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FORMULATION AND EVALUATION OF ZIPRASIDONE HCL CHITOSAN MICROSPHERES FOR NASAL DRUG DELIVERY

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Keywords:

Ziprasidone HCL, Microspheres, Single Emulsification Crosslinking

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ABSTRACT

In this study, the use of chitosan as a polymer for microencapsulation of Ziprasidone HCL using Single Emulsification Crosslinking technique was investigated. Chitosan was selected as a polymer as it is an attractive material for intranasal drug delivery because of its biocompatibility, biodegradability and non toxicity together with its antimicrobial activity and low immunogenicity. Five different batches of microspheres were prepared by varying the quantities of polymer, Glutaraldehyde and stirring speed of mechanical stirrer. The microspheres were characterized for drug content, percentage yield, encapsulation efficiency, particle size and surface morphology. It was observed that on increasing the quantity of polymer, the mean particle size increases and while increasing the stirring speed of mechanical stirrer, the mean particle size decreases whereas on increasing the glutaraldehyde quantity with increasing time interval, the mean particle size of microspheres increases. The effect of polymer quantity on the *in vitro* release of Ziprasidone HCL microspheres was also discussed. It can be studied that by increasing the polymer quantity, the rate of drug release decreases dramatically.

1. INTRODUCTION

Intranasal Therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. Nowadays many drugs have better systemic bioavailability through nasal route as compared to oral administration [1]. Biotechnological advancement has lead to the development of a large number of protein and peptide drug for the treatment of several of diseases. Oral administration of these drugs is not possible because they are significantly degraded in the gastrointestinal tract or considerably metabolized by first pass effect in the liver. Intranasal drug delivery offers a promising alternative route for administration of such drugs [2]. However, although the oral route remains the most popular for systemic drug administration, low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery [3]. In the last few years, the nasal route has received a great deal of attention as a convenient and reliable method for the systemic administration of drugs, especially those which are ineffective orally and must be administered by injection [4]. The microspheres are characteristically free flowing powders consisting of proteins and synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200µm. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug [5,6]. Ziprasidone was the fifth atypical antipsychotic to gain approval (February 2001) in the United States. It is approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia, and acute mania and mixed states associated with bipolar disorder. The oral form of Ziprasidone is the hydrochloride salt, Ziprasidone Hydrochloride. The intramuscular form, on the other hand, is the mesylate salt [7,8]. Chemically Ziprasidone HCL is a 5-[2-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1,3dihydroindol-2-one hydrate hydrochloride. The Half life of drug is 7 hours and bioavailability is 60%. Thus to achieve maximum therapeutic effect with low risk of adverse effects and to improve patient compliance, a controlled release formulations of Ziprasidone HCL is required.

2. OBJECTIVES

The purpose of the present work was to prepare and evaluate Ziprasidone HCL Chitosan microspheres for nasal drug delivery. Nasal drug delivery system is acceptable for those categories of drugs which are unstable on oral administration as they degrade in G.I.T or

metabolized by first pass effect in liver and it is also beneficial long term therapy. To optimize the various processes and formulation parameters such as drug polymer ratio and stirring speed for maximizing the entrapment and prolonged release. To evaluate the drug content, *in vitro* drug release, drug polymer interactions and surface morphology.

3. MATERIALS AND METHODS

Ziprasidone HCL was procured as a gift sample from Ramdev Chemicals Pvt. Ltd. E-41 & 129. M.I.D.C., Tarapur, Boisar, Distt. Thane. Chitosan was purchased from Hi –Media Labs, Mumbai and liquid paraffin, glutaraldehyde, acetic acid, span 80, acetone, petroleum ether were purchased from S.D Fine Chemicals, Mumbai.

Prepration of Microspheres By Single Emulsification Crosslinking Method

Accurately weighed quantity of chitosan 100 mg was dissolved in aqueos solution containing 1ml acetic acid by stirring overnight on a Mechanical stirrer. Thereafter 25 mg of drug was dissolved in the DMSO and mixed well in polymeric solution using mechanical stirrer. The resulting solution was added drop wise through syringe (needle no: 20) into 40 mL of dispersion medium composed of 1:1 ratio of light and heavy liquid paraffin containing 0.4 ml of span-80 with stirring on mechanical blade stirrer at high speed. After 30 min., glutaraldehyde (1ml) was added and stirring was continued for 5 hours at 2100 rpm. Microspheres thus obtained were filtered and washed 3 times with petroleum ether to remove traces of oil and then they were finally washed with acetone to remove excess amount of glutaraldehyde. The microspheres were then dried at room temperature for 24 hours.

4. CHARACTERIZATION AND EVALUATION OF MICROSPHERES

All formulations having different ratio of drug:polymer were subjected to following evaluation tests

- **Particle Size**

The size of microspheres was measured using a microscope with the help of optical microscope, and the mean particle by means of a calibrated stage micrometer with eye piece micrometer. Calibrate the eye piece micrometer using stage micrometer and find out the length of one division of eye piece micrometer. Prepare the slide by using a small quantity of treated microspheres and mount a drop of glycerin and cover with cover slip. Replace the stage

micrometer with the prepared slide. Measure the diameter of the microspheres by observing the no. of divisions covered by microspheres [9].

- **Surface morphology**

Surface morphology and surface appearance of microspheres before and during degradation studies were examined by scanning electron microscope (FESEM, S-4300, Hitachi, Japan). Samples for SEM were freeze dried, mounted on metals with double sided tape. Pictures were taken and examined for surface morphology and surface appearance of microspheres [9].

- **Percentage yield (% production yield)**

The yield was calculated as the weight of the microspheres recovered from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100.

All the experimental units were analyzed in triplicate (n=3).

The production yield (PY) was calculated by the equation,

$$PY = (Pc / Tc) X 100$$

Where:

Pc - Practical content,

Tc - Theoretical content [10,11].

- **Determination of drug content and entrapment efficiency**

100 mg of microspheres were crushed in glass mortar and pestle and the powdered microsphere were suspended in 100 ml of phosphate buffer 6.8. After 12 hrs the solution was filtered and the filterate was analysed for drug content using UV spectrophotometer at 267nm. All the experimental units were analyzed in triplicate (n=3). The drug loading and entrapment efficiency (EE) were calculated as follows:

$$D.L. = \frac{m'_{\text{drug}}}{m'_{\text{ms}}} \times 100\%$$

$$E.E. = \frac{m_{\text{ms}} \times D.L.}{m_{\text{drug}}} \times 100\%$$

where DL(%) is drug loading or drug content, m'_{drug} (g) is the mass of drug measured in the sample microspheres, m'_{ms} (g) is the mass of the sample microspheres used to determine the drug loading, EE(%) is encapsulation efficiency, m_{ms}(g) is the mass of all the microspheres obtained in each experiment and m_{drug} (g) is the total mass of drug used in each experiment.

- ***In vitro* drug release studies**

In vitro drug release studies were carried out for prepared microspheres by using USP dissolution rate test apparatus-II (37±0.5°C). An accurately weighed amount of microspheres equivalent to 10 mg of the drug were taken. The dissolution medium was phosphate buffer (900ml, pH 6.8) for 8 hrs. 5 ml of the samples were withdrawn at specified time intervals (0, 1, 2, 3, 4, 5, 6, 7, 8, hrs.) and equal volume of fresh medium was replaced immediately. After a suitable dilution, samples were analyzed by UV spectrophotometry. All the studies were carried out in triplicate [12].

- **Release models and kinetics**

Release kinetics can be studied by putting the value in all the equations which are given in the (Table No. 1) [13].

Table No. 1 Equations for different model.

Zero order	$Q_t = Q_0 + K_0 t$
First order	$\ln Q_t = \ln Q_0 + K_1 t$
Higuchi	$Q_t = K_H \sqrt{t}$
Korsmeyer-Peppas	$Q_t / Q_\infty = K t^n$

- **Stability of Ziprasidone HCL Loaded microspheres**

The stability of the Ziprasidone HCL encapsulated in to polymer Chitosan was evaluated (According to ICH guidelines) in a period for 60 days aiming to establish the formulation durability. The microspheres powders were put in to a bottle stored for 60 days at 40±2°C/75RH respectively. The physical properties and drug content were examined periodically. The drug content was assessed by the above mentioned UV-VIS spectrophotometric method [14].

5. RESULTS AND DISCUSSION

The present research was executed in two phases. In the first phase, preformulation study was carried out to characterize the drug and to study drug- excipient compatibility. In the second phase, microspheres were prepared to optimize the polymer and its concentration.

Table No. 2: Ingredients used for drug loaded Chitosan microspheres.

Sr. No.	Ingredients	Quantity				
		F_1	F_2	F_3	F_4	F_5
1.	Ziprasidone HCL	25mg	25mg	25mg	25mg	25mg
2.	Chitosan	50mg	100mg	150mg	200mg	250mg
3.	Glacial Acetic acid	1 ml	1 ml	1 ml	1 ml	1 ml

4.	Liquid Paraffin (Heavy+Light)	40 ml	40 ml	40 ml	40 ml	40 ml
5.	Glutaraldehyde	1 ml	2 ml	3 ml	4 ml	5 ml
6.	Span-80	0.4 ml	0.4 ml	0.4 ml	0.4 ml	0.4 ml
7.	Petroleum Ether	20 ml	20 ml	20 ml	20 ml	20 ml
8.	Acetone	20 ml	20 ml	20 ml	20 ml	20 ml

Table No. 3: Physicochemical parameters of microspheres.

Formulation code	Drug:Polymer ratio	Production yield	Entrapment efficiency	Particle size	Cumulative % drug release*
F1	1:2	70.45± 0.26	89.93 ± 0.23	2.23 ± 0.38	87.08
F2	1:3	71.50 ±1.85	90.40 ± 0.35	2.93 ± 0.19	84.96
F3	1:4	69.44 ±0.29	92.55 ± 0.53	3.18 ± 0.26	81.53
F4	1:5	73.39 ±0.26	87.91 ± 0.19	3.37 ± 0.17	80.31
F5	1:6	75.93 ±0.89	85.89 ± 0.25	4.13 ± 0.48	77.18

*All values are given as Mean ± SD;n=3

Table No. 4: *In-vitro* drug release models for different Ziprasidone HCL microspheres formulations.

Formulation code	Zero order	First order	Higuchi model	Koresmeyer peppas model	
	R^2	R^2	R^2	R^2	'n'
F1	0.987	0.886	0.901	0.973	0.805
F2	0.982	0.922	0.928	0.970	0.725
F3	0.995	0.961	0.936	0.993	0.838
F4	0.993	0.976	0.947	0.998	0.850
F5	0.986	0.982	0.956	0.995	0.832

Table no. 5: Stability studies of formulation F1 at 40 ± 2°C/75 RH.

Sampling intervals (days)	Storage condition (40 ± 2°C/75 RH)
	Drug Content (%age)
01	84.95±0.45
07	84.34±0.23
15	83.74±0.33
21	83.16±0.12
30	82.67±0.56
45	82.09±0.41
60	81.77±0.82

All values are given as Mean ± SD; n=3.

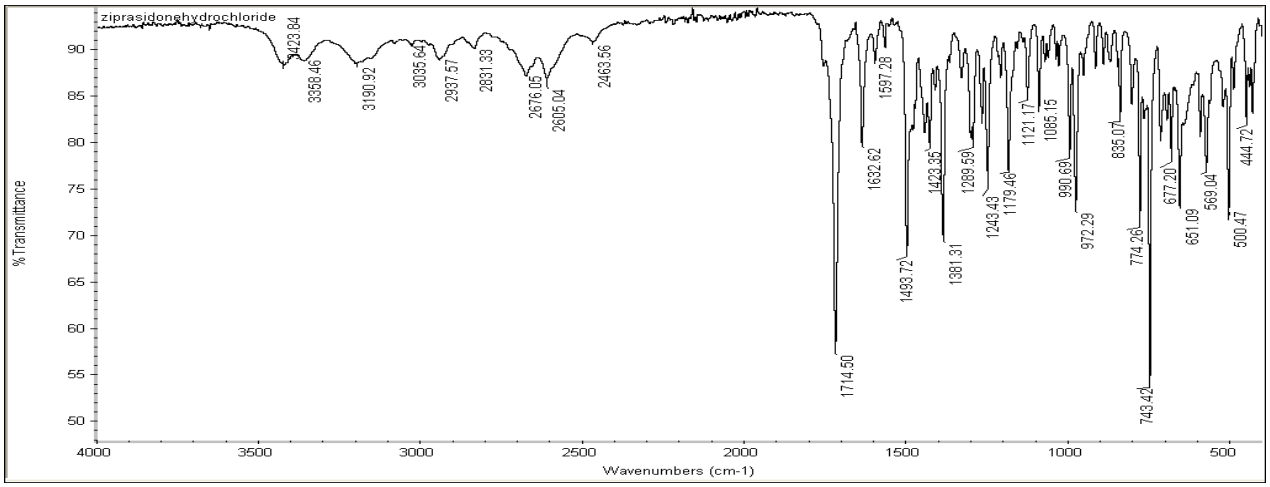

Figure No. 1: FTIR Spectra of Ziprasidone HCL

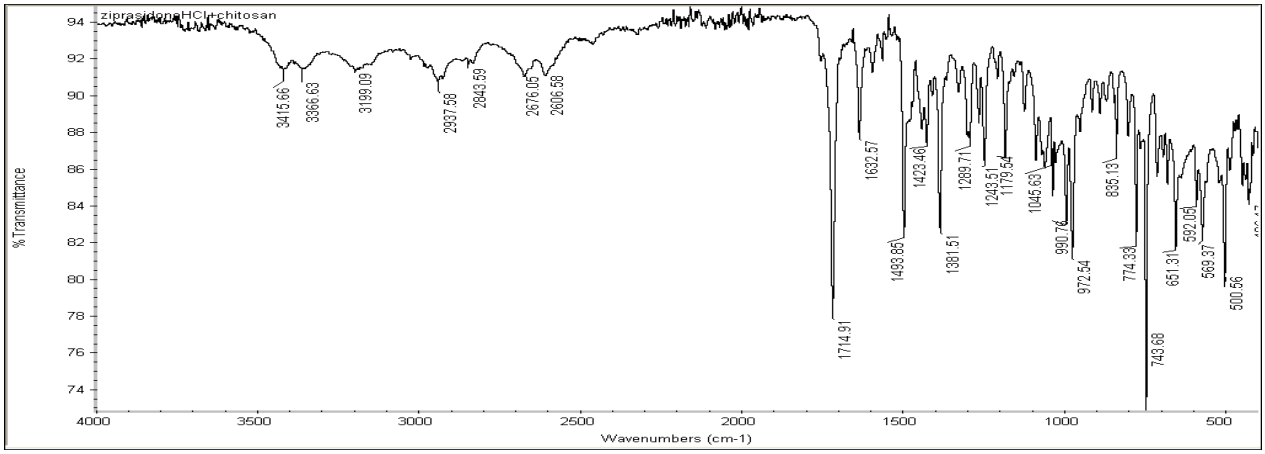

Figure No. 2: FTIR Spectrum of Ziprasidone HCL + Chitosan

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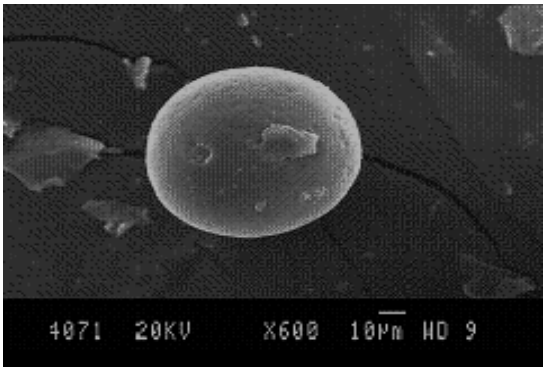
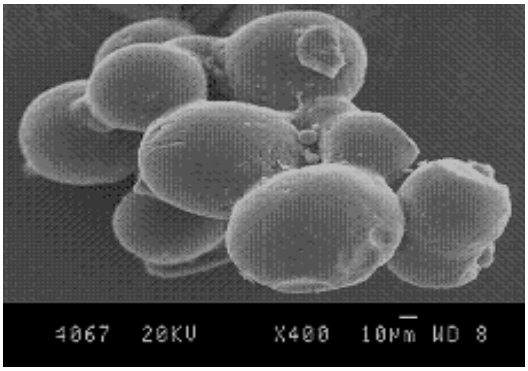
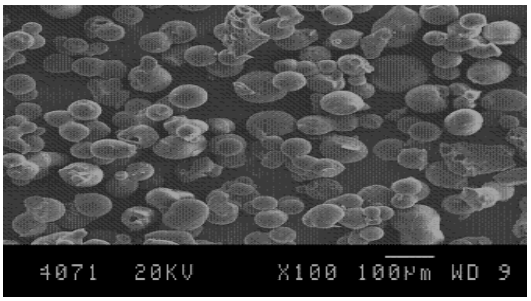


F1(a)



F1(b)



F1(c)

Figure no. 3: SEM of drug loaded Chitosan microspheres of Formulation F1

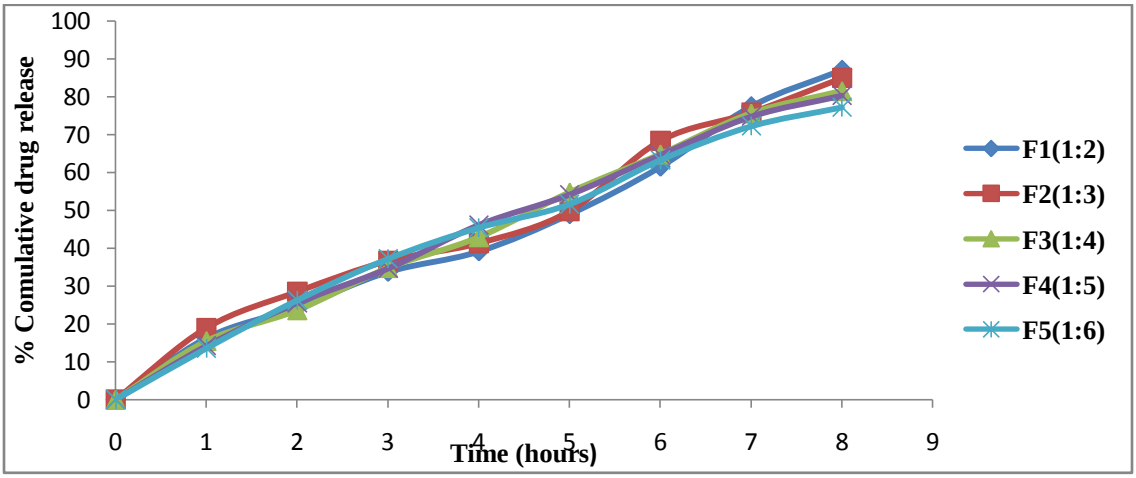


Figure No. 4: *In vitro* release rate profiles of Ziprasidone HCL from Chitosan microspheres in PBS of pH 6.8 at 37 + 0.5°C.

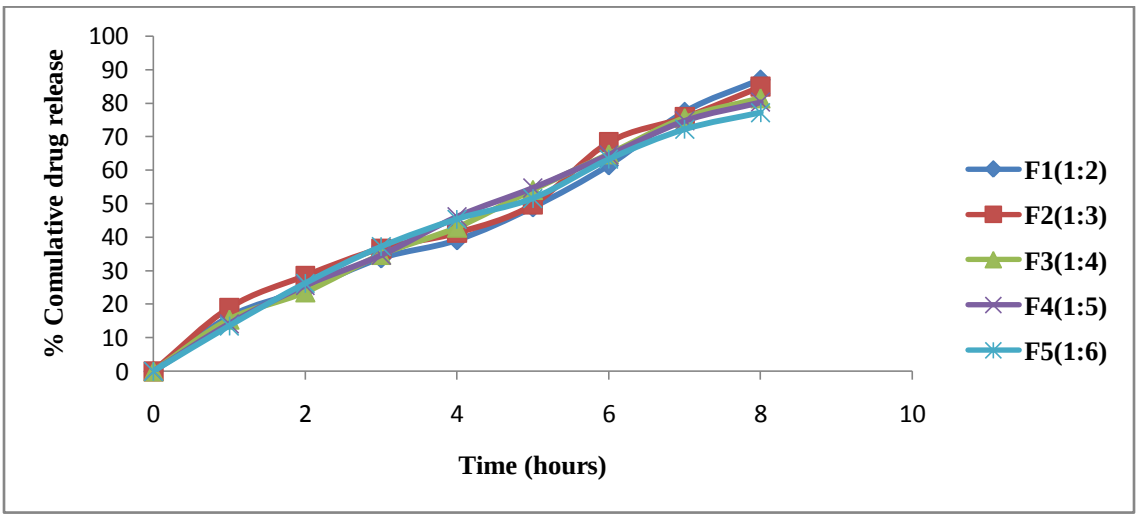


Figure No. 5: Zero order plots of different formulations of Ziprasidone HCL microspheres.

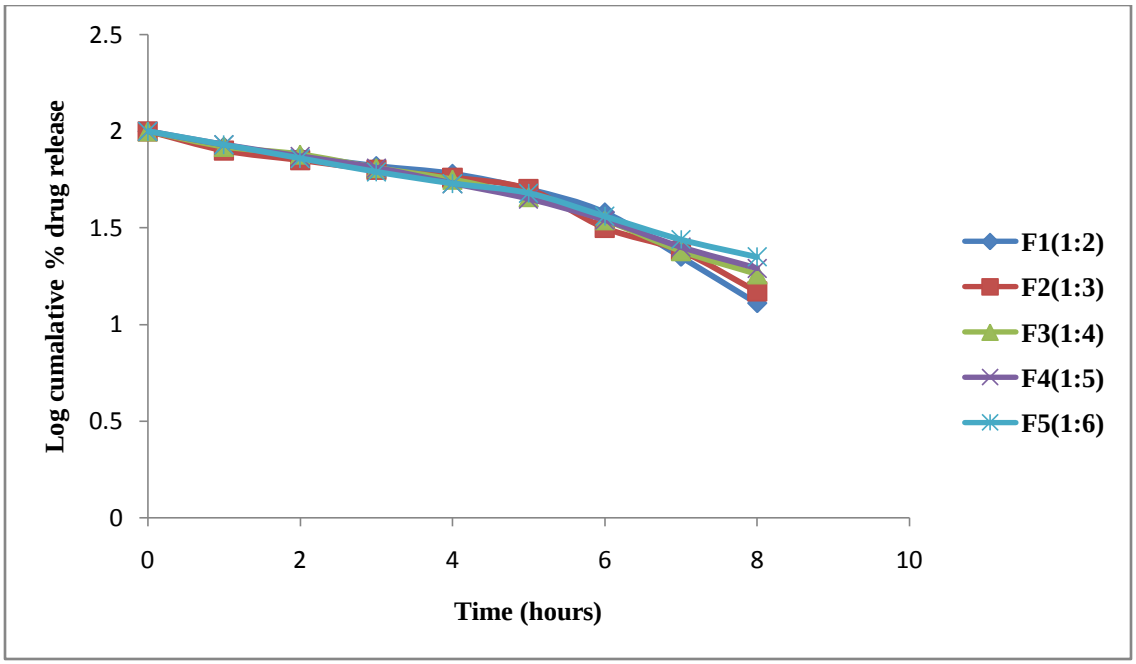


Figure No.6: First order plots of different formulations of Ziprasidone HCL microspheres.

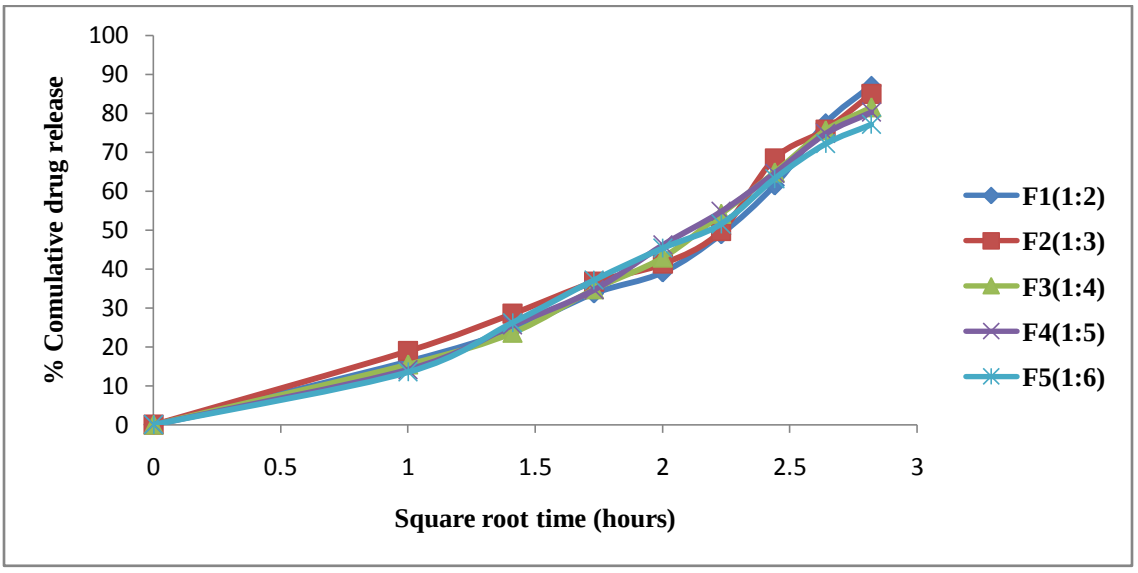


Figure No. 7: Higuchi model plots of different formulations of Ziprasidone HCL microspheres

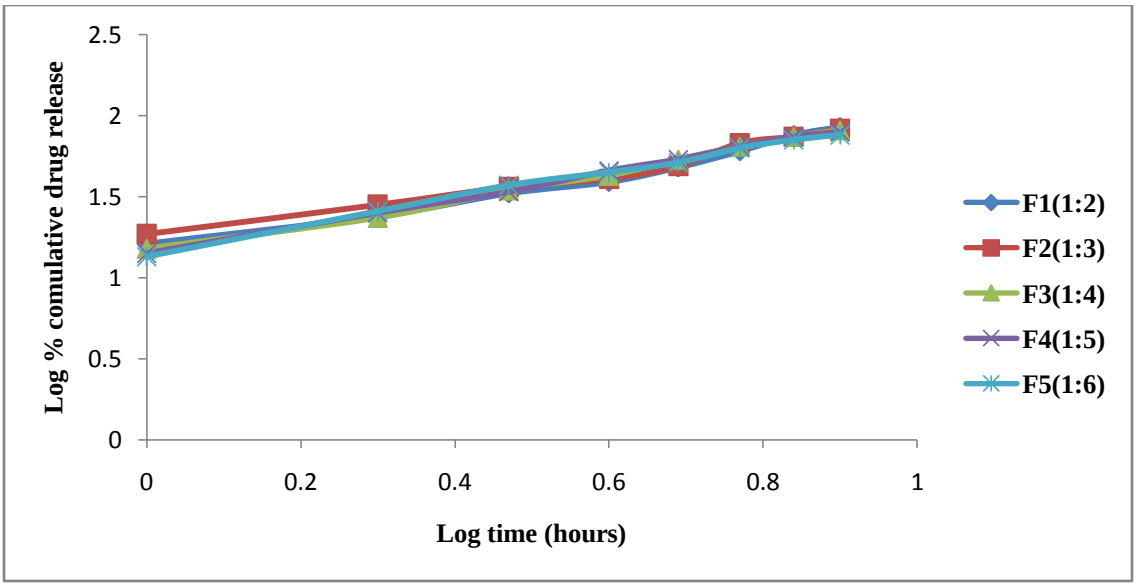


Figure No. 8: Koresmeyer peppas model plots of different formulations of Ziprasidone HCL microspheres.

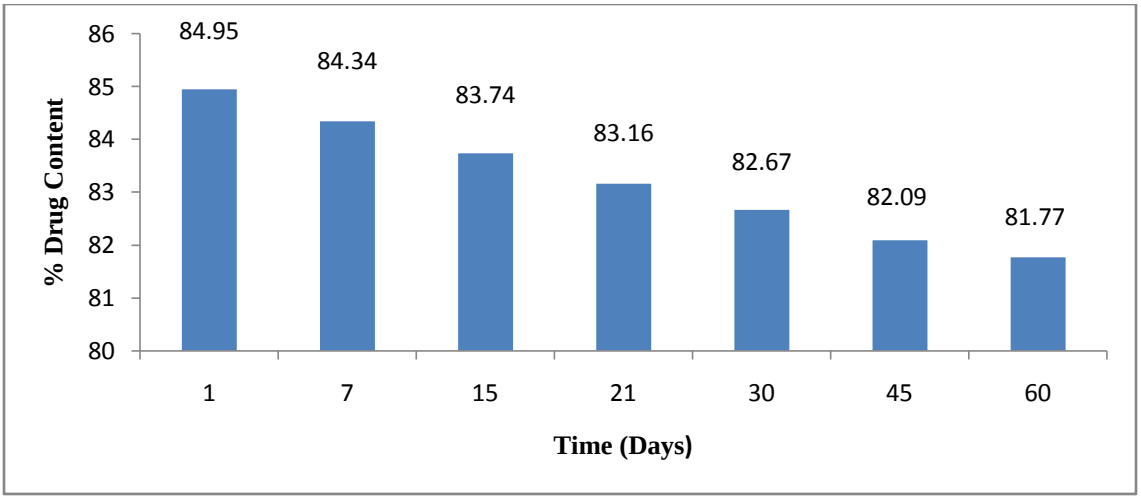


Figure no. 9: Stability Studies of Percentage drug content for formulation F1 at (40 ± 2ºC/75 RH)

6. EVALUATION OF MICROSPHERES

➢ Particle Size Determination

The mean size increased with increasing polymer quantity 50mg - 250 mg with respect to drug (25mg) and glutaraldehyde quantity (1ml) which was kept at constant and stirring speed fixed at 2100 rpm for 5 hours, which produce a significant increase in viscosity, leading to the formation

of larger size droplets and finally a higher microsphere size. (As shown in Table No. 3) The mean size was also influenced by the content and type of polymer used and its ratio in the formulations. As the viscosity of the medium increases, this result in enhanced interfacial Tension. Shearing efficiency is also diminished at higher viscosity [15].

- **Surface morphology**

Scanning electron microscopy (SEM) of Ziprasidone HCL - loaded microspheres showed spherical shaped micro particles with a relatively smooth and non-porous surface, as depicted in (Figure No. 3) for formulations F1.

- **Percentage yield**

The production yield was found to be between 69.44 - 75.93% for F1-F5. The highest production was found in formulation F5 (1:6) 75.93%. The yield of formulation F3 (1:4) was less i.e. 69.44 %.due to flocculation and aggregation of microspheres as the viscosity increase with increase in quantity of polymer.

- **Drug content and entrapment efficiency**

It can be concluded that the highest entrapment efficiency of drug loaded microspheres was found to be 92.55±0.53 for formulation F3 (1:4). The entrapment efficiency was found to be 89.93%, 90.40%, 92.55%, 87.91%, 85.89% for F1, F2, F3, F4, F5 formulation respectively. The entrapment efficiency of formulation F4 and F5 (87.91±0.19%, 85.89%) were found to be less as compared to F3 formulation (92.55±0.53%). This may be due to increased amount of chitosan as it may decrease interfacial tension between the drug and the aqueous phase, motivate its apparent solubility in aqueous phase resulting in loss of drug as shown in table no. 3 [16].

- ***In vitro* drug release studies**

The different microspheres formulations were subjected to *in- vitro* release studies using USP dissolution rate test apparatus-II (37 + 0.5°C). It was observed that for each formulation the drug release decreased with increase in the amount of polymer as shown in table no. 3. This may be due to the fact that the release of drug from the polymer takes place after complete swelling of the polymer and as the amount of polymer in the formulation increases the time required to swell also increases.

- **Drug release kinetics**

The regression coefficient values of different microspheres formulations namely F1-F5 was found to be between 0.982 – 0.995 respectively for zero order model; 0.886– 0.982, respectively for first order model and 0.901-0.956, respectively for Higuchi model and 0.970 – 0.993 for koresmeyer peppas model. The R^2 values were much closer to one for the Zero model as shown in table no. 4. From the correlation coefficient values it was concluded that the drug release form the different microspheres formulations follow Zero model.(which indicated that the mechanism of drug release was diffusion controlled) Higuchi model explained the matrix diffusion mechanism of drug release. The correlation coefficient values for Higuchi model confirmed that drug release followed matrix diffusion mechanism or Higuchi pattern release which was due to the fact that no swelling or no erosion of microspheres takes place during drug release experiments [17].

The mechanism of drug release of the all microspheres formulation was studied by fitting the release data to Korsemeyer equation. The n values for formulations F1 – F5 was found to be between 0.725-0.850, respectively. The n values for Korsemeyer – Peppas model was found to be between 0.5 – 1.0 indicative of non-fickian diffusion.

7. CONCLUSION

The study conducted so far on "Formulation and Evaluation of Ziprasidone HCL Chitosan Microspheres for Nasal Drug Delivery" reveals following conclusions:

- Ziprasidone HCL microspheres can be prepared successfully containing Chitosan, Glutaraldehyde, Span-80, Acetic acid by Single emulsification crosslinking method.
- The SEM study shows that Chitosan microspheres containing Ziprasidone HCL were spherical in shape with a smooth and non-porous surface.
- The FTIR studies confirmed that no chemical interaction took place during encapsulation process.
- The mean particle size of microspheres was in range of 2.23 - 4.13 µm depending upon the quantity of polymer used. The particle size increased as polymer quantity increased. The different size of the produced microspheres will affected significantly the drug loading efficiency, the release profiles and the dose of the released drug.

- Entrapment efficiency was in range of 85.89 to 92.55%. A higher encapsulation efficiency of drug are obtained at a 1:2 drug: polymer ratio. Amount of polymer affected the entrapment efficiency as amount of polymer increased entrapment efficiency was also increased.
- *In -vitro* release of Ziprasidone HCL was slow and prolonged for more than 8 hrs. The study indicated that the amount of drug release decrease with an increase in the polymer concentration.
- So it was concluded that the formulation F1 was best with 2.23±0.38 µm particle size and 87.08 % drug release.

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