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Formulation development and in-vitro evaluation of controlled release dalfampridine hydrogel beads

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A B S T R A C T

The concept of formulating hydrogel beads containing Dalfampridine offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. In present work, hydrogel beads of Dalfampridine were prepared successfully by ionotropic gelation method using different polymers. Formulated beads were evaluated for SEM, Percentage Drug content & In-vitro dissolution studies. Pre-formulation studies like melting point, solubility and UV analysis complied with standards. The FT-IR Spectra revealed that, there was no interaction between Dalfampridine and polymers. Surface smoothness of the Dalfampridine beads was confirmed by SEM. As the ratio of polymer was increased, the mean particle size of Dalfampridine floating beads was decreased. Dalfampridine floating beads with normal frequency distribution were obtained. From in-vitro dissolution studies, F3 formulation containing Carbopol 940 shows prolonged and controlled release up to 20 hrs. Which follows zero order release with super case transport mechanism.

Keywords: Dalfampridine, HPMC K100M, HPMC K30M, Carbopol 940, controlled release

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Multi particulate systems have been paid considerable attention since several years in controlling and sustaining of release rate of many active pharmaceutical ingredients and use of natural biodegradable and synthetic polymers as rate controlling agents also has been enormously increased. Recently, dosage forms that can precisely control the release rates and targets drugs to a specific body site have made enormous impact in the formulation and development of novel drug delivery systems. Oral multiunit dosage forms such as microcapsules and microspheres have received much attention as modified/ controlled drug delivery systems for the treatment of various diseases without major side effects. Additionally, the beads maintain functionality under physiological conditions, can incorporate drug to deliver locally at high concentration ensuring that therapeutic levels are reached at the target site while reducing the side effects by keeping systemic concentration low. It will therefore be advantageous to have means for providing an intimate contact of the drug delivery system with microbeads. Delivery systems for the treatment of various diseases without major side effects. Additionally, the beads maintain functionality under physiological conditions, can incorporate drug to deliver locally at high concentration ensuring that therapeutic levels are reached at the target site while reducing the side

effects by keeping systemic concentration low. It will therefore be advantageous to have means for providing an intimate contact of the drug delivery system with microbeads.

2. Materials and Methods

Materials

Dalfampridine procured by Spectrum Pharma Labs Hyderabad. Sodium alginate, HPMC K100M, HPMC K200M, Carbopol 940 and Calcium chloride purchased from Loba Chemie Pvt. Ltd., Mumbai & S D fine chemical Ltd, Mumbai respectively.

Method of Preparation of Hydrogel beads by Ionotropic gelation method

Accurate quantity of polymer was dissolved in 25ml of distilled water and stirred to form dispersion. Drug was added to the above dispersion and again stirred for uniform distribution and stirred until a homogenous mixture was obtained. The mixture was extruded through a 23G syringe needle into calcium chloride solution (2% w/v). The beads were allowed to remain in the same solution for 30 min to improve their mechanical strength. The formed beads were separated, washed with water and allowed to dry at room temperature overnight.

Evaluation parameters of Hydrogel beads

The Hydrogel beads was evaluated for various parameters

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). Dry Dalfampridine gel beads were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of Dalfampridine hydrogel beads were taken by random scanning of the stub.

Percentage yield

Percentage practical yield of Dalfampridine hydrogel beads was calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Dalfampridine beads recovered from each batch in relation to the sum of starting material.

Drug Content

To determine the drug content and encapsulation efficiency of the beads, 10 mg beads were crushed using a porcelain mortar and a pestle, and dispersed in suitable solvent. 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, and drug content assayed using a UV-visible spectrophotometer at λ-max of 257 nm. The drug content of each formulation was recorded as mg / 10 mg of gel beads.

Drug Entrapment Efficiency

The drug entrapment efficiency of prepared beads was determined by using the following equation.

EE (%) = Actual Drug Content/ Theoretical Drug Content X 100

Dissolution Study

Dissolution Parameters

Medium: 900ml, 0.1N HCL for 2hrs and 6.8pH phosphate buffer for 10hrs.
Apparatus: Paddle (USP-II)
RPM : 100
Temperature: 37^{o} C±0.5

Procedure

The release rate of Dalfampridine Hydrogel beads was determined by employing USP XXIII apparatus II (paddle method). The dissolution test was performed using 900 ml 0.1N HCL, for 2hours and at 6.8pH Phosphate buffer for 10hours, at 37 ±0.5°C at 50 rpm. Dalfampridine h y d r o gel beads equivalent to 10 mg of Dalfampridine was used for the study. At various time points (hourly) 5ml of the sample solution was withdrawn from the dissolution apparatus for up to 12 hrs., and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at 260 nm. Dissolution profiles of the formulations were analyzed by plotting cumulative percentage drug release versus time. The data obtained were also subjected to kinetic treatment to understand release mechanism.

3. Results and Discussion

Determination of absorption maximum (λ-Max)

Determination of Dalfampridine λ-max was done in 6.8 pH phosphate buffer for accurate quantitative assessment of drug dissolution rate. The Dalfampridine peak value is 260. The linearity was found to be in the range of 5- 30 µg/ml in 6.8 PH buffer. The regression value was closer to 1 indicating the method obeyed Beer- lamberts' law.

Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Evaluation of Dalfampridine Hydrogel beads

The Hydrogel beads was prepared by Ionotropic gelation method using HPMC K100M, HPMC K200M & Carbopol 940 as rate retarding polymers, Sodium alginate as gelling agent and calcium chloride as crosslinking agents. The prepared Hydrogel beads were evaluated for its different parameters which revealed many interesting results for efficient preparation of the Hydrogel beads. FT-IR spectroscopy analyses indicated the chemically stable, amorphous nature of the drug in these Hydrogel beads. SEM photographs revealed the spherical nature of the Hydrogel beads in all variations. The formulation F3 has better results than other eight formulations. F3 have its particle size 500nm, drug content 90.26%, drug release 88.59% in 12 hours. The optimized formulation F3 has coefficient of determination (R^2) values of 0.992, 0.948, 0.947 and 0.835for Zero order, First order, Higuchi and Korsmeyer Peppas respectively. A good linearity was observed with the Zero order, the slope of the regression line from the Korsmeyer Peppas equation which showed linearity with n value of 1.33 for optimized formulation (F3). Thus, n value indicates the super case transport mechanism.

Table 1: Formulation design for Dalfampridine H y d r o gel beads using different ratios of drug and polymers.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dalfampridine	50	50	50	50	50	50	50	50	50
Sodium alginate	200	450	700	200	450	700	200	450	700
HPMCK30	250	500	750	250	500	750	250	500	750
HPMC K100	100	150	200	100	150	200	100	150	200
Carbopol 940	50	100	150	50	100	150	50	100	150
Calcium chloride	2	2	2	2	2	2	2		2

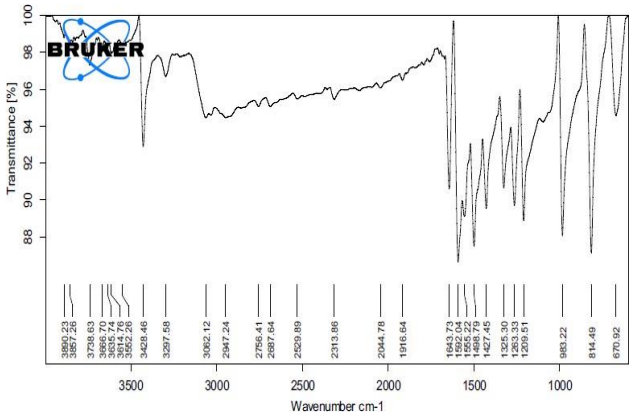

Fig 1: Drug and excipient compatibility studies

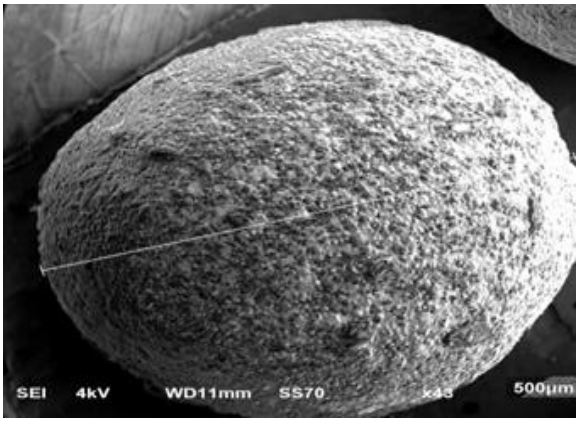

Fig 3: Surface Morphology of Beads

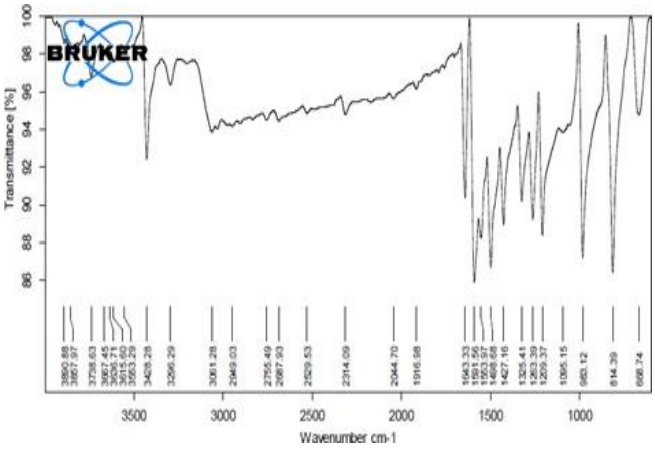

Fig 2: Drug and excipient compatibility studies

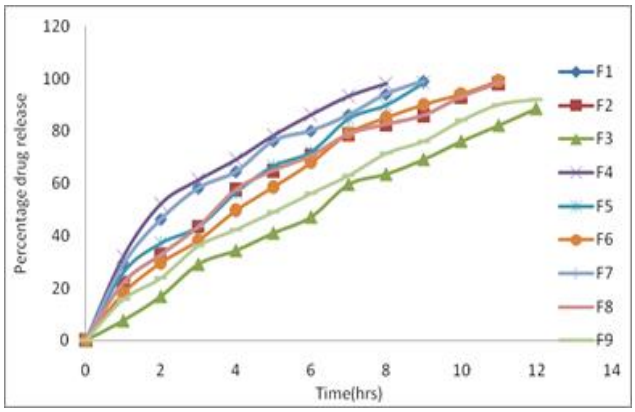

Fig 4

4. Conclusion

From the evaluation studies it can be concluded that Dalfampridine loaded Hydrogel beads using ionotropic gelation method were formulated by using HPMC K100, HPMC K30 & Carbopol 940 as rate retarding polymers among them Carbopol 940 with higher concentration showed sustained release than HPMC K100M & HPMC K100M.

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