Formulation and Evaluation of Controlled Release Floating Tablet of Cinnarizine for Enhancement of Bioavailability

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Abstract: *The aim of the present work is formulation and evaluation of controlled release floating tablets of cinnarizine for enhancement of bioavailability. Cinnarizine floating tablet were prepared by direct compression method using HPMC K4M as matrix formers, sodium bicarbonate as gas generating agent. It is used for the treatment of nausea, vomiting, motion sickness, inner ear disorders, migraine and epilepsy. Floating drug delivery system is a delivery system which has limited absorption window sparingly soluble and insoluble drugs, drugs which locally release in stomach and shows degradability in colon or poor colonic absorption. It comes under gastro retentive drug delivery system (GRDFs)that provides pharmaceutical approaches used in enhancing the Gastric Residence Time (GRT).This system is very helpful to overcome the problem during the formulation of different dosage form. This article shows the recent technological development in floating drug delivery systems based on the principal mechanism of floatation and advantages of achieving gastric retention, on various polymers employed for floating drug delivery systems. This article also summarizes In–Vitro studies to evaluate their performance and also their future potential.*

Key Words: *Cinnarizine, Floating drug delivery system, Floating duration/ Gastric residence time, Gastro retentive drug delivery systems, In-Vitro studies.*

1. INTRODUCTION:

Oral administration is the most important route of any drug delivery to the systemic circulation. The pharmaceutical dosage forms like tablets, capsules, pills creams, liquids, ointments, aerosols, injectable and suppositories are used for delivery of drug to the patients in treatments of acute or chronic disease. Cinnarizine (1-diphenylmethyl-4-(3-phenyl-2-propenyl) piperazine) inhibit the MgATP-dependent generation of a transmembrane proton electrochemical gradient in chromaffine granule. Cinnarizine are classified as antihistamines, calcium channel blockers and anti-epileptics and used for the treatment of variety of diseases like migraine and epilepsy and nausea. Cinnarizine is pharmaceutically used in conditions with vestibular vertigo such as Meniere's disease. It is used for the control of vestibular disorders such as vertigo, tinnitus, nausea and vomiting.It is also effective in the control of motion sickness. Drug delivery systems are used for maximizing therapeutic index of the drug and reduction in side effects due to site-specific drug delivery. This reduces the frequency of administration of medicament. Floating dosage forms are emerging as a promising novel dosage forms. Floating dosage forms can be prepared as tablets, capsules by incorporating suitable excipients as well by adding certain gas generating agents, which in turn give the buoyancy to the dosage form in gastrointestinal fluids. FDDS are retained in the stomach for a prolonged period of time by virtue of their floating properties. The residence of a drug delivery system in the upper part of the gastrointestinal tract (GIT) can be accomplished by several drug delivery systems, such as intra gastric floating systems, swelling and expandable systems, bio adhesive systems, modified shape systems, high-density systems, delayed gastric-emptying systems and low-density super porous systems. The gastric residence time (GRT),which decides the retention time of oral dosage form in GIT, thegastric emptying (GE) of liquids in the fasted state is a function of the volume administered.[1-5]

Controlled release drug delivery systems (CRDDS) are to maintain therapeutically effective plasma drug concentration levels for a longer duration thereby reducing the dosing frequency and to minimize the plasma drug concentration fluctuations at steady state by delivering drug in a controlled and a reproducible manner. Dosage forms having density lower than that of the gastric fluids experience the floating behavior. The de novo design of an oral controlled drug delivery system (DDS) is used to predictable and increased bioavailability of drugs. DDS leading to increases efficacy of the administered dose. Oral controlled-release (CR) dosage forms possessing gastric re-tention capabilities. The size of the dosage form is another factor influencing gastric retention. Food intake, the nature of the food, caloric content, and frequency of feeding has profound effect on the gastric

retention of the dosage form. The non-effervescent FDDS based on mechanism of swelling of polymer or bio adhesion to mucosal layer in GI tract. Effervescent systems include use of gas generating agents, carbonates or any other organic acid present in the formulation to produce carbon dioxide gas, which are incorporated in the dosage form, thus reducing the density of the system and making it float on the gastric fluid.[6-8]

2. MATERIALS AND METHODS:

Cinnarizine Was Gift Sample from Torrent Pharmaceuticals Ltd., Gujarat. Crospovidone, Sodium Starch Glycolate HPMC (K100, k15, k10, k5), NaHco3, Citric acid, Magnesium Stearate, StarchTalc, Potassium Dihydrogen Phosphate, Sodium Hydroxide, n-Octanol, Methanol AR, Acetone LR, Aluminum Foil, Talc chemicals used were of pharmaceutical grade.

3. Preformulation study:

It includes:

3.1.Identification Test:

Scanning of Drug (Cinnarizine) in0.1 N hydrochloric acid (HCl):

A solution containing 10µg/ml cinnarizine by using 0.1N HCL and scanned overdouble beam UV spectrophotometer by using wavelength range of 200 nm to 350 nm taking 0.1 N HCL as a blank. The plot of absorbance v/s wavelength was recorded.

By using polymers

A polymer [Hydroxypropyl Methylcellulose (HPMC)] is used to find out apparent viscosity of cinnarizine. In this, 2gm of polymer were taken and added in 98ml of water then heated the mixture at 80 to 90°C. The mixture was stirred and allowed to cool until the solution was formed. The viscosities of the resulting solution were measured using Brook Field viscometer.

3.2. Fourier transforms infrared (FTIR) spectroscopy:

Powdered samples was taken and intimately mixed with dry powdered potassium bromide. The mixture was taken in a diffuse reflectance sampler and the spectra recorded by scanning in the wavelength region of 2.5 to 25 µ in a FTIR spectrophotometer (Jasco 460 plus, Japan). The IR spectrum of drug was compare with that of the physical mixture to check for any possible drug-excipients interaction.

Evaluation of tablets

Tablet was evaluated for hardness, friability, weight variation, thickness, drug content, I*n-vitro* buoyancy study, swelling index, *In-vitro* dissolution studies and stability study. The Monsanto hardness tester and Roche friabilator was used to identified the hardness and friability. In weight variation test, 20 tablets were weighted and average weight is calculated by using electronic balance. Thickness was determined by dial caliper. For Drug content analysis, 10 tables were taken and powdered. The powder equivalent to 10mg of cinnarazine was dissolved in 0.1N HCl. After that filtration was done and analysis by double beam UV spectrophotometer at 254nm wavelength. For in-vitro studies, 900ml of 0.1N HCl were taken and dissolution of cinnarazine tablets done at 37 ± 0.5 °C at 50rpm. The samples were taken out at every 1hour time interval. The samples were tested by using spectrophotometer at 254nm wavelength. According to ICH guidelines, the stability studies of the tablets were carried by storing tablets in solubility chamber. For Long-Term Testing: 25°C ± 2°C / 60 % RH ± 5 % for 12 months. For Accelerated Testing: 40°C ± 2°C / 75 % RH ± 5 % for 6 months.

4. RESULTS AND DISCUSSION:

UV spectrum of cinnarizine in 0.1 N HCl (**Fig.1**) shows that the drug hasλ_{max} of 254.0 nm. The viscosity of HPMC K4M was found to be 4100 cps.IR spectra of drug and Physical mixture of drug-excipients is shown in **Fig.2a and Fig.2b**The spectrum of cinnarizine was shown to exhibits the characteristic peaks at 3022-3067 cm^{-1} for C-H (aromatic) stretching, 2934-2957 cm^{-1} for C-H (aliphatic) stretching and 1450 cm^{-1} for C-H bending. The characteristic peaks due to the drug were also observed in the spectrum of physical mixture at 3020-3068 cm^{-1} for C-H (aromatic) stretching, 2934-2958 cm^{-1} for C-H (aliphatic) stretching and 1449 cm^{-1} for C-H bending. The hardness (Kg.) of tablets of different batch was found to be in range of 3 to 4 Kg.

The percentage friability of different batches of tablets was found to less than 1 %.The *in-vitro* drug release results suggest that, the drug was released by mixed order kinetics. To ascertain, the drug release mechanism the *in-vitro* release data were also subjected to Higuchi's diffusion and Peppa's plots by taking log cumulative percent drug released versus log time. Result shows the kinetic plot and n value, that the drug was release by Fickian control with swelling. The *in-vitro* buoyancy of formulations fromK1 to K9 containing HPMC K4M was >12 hrs. Dissolution parameter values are showed in figure 4 to figure 7.

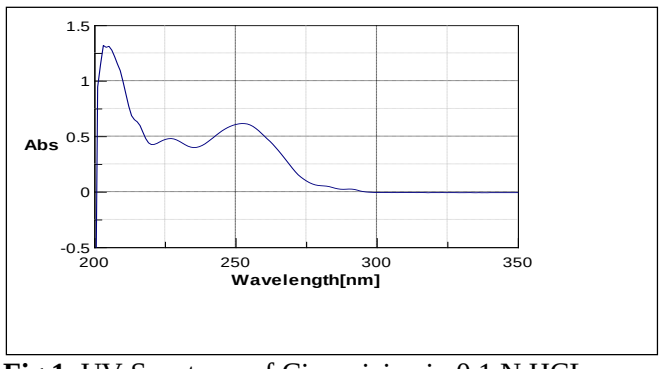

Fig.1. UV Spectrum of Cinnarizine in 0.1 N HCL

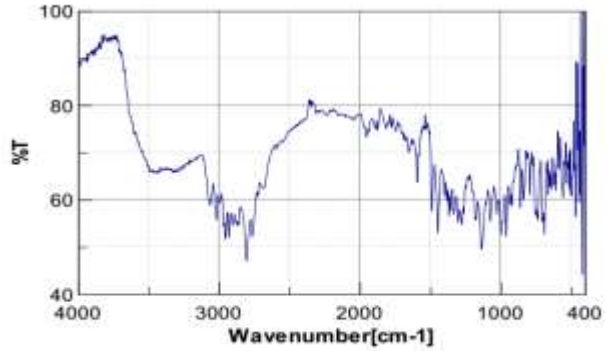

Fig.2a. IR spectrum of Cinnarizine

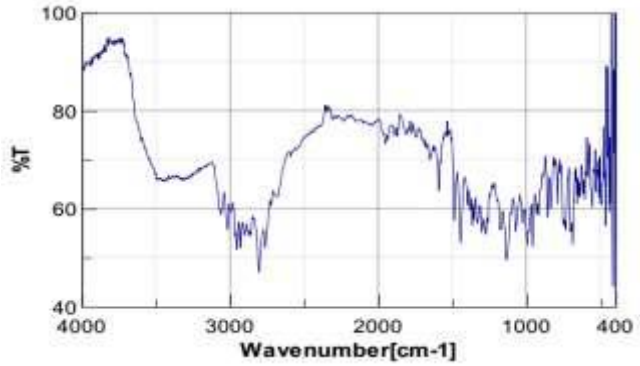

Fig.2b. IR spectrum of Physical mixture of drug-excipients

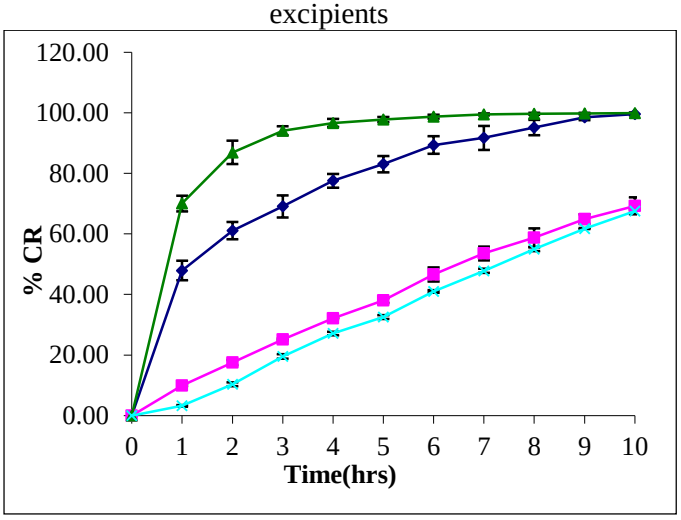

Fig. 3.Dissolution data of F1 to F4

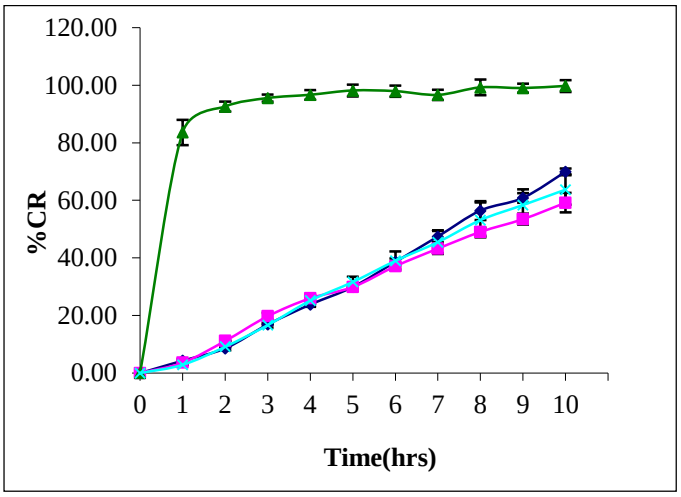

Fig. 4. Dissolution data of F5 to F8

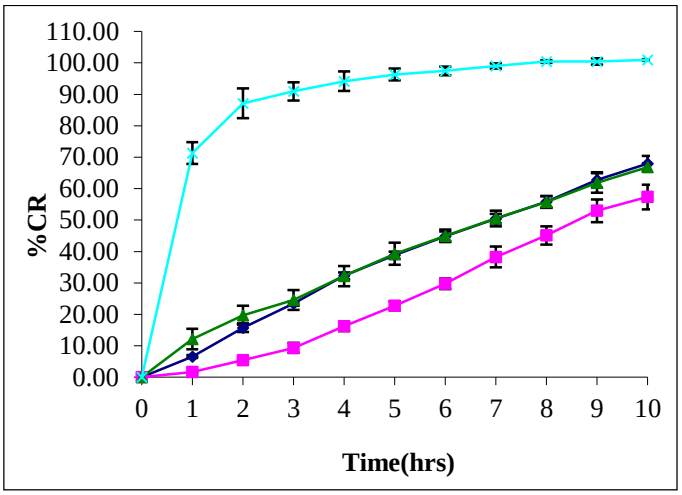

Fig. 5.Dissolution data of F9 to F12

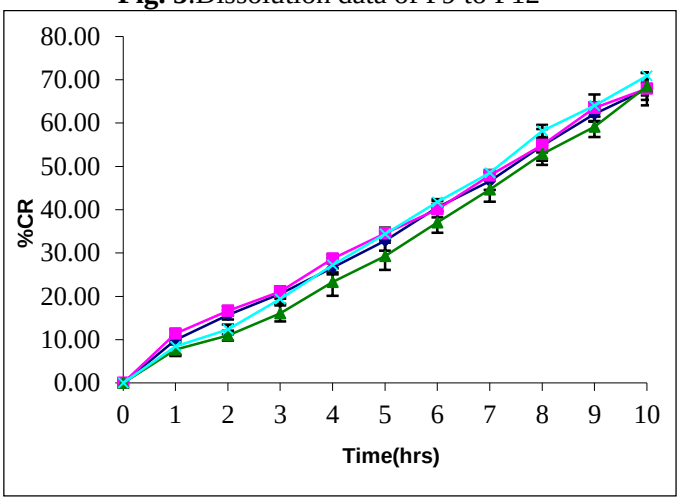

Fig. 6. Dissolution data of F13 to F16

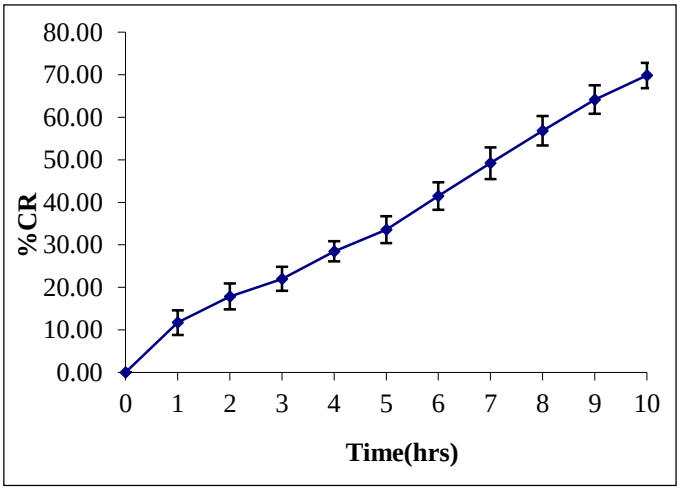

Fig. 7. Dissolution data of F17

5. CONCLUSION:

Gastric retention time (GRT) of Cinnarizine can be increased by formulating it in a floating dosage form using optimum amount of HPMC, $NaHCO_3$ and citric acid. The produced tablets exhibited good floating time and controlled drug release over a period of 10 hours. The floating tablets released drug in stomach to enhance bioavailability of Cinnarizine. It can be

concluded that the application of optimization technique, optimized formulation can be obtained with minimum expenditure time and money. A floating tablet with good flow property and controlled release property can be obtained by optimizing amount of HPMC, $NaHCO_3$ and citric acid. The number of experimental trials carried out to produce the optimized formulation was considerably reduced thereby substantially cutting down the expenditure on time and money.

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