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Design and Evaluation of Levofloxacin Effervescent Floating Tablets

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ABSTRACT

Recently many drugs are formulated as floating drug delivery systems with an objective to sustain release and restrict the region of drug release to stomach. The purpose of the investigation was to prepare a gastro retentive drug delivery system of Levofloxacin. Levofloxacin is a synthetic chemotherapeutic agent used to treat severe or life-threatening bacterial infections. Levofloxacin belongs to the class of fluoroquinolone (or quinolone) anti-infectives. Levofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division. Different formulations were formulated using various concentrations of HPMC (hydrophilic polymer), sodium bicarbonate (gas generating agent) and citric acid. The formulations were evaluated for quality control tests and all the physical parameters evaluated are within the acceptable limits of IP. All the five formulations were subjected to in vitro dissolution studies. In vitro drug release studies of these tablets indicated sustained release for levofloxacin and 80 to 85% release at the end of 6th hour. Hence it is evident from the investigation that floating tablets could be a promising delivery system for levofloxacin with sustained release action and improved drug availability.

KEY WORDS: Levofloxacin, Floating tablets, Controlled release, Gastro retentive.

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INTRODUCTION [1]

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached. Most of the drug absorption is unsatisfactory and highly variable among and between individuals, despite excellent *in vitro* release patterns. The reason for this is essentially physiological and usually effected by GI transit of the dosage form. Especially its gastric residence time (gut), which appears to be one of the major causes of the overall transit time variability. Over the past three decades, the pursuit and exploration of systems designed to be retained in the part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity of encompassing a variety of systems and devices such as floating system, raft system, expanding systems, swelling systems, bio adhesive system and low density systems. Gastric retention will provide advantages such as the delivery of the drugs with narrow absorption windows in the small intestine region also, longer residence time in the stomach could be advantages for the locally acting drug in the upper part of the small intestine, for example drug used in the treatment of peptic ulcer disease.

Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon the release in the GI tract. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorized as once a day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.

Certain types of drugs have benefit by using gastric retentive devices. These include

- acting locally in the stomach
- primarily absorbed in the stomach
- poorly soluble at an alkaline pH
- narrow therapeutic window of absorption
- absorbed rapidly from the GI tract
- degrade in the colon

Physiological considerations [2]

Anatomically the stomach is divided into 3 regions: fundus, body, antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, where as the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an inter digestive series of electrical events takes place, which cycle both through stomach and intestine every 2 to 3 hours. This is the inter digestive myoelectric cycle or migrating myoelectric cycle(mmc), which is further divided into following 4 phases as described by Wilson and Washington.

1. Phase 1 (basal phase) lasts from 40 to 60minutes with rate contractions
2. Phase 2 (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intestine and the frequency also increases gradually.
3. Phase 3 (burst phase) lasts for 4 to 6 minutes. It includes intestine and regular contractions for short period. It is due to this wave that all undigested material is swept out of the stomach down to the small intestine. it is also known as housekeeper wave
4. Phase 4 lasts for 0 to 5 minutes and occurs between phases 3 and 1 of consecutive cycles. After the ingestion of a mixed meal, the pattern contractions changes from fasted to that fed state. These contractions results in reducing the size of the food particles which are propelled towards the pylorus in a suspension form. During the fed state onset of action is delayed resulting in slowdown of gastric emptying rate.

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

Different parameters in the stomach region [1]

- Gastric pH: fasted healthy subject 1.1 ± 0.15 . Fed healthy subject 3.6 ± 0.4
- Volume: resting volume is about 25-50 ml
- Gastric secretion: acid, pepsin, gastrin, mucus and some enzymes about 60 ml with appropriately 4 mmol of hydrogen ions per hour.

Advantages of FDDS [3]

Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose maintenance. Therapeutic levels minimizing the risk of resistance especially in the case of antibiotics retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time thereby increasing bioavailability of sustained release systems intended for once-a-day administration.

Disadvantages [3]

- They require a sufficiently high level of fluids in the stomach for the drug delivery buoyancy, to float there in and to work efficiently

- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluid
- Drugs such as nifedipine, which is well absorbed along the entire GI tract and which undergoes significant first-pass metabolism, may not be desirable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability
- Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa

Types of FDDS [4-6]

Based on the mechanism of buoyancy, two different technologies have been utilized in the development of FDDS. They are

1. Non effervescent FDDS
2. Effervescent FDDS

1) Non effervescent FDDS

The most commonly used in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. When dosage forms come in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. It maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier.

2) Effervescent FDDS

These buoyant delivery systems utilize matrices prepared with swellable polymers such as methocel or polysaccharides, ex: chitosan and effervescent components .ex: sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquids that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the activity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form to float on the chyme.

Stockwell .et al prepared the floating capsule by filling it with a mixture of sodium alginate and sodium bicarbonate. The systems were shown to float during in-vitro tests as a result of the generation of carbon dioxide that was trapped in the hydrating gel network on exposure to an acidic environment. The carbonates, in addition to imparting buoyancy to these formulations, provide the initial alkaline microenvironment for polymers to gel. The release of carbon dioxide helps accelerate the hydration of the floating tablets which is essential for the formation of a bio-adhesive hydrogel. This provides an additional mechanism for retain in the

dosage form in stomach, apart from floating. Floating dosage forms with an in-situ gas generation mechanism are expected to have greater buoyancy and improved drug release characteristics. However, the optimization of the drug release may alter the buoyancy and therefore, it is sometimes necessary to separate the control of buoyancy from the drug release kinetics during formulation optimization.

Applications of floating drug delivery systems [7-10]

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained drug delivery

The problem of short gastric residence time encountered with an oral formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Recently sustained release floating capsules of nifedipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional Nifedipine capsules (8 hours) using rabbits. Similarly a comparative study between the Madopar SR and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case.

Site-specific drug delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg: Riboflavin and Furosemide. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.

A bilayer-floating capsule was developed for local delivery of mesoprostol, which is a synthetic analogue of prostaglandin used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of mesoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced.

Absorption enhancement

Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available lasix tablets (33.4%) and enteric-coated lasix-long product (29.5%).

MATERIALS AND METHODS

Materials

The pure drug levofloxacin was received as a gift sample from Rapson Pharmaceuticals, Chennai, India. Remaining ingredients like sodium bi carbonate, HPMC, citric acid, PVP K30, magnesium stearate and talc which were used in the formulation trial were of lab grade.

Method of Tablet Preparation

Table 1. Formulation trial

Ingredients (mg/tab)	Various Trials of Levofloxacin Tablet				
	F-I	F-II	F-III	F-IV	F-V
Levofloxacin	500	500	500	500	500
Sodium Bicarbonate	200	200	200	200	200
HPMC	0	100	200	100	200
Citric Acid	20	30	30	20	20
PVP	75	75	75	75	75
Magnesium Stearate	15	15	15	15	15
Talc	10	10	10	10	10

Tablets were prepared by wet granulation method using sodium bi carbonate as gas generating agent and HPMC as hydrophilic matrix in each formulation. The composition of formulation is given in table 1. The composition with respect to polymer was selected based on trial preparation of tablet (with HPMC k30). The ingredients except glidant and lubricant were thoroughly mixed and granulation was done with a solution of calculated quantity of PVP k30 in sufficient isopropyl alcohol. The wet mass was passed through sieve no 10 and dried at 45 to 55°C for 2 hours in tray drier. The dried granules were sized by passing through sieve no 22 and the granules retained on sieve no 44 were collected, 10% of the fines were added, mixed with magnesium stearate and talc. Granules were then compressed to tablets in rotary tablet punching machine.

EVALUATION PARAMETERS

Weight variation

10 tablets were weighed collectively and individually. From the collective weight average weight was calculated. The weight of each tablet was then compared with average weight to ascertain whether it is within the permissible limit or not. the weight of not more than two tablets must not deviate from the average weight and no tablet deviate by double the percentage.

Test for hardness and thickness

The hardness of the tablet was evaluated using the Monsanto hardness tester. The tester contains a barrel, containing a compressible spring held between two plungers. The lower plunger was placed in contact with tablet and '0' reading was taken. The upper plunger was forced against a spring by turning the threaded bolt until the tablet fractures. The force of fracture was recorded and the zero force reading was detected from it. If the tablet with stand a force of about 5 kg, it is considered as good tablet. Tablet thickness can be measured by micrometer or by other device. Tablet thickness should be controlled within a $\pm 5\%$ variation of standard value.

Test for friability

It was measured by using Roche friabilator. 6 tablets were subjected to combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping tablets at a distance of 6 inches on each revolution. A pre-weighed sample was placed in the friabilator which was then operated for 100 revolutions. The tablet were then dusted and reweighed. The friability loss was calculated using the difference in weight. The tablet passes the test, if the loss is less than 1% of the original weight.

In vitro buoyancy studies

Floating time was determined using electro lab dissolution tester (USP) at 100 rpm using 900 ml of 0.1 N HCl and temperature was maintained at 37^oc throughout the study. The duration of the floating is the time the tablet floats in the dissolution medium (including buoyancy lag time).

In vitro dissolution studies

Drug release was studied using USP 24 paddle dissolution test apparatus in 900 ml of 0.1 N HCl at 100 rpm at 37^oc. 10 ml of the sample was withdrawn at regular intervals (for every 1 hr) and the same volume of fresh dissolution medium was replaced. The sample withdrawn was filtered and 1ml of the filtered sample was withdrawn and made up to 100 ml with 0.1 N HCl. The absorbance of the samples was determined by Perkin Elmer UV spectrophotometer at 276

nm and the absorbance and concentration of drug release at various time intervals were tabulated.

RESULTS

Table 2. Results of evaluation parameter

Formulation	Buoyancy (in Hours)	Hardness (kg/cm ²)	Thickness (cm)	Friability (%)
I	0	6.54	0.65	0.56
II	3	6.54	0.65	0.56
III	4	6.28	0.65	0.37
IV	8	7.1	0.65	0.75
V	8	6.78	0.65	0.93

Table 3. Dissolution studies

Time in hours	Percentage drug release				
	I	II	III	IV	V
1	57.66	13.2	14.54	16.5	18.08
2	82.58	24.41	26.29	28.09	30.08
3	57.66	32.61	37.28	40.64	41.937
4	54.83	46.28	49.68	51.76	54.53
5	34.61	55.77	64.35	64.81	66.88
6	25.21	80.48	83.69	84.11	85.32
7	13.7	53.97	58.68	60.33	64.79

DISCUSSION

Table 2 depicts the physical parameters (hardness, thickness, friability, buoyancy and weight variation) of all the fabricated tablets. Table 3 reflects the in vitro release of the drug from these tablets. Absence of polymer in Formula I has shown lesser buoyancy, the floating time was reduced, the in vitro drug release studies shown maximum bio availability in second hour. 82.58% of the drug was released in the second hour. All the remaining four formulations floated beyond 8 hours. As per IP requirements, formulation I failed to show satisfactory result in weight variation test as well as in floating buyonancy. Formulation II to V passed the test. Hardness of all the formulations was in the range of 5 to 7.1 kg/cm² and they have passed the test. The thicknesses of the tablets prepared were in the range of 5.5 to 6.5 mm and passes the test as per IP. Drug release pattern of formula II to III showed satisfactory and sustained release. Increase in the concentration of citric acid disturbs monolithic layer of tablet (in formulation II and III) moreover floating time of the tablet was less. The incorporation of citric acid in lower concentration and increment of polymer concentration in formulation IV and V were found to be more suitable to give a good floating ability having better drug release characteristics and consistency. Comparative to Formulation IV Formulation V has more polymer concentration and it has got good drug release characteristics and it gave the best in vitro drug release of 85.32% in 6 hours.

CONCLUSION

Present work focuses on development of prolonged release oral dosage form with gastro retentive properties containing levofloxacin as active ingredient. A floating tablet of levofloxacin was formulated by wet granulation method. The optimum quantity of swellable polymer and gas generating agent was required to impart buoyancy to the system and desirable dimension after swelling. This formulation would enhance absorption of levofloxacin and hence it improves bio availability. All the formulation trials were produced under similar conditions to avoid processing variables. All the prepared formulations fulfilled the official requirement of weight variation test except formulation I. Hardness of the tablet were maintained in the range of 5.0 to 7.1kg/cm². Dissolution media of 0.1 N HCl was found to be suitable for providing adequate sink condition for the gastro retentive levofloxacin tablet. Among all the formulation trial, formulation V was found to be satisfactory. Almost 2:1ratio was found to provide the granules with good buoyancy and satisfactory release. Hence on the basis of buoyancy behaviour and in vitro release studies it can be concluded that formulation V containing 200 mg of HPMC and 75 mg of PVP K30 polymer was the optimized formulation. In future, the optimized formulation can be subjected to stability studies as per ICH guidelines.

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