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Pioglitazone HCl solid dispersion formulations combining five polymers to improve dissolving profile

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Abstract

Many medicines with therapeutic promise are never developed because of their low water solubility. There are a variety of approaches that have been taken to increase the solubility of medications in water. Poorly water-soluble pharmaceuticals may have their solubility and, by extension, their bioavailability enhanced by the use of solid dispersion. The purpose of this research was to examine the influence of different polymers on the solubility of pioglitazone HCl by preparing solid dispersions of the drug using PEG 6000, PVP, Poloxamer 407, Eudragit EPO, and HPMC. Pioglitazone HCl solid dispersion was made by solvent evaporation technique. The yield, drug content, FT-IR spectrum, and in vitro dissolution investigations of the solid dispersions were analyzed. The reliability of the experiment is guaranteed by the histogram of responses and the descriptive statistics of responses. The findings obtained demonstrate that the dissolving profile of Pioglitazone HCl solid dispersion was greatly improved. After 30 minutes, the release of Pioglitazone HCl from solid dispersions including PVP K30, HPMC, PEG 6000, Eudragit EPO, and Poloxamer 407 is 75%, 74%, 100%, 50%, and 62%, respectively, whereas the release from Pioglitazone HCl alone is only 12.05%. The findings suggest that the solid dispersion approach is a viable option for enhancing the dissolving profile of weakly water soluble drugs.

Key-Words: Solid dispersion, Pioglitazone HCl, Eudragit EPO, PEG 6000

INTRODUCTION

Using cutting-edge molecular screening techniques, numerous promising new medication candidates have been found recently. Many medicines with therapeutic promise are never developed because of their low solubility in water. The main issue with weakly water soluble drugs is their low bioavailability due to their partial absorption. The dissolution rate of weakly water soluble medications has been increased using a variety of approaches, including salt creation, complexation with cyclodextrins, solubilization of pharmaceuticals in solvents, and particle size reduction. However, there are certain restrictions with these methods. [1-2]Dissolution characteristics and bioavailability of weakly water-soluble medicines may be greatly enhanced by using solid dispersions (SDs).[4-6,19] Using either the fusion, solvent, or solvent-fusion technique, one or more active substances may be dispersed in a solid state hydrophilic carrier or matrix.[3] SDs of weakly water-soluble medicines with the different pharmacologically inert carriers have been the subject of much research since 1961.[8].

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To increase the bioavailability of poorly soluble medicines, the kneading and physical combination approach is often used to generate solid dispersions. [3]Several researchers have speculated on the processes that might speed up the disintegration of SDs. Particle size reduction and surface area augmentation may be achieved by molecular dispersion of medication in polymeric carriers, leading to increased solubility. The drug's crystal lattice may be broken during the dissolving process without any additional energy expenditure, and the drug's solubility and wettability can be enhanced by the hydrophilic environments in which it is found.carriers.[10,18] Reduction or lack of aggregation and agglomeration may also lead to greater dissolution. In our work water soluble carriers such as PEG 6000, PVP, Poloxamer 407, Eudragit EPO and HPMC are employed as carriers for increase of aqueous solubility. Increased insulin-dependent glucose clearance and reduced hepatic glucose output may be achieved with the use of the thiazolidinedione antidiabetic drug pioglitazone hydrochloride.[11] Among agonists for peroxisome proliferator-activated receptor-gamma, pioglitazone is both powerful and selective.[12] Pioglitazone, when formulated as a solid dispersion, is effective in treating gastrointestinal distress, headache, dizziness, exhaustion, and sleeplessness.[13] The purpose of this research was to investigate the influence of different polymers on the solubility of pioglitazone HCl by preparing solid dispersions of the drug using PEG 6000, PVP, Poloxamer 407, Eudragit EPO, and HPMC.

Material and Methods

Materials

Pioglitazone HCl was a generous gift form Beximco Pharmaceutical Pvt. Ltd. (Dhaka, Bangladesh). PVP K30 (BASF), HPMC (BASF), PEG 6000 (Merck Chemicals), Poloxamer 407(BASF), Eudragit EPO (BASF) used as hydrophilic polymer. All other chemicals and reagents used were of analytical grade and procured from authorized dealer.

Preparation of solid dispersion by solvent evaporation method

Preparation of solid dispersion of Pioglitazone HCl by solvent evaporation method includes two steps; first preparation of a solution containing both the hydrophilic polymer and hydrophobic drug and Evaporation of solvent and formation of solid dispersion.

To dissolve both drug and hydrophilic polymer a mixed solvent system of acetone and ethanol was used in a ratio of 1:4(v/v). The drug and the polymers show an effective solubility in this solvent mixture. Throughout the experiment drug polymer ratio was 1:3.Formulation containing only pure drug was coded as F-P and five solid dispersion with hydrophilic carrier were coded as F-1, F-2, F-3, F-4, and F-5 respectively. According to formulation (Table no 1) PVP K30, HPMC, PEG 6000, Eudragit EPO, and

Poloxamer 407 were added to a solution of Pioglitazone HCl in acetone and ethanol of 1:4(v/v). The solution was stirred at room temperature for 2 hours, and the solvent was removed under vacuum at 60^0C in a rotary evaporator. Solid residue was dried ina vacuum oven for 18 hours at 50^0 C temperature, pulverized, and sieved using a set of sieves. Powders samples were stored in a closed container away from the light and humidity until use.

Standard curve preparation

The following concentration of 1µg/ml , 5 µg/ml,10 µg/ml, 20 µg/ml, 40 µg/ml, 50 µg/ml, 60µg/ml,80 µg/ml ,of Pioglitazone HCl was prepared first. The solutions were then properly mixed. The absorbance values of the solutions were determined at λmax 268 nm by a UV spectrophotometer. As a control or reference sample, 0.1 HCl was used. The standard curve

(Figure: 1) was obtained by plotting the absorbance values against the corresponding concentrations.

Evaluation of solid dispersion

Determination of Percent Yield

The percent yield of pioglitazone solid dispersions can be determined by using the following formula:

Determination of Percent Drug Content

Solid dispersions of Pioglitazone HCl (99 mg) were placed in 25 ml volumetric flask. Ethanol (10 ml) was added, mixed thoroughly using a rotating shaker for 1 hour. The volume was made up to the mark with ethanol. The solution was suitably diluted with ethanol and spectrophotometrically assayed for drug content at 268 nm using the following formula:

FT-IR study of Pure drug and the formulation. Physicochemical characterization was performed using Fourier transform–infrared (FTIR) spectroscopy. For this purpose, samples were reduced to powder andanalyzed as KBr pellets by using a FTIR spectrometer(Shimadzu Corporation, Japan).

In vitro Dissolution studies

Dissolution study was performed for all six formulations. Dissolution was carried out using USP apparatus-II (Paddle) at 37 ± 0.5°C in 900 ml 0.1N HClmedium at 70 rpm. After definite time intervals (5, 15, 30, 60 minute) 5 ml of sample was withdrawn and filtered through Whatman filter No 3. Samples were analyzed spectrophotometrically at 268 nm.

Statistical Evaluation of the Experimental data Histogram Response and Descriptive Statistic of Response

In regression study it is advantageous if the data of response variable is normally distributed or so. The histogram shows that the response is approximately normally distributed. [16] (Fig 2.1). The descriptive statistic tool comprises a type of graph called Box-Whisker plot. When the data is normally distributed theantenna like Whisker attached with box are same in length. The Box-Whisker plot shows that the responseis approximately normally distributed. [17] (Fig. 2.2) **Results and Discussion**

Percent Yield and Drug Content

Various Pioglitazone HCl solid dispersions containing hydrophilic carrier HPMC, PVP K30, PEG 6000, Poloxamer, Eudragit were prepared by solvent evaporation technique to increase solubility and/or dissolution of poorly aqueous soluble drug, Pioglitazone HCl. The percent yield of various Pioglitazone HCl solid dispersions were within the range of 80.43 % to 92.63 (Table 2).

The percentage drug content in different Pioglitazone HCl solid dispersions ranged from 91.68 % and 98.68

%, This indicated that Pioglitazone HCl was uniformly distributed in all of these prepared solid dispersions.

FT-IR Spectroscopy Analysis

Fig. 2 displays the FTIR spectra of pioglitazone, and five different solid dispersion with five htdrophilic polymers. IR spectrum of pure pioglitazone (Fig. 3(a))is characterized by 3364 cm–1 (N-H stretching amide),3084 cm–1 (aromatic C-H stretching), 2928 cm-1(aliphatic C-H stretching asymmetric), 1743 cm-1(amide C = O stretching), 1616 cm-1 (C=C), 1460 cm-1 (ring C-N stretching), 1242 cm–1 (C-S stretching),1084 cm-1 (aliphatic C-O-C) and 850 cm-1 (para disubstituted aromatic ring). The IR bands of pure and solid dispersion showed no significant change ((Fig. 3(a,b,c,d,e,f). However, some of the peaks ofpioglitazone were slightly shifted and found to be attenuated. Significant changes were recorded in IRspectrum of different solid dispersion (Fig. 3 b,c,d).Almost all peaks of pioglitazone were smoothened indicating strong physical interaction between pure drug and hydrophilic carriers. The peak of amidecarbonyl was appeared with decreased peak intensity. **Effect of hydrophilic carriers on the dissolution of Pioglitazone solid dispersion**

The results of dissolution data for different formulationare presented in (Table 3) and (figure 4). Formulation containing pure Pioglitazone (F-P) shows very low dissolution profile which is due to its poor water solubility. It was observed that only 2% and 12% drug were released adrug was released after 5 minutes and 60 minutes of dissolution.

Compared to pure drug, formulation F-1 and F-2 showsvery significant increase in dissolution since after 60 minutes 99.9% and 102% of drug were released from these formulation. This response can be attributed to the incorporation of hydrophilic carriers HPMC and PEG 6000 in formulation F-1 and F-2.

Incase of formula F-3 containing PVP as carrier, the drug release were 61.98% and 87.5% after 5 and 60minutes respectively. It shows that the release was fast initially but the rate of release was increased slowly with time.

Formulation F-4 contain Poloxamer shows the lowest dissolution profile among the solid dispersions. Because only 12.2% and 75% drug were released after 5 and 60 minute respectively. Poloxamers are nonionic tri block copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)). The poor drug release may be resulted because of the central hydrophobic chain of polyoxypropylene.

Formulation F-5 shows the dissolution profile of

solid dispersion of pioglitazone with Eudragit EPO. EudragitE PO is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. It has been shows that after
60 minutes 100.52% drug was released and the released was doubled between the interval of 30 and 60minutes. The reasons for the slow release of the drug from the formulation might be the sustained release properties of the carrier.
Solid dispersions prepared from hydrophilic polymers using solvent evaporation method were effective in improving drug dissolution. The study revealed that optimum levels of hydrophilic carrier ensure a prompt and complete dissolution of Pioglitazone from solid dispersions that are used in oral pharmaceutical formulations. It is, however, suggested that further research on large scale be carried out by using other hydrophilic carrier.
One major focus of future research will be the identification of new surface-active and self-emulsifying carriers for solid dispersions. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may the inadequate drug solubility carriers, so a wider choice of carrier will increase the success of dosage form development. Research should be directed towards identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention must also be given toany physiological and pharmacological effects of the carrier used.

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