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Solid dispersion formulations of Pioglitazone HCl using five different polymers for enhancing dissolution profile

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Abstract

Many drugs are abandoned due to poor aqueous solubility, although having a potential therapeutic effect. Numerous methods have been followed to improve the dissolution rate of poorly water soluble drugs. Solid dispersion is successfully applied to improve the solubility and consequently the bioavailability of poorly water soluble drugs. The aim of present study was to prepare solid dispersions of Pioglitazone HCl with PEG 6000, PVP, Poloxamer 407, Eudragit EPO and HPMC and determine the effect of those polymers on dissolution of pioglitazone HCl. solid dispersion of Pioglitazone HCl was prepared by solvent evaporation method. Solid dispersions were evaluated with respect to their yield percentage, percent drug content, FT-IR spectra and in vitro dissolution studies. The histogram response, descriptive statistics of response ensure the fitness of the experiment. The result obtained show that the dissolution profile of Pioglitazone HCl solid dispersion was considerably improved. Solid dispersions of Pioglitazone HCl with PVP K30, HPMC, PEG 6000, Eudragit EPO and Poloxamer 407 shows 75%, 74%, 100%, 50% and 62% release respectively after 30 minutes where as Pioglitazone HCl shows only 12.05%. Based on the result solid dispersion technique can be an acceptable method for improving the dissolution profile of poorly aqueous soluble drug.

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

Introduction

Recently many potential drug candidates have been identified using advance molecular screening method. It is a common fact that though having a potential therapeutic effect many drugs are abandoned due to poor aqueous solubility. Partial drug absorption resulting in poor bioavailability is the major problem associated with poorly water soluble drug. Numerous methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvents, and particle size reduction has been followed to improve the dissolution rate of poorly water soluble drugs. But these techniques have several limitations. [1-2]

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Solid dispersions (SDs) traditionally have been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs.[4-6,19] Solid dispersion is defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix at solid state prepared by the fusion, solvent or solvent–fusion method.[3] Since 1961, many investigators have studied SDs of poorly water-soluble drugs with the various pharmacologically inert carriers to increase the dissolution[8]. Solid dispersions prepared by kneading and physical mixture method are widely and successfully applied to improve the solubility and consequently the bioavailability of poorly soluble drugs. [3]

The mechanisms for the enhancement of dissolution rate of SDs have been proposed by several investigators. Molecular dispersion of drug in polymeric carriers may lead to particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process and improvement in drug solubility and wettability due to surrounding hydrophilic

carriers.[10,18] Reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. In our study water soluble carriers such as PEG 6000, PVP, Poloxamer 407, Eudragit EPO and HPMC are used as carriers for enhancement of aqueous solubility. Pioglitazone hydrochloride is a thiazolidinedione antidiabetic agent that decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.[11] Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma.[12] The solid dispersions of Pioglitazone solve the problems like gastro-intestinal disturbances, headache, dizziness, fatigue and insomnia.[13] The aim of present study was to prepare solid dispersions of Pioglitazone HCl with PEG 6000, PVP, Poloxamer 407, Eudragit EPO and HPMC and determine the effect of those polymer on dissolution of pioglitazone HCl.

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 in a 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, 60 µg/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:

$$Percent\ yield = \frac{weight\ of\ the\ prepeared\ solid\ dispersion}{total\ weight\ of\ drug\ and\ carrier} \times 100$$

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:

$$Percent\ Drug\ Content = \frac{Practical\ drug\ content\ in\ Solid\ dispersion}{Theoritical\ drug\ content\ in\ Solid\ dispersion} \times 100$$

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 and analyzed 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 HCl medium 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 the antenna like Whisker attached with box are same in

length. The Box-Whisker plot shows that the response is 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 of pioglitazone were slightly shifted and found to be attenuated. Significant changes were recorded in IR spectrum 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 amide carbonyl was appeared with decreased peak intensity.

Effect of hydrophilic carriers on the dissolution of Pioglitazone solid dispersion

The results of dissolution data for different formulation are 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 shows very 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 60 minutes 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. Eudragit E 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 60 minutes. 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 to any physiological and pharmacological effects of the carrier used.

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Table 1: Formulation design of Pioglitazone solid dispersion with different polymers

Formulation Code	Ammount of drug	Name of the polymer	Ammount of polymer
F-P	33mg	No polymer present	0
F-1	33mg	HPMC	66mg
F-2	33mg	PEG 6000	66mg
F-3	33mg	PVP K30	66mg
F-4	33mg	Poloxamer	66mg
F-5	33mg	Eudragit EPO	66mg

Tabel 2: Percent Yield and Drug Content

Formulation Code	Hydrophilic carrier	Percent yield (%) (n=3)	Percent drug content (%) (n=3)
F-1	HPMC	88.13 ± 7.53	92.68 ± 2.9
F-2	PEG 6000	87.18 ± 3.19	98.68 ± 1.91
F-3	PVP K30	80.43 ± 2.43	91.68 ± 1.19
F-4	POLOXAMER 407	92.63 ± 3.62	96.68 ± 2.13
F-5	EUDRAGIT EPO	81.09 ± 2.13	97.68 ± 0.99

Table 3: Dissolution data of different formulation

	Formulation Code Dissolution data(%release)					
Time	F-P	F-1	F-2	F-3	F-4	F-5
5	2 ±.01	24.79±.91	50.39±.31	61.98±1.3	12.39±4.1	24.79±.89
15	8±3.54	38.68±2.6	87.08±3.5	62.32±1.9	49.64±2.1	37.31±2.1
30	10.2±2.1	74.75±1.5	99.9±2.6	75±2.1	62±2.2	50±1.8
60	12.05±1.2	99.92±4.5	102.43±1.6	87.51±2.8	75.05±2.3	100.52±2

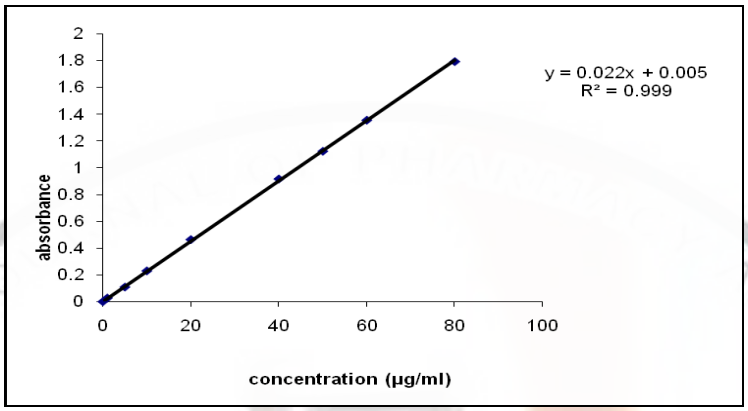


Fig. 1: Standard curve of pioglitazone HCl in 0.1 N HCl

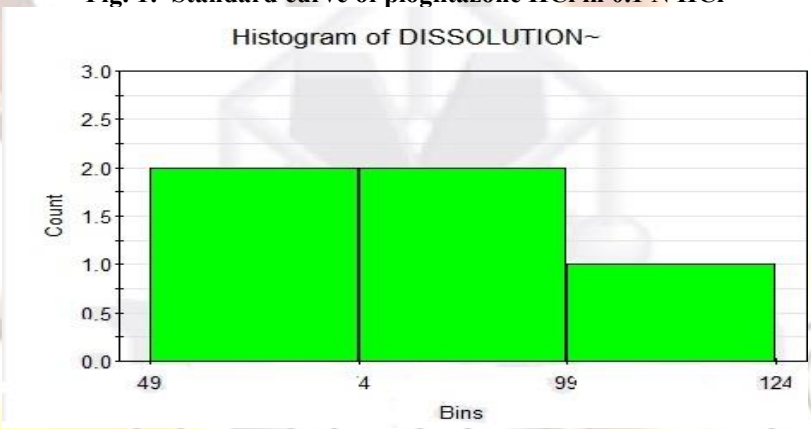


Fig. 2.1: Data distribution Histogram

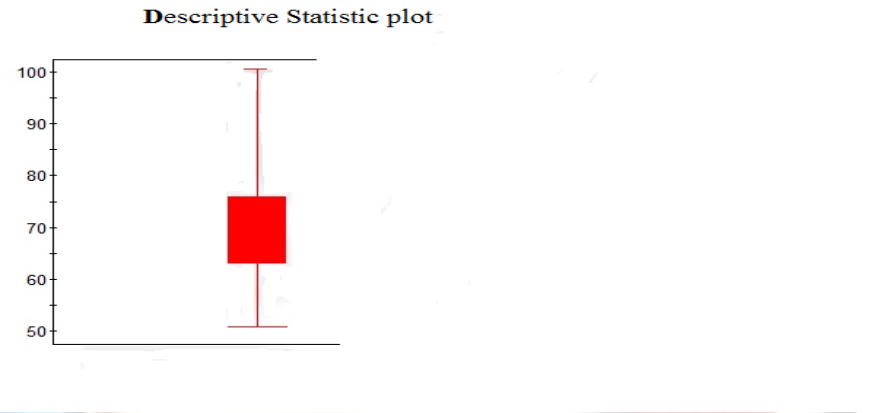
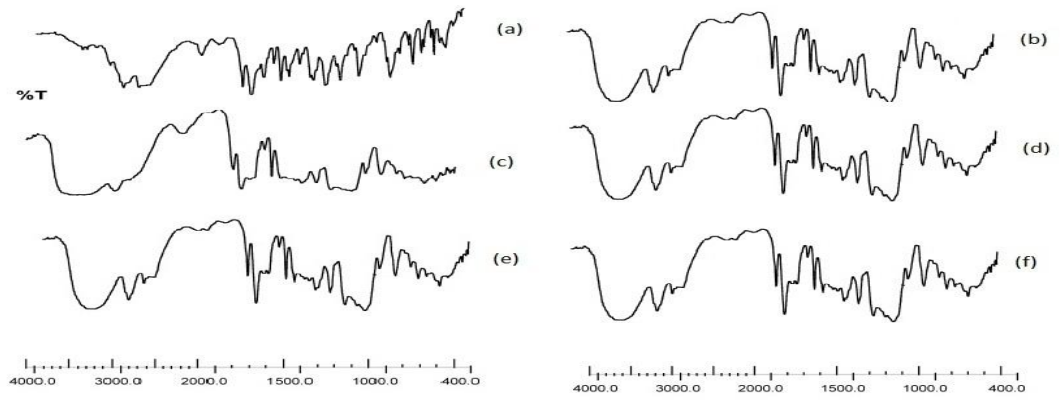


Fig. 2.2: Descriptive Statistic of Response



(a) pure drug (b) F-1 (HPMC as carrier) (c) F-2 (PEG 6000 as carrie)
(d) F-3 (PVP K 30 as carrier) (e) F-4 (Polaxamer as carrier) (f) F-5 (Eudragit E PO as carrier)

Fig 3: FT-IR spectroscopy of different Solid dispersions

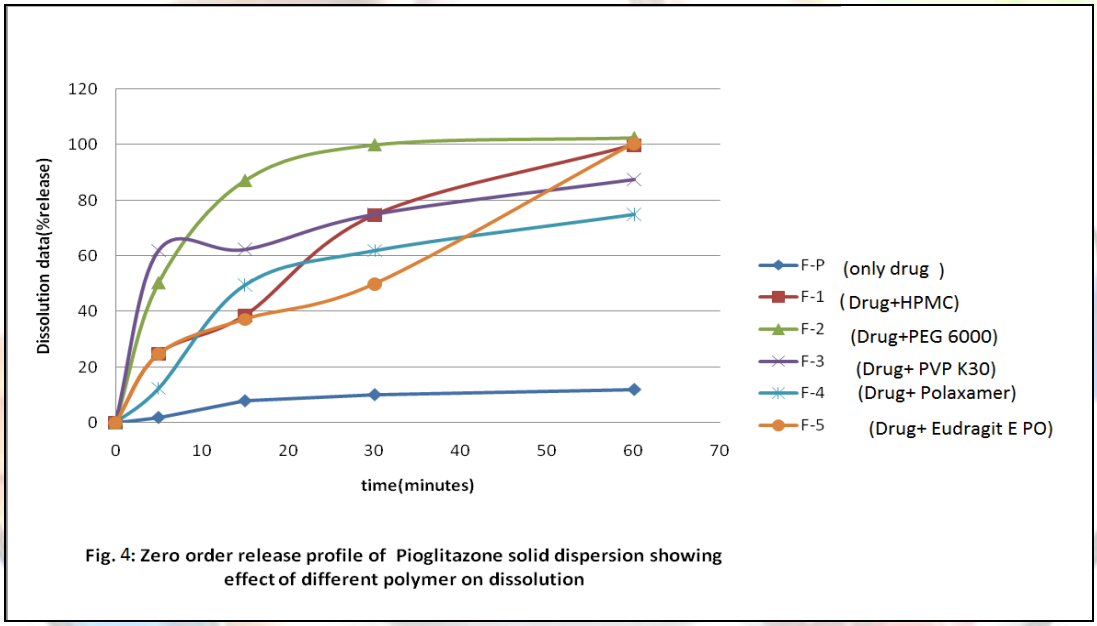


Fig. 4: Zero order release profile of Pioglitazone solid dispersion showing effect of different polymer on dissolution

Fig. 4: Zero order release profile of Pioglitazone solid dispersion showing effect of different polymer on dissolution