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Research Article

FORMULATION OF MICROSPONGES OF RISPERIDONE HCl

Chaitali R Bhandare[1] and Suvarna A Katti [2*]

[1]Department of Quality Assurance Techniques, M.G.V's Pharmacy College, Panchavati, Nasik-422005, Maharashtra, India.

[2]Department of Pharmaceutical Chemistry, M.G.V's Pharmacy College, Panchavati, Nasik-42200, Maharashtra, India.

ABSTRACT

The aim of the present study was to formulate microsponge based drug delivery system containing Risperidone for controlled release. Risperidone is a potent antipsychotic drug which is mainly used to treat schizophrenia, schizoaffetive disorder, mixed and manic states associated with bipolar disorders and irritability in people with autism. By this therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better patient compliance. Ethyl cellulose and Eudragit RS 100 based microsponges were prepared using Quasi-Emusion solvent diffusion method. To design suitable formula, the effect of drug:polymer ratio, inner phase solvent amount, stirring time and speed on physical characteristics of microsponges were investigated. Microsponges were characterized on the basis of drug-excipient compatibility, thermal behaviour, particle size, surface morphology, drug content, encapsulation efficiency and invitro drug release as well. By compatibility study there is no chemical interaction between drug and excipients used. The average particle size was found to be 385.9 nm having roughly spherical and porous structure. Drug content and encapsulation efficiency was obtained as 82.21% and 74.88% respectively. In vitro dissolution results showed that the drug release rate of Risperidone was modified in all formulations. Formulation containing both Ethyl cellulose and Eudragit gave better drug release and encapsulation efficiency as compared to their single use in formulation.

Keywords: Microsponge drug delivery system, Quasi emulsion solvent diffusion method.

INTRODUCTION

Microsponge drug delivery system consists of polymeric system of tiny sponge like uniform, spherical particles with large porous surface microspheres. Microsponges consisting of non-collapsible structure through which active ingredients are released in controlled manner. The average diameter of microsponges is 10-25 microns. The average diameter of a nanosponge is below 1µm but fractions below 500 nm can be selected. They are designed to deliver an active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects and modify drug release profile. The microsponge based novel drug delivery systems, are developed to modify and control the release behaviour of the drugs. By incorporation in to carrier system, it is possible to amend the therapeutic index and duration of the activity of drugs.

Microsponges are prepared by several methods utilising emulsion system as well as by suspension polymerisation in a liquid–liquid system. The most common emulsion system used is oil in water (o/w), with the microsponges being produced by the emulsion solvent diffusion (ESD) method.

Risperidone is a potent antipsychotic drug which is mainly used to treat schizophrenia (including adolescent schizophrenia), schizoaffective disorder, the mixed and manic states associated with bipolar disorder, and

irritability in people with autism. Risperidone, a benzisoxazole derivative, is an atypical antipsychotic drug with high affinity for 5-hydrotryptamine (5-HT) and dopamine D2 receptors. It is used primarily in the management of schizophrenia, inappropriate behavior in severe dementia and manic episodes associated with bipolar I disorder. Risperidone is effective for treating the positive and negative symptoms of schizophrenia owing to its affinity for its "loose" binding affinity for dopamine D2 receptors and additional 5-HT antagonism compared to first generation antipsychotics, which are strong, non-specific dopamine D2 receptor antagonists. According to BCS, Risperidone is a class II compound, that it has poor water solubility and consequently, a dissolution rate-limited absorption through the gastrointestinal tract (GIT), so there is a need to develop suitable dosage form which will give better solubility & bioavailability. The absolute oral bioavailability of Risperidone is 70% (CV=25%). It is extensively metabolized by hepatic cytochrome P450 2D6 isozyme to 9-hydroxyrisperidone, which has approximately the same receptor binding affinity as Risperidone. It is having half life 20 hours (oral), 2.9-6 days (IM).

The present study is aimed at developing microsponge based novel drug delivery system containing Risperidone. Microsponges of Risperidone has been developed using Quasi Emulsion Solvent Diffusion method and evaluated to provide a sustained release action to treat schizophrenia, mixed and manic states associated with bipolar disorders. Therapeutically effective concentrations can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients.

MATERIALS AND METHODS

MATERIALS

Risperidone was obtained as gift sample from Mylan Laboratories Ltd. Sinner, Nashik. Ethyl Cellulose was obtained from Morden lab, Nashik. Eudragit RS100 was obtained as gift sample from Evonik Pharma, Ind, Mumbai. Polyvinyl Alcohol molecular weight 130000 was obtained as gift sample from IPCA Laboratories, Mumbai. All other chemicals and solvent were of analytical grades.

METHOD

Pre-formulation study

Differential scanning calorimetry (DSC)

Thermogram of Risperidone HCl formulation was obtained using differential scanning calorimeter (figure2). Sample was kept in aluminium pan, sealed and heated at constant rate of 10°C/min over temperature range of 10 to 200°C. By purging nitrogen with flow rate of 10 ml/min inert atmosphere was maintained.

Infrared spectroscopy

FTIR spectrum of procured Risperidone HCl was recorded (Figure3) and spectral interpretation was done. The characteristics IR absorption peaks of Risperidone were studied.

Drug-excipient interaction study

To check out any possible interaction between drug and excipients used, compatibility study using DSC and FTIR was carried out. It was done using Fourier Transform Infrared Spectrophotometer using KBr pellet method. DSC thermogram and FTIR spectra of physical mixtures of Risperidone, ethyl cellulose and Eudragit RS 100, PVA was recorded.

Formula design

Variables considered for designing the formula includes

1. Drug-polymer ratio: Effect of drug-polymer ratio in internal phase on microsponge formulation was studied. Eight different ratios of drug to polymer were employed to determine the effect of drug-polymer ratio on physical characteristics and dissolution properties of microsponges. In each formulation the amount of drug was kept constant at 0.1 gm and type and amount polymer were changed as per formula.
2. Volume of internal phase: Effect of internal phase solvent amount on microsponge formulation was studied. The amount of solvent used was determined by considering the viscosity of internal phase and dissolution of drug in solvent. Increased viscosity of internal phase reduces the drug mobility outside the formed droplets, and hence entrapping the higher amount of drug. On trials, the internal phase solvent amount was optimised to 10 ml.
3. Amount of polymer in external phase: Effect of amount of polymer in external phase on microsponge formulation was studied. The concentration of PVA was optimised from 0.5% and 0.75% PVA solutions by considering entrapment efficiency.
4. Stirring time and speed: Effect of stirring time and speed on microsponge formulation was studied. Different stirring time (60min, 2 hour

and 3 hours) and speed (low, medium and high) were employed for batch 1 and 2. From which 3 hours stirring time and high speed was selected.

Preparation of Risperidone Microsponges

Microsponges were prepared by Quasi Emulsion Solvent Diffusion method using different polymers in different amounts.

Table 1: Formulas for batch B1 –B8

Batch	Drug:Polymer ratio	Drug (Risperidone) gm	Ethyl Cellulose (EC) gm	Eudragit (EU) gm	Ethyl alcohol (ml)	% PVA (in 100ml water)
B1	1:2	0.1	0.2	-	10	0.5
B2	1:2	0.1	-	0.2	10	0.5
B3	1:3	0.1	0.2	0.1	10	0.5
B4	1:3	0.1	0.1	0.2	10	0.5
B5	1:3	0.1	0.1	0.1	10	0.5
B6	1:4	0.1	0.2	0.2	10	0.5
B7	1:4	0.1	0.4	-	10	0.5
B8	1:4	0.1	-	0.4	10	0.5

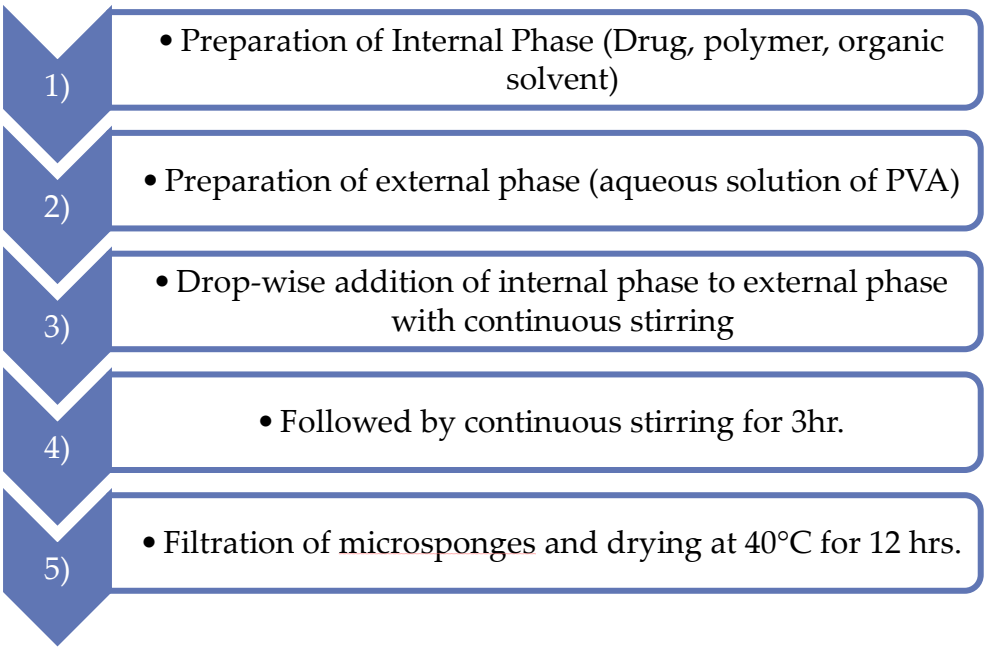

Fig. 1: The processing flow chart

To prepare internal phase, ethyl cellulose or Eudragit RS100 was dissolved in ethyl alcohol. Then, Risperidone was added to solution and dissolved under ultrasonication at 35-40ºC. The external phase was prepared by dissolving polyvinyl alcohol (aqueous solution of PVA). Internal phase was drop-wise poured into external phase followed by three hours of continuous stirring. The mixture was filtered to separate the microsponges. The microsponges were dried in oven at 40°C for 12 hours. Each formulation was carried out in triplicate to optimise formulation parameters and process factors.

Evaluation of Risperidone microsponges

Production yield

Microsponges production yield was determined by formula mentioned below:

Production Yield (PY) = Practical Mass of Micrsponges / Theorotical Mass (Polymer + Drug)* 100

Actual drug content and encapsulation efficiency

Precisely weighed quantity (10 mg) of microsponges containing drug was kept in 100 ml of 0.1N HCl solution for an hour with continuous stirring. Filtered samples were further analysed at 276 nm next to blank using UV spectrophotometer.

Estimation of drug content and encapsulation efficiency for all batches were done using following expressions:

Actual Drug content (%) = (M_{act} / M_{ms}) * 100

Encapsulation Efficiency (%) = (M_{act} / M_{the}) * 100

Where M_{act} = actual Risperidone content in weighed quantity of microsponges,
M_{ms} = weighed quantity of microsponges and
M_{the} = theoretical Risperidone content in microsponges.

Particle size analysis
Particle size analysis of prepared microsponges was carried out using particle size analyser. Particle size analysis is carried out using Malvern Zetasizer Ver. 602 (MAL1051945).

In-vitro drug release study
The in vitro drug release study of microsponges (equivalent to dose of Risperidone filled in capsule) was carried out in the USP Dissolution apparatus type I (Electrolab). Phosphate buffer pH 6.8 was used as a dissolution medium. Temperature was maintained at 37±0.5°C and basket was rotated at the speed of 50 rpm. Drug release was monitored for 30 min and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours. Five ml of samples was withdrawn at each time intervals and sink condition was maintained by replacing an equal amount of fresh dissolution medium. Samples were filtered and analysed by UV-Visible Spectroscopy at 276 nm.

Dissolution kinetics
The dissolution profile of optimized formulation was subjected to various models such as Zero order kinetics, First order kinetics, Higuchi, Korsemeyer-Peppas and Hixson-Crowell to assess the kinetics of drug release from prepared Risperidone loaded microsponges.

Differential scanning calorimetry (DSC)
Thermogram of Risperidone microsponge formulation (B3) was obtained using differential scanning calorimeter. Microsponge samples were kept in aluminium pan, sealed and heated at constant rate of 10°C/min over temperature range of 10 to 200°C. By purging nitrogen with flow rate of 10 ml/min inert atmosphere was maintained.

Infrared spectroscopy
The FTIR spectrum of Risperidone microsponge formulation (B3) was recorded in the wavelength range of 4000 to 400 cm-1. The characteristics IR absorption peaks of Risperidone were studied.

Scanning electron microscopy (SEM)
For assessing morphology and surface topography, prepared microsponges (B3) were examined under scanning electron microscope.

RESULT AND DISCUSSION
Characterization of pure drug
Differential scanning calorimetry (DSC***):*** As reflected by DSC thermogram shown in Figure.2, sharp endothermic peak was observed at 167.48ºC corresponding to melting point of drug in crystalline form; reflecting purity of Risperidone HCl.
FTIR spectroscopy: FTIR spectrum of procured Risperidone was recorded Figure.3 and spectral interpretation was done. The characteristics IR absorption peaks of Risperidon at 3070cm^{-1} (C-H bending), 1651 cm^{-1} (C=O Amide/pyridopyrimidinone), 1130 (C-F stretch Fluoride), 2804 cm^{-1} (C-H stretching) and1060 cm^{-1} (C-N Amines) were there in drug sample spectrum; which confirmed the purity of Risperidone.
Drug-excipient interaction study: To check out any possible interaction between drug and excipients used, compatibility study using DSC and FTIR was carried out. DSC results reflected similar thermal behaviour of physical mixture as that of pure drug. A sharp endothermic peak noted at 170.14°C in case of Risperidone, indicative of its melting point (Figure.4). FTIR spectroscopic study results discovered no any new peak appearance or disappearance of existing peaks, discarding any chemical interaction probability amongst drug and polymer used. The characteristic peaks at 3070cm^{-1} (C-H bending), 1651 cm^{-1} (C=O Amide/pyridopyrimidinone), 1130 (C-F stretch Fluoride), 2804 cm^{-1} (C-H stretching) and1060 cm^{-1} (C-N Amines) were recognized in all spectra (Figure.5). All characteristic peaks of Rispridone were experiential in physical mixture spectrum. Thus, IR spectroscopy results depicted that Risperidone was compatible with selected polymer, excipients and possess good stability.

Characterization of Risperidone microsponges
The encapsulation efficiency, actual drug content, particle size and production yield of microsponges formulations are given in table.2. The actual drug content of all microsponge formulation varied between 11% and 30% to that of theoretical drug content. Encapsulation efficiency of all microsponge formulation was found in between 55% to 90%. Drug content and Encapsulation efficiency were found above 70% in all formulation batches except B5 and B6. Production yield was obtained in between 10-50% for all batches of formulations. It is lower in B5 i.e. 10.33% and higher in B7 i.e. 53.89%. Mean particle size of all formulation batches

was obtained from 300 nm and 1000nm. PDI value ranges from 0.3 to 1.0.

The Risperidone release from microsponge formulation batches are shown in figure 6, 7 and 8. From all batches, B3, B6 and B8 exhibited drug release up to 98-100% up to 12 hrs to provide extended release action. Amongst this three batches, B6 and B8 showed immediate drug release up to 30-40% within one hour and then gradual increase in drug release. And B3 showed steady state continuous controlled release of drug from microsponge formulation up to 12 hrs. The in-vitro drug release data was subjected various release kinetic models, namely zero order, first order, Higuchi, Korsemeyer-peppas which is shown in table 4. And by highest R^2 values best fit model was decided. Korsemeyer peppas model was found to be best fit for most of the formulations. For all formulations N exponent values was found in between 0.3 and 0.8 which is indicative of anomalous non-fickian diffusion i.e. rate of solvent penetration and drug release are in the same range. The drug release controlling element is a non-swellable water insoluble polymer such as Ethyl cellulose or polymethacrylate which controls drug release through the micropores present in their membrane or matrix structure.

Based on encapsulation efficiency, drug content, particle size and steady state drug release in dissolution studies, B3 was selected and subjected for further investigations. DSC thermogram of Risperidone loaded microsponge (figure.9) showed a wide melting endotherm at 168.03ºC indicates that drug was embedded in matrix of polymer used without any change in its entire structure.

FTIR analysis of microsponge formulation was shown in figure 10. Similar vibrational peaks of Risperidone were detected in Risperidone loaded microsponge with minor differences in frequencies. This suggested that Risperidone was compatible with EC and Eudragit and it was apparently stable in microsponges.

SEM photogragh of microsponge (B3) is shown in figure11. It was observed by SEM that the prepared microsponges were roughly spherical in shape and having porous structure containing void spaces.

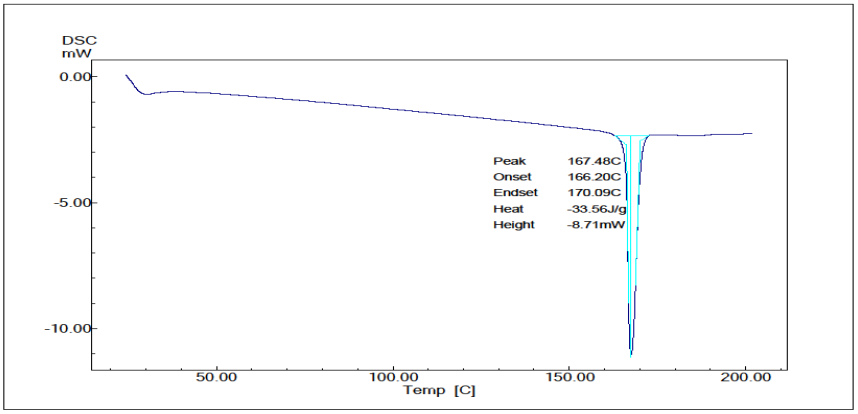

Fig. 2: DSC thermogram of Risperidone HCl

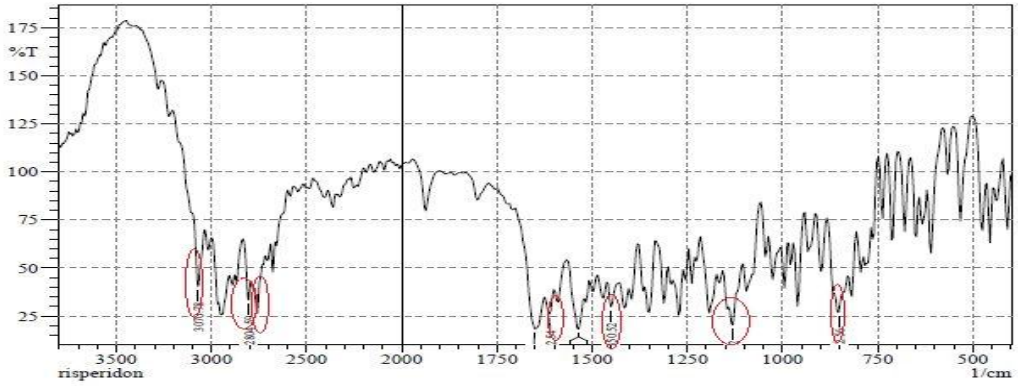

Fig. 3: FTIR spectrum of Risperidone HCl API

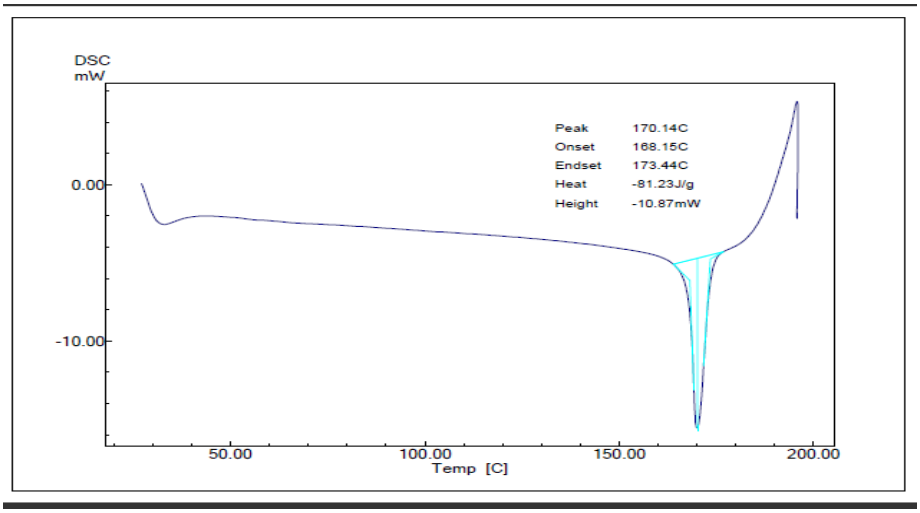

Fig. 4: DSC thermogram of physical mixture of Risperidone and excipients

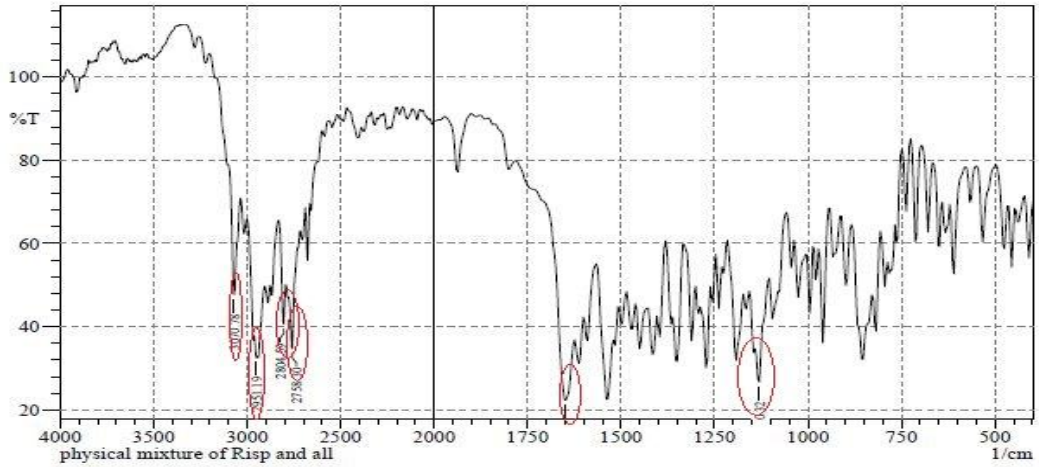

Fig. 5: FTIR spectrum of physical mixture of Risperidone and excipients

Table 2: Actual drug content, encapsulation efficiency and production yield

Batch	Theoretical drug content (%)	Actual drug content (%) mean±SD	Encapsulation Efficiency % Mean±SD	Production Yield %
1	33.33	30.12±0.999	90.39±0.9777	43.33
2	33.33	26.64±0.94	79.94± 2.94	12.00
3	**25.00**	**21.28±1.23**	**74.88 ±2.74**	39.77
4	25.00	18.19±1.21	72.79 ±2.21	14.83
5	33.33	21.94±2.59	65.84 ±0.15	10.33
6	20.00	11.09±3.01	55.46± 3.11	16.67
7	20.00	18.18±0.42	90.94 ±0.32	53.89
8	20.00	15.17±0.96	78.55 ±2.83	39.66

Table 3: Mean Particle Size

Batch	Particle Size (nm)	PDI
1	625.6	0.874
2	325.2	0.394
3	**385.9**	**0.629**
4	392.7	0.631
5	876.0	1.0
6	593.2	0.957
7	476.3	0.515
8	368.6	0.590

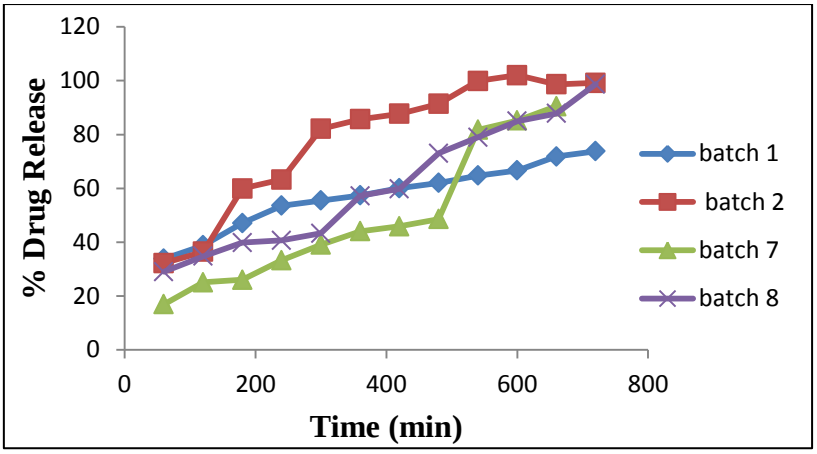

Fig. 6: Comparative *in vitro* drug dissolution profiles of Risperidone Micosponges (B1,2,7,8)

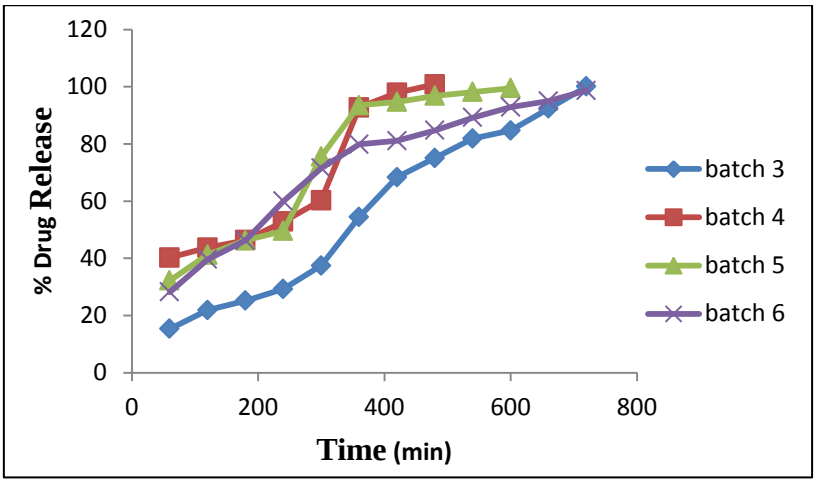

Fig. 7: Comparative *in vitro* drug dissolution profiles of Risperidone Micosponges (B3,4,5,6)

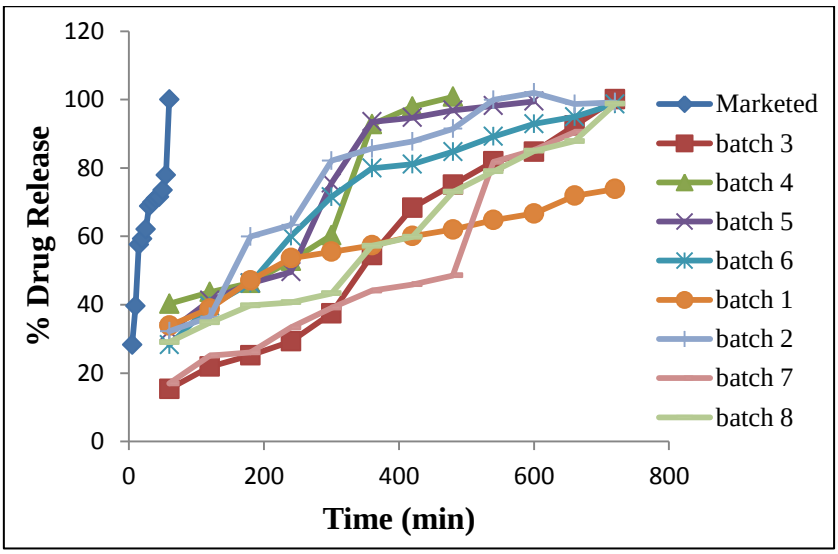

Fig. 8: Comparative *in vitro* drug dissolution profiles of prepared Risperidone Micosponges and Marketed Risperidone Tablet (Sizodon 4)

Table 4: dissolution kinetics

Batch	Zero	First	Highuchi	Korsemeyer-peppas	N (release exponent)	Hixson- crowell	Weibull
1	0.9489	0.9703	0.9835	**0.9856**	0.3132	0.9623	0.9294
2	0.8562	0.9179	0.9305	0.9420	0.5093	**0.952**	0.7726
3	0.9759	0.9416	0.9469	**0.9775**	0.8088	0.9445	0.623
4	0.8694	0.8813	0.8876	0.8719	0.4849	**0.9017**	0.7578
5	0.8701	**0.9519**	0.9151	0.9266	0.5431	0.8722	0.803
6	0.9221	0.8370	0.9752	**0.9833**	0.5243	0.9822	0.8614
7	0.9008	0.6674	0.8513	**0.9253**	0.7263	0.6133	0.4333
8	0.9765	0.9703	0.926	**0.9043**	0.5138	0.9623	0.9294

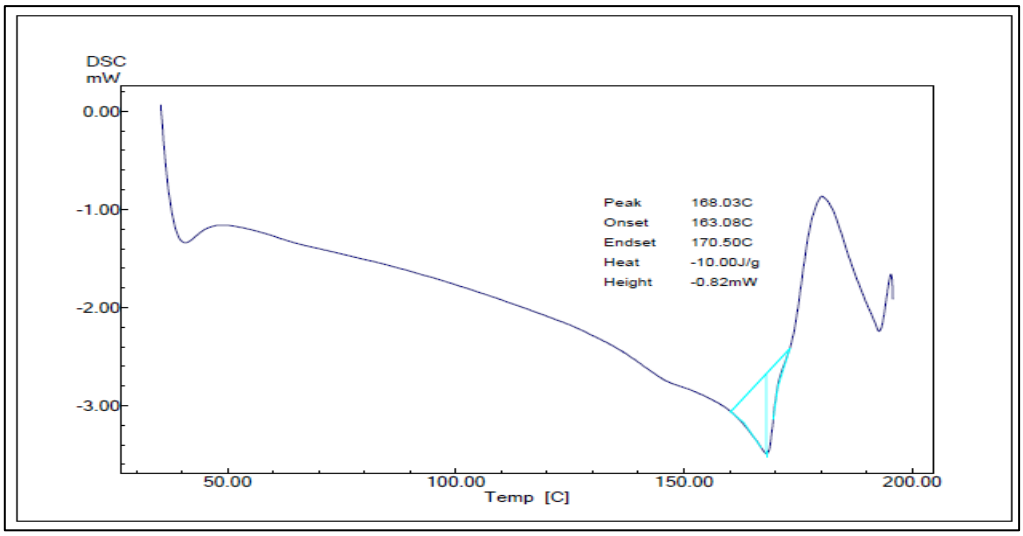

Fig. 9: DSC thermogram of microsponge formulation batch 3

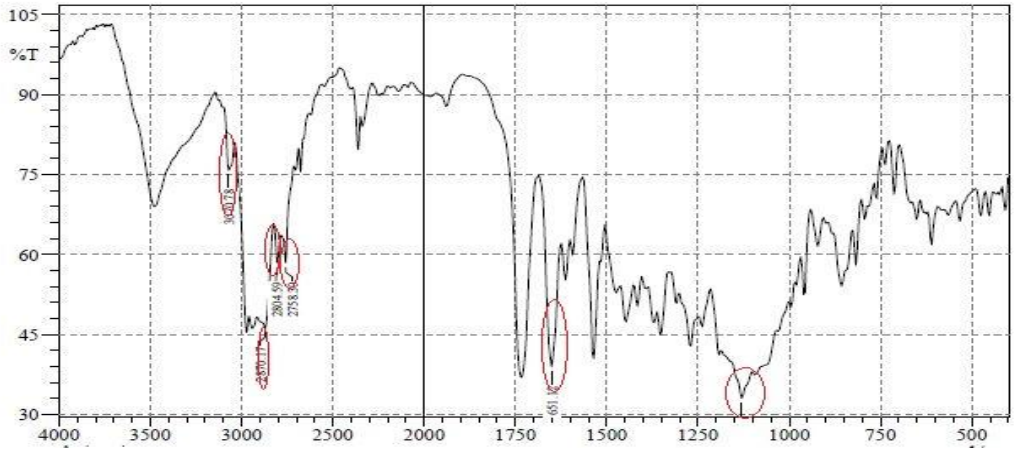

Fig. 10: FTIR analysis of Microsponge formulation batch 3

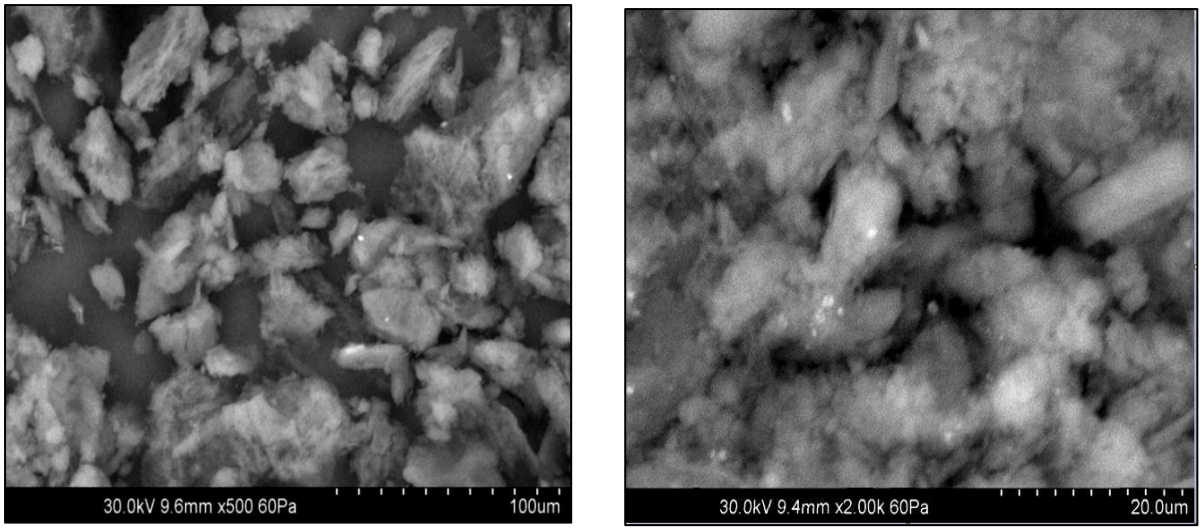

Fig. 11: SEM analysis of microsponge formulation batch 3

Table 5: Results of optimised batch B3

S. No.	Evaluation parameter	Results
1	Drug content	21.28 ± 1.23 (85.21%)
2	Encapsulation efficiency	74.88 ± 2.74%
3	Mean particle size	385.9nm
4	Production yield	39.77%
5	Dissolution and drug release kinetics	100.07% DR in 12 hrs. with R^2 =0.9775 and N=0.8088 (non fickian transport diffusion mechanism)
6	DSC	168.03ºC
7	SEM	Roughly spherical and having porous structure.

CONCLUSION

Microsponges of Risperidone has been developed using Quasi Emulsion Solvent Diffusion method to provide a control release action to treat schizophrenia, mixed and manic states associated with bipolar disorders. Drug content and encapsulation efficiency for optimised batch was found to be 85.21% (i.e. 21.28±1.23% with respect to theoretical drug content) and 74.88±2.74% respectively. Production yield was 39.77%. Mean particle size was observed as 385.9nm. Drug release was obtained up to 100.07% in 12 hrs with R^2 =0.9775 and N=0.8088 showing non fickian transport diffusion mechanism. SEM photographs showed roughly spherical structure having porous surface. Increase in drug-polymer ratio has been found to result as increase in production production yield; while drug content, encapsulation efficiency and percent drug release were found to be decreased. Concerning polymer type, ethyl cellulose significantly increased the drug entrapment efficiency when compared to Eudragit RS 100 but drug release was found to be decreased. Formulation containing both Ethyl cellulose and Eudragit gives better drug release and encapsulation as compared to their single use in formulation. Increased viscosity of internal phase reduces the drug mobility outside the formed droplets, and hence entrapping the higher amount of drug. Concerning the PVA concentration, the negative influence of PVA concentration used on the entrapment efficiency of drug may be attributed to the non-ionic nature of the emulsifier. The molecules may associate away from the oil water interface at higher concentration forming an alternative hydrophobic region which can dissolve some portions of the drug resulting in a reduction of the entrapment efficiency. Therapeutically effective concentrations can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Concerning the effect of formulation variables like drug:polymer ratios, inner phase solvent amount, stirring time and speed on Entrapment efficiency, Drug Content, Particle Size and drug release further attempts have made to increase production yields.

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