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DEVELOPMENT AND EVALUATION OF METOPROLOL SUCCINATE LOADED SUPERPOROUS HYDROGEL IN A CAPSULE: AS A GASTRORETENTIVE DRUG DELIVERY DEVICE.

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ABSTRACT

The present study aims to develop a gatroretentive drug delivery device of metoprolol succinate (M.S) loaded superporous hydrogel (S.P.H) in a capsule. Swelling ratio, apparent density, drug content, and drug release in 0.1N HCL were evaluated for these M.S loaded S.P.H. Hydroxy propylmethyl cellulose is used to form a gel barrier around superporous hydrogel and helps to retard drug release for 12h. A 3^2 factorial design was applied for optimization purpose. D.S.C result shows no interaction between superporous hydrogel forming polymers and the drug. M.S. Stability data shows no comparable differences in physical parameters and the drug release after 3 months of accelerated stability study. ANOVA for Response Surface shows The "Pred R-Squared" of 0.9878 is in reasonable agreement with the "Adj R-Squared" of 0.9975.Hence, the developed M.S loaded superporous hydrogel (S.P.H) in a capsule of improved efficacy can perform better therapeutically.

KEYWORDS: Metoprolol succinate, gatroretentive drug delivery device, superporous hydrogel, capsule, surface response methodology.

1. INTRODUCTION

Hydrogels are the 3D structures used mainly in sustain release drug delivery. Specifically the dried hydrogels are used which have cross-linked network of polymers. The rate limiting factor is the slow swelling property of the hydrogels, as it takes several hours to attain equilibrium swelling. In order to overcome this slow swelling problem, Super Porous

hydrogels have been invented.[1] The super porous hydrogel is developed as novel drug delivery system for drugs having absorption window in stomach and upper part of GIT.[2] Super Porous Hydrogels have numerous supersize pores and the 3D network of hydrophilic polymers that are not soluble and absorbs large amount of water in short period due to the interconnected polymer network.[3,4,5]Superporous hydrogels differ from micropores, as these does not only have fast swelling but also have properties like slipperiness, biodegradability, high mechanical strength, high swelling capacity and stability in acidic condition in stomach.[6] Since these have a super porous nature, one can easily reduce its dry volume, so as to make it small enough to be administered easily via oral route. The swelling properties of the SPH is responsive to the nature of the environment in the body as shown below:

Sr.no	Type of environment	Degree of swelling	Reason
1.	Acidic	Lower	Ionization of acrylic acid on polymer chain.
2.	Basic	Higher	Non-ionization

Though small, the swollen size of SPH is large enough and so also its density is sufficient to float in simulated gastric fluid, and to retain itself in stomach after administration.

Metoprolol succinate (MS) is a b1-selective adrenergic blocking agent.[7] Since the half-life of MS is ~3 to 4 h[9] multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. It has also been reported that MS absorption mainly takes place in the duodenum and jejunum and is directly proportional to the dose available.[9] A gastroretentive dosage is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments.[10]

S.A. Abdel Halim et.al, developed chromium picolinate (CP) loaded gastroretentive device using superporous hydrogel (SPH) and superporous hydrogel composite (SPHC). The drug was considered as good candidate for such systems owing to its narrow absorption window. Swelling ratio, apparent density, scanning electron microscopy (SEM), drug content and drug release in pH 1.2 were evaluated for hydrogels. SEM of hydrogels showed interconnected pores with extensive capillary insertion. Swelling ratio for CP-SPH was higher than that of SPHC while apparent densities were lower.[11]

In the present study we have studied the effect of bisacrylamide (BIS) and HPMC on the % drug release of MS. The objective of this study was to develop an optimized metoprolol

succinate loaded superporous hydrogel in a capsule and aims at[1] understanding the mechanism of drug release from such systems with (acrylamide and bisacrylamide) polymers and other formulation ingredients,[2] optimization of formulation by response surface methodology,[3] evaluation of % drug release at 12h from the optimized formulation by applying a 3^2 factorial design.

2. MATERIALS AND METHODS

2. Materials

2.1. Chemicals

Metoprolol Succinate was obtained as a gift sample from Wockhardt limited, Aurangabad, Acrylamide (AM), N,N'-methylenebisacrylamide (Bis), N,N,N',N'-tetramethylethylenediamine (TEMED) were purchased from spectrochem Pvt. Ltd, Mumbai, Hydroxy propyl methylcellulose (HPMC) K100M, Poloxamer 188, Sodium metabisulfite, Sodium bicarbonate ($NaHCO_3$), were obtained as a gift sample from Colorcon, Ind Pvt. Ltd, Goa. All other solvents and reagents were purchased from Thermofischer scientific Pvt. Ltd, Mumbai, and were of analytical grade.

2.2. METHOD

2.2.1 Calibration curve for Metoprolol Succinate: It was obtained in 0.1N HCL. Between the linearity range of (2-10µg/ml) and correlation coefficient (r^2) of determination was obtained at 222 nm (R = 0.9985), using a UV-Visible spectrophotometer (Shimadzu UV-1800, Japan). The calibration curve in 0.1N HCl was used for dissolution studies.

2.2.2 Formulation of Superporous hydrogels

Superporous hydrogel was synthesized using vinyl monomer i.e acrylamide. Table 2 shows different ingredients to formulate a superporous hydrogel. In general, to make superprous hydrogel, a monomer, cross-linker, deionized distilled water (DDW) (if necessary), foam stabilizer, acid, polymerization initiator, initiation catalyst (if any), and foaming agent were added sequentially to a small glass beaker. The beaker was shaken to mix the solution after each ingredient was added. The pH of the monomer solution was adjusted to 5 using hydrochloric acid (HCL). When sodium bicarbonate was added the whole mixture was stirred instantaneously using glass rod for several seconds to evenly distribute the generating gas bubbles. Synthesized superporous hydrogels were removed from beaker after 10 min and allowed to swell in water before drying, then dried overnight.

Fig.1 synthesized superporous hydrogel before drying.

This dried S.P.H was filled in a capsule, and HPMC K100M was added to it, this makes a complete formulation of M.S loaded S.P.H in a capsule dosage form.

Table 1. Factorial design of selected variables.

Levels	X1- Cross-linker (2.5 % Bis) (µL)	X2- HPMC K100M (mg)
Upper(+1)	500	60
Middle(0)	400	50
Lower(-1)	300	40

Table 2: Composition of MS loaded S.P.H in a capsule.

Formulation code	X1- Cross-linker (2.5 % Bis) (µL)	X2- HPMC K100M (mg)
F1	+1	+1
F2	+1	0
F3	+1	-1
F4	0	+1
F5	0	0
F6	0	-1
F7	-1	+1
F8	-1	0
F9	-1	-1

All other ingredients, such as, MS=25 mg, Acrylamide (AM) =600(µL) (50 % AM), Water=400(µL), Foam stabilizer (10 % Poloxamer 188) (µL) =100, Acid (µL) = 45, Initiator (20 % sodium metabisulfite) (µL) =40, Initiation catalyst (20 % TEMED) (µL) =40, NaHCO3=25 mg, were kept constant in all the formulations.

2.2.3 Drying of superporous hydrogels

Superporous hydrogels were dried under two different conditions. Under first condition (a) swollen superporous hydrogels were dried for one day in an oven at 50 °C. Under second condition (b) swollen superporous hydrogels were dehydrated first by applying about 10 mL

of absolute ethanol per each gel. After this initial dehydration step, superporous hydrogels were dehydrated further by placing them in 50 mL of absolute ethanol several times to ensure replacement of all the water by ethanol. After the dehydration was completed, the excess ethanol in dehydrated superporous hydrogels was removed by draining using filter paper. Then the superporous hydrogels were dried in an oven at 50°C for one day.

2.2.4 Incorporation of metoprolol succinate into superporous hydrogels

The same procedure for synthesis of superporous hydrogel was followed. Drug was added to the beaker directly before sodium bicarbonate and stirred thoroughly using glass rod, then just after the addition of sodium bicarbonate, the whole mixture was stirred using thin glass rod for several seconds to evenly distribute the generating gas bubbles. Synthesized metoprolol succinate superporous hydrogel was removed from beaker after 10 min and allowed to swell in water before drying using condition (b), then filled in a capsule with HPMC K100M to retard the drug release of M.S.

2.2.5 Evaluation of superporous hydrogels

1. Swelling studies

The dry samples were placed on weighing sieve[12] The weighing sieve containing the dry sample was immersed in excess deionized distilled water at room temperature. The weighing sieve was taken out to drain the free water from the sieve and a paper towel was used to remove excess water from underneath the sieve. Then the weight of the swollen sample was measured by subtracting the sieve weight from total weight. This method avoided direct handling of the gel. The weights of hydrating samples were measured at predetermined time intervals at 37 ºC. The swelling ratio (Q)[13] is defined as: Q = Ws/Wd, where Ws is the weight of swollen sample and Wd is the weight of dried sample.

2. Determination of apparent density

Densities of the dried superporous hydrogels were determined from direct mass and dimensional measurements[14] The density (d) of a dried sample was calculated by dividing the weight of a dried sample (Wd) with the volume of the dried sample (Vd). The volume (Vd) was calculated by a solvent displacing method. Briefly, with the use of forceps, a dried sample was immersed in a predetermined volume of hexane in graduated cylinder and the increase in the hexane volume was measured as the volume of the dried sample.

3. Estimation of drug loading

An accurately weighed amount (0.1 g) of the dried MS superporous hydrogel was added to a beaker containing 250 mL 0.1N HCL and kept for 24 h, filtered then made volume upto 250 mL with 0.1N HCL. The absorbance of the solution was determined after carrying an appropriate dilution at λmax 222 nm using 0.1N HCL as a blank. All experiments were carried out in triplicates.

2.2.6 In-vitro buoyancy studies

The *in vitro* buoyancy studies were carried out by observing the floating behavior. The capsules were placed into a beaker containing 100 ml of 0.1N HCL. The floating duration of a capsule along with the gel expansion was noted by visual observation.

2.2.7 In vitro Dissolution Study

A dissolution test was carried out for 12 h using the dissolution apparatus Elecrolab TDT-06L according to United States Pharmacopoeia.[15]Each vessel contained 500 ml of 0.1N HCL, and the paddle apparatus with 75rpm speed was used, while the temperature was kept stable at 37 ^{0}C ± 0.5 ^{0}C. At every time interval, 5 ml of media was withdrawn and measured by UV-VIS spectrophotometer at 222 nm. Furthermore, 5 ml of 0.1N HCL was replaced to keep the volume stable. The dissolution was taken in triplicate for each formulation and % release was calculated using PCP diss. Software.

2.2.8 Mathematical drug release models

The different mathematical models may be applied for describing the kinetics of a drug release process from MS loaded S.P.H in a capsule. The kinetics of MS release from capsule formulations were determined by finding the best fit of release data to zero order, first order, Hixson–Crowell, Higuchi, and Korsmeyer–Peppas plots, respectively.

2.2.9 Differential scanning calorimetry (DSC)

The DSC was carried out for acrylamide and dried S.P.H, using a SHIMADZU DSC-60 plus differential scanning calorimeter. The system was calibrated with a high purity sample of Indium. Sample was scanned at the heating rate of 10°C/min over a temperature range of 50 to 250°C under nitrogen gas using aluminum pans. Peak transitions and enthalpy of fusion were determined for the samples using TA60 integration software.

2.2.10 Accelerated Stability Studies

The stability of formulation (F3) was studied for a period of 90 days, at the temperature of 40° ±2°C and 75% ±5% relative humidity. The formulation was then evaluated for various parameters viz. swelling ratio, apparent density, drug content and release studies.

3. RESULTS AND DISCUSSION

Superporous hydrogels prepared by the gas blowing technique also were called "hydrogel foams" due to the foaming process used in the preparation [16, 17]. In this study, porous hydrogels were synthesized with open channels using the gas blowing (or foaming) technique [18]. To be practical, the swelling had to be completed in less than 30 min, most preferably in less than 5 min. Thus, our efforts have been focused on the synthesis of hydrogels that swell to equilibrium sizes in less than a few minutes.

3.1. Formulation of Superporous Hydrogels

Superporous hydrogels were prepared by cross-linking polymerization of monomers in the presence of gas bubbles. Carbon dioxide gas bubbles were generated by reaction of sodium bicarbonate with acid (acrylic acid (AA) or HCL). The foam size was determined by the amount of released gas bubbles, which in turn, was determined by the amount of acid and NaHCO3. To make superporous hydrogels with homogeneously distributed gas bubbles, polymerization and foaming processes had to occur simultaneously. Thus, control of timing of the two processes was critical. Since stabilizing foam longer than a few minutes was difficult, the gelling had to start within a few minutes after the beginning of foaming (e.g., after addition of NaHCO3 to the monomer mixture). The fast gelling could be achieved by a careful choice of monomers (type and concentration), initiators (type and concentration), temperature, and solvent.

3.2. Polymerization and foaming processes

For making homogeneous superporous hydrogels, the timing of foam formation and polymerization process was very critical. The timing for the addition of the foaming agent and the onset of gelling had to be controlled carefully. The NaHCO3/acid system used in our study provided a special trigger system that made controlling the timing rather easy.

3.3. Evaluation of Superporous hydrogel formulae

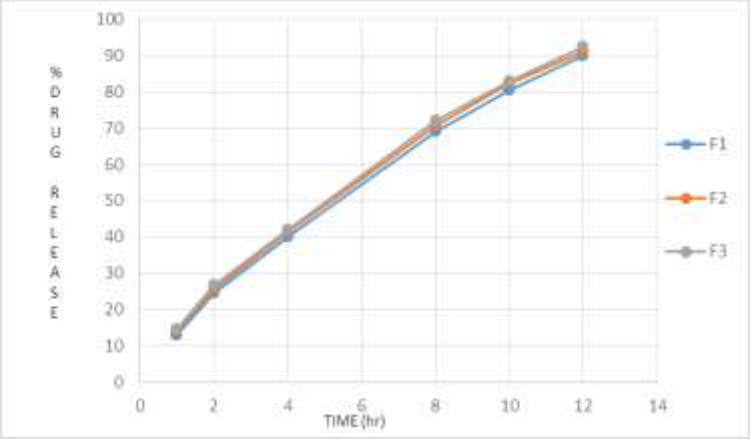
Different parameters like swelling ratio, apparent density, drug content, floating behavior were determined for all 9 formulations of 3^2 factorial design and the results of them are tabulated in table 3.

Table 3. Physical parameters of MS loaded SPH prepared by factorial design.

Formulation code	Swelling ratio	Apparent density(g/cm^3)	Drug content %	Floating time (h)
F1	2.691	0.314	98.66	>12
F2	2.315	0.334	95.24	>12
F3	2.541	0.329	105.24	>12
F4	2.951	0.305	97.22	>12
F5	2.664	0.324	99.35	>12
F6	2.224	0.347	100.66	>12
F7	2.651	0.327	105.36	>12
F8	3.015	0.241	94.35	>12
F9	2.854	0.310	99.25	>12

3.4. In vitro Dissolution Study

The drug dissolution data of all 9 formulations prepared by 3^2 factorial design is shown in (fig.2), it is clear from the graph that all the formulations have succeeded in drug release retardation for 12h.It was found that there is not much difference between F1,F2, and F3 formulations and there is gradual increase in % drug release with time as the concentration of X2 decreases. In formulation F4, F5, F6 there is again increase in % drug release with time as the concentration of X1 and X2 decreases, but formulation F7 shows slight decrease in drug release as compared to F6 and this could be because of slight increase in X2 concentration, which might have been effected the % drug release of the formulation.



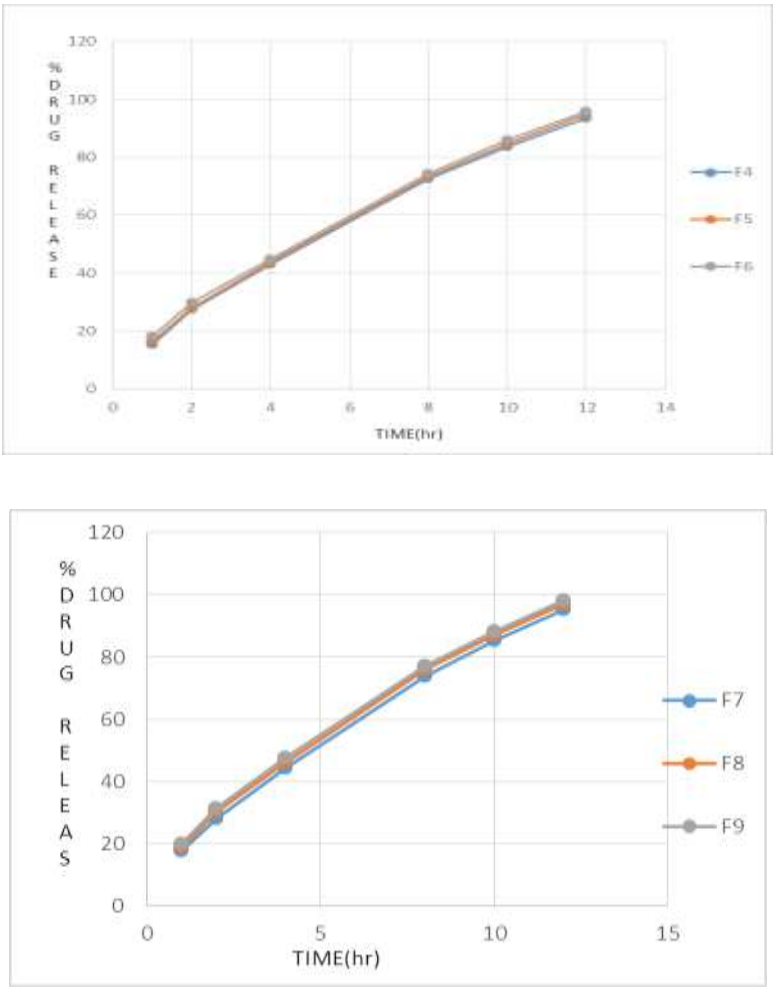


Fig. 2: Dissolution profile of factorial batches F1–F9 in 0.1 N HCL (dissolution medium).

3.5 Mathematical Drug Release Kinetics

In order to develop an ideal kinetic model and to interpret *in vitro* drug dissolution rate data in terms of meaningful parameters, various kinetic models were applied to get the best fit of the data. It was found that release had been realized in accordance with Korsmeyer-Peppas for all the formulations.

The n value of the optimized formulation F3 is 0.7343 and for all other formulations is between 0.61 to 0.74, which shows that the drug release could be probably by "combination of swelling, erosion, and diffusion".[19,20]

3.5 Differential Scanning Calorimetry

The DSC thermogram of Acrylamide indicates a sharp peak at 83.28 °C which corresponds to the melting point of Acrylamide (Fig.3). The thermogram of SPH without MS shows no peak of acrylamide and other polymers indicating, cross-linkage of polymers and gel formation.

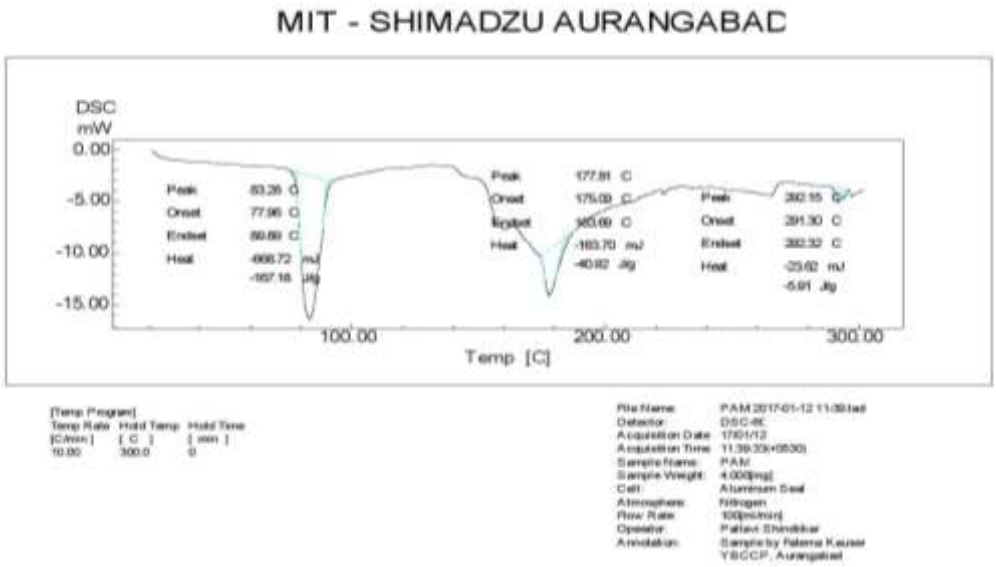


Fig. 3: DSC thermogram of Acrylamide.

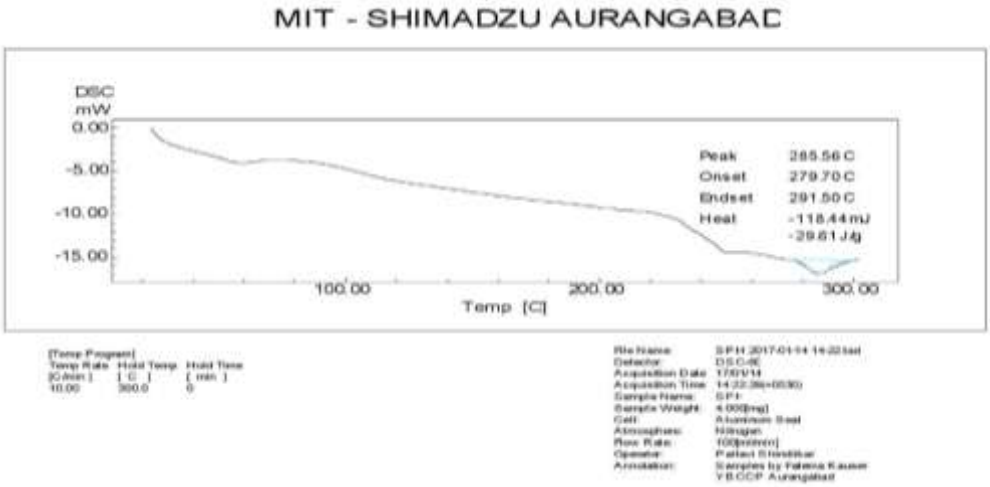


Fig. 4: DSC thermogram of SPH.

3.6 Analysis of ANOVA, model equation and response surface plot

The Model F-value of 790.62 implies the model is significant. Values of "Prob > F" less than 0.0500 indicate model terms are significant.

The fit summary (Table 4) for Rel12h of MS suggested the quadratic relationship where some of the additional terms are significant ($p \leq 0.05$). The regression equation represented best

description of response after the non-significant parameters (P > 0.05) were eliminated from the result as summarized in Table. The lack-of-fit F value indicated non significance (P > 0.05) as desired.

Table 4. ANOVA for response Rel$^{12th\ h}$

Source	Sum of squares	df	Mean square	F value	P Value	Prob > F
Model	60.92	5	12.18	790.62	< 0.0001	significant
A-BIS	*49.47*	1	49.47	3210.18	*< 0.0001*	
B-HPMC	10.09	1	10.09	654.59	*< 0.0001*	
AB	0.095	1	0.095	6.16	*0.0558*	
A^2	1.09	1	1.09	71.01	*0.0004*	
B^2	0.015	1	0.015	0.94	*0.3761*	
Residual	0.077	5	0.015			
Lack of Fit	0.077	3	0.026			Not significant
Pure Error	0.000	2	0.000			
Cor Total	61.00	10				

In this case A, B, A^2 are significant model terms.

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor.

The "Pred R-Squared" of 0.9878 is in reasonable agreement with the "Adj R-Squared" of 0.9975; i.e. the difference is less than 0.2.

Following equation is obtained after removing insignificant terms from ANOVA results. In this case A, B, A^2, are significant model terms.

$$R1 = 94.71-2.87.A-1.30.B+0.15.AB-0.66A^2 -0.076.B^2$$

The negative regression coefficient on A and B implies that an increase in the factor A and B causes decrease in % release within the studied levels. As a main factor, A and B has positive significant effect. Predicted response values were in good agreement with the experimental response values.

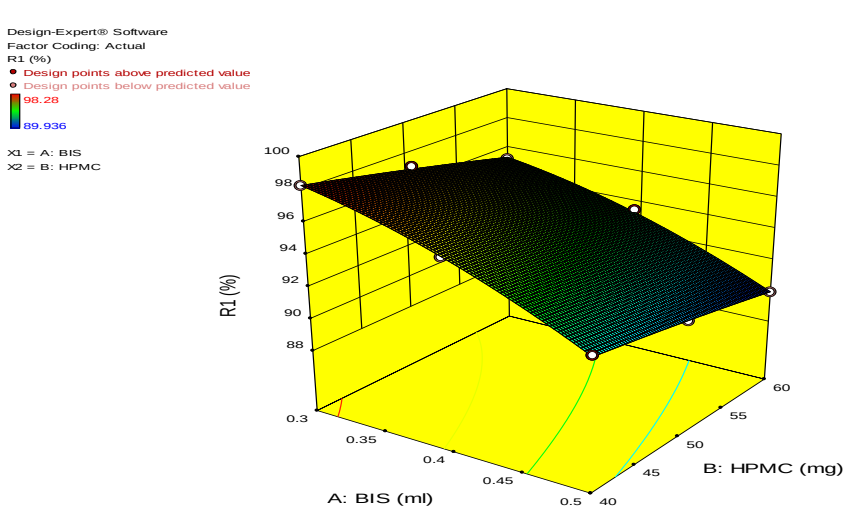


Fig. 5 Response surface plot showing the effect of polymer composition on 'drug release in 12 h' (Rel_{12th} h) from MS loaded SPH in a capsule.

3.7 Accelerated Stability Studies

The stability of formulation (F3) was studied for a period of 90 days, at the temperature of 40° ±2°C and 75% ±5% relative humidity. The formulation was then evaluated for various parameters viz. swelling ratio, apparent density, drug content and release studies.

It was found that (table 5) there is a negligible change in the parameters like swelling ratio, apparent density, drug content and drug release of F3 formulation after an accelerated study of 3 months.

Table 5: Parameters for Floating capsule of F3 Formulation after Stability studies of 3 Months.

Time Interval	swelling ratio	apparent density(g/cm^3)	drug content	%Drug release at 12h
Initial	2.541	0.329	105.24	92.324
1 month	2.544	0.321	105.22	92.296
2 month	2.542	0.324	104.65	92.222
3 month	2.539	0.332	103.21	92.201

4. CONCLUSION

Based on the in vitro evaluations, it was concluded that MS loaded SPH in a capsule would optimize the therapy of this drug. This enabled the desired therapeutic concentration to be achieved in a controlled and sustained manner providing continuous supply of the drug to its absorption site in the small intestine, and yielding a sustained and prolonged MS input to the systemic circulation. Thus these controlled release gastroretentive dosage form could be a

good candidate for novel drug delivery device to improve the systemic circulation of narrow absorption window drugs.

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