RESEARCH ARTICLE

Formulation and *In-vitro* Evaluation of Super Porous Hydrogel Composite of Baclofen

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ABSTRACT

Baclofen (BCN) is a centrally acting muscle relaxant that act by inhibiting the transmission of the reflexes at the spinal cord level. It is used to treat spastic movement particularly in the case of spinal cord injury and multiple sclerosis. The major objective of the present study is to formulate a gastroretentive drug delivery system of super porous hydrogel composite (SPHC) of baclofen to increase its residence time in the stomach to increase its absorption because baclofen has a narrow absorption window limited in the stomach and upper part of small intestine. Gas blowing technique is the method used for the formulation of different formulas of baclofen super porous hydrogel composite by using polymers such as acrylic acid 40%, acryl amide 40%, and poly vinyl alcohol (PVA) in different amounts of 10, 15, 20, 25 and 30 mg, the positive and encouraging results was obtained by the using of acryl amide (AM) and PVA as a monomers. N, N-Methylene-Bis-Aacrylamide (MBA) used as a cross linker. Crospovidone (COP) used as a composite agent. Sodium bicarbonate has been used as the CO_2 generating agent to assist to the formulation. The effect of monomer and cross linker agent amounts on the percent of drug release has been studied. The formulas were investigated for their swelling ratio, mechanical strength, porosity, density, drug content and drug release. The formula of 30 mg PVA, 300 µL of 40% AM, 50 mg CRP and 50 mg Sodium bicarbonate has a mechanical strength of 277gm with a percent of drug release reached to 98.5% within 12 hours. that indicate a sustained release of the baclofen drug. The selected formula then evaluated for scanning electron microscopy and fourier transform infrared spectroscopy (FTIR) study to investigate the compatibility of the drug with the polymers used and the results showed there is no incompatibility between the drug and the materials used.

Keywords: Acryl amide (AM), Baclofen (BCN), Drug release, Poly vinyl alcohol (PVA), Methylene-Bis-Aacrylamide (MBA), Super porous hydrogel composite (SPHC), Swelling ratio, Mechanical strength.

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INTRODUCTION

Oral drug delivery systems are the most favored and convenient rout for delivering the drug to the systemic circulation.[1] Oral controlled release drug delivery has recently gained popularity in the pharmaceutical industry to achieve enhanced therapeutic benefits such as ease of dosing administration, patient compliance, and formulation versatility.[2]

Drugs with short half-lives and easy absorption from the gastrointestinal tract (GIT) are rapidly removed from the systemic circulation. To achieve adequate therapeutic efficacy, these medications must be dosed frequently.[3] To overcome this restriction, oral sustained-controlled-release formulations are being developed to slowly release the medication into the GIT and retain an adequate drug concentration in the systemic circulation for a long time.[4]

Gastroretentive dosage form types can be stored in the gastrointestinal tract and avoid rapid gastric emptying. These systems are ideal for medications that have an absorption window restriction.[5] They are manufactured as modified release drug delivery system formulations with the ability to monitor the release rate and site to confine the dosage type to the GIT's targeted region (stomach).[6]

One of most important approaches that are formulated and developed for increasing drug residence time in the upper part of the GIT are the gastroretentive drug delivery systems.[7] Super porous hydrogel (SPH) is one of the types of these systems that is designed and then developed for the purpose of maintaining the drug for a long period of time in the stomach as much as possible without affecting on its efficacy, absorption, stability, and its mechanical strength to resist the stomach contractions and the harsh gastric environment.[8]

SPHs can be defined as a cross-linked or three-dimensional network consisting of polymers of a hydrophilic nature. These polymers have the ability of absorption of a sizeable amount of

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water within a very short period.[9] This ability is because of the presence of many pores that have a diameter with a range from micro to millimeters scale.[10]

The numerous pores in the super porous hydrogels are connected by forming an opened channels structure, the water molecules can enter to these channels by capillary wetting phenomena rather than by diffusion mechanism.[11] This capillary wetting force makes the swelling of the dried SPH very fast that can take just few minutes regardless of the size of the dried form of the SPH.[12]

The BCN is centrally acting muscle relaxant act by inhibiting of the transmission of the reflexes at the spinal cord level. It is used to treat spastic movement, particularly in the case of spinal cord injury and multiple sclerosis.[12]

The major objective of the present study is to formulate a gastroretentive drug delivery system of super porous hydrogel composite (SPHC) of baclofen to increase its residence time in the stomach to increase its absorption baclofen has a narrow absorption window limited in the stomach and upper part of small intestine.

MATERIALS

Hyper-Chem. LTD CO. (China) provided BCN and COP, HIMEDIA.(India) provided Acryl amide AM, BDH chemicals Ltd. (England) provided Acrylic acid AA, Thomas Baker Chemicals. (India) provided Ammonium persulphate (APS), and N,N-Methylene-Bis-Aacrylamide (MBA), MESE Ltd. (Germany) provided PVA, Alpha chemical. (India) provided Tween 20 **(**T20**),** Sodium metabisulfite SMB and Sodium bicarbonate.

METHODS

Preparation of Baclofen Super Porous Hydrogel Composite

Gas blowing technique was used in this study as a method for preparation of BCN as SPHC. The monomers used in this study are acrylic acid (AA), acryl amide (AM) and poly vinyl alcohol (PVA). N, N`- methylene Bisacryl amide (MBA) was used as cross linker, Tween 20 was used as foam stabilizing agent. Ammonium persulfate (APS)/Sodium metabisulfite pair was used as polymerization initiator pair. Crospovidone was used as a composite agent. Sodium bicarbonate was used as gas generating or foaming agent.[13]

The monomers AA and AM or AA and PVA were added to a test tube of 10 mm diameter and 75 mm in length then (MBA) and tween 20 was added to the mixture with shaking in the sonicator for 5 minutes. In the next step of the formulation crospovidone was added then the polymerization initiation pair was added with vigorous shaking of the test tube for at least 5 minute. Before the addition of sodium bicarbonate the BCN powder of 20 mg was added. Finally, the gas generating agent was added with shaking to ensure the homogeneous distribution of CO_2 bubbles.[13]

The synthesized SPHC can be removed from the test tube by adding 2 mL of absolute ethanol and drowned carefully using suitable forceps. The formed BCN SPHC was1 dried in 1oven at 160°C for 48 hours, later can be used and evaluated for further evaluation tests.[14]

Characterization and Evaluation of SPHC Formulations

Determination of Equilibrium Swelling Ratio

The completely dried SPHC was weighed and then placed more than the swelling medium of 0. N HCl solution at room temperature. The weight is measured at different time intervals until reaching a state where no change in weight can be obtained.[15]

The equilibrium swelling ratio can be calculated by using the following equation:

$$Qs = \{Ws - Wd|Wd\} * 00\%$$ [16]

Here,
Qs is the equilibrium swelling ratio
Ws is the weight of swelled SPHC
Wd is the weight of dried SPHC

Table 1: Formulas of SPHC of BCN prepared by gas blowing technique

Formulas	*BCN mg*	*AA µL*	*AM µL*	*PVA mg*	*MBA 40 µL (%)*	*T20 µL*	*COP mg*	*SMB µL*	*APS µL*	*$NaHCO_3$ mg*
F1	20	200	300		1	200	50	40	40	50
F2	20	200	300		1.5	200	50	40	40	50
F3	20	200	300		2	200	50	40	40	50
F4	20	200	300		2.5	200	50	40	40	50
F5	20	200	300		3	200	50	40	40	50
F6	20	200	300		3.5	200	50	40	40	50
F7	20		300	10	2.5	200	50	40	40	50
F8	20		300	15	2.5	200	50	40	40	50
F9	20		300	20	2.5	200	50	40	40	50
F10	20		300	25	2.5	200	50	40	40	50
F11	20		300	30	2.5	200	50	40	40	50
F12	20	200	300		2.5	225	50	40	40	50
F13	20	200	300		2.5	250	50	40	40	50
F14	20	200	300		2.5	275	50	40	40	50
F15	20	200	300		2.5	300	50	40	40	50

Determination of Equilibrium Swelling Time

Swelling time is a very important criterion of the SPHC. It can be determined by placing the SPHC in the swelling media of 0.1 N HCL solution then the time for complete swelling (or constant weight) can be measured and recorded.[16]

Measurement of Density

Solvent displacement method was employed for density determination of SPHC. The dried piece of SPHC was weighed and its weight was recorded then, this piece was immersed in a predetermined volume of n-hexane as a hydrophobic solvent in a graduated cylinder. The difference between the initial and the final volume of the solvent was considered as the volume of the SPHC, and the density can be calculated from the following equation.[17]

$$Density = {}^{W\ SPHC}/_{V\ SPHC} \quad [18]$$

Here,
W_{SPHC} is the weight of dried SPHC
V_{SPHC} is the volume of SPHC

Measurement of Porosity

Solvent replacement method is used to determine the porosity of SPHC. The dried SPHC was immersed in absolute ethanol overnight and it absorbed ethanol and swelled. After the full blotting of ethanol on the surface, the porosity is calculated from the following equation.[17]

$$Porosity = {}^{M2 - M}/_{PV} \quad [18]$$

Here,
M2 and M are the masses of SPHC after and before the immersion in absolute ethanol respectively.
P is the density of absolute ethanol, V is the volume of SPHC

Determination of the Mechanical Strength

Mechanical strength of the SPHC was determined by applying weight on the swelled SPHC by using TA-XT2i texture analyzer (Stable Micro Systems, Haslemere, UK). The weight in gram (gm) needed for the fracturing of the SPHC was recorded as the mechanical strength.[18]

Determination of Drug Content

Five units of dried SPHC was placed in a mortar and powdered. An amount of drug equivalent to 20 mg was extracted with 100 mL of 0.1N HCl and placed in sonicator for 15 minutes. Then the solution was filtered and diluted properly with 0.1N HC1 solution then the BCN content was measured using UV-visible spectrophotometer at the λ_{max} of the drug.[19]

In-vitro Drug Release

Dissolution apparatus (USP type Π) was used to study the release of BCN drug in this study. The paddle was stirred at a rate of 100 RPM in a 900 mL of the dissolution medium of 0.1N HCl at 37 ± 0.5°C. A sample of 5 mL was withdrawn at specific time intervals from 0.5 to 12 hours, then after each withdrawing process, a fresh amount of 5 mL of the medium solution was substituted. At the λ_{max} of the drug, the absorbance of each sample was measured by using UV-visible spectrophotometer. Drug concentration and the percent of drug release were obtained and calculated by using the standard calibration curve.[20]

Fourier Transform Infrared (FTIR) Analysis

The compatibility of the BCN with the polymers was investigated using the FT-IR spectra of BCN, polymers used, physical mixture and the selected SPHC formula. The powdered sample (2–3 mg) was combined with potassium bromide (KBr) at a 1:5 ratio, and the KBr disc was created by compressing the powder at 5 tons of pressure for 5 minutes in a hydraulic press. Using an FT-IR spectrometer, the scanning range is 4000–400 cm^{-1}.[21]

Scanning Electron Microscopy (SEM)

Hummer sputter coater was used to observe the morphology of the selected dried SPHC formula and to assure the porous structure generated during the formulation process of the SPHC. A QUANTA 450 scanning electron microscope was used to plate samples on the home stage and take images using a digital capture card and digital scan generator.[22]

RESULTS AND DISCUSSION

Effect of Cross Linker Concentration

To investigate the effect of MBA concentration as a cross linker on the properties of the SPHC formulas F1-F6 were prepared and then evaluated. The results are listed in the Table 2 as shown below.

As shown in Table 2, when the concentration of the cross linker increased, the density of the SPHC was increased because of the network space will be diminished, also the porosity will be decreased due to stronger bonds formed between the two monomers and the cross linker, and this will reduce the sizes of interconnecting pores.[23]

Table 2: Effect of MBA as (cross linker) concentration

Formula number	*Swelling time (min)*	*Swelling ratio*	*Mechanical strength (gm.)*	*Density (g/cm^3)*	*Porosity*	*Drug content (%)*
F1	19	18.4	109	1.3 ± 0.023	0.42 ± 0.023	93
F2	15	21.6	130	1.33 ± 0.012	0.4 ± 0.016	96
F3	12	25.3	165	1.35 ± 0.031	0.37 ± 0.04	97
F4	10	37.5	220	1.36 ± 0.012	0.31 ± 0.012	99
F5	9	33.8	230	1.38 ± 0.022	0.27 ± 0.016	101
F6	9	33.3	231	1.39 ± 0.021	0. 23 ± 0.02	92

The swelling ratio of formulas F1-F4 will increase as the cross linker's concentration increased because MBA is a hydrophilic monomer. While in formula F5-F6 there is no significant effect of increased concentration of the cross linker on the swelling ratio, this belongs to at concentrations of MBA of 2.5% and below, MBA considered as hydrophilic monomer as itself. For this reason, the swelling ratio will increase because the hydrogel will absorb more water. However, at concentrations of more than 2.5%, there is a slight decrease in swelling ratio due to the density increase of the crosslinking in the hydrogel, and it will lead to lower the average molecular weight between the crossed links. It will decrease the free volume accessible for the penetration of the water molecules, for these reasons, the concentration of 2.5% of MBA will be chosen for further study.[18]

The swelling time will be decreased significantly for formulas F1-F4 as the concentration of MBA was increased, this is because the total swelling time of the dried SPHC will be determined by a capillary action more than by the thickness of the cell walls and the spokes because of the spokes and the cell walls have a very short swelling time.

The mechanical strength for formulas F1-F4 was increased significantly as the concentration of the cross linker was increased because the high amount of cross linker will maintain the pores integrity and the interconnected channels in the SPHC, i.e., at high density of cross linking, the networks of the polymers become more rigid, so, the two polymer chains will be attached more strongly to each other.[18]

At higher concentrations of MBA >2.5%, there is no significant effect on the mechanical strength as shown in formulas F5-F6 because the hydrogel chains become too inflexible that the mechanical strength becomes independent on the amount of cross linker MBA used.

Drug content within acceptable limits because of the compatibility of the BCN with the used polymers.

Figures 1 and 2 shows the effect of cross linker concentration on the swelling ratio, and mechanical strength of SPHC, respectively:

Effect of Polyvinyl Alcohol (PVA) Concentration

Poly vinyl alcohol is considered as a second option monomer that can be used instead of acrylic acid in the formulation of the SPHC and also can be considered and used as a composite agent.[24]

To investigate the effect of PVA amount as a monomer on the properties of the SPHC, formulas F7-F11 were prepares and tested and the results will be shown in the Table 3 as follow:

The results in Table 3 show a significant increase in the density and mechanical strength because there is an increase in the fibers of cellulosic nature in the polymer structure. Porosity and swelling ratio are decreased significantly due to increase in the viscosity of the solution during the gelation process.[25]

The drug content was in an acceptable limit because there is no drug loss within and after the formulation process and there is a drug-polymer compatibility.

Figures 3 and 4 below will show the effect of PVA concentration on the swelling ratio, and mechanical strength of the SPHC, respectively:

Effect of the Amount of Foam Stabilizing Agent (Tween 20)

Tween 20 was used in this study as a foam stabilizing agent to stabilize the foaming process and control the number of gas bubbles generated. As the gas bubbles are controlled and preserved, and uniformly distributed, the internal structure of the SPHC will become less random and enhanced because the uniform distribution of the intercellular capillary channel network, which is necessary for fast and good swelling and this will lead to an increased mechanical strength by increasing the viscosity of the monomers that were used during the formulation process with improving the swelling properties.[25]

Depending on above-mentioned facts, formulas F4, F12, F13, F14 and F15 were prepared to contain Tween 20 in an amount of (200, 225, 250, 275 and 300 mg), respectively and the results are shown in Table 4.

The results in Table 4 shows the decrease in porosity and increase in density that leading to the increase in the mechanical strength and a decrease in the swelling ratio significantly and this results is compatible with the facts mentioned in the previous page. It will be enhanced because of the uniform distribution of the gas bubbles that is lead to uniform intercellular capillary network with fast swelling (lower swelling time) with lower swelling ratio.[25]

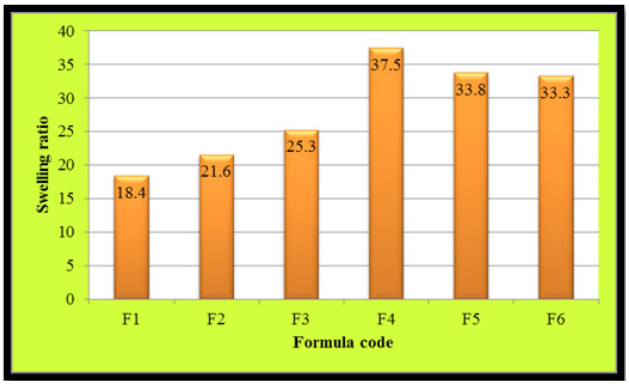

Figure 1: Effect of cross linker concentration on the swelling ratio of SPHC

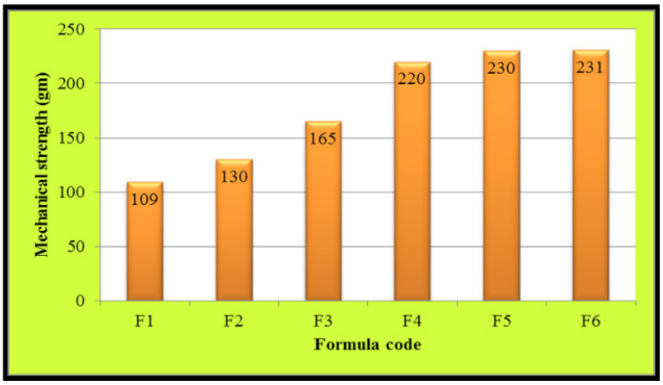

Figure 2: Effect of cross linker concentration on the mechanical strength of SPHC

Table 3: Effect of PVA concentration on SPHC properties

Formula number	*Swelling time (min)*	*Swelling ratio*	*Mechanical strength (gm.)*	*Density g/cm^3*	*Porosity*	*Drug content (%)*
F7	19	31.9	245	1.37 ± 0.012	0.26 ± 0.014	96
F8	21	27.1	252	1.39 ± 0.013	0.22 ± 0.012	99
F9	22	23.4	261	1.42 ± 0.022	0.21 ± 0.013	97
F10	25	21.8	269	1.46 ± 0.012	0.17 ± 0.013	99
F11	27	18.6	277	1.49 ± 0.011	0.15 ± 0.011	95

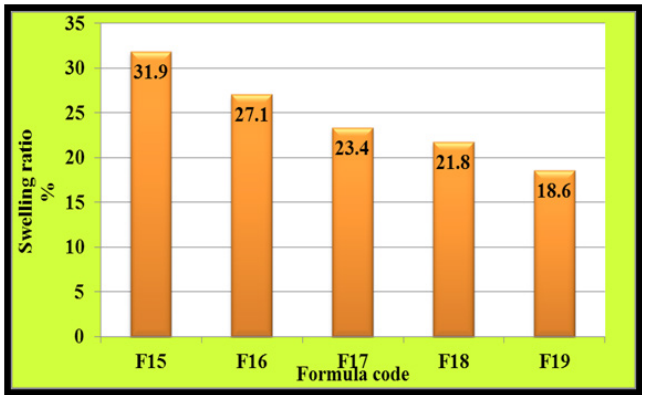

Figure 3: Effect of PVA concentration on the swelling ratio of the SPHC

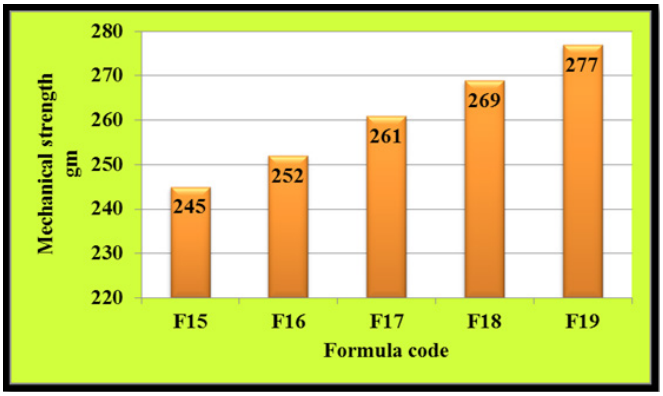

Figure 4: Effect of PVA concentration on the mechanical strength of the SPHC

Table 4: Effect of Tween 20 amount on SPHC properties

Formula number	*Swelling time (min)*	*Swelling ratio*	*Mechanical strength (gm.)*	*Density g/cm^3*	*Porosity*	*Drug content (%)*
F4	10	37.5	220	1.36 ± 0.012	0.31 ± 0.012	99
F12	9	34.3	222	1.38 ± 0.012	0.29 ± 0.012	97
F13	7	31.7	228	1.42 ± 0.02	0.28 ± 0.014	99
F14	6	30.5	232	1.44 ± 0.012	0.26 ± 0.013	97
F15	4	29.2	237	1.48 ± 0.014	0.23 ± 0.011	98

Drug contents for all formulas (F4, F12, F13, F14, F15) were in the acceptable limits indicating no drug lose within and after the formulation process of the SPHC, indicating the compatibility of BCN with the polymers and the materials used in this study.

In-vitro Drug Release

Figure 5 will show the release profile of the formulas (F7-F11) and the effect of the concentration of PVA as a second monomer on it.

The results in the Figure 3 and 4 shows that the release profile of the formulas (F7–F11) was extended for 12 hours for all formulas indicating a slow and sustained rate of release of the BCN drug from SPHC.

The reason for that was there is a relatively high mechanical strength with a decrease in the porosity and swelling capacity of the SPHC as the amount of the PVA was increased because PVA was produce a high viscous solution and it can act as a composite agent causing an increase in the crosslinking between the monomers themselves leading to enhancing of the dispersion force over the osmotic force that cause a delay in the penetration of the swelling media (osmotic force) and hence an increasing in the time period requiring for the complete of the release of the BCN drug from the SPHC.[24,25]

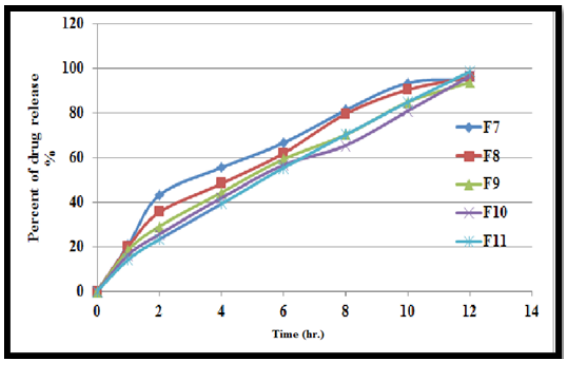

Figure 5: Effect of the concentration of PVA as a second monomer on the release profile of formulas (F7-F11)

Fourier Transform Infrared (FTIR) Study

Bruker optics (Germany) FTIR Spectroscope was used for the analysis of BCN SPHC. The FTIR was considered an

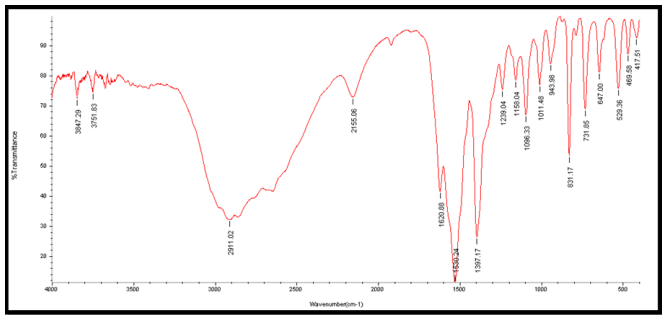

Figure 6: FT-IR spectra for pure BCN

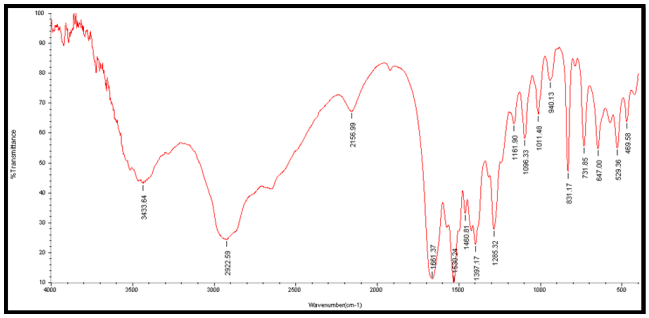

Figure 7: FT-IR spectra for physical mixture of BCN, PVA and CRP in a ratio of 1:1.5:2.5

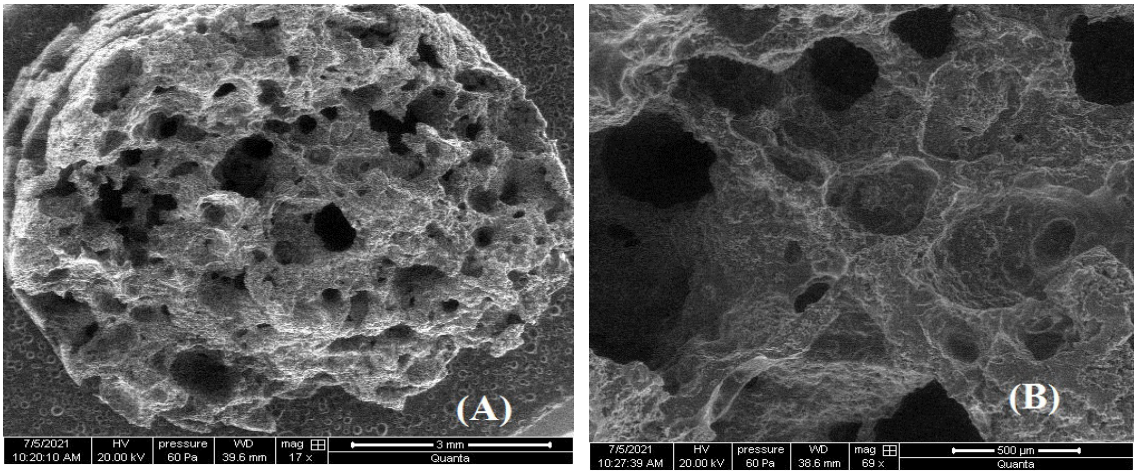

Figure 8: Scanning electron microscopy (SEM) for the selected formula (F11) at different magnification powers A- ×17, B- ×69

important procedure to identify compounds and determine the compatibility of BCN with the polymers used in the formulation process of the SPHC. Figures 6 and 7 will show the FT-IR spectra of pure BCN and physical mixture of BCN with polymers in a ratio of 1:1.5:2.5, respectively. The results indicate no chemical incompatibility between BCN and the polymers as the peaks of the BCN appear in the spectra of the physical mixture.

Scanning Electron Microscopy (SEM)

Quanta 450 FEI (Netherlands) Scanning electron microscope was used to study the outer and inner morphology of BCN SPHC. The study of the scanning electron microscopy of the selected formula (F11) at different magnification powers can be shown in Figure 8.

CONCLUSION

It can be concluded that super porous hydrogel composite can be used to sustain the release of baclofen in the stomach and upper part of the small intestine. Also, SPHC can delay the gastric residence time of the drug in the region of its narrow window of absorption. The increase of the amount of cross linker and PVA can increase the mechanical strength and density with a decrease in the swelling ratio of the SPHC. As the concentration of gas-generating agents increases, the swelling ratio will increase with the decreasing mechanical strength and density. There is a compatibility between the drug and the excipients used, as is clear in the FT-IR examination.

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