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FORMULATION DEVELOPMENT AND CHARACTERIZATION OF SUPERPOROUS HYDROGEL OF ITOPRIDE HYDROCHLORIDE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Aim of this research was development and characterization of Itopride hydrochloride superporous hydrogel to extend drug release. Synthesis of superporous hydrogel composites was carried out by solution polymerization using sodium bicarbonate as gas blowing agent. 50% acrylamide solution (AM) and 50% acrylic acid solution (AA) as a monomer, 2.5% N,N'-methylene bisacrylamide (BIS) as a cross linker, 20% Ammonium persulphate (APS) and 20% N,N,N',N'-Tetramethylethylene diamine (TEMED) as a polymerization initiator pair, 10% Pluronic F127 solution as a foam stabilizer used for synthesis of superporous hydrogel composites. Its characterization performed by density, water retention capacity, *in-vitro* buoyancy study, floating time, swelling ratio, swelling time, porosity, scanning electron microscopy, *in-vitro* drug release and stability. The drug release profiles were fitted to various kinetic models to determine drug release pattern. Density was found to be less than gastric content, swell within time limit, also show degradation kinetics, float within few seconds and floating time more than 12 h. FTIR studies shows all prominent peaks of drug in formulation F-8 and DSC indicate cross linking. The drug release profiles was fitted to korsmeyer-peppas model (R^2=0.9967) and n values were found within limit 0.3724 (e.g. Less than 0.45) suggesting probable release by fickian diffusion (Higuchi matrix). Also stability study for formulation F-8 carried out at 40 ºC and 75% RH for one month, formulation found to be stable. The prepared systems can be effective for extending drug release reducing the dosing frequency and may improve the bioavailability of Itopride hydrochloride.

KEYWORDS: Superporous hydrogel, Gastroretentive drug delivery, Gas blowing technique.

INTRODUCTION

The drugs for oral delivery have their own convenience for ease and economic administration, but the general problem is the loss of their functions due to the short residence in the body. General problems for all oral dosage forms that are encountered in the gastric residence time. About 80% drugs are excreted without being absorbed.[1] Dosage form retention in the stomach with the intention of prolonging oral gastrointestinal transit time to achieve and improve drug bioavailability is the current target.[2] Itopride hydrochloride is a novel gastroprokinetic agent used in treatment of non ulcer dyspepsia, gastritis,diabetic gastroparasis, gastroesophageal reflux disease and functional dyspepsia. The recommended oral dose of Itopride hydrochloride is 50 mg thrice a day. A dosage form that can extend the release of Itopride hydrochloride would be beneficial in such cases. Itopride hydrochloride shows dual action, it increases acetylcholine concentration by inhibiting dopamine D2 receptors and acetylcholine esterase. Higher the level of acetylcholine increases the gastrointestinal peristalsis, increases the lower oesophageal sphincter pressure, stimulates gastric motility, accelerate gastric emptying and improves gastro-duodenal co-ordination. On oral administration of Itopride hydrochloride, it was observed that it rapidly and extensively absorbed and peak plasma concentration achieved within 34 min after oral dosing. Thus it has rapid onset of action unlike other prokinetic agent like cisapride and mosapride which take 60 min to achieve serum concentration. Presence of food not affects its absorption. Mean peak plasma concentration, Cmax, Tmax, AUC and $t_{½}$ for Itopride hydrochloride was 0.28 ± 0.02 µg/ml, 0.58 ± 0.08 h, 0.75 ± 0.05 µg h/ml, 5-6 h.

Itopride hydrochloride is rapidly distributed, except in the CNS (central nervous system) and spinal cord. Itopride Hydrochloride was about 96% protein bound. Albumin accounts for most protein binding. Metabolised in the liver by N- oxidation to inactive metabolites by the enzyme flavin-containing monooxygenaze (FMO_3) and excreted mainly by the kidneys as metabolites and unchanged drugs.A Gastroretentive drug delivery system that can be retained in stomach and increase the local delivery would also be very useful.[3-9] The rigid crystalline structure and low elasticity in polymer lead to slow swelling of hydrogels and they take few hour to day for complete swelling. Diffusion of water through glassy matrix structure of hydrogel is the reason for its slow swelling. This property of hydrogel is responsible to make

a controlled release dosage form. Fast swelling may not serve the purpose. This is the reason behind the development of a new generation of hydrogels namely a superporous hydrogel.

MATERIALS AND METHODS

Materials

The following materials were used in this study. Acrylic Acid (AA), Acrylamide (AM), N,N Methylene bisacrylamide (BIS), Ammonium Persulphate (APS), N,N,N,N-Tetramethyl ethylene diamine (TEMED) were the generous gift samples from Gennova Biotech, Pune. Pluronic F 127, Sodium carboxy methyl cellulose (Ac-Di-Sol) from Maple Biotech, Pune and Gellan Gum, Carbopol 934P and Sodium bicarbonate from Research Lab, Pune. Guar gum and Xanthan Gum from Research lab, fine chem industry, Mumbai. Chitosan from GM Supplier - V.Kumar and Sons, Aurangabad. Itopride hydrochloride was obtained from Symed Labs Limted, Hyderabad. All other chemicals used were analytical grade.

Methods

Superporous hydrogel composites were synthesized by preparing 50% acrylamide solution (AM) and 50% acrylic acid solution (AA) as a monomer, 2.5% N,N'-methylene bisacrylamide (BIS) as a cross linker, 20% Ammonium persulphate (APS) and 20% N,N,N',N'- Tetramethylethylene diamine (TEMED) as a polymerization initiator pair, 10% Pluronic F127 solution as a foam stabilizer are prepared in double distilled water except 6% Chitosan solution prepared in 0.1 N Acetic acid. All above solutions were added subsequently in a test tube. Test tube must be shaken after addition of each ingredient. Adjust the pH 5 of mixture by using 2M NaOH. After addition of all ingredients add Sodium bicarbonate as a foaming agent (gas blowing agent) in solid state only. Before addition of $NaHCO_3$ add 100 mg of Itopride Hydrochloride or physical mixture of drug and polymer in 1:1 and ratio passed through 60# sieve and allow to polymerize for 10 min. Ac-Di-Sol and Carbopol 934P as a composite material were added in a solid state leads to uniform distribution of gas bubbles. Due to addition of $NaHCO_3$ pH of mixture increases and accelerates the polymerization reaction. The synthesized SPH removed from test tube with the help of forcep. Pore may get collapse should be avoided by placing SPH in absolute ethanol. Formed SPHs were air dried.

Composition of floating superporous hydrogel

Table 1: Composition of different Formulations

Sr No.	Formulations Code ⇨ Ingredients ⇩	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	Itopride Hydrochloride (mg)	100	100	100	100	100	100	100	100
2	Acrylamide (µl)	200	200	200	200	200	200	200	200
3	Acrylic acid (µl)	70	70	70	70	70	70	70	70
4	N,N'-methylene Bisacrylamide (µl)	250	250	250	250	250	250	250	250
5	Pluronic F 127 (µl)	50	50	50	50	50	50	50	50
6	Ac-Di-Sol (mg)	500	-	-	500	500	500	500	500
7	Carbopol 934P (mg)	-	100	100	100	100	100	100	100
8	N,N,N',N'-Tetramethylethylene diamine (µl)	30	30	30	30	30	30	30	30
9	Ammonium persulphate (µl)	30	30	30	30	30	30	30	30
10	Water (µl)	10	10	10	10	10	10	10	10
11	Gellan Gum (mg)	-	-	-	-	100	-	-	-
12	Guar Gum (mg)	-	-	-	-	-	100	-	-
13	Xanthan Gum (mg)	-	-	-	-	-	-	100	-
14	Chitosan (µl)	-	-	500	-	-	-	-	500

Evaluation of Itopride Hydrochloride Superporous Hydrogel Composite

Density

It is difficult to measure the density of superporous hydrogel directly. Density of superporous hydrogel was determined by solvent displacement method. Actually it is a apparent density. Mass of SPH was measured then this SPH placed in graduated cylinder containing measured volume of absolute hexane. Density was calculated by following equation.[10-11]

$$\text{Density} = M_{SPH} / V_{SPH} \quad (1)$$

Where, M_{SPH} = Mass of SPH

V_{SPH} = Volume of SPH

Swelling studies

Swelling time was calculated by placing SPH in deionised water until it attains equilibrium swelling. Time required for equilibration is noticed. The dried SPH was allowed to hydrate in excess of deionised water at room temperature. The weight of fully swollen hydrogel was

measured at different time interval, remove excess of water from surface by gental blotting. The swelling ratio was determined by following equation.[12]

Qs = (Ms-Md/Md)X100 (2)

Where,

Ms=Mass of fully swollen SPH

Md= Mass of dried SPH

Water Retention

Water retention capacity as a function of time determined from the following equation[13-14]

Wrt = (Wp – Wd) / (Ws – Wd) X100 (3)

Where,

Wd = weight of the dried hydrogel,

Ws = weight of the fully swollen hydrogel, and

Wp = weight of the hydrogel at various exposure times.

For determination of the water-retention capacity of the hydrogels as a function of time of exposure at 37ºC, the water loss of fully swollen polymer at time intervals was determined by gravimetry.

***In-vitro* Buoyancy studies**

Buoyancy studies were performed by placing piece of superporous hydrogel in a beaker containing 100 ml of 0.1N HCl and at 37°C ± 0.5°C. Time taken by piece of hydrogel to rise on surface and float was taken as a floating lag time. The time for which it remains float is called total floating time.[10]

Porosity measurement

The porosity of superporous hydrogel measured by immersing dried SPH in absolute ethanol over night and weighed after excess of ethanol on the surface was blotted. The porosity was measured as follows[10]

Porosity = $(M_2 – M_1/ V \rho) X 100$ (4)

Where,

M_2: Mass of SPH in swollen state

M_1-: Mass of SPH in dride state

P: Density of ethanol

Volume (V) was measured from its displacement volume.

Compatibility Studies

Compatibility Study by IR Spectroscopy

IR is the most powerful analytical technique to identify functional groups of a drug. The most important part of pharmaceutical dosage form is the proper selection of excipients on which dosage forms action depends.

Method

The Pure drug and physical mixture of polymer were subjected to IR studies. In the present study, disc (pellet) of potassium bromide (KBr) method was employed.[15-16]

Compatibility study by DSC

Thermogram of drug and formulation were obtained. Crushed samples were sealed in flat bottomed aluminium pan and heated (3 mg) over a temperature range of 50-300ºC at a rate of 10 ºC/min. in a nitrogen atmosphere at flow rate of 50 ml/min.

Determination of Drug Content

Six SPH units of formulation were finely powdered and quantities of the powder equivalent to 100 mg of Itopride hydrochloride were accurately weighed, transferred to a 100ml volumetric flask. Drug treated with 10ml of 0.1N HCl mixed well and make up the volume upto 100 ml with 0.1 N HCl. In order to ensure complete solubility of ITH stock was placed on sonicator. Then filter the solution, make dilutions and take absorbance at 258 nm using UV visible spectrophotometer.[10,17-18]

Scanning Electron Microscopy

The morphology or texture of superporous hydrogel was examined with scanning electron microscopy (SEM). In order to ensure that porous structure generated during SPH synthesis. Dried superporous hydrogel composite cut into pieces to expose their inner structure and imaged in a Zeiss EVO LS 10 SEM.[11,14,19]

***In-vitro* release Study**

Drug release from superporous hydrogel drug delivery system was carried out using dissolution test apparatus (USP type II). The dissolution test performed using 900 ml 0.1N HCl, at 37°C ± 0.5°C and at 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at different time interval. The samples were replaced with fresh

dissolution medium of same quantity. Drug release was analyzed at 258 nm wavelength using 0.1N HCl as a blank using UV Visible spectrophotometer. Drug release was calculated.

Different Models For drug release[9,10,20-22]

Zero order kinetics

$Q(t) = K_0 t$ (5)

Q(t) is a percent of drug release as a function of time and K_0 describes dissolution rate constant for zero order drug release . A plot of % drug released against time will be linear if the release obeys zero order release kinetics. Rate constant (K_0) calculated from slope of plots.

First order kinetics

$\text{Log } Qt = \log Q_0 + K_1 t / 2.303$ (6)

First order equation describes the release from system. Rate of drug release depends on concentration. Q_0 is initial amount of the drug, t is time, K_1 is dissolution rate constant. A plot of log of % drug remained against time will be linear if the release obeys first order release kinetics.Rate constant (K_1) calculated from slope of plots.

Higuchi Model

$Q(t) = K_H t^{1/2}$ (7)

Q(t) is % of drug dissolved , t is time , K_H is dissolution rate constant for square root of time. A plot of the fraction of drug released against square root t will be linear if the release obeys Higuchi model release kinetics. Rate constant (K_1) calculated from slope of plots.

Hixon crowell cube root law

$Wo^{1/3} - Wt^{1/3} = K_H t$ (8)

Where Wo: Initial amount of drug in dosage form

Wt: remaining amount of drug at time t

This law describes the release from system where there is a change in surface area and diameter of the particle.

Korsemeyer-Peppas Model

Fickian and non-fickian diffusion- In order to define a model which will represent a better fit for the release from tablet formulations dissolution data upto 60 % can be further analysed

using Peppas – Korsemeyer equation. To evaluate the contribution of the release mechanism other than diffusion, other models of release kinetics were employed.

This model is widely used, when the release mechanism is not well known or when more than one type of release phenomena could be involved. The 'n' could be used to characterise different release mechanism as follows:

Table 2: Different mechanism of drug release for cylindrical shape[9]

Sr.No.	'n'	Mechanism
1	0.45	Fickian diffusion (Higuchi matrix)
2	0.45 < n <0.89	Anamalous transport (non fickian diffusion)
3	0.89	Case –II Transport (Zero order release)
4	n > 0.89	Super case-II Transport

Stability studies

Stability study being the part of drug discovery and ends with demise of compound or commercial product. The samples of optimized formulation were kept at 40°C ± 2°C and 75% ± 5% relative humidity for one month in HDPE bottle. Then samples were withdrawn and analysed for drug content, SEM and *in-vitro* drug release.[19]

RESULTS

All formulations of superporous hydrogels were evaluated for Density, Swelling ratio, Swelling time, Water retention capacity, Floating time, Buoyancy time, Porosity, Images of SPH, Drug content, Scanning Electron Microscopy (SEM), Drug excipient interaction study, *In-Vitro* drug release.

Density, Swelling ratio, Swelling time

Table 3: Density, Swelling ratio, Swelling time

Sr. No.	Formulations	Density ± SD (gm/cc)	Swelling Ratio ± SD	Swelling Time ±SD (min)
1	F-1	0.353 ±0.005	17.62 ±0.3	4.33 ±1.154
2	F-2	0.29 ±0.01	27.37 ±2.05	3.00 ±1
3	F-3	0.35 ±0.04	15.67 ±2.5	3.67 ±1.154
4	F-4	0.33 ±0.07	16.18 ±2.6	3.33 ±1.52
5	F-5	0.45 ±0.01	14.83 ±3.47	6.67 ±1.154
6	F-6	0.37 ±0.03	13.30 ±2.21	4.33 ±0.577
7	F-7	0.35 ±0.01	16.74 ±0.650	12 ±2.645
8	F-8	0.40 ±0.04	15.98 ±1.69	5.00 ±1

SD=Standard deviation (n=3)

Table 4: Water retention capacity, Floating time, Buoyancy time,%Porosity

Sr. No.	Formulations	Water Retention capacity (%)	Floating Time (h)	Buoyancy time (sec)	% Porosity
1	F-1	75	>12	60	81
2	F-2	78	>12	0	74
3	F-3	53	>12	0	70
4	F-4	65	>12	8	68
5	F-5	36	>12	44	54
6	F-6	40	>12	0	58
7	F-7	49	>12	0	65
8	F-8	59	>12	0	71

Images of Superporous hydrogel

a. **Superporous hydrogel in dried state:** Superporous hydrogel in dried state is as shown in fig.1

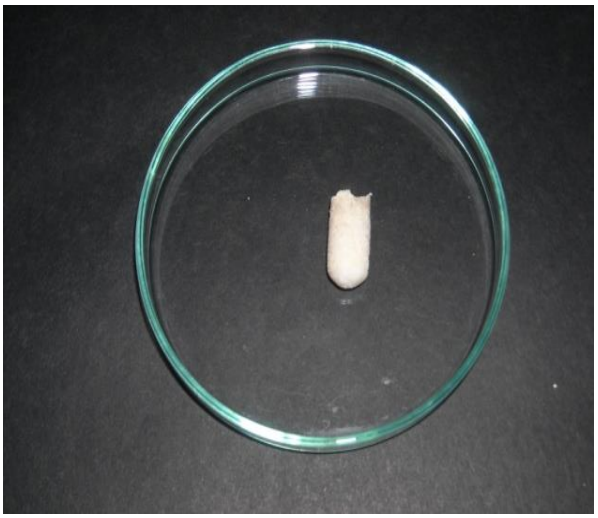


Fig. 1: Superporous hydrogel in dried state

b. **Swollen superporous Hydrogel :** Superporous hydrogel in swollen state is as shown in fig.2

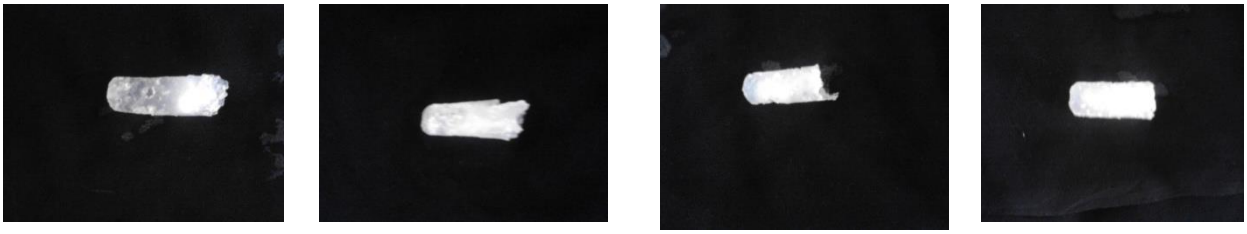
c.

Formulation :F-1

Formulation :F-2

Formulation F-3

Formulation F-4



Formulation F-5 **Formulation F-6** **Formulation F-7** **Formulation F-8**

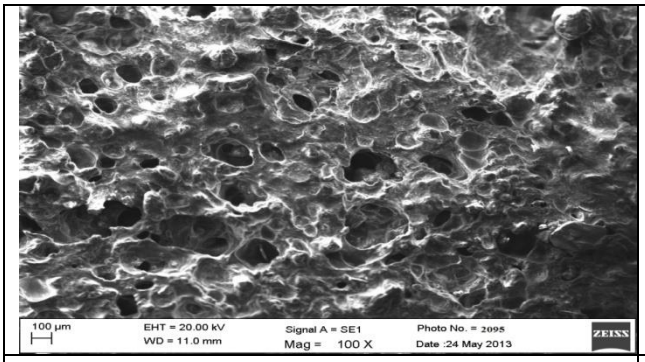
Fig. 2: Images of swollen superporous hydrogels (Formulation: F-1 to F-8)

Drug content

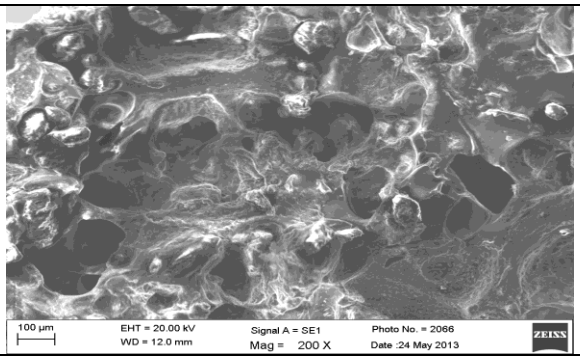
Table 5: Drug Content of all Formulations

Sr. No.	Formulations	Drug Loaded (mg)	% Drug Content ± SD
1	F-1	100	99.6 ± 0.008
2	F-2	100	100 ± 0.0006
3	F-3	100	98.7 ± 0.001
4	F-4	100	100 ± 0.004
5	F-5	100	95.5 ± 0.02
6	F-6	100	97.7 ± 0.002
7	F-7	100	98.3 ± 0.01
8	F-8	100	99 ± 0.004

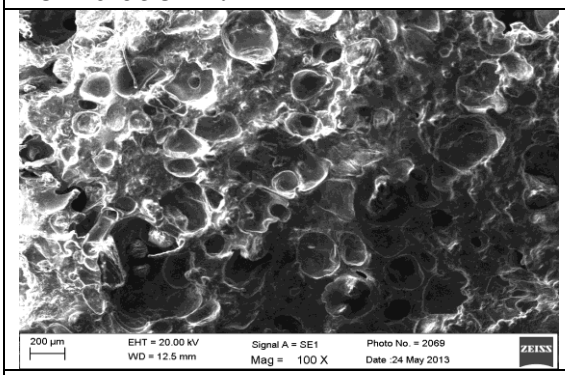
Scanning Electron Microscopy (Fig.3)



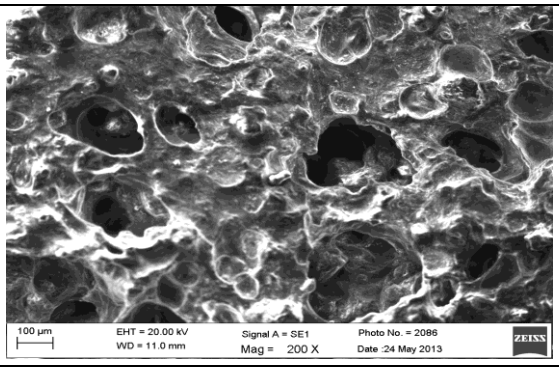
Formulation F:1



Formulation : F-2



Formulation F:3



Formulation F:4

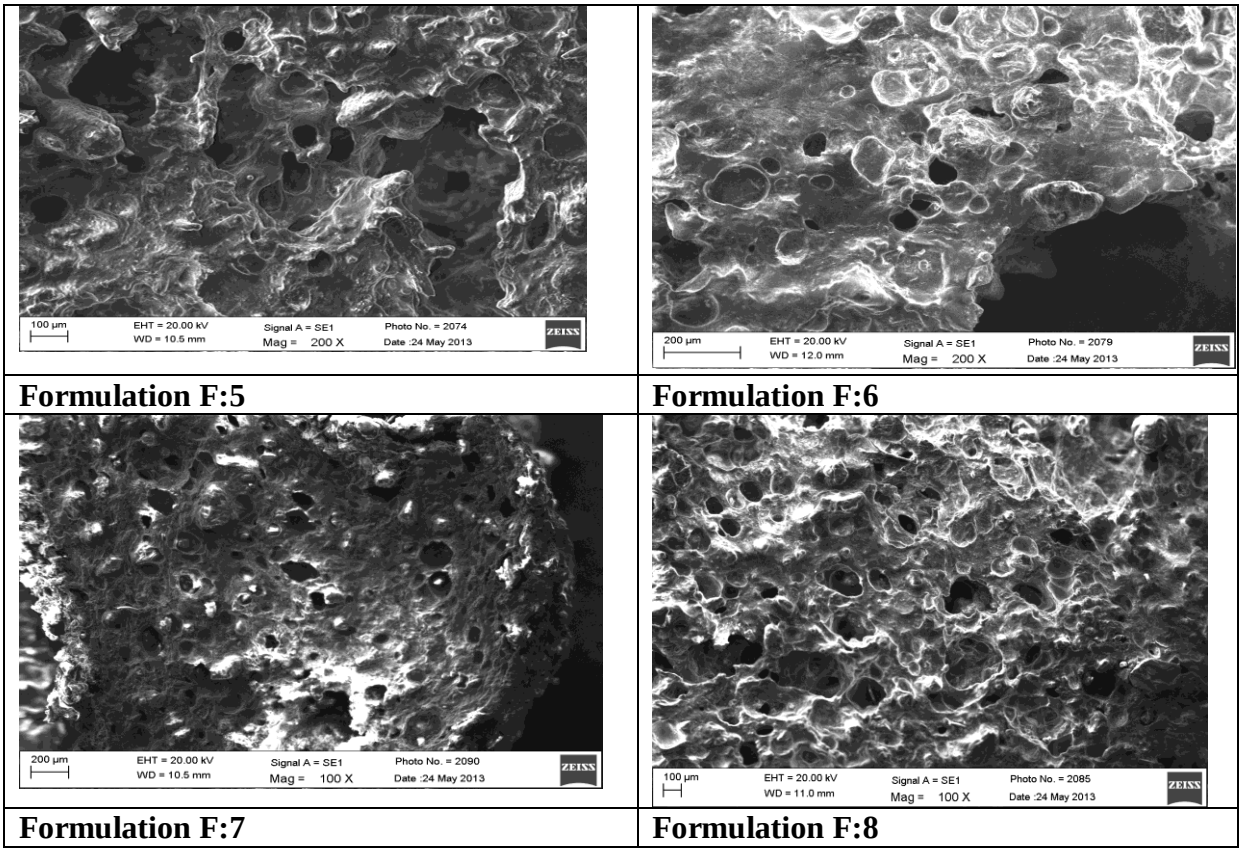


Fig 3 : Scanning electron microscopic images for F-1 to F-8 formulations

Drug excipient interaction study

Drug polymer interaction studies were performed using FTIR (KBr pellet method) and DSC studies.

FTIR Spectroscopy (Fig 4 and Fig 5)

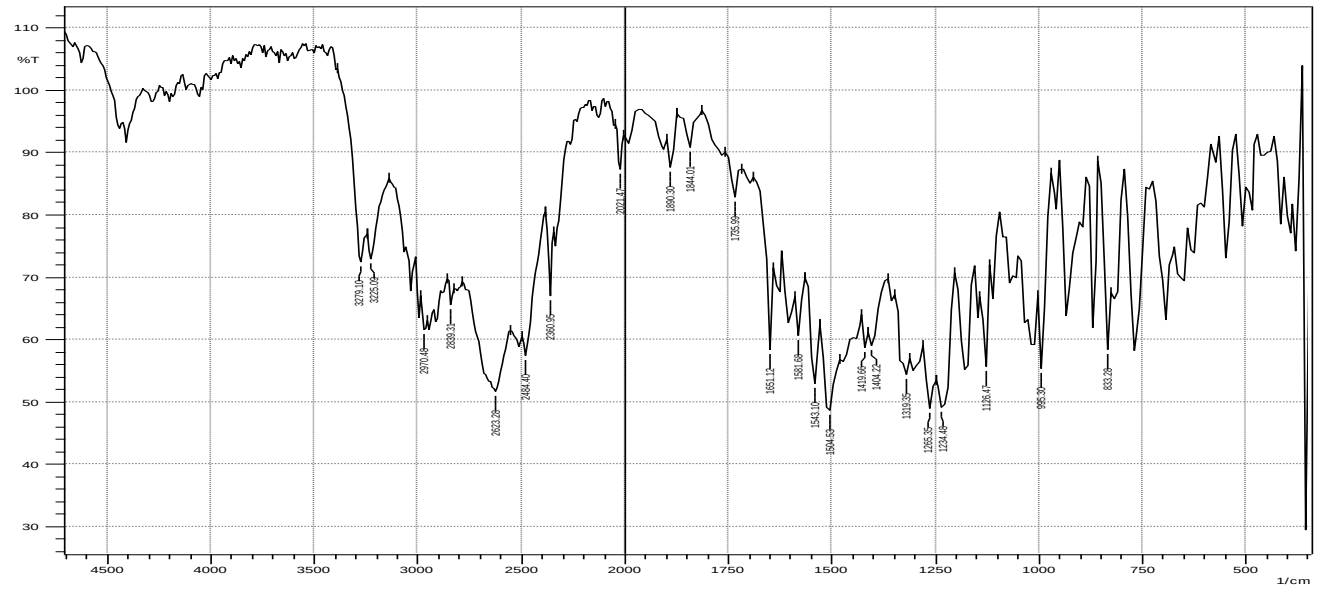


Fig. 4: IR spectra of Itopride Hydrochloride

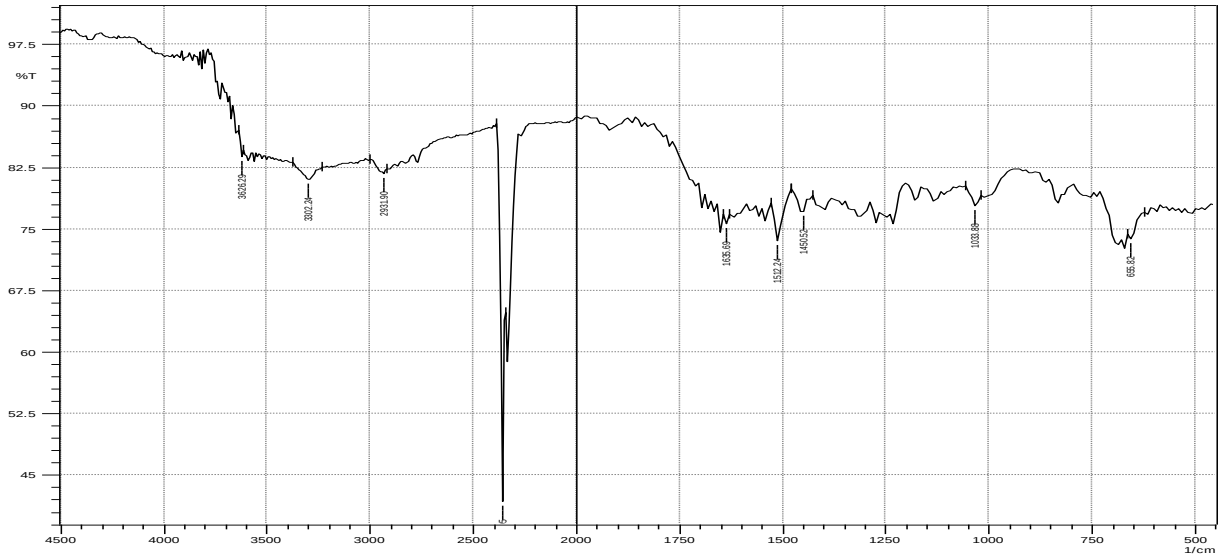


Fig.5: IR spectra of Formulation F-8

Table 6: Interpretation of IR spectra of Itopride Hydrochloride

Sr. No.	Groups	Peaks for pure drug(cm^{-1})	Peaks for F-8 formulation(cm^{-1})
1	N-H asymmetric structure	3279.10	3302.24
2	C-H structure of methyl group	2970.48	2931.90
3	C=O bending	1651.12, 1581.68, 1543.10	1697.41, 1681.98, 1651.12
4	C=C aromatic structure	1504.53	1512.24
5	C-N aromatic structure	1234.48	1234.48

Differential Scanning Calorimetry (DSC)

DSC thermogram of Itopride Hydrochloride and Formulation F -8 shown in fig.6 and fig.7 respectively.

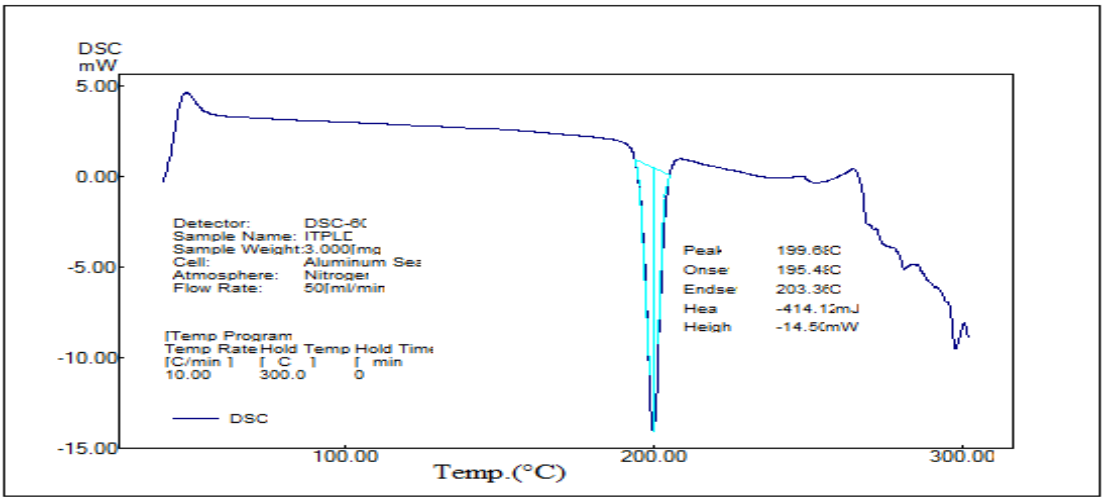


Fig. 6: DSC Thermogram of Itopride Hydrochloride

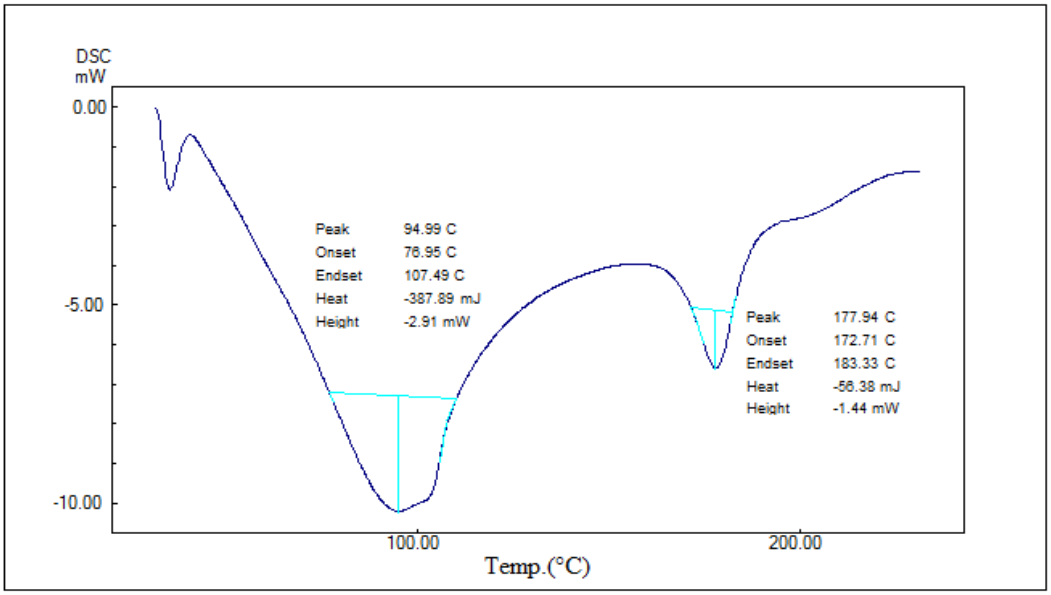


Fig. 7: DSC thermogram of formulation F-8

Table 7: Thermal characteristics of Itopride Hydrochloride

Sr. No.	Thermal characteristics	Temperature (pure drug)	Temperature (F-8 formulation)
1	Onset temperature (To)	195.48ºC	172.71 ºC
2	Peak temperature(Tp)	199.68 ºC	177.94 ºC
3	Endset temperature(Tb)	203.36 ºC	183.33 ºC

***In-vitro* drug release profile (Fig.8 and Table 8)**

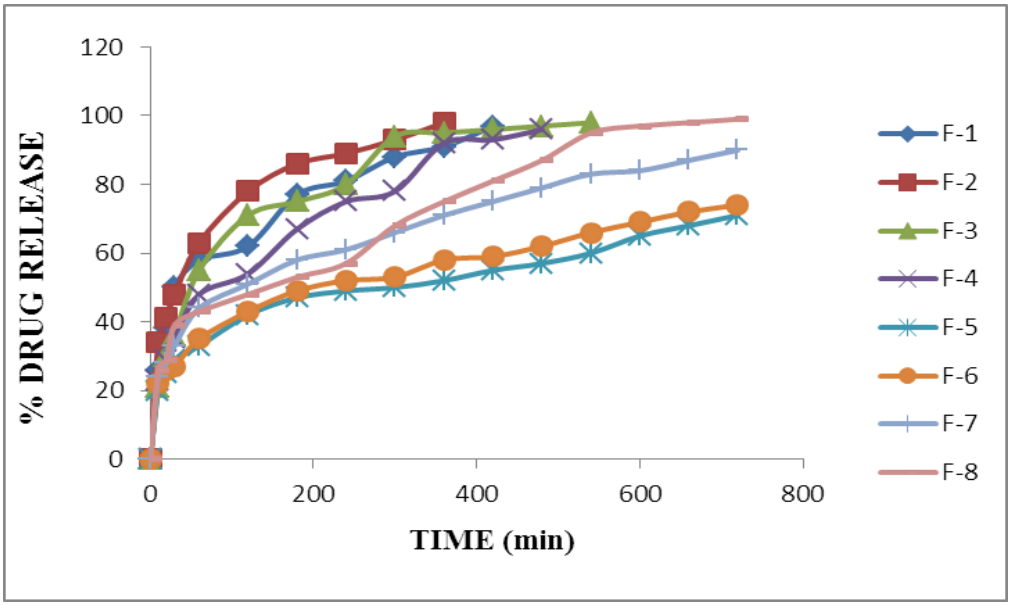


Fig. 8: In Vitro Drug Release for F-1 to F-8 formulations

Table 8: *In vitro* drug release profile of Itopride Hydrochloride from F-1 to F-8 formulation

Sr. No.	Time (T) (min)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	0	0	0	0	0	0	0	0	0
2	10	26	34	21	23	20	22	24	26
3	20	38	41	30	29	25	26	28	29
4	30	50	48	36	35	29	27	33	39
5	60	58	63	55	48	33	35	44	43
6	120	62	78	71	54	42	43	51	48
7	180	77	86	75	67	47	49	58	53
8	240	81	89	80	75	49	52	61	57
9	300	88	93	94	78	50	53	66	68
10	360	91	98	95	92	52	58	71	75
11	420	97	-	96	93	55	59	75	81
12	480	-	-	97	96	57	62	79	87
13	540	-	-	98	-	60	66	83	95
14	600	-	-	-	-	65	69	84	97
15	660	-	-	-	-	68	72	87	98

Table 9: R^2 and k values for different kinetic models for all formulations

Sr. No.	Formulations	Zero Order		First Order		Higuchi		Peppas	
		R^2	K	R^2	K	R^2	K	R^2	K
1	F-1	0.4294	17.29	0.9583	-0.4242	0.9205	40.68	0.9793	53.01
2	F-2	0.3341	21.12	0.9696	-0.6113	0.9133	46.37	0.9945	59.57
3	F-3	0.5989	14.53	0.9879	-0.4734	0.9497	38.33	0.9863	47.49
4	F-4	0.7364	14.89	0.9808	-0.3782	0.9784	36.65	0.9781	43.696
5	F-5	0.3185	7.077	0.7992	-0.1092	0.8950	21.45	0.9909	33.74
6	F-6	0.4558	7.669	0.8611	-0.1252	0.9232	23.188	0.9944	35.804
7	F-7	0.5614	9.430	0.9560	-0.1975	0.9453	28.441	0.9964	41.784
8	F-8	0.7246	10.32	0.9612	-0.3229	0.9644	30.762	0.9967	44.61

Table 10: Diffusion exponent (n) and k values for best fit Korsemeyer peppas model

Sr. No.	Formulations	Best fit model	Correlation coefficient (R^2)	n Value	k Value
1	F-1	Peppas	0.9793	0.3169	53.01
2	F-2	Peppas	0.9945	0.3007	59.56
3	F-3	Peppas	0.9863	0.3823	47.49
4	F-4	Peppas	0.9781	0.3099	43.696
5	F-5	Peppas	0.9909	0.2650	33.74
6	F-6	Peppas	0.9944	0.2735	35.804
7	F-7	Peppas	0.9964	0.3010	41.784
8	F-8	Peppas	0.9967	0.3724	44.61

Stability study (40°C ± 2°C and 75% ±5% RH / One Month)

Table 11: Drug content of F-8 Formulation (Stability study)

Sr. No.	Formulation	Drug loaded (mg)	Estimated Value (mg)	Drug content ± SD
1	F-8	100	98.9	98.9 ± 0.001

***In vitro* drug release for F-8 Formulation** (stability study: Fig.9 and Table 12)

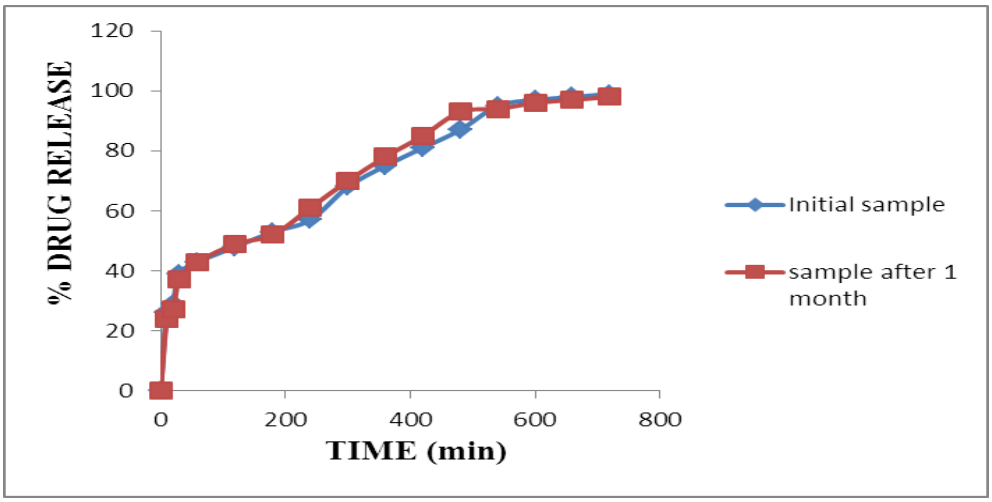


Fig.9: Dissolution profile for Initial and stability sample for formulation F-8

Table 12: In vitro drug release for F-8 Formulation (stability study)

Sr. No.	Time (T) (min)	% Drug Release Initial sample	% Drug Release at 40°C and 75% RH
1	0	0	0
2	10	26	24
3	20	29	27
4	30	39	37
5	60	43	43
6	120	48	49
7	180	53	52
8	240	57	61
9	300	68	70
10	360	75	78
11	420	81	85
12	480	87	93
13	540	95	94
14	600	97	96
15	660	98	97
16	720	99	98

DISCUSSION

Superporous hydogel (SPH) and superporous hydrogel composites (SPHC) were synthesized by a solution polymerization technique using acrylic acid and acrylamide as a monomers,

ammonium persulphate (APS) and N,N,N,N,- tetramethylethylene diamine (TEMED) as initiator pair. TEMED act as a catalyst also. N,N-methylene bisacrylamide (BIS) as a crosslinker. Pluronic F-127 was a surface active agent which acts as a foam stabilizer to create porous structure.

For the synthesis of SPH and SPHCs with well distributed pores, polymerization and foaming involve in the preparation of polymers must be carefully controlled. The lifetime of foam is short but foam stabilization is important. The monomers can be polymerized or water soluble polymer chains can crosslinked around gas bubbles generated by blowing agent sodium bicarbonate ($NaHCO_3$).

Adjustment of pH plays important role in formulation of SPH. pH should be in the range of pH4.5-5 to improve mechanical strength and homogeneous pore formation. Ac-Di-Sol improves mechanical strength as it is compositing agent. Carbopol 934P shows important role in stabilizing foam during synthesis. Due to addition of carbopol 934P foam generated was fine and uniform. Heat of polymerization was better dissipated in the presence of carbopol 934P because formation of gel is an endothermic process. As a rule, temperature increases bubble size increases this result in reduction of thickness and strength of foam film and diffusion of interbubble gas leads to decrease in foam stability. Chitosan enhance the viscosity of stock solution, which efficiently prevented bubbles escaping from solution and residual gas bubbles were able to form interconnected channels.

Density: Superporous hydrogel (SPH) and superporous hydrogel composites (SPHCs) posses number of pores. Density of these should be lower than conventional hydrogels. Density of synthesized Itopride hydrochloride SPHC was found within range of 0.29±0.01 to 0.45±0.01 gm/cc as shown in table 3. Due to addition of Ac-Di-Sol and Carbopol 934P density of SPHC decreased. When Ac-Di -Sol and Carbopol 934P were mixed with monomer solution. It swells so that monomers and crosslinker were absorbed into cellulose network.

Chitosan increase apparent density and prevents bubble escaping from solution mixture as well as it decreases pore size of SPHC. At same time number of interconnected pores were increased leads to increase in volume occupied. Density of formulation F-5 to F-8 was more compare to formulation F-1 to F-4 may be due to cross linking of natural polymers. All formulations F-1 to F-8 showed density lower than gastric content, which makes them able to float in gastric environment.

Swelling Ratio

The important characteristic of SPHC is fast swelling ability. Swelling ratio of SPHCs in distilled water were found to be in the range of 13.30 ± 2.21 to 27.37 ± 0.05 shown in table 3. Ac-Di-Sol and Carbopol 934P slows down swelling and decrease equilibrium swelling ratio of SPHCs. Through entanglement with crosslinked Ac-Di-Sol network, flexibility of the polymeric chains was greatly restricted. Bonds between Ac-Di-Sol and P(AA-CO-AM) reduced the ability of polymer to form hydrogen bonds with water molecules, thus limiting its water absorption. Therefore a dense Ac-Di-Sol network would further restrict the swelling of polymer. Increase in Ac-Di-Sol concentration dramatically decreased swelling time. The reason for fast swelling was hydrophilicity and high wettability of Ac-Di-Sol. Presence of chitosan leads to slower swelling and leads to decreasing equilibrium swelling ratio of SPHCs.

Swelling Time

Swelling time is most important parameter of SPH, it is time taken by SPH to swell to its equilibrium size. Swelling time of all formulation was found within the range 3 ± 1 to 12 ± 2.645 min.

Water Retention Capacity

The interconnected pores allow polymers to hold more water by capillary force. Water retention capacity also explains degradation kinetics. Water retention capacities of all formulations (F-1 to F-8) were 75, 78, 53, 65, 36, 40, 49, 59% at forth hour (table 4) and there was loss of weight is observed at 24 h for all formulations.

Floating Time

The time period for which formulations remain float is known as floating time. Duration of all prepared SPHCs formulations (F-1 to F-8) remained buoyant upto 12 h.

***In-vitro* buoyancy**

Buoyancy studies were performed using 0.1N HCL solution at 37ºC. SPHCs floated and remain buoyant. Formulation F-1, F-5 and F-6 take 60 sec., 8 sec. and 44 sec. respectively to float, while other remains buoyant.

Porosity

Addition of compositing agent in a superporous hydrogel leads to decrease in porosity of formulation compared with conventional hydrogel. Chitosan prevent the bubble escaping from the solution mixture as well as decreased pore size of SPHC due to accumulation of compositing agent at periphery of pore. Percent porosity of all formulations shown in table 4. Due to use of compositing agent blockage of some capillaries and solvent could not penetrate well. Porosity may decrease due to increased cross linking density.

Images of SPHC: Images of SPHC after swelling indicate their consistency in the structure. This represents their mechanical strength in harsh stomach environment. Formulation F-1, F-2, F-4 were difficult to handle after their equilibrium swelling. They were broken while lifting. Formulation F-3, F-5, F-6, F-7, F-8 were maintain their integrity and remain in intact form as shown in figure 2.

Drug Content: It was found in the range of 95.5 ± 0.02 to 100 ± 0.004 (table 5). It complies the limit.

Scanning Electron Microscopy

The pictures shown in figure 3 clearly indicates the formation of pores within structure. These pores mainly responsible for swelling of SPH. Superporous hydrogel composite shows number of small size pores of which number of pores observed to be blocked due to presence of compositing agent like Ac-Di-Sol, carbopol 934P. Fully swollen superporous hydrogel composite shows white fibers could be the chitosan molecules while some SPH shows transparency after swelling which primarily confirms its distribution in superporous hydrogel composite.

Fourier Transform Infrared Spectroscopy (FTIR)

All the prominent peaks of drug such as, N-H, C-H methyl group, C=O, C=C aromatic structure, C-N aromatic structure, C-O aromatic structure were observed in FTIR spectra of formulation F-8 shown in figure 4-5 and table 6. It indicates that all the polymers and reagents used in formulation of superporous hydrogel and its composites were compatible/having no interaction with Itopride Hydrochloride.

Differential Scanning Calorimetry (DSC): The thermogram of Itopride hydrochloride showed a single sharp endothermic peak with an onset temperature (To) of 195.48ºC, peak

temperature (Tp) of 199.68 ºC and recovery to base line (Tb) at 203.36 ºC (table 7 and figure 6). The peak temperature represents the melting of Itopride hydrochloride.

The thermogram of F-8 formulation (figure 7), showed decrease in sharpness of peak of Itopride hydrochloride with onset at 172.71 ºC and peak at 177.94 ºC this simply reflects a parallel shift of melting endotherm to left. Also there is decrease in peak height from -14.5 to -1.44 due to dilution effect of excipients. Indicating interaction between drug and excipient which cannot be considered as a significant incompatibility between Itopride Hydrochloride and other excipient. It also indicates that the changes occurring in the prominent thermogram of Itopride hydrochloride is due to cross-linking and polymerization during synthesis of SPH.

***In-vitro* drug release**

In-vitro drug release study was performed by using USP type -II (Paddle) dissolution test apparatus at 50 rpm and 37 ± 0.5ºC using 0.1 N HCl as dissolution medium. Drug release profile for all formulations is shown in table 8 and % drug release for all formulations is shown in figure 8. Formulation F-1 to F-4 shows maximum drug release but within 12 h, while F-5 to F-8 shows upto 12 h. F-8 formulation shows 99% drug release upto 12 h.

Curve fitting Analysis

In vitro drug release data obtained was subjected to Zero order, First order, Higuchi, Korsemeyer-Peppas, Hixon-Crowel model in order to establish drug release mechanism and kinetics of drug release from prepared superporous hydrogel composite. To obtain a better understanding residual analysis of said models was performed. The goodness of fit was evaluated using regression coefficient (R^2). Good linearity was observed with greater value of R^2. The value of release exponent 'n' is an indicative of release mechanism. The value 'n' obtianed for all formulations was in the range of 0.2650-0.3823 as shown in table 10. This indicates fickian diffusion as it was less than 0.45.

All formulations follows korsemeyer-Peppas model as it shows maximum R^2 values for all formulations. R^2 Values for all formulations ranges from 0.9781 to 0.9967 as shown in table 9. Formulation F-8 was found to achieve the objective.

Stability study (40°C ± 2°C and 75% ±5% RH / One Month)

Stability of formulation F-8 was carried out at 40°C ± 2°C and 75% ± 5% RH for one month.

Drug content

Drug Content: Sample evaluated after one month stability shows drug content 98.9 ± 0.001, which was within acceptable limit. As shown in table 11.

***In-vitro* drug release:** *In- vitro* drug release was 98% at 12 h as shown in table 12 and figure 9 indicating similarity of dissolution profile before and after stability.

CONCLUSION

In the present study Itopride hydrochloride loaded superporous hydrogel as a gastroretentive drug delivery system developed by gas blowing technique. As SPHC posses pores, so density of SPHC was found to be less than the gastric content this factor has more intact on gastric retention. Compositing and cross linking agent decreases the density. Equilibrium swelling ratio decreased due to cross linking agent and compositing agent restrict hydrogen bonding. All formulations shows swelling time within few minutes which is an important parameter for floating behaviour. Water retention capacity also explains degradation kinetics there was loss of weight after 24 h. All prepared SPHC formulations remained buoyant up to 12h. From *in-vitro* buoyancy study it was found that all formulations take few seconds to float. Porosity of all formulations decreases due to addition of compositing agent. *In-vitro* drug release of formulation F-8 shows nearly 100% drug release up to 12 h. Formulation F-8 shows higher regression coefficient 0.9967 and follows Korsmeyer-peppas model, it was found that F-8 formulation achieve the main objective of drug release. n values were found within limit 0.3724 (e.g. Less than 0.45) suggesting probable release by fickian diffusion (Higuchi matrix).

All formulations shows desired properties for gastric retention and floating such as density was found to be less than gastric content, swell within time limit, also show degradation kinetics, float within few seconds and floating time more than 12 h. Formulation F-8 shows satisfactory results to achieve desired drug release profile. Also stability study for formulation F-8 carried out at 40 ºC and 75% RH for one month, formulation found to be stable.

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