



Development of two Novel Techniques for Enhancing the Dissolution rate of Pioglitazone

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ABSTRACT

The antidiabetic drug pioglitazone is hydrophobic and having dissolution rate limited bioavailability. Several attempts were made to enhance its dissolution rate. In this investigation the two well known techniques viz., microcapsules and compression coating originally designed for sustained drug delivery were used for enhancing the dissolution rate of Pioglitazone. The polymer eudragit E100 was reported as a taste masking material for bitter drugs. However this research work is aimed to exploit eudragit E100 as dissolution enhancer by virtue of its acid solubility. The polymer was incorporated as a carrier for preparation of solid dispersion, coating material in microcapsules and compression coated tablets. The prepared formulations were evaluated for various parameters including the compatibility studies with IR spectra and drug dissolution studies. The drug Pioglitazone was found to be compatible with eudragit and dissolution rate was also increased in presence of the polymer. The dissolution rate was increased in presence of the polymer and dependent on the technique employed. High dissolution rate of Pioglitazone was observed from the tablets coated with the polymer eudragit E100.

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Introduction

The micro environmental pH¹ surrounding the drug molecule was found to influence the solubility, dissolution rate and performance of a drug. pH dependent polymers are used to prepare fast dissolving tablets, sustained/controlled^{2/} targeted^{3/} enteric coated⁴ formulations, stabilize the drugs and to mask the taste. Eudragit E100 is most commonly used to mask the taste of bitter drugs. This polymer solubility is pH dependent and more soluble in acidic conditions. This polymer was not reported as dissolution enhancer.

Eudragit E100 is a (cationic copolymer based on dimethyl amino ethyl methacrylate) polymethacrylate with pH dependent solubility, specifically used for taste masking. It is soluble in gastric fluid up to pH 5.0 and is swellable and permeable above pH 5.0⁵.

Pioglitazone Hcl 5-({4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl}methyl)-1,3 thiazolidine-2,4-dione is an antihyperglycaemic agent that in the presence of insulin resistance, increases hepatic and peripheral insulin sensitivity thereby inhibiting hepatic gluconeogenesis and increase peripheral and splanchnic glucose uptake. Pioglitazone selectively stimulates the nuclear receptor PPAR γ . This activation increases insulin sensitivity and thus effect the glucose and lipid metabolism. Primary metabolites are pharmacologically active and half life of approximately 24hr. This allows for once daily administration of pioglitazone⁶.

The solubility of the poorly soluble drugs were found to be increased in presence of hydrophilic polymers⁷⁻⁹ such as PEG and PVP, but the attempts with the pH dependent polymers was scanty. So studies were carried out to determine the effect of these polymers on dissolution rate of poorly soluble drug Pioglitazone. The polymers are used as carriers in the

preparation of solid dispersions¹⁰⁻¹¹ and as a coating material in the preparation of microcapsules¹²⁻¹⁵ and compression coated tablets. Much of earlier reports indicated that the microcapsules and compression coated tablets are designed for slow release. Eudragit E100 is incorporated in to the formulations with three different techniques viz., solid dispersion, compression coating and microcapsules.

However in this research work, an attempt was made to exploit these techniques for possible improvement in dissolution.

Materials And Methods

Pioglitazone Hcl, Eudragit E100, pvp k30, IPA, magnesium stearate, talc. All the materials used in this study comply with the pharmaceutical and analytical standards, respectively. Multistation tablet press (CDM-3-16, Cadmach machinery .co.pvt), Disintegration test apparatus (2-USP-305, Campbell electronics), Dissolution test apparatus (DT 03071009, Lab India 2000) and UV-visible spectrophotometer (SL159, Elico .Ltd) were used in this research work.

IR studies:

In this study, KBr disc method was employed to conduct IR spectral studies on pure drug and formulations. The sample was powdered and mixed with KBr (1:100). The mixture was then compressed into transparent disc under high pressure using hydraulic pellet press. This disc was placed in IR spectrophotometer using sample holder and IR spectrum was recorded.

Analysis of pioglitazone Hcl using a UV-Visible spectrometer:

First, 10 μ g ml⁻¹ stock solution was prepared and further dilutions were made with 0.1 N Hcl to get a concentration range 5-25 μ g ml⁻¹. Absorbance of these solutions were measured at

270nm by using UV-Visible spectrophotometer. The calibration curve was constructed in between concentration and absorbance. The method was validated as per ICH guide lines.

Preparation of solid dispersion:

Solid dispersions were prepared by solvent evaporation technique. Drug and Eudragit E-100 were weighed in different ratios (1:1, 1:2, and 1:3) and dissolved in a common solvent 1NHCl. The resulting solution was subjected to evaporation at 60°C. The dried residue was passed through sieve no 60.

Drug content determination:

The solid dispersion containing equivalent to 10 mg of drug was weighed and it was dissolved in 10ml of 0.1NHCl. Suitable dilutions were made and analysed spectrophotometrically at 270nm. Drug content was determined from standard graph.

Preparation of fast dissolving tablets:

The solid dispersion equivalent to 30 mg of drug was weighed. Required quantity of excipients were weighed and mixed thoroughly. Tablets were prepared by direct compression technique. The blend was compressed using 9mm round shaped tablet tooling set of multi Station tablet press. The composition of the tablet was given in the Table .1.

Preparation of microcapsules:

Microcapsules were prepared by coacervation phase separation technique. The coacervation was achieved by exploiting the principle influence of pH on solubility of the polymer. In this research work, coacervation was induced by changing the pH of the liquid manufacturing vehicle (LMV). Required quantity of Eudragit E-100 was dissolved in its liquid manufacturing vehicle (10 ml of 1NHCl) by using a cyclomixer and 250 mg of accurately weighed Pioglitazone was dispersed in another 10 ml of 1NHCl. Both the solutions were mixed. 1N NaOH solution was added drop by drop until neutral pH was attained and it was checked by immersing the electrodes in the LMV containing the drug- polymer mixture. The separated Eudragit E-100 was allowed to deposit on the dispersed drug particles. The resulting microcapsules were separated by decantation and dried 60°C for 4 hr.

Preparation of tablets:

Microcapsules equivalent to 30 mg was weighed. Required quantity of excipients were weighed and mixed thoroughly. Tablet was prepared by direct compression. The blend was compressed using 9mm round shaped tablet tooling set of multi Station tablet press. The composition of the tablet was given in the Table .1

Drug content determination:

Microcapsules equivalent to 10 mg was weighed and it was dissolved in 10ml of 0.1NHCl. Suitable dilutions were made and analysed spectrophotometrically at 270nm. Drug content was determined from standard graph.

Compression coating:

Preparation of Uncoated tablets: Required quantity of excipients and drug were weighed. Tablet was prepared by direct compression. The materials were weighed, mixed and passed through a mesh (250µm) to ensure complete mixing. The tablets were prepared by compressing the thoroughly mixed materials using 6 mm round shaped tablet tooling set of multi Station tablet press.

Preparation of coated tablets: The compression coating was provided by placing half the quantity of coating material in the die cavity, then the core tablet was carefully positioned in the centre and filled with the other half of the coating material. The coating material was compressed using 9mm round round

shaped tablet tooling set of multi station tablet press. The composition of tablet was given in table-1

Determination of drug content:

Twenty tablets were powdered and the quantity of powder equivalent to labelled amount of Pioglitazone was utilized for assay. The drug was extracted using 10 ml methanol. The solution was filtered, made up to volume with methanol and analyzed spectrophotometrically by measuring the absorbance at 269.5 nm.

Evaluation of tablets:

Pre compression parameters:¹⁶

The following micromeritic properties of blend containing drug and diluents were studied.

a) Bulk density (g/ml):

About 5 g of blend containing the complex along with the excipients mentioned in the above table was weighed and transferred to a measuring cylinder. The bulk volume was noted. The bulk density was calculated by the formula.

$$\text{Bulk density} = \frac{\text{mass}}{\text{bulk volume}}$$

b) Carr's index (%)

About 5g of blend containing the complex along with the excipients mentioned in the above table was weighed and transferred to a measuring cylinder and then it was subjected to 100 tapings. The Carr's index was calculated by the formula.

$$\text{carr's index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

c) Hausner's ratio:

About 5g of blend containing drug and excipient was weighed. It was transferred to a 25 ml measuring cylinder and subjected to 100 tapings. The Hausner's ratio was calculated by the formula.

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

d) Angle of repose:

About 5g of blend containing drug and excipient was weighed and it was kept in an open cylinder which was placed on a graph sheet. Then the cylinder was slowly lifted. The angle of repose was calculated by the formula

$$\text{Angle of repose } (\theta) = \tan^{-1} \frac{h}{r}$$

Post compression parameters:^{17, 18}

Hardness:

The prepared tablets hardness was measured by using Monsanto hardness tester. The hardness was measured in terms of kg/cm².

Weight variation:

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. The percentage deviation was calculated.

Friability:

Ten tablets were weighed collectively and placed in the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively.

Wetting time:

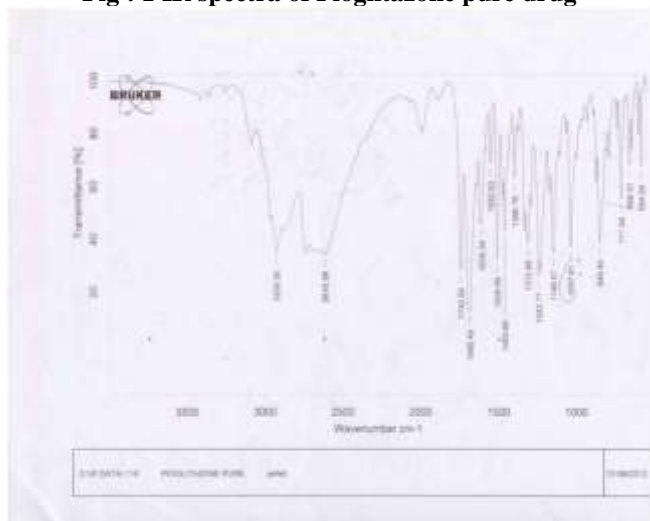
A piece of tissue paper folded twice was placed in a small petridish (Internal diameter of 5 cm) containing 6 ml of distilled water. A tablet was placed on the paper, and the time required for complete wetting of the tablet was measured.

In vitro disintegration time:¹⁹

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water was maintained at a temperature of $37 \pm 2^\circ\text{C}$ and time taken for the entire tablet to disintegrate completely was noted.

Results And Discussion

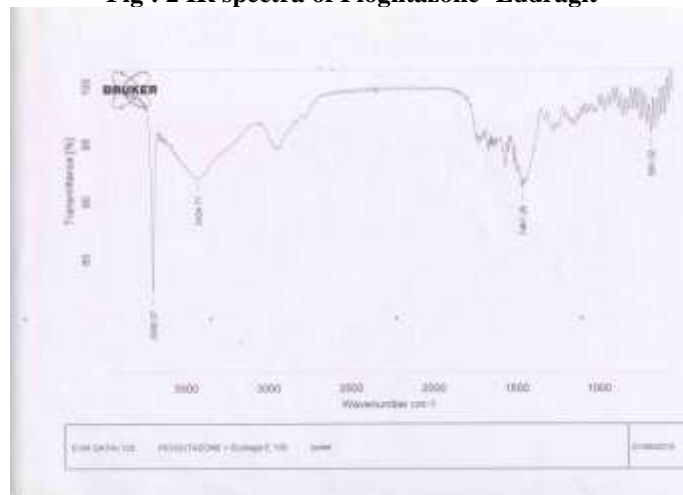
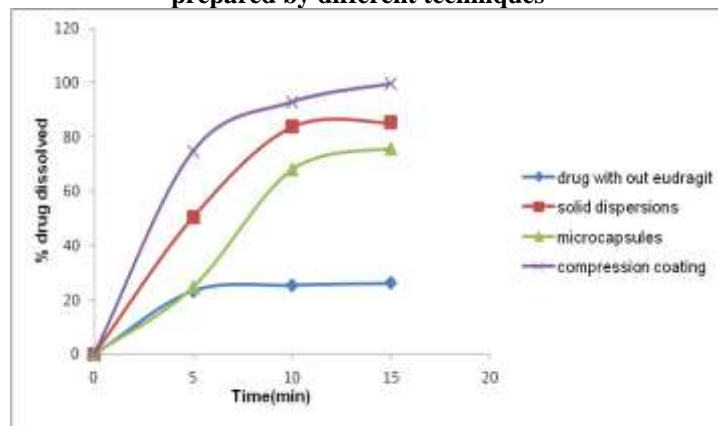
This research work is aimed to design, develop and formulation of fast dissolving tablets for Pioglitazone. The drug Pioglitazone belongs to class II of bio classification system. To enhance the dissolution rate of Pioglitazone, three different approaches such as solid dispersions, compression coating and microcapsules were employed in this investigation. Generally the microcapsules and compression coating are designed for sustained or control release formulations. However in this investigation an attempt was made to use these technologies for dissolution enhancement. Solid dispersions usually contain a hydrophilic carrier, where as in this research work the pH dependent polymer was used to improve the dissolution rate. Drug: polymer ratio 1:3 was maintained in all cases. Solid dispersions were prepared by solvent evaporation technique and evaluated for drug content and subjected to compression. Microcapsules were prepared by coacervation phase separation technique. The reported techniques for coacervation phase separation were temperature change, incompatible polymer addition, Non solvent addition, salt addition, polymer-polymer interaction. The Microcapsules were evaluated for drug content and subjected to compression in presence of the cushioning agent i.e., the direct compressible diluent DCP. The compatibility between the drug and the polymer Eudragit E100 was investigated with IR spectral studies. The IR spectra are showed in fig.1

Fig : 1 IR spectra of Pioglitazone pure drug

The following characteristic peaks were observed in spectra of pure Pioglitazone Hcl as well as the mixture containing the drug and polymer. Thus these studies clearly indicated that the interactions do not exist between the drug and polymer.

1. 2928.05 cm^{-1} --C-H stretching
2. 1742.60 cm^{-1} --ketone stretching(C=O) 5 membered ring
3. 1685.45 cm^{-1} -- α, β unsaturated 6 membered ring, carbonyl stretching(saturated)
4. 1509.69 cm^{-1} --N-H bending vibration (Amino salts)
5. 1148.57 cm^{-1} --S-H stretching (sulfur compounds)
6. 711.55 cm^{-1} ----Aromatic

Various Micromeritic properties were evaluated for the blends containing drug polymer and other excipients prior to compression. The resulting data is showed in table.2. The blend exhibited the desired flow properties and hence subjected to compression. The formulated tablets were evaluated for various quality control tests and the results are documented in table.3. All the prepared tablets satisfied the quality control requirements. The formulated tablets were further subjected to *in vitro* dissolution studies in 0.1NHcl. The corresponding dissolution profiles are showed in fig.3.

Fig : 2 IR spectra of Pioglitazone- Eudragit**Fig: 3 dissolution profile of pioglitazone-Eudragit tablets prepared by different techniques**

Various *in vitro* dissolution parameters were computed and depicted in table .4. The dissolution rate was found to be increased in presence of the polymer Eudragit and dependent on the method of incorporation of Eudragit E100 in to the formulation. The dissolution rate observed from the three techniques was treated statistically with one way ANOVA and a significance differences in dissolution rate ($p < 0.05$) was observed. Among the three techniques, compression coating was found to be more suitable to enhance the dissolution rate. It may be due to the high penetration of gastric fluids in to the tablet and possible solubility of the coating material in gastric fluid. The effective surface area available in case of tablets formulated with solid dispersions is less compared to the compression coated tablets. The formulation containing microcapsules may lose the coating material during compression and handling.

Conclusion

This research investigation concludes that the deposition of Eudragit E100 over the uncoated tablet containing Pioglitazone improves the dissolution rate of poorly soluble drug Pioglitazone.

Table No. 1 Composition of tablets

S.no	Ingredients	Quantity per one tablet (mg)			
		F1	F2	F3	F4
1	Drug- Eudragit	120mg equivalent to 30 mg of pure drug	120mg equivalent to 30 mg of pure drug	30mg drug 90mg polymer	30 mg drug
2	Crosspovidone	15.6	15.6	15.6	15.6
3	Dicalcium phosphate	157	157	157	157
4	Magnesium stearate	2	2	2	2
5	Talc	2	2	2	2
6	Total weight	296.6	296.6	296.6	206.6

F1-solid dispersion F2- Microcapsules F3- compression coating F4-drug with out Eudragit

Table No. 2 Micromeritic properties of the blend containing pioglitazone-Eudragit

Formulation	Carr's index	Hausner's ratio	Angle of repose ⁽⁰⁾	% drug content
Solid dispersion(1:3)	13	1.24	25	98.4
microspheres	12	1.23	27	96.2
Compression coating	14	1.25	26	98.9

Table No. 3 Post compression parameters of the

Formulation	Average weight(mg)	Hardness (kg/cm ²)	%friability	Disintegration time(sec)	Wetting time (sec)
Solid dispersion(1:3)	296±0.04	3.4±0.02	0.59 ±0.03	56±1.00	12±1.00
microspheres	296±0.06	3.6±0.02	0.51±0.04	53±1.00	13±1.00
Compression coating	296±0.05	3.2±0.02	0.64±0.04	52±1.00	16±1.00

Table No. 4 *In vitro* dissolution kinetics of Pioglitazone-Eudragit tablets observed in 0.1N Hcl

Formulation	Correlation coefficient (r)		DE ₁₀	K (min ⁻¹)	T ₅₀ (min)
	Zero order	First order			
pure drug	0.606	0.629	16.56	0.0184	37.7
Solid dispersion(1:3)	0.9126	0.9594	46.22	0.1443	4.8
microcapsules	0.9392	0.9733	29.36	0.1241	5.6
Compression coating	0.8456	0.9768	60.57	0.3276	2.1

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