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Formulation and Evaluation of Chitosan Microspheres for Intranasal Delivery of Zolmitriptan.

Digambar Mali*[1], Sachin Bedse[1], Tushar Bhambere[1], Rekha Dighe[1], Swati Talele[1], GhanashyamChaudhari[1]

1. Sandip Institute of Pharmaceutical Sciences, Mahiravani, Nasik, Maharashtra, India.

ABSTRACT

Chitosan based microspheres containing were prepared by the emulsion cross linking method for nasal delivery of zolmitriptan. Nasal microspheres offer significant advantages over other type of drug delivery system. It modulates absorption characteristics of the drug by enhancing drug residence time in the nasal cavity and subsequently may increase bioavailability profile of administered drug. For the present study, Chitosan was selected as a mucoadhesive polymer. The microspheres were evaluated with respect to the particle size, production yield, encapsulation efficiency, shape and surface properties, drug and polymer interaction, mucoadhesive property, *in vitro* drug release. To optimize the microsphere formulation, 2^3factorial design was employed for investigating the effect of three factors, polymer concentration (chitosan), emulsifier concentration (Span 80) and cross-linking agent (gluteraldehyde) on response variable, which are encapsulation efficiency, in vitro drug release.

Keywords: Microspheres, Nasal Drug Delivery, Mucoadhesive

*Corresponding Author Email digambar22mali@gmail.com
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INTRODUCTION

Micro-carriers (Microspheres) shows features like controlled release, improvement in the residence time and thus enhancing bioavailability of administered drug. Nasal drug delivery is the promising route for drugs which show large first-pass metabolism after oral administration and poor stability in the gastrointestinal tract. Nasal route offers several merits like porous endothelial membrane, highly vascularized mucosa, large surface area presence of microvilli structure of the epithelial cells, absence of first-pass hepatic metabolism, easily accessible and has good patient acceptability. This route suffers from drawbacks like mucociliary clearance, low bio-availability for large proteins, unsuitability of drug and other excipients in the formulations irritating to the mucosa, enzymatically active nature of nasal mucosa. Nasal absorption of drug is mainly affected by Physico-chemical factors like molecular weight, drug solubility and dissolution, Pka and partition coefficient of drug, polymorphism, Prodrug, particle size and morphology, design of dosage form etc.[1-4]. The objective of this study was the possible application of natural polymer for the preparation of mucoadhesive nasal microspheres by emulsion Crosslinking technique, with the ultimate intent of enhancing the bioavailability of the nasal Zolmitriptan formulation by improving the residual time of the drug in the nose. Patients with migraine generally suffer from nausea and vomiting; oral treatment can therefore be inconvenient or could fail. Zolmitriptan, 4S-4- ({3-[2-(dimethylamino) ethyl]-1H-indol-5-yl} methyl)-1, 3-oxazolidin-2-one,is a second generation triptan prescribed for patients with migraine attacks, with or without an aura, and cluster headaches. It has a selective action on serotonin (5-HT1B/1D) receptors and is very effective in reducing migraine symptoms, including pain, nausea, and photo- or photophobia.[5-8]

MATERIALS AND METHOD

Materials

All the chemicals like chitosan, glacial acetic acid, span-80, gluteraldehyde, chloroform, cyclohexane used were of analytical reagent grade.

Preparation of Microspheres

Cross-linked Zolmitriptan microspheres were prepared by Emulsion-Crosslinking method. The aqueous phase was prepared by dissolving specified quantity of chitosan in 2% glacial acetic acid by stirring. The aqueous phase was pre-emulsified in cyclohexane: chloroform mixture (4:1, v/v) containing Span-80. The emulsion was homogenized by high-speed homogenizer for 3 min. Further, a suitable amount of gluteraldehyde was added under magnetic stirring at 500 rpm. The

stirring was maintained for 3 hr at 40^0C. Microspheres were isolated by washing twice with cyclohexane. Finally microspheres were air dried and kept in a closed container. Formulation variables such as concentration of polymer, concentration of surfactant & concentration of crosslinking agent were evaluated to obtain the microspheres of optimum properties[9].Composition of variable is given in Table 1.

Table 1: The various batches of microspheres.

Sr No	Formulation Code	Drug (mg)	Chitosan (mg) X1	Span 80 (%) X2	Gluteraldehyde(ml) X3
1	F1	100	200	1	1
2	F2	100	400	1	1
3	F3	100	200	3	1
4	F4	100	400	3	1
5	F5	100	200	1	1.5
6	F6	100	400	1	1.5
7	F7	100	200	3	1.5
8	F8	100	400	3	1.5

Preformulation Studies

Fourier Transforms Infrared Spectroscopy (FT-IR) Analysis

A. Drug

The FT-IR spectra of dry sample of Zolmitriptan was taken and analyzed between 4000 cm^{-1} – 400 cm^{-1}.

B. Polymer

The FT-IR spectra of dry sample of chitosan was taken and analyzed between 4000 cm^{-1}- 400 cm^{-1}.

C. Drug Polymer Interaction Study

Drug polymer interaction testing was performed by mixing drug with polymer in equal proportion and then IR spectrum was noted for physical mixture. The FT-IR spectrum was analyzed between 4000 cm^{-1}- 400 cm^{-1}.[16]

Differential Scanning Calorimetric (DSC)

The DSC measurements were performed on a DSC-61000 (Metller Toledo USA) Differential Scanning Calorimeter with thermal analyzer. The DSC measurements were performed on drug, polymer, physical mixture of drug and polymer (1:1). All accurately weighed samples (about 2 mg of samples) were placed in a sealed aluminum pan, and the samples were heated under nitrogen flow (10 ml/min) at a scanning rate of 10^0C per min from 25 to 300 ^{0}C. An empty aluminum pan was used as reference[17].

FORMULATION STUDIES

Micromeritic Properties. [10-11]

Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. The angle of repose was determined by the funnel method. A glass funnel was secured with its tip at a given height (H) above a piece of graph paper placed on a horizontal surface. Powder was poured through the funnel until the apex of the conical pile touched the tip of the funnel. The angle of repose was calculated with the formula:

$$\text{Tan } \Theta = H / R$$

Where, H = Pile Height, R = Radius of Pile

Bulk Density

Bulk density of all batches of microcapsules was determined by pouring gently 1 g of sample through a glass funnel into a 10 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated as per given formula.

Bulk density= Mass of sample (mg)/ Apparent unsettled volume (ml)

Tapped Density

The tapped density was determined by pouring microcapsules (1 g) through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from a height of 2 inches until a constant volume was obtained. The volume occupied by the sample after tapping was recorded .The values for tapping density was calculated as per given formula

Tapped density = Weight of sample (mg)/ Volume occupied by sample (ml)

Compressibility index

The compressibility indices of the formulation blends were determined using Carr's compressibility index formula.

Carr's Index = (Tapped density- Bulk density) /(Tapped density) *100

Hausners ratio

It provides an indication of the degree of densification which will result from vibration of feed hopper. Lower the Hausners ratio better is the flow ability.

Hausners ratio = Tapped density/ Bulk density

Percentage yield.[12-13]

The percentage yield of different formulations was determined by weighing the microspheres after drying. The percentage yield was calculated as follows

%Yield =Total weight of microspheres/ Theoretical weight of drug and polymer*100

Drug content[14]

The various batches of the microspheres were subjected for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres (50mg) were dissolved in adequate quantity (500ml) of phosphate buffer PH 6.8& then filter. The UV absorbance of the filtrate was measured using a UV spectrometer at 222.5nm.

Drug content (%) = Actual amount of Zolmitriptan in microspheres (mg)/ Amount of microspheres taken (mg) *100

Entrapment efficiency[14]

Microspheres (50 mg) were crushed in a glass mortar and pestle and the powdered microspheres were dispersed in 500 ml of water. After 24 hours, the dispersion was sonicated to break up the microspheres completely and cause them to discharge their contents. It was then filtered and filtrate was analyzed for the drug content using a UV- spectrophotometer at 221.5 nm (Cary 60, Agilent Technologies).

EE (%) =Actual amount of zolmitriptan in microspheres (mg) /Theoretical amount of zolmitriptan in microspheres (mg)*100

Particle size analysis[12-13]

The particle size analysis was carried out using microscopic image analysis technique. The particle size was determined in a Motic digital microscope equipped with a 1/3" CCD camera imaging accessory and computer controlled image analysis software (Motic image plus 2).

***In-Vitro* drug release study**[15]

In vitro drug release study of Zolmitriptan for a period of 8 hrs was carried out using self prepared assembly. To study the drug release behavior of formulation, microspheres was transferred into the open ended test tube tied at one end with cellophane membrane of 0.22µm. The test tube was dipped from membrane side in a beaker containing 200 mL phosphate buffer pH 6.8. The temperature and stirring rate were maintained at 37 ± 5^0C and approx. 200 rpm, respectively. Samples (5 ml) were withdrawn periodically and replaced with an equal amount of phosphate buffer pH 6.8 to maintain the sink condition. Withdrawn samples were filtered through Whatman filter paper and then analyzed spectrophotometrically at 222.5 nm wavelength.

***In Vitro* mucoadhesive strength**[12-13]

A freshly cut 2cm^2 piece of goat nasal mucosa was obtained and cleaned by washing with isotonic saline solution. 100 milligram of microparticles was placed on mucosal surface which was fixed over glass slide. About 100µl of simulated nasal electrolytes (SNES: aqueous solution containing 8.77 mg/ml NaCl, 2.98mg/ml KCl and 0.59 mg/ml CaCl2) was placed on

microspheres and this plate was incubated for 15min in desiccators to allow the polymer to interact with the membrane. The support was then fixed at an angle of 45º relative to the horizontal plane. The nasal mucosa was thourghly washed with phosphate buffer (pH 6.8) at the rate of 1ml /min using burette. Sixty min after application of microspheres, the concentration of drug in collected perfusate was spectrophotometrically determined. The microsphere amount corresponding to the drug amount in perfusate was determined. The adhered microspheres amount was estimated from the difference between the applied microparticles amount and the flowed microparticles amount.

$$\% \text{ Mucoadhesion} = (Wa-W_l) /Wa* 100$$

Where, Wa = weight of microspheres applied; W_l = weight of microspheres leached out.

Degree of swelling[s12]

The swellability of microspheres in physiological media was determined by allowing the microspheres to swell in the phosphate buffer pH 6.8. 100 mg of accurately weighed microspheres were immersed in little excess of phosphate buffer saline of pH 6.8 for 24 h and washed thoroughly with deionized water.

$$\alpha = Ws–Wo/ Wo$$

Where,

α is the degree of swelling; Wo is the weight of microspheres before swelling and Ws is the weight of microspheres after swelling.

Surface characterization of microspheres by Scanning Electron Microscopy (SEM)[16]

The obtained microspheres were subjected for surface morphology using scanning electron microscope. SEM study was performed at DIYA Labs, Navi Mumbai by Scanning Electron Microscopy (SEM) using TEOL 5400 Model, Japan.

RESULTS AND DISCUSSION

Preformulation Studies

Fourier Transforms Infrared Spectroscopy (FT-IR) Analysis

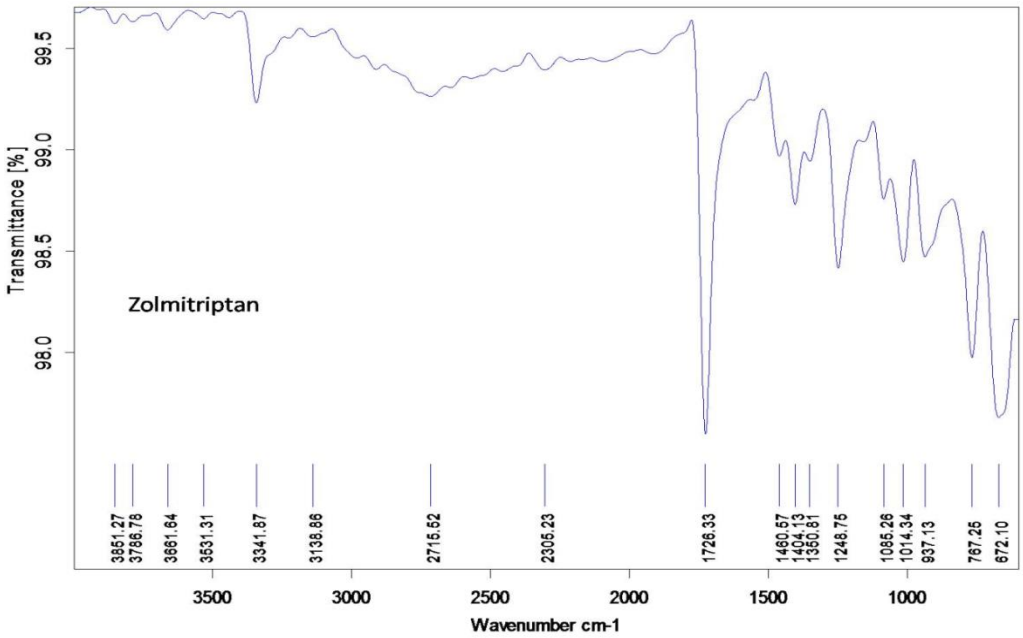

Figure 1: FT-IR spectra of Zolmitriptan.

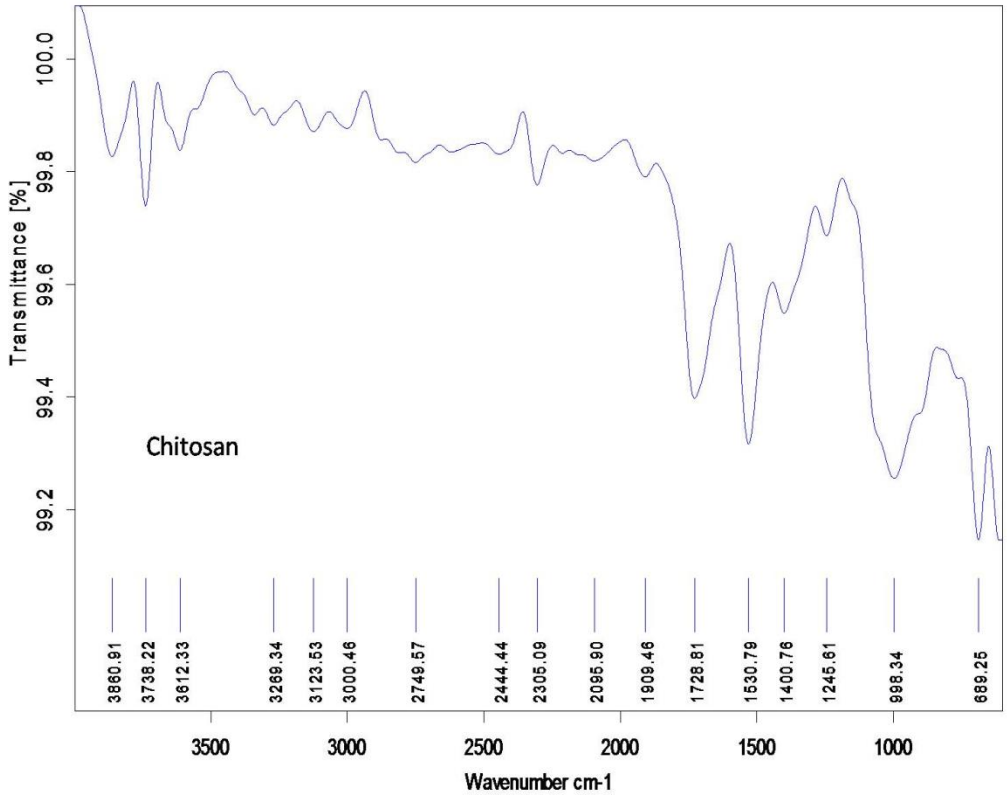

Figure 2: FT-IR spectra of Chitosan

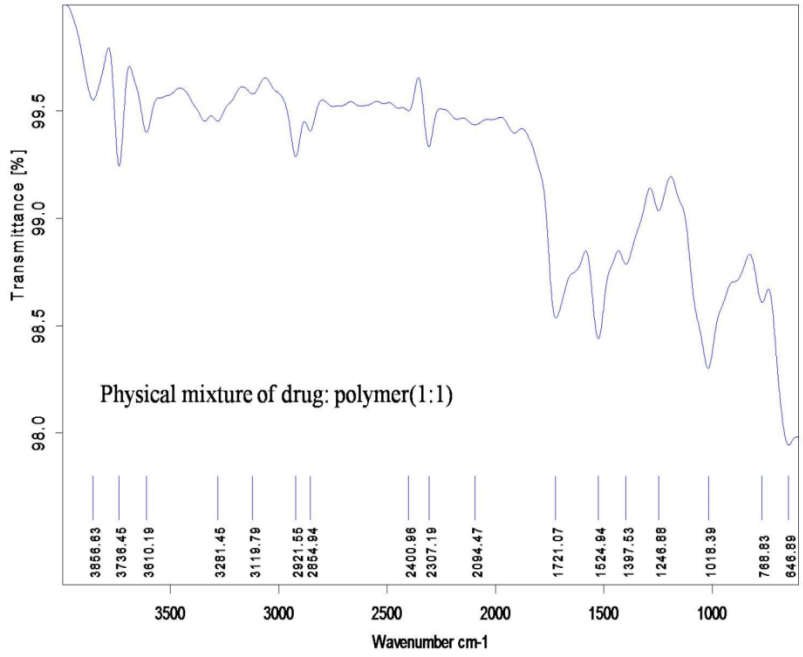

Figure 3: FT-IR spectra of Zolmitriptan and chitosan (Physical mixture)

The FTIR spectra of physical mixture of zolmitriptan and chitosan has not shown any extra peak or deletion of any peaks which are observed in individual spectra of zolmitriptan and chitosan. FT-IR Frequencies for Zolmitriptan, chitosan & physical mixture were given in table 2, 3, and 4 respectively.

Table 2. FT-IR Frequencies for Zolmitriptan

Sr no	Frequency (cm-1)	Type of Vibration
1	3341.87	N-H $_{str}$
2	1726.33	C=O $_{str}$
3	1460.57	=CH2 $_{bend}$

Table 3: FT-IR Frequencies for Chitosan

Sr no	Frequency (cm-1)	Type of Vibration
1	3612.33 & 3738.22	O-H $_{str}$
2	1728.81	C=O $_{str}$
3	1530.79	N-H $_{bend}$
4	998	C-H $_{bend}$

Table 4: FT-IR Frequencies for Physical mixture of Drug and Polymer (1:1).

Sr no	Frequency (cm-1)	Type of Vibration
1	3610.19 & 3736.45	O-H $_{str}$
2	2912.55	C-H $_{str}$
3	1721.07	C=O $_{str}$
4	1524.94	N-H $_{bend}$
5	1018.39	C-H $_{bend}$

Differential Scanning Calorimetry (DSC)

DSC curve of Zolmitriptan shows a sharp peak at 138.62ºC, due to melting of the drug, indicating its melting point. The pure polymer (chitosan) exhibits a peak at 202.01ºC, referring to the relaxation that follows the glass transition. The DSC Thermogram of physical mixture of drug and polymer shows peaks at 138.80 ºC and 194.41ºC respectively, showing no sign of interaction. DSC Thermogram of drug, polymer and Physical mixture of Drug and Polymer (1:1) are shown in figure 4, 5, 6.

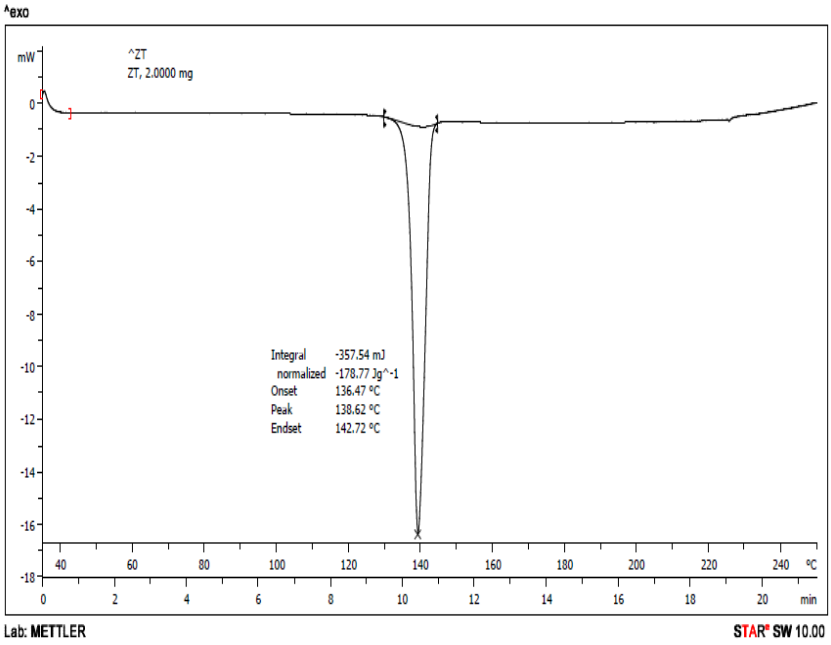

Figure4:DSC Thermogram of Zolmitriptan.

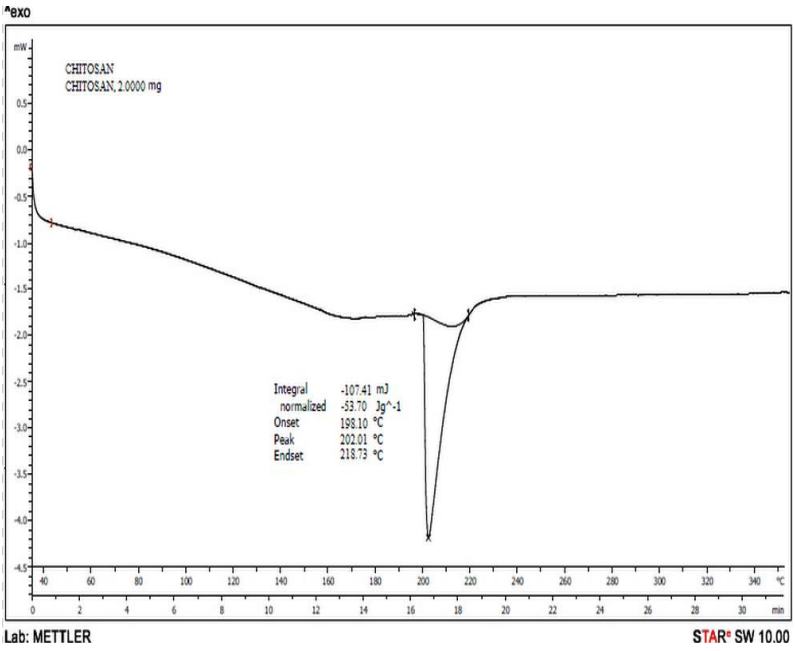

Figure 5:DSC Thermogram of Chitosan.

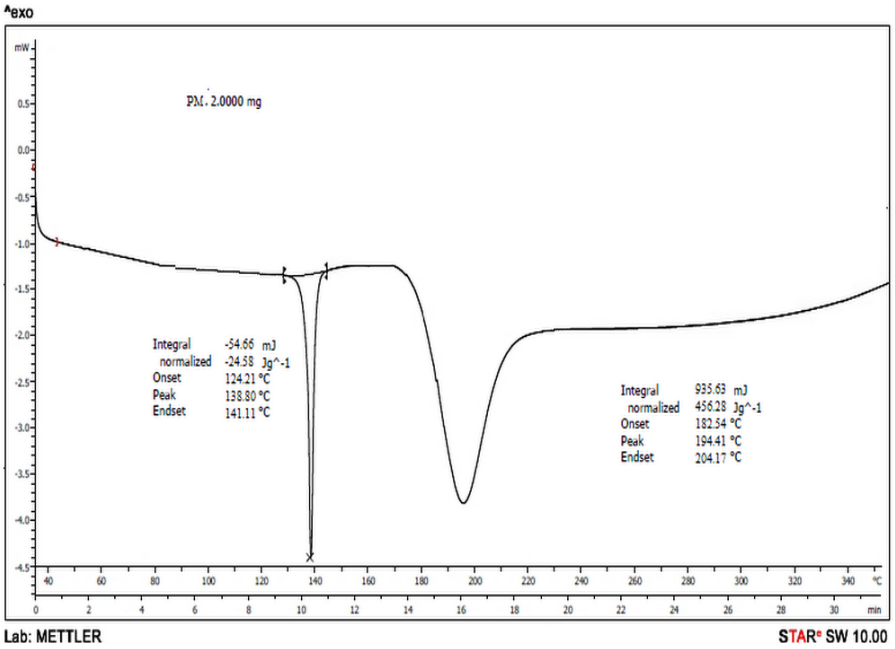

Figure 6: DSC Thermogram of Physical mixture of Drug and Polymer (1:1).

Formulation Studies

Micromeritic Properties

The microspheres for all eight formulations were evaluated. The angle of repose was found to be of all batches in range of 19˚.62 ± 0.63 to 22˚.61 ± 0.60 exhibiting good flow properties. Bulk density was found to be in range of 0.46 ± 0.003 to 0.56 ± 0.008 (gm/cm3). The outcome of tapped density was in the range of 0.5 ± 0.008 to 0.61 ± 0.01 (gm/cm3). Carr's index was found in the range of 8.00 ± 2.7 % to 12.55 ± 1.4 % which confirms excellent flow properties. The Hauser's ratio was found in the range of 1.08 ± 0.01 to 1.14 ± 0.01 which also confirms good flow properties of microspheres. Results of micromeritic properties were depicted in table no 5.

Table 5: Micromeritic properties of different batches of microspheres.

Sr No	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hauser's ratio	Angle of repose(θ)
F1	0.51 ± 0.01	0.58 ± 0.009	12.55 ± 1.4	1.14 ± 0.01	19.62 ± 0.63
F2	0.49 ± 0.003	0.54 ± 0.004	8.78 ± 0.74	1.09 ± 0.008	22.45 ± 0.46
F3	0.51 ± 0.01	0.56 ± 0.01	8.00 ± 2.7	1.08 ± 0.03	20.46 ± 0.23
F4	0.5 ± 0.007	0.55 ± 0.004	9.00 ± 2 1.5	1.09 ± 0.01	20.13 ± 0.24
F5	0.56 ± 0.008	0.61 ± 0.01	8.10 ± 1	1.08 ± 0.01	21.79 ± 0.80
F6	0.48 ± 0.003	0.53 ± 0.004	9.72 ± 1.26	1.1 ± 0.01	22.61 ± 0.60
F7	0.46 ± 0.003	0.5 ± 0.008	8.23 ± 1.88	1.09 ± 0.02	20.13 ± 0.24
F8	0.55 ± 0.013	0.61 ± 0.01	8.68 ± 0.70	1.09 ± 0.008	21.46 ± 0.47

Percentage Yield.

The percentage yield of different batches was determined by weighing the microspheres after

drying. The percentage yields of different formulations were found to be in range of 87 % - 96.4%.Results were given in table no 6.

Table 6: Percentage yield of different batches of microspheres

Sr No.	Batch	Yield (%)
F1	F1	93.33333
F2	F2	95
F3	F3	89.66667
F4	F4	93.4
F5	F5	95
F6	F6	93.2
F7	F7	87
F8	F8	96.4

Average of three values ± S.D.

Drug Content Determination

The various batches of the microspheres were subjected for drug content analysis & obtained results were summarized in table no 7. The powdered microspheres (50mg) were dissolved in adequate quantity (500ml) of phosphate buffer PH 6.8 then filter. The UV absorbance of the filtrate was measured using a UV spectrometer at 222.5nm. Drug content was found in the range of 13.16 ± 0.07 to 15.14 ± 0.13. Maximum drug content was observed for batch F5 (15.14 ± 0.13).

Table 7: Drug content values of different batches of microspheres.

Sr No	Batch	Drug content (%)
1	F1	14.82 ± 0.17
2	F2	13.86 ± 0.11
3	F3	13.82 ± 0.25
4	F4	13.16 ± 0.07
5	F5	15.14 ± 0.13
6	F6	14.1 ± 0.13
7	F7	14.42 ± 0.27
8	F8	13.73 ± 0.27

Average of three values ± S.D

Drug Entrapment Efficiency (E.E.)

The drug entrapment efficiency of different batches of microspheres were shown in table 8 below. Drug Entrapment Efficiency was found in the range of 41.48 ± 0.77 to 70.52 ± 0.68. Maximum drug content was observed for batch F6 (70.52 ± 0.68). From the obtained results it was observed that by increasing the concentration of polymer drug entrapment efficiency also increases.

Table 8: Entrapment efficiency of different batches of microspheres.

Sr No .	Batch	Entrapment efficiency (%)
1	F1	44.49 ± 0.53
2	F2	69.33 ± 0.55
3	F3	41.48 ± 0.77
4	F4	65.8 ± 0.36
5	F5	45.44 ± 0.39
6	F6	70.52 ± 0.68
7	F7	43.3 ± 0.81
8	F8	68.67 ± 1.36

Average of three values ± S.D.

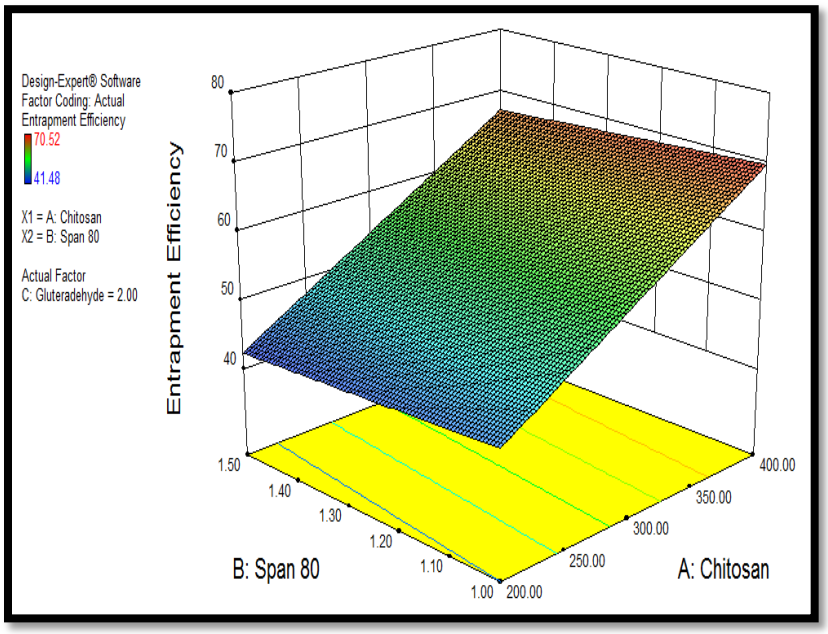

Figure 7: Three dimensional View of % Entrapment efficiency with respect to the concentration of polymer and surfactant.

Particle Size Analysis

The average Particle size was obtained in range of 8.36 ± 2.2 µm to 10.99 ± 2.82 µm. The Change in the concentration of polymer and surfactant results in variation of particle size of microspheres. The average particle size of formulation batch F3 showed minimum particle size(8.36 ± 2.2µm) while formulation batch F6 showed maximum particle size (10.99 ± 2.82 µm). Increase in the concentration of surfactant leads to decrease in the particle size of microspheres i:e average particle size obtained for batch F3 was 8.36 ± 2.2 utilizing 3% surfactant concentration. While greater particle size was obtained for batch F6 (10.99 ± 2.82) utilizing 1% surfactant concentration. Another effect which observed was with increase in the concentration of polymer, the particle size for microspheres also increases. Formulation batches

containing higher concentration of polymer i: e 400mg showed comparatively larger particle size (10.99 ± 2.82, 10.99 ± 2.82) for F2 and F6 respectively than those containing low concentration of polymer. The obtained particle size ranges for microspheres were shown in table 9.

Table 9: Particle size of different batches of microspheres

Sr. No.	Formulation code	Particle size (µm)
1	F1	9.12 ± 2.52
2	F2	10.67 ± 2.71
3	F3	8.36 ± 2.2
4	F4	9.43 ± 2.66
5	F5	9.33 ± 2.59
6	F6	10.99 ± 2.82
7	F7	8.65 ± 2.31
8	F8	9.92 ± 2.7

Average of three values ± S.D.

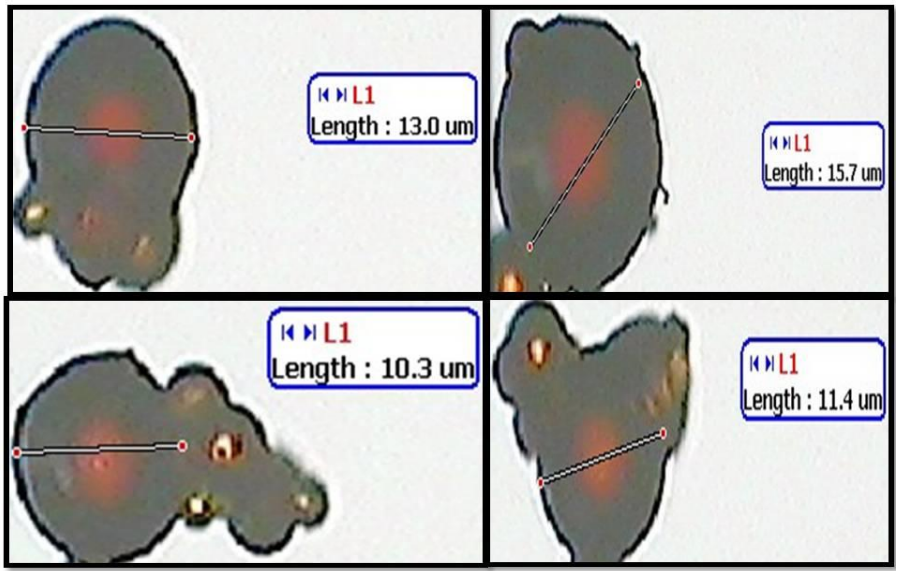

Figure 8: Motic microscopic images of microspheres

***In-Vitro* Drug Release Study**

In vitro drug release for Zolmitriptan loaded microsphere for a period of 8 hrs was carried out using self prepared assembly by using Phosphate buffer (pH 6.8) at 37 ± 5^0C using cellophane membrane of 0.22µm. From the dissolution profile of formulations F1 to F8, it is concluded that formulation batch F2 shows better drug release profile (76.90±3.03) than other formulations. Cumulative % release has been shown for average of three preparations. Cumulative % drug release for all the formulations are depicted in the table 10.

Table 10: *In- vitro* drug release studies of different batches of microspheres

Time	F1	F2	F3	F4	F5	F6	F7	F8
15 min	30.22±2.17	21.50 ± 1.63	34.85 ± 1.18	32.45 ±2.65	19.80 ±0.24	21.00 ± 3.2	30.35 ± 3.47	18.49 ±1.51
30 min	37.20 ± 5.18	28.55 ±3.51	38.99 ± 1.43	43.74 ± 7.29	28.26 ±1.71	23.65 ±3.67	37.26 ±2.74	27.66 ±2.34
60 min	46.02 ± 2.16	36.78 ± 6.60	40.77 ± 1.74	47.20 ±7.56	34.95 ±0.91	27.07 ±4.1	41.89 ±1.63	38.84 ±1.01
120 min	50.23 ± 1.81	54.61 ± 1.27	45.90 ± 1.17	51.01 ±8.21	40.02 ±0.93	29.89 ±1.98	45.82 ±1.14	43.44 ±1.78
180 min	53.45 ± 1.06	59.26 ± 1.53	51.03 ±0.85	54.28 ±9.62	42.74 ±0.93	39.20 ± 4.19	49.18 ± 1.53	46.26 ±1.83
240 min	56.24 ± 1.03	63.63 ± 2.68	54.85 ±0.69	57.78 ±8.02	44.80 ± 0.25	44.59 ± 2.63	51.38 ±1.22	50.95 ±2.79
300 min	61.40 ± 1.18	67.19 ± 1.96	60.37 ± 1.42	61.76 ±5.23	48.45 ± 1.18	48.80 ± 1.35	53.31 ±0.87	55.83 ±4.23
360 min	65.88 ± 1.44	69.90 ± 1.45	62.90 ±1.07	64.57 ±3.95	52.10 ± 0.34	53.40 ±2.18	57.84 ± 0.55	60.73 ± 4.02
420 min	69.63 ± 1.46	73.47 ±1.67	66 ± 0.87	67.30 ±2.94	59.36 ± 2.78	57.59 ±2.73	63.63 ± 0.96	63.01 ± 3.28
480 min	71.01 ± 2.12	76.90 ± 3.03	69.97 ±1.42	70.21 ±1.51	62.96 ± 0.23	61.09 ±1.44	69.59 ± 2.77	66.13 ± 3.27

Average of three values ± S.D.

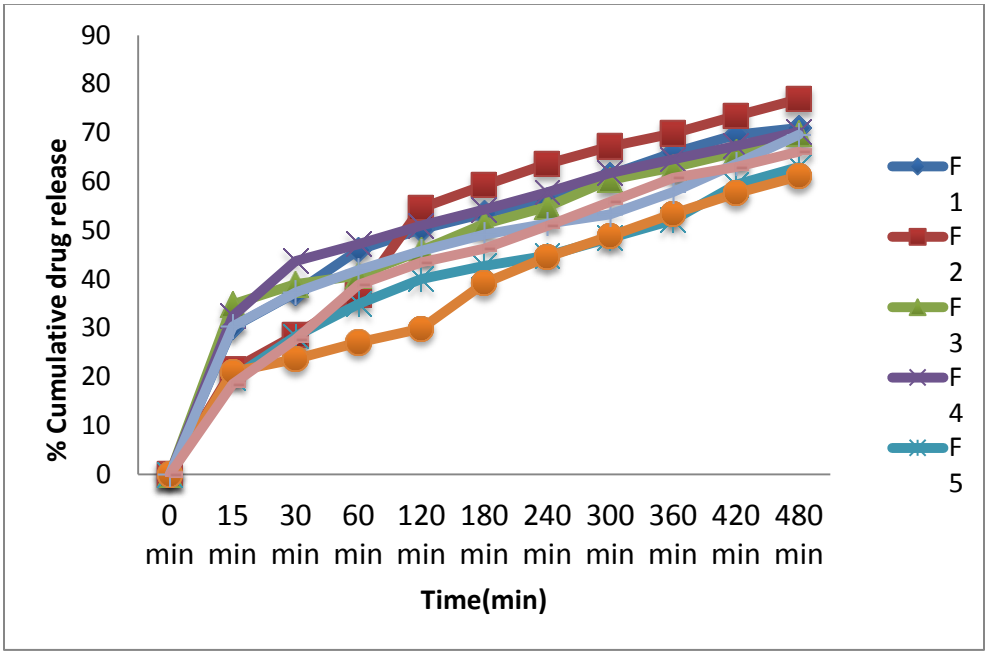

Figure 9: Graphical presentation of comparative drug release profile of 8 formulations.

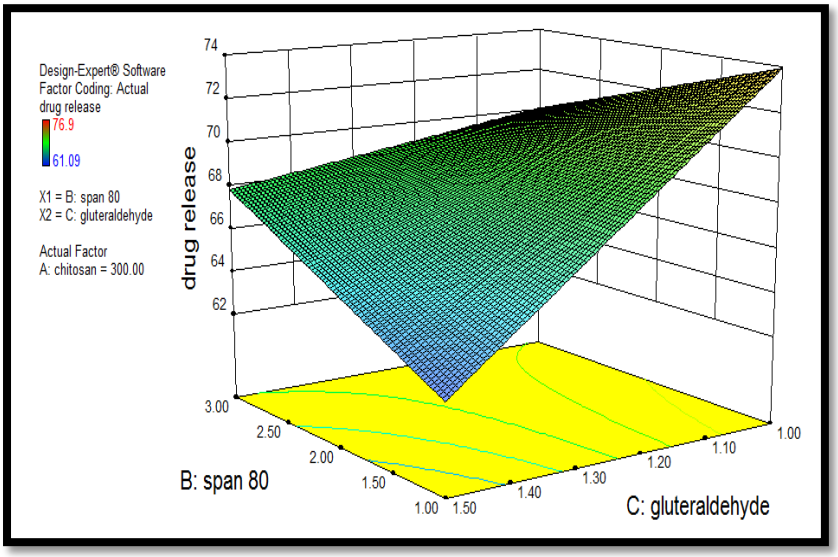

Figure 10: Three dimensional View of % drug release with respect to the concentration of surfactant and cross-linking agent.

Microspheres prepared with chitosan polymer effectively sustained the drug release to 8 hr. The effect of different polymer concentration on the release rate was also studied. The rate and extent of zolmitriptan release from microspheres significantly decreased with an increase in polymer concentration. Formulation batch F2 showed best appropriate balance between drug release rates. Cumulative % release has been shown for average of three preparations.

***In-vitro* Mucoadhesion Study**

Mucoadhesion studies were followed to ensure the adhesion of the formulation to the nasal mucosa for a prolonged period of time at the site of absorption. Mucoadhesion was found to be increased with increase in the concentration of polymer shown in table 11. The percentage mucoadhesion was found in the range from 65.72±0.79 to 82.11±1.6.

Table 11: *In vitro* mucoadhesive strength of different batches of microspheres

Sr No	Batch	*In-vitro* mucoadhesion (%)
1	F1	71.6±0.73
2	F2	82.11±1.6
3	F3	69.54±0.78
4	F4	79.22±0.87
5	F5	65.72±0.79
6	F6	75.31±1.19
7	F7	70.48±2.62
8	F8	71.71±1.35

Average of three values ± S.D.

***In Vitro* Degree of Swelling**

In vitro swelling properties of the microspheres are expressed as degree of swelling. Swelling

capacity of microspheres was determined by determined by allowing the microspheres to swell in the phosphate buffer pH 6.8 for 24 hrs. The maximum swelling (degree of swelling) 2.89 ±0.03 was observed with microspheres containing highest concentration of polymer. The degree of swelling of microspheres was found in the range of 2.05 ± 0.04 to 2.89 ±0.03.

Table 12: *In vitro* swelling capacities of different batches of microspheres

Sr No	Batch	Degree of swelling
1	F1	2.07 ±0.02
2	F2	2.69 ±0.02
3	F3	2.11 ±0.03
4	F4	2.9 ±0.03
5	F5	2.17 ± 0.02
6	F6	2.84 ± 0.04
7	F7	2.05 ± 0.04
8	F8	2.89 ±0.03

Average of three values ± S.D.

Scanning Electronic Microscopy

The microspheres were spherical in shape with smooth surface of microspheres. All microspheres were spherical with smooth surfaces.

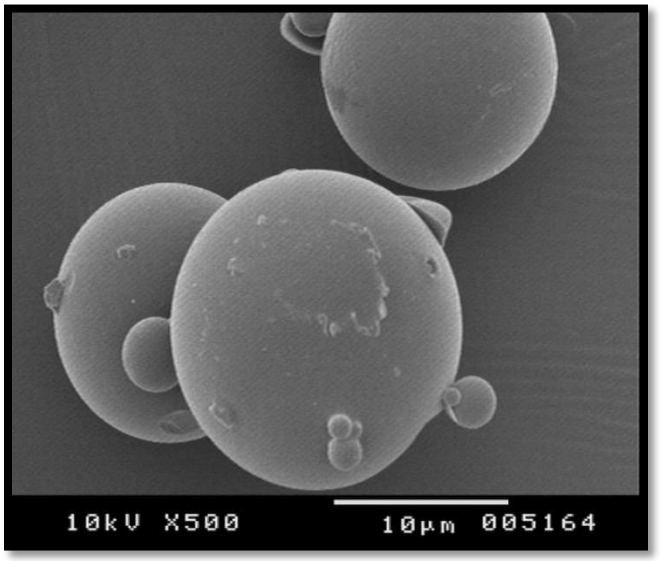

Figure 11: Scanning Electron Microphotograph of optimized formulation.

CONCLUSION

The emulsion Crosslinking technique is found to best suitable method for preparation of zolmitriptan microspheres. Prepared microspheres showed good entrapment efficiency with optimum drug release. Outcome of study concluded that chitosan can be employed as mucoadhesive polymer for nasal drug delivery system.

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