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Formulation and *in-vitro* evaluation of directly compressed controlled release matrices of Losartan Potassium using Ethocel Grade 100 as rate retarding agent

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ABSTRACT

Current study was aimed to develop 200 mg controlled release matrix tablets of Losartan Potassium using Ethocel 100 Premium and Ethocel 100 FP Premium as rate controlling polymer. *In-vitro* studies were performed according to USP Method-I in phosphate buffer (PH 6.8) using pharma test dissolution apparatus. The temperature of the dissolution medium was kept constant at 37 ± 0.5 °C at 100 rpm. Flow properties, physical quality control tests, effect of polymer size and drug-to-polymers ratios were studied using different kinetics models such as 1st-order, zero-order, Hixon Crowell model, Highuchi model and Power law. Difference factor f_1 and similarity factor f_2 were applied for dissolution profiles against Cardaktin® tablets used as a reference formulation. The matrices with polymer ethocel 100 FP Premiums have prolonged the drug release rate as compared to polymer ethocel 100 Premiums. The *n* values matrices with polymer ethocel grade 100 ranged from 0.603 to 0.857 indicating that the drug release occurred by anomalous non fickian diffusion kinetics while then value of reference Cardaktin® tablet was measured as 0.125 indicating that these tablets do not follow power law. The dissolution profiles of test formulations were different than that of reference Cardaktin®. This suggests the polymer Ethocel grade 100 can be proficiently incorporated in fabrication and development of once a day controlled release matrix tablets.

1. Introduction

The of acute and chronic diseases has been managed for many decades by delivery the drugs to the patients using different dosage forms such as pills, tablets, capsules, aerosols, suppositories, creams, ointments and injectable. Remarkable advancements have been achieved in delivering the drugs through other routes but delivery of drugs by oral route is the most preferable (Aggarwal et al., 2013). The conventional oral dosage forms have several disadvantages such as frequents administration of short half-life drug, drug fluctuation in blood and poor patient compliance (Modi et al., 2011). Extended dosage forms follow zero-order drug release kinetics and provides constant amount of drug over an extended duration and optimize the therapeutic effects of the drug (Madhusudhan and Nazeer, 2010; Remington, 2002; Robinson and Lee, 1987). Controlled drug delivery is of mainly two types either dissolution controlled or diffusion controlled (Chien, 1992). Orally administered controlled release devices providing constant drug delivery (Dahiya and Gupta, 2011). Controlled release dosage forms provide benefits such as reducing multiple-dosing, maintaining constant drug level in blood, minimizing wastage of drug. Thus patient can take drug conveniently and improve patient compliance as compared to conventional dosage forms (Pahade et al., 2010). Polymers have been used to modify the drug release rates from different controlled release dosage forms. Polymers have many applications such as taste masking, binding, coating, stabilizing and matrix forming agents used in the development of pharmaceutical dosage forms (Pillai and Ramesh, 2001). In novel drug delivery system, introduction of matrix tablet as sustained release provide new innovation in the pharmaceutical research. It eliminates multifaceted processes like coating and pelletization

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during the process of dosage form development. The rate of drug release can be well controlled by the polymer incorporated (Vidyadhara et al., 2004; Mohammed et al., 1999). Moreover, matrix tablets most frequently used due to their flexibility and cost effectiveness as oral controlled drug delivery systems (Emami et al., 2008). In matrix tablet, drug is uniformly dispersed throughout the polymer matrix. In designing and development matrix devices, different polymeric materials are used such as ethylcellulose, hydroxyproply methylcellulose, poly ethylene oxide and xanthan gum (Raju et al., 2010). Polymer Ethocel is ethylcellulose ether derivatives acts as coating material for granules, matrix forming material for designing of controlled release matrix tablets, act as binder in tablets and used in the preparation of microcapsule (Shah et al., 2012). Metformin HCl sustained release matrices are evaluated using HPMC and HPC as rate altering polymers (Uma and Rathore, 2014). Other authors designed and evaluated controlled release matrices of Flurbiprofen with polymer (Eudragit) and determined the *in-vitro* drug release patterns of various formulated matrices. (Bhateja et al., 2012) investigated the drug release profiles of newly developed sustained release matrices of Aceclofenac. (Husen et al., 2012) evaluated the controlled release matrix tablets of Metoclopramide HCl using different polymers such as guar gum, xanthan gum and carbopol 934. Nicorandil extended release once a day matrices were prepared and evaluated (Pahade et al., 2010). (Enayatifard et al., 2009) prepared and evaluated Diltiazem HCl controlled release matrix tablets using ethylcellulose. Losartan Potassium has inhibitory action on angiotensin II receptors and has short half-life of 2 h. It is used in the management of hypertension, minimizing risks of strokes in hypertensive and patient with left ventricular-hypertrophy (Nayak et al., 2011; Behera et al., 2010).

2. Materials and methods

2.1. Chemicals

Losartan Potassium gifted (Well and Well Pharmaceutical, Islamabad), Cardaktin® Tablets (Hygeia Pharmaceutical, Islamabad, Pakistan) were purchased from local market and were immediate release tablets containing 100 mg of Losartan Potassium as controlled release tablets of Losartan Potassium were not available in the Pharma market of Pakistan. Ethocel 100 Premium and Ethocel 100 FP Premium (Dow Chemical Co., Midland USA), Magnesium Stearate and Spray Dried Lactose (BDH chemical Ltd., Pool England), Sodium Hydroxide (NaOH), Starch and Monobasic Potassium Phosphate (Fluka, Germany) The chemicals used were of analytical grade and were used without any further purification.

2.2. Equipments

Digital Electronic Balance (AX-200, Japan), UV–vis Spectrophotometer (UVIDEC-1610, Shimadzu, Japan), Pharma Test Dissolution Apparatus, (D-63512, Germany), Single Punch Tableting Machine (Erweka AR 400, Germany), Friabilatior (Erweka TA3R, Germany), Hardness Tester (Erweka Apparatus TB24, Germany), Test Tubes, 100 ml Conical Flasks, 100 ml, 200 ml and 1000 ml Volumetric Flasks, Micro-pipette, 100 ml Beakers, 100 ml Graduated Cylinders (Pyrex, Japan).

2.3. Construction of Losartan Potassium analytical curve

Losartan Potassium 100 mg was dissolved in 100 ml of phosphate buffer (pH 6.8) and from this stock solution 50 ml was diluted to 100 ml with the same buffer solution to obtained Ist-dilution. In the same manner 2nd, 3rd, 4th and 5th dilutions were prepared. The dilutions were analyzed spectrophotometrically at measuring wave length of 205 nm.

Table 1
Losartan potassium controlled release matrices using Ethocel Grade 100.

Drug-to-polymer ratio	Ethocel 100 P (mg)	Ethocel 100 FP (mg)	Filler (spray dried lactose) (mg)
10:3	30	–	69
10:3		30	69
10:4	40	–	59
10:4	–	40	59
10:5	50	–	49
10:5	–	50	49

2.4. Tablet formulation

Controlled release matrix tablets containing Losartan Potassium (100 mg) and polymer (Ethocel grade 100) were formulated at dug-to-polymer ratio (D:P) ratios of 10:3, 10:4 and 10:5. The fixed amount of drug and magnesium stearate, *i.e.*, 100 mg and 1 mg, respectively was added. Filler (spray dried lactose) was also incorporated. The sizes of pilot batches were 100 tables of each type of the formulations as given in Table 1.

2.5. Tablet preparation and development

Losartan Potassium, polymer and other excipients were weighed separately with the help of digital electronic balance (AX-200, Japan). Drug and polymer were mixed geometrically using pestle and mortar and was passed through No-32 mesh screen. Lubricant (magnesium stearate 0.5%) was added and again these mixtures were passed twice through the same mesh screen. The powder mixtures were directly compressed into tablets using single punch machine (Erweka, Germany).

2.6. Flow characteristics of different formulations

The flow characteristics of different formulations and of powdered drugs are very important for designing and development of elegant matrices. In order to determine the flow characteristics such as angle of repose, compressibility index and Hausner's ratios were determined according to the standard procedures given in USP (USP, 2007).

2.7. Influence of particle size

The impact of polymers particle size on the drug release rates was studied as Ethocel 100 Premium is available the granular form and Ethocel 100 FP Premium is in the form of fine particles.

2.8. Influence of drug-to polymer ratios

The influence of concentration of polymers or drug-to-polymer ratios was also investigated as the polymer concentration increased from 30 to 50 mg as the drug-to-polymer ratios were increased from 10:3 to 10:5. The polymers concentrations may influence the drug release rates from the polymeric tablets while keeping the drug amounts constant in all matrices.

2.9. Physical characteristic of tablets

Physical characteristics like appearance, thickness, diameter, friability, weight variation and hardness were determined according to standard procedures. Thickness and diameter of 10 tablets was determined by using vernier caliper (Erweka, Germany). Harnesses of 10 tablets were determined with help of

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