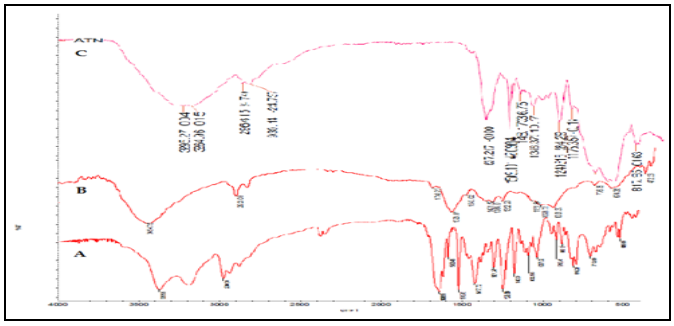

FIG. 5: OVERLAIN FT-IR SPECTRA OF (A): PURE ATENOLOL; (B): PURE CHITOSAN & (C): SPH BATCH IV

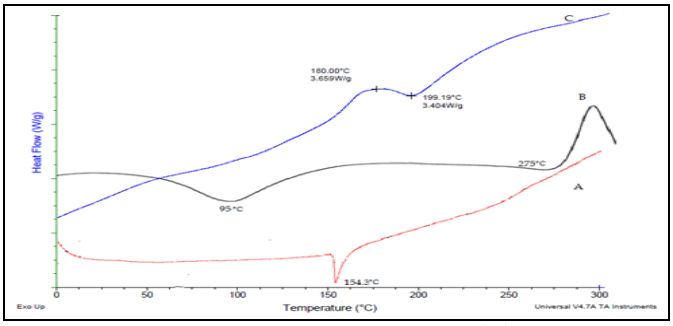

FIG. 6: DSC THERMOGRAMS OF (A): PURE ATENOLOL; (B): PURE CHITOSAN & (C): SPH BATCH IV

The thermogram of pure atenolol showed sharp endothermic with melting peak at 154.36 ºC.

Thermogram of an optimized formulation containing chitosan showed an endothermic peak at 186.20 ºC. A slight shift in of endothermic peaks on the right hand with decreased in its intensity indicates increased amorphization of drug thus increased the release of the drug.

Powder X-ray Diffractometry Studies: The powder X-ray diffraction patterns were recorded using an X-ray Diffractometer (PW1729. Philips, Netherland) with Cu as an anode material and crystal graphite on ochromator operated at a voltage of 30 kV and a current of 30 mA. The samples were analyzed in the 2θ angle range of 2 to 50º. The range and the chart speed were 5 × 10^3 CPS and 10 m/2θ, respectively.

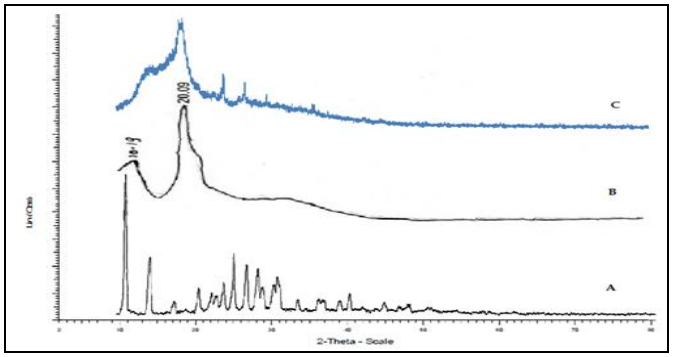

FIG. 7: XRD PATTERNS OF (A): PURE ATENOLOL; (B): PURE CHITOSAN; (C): SPH BATCH IV

PXRD study gives information about the crystallographic structure and composition of materials. The overlain XRD spectrums of pure drug and its formulations are shown in **Fig. 7**.

The analysis of XRD pattern reveals sharp intensity peaks of the crystallinity of the pure drug and pure excipients, but when it was incorporated into the polymer matrix, the intensities of the peaks were decreased due to decreased crystallinity of the drug. Thus amorphization of drug causes increased the release of the drug.

D. Stability Studies: Stability studies of optimized Batch-IV were carried out as per ICH guidelines at specific conditions of temperature (40 ºC) and relative humidity (75%) for three months. The sample was withdrawn at an interval of 30 days and evaluated for drug content, percent drug release, Differential scanning calorimetry analysis and Powder X-ray diffraction analysis.

Drug Content and Dissolution Data of Stability Studies: Batch-IV evaluated for drug content and dissolution profile at 30th day, 60th day and 90th day of stability. The results of drug content and dissolution profile for stability are mentioned in below **Table 7** and **Fig. 8** respectively.

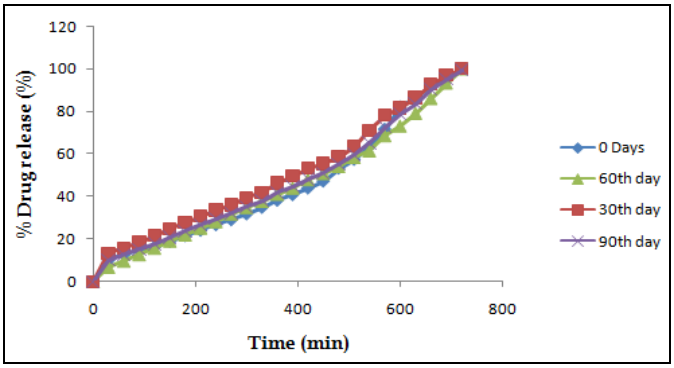

FIG. 8: DISSOLUTION PROFILE OF STABILITY STUDIES

TABLE 7: DRUG CONTENT DATA OF STABILITY STUDIES

S. no.	Trial no.	0 Day	30th Day	60th Day	90th Day
1	1	99.99	99.84	99.86	99.79
2	2	99.98	99.88	99.78	99.65
3	3	99.99	99.91	99.43	99.72
4	Mean	99.99	99.87	99.69	99.72

Results of drug content and dissolution studies at 30th day, 60th day and 90th day of stability indicated that there were no significant changes observed in drug content and dissolution profile of Batch-IV. It concluded that Batch-IV was stable for three months at specified conditions of temperature (40 ºC) and relative humidity (75%).

Differential Scanning Calorimetry Studies: DSC of Atenolol, freeze-dried optimized hydrogel batch were obtained using DSC (DSC 60 Schimadzu) equipped with an intracooler. A platinum crucible used with alpha alumina powder as a reference to calibrate the DSC temperature and enthalpy scale. The powder samples were hermetically kept in the aluminum pan and heated at a constant rate of 10 °C per min, over a temperature range of 35 °C to 200 °C. The inert atmosphere was maintained by purging nitrogen at the flow rate of 150 ml/min. DSC thermograms of optimized Batch-IV at 0day, 30th day, 60th day and 90th day are given in **Fig. 9**.

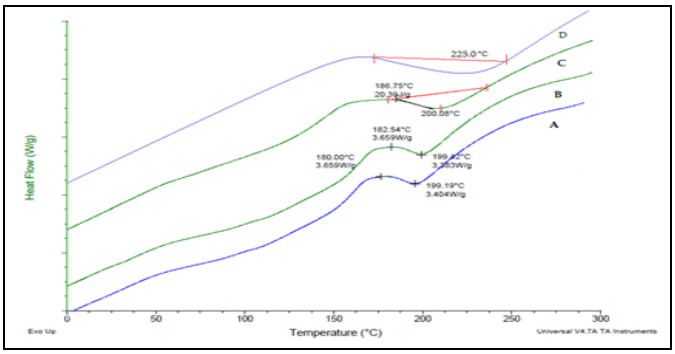

FIG. 9: DSC THERMOGRAMS OF BATCH-IV FOR STABILITY (A): AT 0 DAY; (B): AT 30th DAY; (C): 60th DAY AND (D): AT 90th DAY

The results of differential scanning calorimetric studies of optimized batch showed that there were no significant changes in DSC spectra and melting points of optimized Batch-IV after 30th day, 60th day and 90th day of stability. Thus it is concluded that Batch-IV was stable for three months at specified conditions of temperature (40 ºC) and relative humidity (75%).

Powder X-ray Diffraction Studies: The powder X-ray diffraction patterns were recorded using an X-ray Diffractometer (PW1729. Philips, Netherland) with Cu as an anode material and crystal graphite on ochromator operated at a voltage of 30 kV and a current of 30 mA. The samples were analyzed in the 2θ angle range of 2 to 50º. The range and the chart speed were 5×10^3 CPS and 10 m/2θ, respectively. XRD patterns of Batch-IV are given in **Fig. 10**.

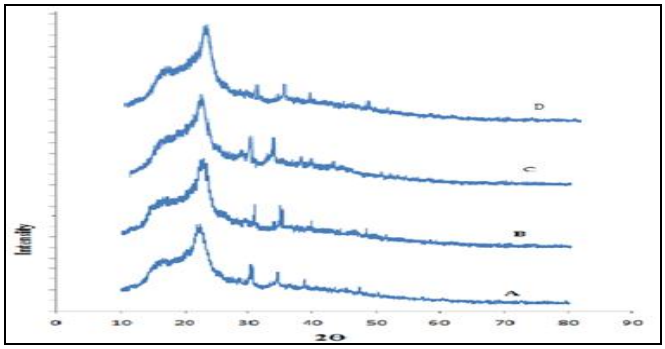

FIG. 10: XRD PATTERNS OF OPTIMIZED BATCH-IV FOR STABILITY (A): AT 0 DAY; (B): AT 30th DAY; (C): AT 0th DAY AND (D): AT 90th DAY

CONCLUSION: Gastro retentive drug delivery system offers a valuable dosage form which delivers the drug at a controlled rate and a specific site. The SPH tablets of atenolol provide a better option for increasing the bioavailability and reliability for treatment of hypertension by allowing better control of fluctuations observed with conventional dosage forms. From the FTIR spectra, we concluded that there was no any permanent interaction between drug and excipients. Thus all excipients were compatible with the drug. The optimized formulation IV containing 160 mg chitosan, 400 mg glyoxal, and 400 mg polyvinyl alcohol can be considered as a promising gastro retentive drug delivery system of atenolol, providing zero-order drug release throughout 12 h. It indicated that drug was released in a controlled manner over the prolonged period through gastroretention. This would help in enhanced bioavailability of the drug.

The optimized formulation IV was found to be stable for three months at specified conditions of temperature and relative humidity. Thus, the superporous hydrogel tablets of atenolol have been successfully prepared with prolonged drug release through gastroretention and to enhance bioavailability of the drug.

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CONFLICT OF INTEREST: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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