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Research on Formulation and Evaluation of Floating Microspheres

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Abstract: *The purpose of this study is to design and evaluate a floating multipart oral delivery system for diltiazem hydrochloride that can provide sustained release. The aim of the work is also to study various parameters that influence the behaviour of floating multiparticles in an oral dosage form. Floating microspheres were prepared by a non-aqueous emulsifying solvent evaporation technique using ethyl cellulose and Eudragit RS-100 asthe rate-controlling polymer. In vitro activity was evaluated using standard pharmacopoeia and other tests such as drug-polymer compatibility, (%)yield, particle size analysis, drug entrapment efficiency, surface topography, in vitro buoyancy and release studies. The results show that the mixing ratio of the components in the organic phase affected the size, size distribution (199-320 µm), drug concentration(59-84%), percent yield (57-77%) and drug. Liberation microsphere (45-99aftern12 hours) and swimming time > 12 hours. The best results were obtained in the ratio drug: polymer Eudragit RS-100 (1:3). Good in vitro floating behaviour was observed in most cases, and various drug release patterns could be achieved by varying the polymer ratio, which was optimized to match the target release profile. Stability studies showed no significant change in the drug content of the formulation even after 3months. The data obtained in this study therefore suggest a floating dose of micro particles*

Keywords: Floating Microspheres

I. INTRODUCTION

Floating microspheres are enteral drug delivery systems based on a bubble-free approach. They are spherical hollow particles without a nucleus. These microspheres are typically free-flowing powders composed of light or synthetic polymers ranging from 1 µm to 1000 µm in diameter. Hydro dynamically controlled drug delivery systems (floating Drug delivery systems) are low-density systems that have sufficient buoyancy above the stomach contents and remain suspended in the stomach without affecting the gastric emptying rate for long periods of time.

Sustained drug release from floating systems improves drug retention in the stomach and reduces fluctuations in plasma drug concentration. Polymers used to produce floating microspheres include polycarbonate, HPMC, cellulose acetate, calcium alginate, Eudragit S, chitosan, etc. Therefore, floating microspheres are considered one of the most promising floating systems. They have the unique advantages of multi-device systems and also have better floating functionality. [1,2]

Common methods used to prepare them include emulsion solvent evaporation and emulsion solvent diffusion. Drug release and better floating properties largely depend on the type of polymer, plasticizer and solvent used in the formulation..

The oral route of administration is considered a very convenient route of administration and is often used for drug administration due to its ease of administration, patient compliance and formulation flexibility. The success of an oral controlled delivery system

Depends on better absorption of the drug from the gastrointestinal tract. However, the biggest problem with conventional dosing is keeping the drug Concentration within the therapeutically effective concentration, which can only be achieved with multiple daily administrations.

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Although attempts have been made to develop controlled release systems for the oral route of administration, various limitations such as variable drug absorption, uncontrolled gastric transit time, have indicated the need for more intelligent drug delivery systems that can improve drug delivery and transit. Time drug or provide an effective concentration locally. Gastrointestinal drug delivery systems can be retained in the stomach and help improve oral continuous delivery of drugs that have an absorption window in a specific region of the gastrointestinal tract.[3]

Various methods have been developed to increase gastric residence time (GRT), including: floating drug delivery systems (FDDS), inflatable or expandable systems, mucosal adhesive systems and high density systems. These systems improve the bioavailability of drugs with a narrow absorption window, reduce drug waste and improve solubility

Drugs that are less soluble in high pH environments. It also has applications for local drug delivery to the stomach and proximal small intestine. The most popular route of drug administration is oral because of patient consent and ease of consumption and cost effectiveness. Many different techniques have been developed, such as tablet capsule syrups, etc., to deliver a significant amount of drug to a specific location in a prearranged and systematic manner, but there are many physiological problems along the way, Such as bypassing. The GIT is the main site of absorption (stomach and upper intestine) due to its high density and low retention time, resulting in incomplete drug release and low.[4]

Floating systems are low-density systems that have sufficient buoyancy to float on the stomach contents and remain floating in the stomach without affecting the rate of gastric emptying for long periods of time, causing insufficient release of drugs over the stomach contents. Absorption. In recent decades, several gastric-retaining drug delivery systems have been developed, including high-density systems that remain in the lower part of the stomach, with lower densities that cause gastric fluid and mucosal buoyancy. . adhesive systems that cause bio adherence to the gastric mucosa, opening, expanding or swelling systems that can limit the emptying of dose forms through the pyloric sphincter, ultra porous hydrogel systems, magnetic systems, etc..

For oral solid delivery systems, drug absorptionis unsatisfactory and varies greatly between individuals. Despite excellent in vitro release patterns. A major concern is physiological variability such as gastrointestinal (GI) transit in addition to gastric retention time, as the latter plays a dominant role in the overall transport of the dosage form. Although sustained release can be achieved with an oral controlled release system, the drug is released within less than 12 hours after passing the site of absorption. Therefore, It is not possible to administer the drug orally for more than 12 hours. This led researchers to keepthe drug delivery system in the stomach for a long timeand predictably. Such long-term gastric retention Controls not only time but also Space in the stomach, keeping the delivery system Stableand Delivering the medicine correctly. Floating drug delivery systems are essentially Prepared to increase gastric residence time which in turn increases the bioavailability of drugs that are strongly absorbed in the stomach and poorly absorbed in the lower part of the digestive tract. [5]

Diltiazem hydrochloride is a calcium channel blocker used as a medicine for hypertension, angina pectoris, etc. It has poor Bioavailability (30-50%) and an absorption window in the upper gastrointestinal tract, so it has been proposed to develop a drug delivery system that Obstructs the gastrointestinal tract to improve drug absorption, to increase drug bioavailability.

II. LITERATURE REVIEW

a. Introduction

- A Brief Overview of Drug Delivery Systems
- Importance of In-wax Buoyant Drug Delivery Systems
- Need for a Flotation System for Diltiazem Hydrochloride.

b. Physiology of the Stomach

- Factors affecting gastric emptying
- Rationale for using flotation systems to increase gastric retention time.

c. Formulation Approaches

- Different Polymers Used in floating Systems

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- Formulation Aspects of Diltiazem Hydrochloride
- Manufacturing Methods for Suspension Drug Delivery Systems.

d. Evaluation Parameters

- In vitro methods for evaluation of floating systems (eg, floating delay, floating duration, drug release)
- In vivo evaluation methods (if applicable)
- Characterization of diltiazem-loaded floating systems

e. Studies on Floating Drug Delivery Systems of Diltiazem Hydrochloride

- Summary of Related Studies
- Formulation Strategies and Results
- Comparative Analysis of Different Formulations

f. Challenges and Future Perspectives

- Challenges in the Design and Evaluation of Diltiazem Hydrochloride Flotation Systems
- Future Research Directions and Innovations in the Field

III. MATERIALS AND METHODS

Materials

Diltiazem hydrochloride , Ethyl cellulose and Eudragit RS-100 m.All chemicals used in the study were of analytical grade.

Methods

Preparation of floating microspheres:

Microspheres were prepared by evaporation of a non-aqueous emulsifying solvent. In short, drug and polymer i.e. Diltiazem HCl and Eudragit RS 100, ethyl cellulose were mixed in acetone in different proportions using mixing solvent viz. Isopropyl alcohol. The suspension was added to 200 mL of liquid paraffin, stirring for 2 h with a mechanical stirrer at 1200 rpm to completely evaporate the solvent, and the microspheres were collected by filtration. The microspheres were repeatedly washed with petroleum ether at 40–60 °C until they became oil-free. The collected Microspheres were dried for 1 hour at room temperature and then stored in a desiccator.[6]

Evaluation of floating microspheres

Micrometric studies of floating microspheres:

Microspheres are characterized by their micrometric Properties such as particle size, tap density, Carr's Compressibility index and flow property.

Table 1: Drug and polymer combination in solvent mixture of acetone and isopropyl alcohol

Batches→ Ingredients↓	A1	A2	A3	A4
Ethyl cellulose (mg)	500	1000	1500	2000
Diltiazem HCL (mg)	500	500	500	500

Table 2: Micromeritic study

Parameters → Batches ↓	Average particle size (µm)	Tapped density (g/cm3)	Bulk density (g/cm3)	% compressibility Index	Hausner's Ratio	Angle of repose (θ)
A1	240.2 ± 16.3	0.814	0.783	15.2	1.03	41°29'
A2	248.0 ± 11.7	0.802	0.771	12.5	1.04	39°16'
A3	280.0 ± 9.6	0.794	0.770	13.1	1.03	39°21'
A4	319.5 ±12.9	0.788	0.746	15.8	1.05	32°78'

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Table 3: Percentage yield and percent buoyancy:

Batch no.	Percentage yield	Percentage Buoyancy	% drug entrapment
A1	70.86	52.12	75.26
A2	69.56	48.34	72.87
A3	64.45	39.56	74.56
A4	66.45	41.65	62.26

Percent yield of microspheres formed (i.e. recovery):
The measured mass of microspheres produced was divided by the total amount of non-volatile components used to make the microspheres, giving the total floating microsphere yield in percentage..

Study of floatation behaviour (or buoyancy) of Microspheres:
Flotation studies were carried out to determine the flotation behaviour of different polymer combinations. The beak method was originally used to gain insight into the flotation behaviour of a proposed dosage form.50 mg of suspended micro particles were placed in each of four 50 mL beakers containing 20 mL of 0.1 N HCl containing 0.02% Tween 80. The beakers were shaken in a biological shaker at 37°C ± 0.5°. C with a speed of 40 revolutions per minute. Floating microspheres were collected after 3, 6, 9 and 12 h and dried to constant weight. The percentage of floating microspheres was calculated using the following equation:
% Floating Microspheres: weight of floating microspheres after time *t*×100
Initial weight of floating microspheres

% Drug entrapment determination:
50 mg of suspended microspheres were finely crushed mechanically. These powders were dissolved in 50 mL of 0.1 N HCl and filtered through filter paper. 5 mL of this solution was then diluted to 50 mL and absorbance was recorded at 203.2 nm against 0.1 N HCl as a blank.[7] The percentage of drug retained was calculated using the following formula:
% Drug Entrapment: Calculated drug concentration ×100
Theoretical drug concentration

Dissolution test (in-vitro drug release) of microspheres:
The dissolution test was performed using a six-station USPXXVII Type I (Electro lab Tablet Dissolution Tester USP, TDT-06P). 900 mL of 0.1 N HCl(pH 1.2) diltiazem-HCl was filled into the dissolution vessel and the medium temperature was set at 37+0.5 °C and the blade rotation speed was used as the dissolution medium. Customized set at 100 rpm. At predetermined time intervals of 12 h, 5 µl samples were taken and replaced with the same amount of fresh medium. The sample taken was diluted and analysed with a UV-Spectrophotometer (Shimadzu UV-1700) with corresponding Λmax values for diltiazem HCl (203.2 nm). Drug concentration was calculated using an equation generated from the standard curve.

Morphological study using scanning electron microscopy:
Scanning Electron Microscopy (SEM): Uncoated and coated (optimized)microsphere
Surface topography and cross-section of optimized microsphere were examined using aFEI-Philips XL-30 analytical electron microscope (IICT,Hyderabad). The sample was loaded into a copper sample and sputtered with carbon and then gold.[8]

Drug polymer interaction:
The drug-polymer interaction was studied by FTIR (Shimadzu, Japan. Model-8400S)[9]

Stability studies:
Stability studies were conducted at 40±2°C and 75±5% relative humidity for 90 days.[10]

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IV. RESULTS AND DISCUSSION

The average particle size of the different batches is 200-350 µm. With a Carr's index Ranging from 9-16% and a Hausner ratio of 0.5 and an angle of repose Of 30°-45° was observed, which is a Significant limit to show the flow properties of microspheres When formulated into a dosage form [Table 2].[11,12]

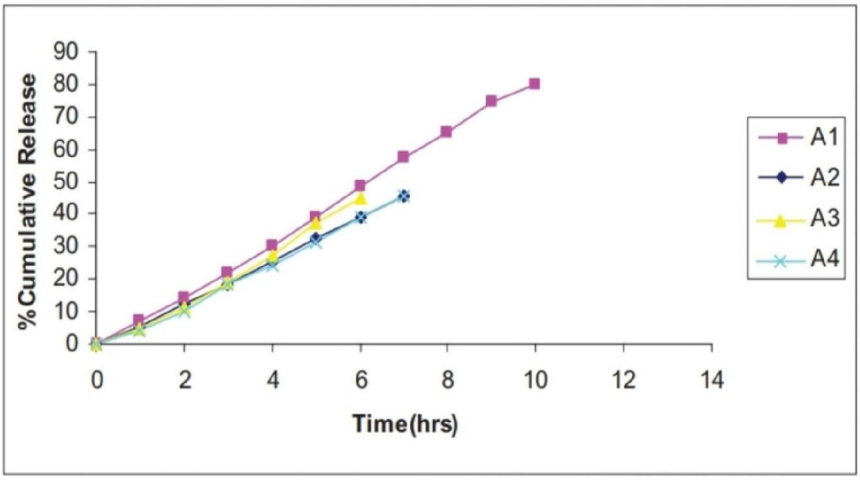

Fig. 1:- In-vitro drug release of batches A1-A4

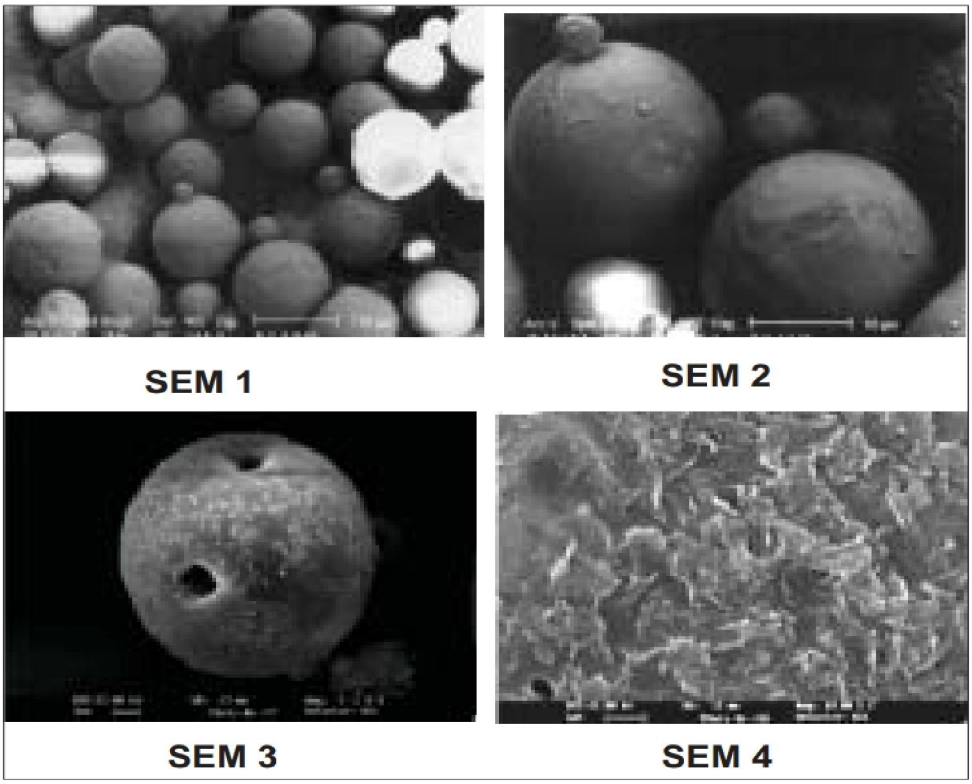

Fig.3: SEM photomicrographs of floating microspheres SEM 1 shows size range of floating microspheres. SEM 2 shows Smooth texture of floating microspheres. SEM 3 shows dents on the Surface. SEM 4 shows surface morphology of floating microspheres.

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The microspheres of batch B3 were found to have a buoyancy of 52.12%, indicating that most of the microspheres were still floatable after 12 hours due to low density and internal Voids [Table 3].[13,14,15]

Microspheres from batch A1 formulation showed 75.26% entrapment, while formulations A2, A3 and A4Showed less entrapment than the optimized formulation. This can be attributed to the permeability properties of each polymer used, which can facilitate the diffusion of Part of the trapped drug into the surrounding environment during the preparation of suspended microspheres[Table 3].[16,17,18]

Drug release from floating microspheres was evaluated at pH 1.2 using diltiazem-HCl as a model drug. The drug release rate of diltiazem-HCl was almost linear during the first 10 hours and then gradually decreased [Fig.1].[19,20,21]

Different kinetics were used to interpret the release rate of diltiazem-HCl from microspheres of sustained-release suspension formulations. Determination of the coefficient (R2=0.9573) shows that the release of lot A1 best fits the Korsmeyer model.[22,23,24]

The surface topography showed a spherical surface and a circular cavity surrounded by an outer shell of drug and polymer for all formulations. They appeared to be hollow, presumably due to the rapid escape of volatile[25,26,27]

Solvent from the polymer matrix. This hollow nature was also responsible for the floating microspheres in simulated gastric fluids . Infrared interpretation Showed that there are no interactions between the drug and Polymers. The stability study showed that the degradation of the drug was less than 5%, which means that the formulation was stable and slightly degraded for 3 months.[28,29,30]

V. CONCLUSION

A micro meter study shows good results for suspended Microspheres. BatchA1 floating microspheres proved to be satisfactory in terms of drug release, buoyancy and drug entrapment and can be used as an alternative to conventional dosage forms. The maximum in vitro drug release was 98.89% after 12 hours BatchA1 floating microspheres. Swimming was achieved during the study period.

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