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Research Article

Formulation and Evaluation of Particulate Nasal Drug Delivery System for the Treatment of Migraine

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ABSTRACT

The intranasal delivery is preferable route for the administration of the drug for local systemic as well as central nervous system drug delivery. Microparticulate drug delivery system provides numerous advantages like, increased surface area, modified release pattern, improved bioavailability etc. The aim of the present study is an attempt to formulate and evaluate microspheres drug delivery system of Zolmitriptan by using Ethyl Cellulose as polymer for the treatment of migraine. The Zolmitriptan microspheres were prepared by quasi emulsion solvent diffusion method using methanol and dichloromethane system. The formulation parameters and processing parameters like ratio of drug polymer (1:2, 1:3, 1:4, 1:5, 1:6, 1:7), volume of water and stirring speed, time were optimized. The prepared microspheres were characterized for its drug content, percentage yield, compatibility study, powder characteristics, percent moisture content, *in-vitro* drug release, Ex-vivo mucoadhesion study. Based on In-vitro drug release the batch F4 is selected as optimized batch. Having drug: polymer ratio is 1:5 (Zolmitriptan 50 mg: ethyl cellulose 250mg). The *in-vitro* % drug release of batch F4 was 99.6.

Keywords: Zolmitriptan, mucoadhesion

1. INTRODUCTION

Intranasal drug delivery system is suitable for the local and systemic delivery of diverse therapeutic compounds. Among the non-invasive routes, nasal administration offers promising potential as a variable alternative for the delivery of some drugs. Hence, a surge of interest led to many investigations involving the cavum as a possiblewebsite for the administration of a lot of therapeutic agents. The nasal route is conventionally used for drug delivery for treatment of local disease. Now a days this route has received special attention as a conventional and reliable method for systemic delivery of drugs, especially those that are ineffective by route due to their metabolism in the GI tract being prone to first pass metabolism. The objective of present study is to prepare the sustained release microspheres. A sustained, constant drug level at the therapeutic optimum is needed in the blood in number of pathological conditions. Therefore the preparation of controlled and targeted drug delivery system is most important. The microparticulate delivery systems include mainly microspheres, liposomes, suspension and microemulsion.

Biodegradable and biocompatible polymer materials as drug carriers have been investigated in the recent 15 years in large number of studies in various drug delivery systems. Microparticles, have controlled diffusion through the matrix structure and also sensitive materials (drugs, peptides, hormones, vaccines, pDNA) can be protected against the external environment. The present work was aimed to formulate and evaluate

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microsphere of Zolmitriptan Microspheres prepared by quasi emulsion diffusion method using ethyl cellulose as polymer. Prepared microspheres were expected to adhere to the nasal mucosa and can be utilized for controlled release of Zolmitriptan for an extended period in the treatment of migraine. To achieve the objectives the plan is executed to improved therapeutic efficiency, provide prolonged contact with nasal mucosa enhances absorption and bioavailability, improvement in the resistance time, it has very effective in reducing migraine, avoid first pass metabolism and used for sustained release.

2. MATERIAL AND METHODS

2.1. MATERIALS

Zolmitriptan, Ethyl cellulose (Lobachemie Mumbai), Dichloromethane (Lobachemie Mumbai), methanol (Lobachemie Mumbai), Sodium hydroxide (Lobachemie Mumbai), Potassium dihydrogen phosphate (Lobachemie Mumbai), Ethanol (Lobachemie Mumbai).

2.2. METHODS

2.2.1. Preparation of Calibration curveof Zolmitriptan in phosphate buffer pH 6.6.

The 10 mg of drug dissolved in 100 ml of PBS (pH 6.6) respectively to get 100 µg/ml. concentration solutions and stock solution was farther diluted to obtain final standard solution in the range from 5-30 µg/ml. All the solutions were scanned through UV spectrophotometer (Pharmaspec UV 1700, Shimadzu) and absorbance were taken against PBS (pH 6.6) respectively as a blank at 227 nm. The values of absorbance were plotted graphically against the concentration.

2.2.2. Preparation of microspheres by quasi emulsion diffusion method

Microspheres were prepared by quasi-emulsion diffusion method. The weighed amount of Zolmitriptan was dissolved with polymer Ethyl cellulose in solution of dichloromethane and methanol. The resultant drug-polymer suspension was poured in 95 ml of distilled water. Under agitation 400-800 rpm and thermally controlled at 38^0C.

The agitation was continued for 40 min until the translucent quasi emulsion droplet turned into opaque microspheres. The solidified microspheres were recovered by filtration and washed with water. The resultant microspheres were dried at room temperature for half hour. The formulated batches were coded as F1, F2, F3, F4, F5, and F6

Table 1: Composition of microspheres

Sr. No.	Batches	Drug (mg)	Polymer(mg)	Solvent(ml)	Bridging liq.(ml)
1.	F1	50	100	3	2
2.	F2	50	150	3	2
3.	F3	50	200	3	2
4.	F4	50	250	3	2
5.	F5	50	300	3	2
6.	F6	50	350	3	2

2.2.3. Characterization of Zolmitriptan microspheres.

- **Drug content determination**

The all batches of microspheres were subjected to drug content determination. The microspheres (10mg) were dissolved in (900ml) phosphate buffer 6.6 and then filtered. The UV absorption of the filtrate was measured using UV spectrometer at 227 nm.

$$\text{Drug Content (\%)} = \frac{Actual\ amount\ of\ Zolmitriptan\ in\ microspheres\ (mg)}{Amount\ of\ microspheers\ taken\ (mg)}\ X\ 100$$

Theoretical and practical drug content determined was given in table no.

Table 2: Theoretical and practical drug content and % drug recovery of the quasi emulsion diffusion method microspheres for various batches

Sr. No.	Batch code	Theoretical Drug content(mg/50mg)	Practical Drug content(mg/50mg)	% Recovery of drug
1	F1	50.00	49.96± 0.011	98.99±0.021
2	F2	47.66	46.63± 0.010	91.11±0.016
3	F3	42.42	41.41± 0.016	99.27±0.001
4	F4	40.17	40.13± 0.021	99.97±0.009
5	F5	45.03	44.01± 0.09	98.01±0.017
6	F6	43.12	41.21±0.012	99.21±0.014

* Each value is average of three separate determinations ±SD

- **Moisture content determination**

To determine the moisture present in quasi emulsified microspheres exactly 100 mg of powder was weighed and was dried at the hot air oven at 60 ^{0} C till constant weight. Percentage moisture content was the calculated.

$$\text{\% moisture content} = \frac{Initial\ weight\ -\ Final\ Weight}{Initial\ Weight}\ X\ 100$$

Percentage moisture content in various batches of the quasi emulsion diffusion microspheres determined by hot air oven is given in table no. 3

Table 3: % Moisture content in various batches determined by hot air oven

Batch code	% Moisture content*
F1	1.86±0.0324
F2	1.55±0.0905
F3	1.84±0.0056
F4	2.32±0.0245
F5	1.96±0.0133
F6	1.89+0.0122

* Each value is average of three separate determinations ±SD

- **Drug-excipient compatibility study**
- **Infrared spectroscopy**

Fourier transform – infrared spectra of drug and formulation batch F4 were obtained. The spectra were scanned over the range of the wave number range from 4000 – 400 cm^{-1}. FT-IR spectra of pure drug and formulation were shown in fig. no. 1 and 2 respectively.

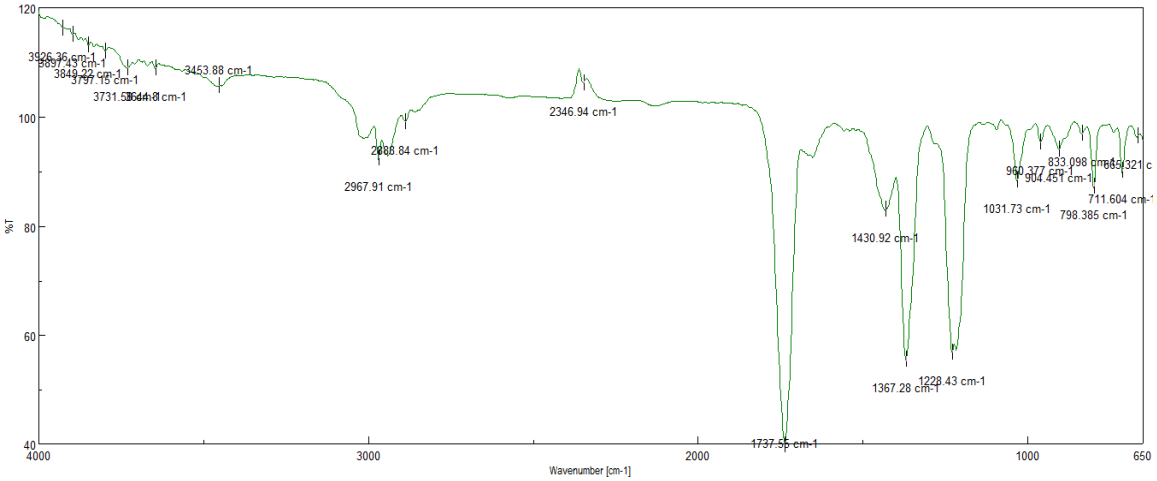

Fig. 1: IR Spectra of Zolmitriptan

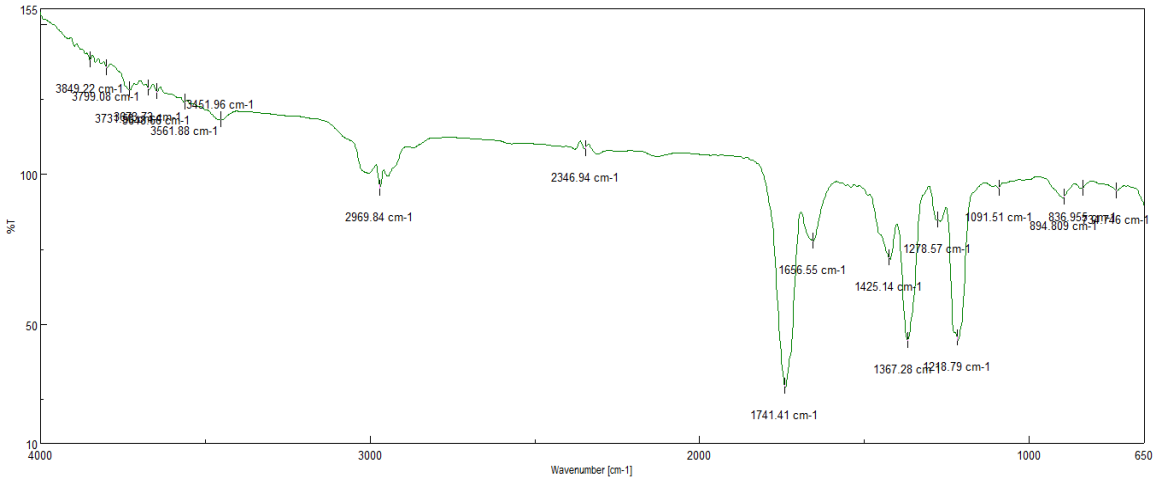

Fig. 2: IR Spectra of Formulation F4

- **Differential scanning calorymetry**

Thermal analysis of drug and formulation was performed by differential scanning calorimetry. DSC thermogram of pure drug and formulation was shown in fig. no. 3 and 4 respectively.

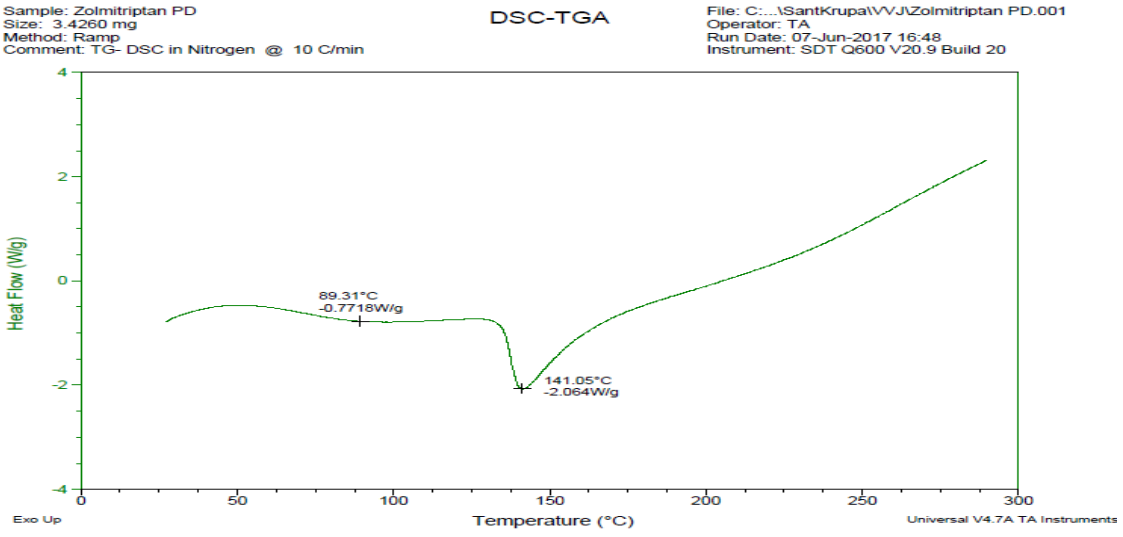

Fig. 3: DSC Graph of pure drug Zolmitriptan

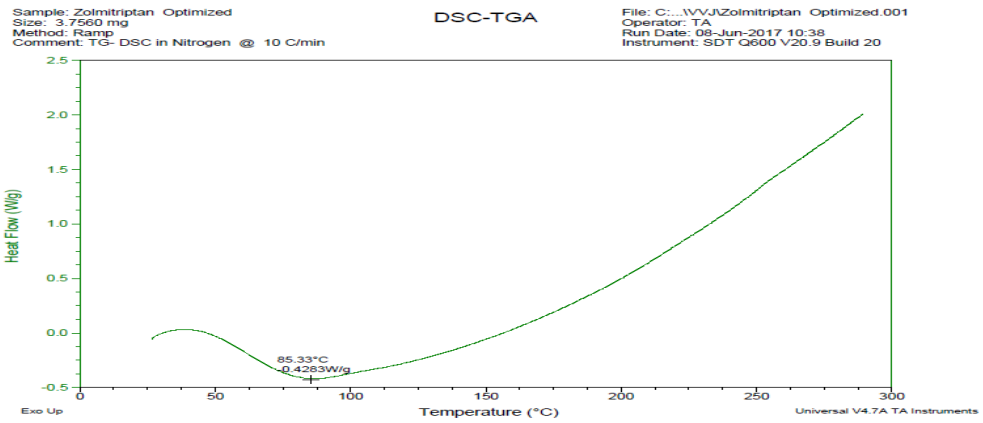

Fig. 4: DSC Graph of For Formulation F4

- **Powder X-RAY diffraction study**

To obtain the change in the crystallanity of the microspheres prepared, the PXRD study was carried out by using X ray diffractometer. For this sample of pure drug, formulated batch were irradiated with monochromatisedCuKα radiation and analyzed between from 5^0 to 60^0 (2θ). Powder X ray diffractrograms of pure drug and formulated batch shown in fig. no. 5 and 6

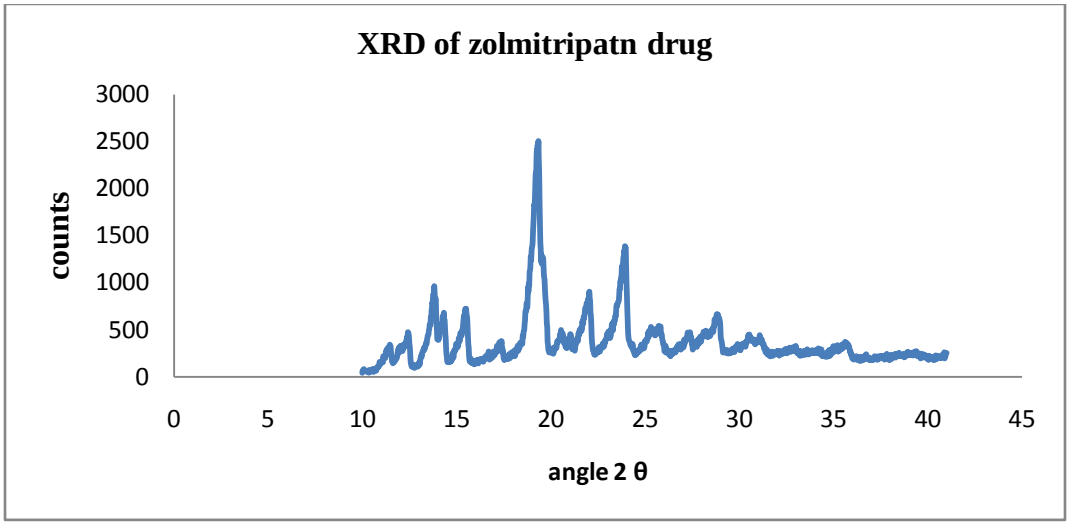

Fig 5: Powder X ray diffractograms of Zolmitriptan drug

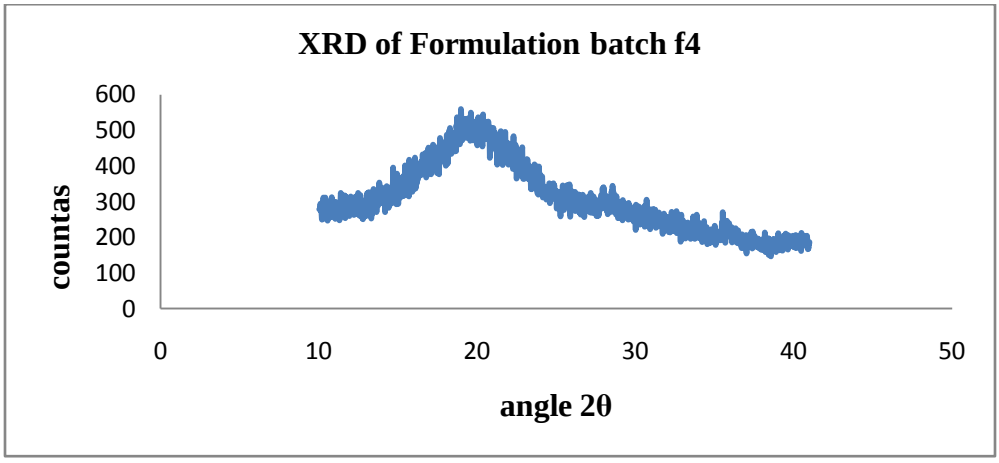

Fig. 6: Powder X ray diffractograms of formulation F4

- **In-vitro release study**

In-vitro drug release studies were performed with aUSP (type 2) dissolution apparatus. Sample of microspheres containing 50 mg of Zolmitriptan were tested in phosphate buffer 6.6. The rotational speed was set at 30 rpm and temperature for dissolution medium was set at 37^0 C. sample (5ml) were withdrawn at predetermined time points (0.5, 1, 1.5, 2, 2.5, 3, 3.5, up to 8 hrs.) and for each withdrawal the corresponding volume was replaced with fresh phosphate buffer of same temperature. Samples were filtered (watman filter paper) and assayed spectrophotometrically for Zolmitriptan at 227 nm dissolution profile of formulation batches is given in fig. no. 7

Table 4: In-vitro drug release studies of Zolmitriptan microspheres

Sr. No.	Time (Hrs.)	F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	0.5	46.25±0.002	42.33±0.40	37.68±0.84	19.13±0.3	16.83±0.24	15.57±0.36
3	1	52.99±0.031	50.1±0.48	44.47±0.37	38.32±0.4	28.28±0.36	22.09±0.08
4	1.5	63.21±0.004	59.32±0.48	56.91±0.18	42.85±0.2	37.21±0.1	31.79±0.41
5	2	71.24±0.21	68.03±0.45	64.42±0.21	47.49±0.6	44.17±0.08	37.92±0.48
6	2.5	82.93±0.44	73.6±0.58	78.9±0.16	51.81±0.3	47.2±0.42	42.6±0.40
7	3	95.01±0.85	79.35±0.45	81.82±0.26	53.6±0.2	48.27±0.11	49.3±0.36
8	3.5	95.02±0.41	84.24±0.51	87.38±0.12	57.8±0.4	50.58±0.42	55.47±0.39
9	4	95.01±0.35	97.32±1.16	91.55±0.28	59.28±0.66	55.72±0.46	58.61±0.33
10	4.5	95.01±0.65	97.32±016	96.20±0.49	71.9±0.5	61.81±0.40	63.04±053
11	5	95.013±0.27	97.33±0.36	96.43±0.91	79.8±0.5	68.91±0.51	69.95±0.50
12	6	95.01±0.41	97.31±0.69	96.44±0.36	88.95±0.4	74.53±0.40	71.8±0.77
13	7	95.01±0.39	97.32±0.48	96.45±0.37	99.6±0.61	81.67±0.37	75.4±0.75

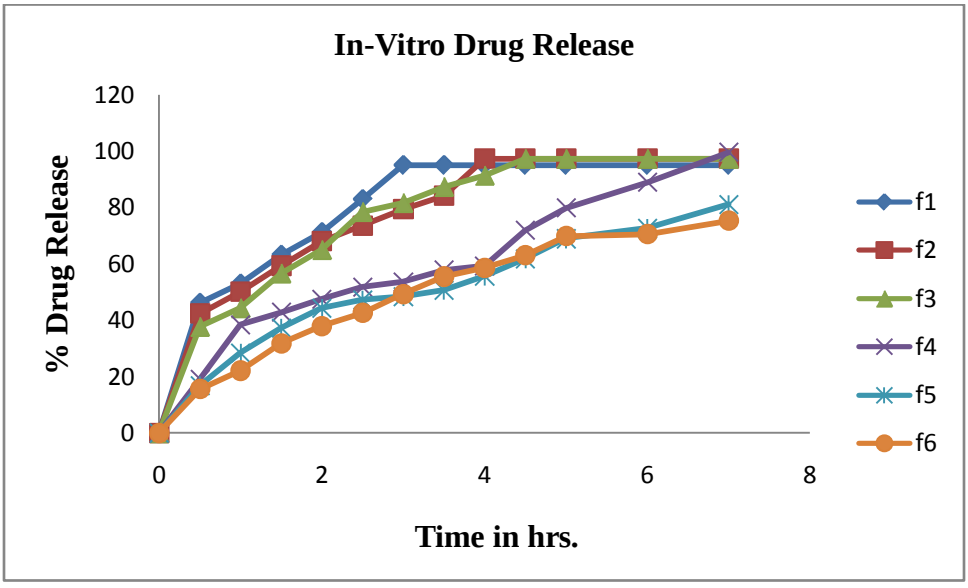

Fig. 7: Graph of In-vitro Drug release

- **Ex-vivo mucoadesion study**

To study the drug permeation through the nasal mucosa, ex-vivo study using Goat nasal mucosa (obtained from Slaughter house) was performed using Franz diffusion cell. Nasal mucosa was washed with phosphate buffer pH 6.6 and size of contact area 1.55 cm^2 was mounted on the receptor compartment of the Franz diffusion cell (diameter 10 mm, 15ml volume), with dermal face in contact with the phosphate buffer (pH6.6). two experimental sets in triplicate were performed keeping the temperature 37±0.5 ^{0}C, at speed of 100 rpm. The Zolmitriptan microspheres were resuspended in 2ml phosphate buffer pH 6.6 and paced on surface of nasal mucosa. 2 ml sample was withdrawn from replaced compartment at 0min, 15min, 30min, 1h, 2h, 4h, 6h, 8h, 16h, and 24hrs. and replaced with 2 ml of fresh phosphate buffer to maintain sink condition. The pure drug aqueous solution was taken as control group. Sample was analyzed by UV-spectroscopy at 227nm for the estimation of amount of drug permeated with time. The ex-vivo mucoadhesion study was shown in fig no. 8

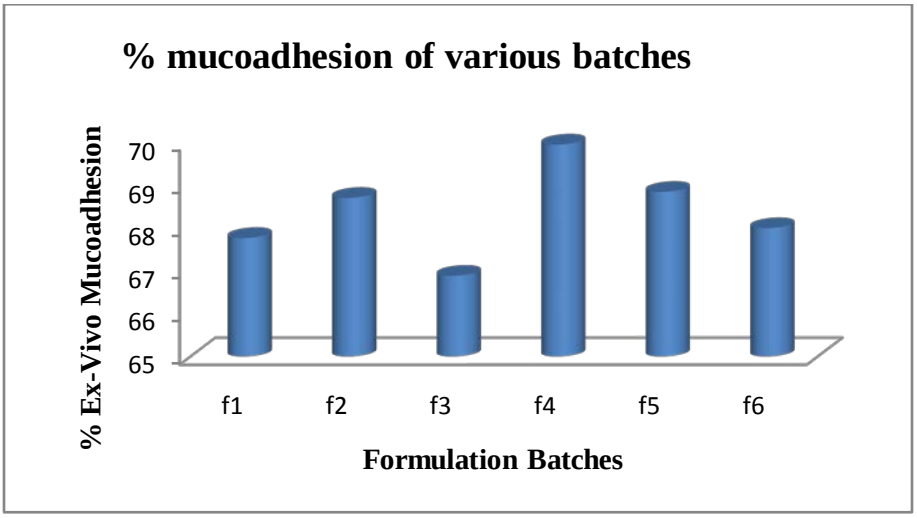

Fig. 8: Percent mucoadhesion Zolmitriptan microspheres of batches (F1-F6)

Table 5: Percent Ex-vivo mucoadhesion of various batches

Sr. no.	Batch Code	% Ex-vivo mucoadhesion
1	F1	67.76±0.02
2	F2	68.7±1.02
3	F3	66.74±1.05
4	F4	69.95±0.99
5	F5	68.84±0.56
6	F6	67.99±1.06

- **Stability study**

Stability studies were carried out according to ICH guidelines by storing the formulation F4. The accelerated studies were done 40^{0}c± 2^{0}c / 75%±5% for a period of three months in a programmed environmental test withdrawn (CHM-10S, Remi instrument Ltd. Mumbai, India). The sample were withdrawn at 0 and 30 days and analyzed for the drug content and in-vitro drug release.

Table 6: Conditions for stability studies:

Sr. no.	Study	Storage Conditions	Min. time for recovery of data at submission
1	Accelerated	40^{0}C ± 2^0 C /75% ±5% RH	3 months

Table 7: Stability study of formulation Batch F4

Time	Drug content (mg)	Drug release
Zero month	2.848±0.063	98.25±1.75
Third month	2.93±0.091	97.01±1.62

RESULT AND DISCUSSION

Drug content determination

The drug content of batches containing polymer Ethyl cellulose and Zolmitriptan was determined by UV spectroscopic method. The amount of drug microspheres was found proportionately near to that of incorporated drug. Theoretical and practical drug content and % drug recovery of various batches of quasi emulsion diffused particles are shown in table no. 2

Moisture content determination

The moisture content of the formulated batches was found to 1.55-2.32%. The moisture content found to be is given in table no. 3

Drug excipient compatibility study

FTIR study

FTIR spectra of pure drug Zolmitriptan and formulation were shows no any interaction between drug and polymer. It shows no any change in principal peaks. It shows the peaks at NH Stretching 3457.96, C=O-O 1656.55, CH_2 group 1425.14, C-H Stretching 2969.84, CH_3 Stretching 1367.28, Cyclic ring 2346.94. FTIR spectra of pure drug and formulated batch F4 is shown in fig. no. 1 and 2

Differential Scanning Calorimetry

Thermal analysis of Zolmitriptan and formulated batch F4 was performed by using DSC. The thermograms of pure drug and formulated batch F4 was in fig no. The drug shows the endothermic peak at 141^0 C. The thermogram of batch F4 shows the peak of formulation was dramatically reduced in the DTA at 85.33^0 C. This result suggests that the crystalline structure of Zolmitriptan was transferred into an amorphous state during the quasi emulsion diffusion method and the drug was molecularly dispersed inside the microspheres as supported by X-ray study.

X-RAY diffraction study

The X-ray diffracatograms of pure drug and formulated batch F4 is shown in fig. The X-ray diffraction pattern for Zolmitriptan displayed the presence of numerous distinct peaks at 2θ angle 19.25^0, 20.44^0, 22.21^0, 24.23^0, 26.54^0. The molecular state of Zolmitriptan in the microspheres was changed from crystalline state to amorphous state. This shoes that entrapped drug molecule is monomolecular dispersed in the polymer matrix. This amorphous nature of microspheres is useful for entrapment of its bio-availability from nasal route of administration.

In-vitro release study

In-vitro drug release were carried out and enumerated in fig no. from the in-vitro drug release study results the maximum percentage drug release (99.6%) at the end of 8 hrs. was observed with trial F4 batch which contains 250 mg of ethyl cellulose. Below 250 mg of ethyl cellulose concentration the drug release is observed within 3 to 5hrs. And the drug release from the batches F5 and F6 shows the more time to drug release that more than 8 hrs. From all the batches F4 batch is selected as best formulation due to drug release pattern. The drug: polymer is in the ratio 1:5 (Zolmitriptan 50mg: 250mg Ethyl cellulose).

Ex-vivo mucoadhesion study

Ex-vivo drug permeation studies Goat nasal mucosa was selected as biological membrane for permeation studies using Franz diffusion cell. The ex-vivo mucoadhesion indicates that microspheres had good mucoadhesive property and could adequately adhere on nasal mucosa. It was observed that increase in proportion of polymer, ethyl cellulose increased mucoadhesive strength of microspheres. This can be due to modification of the permeability of the nasal membrane by employment of absorption enhancers such as ethyl cellulose which can increase the absorption of

drugs and the use of mucoadhesive systems such as bioadhesive liquid formulations, microspheres, powders and liquid gelling formulation that decrease mucocilliary clearance of the drug formulation and thereby increase the contact time between the drug and site of absorption. Percent ex-vivomucoadhesion is given in table no. 5

Stability study

Stability studies were conducted for the best formulation (F4) for three months according to ICH guidelines and evaluated for drug assay, *in vitro* release studies. Accelerated stability studies were conducted. After subjecting the samples for different temperature and humidity conditions there was not much difference found in the drug content at the various time intervals. The *in vitro* drug release profiles were super imposable which confirms the stability of the product.

SUMMARY AND CONCLUSION

The Zolmitriptan microspheres were prepared successfully by quasi emulsion diffusion method. The prepared microspheres show the good mucoadhesion, it shows good compatibility study. The drug release from the batch F4 is 99.6% within 8hrs. Having drug: polymer ratio is 1:5. The API Zolmitriptan was evaluated for its organoleptic properties and solubility. The results found are satisfactory. Hence it can be concluded that formulated controlled release microparticulateddrug delivery system of Zolmitriptan may be ideal and effective to control migraine attacks by allowing the drug to release continuously for 8 hrs. The quasi emulsion diffusion method is found to be best suitable method for the preparation of microspheres showed good mucoadhesion with optimum drug release. The outcome of study concluded that ethyl cellulose can be employed as mucoadhesive polymer for nasal drug delivery system.

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