IJPSR (2020), Volume 11, Issue 8 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 August 2019; received in revised form, 11 January 2020; accepted, 05 March 2020; published 01 August 2020

FORMULATION AND *IN-VITRO* CHARACTERISATION OF CONTROLLED RELEASE LAFUTIDINE SUPER POROUS HYDROGEL TABLETS

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Keywords:

Super Porous Hydrogel (SPH), Chitosan, Swelling, Floating

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ABSTRACT: The aim is to design, develop & characterize a desired gastro retentive super porous hydrogel (SPH) formulations containing lafutidine is histamine H2-receptor antagonist that may be used alone or with other agents to treat inhibits stomach acid production. SPH's synthesized employing various composite agents *viz*., sodium alginate, pectin, Carbopol, and chitosan were subjected to density and swelling property (swelling time, swelling ratio) characterization. Pectin, Carbapol, and chitosan have shown the best results; they were optimized for further characterization. As a hybrid agent is responsible for maintaining the capillary structure required for fast swelling of SPH, the effect of optimized hybrid on mechanical characters and swelling behavior of SPH was assessed. As the hybrid chitosan concentration increased, there was an extensive variation in swelling properties. Swelling time was gradually decreased from 45 to 16 min. SPHH-CN1 to SPH-CN7 lafutidine combined formulations were developed with dried SPH-CN5 powder. Drug release studies for formulations F1- F7 was carried out, and based upon release and retarding capacity, the effect of sodium bicarbonate F4 is the optimized formulation for present work. No prominent difference was observed in the principal IR peaks of lafutidine optimized polymer (chitosan), no prominent enthalpy changes were observed in the DSC endotherms of lafutidine, optimized polymer (chitosan), physical mixture formulations upon comparison with the peaks of drug and polymer alone, which may be considered that lafutidine and chitosan are compatible enough without any interactions. SEM photograph clearly reveals the presence of the swollen pores on the surface of the super porous hydrogel hybrid drug delivery systems.

INTRODUCTION: Despite the extensive absorption properties of the duodenum and jejunum, the extent of absorption at these sites is limited because the passage through this region is rapid.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(8).3745-62

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(8).3745-62

Enhancing the gastric residence time (GRT) of a narrow absorption window drug may significantly improve the net extent of its absorption [1]. The small intestinal transit time is an important parameter for drugs that are incompletely absorbed [2].

Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [3]. Super porous hydrogel systems [4] are swellable systems that differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous

hydrogels of average pore size >100 micrometer, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand the pressure by gastric contraction. This is advised by the co-formulation of hydrophilic particulate material. Hydrogels are cross-linked hydrophilic polymer chains with a network structure consisting of acidic, basic, or neutral monomers, and are able to imbibe large amounts of water. The hydrogel swelling properties are mainly related to the elasticity of the network, the extent of cross-linking, the presence of hydrophilic functional groups (such as -OH, -COOH, $-CONH_2$, $-SO_3H$) in the polymer chains, porosity of the polymer [5], manufacturing process, and materials used [6] and their swelling takes more time [7]. Japanese researchers have created a rapidly self-healing hydrogel material, forming a gel in seconds and useful in regenerative medicine and green chemistry [8].

A super porous hydrogel (SPH) is a three-dimensional network of hydrophilic polymer chains, and their complete swelling occurs in less than 30 sec. The formulation of super porous hydrogels involves components like cross-linking agents, initiators for initiation of polymerization, foaming agents like inorganic carbonates such as Na_2CO_3 and $NaHCO_3$. These inorganic carbonates are safely used as a gas-forming ingredient in effervescent tablets for antacids. They are safe, cheap, and easy to use [9] Preparation of super porous hydrogels is as follows.

Gas Blowing/Foaming Method: Porous hydrogel is formed by cross-linking polymerization of vinyl monomers, thereby producing gas bubbles. In a test tube, monomer, initiator and crosslinker are added. The monomer solution is made slightly acidic to retard the polymerization process. The addition of sodium bicarbonate generates carbon dioxide bubbles making the foam rise. The addition of sodium bicarbonate increases the pH, resulting in faster polymerization of vinyl monomers. Completion of polymerization while the foam is still stable results in the formation of super porous hydrogels. The three-dimensional structure of super porous hydrogels of any shape can be easily made, and they can be synthesized in any moulds shows a scanning electron microscopic picture of a porous hydrogel showing interconnected pores. The size of pores produced by the gas blowing (or foaming) method is in the order of 100 mm and larger. Macroporous hydrogels possess pores in the size range of 100 nm to 10 mm range; the new porous hydrogels were named super porous hydrogels.

Mechanical Blowing Method: For large-scale production of super porous hydrogels, mechanical blowing through one or more atomizers may be a better choice than the chemical blowing method. This is because it may not be desirable to complete a polymerization in a few minutes since the heat generated during polymerization may not be dissipated quickly. Thus, a smaller amount of initiator may be used to delay the gelling time (*e.g.*, more than 10 min). Since, mechanical blowing can start at any time for any duration, the foaming process may begin at the desired time and foam height can be maintained as necessary. Accurate timing control is possible by mechanical blowing in the large-scale production of super porous hydrogels [10].

Porosigen Technique: Porous hydrogels are prepared in presence of dispersed water soluble porosigen. Porosigens are hydrophilic in nature and come in contact with water to generate porous structure in hydrogel *e.g.* micronized (sucrose, lactose, cellulose), sodium chloride. Pore size generates in hydrogel depends on the size of porosigens [11]. Phase separation technique: Phase separation is very critical process in generating superporous hydrogel because there is no much control over the porosity. So, this method use in limited type of hydrogel prepared by HEMA (Hydroxy ethyl methyl acrylate) and NIPAM (N-isopropyl acrylamide) [12].

Gastroretentive Tablets: Dry blending and direct compression[13-14] is used to make gastroretentive tablets. The SPH particles of acrylic acid/ sulfopropyl acrylate copolymers are mixed with gelatin and tannic acid, and then tableted by direct compression. Formation of hydrogen bond between gelatin and tannic acid, as well as the carboxyl groups on the polymeric carrier, produce an integrated matrix, which is shown to be stable after swelling. The gastroretentive tablet can swell up to

22 times its own volume within a 40 min period maintaining its original shape [15].

Lafutidine is a newly developed second generation histamine H2-receptor antagonist. It is absorbed in the small intestine, reaches gastric cells via the systemic circulation and then directly and rapidly binds to gastric cell histamine H2 receptors, resulting in immediate inhibition of gastric acid secretion. Lafutidine is used in the treatment of gastric ulcers, duodenal ulcers, and gastric mucosal lesions associated with acute gastritis and acute exacerbation of chronic gastritis. It has been shown to have mucosal protective action throughout the gastrointestinal tract. In clinical studies, lafutidine has been shown to inhibit gastric acid secretion during the day time as well as during the night. Lafutidine possesses a potent and long lasting gastric antisecretory effect mediated by H2-receptor blockade in animals. Lafutidine has a receptor binding affinity which is 2-80 times higher than other representative H2-receptor antagonists (*e.g.* famotidine, ranitidine, and cimetidine). In addition, lafutidine exerts gastro protective effects independent of its antisecretory action [16].

Lafutidine is freely soluble in acetic acid, slightly soluble in methanol, very slightly soluble in diethyl ether and practically insoluble in water. When 10 mg of lafutidine is orally administered to normal adult males, fasting plasma concentration of unchanged drug observed as T_{max}: 0.8 ± 0.1 h; C_{max}: 174 ± 20 ng/ml; $T_{1/2}$: 3.30 h. The total excreation rate of lafutidine in urine is approximately 20% of given dose [17].

MATERIALS AND METHODS: The main material lafutidine were obtained from Cadila Health Care, Baddi, India. Chemicals and other materials used like chitosan, pectin, sodium alginate, Carbopol 940 were procured from S.D. Fine Chem. Limited, Mumbai, India. Sodium bicarbonate, microcrystalline cellulose, magnesium stearate, acrylic acid, ammonium persulphate, talc were procured from Merck, India.

Methods:

Construction of Calibration Curve using 0.1 N HCl (pH 1.2): Accurately weighed 10 mg of lafutidine was dissolved in methanol taken in a clean 10 ml volumetric flask. The volume was made up to 10 ml with ethanol, which gives a concentration of 1000 µg/ml. From this standard solution, 1 ml was pipette out in 10 ml volumetric flask, and volume was made up to 10 ml using 0.1N HCl to obtain a concentration of 100 µg/ml. From the above stock solution, aliquots of 0.4, 0.6, 0.8, 1.0, 1.2 and 1.4 ml each was transferred to a separate 10 ml volumetric flask and solution was made up to 10 ml using 0.1N HCl to obtain a concentration of 4, 6, 8, 10, 12 and 14 µg/ml respectively. The absorbance of each solution was measured at 279 nm.

Preparation of Various SPHH: 2 gm of a polymer selected was dissolved in 100 ml of 0.1M acetic acid. 3 ml of the polymer solution was transferred in petriplate. To this, add cross-linking agent Glyoxal (10%) solution at (50 µl) concentration, respectively. To this, add 20 µl of span 80 foam stabilizer, 200 µl of acrylic acid as a monomer, and 15 µl of ammonium persulphate (ml) as a polymerization initiator. Then add 100 mg of sodium bicarbonate to the above-prepared complex and mixed thoroughly to get a uniform mixture. Polymerization was allowed to continue for approximately 5 min synthesized SPH was allowed to dry in an oven at 60 °C or air-dried for 48 h in a closed petri plate.

TABLE 1: FORMULA FOR SYNTHESIS OF SPH AND THEIR HYBRIDS

Ingredients	SPH	SPH-H1 Sodium alginate	SPH-H2 Pectin	SPH-H3 Carbapol	SPH-H4 Chitosan
Acrylic acid	200 µl	200 µl	200 µl	200 µl	200 µl
Glyoxal	50 µl	50 µl	50 µl	50 µl	50 µl
Span 80	20 µl	20 µl	20 µl	20 µl	20 µl
Ammonium persulphate	15 µl	15 µl	15 µl	15 µl	15 µl
Sodium alginate	-	2%	-	-	-
Pectin	-	-	2%	-	-
Carbapol 934P	-	-	-	2%	-
Chitosan	-	-	-	-	2%
Sodium bicarbonate	100 mg	100 mg	100 mg	100 mg	100 mg

Evaluation of Superporous Hydrogels:

Scanning Electron Microscopy: Scanning electron microscope (SEM) was used for the determination of the morphology of super porous hydrogel. SEM study is useful in the determination of porous structure and pore size of super porous hydrogel [18-19].

Fourier Transform Infrared Spectroscopy: In FTIR spectroscopy investigation of super porous hydrogels, the FTIR spectrum was recorded over the range of 4000-400 cm^{-1}. KBr pellet is a method of choice in which Transform Infrared FT-IR spectrophotometer are generally used [20]

Measurement of Density: For density measurement, the solvent displacement method was used. The dried super porous hydrogel was used for density measurement, which actually showed the apparent density of the super porous hydrogel. The dried super porous hydrogel is treated with different solvents, which actually gives apparent densities of super porous hydrogels. A piece of hydrogels is weighed for mass. With forceps, that piece is immersed in a predetermined volume hydrophobic solvent such as hexane that is not absorbed by super porous hydrogels in a graduated cylinder, and measurement in the hexane volume is measured as the volume of the polymer [21].

Determination of Drug Content: Superporous hydrogel required amount is taken in a 100 ml volumetric flask. About 10 ml of the buffer is added, mixed well, and makeup to volume. This mixture is filtered, and drug content is determined using a UV-visible spectrophotometer at appropriate wave-length [22.]

Drug Excipients Compatibility: FT-IR spectroscopy is used. The prepared super porous hydrogel is subjected to FT-IR analysis by the KBr pellet method using the Fourier-Transform Infrared spectrophotometer and recorded over a range of 400-4000 cm^{-1} [23].

Mechanical Strength: Quantifying super porous hydrogel mechanical properties is challenging is measure by applying weight on swelled super porous hydrogel until it breaks. Mechanical strength is measure by using bench comparator and gastric simulator. A gastric simulator, based on the water hammer theory, utilizes a controlled amount of different types of stresses on objects immersed in the testing fluid to simulate forces that a sample might receive upon ingestion in body [24].

Determination of Void Fraction: Void fraction can be calculated by the following equation

Void Fraction = Dimensional volume of hydrogel / Total volume of pores

Void fraction is determined by immersing hydrogels in the HCl solution (pH 1.2). Dimensions of swollen hydrogels are measured, and by using these data, sample volumes are determined as dimensional volume. In the meantime, the amount of absorbed buffer into hydrogels is determined by subtracting the weight of dried hydrogel from the weight of swollen hydrogel and resulting values are assigned as total volume of pores in hydrogels [25].

Water Retention: Following equation is used to determine water retention capacity (W_{Rt}) as a function of time

$$W_{Rt} = (Wp - W_d) / (Ws - W_d)$$

Where W_d is the weight of dried hydrogel, Ws is weight of fully swollen hydrogel, and Wp is weight of hydrogel at various exposure times. Water loss of fully swollen polymer at timed intervals was determined by gravimetric at 37 °C [25].

Porosity Measurement: For Porosity measurement, the dried super porous hydrogel was immersed in absolute ethanol overnight and weighed. It absorbed ethanol and swollen, which leaded to the blotting of ethanol on the surface. Porosity is calculated from the following equation

$$Porosity = (M - M1) / \rho V$$

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

Swelling Property: Superporous hydrogels are characterized by their swelling and mechanical properties. The most important factors are ionic strength, pH, salts, organic solvents, and pressure.

Equilibrium Swelling Time: Swelling time is the 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 super porous hydrogel is allowed to hydrate in excess of swelling medium (25 ml) at room temperature.

At various time intervals, the hydrogel is removed from the solution and weighed after excess solution on the surface is blotted.

Equilibrium Swelling Ratio: Measured weight of dried super porous hydrogel and allowed to hydrate in distilled water at room temperature. At various time intervals, measured weight. Equilibrium swelling ratio is calculated by using this formula;

$$Q_S = (W_S - Wd) / (Wd \times 100)$$

Ws is weight of welled hydrogel, Wd is weight of dried hydrogel and Qs is equilibrium swelling ratio. Swelling/deswelling behaviors of superporous hydrogels are examined by repeating the same experiments at two different pH like 7.0 and 1.2 [25].

Swelling Reversibility: Pulsatile pH-dependent swelling of super porous hydrogels is evaluated by an alternation of swelling medium between the 0.1N HCl solution (pH 1.2) and Phosphorus buffer solution (pH 7.4). Hydrogels are first swollen in pH 1.2 HCl solutions for 30 min and weighed at a given time, then transferred to the phosphorous buffer solution. The same procedures are performed for swelling in a phosphorous buffer solution before transferring swollen hydrogels back to the HCl solution. Hydrogels are transferred to alternating solutions every 30 min [25].

Stability Studies: Sample is kept in airtight containers and stored in a stability chamber at 40 °C/ 75% RH for three months. *In-vitro* dissolution study data obtained after three months will be compared with the data obtained at the time of preparation [25].

Gelation Kinetics: As polymerization reaction proceeds, viscosity continuously increases until full network gel structure is formed. Gelation time is measured by a simple tilting method after adjustment of pH to 5.0 with acetic acid. It is determined by the duration of time taken by reactant mixture to become vicious, and henceforth viscous solution no longer falls in tilted tube position [26-27].

***In-vitro* Drug Release Studies:** The release rate of the drug from super porous hydrogels is carried out at 37 ± 0.5 °C in 900 ml simulated gastric fluid SGF of 0.1N HCl using USP paddle type. Medium is stirred at 50 rpm, and 5 ml aliquots are withdrawn at specified time intervals, maintain sink conditions, then assayed spectrophotometrically to get a cumulative percentage of drug release.

TABLE 2: EFFECT OF PECTIN ON CROSS LINKING AGENTS

Ingredients	SPH-H-Pectin					
	P1	P2	P3	P4	P5	P6
Arcylicacid (µl)	200	200	200	200	200	200
Glyoxal (%)	1.5	1.75	2	2.25	2.5	3
Span 80 µl	20	20	20	20	20	20
Ammonium persulphate (µl)	15	15	15	15	15	15
Pectin (%)	2	2	2	2	2	2
Chitosan (%)	-	-	-	-	-	-
Carbapol 934P (%)	-	-	-	-	-	-
Sodium bicarbonate	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

TABLE 3: EFFECT OF CARBAPOL ON CROSS LINKING AGENT

Ingredients	SPH-H-Carbapol					
	CL1	CL2	CL3	CL5	CL6	CL7
Arcylicacid (µl)	200	200	200	200	200	200
Glyoxal (%)	1.5	1.75	2	2.25	2.5	3
Span 80 (µl)	20	20	20	20	20	20
Ammonium persulphate (µl)	15	15	15	15	15	15
Pectin (%)	-	-	-	-	-	-
Carbapol(%)	2	2	2	2	2	2
Chitosan (%)	-	-	-	-	-	-
Sodium bicarbonate	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

TABLE 4: EFFECT OF CHITOSAN ON CROSS LINKING AGENT

Ingredients	SPH-H-chitosan					
	CN1	CN2	CN3	CN4	CN5	CN6
Arcylic acid (µl)	200	200	200	200	200	200
Glyoxal (%)	1.5	1.75	2	2.25	2.5	3
Span 80 (µl)	20	20	20	20	20	20
Ammonium persulphate (µl)	15	15	15	15	15	15
Pectin (%)	-	-	-	-	-	-
Chitosan (%)	2	2	2	2	2	2
Carbapol 934P (%)	-	-	-	-	-	-
Sodium bicarbonate	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

Optimization of Chitosan Concentration: Chitosan as an optimized hybrid is responsible for maintaining the capillary structure required for fast swelling, hence the effect of these polymers on the behavior of SPH was assessed by increasing its concentration from 1- 3.5%.

TABLE 5: OPTIMIZATION OF CHITOSAN CONCENTRATION

Ingredients	SPH-H-Chitosan					
	CN1	CN2	CN3	CN4	CN5	CN6
Arcylicacid (µl)	200	200	200	200	200	200
Glyoxal (%)	1.5	1.75	2	2.25	2.5	3
Span 80 (µl)	20	20	20	20	20	20
Ammonium persulphate (µl)	15	15	15	15	15	15
Chitosan (%)	1	1.5	2	2.5	3	3.5
Sodium bicarbonate	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

Formulation and Evaluation:

Preparation of SPHH Based Drug Delivery Systems:

SPH for Chitosan: 2 gm of chitosan was dissolved in 100 ml of 0.1M acetic acid. 3 ml of chitosan solution was transferred to Petri plate. To this, add crosslinking agent Glyoxal (10%) solution at 50 µl concentration, respectively. To this, add 20 µl of span 80 foam stabilizer, 200 µl of acrylic acid as monomer and 15 µl of ammonium persulphate (ml) as polymerization initiator. Then add 100 mg of sodium bicarbonate to above-prepared complex. Finally stir it well and kept for overnight in hot air oven at 45 °C.

Drug Loading: The method of soaking equilibrium was employed for drug loading in this method the amount of buffer necessary for complete swelling of superporous hydrigel was first determined. After that 15 ml of drug solution (25 mg of lafutidine in 15 ml of (0.1N HCl) was prepared. The weighed quantity of super porous hydrogel was placed in the drug solution and left until the drug solution was sucked up. Finally, the completely swollen super porous hydrogel loaded with the drug was dried in an oven at 30 °C overnight.

Method of Formulation: The super porous hydrogel tablets of lafutidine was formulated by taking the dried SPH formed and to this microcrystalline cellulose was utilized as diluents, magnesium Stearate as a glidant, talc as lubricant respectively, the powder blend was mixed for ten minutes after obtaining a uniform mix it is passed through no. 60 sieve and was prepared for compression.

The compression was carried out in (16 stations) punch of 9 mm and adjusting thickness and hardness accordingly.

TABLE 6: COMPOSITION OF TABLETS PREPARED BY DIRECT COMPRESSION METHOD (300 mg)

Ingredients (mg)	TF1	TF2	TF3	TF4	TF5	TF6	TF7
Lafutidine + SPH CN5 Powder	100	125	150	175	200	225	250
Mg stearate	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5
Micro crystalline cellulose	180	155	130	105	80	55	30
Total	300	300	300	300	300	300	300

RESULTS AND DISCUSSION:

Characterization of SPHH'S:

Measurement of Initial Size: The so formed final SPHH's are rigid and brittle and when they were in contact with water swells to 10-15 times of its original volume. Measurements were given in **Fig. 1**.

FIG. 1: THE FINAL, DRIED HYDROGEL IS RIGID AND BRITTLE (LEFT); IT SWELLS TO ABOUT 10 TO 15 TIMES OF ITS OWN VOLUME IN WATER (RIGHT)

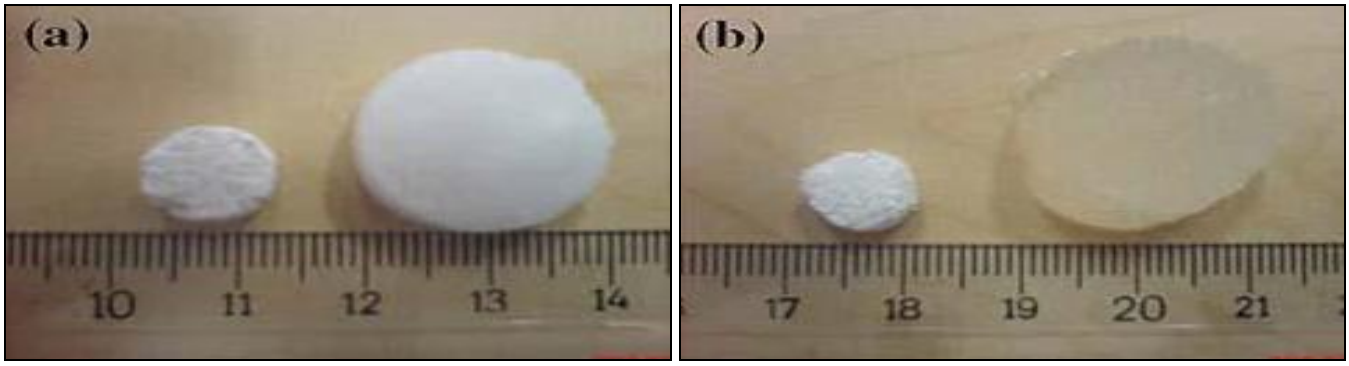


FIG. 2: PHOTOGRAPHS OF (A) SPHH IN DRIED (LEFT) AND SWOLLEN STATE (RIGHT), (B) SPH IN DRIED (LEFT) AND SWOLLEN STATE (RIGHT)

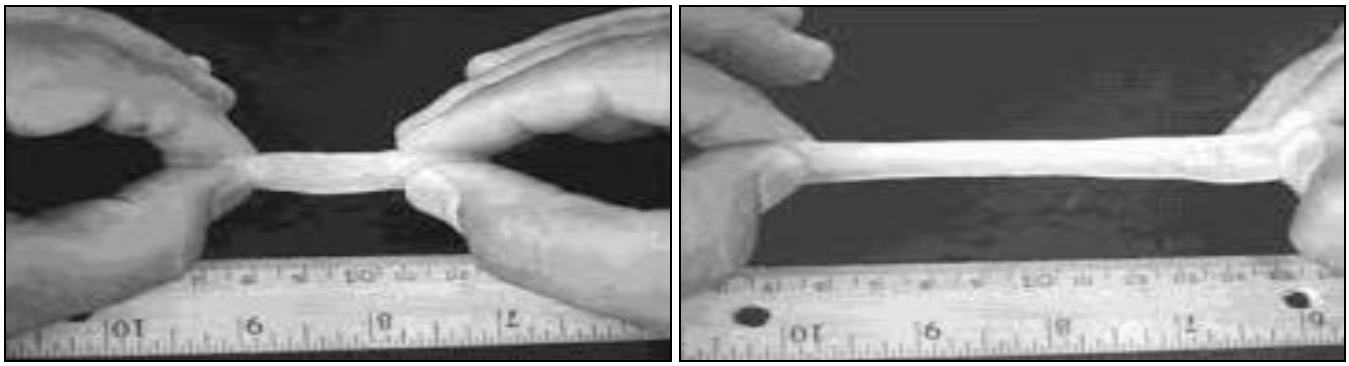


FIG. 3: TYPICAL SWELLING AND MECHANICAL PROPERTIES OF THIRD GENERATION SPHHS

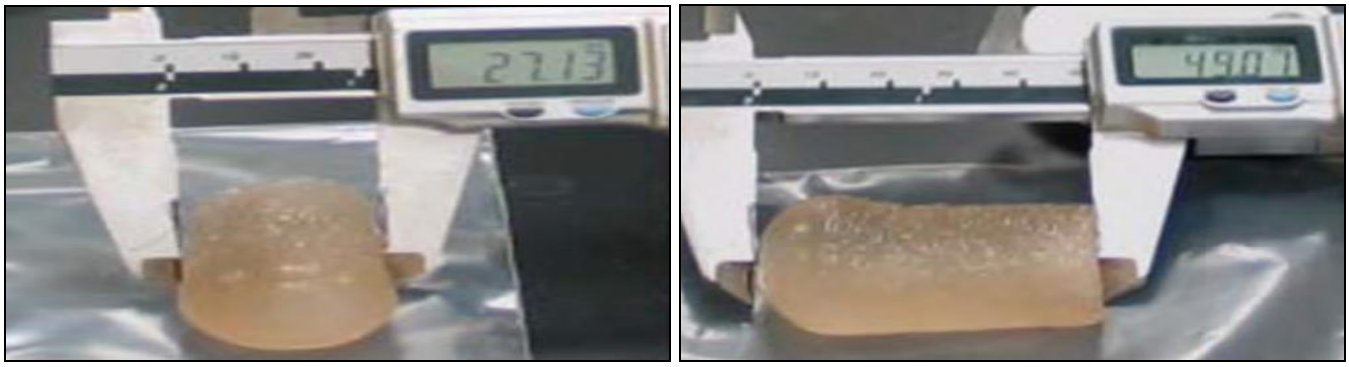


FIG. 4: SIZE DETERMINATION BY VERNIER CALIPERS

Optimization of SPH Hybrid Material Based on Swelling Characteristics and Density:

TABLE 7: OPTIMIZATION OF SPH COMPOSITE

Specification	Sodium alginate	Pectin	Carbapol	Chitosan
Density (gm/cm^3)	1.52 ± 0.16	1.41 ± 0.11	1.37 ± 0.24	1.12 ± 0.36
Swelling time (min)	83 ± 14	79 ± 10	70 ± 13	58 ± 12
Swelling ratio (Q)	210 ± 18	230 ± 23	255 ± 19	280 ± 32

(n=3); Mean ± S.D

SPH's synthesized employing various hybrid agents sodium alginate, pectin, Carbapol, chitosan were subjected to density and swelling property (swelling time, swelling ratio) characterization. According to the results, SPH employing chitosan hybrid agents has shown less density compared to other three. Upon assessment of swelling properties, Carbapol and chitosan employing SPH's has shown comparatively equal results with respect to swelling time and swelling ratio. As pectin, Carbapol, and chitason have shown the best results, they were optimized for further characterization.

Effect of Crosslinking Agent on SPH Hybrids: From porosity and void fraction measurement, it was observed porosity was gradually decreased as the concentration of glyoxal increased. The void fraction of SPH was decreased by the increase in the amount of glyoxal.

TABLE 8: EFFECT OF GLYOXAL ON PECTIN

Formulation	Porosity (%)	Void fraction (ml/g)	Swelling studies		Mechanical strength (gm)
			Swelling time (min)	Swelling ratio	
P1	32.6 ± 10	0.87 ± 0.2	98 ± 10	251 ± 11	130 ± 26
P2	43.4 ± 12	0.73 ± 0.8	86 ± 11	242 ± 15	136 ± 12
P3	56.3 ± 15	0.64 ± 0.6	79 ± 14	232 ± 24	145 ± 21
P4	64.5 ± 11	0.53 ± 0.2	85 ± 12	225 ± 22	160 ± 23
P5	72.6 ± 14	0.41 ± 0.1	88 ± 11	219 ± 15	155 ± 21
P6	78.9 ± 18	0.32 ± 0.8	96 ± 16	215 ± 11	150 ± 16

TABLE 9: EFFECT OF GLYOXAL ON CARBAPOL

Formulation	Porosity (%)	Void fraction (ml/g)	Swelling studies		Mechanical strength (gm)
			Swelling time (min)	Swelling ratio	
SPH CL1	73.8 ± 10	1.47 ± 1.1	86 ± 23	278 ± 22	115 ± 12
SPH CL2	60.2 ± 13	1.38 ± 1.3	80 ± 22	269 ± 25	125 ± 23
SPH CL3	51.4 ± 17	1.30 ± 1.3	70 ± 25	255 ± 23	135 ± 29
SPH CL4	47.35 ± 19	1.26 ± 1.2	64 ± 12	272 ± 26	145 ± 13
SPH CL5	42.1 ± 16	1.21 ± 1.2	56 ± 16	293 ± 21	160 ± 19
SPH CL6	38.9 ± 13	1.11 ± 1.1	50 ± 17	291 ± 16	175 ± 17

TABLE 10: EFFECT OF GLYOXAL ON CHITOSAN

Formulation	Porosity (%)	Void fraction (ml/g)	Swelling studies		Mechanical strength (gm)
			Swelling time (min)	Swelling ratio	
SPH CN1	80.3 ± 12	1.38 ± 1.1	74 ± 14	265 ± 16	135 ± 21
SPH CN2	74.8 ± 12	1.31 ± 1.1	65 ± 16	277 ± 15	145 ± 12
SPH CN3	65.9 ± 11	1.26 ± 1.3	58 ± 10	280 ± 13	165 ± 14
SPH CN4	52.3 ± 10	1.18 ± 1.2	46 ± 21	289 ± 17	180 ± 13
SPH CN5	41.2 ± 19	1.09 ± 0.9	38 ± 12	279 ± 21	195 ± 16
SPH CN6	29.7 ± 11	0.96 ± 0.8	45 ± 16	271 ± 19	220 ± 10

(n=3); Mean ±S.D

To investigate the effect of crosslinker on the swelling characteristics of the gel, the concentration of glyoxal in the feed mixture was varied in the range of 1.50- 3.0%. The results are recorded, which indicates that the swelling ratio increases when the concentration of glyoxal is in the range 2.5%, while beyond 2.5% w/v the swelling ratio slightly decreases. The initial increase in the swelling time is because glyoxal itself is a hydrophilic monomer and, therefore, the swelling ratio increases with increasing concentration of glyoxal.

However, beyond 2.5%, the slight decrease is due to increasing cross-linking density in the hydrogel, which lowers the average molecular weight between cross-links, and this curtails the free volumes accessible to the penetrating water molecules. At higher amounts of glyoxal, the hydrogel network chains become so inflexible that the swelling ratio is independent of the amount of glyoxal concentration.

By carrying out mechanical properties evaluation, it was observed that the Mechanical strength was gradually increased with an increase in glyoxal concentration, which was clearly evident that as the fracture of gels happened at high weights. Also, the penetration pressure was found to be gradually increased with glyoxal concentration, thus increasing the mechanical stability. This entanglement significantly improved the structural integrity of the hydrogel and decreased stress relaxation, which enhanced its ability to withstand pressure.

Evaluation of Degradation Kinetics:

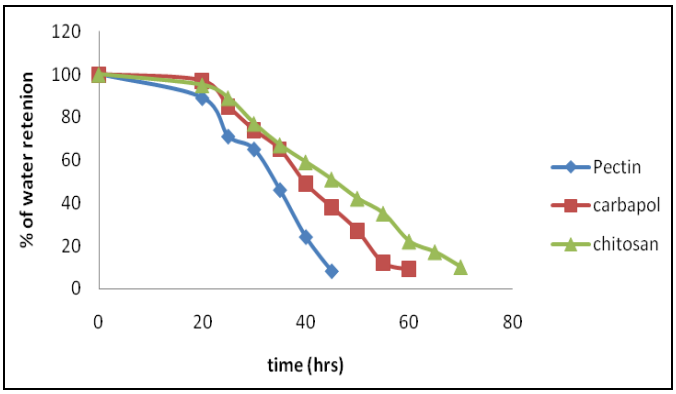


FIG. 5: WATER RETENTION STUDIES

The weight loss of pectin, carbapol, and chitason hydrogels occurred after 12 h lower the concentration of the crosslinking agent, the faster was the loss of water from the superporous hydrogel. In an acidic environment, superporous hydrogels kept equilibrium swelling ratios for a certain period of time, 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 a 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.

Gelation Kinetics: The gelation kinetics gives good information determining the introduction time of the blowing agent (sodium bicarbonate). For making homogeneous superporous hydrogels, the timing of foam formation and polymerization processes was very important. In order to produce large and uniform pores, the blowing agent must be introduced when the reactant system has appropriate viscosity. Bubbles cannot maintain their shapes by the completion of reaction when the blowing agent is introduced too early, and they cannot even be formed when introduced too late. The sol-gel transition time for various formulations was between 18- 22 sec. This clearly indicated that the blowing agent must be introduced immediately after the adjustment of pH to 5.0 with sodium hydroxide solution. At the beginning of polymerization, all the ingredients except sodium bicarbonate were mixed.

The presence of acid reduced the pH to an acidic level (pH 2.0- 3.0). At such a low pH, gelation and foaming do not occur. The gelation reaction took place only at pH of 6.0- 7.0. On the other hand, the foaming reaction took place only at the acidic condition (pH 5.0- 5.5). Hence, the pH was adjusted to 5.0 by the addition of sodium hydroxide solution (200-250 µl). At this pH, the slow polymerization occurs.

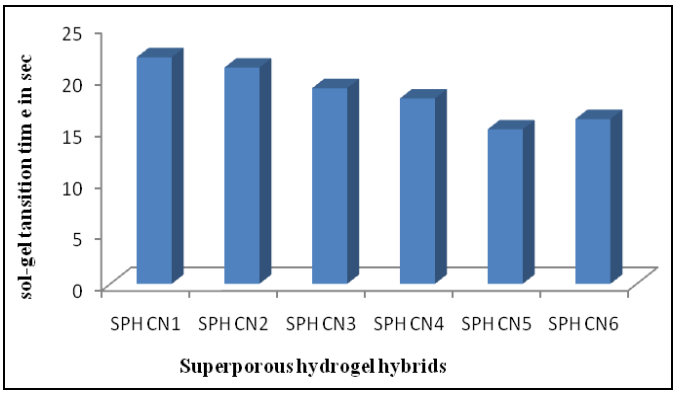


FIG. 6: GELATION KINETICS

Effect of Drying Conditions and Wetting Agents on Behavioral Characteristics of Optimized SPH Hybrids:

TABLE 11: EFFECT OF DRYING AND WETTING CONDITION ON SPH HYBRIDS

Drying condition	SPH	Wetting agent (surfactant)	Size in dried state	Density (gm/cm^3)	Swelling characters	
					Swelling time (min)	Swelling ratio
Water	SPH-CL6	-	4×2	1.37 ± 0.4	50 ± 1.2	317 ± 2.3
	SPH -CN5	-	5×3	1.12 ± 0.9	38 ± 2.3	293 ± 2.5
n-hexane	SPH-CL6	-	6×3	1.29 ± 0.8	42 ± 5.6	326 ± 4.2
	SPH-CN5	-	7×2	1.04 ± 0.2	25 ± 4.2	321 ± 1.3
Ethanol	SPH-CL6	-	9×3	1.20 ± 0.6	30 ± 2.5	342 ± 4.6
	SPH-CN5	-	10×2	0.93 ± 0.8	18 ± 2.4	338 ± 5.2
Ethanol with	SPH-CL6	2% SLS	10×3	1.15 ± 0.6	26 ± 3.6	358 ± 1.3
2% SLS	SPH-CN5	2% SLS	11×4	1.26 ± 0.2	12 ± 4.6	349 ± 4.2

To find the optimum drying condition that did not alter the swelling ratio of dried super porous hydrogels, few drying conditions were examined, the swelling ratios and swelling times of conventional and super porous hydrogels dried at four different conditions. The density of dried conventional hydrogels was 1.38 ± 0.08 $g/cm^{3,}$ while the densities of super porous hydrogels were less than 1 and as low as 1.14. There was little difference in the equilibrium swelling ratios among super porous hydrogel resulting from changes in drying conditions or the wetting agent used. However, depending on the drying condition, the super porous hydrogel showed dramatic differences in the time it took them to reach equilibrium swelling (Swelling time). When the swollen super porous hydrogels were dried at 60 °C overnight (condition II), the swelling time was around 12 min. Although this swelling time was much faster than that of the conventional hydrogels, the swelling was still too slow to be useful for our intended applications. When a super porous hydrogel dried under condition II was placed in n-hexane, the outer region swelled to equilibrium only seconds after contact with water.

This swelling changed the outer region from opaque to clear. With the penetration of water, the clear region gradually expanded towards the center. This penetration step was quite slow and took most of the swelling time. The center part remained opaque until water penetrated through. Once the water reached the center, the central region became clear and swelled to the fully swollen state in just a few seconds. The slow penetration into the center of the dried super porous hydrogels indicated that the drying under condition II somehow disrupted the capillary channels.

The inner structure of the super porous hydrogels under SEM showed that many of the capillary channels were closed or partially blocked, forming dead-end structures. Since a small percentage of closed pores can result in overall poor capillary action, the slow swelling of the super porous hydrogels was understandable. It is likely that the removal of water during drying resulted in the collapse of polymer chains and the pores due to the high surface tension of water. Such a collapse brought substantial shrinkage of the gel, as indicated by rather a high density of 1.24 g/cm^3. For this reason, we examined a method of drying in the absence of water to maintain intact capillary channels even after drying. When the super porous hydrogels were dried under condition (*i.e.*, dehydrated in ethanol first before drying), the swelling time was reduced to about 18 min.

This is an order of magnitude reduction in the swelling time pores remained intact, and no signs of pore collapses were seen. During ethanol dehydration, the super porous hydrogel became rigid, probably due to precipitation of polymer chains in a poor solvent. This rigid structure might have contributed to better maintenance of the pore structures during drying, as indicated by the low density of $0.93g/cm^3$.

Since good capillary action requires surfaces with good wettability, the effects of wetting agents on swelling kinetics were examined to see whether the swelling time could be further shortened. When super porous hydrogels were dehydrated with ethanol containing 1% SLS before drying, the swelling time was reduced even further to less than 5 min. Density was slightly increased with the presence of SLS from 0.73 to 1.26 g/cm^3. While

there was some advantage to using SLS, the decrease in the swelling time and it was reasoned that the best wetting agent would be water itself, and so moisture was absorbed into the dried super porous hydrogels in a controlled manner using a moistening chamber.

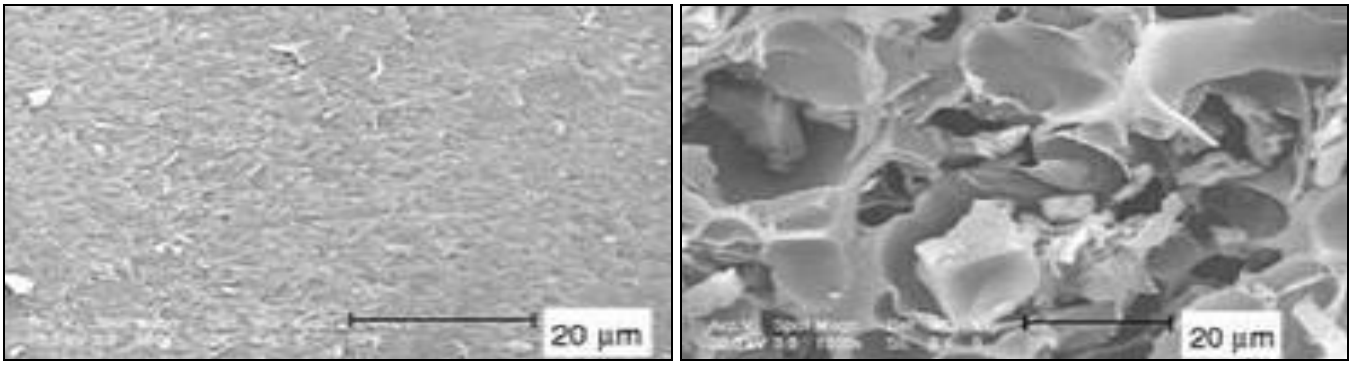


FIG. 7: SEM PHOTOGRAPHS OF CONVENTIONAL HYDROGEL (A) AND ETHANOL TREATED SPH (B)

Effect of Calcium Carbonate on Bulk Density (ρ) & Swelling Characteristics of SPH Hybrids:

TABLE 12: EFFECT OF $CACO_3$ ON BULK DENSITY (ρ) AND SWELLING CHARACTERISTICS OF SPH. HYBRIDS

SPH	Calcium carbonate (gm)	ρ (gm/cm^2)	Swelling ratio
SPH -H CN1	0.0	1.18	336
SPH- H CN2	0.50	0.92	338
SPH- H CN3	1.25	0.96	342
iSPH- H CN4	2.5	0.72	349

As shown in **Table 13**, the increase in $CaCO_3$ content has a big influence on the density of the hydrogels. The results reveal that the increase in $CaCO_3$ causes a decrease in the density of the hydrogels. The decrease in density can be attributed to the pores containing air. Using the high content of $CaCO_3$ to synthesize of hydrogel causes the high number of produced pores, and subsequently, the density will be decreased. So, the decrease in density can be attributed to the increase in porosity. The equilibrium of water content and dynamic swelling behavior of hydrogels as a function of the $CaCO_3$ amount was assessed. By using the $CaCO_3$ in the feed mixture, the water absorbency of the hydrogels increases.

This may be attributed to the fact that using $CaCO_3$ in the hydrogel makes pores in the hydrogel structure and results in high water uptake. Also, hydrogels absorb a higher amount of water with increasing $CaCO_3$ amount in reaction feed that may be due to an increase in pore number. Also, the effect of $CaCO_3$ content on the swelling kinetics of the hydrogels was investigated. A preliminary study was conducted on the hydrogels swelling kinetics.

The rate of water uptake in porous hydrogels is higher than that of a non-porous hydrogel. An increase in the rate of absorption would be expected from the increase in surface area with increasing porosity of hydrogels.

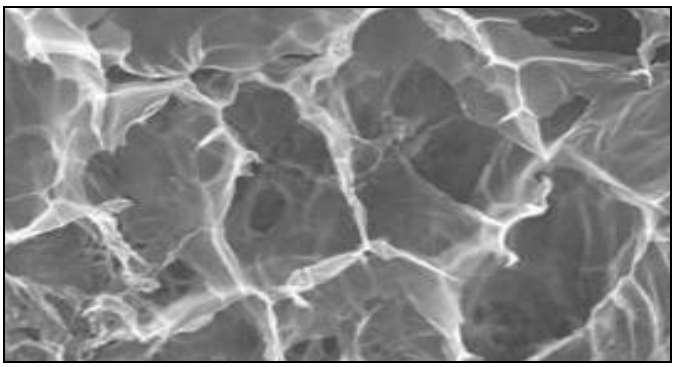
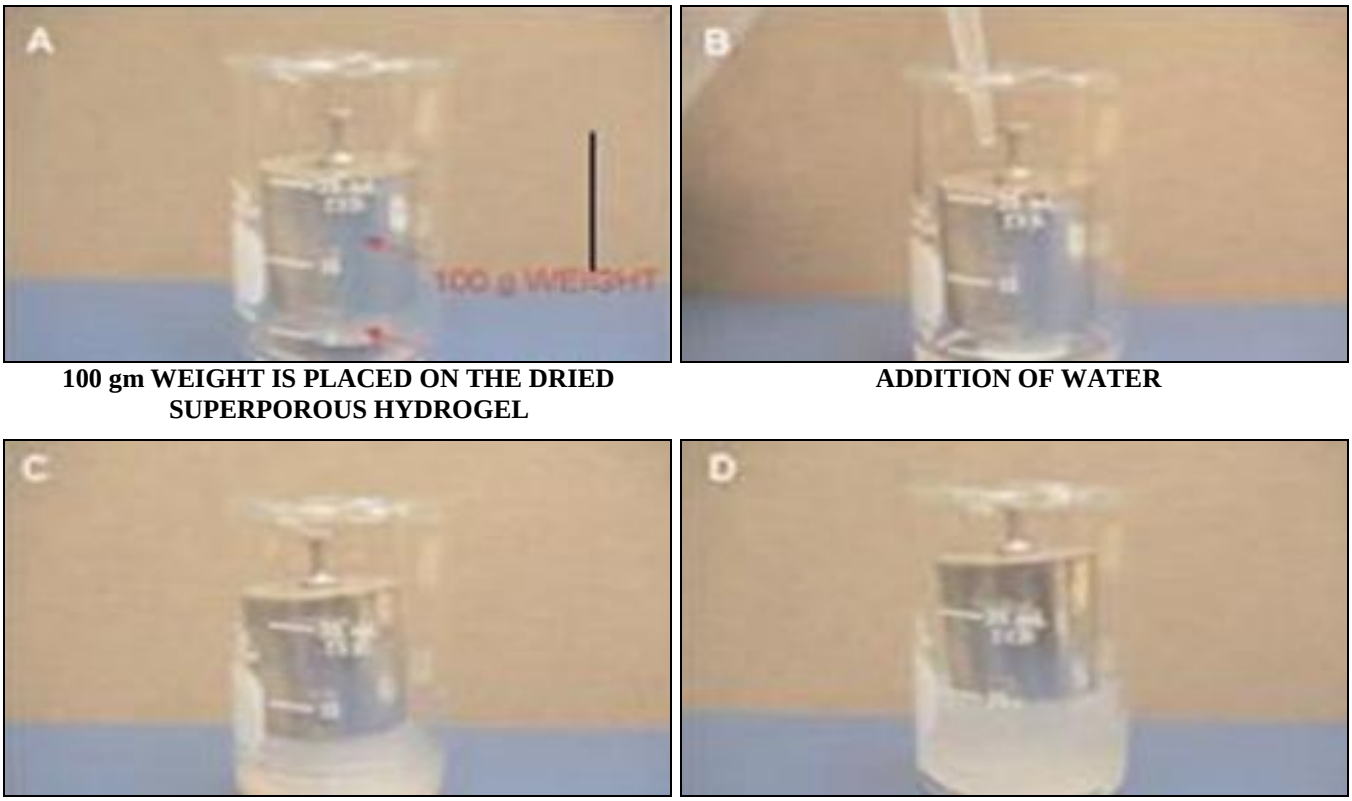


FIG. 8: SEM PHOTOGRAPH OF $CaCO_3$ TREATED SPH-HYBRIDS

Swelling Reversibility Study Comparison Between Carbapol and Chitosan Formulation: Pulsatile pH-dependent swelling of the super porous hydrogels was evaluated at 37 °C by an alternation of the swelling medium between the HCl solution (pH 1.2) and phosphate-buffered solution (PBS, pH 7.4). The swelling reversibility of the super porous hydrogel between pH 1.2 and pH 7.4 solutions. They were able to absorb and reabsorb the swelling medium quickly upon the pH change from acidic to basic conditions quickly and *vice versa*. The structure of the super porous hydrogel with large numbers of pores connected to one another to form capillary channels was favorable for easy diffusion of the swelling medium into the polymeric matrix, thus contributing to its quick response toward pH change.

The time for swelling was longer than that for deswelling of the hydrogels, which might be due to the restricted chain mobility of the hydrogels which was anchored at several points through molecular entanglement with the PVA network because the fast pH-sensitive behavior of hydrogels was based on the freely mobile side chains.

Mechanical Properties: As a hybrid agent is responsible for maintaining the capillary structure required for fast swelling of SPH, the effect of optimized hybrid on mechanical characters and swelling behavior of SPH was assessed. chitosan was increased from 1%-3.5% in CN-1 to CN-6 SPH's. As the hybrid chitosan conc. Increased, there was an extensive variation in swelling properties. Swelling time was gradually decreased from 45 min to 16 min. As the amount of chitosan increases the mechanical strength increases due to increased cross-linking density of the super porous hydrogel.



100 gm WEIGHT IS PLACED ON THE DRIED SUPERPOROUS HYDROGEL

ADDITION OF WATER

IMMEDIATE SWELLING OF SUPERPOROUS

LIFT OF 100 gm WEIGHT

FIG. 9: MECHANICAL PROPERTIES OF OPTIMIZED SPH- HYBRIDS

Optimization of Chitosan Concentration: As a hybrid agent is responsible for maintaining the capillary structure required for fast swelling of SPH, the effect of optimized hybrids on mechanical characters and swelling behavior of SPH was assessed. Chitosan conc. was increased from (1-3.5%), respectively, from SPH CN1-SPH CN6.

TABLE 13: RESULTS DESCRIBING EFFECT OF CHITOSAN ON SWELLING RATIO AND MECHANICAL STRENGTH

Formulation code	Swelling studies		Mechanical strength (gm)
	Swelling time (min)	Swelling ratio (n=3); mean ± S.D	
SPH CN 1	45 ± 9.2	265 ± 19	136 ± 13
SPH CN 2	39 ± 3.6	279 ± 20	148 ± 10
SPH CN 3	31 ± 8.3	286 ± 25	162 ± 11
SPH CN4	29 ± 1.2	291 ± 14	185 ± 21
SPH CN5	19 ± 1.5	294 ± 14	193 ± 16
SPH CN6	16 ± 1.2	304 ± 16	220 ± 18

As the hybrid chitosan concentration increased, there was an extensive variation in swelling properties. Swelling time was gradually decreased from 45 min to 16 min from SPH CN1-CN6 and

swelling ratio has gradually increased with an increase in HYBRID agent conc. This indicates that CHITOSAN improved the structural integrity of the super porous hydrogel by an entanglement of the polymer chains with the chitosan fibers. It also provides intrafibers capillary channels in its hollow lumen. This effect causes a reduction in swelling time. One of the most important requirements for gastric retention super porous hydrogel is its structural integrity. A super porous hydrogel should be able to withstand the pressure expected in the stomach during repeated gastric contraction. As the amount of chitosan increases the mechanical strength increases due to increased cross-linking density of the super porous hydrogel. When more than 2.5% chitosan was incorporated, due to the increase of solution viscosity, good mixing of all the ingredients becomes difficult. Thus, 2.5% of Chitosan (SPH CN 5) was used as the optimum concentration.

TABLE 14: WATER UPTAKE STUDY (SWELLING INDEX)

FC	Swelling index	Density of dried SPH (gm/cm^3)
F1	47.35 ± 0.23	298 ± 2.5
F2	58.00 ± 0.14	299 ± 3.2
F3	40.00 ± 0.12	296 ± 2.7
F4	72.60 ± 0.80	299 ± 2.5
F4	52.75 ± 0.56	298 ± 3.2
F6	74.50 ± 0.20	299 ± 3.5

TABLE 15: POROSITY, VOID FRACTION, PENETRATION PRESSURES AND WATER RETENTION OF SUPERPOROUS HYDROGEL FORMULATIONS

Formulations	Porosity (%)	Void fraction (ml/g)	Penetration pressure (g/cm^2)	Water retention capacity
F1	38.3 ± 2.2	1.42 ± 0.03	52 ± 3	0.63468
F2	58.3 ± 3.1	1.25 ± 0.04	78 ± 5	0.77567
F3	66.4 ± 2.5	1.15 ± 0.01	103 ± 6	0.52869
F4	73.2 ± 4.2	0.93 ± 0.03	126 ± 8	0.97423
F4	44.2 ± 3.3	1.33 ± 0.02	62 ± 3	0.70496
F6	79.2 ± 1.5	0.85 ± 0.04	165 ± 11	0.70945

In-vitro **Buoyancy Studies:** The Prepared SPH-chitosan formulations were placed in a 100 ml glass beaker containing 0.1 N Hydrochloride.

TABLE 16: FORMULA OF DOSAGE FORM TO CARRY OUT *IN-VITRO* BUOYANCY STUDY

Ingredients	SPH-CN1	SPH-CN2	SPH-CN3	SPH-CN4	SPH-CN5	SPH-CN6
Glyoxal (µl)	50	50	50	50	50	50
Potassium persulphate (µl)	20	20	20	20	20	20
Span 80 (µl)	15	15	15	15	15	15
Sodium bicarbonate (mg)	100	100	100	150	175	200
Chitosan (%)	2.5%	3%	3.5%	2.5%	3%	3.5%

TABLE 17: *IN-VITRO* BUOYANCY STUDY

Formulation	Floating lag time (min)	Floating time (h)
CN1	36	>12
CN2	42	>12
CN3	46	>12
CN4	32	>12
CN5	41	>12
CN6	53	>12

The formulae CN1, CN2 and CN3 contain constant $NaHCO_3$ and they have polymer ratio 2.5-3.5 w/w, respectively. In the study it was observed that CN1 which had the least polymer ratio, had significantly shorter buoyancy lag time of 36 sec. whereas the formulae CN2 & CN3 containing 3% and 3.5% w/w of the polymer respectively showed buoyancy lag times of 42 & 47 sec, respectively. The F1 lag time was shorter than that observed with other formulae containing increasing concentrations of 2.5% (formulae CN2 & CN3). This could be explained with regard to the rate of the test medium penetration into these matrices and, consequently, the time required for gel formulation. In the formulae, CN4, CN5, and CN6, the $NaHCO_3$ ratio maintained were 125,150,175 mg, and the release retarding polymer was placed in the ratio of 2.5, 3, and 3.5% respectively. In these formulations to it was observed that the formulae CN4 containing the least amount of the polymer has shown shorter buoyancy lag time of 32 sec, whereas the formulation CN5 & CN6 containing 3% and 3.5% w/w of the polymer respectively has shown buoyancy lag time in ascending fashion (41 and 53) *i.e.*, as the polymer ratio increased the floating lag time also increased.

Dissolution and *in-vitro* Evaluation: Lafutidine SPH-Chitosan drug delivery systems (SPH- CN1 to SPH-CN7) were prepared according to the procedure given in section 6 of Chapter 6 and subjected to *in-vitro* dissolution studies for 12 hours duration.

Dissolution Study: The rate retarding polymer selected for the formulation is Lipoidal in nature since comparatively, they have less density and may not affect the buoyant characters of the SPH-Hybrid systems. SPH-HF1 to SPH-HF7 combined formulations were developed employing different concentrations of CN5 powder, increasing from 100-250 mg, 5 mg of mg. stearate, 5 mg of talc, and remaining weight of mcc to make 300 mg total weight of the tablet. All the lafutidine CR formulations developed *viz*., SPH-C, SPH-HF1 to SPH-HF7 were subjected to *in-vitro* dissolution studies using USP XVI paddle-type dissolution apparatus for 12 h duration. All the samples were U.V analyzed. Lafutidine SPH-HF1 formulation employing 100mg Chitosan as polymer has shown less retardancy by releasing 100.15% of lafutidine by 9 h itself because of the low concentration of polymer. Lafutidine SPH-HF2 formulation employing 125mg Chitosan has a comparatively less controlling effect by releasing 99.44% in 10 h.

Lafutidine SPH-H3 formulation employing 150 mg has released 98.12% lafutidine at the end of 11 h. Lafutidine SPH-HF4 formulation employing 175 mg of Chitosan polymer has shown much more retardancy than SPH-HF1 by releasing only 96.51% of lafutidine at the end of 12 h, which shows the high retarding ability of the polymer. Lafutidine SPH-HF5 formulation employing 200 mg of **c**hitosan polymer has also shown good controlling ability by releasing only 84.26% of lafutidine at the end of 12 h. But lafutidine daily dose seems to be two times a day. Hence, the optimum drug is not released as required within 12 h because of the high retarding capacity of Chitosan concentration.

Lafutidine SPH-HF6 formulation employing 225 mg of polymer has shown less retardancy than SPH-HF1 and HF-5 by releasing 98.15% of drug in 10 h which shows the high retarding ability of the polymer has been overcome with low concentration of mcc, *i.e.*, below 20% hence HF5 having 10% which acts as super-disintegrant and so tablet integrity is not maintained for much time.

Lafutidine SPH-H7 formulation employing 250mg of polymer failed to release the drug up to 12 h, 99.15% of lafutidine were released in 8 h has shown much less retardancy than SPH-HF1and HF-5 which shows the high retarding ability of the polymer has been overcome with low concentration of mcc *i.e.*, below 20% having 18% which acts as super disintegrant and so tablet integrity is not maintained for much time. Except for F6 and F7, all other formulations have shown consistently controlled release of medication, which may suggest being chitosan is supporting polymer to super porous hydrogel hybrid formulation.

Upon comparison of *in-vitro* release profiles of all the formulations, SPHH DDS employing 175 mg of Chitosan with 35% of microcrystalline cellulose as rate controlling polymer has shown maximum retarding ability beyond 12 h. Dug release profiles are shown in **Fig. 10**.

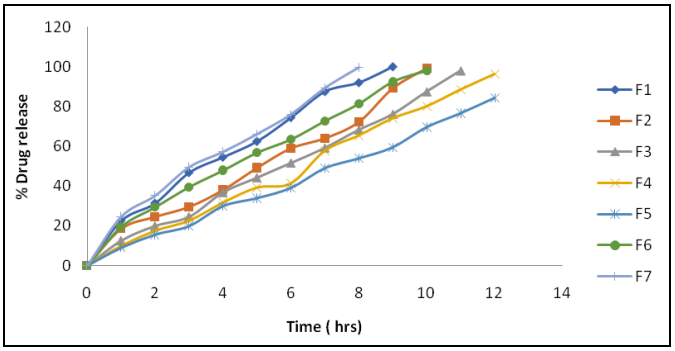


FIG. 10: CUMULATIVE% RELEASE PROFILE OF LAFUTIDINE CHITOSAN FORMULATION F1-F7

Analysis of the Release Data: The order of drug release from matrix systems was described by using zero-order or first-order kinetics. The mechanism of drug release from matrix systems was studied by using the Higuchi equation and erosion equation and Peppas-Korsmeyer equation. All the formulations were found to be following zero-order kinetics, which was evident from the higher r^2 values compared to that of the first-order plots. In order to assess the release mechanism, all the formulations dissolution data were fitted to Higuchi and Erosion plot; r^2 values of Higuchi plots were found to be more than that of erosion plot, which indicates Higuchian diffusion as the release mechanism. The dissolution data of all

SPHH formulations were fitted to the Power law (Korsemeyer Pappas model), and all the exponent - n values were found to be between 0.5-1, which indicates all the formulations were following Non-Fickian mode of drug release and are shown in **Table 19**.

TABLE 18: REGRESSION COEFFICIENT & EXPONENTIAL VALUES OF LAFUTIDINE SPH – FORMULATIONS F1- F7

Formulation	Zero Order	First-order	Higuchi	Erosion	Korsmeyer Peppas		Hixson Crowell
					R^2	"n"	
F1	0.976	0.901	0.969	5.976	0.651	0.829	0.975
F2	0.988	0.795	0.918	5.536	0.702	0.756	0.983
F3	0.997	0.84	0.922	5.324	0.781	0.676	0.995
F4	0.993	0.909	0.914	5.217	0.824	0.601	0.995
F5	0.996	0.92	0.915	5.018	0.829	0.824	0.996
F6	0.987	0.852	0.964	5.945	0.678	0.806	0.98
F7	0.977	0.889	0.974	5.893	0.617	0.840	0.972

Drug-Polymer Compatibility Studies:

IR Spectroscopic Studies: Lafutidine pure, Lafutidine Optimized Polymer physical mixture, Optimized Polymer formulations were subjected to IR spectroscopic studies to check the compatibility among them.

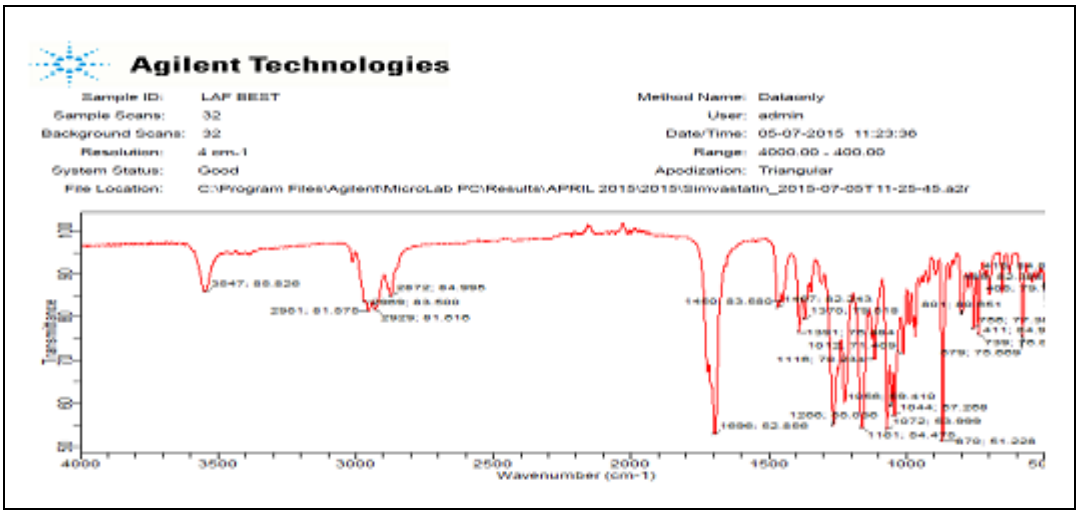


FIG. 11: IR SPECTRA OF LAFUTIDINE + CHITOSAN BEST FORMULATION

No prominent difference was observed in the principal IR peaks of lafutidine, Optimized Polymer (Chitosan), physical mixture formulations upon comparison with the peaks of drug and polymer alone, which may be considered that Lafutidine + Chitosan are compatible enough without any interaction and are shown in **Fig. 11**.

Differential Scanning Calorimetric (DSC) Studies: Differential Scanning Calorimetry is a technique by which the heat flows to or from a reference is monitored as a function of temperature or time, while the sample is subjected to a controlled temperature program. Lafutidine pure drug, optimized polymer chitosan, lafutidine optimized polymer physical mixture, lafutidine Optimized polymer (chitosan) formulations were subjected to DSC studies to check the compatibility among them.

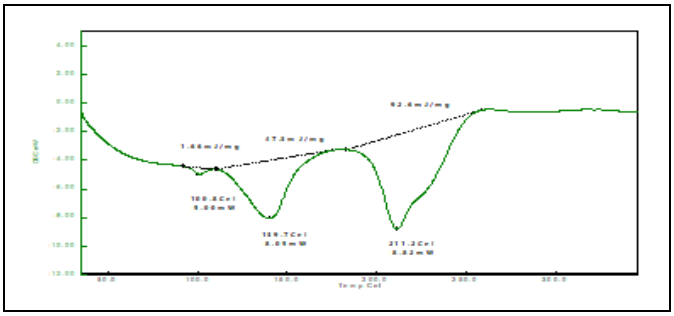
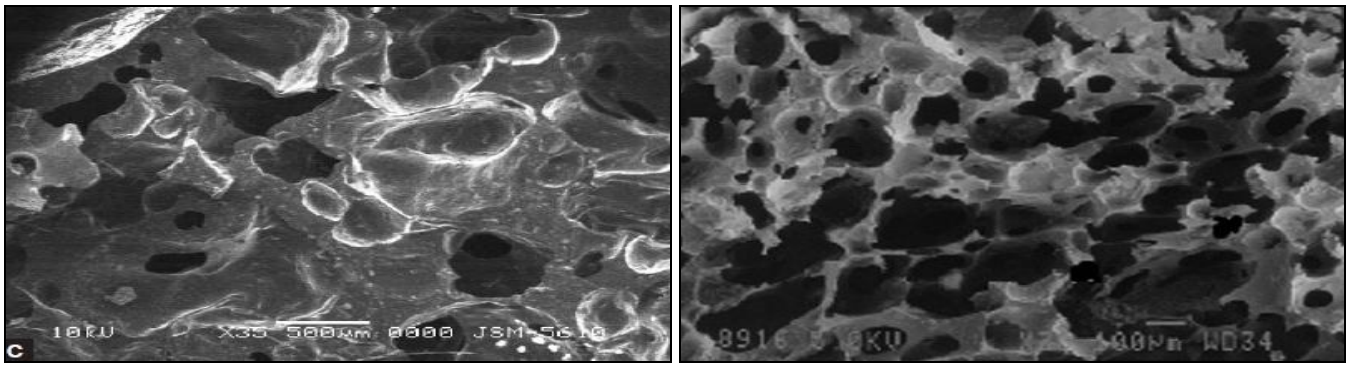


FIG. 12: DSC THERMOGRAM OF LAFUTIDINE BEST FORMULATION

No prominent enthalpy changes were observed in the DSC endotherms of Lafutidine, Optimized Polymer Chitosan, physical mixture formulations upon comparison with the peaks of drug and polymer alone, which may be considered that lafutidine and chitosan are compatible enough without any interactions. FTIR spectra were given in **Fig. 12**.

Scanning Electron Microscopy: The SEM images of SPH possessed large numbers of interconnected pores, indicating that formation hydrogel with the super porous structure. In the structure of SPH, the inner surface contained large numbers of the pores connected to each other. It can be observed in the SEM image, which shows structures with great penetration of the medium into the system with pores that form connections (channels) with the interior of the structure. The capillary channels were clearly observed from SEM image, and this may enable water to enter into the hydrogel networks or drug molecules to diffuse out of them. The optimized formulation was subjected to surface Topography studies using Scanning electron Microscopy studies to assess the surface characteristics of the optimized formulation. The scanning electron microscopic photograph of super porous hydrogel shown in **Fig. 13** clearly indicates the presence of pores on the surface. The super porous hydrogel has high porosity and is responsible for faster swelling of super porous hydrogels. The mechanical strength was significantly increased.



SPHH, ×35 MAGNIFICATION WITH SCALE BAR OF 500µm

PHH, ×100 MAGNIFICATION WITH SCALE BAR OF 500µm

FIG. 13: SEM PHOTOGRAPH REVEALS THE PRESENCE OF THE SWOLLEN PORES ON THE SURFACE OF THE SUPERPOROUS HYDROGEL COMPOSITE DRUG DELIVERY SYSTEMS

Scanning electron microscopic photograph of formulation IV recorded at various magnification. The pictures were taken at an excitation voltage of 10 kV. SEM pictures of SPHH and SPHH particles. SEM photograph reveals the presence of the swollen pores on the surface of the super porous hydrogel composite drug delivery systems.

TABLE 19: ACCELERATED STABILITY STUDY

Parameters	After 15 days	After 30 days	After 45 days
Physical appearance	No change	No change	No change
Weight variation (mg)	298 ± 1.6	299 ± 2.70	298 ± 1.30
Thickness (mm)	4.19 ± 1.87	4.21 ± 2.86	4.23 ± 3.98
Hardness (kg/cm^2)	7.24 ± 0.23	7.20 ± 0.64	7.20 ± 0.99
Friability (%)	0.56 ± 0.05	0.57 ± 0.08	0.57 ± 0.06
Drug content (mg/Tab)	98.34 ± 0.34	98.21 ± 0.29	98.01 ± 0.87
Buoyancy lag time (sec)	32 ± 1.60	33 ± 2.8	33 ± 3.10
Duration of buoyancy (hr)	>12	>12	>12
Swelling time	19 ± 1.2	21 ± 1.6	18 ± 1.4

Determination of shelf life accelerated stability studies were carried out at required conditions for 45 days all the parameters like physical appearance, weight variation, thickness, hardness, friability, drug content, buoyancy lag time, floating time, swelling time were found to be within limits.

CONCLUSION: The results conclusively demonstrated that super porous hydrogel tablets of lafutidine were effectively prepared with desired properties. Super porous hydrogel tablets of lafutidine were prepared by the direct compression method. The directly compressed formulations exhibited better *in-vitro* drug release profiles.

The formulation F4 prepared by direct compression containing chitosan-based glyoxal prepared by cross-linking technique exhibited useful swelling index and maximum rate of drug release. So, this formulation was considered to be the optimized

formulation. The prepared tablet formulations are evaluated for different pre-compressional and post compressional parameters; the results revealed that all formulations show good pre-compressional properties showing better flowability, hardness is maintained in the range of 4.9 to 6.9 kg/cm^2 which provides good mechanical strength to the tablet.

Other parameters like weight variation, friability, thickness, drug content are in the range of prescribed limits of IP. Thus, the formulated super porous hydrogel tablets of lafutidine offer a superior alternative over conventional marketed dosage forms in regards to Localized action and Sustained release of the drug. FTIR studies, combined with stability studies, proved the integrity of the developed tablets along with SEM analysis gives improved information of the formulation by showing porous formation. The mechanical stability of SPHC in Gastric fluid is significantly enhanced and depends on the chitosan content. SPHC-DDS is mechanically stable, low dense has a good swelling capacity, and is pH-dependant.

The zero-order best explains the *in-vitro* drug release from SPHC. SPHC-DDSs are found to be stable for three months. A sustained release lafutidine drug delivery system has been prepared successfully using an SPHC, with Chitosan as a composite material.

ACKNOWLEDGEMENT: The authors are thankful to the Hindu College of Pharmacy for providing support to this research.

CONFLICTS OF INTEREST: There is no conflict of interest during this research.

REFERENCES:

1. Hoffman A, Stepensky D, Lavy E, Eyal S, Klausner E and Friedman M: Pharmacokinetic and pharmacodynamic aspect of gastroretentive dosage forms. International Journal of Pharmaceutics 2004; 277(1-2): 141-53.
2. Klausner EA, Lavy E, Friedman M and Hoffman A: Expandable gastro retentive dosage forms, Journal of Controlled Release 2013; 90(2): 143-62.
3. Arora S, Ali J, Ahuja A, Khar RK and Baboota S: Floating drug delivery system: a review. AAPS Pharm Sci Tech 2005; 6(3): 373.
4. Desai S and Bolton S: A floating controlled release drug delivery system: an *in-vitro-in-vivo* evaluation. Pharmaceutical Research 1993; 10(9): 1321-25.
5. Gupta NV and Shivakumar HG: pH-sensitive super porous hydrogels composed of methacrylic acid and acrylamide: preparation and properties. Acta Pharmaceutica Sciencia. 2010; 52(3): 239-46.
6. Omidiana H, Rocca JG and Park K: Advances in super porous hydrogels .Journal of Controlled Release. 2005; 102(1): 3-12.
7. Park K: Super porous hydrogels for pharmaceutical and other applications. Drug development and Delivery 2002; 2(5): 1-19.
8. Li YK, Guo CG, Wang L, Xu Y, Liu CY and Wanga CQ: self-healing and multi-responsive hydrogel based on biodegradable ferrocene-modified chitosan. Royal society of Chemistry 2014; 4: 55133-38.
9. Qiu Y and Park K: Superporous IPN Hydrogels Having Enhanced Mechanical Properties. AAPS Pharm Sci Tech 2003; 4(4): 402-06.
10. Dorkoosh FA, Borchard G, Rafiee-Tehrani M, Verhoef JC and Junginger HE: Evaluation of superporous hydrogel (SPH) and SPH composite in porcine intestine ex-vivo: assessment of drug transport, morphology effect, and mechanical fixation to intestinal wall. European Journal Pharmaceutics and Biopharmaceutics 2002; 53(2): 161-66.
11. Bagadiya A, Kapadiya M and Mehta K: Superporous hydrogel: a promising tool for gastro retentive drug delivery system, International Journal of Pharmacy &Technology 2011; 3(4): 1556-71.
12. Nagpal M, Singh SK and Mishra D: Superporous hydrogels as gastroretentive devices, Acta Pharmaceutica Sciencia, 2011; 53(1): 7-24.
13. Patel NP, Pandya VM and Bharadia PD: Recent development in superporous hydrogel, International Journal of Universal Pharmacy and Life Sciences 2012; 2(3): 147-59.
14. Omidian H, Zohuriaan-Mehr MJ, Kabiri K and Shah K: Polymer chemistry attractiveness: Synthesis and swelling studies of gluttonous hydrogels in the advanced academic laboratory. J of Polymer Materials 2004; 21(3): 281-92.
15. Dewan B and Chimata R: An open-label, randomized, cross-over bioequivalence study of lafutidine 10 mg under fasting condition. World Journal of Gastrointestinal Pharmacology and Therapeutics 2010; 1(5): 112-18.
16. Haruki S, Matsumoto H, Kodama K, Tanabe M, Takayanagi H and Cyong J: Pharmacokinetic studies of lafutidime (FRG–8813) in man. Japan Pharmacology and Therapeutics 1995; 23: 3049-59.
17. Chowdary KPR, Prakasarao KS and Madhuri D: Formulation and evaluation of etoricoxib tablets employing cyclodextrin- Poloxamer 407- PVP K30 inclusion complexes. International Journal of Applied Biology and Pharmaceutical Technology 2011; 2(4): 43-48.
18. Kovvasu SP, Kunamaneni P and Janjanam KC: Formulation and optimization of controlled-release paroxetine hydrochloride tablets using response surface methodology. Journal of Global Trends in Pharmaceutical Sciences 2016; 7: 3520-34.
19. Chowdary KPR, Sundari PT and Prakasarao KS: Formulation and evaluation of piroxicam and aceclofenac tablets employing Prosolve by direct compression method. Asian Journal of Chemistry 2009; 21(8): 5847-50.
20. Kovvasu SPR and Chowdary KPR: Formulation development and *in-vivo* evaluation of pioglitazone inclusion complexes: A factorial study. International Journal of Applied Pharmaceutics 2018; 10(3): 49-55.
21. Gupta NV and Shivakumar HG: Preparation and characterization of superporous hydrogels as pH-sensitive drug delivery system for pantoprazole sodium. Current Drug Delivery 2009; 6(5): 505-10.

22. Ray D, Sahoo PK and Mohanta GP: Designing of superporous cross-linked hydrogels containing acrylic-based polymer network. Asian Journal of Pharmaceutics 2008; 2(2): 123-27.
23. Kumar A, Pandey M, Koshy MK and Saraf SA: Synthesis of fast swelling superporous hydrogel: effect of concentration of crosslinker and acdisol on swelling ratio and mechanical strength. International Journal of Drug Delivery 2010; 2(2): 135-40.
24. Shwetha K and Swamy NGN: Development and evaluation of superporous hydrogels for metoprolol tartrate as a gastro retentive system. Indian Journal of Novel Drug Delivery 2012; 4(2): 104-09.
25. Bagadiya A, Kapadiya M and Mehta K: Superporous hydrogel: a promising tool for gastro retentive drug delivery system. International Journal of Pharmacy &Technology 2011; 3(4): 1556-1571.
26. Gupta NV and Shivakumar HG: Preparation and characterization of superporous hydrogels as gastro retentive drug delivery system for rosiglitazone maleate. Journals tums ac ir 2010; 18(3): 200-10.
27. Patel PK, Mistry SN, Patel GJ, Bharadia PD, Pandya VM and Modi DA: Recent in controlled drug delivery system: superporous hydrogels. Journal of Pharmaceutics and Cosmetology 2011; 1(5): 53-65.

How to cite this article:
Ramya MG, Akki R and Kathirvel S: Formulation and *in-vitro* characterisation of controlled release lafutidine super porus hydrogel tablets. Int J Pharm Sci & Res 2020; 11(8): 3745-62. doi: 10.13040/IJPSR.0975-8232.11(8).3745-62.