Abstract

Multi-layer floating tablet of ciprofloxacin were designed based on gas formation technique. The core tablet contain ciprofloxacin hydrochloride coated with hydroxypropyl methyl cellulose (protective coat), with sodium bicarbonate and citric (effervescent layer), and Eudragit® RL 30D (gas entrapped membrane), respectively. Eudragit® RL 30D is a good candidate for the gas entrapped membrane because it have high flexibility, high puncture strength and high (two time than Eudragit® RS 30D) water permeability. When the system placed in dissolution medium (0.1N HCl) the gas entrapment membrane allow the acidic water to come inside the membrane react with sodium bicarbonate and generate the CO₂ this CO₂ entrapped into the outer polymeric gas entrapment membrane and decrease the density of the tablet less than 1gm/ml and the tablet become float. The formulation variables which affect the floating properties and drug release are investigated. The tablets which are prepared by direct compression have the shorter lag time as compare to tablet by wet granulation. Higher amount of HPMC also delay the drug release from the tablet. Excessive amount of gas forming agent did not affect the lag time but increase the rate of drug release and increase weight of the tablet and also increase the coating level of gas entrapment layer. The plasticizer also play an important role here as the amount of plasticizer increase the lag time also increase but using the plasticizer more than 25% w/w the gas entrapment coat goes to break when placed in dissolution medium. Decrease the amount of plasticizer also decrease the lag time (shorter lag time) but decreasing the amount of plasticizer less than 13% w/w the tablet unable to float and the gas entrapment coat goes to break. Finally a good floating and sustain release tablet seems to be a promising gastro retentive drug delivery system.

Keywords: Gastro retentive drug delivery system; floating tablet; Lag time; Total lag time.

Introduction

As we know that gastric residence time (GRT) is one of the important factor affecting the drug bioavailability of the pharmaceutical dosage form. Short gastric emptying time or short gastric residence time can result in incomplete drug absorption and release from the dosage form particularly dosage form which have absorption window in the upper part of the gastro intestinal tract (GIT) or have a narrow absorption window. Floating drug delivery system (FDDS) is one of the gastroretentive drug delivery system which can increase the gastric residence of the dosage form and the dosage form remain in gastric region for long period of time with continuous drug release and absorption. Drugs which have absorption window through out the GIT or drugs which cause gastric irritation or drugs which are unstable in acidic medium are not a good candidate for gastro retentive drug delivery system. Drugs which are stable in acidic medium or have narrow absorption window or have absorption window at upper part of GIT or drugs which act locally in the gastric region are good candidate for gastro retentive drug delivery system. Floating drug delivery system float in the gastric fluid because of its lower bulk density (<1 gm/ml) as compare to gastric fluid.

Classification of Floating Drug Delivery Systems (FDDS)
1. Effervescent Floating Dosage Forms.
2. Non- Effervescent Floating Dosage Forms.

Factors Affecting Gastric Retention:
1. GRT is a function of dosage form buoyancy that is dependent on the density.
2. Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.
3. Shape of dosage
4. Fed or unfed state: under fasting conditions: GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC)

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International Journal of Contemporary Research and Review

April, 2011|Volume 01|Issue 04|
that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

5. Nature of meal: feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

6. Caloric content: GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

7. Frequency of feed: the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

8. Gender: Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

9. Age: Elderly people, especially those over 70, have a significantly longer GRT.


## Material and Methods

### Material

Ciprofloxacin hydrochloride was used as a model drug which is predominantly absorbed in the upper part of the GI tract. Microcrystalline Cellulose (Avicel® Ph 113, FMC) LOD less than 2%W/W and Lactose DCL22 (Anhydrous, DMV) were used as component of core tablet. Magnesium stearate used as a lubricant and Aerosil® 200 used as a glidant. HPMC 15pcs was used as a protective layer and also used as a binder with sodium bicarbonate (NaHCO₃, Merk) as a gas forming agent and citric acid (Merk) as an acidifier. Eudragit® RS 30 D (Evonik Industries, Germany) or Eudragit® RL 30 D (Evonik Industries, Germany) used as gas-entrapped membrane plasticized with water insoluble plasticizer myvacet (acetylated monoglycerides). EUDRAGIT® RL 30 D is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups.

### Preparation of floating tablets

The core tablet contains ciprofloxacin hydrochloride, Microcrystalline Cellulose (Avicel® Ph 112, FMC) and Lactose anhydrous (FMC). In wet granulation method the core tablet excipients are mixed in a V-blender for 10 minutes than this blend goes for hand granulation and dried at 50 °C in oven until the LOD comes below 2%w/w. Once the LOD come below 2%w/w the material pass through sieve no. 40 (mesh size 425 μm) and collect the blend. Extra granulators magnesium stearate (1%w/w) and Aerosil® 200 (0.5%w/w) both are pass through sieve no. 60 (mesh size 425 μm) the granulated blend and extra granulators are mixed for further 5 minutes in V-blender and collect. The ready for compression material goes for compression. In dry granulation the

### Marketed Products of GRDDS

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Delivery system</th>
<th>Drug (dose)</th>
<th>Company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valrelease®</td>
<td>Floating capsule</td>
<td>Diazepam (15mg)</td>
<td>Hoffmann-LaRoche, USA</td>
</tr>
<tr>
<td>Madopar® HBS (Prolup® HBS)</td>
<td>Floating, CR capsule</td>
<td>Benserazide (25mg) and L-Dopa (100mg)</td>
<td>Roche Products, USA</td>
</tr>
<tr>
<td>Liquid Gaviscon®</td>
<td>Effervescent Floating alkali preparation</td>
<td>Al hydroxide (95 mg), Mg Carbonate (358 mg)</td>
<td>GlaxoSmithkline, India</td>
</tr>
<tr>
<td>Topalkan®</td>
<td>Floating liquid alkali preparation</td>
<td>Al – Mg antacid</td>
<td>Pierre Fabre Drug, France</td>
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<tr>
<td>Almagate Flot coat®</td>
<td>Floating dosage form</td>
<td>Al – Mg antacid</td>
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<tr>
<td>Conviron®</td>
<td>Colloidal gel forming FDDS</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Cytotech®</td>
<td>Bilayer floating capsule</td>
<td>Misoprostol (100µg/200µg)</td>
<td>Pharmacia, USA</td>
</tr>
<tr>
<td>Cifran OD®</td>
<td>Gas-generating floating form</td>
<td>Ciprofloxacin (500mg)</td>
<td>Ranbaxy, India</td>
</tr>
</tbody>
</table>
excipients for core tablet goes for slugging (preparation of large tablet) the slugs are prepared by using REMEK (Mini Press II), 13mm flat punches compressed in. The slugs are passed through cromill (Cronimo) using 0.5mm screen. The screened blends than pass through the 40# sieve and mixed with magnesium stearate (1%w/w) and Aerosil®200 (0.5%w/w) for further 5 minutes in a V-blender and collect. The ready for compression was compressed in a Compression Machine (Sviac, PR6) Compression parameters are below.

Coating of core tables
Three successive layering over the core tablets; inner protective layering using HPMC, a gas forming layering using sodium bicarbonate and outer most gas entrapped membrane.

Protective coating: solution of HPMC plasticized by polyethylene glycol (PEG 6000), plasticizer used 8% w/w of the polymer and the concentration of the final coating solution is 10%w/w. before protective coating the tablets are preheated using INSTACOAT (Pharma R&D Coater) to remove the excessive moisture. The protective coat weight build up is 2%w/w. After completion of preheating or before going for protective coating, takes 20 tablets randomly for three time and calculate the initial average weight of the 20 tablets.

Gas forming layering: sodium bicarbonate in HPMC 15cps solution plasticized with Polyethylene glycol (PEG 6000). HPMC 15cps is used as a binder the ration of sodium bicarbonate to HPMC were 2:8, 5:5, 8:2 w/w. plasticizer used 8% w/w of the polymer content. Final concentration of coating solution is 10%w/w. Takes 20 tablets randomly for three times and calculate the initial average weight of the 20 protective coated tablets.

<table>
<thead>
<tr>
<th>Protective coating parameter</th>
<th>Desired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed temperature</td>
<td>30-34 °C</td>
</tr>
<tr>
<td>Heater temperature</td>
<td>35-38 °C</td>
</tr>
<tr>
<td>Pan speed</td>
<td>4-6 rpm</td>
</tr>
<tr>
<td>Pump speed</td>
<td>2-4 rpm</td>
</tr>
<tr>
<td>Spray rate</td>
<td>0.25-0.50 gm/minutes</td>
</tr>
<tr>
<td>Weight build up</td>
<td>2%w/w</td>
</tr>
</tbody>
</table>

Gas entrapped membrane coating

<table>
<thead>
<tr>
<th>Gas entrapped membrane coating</th>
<th>Desired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed temperature</td>
<td>28-32 °C</td>
</tr>
<tr>
<td>Heater temperature</td>
<td>35-40 °C</td>
</tr>
<tr>
<td>Pan speed</td>
<td>10-15 rpm</td>
</tr>
<tr>
<td>Pump speed</td>
<td>2-3 rpm</td>
</tr>
<tr>
<td>Spray rate</td>
<td>0.25-0.40 gm/minutes</td>
</tr>
<tr>
<td>Weight build up</td>
<td>6,12 %w/w</td>
</tr>
</tbody>
</table>

Outer most gas entrapped membrane; the two layer coated tablet now ready for gas entrapped membrane coating. Eudragit® RL 30 D and Eudragit® RS 30 D are different only on the basis of amount of quaternary ammonium groups and quaternary ammonium groups directly responsible for the permeability of the membrane, Eudragit® RS 30 D contain one half quaternary ammonium as compare to Eudragit® RL 30 D. Eudragit® RL 30 D membrane have high permeability. Eudragit® RL 30 D and Eudragit® RS 30 D both are marketed as 30%w/w aqueous dispersion. The gas forming layered tablets are divided into two batches, one coated with Eudragit® RL 30 D and another coated with Eudragit® RS 30 D, both are plasticized by water insoluble polymer Myvacet (10, 15, 20, 25, 30%w/w). After addition of plasticizer the solution gently stirred for 20-30 minutes. Final concentration of coating solution is 12%w/w. As sodium bicarbonate is very sensitive against the moisture which will create the stability problem. So the process condition is considerable, RH of the processing area should be < 40 &. <30 °C. After preheating calculate the average 20 tablet weight. Collect the tablets when weights build up achieved (6, 12 w/w).

Curing; once the desired weights build up achieved the pump is off and tablet are rotated in the pan to remove the excessive moisture from the tablet then collect the tablets.

Evaluation of floating tablets
Tables from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. Hardness; using tablet hardness tester [Dr. Schleuniguek (Phamatorn)]. Friability; using friabilator USP (Electrolab).

In vitro buoyancy studies:
In vitro buoyancy studies were performed for all the formulations as per the method described by Rosa et, al. The randomly selected tablets from each formulation were kept in a 100ml beaker containing 0.1N hydrochloric acid.

Floating lag time (FLT): The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT).

Total floating time (TFT): The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

Drug Content:
The drug content in each formulation was determined by triturating 20 tablets and
powder equivalent to average weight was added in 100ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45μ membrane filter, diluted suitably and the absorbance of resultant solution was measured U.V. spectrophotometrically at 277nm using 0.1 N hydrochloric acid as blank.

Drug Release:  
The release rate of ciprofloxacin hydrochloride from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45μ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 277 nm using UV spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Result and discussion

Floating properties:  
The system coated with Eudragit® RS 30D as gas-entrapped membrane did not float even when high amount of gas forming agent (12% w/w weight gain of HPMC: NaHCO₃, 2:8 w/w) and low weight gain (5%w/w low weight gain, HPMC : NaHCO₃, 2:8 w/w). Eudragit® RS 30D is less permeable to water vapor and low amount of dissolution fluid able to penetrate inside the gas-entrapped membrane to induce the effervescent reaction and generate sufficient amount of CO₂ to make the system float. Eudragit® RL 30D contain twice as many quaternary ammonium groups in Eudragit® RS 30D therefore the Eudragit® RL 30D membrane hydrated quickly and gas generate faster, therefore only Eudragit® RL 30D was taken as gas-entrapped membrane in this study.

Formulation variable:  
Ciprofloxacin is unstable with sodium bicarbonate so need to separate the core containing ciprofloxacin from bicarbonate layer using HPMC as a protective coating.

Method of core preparation:
Core tablet containing ciprofloxacin hydrochloride was prepared by both wet granulation and direct compression. In wet granulation PVP29/30 (polyvinyl pyrolidine) solution is used as a granulating fluid. In direct compression the blend for core is directly compressed.
granulation containing PVP are shows delayed drug release but no significant change in lag time and other hand the tablets prepared by direct compression shows faster drug release. The directly compressed core disintegrates with in 50 second whereas the wet granulation core takes 100 second for disintegration.

Affect of gas forming agent: 
Increasing the amount of gas forming agent (NaHCO₃) more than 20%w/w did not significantly affect time to float. However increasing the amount of NaHCO₃ increase the rate of drug release. HPMC play an important role, seemed to retard the drug release.

Gas-entrapped membrane coating: 
The time to float was longer with increased coating level of gas-entrapped membrane. The higher level of membrane coating represents the higher thickness of the membrane and caused the lower water permeability of the film. Decreasing the water permeability decrease the drug release.

Amount of plasticizer: 
Increasing the amount of plasticizer (>25%w/w) delayed the lag time and also delayed the drug release and provides excess elasticity to the film and the film is going to break after 1 hr. Decreasing the amount of plasticizer (20% w/w, < 20%w/w) increase the lag time but decreasing the amount less than 15%w/w show no floating because the film have not sufficient flexibility, gas is generated but due to the lack of flexibility and pressure of CO₂ the tablet goes bust.

Conclusions: 
The floating multi-layer tablets of ciprofloxacin were developed. The system consists of drug-containing core tablets coated with a protective layer, a gas forming layer and a polymeric membrane, respectively. The polymeric film with high flexibility (Eudragit® RL 30D) plstisized with 18%w/w plasticizer had high capability to entrap generated CO₂ and the subsequent good floating properties. These tablets enable to float due to the formation of CO₂ and the entrapment of generated CO₂ by the outer polymeric membrane. The floating properties and the drug release from the floating tablet were depend on the core preparation method (the core tablet should have disintegration time very less), the amount of gas forming agent (ratio of NaHCO₃ to HPMC) and the level of gas entrapment layer membrane.

The tablet with good floating properties (time to float less than 10 minutes, floating time more than 12 hr.) and sustained drug release were obtained. These floating multi-layer coated tablets seem to be a promising gastro retentive drug delivery system.

References:
Research

Chandola V et al.: Formulation and Evaluation of Multilayer Floating Tablet

ISSN 0976 – 4852
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