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Formulation and Evaluation of Mucoadhesive Microspheres of Ziprasidone Hydrochloride for Oral Controlled Release.

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Abstract
Mucoadhesive microspheres of Ziprasidone HCL were prepared using sodium alginate as a shell forming polymer and HPMC-E5 as a mucoadhesive polymer for the potential use of treating schizophrenia. These were achieved by injection molding technique (Ionic cross linking). The microspheres exhibited good mucoadhesive properties and drug release from mucoadhesive microspheres was slow and extended over a longer period of time, depending on the composition of sodium alginate coat. The present investigation is aimed to prepare the sustained release mucoadhesive microspheres of Ziprasidone HCL using polymers like HPMC-E5 and sodium alginate. The drug to polymers ratio (Ziprasidone HCL, HPMC-E5 and sodium alginate) in optimized batch M 1 was kept at 1: 1: 3. The prepared beads were characterized for its particle size distribution, percent drug content, mean diameter and crushing strength, surface morphology (SEM), *in vitro* wash off test and *in vitro* drug release. The prepared beads were found to be optimal in terms of particle size and entrapment efficacy. There were no compatibility issues and the crystallinity of drug was found to be reduced in prepared microspheres, which were confirmed by DSC and PXRD studies. The time to release 90% of drug in the optimized batch M1 was 10 hr. Further investigations are required to reduce the amount of polymer in microspheres that can provide maximum drug loading and acceptable dosage form.

Key Words
Ziprasidone hydrochloride, mucoadhesive microspheres, controlled release.

Introduction
Microspheres are ideal carriers for delivery of the drug in both oral and parental routes of administration. Microspheres have been developed for not only sustaining the drug release profile but have also been used to enhance the extent of drug release. Most of the newly investigated drug molecule or those available in market possess either solubility or permeability related pharmacokinetic problems. The most important and common problem associated with them are generally low aqueous solubility of drug not only in dissolution media but also in gastrointestinal fluid. Many oral controlled drug release systems have been developed to improve drug bioavailability and release the drug for prolonged period of time. The main objective of such a drug delivery system is to control the release profile of the drug and also to sustain the drug release.

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Moreover, the drug must be released from the delivery system in the absorption window, where the drug gets maximum absorption. Most of the drug delivery carrier systems such as microspheres and nanoparticles have been developed to improve the bioavailability and to enhance the pharmacokinetic properties, which can lead to improve the patient compliance. Microspheres by various polymers and its applications are described in standard textbooks, has been accepted as a process to achieve controlled release and drug targeting. Mucoadhesion has been a topic of interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs. Several studies reported mucoadhesive drug delivery systems in the form of tablets, films, patches for oral, buccal, nasal, ocular, and topical routes; however, very few reports on mucoadhesive Microspheres are available.

Objective of this article is to formulate and evaluate mucoadhesive microspheres of Ziprasidone HCL to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to prolonged gastrointestinal absorption and enhance the bioavailability of drugs.

Materials and Methods

Materials

Commercial Ziprasidone hydrochloride was gift sample from Pharma R&D Macleods Pharmaceutical Ltd. Andheri (East), Mumbai. Methocel E3 LV from Dow chemicals and Sodium alginate from Loba Chemical Pvt. Ltd. Mumbai. All other chemicals used were of analytical grade.

Preparation of Microspheres

Ziprasidone Hydrochloride Microspheres were prepared by using different ratios of mucoadhesive polymer HPMC-E5 and shell forming polymer sodium alginate shown in table 1. These were dissolved in purified water to form homogeneous polymer solution. The drug was added to the polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added manually drop wise into calcium chloride (5%w/v) solution through a syringe (needle no.18) and kept for 15 mins to produce spherical rigid spheres, and collected by decantation, washed repeatedly and dried at room temperature. Mucoadhesive microspheres of Ziprasidone hydrochloride with a coat consisting of a mucoadhesive polymer HPMC-E5 and Sodium alginate in 1:3, 1:1 and 3:1 ratio could be prepared by the orifice-ionic gelation process. Microspheres with a coat of mucoadhesive polymer alone could not be prepared because of their water-soluble nature. The microspheres were found to be discrete, spherical, free-flowing, and of the monolithic matrix type. The microspheres were uniform in size, with a mean size of 1.2 mm. This technique has been used for encapsulation of drug in sodium alginates. Gelation occurs by cross-linking of the uronic acids with divalent cations, such as Ca^{2+}. The microspheres are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. Sodium alginate was used as a matrix-forming agent for preparation of microspheres. A hydrophilic polymer such as HPMC-E5 was used to achieve the desired mucoadhesion. It forms a strong mucoadhesive bond with the gastrointestinal mucosa and also forms a barrier around drug core so that drug is diffused slowly through this membrane. The present study revealed that the inotropic gelation method was found to be suitable for preparation of Ziprasidone hydrochloride mucoadhesive microspheres for oral controlled release formulation.

Pharmaceutical Characterization

Drug Content

Ziprasidone hydrochloride content in the microspheres was estimated by a UV spectrophotometric (Jasco V500, Japan) method based on the measurement of absorbance at 254 nm in phosphate buffer of pH 7.5 with 2% sodium lauryl sulphate. The method was validated for linearity, accuracy, and precision. The method obeyed Beer's law in the concentration range 1 to 10 mg/mL. Accurately weighed quantity of the microspheres (30 mg) were dissolved in 10 ml methanol and sonicated for 15 minute. Solution was filtered through 0.45um membrane filter and appropriate dilutions were done in phosphate buffer of pH 7.5 with 2% sodium lauryl sulphate.

Encapsulation Efficiency

Encapsulation efficiency was calculated using the following formula,

$$\text{Encapsulation efficiency} = \frac{\text{Estimated percent drug content}}{\text{Theoretical percent drug content}} \times 100$$

Mucoadhesion Testing by *In Vitro* Wash-Off Test

The mucoadhesive property of the microspheres was evaluated by an in vitro adhesion testing method known as the wash-off method. The muco-adhesiveness of these microspheres was determined by comparing mucoadhesive microspheres (prepared with HPMC and sodium alginate) with that of non-mucoadhesive microspheres (prepared with sodium alginate only). In this method freshly excised intestinal mucosal membrane (3 × 2 cm) of sheep was taken and mounted on paddle of USP dissolution test apparatus with thread shown in figure 3. About 30 both type of microspheres (mucoadhesive and non mucoadhesive) were spread onto each wet rinsed tissue specimen, and immediately thereafter the support was hung onto the arm of a USP dissolution test apparatus. Operate the USP dissolution test apparatus at 25 rpm of paddle in both gastric pH (0.1N HCl, pH 1.2) and

intestinal pH (phosphate buffer, pH 6.2) at 37.5 ± 0.5°C. At the end of 30 minutes, 60 minutes, and at hourly intervals upto 6 hours, the apparatus was stopped and the number of microspheres still adhering to the intestinal mucosal membrane was counted.

Crushing Strength

Crushing Strength of microspheres was determined by mercury load cell method using 20ml hypodermic glass syringe. Microspheres were randomly sampled and subjected to crushing strength determination.

Particle size analysis

Particle size of 50 beads was measured with digital microscopy, Inverted Microscope (Nikon Eclipse E 600 Pol Japan). The prepared microspheres were subjected for particle size analysis. Microspheres were suspended in liquid paraffin and particle size was measured.

Scanning electron microscopy

The surface topography of the beads were examined using optical microcopy and scanning electron microscope (Cambridge Stereoscan 120 UK) Samples were coated with gold film under vacuum using a sputter coater (SPI Sputter™ Coating Unit, SPI Supplies, Division of Structure Probe, Inc., PA, and USA) and then investigated

***In Vitro* Dissolution Study**

In vitro drug release of Ziprasidone hydrochloride from the microspheres were performed in media of phosphate buffer of pH 7.5 with 2% sodium lauryl sulphate in 900 mL using a USP type II apparatus with a rotating paddle stirrer at 75 rpm and 37°±0.5°C. A sample of microspheres equivalent to 20 mg of Ziprasidone hydrochloride was used in each test. A Jasco V500 (Japan) UV spectrophotometer, operating at 318 nm and using 10mm quartz cells was used to assay the dissolution media.

Results and Discussion

Drug Content

The study revealed that drug content was reduced with reducing of sodium alginate concentration. The drug content was found to be in the range of 20 % to 28 % shown in Table 1 and highest in batch M1.

Encapsulation Efficiency

The study revealed that encapsulation efficiency was reduced with reducing of sodium alginate concentration. It reveals that sodium alginate responsible for microspheres formation. The encapsulation efficiency was found to be in the range of 60 % to 84 % shown in Table 1 and highest in batch M1.

Mucoadhesion Testing by *In Vitro* Wash-Off Test

Microspheres with a coat consisting of alginate and a mucoadhesive polymer exhibited good mucoadhesive properties in the in vitro wash-off test when compared to a non mucoadhesive microspheres, (without HPMC-E5). The wash-off was slow in the case of microspheres containing alginate-mucoadhesive polymer as coat of batch M3, then M2 and then M1, when compared to that of non mucoadhesive microspheres as a batch NM shown in table 2.The rapid wash-off observed at intestinal pH 7.5. It may be due to pH-partition hypothesis ionization of carboxyl and other functional groups in the polymers at this pH, which increases their solubility and reduces adhesive strength. The results of the wash-off test indicated that the microspheres had fairly good mucoadhesive properties.

Crushing Strength

Concentration of HPMC E5 and sodium alginate both showed positive influence on crushing strength, high concentration of HPMC E5 shows slower breakdown means high crushing strength. The crushing strength of beads is determined by various interparticular forces. The liquid bridges in wet beads between insoluble solid particles of talc and or drugs are influence on agglomeration of particles during the formation of beads. The strength of dry beads depends on formation of solid bridges due to drying of alginate solution that hold insoluble particle strongly. The formation of interparticular bridges also depends on the surface area provided by the particles and beads have limited increase in crushing strength.

Scanning electron microscopy

SEM photography and typical surface morphology of batch M1, M2 & M3 were shown in figure 4. The M1 batch showed spherical appearance with smooth outer surface (Fig. 4A). The M2 Batch (Fig. 4B) was spherical in nature with rough surface. The M3 Batch (Fig. 4C) was spherical in appearance showing more or less rough surface. The solid state SEM analysis also revealed that the prepared microspheres were found to devoid of aggregation particles and hence posses negligible surface charges, and hence the beads were found to be physically stable.

In Vitro Drug Release Study

Dissolution testing is a frequently used quality control method for assessing drug release from oral dosage forms and is essential to assess how the release of the model drug would occur *in vivo*. In vitro drug release study of Ziprasidone hydrochloride mucoadhesive microspheres revealed a slow and extended release over a period of 10 hours. The release followed zero order kinetics (R^2>0.90) after a lag period of 1 hour. The drug release of Ziprasidone loaded microspheres with different proportion of HPMC E5 and Sodium Alginate was carried out in phosphate buffer of pH 7.5 with 2 % sodium lauryl sulphate in 900 mL using a USP type II apparatus with a rotating paddle stirrer at 75 rpm and 37°±0.5°C. The drug release patterns were shown in Table 3. The initial release within the first 15 min was observed in all the batches which may be due to presence of drug on the surface of microspheres as well as faster penetration of dissolution medium. The response surfaces of the obtained result were also plotted (Fig. 3). Higher concentration of Sodium Alginate and lower concentration of HPMC E5 showed positive influence on drug release for 10 hrs testing period. The optimized batch (M1) showed maximum drug release profile as compared to other batches**.** Thus the prepared Ziprasidone Hydrochloride microspheres were found suitable for oral controlled release formulation.

Conclusion

Thus, our attempt to prepare extended release mucoadhesive microsphere of Ziprasidone Hydrochloride was successful in delivering the drug for a longer period of time in a zero ordered fashion with good mucoadhesion as desired. The inotrpic gelation method was utilized in the preparation of Ziprasidone microspheres. The microspheres prepared by this method were found to be more uniform in size and provided better-extended release profile of Ziprasidone. The percent drug content was depends upon the amount of sodium alginate and HPMC E5 ratio. Crushing strength depend more on concentration of HPMC E5 than sodium alginate. SEM study showed a significant difference on microsphere surface. Batch M1 showed smooth surface and Batch M2 showed rough surface due to leaching of drug in counter ion solution during preparation.

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Fig. 1: Mucoadhesive Microspheres.

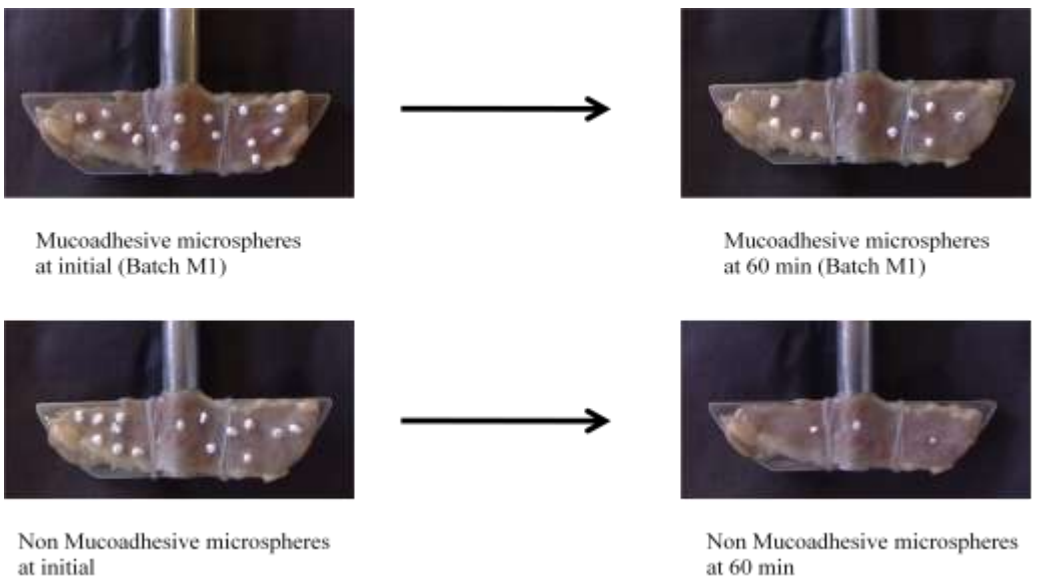

Fig. 2: *In vitro* wash off test.

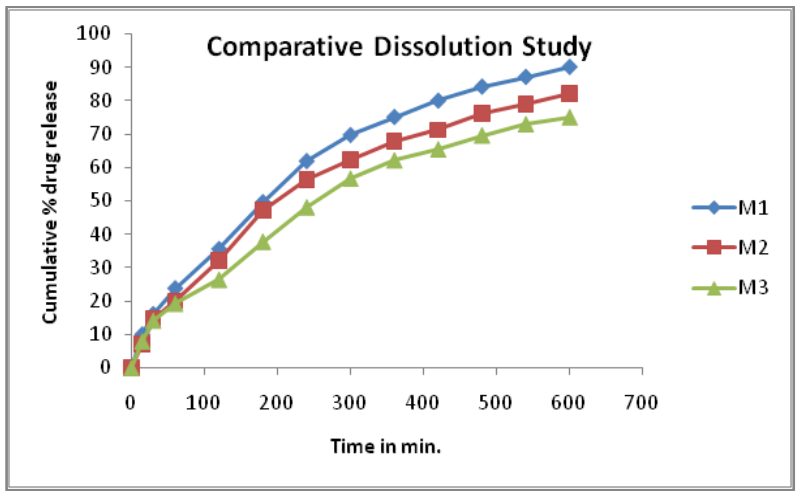

Fig. 3: Release profile of Ziprasidone hydrochloride microspheres (♦1:3, ■1:1, ▲3:1) in phosphate buffer, pH 7.5 containing 2% SLS.

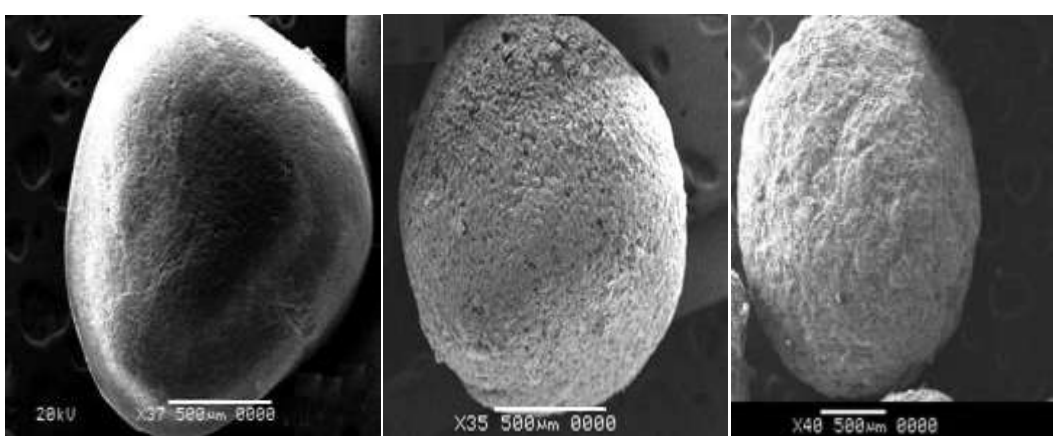

Fig. 4A: Batch M1 **Fig. 4B:** Batch M2 **Fig. 4C:** Batch M3

Table 1: Drug content and Encapsulation efficiency.

Batch	HPMC-E5 : SA	Drug content (%)	Encapsulation efficiency (%)
M1	1 : 3	27.98	83.94
M2	1 : 1	25.06	75.18
M3	3 : 1	20.06	60.18

Table 2: *In vitro* wash off test.

Time (h)	Percentage of Microspheres Adhering to Tissue							
	M1	M2	M3	NM*	M1	M2	M3	NM*
	In 0.1N HCl, pH 1.2				In Phosphate Buffer, pH 6.2			
0	100	100	100	100	100	100	100	100
0.5	27	26	30	30	21	19	27	28
1	21	22	24	15	19	15	24	17
2	19	20	19	5	17	12	20	5
3	8	11	15	-	7	7	16	-
4	3	4	13	-	2	2	11	-
5	-	-	6	-	1	-	6	-
6	-	-	2	-	-	-	1	-

***** Non Mucoadhesive

Table 3: Cumulative % drug release from Ziprasidone hydrochloride microspheres.

Time (in min.)	M1	M2	M3
0	0	0	0
15	10.1	7.2	8
30	16.2	14.6	14.2
60	23.9	20.1	19.3
120	35.7	32.1	26.5
180	49.7	47.3	37.9
240	62	56.3	48.2
300	69.8	62.3	56.8
360	75.2	67.8	62.3
420	80.1	71.2	65.6
480	84.3	76.2	69.8
540	87.2	78.9	73.1
600	90.2	82.1	75.2

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