RESEARCH ARTICLE

Development and Statistical Optimization of Food Protein-Stabilised Irbesartan Microsponges: An Effect of Lyophilisation

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ABSTRACT
Microsponges are porous microscopic particles that are rapidly becoming an emerging drug delivery route. They are small, rounded grains and have a sponge-like appearance and a very large porous surface that can release the drug in a predetermined and anticipated fashion. Irbesartan is a medication with limitations such as poor bioavailability due to a high first-pass effect, poor water solubility/dissolution rate, low stability, etc. An improvement in the interaction or no interaction was observed between the drug and the excipients, as shown in an IR spectrum and standard curve of the pure drug formulation and placebo formulation. Microsponges of various ratios were developed via the solvent method, and the volume of polymer (ethyl cellulose) (X1) and crosslinker (dichloromethane) (X2) were kept different, along with the stirring speed (X3) being retained in different groups. The factors were selected as independent variables, and % Entrapment efficiency, Particle size, and % cumulative drug release were chosen as dependent variables. The whey protein is taken as a stabilizer an optimum batch among eight formulations was determined through 23 factorial design and tested on bulk density, tapped density, angle of repose, compressibility Index, Carr's index, dissolution studies, Entrapment efficiency, production yield, compatibility studies, powder x-ray diffraction (P-XRD), Differential scanning colorimetric (DSC) and particle size analysis. Therefore, microsponge formulation with a wide range of polymers is a favourable alternative method of enhancing the dissolution rate of Irbesartan.
Keywords- Particle size, Entrapment Efficiency, whey protein, cumulative drug release, factorial design, antihypertension.
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INTRODUCTION

The most feasible and commonly used method of drug administration is the oral route. Medications with a short half-life, which are readily absorbed gastrointestinally, are easily removed by circulating in the blood. Rally controlled release formulations, which release the drug into the digestive system gradually and help keep a constant concentration of the drug in the serum over a longer period without the need for frequent administrations, have been formulated to overcome these complications. Because of their simplicity, regular usage, proper administration in relieving pain, correct dosage, and above all, patient convenience, the range of oral solid dosage forms makes up 50 to 60 percent of the medications. Tablets and capsules are the most common solid dosage forms and can be found in many novel drug delivery techniques such as nanospheres, microparticles, nanoparticles, microspheres, and microsponges[1-3].

The Microsponge Delivery System (MDS) consists of porous, polymeric microparticles that are strongly cross-linked and capable of holding various active substances, releasing them gradually into the skin in response to triggers. This approach was initially proposed to improve drug performance. It is a cutting-edge drug delivery system that utilises microporous beads filled with active ingredients[4,5].

MATERIALS AND METHODS

Materials

Irbesartan (IRB) was obtained as a gift sample from CTX Lifesciences Pvt. Ltd., Sachin, Surat, Gujarat, India. Ethyl cellulose, Polyvinyl alcohol, and Dichloromethane were obtained from Loba Chemie Pvt, Ltd. Whey protein from Ana Lab Fine Chemicals, Mumbai, India.

Methods

Analytical Study

UV-VIS Spectrophotometry Method for Irbesartan

Spectra Analysis and Choice of Analytical Wavelengths

The quantity of the reference standard corresponding to 10 mg IRB was placed into a 100 ml volumetric flask. RB was dissolved in about 25ml of methanol in a 100ml volumetric flask with vigorous agitation, followed by ultrasonication for approximately 5 minutes. The volume under analysis was then made up to the mark with the same solvent to obtain standard stock solutions containing a concentration of 100 µg/ml. The standard stock solution was diluted appropriately to give the desired concentrations of Irbesartan. The conventional solutions were then analysed

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Table 1: Variables Selected to Perform Optimization

Factors	Variables	Low level	High level
X1	Ethyl cellulose	1000mg	2000mg
X2	Dichloromethane	10ml	20ml
X3	Stirring speed	500rpm	4000rpm

Table 2: Coded Levels

Coded levels	Actual values		
	X1 (mg)	X2 (ml)	X3 (rpm)
-1 (Low)	1000	10	500
1 (High)	2000	20	4000

in the spectrum mode of the instrument at a range of 400 nm to 200 nm, and the spectrum was noted, and the λ max was recorded[6-11].

Study of Beer's Law

Prepare standard curves of Irbesartan in distilled Water, in acidic buffer pH 1.2, in phosphate buffer pH 7.4, and in phosphate buffer pH 6.8, respectively.

Saturation Solubility Experiments

The saturation solubility of Irbesartan in various solvents, i.e. distilled water, acidic buffer (pH 1.2), phosphate buffer (pH 7.4), and phosphate buffer (pH 6.8) was determined. A weighed amount of Irbesartan was placed into the conical flask containing 20ml of the solvent and stirred after 48 hours. The mixture was then filtered on a rotary shaker using Whatman filter paper. Irbesartan was soluble, and its solubility was obtained by the spectrophotometric method at 220 nm.

Table 3: 2^3 Full Factorial Designs Actual values

Formulations	Actual values		
	Ethyl cellulose X1 (Mg)	Dichloromethane X2 (ML)	Stirring speed X3 (RPM)
F1	+1	-1	+1
F2	+1	+1	-1
F3	-1	-1	-1
F4	-1	+1	+1
F5	+1	-1	-1
F6	-1	-1	+1
F7	+1	+1	+1
F8	-1	+1	-1

Preformulation Studies

The physical appearance, colour, odour, solubility and test of the drug sample of Irbesartan were analysed.

Determination of Melting Point

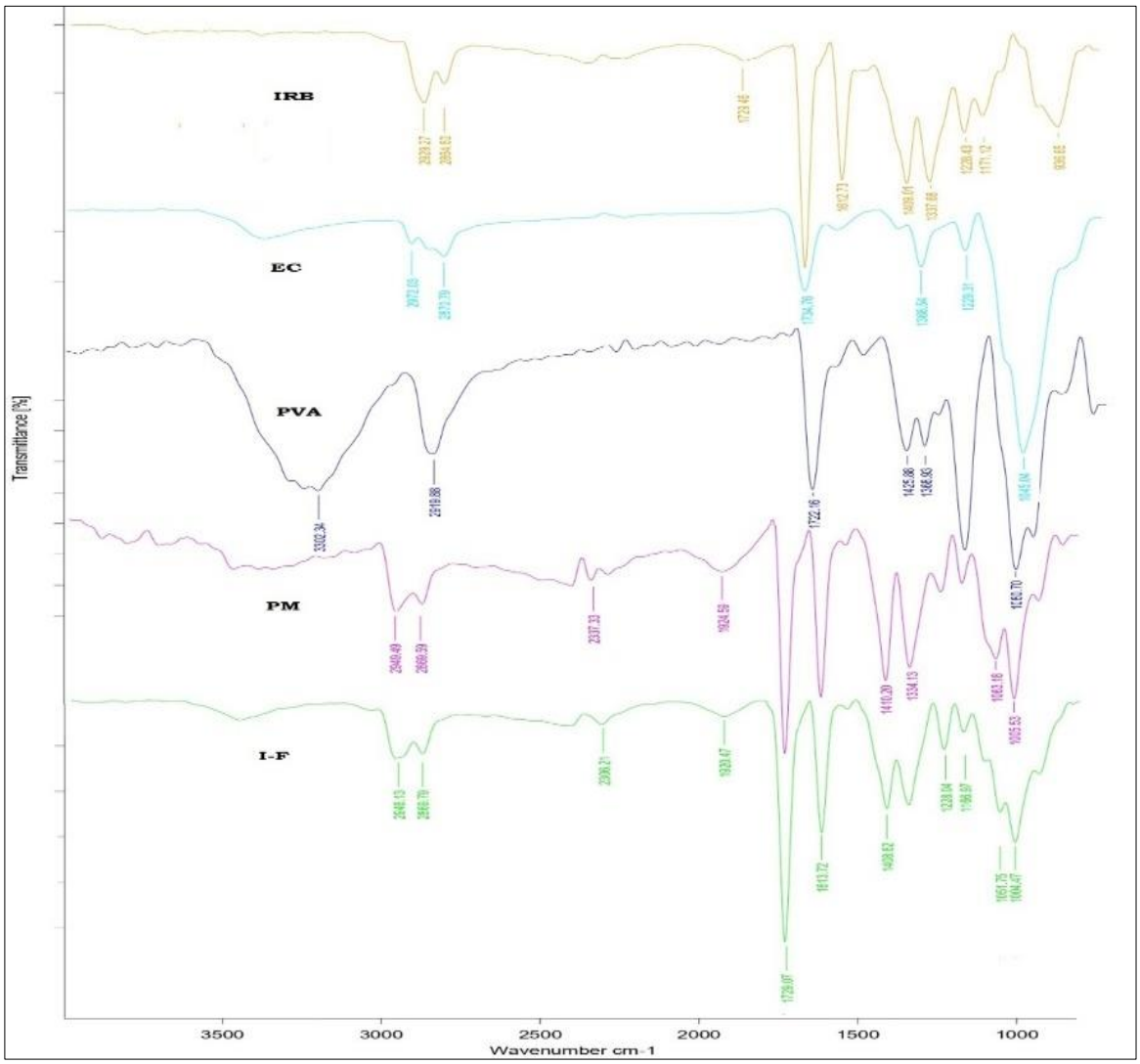

Figure 1: FTIR overlay of Irbesartan+EC+PVA+PM+IRB-F

The melting point of Irbesartan was determined by using a melting point apparatus (Veego, Model VMP-D, India).

Spectroscopic Studies

Compatibility Study between the Drug and Excipients

Interpretation of FT-IR Spectrum

In the ratio of 100:1, the dry red sample of Irbesartan was mixed with the KBr of IR grade. The mixture was transformed into a pellet shape by applying 10 tons of pressure in the hydraulic press. The pellets were scanned at 400-4000 cm^{-1} wavenumbers using the (Perkin Elmer, Spectrum BX, and USA) FTIR instrument. The spectral data were interpreted by comparing the test sample spectra of Irbesartan with a standard Irbesartan spectrum, as well as comparing the peak of the absorption with the standard absorption of the functional groups[12-15].

Table 4: Saturation Solubility of Irbesartan in Different Solvent

Media	Solubility
Distilled water	~2.6 folds
Acidic buffer (pH 1.2)	~9.8 folds
Phosphate buffer (pH 6.8)	~5 folds
Phosphate buffer pH 7.4	~5.1 folds

Differential Scanning Calorimetry (DSC)

The sample was precisely weighed in aluminium pans and hermetically sealed with aluminium lids.

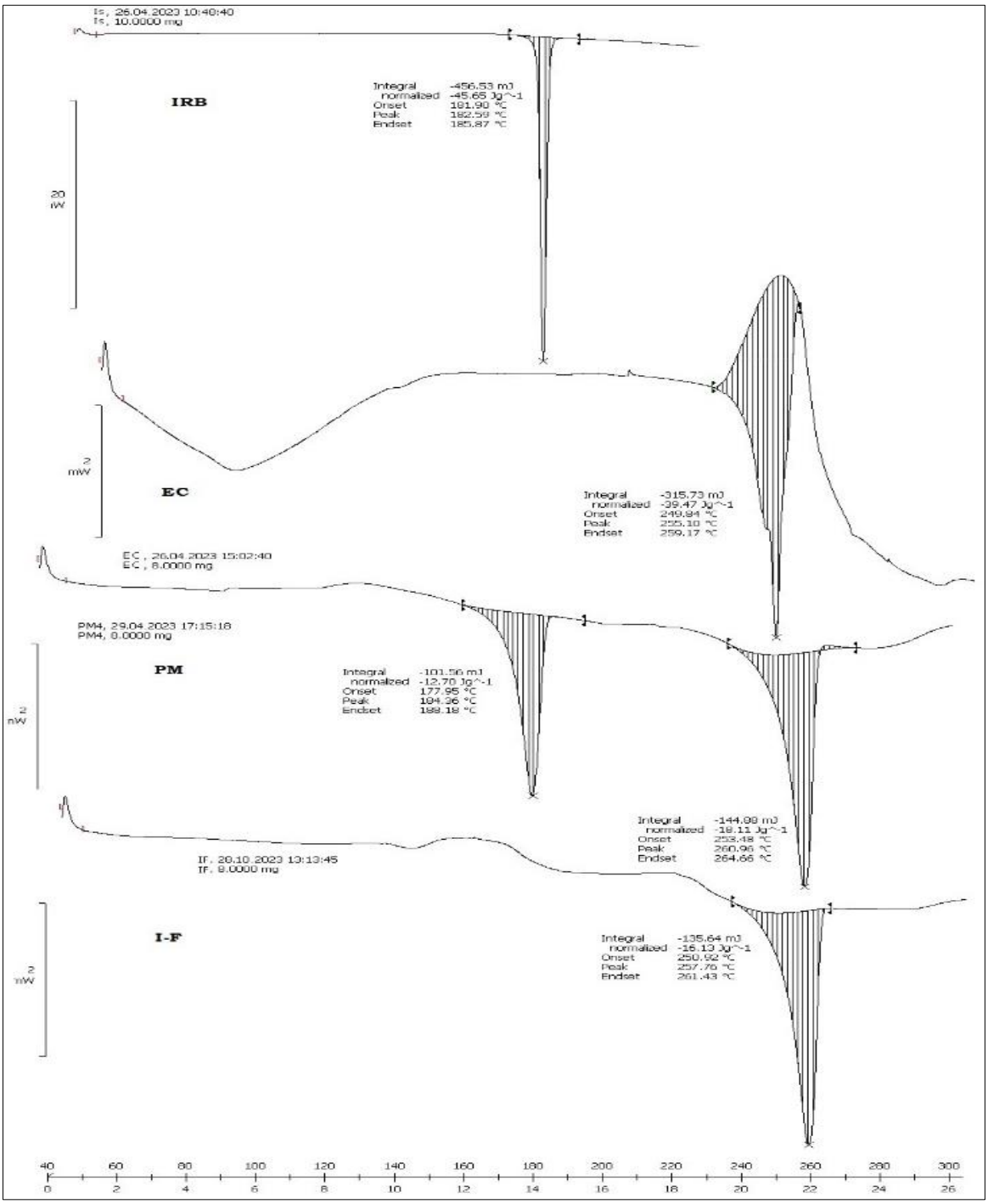

Figure 2: DSC thermogram Overlay of I-F, PM, EC, IRB

Thermogravimetry was performed at a scanning rate of 10 °c/min over the temperature range of 30-300 °c in liquid N_2 (flow rate of 10 ml/min). The lyophilised samples in various forms of preparation were analysed by thermogravimetry. As a reference, an empty aluminium pan was used. DSC measurements were taken using an aluminium sealed pan at a heating rate of 5 °C/min over a temperature range of 25 to 250 °c. Each measurement involved a sample size of 5-10mg. During the measurement process, the sample cell was purged with nitrogen[16-19].

Method of Microsponge Preparation

A set of varying ratios of polymer including ethyl cellulose, polyvinyl alcohol/whey protein as ethyl cellulose, polyvinyl alcohol/whey protein prepared to formulate Microsponges.

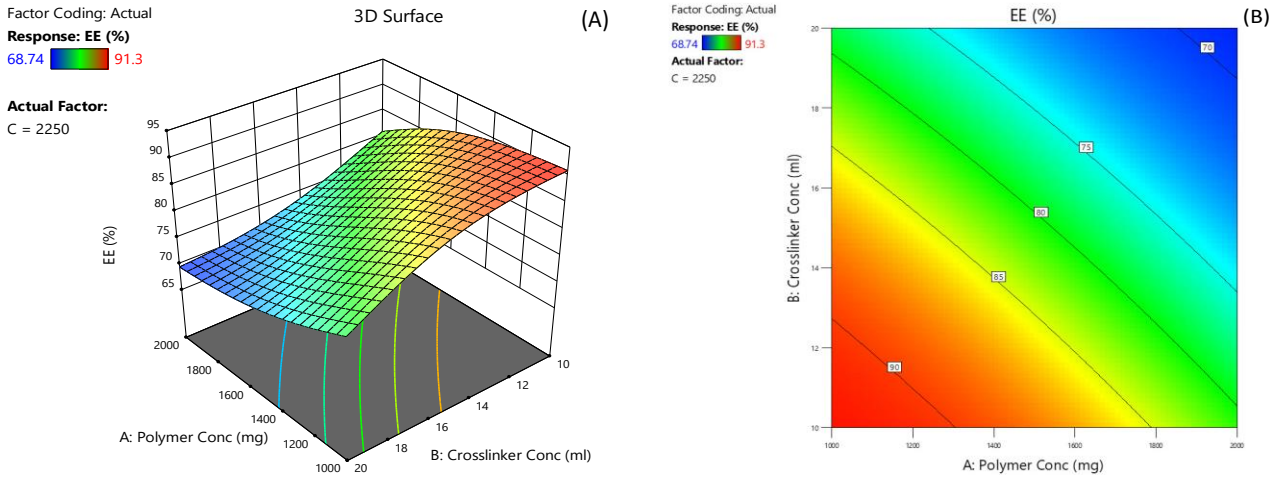

Figure 3: (A) Response Surface plot and (B) contour plot showing the effect of polymer & crosslinkers on % entrapment efficiency

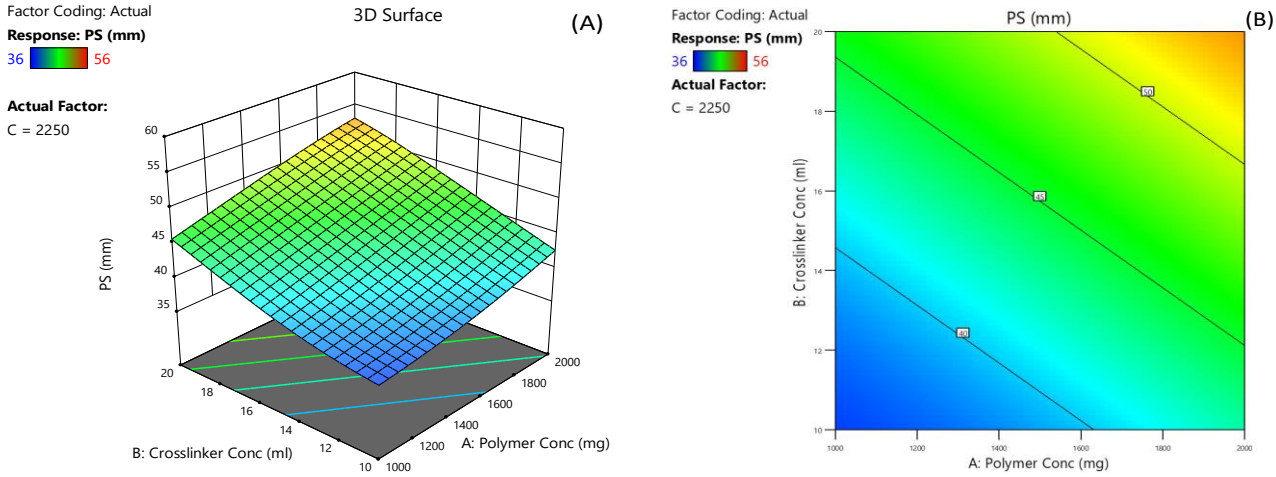

Figure 4: (A) Response Surface plot and (B) contour plot showing the effect of polymer & crosslinkers on Particle size

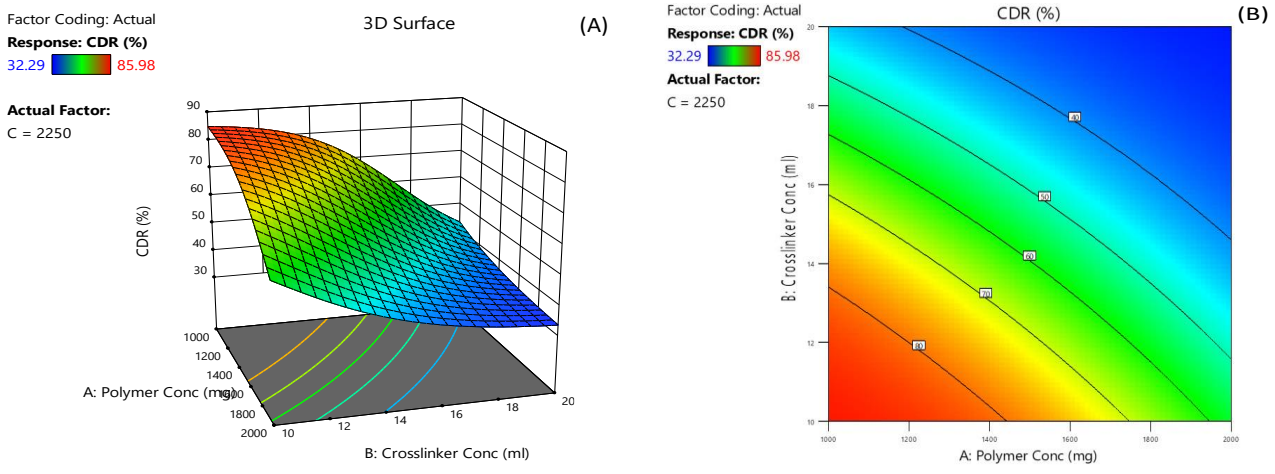

Figure 5: (A) Response Surface plot and (B) contour plot showing the effect of polymer & crosslinkers on % Cumulative Drug Release

Cross linking was done using Dichloromethane. In the first beaker, Irbesartan and ethyl cellulose were added to the dichloromethane. In the second step, the polyvinyl alcohol/Whey protein was added to distilled water. The reaction mixture from the second beaker was added to the first beaker. This reacted blend was agitated at 1 RPM for a time of 2 Hours. To purify, a filtration process was performed, and the Microsponges were collected after filtration. The sample was freeze-dried at -20 o C for 24 hours and stored at ambient conditions until further use[20,21].

2^3 Factorial Designs

"A factorial design of 23 replicates consisting of Ethyl cellulose (X1), dichloromethane (X2) and stirring speed (X3) as independent variables and % Entrapment efficiency, Particle size, and % cumulative drug release were the dependent variables. Various matrix parameters that were exhibited in Table 1-3[22].

Evaluation and Characterization

Particle Size Analysis and Zeta Potential

"Irbesartan-loaded Microsponges. Particle size was determined using photon correlation spectroscopy using Zeta sizer (PCS3000, Malvern, England). Samples were diluted adequately in water containing 1 per cent of F68 and 20 per cent sugar. A measure of surface charge is called the Zeta potential. It is measurable with the aid of an additional electrode in the particle sizing apparatus. Measurement of zeta potentials Samples of the Microsponges diluted in 0.1 mol/L KCl were introduced into the electrophoretic cell and an electric field of approx. 15 V/cm applied. The average hydrodynamic diameter and polydispersity index were then calculated using cumulated analysis following averaging of the readings[23].

Micromeritics Study

Angular Repose

All the repose angles were done using the glass funnel method. The angle of repose is then determined by measuring the height of the cone-shaped powder together with the radius of the circular-shaped base of the powder heap. A formula can compute the angle of repose[24].

$$\emptyset = \tan^{-1}(\frac{h}{r})$$

Bulk Density

Bulk density of previously weighed mass of microsponge in a graduated measuring cylinder.

Bulk density = weight of Microsponges in g/bulk volume of Microsponges[25].

Tapped Density

Tapped density = wt of Microsponges in grams/ volume of Microsponges after tapping[26].

Carr's Compressibility Index

$$\text{Carr's compressibility index} = ((\text{Tapped density} - \text{Bulk density}))/(\text{Tapped density}) \times 100$$

Hausner's Ratio

Hausner's ratio: Tapped density/ Bulk density

Powder X-ray Diffraction (PXRD)

The PXRD patterns were measured in a Bruker Axs-D8 Advance X-ray diffractometer. The samples were bombarded using mono-chromatized CuKa and studied at 2-80 ºC 2 pil. The patterns were scanned at a voltage of 30kV and at 30mA current, respectively. The scanning speed was set at 10°C/min[27].

Field Emission Scanning Electron Microscopy (FE-SEM)

Such tools are used to analyse the shape and the size of the particles and to obtain morphological data concerning the drug delivery system in question. EMEM is a method that entails transmission of conductivity on the produced particles under vacuum to a focused electron beam. In case wet samples need to be examined, FESEM can be utilised[28-30].

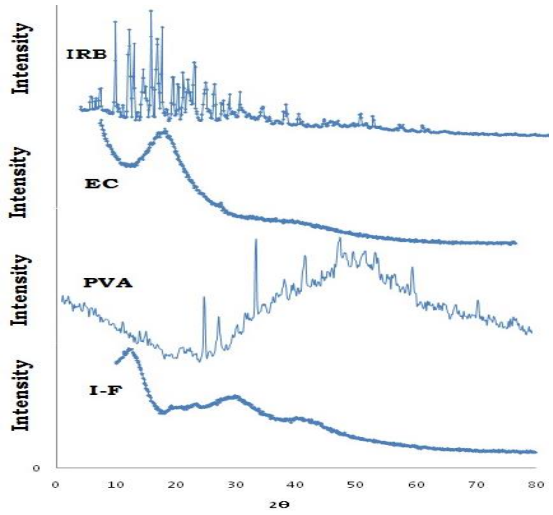

Figure 6: Powder X-ray diffractogram Overlay of I-F, PVA, EC, IRB

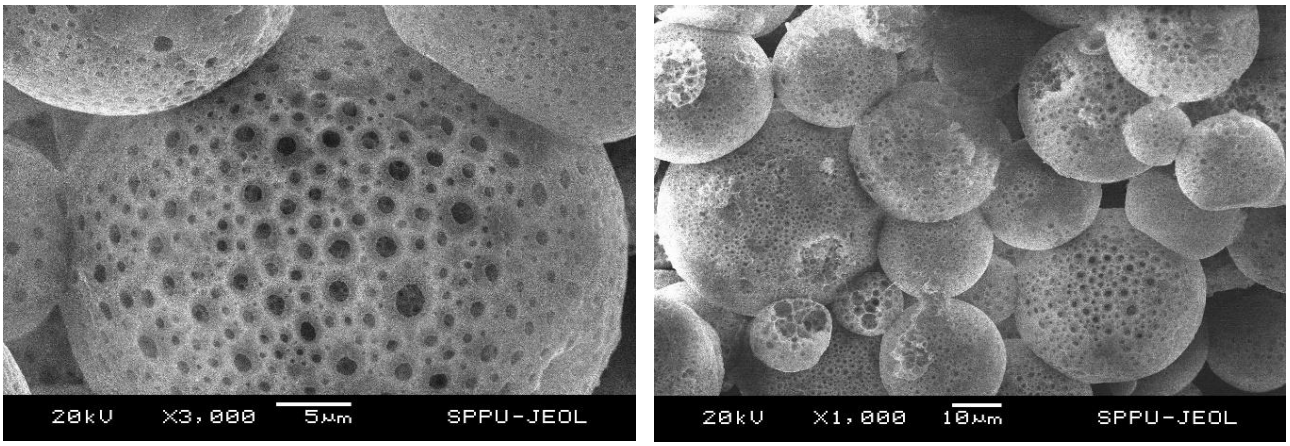

Figure 7: SEM of optimized F5 batch at 5 µm and 10 µm

Transmission Electron Microscopy

Structural investigation of Microsponges was done by the use of an electronically transmitted microscope "(PHILIPS CM-200; London; operating voltages: 20-200kv; Resolution: 2.4 Åo)". In TEM images, the electrons are used as the coupling medium (instead of visible light) and can achieve magnification as high as 1,000,000 x and a resolution of 10 Å. The pictures can be deciphered on both a fluorescent screen and photographic film[31-33].

Entrapment Efficiency

Entrapment efficiency (Ee) and Drug loading (DL) were calculated by weighing a prepared amount of Microsponges (25mg) into a 25ml volumetric flask and adding 0.1N HCL to bring the volume to 25ml. After shaking, the suspension was allowed to incubate for 24 hours at room temperature and shaken in between. Suspension was filtered, and the drug content in the filtrate was determined by using a UV/VIS spectrophotometer at the appropriate wavelength (210nm). Entrapment efficiency of each batch was defined in terms of entrapment percentage using the following formula. EE (Wa Ws)/ Wa x 100, where Wa, Ws and WI were the weight of the drug added in the system, the analytic weight of the drug in supernatant and the weight of the polymer added in the system, respectively[34].

% Cumulative Drug Release Study

Dissolution studies *in vitro* were accomplished in USP type I Apparatus The loaded Microsponges of weighed amounts of drug were dispersed into semipermeable membrane (Two ends closed small permeable bag) were ends closed by clamps. This membrane was added into the dissolution apparatus utilizing 900 ml of phosphate buffer as the dissolution medium maintaining the temperature of 370C at a rate of 50 RPM. "Withdrawn after pre-determined time intervals and the same volume of fresh dissolution medium was replaced to sustain sink condition. Concentrations of drug present in the samples were determined spectroscopically at 210 nm.

Accelerated Stability Study

The formulation was subjected to stability studies under the following conditions. 40°C ± 2 °C / 75% ± 5% RH, at room temperature, and in a refrigerator. The formulation was subjected to stability for a period of six months. The samples were withdrawn at 0 days, 3, and 6 months[35,36].

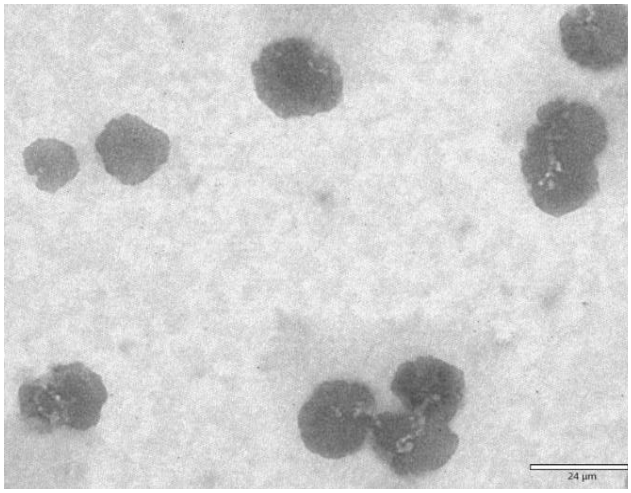

Figure 8: TEM image of dried IRB-MSGs (F5)

RESULTS AND DISCUSSION

Analytical Study

UV-VIS Spectrophotometry Method for Irbesartan

Description: The sample of Irbesartan was found to be a white crystalline powder.

Analysis of Spectra and Choice of Wavelengths of the Analysis

The UV spectrum of Irbesartan showed λmax at 220 nm, which complies with the value.

Study of Beer's Law

A standard curve was drawn by preparing stock solutions of Irbesartan in acidic buffer (pH 1.2), distilled water, phosphate buffer (pH 6.8), and phosphate buffer (pH 7.4), respectively. The results showed the curve to be linear within the concentration range of 2-16 mcg/ml at 220.0 nm $\lambda_{max.}$

Saturation Solubility Study

"Saturation Solubility was determined in distilled water, acidic buffer pH 1.2, phosphate buffer pH 6.8 and phosphate buffer pH 7.4, respectively and which was depicted in table no. 4".

Preformulation Studies

Spectroscopic Studies

FT-IR Spectrum Interpretation

IR spectra of physical combination of API and additives were recorded to observe the interaction of drug and polymer. The pellets were prepared in KBr press using combination of API and polymer in 1:1 proportion and after that the drug was blended separately with each excipient individually. The FT-IR spectrum of that resultant product was taken and compared with the spectrum of standard drug.

Compatibility Study between Drug and Excipients

FT-IT spectrum of (A) Irbesartan and (B) Ethyl cellulose showed characteristic peaks which were exactly revealed the similarity as that of reported spectrum in regards with the frequencies. All characteristic peaks in IRB, EC, and PVA were observed in PM which reveals the compatibility of all excipients with each other.

The spectral pattern of RB illustrates an extended band in the spectral dimension 3450-1600 cm -1, due to the presence of crystallization water that is overlaid in certain sharp points, such as the ones at 2946.13 cm -1 (C-H stretching, alkane), 2869.79 (N-H stretching, alkane), 1920.47 (Carbonyl stretching, saturated aliphatic), 1729.07 (C= The corresponding bands given above may be assumed to represent the so-called reactive functional groups of the types of IRB, EC, PVA etc that were found in this spectrum of dried IRB-MSGs as shown in figure 1. One of the reasons of this could be due to possible interaction between drug, polymer and the cross-linker through hydrogen bonding. Besides, their existence was evaluated in the spectra of binary mixes with excipients.

Differential Scanning Calorimetry (DSC)

The RB shows a distinct characteristic endothermic peak centred at 182.59 ºC. Physical mixture of IRB, Ethyl Cellulose (EC), polyvinyl alcohol (PVA), and whey protein isolate (WPI) displayed sharp endothermic peaks at 184.36 ºC, devoid of any crystal form. Differently, in the dried

powder of IRB-MSGs there is an endothermic peak at an onset temperature of 250.92 ºC, a peak 257.76 ºC and the conclusion of 261.43 ºC of temperature corresponding to the recrystallization of the melt other than the decomposition of the same with an endothermic peak. The total loss of an endotherm peak representing irbesartan occurred in IRB-MSGs, reflecting the formation of an amorphous inclusion complex and loss of crystallinity, which can be attributed to the embedding of IRB within the polymer structure. It was therefore concluded that the molecular encapsulation of the IRB into the EC cavity successfully occurred as indicated in figure 2.

Formulation of Microsponges

The ratios of ethyl cellulose and polyvinyl alcohol were taken in various proportions in solvent method. The dispersed phase including ethyl cellulose and drug was dissolved in dichloromethane and gradually introduced into a certain quantity of polyvinyl alcohol in distilled water as a water-dissolved continuous phase. The mixture in the reaction vessel was stirred at a speed of 1000 rpm in 2 hrs. The resultant Microsponge was removed by lyophilization Abbreviations concerning the different concentration of the independent variables were stated in table no. 5.

Response Surface Analysis (RSA)

Response 1: % Entrapment Efficiency (%EE)

Final Equation in Terms of Coded Factors

$\%EE = +0.1552 - 1.77X_1 - 2.00X_2 - 2.00X_3 + 0.2014X_1X_2 - 1.96X_1X_2X_3$

Response 2: Particle Size

Final Equation in Terms of Coded Factors

$PS = -0.4892 + 1.08X_1 + 1.49X_2 + 1.36X_3 + 1.37X_1X_2X_3$

Response 3: % Cumulative Drug Release

Final Equation in Terms of Coded Factors

$\%CDR = -0.3427 - 1.60X_1 - 2.20X_2 - 2.43X_3 + 0.4130X_1X_2 - 2.36X_1X_2X_3$

Entrapment Efficiency (%EE) and Drug Loading (%DL)

"% Encapsulation efficiency of IRB-MSGs varied from 68.74±0.51 % to 91.30±0.47% and % drug loading varied from 3.44% to 8.48%. Encapsulation efficiency increased with increasing concentration of cross-linker but in higher EC concentration batches it was found to be decreased. The highest drug encapsulation was found with batch F5 (1-3)".

Powdered X-Ray Diffraction Pattern

The diffraction spectrum of plain IRB exhibited a series of high peak intensities in the region 9–27° of 2Θ, indicating the crystalline state of IRB. The peak intensity of plain IRB was considerably higher than that of the physical mixture. There was a significant change in the intensities of powder, 2θ values between the physical mixture and IRB–MSGs. The crystalline feature of IRB in IRB–MSGs was significantly distorted. This indicates that the IRB was successfully entrapped in a solid polymer core.

Field Emission Scanning Electron Microscopy

Micrographs of optimized formulation (F5) showed that IRB–MSGs were of spongy, unvarying, and ovate/sphere-shaped. SEM image revealed the highly porous structure of IRB–MSGs image. The image illustrates the creation of spherical pores. The morphological investigation of optimized formulation revealed a larger variety of pores, indicating that maximal drug accommodation may be entrapped into the aforesaid cavities.

Transmission Electron Microscopy (TEM)

It shows that the particles had almost round and uniform shapes.

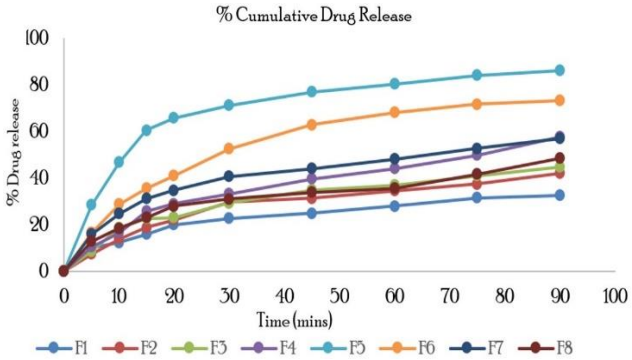

Figure 9: *In-vitro* dissolution study of plain IRB, and dried IRB-MSGs (F1-F8)

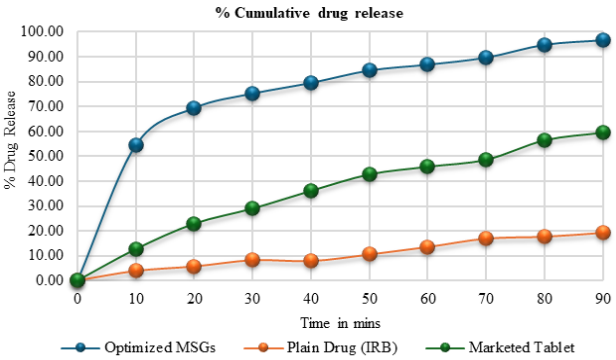

Figure 10: *In-vitro* dissolution study of plain IRB, Marketed tablet, and dried IRB-MSGs

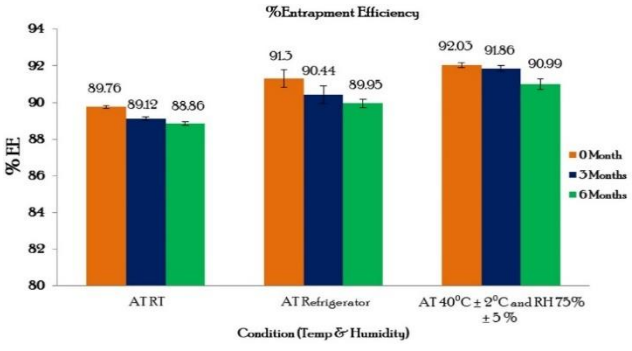

Figure 11: % Entrapment efficiency at different Temperature conditions

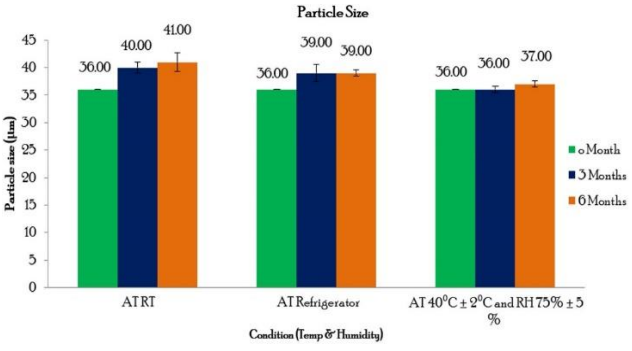

Figure 12: Particle size at different Temperature conditions

Table 5: Factorial Design of Irbesartan Microsponges

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
Weight of drug (mg)	200	200	200	200	200	200	200	200
PVA:EC (%w/w) (X1)	1:2	1:1	1:1	1:2	1:1	1:2	1:2	1:1
DCM (ml) (X2)	20	20	20	10	10	20	10	10
DW (ml)	150	150	150	150	150	150	150	150
SS (RPM) (X3)	4000	4000	500	4000	500	500	500	4000

The mean diameter of IRB-MSGs i.e for optimized formulation (F5) was found to be 24 µm in size which is depicted in Fig 8.

In-vitro Dissolution Study

The % release of drugs was not comparable in all the formulations (F1-F8). In the first 30 min, the MSGs demonstrated instantaneous liberation of IRB, which could be attributed to instant excretion of the compound immobilised on the surfaces of MSGs. Subsequently, there was a slow and progressive liberation of IRB encapsulated in microsponges. The release of IRB-MSGs (F5) was determined to be 85.98 % and that of the control as 94.74 %.

The dissolution diagrams of IRB, marketed tablet, and dried IRB-MSGs in acidic buffer pH 1.2 at 37°C shown in Figure 7. It was evident that the marketed tablet showed significant improvement in dissolution rate concerning IRB alone. Furthermore, the dried IRB-MSGs (F5) exhibit faster dissolution as compared to plain IRB as well as marketed formulation and it was found to be 96.69%.

Accelerated Stability Study

Appearance

Formulation kept for stability studies were removed and examined. The color of Formulation was similar before and after stability studies.

% Entrapment Efficiency

"No significant difference was found in the % entrapment efficiency revealed in the formulation when exposed even at different temperature and humidity conditions. Hence, the formulation was found to be stable over a period of time".

Particle Size

There is no important distinction that has been exhibited in the formulation when subjected even to varied temperature and humidity condition.

The zeta potential was also observed before (-28.4 mV) and after stability (-25.9 mV). Thus, it is concluded that the IRB-MSGs formulation was observed to be steady over the period of time.

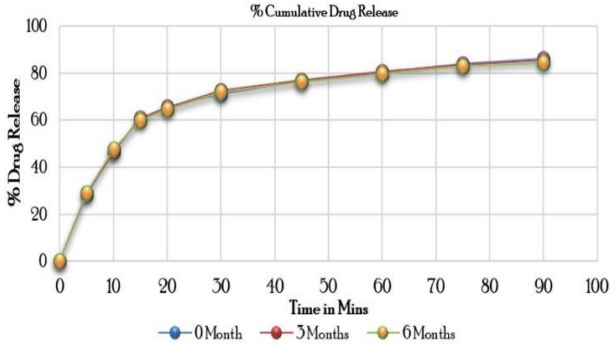

Figure 13: % Cumulative Drug Release at 0, 3, and 6 months' conditions

Table 6: Percent drug encapsulation and drug loading of MSGs

Run	Percent drug encapsulation (%)	Unentrapped drug (%)	Drug Loading (%)
F1	68.74 ±0.51	31.26 ± 0.51	3.44
F2	77.20 ± 0.58	22.80 ± 0.58	3.86
F3	79.71 ± 0.53	20.29 ± 0.53	7.97
F4	81.91 ± 0.50	18.09 ± 0.50	8.19
F5	91.30 ± 0.47	8.70 ± 0.47	4.57
F6	84.76 ± 0.59	15.24 ± 0.59	8.48
F7	80.26 ± 0.97	19.74 ± 0.33	4.01
F8	82.95 ± 0.33	17.05 ± 0.33	8.30

% Cumulative Drug Release

The CDR study showed no significant difference with that of initial CDR profile of optimized freeze-dried IRB-MSGs, and it was revealed that drug release was 84.20%. Thereby, one can conclude that the IRB-MSGs formulation was stable during the time period.

CONCLUSION

The current study has demonstrated that the microsponges can be made using the emulsion solvent diffusion process. The preparation of IRB-loaded microsponges by the use of quasi emulsion solvent diffusion method was initiated experimentally. In this case it was implemented with 8 potential preparations. Eight formulations (i.e. F1, F2, F3, F4, F5, F6, F7, and F8) formulations were prepared using different combinations of polymers, crosslinkers, and stabilizers. A relatively high Entrapment Efficiency, Particle Size, & Drug Loading of the optimized formulation, i.e., F5, was obtained. Moreover, the IRB-MSGs have good appeal to numerous potential uses due to the submicrometer dimension and size distribution, or rather, the biodegradability in structure. The solubility and rate of dissolution IRB of its formulation were significantly higher than the drug alone. Thus, according to the results obtained based on the above, it was concluded that through preparing MSGs, the bioavailability of IRB could be increased significantly. The F5 formulation was made, and it was observed that no significant change in terms of the % entrapment efficiency, size of the particles as well as the % cumulative drug release was found after stability. The stability analyses showed that formulations could be kept with stability over time.

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