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FORMULAION AND *INVITRO* EVALUATION OF ZOLMITRIPTAN HYDROGEL BEADS

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ABSTRACT

A sustained release system of Zolmitriptan was formulated to increase the residence time in intestine and to modulate the release behavior of the drug. Hydrogel drug delivery has significant ability to control the drug release. Drug and polymer compatibility was studied by subjecting physical mixtures of drug and polymers to FTIR spectrophotometry. The beads were prepared by Ionotropic gelation method. By using Sodium alginate, pectin and karaya gum in 1:1, 1:2, 1:3 ratios. The beads were evaluated for percent drug entrapment efficiency, and *in vitro* drug release. The *in vitro* drug release study of the beads was carried out in PH 6.8 Phosphate buffer by USP dissolution method and in a flow through cell apparatus and the results were compared. In the modified flow through dissolution method, Beads formulated employing Sodium alginate alone could not sustain the drug release, whereas beads formulated with mixture of Sodium alginate and copolymers demonstrated sustained release of Zolmitriptan for 12hrs.

Key words: Zolmitriptan, Inotropic gelation, Hydrogel, Pectin, Karaya gum.

INTRODUCTION

High patient compliance and flexibility in designing dosage forms attracted the oral drug delivery systems to be the most convenient mode of drug administration when compared to other dosage forms. Of these, matrix systems have gained widespread importance in controlled drug delivery due to cost-effective manufacturing technology [1]. The swellable matrices for oral administration are commonly prepared as tablets by compression of hydrophilic micro particulate polymers. Many natural polysaccharides like chitosan [2], alginate [3] and gums/mucilage like Xanthan [4], gaur gum [5] more sustain the release of drug from matrix system than widely used synthetic materials like methylcellulose, hydroxypropyl methyl cellulose and sodium carboxymethyl cellulose. These natural or synthetic polysaccharides form hydrogel in aqueous media [6]. Over the past few decades, advances in hydrogel technologies have spurred development in many biomedical applications including controlled drug delivery [7]. Hydrogels are very versatile materials and have attracted significant attention recently as drug delivery system. The hydrogels are entangled polymer networks that trap a large amount of water without dissolving. Hydrogels are comprised of cross-linked polymer networks that have a high number of hydrophilic group or domains. These networks have a high affinity for water, but are prevented from dissolving due to the chemical or physical bonds formed between the polymer chains and water penetrates these networks causing swelling, giving the hydrogel its form. The development of hydrogels from a variety of synthetic and natural material has provided a great deal of flexibility in fabricating of modified release system [8].

Biocompatible & biodegradable hydrogels have been designed using natural polymers and various gums due to low toxicity and susceptible to enzymatic degradation or using synthetic polymers that possess hydrolysable moieties [9]. The hydrogels from these natural polymers have been prepared with a variety of different shapes and formulations that include liquid gel, powders, beads, films, tablets, capsules, microspheres and sponge [10].

Migraine is a mysterious disorder characterized by pulsating headache, usually restricted one side,

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which comes in attacks lasting 4-48 hrs. Zolmitriptan is a synthetic tryptamine derivative and appears as a white powder that is readily soluble in water. Zolmitriptan is used for the acute treatment of migraine with or without aura in adults. It has a half life of 2.5 -3 hrs .Zolmitriptan formulating into hydrogel beads is a modern and a more innovative approach used to prolong the drug release pattern. Thus to sustain the drug release and to reduce the dosing frequency hydrogel beads are developed.

MATERIALS AND METHODS

Materials

Zolmitriptan was obtained from Dr. Reddy's Lab, Hyderabad, India. SODIUM ALGINATE was purchased from Krishna Pectins Pvt. Ltd, India , Pectin was obtained from S.D. Fine Chem. Ltd, India, Karaya gum was obtained from Colorcon Industries, India CALCIUM CHLORIDE was taken from B. F. Goodrich Chemicals Co., USA ,WATER was from Universal Medicare Pvt. Ltd, Mumbai.

Methods

FTIR spectroscopy The drug - excipients interaction were studied using Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA). An IR spectrum for the drug was recorded in a FTIR for pure drug and physical mixtue of pure drug and polymers with Potassium Bromide (KBr) pellets. The spectra were scanned over the 3600 to 400 cm-1 range.

FORMULATION DESIGN

Preparation of Hydrogel beads: Ionotropic gelation technique

Hydrogel of were prepared by Ionotropic gelation technique. In the present work three sets hydrogel beads were prepared by using (1:1,1:2,1:3) sodium alginate alone in different concentrations and with different concentrations of polymers like, Pectin ,Karaya gum and Calcium chloride as counter ion. The detailed composition of the various formulations prepared is as mentioned in Table 1.

Preparation of Hydrogel beads

The beads were prepared in three batches. In the first set three formulations of microbeads were prepared (F1, F2, F3). Solutions of Sodium alginate in different ratios were used. In the second set another three formulations were developed with Pectin and Sodium alginate in different ratios (F4,F5,F6). In the third set Karaya gum was used along with the sodium alginate in different ratios (F7,F8,F9).a polymer solution was prepared in 100ml of deionized water. In 50ml of polymer solution, weighed quantity (250mg) of Zolmitriptan was dispersed uniformly in all three solutions saparetly. Bubble free dispersion was dropped through a syringe into 100ml aqueous calcium chloride solution and stirred at 100rpm. After stirring for 10minutes, the gelled beads were separated by filtration, washed with distilled water, air dried and finally dried at 60^0 for 6 hours in oven.

EVALUATION OF PHYSICOCHEMICAL PARAMETERS OF FLOATING BEADS

Determination of bead diameter

The diameter of a sample of gel beads (25 beads) of each formulation was determined using a dial thickness meter. Measurement for each sample was repeated ten times. Mean diameter and standard deviations were recorded.

Surface morphology (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). The samples were gold coated prior to the scanning. For examination of the internal structure of the beads, they were cut in half with a steel blade.

Drug Entrapment Efficiency

200 mg beads were crushed using a porcelain mortar and a pestle, and dispersed in suitable solvent (p^H 6.8 phosphate buffer). The dispersion was sonicated for 15 minutes and left overnight for 24 hrs, then the dispersion was filtered. A 1 ml sample was taken and diluted with suitable solvent (p^H 6.8 phosphate buffer), and analysed using a UV-visible spectrophotometer at λmax of 215 nm

The percentage drug entrapment efficiency (%EE) of each bead formulation was calculated using the following equation:

$$EE\ (\%) = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

IN VITRO DRUG RELEASE STUDIES

In vitro release characteristics of gel beads were evaluated employing USP XIV dissolution testing apparatus 2 (paddle method). The dissolution test was performed using 900 ml of p^H 6.8 phosphate buffer as dissolution medium maintained at 37±0.5 ºC. The contents were stirred at 50 rpm. A 5 ml aliquot of the solution was withdrawn at predetermined time intervals for 12 h and fresh 5ml dissolution media was replaced to maintain sink condition. The sample aliquots were analyzed spectrophotometrically at a wavelength of 215 nm (UV spectrophotometer, 1601, Shimadzu, Japan).

STABILITY STUDIES

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

RESULT AND DISCUSSION

FTIR spectroscopy Compatibility studies were performed using FTIR spectrophotometer. The FT IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption peaks shown that they are in official limits (±100 cm^{-1}) the drug is compatible with excipients (Fig 1 & Fig 2).

Scanning electron microscopy

The1 scanning electron microscopy of blank and drug loaded beads are shown in fig 3

SEM analysis of the F8 formulation shown the smooth external morphology as in the fig 3

Determination of beads diameter

Diameter was determined using dial thickness meter**.** The prepared beads were almost spherical and translucent. The mean surface diameter of 9 formulations was between 1.693±0.015(SD) and 1.793±0.015(SD) (Table 2). It was found that the incorporation of copolymers (Sodium alginate,Pectin and Karaya gum) increased the bead diameter in formulations F1 to F9. As the process parameters were kept constant, the added materials were responsible for the changes in the size of the beads.

Drug entrapment efficiency

Entrapment efficiency was determined as per the procedure and results are shown in the Table .2 .The Formulation F8 shown the highest drug entrapment and formulation F1 showed the lowest entrapment. As the copolymers concentration increased the entrapment efficiency of various Zolmitriptan hydrogel beads was found to be increased in each batch.

IN VITRO RELEASE PROFILE

In-vitro drug release study of Zolmitriptan hydrogel beads was carried in pH 6.8 phosphate buffer for a period of 12hrs. In the pH 6.8 phosphate buffer the beads exhibited a biphasic release profile as an initial rapid drug release phase (burst effect) was followed by a sustained, gradually increasing drug release phase after 1h extending upto14h. Formulation F9 contained sodium alginate, karaya gum could sustain. The zolmitriptan release upto14h. It released complete drug at the end of 14h. Whereas formulations contained Sodium alginate F1, F2 and F3 released 98.41%, 99.89% and 100.2% of drug respectively at the end of bellow10h. The formulations contained pectin; F4, F5 and F6 released 100.84%, 100.63% and 98.62% of the drug at the end of 12h respectively. The formulations contained karaya gum; F7, F8 and F9 released 97.85%, 99.93% and 98.15% of the drug at the end of 14 h respectively.

STABILITY STUDIES

Stability studies were conducted for the best formulation (F8) for six 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.

Table 1. Formulation Design of Microbeads

S.NO	INGREDIENTS	FORMULATIONS								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	SUMATRIPTAN	1	1	1	1	1	1	1	1	1
2	SODIUM ALGINATE	1	2	3	0.5	1	1.5	0.5	1	1.5
3	PECTIN	-	-	-	0.5	1	1.5	-	-	-
4	KARAYA GUM	-	-	-	-	-	-	0.5	1	1.5

Table 2. Characterization of Zolmitriptan beads

Formulation code	Mean Diameter ± SD (mm)	% EE
F1	1.693±0.015	61.50
F2	1.740±0.020	62.38
F3	1.700±0.026	65.95
F4	1.793±0.015	70.97
F5	1.720±0.030	72.38
F6	1.727±0.021	76.83
F7	1.723±0.015	79.78
F8	1.707±0.015	82.90
F9	1.783±0.021	80.78

Table 3. Kinetics of release pattern of F8

S.NO	Formulation Code	r^2 value for zero order equation	r^2 value for first order equation	r^2 for Higuchi equation	r^2 for Peppas equation	n value for Peppas equation
1	F4	0.979	0.876	0.951	0.8278	0.7

Table 4a. Conditions for stability studies

S.no	Study	Storage conditions	Min. time forrecovery of data at submission
1	Accelerated	40^0c ±2^0c /75% ±5% RH	3 months

Table 4b. Stability study of formulation F8

Time	Drug content (mg)	Drug release
Zero month	2.908±0.057	97.55±1.61
Third Month	2.923±0.096	96.91±1.78

Fig. 1. FT-IR Spectra of pure drug (Zolmitriptan)

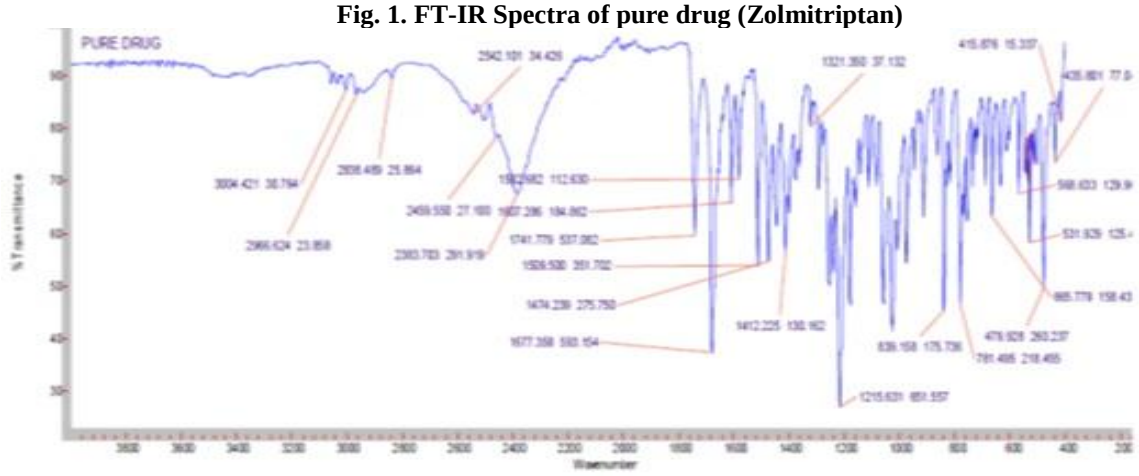


Fig 2. FT-IR Spectra of physical mixture of polymers and drug

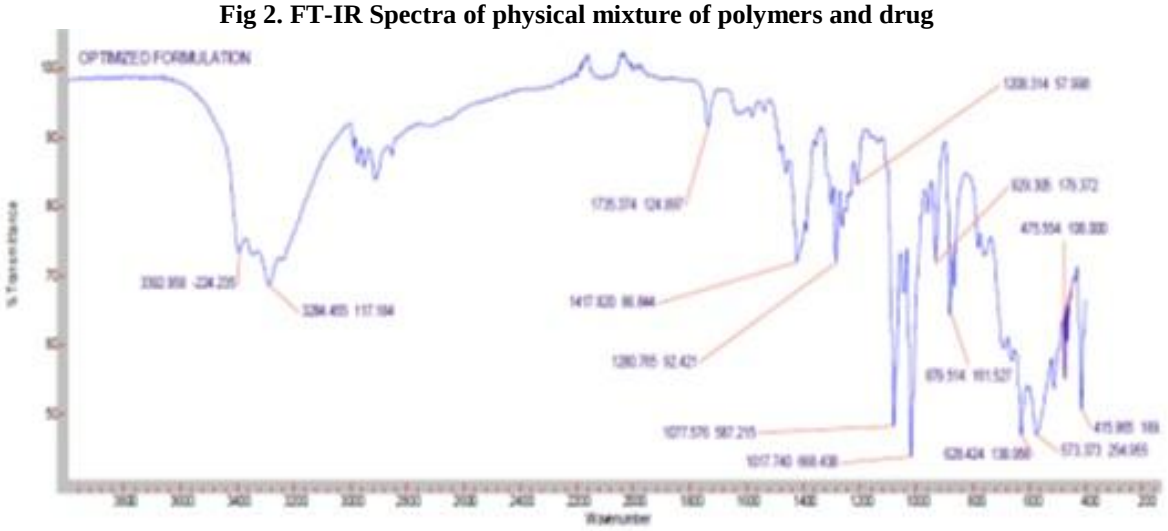


Fig 3. Scanning electron microscopy of (a) blank and (b) drug loaded beads (F8)

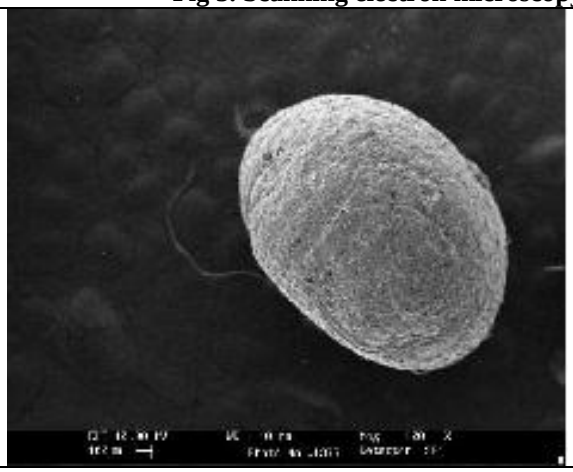


Fig 4. *In Vitro* Release of FormulationsF1-F9

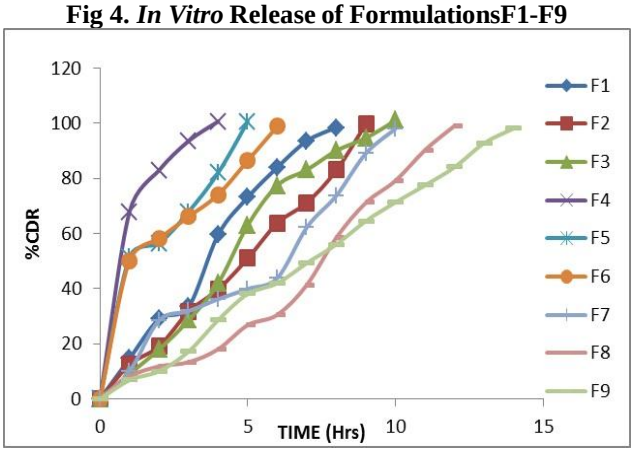


Fig 5. Zero order kinetics:F8

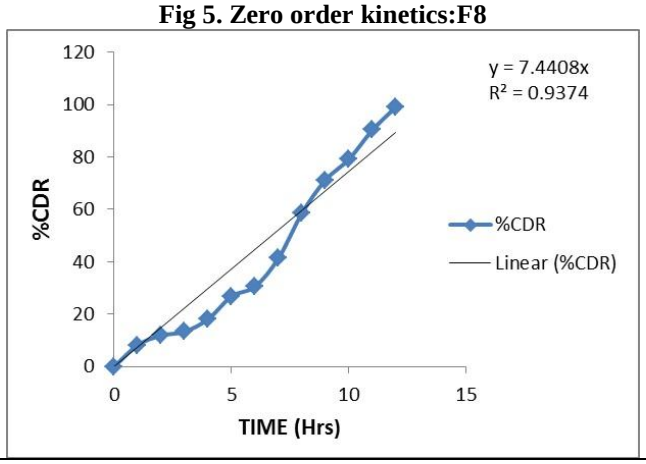
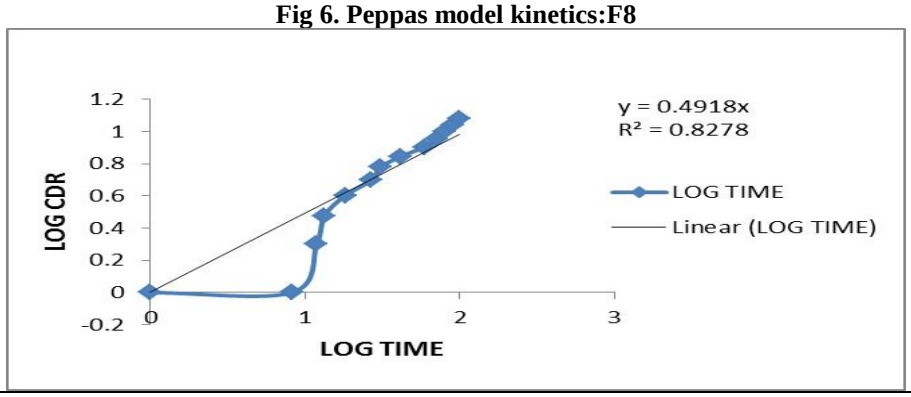


Fig 6. Peppas model kinetics:F8



CONCLUSION

All the preformulation and post formulation evaluations were conducted and the results were satisfactory. The results also shown that beads formulated with mixture of Sodium alginate and karayagum (F8) shown the highest drug release compared to other formulations. So the formulation F8 was selected for stability studies and surface morphological studies by scanning electron microscopy. To analyze the mechanism of drug release from the beads, the *in vitro* release data was fitted into various release models. It was observed that the release of the drug followed Zero Order kinetics and peppas model mechanism of drug release .Stability study results show that formulation was stable.

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