Open access Journal International Journal of Emerging Trends in Science and Technology
IC Value: 76.89 (Index Copernicus) Impact Factor: 4.219 **DOI:** https://dx.doi.org/10.18535/ijetst/v4i8.03

Mucoadhesive Microspheres Based Formulation Development of Ziprasidone Hydrochloride for Nasal Delivery

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Abstract
The most important criteria for developing novel drug delivery system are to achieve clinical efficacy. Mucoadhesive polymer like chitosan can be employed to increase the residence time of formulation in the nasal cavity. The study was undertaken to develop chitosan based mucoadhesive microsphere of Ziprasidone Hydrochloride (fifth generation antipshychotic) as simple w/o emulsification-cross linking process using liquid paraffin as external phase.Ten different formulations were developed. Results show that as the concentration of polymer increases it affects the particle size, production yield, encapsulation efficiency, swelling index, in-vitro mucoadhesion and in-vitro drug release of mucoadhesive microspheres. The in vitro mucoadhesion of microspheres was investigated using freshly isolated goat nasal mucosa. The mucoadhesion for M0, M1, M2, and M9 was tested. The Mucoadhesion property was satisfactory. The M2 exhibited lowest mucoadhesion of 68.9%, and M0 displayed highest mucoadhesion of 87.5%. The In Vitro release studies it revealed that 84.1% of drug release from formulation M1 at 7hrs. The 50% of the drug was released from the formulation M2 and 70.67% from formulation M9.This formulations were further used for SEM for particles size analysis, mucoadhesion test and in-vitro drug release. The In-vitro % drug release data suggest that the maximum and sustained drug release was obtained for formulation M1. Conclusively, the present study showed that Ziprasidone hydrochloride chitosan microspheres can deliver intanasally which can improve the therapeutic outcome for the Epileptic seizure.

Keywords: - Drug entrapment efficiency, In-vitro mucoadhesion study, Ziprasidone hydrochloride, Mucoadhesive microspheres, Residence time

1. Introduction

Nasal drug delivery is increasingly important as an alternative to the oral and parenteral route for systemic drug delivery. There has been increasing interest in using the nose as a route for an administration of systemically active drugs. There are number of research and review articles on nasal drug delivery. The direct drug transport into the systemic circulation, thereby avoiding hepatic first-pass metabolism and irritation of gastrointestinal membrane [1,2]. Also nasal route is non-invasive, therefore, reduced risk of infection, ease of convenience and self-medication resulting in improved patient compliance [3]. Although nasal administration of drugs has many advantages, it is usually limited by the specific nasal morphological and physiological characteristics. One of the most important is nasal mucociliary clearance that limits the time allowed for drug absorption to occur [4, 5]. Intranasal delivery is suitable for the local and systemic delivery of diverse therapeutic compounds. Among the non-invasive routes, nasal administration offers promising potential as a viable alternative for the delivery of some drugs. Recently, microsphere technology has been applied in designing formulations for nasal drug delivery [6]. The primary rationale behind selection of microspheres is to provide a better chance for the drug to be absorbed by allowing a more intimate

and prolonged contact between the drug and the mucosal membrane [7]. Ziprasidone hydrochloride was the fifth a typical antipsychotic for the treatment of schizophrenia, and the intramuscular injection form of ziprasidone is approved for acute agitation in schizophrenic patients[8]. Chitosan is a natural polymer that has mucoadhesive properties because of its positive charges at neutral pH, which enable an ionic interaction with the negative charges of sialic acid residues on the mucus [9, 10]. This highly mucoadhesive characteristics of chitosan provide a longer contact period for drug transport through nasal mucosa and prevents the clearance of the formulation via mucociliarly clearance mechanism [11]. Therefore, chitosan microspheres have been extensively evaluated as a drug delivery system [12,13,14,15]. The objective of the present study is to formulate and evaluate mucoadhesive microspheres of Ziprasidone hydrochloride that will increase residence time in the nasal cavity and at the same time increase the local of absorption of drug and reducing systemic side effects and also to develop unique controlled delivery system for patients suffering from allergy and rhinitis. The microspheres were prepared by emulsification cross linking method in different ratio by using mucoadhesive polymer, chitosan.

2. **Materials and methods**

2.1 Reagents and chemicals

Ziprasidone hydrochloride was received as a kind gift from CADILA Pharmaceutical Pvt. Ltd., Ahmedabad, Gujarat, India. Chitosan was provided by Chemika Biochemika Reagents, India, liquid paraffin (Kasliwal Bros, Indore, India). All other ingredients used were of analytical grade and were used without further purification. Spectrophotometric studies were carried out by using double-beam UV-spectrophotometer, Shimadzu, Pharma Spec 1700, Kyoto, Japan.

2.2 Identification of Ziprasidone Hydrochloride and Chitosan

Identification of Ziprasidone Hydrochloride by FTIR

The bulk drug samples were identified by matching their IR spectra. The instrument used for this purpose was, FTIR-8400 S, Shimadzu Corporation (Japan). Further, confirmation of drugs was done by observing their melting points (by Thiele's tube method). The observed melting points of these drugs were matching with the reported melting points[16].

Determination of melting point of Ziprasidone Hydrochloride

Melting point of pure Ziprasidone Hydrochloride was found to be 307^0C[17].

Identification by thermal analysis (DSC)

Melting point of Ziprasidone Hydrochloride was confirmed with its individual DSC thermogram and was found satisfactory[16,18].

2.3 Identification of Drug by UV spectrophotometry

Assay of Ziprasidone Hydrochloride by UV spectrophotometry

The Ziprasidone Hydrochloride was identified by UV spectroscopy method. The Ziprasidone Hydrochloride exhibited maximum absorption at 521 nm. After scanning the λ_{max} of the Ziprasidone Hydrochloride with methanol it matches with that of the standard λ_{max} given in the articles (521nm). This wavelength was considered as λ_{max} for samples and all the observations by UV spectrophotometer to calculate the amount of drug was taken at this wavelength.

Preparation of Calibration Curve of Ziprasidone hydrochloride

The standard stock solution was prepared by dissolving 50 mg Ziprasidone Hydrochloride in 30ml methanol by sonication for 10 minutes and volume was made up to the 50 mL mark using methanol. From the standard stock solution (1000 µ g/ml), different aliquots were diluted with distilled water separately to prepare a series of concentrations from range 2-10 µg/ml. The standard solution of Ziprasidone Hydrochloride (10 µ g/ml) was scanned in the range of 600-400 nm against distilled water as a blank. The λmax of

this solution was found to be 521 nm. Absorbance of all solutions was measured at 284 nm against distilled water as a blank. The calibration curve was prepared by plotting absorbance versus concentration of drug[16,17].

2.4 Preparation of mucoadhesive microspheres

Ziprasidone Hydrochloride loaded chitosan microspheres were prepared by simple w/o emulsification-cross linking process using liquid paraffin (heavy and light, 1:1) as external phase. Firstly, Ziprasidone Hydrochloride was dissolved in 2ml of acetone and sonicated it till a clear solution is obtained. Chitosan was dissolved in 2% aqueous acetic acid solution by continuously stirring and then solution of chitosan was added in the drug solution with continuous stirring at constant speed until a homogeneous solution was obtained. This solution was added slowly to liquid paraffin (heavy and light, 1:1) containing 0.2% (w/v) of SLS as stabilizing agent under constant stirring at 1800 rpm speed for 15 min using a high speed mechanical stirrer. To this w/o emulsion, GA was added slowly and stirring was continued for 2 h. The hardened microspheres were separated by vacuum filtration and washed several times with hexane to remove oily part. Finally, microspheres were washed with distilled water to remove unreacted GA. The microspheres were air dried for 24 h and then stored in desiccator until further use[19,20].

To investigate the effect of different formulation and process variables on particle size, encapsulation efficiency, drug loading etc., various batch of formulations were prepared by varying one parameter and keeping the others constant as given in Table 1.

Table 1: Formulation composition of Ziprasidone hydrochloride mucoadhesive microspheres

F.No.	Drug: Polymer (Ratio)	Aqueous : Oil (Ratio)	GA	SLS	Stirring Rate (rpm)	Cross Linking Time (Hrs)
M0	0:10	10:100	2 ml	0.2%	1800	2
M1	1:9	10:100	2 ml	0.2 %	1800	2
M2	2:8	10:100	2 ml	0.2 %	1800	2
M3	3:7	10:100	2 ml	0.2 %	1800	2
M4	1:9	20:100	2 ml	0.2 %	1800	2
M5	1:9	10:100	1 ml	0.2 %	1800	2
M6	1:9	10:100	2 ml	0.2 %	1200	2
M7	1:9	10:100	2 ml	0.2 %	1500	2
M8	1:9	10:100	2 ml	0.1 %	1800	2
M9	1:9	10:100	2 ml	0.2 %	1800	3

2.5 Characterization of Microspheres

a) Production yield (%)

The production yield of microspheres of various batches were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of microspheres and % production yields were calculated as per the formula mentioned below.[21]

$$PY(\%) = \frac{\text{Amount of Microspheres Wo}}{\text{Amount of Drug + Polymer } W_T} X\ 100$$

Where PY = Production Yield; W_O = Practical mass (microspheres) and

W_T = Theoretical mass (Polymer + Drug).

b) Encapsulation/Entrapment efficiency

To determine the amount of drug encapsulated in microspheres, a weighed amount (50 mg) of

microspheres was suspended into 50 ml of methanol and sonicated for 15 min in order to extract the entrapped drug completely. The solution was filtered through whatman filter paper. 1 ml of this solution was withdrawn and diluted to 50 ml with pH 6.4 phosphate buffer solution. This solution was assayed for drug content by UV spectrophotometer [19] at 284 nm.

Encapsulation efficiency was calculated as:[22]

$$\text{Encapsulation Efficiency}(\%) = \frac{\text{Practical drug content (ED)}}{\text{Theoritical drug content (AD)}} \text{X } 100$$

Where EE= Encapsulation efficiency; ED= Amount of encapsulated drug and
AD= Amount of drug added.

c) Degree of swelling

The swell ability of microspheres in physiological media was determined by swelling them in the PBS pH 6.4.

The swelling ratio (SR) was calculated according to the following equation [23]

$$\propto = \frac{W_S - W_0}{W_0}$$

Where $\propto$ = degree of swelling; W_O = weight of microspheres before swelling and
W_S = weight of microspheres after swelling.

d) External morphological evaluation

Optical microscopy: All batches of microspheres were studied for shape and size by optical microscopy (Olympus Microscope, Olympus Optical Co. Ltd., Japan). The samples were studied in the form of dispersion in paraffin oil.

2.6 In vitro mucoadhesion studies

Mucoadhesion of microspheres was assessed using the method reported with little modification. The in vitro mucoadhesion of microspheres was investigated using freshly isolated goat nasal mucosa. The tissues were cut into the size of 1×1 cm and were mounted onto the glass slide and accurately weighed microspheres (10 mg) were sprinkled on the mucosa. This glass slide was kept in desiccator for 15 min to allow the polymer to interact with the membrane and finally placed in the cell that was attached to the outer assembly at an angle of 45^o. Phosphate buffer solution pH 6.4, previously warmed to 37 ± 5^0C was circulated all over the microspheres and membrane at the rate of 1 ml/min. Washings were collected at different time intervals and microspheres were collected by centrifugation followed by drying at 50^0C. The weight of washed out microspheres was determined and percent mucoadhesion was calculated by following formula(23):

$$\text{Mucoadhesion } (\%) = \frac{(W_2 - W_1)}{W_2} \text{ X } 100$$

Where, W_2 = weight of microspheres applied and W_1 = weight of microspheres leached out.

2.7 In-vitro Release Studies

The drug release study was performed using USP XXIV basket apparatus at 37°C ± 0.5°C at 50 rpm using 900 mL of phosphate buffer (pH 6.8) as a dissolution medium as per USP XXVI dissolution. Microspheres equivalent to 10 mg of ZIPRASIDONE HYDROCHLORIDE drug were used for the test. 0.5ml of sample solution was withdrawn at predetermined time intervals, filtered through a Whatmann filter paper, diluted suitably, and analyzed spectrophotometrically. An equal amount of fresh dissolution medium was replaced immediately after with drawl of the test sample. Percentage drug dissolved at different time intervals was calculated at 521.0 nm[24].

In order to investigate the drug release mechanism, the release data were fitted to model representation: zero order as cumulative amount of drug released vs time.[25]

Zero order

$C = K_0 t$

Where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in minutes. A graph of concentration Vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

2.8 Stability Studies

Stability is defined as ability of particular drug or dosage form in a specific container to remain with its physical, chemical, therapeutic and toxicological specifications. Stability tests are the series of tests designed to obtained information on the stability of the pharmaceutical product in order to define its shelf life and utilization period under specified packaging and storage conditions. The purpose of stability testing is to provide information on how the factors such as temperature, humidity and light, and to establish a shelf life for the drug product at recommended storage conditions.

Procedure

From the batches of Ziprasidone Hydrochloride loaded microspheres, formulation M0, M1, M2 and M9, were tested for stability studies. The formulation were divided into 3 sample sets and stored at: 1. 4±1˚C 2. 25±2˚C and60±5%RH 3. 37±2˚C and 65±5%RH After 30 days, the drug release of selected formulations was determined by the method discussed previously in vitro drug release studies and percentage entrapment efficiency was also carried out for the same formulation[26].

3 **Result and discussion**

3.1 FTIR of drug loaded microspheres

FTIR absorption spectra of pure drug, polymer used and the combination of drug and polymers were taken to confirm the identity of the drug and to detect the interaction of the drug with the excipients.The individual FTIR spectra of pure drug and polymer as well as the combination spectra of the drug and the polymer show no significant interaction between Ziprasidone Hydrochloride and chitosan when compared with FTIR spectrum of pure drug. The obtained spectra were shown in the figure 1 to 2.

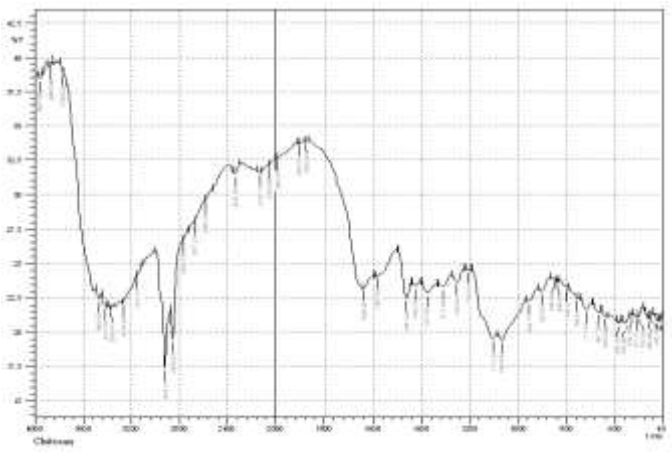


Figure 1:- FTIR spectra of Chitosan

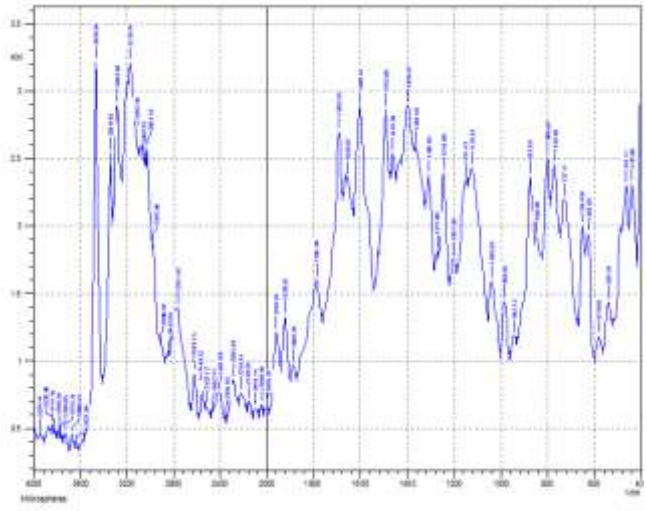
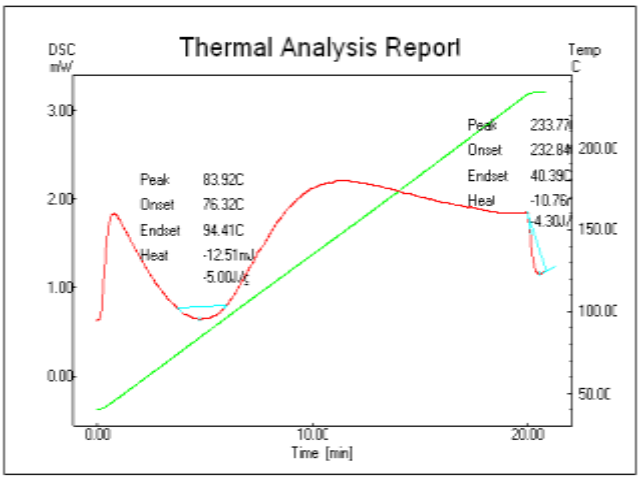


Figure 2:- FTIR spectra of Drug loaded Microspheres

3.2 DSC of drug loaded microspheres

The DSC of drug alone, chitosan alone, blank chitosan microspheres without drug and chitosan microspheres loaded with drug were performed to validate the physical state of the drug in the microsphere. The drug and chitosan depicted endothermic peak at 307.9 ºC and 95.25 ºC respectively. The melting point of pure Ziprasidone Hydrochloride was in the range of 2304 to 306nm and almost near has been found in the DSC thermogram. This confirms that the sample used for experimental studies was pure drug. The blank chitosan microspheres without drug exhibited endothermic peak at 83.92 ºC in figure-3. The chitosan microspheres loaded with drug exhibited endothermic peak at 115.45 ºC so

the chitosan microspheres loaded with drug was investigated in order to obtain information about the physical state of drug in chitosan matrix in figure-4.



. Figure-3: DSC thermogram of Blank Chitosan Microspheres without Drug

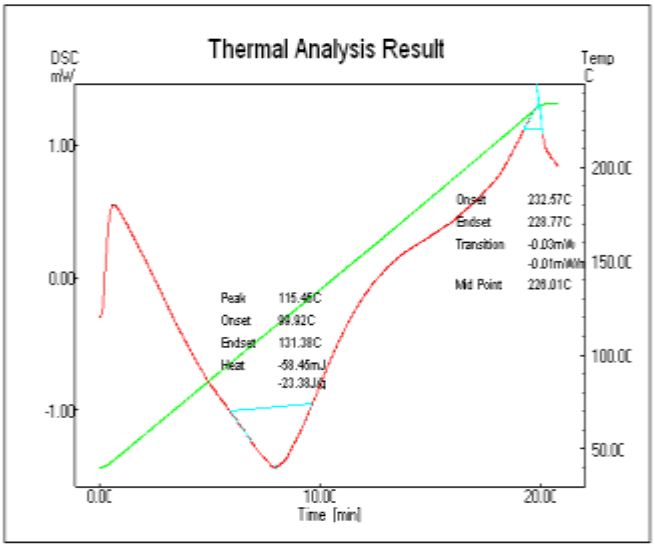


Figure-4: DSC thermogram of Chitosan Microspheres loaded with Drug

3.3 Preparation of Calibration Curve of Ziprasidone hydrochloride

Absorbance of all solutions was measured at 284 nm against distilled water as a blank. The calibration curve was prepared by plotting absorbance versus concentration of drug.

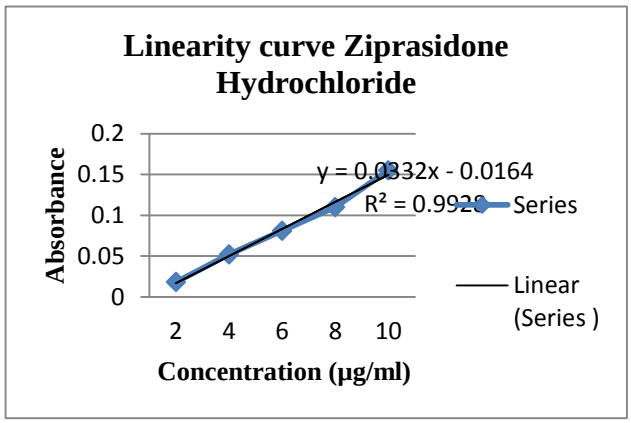
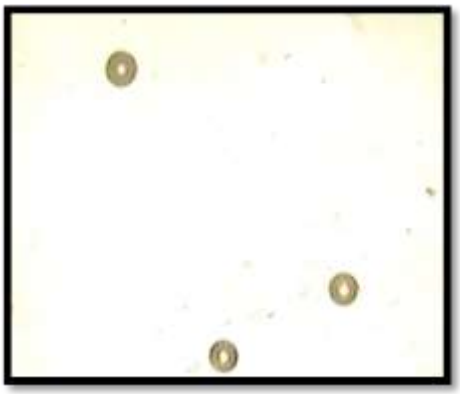


Figure 5:- Calibration curve of Ziprasidone Hydrochloride drug in methanol

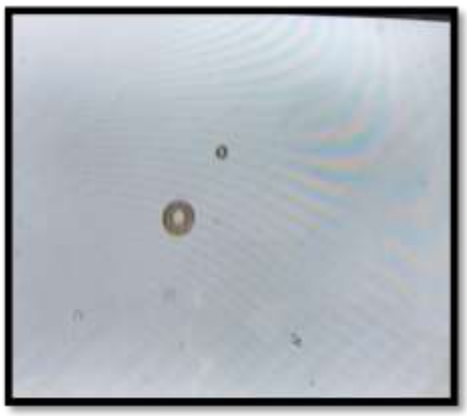
3.4 Optical microscopy

Optical microscopy of drug loaded microspheres depicted irregular geometry in some batches due to which those batches fails to achieve better encapsulation. The findings of optical microscopy suggest that the particle of microspheres of M0 (a), M1(b), M2(c) and M9(d) were satisfactory.

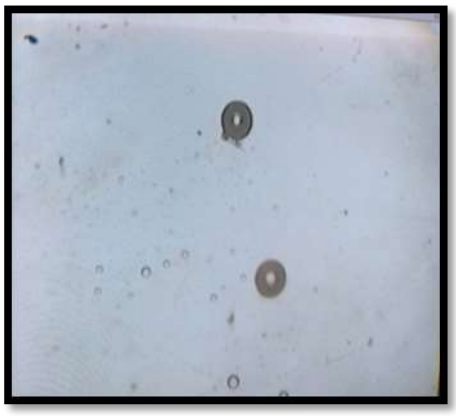
(a)



(b)



(c)



(d)

Figure 6:- Geometrical photographs M0 (a), M1(b), M2(c) and M9(d)

3.5 Production yield (%)

It was observed that as concentration of polymer increases production yield decreases, since increase in polymeric concentration make solution more viscous this was difficult to pour and get sticked on the wall of the beaker. The % production yield of microspheres was found to be maximum for M3 (74.59%) having lowest amount of polymer. Lowest % yield was of formulation M4 (51.56%). Stirring rate also affects production yield.

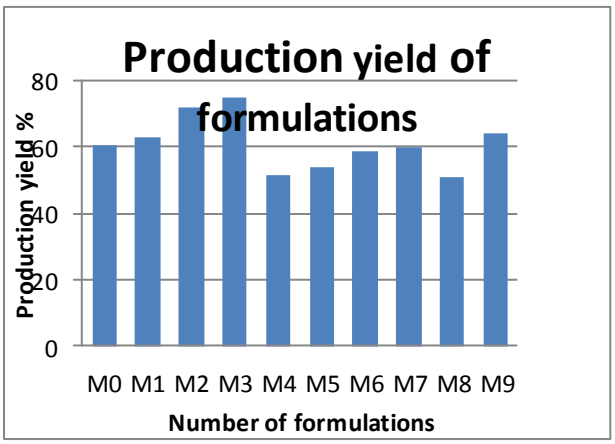


Figure 7:- Representation of Production yield of all the formulations

3.6 Entrapment efficiency (%)

The entrapment efficiencies of drug were recorded in the range of 48.05% to 79% for M1 to M9. The M8 revealed lowest entrapment efficiency of drug i.e. 48.09%, while M1 displayed 79% highest drug entrapment efficiency when compared to other formulations. From results it has been observed that on increasing the polymer ratio the drug entrapment efficiency increases.

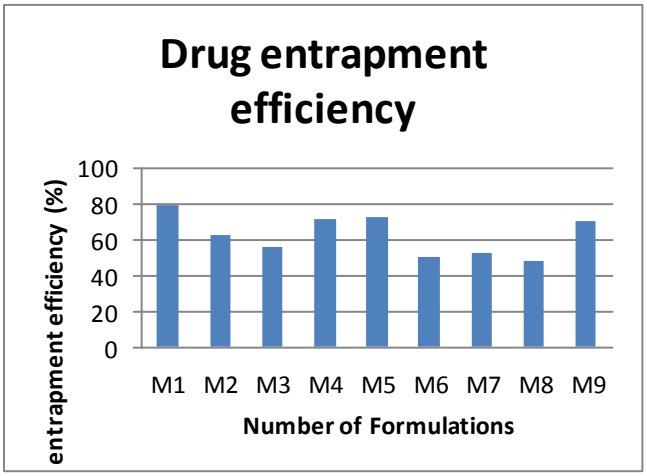


Figure 8:- Representation of entrapment efficinecy of all the formulations

3.7 Degree of swelling index

The degree of swelling was ranged from 0.36 to 1.66% for formulations M0 to M9. The lowest degree of swelling was observed in M3 (0.36%) and the highest degree of swelling was noticed in M0 (1.66%).

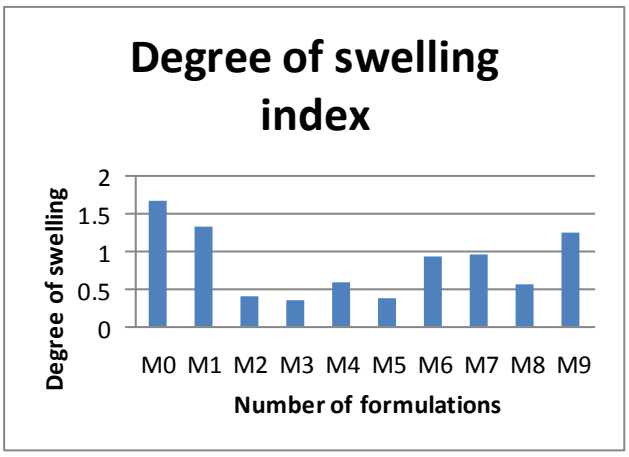


Figure 9:- Represents Degree of swelling of microspheres in all the formulations

The results of the studies revealed that, swelling ratio of the microspheres increased with increasing the ratio of the polymer which could be due to more amount of polymer present in the microspheres that may be responsible for higher swelling.

3.8 Mucoadhesion test or In-vitro wash off test

On the bases of above evalution only four formulations were selected for further tests. The mucoadhesion for M0, M1, M2, and M9 was tested. The Mucoadhesion property was satisfactory. The M2 exhibited lowest mucoadhesion of 68.9%, and M0 displayed highest mucoadhesion of 87.5%.

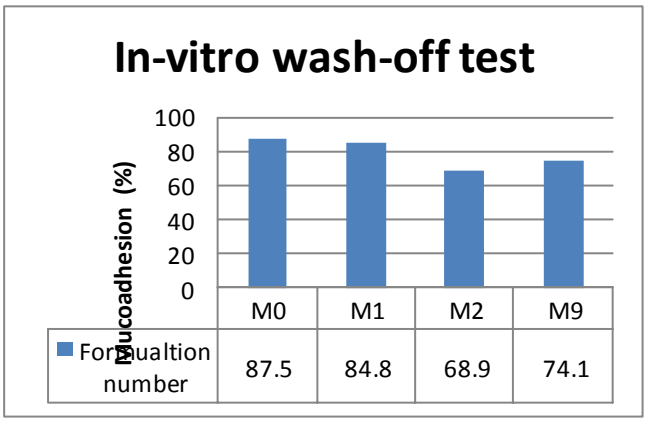


Figure 10:- Representation of mucoadhesion strength of formulation microspheres

The results showed that M0, M1, M9 had satisfactory mucoadhesive strength and could adequately adhere to nasal mucosa. tensile studies performed with ziprasidone hydrochloride loaded microsphere showed that drug/polymer ratio significantly influenced the mucoadhesive properties of the microspheres. Hence high concentration of polymer imparts larger penetration with maximum adhesion Thus, formulation M0, M1 and M9 satisfy the Mucoadhesion.

Morphological characteristics of microsphere by SEM

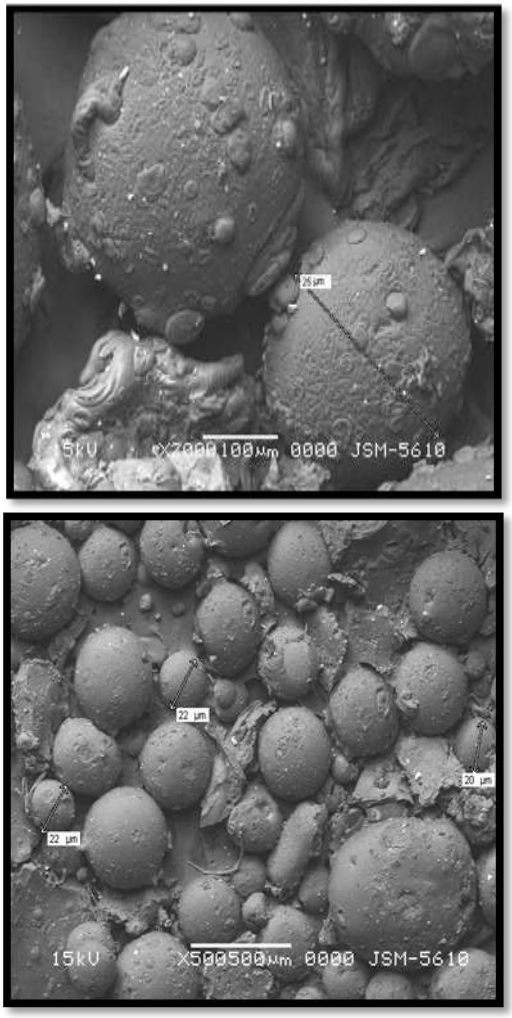


Figure 11 and 12:- Microspheres of formulation M1 and M2 respectively.

Figure 13:- Microspheres of formulation M9

At higher polymer concentration (M1) the microsphere with smooth surface was obtained but at lower polymer concentration (M2)spherical with slightly rough and wrinkled surface of microspheres were obtained .At the higher cross linking time, little furrowed but spherical microspheres with small pits were obtained M9.

Based on the SEM study we continued with M1, M2 and M9 for *in vitro* release study.

3.9 In vitro drug release studies

From the in vitro release studies it revealed that 84.1% of drug release from formulation M1 at 7hrs. The 50% of the drug was released from the formulation M2 and 70.67% from formulation M9.

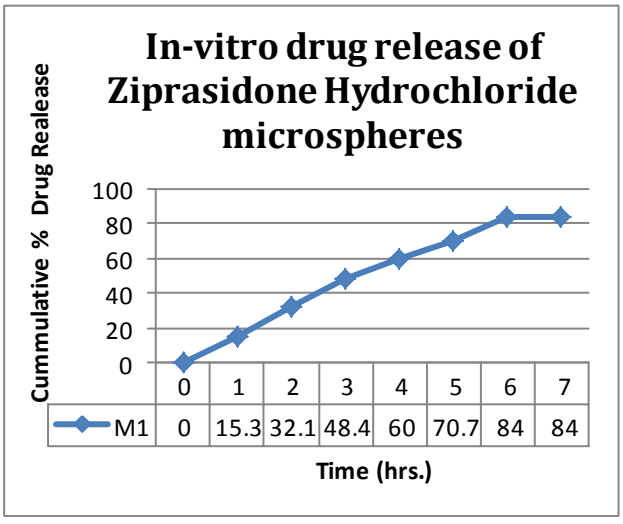


Figure14:- Cummulative drug release of formulation M1

From above finding it has been noticed that on increasing the concentration of chitosan it decreased the drug release from microspheres. The high stirring rate, high concentration of chitosan and GA make the microsphere stiff. This hardness of microsphere decreases the rate of drug release from microspheres. Thus formulation M1 exhibited the sustained release of drug from microspheres in comparison to others.

4. **Conclusion**

Different formulation batches were evaluated for various parameters like production yield, entrapment efficiency, swelling Index and particle geometry determination were found to get a better result for formulation M1, M2 and M9.This formulations were further used for SEM for particles size analysis, mucoadhesion test and in-vitro drug release.

In conclusion, the present study showed that Ziprasidone Hydrochloride chitosan microspheres can deliver intanasally which can improve the therapeutic outcome for the Epileptic seizure.

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