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Research Article

FORMULATION AND IN VITRO EVALUATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM FOR OFLOXACIN

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ABSTRACT

Sustained release (SR)-gastroretentive dosage forms (GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. A new strategy is proposed for the development of gastroretentive dosage forms for ofloxacin preferably once daily. The design of the delivery system was based on the sustained release formulation, with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems. Different polymers, such as psyllium husk, PMC K100M, crospovidone and its combinations were tried in order to get the desired sustained release profile over a period of 24 h. Various formulations were evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, drug content and in vitro drug release profile. It was found that dimensional stability of the formulation increases with the increasing psyllium husk concentration. It was also found that in vitro drug release rate increased with increasing amount of crospovidone due to the increased water uptake, and hence increased driving force for drug release. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines.

Keywords: Ofloxacin; Sustained release; Psyllium husk; Gastroretentive.

INTRODUCTION

Oral sustained release dosage forms have been developed due to their considerable therapeutic advantages (Hoffman, 1998). This approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract. This is due to the relatively short transit time of the dosage form in these anatomical segments. Thus, after only a short period of less than 6 h, the sustained release dosage form has already left the upper gastrointestinal tract and the drug is released in non-absorbing distal segments of the gastrointestinal tract. This results in a short absorption phase that is often accompanied by lesser bioavailability.

It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of these drugs. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a sustained manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of SR-DFs for these drugs (Hwang et al., 1998; Hoffman and Stepensky, 1999).

The need for gastro retentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems (Deshpande et al., 1996 The objective of present work was to develop gastroretentive formulation, which releases drug in the stomach and upper gastrointestinal (GI) tract, and form an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract. Example of substance whose bioavailability is strongly dependent on the local physiology in the GI tract and which preferably is absorbed in the higher sections of the intestine is ofloxacin. Ofloxacin is readily soluble in the acidic environment of the stomach. In the intestine, where neutral to slightly alkaline pH conditions prevail; however, precipitation of the active compound occurs, which adversely affects absorption in the lower sections of the intestine. There is a need for systems that reside in the stomach over a relatively long time and release the active compound there in a sustained manner (Sen and Kshirsagar, 2002). This led to the formulation of sustained release gastro retentive drug delivery system for ofloxacin using suitable polymers.

2. MATERIALS AND METHODS

2.1. Materials

Ofloxacin and psyllium husk were gifted by Macleoid Pharmaceuticals, India. HPMC K100M, HPMC K4M, PVP K30 and Crospovidone were obtained as gift samples from DR.REDDY'S India. Talc and magnesium stearate were gifted by M/s Bayer India Ltd., India. All other solvents and reagents were purchased
from Ranbaxy chemicals, India, and were of analytical grade.

2.2. Methods

2.2.1. Manufacturing of sustained release formulation of ofloxacin

Typical sustained release formulations of ofloxacin are listed in Tables 1 and 2. Tablets were made by using psyllium husk (gelling agent), HPMC K100M, HPMC K4M(hydrophilic polymer), crospovidone (swelling agent), sodium bicarbonate (gas-generating agent) Tablets were made by using wet granulation process with PVP K30 (5%, w/v, isopropyl alcohol). Compression was done on a Cadmach single station tablet press using caplet shaped punches

Table 1: Formulation composition to study the effect of HPMC K4M and HPMC K100M on in vitro release of ofloxacin

Composition(mg/tablet)	F1	F2	F3	F4	F5
Ofloxacin	250	250	250	250	250
HPMC K4M	40	75	100	75	75
HPMC K100M	25	25	25	20	25
Sodium bicarbonate	40	40	40	40	40
Crospovidone	125	125	125	125	125
PVPK 30	20	20	20	20	20

Table 2: Formulation composition to study the effect of Psyllium husk and Betacyclodextrin on in vitro release of ofloxacin

Composition(mg/tablet)	F6	F7	F8	F10	F11	F12	F13	F14
Ofloxacin	250	250	250	250	250	250	250	250
HPMC K4M	75	75	75	75	75	75	-	-
HPMC K100M	25	25	25	25	25	25	-	-
Psyllium husk	-	-	-	-	-	-	50	60
Sodium bicarbonate	40	40	35	45	40	40	40	40
Crospovidone	0	50	100	100	100	100	100	100
PVPK 30	10	10	10	10	10	10	10	10
β Cyclodextrins	-	-	-	-	50	100	40	10

2.2.2. In vitro release study

The release of ofloxacin from the tablets was studied using USP dissolution Apparatus I. The dissolution medium was phosphate buffer pH 1.2 for first 2 h, Phosphate buffer pH 4.5 for next 2 h and pH 7.4 for remaining hours (Wang, 1978), the volume being 900 ml. The temperature was maintained at 37 ± 0.5 °C. The rotation speed was 100 rpm. Five milliliters of aliquot were withdrawn at predetermined time intervals of 1, 2, 3, 4, 6, 8, 10, 12, 14, 16 and 24 h. The medium was replenished with 5 ml of fresh buffer each time. Sample was analyzed by using UV spectrophotometry at 294 nm.

2.2.3. Buoyancy lag time and the duration of buoyancy

The buoyancy lag time and the duration of buoyancy were determined in the USP dissolution Apparatus II in an acid environment. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as buoyancy lag time and the duration of buoyancy was observed visually (Yang et al., 1999).

3. RESULTS AND DISCUSSION

3.1. Effect of psyllium husk on in vitro drug release and integrity of formulations

Effect of different concentrations of Psyllium husk on in vitro release of Ofloxacin was studied. Initially, tablet containing 40 mg of Psyllium husk (F1) could not retain its physical integrity for desired period (24 h) of time. As the concentration of psyllium husk increases (F2 and F3), it retains integrity up to desired period of time (24 h). It is important to maintain the physical integrity of the tablet in case of once daily formulations. If it does not maintain its physical integrity, tablet could be broken down into smaller fragments and escape from the upper part of the GI tract. Hence, an attempt was made in order to increase the physical integrity of the tablets using psyllium husk. Further, formulation (F1) provided higher burst drug release as compared to the marketed formulation as shown in Fig. 1In case of F1 and marketed formulations; burst drug release after 2 h was 34.06 ± 0.52 and 31.08 ± 0.89%, respectively. Therefore, amount of psyllium husk was increased to 100 (F2) and 125 mg/tablet (F3). As the concentration of psyllium husk increases, initial burstdrug release as well as drug release in the latter hours decreases as compared to the marketed formulation. In case of F2 and F3 formulations, burst drug release after 2h was found to be 28.22±0.96 and 24.22±1.28%, respectively. In case of formulation F1 and F3, cumulative drug release at the end of 24 h was found to be 53.60 ± 1.86 and 47.20 ± 1.74%, respectively. This might be due to the gelling properties of psyllium husk. Psyllium husk forms thick gel at higher concentrations, which could have contributed to the decrease in drug release. Drug associated with the surface of tablet matrix could have also contributed to the initial burst release. As the surface associated drug was released, psyllium husk matrix could have contributed to the slower drug release over a period of 24 h. Formulation(F2) containing 100 mg of psyllium husk maintained its physical integrity for 24 h and showed similar pattern of drug release as compared to the marketed formulation, hence, selected for the further studies.

Ofloxacin is soluble in aqueous solution with pH between 2 and 5. It is sparingly to slightly soluble in aqueous solution with pH 7. Hence, developed formulations as well as marketed formulation could not release total amount of the drug into the dissolution medium by pH change method.

3.2. Effect of HPMC K100M on in vitro release of Ofloxacin

Initially, HPMC K100M was tried in concentration of 30 mg/tablet (F4). The formulation provided higher burst drug release as compared to marketed formulation as shown in Fig. 2. In case of F4 and marketed formulations, burst drug release after 2 h was found to be 34.08 ± 0.92 and 31.08 ± 0.89%, respectively. Therefore, amount of HPMC K100M was increased to40 mg/tablet (F2), the formulation provided burst drug release comparable to the marketed formulation. Further increase in amount of HPMC K100M to 50 mg (F5) provided low burst drug release as compared to the marketed tablets. Formulation (F5) showed 24.01 ± 1.23% of burst drug release at the end of 2 h. High HPMCK100M content results in a greater amount of gel being formed. This gel increases diffusion path length of the drug. Its viscous nature also affects diffusion coefficient of the drug. As a result, reduction in drug release is obtained. Thus, 40 mg (F2) HPMC K100M was selected for further studies.

3.3. Effect of crospovidone on in vitro release of Ofloxacin

In order to improve the release profile of the formulations, concentration of crospovidone was increased. Crospovidone acts as a swelling agent, which is capable of swelling greater than its original volume and preferably to at least twice its original volume when coming into contact with an aqueous fluid, such as gastrointestinal fluid. The swelling agent, which normally swells to several times its original volume in water, exhibits a controlled swelling in the presence of water soluble hydrophilic polymers (Talwar and Staniforth, 2001, WO 01/64183). Three concentrations 0 mg (F6), 100 mg (F7) and 200 mg (F2) of crospovidone were tried. As the concentrations of crospovidone increases from 0 to 200 mg/tablet, drug release has increased as shown in Fig. 3. Formulation (F6), which does not contain crospovidine, showed 38.71 ± 1.64% of cumulative drug release at the end of 24 h. Formulation containing 100 mg (F7) showed 49.64 ± 1.32% cumulative drug release whereas formulation containing 200 mg (F2) showed 52.55 ± 1.02% cumulative release at the end of 24 h. As the concentration of crospovidone increases, water uptake capacity of the formulation increases (data not shown). This increases the porosity of the matrix, which results in increased drug release from the matrix system.

3.4. Effect of gas-generating agent on in vitro release of ofloxacin

As the concentration of sodium bicarbonate increases from 60 to 80 mg/tablet, drug release decreases as shown in Fig. 4. This might be due to the alkaline nature of sodium bicarbonate. Sodium bicarbonate creates an alkaline environment round the tablet. Ofloxacin is less soluble in alkaline environment that decreases the drug release from the formulation. Formulation containing 60 mg sodiumbicarbonate (F8) showed 54.91 ± 1.30% cumulative drug release whereas formulation containing 80 mg of sodium bicarbonate (F9) showed 47.20 ± 1.35% cumulative drug release at the end of 24 h. Formulation containing 70 mg sodium bicarbonate (F2) showed 52.55 ± 1.02% cumulative drug release at the end of 24 h In such systems, sodium bicarbonate acts as a gas generating agent. It generates gas when it comes into contact with an acidic environment of the stomach. This gas entraps into the matrix of water-soluble polymers and the formulation floats in an acidic environment of the stomach. As the concentration of sodium bicarbonate increases from 60 (F8) to 80 mg/tablet (F9), floating lag time has reduced to 25 s. As the concentration of sodium bicarbonate increases from 60 to 80 mg/tablet, duration of floating has also been increased from 18 to24 h .This might be due to the gas generated by 60 mg sodium bicarbonate might not be sufficient to keep formulation floating for prolonged period of time whereas in case of gas generated by80 mg sodium bicarbonate was sufficient to keep formulation floating for 24 h.

4. CONCLUSION

We conclude that psyllium husk and HPMC K100M increases the dimensional stability of the formulations, which is necessary in case of once daily formulations. Sodium bicarbonate acts as a gas-generating agent, which is necessary in case of gastroretentive dosage forms. Crospovidone improved the drug release profile and swelling factor of psyllium husk based formulations. We also conclude that channeling agents, such as betacyclodextrin are useful to increase the initial burst release from psyllium husk based formulations. The optimized formulation was found to be stable at all the stability conditions. Based on the in vivo performance in a parallel study design in healthy subjects, the developed formulation shows promise to be bioequivalent to the marketed product (Zanocin).

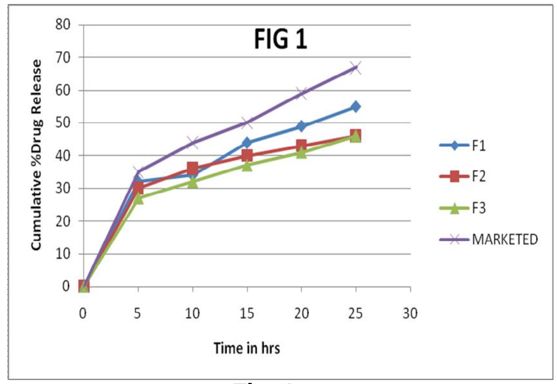

Fig. 1:

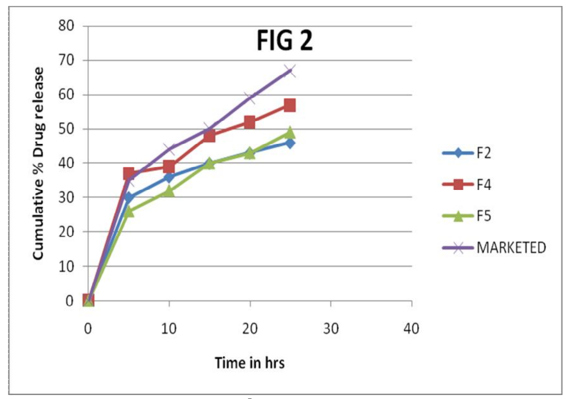

Fig. 2:

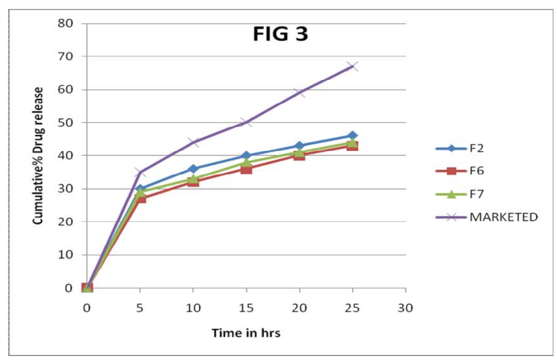

Fig. 3:

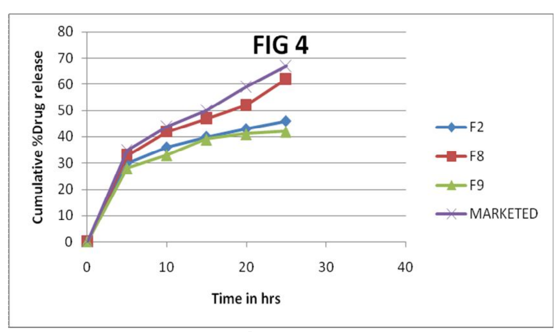

Fig. 4:

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