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Formulation and evaluation of floating microbeads of ciprofloxacin HCl by emulsion gelation method

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ABSTRACT

The objective of this investigation is to develop a multi-unit gastro retentive sustained release dosage form of a water soluble drug, Ciprofloxacin, from a completely aqueous environment avoiding the use of any organic solvent. A new emulsion gelation technique is used to prepare emulsion gel beads using sodium alginate as the polymer. The gel beads containing is prepare by gently mixing or homogenizing oil and water phase containing sodium alginate which is then extruded in to calcium chloride solution. The effects of factors like concentration of oil, curing time, drug: polymer ratio, alginate: pectin ratio and curing agent on drug entrapment efficiency, floating lag time, morphology and drug release are study. Minimizing the curing time of beads leaded to enhanced drug entrapment efficiency. The use of sodium alginate and combinations of sodium alginate and pectin are used to study the effect on the sustaining property of the formed beads. It is found that sodium alginate was not sufficient to sustain the drug release at gastric pH. Instead of it, appropriate combination of alginate and pectin could provide the sustain release of drug. The results show that these beads can entrap even a water soluble drug as Ciprofloxacin in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time.

Key words: Floating Lag Time; Immediate release; Floating Lag time; Drug release.drug entrapment efficiency.

INTRODUCTION

Oral controlled release (CR) formulations have been developed in an attempt to release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation. Approaches to increase the GRT include: (i) bioadhesive delivery systems, ii) swellable delivery systems and (iii) density-controlled delivery systems, which either float or sink in gastric fluids. The floating system is intended to float in and over the gastric contents resulting in prolonged GRT. Furthermore, as the total gastrointestinal transit time of the dosage form is increased by prolonging the gastric residence time, these systems can also be used as sustained release devices with a reduced frequency of administration and therefore, improved patient compliance. Unfortunately, floating devices administered in a single-unit form such as hydrodynamically balanced systems (HBS) are unreliable in prolonging the GRT owing to their 'all-or none' emptying process and, thus, they may cause high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GIT. In contrast, multiple-unit particulate dosage forms (e.g. microspheres, gel beads) have the advantages that they pass uniformly through the GIT to avoid the vagaries of gastric emptying and provide an adjustable release, thereby, reducing the intersubject variability in absorption and risk of local irritation. Various types of drug delivery systems for oral administration such as drug release rate-controlled delivery systems, time-controlled delivery systems and site-specific delivery systems have been extensively developed. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. An important requisite for the successful performance of oral CRDDS is that the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion, to ensure continuous absorption of the released drug. The average time required for a dosage unit

to traverse the GIT is 3–4 h, although slight variations exist among various dosage forms. Certain types of drugs can benefit from using gastro retentive devices. These include: Drugs acting locally in the stomach, Drugs that are primarily absorbed in the stomach, Drugs those are poorly soluble at an alkaline pH, Drugs with a narrow window of absorption, Drugs absorbed rapidly from the GI tract, Drugs that degrade in the colon. Thus, when a drug possesses a narrow 'absorption window, design of the controlled release preparation requires both prolongation of gastrointestinal transit of the dosage form and controlled drug release.[1] The prolongation of gastric residence time (GRT) is expected to maximize drug absorption from Floating Drug Delivery Systems (FDDS) due to increased dissolution of drug and longer residence at the most favorable sites of absorption. It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time. Gastro retentive Dosage Forms (GRDFs) will provide us with new and important therapeutic options.[2] Thus control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drug exhibiting an 'absorption window' in the GI tract. The intimate contact of the DDS with the absorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption. These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Drug may not be absorbed uniformly over the length of the gastrointestinal tract, because dosage form may be rapidly transported from more absorptive upper regions of the intestine to lower regions where the drug is less absorbed and drug absorption from colon is usually erratic and inefficient. Moreover, certain drugs are absorbed only from the stomach or the upper part of small intestine.[3] The rate of drug absorption may not be constant in spite of the drug delivery system delivering the drug at constant rate into the gastrointestinal fluids. The drug is absorbed only from specific regions of the stomach or upper parts of the small intestine in case when the drug has a clear cut "absorption window".[4] Absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of CDDS. It is apparent that for a drug having such an absorption window, an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the upper parts of the gastrointestinal tract for a long period of time. The real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hrs but also to prolong the presence of dosage forms in the stomach or somewhere in the upper part of small intestine.[5]

MATERIALS AND METHODS

Materials

Ciprofloxacin Hcl was obtained as a gift sample from Alpa Pharmaceutical Ltd. Indore. Sodium alginate was purchased from, Alpa Pharmaceutical Ltd. Indore HPMC K100M was purchased from Peekay Scientific Center, Bhopal the other chemicals and reagents used in the study were of analytical grade.

METHODS

Emulsion GELATION method

Ciprofloxacin micro beads are prepared by emulsion GELATION method.

Sodium Alginate (4%) was dissolved in distilled demineralised water with agitation. Ciprofloxacin and different concentrations of mineral oil are added to the solution.

This solution (2.5g) containing Ciprofloxacin (125 mg) and oil (0-40% (w/w)) is dropped through 21 G needle in to 1%calcium chloride (10 ml) and left at room temperature for2 h.

The resultant hydro gel beads are washed twice with distilled water and kept for drying at room temperature up to 12 hours.

Preformulation of Ciprofloxacin HCl Hydrochloride

Preformulation studies for the selected drug Ciprofloxacin HCl include test for identification (examination of physical appearance, melting point determination, IR spectroscopy, solubility studies.

Quantitative estimation of drugs
UV spectrophotometric method was used to estimate the drug concentration in 0.1N HCl (1.2 pH).

DETERMINE THE WAVELENGTH OF MAXIMUM ABSORBANCE IN 0.1N HCl (1.2PH)
Ciprofloxacin HCl, 10mg was taken in upto 10ml 0.1N HCl in volumetric flask, sonicated for 10min to dissolve the sample. The prepared sample was 1000µg/ml. Than 1 ml of above solution was then transferred to another 10 ml volumetric flask and diluted it upto the mark with 0.1N HCl, This sample was 100µg/ml. The solution prepared was scanned in the range of 200 to 400 nm using 0.1N HCl as a reagent blank in UV spectrophotometer to the determine the λ_{max}.

PREPARATION OF CALIBRATION CURVE IN 0.1N HCl
Preparation of 0.1N HCl (1.2) buffer solution
0.85 ml concentrated hydrochloric acid is dissolved in a 100 ml distilled water Sonicated for 10 minutes to dissolve the hydrochloric acid, than check the pH at 1.2. Fianally 0.1 N (1.2 pH) solution is prepared and used as a blank solution.

Preparation of stock solution
Approximately 10 mg of Ciprofloxacin HCl was weighed accurately and transferred to 10 ml of volumetric flask, than 0.1 N HCl was added to dissolve the Ciprofloxacin HCl completely. The volume was made up to 10 ml with 0.1 N HCl. The prepared sample was 1000 µg/ml. 1ml of above solution was then transferred to another 10 ml volumetric flask and diluted it upto the mark with 0.1 N HCl. This sample was prepared strength of 100µg/ml.

Preparation of working standard
Working standard solution having conc. of 2 to 10 µg/ml was prepared by appropriately diluting the stock solution with 0.1 N HCl. The absorbance of each working standard was measured at 277 nm in UV spectrophotometer using 0.1 N HCl as a blank.

COMPATIBILITY STUDIES
FOURIER TRANSFORM INFRARED (FT-IR ANALYSIS)
The FT-IR analysis of the Ciprofloxacin HCl was carried out for qualitative compound identification. To check the compatibility of the drug with various polymers, IR spectra of drug, polymers and combination of the drug and polymers were taken on a FT-IR spectrophotometer in the wave number region of 4000-400 cm^{-1}.The IR spectra of drug, polymers and their combination are shown in spectra.

RESULTS AND DISCUSSION

ORGANOLEPTIC PROPERTIES
The properties are shown in table no. 1.

Table 1: Organoleptic Properties

Content	Character
Colour	A Pale yellow
Crystalinity	Crystalline powder
Taste	Slightly bitter in taste
Odour	Odourless

SOLUBILITY PROPERTIES
The properties was done in different solvents and result is shown in table no.2

Table 2: Solubility of Ciprofloxacin HCl in different solvent

Solvents	Solubility Properties of the drug (1gm)
Water	Soluble in water
Acetic acid and Methanol	Slightly soluble
Ethanol	Very Slightly soluble in ethanol

COMPATIBILITY STUDIES
FOURIER TRANSFORM INFRARED (FT-IR) ANALYSIS
The combinations were compared with the spectra of pure drug and individual polymers. The principle peak obtained for the combinations were almost similar to that of the drug. The IR spectra of the Drug-HPMC and Drug-

Sodium Alginate did not show any changes. The possibility of interaction was ruled out as there was no major shift in the absorption bands of drug and the formulation. **(Fig. 1,2,3) (Table no. 3,4,5)**

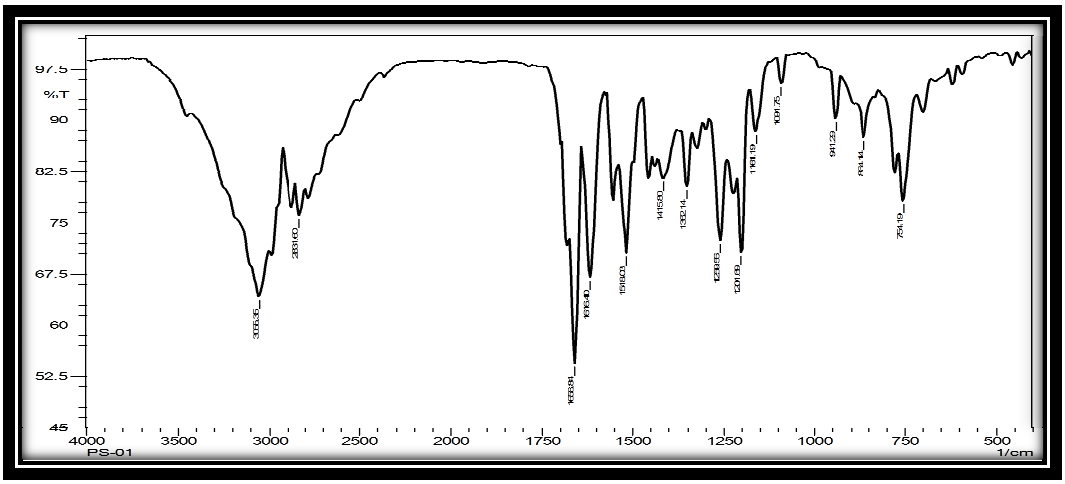

Figure 1: FT-IR Spectra of Ciprofloxacin HCl

Table 3: Interpretation of FT-IR spectra of Ciprofloxacin HCl

Functional group	Wave number (c.m.$^{-1}$)
C-H (Str)	2831.60
C=C (Str)	1658.84
N-C	1616.40
C=O	1518.03

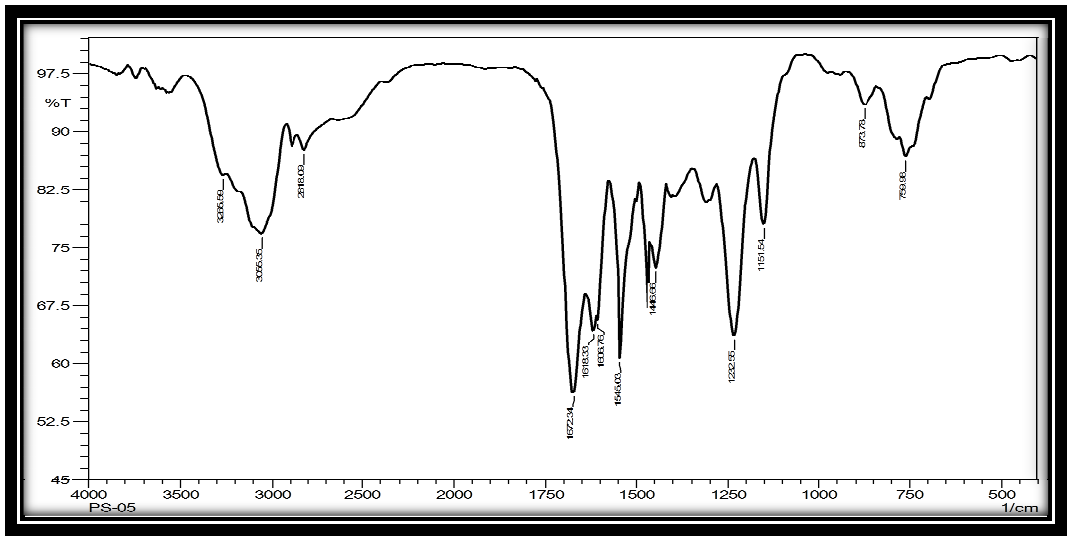

Figure 2: FT-IR Spectra of HPMC K4M

Table 4: Interpretation of FT-IR spectra of HPMC K4 M

Functional Group	Wave Number (C.M.$^{-1}$)
=CH-	3055.35
-C=O (str)	1672.34
Ether or alcohol	1545.03
Ether or alcohol	1232.55

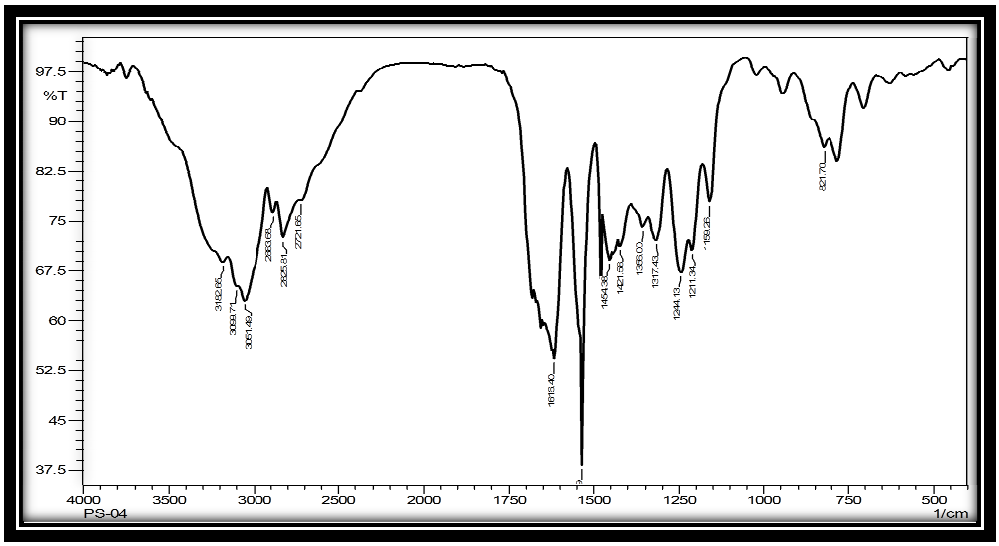

Figure 3: FT-IR Spectra of Sodium Alginate

Table 5: Interpretation of FT-IR spectra of sodium alginate

Functional Group	Wave Number (C.M.$^{-1}$)
-OH or OR (Str)	3051.49
Ether or alcohol	1454.38
Ether or alcohol	1317.43
Ether or alcohol	1244.13

UV-SPECTROPHOTOMETRIC STUDIES

UV spectrophotometric study was carried out in 0.1 N HCl medium in a scanning range of 200-400 nm. The λ_{max} was obtained 277 nm and comparison with the literature value authenticated the study **(Fig. 4).** The range was found to 2-10 µg/ml **(Table.6)** and linerty was found 0.9974 **(Fig. 5).**

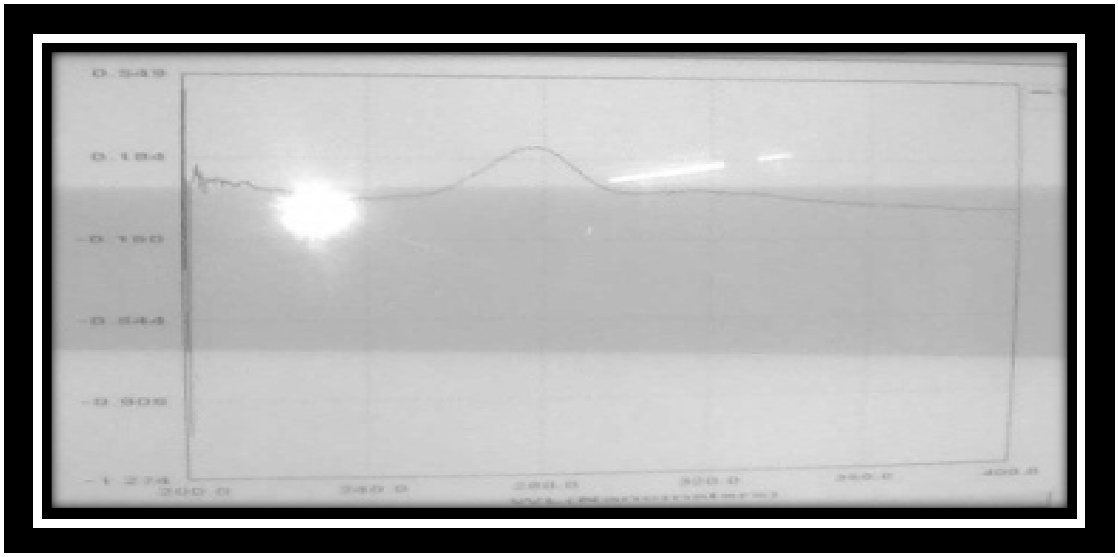

Figure 4: UV-Spectrum of Ciprofloxacin HCl in 0.1N HCl

PREPARATION OF CALIBRATION CURVE

Table 6: Data for standard calibration curve of Ciprofloxacin HCl in 0.1N HCl

Concentration (µg/ml)	Absorbance at 277 nm
2	0.227
4	0.502
6	0.715
8	0.960
10	1.245

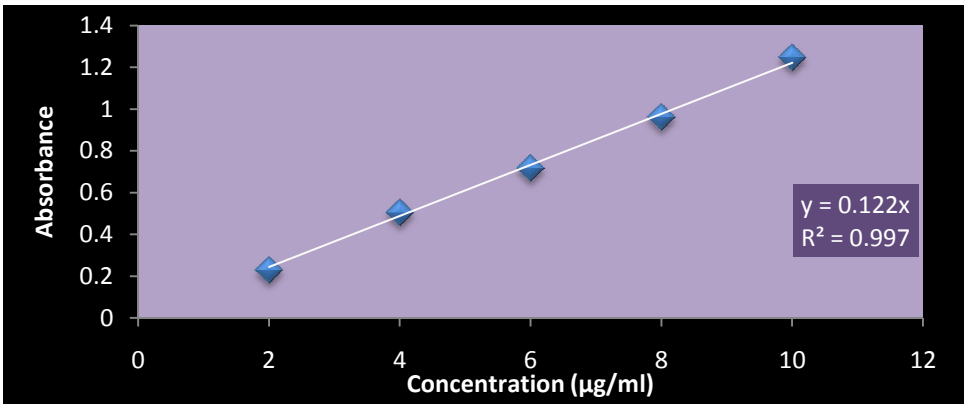

Figure 5: Calibration Curve of Ciprofloxacin HCl in 0.1 N HCl

INTERPRETATION

Calibration curve (Ciprofloxacin HCl) was found to obey the Beer- Lambert law. The absorbance value of standard concentration of 2-10 µg/ml were plotted and linearity was observed with R^2= 0.9974 in 0.1 N HCl (1.2 pH). The calculation of drug content and in-vitro drug release was based on this calibration curve.

CONCLUSION

The Ciprofloxacin HCl was obtained as a gift sample from Alpa Pharmaceuticals, Indore (M.P.). The Physical appearance and melting point of drug were found to be concordant with that mentioned in USP, 29 and Clarke's Analysis of Drugs and Poisons, 2006 respectively which shows the purity of the sample. IR spectrum of the drug sample was obtained by FT/IR. Its characteristic absorption bands proved its identity.

Solubility of Ciprofloxacin HCl was determined in various aqueous and non-aqueous solvents. The drug was found to be soluble in distilled water, ethanol, methanol, acetic acid, 0.1N HCl (pH 1.2).

Absorption maxima of the drug were determined by UV spectrophotometric method using UV/Visible spectrophotometer (shimadzu-1800). The λmax for drug in 0.1N HCl was 277 nm (pH 1.2). The standard curves of drug were prepared in 0.1N HCl in the concentration range of 2 to 10 µg/ml. A straight line with R^2=0.9974 for 0.1N HCl (pH 1.2) was found indicating that the drug follows Beer's law within the specified concentration range.

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