IJBPAS, August, 2022, 11(8): 3657-3666

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

PREPARATION, CHARACTERIZATION AND EVALUATION OF RISPERIDONE CONTROLLED RELEASE MICROSPHERES BY USING SOLVENT EVAPORATION TECHNIQUE

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Received 15th July 2021; Revised 20th Aug. 2021; Accepted 6th Nov. 2021; Available online 1st Aug. 2022

https://doi.org/10.31032/IJBPAS/2021/11.8.6290

ABSTRACT

Back ground: It is a challenge to provide the constant drug concentration in blood there by increasing the patient compliance it can be overcome by the microspheres.

Objective: The primary objective of the research work was to prepare, characterize and evaluate controlled release microspheres of risperidone.

Method: The method used for preparation of risperidone microspheres is by using non-aqueous solvent evaporation technique to facilitate the delivery of the drug at a predetermined rate for a specific period of time.

Results: All the formulated microparticles were subjected to various evaluation parameters such as particle size analysis, micrometric properties, drug entrapment efficiency, percentage drug loading, percentage yield and *in vitro* drug release study. The compatibility of the drug and polymers was confirmed by physical compatibility study, fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC). The formation of the most optimized batch of the microsphere (F9) was confirmed by scanning electron microscopy (SEM), DSC, FTIR.

Conclusion: As a result, the current work demonstrates the successful formulation of controlled release microspheres of risperidone using the solvent evaporation method and

appropriate polymers such as hydroxy propyl methyl cellulose and ethyl cellulose. This study has been a satisfactory attempt to formulate a micro-particulate system of risperidone with a view of controlled delivery of the drug.

Keywords: Risperidone, Microspheres, Hydroxy propyl methyl cellulose, Ethyl cellulose

INTRODUCTION

The design of innovative delivery systems for the regulated release of medications and their distribution at the intended spot in the body to reduce side effects and enhance therapeutic efficacy of drugs is one of the most demanding areas of pharmaceutical research **[1-3]**. The basic principle behind the controlled drug delivery system is to enhance the biopharmaceutic, pharmacokinetic, and pharmacodynamic properties of a drug in such a way that its efficacy is optimised by reducing side effects, dose frequency, and curing the disease in a short period of time by administering a small amount of drug via the most appropriate route **[4]**. Controlled drug delivery by encapsulating the drug inside the polymeric carriers has achieved great progress in the last two decades. A steady-state plasma concentration can be achieved by this system. It also enhances the drug release and decreases side-effects by drug localization at the site of action and by controlling the drug release **[5]**. Microsphere, as carrier for drug is one of the various approaches of drug delivery which maximizes the drug concentration at the target site **[6]**. Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles. It can also be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level with particle size range of 1-100 µm **[7, 8]**. Risperidone is a second-generation antipsychotic medication used to treat a number of mental health disorders including schizophrenia, bipolar mania, psychosis, or as an adjunct in severe depression **[9-11]**. D2 dopaminergic receptors are transiently inhibited by risperidone, reducing dopaminergic neurotransmission, therefore decreasing positive symptoms of schizophrenia, such as delusions and hallucinations. Risperidone binds transiently and with loose affinity to the dopaminergic D2 receptor, with an ideal receptor occupancy of 60-70% for optimal effect **[12-16]**. The rationale behind this study was to prepare the microspheres of risperidone encaps-ulated in the Hydroxy propyl methyl cellulose, Ethyl cellulose, Tween80 and Dichloro methane polymer to control the

release of the drug. HMPC pH independent whereas ethyl cellulose is a pH-dependent polymer. In addition, the drug release kinetics for the formulations developed was also evaluated.

MATERIALS AND METHODS

Materials:

Rispiridone was generously gifted by Central Drug Laboratory, Kolkata, India. Polymers like Hydroxy propyl methyl cellulose and ethyl cellulose were purchased from Merck chemicals Germany. Tween 80 from Lobachemie, Mumbai. The pure dug was of standard quality complying with official monographs. All the chemicals used for the analysis were of analytical grade complying with the official monograph. Deionised water (distilled) was used throughout the experimental procedure.

Method:

Initially, the risperidone and its physical mixture with polymers were white in color. Stability study between the drug and the polymer was conducted after the 15th and 30th day. No visible interaction between the drug and polymer was noticed. According to a previous study, change in temperature and humidity may lead to the physical changes. So, proper storage conditions were maintained for 30 days.

Preparation of risperidone microspheres:

Risperidone loaded EC/HPMC microspheres were prepared by solvent evaporation method using water as a continuous phase. Various concentrations of EC (0.2-2.0 gm) were first dissolved in 50 ml dichloromethane (DCM) at room temperature and 200 mg risperidone was added to it. The mixture was sonicated for 20 minutes to form uniform dispersion of drug in polymers. This solution was poured into 400 ml of pure water previously containing various concentrations of dissolved HPMC (0.2-1.8 gm) and 0.5% tween 80. DCM was removed by stirring at 1,000 RPM at 20°C for 1 hour. After the removal of DCM, microspheres were collected on filter paper (Whatman filter paper No 40) by filtration method. These collected microspheres were washed 3 times with pure water and dried in a vacuum silica desiccator at room temperature until a constant weight of microspheres was achieved. This ensured the removal of any trace solvent left in the formulated microspheres. All formulations were prepared at least 3 times and resulting batches were batches and composition of risperidone microspheres were shown in **(Table 1)** were analysed for further characterization.

Construction of standard graph:

Preparation of stock solution:

100mg of the pure drug was weighed and transferred to a 100ml volumetric flask, 50ml of pH 7.4 phosphate buffer was added to the above flask and dissolved, the

volume was made up with the pH 7.4 phosphate buffer.

Preparation of sample solution:

The average weight of the tablets were determined by weighing 10 tablets and these were powdered. Tablet powder equivalent to 2mg of risperidone was weighed and transferred to a 100ml volumetric flask. About 20ml of pH 7.4 phosphate buffer was added and sonicated for15 min for complete dissolution of drugs, the volume was made up with pH 7.4 phosphate buffer and mixed well, and then the above solution was filtered through Whatmann filter paper. Dilutions were made with 7.4 Phosphate buffer to attain a concentration of 4g/ml **(Table 2, Figure 1)**.

Table 1: Composition of Risperidone microspheres

Composition (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	1	1	1	1	1	1	1	1	1
Ethyl cellulose	40	80	80	120	140	120	160	160	200
Hydroxyl propyl methyl cellulose	100	60	140	20	20	180	60	140	100

Table 2: Standard curve

Concentration (µg/ml)	Absorbance
2	0.0799
3	0.1101
4	0.1519
5	0.198
6	0.232

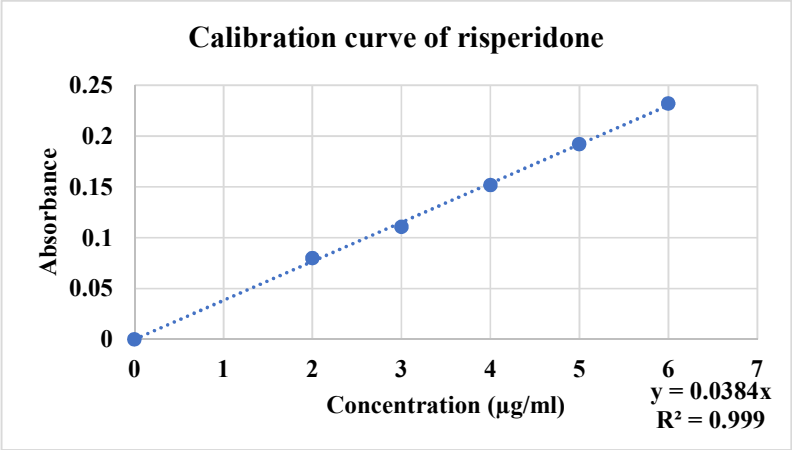

Figure 1: Calibration curve of risperidone

RESULTS AND DISCUSSIONS

Drug-polymer compatibility study

Physical compatibility study initially, the risperidone and its physical mixture with polymers were white in color. Stability study between the drug and the polymer was conducted after the 15th and 30th day. No visible interaction between the drug and polymer was noticed. According to a previous study, change in temperature and humidity may lead to the physical changes. So, proper storage conditions were maintained for 30 days (**Table 3**).

Determination of particle size of microspheres:

All the microspheres obtained from non-aqueous solvent evaporation technique were discrete and spherical in shape. The optical microscopic study of particle size distribution revealed that the microspheres were uniform in size in each formulation with average diameter ranged from 90.01±3.00-130±4.16 µm. The particle size was maximum for the F8 batch with a maximum concentration of hydroxy propyl methyl cellulose and ethyl cellulose. According to a previous study, it was reported that the particle size increased with increase in ethyl cellulose concentration. It was shown in **(Table 4)**.

Determination of percentage drug entrapment efficiency:

The percentage drug entrapment efficiency ranged from 36.24% to 95.07%. The effect of the combination of the polymers over encapsulation efficiency was convincing. The entrapment efficiency was found to be abruptly increasing when a combination of polymers was used and the maximum entrapment efficiency of 83.56% was noted for the batch F4 with a high drug-polymer ratio of 4:2 containing a combination of hydroxy propyl methyl cellulose and ethyl cellulose. This ratio of polymers was found to be efficient of encapsulating maximum drug than any other batches. An increase in the concentration of polymer in a fixed volume of organic solvent resulted in an increase in encapsulation efficiency .It was shown in **(Table 4)**.

Determination of percentage drug loading:

The percentage drug loading ranged from 35.52% to 94.50%. Higher drug loading was observed in F8 is 88.95% containing a combination of hydroxy propyl methyl cellulose and ethyl cellulose in the ratio 4:2. A higher percentage of loading was obtained by the addition of ethyl cellulose polymer and by increasing the amount of polymer with respect to the drug. A study reported that various factors such as the drug to albumin ratio, the concentration of surfactant, stirring rate of the emulsion and average size of microspheres could affect drug loading. It was shown in **(Table 4)**.

Determination of percentage yield:

Percentage yield of all the formulations prepared from solvent evaporation technique was found in the range 55.67 to 80.09 % which is sufficiently high. As experimental result revealed percentage yield value was directly related to polymeric concentration rather than the combination of polymers used. According to a previous study, as the polymer concentration increased, percentage inverse also increased. It was shown in **(Table 4)**.

Rheological properties:

The angle of repose, bulk density, tapped density; Carr's index and Hausner's ratio

were determined to assess the flow-ability of the prepared microspheres.

Angle of repose:

It was measured by fixed funnel standing method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured it was calculated and tabulated **(Table 5)**.

Bulk density:

Apparent bulk density (ρb) was measured by pouring the pre-weight (M) blend into a graduated cylinder. The bulk volume (Vb) of the blend was determined **(Table 5)**. Then the bulk density was calculated by using the formula: $\rho_{b=}\frac{M}{V_b}$

Tapped density:

The measuring cylinder containing a known mass (M) of the blend was tapped for a fixed time, and the minimum volume (V_t) occupied in the cylinder was measured **(Table 5)**.

Carr's index:

Carr's index of the powder was determined for the determination of flow of the powder **(Table 5)**. In Carr's index, the value below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicates poor flow-ability.

Hausner's ratio:

It gives information about flow-ability of the powder. It is determined by comparing the tapped density to the bulk density **(Table 5)**. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

In vitro drug release:

In vitro release studies were performed by using USP-II type dissolution apparatus (paddle type). An accurately weighed sample (75 mg) of microspheres was suspended into 900 ml of phosphate buffer (pH 7.4) maintained at a temperature of 37 °C±0.5 °C and stirred at a speed of 100 rpm (round per minute). At predetermined time intervals, a 5 ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37 °C. The absorption of the filtered withdrawn sample was measured by UV spectrophotometer (Shimadzu 1700, Japan) with suitable dilution and the corresponding concentration was determined from the respective calibration curve. The temperature was maintained at 37 °C throughout the studies.

Scanning electron microscope (SEM):

Scanning electron microscopy was carried out to study the morphological characteristics of risperidone microspheres of F9 formulation batch. It was carried out by sprinkling the microspheres on one side

of an adhesive stub. The dried microspheres were coated with gold (100 Å) under an argon atmosphere in a gold coating unit and scanning electron micrographs (JEOL MAKE UK; MODEL-JSM 6360) were observed **(Figure 2)**. The formulated microsphere were smooth surface. They are not poses any porous nature. Moreover the formed microsphere were mostly spherical shape.

Differential scanning calorimetry (DSC): The DSC thermogram of pure drug and formulation batch (F9) was generated and investigated on a Perkin Elmer (Singapore); MODEL– Pyris diamond TG/DTA. A sample weight of 10±2 mg was used in each experiment. The samples were heated from 30 °C to 400 °C at a heating rate of 10 °C/min in the nitrogen atmosphere (flow rate 150 ml/min) to investigate the presence of additional peaks or absence of peaks indicating the uniform dispersion of drug in the polymer **(Figure 4)**. Absence of primary peak of the drug showed that drug are well encapsulated in microspheres.

Fourier-transform Infra-red spectroscopy (FTIR): The pure drug of risperidone showed sharp characteristic FTIR peak at 2939.08 cm-1 because of the stretching of (-OH) groups (Carboxylic Acid), while, peak at 2939.08 cm-1 also showing the (–C-H) stretching vibration. The peak at 1642.33 cm-1 indicated (C=C) stretching's vibrations due to the presence of aromatic ring/alkene which is completely substituted , peaks at 1531.52 cm-1 and 1349.33 cm-1 could be suggested to (–CH2) scissoring and (–OH) bending vibration, respectively, peak at 1150 cm-1 indicated the presence of (–CH-OH) group. The peak at 1128 cm-1 indicated (–CH-O-CH-) stretching. It shows that there was no alteration in the properties of the drug and polymers during the formulation. Hence the drug and polymers were compatible with each other**.** The IR spectrum was recorded using an FTIR spectrophotometer by the ATR method. The spectra obtained for risperidone and formulation batch (F9) were compared **(Figure 4)**. In this method peak of the pure drug was matched with that of the formulations in the range of 4000-400 cm-1 for 100 scans.

Table 3: Physical compatibility studies

Composition	Description		
	Initial colour	After 15 days	After 30 days
Risperidone	White	No change	No change
Risperidone and hydroxy propyl methyl cellulose	White	No change	No change
Risperidone and ethyl cellulose	White	No change	No change

Table 4: Determination of particle size

Formulation code	Average particle size(µm)	%Drug entrapment efficiency	% Drug loading	% Yield
F1	102.34±4.58	36.24±1.03	35.25± 0.57	55.67± 0.34
F2	92.05±3.35	47.92 ± 0.44	46.75± 0.67	63.34±0.28
F3	101.26±4.16	60.25± 0.92	59.03 ± 1.03	70.00±0.62
F4	100.56±3.05	83.56± 0.66	82.30± 0.45	74.00 ±1.15
F5	94.62±2.00	45.69± 1.06	44.45± 0.64	56.88±0.64
F6	95.64±2.48	53.72± 0.43	52.45± 0.55	64.92±1.10
F7	95.01±4.42	67.45± 0.33	66.84± 0.72	72.36± 0.55
F8	90.01±3.00	89.52± 0.25	88.95± 0.89	76.02 ±0.82
F9	94.72±2.64	39.65± O.69	38.10 ± 0.99	58.65 ±0.98

Table 5: Rheological characteristics of Angle of repose risperidone formulations F1 to F9

Formulation code	Angle of repose(^{0})	Tapped density (g/cm^3)	Bulk density (g/cm^3)	Carr's Index	Hausner's ratio
F1	30.10±2.27	0.76±0.007	0.66±0.003	13.15±0.36	1.15±0.072
F2	32.24±1.16	0.76±0.007	0.66±0.003	13.15±0.36	1.15±0.072
F3	31.33±3.13	0.77±0.007	0.65±0.001	15.58±0.14	1.18±0.010
F4	33.42±1.14	0.75±0.015	0.67±0.013	10.66±0.52	1.11±0.004
F5	32.37±1.15	0.73±0.014	0.65±0.001	10.95±0.66	1.12±0.002
F6	30.12±3.32	0.76±0.007	0.67±0.013	11.84±1.03	1.13±0.008
F7	35.66±3.02	0.79±0.002	0.68±0.007	13.92±0.44	1.16±0.001
F8	34.69±2.49	0.75±0.005	0.66±0.003	12.00±0.59	1.13±0.004
F9	32.40±1.98	0.77±0.007	0.67±0.013	12.98±0.72	1.14±0.020

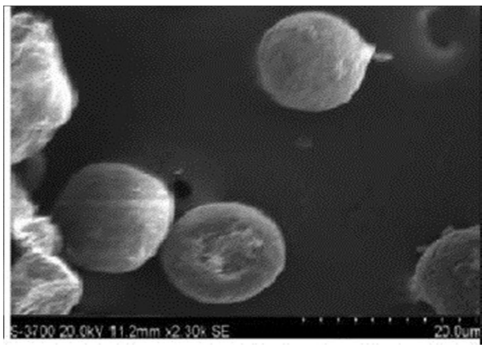

Figure 2: Scanning electron micrograph

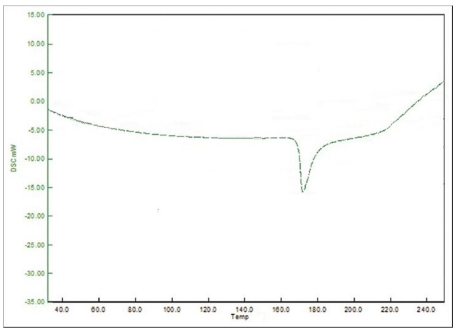

Figure 3: DSC thermograms of risperidone and formulation F9 microspheres

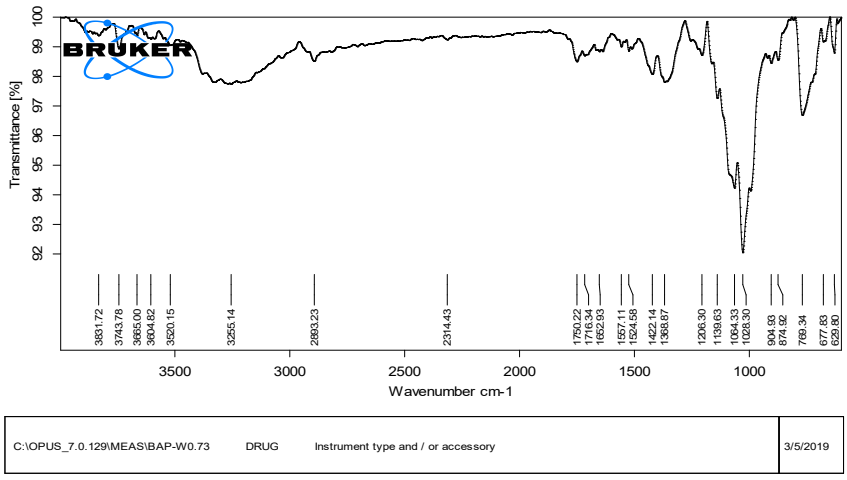

Figure 4: FTIR spectra of risperidone and formulation F9 microspheres

CONCLUSION

The present work, therefore, shows the successful formulation of controlled release microspheres of risperidone by the solvent evaporation method using hydroxy propyl methyl cellulose and ethyl cellulose as suitable polymers. This study has been a satisfactory attempt to formulate a micro-particulate system of risperidone with a view of controlled delivery of the drug. In the formulation, the combination of cost-effective and bio- compatible polymers of hydroxy propyl methyl cellulose and ethyl cellulose had been successfully used and there is a scope of scale-up of the batches to the commercial level. Physical compatibility study, FTIR and DSC studies used for drug-polymer compatibility study confirmed the absence of any physiochemical interaction between the drug and polymers. The formulation was found to be efficient with good percentage entrapment efficiency, percentage drug loading and percentage yield. The surface structure, particle size and flow analysis revealed that the microspheres showed good flow and pack- ability, indicating that it can be successfully handled and filled into a capsule dosage form. *In vitro* drug release showed a prolonged and controlled release of risperidone. The drug release was found to be polymer concentration dependent. SEM analysis showed a rough and porous surface with the spherical appearance of microspheres. FTIR studies showed that risperidone did not undergo any chemical changes while forming the microspheres. DSC thermograms revealed that the drug particles were dispersed uniformly at the molecular level in the polymer matrix. Hence, the controlled release microsphere formation of risperidone may provide a convenient dosage form for achieving best performance regarding flow, drug entrapment, and release. Further, their potential to improve the bioavailability of risperidone in human needs to be investigated in further studies.

ACKNOWLEDEGMENT: I am grateful to Mr. Vasu Naik for guiding me to do the research work and very grateful to Hindu College of Pharmacy, Amaravati road, Guntur for providing support, facilities and guidance.

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