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Development and Characterization of Superporous Hydrogels for Enhanced Bioavailability of Ramipril: In-vitro Evaluation

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Abstract

This synthesis method involves the use of a gas blowing technique, where acrylamide and acrylic acid are used as hydrophilic monomers, bisacrylamide (BIS) as a cross-linker, and distilled deionized water and pluronic F-127 as foam stabilizers. Propranolol Hydrochloride was used as a model drug to evaluate the pre-compressional and post-compressional properties of the superporous hydrogel, and the results showed good properties. Compatibility studies were conducted to ensure that the drug and the superporous hydrogel are compatible with each other and do not undergo any chemical reactions that could affect the drug's effectiveness. Stability studies were also conducted to evaluate the shelf-life of the optimized formulation, and the results indicated that the formulation is stable. Overall, the synthesis of superporous hydrogels of Ramipril has been successful in enhancing the drug's bioavailability, which could potentially improve its therapeutic effectiveness. This demonstrates the potential of superporous hydrogels as drug delivery systems and the importance of optimizing their formulation to ensure their stability and compatibility with the drug.

Keywords: Superporous hydrogel, gas blowing technique, Ramipril, hydrophillic monomers

Full-length article

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1. Introduction

Superporous hydrogels (SPHs) are a type of hydrogel that have an open porous structure with a large volume of interconnected pores. They were initially developed as a drug delivery system for drugs with an absorption window in the stomach and upper gastrointestinal tract. SPHs can swell immediately in the stomach, and their integrity can be maintained in the harsh stomach environment, while the active pharmaceutical ingredient is being released [1].

The immediate and fast swelling property of SPHs is due to the capillary force that causes water to be absorbed through the open porous structure. However, conventional SPHs (CSPHs) have poor mechanical strength, which limits their use as drug delivery systems. This limitation was overcome by developing the second-generation SPH composites (SPHCs) and third-generation SPH hybrids (SPHHs) [2]. SPHCs are made by incorporating reinforcing materials such as fibers or particles into the SPH structure to enhance their mechanical properties[3]. SPHHs, on the other hand, are made by combining two or more types of hydrogels, such as a fast-swelling hydrogel and a slow-swelling hydrogel, to create a hybrid with improved mechanical strength and drug release properties [4].

The advantages of SPHs as drug delivery systems include their ability to provide controlled drug release, protect the drug from degradation in the harsh stomach environment, and increase the bioavailability of drugs with an absorption window in the stomach and upper gastrointestinal tract [5]. However, there are also some disadvantages, such as the difficulty in loading hydrophobic drugs and the potential for gastrointestinal obstruction if the SPHs remain in the stomach for too long [6]. There are several techniques for loading drugs into SPHs, including physical entrapment, chemical conjugation, and electrostatic interaction. The characterization of SPHs involves evaluating their swelling properties, mechanical strength, pore size, and drug release kinetics [7]. The applications of SPHs extend beyond drug delivery to include tissue engineering, wound healing, and environmental remediation. Overall, the development of SPHs has opened up new possibilities for drug delivery and other biomedical applications [8].

2. Materials and Methods

Ramipril was a gift sample received from Piramal Enterprises Ltd. , Pithampur, India., Chitosan (High molecular weight) &Ethanol were obtained from Qualikems Fine chem. Pvt. Ltd. Cholesterol, Disodium hydrogen

phosphate, Potassium dihydrogen orthophosphate (KH2PO4),Sodium chloride (NaCl),Acetone, Methanol, Ethe, Potassium chloride (KCl) Glacial acetic acid, Hydrochloric acid (HCl),Ammonium per sulphate, Acrylic acid, N,N-Methylene-bis-acrylamide, Acrylamide Sigma-Alderich, N, N, N', N'-tetramethyl-ethylenediamine, Pluronic F-127,Sodium bicarbonate (NaHCO3) were purchased from Qualikems Fine Chem. Pvt. Ltd.

2.1. Drug - excipients compatibility study

Drug - excipients interaction study was done to check any interaction between the drug and excipients**.** This study for Ramipril was carried out by using FT-IR spectrophotometer by NaCl pallet method. The samples of drugs, Chitosan, acrylamide, pluronic F-127, ammonium per sulphate (APS), N, N, N', N'-tetramethyl-ethylenediamine (TEMED) and their physical mixture were mixed with hard liquid paraffin and the spectra were obtained using FTIR spectrophotometer. The spectrum was scanned over a frequency range 4000-500 cm-1 (182) [10].

2.2. Formulation and evaluation of superporous hydrogel hybrid(sph)

A superporous hydrogel was prepared for Ramipril using a gas blowing technique with slight modifications. In a test tube (20 mm outer diameter × 150 mm in length), a monomer solution of acrylamide (50% w/v), acrylic acid (50% w/v), bisacrylamide (BIS) (2.5% w/v) as a cross-linker, distilled deionized water, and Pluronic F-127 (10% w/v) as a foam stabilizer were sequentially added. High molecular weight chitosan was added at varying concentrations of 0.5, 1.0, 1.5, and 2.0% w/v as a secondary polymer. Ammonium persulfate (APS) (20% w/v) was added as a reaction initiator and N,N,N',N'-tetramethyl-ethylenediamine (TEMED) (20% w/v) was used as a catalyst (Table 1.1). The test tube was shaken after each ingredient was added to ensure proper mixing. The pH of the monomer solution was adjusted to 5.0 using HCl buffer (pH 1.2) and 1M NaOH solution. Sodium bicarbonate (100 mg) was then added as a foaming agent to the composition. The shaking was continued during the addition of all ingredients to ensure proper mixing and distribution of gas bubbles throughout the formulation. After gelation, the superporous hydrogel (SPH) formulation was treated with absolute ethanol to retrieve it from the test tube. The SPH was then kept at 60˚C in an oven overnight. The effect of different concentrations of chitosan and cross-linker on various parameters of the formulation, such as apparent density, porosity, swelling properties, and mechanical strength, was evaluated.[9]

2.3. Characterization of SPH

2.3.1. Measurement of gelation kinetics

Gelation kinetic of developed formulation was determined by tilting method. In this process test tubes were tilted in slight decline position and ensure that solution in the test tube mixture were no longer downward [10].

2.3.2. Swelling ratio

To determine the swelling ratio, a fully dry SPH was weighed and then dipped in swelling medium. Swelling ratio was determined in HCl buffer (pH 1.2). At regular time periods, the SPH disc was taken out from the medium and again weighed after excessive swelling medium on the surface was blotted. Measurements were carried out in triplicate. Swelling ratio for the entire formulation batch with respect to changing concentration of BIS and chitosan were calculated. Results were determined based on the following equation:

$$\text{Swelling ratio } (Q) = \frac{Ms - Md}{Md \times 100}$$

Where Q - Swelling ratio, Ms - Mass of swollen SPH and Md - Mass of dried SPH.[11]

2.3.3. Apparent density, porosity and void fraction

The dried SPH was immersed in predetermined amount of hexane in the graduated measuring cylinder by using forceps. After that increase in hexane volume was noted [12].

Density was calculated by following equation:

Apparent density (ρ) = MSPH/VSPH

Where MSPH is the mass of dried SPH and VSPH is the volume of hexane displaced by SPH.

Porosity was measurement by following solvent replacement method. SPH in dried state were dipped overnight in absolute ethanol and weighed was taken after excess ethanol on the surface was blotted. The porosity was calculated from the following equation [13].

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

Where M1 is mass of dried SPH before dipping in ethanol and M2 are the mass of the swollen SPH after immersion in absolute ethanol; ρ relates density of absolute ethanol and V denotes volume of the swollen SPH [13]. Void fraction determination of SPH was carried out by keeping the SPH in hydrochloric acid buffer (pH 1.2) overnight and dimension of swollen hydrogel was calculated. During this period total volume of pore was calculated by subtracting the dried SPH mass from swollen SPH mass. [14]

Void space was calculated by following formula:

$$\text{Void fraction} = \frac{\text{Dimensional of SPH}}{\text{Total pores volume}}$$

2.4. Estimation of drug loading

Drug content in SPH was estimated by using multiple extraction method. For this, Ramipril loaded SPH was placed in a beaker containing 50 ml of HCl buffer pH1.2 for extraction and stirred for few minutes. Process was repeated many times until the entire drug was not extracted. After that solution was passed through 0.45 µm filter and drug content was estimated by UV-VIS spectrophotometer at 290 nm [15].

2.5. In vitro, release study

The drug release from prepared SPH formulation was estimated with USP dissolution apparatus II (Paddle type) at 37 ± 0.5 ˚C in 900 ml of HCl buffer pH 1.2 for stated period of time.[16] The paddle was rotated at 100 rpm and withdrawing 10 ml aliquot from the medium at predetermined time of interval. The withdrawing samples were replaced with fresh buffer. The aliquots sample was passed through 0.45 µm nylon filter and assayed spectrophotometrically at 210 nm [17].

2.6. Scanning electron microscopy (SEM)

The morphological studies of SPH were carried out by using SEM. For this dried SPH disc were cut to expose their internal structure. The samples were prepared separately on sample holders.[18] These holders were stained with gold palladium using sputter coater for one minute under inert argon gas before electron microscope scanning. Microscopic image of SPH was taken by using SEM [10].

2.7. Effect of different pH media on swelling

Swelling of SPH formulations were evaluated for their sensitivity towards different pH range. For determine the pH dependent swelling behaviour of SPH, various media of different pH media viz: pH 1.2, 3.0, 4.9 and 7.4 were prepared [20]. SPH formulations were kept in different pH media until equilibrium swelling and evaluated with respect to their swelling behaviour [21].

2.8. *Differential scanning colorimetr*y

Thermal analysis of both drugs and their SPH formulations were performed using thermal analyzer (PHOENIX DSC- 204 F1, Netzsch- Geratebau GmbH, Germany) [22]. Temperature axis and cell constant were calibrated by utilizing indium (In). Accurately weighed drug (2 mg) was transferred to aluminium pans and sealed. Sample was heated over a temperature range of 30-350˚C, under dry nitrogen purging (50 ml/min) in pinholed aluminium pans [23].

3. Results and discussion

Drug - excipients compatibility study

3.1. Measurement of gelation kinetics

Gelation kinetic study provides information of time of introducing foaming agents in the solution mixture of monomers. The pH of the solution mixture should be maintained 5.0 before adding foaming agents. Foaming agents should not be added too early or too late after the polymerization process start. This is because during polymerization process viscosity of the monomer solution increased and when foaming agents are added too late then bubble will not be formed and if foaming agents would be added too early then bubble so formed will not be able to maintain for long time. Hence foaming agents should be added few seconds after the gelation process start.

3.2. Swelling ratio

Swelling ratio of SPH in HCl buffer solution pH 1.2 was determined at different time of interval **(Table 1.6)**. Fully swollen SPH formulations were shown in **figure 1.6** and **figure 1.7** The effects of concentrations of chitosan and cross linker (BIS) on swelling ratio were determined.

3.3. Estimation of drug loading

Drug loading (%w/w) inside SPH formulations were estimated at 2.06; 2.17; 2.13; 2.08; 2.04; 1.98 and 1.79 %w/w of formulations. Thus, Ramipril content was found to be 20.62; 21.79; 21.31; 20.80; 20.41; 19.82 and 17.93 µg per mg of SPH formulation for FA, FB, FC, FD, FE, FF and FG respectively. Highest drug loading inside FB formulation was observed due to highest swelling ratio and strong interpenetrating network formation.

3.4. In vitro release study

It was observed from the data as shown in **table 1.8** that drug release from SPH was found to be varied as increase in the concentration of chitosan and BIS. At initial (lower) chitosan concentration (0.5%) drug release showed burst effect and release the drug faster due to less strong wall structure of SPH and fast diffusion of drug from matrix. As increasing in concentration of chitosan from 0.5 to 1% w/v, reduced and prolonged drug release was recorded up to 12 hrs. On further increasing the concentration of chitosan from 1 to 1.5 and 2% w/v, drug release was retarded and was observed till 12 hrs. However, drug release was found to be less than that of 1% w/v chitosan concentration at each time point **(figure 1.8 a)**. It was due to the fact that increasing chitosan concentration enhanced the viscosity of the formulation and rigid the integrity of structure that resist the back diffusion of drug.Further, increasing the concentration of cross linker also affects the release characteristics of the drug from SPH **(figure 1.8 b)**. It was observed from the **figure 1.8 b** that on increasing concentration of BIS from 2 to 3.5% w/v, decreased drug release was recorded. At minimum concentration of cross linker (2% w/v), burst effect was observed due to weaker cross-linking density however, while increasing cross linker concentration from 2 to 3.5% w/v drug release was decreased and provide for prolong period of time. It might be due to the fact that with increase in cross linker concentration the cross-linking density was increased and hence results in denser network of SPH.

3.5. Scanning electron microscopy (SEM)

Morphological characterization of SPH was carried out with the help of scanning electron microscopy (SEM) at different magnifications as shown in **figure 1.9**. It was observed that SPH exhibited tubular structure at low magnification and when magnification was increased then higher porous structure were shown. Highly porous nature of SPH responsible for more penetration of swelling media inside them and hence result in faster and higher swelling. Highly porous structure of SPH is also responsible for effective drug release as swelling media dissolve the drug and taken out from the structure in a controlled way.

3.6. Effect of different pH media on swelling

It was depicted from the results as shown in **table 1.9** that swelling capacity was higher in acidic condition and reduced on exposure of SPH to basic media. Maximum swelling was observed at pH 3 whereas least swelling was obtained at pH 7.4. Chitosan and acrylic acid are responsible for their swelling capacity **(figure 1.10)**. Based on the pKa of chitosan (6.5) and acrylic acid (4.7) swelling capacity was obtained. Under acidic condition (pH~3) amino (-NH2) group comes into consideration and undergoes protonation (NH3+). Thus, at this pH NH3+- NH3+ electrostatic repulsion takes place that result in increased in swelling

3.7. Differential Scanning Colorimetry (DSC)

DSC – profile of drug Ramipril was determined alone and Ramipril loaded SPH formulation and results were shown in figure 1.11. DSC thermogram of Ramipril represented the sharp endothermic peak at 113.9 and thermogram of drug loaded SPH showed endothermic peaks at 119.9 which is almost nearer to the endothermic peak of drug.

Table 1.1: Composition of SPH formulations containing Ramipril

Ingredients	Formulation Code						
	FC_1	FC_2	FC_3	FC_4	FC_5	FC_6	FC_7
Acrylamide (µl) (50%w/v)	200	200	200	200	200	200	200
Acrylic acid (µl)(50%v/v)	200	200	200	200	200	200	200
BIS (%w/v) (70µl)	2.5	2.5	2.5	2.5	2	3.0	3.5
Water (µl)	100	100	100	100	100	100	100
PF-127 (µl) (10%w/v)	100	100	100	100	100	100	100
Chitosan(%w/v) (200 µl)	0.5	1.0	1.5	2.0	1.0	1.0	1.0
APS (µl) (20% w/v)	40	40	40	40	40	40	40
TEMED (µl) (20% w/v)	40	40	40	40	40	40	40
$NaHCO_3$(mg)	100	100	100	100	100	100	100
Ramipril (mg)	20	20	20	20	20	20	20

Table 1.2: Characteristics peaks for functional group in Ramipril pure drug

Reported peaks (cm^{-1})	**Observed peaks (cm^{-1})**	**Inference**
3500-3300	3445	N-H stretching
3400-3200	3273	O-H stretching
1260-1000	1186	C-O stretching
1750-1735	1738	Ester

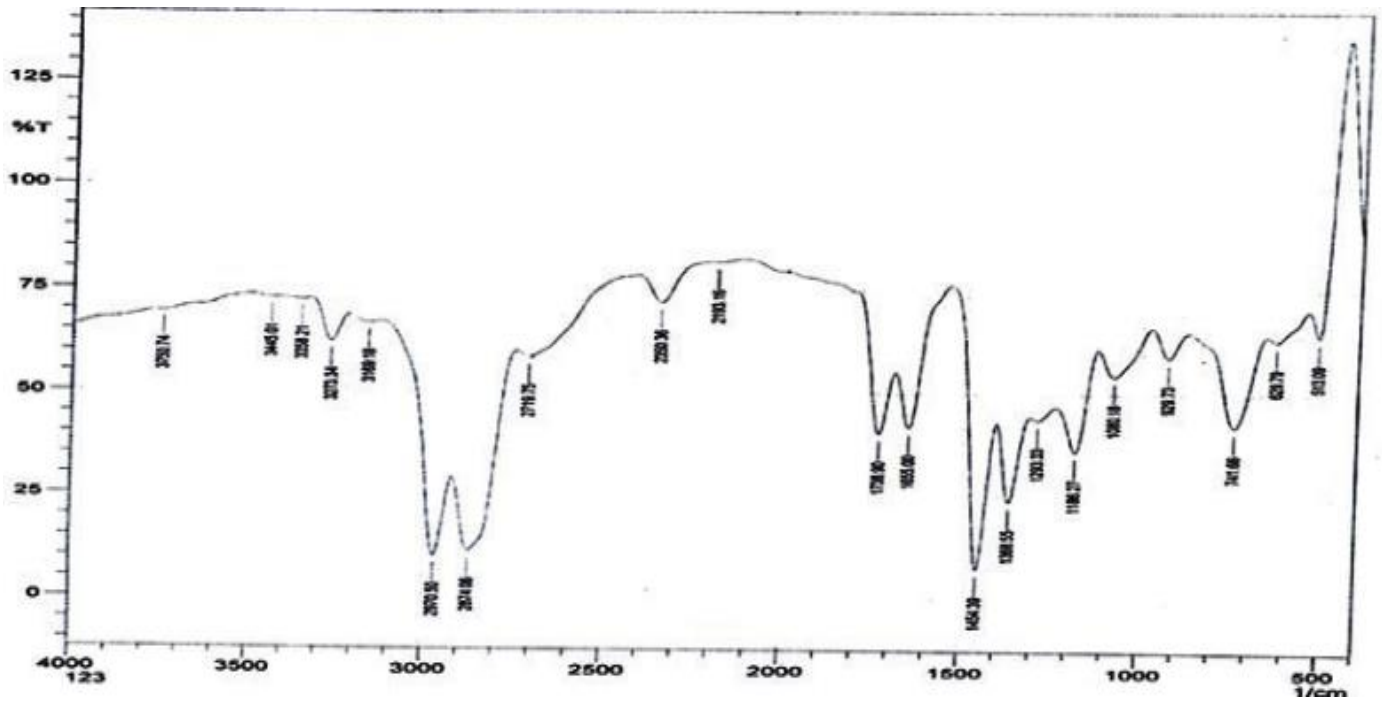


Figure 1.1: IR Spectrum of Ramipril Drug

Table 1.3: Characteristics Peaks for functional group in Chitosan

Sr. no.	Observed peaks (cm^{-1})	Inference
1	3724	C-O stretching
2	3352	N-H stretching
3	1147	O-H stretching

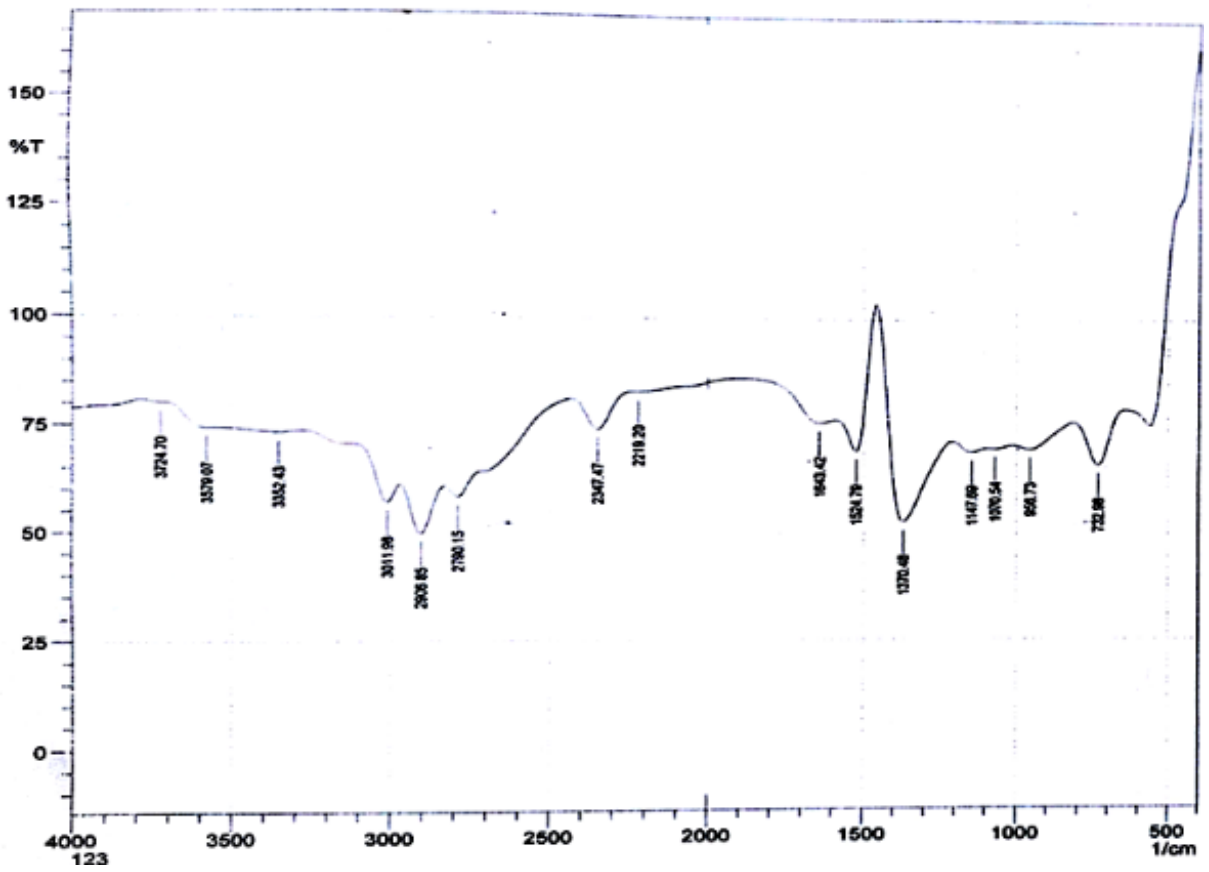


Figure 1.2: IR Spectrum of chitosan

Table 1.4: Characteristics Peaks for functional group in Acrylic acid

Sr. no.	Observed peaks (cm^{-1})	Inference
1	3255-2755	O-H broad stretching
2	1719	-C=O stretching
3	1404	C-O-H stretching

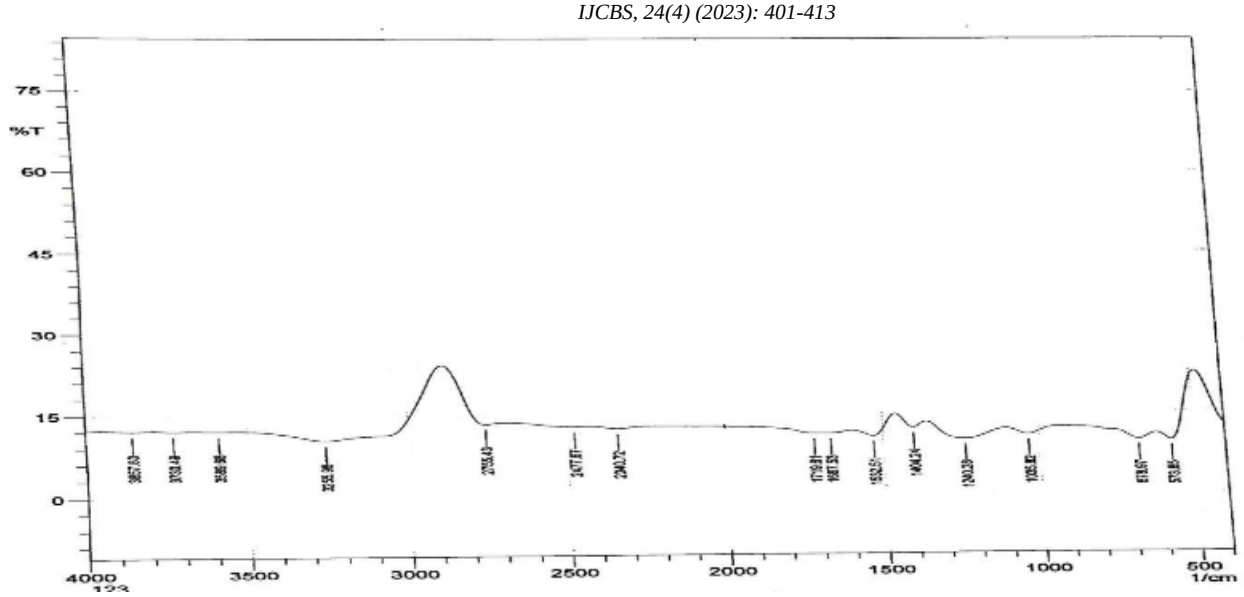


Figure 1.3: IR Spectrum of Acrylic acid

Table 1.5: Characteristics Peaks for functional group in Acrylamide

Sr. No.	**Observed peaks (cm^{-1})**	**Inference**
1	3214-3350	N-H stretching
2	1674	-C=O stretching
3	1118	C-N stretching

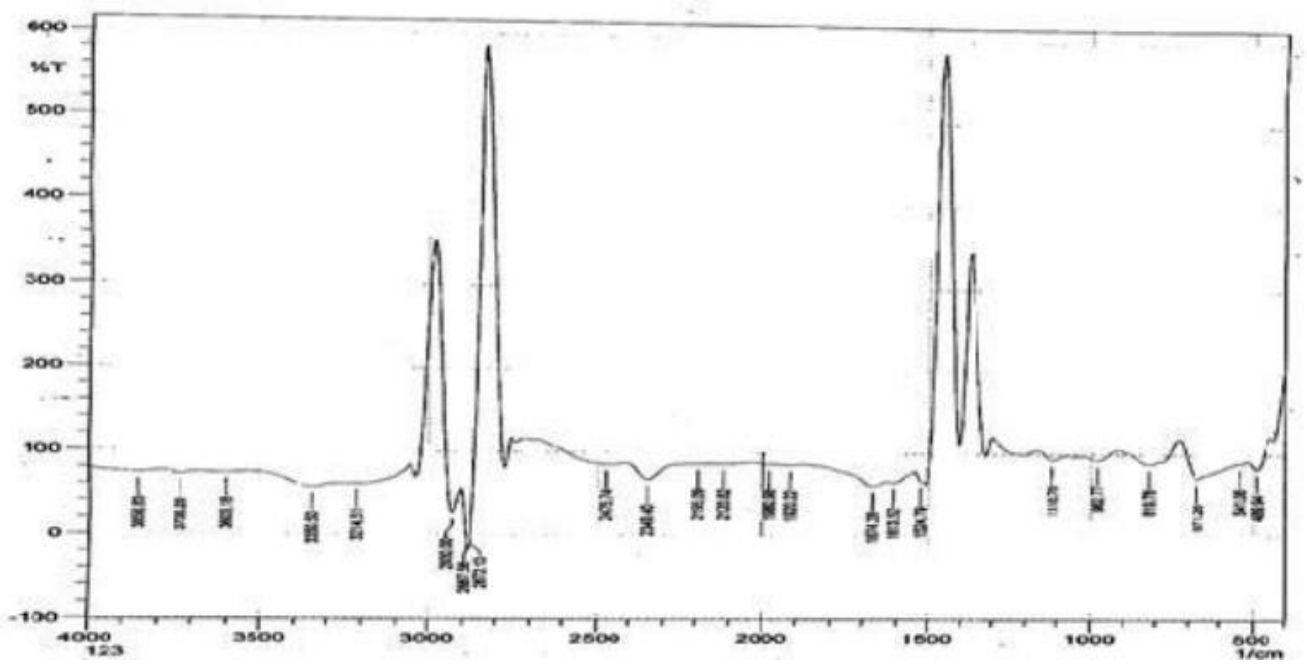


Figure 1.4: IR Spectrum of Acrylamide

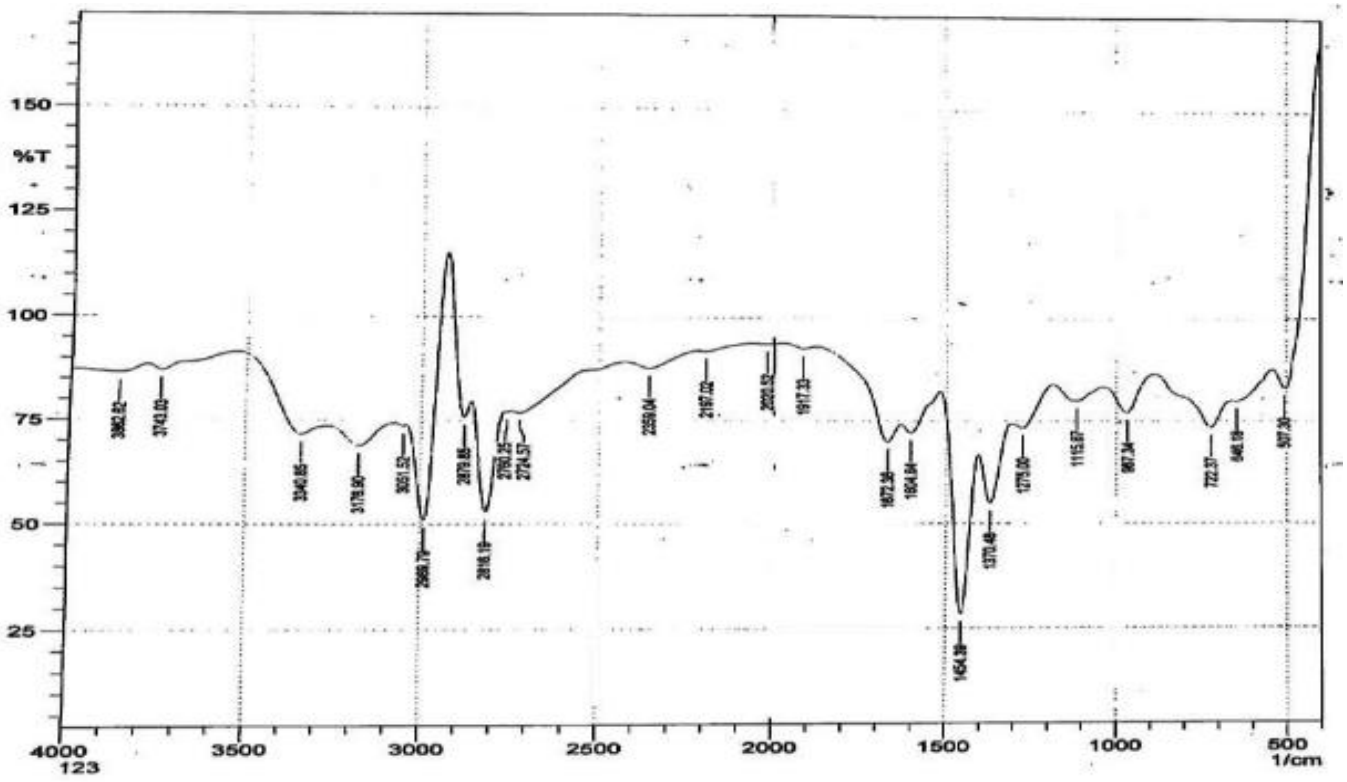


Figure 1.5: IR Spectrum of a) Ramipril b) Chitosan c) Acrylamide d) Acrylic Acid and e) physical mixture of PROP HCl and polymers

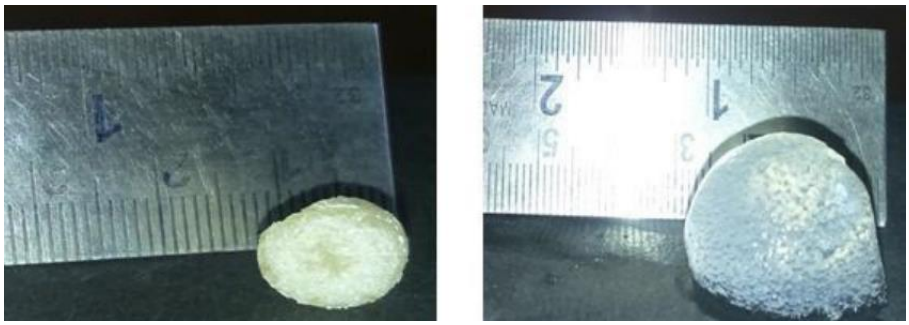


Figure 1.6: Scaling of Ramipril in a) dried and b) swollen form

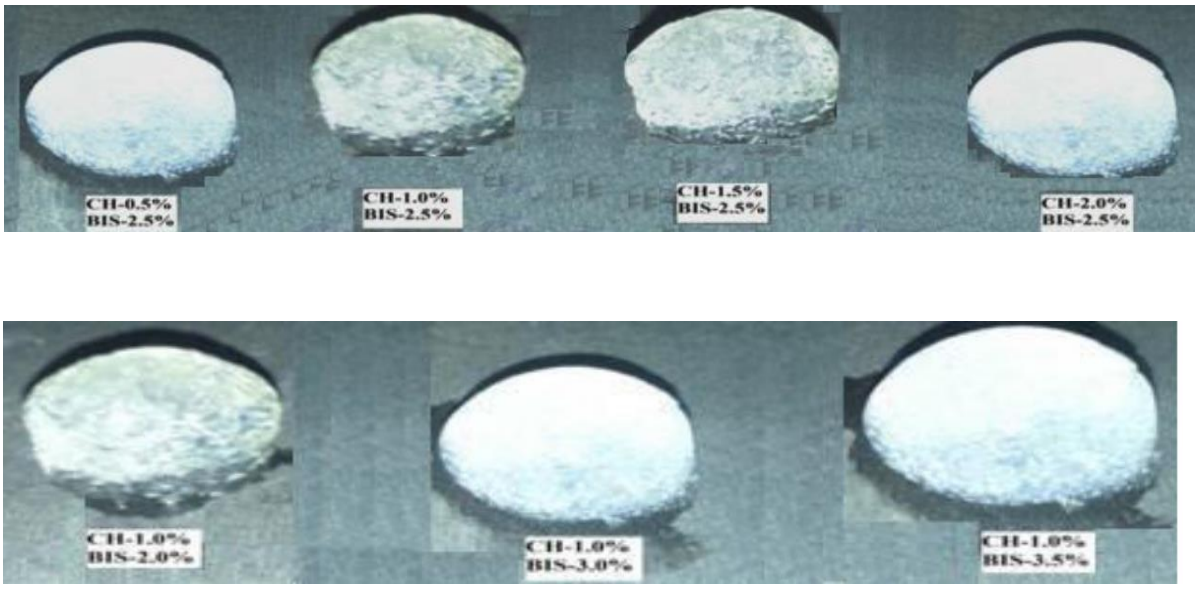


Figure 1.7: Ramipril SPH formulations after complete swelling

Table 1.6: Swelling ratio of all SPH formulation of Ramipril at different time interval

Time (mins)	**Formulation code**						
	FA	**FB**	**FC**	**FD**	**FE**	**FF**	**FG**
2	9.54±0.3	11.72±0.5	8.94±0.7	6.15±0.9	9.58±0.8	4.63±0.7	2.39±0.6
4	18.25±0.5	23.98±0.7	17.11±0.6	14.65±0.7	18.93±0.6	8.67±0.8	6.18±0.8
6	37.98±0.8	45.72±0.4	33.84±0.4	33.71±0.4	38.88±0.3	21.43±0.5	15.19±0.3
8	42.29±0.3	53.71±0.6	40.63±0.7	39.52±0.8	43.54±0.7	33.74±0.3	25.65±0.5
10	48.56±0.5	65.13±0.8	46.11±0.3	46.84±0.5	49.32±0.4	41.76±0.6	31.91±0.6
12	61.97±0.4	70.15±0.3	59.88±0.7	57.81±0.6	63.79±0.6	49.18±0.4	41.37±0.4
14	70.67±0.6	84.78±0.5	65.83±0.5	61.94±0.3	72.81±0.5	55.47±0.7	53.17±0.3
16	86.39±0.3	98.31±0.7	85.39±0.3	79.16±0.5	92.68±0.9	70.67±0.8	64.13±0.6
18	109.89±0.7	121.19±0.4	108.34±0.5	97.94±0.6	115.95±0.4	85.62±0.3	77.39±0.5
20	119.19±0.4	129.11±0.6	115.87±0.3	106.32±0.4	123.43±0.3	93.61±0.4	84.16±0.3
22	128.97±0.3	135.18±0.3	122.46±0.2	113.67±0.3	132.89±0.4	100.36±0.6	89.94±0.3
24	130.87±0.2	137.95±0.2	124.19±0.2	117.1±0.3	134.11±0.3	106.46±0.5	91.71±0.2
26	131.94±0.1	138.13±0.3	126.56±0.1	118.14±0.1	135.21±0.2	107.12±0.2	92.64±0.2
28	132.89±0.1	139.54±0.1	128.09±0.2	119.67±0.2	136.88±0.1	108.67±0.2	94.11±0.1
30	133.03±0.1	139.96±0.1	128.71±0.1	119.81±0.1	137.01±0.1	109.02±0.1	94.97±0.1

Table 1.7: Apparent Density, Porosity and Void Space of all formulations

Formulation codes	**Apparent density (g/cm3)**	**Porosity (%)**	**Void fraction (ml/g)**
FA	0.39 ± 0.02	41.85 ± 0.02	1.48 ± 0.02
FB	0.28 ± 0.01	59.92 ± 0.02	1.69 ± 0.02
FC	0.42 ± 0.02	38.39 ± 0.01	1.43 ± 0.01
FD	0.48 ± 0.01	31.56 ± 0.02	1.39 ± 0.01
FE	0.37 ± 0.01	48.33 ± 0.02	1.53 ± 0.01
FF	0.53 ± 0.02	27.36 ± 0.01	1.27 ± 0.01
FG	0.58 ± 0.01	21.33 ± 0.01	1.21 ± 0.02

Table 1.8: *In vitro* drug release data of SPH formulations

Time (min)	Formulation code						
	FA	FB	FC	FD	FE	FF	FG
2	19.14±0.2	11.36±0.4	6.73±0.4	5.71±0.2	29.66±0.3	4.16±0.5	3.42±0.3
4	34.79±0.4	24.9±0.2	16.55±0.3	11.78±0.3	46.21±0.2	11.79±0.3	9.64±0.4
6	48.83±0.32	33.78±0.5	26.39±.5	25.93±0.6	61.91±0.4	22.87±0.7	17.89±0.2
8	61.39±0.3	52.34±.5	38.71±0.6	46.42±0.6	71.65±0.4	39.94±0.2	25.07±0.1
10	81.76±0.5	69.84±0.6	62.11±0.6	58.16±0.4	82.87±0.6	52.63±0.2	39.98±0.1
12	93.16±0.3	86.66±0.4	78.27±0.4	72.94±0.1	96.90±0.2	67.19±0.1	55.08±0.5
14	94.04±0.1	94.92±0.2	88.68±0.3	80.21±0.2	97.44±0.2	71.44±0.2	66.49±0.3
16	-	95.08±0.1	89.32±0.2	81.93±0.1	-	72.17±0.1	67.89±0.1

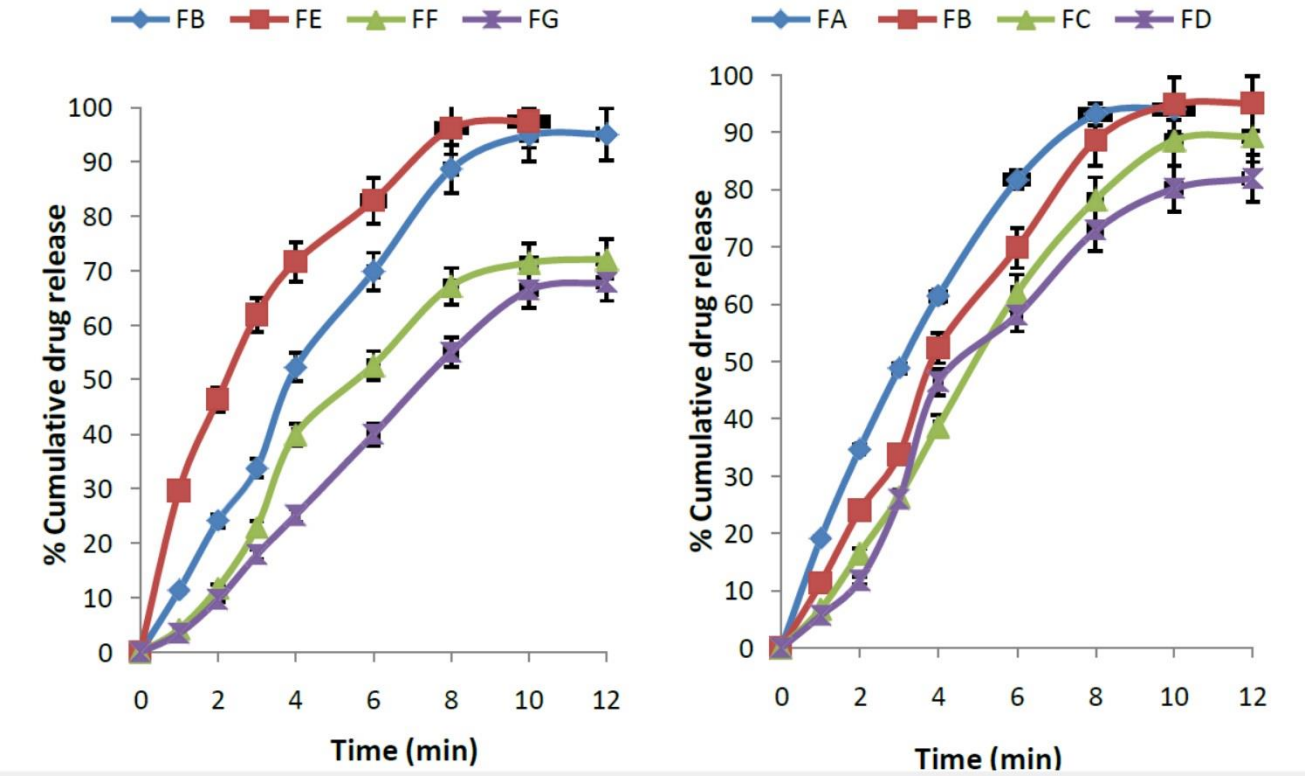
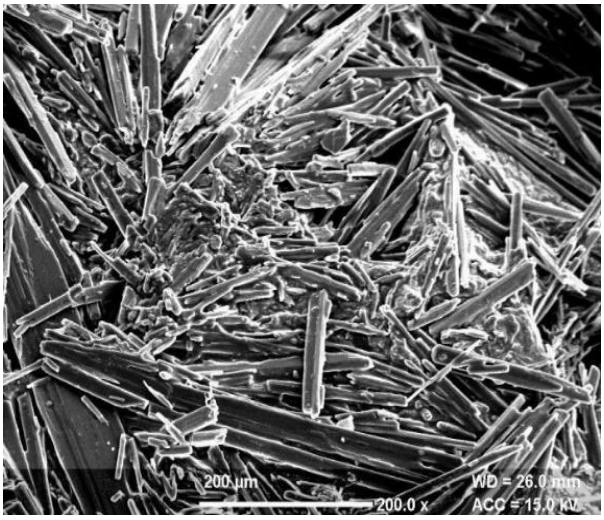


Figure 1.8: *In vitro* drug release data of SPH formulations with changing a) Chitosan and b) Cross linker concentrations

(i)



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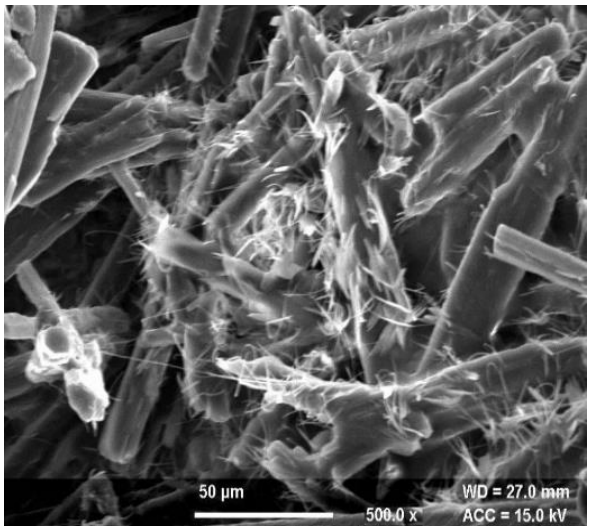

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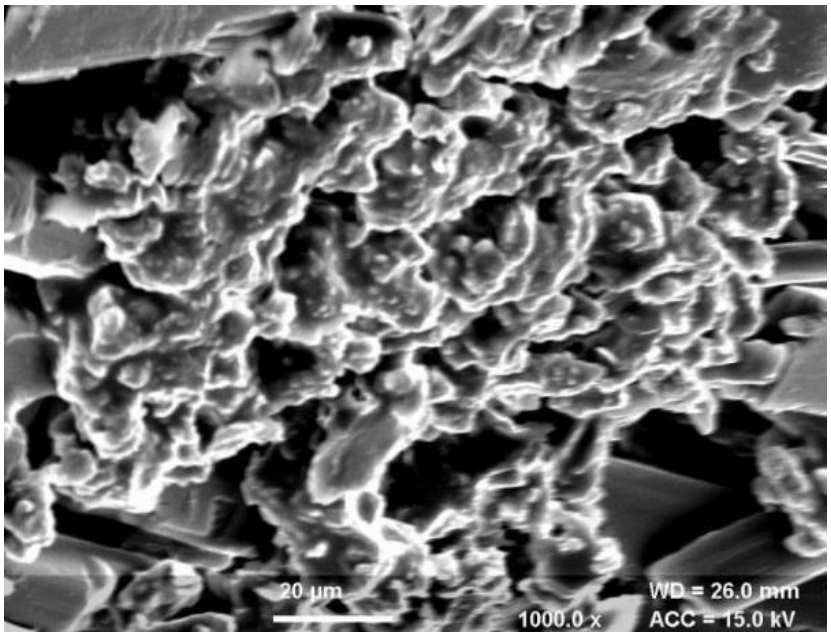

(iii)

Figure 1.9: Scanning Electron Microscopy (SEM) of FB formulation at i) 200x, ii) 500x and iii) 1000x

Table1.9: Effect of pH on swelling ratio of SPH formulation

Time (Mins)	Swelling ratio (%)			
	pH 1.2	pH 3.0	pH 4.9	pH 7.4
0	0	0	0	0
2	10.05± 0.3	13.67± 0.6	8.22± 0.5	5.31± 0.7
4	14.72± 0.5	21.02 ± 0.4	10.54 ± 0.4	8.07± 0.5
6	29.09 ± 0.6	39.13± 0.3	24.18± 0.4	13.34 ± 0.3
8	37.52± 0.4	51.28 ± 0.7	31.07 ± 0.3	19.44± 0.4
10	48.42± 0.5	61.14± 0.4	38.21± 0.7	27.17 ± 0.2
12	61.17 ± 0.3	73.13 ± 0.3	45.02 ± 0.9	34.74± 0.6
14	72.64± 0.7	84.29± 0.2	52.36 ± 0.5	41.18 ± 0.3
16	98.09 ± 0.5	107.44 ± 0.5	66.94 ± 0.4	57.52± 0.4
18	116.84± 0.9	127.11± 0.4	76.37± 0.3	68.41 ± 0.6
20	123.17 ± 0.3	139.55 ± 0.4	98.71 ± 0.7	87.38± 0.1
22	139.87± 0.4	154.62± 0.1	117.33± 0.4	96.81 ± 0.3
24	142.27 ± 0.2	156.59 ± 0.3	119.97 ± 0.2	101.93± 0.1

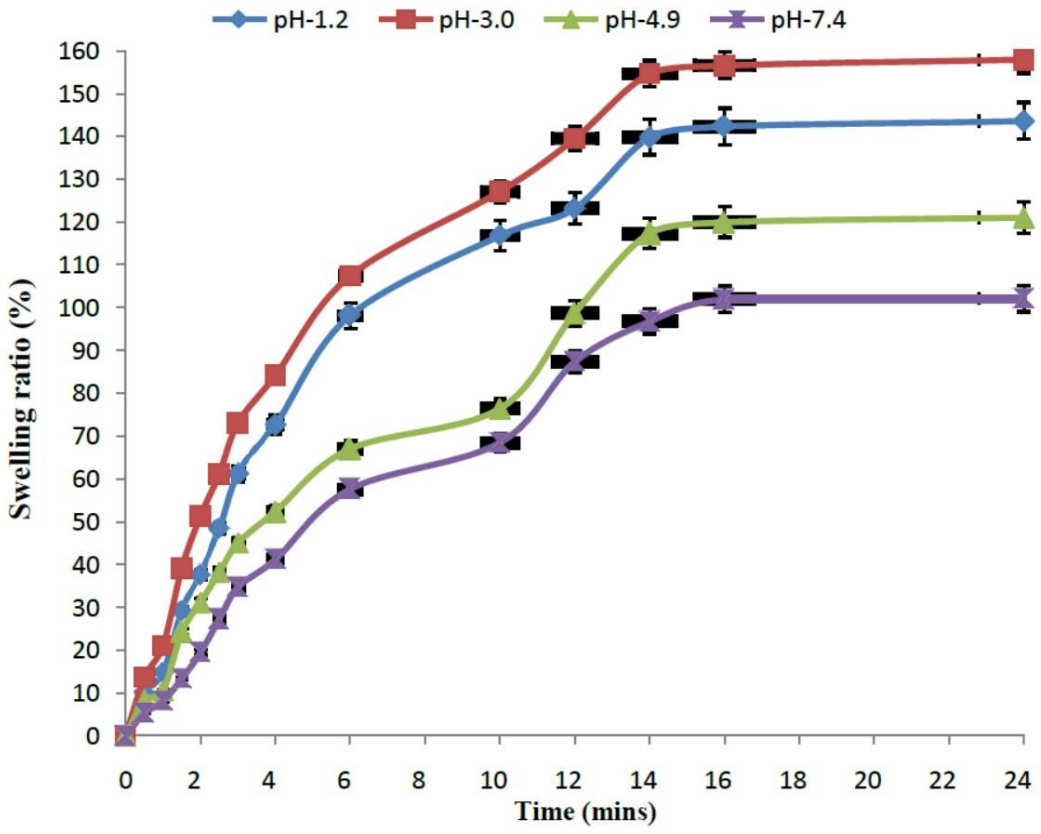

Figure 1.10: Effect of pH on swelling ratio of Ramipril SPH formulation

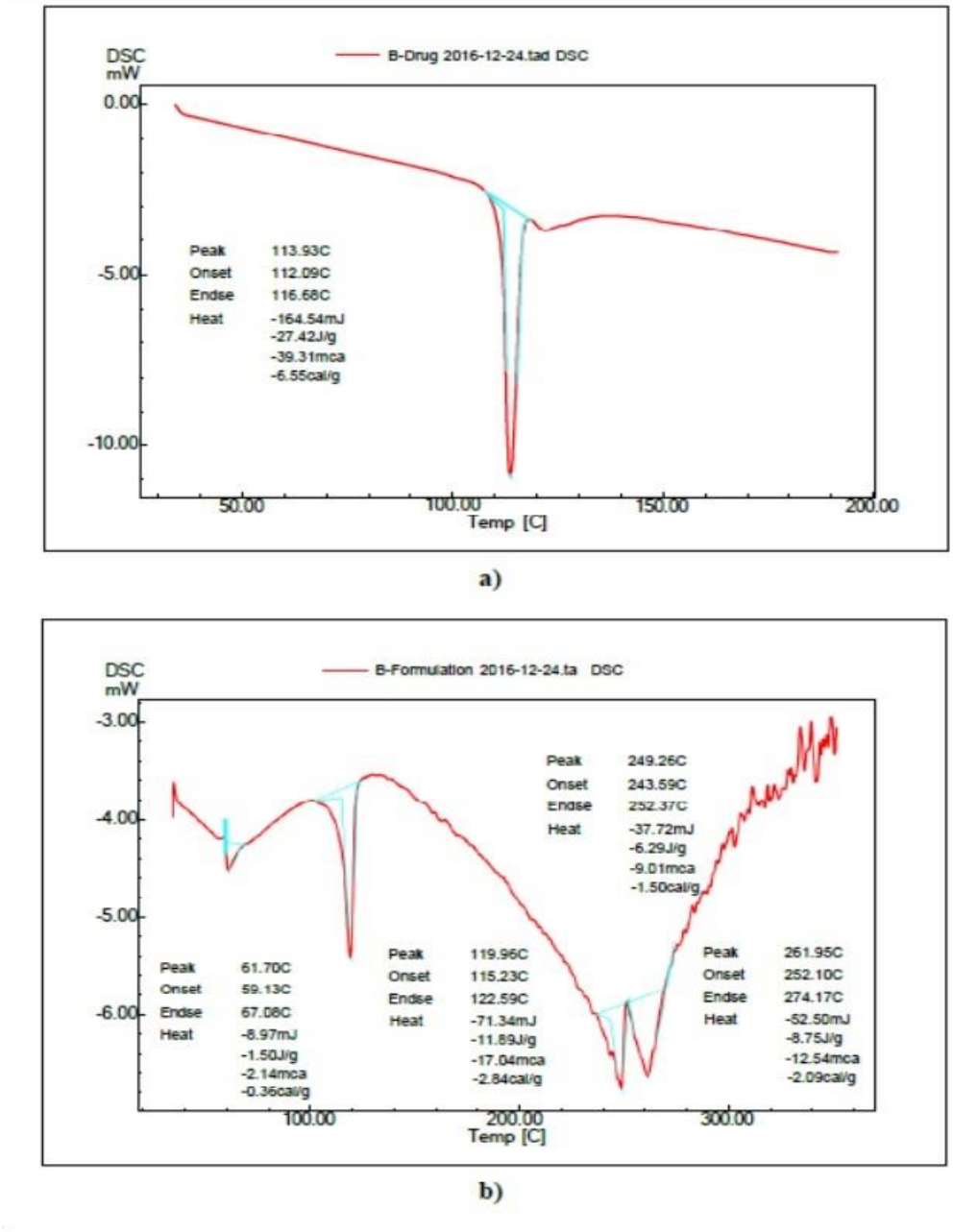

Figure 1.11: DSC Thermogram of a) Ramipril and b) Ramipril SPH

Since DSC profile of both drug as well as drug loaded SPH depicted the endothermic peaks nearest to each other that indicated that no physical interaction between drug and polymers.

4. Conclusion

The aim of this study was to develop a superporous hydrogel formulation of Ramipril for oral disintegrating delivery. Superporous hydrogels were chosen due to their highly porous nature, which allows them to swell significantly upon absorbing swelling media. In addition, superporous hydrogels possess greater tensile strength due to their elastic properties, making them an advanced generation of hydrogel system. Ramipril was selected for its good solubility in acidic media and its ability to achieve peak plasma concentration within 1-4 hours after oral administration. However, its short half-life of 3-4 hours requires frequent dosing with conventional tablets, which can cause various side effects such as dizziness, uneven heartbeats, and shortness of breath. Furthermore, Ramipril's solubility is better in acidic media but degrades in alkaline media.

References

[1] J. Chen, H. Park, and K. Park. (1999). Synthesis of Superporous Hydrogels: Hydrogels with Fast Swelling and Superabsorbent Properties. Journal of Biomedical Material and Research. 44(1): 53-62.

[2] K. Park, J. Chen, and H. Park. (2001). Hydrogel Composites and Superporous Hydrogel Composites Having Fast Swelling, High

Mechanical Strength, and Superabsorbent Properties. US Patent No. 6271278.

[3] F.A. Dorkoosh, J.C. Verhoef, G. Borchard, M.R. Tehrani, and H.E. Junginger. (2001). Development and Characterization of a Novel Peroral Peptide Drug Delivery System. Journal of Controlled Release. 71: 307–318.

[4] M. Nagpal, S.K. Singh, and D. Mishra. (2013). Superporous Hybrid Hydrogels Based on Polyacrylamide and Chitosan: Characterization and In Vitro Drug Release. International Journal of Pharmaceutical Investigation. 3(2): 88-94.

[5] A. Kumar A, Pandey M.K. Koshy, A.S. Shubhini. (2010). 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: 135-140.

[6] V.N. Gupta and H.G. Shivakumar. (2010). Preparation and Characterization of Superporous Hydrogels as Gastroretentive Drug Delivery System for Rosiglitazone Maleate. DARU Journal of pharmaceutical science. 18(3): 200-210.

[7] S. Yang, Y. Fu, S.H. Jeong, and K. Park. (2004). Application of Poly (Acrylic Acid) Superporous Hydrogel Microparticles as a Super-Disintegrant in Fast-Disintegrating Tablets. Journal of Pharmacy and Pharmacology. 56(4): 429-436.

[8] H.V. Chavda, R.D. Patel, I.P. Modhia, and C.N. Patel. (2014). Role of Superporous Hydrogel Particles as A Superdisintegrant In Fast Disintegrating Tablet of Glipizide. Chronicles of Young Scientists. 5 (1): 11-19.

[9] D. Cetin, A.S. Kahraman, and M. Gumusderelioglu. (2011). Novel Scaffolds Based on Poly (2- Hydroxyethyl Methacrylate) Superporous Hydrogels for Bone Tissue Engineering. Journal of Biomaterials Science. Polymer Edition. 22(9): 1157-1178.

[10] S. Kubinova, D. Horak, and E. Sykova. (2009). Cholesterol-Modified Superporous Poly (2-Hydroxyethyl Methacrylate) Scaffolds for Tissue Engineering. Biomaterials. 30: 4601-4609.

[11] A. Jayakrishnan, M. Mohanty, R. Mandalam, and V.P.K. Rao, A.K. Gupta, and S. Joseph. (1994). Endovascular Embolization Using Hydrogel Microspheres. Journal of Materials Science Materials in Medicine. 5(9): 723-727.

[12] H. Park. (2002). Superporous Hydrogels for Pharmaceutical and other Applications. Drug Delivery Technology. 2: 38-44.

[13] J.M. Turakhiya, H.D. Savani, J.M. Patel, and B.V. Akbari, N.G. Prajapati and V.S. Shah. (2013). A Review Superporous Hydrogel (SPH) - An Approach for Controlled Drug Delivery. Universal Journal of Pharmacy. 2(1): 47-58.

[14] A.V. Chobanian, G.L. Bakris, H.R. Black, W.C. Cushman, L.A. Green, J.L. Izzo, D.W. Jones, B.J. Materson, S. Oparil, J.T. Wright, and E.J. Roccella. (2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Jama. 289(19): 2560-2572.

[15] J.A. Oates and N.J. Brown. (2001). Antihypertensive Agents and the Drug Therapy of Hypertension, In, "Goodman and Gillman's "The Pharmacological basics of Therapeutics. 10: 871-900.

[16] J.Y. Mukund, B.R. Kantilal, and R.N. Sudhakar. (2012). Floating Microspheres: A Review. Brazilian Journal of Pharmaceutical Sciences. 48 (1): 17-30.

[17] K. Rajkumar, R.S. Goud, P.S. Sowjanya, P. Anusha, A.S. Lavanya, E.R. Reddy. (2012). A review article on Floating Microspheres of Novel approach on Drug Delivery. Journal of Drug Delivery Research. 1 (4): 1-20.

[18] E.A. Klausner, E. Lavy, M. Friedman, and A. Hoffman. (2003). Expandable Gastroretentive Dosage Forms. Journal of Controlled Release. 90(2): 143-62.

[19] S. Bansal, M. Bansal, G. Shilakari, and A. Asthana. (2013). Gastroretentive Drug Delivery System: Recent Trends and Advances. Inventi Rapid Pharmaceutical Technology. 2: 1-11.

[20] P.R. Hari, T. Chandy, and C.P. Sharma. (1996). Chitosan/Calcium-Alginate Beads for Oral Delivery of Insulin. Journal of Applied Polymer Science. 59: 1795-1801.

[21] R.B. Gandhi, and J.R. Robinson. (1988). Bio-adhesion in Drug Delivery. Indian Journal of Pharmaceutical Science. 50: 145-152.

[22] A. Ahuja, R.K. Khar, and J. Ali. (1997). Mucoadhesive Drug Delivery Systems. Drug Development and Industrial Pharmacy. 23: 489-492.

[23] J. Russel, and P. Bass. (1985). Canine Gastric Emptying of Polycarbophil: An Indigestible Particulate Substance. Gastroenterology. 89: 307-312.