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Research Article

Formulation development studies on pioglitazone- β-cd matrix tablets for controlled release

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ABSTRACT

The aim of the present investigation was to enhance the solubility and impart a controlled release pioglitazone - βCD matrix tablets; pioglitazone is an oral hypoglycemic agent, which belongs to Class II of BCS with relatively short elimination half life. Inclusion complex of pioglitazone with β-cyclodextrin was prepared by kneading, co-precipitation, physical mixture and evaluated for its *in-vitro* release. The dissolution study of kneading complex shows significant increase in the drug release from kneading complex than pure drug and physical mixture. Matrix tablet complex equivalent to 30 mg pioglitazone were prepared by using ethylene vinyl acetate (EVA), ethyl cellulose (EC) and starch acetate (SA) evaluated for various tablet properties and *in-vitro* dissolution studies. The feasibility of employing βCD complexes in the design of controlled release matrix tablets of pioglitazone for obtaining slow controlled and complete drug release in 24 h.

Keywords: pioglitazone; β-cyclodextrin; inclusion complex; ethylene vinyl acetate; ethyl cellulose; starch acetate; matrix tablets.

INTRODUCTION

The objective of any drug delivery system is to provide therapeutic amount of drug to targeted site in body to achieve the desired therapeutic effect In recent years, attention has been focused on the development of new drug delivery system rather than invention of new molecules (Robinson J.R. & Lee V.H.L, 1987; Khan G.M, 2001). Pioglitazone is an oral antidiabetic, belonging to the thiazolidinedione group of drugs. Pioglitazone commonly prescribing drug for patients with type II diabetes and it belongs to class II of Biopharmaceutical Classification System (BCS) having low water solubility which is rate limiting step in absorption of drug in Gastrointestinal tract (Ram Chand Dhakar et al., 2011). Pioglitazone is having short biological half-life need to be administered more than once a day, which increases the possibility of non-compliance and produce greater fluctuations in plasma drug levels both above and below therapeutic range (Higuchi T. and Conners K.A, 1961; Rathore M.S et al., 2007).

Matrix controlled tablet there is strong need to use of any technique to enhance the solubility of class II drug. Inclusion complex of pioglitazone with β-Cyclodextrin increase the solubility in phosphate buffer and water also the formation of the inclusion compounds greatly modifies the physical and chemical properties of the guest molecule, mostly in terms of water solubility. This is the reason why Cyclodextrin have attracted much interest in many fields, especially pharmaceutical applications: because inclusion compounds of Cyclodextrin with hydrophobic molecules are able to penetrate body tissues, these can be used to release biologically active compounds under specific conditions. In most cases the mechanism of controlled degradation of such complexes is based on pH change of water solutions, leading to the cleavage of hydrogen or ionic bonds between the host and the guest molecules. Inclusion complex of Glipizide with β-cyclodextrin was prepared by kneading, co-precipitation, physical mixture and evaluated for its in-vitro release. The dissolution study of kneading complex shows significant increase in the drug release from kneading complex than pure drug and physical mixture (Patidar Deepak et al., 2011).

The objective of the present investigation is to design pioglitazone matrix tablets with βCD. pioglitazone is widely prescribed and effective ant-diabetic drugs were selected for formulation into controlled release drug delivery system in the form of matrix tablets employing three polymers namely (i) ethylene vinyl acetate copolymer (EVA) (ii) ethyl cellulose (EC) and (iii) starch acetate (SA).

MATERIAL AND METHOD

Pioglitazone was gift sample from Dr.Reddy's Laboratories Ltd., Hydrabad. Ethylene Vinyl Acetate Copolymer

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Table 1: List of pioglitazone matrix tablets prepared employing pioglitazone alone and pioglitazone -βCD Inclusion complexes

S.No	Drug Form	Matrix Polymer	Code
1	Pioglitazone	EVA	PTEVA1
2	Pioglitazone-βCD (1:1)	EVA	PTEVA2
3	Pioglitazone	EC	PTEC1
4	Pioglitazone -βCD (1:1)	EC	PTEC2
5	Pioglitazone	SA	PTSA1
6	Pioglitazone -βCD (1:2)	SA	PTSA2

Table 2: Formulae of piogltazone matrix tablets prepared

Ingredient (mg/tablet)	Matrix Tablet Formulation					
	PTEVA1	PTEVA2	PTEC1	PTEC2	PTSA1	PTSA2
Pioglitazone	30	--	30	--	30	--
Pioglitazone -βCD (1:1) Inclusion complexes	--	60.0	--	60.0	--	60.0
EVA	11.0	11.0	--	--	--	--
EC	--	--	11.0	11.0	--	--
SA	--	--	--	--	11.0	11.0
Lactose	170.2	140.2	170.2	140.2	170.2	140.2
Talc	4.4	4.4	4.4	4.4	4.4	4.4
Magnesium stearate	4.4	4.4	4.4	4.4	4.4	4.4
Total weight of Tablet (mg)	220	220	220	220	220	220

(Grade 1408), Ethyl Cellulose (BDH ; having an ethoxyl content of 47.5% by weight and viscosity of 22 cps in a 5% concentration by weight, in a 80:20 tolune-ethanol solution at 25°C. Starch acetate (D.S: 2.75) were procured from commercially. All other materials used were of Pharmacopoeial grade.

PREPARATION OF MATRIX TABLETS

Among the various approaches, preparation of drug-embedded matrix tablets is one of the least complicated approaches for obtaining controlled release and is widely used in industry. In the present study Matrix tablets of pioglitazone alone and pioglitazone - βCD (1:1) Inclusion complexes was formulated employing (i) Ethylene Vinyl Acetate (EVA) (ii) Ethyl Cellulose (EC) (iii) Starch acetate (SA) in different proportions of drug and polymers and tablets were evaluated for drug release kinetics and mechanism.

Method of Preparation of Matrix Tablets

Matrix tablets of pioglitazone were prepared as per the formulae given in Table 1 and2. The required quantities of medicament, lactose and matrix forming polymer were mixed thoroughly in a mortar by following geometric dilution technique. The granulating fluid (solvent blend of water and alcohol in 1:1 ratio) was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60^0C for 4 h. The dried granules were passed through mesh No. 16 to break aggregates. The lubricants talc and magnesium stearate were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary tablet punching machine (M/s Cadmach machinery Co. Pvt. Ltd., Mumbai) to a hardness of 8 kg/sq.cm. Using 9 mm round and flat punches.

Evaluation of Tablets

Hardness of the matrix tablets prepared was tested using a Monsanto Hardness Tester. Friability of the matrix tablets prepared was determined in a Roche friabilator. Disintegration time was determined in Thermonic tablet disintegration test machine using water, 0.1 N HCl and phosphate buffer of pH 7.4 as test fluids (Table 3).

Estimation of drug content in tablets

Five tablets were accurately weighed and powdered. Tablets powder equivalent to 30 mg of the drug was taken for assay into 25 ml volumetric flask and 20 ml of methanol were added. The mixture was shaken thoroughly for about 30 min. to extract pioglitazone. The solution was then made upto volume with methanol. The methanolic solution was subsequently diluted suitably with phosphate buffer of pH 7.4 and assayed at 223 nm for pioglitazone.

Drug release study on Pioglitazone Matrix Tablets

Release of Pioglitazone from the matrix tablets prepared was studied in 0.1N hydrochloric acid (900 ml) using an eight station dissolution rate test apparatus (model, TDT-08L, M/s.Electrolab) with a paddle stirrer at 50 rpm and 37 ± 0.5°C.

One tablet containing 30 mg of pioglitazone was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and were assayed at 269 nm for pioglitazone using a Schimadzu UV-150 double beam spectrophotometer. The sample (5 ml) taken at each sampling

Table 3: Weight Variation, Hardness, Friability, Disintegration Test and Drug Content of pioglitazone Matrix Tablets

Formulation code	Weight variation (%)	Friability (%)	Hardness (Kg/cm^2)	DT (min.)	Pioglitazone content (%) ($\bar{x}$ ± s.d)
PTEVA1	215.0 ± 1.12	0.31 ± 0.12	5.51 ± 0.41	Non-disintegrating	98.85 ± 0.59
PTEVA2	219.1 ± 1.28	0.43 ± 0.11	6.03 ± 0.73	Non-disintegrating	96.03 ± 0.37
PTEC1	219.7 ± 1.25	0.34 ± 0.14	5.01 ± 0.31	Non-disintegrating	94.12 ± 0.45
PTEC2	219.8 ± 1.09	0.52 ± 0.16	6.10 ± 0.51	Non-disintegrating	95.02 ± 0.86
PTSA1	217.2 ± 1.14	0.61 ± 0.15	5.10 ± 0.91	Non-disintegrating	96.53 ± 0.62
PTSA2	218.8 ± 2.61	0.53 ± 0.17	6.90 ± 0.35	Non-disintegrating	95.98 ± 0.81

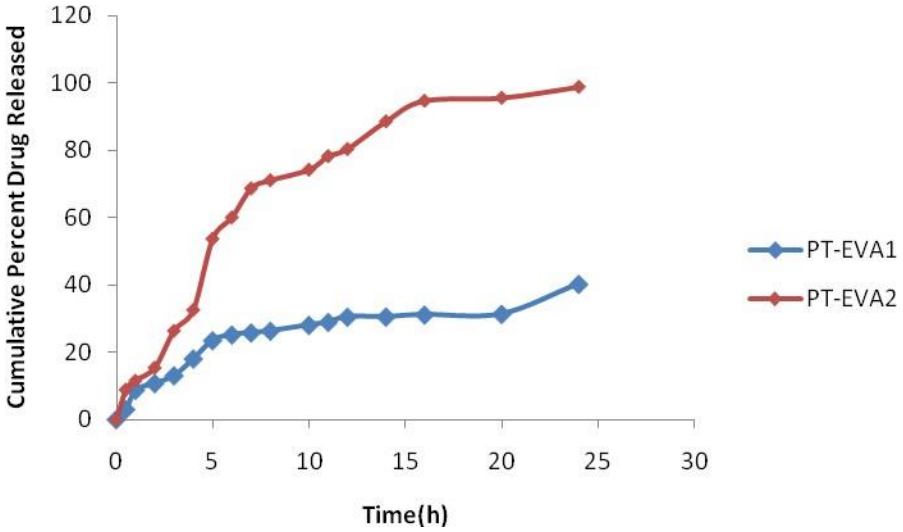

Figure 1: Release Profiles of Pioglitazone Matrix Tablets Prepared Employing Ethylene Vinyl Acetate (EVA) Using Lactose as Diluent

time was replaced with fresh dissolution medium (5 ml). The drug release experiments were conducted in triplicate. (Fig 1, 2&3).

RESULTS AND DISCUSSION

Matrix tablets were formulated employing pioglitazone alone and their βCD complexes with an objective of evaluating the feasibility of employing drug-βCD complexes in the design of controlled release tablet formulations for obtaining slow, controlled and complete drug release in 24 h. All the matrix tablets formulated contained 100 ± 5.0 % of the labeled claim. All the matrix tablets were found to be non- disintegrating in water, acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such, the formulated matrix tablets were of good quality with regard to drug content, hardness and friability. As the matrix tablets formulated employing ethylene vinyl acetate copolymer (EVA), ethyl cellulose (EC) and starch acetate (SA) were non-disintegrating in acidic and alkaline fluids, they are considered suitable for oral controlled release.

Drug Release Characteristics of Pioglitazone Matrix Tablets

Pioglitazone release from the matrix tablets formulated was slow and spread over more than 24 h and depended on the drug form used in the matrix tablets and the polymer used. Pioglitazone release from the matrix tablets formulated employing pioglitazone alone was very slow with all the three polymers. Percent pioglitazone released in 24 h was found to be 40.28, 29.76 and 27.48 respectively with tablets formulated employing ethylene vinyl acetate (PTEVA1),ethyl cellulose (PTEC1) and starch acetate (PTSA1) as matrix forming polymer. When pioglitazone- βCD complexes were used in the matrix tablets drug release was improved and percent drug released in 24 h was found to be 98.78, 98.16 and 99.32 respectively with tablets formulated employing ethylene vinyl acetate (PTEVA2),ethyl cellulose (PTEC2) and starch acetate (PTSA2) as matrix forming polymer. Thus with all the three matrix forming polymers, pioglitazone release from the matrix tablets was slow, controlled and com-

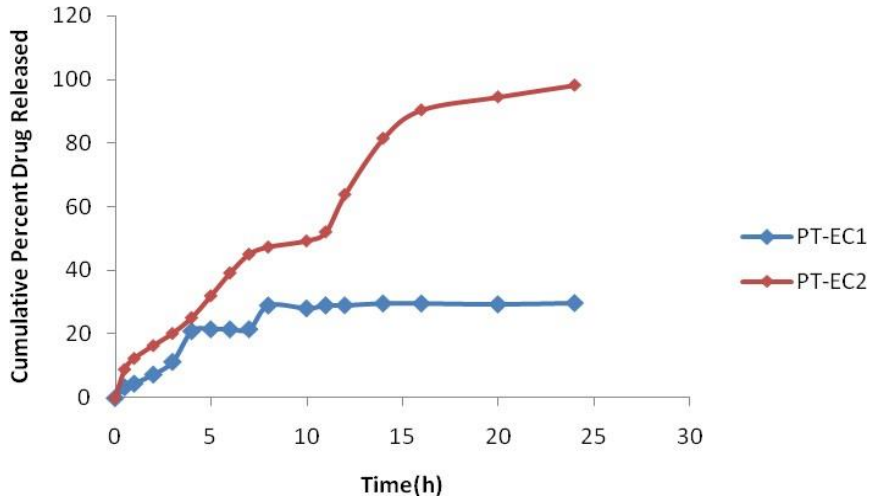

Figure 2: Release Profiles of Pioglitazone Matrix Tablets Prepared Employing Ethyl Cellulose (EC) Using Lactose as Diluent

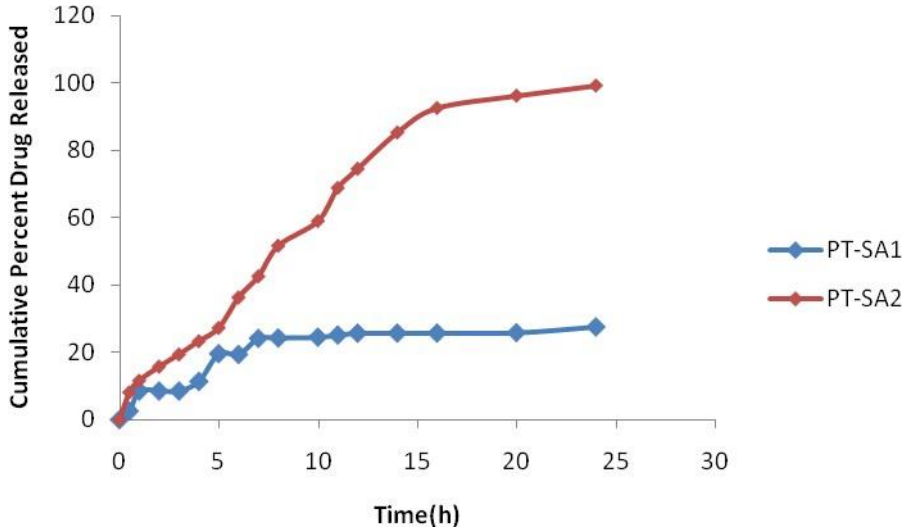

Figure 3: Release Profiles of Pioglitazone Matrix Tablets Prepared Employing

plete in 24 h when pioglitazone- βCD complexes were used. Pioglitazone release rates were much higher in the case of matrix tablets containing Pioglitazone– βCD complexes when compared to those containing pioglitazone alone.

Analysis of release data as per zero order and first order kinetics models indicated that both the zero order and first order kinetic models are equally applicable to describe the release data. The correlation coefficient (r) values were nearly the same in both zero order and first order kinetic models.

Plots of percent released versus square root of time were found to be linear with (r > 0.9163) with all the matrix tablets formulated indicating that the drug release from these tablets was diffusion controlled.

CONCLUSION

Pioglitazone release from the matrix tablets formulated was slow and spread over more than 24 h and depende d on the drug form used in the matrix tablets and the polymer used. Pioglitazone release from the matrix tablets formulated employing pioglitazone alone was very slow with all the three polymers. Percent pioglitazone released in 24 h was found to be 40.28, 29.76 and 27.48 respectively with tablets formulated employing ethylene vinyl acetate (PTEVA1), ethyl cellulose (PTEC1) and starch acetate (PTSA1) as matrix forming polymer.

When pioglitazone- βCD complexes were used in the matrix tablets drug release was improved and percent drug released in 24 h was found to be 98.78, 98.16 and 99.32 respectively with this tablets. Thus with the entire three matrixes forming polymers, pioglitazone release from the matrix tablets was slow, controlled and complete in 24 h when pioglitazone- βCD complexes were used. Pioglitazone release rates were much higher in the case of matrix tablets containing Pioglitazone– βCD complexes when compared to those containing pioglitazone alone.

RECOMMENDATIONS

Hence complexation with β cyclodextrin (βCD) is recommended for the formulation of controlled release

products of BCS class II anti diabetic drugs to achieve slow, controlled and complete drug release in 24 h for once a day administration. The significant achievement of the present investigation is development of controlled release formulations of poorly soluble BCS class II drugs employing their βCD complexes which is not possible with the poorly soluble drugs alone.

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