Formulation and Evaluation of Gastro retentive Floating Drug Delivery System of Ofloxacin

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ABSTRACT

The objective of this present study is to formulate and evaluate the gastroretentive floating drug delivery system (GRFDDS) of ofloxacin prepared by using synthetic and natural polymers (polyethylene oxide and gum karaya). Formulations were prepared by wet granulation technique and sodium bicarbonate (10% w/w) was incorporated as gas generating agent. Tablets were evaluated for hardness, in vitro buoyancy, drug content and in vitro drug release studies. Release data obtained was subjected to analysis using different mathematical models namely — zero order flux, first order, erosion plot, Higuchi and Korsmeyer peppas equations. All formulated tablets irrespective of polymer used had hardness and friability values >5.0kg/cm2 and <0.68%. The in vitro lag time and total buoyancy time for all the formulations were between 45 to 183secs and 5 to 16 hrs respectively. As the concentration of the polymers in the formulations increased the drug release decreased. Formulations made with gum karaya exhibited first order kinetics, non- fickian diffusion and the formulations like OGRK3 and OGRK4 followed first order and erosion mechanism. Whereas polyethylene oxide based formulations OP2,OP4 and OP5 exhibited zero order, non fickian diffusion and remaining formulations followed first order, erosion mechanism. GRFDDS of ofloxacin using synthetic (polyethylene oxide) and natural polymer (gum karaya) with drug to polymer ratio 1:0.5 and 1:0.625 respectively are final optimized formulations. These were further characterized by Fourier transform infrared spectroscopy (FTIR) which indicated that there was no interaction between drug and polymers.

Keywords: Floating drug delivery, Gastroretentive drug delivery system, Gum Karaya, Ofloxacin, Polyethyloxide, Release kinetics.

INTRODUCTION

Gastroretentive floating drug delivery systems (GRFDDS) are systems which increase the gastric retention time of the dosage form at the stomach and upper parts of the small intestine and suitable for the drugs having site-specific absorption from the above site [1]. The released drug from the drug system at the stomach maintains the drug concentration at the desired site. This system provides the drug concentration and prevents the premature absorption of the drug from the upper intestinal tract.

Many attempts have been made in recent years to provide a dosage form with a longer gastric retention time and therefore a more efficient absorption [2]. Several approaches have been developed to increase the duration of oral dosage forms in the stomach. These include floating drug delivery systems, swelling and expanding systems, polymeric bio adhesive systems; modified-shape systems, high-density systems and other delayed gastric emptying devices [3-4]. Of all these approaches, the gastric floating drug delivery system (GFDDS) has provided several advantages, as shown by the encouraging results reported earlier [5].

Ofloxacin is a synthetic second generation chemotherapeutic antibiotic of the fluoroquinolone drug class which is mainly indicated for the treatment of serious and life threatening bacterial infections [6]. Ofloxacin is readily soluble in the acidic environment of the stomach. In the intestine, where neutral to slightly alkaline pH conditions prevail, precipitation of the active compound occurs, which adversely affects absorption in the lower sections of the intestine [7]. Its chemical formula is (S)-9-fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrind[1, 2, 3-de]-1, 4-benzoxazine-6-carboxylic acid with a bioavailability of about 98%. Hence, there is need for this system to reside in the stomach over a relatively longer time and release the active compound in a sustained release manner. This necessitated the design and development of sustained release gastro retentive drug delivery system of ofloxacin using suitable polymers.

Gum Karaya (GK) is a polysaccharide which on hydrolysis yields the monosaccharides, L-rhamnose, D-galactose, D-galacturonic acid units in S.ures, S. villoa in S. setigera gum, in addition to these monosaccharides another minor hexose component, d-tagatose is also present in S.ures, the proportion of various components is 43% D-galacturonic acid, 13%, D-galactose and 15% L-rhamnose [8].

The GRFDDS of the present investigation are designed to retain in the stomach for longer periods of time and deliver the ofloxacin effectively. It is thought that this system studied would provide increased absorption of the ofloxacin at a rate such that effective plasma levels can be achieved and maintained for a prolonged duration.

In the present investigation, GRFDDS ofloxacin were prepared by using natural and synthetic polymers like gum karaya (GK) and polyethylene oxide (PEO) respectively by effervescent floating technique.

MATERIALS AND METHODS:

Ofloxacin was a gift sample from Ipca Labs Pvt. Ltd., Mumbai, India. Polyethylene oxide (PEO) WSR 303 was a gift sample from Wockhardt Ltd. Aurangabad, India. Gum Karaya was purchased from Girijan Co-operative Corporation Ltd., Visakhapatnam, India. Sodium bicarbonate, povidone K 30, talc and magnesium stearate were purchased from S.D. Fine Chemicals Ltd., Mumbai. All the chemicals were analytical grade.

Methods:

Preparation of tablets:

All the ingredients according to the formulae as mentioned in Table 1 were passed through the sieve No. 40. Drug was geometrically mixed with polymer until a homogenous blend was achieved. Granules were prepared by using 10% w/v solution of polyvinyl pyrolidline (PVP) in 70% isopropl alcohol (IPA) as binder solution. The wet mass was dried at 50° C and the dried granules were sifted through sieve no.24. The required quantity of sodium bicarbonate and magnesium stearate were added and mixed thoroughly. The formula of the composition of the different ingredients and quantity used is shown in table 1. The final blend was compressed into tablets on a 16- stationary rotary tablet punching machine (M/S. Cadmack Machinery Co. Pvt. Ltd., India) fitted with 12 mm standard concave punches maintaining the hardness at 4-6 Kg/cm². The weights of the tablets varied depending on the composition (See Table 1).

Evaluation of tablets:

The prepared floating tablets were evaluated for floating properties like floating lag time and total floating time by in vitro buoyancy determination. The tablets were also evaluated for hardness, friability, uniformity of weight and drug content uniformity.

In Vitro Buoyancy Determination:

All the prepared floating tablets of ofloxacin were subjected to in vitro buoyancy test by determining its floating lag time. For this study 3 tablets were used from each batch. The buoyancy lag time and the duration of the buoyancy were determined in 1 Litre glass beaker containing 900 ml of 0.1 N hydrochloric acid (HCl). The media was kept in stagnant condition and the temperature maintained at 37±0.5°C. The time taken for the tablet to rise to the surface and float was determined as floating lag time.
Different drug to polymer ratios (OP 1 to OP 5).

Table 1: Formulæ of GFDDS for Ofloxacin prepared with PEO and Gum Karaya

<table>
<thead>
<tr>
<th>S No</th>
<th>Ingredients (mg/tablet)</th>
<th>OP1</th>
<th>OP2</th>
<th>OP3</th>
<th>OP4</th>
<th>OP5</th>
<th>OGK1</th>
<th>OGK2</th>
<th>OGK3</th>
<th>OGK4</th>
<th>OGK5</th>
<th>OGK6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ofloxacin</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>2</td>
<td>PEO 503</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>Gum karaya</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>NaHCO₃</td>
<td>54</td>
<td>60</td>
<td>66</td>
<td>72</td>
<td>78</td>
<td>54</td>
<td>60</td>
<td>66</td>
<td>72</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>Povidone K 30</td>
<td>27</td>
<td>30</td>
<td>33</td>
<td>36</td>
<td>39</td>
<td>27</td>
<td>30</td>
<td>33</td>
<td>36</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>Magnesium stearate</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Total (mg)</td>
<td></td>
<td>537</td>
<td>596</td>
<td>656</td>
<td>715</td>
<td>775</td>
<td>537</td>
<td>596</td>
<td>656</td>
<td>715</td>
<td>775</td>
<td>834</td>
</tr>
</tbody>
</table>

From each batch, 10 tablets were taken and powder in a glass mortar and the powder extracted with 25 ml of 0.1N hydrochloric acid with vigorous shaking on a mechanical shaker for 1 hour and filtered into a 50 ml volumetric flask through a 0.45 µm millipore nylon filter disc and the filtrate was made up to the mark with 0.1N hydrochloric acid. Further appropriate dilutions were made and the absorbances were measured at 293 nm against blank (0.1N HCl) using an Elicos SL 210 UV-Visible double beam spectrophotometer (Elico, India).

In Vitro Drug Release Studies:

In vitro release of ofloxacin floating tablets was studied using USP XXIV dissolution rate test Apparatus-II (Model: DISSO 2000, M/s. Lab India) employing the paddle stirrer (Apparatus-II). 900 ml of 0.1N HCl was used as dissolution medium maintained at a temperature of 37±0.5°C and the paddle was rotated at 50 rpm. 5 ml of samples were withdrawn by means of a syringe fitted with a prefilter at appropriate time intervals and immediately replaced with 5 ml of fresh medium maintained at 37±0.5°C. The samples were suitably diluted with blank dissolution fluid and analyzed for content of ofloxacin spectrophotometrically at λmax 236nm using an Elicos SL 210 UV-Visible double beam spectrophotometer (Elico, India). The amount released was expressed as a percentage of the drug content in each dissolution medium [11]. The dissolution test was carried out in triplicate and the mean results reported.

Determination of tablet hardness and friability test:

Ten tablets were selected at random and the hardness of each tablet was measured by using a Monsanto hardness tester [8]. The determination was done in triplicate and the mean value was reported. The friability test was carried out in Roche Friabilator. Ten tablets were weighed (w) initially and put in a rotating drum. Then, they were subjected to 100 revolutions of 6 inches height [9]. After completion of rotations, the tablets were again weighed (w'). The friability test was carried out in Roche Friabilator. Ten tablets were selected at random and the hardness of each tablet was measured by using a Monsanto hardness tester [8]. The determination was done in triplicate and the mean value was reported.

Zero order release kinetics [11] is defined as a linear relationship between the fractions of drug released versus time. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics. It is given by equation 2 below:

\[ Q = k_0 t \]

Where, Q is the fraction of drug released at time t and k_0 is the zero order release rate constant.

In first order release kinetics [9], Wagner assumed that the exposed surface area of a tablet decreased exponentially with time during dissolution process, this suggests that drug release from most of the slow release tablets could be described adequately by zero-order, first-order, diffusion, erosion and peppas equations. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation and erosion equation.

Higuchi equation defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time. It is defined by equation 4 below:

\[ Q = k_s \sqrt{t} \]

Where, k_s is the release rate constant. Hence, a plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the fick’s law, square root time dependent.

Erosion equation defines the drug release based on tablet erosion alone (See equation 5).
Q = 1- (1-K^t)^n ..............................5

where, Q is the fraction of drug released at time t, K is the release rate constant. Thus, a plot between [1-(1-Q)^1/t] against time will be linear if the release obeys erosion equation.

In order find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer Peppas model in equation 6.

Mt / M∞ = K t^n ..............................6

Where Mt / M∞ is a fraction of drug released at time t, K is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices. For the case of cylindrical tablets, 0.45 = n corresponds to a Fickian diffusion mechanism, 0.45 < n < 0.89 to non-Fickian transport, n = 0.89 to Case II (relaxational) transport, and n > 0.89 to super case II transport[19].

Fourier Transform Infrared Spectroscopy:

Infrared spectroscopy was carried out using a Perkin Elmer Shimadzu FTIR 8300 Spectrophotometer and the spectrum was recorded in the region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (drug and drug resinate mixture, 1:1 ratio) in KBr (200-400 mg) and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained. Spectra were recorded in duplicate for each of the samples.

RESULTS AND DISCUSSION:

Physicochemical parameters of the tablets

The tabletting physicochemical parameters are presented in Table 2. It was observed that the hardness values of formulations prepared with GK were between 5.0–5.5 kg/cm² while those prepared with PEO were between 5.1–5.6 kg/cm². The friability percentages of all the formulations were less < 0.65. The results showed that all the physicochemical parameters were within acceptable compendia limits[9-10].

In-vitro floating test:

The results of the in vitro buoyancy studies are presented in table 3. It was observed that the floating lag times of formulations prepared with PEO was between 45 to 92secs while those formulated with GK was between 115 to 183 sec. The floating lag time of formulations prepared with PEO were observed to be generally lower compared with those of GK. This may be attributable to the high hydrophilic nature of the water soluble resin PEO used in the formulation compared with the GK. This results in fast influx of dissolution medium (0.1N HCl) into the matrix formulation, which results in the liberate carbon dioxide as the carbamates and bicarbonates interact with the acid medium. The carbon dioxide generated is entrapped in the gelified hydrocollodion, hence resulting in floating. However, it was generally observed that floating lag times increased with increase in polymer concentration irrespective of the polymer used in the formulation. The total buoyancy time also depends on the type and concentration of polymer used (See Table 3).

In-vitro dissolution studies:

The release profiles of ofloxacin from PEO WSR 303 and GK based GFDDs containing different drug to polymer ratios are shown in Figs. 1 and 2. More than 99% of the drug was released from all the formulations. However, the time for maximum release differs, for instance the time for maximum release of OP1,OP2,OP3,OP4 and OP5 are 4, 6, 10, 12 and 14 hrs respectively and for OGK1,OGK2,OGK3,OGK4,OGK5 and OGK6 are 2.4, 8,10,12 and 14 hrs respectively. Generally, as the concentration of the polymers increased in the formulations the drug release was found to be retarded. (t0.125, t0.25, t0.375, t0.5, t0.75, 1.0, 1.25) As polymer concentration increased the drug release was found to be retarded. The results showed that formulations OP4 and OGK5 with drug: polymer concentration of 1: 0.5 and 1: 0.625 retarded the active content up to 12 hrs. These two formulations were therefore taken as the optimised formulation for drug delivery system for ofloxacin. This indicates that there is no chemical interaction between drug and the added excipients during granulation and tabletting used in the study.

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