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FORMULATION AND EVALUATION OF ZOLMITRIPTAN MICROSPHERE

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ABSTRACT

In this work, zolmitriptan microsphere was prepared and evaluated. The zolmitriptan microsphere was prepared by emulsion cross linking method using various concentrations of chitosan polymer. The prepared microsphere were characterized for its drug content, particle size, zeta potential, percentage yield, entrapment efficiency and *in vitro* drug release profile. Based on the *in vitro* drug release profile of Zolmitriptan microspheres formulations (F1, F2, F3 and F4) formulation F4 was selected as the best formulation which contains the particle size of 3.2µm and drug:polymer in the ratio of 1:1.5 (Zolmitriptan 100mg:150mg of Chitosan). The *in vitro* % drug release of F4 formulation was 98.17 and it was found to be suitable formulation for the treatment of migraine patients. Hence it can be concluded that the newly formulated controlled release microparticulate drug delivery systems of Zolmitriptan may be ideal and effective to control the migraine attacks by allowing the drug to release continuously for 24 hrs.

KEYWORDS: Zolmitriptan, Emulsion Cross linking, Zeta potential, Migraine, Nasal route.

INTRODUCTION

A sustained, constant drug level at the therapeutic optimum is needed in the blood in a number of pathological conditions. Therefore the preparation of controlled and targeted drug delivery systems is most important. The microparticulate delivery systems include mainly pellets, microparticles, lipospheres and macroemulsions.[1,2] The aqueous solubility, which becomes for many drugs the main drawback during formulation either in a liquid form or in a controlled release system, has been overcome by microencapsulation techniques. 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 microsphere of Zolmitriptan Microspheres prepared by emulsion crosslinking method using chitosan 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.[3,4] 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.

MATERIALS AND METHODS

Materials Used: Zolmitriptan and chitosan were purchased from Sigma Aldrich, Liquid paraffin, Span 80, Tween 80, Glutaraldehyde was purchased from Loba Chemicals, Mumbai, All other chemicals and reagents used were of analytical grade.

METHODS

Preparation of microsphere by emulsion cross linking method: Chitosan were accurately weighed and mixed in 10 ml of distilled water, preheated to 60˚c followed by the addition of tween 80 (0.1%w/v). To this 0.1gm of zolmitriptan was added and thoroughly mixed to obtain a homogeneous solution. The mixture was maintained at 50˚c and then added dropwise into 100ml of liquid paraffin containing span 80 (0.1%w/v) preheated to 60˚c at constant stirring with three blade stirrer in order to form a w/o emulsion.[5,6]

Glutaraldehyde was added dropwise to the emulsion and stirred for 1 hour at room temperature to stabilize the microsphere. The mixture was then left to cool at between 5 to 10˚c for 30 mints to enhance settling of microsphere. Microspheres were collected by centrifugation. Several batches namely (F1, F2, F3 and F4) were formulated by changing the drug and polymer ratio.[7,8]

Table 1: Formulation Code

S. No	Formulation	Drug (mg)	Polymer Chitosan (mg)	Surfactant Span 80 (ml)	Solvent Liquid Paraffin (ml)	Solvent Glutaraldehyde (ml)
1.	**F1**	100	50	2ml	100	25ml
2.	**F2**	100	100	2ml	100	25ml
3.	**F3**	100	150	2ml	100	25ml
4.	**F4**	100	200	2ml	100	25ml

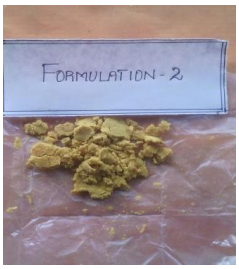
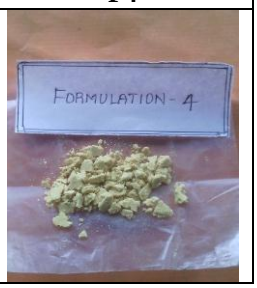
Formulation	F1	F2	F3	F4
Image				

Fig. 1-4: Formulations of Zolmitriptan Microspheres

Characterization of zolmitriptan microspheres

Drug content: 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.

$$\text{Drug content (\%)} = \frac{Actual\ amount\ of\ Zolmitriptan\ in\ microspheres\ (mg)}{Amount\ of\ microspheres\ taken\ (mg)} X100$$

Particle size analysis: Particle size was determined using PCS (S4700 PCS System Zetasizer 6.32, Malveran UK).

Sample preparation for particle size analysis: A known amount of microspheres were dispersed in distilled water (1mg/ml) and subjected to sonication for 5min and vortex mixing before analysis. The size and size distribution of the microspheres plays an important role in determining their fate and therapeutic effects after administration. One of the advantages is their greater ratio of surface area. The size and size distribution are also important to determine their interaction with the cell membrane and their penetration across the physiological barriers. This can be measured by using photon correlation spectroscopy, dynamic light scattering and laser diffraction analyzer. The polydispersity index quantitatively measures the uniform dispersion of the microspheres. Low the poly dispersity indicates the narrow size distribution of particles.

Zeta potential: Surface charge is important in adhesion and interaction of particle with cells. The zeta- potential is used to measure the cell surface charge density. It can be measured using Malveran-mastersizer.

Percentage yield: The percentage yield of different formulations was determined by weighing the microspheres after drying.

$$\text{Percentage yield} = \frac{Total\ weight\ of\ microspheres}{Theoritical\ weight\ of\ drug\ polymer} X100$$

Entrapment efficiency: 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 221.5nm (Cary 60, Agilent Technologies).[10]

***In vitro* drug release studies:** *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 ± 50C 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. From the absorbance values the cumulative percentage drug release was calculated.[9]

RESULTS AND DISCUSSION

Drug content determination

The various batches of the microspheres were subjected for drug content analysis & obtained results were summarized in table. 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 12.80 to 15. Maximum drug content was observed for batch F3(15.14).

Table.2: Drug Content of Microspheres

S. No	Batch	Content (%)
1.	F1	12.80
2.	F2	13.16
3.	F3	15.14
4.	F4	14.82

Drug entrapment efficiency: Drug Entrapment Efficiency was found in the range of 56.67 to 90.12 Maximum drug content was observed for batch F3 (90 ± 1.9). From the obtained results it was observed that by increasing the concentration of polymer drug entrapment efficiency also increases.

Table 3: Drug Content of Microspheres

S. No	Batch	Drug: polymer ratio	% drug entrapment
1.	F1	1:1	56.67
2.	F2	1:2	67.50
3.	F3	1:3	90.12
4.	F4	1:4	82.40

Percentage yield: The percentage yield of different batches was determined by weighing the microspheres after drying.

Table 3: Percentage Yield Values of Microspheres

Batch	Drug: Polymer ratio	% YIELD
F1	1:1	60
F2	1:2	52
F3	1:3	87
F4	1:4	90

Zeta Potential

Table 4: Zeta Potential Values of Microspheres

S:No	Batch	Zeta potential values
1	F1	-3.20
2	F2	-18.6
3	F3	3.70
4	F4	-2.88

Size distribution

Table 5: Size Distribution of Microspheres

S:No	Batch	Particle size (µm)
1	F1	1.1
2	F2	2.3
3	F3	3.2
4	F4	4.8

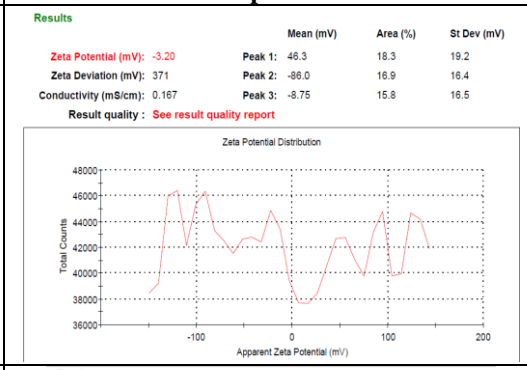
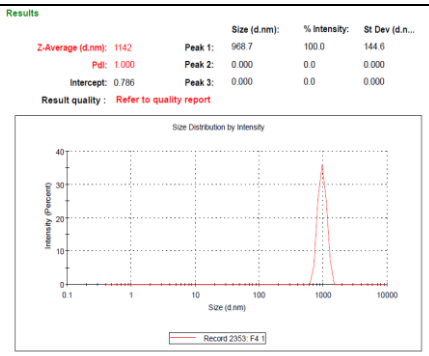
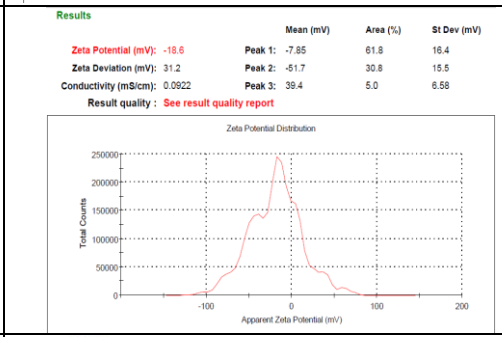
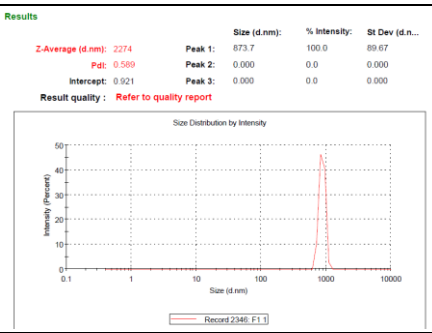
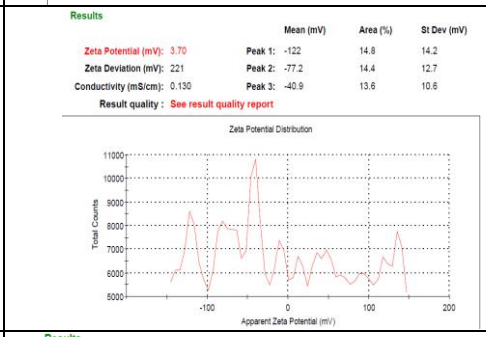
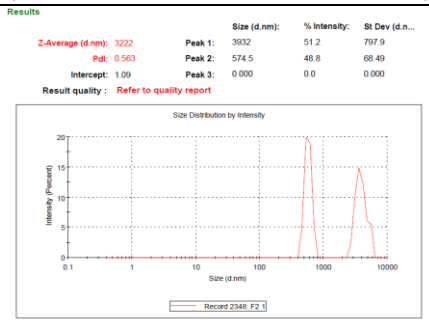
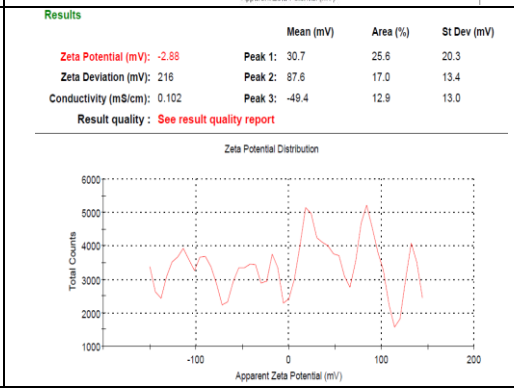
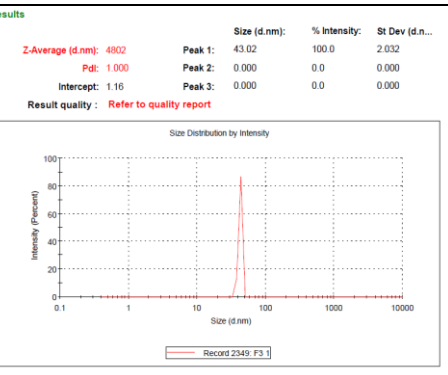
Batch	Zeta potential	size distribution
F1		
F2		
F3		
F4		

Fig.5-12: zeta potential and size distribution

***In vitro* drug release studies[52]**

Table 6: *In vitro* Release Studies Of Zolmitriptan Microspheres

S. No	Time in hours	%Cumulative Drug Release			
		F1	F2	F3	F4
1	0.5	30.26	20.72	17.86	10.64
2	1	40.67	35.61	31,34	26.73
3	6	78.46	65.24	60.29	52.61
4	12	93.52	85.48	75.55	64.29
5	16	**97.23**	91.35	88.67	71.28
6	20	**97.22**	**97.25**	92.49	81.37

7	24	**97.21**	**97.18**	**98.17**	90.36

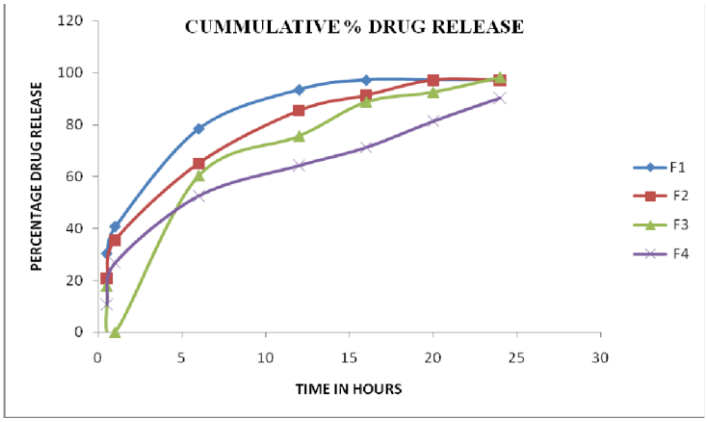


Fig.13: *In vitro* drug release

From the *in vitro* drug release study results, the maximum percentage drug release (98.17) at the end of 24hwas observed with trial F3 which contains 150 mg of Chitosan. Below 150 mg of Chitosan concentration as in the case of trials F1 and F2 the maximum percentage drug release 97.23 and 97.25% were obtained at the end of 16 and 20hours respectively which was not desirable. Beyond 150 mg of Chitosan concentration, reduction in drug release was observed in the case of trial F4. The maximum percentage drug release for F4 was found to be 90.36% at the end of 24h were obtained. From the *in vitro* drug release data for F1- F4, it was observed that increase in Chitosan concentration delays the drug release due to increased particle size and reduced surface area available for drug release. From all the formulations, F3 was selected as best formulation due to its ideal particle size, high entrapment efficiency (90.8%) and desirable drug release (98.17% at 24 h).

SUMMARY CONCLUSION

The active pharmaceutical ingredient Zolmitriptan was evaluated for its Organoleptic properties and solubility. The results obtained were satisfactory.

Zolmitriptan microspheres were prepared by emulsion cross linking technique and the polymer concentrations were optimized by various trials In the present study Chitosan microspheres containing Zolmitriptan were prepared. The effect of increase in polymer concentration in various parameters like particle size and *in vitro* release profile were studied.

The Zolmitriptan microspheres were formulated and evaluated for its *in vitro* drug release profile. The results showed that the *in vitro* drug release for F1, F2, F3 and F4 were found to be 97.23, 97.25, 98.17 and 90.36 respectively.

Based on the *in vitro* drug release profile of Zolmitriptan microspheres formulations (F1, F2, F3 and F4) formulation F4 was selected as the best formulation which contains the particle size of 3.2µm and drug:polymer in the ratio of 1:1.5 (Zolmitriptan 100mg:150mg of Chitosan).

The *in vitro* % drug release of F4 formulation was 98.17 and it was found to be suitable formulation for the treatment of migraine patients. Hence it can be concluded that the newly formulated controlled release microparticulate drug delivery systems of Zolmitriptan may be ideal and effective to control the migraine attacks by allowing the drug to release continuously for 24 hrs.

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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