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Original Article

DEVELOPMENT OF A PROLONGD RELEASE GASTRORETENTIVE TABLET FORMULATION OF LEVOFLOXACIN

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ABSTRACT

Objective: The present investigation concerns the design and evaluation of floating tablets of Levofloxacin, which after oral administration prolong the gastric residence time and increased drug bioavailability.

Methods: Levofloxacin is a synthetic chemotherapeutic agent used to treat severe or life-threatening bacterial infections. The present work was designed to formulate floating tablet of Levofloxacin with various swelling agents. Formulations were prepared using various concentrations of Guar gum, Carbopol, hydroxy propyl methyl cellulose and Ethyl Cellulose by direct compression technique. The selected batches were evaluated for various parameters like weight variation, thickness, diameter, friability, floating lag time, duration of floating, swelling index, content uniformity and *in-vitro* drug release. The data obtained from the *in-vitro* dissolution studies of optimized batch F**7** were fitted in different models.

Results: The optimized formulation F7 showed 99.25% drug content, floating lag time of 10 min and swelling index of 40%. Drug release mechanism was found to be zero order along with higuchi release kinetics exhibiting diffusion along with dissolution of the drug from the tablet by non fickian mechanism.

Conclusion: Levofloxacin floating tablets exhibited increased gastric residence time, there by improved bioavailability and therapeutic effect of the drug.

Keywords: Levofloxacin, Gastro retentive, Guar gum, Hydroxy propyl methyl cellulose, Ethyl Cellulose, Carbopol.

INTRODUCTION

Oral controlled drug delivery system provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of Gastro Intestinal (GI) transit. Conventional oral controlled dosage forms suffer from mainly two adversities the short gastric retention time and unpredictable gastric emptying time [1]. A relatively short GI transit time of most drug products impedes the formulation of single daily dosage forms. Altering the gastric emptying can overwhelm these problems. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time using gastro retentive dosage forms that offer a new and better option for drug delivery [2].

Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment [3]. Gastro retentive floating tablets have been emerged as an efficient means of enhancing the bioavailability of many drugs. Rapid gastro-intestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of administered dose [4].

Levofloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class and is used to treat severe or life-threatening bacterial infections or bacterial infections that have failed to respond to other antibiotic classes [5]. Levofloxacin is a broad-spectrum antibiotic, inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division [6].

The bioavailability of Levofloxacin hemihydrate is above 99% with a plasma half-life of 6–8 h. It is freely soluble in pH 0.6 to 5.8 ranges. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 and above which the solubility decreases and reaches a minimum value at a pH of approximately 6.9. Thus solubility of the drug is reduced in intestinal alkaline pH. [7] Hence, it was selected in the present investigation as a suitable candidate for the design of gastric floating drug delivery system for improved retention time and bioavailability.

The present study is to develop a floatable drug delivery system of Levofloxacin using hydroxy propyl methyl cellulose, Guar gum, Carbopol, Ethyl cellulose for sustained drug delivery and gastric retentive property. Thus the study aims to improve the oral bioavailability of the drug and to achieve extended retention in the stomach which may result in prolonged absorption

MATERIALS AND METHODS

Materials

Levofloxacin was received as a gift sample from Srini Pharmaceuticals, Nalgonda. Guar gum was obtained as a gift sample from Colorcon Asia Pvt. Ltd, Goa, India. Hydroxy Propyl Methylcellulose, Micro Crystalline Cellulose, Magnesium stearate, Sodium bicarbonate, Talc, Carbopol, Ethyl cellulose, Poly vinyl pyrolidone K 30 were procured from S. D. Fine Chem. Ltd, Mumbai, India.

Preparation of floating tablets of levofloxacin

Levofloxacin floating tablets were prepared by direct compression method employing sodium bicarbonate as gas-generating agent. Guar gum, Carbopol and Ethyl cellulose were used as rate controlling polymers. The concentrations of the excipients were optimized as showed in table 1. The drug was mixed with the rate retarding polymers and other excipients in ascending order of their weights. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then magnesium Stearate and Talc were added. About 650 mg of the powder mix was weighed accurately and fed into the die and compressed using 12 mm round surface punches [8].

Evaluation of levofloxacin floating tablets

Levofloxacin floating tablets were subjected to post compression parameters like weight variation, hardness, friability, floating time, total floating time, in-vitro dissolution, swelling index, in-vitro buoyancy, drug content and stability studies.

Weight variation

The formulated tablets were tested for weight uniformity. 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with the average weight to ascertain whether it is within permissible limits or not [9].

Table 1: Composition of levofloxacin floating tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Levofloxacin	250	250	250	250	250	250	250	250	250	250	250	250
Hydroxy propyl methyl cellulose	20	-	-	-	-	-	-	-	-	-	-	-
Guar gum	-	20	-	20	10	-	30	35	30	35	40	40
Carbopol	-	-	20	10	-	20	-	5	-	-	-	-
Ethyl cellulose	-	-	-	-	5	5	5	5	10	10	5	10
Sodium bicarbonate	15	15	15	15	15	15	15	15	15	15	15	15
Poly vinyl pyrolidone K 30	5	5	5	5	5	5	5	5	5	5	5	5
Microcrystalline cellulose	55	55	55	45	60	50	40	30	35	30	30	25
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	650	650	650	650	650	650	650	650	650	650	650	650

Hardness

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Pfizer tablet hardness tester.

Friability

The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The percentage friability was calculated using the formula [10].

$$\% \text{ Friability} = \frac{\text{Initial weight (gm)} - \text{Final weight (gm)}}{\text{Initial weight (gm)}} \times 100$$

Determination of swelling index

The swelling index of tablets was determined in 0.1N Hcl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 h. The swelling index (SI), expressed as a percentage, and was calculated from the following equation [11].

$$SI = \frac{\text{Weight of Swollen tablet-Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

***In vitro* buoyancy studies**

In-vitro buoyancy studies were performed for all the twelve formulations as per the method described by Rosa *et al.* The randomly selected tablets from each formulation were kept in a 100 ml beakers containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of the medium was determined as the total floating time (TFT) [12].

Drug content estimation

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to an average weight was added in 100 ml of 0.1N HCL, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant the solution was measured spectrophotometrically at 288 nm using 0.1 N HCL as blank.

***In-vitro* dissolution studies**

In-vitro drug release of the samples was carried out using USP–type II dissolution apparatus at 37±0.5ºc using 900 ml of 0.1N Hcl as the dissolution medium at 50 rpm speeds. One Levofloxacin tablet was placed in each basket and was allowed to run for 12 hours. Aliquot of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume. Collected samples were suitably diluted with 0.1N Hcl and analyzed at 288 nm using 0.1N Hcl as blank. The drug content was calculated using the equation generated from the standard curve. The %cumulative drug release was calculated [13].

Study of release kinetics

The dissolution data were fitted into various kinetic models to determine the release mechanisms. Different kinetic equations (zero order, First order, and Higuchi's equations) were applied to interpret the release rate of the drug from the matrix system. For prediction of the mechanism of drug release through polymeric system Korsmeyer and Peppas, developed a mathematical equation, relating exponentially the drug released to the elapsed time. It is a simple semi empirical equation also called as *Power law.*

$M_t/M_\infty = Kt^n$

Where, M_t/M_∞ is the fraction of drug released at time' t' and infinite time,' k' is the kinetic constant, n is the drug release exponent, indicative of the mechanism of drug release.

Exponent, n			Drug Release Mechanism
Thin Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian Diffusion
0.5<n<1.0	0.45<n<0.89	0.43<n<0.85	Anomalous Transport
1.0	0.89	0.85	Case II transport

Mean dissolution time (MDT) is used to characterize the drug release rate from the dosage form and retarding efficiency of the polymer. MDT was calculated using the equation:

$$MDT = n/(n+1) * k^{-1/n}$$

Where' n' is the release component and' k' is the kinetic constant calculated from the power law [14].

RESULTS AND DISCUSSION

Levofloxacin floating tablets were developed to increase the gastric residence time of the drug, so that they can be retained in the stomach for longer time and help in controlled release of the drug to a minimum of 12h. The tablets were made using different gel forming polymers such as Guar gum, carbopol and ethyl cellulose by direct compression method. When a combination of gas entrapping as well as controlled release system is there, the use of disintegrating agent is important which does not quickly break the matrix and allows slow disintegration of the swollen matrix. Poly vinyl pyrolidone K 30 in an optimized concentration was employed for such unique disintegration properties. Talc and magnesium stearate were employed for their glidant and lubricant property. The prepared formulations were evaluated for physical characters like tablet hardness, friability, weight variation buoyancy lag time, total floating time, in-vitro drug release and drug release kinetics.

Table 2: Post compression evaluation of levofloxacin floating tablets

Formulation code	Weight variation [a] (mg)	Thickness [b] (mm)	Hardness[a] (kg/cm²)	Friability[a](%)
F1	651±2.33	4.15±0.10	6.3±0.05	0.33±0.10
F2	650±2.94	4.13±0.05	6.5±0.10	0.30±0.04
F3	649±3.77	4.16±0.05	6.3±0.12	0.33±0.07
F4	650±1.50	4.14±0.10	6.5±0.05	0.34±0.17
F5	649±3.30	4.17±0.05	6.2±0.10	0.36±0.08
F6	647±2.83	4.12±0.10	6.6±0.05	0.41±10.12
F7	648±2.33	4.18±0.06	6.2±0.09	0.42±0.05
F8	650±3.11	4.14±0.05	6.4±0.04	0.35±0.12
F9	652±2.56	4.16±0.09	6.3±0.10	0.37±0.04
F10	650±2.14	4.14±0.05	6.5±0.05	0.40±0.08
F11	651±1.85	4.18±0.05	6.2±0.04	0.38±0.12
F12	649±2.35	4.13±0.05	6.4±0.10	0.42±0.07

[a]Data shown are as an average n = 20, [b]Data shown are as an average n = 10

Table 3: Evaluation of drug content, floating lag time, swelling index and total floating time for the prepared formulations

Formulation code	Drug content (%) n = 20	Floating lag time (Min)	Swelling index (%)	Floating duration (H)
F1	99.49±0.91	5 min 25 sec	--	Fail
F2	99.55±0.92	4 min 33 sec	38.09	8
F3	99.41±0.34	3 min 32 sec	--	Fail
F4	99.72±1.39	3 min 22 sec	--	Fail
F5	99.84±1.69	15 min 12 sec	--	Fail
F6	99.30±1.07	15 min 34 sec	--	Fail
F7	99.25±1.81	10 min 12 sec	40.90	12
F8	99.54±0.37	10 min 24 sec	40.20	12
F9	98.50±0.91	2 min 21 sec	--	Fail
F10	99.26±1.65	5 mins	36.83	12
F11	98.30±0.85	3 mins 23 sec	22.05	12
F12	99.45±0.98	12 mins	27.69	12

Post compression parameters of Levofloxacin tablets

Levofloxacin floating tablets were evaluated for post compression parameters like weight variation, thickness hardness, and friability. All the formulations remained off white, smooth, flat faced circular with no visible cracks. The results are shown in table 2.

Weight variation

The prepared tablets were evaluated for weight variation and were in the range of 647±2.83 to 651±2.33. The percent deviation from the average weight was found to be within the prescribed official limits.

Thickness

The thickness of the tablets was measured using vernier callipers. The thickness of the tablets ranged between 4.12±0.10 to 4.18±0.06 mm.

Hardness

Hardness of the tablets was measured by Monsanto tester. Tablet hardness reflects differences in tablet density and porosity, which are supposed to result in difference release patterns of the drug by affecting the rate of penetration of the dissolution fluid at the surface of the tablet. Hardness of the tablets was found to be between 6.2 to 6.6 kg/m². The tablets were found to be of good tensile strength.

Friability

Friability was measured by Roche Friabilator and found to be 0.30 to 0.42, the friability of all the tablets was to be less than 1% which is an indication of satisfactory mechanical resistance of the tablets.

Drug content

The drug content was in the range of 98.30±0.85 to 99.84±1.69% which reflects good uniformity in drug content among different formulations.

Floating lag time

The time taken for the tablets to rise to the surface and float is the floating lag time. The gas generated is trapped and protected within the gel, formed by hydration of the polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1, the tablet became buoyant. The floating lag time ranged between 2 min 21 sec to 15 min 34 sec.

***In-vitro* dissolution studies for the prepared formulations**

The in-vitro dissolution was carried out for all the batches for 12 h. Formulations F1, F3, F4, F5, F6 and F9 showed no floating properties as they are containing high amount of carbopol which lead to formation of a viscous gel. Large concentration of high viscosity polymer induces the formation of strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix, which may result in retardation or decreases the drug release. The percentage release of drug varied for different batches. Formulation F7 containing 30% of Guar gum and 5% ethyl cellulose showed 98.79% of drug release at the end of 12 h.

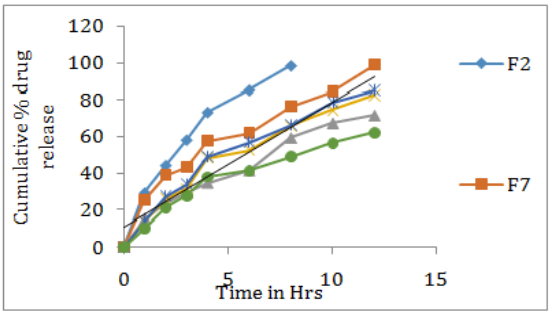

Fig. 1: *In-vitro* release profile for F2, F7, F8, F10, F11 and F12 formulations

Release kinetics

The data obtained from the *in-vitro* dissolution studies of optimized batch F**7** were fitted in different models viz. Zero order, first order, Korsemeyer-Peppa's model, Higuchi model and Hixson-Crowell model. Release kinetics results as shown in table 4.

Table 4: Release kinetics of F7 formulation

Formulation code	Zero order	First order	Higuchi model	Peppas model
F7	0.926	0.797	0.990	0.570

It was found that, all the tablet formulations follow diffusion, dissolution mechanism for all drug release. F7 formulations followed diffusion along with dissolution of the drug from the tablet by non fickian mechanism. Drug release mechanism was found to be zero order along with higuchi release kinetics exhibiting diffusion along with dissolution of the drug from the tablet by non fickian mechanism.

CONCLUSION

Gastro-retentive controlled drug delivery system of Levofloxacin was prepared to increase the therapeutic effect of the drug by releasing the drug at the proximal part of the small intestine. Levofloxacin is used in eradication of Helicobacter Pylori and other bacterial infections. Levofloxacin floating tablets were prepared using of Guar gum, carbopol, hydroxy propyl methyl cellulose and Ethyl Cellulose in various ratios by direct compression technique employing sodium bicarbonate as gas-generating agent. According to the above results, formulation F7offered best controlled release along with floating lag time of 10 min 12 sec and total floating time of 12 h and in-vitro drug release of 98.79% at the end of 12 h.

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CONFLICT OF INTERESTS

Declared None

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