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PREPARATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM (FDDS) CONTAINING AN ANTIVIRAL DRUG

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Abstract

Acyclovir, an antiviral drug has low oral bioavailability of about 15-30%. It shows more absorption in the upper gastro intestinal tract. The main objective is to evaluate the potential of floating alginate beads as a drug carrier for acyclovir to prolong gastric residence time of drug in its absorption window. Floating beads were prepared from sodium alginate solution containing $CaCO_3$ as gas-forming agent using Ionotropic gelation method. To overcome the limitation of drug leaching during preparation and to have improved sustained release characteristics, alginate beads were prepared with the addition of polymers like Hydroxy propyl methyl cellulose (HPMC K4M), Eudragit RL 100 and Xanthan gum. Beads were also prepared by using Pectin (polyelectrolyte) containing cross linking solution. The compatibility of drug with the polymer was confirmed through the FT-IR studies. The prepared beads were evaluated for percentage drug loading, entrapment efficiency, surface morphology and in vitro release characteristics to know the effect of addition of these polymers to alginate solution and the addition of Pectin to cross linking solution. Pectin treated beads prepared with Xanthan gum & Pectin not only showed improved percentage drug loading but also exhibited sustained drug release in the pH 1.2. So these floating alginate beads may act as a promising carrier for acyclovir to improve its oral bioavailability.

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Introduction

The oral route represents the predominant and most preferable route for drug delivery. It allows ease of administration by the patient and is highly convenient way for substances to be introduced into the human body. Oral drug delivery systems (DDS) are divided into immediate release and modified release systems.

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery system (GRDDS). These are the systems which can remain in gastric region for several hours and significantly prolongs the gastric residence time of drug. After oral administration, such a delivery system would be retained in stomach. It will release the drug there in a controlled & prolonged manner, so that the drug could be supplied continuously to absorption site in gastrointestinal tract (GIT).

The goal in designing sustained and controlled release is to reduce frequency of dosing or increase effectiveness of the drug by localization at site of action. The controlled release technology had made it possible to release drug at constant rate for a longer period of time that is the development Of gastroretentive drug delivery system. Besides being able to continually and sustainably deliver drugs to the small intestinal absorption window, the improvements provided from gastroretentive drug delivery systems include: achieving a greater and prolonged therapeutic effect and thus reducing the frequency of administration periods, providing a more effective treatment of local stomach disorders, and minimizing both lower-tract inactivation of the drug and drug effects on the lower intestinal flora .Depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 h. This variability, may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine. Thus, control of placement of Oral drug delivery systems (DDS) in a specific region of the gastrointestinal tract (GIT) offers numerous advantages, especially for drugs exhibiting an absorption window in the gastrointestinal tract (GIT) or drugs with a stability problem. Overall, the intimate contact of the Oral drug delivery systems (DDS) with the absorbing

membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption.

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low- density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric residence times and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal [1- 4].

Materials and Method

All the chemicals used in the study were of analytical grade.

Preformulation Study

Preformulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. preformulation study is the first step in formulation study. Determination of melting point using capillary method and digital melting point apparatus, solubility of acyclovir, compatibility studies (FT-IR Spectroscopy) were carried out.

Preparation of floating beads:

Drug was dispersed in the alginate solution (3%w/v) and calcium carbonate was added in the ratio of 0.5:1 (CaCO3: alginate wt/wt). The resulting solution was dropped through a 26 gauge needle in to the 100 ml cross linking solution (calcium chloride (1%w/v) + acetic acid (10%v/v)). For Preparing alginate/HPMC, alginate/Eudragit RL 100 and alginate/Xanthan gum beads, HPMC (0.5%, 1%, 1.5%W/), Eudragit RL 100(1% W/N) and Guar gum (0.5%, 1%, 1.5%W/V) were added to drug /alginate/CaCO3, solution and dropped in to cross linking solution. For preparing the Pectin treated alginate beads the drug/polymer solution was dropped in to the cross linking solution containing 0.5%wlv pectin. The beads were allowed to remain in the solution for 30 min. Then the beads were separated, washed with water thrice and air dried.

F. C	Na alginate (%)	Acyclovir (Mg)	HPMC K4M (%)	Xanthan gum (%)	Eudragit R L 100 (%)	CaCO3 alg	CaCl2 (%)	Pectin (%)
F1	3	250	1	-	-	0.5:1	1	-
F2	3	250	-	1	-	0.5:1	1	-
F3	3	250	-	-	1	0.5:1	1	-
F4	3	250	0.5	-	-	0.5:1	1	-
F5	3	250	-	0.5	-	0.5:1	1	-
F6	3	250	1.5	-	-	0.5:1	1	-
F7	3	250	-	1.5	-	0.5:1	1	-
F8	3	250	0.5	-	-	0.5:1	1	0.5
F9	3	250	-	0.5	-	0.5:1	1	0.

Table no: 3 formulation design

Evaluation of the Floating Beads:

Study of size and uniformity of alginate beads:

To prepare uniform beads (i.e., of the same size and density) it is essential that synthesis conditions such as viscosity, rate of falling of drops, stirring rate and distance between surface and gelation medium, be maintained constant.

The diameter of beads was determined by screw gauge. 20 dried beads were randomly selected from each batch and the mean diameter was determined. The least count of screw gauge was 0.005 mm. Colour and shape of dried beads of each batch was noted.

Percentage entrapment efficiency

200 mg of acyclovir loaded Calcium alginate beads was dissolved in 250 ml of 0.1N HCL by stirring for 6 h and filtered using 0.45 m Millipore filter. l ml was pipetted out and made up to 10 ml. Acyclovir content was determined spectrophotometrically at 256 nm. The determinations were made in triplicate and the percentage entrapment efficiency (EE) was calculated as follows.

EE (%) = Practical drug loading/Theoretical drug loading× 100

Percentage yield

The prepared alginate beads of all batches were accurately weighed and the percentage yield was calculated by using following equation,

% Yield= Actual weight of product/ Total weight of excipients and drug X 100

Buoyancy of the Alginate beads

The floating ability was determined using USP dissolution test apparatus II. Fifty beads were put in the vessel and the paddle was rotated at 50 rpm in 900 ml 0.1 N HCL, maintained at 37±0.5 °C for 12 hours. The floating and the settled portion of beads were recovered separately. Buoyancy percentage was calculated. The floating ability of the beads was measured by visual observation and the percent of floating beads was taken as the average of three determinations. The preparation was considered to have buoyancy, only when all beads floated on the test solution immediately or within a lag time which did not exceed 2 min [14].

Buoyancy % = $W_f / (W_f+W_s) \times 100$

Where W_f and W_s, are the weight of the floating and settled alginate beads.

Morphological Analysis

Surface morphology of the beads was examined with a scanning electron microscope.

In-vitro Drug Release Study

The drug release rate from floating Alginate bead was carried out using six basket dissolution apparatus USP type I. A weighed amount of floating alginate beads was filled into a capsule and placed in 900ml of 0.1N HCI dissolution medium. Temperature was maintained at 37 ± 0.5°C at a rotating speed of 100rpm. 5 ml aliquots were withdrawn at predetermined time intervals for 12hrs, filtered and analyzed by UV spectrophotometer at 256 nm after suitable dilution. The withdrawn volume was replaced with an equal volume of fresh 0.1NHCI. The cumulative % drug release was calculated using standard calibration curve.

Drug Release Kinetics:

To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted into Zero order, First order, Higuchi model, Korsmeyer-Peppas model and Hixson Crowell model. By comparing the R-values obtained, the best fit model was selected.

Stability studies

The stability studies for beads were done by keeping the sample beads from optimized batches at room temperature for 90 days. The selected batch for stability study was batch F9. The product was evaluated for in vitro drug release and drug content.

RESULTS AND DISCUSSION

Preformulation study conclude that Acyclovir is slightly soluble in water, insoluble in ethanol and the organic solvents, soluble in dilute aqueous solutions of alkali and mineral acids. The melting point was found to be in the range of 256.5-257°C. FT-IR study confirmed that the drug is compatable with the excipients used in the formulation.

The alginate beads are spherical in shape. The flow rate, flow time, viscosity, stirring and shape are responsible for the uniformity of the beads. The percentage entrapment efficiency were found to be between 65.48-87.32%. Xanthan gum is found to be more viscous than the other polymers and it showed maximum drug entrapment. Pectin is used as polyelectrolyte. It showed a more improved drug release profile than the simple lonotropic gelation method. The floating time of the formulations were found to be more than 20 hrs. The percentage buoyancy was found to be in the range of 57.64-87.01%, being the highest for formulation F4 and lowest for F7. As the polymer concentration has increased, buoyancy decreased due to increase in the viscosity of the polymer.

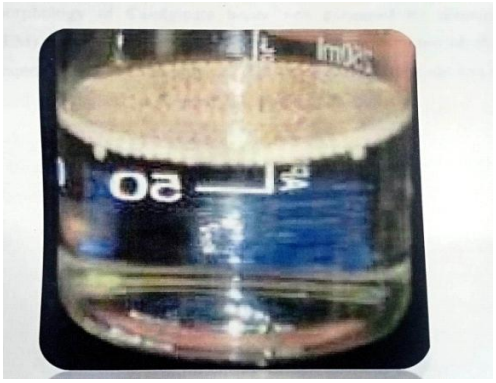

Figure no. 1

From the Morphological analysis (SEM analysis), the smooth surface of beads shows complete homogeneity of drug and polymer.

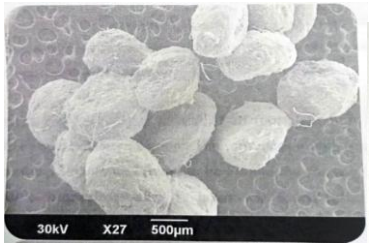

Figure no.2

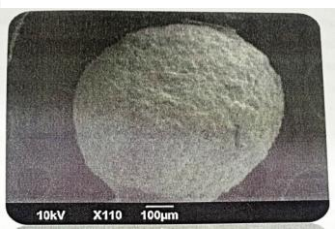

Figure no.3

The percentage cumulative drug release of all formulations is found to be in the range of 52.342-99.65 % w/w after 12 hours. The formulation with maximum percentage cumulative release after 12 hours was found to be F9 (xanthan gum/pectin treated beads)

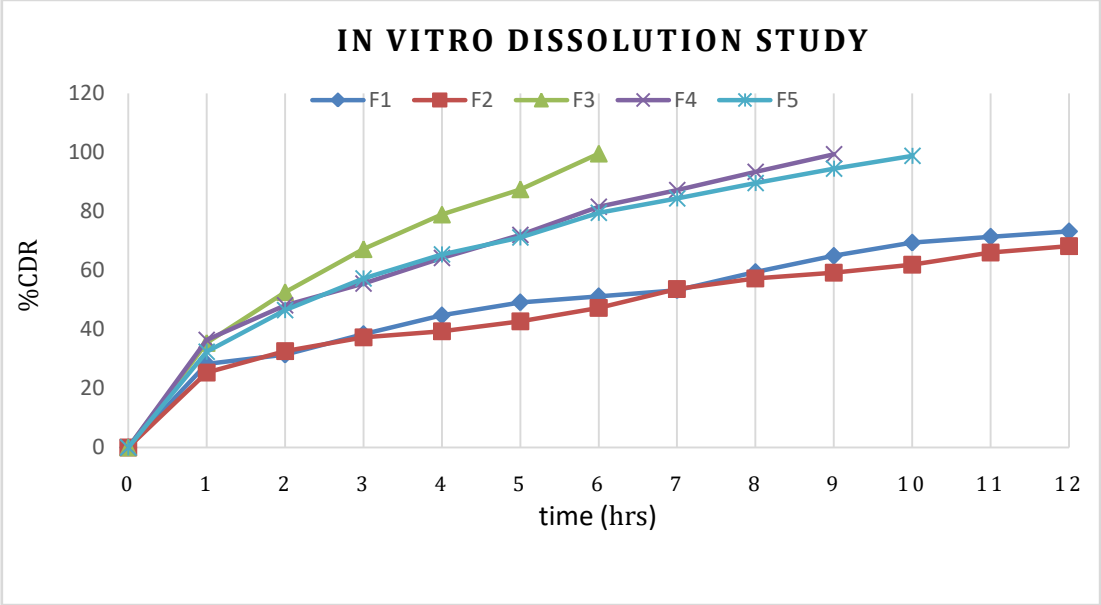

Figure 4: In vitro dissolution study (F1-F5)

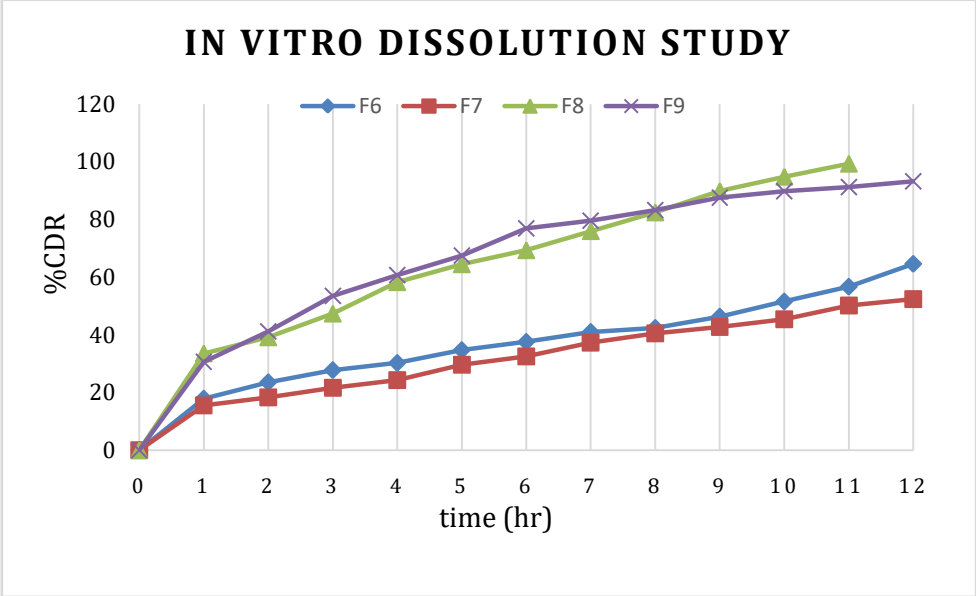

Figure 5: In vitro dissolution study (F6-F9)

Evaluation studies conducted suggests that floating alginate beads may act as a promising drug carrier for acyclovir.

Conclusion

Acyclovir is the first specific antiviral drug to become widely used against herpes particularly Herpes Simplex Viruses (HSV) types I and II and Varicella Zoster. In the present study Acyclovir floating beads were formulated to achieve sustained release of drug in the absorption window of GIT. An attempt has been made to validate the release retardant property of HPMCK4M, EUDRAGIT RL 100 and XANTHAN GUM on in vitro release of Acyclovir. Three concentrations were selected for each polymer, i. e 0.5%, 1% and 1.5%. Sodium alginate beads prepared with xanthan gum and treated with pectin not only showed improved percentage drug loading but also exhibited sustained drug release in the pH 1.2. So these Floating alginate beads may act as a promising carrier for acyclovir to improve its oral bioavailability.

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Conflict of interest

Authors are declared that no conflict of interest.

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Ethical consideration and inform consent

Not applicable

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