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FORMULATION AND EVALUATION OF FLOATING ORAL IN SITU GEL OF MICROWAVE INDUCED PIROXICAM-CYCLODEXTRIN SOLID DISPERSION

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ABSTRACT

The objective of the present study was to formulate and evaluate floating oral in situ gel of piroxicam-cyclodextrin solid dispersion. Piroxicam is used in long term treatment of gout, rheumatoid arthritis and osteoarthritis. At the same time the drug is always associated with elevated risk of gastrointestinal toxicity. In situ oral gels not only prevent direct contact of the drug with gastric mucosa but also it sustains the release of drug leading to better treatment, efficacy, safety and patient compliance. Piroxicam is categorized as BCS class 2. Hence to increase solubility, solid dispersion of piroxicam is prepared by using cyclodextrin. The prepared dispersions were formulated as in situ gel by using sodium alginate (F1, F2, F3 and F4). All these were characterized for various evaluation studies. It was observed that formula code F1 showed better results and it can assume that F1 as the best formulation. The prepared in situ gel could float in gastric condition and releases drug in controlled manner.

INTRODUCTION

Oral in situ gel forming system is also known as stomach specific controlled drug delivery system with enhanced gastro retention. This system is a liquid before administration and then converts into gel form that will float on stomach when it comes in contact with it.

There are different approaches for the development of in situ gelling system. Examples are ionic cross linking, pH dependent, and temperature dependent. Simply alginic acid undergoes gelation in presence of divalent or polyvalent ions like calcium and magnesium.[1,2]

Piroxicam is a Non Steroidal Anti Inflamatory Drug act by blocking cyclooxygenase enzyme. The drug is very much used in various inflammatory conditions. The high ulcerogenic activity of this drug limits it to widespread used as a NSAID. And the other aspect of this drug is , it is associated with poor aqueous solubility. Piroxicam is belongs to Biopharmaceutical Classification System(BCS) class II , characterized by low solubility and high permeability. [3]

Extensive review of literature indicates that physiological carrier like cyclodextrin has been used in solid dispersion preparation to improve solubility of Piroxicam. The present study was directed towards development of solid dispersions by incorporating microwaves.[4]

The present study attempted to give dual results that one is to increase the bioavailability of BCS class II drug Piroxicam, and to release the drug in controlled manner without acidic irritations by developing them into in situ gelling system. The system will float on stomach and may be promisingly useful for patients who cannot administer solid dosage forms

MATERIALS AND METHODS [5,6,7,8,9,10]

Materials

Piroxicampharma grade (supplied by Yarrow chemicals Mumbai), sodium alginate(SA),hydroxyl propyl methycellulose(HPMC), cyclodextrin supplied by Balaji chemicals,and calcium carbonate. All other reagents were of analytical grade.

Methods

Development of Piroxicam- Cyclodextrin solid dispersion:

Piroxicam and cyclodextrin in the ratio 1:7.5 has taken in a glass beaker and subjected to microwaves for 5 minutes at the power of 700 W in a domestic microwave oven. After 5 minutes, the beaker allowed to cool to room temperature and pulverized and sieved.

Preparation of *In-situ* Gel

Floating *in situ* gel formulations of Piroxicam were prepared using compositions given in Table 1. In around 75ml of water, a measured quantity of sodium alginate (SA) required to make a 2 %

(w/v) solution was dissolved and temperature was maintained at 60°C using a heating magnetic stirrer . After cooling to below 40°C, appropriate amounts of polymer (HPMC), methyl paraben and propyl paraben (ratio of 9:1), the solid dispersion equivalent to 20mg drug,along with gas generating agent (calcium carbonate) were dissolved/ dispersed uniformly into the sodium alginate solution with continuous stirring. The stirring was continued after complete addition until a uniform dispersion was obtained and the dispersion was allowed to cool at room temperature. Finally, the volume was adjusted to 100ml with distilled water.

Table 1: FORMULA FOR IN SITU GELLING SYSTEM

Ingredients	F1	F2	F3	F4
Piroxicam	0.2 gm	0.2gm	0.2gm	0.2gm
Sodium alginate	2gm	2gm	2gm	2gm
HPMC	0.5gm	0.6gm	0.8gm	1gm
Calcium carbonate	0.5gm	0.6gm	0.8gm	1gm
Methyl paraben	0.09gm	0.09gm	0.09gm	0.09gm
Propyl paraben	0.01gm	0.01gm	0.01gm	0.01gm
Distilled water upto	100ml	100ml	100ml	100ml

(Drug 200mg has taken for 100ml preparation, which is equivalent to 20mg therapeutic dose when 10ml preparation has taken)

EVALUATION STUDIES:

Evaluation of solid dispersion:

Phase solubility study of solid dispersion:

The prepared dispersion was added to 100ml deaerated water in a stoppered flask. The solution was equilibrated by intermittent shaking for 48 hours maintained at 37^0 c and filtered. The solution was then analyzed by spectrophotometer at 253nm.

Drug content:

Dispersion equivalent to 20mg Piroxicam was added to 100ml standard flask and dissolved in little quantity of isopropyl alcohol and make up the solution to 100 ml 0.1 N HCL. Pipetted out 1ml and make up to 100 ml and solution is scanned at 354nm. Drug content can be calculated from standard plot of Piroxicam in 0.1N HCL.

Evaluation of In- situ gel formulations:

Determination of drug content

Accurately, 10 mL of formulation (containing the equivalent of 20 mg Piroxicam) from different batches was measured and transferred to 100 mL volumetric flask. To this 50-70 mL of 0.1 N HCl was added and sonicated for 30 min. Volume was adjusted to 100 mL. Complete dispersion of

contents was ensured visually and the dispersion was filtered using Whatman Filter Paper. From this solution, 10 mL of sample was withdrawn and diluted to 100 mL with 0.1 N Hcl. Contents measured at 354 nm.

pH Measurement

The pH of the prepared formulations was measured using a calibrated digital pH meter (Schott Gerate, Germany).

***In-vitro* gelation study**

To evaluate the formulations for their *in-vitro* gelling capacity, accurately measured 10 mL of formulation was added to 100 mL of 0.1 N HCL at 37^0c in a beaker with mild agitation.

***In vitro* floating study**

The *in-vitro* floating study was carried out by introducing 10 mL of formulation into a beaker containing 100 ml of 0.1N HCl, (pH 1.2) at 37 °C without much disturbance. The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on surface of the dissolution medium (duration of floating) were recorded.

***In vitro* drug release study**

The dissolution studies were performed in triplicate using a type II (paddle method) dissolution apparatus. The dissolution medium used was 900 ml of 0.1 N HCl (pH 1.2), maintained at 37 ºC. The stirring rate was adjusted to 50 rpm. Speed was believed to simulate the *in vivo* existing mild agitation and was slow enough to avoid the breaking of gelled formulation. At predetermined time intervals, 10 mL samples were withdrawn and replaced by fresh dissolution medium, filtered through Whatman filter paper, diluted, and assayed at maximum absorbance at 354 nm.

Measurement of viscosity of *in-situ* gelling system

Viscosity of the dispersion was determined using a Brookfield digital viscometer (NDJ-5S Viscometer). The samples (200 mL) were sheared at a rate of 100 rpm/min using spindle number 2 at room temperature. Viscosity measurement for each sample was done in triplicate, with each measurement taking approximately 30 seconds.

RESULTS AND DISCUSSION:

Phase solubility study on solid dispersion:

Solubility studied on Piroxicam control and solid dispersion was carried out. Results of solubility studies reveals that Piroxicam- cyclodextrin solid dispersion resulted in enhanced solubility of 78.07% compared to 34.6% of Piroxicam control.

Drug content determination on solid dispersion:

Drug content estimation of solid dispersion exhibited satisfactory drug content of 94.65% .

Drug content determination on in situ gel formulations:

The drug content estimation of all the in situ formulations were satisfactory and percentage of drug content was found to be 90- 97% for all the formulations.

pH measurement of in situ gel formulations:

All the formulations showed neutral alkaline pH and it was found to be 7- 8..

***In vitro* gelation study:**

All formulations showed immediate gelation upon contact with acidic medium and formed gel.

Viscosity studies:

All formulations were subjected to viscosity studies. All showed sufficient viscosity .

***In vitro* floating study:**

All formulations were subjected to in vitro floating study and it was observed that all formulations showed 12 hours of floating duration.

Table 2: RESULTS OF IN SITU GELLING SYSTEMS

Formulation code	Drug content (%)	pH	Duration of floating(hours)	Viscosity(cps)
F1	95.97%	7.4	>12	216.76
F2	93.56%	7.2	>12	278.43
F3	96.34%	7.4	>12	288.54
F4	92.73%	7.5	>12	275.98

***In vitro* drug release study:**

The study was conducted by using 0.1 N HCL as dissolution medium. It was conducted over a period of 6hours. Formula F1 showed drug release of81.02.% and F2 showed a drug release of 74.67% and F3 showed a drug release of 73.67% but when increase in concentration of viscosity enhancing polymer HPMC above 0.8% it showed better gel integrity but it retards drug release of 71.5% from this it can conclude that formula F1 showed satisfactory drug release.

FIGURE1 : PHOTOGRAPH TAKEN DURING IN VITRO FLOATING STUDY

DISCUSSION

In the study attempted to develop piroxicam in situ gel by modifying the parameter that is concentration of polymer hydroxyl propyl methyl cellulose. The drug content determination of developed solid dispersion which reveals that microwave assisted technology is a stable and suitable method for the preparation of Piroxicam- cyclodextrin solid dispersion. pH measurement which reveals that all formulations can be administered safely which would not cause any irritation to oral mucosa.

In vitro gelation studies showed better gelation.These occurs when calcium carbonate comes contact with acidic medium. It releases carbon dioxide and calcium ions. Released calcium ions interact with sodium alginate and it causes gelation. Viscosity measurements showed that it allows ease of administration. when increase the concentration of polymer it showed viscous gel. The mechanism behind the floating was when calcium carbonate was in contact with acidic medium it releases carbondioxide and calcium ions. The evolved carbon dioxide entrapped in gel causing it to float.

Drug release study showed that when polymer concentration increased the gel formed having high integrity that it retard drug release. Amount of calcium carbonate may be also the reason, when more polymers are available for cross linking it causes drug to release slowly.

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