EFFECT OF NATURAL AND SYNTHETIC POLYMERS ON DRUG RELEASE IN THE FORMULATION EXTENDED RELEASE TABLETS OF ISONIAZID

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ABSTRACT: The objective of the study was to formulate controlled release matrix tablets of losartan Potassium by using a combination of hydrophilic synthetic polymer like poly (ethylene oxides) and natural gums like xanthan gum, karaya gum and guar gum. A combination of synthetic hydrophobic polymers like methacrylates with synthetic hydrophilic polymer like poly (ethylene oxide) was also used in the preparation of matrix tablets and evaluated for their influence on controlled drug release. The matrix tablets were prepared by direct compression process and evaluated for hardness, weight variation, friability, swelling index and for *in-vitro* release of the drug. Preliminary evaluations showed that matrix tablets containing xanthan gum, guar gum and sodium alginate alone or in combination could not efficiently retard the drug release for prolonged period of time. The tablets containing combination of natural polymers and poly (ethylene oxides) and also methacrylates and poly (ethylene oxides) exhibited controlled release for a prolonged period of time. All the physical characteristics evaluated for the tablets were found to be within the acceptable limits.

Keywords: Losartan potassium, Matrix tablets, Natural gums, Synthetic polymers.

INTRODUCTION

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the polymer may undergo relaxation process so that the polymer chains become more flexible and the matrix swells. This could allow the encapsulated drug to diffuse rapidly out of the matrix.

On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling . In the preparation of matrix tablets when a combination of hydrophilic polymers and gums are used, when the tablet is exposed to the dissolution medium the polymers absorb the medium and swells by interacting with each other. This may result in an increase in the viscosity, which

becomes greater than the viscosity of each polymer individually. This can be used for extending the drug release for prolonged period of time.

From the wide choice of possible matrix materials used in the preparation of controlled release formulations are , poly (ethylene oxides), methacrylic polymers, guar gum, xanthan gum, sodium alginate, chitosan, poly (acrylic acids), etc. Among the variety of hydrophilic polymers used, poly (ethylene oxides) (PEO) is one of the most important material used in the preparation of the matrix tablets because of its non-toxicity, high water-solubility and swellability.

In a research work it was proved that poly (ethylene oxides) can be used as alternative to HPMC for the preparation of matrix tablets. . Methacrylic polymers (Eudragit) also attracted researchers in fabricating controlled release dosage forms, due to their high chemical stability, good compatibility properties and their ability to sustain the drug release. Natural gums hydrate and swell up on contact with water and these have been used for the preparation of controlled release dosage forms. Their cost effectiveness and regulatory acceptance is also another reason for using them as excipients.

Guar gum (the groundendosperm of guar beans) a polysaccharide derivative with glycoside linkage has been used as matrix former for controlled release of various drugs [8-9]. Xanthan gum (derived from the bacterial coat of *Xanthomonas campestris*), is a high molecular weight extracellular polysaccharide which was initially used as a suspending agent but later it was reported to function as a matrix retardant in solid dosage forms. [10-11] Sodium alginate is a water soluble salt of alginic acid. It is a natural polysaccharide and has been used as a matrix for entrapment of drugs and macromolecules .It's a non-toxic nature and ease of handling makes it an excellent release retardant material.

Up on exposure to aqueous fluids, the natural polymers hydrate to form a viscous gel layer through which the drug is released by diffusion and/or erosion of the matrix. The major drawback of using natural drugs alone in the matrix tablet formulations is, they could not retard the drug release more than 6-10 hrs [2].

Hence, the combination of the natural polymers with synthetic polymers was used in the preparation of matrix tablets in the present study. In the successful formulation of matrix tablets several factors, such as the polymer type and concentration, the drug particle size, presence of additives and excipients in the final formulation can modify the drug release from the matrices [13]. Losartan potassium is a potent, highly specific angiotensin II type 1 receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 h.

The present research work aimed at developing and optimizing an oral controlled release matrix tablet formulations of losartan potassium by employing different types of natural and synthetic polymers. The synergistic effect of mixture of natural gums and synthetic polymer like Poly (ethylene oxide) and poly methacrylates on retarding the drug release of freely soluble drug to achieve steady state release was evaluated.

MATERIALS AND METHODS:

Materials: Losartan Potassium was kindly supplied from Dr.Reddy's Laboratories Ltd (Hyderabad), PEO's {Polygon WSR 303}, Methacrylates (Eudragit L 100 & S 100) were obtained as gift samples from Dow chemical's Asia Pvt., Ltd., Mumbai. Xanthan gum, karayagum and guar gum were procured commercially from Arrow chemicals Pvt. Ltd, Mumbai. All other chemicals were of analytical grade and were used as received.

Preparation of Matrix Tablets: The matrix tablets containing losartan potassium was prepared by a direct compression process. POLYOX WSR 303, Eudragit L 100, Eudragit S 100, xanthan gum, karaya gum and guar gum were used as swellable polymers which control drug release. The controlled release tablet formulations consisted of a drug and polymer were prepared in different ratios. Microcrystalline cellulose was added as diluent at different proportions to the matrix tablets to achieve uniform weight.

The drug, polymers and diluent were screened through #45 sieve and preblended in a lab scale double cone blender. The lubricant such as magnesium stearate in the concentration of 0.5 % was added and the blend was mixed again prior to compression. The drug blends were directly compressed by using cadmach rotary compression machine using 9 mm flat punches with a constant compression force. The different forms of tablets compressed together with their compositions are given in **Table 1**.

Evaluation of Tablets: The prepared tablets were evaluated as per standard procedure for weight variation (n = 20), hardness (n = 6), drug content, thickness (n = 20), friability and for water uptake characteristics. The hardness of the matrix tablets was determined by using a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). Friability test (n = 20) was conducted using Roche friabilator. Thickness of the tablets was measured by digital Vernier caliper. Drug content was determined by taking an accurately weighed amount of powdered losartan potassium from the tablets (100 mg) and was extracted with water and the solution was filtered through 0.45-µ membrane. The absorbance was measured at 205nm after suitable dilution using digital UV double beam spectrophotometer (Elico model SL-218).

TABLE 1: COMPOSITIONS OF VARIOUS MATRIX TABLET FORMULATIONS OF LOSARTAN POTASSIUM

Ingredients [mg/tablet]	FORMULATIONS									
	FL 1	**FL2**	**FL3**	**FL4**	**FL5**	**FL6**	**FL7**	**FL8**	**FL9**	**FL10**
Losartan Potassium	100	100	100	100	100	100	100	100	100	100
Polyox-WSR 303	75	75	75	75	75	75	75	75	75	75
Eudragit L 100	50	75	---	---	---	---	---	---	---	---
Eudragit S 100	---	---	50	75	---	---	---	---	---	---
Xanthan Gum	---	---	---	---	50	75	---	---	---	---
Karaya gum	---	---	---	---	---	---	50	75	---	---
Guar Gum	---	---	---	---	---	---	---	---	50	75
Microcrystalline cellulose	73.5	48.5	73.5	48.5	73.5	48.5	73.5	48.5	73.5	48.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total wt of tablet (mg)	300	300	300	300	300	300	300	300	300	300

Swelling behavior of Matrix Tablets: The extent of swelling for the matrix tablets were measured in terms of % weight gain by the tablet. The swelling behavior for the formulation containing natural gums was studied. One tablet from each formulation was kept in a petri dish containing pH 6.8 phosphate buffer. At the end of 1 hr, the tablet was withdrawn, soaked with tissue paper, and weighed. The process was continued till the end of 24 hrs. % weight gained by the tablet was calculated by formula;

S.I = {(Mt-Mo) / Mo} X 100,

Where, S.I = swelling index, Mt = weight of tablet at time't' and Mo = weight of tablet at time t = 0.

The results of swelling behavior of matrix tablets are depicted in **table 2**.

TABLE 2: SWELLING CHARACTERISTICS OF VARIOUS MATRIX TABLET FORMULATIONS OF LOSARTAN POTASSIUM

Formulation	Swelling Index(%) at various time intervals (Hrs)		
	2	6	12
FL6	11.3	47.9	80.6
FL8	10.2	47.1	71.2
FL10	19.1	58.3	69.3

***In vitro* Drug Release Characteristics:** Drug release from the matrix tablets was assessed by dissolution test (n = 6) using USP type II dissolution apparatus equipped with paddles at 37ºC ±0.5ºC with an rpm of 75. The test was performed using 900 ml of 0.1 N HCL (for 2hrs) and phosphate buffered solution, pH 6.8 (up to 24 hrs) as dissolution media. Dissolution studies were carried out in triplicate, maintaining the sink conditions for all the formulations. A 5 ml aliquot of samples were withdrawn at regular time intervals, filtered and assayed spectrophotometrically at 205 nm. To analyze the mechanism of drug release from the matrix tablets, data obtained from the drug release studies were analyzed according to the following equations of the First-order model, Higuchi model, and the Korsmeyer-Peppas model respectively.

$$InQ=k.t \quad \text{----------1}$$

$$Q = k.t^{½} \quad \text{----------2}$$

$$M_t/M_\alpha = Kt^n \quad \text{----------3}$$

where Q in the equation (1) is Cumulative percent drug remained, while Q in the equation (2) is Cumulative percent drug released, where *Mt*/*Mα* is the fraction of drug released, *t* is the release time and *k* is the constant incorporating the structural and geometrical characteristics of the release device. The values of *n* were obtained by linear regression analysis. A value of *n*=0.45 indicates Case I (Fickian) diffusion or square root of time kinetics, 0.45<*n*<0.89 indicates anomalous (non-Fickian, drug diffusion in the hydrated matrix and the polymer relaxation,) diffusion, *n*=0.89 indicates Case II transport and *n*>0.89 indicates Super Case II transport . Linear regression analysis was performed for all these equations and regression coefficients (R^2) were determined.

Stability Studies: Stability studies on the optimized matrix tablets were carried out as per ICH guidelines at 25ºC ±2ºC/60% ± 5% RH and 40ºC ±2ºC/75% ± 5% RH for 6 months by storing the samples in stability chamber. Further, the matrix tablets were evaluated for appearance, weight variation, hardness, drug content and for *in vitro* drug release profiles over a period of 6 months.

RESULTS AND DISCUSSION: All batches of Losartan potassium matrix tablets were manufactured under similar conditions to avoid the processing variables. The prepared tablets were subjected to various evaluation tests such as weight uniformity, hardness, drug content, friability and thickness. The formulated matrix tablets met the pharmacopoeial requirement in uniformity of weight, hardness, percentage friability

and thickness. All the results obtained for the physical parameters (**table 3**) were satisfactory and within the limits.

TABLE 3: PHYSICAL PARAMETERS OF VARIOUS MATRIX TABLET FORMULATIONS OF LOSARTAN POTASSIUM

Formulation	Weight Uniformity (mg) ± S.D (n = 20)	Hardness (Kg/cm²) (n = 6) ± S.D	Friability (%) (n = 20)	Drug Content (%) (n=6) ± S.D
FL1	300 ± 1.24	4.5 ± 0.25	0.21	98.9 ± 0.50
FL2	301 ± 0.99	4.5 ± 0.50	0.12	99.3 ± 0.42
FL3	300± 1.68	4.6 ± 0.40	0.29	99.4 ± 0.09
FL4	300 ± 1.55	4.5 ± 0.56	0.19	98.8 ± 0.12
FL5	301 ± 2.01	4.4 ± 0.50	0.23	100 ± 0.08
FL6	300 ± 1.15	4.6 ± 0.29	0.12	100 ± 0.21
FL7	301 ± 1.05	4.5 ± 0.50	0.28	99.3 ± 0.24
FL8	300 ± 1.69	4.5 ± 0.30	0.14	99.3 ± 0.09
FL9	300 ± 1.88	4.4 ± 0.40	0.24	99.1 ± 0.09
FL10	301 ± 1.92	4.5 ± 0.50	0.23	99.4 ± 0.06

All formulations of losartan potassium with different polymer compositions were within the weight range of 300-302 mg. Friability loss for all the formulations were in the range of 0.29 to 0.36 and the drug content in all the formulations were uniform and was in the range of 98-100 %. The hardness of all the formulations were maintained in the range of 4.0 to 4.8 (Kg/cm²). The swelling behavior of the selected matrix tablets (Formulations L6, L8, L10 & L12) was studied. The results of the swelling behavior are shown in **Figure 1 & 2**. The swelling behavior indicates the rate at which the matrix tablet absorbs water from dissolution media and swells. The water uptake and swelling started slowly and continued for 13 hours.

Constant and prolonged release of drug will occur in such situation because the increase in diffusion path length due to swelling of the matrix. The formulation containing xanthan gum and guar gum exhibited a high degree of swelling when compared with the formulations containing karaya gum and sodium alginate. Hence, the drug release was extended for prolonged time for the formulation containing xanthan and guar gum.

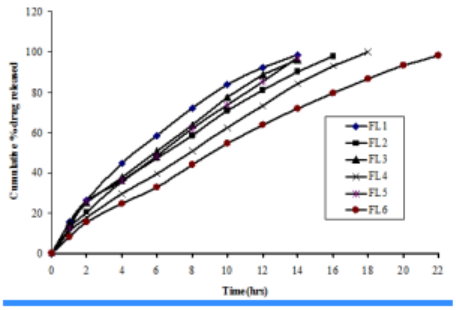

FIGURE 1: DRUG RELEASE PROFILES OF CONTROLLED RELEASE MATRIX TABLET FORMULATIONS OF LOSARTAN POTASSIUM

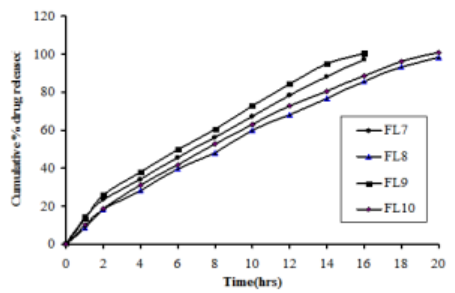

FIGURE 2: DRUG RELEASE PROFILES OF CONTROLLED RELEASE MATRIX TABLET FORMULATIONS OF LOSARTAN POTASSIUM

The tablets appeared swollen from the beginning and a viscous gel layer was formed when they came into the contact with the dissolution medium**.** The *in vitro* drug release studies were conducted for all the matrix tablet formulations. The tablets extended the drug release from 10hrs to 22hrs. In order to investigate the release mechanism, the data were fitted to models representing first-order and Higuchi's square root of time. From the **table 4**, it is concluded that all the fabricated tablets followed Higuchi release kinetics.

TABLE 3: *IN VITRO* PHARMACOKINETIC PARAMETERS OF VARIOUS MATRIX TABLET FORMULATIONS OF LOSARTAN POTASSIUM

Formulations	First order constants (hr^{-1})	Correlation coefficient (R^2)	Dissolution rate constants ($mg/hr^{1/2}$)	Correlation coefficient (R^2)	Peppas constant (n)	Correlation coefficient (R^2)
FL 1	0.268	0.980	32.48	0.996	0.74	0.996
FL 2	0.152	0.986	25.62	0.997	0.69	0.987
FL 3	0.116	0.991	30.12	0.987	0.71	0.990
FL 4	0.199	0.996	26.62	0.999	0.64	0.991
FL 5	0.110	0.995	34.99	0.997	0.63	0.980
FL 6	0.087	0.989	24.32	0.982	0.54	0.993
FL 7	0.238	0.980	38.07	0.995	0.70	0.992
FL 8	0.151	0.996	32.69	0.989	0.65	0.988
FL 9	0.138	0.994	35.42	0.976	0.75	0.992
FL 10	0.195	0.996	28.51	0.986	0.57	0.992

Further, to understand the drug release mechanism, the data were fitted to Peppas exponential equation. In the present study it was observed that all the fabricated tablets followed non-fickian diffusion mechanism (Table 3) which indicates the drug release through diffusion and polymer relaxation. The drug release from the matrix tablets containing PEO'S and eudragits (Formulations FL2 & FL4) showed linear drug release over a period of 18 hrs. For these formulations the initial burst release of the drug was not observed. This may be due to the presence of insoluble eudragit in the matrix which prevented the faster drug diffusion due to the formation of rigid complex [6 & 18] .

The n value calculated from Korsmeyer model was in the range of 0.67-0.74 indicating anomalous or non-fickian transport. Therefore, both diffusion and erosion mechanisms influenced the release of losartan from matrix tablets. The drug release form the tablets containing PEO and xanthan gum (Formulations L5 & L6) showed controlled release up to 22 hrs than the formulations with karaya gum, guar gum and sodium alginate.

This is due to high degree of swelling and slow erosion due to polymer relaxation for xanthan gum than other gums which has been observed from the swelling index studies. The critical value of 'n' calculated from korsmeyer-peppas model for determining the drug release mechanism for these formulations indicated non-fickian diffusion i.e., the drug release is by diffusion from the hydrated matrix and by polymer relaxation. The drug release from the tablets containing PEO, karaya gum and guar gum was extended up to 18 hrs (Formulations L7 - L10).

It was also observed that increase in the concentration of gums, the drug release was extended. This is due the hydrophilic nature of the poly (ethylene oxide) and gums. These tablets showed greater water uptake which resulted in the formation of highly viscous gel layer around the tablet. The formed gel layer resulted in the longer diffusional path length, there by retarding the drug diffusion. The critical value of 'n'

calculated for these formulations indicated non-fickian diffusion i.e., the drug release is by diffusion from the hydrated matrix and by polymer erosion.

The stability studies on selected formulations were carried out for 6 months as per ICH guidelines (Formulations L6, L8 & L10). Under the specific storage conditions, no significant changes in the physicochemical properties viz., weight of the tablet, hardness, friability and drug content of losartan potassium matrix tablets was observed. The result of stability tests suggested that losartan potassium release properties from the prepared tablets were stable under the above storage conditions and no significant changes in their physical attribute was observed.

CONCLUSIONS:

Losartan Potassium controlled release matrix tablets were successfully formulated using the combinations of poly (ethylene oxide) with eudragits and natural gums for delivery of drug over an extended period of time. Previous studies have shown that natural gums like xanthan gum, guar gum, karaya gum and sodium alginate alone in the tablets cannot efficiently control the drug release for prolonged period of time.

This study demonstrates that the combination of hydrophilic natural gums and hydrophobic Eudragits with high molecular weight synthetic polymer like poly (ethylene oxide) led to prolonged release of the drug up to 22 hrs. An important feature of this system is the potential for generating constant drug release.

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