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Research Article

Polysaccharide-Based Superporous, Superabsorbent, and Stimuli Responsive Hydrogel from Sweet Basil: A Novel Material for Sustained Drug Release

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This study is carried out on polysaccharide-based hydrogel extracted from the seeds of *Ocimum basilicum* L. for its evaluation as a superabsorbent and stimuli responsive biomaterial for sustained release drug delivery system. *O. basilicum* (Syn: Basil) seed hydrogel (BSH) expressed high swelling capacity at pH 6.8 and 7.4 and deionized water. Highly reversible on-off switching (swelling-deswelling) behavior of BSH was ascertained in deionized water and ethanol, pH 7.4 and 1.2, and deionized water and normal saline. Scanning electron microscopy (SEM) of BSH has revealed macroporous structure of BSH having average pore size of $1.92 \pm 3.83\ \mu$m noted after swelling and lyophilization. BSH containing tablet formulations showed a sustained release pattern of diclofenac sodium (DS) which is dependent on the concentration of BSH. When comparing with commercially available formulation of DS, even better sustained release behavior of DS was observed in BSH-based formulation. Super case-II transport mechanism is followed by the DS release from BSH matrix tablet. Haemocompatibility studies of BSH were also performed and found it nonhaemolytic and nonthrombogenic.

1. Introduction

Hydrogels are water swellable materials having three-dimensional polymeric network retaining both the cohesive properties of solids and diffusive transport of liquids. They have got great attraction of researchers and technologists due to their extensive biomedical applications [1, 2]. Such hydrogels have interconnected microscopic pores and elasticity, possessing hydrophilic functional groups (hydroxyl, carboxylic acid, amide, and sulphate) which enhance their water holding and swelling capacity [3, 4]. Hydrogels have also reversible volume phase transitions depending on stimuli factors such as temperature, ionic strength, pH, solvent composition, and electric field [5, 6]. These properties made hydrogels promising materials for pharmaceutical, agriculture, and biotechnological applications [7, 8].

Recently, polysaccharide-based hydrogels have gained a lot of interest in drug delivery system due to their extraordinary swelling indices, stimuli responsive properties, biodegradability, biocompatibility, and nontoxicity [9–13].

Ocimum basilicum L., (Syn: sweet basil in English, Babui tulsi in Hindi and Marathi, Rihan in Arabic, Niasabo in Gujrati, Jangli tulsi in Urdu, Tohrakhurasani in Persian, and Okimon in Unani) is a popular culinary and ornamental herb

also used in a folk medicinal value [14–19]. *O. basilicum* L. (OB; sweet basil) seeds (OBS) have the ability to swell 10-12 times of their original volume [20]. The epidermis of OBS when soaked in water rapidly swells and excretes a gelatinous material. The high mucilage content of seeds can make it a good source of edible gum [21]. This mucilage is mainly composed of carbohydrates like D-glucose, D-galactose, D-mannose, L-rhamnose, pectins, and hemicellulose materials. Minor components are protein, minerals, and fat [22]. The polysaccharides extracted from OBS by cold water extraction and alcohol precipitation consist of two major fractions, i.e., an acid-stable core glucomannan and a (1-4) linked xylan having acidic side chains. Glucomannan constitutes a major fraction (43%) having glucose to mannose ratio of 10:2, minor fraction of xylan (24%), and a smaller portion of glucan (2.31%) [23].

We are focused on the extraction of BSH from OB seeds and its utilization as a superabsorbent biomaterial for sustained drug delivery. This study is addressing swelling-deswelling behavior (on-off switching) of BSH in different solvents, salts, and pH to show its network flexibility. We also report on the kinetic analysis of the swelling data recorded in various media. The design of oral formulation of drug in tablet form is also aimed at getting sustained delivery of diclofenac sodium. The morphology of hydrogel and tablets formulation is also being reported. For potential biomedical applications, BSH will be evaluated through blood compatibility studies.

2. Materials and Methods

2.1. Materials. Seeds of *O. basilicum* were purchased from the local market. HCl, ethanol, *n*-hexane, potassium dihydrogen phosphate, and KCl were acquired from Riedel-de Haën, Germany. NaOH (Merck) was standardized with oxalic acid. Avicel® PH-101 and tragacanth gum were purchased from Fluka. Simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) were prepared as described in United States Pharmacopeia (2010). Deionized water was used during all experiments. Tea bags with a 100-mesh nylon screen (i.e., tea bag method [11]) were used for swelling-deswelling experiments.

2.2. Isolation of BSH. BSH was isolated from the seeds of *O. basilicum* as reported elsewhere with some modification [3, 4, 10]. Briefly, seeds of *O. basilicum* (50 g) were soaked in deionized water (1000 mL) for 4 h before warming at 40°C for 45 min. Mucilage/hydrogel was extruded from the seed coat and separated by gentle pressing the seed using nylon gauze. Isolated hydrogel (BSH) was washed three times with *n*-hexane (200 mL) to make it free from nonpolar substances. Finally, BSH was thoroughly washed with deionized water and separated through centrifugation. BSH was dried at 60°C for 48 h in vacuum oven, crushed, and passed through sieve no. 60. BSH powder was stored in vacuum desiccator until further use. Yield of BSH was found as 8.9 g/100 g of dried OB seeds.

2.3. Physical Properties of BSH. Physical properties of BSH, such as bulk density, tapped density, particle size, angle of repose, Hausner ratio, and Carr's index, were determined. Moisture content, water retention capacity, gelation contents, and swelling capacity of hydrogel were also determined [10].

2.3.1. Bulk and Tapped Density. BSH powder (1.0 g) was filled in a graduated cylinder (10 mL) and its bulk volume (V_b) was noted. Tapped volume (V_t) was determined by tapping the filled cylinder for 100 times and noting the final volume. Bulk density (D_b) and tapped density (D_t) were calculated using the following equations, respectively [24]:

$$D_b = \frac{weight\ of\ hydrogel}{volume\ of\ hydrogel\ (Vb)} \tag{1}$$

$$D_t = \frac{weight\ of\ hydrogel}{Tapped\ Volume\ (Vt)}. \tag{2}$$

2.3.2. Angle of Repose. To observe the flow properties of BSH, angle of repose was determined using fixed funnel method [25]. BSH powder was allowed to pass freely through a funnel on a graph paper until the apex of the heap just touched the lower tip of the funnel. The height (h) and radius (r) of the circular heap were noted accurately and angle of repose (θ) was calculated using

$$\tan(\theta) = \frac{h}{r}. \tag{3}$$

2.3.3. Hausner Ratio. It is the ratio of tapped density to bulk density and calculated using the following [24]:

$$Hausner\ ratio\ (H) = \frac{D_t}{D_b}. \tag{4}$$

2.3.4. Carr's Index. To measure the packing arrangements of BSH powder, Carr's index was calculated using the following equation [25]:

$$Carr's\ index\ (C) = 100 \times \left(1 - \frac{D_b}{D_t}\right). \tag{5}$$

2.3.5. Moisture Content. Moisture content of BSH powder was calculated by weighing the BSH powder (1.0 g) before and after heating at 105°C for 60 min in a vacuum oven.

2.3.6. Gelation Contents. BSH (0.1 g) was allowed to swell in deionized water (100 mL) for 24 h at 25°C followed by centrifugation at 3000 rpm for 45 min. Sediment paste was separated, weighed, and dried at 70°C under vacuum. The dried paste is the gelling content of BSH. Gelling contents were calculated using the following equation [26]:

$$Gelling\ contents\ (\%) = \frac{W_f}{W_i} \times 100, \tag{6}$$

where W_f is the dried weight of the sediment paste and W_i is the weight of wet paste.

2.4. Stimuli Responsive Swelling Study of BSH

2.4.1. pH Responsive Swelling of BSH. BSH powder (0.1 g) was accurately weighed and filled in each of the four tea bags (i.e., a 100-mesh nylon screen). These bags were separately dangled in four beakers (100 mL) having buffer solutions of pH 7.4, 6.8, and 1.2 and deionized water. Bags were carefully removed after specific time intervals and hung for some time to drain excess water. Weight of each bag was noted and put again in relevant media to continue the swelling studies. The swelling capacity (g/g) was calculated using the following equation:

$$\text{Swelling capacity}\,(g/g) = \frac{W_t - W_o - W_c}{W_o}, \tag{7}$$

where W_o is the weight of dry BSH filled in the tea bag, W_c is weight of empty wet tea bag, and W_t is the weight of wet tea bag having swollen BSH.

The same swelling procedure was performed in a single step and calculated the maximum swelling capacity after 24 h using (7).

2.4.2. Salt Responsive Swelling of BSH. Solutions of NaCl and KCl were prepared with different concentrations (0.01, 0.05, 0.1, 0.25, 0.5, 1, 1.5, and 2.0 M) and used to determine equilibrium swelling (after 24 h) of BSH. Accurately weighed BSH powder (0.1 g) was filled in each of the eight tea bags (i.e., a 100-mesh nylon screen) and dipped in different concentrations of salt solution. After 24 h, bags were removed from beakers and hung for a while to drain out excessive salt solution and swelling capacity was determined using (7).

2.5. Stimuli Responsive Swelling-Deswelling Behavior of BSH

2.5.1. pH Responsive Swelling-Deswelling of BSH. Accurately weighed BSH powder (0.1 g) was taken in a tea bag and placed in beaker (100 mL) having buffer solution (80 mL) of pH 7.4 for 20 min. Bag containing swollen BSH was removed periodically and weighed after draining excess medium. To observe deswelling behavior of BSH, this bag having swollen BSH was then placed in another similar beaker having buffer solution of pH 1.2 with the same volume for 20 min. Again, the tea bag was removed, drained from the excessive media, weighed, and placed in buffer solution of pH 7.4 for swelling. This swelling-deswelling cycle was performed four times. Swelling capacity was calculated using (7).

2.5.2. Saline Responsive Swelling-Deswelling of BSH. Responsiveness of BSH powder in deionized water and normal saline was noted by alternatively placing the BSH filled tea bag (i.e., a 100-mesh nylon screen) in respective media (deionized water for swelling and normal saline for deswelling) as described in previous section.

2.5.3. Ethanol Responsive Swelling-Deswelling of BSH. Deionized water and ethanol were used as swelling and deswelling media, respectively to determine the response of BSH powder. Time duration for placing BSH powder in each of the swelling and deswelling media was 30 min. The rest of the procedure was the same as given in previous section.

Swelling-deswelling responsive studies of BSH in each medium were carried out three times and the mean values were reported.

2.6. Swelling Kinetics. To check the rate of absorbency by BSH, the weighed amount of BSH was filled in each of the four tea bags and immersed in 80 mL media (pH 1.2, 6.8, and 7.4 and deionized water). At definite time intervals, the quantity of water absorbed by BSH was measured using the following equations [4]:

$$Q_t = \frac{W_s - W_d}{W_d} = \frac{W_t}{W_d} \tag{8}$$

$$Q_e = \frac{W_\infty - W_d}{W_d} = \frac{W_e}{W_d}, \tag{9}$$

where W_d is the initial weight of dried BSH, W_s is the swollen weight after time t, W_t is the weight of water absorbed by BSH after time t, Q_t is the normalized degree of swelling, W_∞ is the weight of swollen BSH at t_∞ when the rate of swelling of BSH became constant, W_e is the quantity of water absorbed by BSH at t_∞, and Q_e is the normalized equilibrium degree of swelling. The kinetics of the swelling can be analyzed through normalized degree of swelling Q_t and normalized equilibrium degree of swelling Q_e at time t. The second-order kinetics was applied on swelling data using (10) [27]. A plot of t/Q_t *vs* t must be linear with the slope of $1/Q_e$ and an intercept of $1/kQ_e{}^2$:

$$\frac{\mathrm{t}}{\mathrm{Q_t}} = \frac{\mathrm{t}}{\mathrm{Q_e}} + \frac{1}{\mathrm{kQe^2}}. \tag{10}$$

2.7. Scanning Electron Microscopy. Morphological analysis of the BSH was performed through scanning electron microscopy (SEM) as described elsewhere [3]. Briefly, dried BSH powder (0.1 wt%) was swollen in deionized water and freeze-dried. Cross sections of the sample were obtained using a sharp blade and observed under SEM (FEI Nova, NanoSEM 450) equipped with a low-energy Everhart-Thornley detector, operated at 10 kV. Each sample was drop casted on a carbon mount and dried at 25°C in a vacuum oven for 24 h prior to analysis. SEM images of the surface of BSH containing tablet formulation were recorded. Furthermore, water swollen and then freeze-dried BSH containing tablet formulations were also examined through SEM.

2.8. Preparation of Tablets. To evaluate BSH as a sustained release material in an oral drug delivery system, diclofenac sodium (DS) was used as model drug. Three tablet formulations (DSF1, DSF2, and DSF3) using different concentrations of BSH were prepared by wet granulation method (Table 1). For comparison, one tablet formulation (DSF) was prepared without BSH (Table 1). Avicel® PH 101 and tragacanth were used as a diluent and binder, respectively. Avicel® PH 101 is microcrystalline cellulose and, being an inert material, it is a widely and most commonly used excipient by pharmaceutical industries for tablet formulations. Similarly, tragacanth is odorless and tasteless material and also used in pharmaceutical industries as a binder in wet granulation process. BSH, DS,

Table 1: Composition (mg) of BSH tablet formulation.

Constituents of formulation	Formulations			
	DSF	DSF1	DSF2	DSF3
BSH	-	100	150	200
DS	100	100	100	100
Avicel® PH 101	250	150	100	50
Tragacanth	40	40	40	40
Magnesium stearate	10	10	10	10

and Avicel® PH 101 were properly mixed after passing through sieve no. 40 and granulated with tragacanth aqueous solution. The wet material was then dried at 60°C for 6 h and passed through sieve no. 20. Dried granules were lubricated with magnesium stearate and compressed in a rotary presser fitted with 9 mm flat surface punch at 400 ± 5 mg. Hardness and thickness of tablets were kept at 6–7 Kg/cm^2 and 4.45–4.56 mm, respectively.

2.9. In Vitro Drug Release Study and Mechanism. Drug release study was carried out in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) using USP dissolution apparatus II. Tablets were kept in SGF (900 mL) for 2 h and then shifted to SIF (900 mL) for 10 h at 37 ± 0.5°C and 50 rpm. After specific time intervals, sample (5 mL) was taken from respective media, filtered, diluted (if required), and analyzed by UV-Vis spectrophotometer (Shimadzu, Japan) at 276 nm. The same quantity of fresh media was replenished. Drug release study was repeated three times and reported the mean value. Furthermore, the same procedure was adopted for commercially available tablet formulation (Voltral® SR 100) to compare the drug release behavior with BSH-DS tablets.

The drug release mechanism from an oral drug delivery system can be explained by different mechanisms, either alone or in combination, i.e., diffusion, swelling, and erosion [28, 29]. Here, the power law in the following was used to determine the drug release mechanism from BSH containing tablet formulations:

$$\frac{M_t}{M_\infty} = K_p t^n, \tag{11}$$

where M_t/M_∞ is the fraction of drug release in time t, K_p is the constant, and n is the diffusion coefficient which is used to find the drug release mechanism. Drug release from polymer matrix followed Fickian diffusion, non-Fickian diffusion, and super case-II transport when the value of $n <$ 0.45, from 0.45-0.89 and > 0.89, respectively [29, 30].

2.10. Swelling Study of Tablets. Swelling capacity of the prepared tablets was determined in deionized water to observe whether the swelling capacity of BSH was retained in tablet formulation or not. The procedure adopted was the same as that described for stimuli responsive swelling study of BSH and swelling capacity was calculated using (7).

2.11. Haemocompatibility Studies of BSH

2.11.1. Thrombogenicity Evaluation. Interaction of BSH with blood was studied by determining its haemolytic potential and thrombogenicity (thrombus formation) as described by International Standard Organization (ISO) (ISO10993-4, 1999). To determine the thrombogenicity, thrombus formation on BSH surface was evaluated using gravimetric method [31, 32]. Hydrogel (0.5 g) was placed in phosphate buffer saline (PBS) for 24 h at 37°C. After removing excessive PBS, citrate blood (2 mL) and $CaCl_2$ (0.2 mL, 0.1 M) were added. After 45 min, distilled water was added in the solution to stop the clotting. Clots were then fixed using formaldehyde solution (36-38%, 5 mL), dried, and weighed. For positive and negative control, the same procedure was adopted without hydrogel and without hydrogel and blood, respectively. PBS was prepared as described elsewhere [33]:

$$\begin{aligned} &\textit{Thrombose}\,(\%) \\ &= \frac{\textit{mass of test sample} - \textit{mass of}\ (-)\ \textit{control}}{\textit{mass of}\ (+)\ \textit{control} - \textit{mass of}\ (-)\ \textit{control}} \\ &\quad \times 100. \end{aligned} \tag{12}$$

2.11.2. Haemolysis Potential. Haemolytic potential is the determination of the extent to which haemolysis occurs when a sample comes in direct contact with blood. Haemolysis test was performed according to the procedure explained by American Society for Testing and Materials (ASTM) [34]. Hydrogel (0.5 g) was placed in PBS at 37°C for 24 h and then washed thoroughly with PBS. Hydrogel was incubated with known amount of citrate blood and PBS for 3 h at 37°C. Hydrogel solution was then centrifuged at 10^4 rpm for 15 min. Supernatant was separated and optical density (OD) was determined at 540 nm using UV-Vis spectrophotometer. For positive and negative control, the same amount of citrate blood was incubated with distilled water and PBS, respectively [32]. Haemolytic potential was calculated using the following equation:

$$\begin{aligned} &\textit{Haemolytic index}\,(\%) \\ &= \frac{\textit{OD of test sample} - \textit{OD of}\ (-)\ \textit{control}}{\textit{OD of}\ (+)\ \textit{control} - \textit{OD of}\ (-)\ \textit{control}} \\ &\quad \times 100. \end{aligned} \tag{13}$$

3. Results and Discussion

3.1. Physical Properties of BSH. Results of physical properties of BSH are depicted in Table 2. Flow parameter, i.e., angle of repose, and compressibility index indicated that the BSH powder has poor flowability and compressibility, respectively. Therefore, necessary measures have to be taken before formulation development, i.e., addition of lubricant and/or glidant, increasing the concentration of binder or replacing the binder, and the use of wet/dry granulation process.

3.2. pH Responsive Swelling Trends of BSH. The swelling response of BSH was observed in deionized water as well

Table 2: Physical properties of BSH.

Physical properties	Results
Moisture contents	8.2 ± 0.05%
Swelling capacity	111 ± 2 g/g
Angle of repose	39.5 ± 1.3
Bulk density	0.212 ± 0.011 g/cm^3
Tapped density	0.311 ± 0.019 g/cm^3
Particle size	≈ 250 μm
Gelling content	28.51 ± 2.23%
Carr's index	31.83 ± 1.05
Hausner ratio	1.47 ± 0.08

as gastrointestinal tract pH using buffer solutions of pH 1.2, 6.8, and 7.4. However, in water, BSH swells rapidly with high swelling index due to its superporous nature and nonionic behaviour of water as compared with its swelling at pH 6.8 and 7.4 buffers. If we closely observe the swelling behavior of BSH in water and at pH 7.4, it is noted that BSH swells less at pH 7.4 than in deionized water due to charge screening effect of excess Na^+ ions (i.e., anion-anion repulsions/shielding of carboxylate anions) [10, 11].

There was a negligible swelling observed under acidic (pH 1.2) condition. This less swelling was due to the existence of protonated form of carboxylate ions (COOH) which exhibit negligible repulsion between anions and lead to the least swelling at pH 1.2 [35].

This BSH appeared to be a rapidly swelling polysaccharide biomaterial which swells to the maximum in 90 min in aqueous environment. Swelling of BSH in slight acidic and slight basic medium appeared to be 35-43% of BSH mass. However, there was also a rapid swelling pattern of BSH. Swelling of BSH, in the first 90 min, was even rapid than already known and famous water swellable polysaccharides from *Mimosa pudica* (touch-me-not) [3], *Linum usitatissimum* (Flax, alsi) [10], *Cydonia oblonga* (Quince) [4], and sodium carboxymethyl cellulose (NaCMC) [36] (Figure 1(b)), etc.

3.3. Swelling Kinetics. The utilization of hydrogel as a sustained release oral drug delivery system mainly depends on rate and extent of swelling, pH of the swelling media, and particle size of the hydrogelable material [37]. The rate of BSH swelling is determined through swelling kinetics when applied on swelling data which was measured at pH 1.2, 6.8, and 7.4 and deionized water (Figure 1(c)). The linearity of the plot between t/Q_t and t with slope of $1/Q_e$ and an intercept of $1/kQ_e{}^2$ showed that the swelling of BSH followed the second-order kinetics [37]. The polysaccharides hydrogels which swell according to 2nd order swelling kinetics are highly valuable for the development of sustained release formulation of NSAIDs [3, 4, 10].

3.4. Evaluation of Swelling Behavior of BSH in Salt Solutions. Polysaccharides-based hydrogelable materials are extensively used in sustained release oral drug delivery system. Presence of different salts in food can alter the swelling ability of these hydrogels which ultimately affects the rate and extent of the release of drug. Therefore, the swelling ability of BSH in the presence of different salts (NaCl, KCl) concentration was investigated in different aqueous molar solutions (0.1 to 2.0 M). Significant decrease in equilibrium swelling was observed when the concentration of salt solutions increased from 0.1 to 0.5 M. Swelling capacity is also affected by the nature and number of functional groups present on polymer chains and their ionization capacity. Presence of cations in the media reduces the anion-anion repulsion due to charge screening effect which results in the decrease of swelling [35]. Furthermore, ionic cross-linking of functional groups present on polymeric chain is also responsible for less swelling of hydrogel [38]. As shown in Figure 2(a), less swelling was observed in KCl aqueous solution as compared to NaCl solution at the same concentration because of high attraction of potassium ion towards counter ions present at the surface of BSH than sodium ions [10].

3.5. Stimuli Responsive Swelling-Deswelling of BSH. Polysaccharides based hydrogelable materials are ideal candidate for development of sustained/controlled release oral drug delivery system and the release of drug from such system mainly depends upon the swelling ability of polysaccharides. Any change in the composition of the surrounding environment may affect the swelling of polysaccharides and, hence, the drug releasing ability. Presence of salt in food and concomitant administration with alcohol and pH of GIT may affect the release of drug. Therefore, it is of utmost importance to study the swelling-deswelling behavior of BSH under different condition [10].

3.5.1. Swelling-Deswelling of BSH in Water and Saline Media. A reasonable swelling capacity (78.1 g/g) of BSH was noticed in deionized water after 20 min, whereas a sudden drop in swelling of BSH was recorded when swollen BSH was shifted to normal saline (0.9% w/v NaCl) (Figure 2(b)). Swelling in water and deswelling in NaCl solution is mainly due to difference of osmotic pressure between polymer chain and its surroundings created due to the presence of sodium ions (Na^+). As a result, water escaped from swollen BSH which resulted in the shrinking of the hydrogel. When hydrogel was again come in to contact with deionized water, the process reversed and BSH swelling was started with diminishing of the existing osmotic pressure [3, 4]. Additionally, the charge screening effect due to the presence of cations generated a nonperfect anion-anion electrostatic repulsion which also decreased the swelling of BSH.

3.5.2. Swelling-Deswelling of BSH in Basic and Highly Acidic Medium. Swelling-deswelling behavior of BSH was determined under basic (pH 7.4) and acidic (pH 1.2) conditions and it was found that the hydrogel swells in basic medium and shrinks drastically in acidic medium (pH 1.2). This swelling and deswelling trend was monitored up to four cycles as shown in Figure 2(c). At pH 7.4, deprotonation of carboxylic acid group generates the carboxylate ions (COO^-). Presence of anion-anion repulsion not only relaxes the polymeric

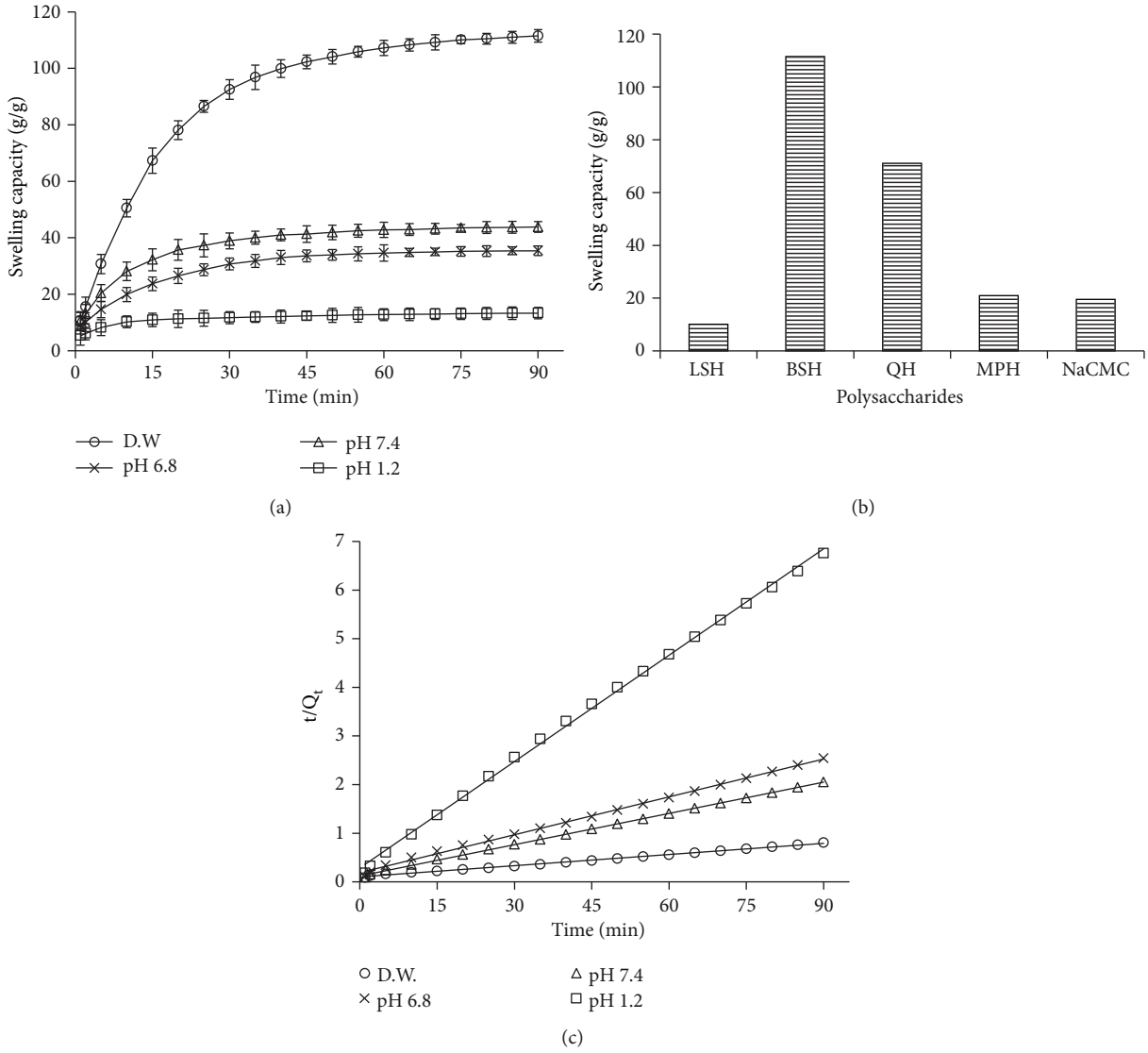

Figure 1: Swelling behavior in deionized water and different pH (a). Comparison of swelling capacity (g/g) of BSH with already reported polysaccharides LSH (Linseed hydrogel) [10], QH (Quince seed hydrogel) [4], MPH (*Mimosa pudica* hydrogel) [3], and NaCMC (sodium carboxymethyl cellulose) [36] in the first 90 min (b). Second-order swelling kinetics of BSH in different media (c).

chains but also allows the media to enter deeply in the polymeric matrix [35]. When this swollen hydrogel is transferred to acidic media, the protonation of carboxylate ion reduces the electrostatic repulsion. Hence, the chains of polymer get closer to each other which develops intermolecular bonding. As a result, the shrinking of polymer becomes evident.

3.5.3. Swelling-Deswelling of BSH in Water and Ethanol Medium. Water swollen BSH when placed in ethanol has shown abrupt deswelling behavior. This drastic fall in swelling capacity after immersing in ethanol is due to the polarity differences between water and ethanol. Further, the ethanol molecules replace water molecules with ease [39]. As a result, water escapes out from hydrogel and deswelling occurs [4, 10]. Four cycles of on-off swelling were recorded and expressed in Figure 2(d). Based on these findings, it can be concluded that BSH-based sustained release formulations may change the drug release pattern in the presence of alcohol. Therefore, special instructions should be passed on to patients that drinking should be avoided during the whole course of treatment.

Concluding, it has been derived from swelling-deswelling results that BSH will give release of drugs in near neutral pH values of GIT and will give negligible release at acidic pH of stomach, in saline condition, and in ethanol (organic media).

3.6. Scanning Electron Microscopy. Morphological analysis of the swollen and then freeze-dried BSH was performed to observe the texture and arrangements of internal porous structures. SEM images of BSH have exposed the macroporous nature of hydrogel (Figure 3). Well dispersed and interconnected macropores were observed in transverse and

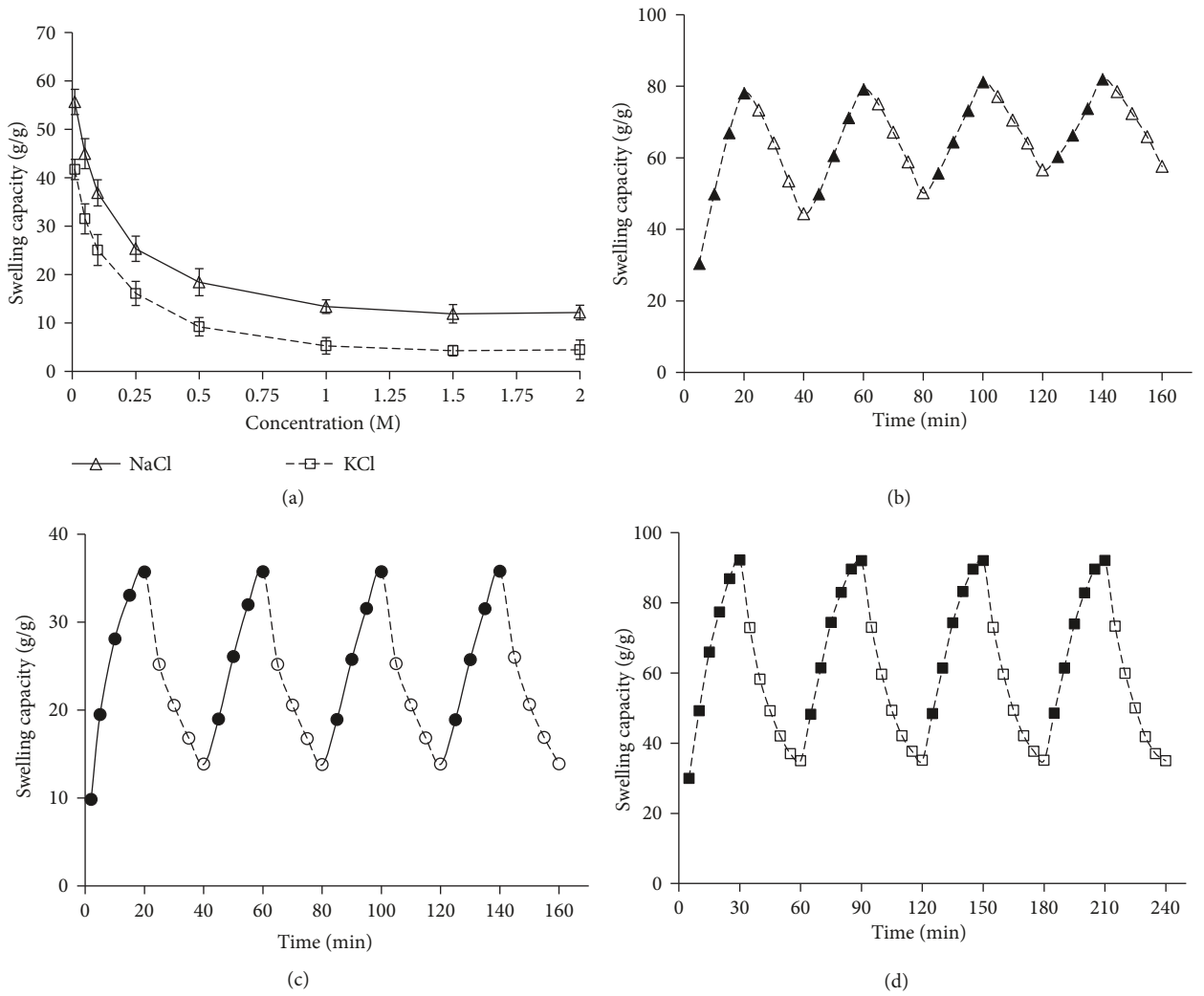

Figure 2: Equilibrium swelling capacity (after 24 h) of BSH in different molar solutions of NaCl and KCl (a). Swelling-deswelling (on-off switching) of BSH in deionized water and normal saline (b), basic (pH 7.4) and acidic (pH 1.2) media (c), and deionized water and ethanol (d).

longitudinal cross sections of hydrogel having average pore size of $1.92 \pm 3.83\ \mu$m. Highly porous nature of BSH provides an easy passage to the solvents which is essential for fast and high swelling of hydrogel. Furthermore, SEM images of the tablet also revealed the presence of microscopic channels of BSH which contributed to the fast and high swelling of BSH even in tablet formulations (Figures 4(d)–4(f)).

3.7. Swelling Study of Tablets. Swelling behavior of three different tablet formulations was carried out in deionized water and results are depicted in Figure 4(a). When the swelling medium comes in contact with polymer chains, the hydrophilic moieties on polymer will exhibit affinity towards the molecules. These moieties then dissociate into ionic form and electrostatic repulsion between these ions relaxes the polymeric chains. As a result, the penetration of swelling medium (water) becomes easier. Therefore, profound swelling of polymer was seen. Swelling of BSH tablets was directly proportional to the concentration of polymer and it was observed in the swelling graph of tablet formulations (Figure 4(a)). DSF3 has high concentration of BSH than DSF2 and DSF1; therefore, more swelling was observed in DSF3 as compared to other formulations. However, less swelling of BSH containing tablet formulations was observed as compared to BSH powder which is mainly due to the compression of BSH into tablet form. During compression process, the particles of BSH are closely and tightly packed which created hindrance in penetration of swelling media [26]. Photographs of the aerial and axial view of tablet during swelling are shown in Figure 4(b).

3.8. In Vitro Drug Release Study and Mechanism. Water swellable hydrogel is an integral component of a controlled/sustained release drug delivery system [4, 40]. *In vitro* DS release studies were performed both in SGF (pH 1.2) for 2 h and in SIF (pH 6.8) for 10 h at 37°C. The drug release from a polymeric material depends upon the swelling and drug loading capability of the polymer followed by the drug

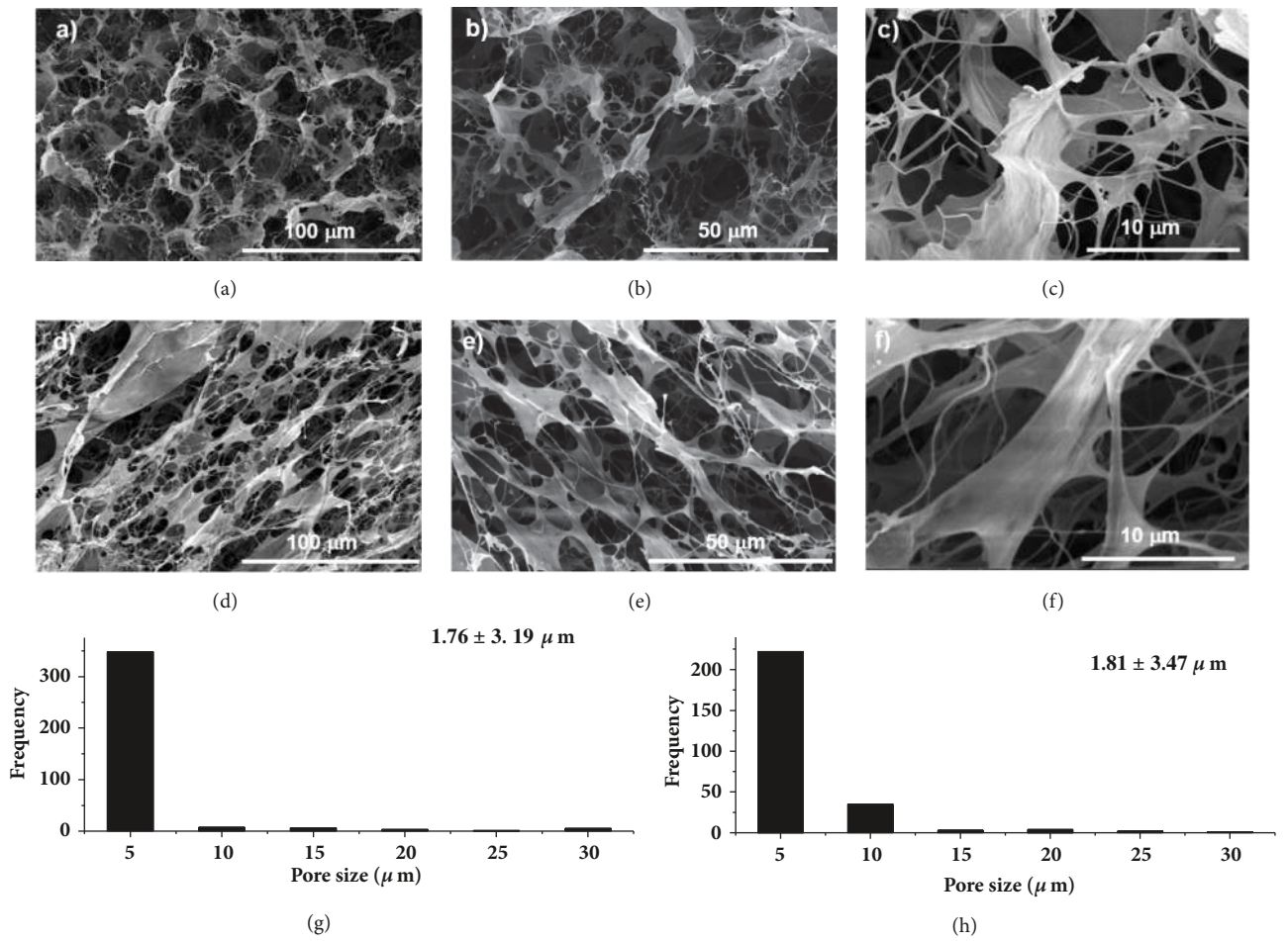

Figure 3: Scanning electron micrographs of transverse (a–c) and longitudinal (d–f) cross sections of swollen and then freeze-dried BSH (with average pore size 1.92 ± 3.83 μm) at different magnifications. Size distribution of macropores (g) and (h) and of transverse (a) and longitudinal (d) cross sections.

solubility in the concerned media [41]. Poor swelling ability of BSH in acidic environment declines the penetration of media and also the drug is not solubilized from polymeric matrix. Therefore, negligible release of drug (4.1, 6.24 and 7.92%) was observed in SGF (after 2 h) from DSF1, DSF2, and DSF3, respectively (Figure 4(c)), whereas a considerable high drug release (99.26, 92.29, and 80.22%) from DSF1, DSF2, and DSF3 was found in SIF (after 10 h), respectively, due to high and fast swelling of BSH at this pH of SIF.

The release of DS from tablets also varies by varying the quantity of BSH in the formulations. The results indicated that drug release from tablets is inversely proportional to the concentration of BSH. As we increased the quantity of hydrogel from 100 to 200 mg/tablet, DS released after 10 h was decreased from 99.26 to 80.22%. Due to high swelling and water holding capacity of BSH, it is difficult for dissolved drug to diffuse out of polymeric matrix. Therefore, a delayed drug release behavior was observed. DS release from BSH is also compared with commercially available formulation, Voltral® SR 100. After 12 h drug release study, 90.51 and 80.22% drug were released from Voltral® SR 100 and DSF3, respectively. Figure 4(c) also showed that a sustained and prolonged drug release behavior from BSH containing formulation, i.e., DSF3, was witnessed as compared to marketed formulation. Additionally, DS was released from DSF (formulation without BSH) in SGF within 2 h which further confirm the sustained release potential of BSH in tablet formulations.

Table 3: Power law values of DSF formulations.

Formulations	K_p	n	r^2
DSF1	5.127	1.402	0.9816
DSF2	4.516	1.344	0.9838
DSF3	3.861	1.295	0.9864

A plot of $\ln M_t/M_\infty$ and $\ln t$ was drawn and values of diffusion exponent (n) and power law constant (K_p) were calculated from the slope and intercept (Table 3). The value of n was found from 1.295–1.402 indicating a super case-II transport, i.e., erosion-based drug release [42].

3.9. Haemocompatibility Studies of BSH. Thrombogenic behavior was measured in terms of the weight of clot formed

Table 4: Results of haemocompatibility studies of BSH.

Parameters	Observations		Inference
Thrombogenicity	Weight of blood clot (g) 0.41 ± 0.03	Thrombose (%) 92.11 ± 2.18	Nonthrombogenic
Haemolysis	OD at λ_{max} = 540 nm 0.37 ± 0.05	Haemolytic index (%) 3.65 ± 0.81	Nonhaemolytic

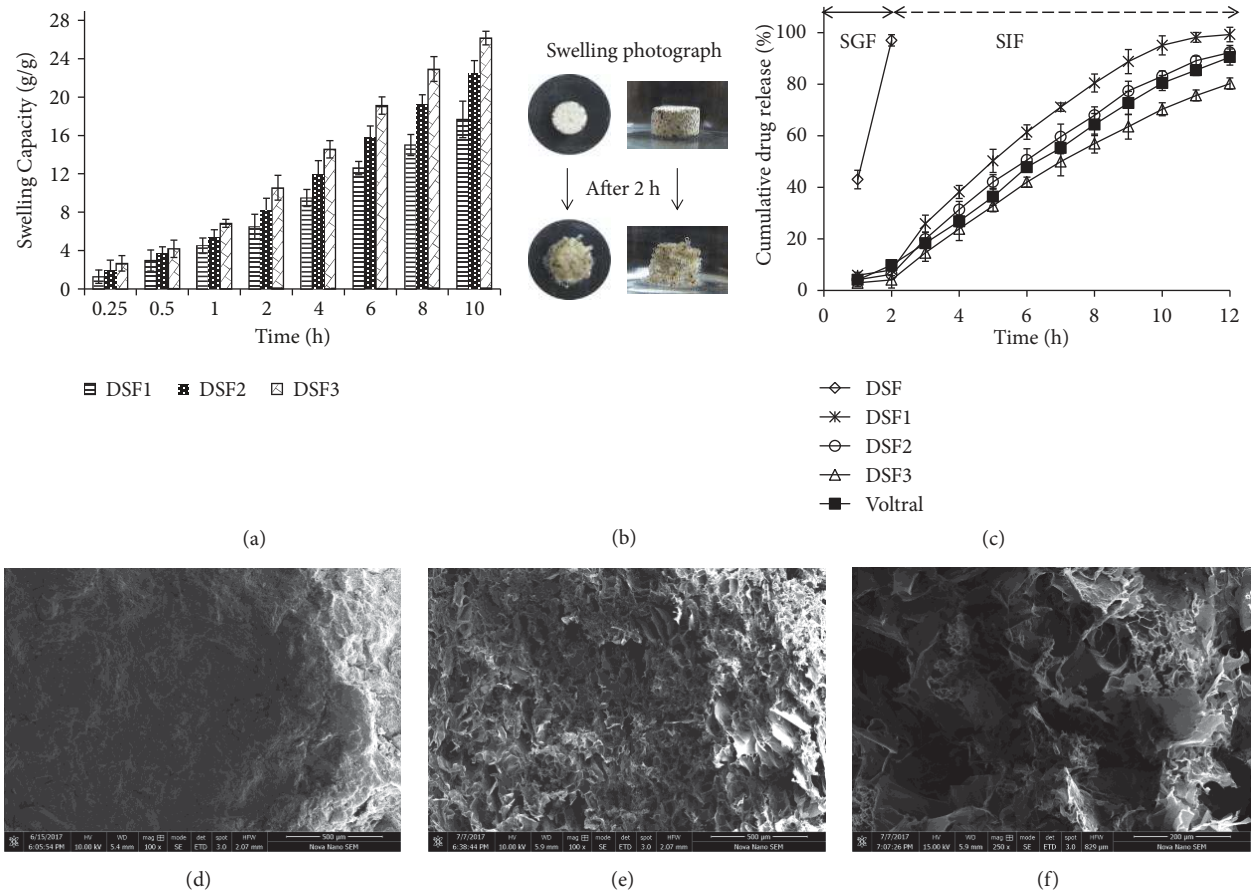

Figure 4: Swelling capacity of different tablet formulation in deionized water after various time intervals (a). Photographs showing swelling of tablets in deionized water (b) and diclofenac sodium release from different formulations, i.e., DSF, DSF1, DSF2, DSF3, and Voltral, in SGF (2 h) and SIF (10 h) (c). SEM images of BSH containing tablet formulation (DSF3); tablet surface (d), tablet surface after swelling in deionized water (e), and magnified image of surface of swollen tablet (f).

during blood-hydrogel interaction and compared to the control [43]. The weight of the clot formed and thrombose (%) was found to be 0.41 ± 0.03 g and 92.11 ± 2.18%, respectively (Table 4). In case of positive control, the weight of clot was greater than clot formed with BSH. These results indicated that the BSH is nonthrombogenic as the clot formation is slow as compared to the control group.

According to the safety standards of ISO document 10993-3 2002 [44], the haemolytic index should be less than 5% to consider a material safe for biomedical applications. The value of haemolytic index was noted as 3.65% (Table 4).

4. Conclusion

Seeds of *Ocimum basilicum* extrude hydrogel which have high swelling capacity in deionized water as well as in pH 6.8 and 7.4. Further, the hydrogel is very responsive in media of pH 1.2, ethanol, and salt solutions of sodium chloride and potassium chloride. Therefore, it is highly suitable for sustained drug delivery systems. The SEM analysis has proven the availability of drug loading sites and release profile confirmed the suitability as a valuable drug carrier. Synthetic/semisynthetic polymers are commonly used in

commercially available sustained release dosage form which can be replaced by naturally occurring polymer, BSH. Due to haemocompatibility, BSH may have many potential biomedical applications.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

There are no conflicts of interest to declare.

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