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Formulation and evaluation of Losartan Potassium matrix tablets for oral controlled release

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Abstract

The aim of the current study was to design oral controlled release matrix tablets of losartan potassium. Tablets were prepared by direct compression and evaluated for hardness, friability, thickness, drug content and in vitro dissolution parameters. Carbopol 934P and HPMC K 100M (hydroxyl propyl methyl cellulose) were used as the polymers . In vitro release studies were conducted in phosphate buffer pH 6.8 for 24 hours. All the formulations showed controlled release of losartan potassium over a period of 24 hours. The release profile of losartan potassium from all the formulations (except F2, F3, F8 which showed first order release) are close to zero order and follow diffusion dependent release. Irrespective of the polymer type and its concentration, the prepared hydrophilic matrix tablets showed non-fickian (anomalous) release, coupled diffusion and polymer matrix relaxation as the values of release exponent (n) are in between 0.584 and 0.8692. Finally it was clear that HPMC K100M and Carbopol 934P are good candidates for preparing controlled release matrix tablets of losartan potassium.

Key Words: Matrix tablets, Losartan potassium, Controlled release.

Introduction

A typical controlled release system is designed to provide constant or nearly constant drug levels in plasma with reduced dose, frequency of administration and fluctuations in plasma concentrations via slow release over an extended period of time[1]. A Matrix device consists of drug dispersed homogeneously throughout a polymer matrix. Two major types of materials are used in the preparation of matrix devices[2],which include hydrophobic carriers like glyceryl

tristearate, fatty alcohols, fatty acids, waxes, carnauba wax, methyl methacrylate, polyvinyl chloride, polyethylene, ethyl cellulose and hydrophilic polymers like sodium carboxymethylcellulose, hydroxylpropylmethylcellulose (HPMC), sodium alginate, xanthan gum, poly ethylene oxide and carbopols.

Matrix systems offer several advantages relative to other extended release dosage forms like easy to manufacture,versatile,effective, low cost and can be made to release high molecular weight compounds[3]. Since the drug is dispersed in the matrix system, accidental leakage of the total drug components is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release.

Losartan potassium is an angiotensin II receptor antagonist. The drug is readily absorbed from the GI tract, following oral administration. The drug undergoes extensive first pass metabolism, hence its bioavailability is only 32%. The drug has a low elimination half life (1.5 to 2.5hours) and hence it is suitable for oral controlled release. Administration of conventional tablets of losartan potassium may exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site. Accordingly, studies on regulation of drug release by formulating its controlled release systems[4]would be advantageous as it would decrease the side effects and improve the patient compliance.

The current study aims at developing oral controlled release tablets of losartan potassium, using hydrophilic matrices HPMC K100M and Carbopol 934P. The developed formulations were evaluated for weight variation, thickness, hardness, friability and in vitro release studies.

Materials and Methods

Materials

Losartan potassium was obtained as a gift sample from Cipla, Goa. HPMC K 100 M, Carbopol 934P and dicalcium phosphate (S.D. Fine chemicals Ltd., Mumbai) were procured commercially. All other chemicals employed were of analytical grade.

Preparation of Compressed Matrices

Table 1 enlists the composition of different formulations prepared using varying amounts of the polymers (i.e. Carbopol 934P and HPMC K4M) and dicalcium phosphate as the diluent, along with the fixed quantity of magnesium stearate as the lubricant. Drug and the excipients were homogeneously blended and subsequently compressed into flat-faced tablets (460mg, 12.9mm diameter) using single-punch tablet compression machine (Cadmach, India).

Tablets Assay and Physical Evaluation

The tablets were assayed for drug content (n=5) using methanol as the extracting solvent, and the samples were analyzed (5)spectrophotometrically (Elico) at 207nm.

Tablets were also evaluated for hardness (n=5), friability (n=20), weight variation (n=20) and thickness (n=5).

***In Vitro* drug release studies**

Dissolution studies[6]were performed for all the formulations in triplicate, employing USP XXVII paddle method and phosphate buffer pH 6.8 as the dissolution medium at 50 rpm and 37±0.5°C. A 5 ml of sample was withdrawn periodically at suitable time intervals and the volume was replaced with an equivalent volume of the blank dissolution medium. The samples were analyzed spectrophotometrically (Elico) at 207nm.

Data analysis

Release data were analyzed as per zero order, first order, higuchi equation and peppas equation models to asses the drug release kinetics and mechanism of release from the tablets.

Results and Discussion

The assayed content of drug in various formulations varied between 98.9% and 100.9% (mean 99.9%). Tablets weights varied between 457.2 and 462.6 mg (mean 459.4 mg), thickness between 2.20 and 2.32 mm (mean 2.25 mm), hardness between 6.1 and 6.8 Kg/cm²(mean 6.5 Kg/cm²) and friability ranged between 0.29% and 0.53%(mean0.34%). Thus all the physical parameters of the compressed matrices were practically with in control.

Drug release from the various controlled release formulations is indicated in table 2. The correlation coefficient (r) values of the formulations is indicated in table 3. In the current study, the values of release rate exponent (n), calculated as per the algorithm proposed by Peppas and Korsemeyer[7], ranged between 0.5840and 0.8962 (table 4). The values of zero order release rate constant k_o(mg/hr) are indicated in table 4. The amount of losartan potassium released from all the formulations until 24hr ranged between 93.4% and 100.3% indicating almost complete drug release from the formulations.

Table 1. Composition of Losartan Potassium Tablets*
Ingredients(mg/tablet)

Formulations	Drug	Carbopol	HPMC	Mag.stearate	Dicalcium phosphate
F1	100	150	-------	5	q.s. 460
F2	100	-------	150	5	q.s. 460
F3	100	50	100	5	q.s. 460
F4	100	50	150	5	q.s. 460
F5	100	50	200	5	q.s. 460
F6	100	100	100	5	q.s. 460
F7	100	100	150	5	q.s. 460
F8	100	100	200	5	q.s. 460
F9	100	150	100	5	q.s. 460
F10	100	150	150	5	q.s. 460
F11	100	150	200	5	q.s. 460

*q.s. Indicates quantity sufficient

Table 2. Dissolution data(mean± S.D., n=3) of losartan potassium matrix tablets

Formulations	1hr	4hr	8hr	12hr	18hr	24hr
F1	11.7±1.22	51.3±0.75	63.4±0.69	74.7±1.9	93.4±1.8	100.1±1.2
F2	12.9±1.25	52.3±1.56	68.9±0.88	82.4±1.5	97.7±0.76	100.1±0.42
F3	13.5±1.2	55.3±1.1	71.3±1.56	82.9±1.14	98.9±1.6	99.7±1.02
F4	5.9±1.52	27.5±0.82	53.8±1.03	65.5±1.4	93.49±0. 6	100.2±1.01
F5	4.6±0.93	25.4±0.71	49.9±1.23	73.4±0.82	91.5±0.82	99.2±1.19
F6	10.18±0.24	41.6±075	60.6±1.9	75.6±0.91	99.5±0.43	100.26±0.79
F7	6.5±0.66	27.2±0.43	48.9±0.77	69.1±1.01	88.2±0.99	98.9±1.23
F8	4.08±0.82	23.9±0.26	45.3±0.72	63.3±1.43	86.6±0.42	98.6±0.99
F9	6.2±0.78	31.2±0.99	51.1±1.07	65.5±1.2	90.6±0.63	98.9±1.25
F10	3.8±1.03	230.3±0.5	42.02±0.70	60.3±1.52	87.2±1.6	96.5±1.3
F11	3.2±0.95	21.17±1.75	39.5±0.66	55.7±1.52	68.9±1.05	93.4±0.52

Table 3. Correlation Coefficient (r) values (from dissolution rate test) of Losartan Potassium tablets

Formulation	Zero order(r)	First Order(r)	Higuchi equation(r)	Peppas equation(r)
F1	0.9104	0.6416	0.9724	0.9282
F2	0.9055	0.9238	0.9975	0.9439
F3	0.8818	0.9323	0.9408	0.9189
F4	0.9553	0.9240	0.9925	0.9864
F5	0.9411	0.9275	0.9832	0.9774
F6	0.9046	0.7625	0.9739	0.9613
F7	0.9604	0.8918	0.9919	0.9851
F8	0.6705	0.8951	0.9921	0.9808
F9	0.9635	0.8942	0.9955	0.9762
F10	0.9792	0.9226	0.9898	0.9772
F11	0.9715	0.8687	0.9888	0.9677

Table 4. Dissolution parameters of Losartan potassium matrix tablets

Formulations	n (peppas eqn.)	k_o(mg/hr)	T50(hr)	T90(hr)
F1	0.6197	0.0387	3.9	15.9
F2	0.6439	0.045	3.78	14.30
F3	0.5840	0.0344	3.8	14.85
F4	0.8102	0.0432	7.5	17.17
F5	0.8566	0.0447	8.9	17.20
F6	0.7255	0.0391	4.8	15.95
F7	0.8352	0.0416	8.35	18.25
F8	0.8692	0.0431	8.95	19.50
F9	0.8304	0.0410	7.85	17.95
F10	0.8644	0.0423	9.78	19.20
F11	0.8231	0.0463	10.20	23.50

Dissolution data of the various matrix tablets is indicated in table 2. The formulated matrix tablets released the drug for 24 hours and follow near zero order release (formulations: F1, F4, F5 to F7, F9 to F11). The formulations: F2, F3and F8 followed first order release. The drug release from the HPMC K100M and Carbopol 934P based matrix tablets decreased with the increase in the polymer level. This effect might be ascribed to an increase in the extent of gel formation in the diffusion layer[6] . All the formulations (F1 to F11) showed marked variation in the drug release at the end of 12 hours. Formulation F3 showed highest release (82.9%) and formulation F11 least release (55.7%) at the end of 12 hours. However, all the formulations (F1 to F11) achieved complete release of the drug (93.4% to 100.3%) at the end of 24 hours. Hence, all the formulations (F1 to F11) were optimized as they achieved slow controlled release for a period of 24 hours.

The values of correlation coefficient(r) and release exponent (n) are indicated in the tables 3 and 4 respectively. Upon comparison of correlation coefficient values (r) of all the optimized formulations, it was indicated that the release rates are closer to zero order, in the case of formulations: F1, F4 to F7, F9, F10 and F11 where as first order in the case of formulations : F2, F3 and F8.

Rate of drug release[8]tended to decrease with increase in the content of either Carbopol or HPMC. The viscosity of the gel layer around the tablet increases with the increase in the hydrogel concentration, thus limiting the release of the active ingredient. As the carboxyl groups of Carbopol dissociate highly at pH above the pKa (6 ± 0.5) electrostatic repulsions between the negatively charged carboxyl groups cause uncoiling and expansion of molecules, resulting in polymer swelling and consequent gel formation[4].

The values of T50 (time taken for 50%release of drug)and T90 (time taken for 90% release of drug) are indicated in table 4.The value of T50 enhanced markedly from 3.78 hours, observed at low levels of both the polymers, to as high as 10.2 hr, observed at high levels of both the polymers (table 4). Similarly,the value of T90 enhanced markedly from 14.3hours, observed at low levels of both the polymers, to as high as 23.5 hr, observed at high levels of both the polymers (table 4). This indicated considerable release retarding potential of the polymer for losartan potassium. Several kinetic models describe the drug release from the immediate and modified release dosage forms. The model that best fits the release data is evaluated by

correlation coefficient(r). The r value was used as criteria to choose the best model to describe the drug release from the controlled release tablets. The r value of the formulations from various models is indicated in table 3. The r value obtained after fitting the drug release data to the higuchi equation indicates that the drug release mechanism from these tablets was diffusion controlled. Irrespective of the polymer type and its concentration, the prepared hydrophilic matrix tablets showed non-fickian (anomalous) release, coupled diffusion and polymer matrix relaxation[8] as the values of release exponent (n) are in between 0.584 and 0.8692.

Hence, all the formulations (F1 to F11) were optimized (suits for commercialization) as they achieved slow controlled release for a period of 24 hours, hence they can be used as once a day controlled release tablet formulation.

Conclusion

From the foregoing investigation it may be concluded that the release rate of drug from the matrix tablets can be governed by the type of the polymer and the concentration of the polymer employed in the preparation of the tablets. Slow, controlled and complete release of losartan potassium over a period of 24hr was obtained from the matrix tablets formulated employing HPMC K 100 M and Carbopol 934P. Hydrophilic matrix tablets of losartan potassium, can successfully be employed as a once a day oral controlled release drug delivery system.

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