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A CONCISE REVIEW ON FLOATING DRUG DELIVERY BY USING DESIGN EXPERT

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ABSTRACT

Floating drug delivery systems have a lower bulk density than gastric fluids and hence remain buoyant in the stomach for an extended period of time without influencing gastric emptying rate. While the system is floating on the gastric contents, the drug is slowly released from the system at the prescribed pace; after drug release, the remaining system is evacuated from the stomach. This leads in extended stomach retention time and better regulation of plasma medication concentration variations. There are two types of floating medication delivery systems. Non-effervescent and Gas-generating systems. Ciprofloxacin HCl floating tablets by using polymers like HPMC K4M, Eudragit 100S, guar gum. The prepared tablets are characterized by using different evaluation parameters like buoyancy lag time, floating time, *in-vitro* drug release, uniformity of drug content, hardness, friability etc. and it is optimized by factorial design using Design Expert Software. The *in-vitro* drug release of the optimized formulation is best fitted and found to follow Hixon crowell erosion kinetics with a higher R^2 value of 0.992.

KEYWORDS: Ciprofloxacin, Floating Tablet, Gastric Emptying Rate, Control release, Optimization.

INTRODUCTION

Over the past few years, scientific and technological advances have been made in the research and development of a controlled rate oral drug administration system. Oral bioavailability of drugs with a window of absorption in the upper gastrointestinal tract is generally restricted with dosage forms such as tablet, capsules and granules. These drugs can be delivered ideally by slow release from the stomach to give a localized effect at the site of action. Gastric

emptying of dosage forms is an extremely variable process which depends upon various factors of the dosage form and the physiology of GIT, so the ability to prolong and control the emptying time is a valuable quality for dosage forms. The residence time is main factor which influencetheabsorptionofdruginthestomachandupperintestine. It also modified *in vitro* & *in vivo* release profile of the oral conventional dosage form. To overcome these issues and to increase the bioavailability of these drugs, sustained drug delivery systems, with a prolonged residence time in the stomach, can be used.[1]

Gastro-retentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients in sustained manner and prolonged release of the drug to the upper part of the gastrointestinal (GI) tract.[2]

Gastro retentive delivery system can be classified as follows

1. Bioadhesive Drug Delivery System
2. Expandable Drug Delivery System
3. Floating Drug Delivery System
4. High density systems

Floating drug delivery systems have a lower bulk density than gastric fluids and hence remain buoyant in the stomach for an extended period of time without influencing gastric emptying rate. While the system is floating on the gastric contents, the drug is slowly released from the system at the prescribed pace; after drug release, the remaining system is evacuated from the stomach. This leads in extended stomach retention time and better regulation of plasma medication concentration variations. There are two types of floating medication delivery systems: (i) Non-effervescent and (ii) Gas-generating systems.[3, 4]

FLOATING SYSTEMS: Floating Drug Delivery Systems (FDDS) have a lower bulk density than gastric fluids and hence remain buoyant in the stomach for a longer period of time without altering the gastric emptying rate. While the system is floating on the gastric contents, the medicine is gently released at the desired pace from the system. The residual system is discharged from the stomach once the medicine has been released. As a result, GRT increases and variations in plasma medication concentrations are better controlled. Non-effervescent and effervescent floating systems are the two types of floating systems.[5, 6]

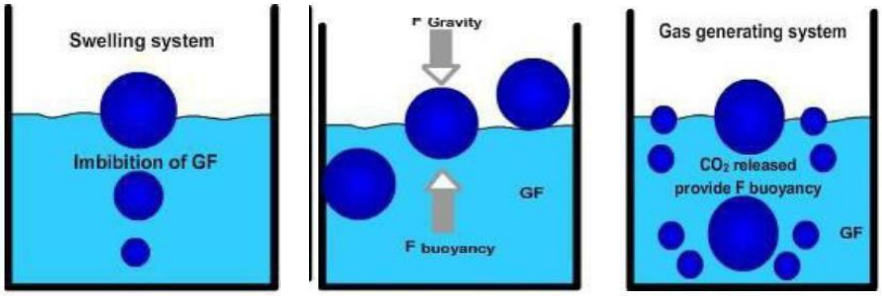

Figure 1: Mechanism of Floating System.

Advantages of FDDS

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

- Improved drug absorption because of increased GRT and more time spent by the dosage form at its absorption site.
- Controlled delivery of drugs.
- Delivery of drugs for local action in the stomach.
- Minimizing the mucosa irritation due to drugs, by drug releasing slowly at controlled rate.
- Treatmentofgastrointestinaldisorderssuchasgastro-esophagealreflux.
- Simple and conventional equipment for manufacture.
- Ease of administration and better patient compliance.
- Site-specific drug delivery.[7]

Ciprofloxacin: Ciprofloxacin is commonly known as broad spectrum antibiotic against both gram positive and gram negative bacteria. It is prescribed in treatment of respiratory and urinary tract infections. Conventionally Ciprofloxacin tablets have been used from the treatment of bacterial infections. It is an acidic drug which is majorly absorbed in stomach. The bioavailability of Ciprofloxacin is 69% and its half life is 4 hours. The Ciprofloxacin HCl floating tablets is proposed.

- To improve half life which shows prolongs action of drug in controlled manner for long period in stomach.
- To increase bioavailability of drug by increasing gastric residue time.
- Ciprofloxacin floating tablets are used to decrease dose frequency of drug also avoid fluctuations that cost by conventional tablets and also it helps to reduce the adverse effects caused by ciprofloxacin at higher doses.[8]

Mechanism of Action: Ciprofloxacin HCl drug has *in vitro* activity against a wide range of gram negative and gram positive organism. Ciprofloxacin inhibits bacterial DNA gyrate, an enzyme Responsible for countering excessive super coiling of DNA during replication of transcription. But the mechanism action of Ciprofloxacin is different from other antimicrobial agents such as Beta lactum, tetracycline, amino glycosides therefore organism resistant to these drug may susceptible to Ciprofloxacin Hcl drug.[9]

Factorial Optimization of Ciprofloxacin in HCl Floating Tablets

To understand the influence of formulation variables on the quality of formulations with a minimal number of experimental trials and subsequent selection of formulation variables to develop an optimized formulation using established statistical tools for optimization.[10]

METHODOLOGY

Preformulation Studies: The Preformulation studies are conducted to establish the physiochemical characteristics of the drug and its compatibility with the excipients used. The Preformulation studies are necessary to formulate drug into stable, safe and effective dosage form.

Compatibility studies: The drug and excipients selected for the formulation are evaluated for physical and chemical compatibility studies.

Drug–Excipients interaction study by FTIR: Infrared spectroscopy can be used to identify a compound and also to investigate the composition of a mixture there by we can study incompatibility with two compounds. Compatibility in between both drug and excipients. The IR spectra of the test samples were obtained by Pressed Pellet technique using Potassium bromide.[11, 12]

Construction of Calibration Curve Ciprofloxacin HCl

From the standard solution aliquots of 2ml, 4ml,6ml, 8ml,10mlwerepipetteout to 100 ml standard measuring flask and made up to 100 ml with 0.1 N HCl. The absorbance of the above solutions was measured in UV-spectrophotometer at λmax 277 nm using 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-axis and Absorbance on Y-axis, which gives a straight line which indicates the drug, is pure and obeys the Beers lamberts Law.

Formulation of Ciprofloxacin HCl Floating Tablet: The proposed formulation of Ciprofloxacin HCl was prepared using Design expert 10 using HPMC K4M, Eudragit 100S and Guar gum as variable and the formulate on design is given in the figure 7 and table.7.

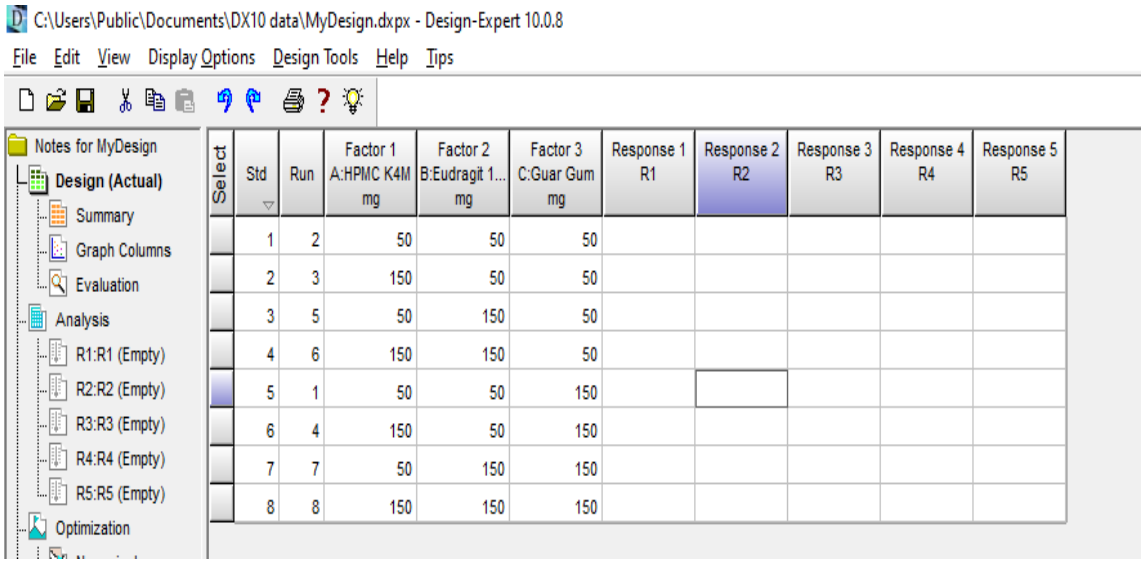

Figure 2: Design Expert 10 Reponses of Formulation Design.

Table 1: Formulation Design of Ciprofloxacin HCl Floating Tablet.

Formulation (mg)	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8
Ciprofloxacin HCl	250	250	250	250	250	250	250	250
HPMCK4M	50	150	50	150	50	150	50	150
Eudragit100S	50	50	150	150	50	50	150	150
Guar Gum	50	50	50	50	150	150	150	150
Sodium bicarbonate	50	50	50	50	50	50	50	50
Citric acid	15	15	15	15	15	15	15	15
Starch mucilage	25	25	25	25	25	25	25	25
Magnesium sterate	10	10	10	10	10	10	10	10
Lactose	300	200	200	100	200	100	100	0

Preparation of Ciprofloxacin HCl Floating Tablet

Floating tablets of Ciprofloxacin HCl were prepared by wet granulation technique using various polymers like HPMC K4M, Eudragit100S, Guar gum with combination of sodium bicarbonate and citric acid as gas generating agent. The composition of each formulationis given in formulation table no - 7.

Totally Eight batches of granules were prepared.

1. Ciprofloxacin Hcl is passed through sieve no.20.
2. HPMCK4M, Eudragit100S, Guargum, sodiumbicarbonate, citricacidpassed through sieve no.40.

3. Magnesium stearateispassedthroughsieveno60.
4. The shifted materials of Ciprofloxacin HCl was geometrically mixed with polymer and sodium bicarbonate and citric acid and blended for 10 minutes.
5. Then starch mucilage was added slowly drop wise manner to form a coherent mass.
6. Theformedcoherentmasswassievedmanuallythroughsieveno.16toform granules.
7. Then the granules are collected and dried in hot air oven at 40ºC±2ºC for 2hours.
8. The dried granuleswerepassedthroughsieveno.20.
9. Magnesium stearate is added to the dried granules then subjected to pre compression studies.
10. After the completion of compression studies, the granules of all formulations were compressed into tablets by using tablets punching machine.

Pre Compression Parameter

Bulk Density (ρb): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/mL and is given by formula.[13]

$$\rho b = \frac{M}{Vb}$$

Where, **M** and **Vb** are mass of powder and bulk volume of the powder respectively.

Tapped Density (ρt): Weighed powder sample was transferredtoa graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (500). The tapped density was determined by the formula.[14]

$$\rho t = \frac{M}{Vt}$$

Where, **M** and **Vt** are mass of powder and tapped volume of the powder respectively.

Angle of Repose (Ɵ): The flow properties were characterized in terms of Angle of repose, Carr's index and Hausner's ratio. For determination of Angle of Repose (Ɵ), the drug and the blends were poured through the walls of a funnel, which was fixed at a position such that its lower tip wasataheightofexactly2.0cmaboveahardsurface.Thedrugortheblendswere poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.[14]

$$\Theta = \tan^{-1}\frac{h}{r}$$

Table 2: Flow Property.

FlowProperties	Angle of Repose(Θ)
Excellent	<25
Good	25-30
Fair/Reasonable	30-40
Flow with difficulty	>40

Carr's Index or %Compressibility: It indicates powder flow properties. It is measured for determining the relative importance of interparticulate interactions.[14]

$$\text{Cl} = \frac{\rho t - \rho b}{\rho t} X\ 100$$

Hausner's Ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.[14]

$$\text{HR} = \frac{\rho t}{\rho b}$$

Where, **ρt** and **ρb** are tapped density and bulk density respectively.

Weight Variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated.

Hardness test: Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken.

Friability test: Friability is the loss of weight of tablet in the container/package due to removal of fine particles from the surface. This test is applicable to compressed tablets and is intended to determine the physical strength of tablets.[15,16]

Estimation of Drug Content: 20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of Ciprofloxacin Hydrochloride was transferred in to a 100 ml volumetric flask and volume made up with 0.1N HCl. Further 1ml of the above solution was diluted to 10 ml with 0.1N HCl and absorbance of the resulting solution was observed at λmax 277 nm.[17]

Floating test: The tablets were placed in a 100ml beaker containing 0.1N HCl. The time between introducing of dosage form and its buoyancy on 0.1N Hcl and the time during at which the dosage form remain buoyant were measured.[17]

Buoyancy lag time*:* The time taken for the dosage form to emerge on surface of medium is Called Floating lag time (FLT). Total duration of time during which the dosage form remains buoyant is called Total floating time (TFT).[18]

***In Vitro* Dissolution Studies of Tablets:** 900ml of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°C + 0.5°C. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 50 rpm.

At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at λmax 277 nm using UV-spectrophotometer.[19]

Factorial Optimization of Ciprofloxacin HCl Floating Tablets: To understand the influence of formulation variables on the quality of formulations with a minimal number of experimental trials and subsequent selection of formulation variables to develop an optimized formulation using established statistical tools for optimization.

Mathematical modeling, evaluation of the ability to fit to the model and response surface modeling were performed with employing Design-Expert® software (Version 10). In full factorial design, all the factors are studied in all the possible combinations. Hence, 2^3 factorial designs were chosen for the current formulation optimization study. Totally eight tablet formulations were prepared employing selected combinations of the two factors as per 2^3 Factorial and evaluated to find out the significance of combined effects of the two factor to select the best combination required to achieve the desired sustained release of Ciprofloxacin HCl tablet.[20,21]

Table 3: Experimental Design.

Factors: Formulation Variables	Levels (mg/tablet)	
	-1	+1
HPMCK4M	50	150
Eudragit100S	50	150
Guar gum	50	150
Response	**Goal**	
Time taken for drug releaseat 50%	Minimize	
Drugreleaseat12thhour	Maximize	

***In vitro* release kinetics** To study the *in vitro* release kinetics of the optimized floating tablets, data obtained from *In vitro* dissolution study was plotted in various kinetic models.[22]

Zero order equation: Time (The zero order release kinetics can be obtained by plotting cumulative % drug released Vs hours). It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C=K_0t$$

Where, K_0=Zero order constant in Conc. /time

First order equation: A graph was plotted with log% cumulative drug remaining Vs Time in hours.

$$Logic = logC_0 – Kt/2.303$$

Where, C_0= Initialdrugconcentration

K=Firstorderconstant

Higuchi kinetics: A graph was plotted with %cumulative drug released Vs Square root of time.

$$Q= Kt_{1/2}$$

Where, **K=** Constant reflecting design variable system (Differential rate constant)

Hixson and Crowellerosion equation: To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and Crowell erosion equation. A graph was plotted with cube root of % drug remaining Vs Time in hours.[23, 24]

$$Q^{1/3} – Q^{1/3} = KHC \times t$$

Where, Q_t=Amount of drug released at time t, Q0 = Initial amount of drug. **KHC**=Rate constant for Hixson Crowell equation.

ABBREVATIONS: DOE: Design of Experiments; API: Active Pharmaceutical Ingredients; Vs: Versus; PBS: Phosphate buffer saline; Pvt. Ltd.: Private limited; TEM: Transmission electron microscopy.

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