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Research Article

Formulation and Evaluation of Alginate Microspheres of Olanzepine

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Abstract

Objective: The objective of this research was to formulate and evaluate microspheres of Olanzepine to achieve a substantial increase in length of stay of the drug in the gastrointestinal tract with sodium alginate for controlled release.

Materials and Methods: The Olanzepine microspheres were prepared by Ionotropic gelation technique. Olanzepine and sodium alginate polymers were individually passed through sieve ≠ 60. The weighed quantity of the Olanzepine was added to 50 ml of purified water containing the sodium alginate polymers and thoroughly mixed with a stirrer at 400 rpm to form a homogenous polymer solution. The resulting homogeneous dispersion was sonicated for 20 minutes to remove any air bubbles. Microspheres were prepared by ionotropic gelation method using calcium chloride as a cross-linking agent. The developed Olanzepine microspheres were characterized for micrometrics properties, morphology, drug entrapment efficiency, mucoadhesive property, *in-vitro* drug release and interaction studies FTIR [Fourier transforms infrared spectroscopy] and differential scanning calorimeter [DSC].

Results: The olanzepine microspheres were free-flowing and discrete. The mean particle size ranged from 338.40±3.90µmto 374.77±3.16 µm and the entrapment efficiencies ranged from 63%.to95.5%. FTIR studies indicated the of olanzepine-polymer interactions in the ideal formulation A2. There was no compatibility issues was found to be olanzepine microspheres, which were confirmed by DSC studies. Among different formulations, the olanzepine Microspheres of batch A2 had shown the optimum percent drug entrapment of microspheres and the controlled release for about 9 hrs. Stability studies were carried out for A2 were within permissible limits.

Conclusion: The results obtained in this present work demonstrate the potential use of sodium alginate polymer for preparation of controlled delivery olanzepine microspheres and prolonged residence at the absorption site.

Keywords: Microsphere, Olanzepine, Gastroretentive, Ionotropic gelation.

1. Introduction

Oral controlled drug delivery system such as microsphere is useful to maintain therapeutically effective plasma drug concentration levels for a longer duration there by reducing the dosing frequency and to minimize fluctuations in the plasma drug concentration at the steady state by delivering the drug in a controlled and reproducible manner. Moreover, it is easy for administration, no patient compliances and flexibility in the formulation. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in

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gastrointestinal tract (GIT) is to control gastric resistance time i.e., gastroretentive drug delivery system, which will provide us with new and important therapeutic options. Microspheres have advantages like efficient absorption, enhanced bioavailability of the drugs, maximum utilization of drugs, much more intimate contact with intestinal cells, better patience compliance and targeting to specific absorption site can be achieved by using suitable polymers on the surface of microcarriers[1-3].

Olanzapine is classified as a thiobenzodiazepines. It is an atypical antipsychotic drug used in the treatment of schizophrenia. It is practically insoluble in water, having only 60% oral bioavailability. Olanzapine undergoes extensive first pass metabolism. In this regard our main focus of this research is to prepare sustain microspheres of Olanzepine which provides slow release in gastrointestinal tract and also assures the presence of dosage form at the site of absorption. Olanzapine has been shown to selectively bind to central dopamine D2 and serotonin (5-HT2c3receptors and is effective against the negative symptoms of schizophrenia with a lower incidence of extra pyramidal symptoms. A second generation atypical antipsychotic, Olanzapine is extensively metabolized in liver (1st pass metabolism) by the cytochrome P450 CYP1A2 and CYP2D6 isoenzymes to about 10 metabolites, some of them are inactive while the others cause many adverse effects, followed by glucuronidation These adverse effects include hypotension, dry mouth, tremors, and somnolence. The drug has a moderate elimination half-life implying that once daily therapy is adequate for treatment of schizophrenic conditions [4-6].

Materials and Methods

Materials

Olanzepine was a gift sample from Enaltec Lab Private Ltd, Mumbai, India. Sodium alginate gift sample from Loba chemical Mumbai and Calcium chloride was purchased from S.B. Fine chemicals Ltd, Mumbai.

Preparation of Olanzepine Microsphere

The olanzepine microspheres were prepared by Ionotropic gelation technique. Olanzepine and sodium alginate were individually passed through sieve no 60. The weighed quantity of the olanzepine was added to 50ml of deionised water containing the sodium alginate and thoroughly mixed with a stirrer at 200 rpm to form a homogenous polymer solution. The resulting homogeneous dispersion was sonicated for 30 minutes to remove any air bubbles. For the formation of microspheres the dispersion was extruded drop-wise from a needle of 20 G in diameter from a height of about 5 cm into aqueous calcium chloride solution (10%) and stirred at 700 rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce spherical rigid olanzepine microspheres. Then the solution containing formed microspheres was filtered by using Whatman filter paper. The microspheres were allowed to dry at 60°C for 6 hrs and stored in well-closed container for further use [7-10]. The composition of various formulations was mentioned in Table 1.

Percentage yield

The percentage yield of olanzepine microspheres of various batches were calculated by using the weight of final product after drying with respect to initial total weight of the olanzepine and polymer used for preparation of olanzapine gastroretentive microspheres [11].

Particle size

Particle size and size distribution of the olanzepine microspheres were calculated by sieve analysis method. [12].

Shape and Surface Morphology

The external and internal morphology of the microspheres were studied by scanning electron microscopy (SEM) in, Pune University .The samples for SEM were prepared by suspended with water and mounted on a glass slide and visualized under optical microscope and scanning electron microscope. Microsphere was obtained spherical in shape and smooth surface [13].

Micromeritic properties

Angle of repose (θ) Accurately weighed 5 g of blend samples were passed separately in a glass funnel of 25 ml capacity with diameter 0.5 cm. The funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample was

allowed to flow from the funnel, so the height of the pile *h* just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters.

Angle of repose was calculated by formula:

$$\theta = \tan -1 (h/r)$$

Hausner's ratio (HR)

HR was obtained by using formula:

$$HR = TD/BD$$

Carr's index (CI)

CI, which is calculated as follows:

$$CI\ (\%) = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Swelling Studies

Microspheres were weighed (W1) and placed in phosphate buffer (pH 6.8) solution. After 10 hours, the microspheres were removed from the buffer and excess surface buffer was carefully removed using the filter paper. The swollen microspheres were then reweighed (W2) and swelling index (SI) was calculated using the following formula [15].

Encapsulation efficiency and drug loading

To determine the amount of drug encapsulated in microspheres, a weighed amount (20 mg) of microspheres was crushed and suspended into l with pH 6.8 phosphate buffer solution for 24 hr and filtered This solution was assayed for drug content by UV spectrophotometer at246 nm. [16].

In vitro Drug Release Studies

The release rate of olanzepine from olanzepine microspheres was determined using USP Type II (paddle) dissolution test apparatus. The dissolution test was performed using 900 ml of dissolution medium of 0.1 N Hydrochloric acid, at 37±0.5°C and a rotation speed of 50 rpm. In specified time intervals an aliquot of 5ml samples of the solution were withdrawn from the dissolution apparatus and with replacement of fresh fluid to dissolution medium. The samples were filtered through filter paper of 0.45 µm. The samples were analyzed at 246 nm for drug content using UV spectrophotometer. The olanzepine release experiment was carried out[17].

Fourier transforms infrared spectroscopy (FTIR) studies

FTIR spectra of the pure olanzepine and olanzepine microspheres were produced using KBr disk method. The samples were analyzed between wave numbers 4000 and 400/cm resolution determined to check the intactness of the drug in the polymer mixture.

Differential scanning calorimeter (DSC) studies

The thermal behavior of pure olanzepineandolanzepine loaded microspheres was studied using a DSC Perkin Elmer DSC at a heating rate of 10°C/minutes. 5 mg samples were accurately weighed into aluminum pans and then sealed. The measurements were performed at a heating range of 25-300°C under nitrogen atmospheres.

Stability study

Stability studies were carried out for olanzepine formulation as per ICH guidelines. The best mucoadhesive microspheres formulation (A2) was sealed in high-density polyethylene bottles and stored at 40±2°C/75±5% relative humidity (RH) for 90 days. The samples (A2) were evaluated for entrapment efficiency and percentage mucoadhesion for every 1 month up to 3 months [18].

Result and Discussion

Percentage yield and micrometric studies

The production yields of microspheres prepared by ionotropic gelation method were found to be between 32.36 % and 95.1 % as shown in Table 2. It was found that production yield of microspheres prepared by A2batch no. was greater than other batches. All olanzepine microspheres formulations were evaluated for micromeritic properties. Results are shown in Table 3. Angle of repose of all microspheres batch varied from 27.11 to 33.00. Carr's index varies from 11.31 to 13.81 %. All formulations results revealed good flow property and compressibility.

Particle size

The average particle size of olanzepine microspheres ranged from 338.40±3.90 to 374.77±3.16 µm. The mean particle size was significantly increases with increasing sodium alginate concentration this may be attributed to high viscosity of sodium alginate solution.

Morphology of microspheres

The morphology of the olanzepine microspheres of best formulation A2 was examined by SEM. The SEM photographs revealed that olanzepine microspheres were discrete and spherical shape with a rough surface morphology (Fig. 1).

Entrapment efficiency

The percentage entrapment efficiency ranged from 63 to 95.5% (Table 2). The entrapment efficiency of the olanzepine microspheres prepared with A2 batch was higher than other batches of microspheres.

***In vitro* dissolution studies**

The *in vitro* Olanzepine release profiles for all batches were shown in Fig. 2. Drug release from these microspheres was slow, controlled release and dependent upon the nature and concentration of sodium alginate polymers used. Among all the formulations A2 showed good dissolution profile with 90.56 % of drug release in 12 hrs. Hence it is considered as the best microsphere formulation, which seems to be a good candidate for controlled release of olanzepine.

FTIR studies

Infrared (IR) spectra of pure drugs sample of olanzepine was compared with IR spectra of olanzepine loaded microspheres, as there was no significant change in the pattern of peaks of pure drug and olanzepine loaded microspheres. Hence, there was no interaction seen in between olanzepine and polymer

DSC studies

The thermal behavior of prepared olanzepine microspheres was studied in comparison with thermo grams of pure olanzepine. The thermogram of pure olanzepine showed a sharp endothermic peak at 199ºC °C, which corresponds to its melting point. The characteristic peak of olanzepine was well recognized in the olanzepine-loaded microspheres. Thus, there was no incompatibility between olanzepine and sodium alginate polymers used in the formulation of microspheres.

Conclusion

In this study, controlled release olanzepine microspheres were prepared using the ionotropic gelation method. It can be conclude from the above investigation that the proper selection of formulation conditions is very important to achieve high encapsulation efficiency and to control the release of olanzepine from alginate microspheres This study has been a satisfactory attempt to formulate a microsphere of an anti-depressant drug olanzepine with a sodium alginate. Interaction studies [FTIR and DSC] data revealed that there was no interaction between sodium alginate polymers and olanzepine, hence they are compatible. The prepared olanzepine microspheres gave good micrometrics properties, percent yield, drug entrapment, mucoadhesive property and *in vitro* release. SEM analysis of the olanzepine microspheres revealed that A2 formulation was spherical shape with rough surface morphology. Among different formulations, the olanzepine microspheres of batch A2 had shown the optimum percent drug entrapment of microspheres and the controlled release. Thus the results demonstrate the potential use of sodium alginate polymer for preparation of controlled delivery olanzepine microspheres for prolonged residence at the absorptions.

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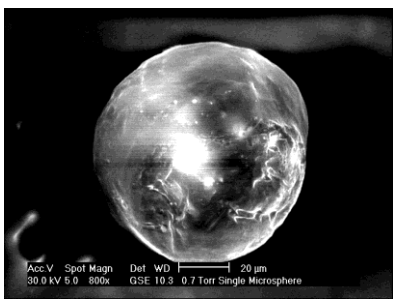


Fig. 1: Scanning electron photomicrographs of the formulation A2:

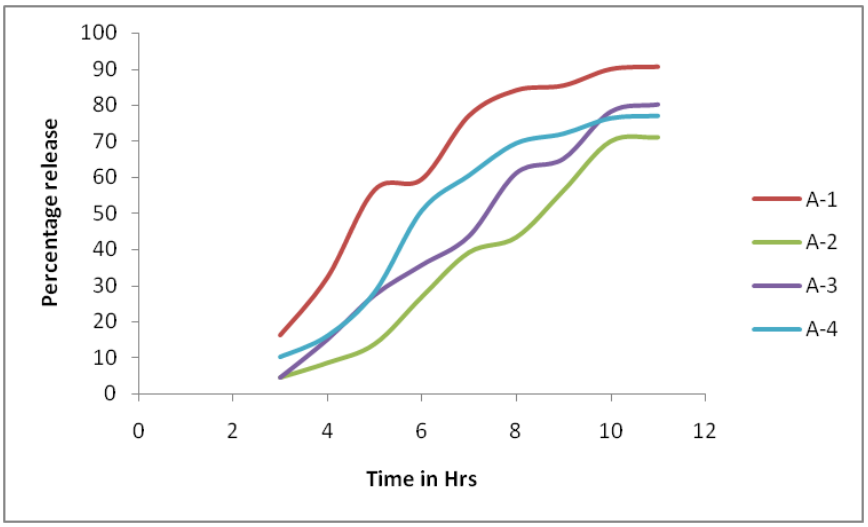


Fig. 2: Comparative release profile of formulation A1-A4.

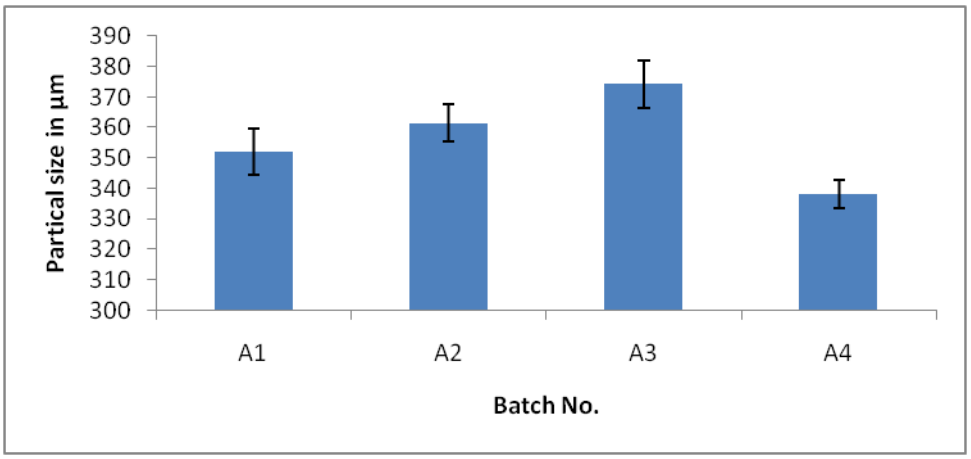


Fig. 3: Particle size analysis of olanzepine microsphere.

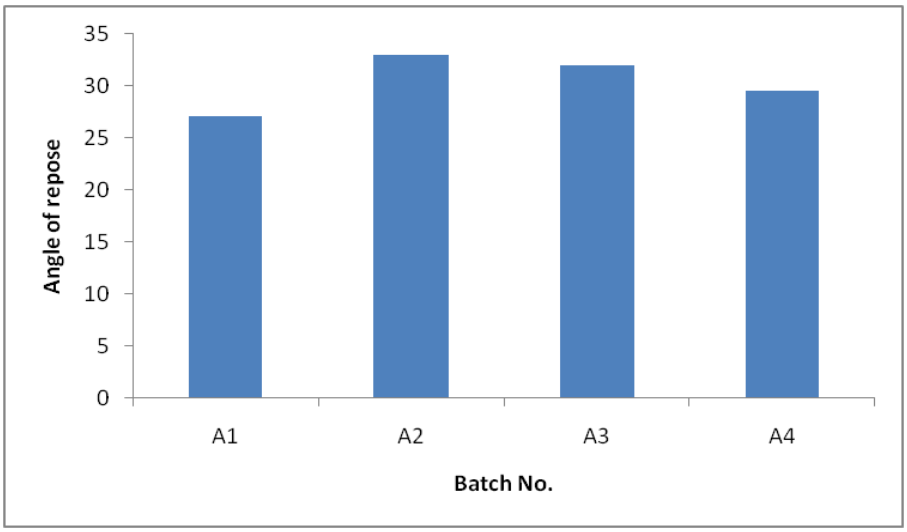


Fig. 4: Angle of repose of Olanzepine microsphere.

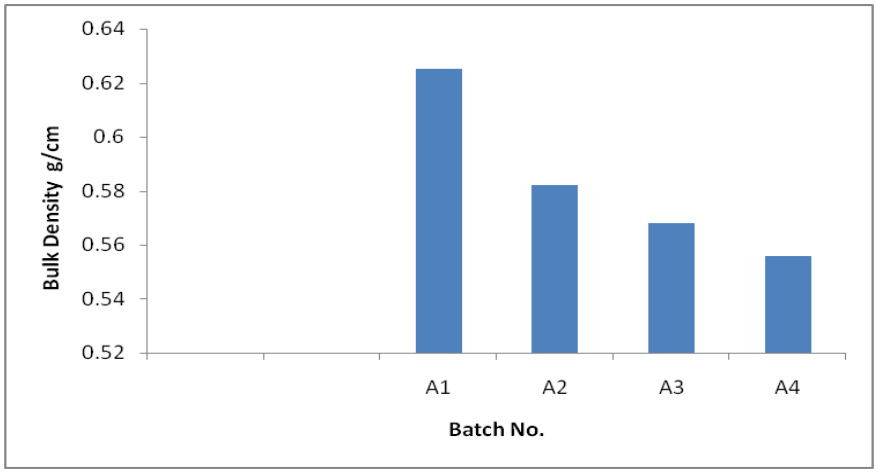


Fig. 5: Bulk density of Olanzepine microsphere.

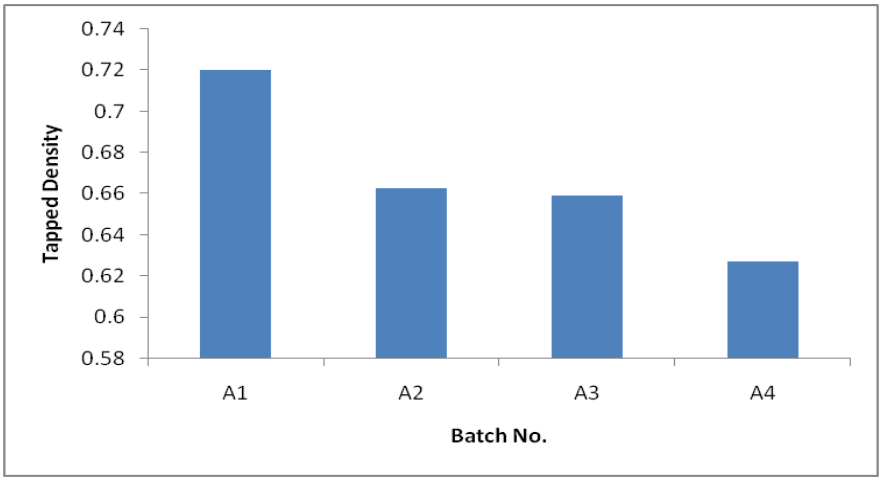


Fig. 6: Tapped density of Olanzepine microsphere.

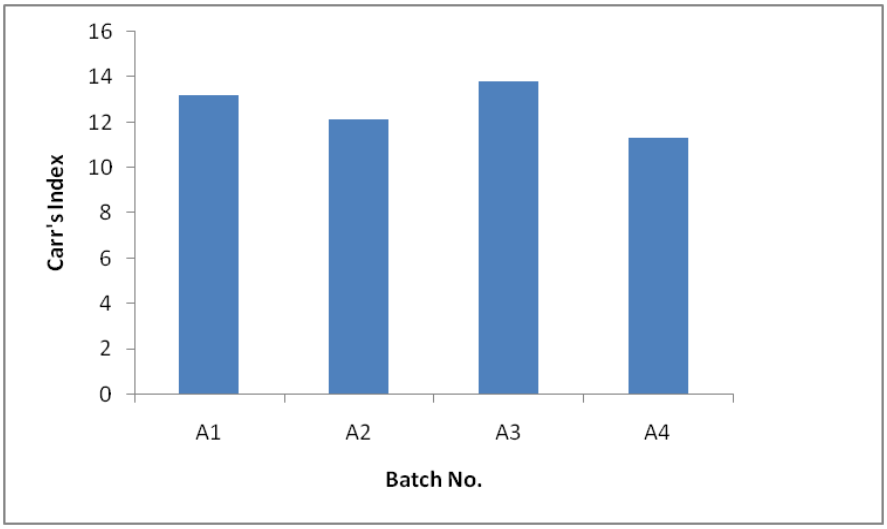


Fig.7: Carr's Index of Olanzepine microsphere.

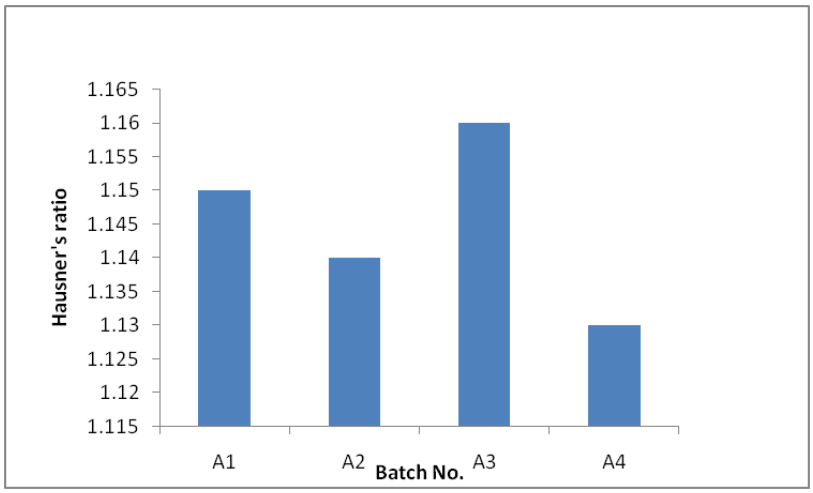


Fig.8: Hausner's ratio of Olanzepine microsphere.

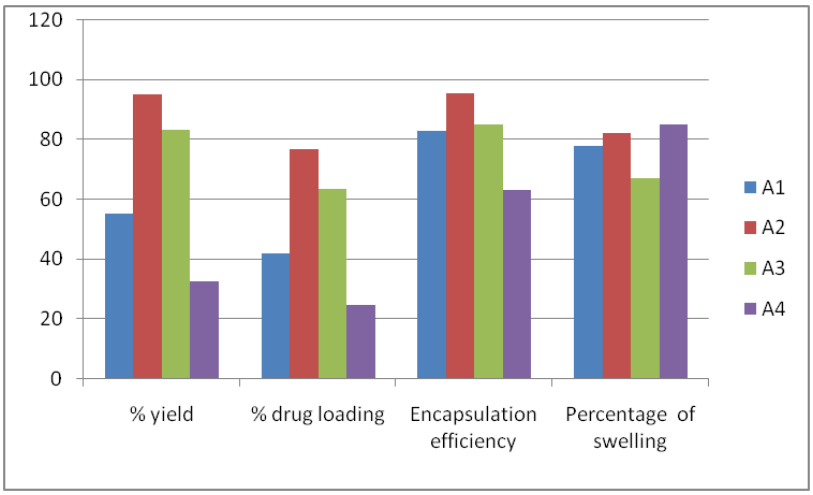
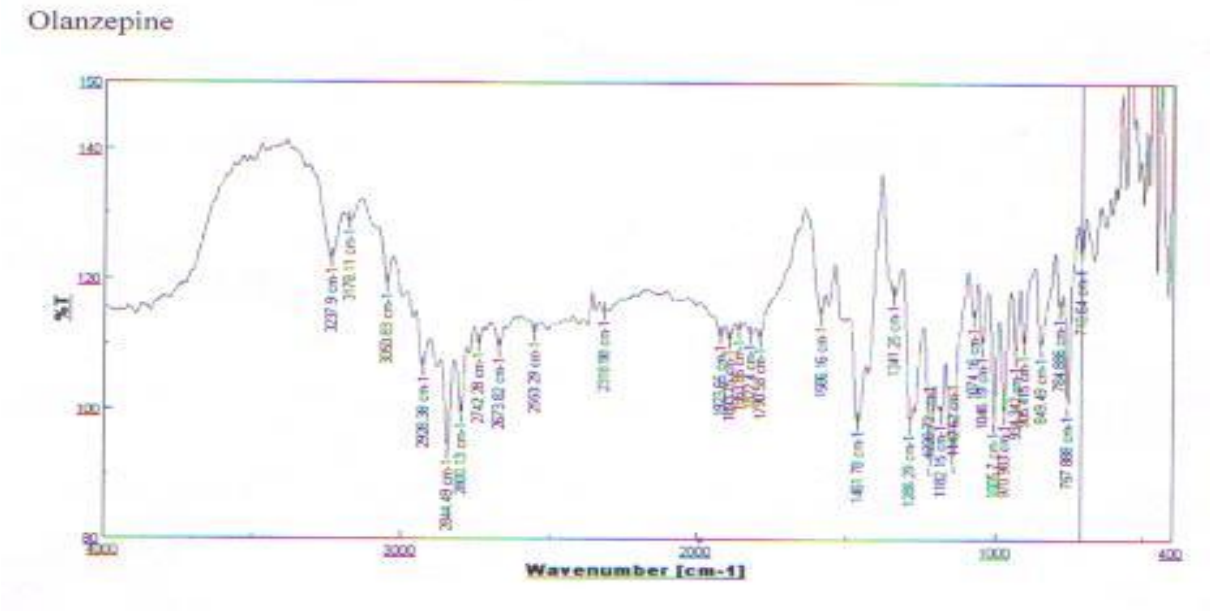
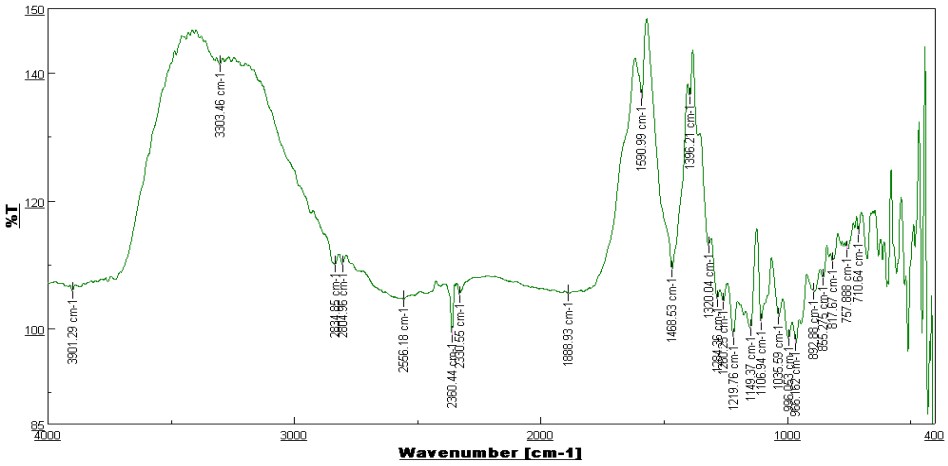


Fig. 9: Physical characteristic Olanzepine microsphere.



(a)



(b)

Fig.10: Fourier transforms infrared spectroscopy spectra of, (a): Pure olanzepine ;(b): Formulation containing sodium alginate (A2).

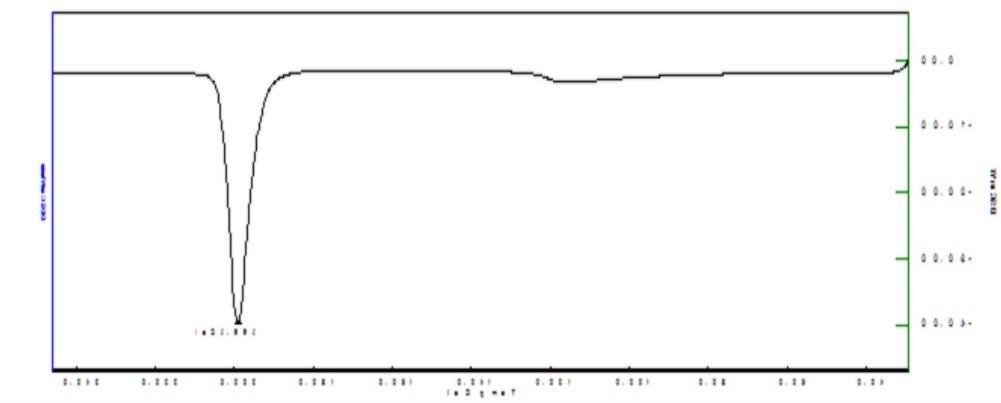


Fig.11: Differential scanning calorimeter thermograms Pure olanzepine

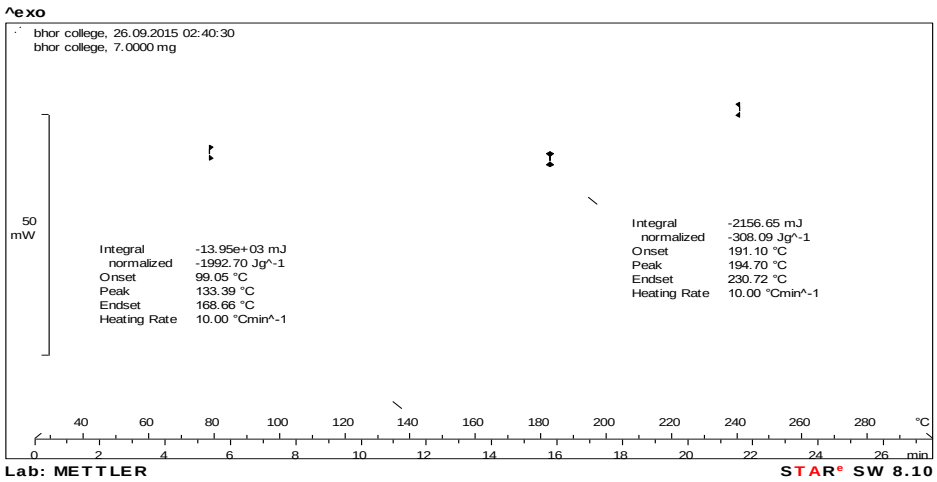


Fig.12: Differential scanning calorimeter thermograms olanzepine microsphere.

Table 1: Composition of olanzepine microspheres.

Sr. No.	Batch code	Drug – polymer ratio
1	A1	1: 0.5
2	A2	1:1
3	A3	1:1.5
4	A4	1:2.

Table 2: Physical characteristic of olanzepine loaded alginate microsphere.

Batch No.	% yield	% drug loading	Encapsulation efficiency	Percentage of swelling
A1	55.27	41.98	83	78%
A2	95.1 %	76.76 %	95.5	82%
A3	83.40 %	63.34 %	85	67%
A4	32.36 %	24.58 %	63	85 %

Table 3: Micromeritic property of formulations olanzepine loaded alginate microsphere.

Batch No.	Particle size (µm)	Angle of repose	Tapped density	Bulk density	Carr's index	Hausner's ratio
A1	352.1 ± 7.5	27.11	0.720	0.625	13.19	1.15
A2	361.4 ± 6.2	33	0.663	0.582	12.12	1.14
A3	374.2 ± 7.8	32	0.659	0.568	13.81	1.16
A4	338.1±4.5	29.5	0.627	0.556	11.31	1.13

Table 4: Dissolution profile of olanzepine loaded alginate microsphere.

Time (hr.)	A-1	A-2	A-3	A-4
0	16.32	4.46	4.49	10.11
1	32.33	8.54	15.04	15.94
2	56.62	13.76	27.34	28.04
3	59.59	26.83	35.64	50.64
4	77.22	39.19	43.65	60.40
5	84.25	43.37	61.11	69.29
6	88..56	56.34	65.08	71.92
7	90.11	70.00	78.11	76.21
8	90.77	71.12	80.11	76.87

Source of Support: Nil.

Conflict of Interest: None declared

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