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Research Article

FORMULATION DEVELOPMENT OF PIOGLITAZONE TABLETS EMPLOYING A NEW CO-PROCESSED EXCIPIENT

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ABSTRACT

An efficient platform for the manipulation of excipient functionality is provided by co-processing two or more existing excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients In the present study a new co-processed excipient consisting of cellulose and ethylcellulose was developed and evaluated for its application in the formulation development of pioglitazone tablets fulfilling the official dissolution rate test specification. Cellulose –EC co-processed excipient was prepared by kneading method and was characterized by determining melting point, solubility, swelling index in water, pH, and micromeritic characters namely particle size, bulk density, tapped density, angle of repose and compressibility index and evaluated for its application as directly compressible vehicle in the formulation of pioglitazone tablets.

Cellulose-EC co-processed excipient prepared by kneading method is granular, discrete and free flowing. It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4. It exhibited slight swelling (24%) in water. Cellulose-EC co-processed excipient has excellent flow properties alone and as blends with the selected drug it exhibited excellent to good flow properties. Pioglitazone tablets prepared by direct compression method employing Cellulose-EC co-processed excipient as DCV were of good quality with regard to drug content, hardness, friability and disintegration time. The tablets formulated disintegrated rapidly within 2 min 40 sec. Pioglitazone tablets prepared gave rapid dissolution of the contained drug and fulfilled the official (IP) dissolution rate test specification prescribed. The formulated tablets also gave rapid and higher dissolution of pioglitazone than the commercial tablets tested. Thus Cellulose-EC co-processed excipient developed in this study was found to be a promising directly compressible vehicle for the preparation of compressed tablets and pioglitazone tablets with rapid disintegration and dissolution characteristics could be developed employing the new co-processed excipient.

Keywords: Cellulose – Ethyl cellulose Co- processed Excipient, Directly compressible vehicle, Co-processed Excipient, Pioglitazone Tablets

INTRODUCTION

An efficient platform for the manipulation of excipient functionality is provided by co-processing two or more existing excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients [1]. Co-processed excipients are prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-drying, kneading and spray drying. Co-processing of excipients in the pharmaceutical industry can be dated back to the late 1980's with the introduction of co-processed microcrystalline cellulose and calcium carbonate[2]. Other co-processed excipients include Cellactose (a co-processed combination of cellulose and lactose) and silicified microcrystalline cellulose (a combination of microcrystalline cellulose and silicon dioxide)[3]. In the present study a new co-processed excipient consisting of cellulose and ethylcellulose was developed and evaluated for its application in the formulation development of pioglitazone tablets. Pioglitazone, a widely prescribed antidiabetic drug is poorly soluble in water and aqueous fluids of g. i. tract and exhibits low and variable dissolution rates from tablet dosage forms. I.P 2010 prescribed a dissolution rate test specification of NLT 70 % in 45 min for pioglitazone tablets to check the quality of commercial brands. The objective of the present study is to develop pioglitazone tablets fulfilling the official dissolution rate test specification employing the new co-processed excipient developed.

MATERIALS AND METHODS

Materials

Pioglitazone was a gift sample from Dr. Reddy Laboratories Ltd., Hyderabad. Cellulose (SDFCL), ethyl cellulose (viscosity at 25^{0}C is 18-24 cps), Crospovidone, talc and magnesium stearate were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Pioglit30 tablets of M/s Sun Pharmaceutical Industries, J & K, Batch No. ADL 0529; Mfg. Date: 04/2012; Exp. Date: 03/2014 were procured from local market.

Methods

Preparation of Cellulose-EC Co-processed Excipient

Ethyl cellulose (0.1g) was dissolved in a solvent blend consisting of dichloromethane and methanol (1:1) in a dry mortar. Cellulose (5g) was added to the ethyl cellulose solution and mixed. The slurry was kneaded for 30 min. The semi solid mass formed was forced through mesh no. 20 to form granular aggregates. The product formed was dried at 60^{0}C in a hot air oven. The dried product was passed through mesh no. 20. The fines formed are removed by sieving through mesh no. 120.

Characterization of Cellulose-EC Co-processed Excipient

Cellulose-EC co-processed excipient prepared was characterized by determining melting point, solubility, swelling index in water, pH, and micromeritic characters namely particle size, bulk density, tapped density, angle of repose and compressibility index.

Solubility

Solubility of Cellulose-EC was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4.

pH

The pH of a 1% w/v slurry was measured.

Melting point

Melting point was determined by using melting point apparatus.

Swelling Index[4]

Cellulose-EC (0.5 g) was added to 10 ml of water and petroleum ether taken in two different graduated test tubes and mixed. The dispersion in the tubes was allowed to stand for 24 hrs. The volumes

of the sediment in the tubes were recorded. The swelling index of the material was calculated as follows.

S.I (%) = (Volume of sediment in water – Volume of sediment in petroleum ether)/ (Volume of sediment in petroleum ether)

Particle size

Particle size analysis was done by sieving using standard sieves.

Bulk density[5]

Bulk density (g/cc) was determined by three tap method in graduated cylinder.

Angle of repose[6]

Angle of repose was measured by fixed funnel method.

Compressibility index[7]

Compressibility index (CI) was determined by measuring the initial volume (V_0) and final volume (V) after hundred tappings of a sample of the product in a measuring cylinder.

CI was calculated using equation,

Compressibility index (CI) = $[(V_0-V)/V_0] \times 100$

Estimation of Pioglitazone

An UV Spectrophotometric method based on the measurement of absorbance at 269 nm in 0.1 N hydrochloric acid was used for the estimation of pioglitazone. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.85 % and 1.4 % respectively. No interference by the excipients used in the study was observed.

Preparation of Pioglitazone Tablets by Direct Compression Method

Tablets of pioglitazone (30 mg) were prepared by direct compression method as per the formula given in the Table 2 employing Cellulose-EC co- processed excipient as directly compressible vehicle. All the materials required as per the formula were blended in a closed polyethylene bag. The blends were compressed into tablets on a 10 station tablet punching machine (Rimek) to a hardness of 6 kg/cm^{2}using 9 mm flat punches.

Evaluation of Tablets

All the tablets prepared were evaluated for content of active ingredient, hardness, friability, disintegration time and dissolution rate. Hardness of tablets was tested using Monsanto hardness tester. Friability of the tablets was determined in a Roche Friabilator. Disintegration time was determined in a Lab India tablet disintegration test machine (model: DT 1000) using water as test fluid.

Estimation of Drug Content in the Tablets

From each batch of tablets prepared 20 tablets were accurately weighed and powdered. Tablet powder equivalent to 50 mg of drug was taken for assay into a 100 ml conical flask and extracted with 3×20 ml quantities of methanol. The methanolic extracts were filtered and collected into a 100 ml volumetric flask and the volume was then made upto 100 ml with methanol. The solution was then suitably diluted with 0.1 N hydrochloric acid and assayed at 269 nm. Drug content of the tablets was calculated using the standard calibration curve.

Dissolution Rate Study

Dissolution rate of the tablets prepared was studied employing USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. Hydrochloric acid, 0.1 N (900 ml) was used as dissolution fluid. One tablet was used in each test. A temperature 37±1^{0}C was maintained throughout. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45 µ) at different time intervals and assayed for pioglitazone at 269 nm. All the dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

The objective of the present study is to prepare and characterize Cellulose – Ethyl cellulose (Cellulose-EC), a new co-processed excipient and to evaluate its application as directly compressible vehicle in the formulation development of pioglitazone tablets. Cellulose –EC co-processed excipient was prepared by kneading method into granular form. The prepared Cellulose –EC co-processed excipient was characterized by determining various physical and micromeritic properties. The Cellulose –EC co-processed excipient prepared was granular, discrete and free flowing. The physical and micromeritic properties of Cellulose –EC co-processed excipient prepared are summarized in Table 1.

The Cellulose –EC co-processed excipient prepared was charred at 210^{0}C. It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4. It exhibited slight swelling in water and the swelling index was found to be 24 %. The flow properties of the Cellulose – EC co-processed excipient prepared were determined by measuring bulk density, angle of repose and compressibility index. The results given in Table 1 indicated that the excipient prepared has excellent flow properties. As the Cellulose –EC co-processed excipient possesses excellent flow properties, it is considered as a promising directly compressible vehicle for direct compression of tablets.

Table 1: Physical and Micromeritic Properties of Cellulose–EC Co-processed Excipient

S. No.	Property/Test	Result
1.	Melting point	Charred at 210^{0}c
2.	Solubility	Insoluble in water and aqueous fluids of acidic and alkaline pHs.
3.	Swelling Index (%)	Slightly Swelling in Water. Swelling Index is 24%
4.	pH (1% aqueous dispersion)	6.5
5.	Particle size (µm)	20/120 mesh (482.5 µ)
6.	Bulk density (g/cc)	0.250
7.	Tapped density (g/cc)	0.279
8.	Angle of repose (^{o})	19.29
9.	Compressibility index (%)	10.39

Blends of Cellulose –EC co-processed excipient and pioglitazone also exhibited excellent to good flow properties. The estimated bulk density values of Cellulose –EC co-processed excipient would also contribute to its good flow.

Pioglitazone (30 mg) tablets were prepared by direct compression method employing Cellulose –EC co-processed excipient as DCV. The tablets were prepared as per the formulae given Table 2. All the tablets prepared were evaluated for content of active ingredient, hardness, friability, and disintegration time and dissolution rate. The results are given in Table 3. Hardness of the tablets was in the range 5.0 – 5.5 Kg/sq.cm. Weight loss in the friability test was 1.52% .The drug content of the tablets was within 100 ± 3% of the labeled claim. Pioglitazone tablets formulated disintegrated rapidly within 2 min 40 sec and the commercial tablets disintegrated in 5 min 20 sec. As such the pioglitazone tablets prepared employing the Cellulose –EC co-processed excipient were of good quality with regard to drug content ,hardness, friability and disintegration time.

Table 2: Formula of Pioglitazone Tablets Prepared By Direct Compression Method Employing Cellulose –EC Co- processed Excipient

Ingredient	Quantity (mg/tablet)
Pioglitazone	30
Cellulose-ECCo-processed excipient (20/120 mesh)	181
Crospovidone	9.4
Talc	4.8
Magnesium stearate	4.8
Tablet weight (mg)	**230**

Table 3: Physical Properties of Pioglitazone Tablets Prepared By Direct Compression Method Employing Cellulose – EC Co-processed Excipient

Formulation	Hardness (kg/sq.cm)	Friability (% weight loss)	Disintegration time (min-sec)	Drug content (mg/tablet)
Pioglitazone Tablets (Formulated)	5.0 - 5.5	1.52	2-40	29.4
Pioglitazone Tablets (Commercial)	5.0 - 6.0	1.25	5-20	29.5

The dissolution profiles of the tablets prepared and commercial tablets are shown in Fig.1. Rapid drug dissolution was observed from the tablets formulated employing Cellulose – EC co-processed excipient as directly compressible vehicle as well as from commercial tablets. Dissolution data were analyzed as per zero order and first order kinetics. Dissolution of pioglitazone from the tablets followed first order kinetics with correlation coefficient (r) values > 0.973. The corresponding first order release dissolution rates (K_1) are calculated from the slope of the first order linear dissolution plots. The dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[8]. The dissolution parameters are summarized in Table 4.

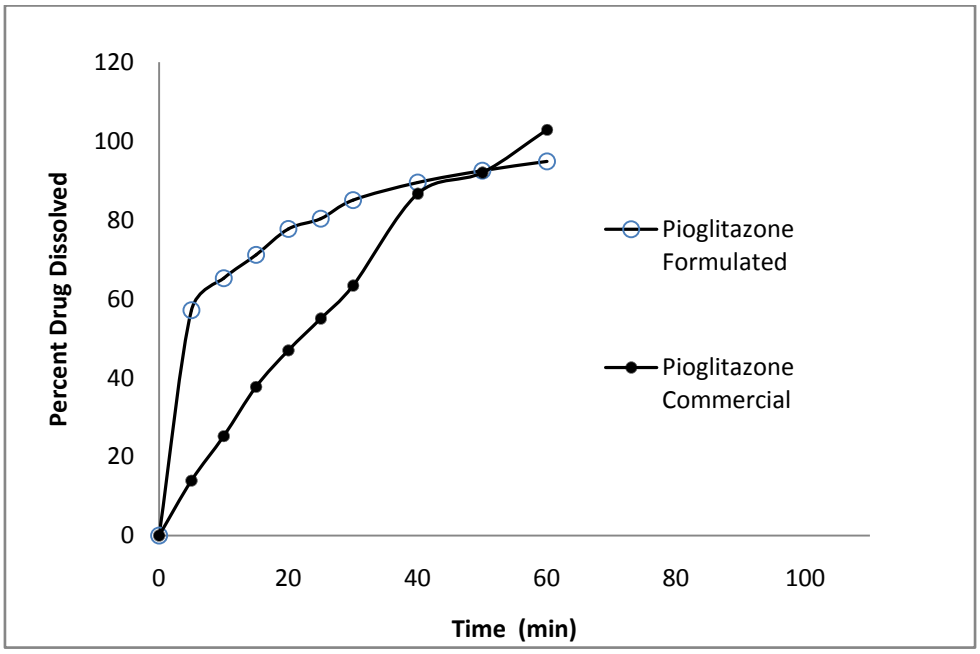

Fig. 1: Dissolution Profiles of Pioglitazone Tablets Formulated Employing Cellulose – EC Co-processed Excipient and Commercial Tablets

Table 4: Dissolution Parameters of Tablets Formulated by Direct Compression Method Employing Cellulose-EC Co-processed Excipient Prepared and Commercial Tablets

Formulation	Dissolution Parameter				Official Dissolution Rate Specification	Dissolution Observed
	PD_{10} (%)	T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})		
Pioglitazone Tablets Formulated	65.24	3.5	65.69	0.0554	NLT **70** % in 45 min in 0.1 N HCl (I.P, 2010)	70% in 15 min
Pioglitazone tablets Commercial	25.24	22.5	34.72	0.0437	NLT **70** % in 45 min in 0.1 N HCl (I.P, 2010)	86.6 % in 45 min

Pioglitazone dissolution from the formulated tablets was rapid and higher than that from commercial tablets. The dissolution rate (K_1) values were found to be 0.0554 and 0.0437min^{-1} respectively in the case of formulated and commercial pioglitazone tablets. Both the formulated and commercial pioglitazone tablets fulfilled the official dissolution rate test specification prescribed for pioglitazone tablets

in I.P 2010. Thus pioglitazone tablets could be formulated employing Cellulose-EC co-processed excipient as directly compressible vehicle. These tablets exhibited rapid disintegration and dissolution rate characteristics and fulfilled the official (I.P) specifications with regard to various physical properties and dissolution characteristics.

CONCLUSION

Cellulose-EC co-processed excipient prepared by kneading method is granular, discrete and free flowing. It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4. It exhibited slight swelling (24%) in water. Cellulose-EC co-processed excipient has excellent flow properties alone and as blends with the selected drug it exhibited excellent to good flow properties. Pioglitazone tablets prepared by direct compression method employing Cellulose-EC co-processed excipient as DCV were of good quality with regard to drug content, hardness, friability and disintegration time. The tablets formulated disintegrated rapidly within 2 min 40 sec. Pioglitazone tablets prepared gave rapid dissolution of the contained drug and fulfilled the official (IP) dissolution rate test specification prescribed. The formulated tablets also gave rapid and higher dissolution of pioglitazone than the commercial tablets tested. Thus Cellulose-EC co-processed excipient developed in this study was found to be a promising directly compressible vehicle for the preparation of compressed tablets and pioglitazone tablets with rapid disintegration and dissolution characteristics could be developed employing the new co-processed excipient.

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