Journal of Drug Delivery Science and Technology 39 (2017) 385–397

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Development and formulation of floating tablet formulation containing rosiglitazone maleate using Artificial Neural Network

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ARTICLE INFO

Article history:
Received 2 April 2017
Received in revised form
23 April 2017
Accepted 23 April 2017
Available online 26 April 2017

Keywords:
Controlled release
Oral drug delivery
Neural networks
Rosiglitazone maleate

ABSTRACT

The aim of this study was to develop a new gastro-retentive formulation that has the capability to maintain the release of rosiglitazone in the gastric medium. For this purpose, we have used formulation by design approach and predicted the formulation characteristics of the final formulation by using Artificial Neural Network. Tablet formulations were prepared by using HPMC K100LV and HPMC K4M for the maintenance of sustained release and sodium bicarbonate and citric acid were used as the gas forming agents for floating. Possible interactions between the rosiglitazone maleate and the excipients were investigated by FT-IR and DCS analyses. Dissolution studies were performed in order to characterize the zero order release pattern of the formulations in three different media as pH:1 hydrochloric acid-potassium chloride, pH 2.5:phthalate and pH:4 acetate buffer solutions, under sink conditions. In the end, Artificial Network Model predicted and experimentally quantified results were compared with each other with f_2 test. As a result, these two profiles are found to be similar with f_2 values of 68.98, 59.98 and 62.99 for pH:1 hydrochloric acid-potassium chloride, pH: 2.5 phthalate and pH:4 acetate buffer solutions, respectively.

1. Introduction

Controlled release drug delivery systems have advantages such as decreasing dosing frequency, increased patient compliance and minimize adverse effects of fluctuations in drug plasma concentration [1]. Controlled release dosage forms deliver the drug to the gastrointestinal tract in a slow manner and provide drug concentration that remains constant for certain period of time in the systemic circulation. Because of the short stomach emptying time and length of stay in the stomach, release of drugs which are soluble and absorbed in stomach and upper gastrointestinal tract can not be completed in the absorption site, which results in the lack of bioavailability of these drugs [2]. Therefore, controlled release systems have been developed, which are specific for absorption site and that could retain in the stomach longer. Prolongation of the residence in the stomach increases bioavailability of certain drugs due to extension of drug release time [3]. In order to prolong the retention time of dosage form in stomach, large number of studies has been previously done by different research groups. Of these, high-density systems [4], low-density systems [5–7] mucoadhesive systems [8], expandable gastroretentive systems [9,10], super porous hydrogel systems [11] and magnetic systems [12] are some examples for these studies.

The primary aim of the study was to develop a gastroretentive drug delivery system that may remain buoyant in the gastric fluid for a certain period of time. For this purpose, rosiglitazone maleate was chosen as a model drug due to its high solubility in acidic medium. It is used in the treatment of type 2 diabetes. Type 2 diabetes occurs depending on partial insulin deficiency and insulin resistance. A member of thiazolidinedione class of antidiabetic drugs rosiglitazone, show anti-hyperglycemic effect by increasing insulin sensitivity. Rosiglitazone is used in the form of maleate salt [13,14]. Depending on the solubility increase of rosiglitazone with the decreasing pH values, it was classified as suitable candidate for gastroretentive drug delivery systems.

In general, for preformulation studies, the effects of the excipients on formulation properties may be characterized by many different techniques, lately named as design of experiments (DoE) or formulation by design (FbD). As the basic principle of these classical techniques, one variable at a time is changed and its possible effects on the formulation properties are explored, without any interaction among the other variables. However, in the last

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http://dx.doi.org/10.1016/j.jddst.2017.04.029
1773-2247/

decade, many different techniques have been successfully used which allow to explore the effects of more than one variables at the same time and their possible interactions among them on formulation characteristics. Among these techniques, factorial design, central composite design and Artificial Neural Network (ANN) are the most commonly used examples having the capability of predicting the outcomes of multiple variables at a time [15–17]. Controlled release dosage forms are the most difficult formulation types with respect to application of the above-mentioned methods, because there exists many release controlling agents that are used to modify the drug release.

ANN models are the one of the most precise methods used to predict formulation characteristics. They have the capability of predicting effects of more than one input factors; and even though they might explore the nonlinear interactions of these input parameters once at a time. They are such models that might learn the interaction relations and develop certain mathematical models for the correction of errors in predicting [1,18]. ANN modeling has been previously used by many other research groups for the prediction of formulation characteristics and for the investigation of their possible combinational interactions [19–21].

In this study, we have formulated floating tablet formulations of rosiglitazone maleate in order to improve its retention time in the gastric medium, since it is highly soluble in the gastric pH values. In addition, we have applied ANN modeling study in order to characterize the possible effects of various combinations of release controlling polymers existing at different ratios within the formulation. The capability of developed ANN model was also validated by using an external set of data, which has not been used in the learning process of the model.

2. Materials and methods

2.1. Materials

The active ingredient rosiglitazone maleate was obtained from Dr. Reddy's Laboratories Ltd. (Hyderabad, India). The polymers (Hydroxypropyl methyl cellulose K100LV-HPMC K100LV- and Hydroxypropyl methyl cellulose K4M-HPMC K4M-) that were used in the formulation of floating tablets were purchased from Colorcon, Germany. The other excipients were as lactose monohydrate from Borculo Domo Ingredients, Netherlands magnesium stearate from Meck, Germany; citric acid from Carlo Erba, Italy; Sodium acetate trihydrate from Anreac Químıca, Spain and sodium bicarbonate from Merck, Germany. All other chemicals used in the research studies were analytical grade and used without further purification.

2.2. Quantification of rosiglitazone maleate

The quantification of rosiglitazone maleate was evaluated by using a high pressure liquid chromotography (HPLC) method. In this method the mobile phase was composed of a mixture of 0.01 M pH:3 phosphate buffer; acetonitrile and methanol at the ratio of 75:20:5 (v:v:v). UniverSil C_{18} revers phase column (150 mm x 4.6. mm i. d.) was used for the separation of rosiglitazone maleate, which has been previously conditioned at 35 °C. The flow rate of the mobile phase was set as 1 ml per minute and the detection was performed with a UV detector at λ: 240 nm. The method was validated through the parameters of linearity, accuracy, precision, selectivity and system suitability.

2.3. Solubility studies

The solubility of rosiglitazone maleate has been determined in three different media as pH:1 hydrochloric acid-potassium chloride, pH: 2.5 phthalate and pH:4 acetate buffer in order to determine the sink conditions for dissolution studies. For this purpose, excess amount of rosiglitazone maleate was added in glass vials containing 15 ml of the above-mentioned buffer solutions. Afterwards the vials were tightly capped and place in a horizontal shaker at 37 ± 0.5 °C and the speed of this shaker was set at 20 rpm per minute. Samples were withdrawn at 1 and 24 h in order to determine the amount of rosiglitazone maleate and analyzed with HPLC.

2.4. Fourier transform infrared analysis

In order to investigate any possible interactions between rosiglitazone maleate and polymers, Fourier transform infrared (FT-IR) analysis were used. For this purpose, mixture of rosiglitazone maleate with HPMC K100LV and HPMC K4M; and also, rosiglitazone maleate alone was analyzed. The infrared spectra were detected over a range of 500–4000 cm^{-1}.

2.5. Differential scanning calorimetry analysis

As a complementary part to FTIR analysis, differential scanning calorimetry (DSC) analysis was done for any possible drug polymer interactions. Samples of rosiglitazone maleate; mixture of rosiglitazone maleate with HPMC K100LV and HPMC K4M; and mixture of HPMC K100LV and HPMC K4M were analyzed by using DSC Q 100 (TA Instruments; USA). Approximately, a sample of 5–10 mg was weighed in an aluminum pan and a heating rate of 10 °C/min was employed in the range of 10–250 °C. Analyses were performed under a nitrogen purge. Empty aluminum pans were used as a reference. The change of in the heat of samples was monitored with respect to change in temperature.

2.6. Preparation of tablet formulations

The formulations were prepared by using two different types of polymers having different viscosities for maintaining the sustained release of rosiglitazone maleate, which were HPMC K100LV and HPMC K4M. In order to prepare a floating dosage form; gas forming agents (sodium bicarbonate and citric acid) were added in the formulation. Magnesium stearate was used as the lubricant and lactose monohydrate served as the filling agent in the formulation. Three different levels of HPMC K100LV and HPMC K4M were used in preparation of the tablets and with respect to these levels, nine different formulations were prepared by keeping the final tablet weight constant as 400 mg by only changing the amount of lactose mohydrate. The amounts of all other excipients were kept constant. The tablets were prepared by direct compression method and the tablet hardness was set within the range of 102–105 N. The composition of tablet formulations was briefly summarized in Table 1 with the amounts of all levels of ingredients.

2.7. In-vitro floating test

The floating capabilities of the formulations were tested in the same media, in which dissolution studies were performed. For this purpose, tablet formulations were dropped in beakers containing 250 ml of pH:1 hydrochloric acid-potassium chloride, pH:2.5 phthalate and pH:4 acetate buffer solutions and the time was recorded as zero for this point. Afterwards, the time for the beginning of floating and the total time of floating were recorded for all formulations.