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DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE LOSARTAN POTASSIUM FORMULATION USING DIFFERENT POLYMERS

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ABSTRACT

The present study was undertaken to develop and evaluate controlled release formulations of Losartan potassium by using different polymers in various drug to polymer ratios [1:1, 1:2 &1:3]. Polymers used were Eudragit RS100, Eudragit L100, Eudragit S100, Ethyl cellulose and Hydroxypropylmethylcellulose (HPMC). Fourier Transform Infrared spectroscopy (FT-IR) as well as Differential Scanning Calorimetry (DSC) studies revealed no chemical interaction between the drug and polymer used. The micromeritic properties of the prepared formulations proved that by increasing the ratio of the polymer in the blend, it was followed by decreasing the angle of repose (from 40.20 0 of the plain drug to 29 0), Carr,s index (from 31.40% of the plain drug to 9%), Hausner ratio (from 1.46 of the plain drug to 1.02). Drug release from the prepared formulations was followed at three pH values [1.0, 6.8 &7.4] representing the main segments of G I T. It was revealed that by increasing the concentration of the polymer in the blend a retarding effect of the drug release was observed in the orded 1:3> 1:2>1:1. Mixing the plain drug with solid dispersion system of Eudragit L100 (that offers drug release at pH6.8) and solid dispersion system of Eudragit S100 (that offers drug release at pH7.4) in a physical mixture offers both immediate and controlled release thus increase the patient compliance.

KEYWORDS: Losartan potassium, solid dispersions, controlled release.

1 INTRODUCTION

The objective of an ideal drug delivery systems is to deliver an adequate amount of drug for an extended period for its optimum therapeutic activity. Most drugs are inherently not long- lasting in the body, and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity.[1]

Controlled release dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administration.[2] The most important aim for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance. Losartan potassium is an orally active angiotensin-II receptor antagonist used in treatment of hypertension due to mainly blockade of AT1 receptor.[3]

Losartan potassium is widely used to delay progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes[4], and microalbuminuria (>30mg/ 12h) and proteinuria(>900mg/ 24h). Losartan potassium is freely soluble in water, slightly soluble in acetonitrile and also soluble in isopropyl alcohol. It is readily absorbed from gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half life ranges between 1.5-2.5 hours.

Administration of convential tablets of Losartan potassium may exhibit fluctuation in the plasma drug levels, resulting either in manifestation of side effects and reduction in drug concentration at the receptor site. Accordingly, studies an regulation of drug release by formulating its controlled release system[1,5-7], would be advantageous as it would decrease the side effects and improve patient compliance. Administration of Losartan potassium in a sustained release dosage form with dual characteristics, that is, burst release, followed by an extended release over 8 hours would be more desirable; as these characteristics would allow rapid onset followed by protracted therapeutic effects.

Different techniques were used to control the release of Losartan potassium, these include the development of floating tablets[8], preparation of matrix tablets or beads.[9] The current study aims at developing oral controlled release formulations containing Losartan potassium in combination with Eudragit RS100 (pH-independent polymer), Eudragit L100, Eudragit S100 (pH –dependent polymer), Ethyl cellulose (EC) as well as hydroxypropylmethylcellulose (HPMC). The prepared

matrices were in concentrations of (1:1, 1:2 and 1:3) drug to polymer ratios and the solid dispersion was the technique of choice for the preparation of such systems.

2- MATERIALS AND METHODS

2.1. Materials

Losartan potassium was a gift sample kindly supplied by Mepaco pharmaceuticals industries, Egypt.
Eudragit RS100, Eudragit L 100 and Eudragit S 100 and (HPMC) Hydroxypropylmethylcellulose were purchased from RÖhmPharma GMPH, Darmstadt (Germany).
Ethyl cellulose was obtained from Sigma- Aldrich Chemi (Germany).
All other reagents were analytical or pharmaceutical grade and used as received.

2.2 Preparation of solid dispersion

Five formulations based on the solid dispersion technique were prepared containing Losartan potassium with Eudragit RS100, EudragitL100, EudragitS 100, Ethyl cellulose and Hydroxypropylmethylcellulose (HPMC) (in ratios of 1:1, 1:2 and 1:3) drug to polymer. The method was achieved by dissolving the required weight of polymer in a mixture of ethanol: dichloro-methane in a ratio of (1:1) in a glass vessel at 40 oC using Vortex Mixer (Maxi mix 11, Thermolyne Corporation, U.S.A.). The mixture was stirred at 400 rpm in a water bath (KOWELL N4, Germany) over 20 min. The drug was gradually added to the above mixture with stirring tuntil completely dissolved. Stirring was continued on a water bath until the solvent mixture was evaporated. The dry film obtained was pulverized and passed through a 60 mesh sieve in order to obtain a homogenous particle size (10, 11). Table (1) shows the different formulations (F1-F16) which represents different drug to polymer ratios.

2.2.1 Preparation of a physical mixture containing plain Losartan and solid dispersion systems of Eudragit L100(1:3) and Eudragit S100(1:3).

This mixture is prepared by well mixing of 50 mg of plain Losartan potassium with a weight equivalent to 25mg Losartan from solid dispersion system of Eudragit L100 as well as a weight equivalent to 25mg Losartan from solid dispersion system of Eudragit S100 (both solid dispersions were in the ratio of 1:3 drug to polymer ratio).

Table 1: Composition of different formulations containing Losartan potassium- polymer in different ratios.

Polymer used	Formula code	(Losartan : polymer) ratio
Eudragit RS100	F1	1:1
	F2	1:2
	F3	1:3
Eudragit L100	F4	1:1
	F5	1:2
	F6	1:3
Eudragit S100	F7	1:1
	F8	1:2
	F9	1:3
Ethyl cellulose	F10	1:1
	F11	1:2
	F12	1:3
HPMC	F13	1:1
	F14	1:2
	F15	1:3
Physical mixture	F16	50mg Losartan + 100mg of F6 +100mg of F9

3. Pre formulation studies of the prepared Solid disperssions

3.1 FTIR study

The compatibility between drug and resins was detected by IR spectra obtained on FTIR Tensor 27(Bruker). The pellet was prepared on KBr pellet press (HORIZON WC-56). The spectra were recorded over the wave number range of 4000 to 500cm-1**.**

3.2 DSC study

Further the compatibility between drug and polymer was detected by DSC study. Thermograms were obtained by using a differential scanning calorimeter (DSC6, Perkin-Elmer, USA) at a heating rate 10 oC /min over a temperature range of (35-250 oC). The sample was hermetically sealed in an aluminium crucible. Nitrogen gas was purged at the rate of 10 ml/ min for maintaining inert atmospheres.

4. Micromeritic properties of free losartan and solid dispersions

4.1 Angle of repose

Angle of repose was determined using fixed funnel method. The accurately weighed samples were taken in a funnel which was held in place with a clamp on a ring support over a glass plate. The height of the funnel was

adjusted in such away that the tip of the funnel is just touching the apex of the heap of the sample. Approximately 1 gm of the sample is transferred into the funnel keeping the orifice of the funnel blocked by the thumb. The sample was allowed to flow through the funnel freely onto the surface. When the sample is emptied from the funnel, the angle of the heap to the horizontal plane is measured using the following equation.[12]

Angle of repose (θ) = tan-1 (h/r)

Where, "h" is height of the sample cone, and "r" is the radius of the sample cone.

4.2 Bulk density

Tapped bulk density (TBD) as well as Loose bulk density (LBD) were determined by using 5 gm of the sample from each prepared formula previously lightly shaken to break any aggregates formed; and was placed into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from a height of 2.5 cm at 2 second intervals. The reading of tapping was continued until no further change in the volume of sample was noticed. TBD and LBD were de termined by using the following equations.[13]

TBD= weight of the sample (W) / tapping volume of the packing (V)
LBD= weight of the sample (W) / volume of the packing (V)

4.3 Carr's index

The Carr,s index (CI) is an indication of the compressibility of the powder. It is based on the apparent bulk density and the tapped density, the percentage compressibility of the sample mixture was determined by the following formula.[14]

$$CI = \frac{BD - TD}{BD} \times 100$$

Where, BD is the freely settled bulk density of the sample, and TD is the tapped bulk density of the sample.

4.4. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by.

H = BD / TD

Where, BD is the freely settled bulk density of the sample, and TD is the tapped bulk density of the sample.[15-17]

4.5. Drug content estimation

A certain amount from each formulation was weighed and ground in a mortar with a pastele to get fine powder. From the mixture a quantity equivalent to 50 mg of Losartan potassium was accurately weighed and extracted thoroughly with 100 ml water by sonication for 30 min.[18, 19] The solution was filtered through 0.45 µm membrane filter and then suitably diluted. Absorbance of the obtained solution was measured using UV spectrophotometer (Thermo, Evo300pc, U.S.A) at wavelength of 234 nm.

4.6. *In –vitro* release studies

In –vitro release of prepared samples was carried out Using type II USP dissolution apparatus (paddle type, Coply, NG42JY, Nottingham, UK), the release medium 900ml of either pH1.2 for 3 hrs, pH 6.8 as well as pH 7.4 for 6-15 hrs placed into the dissolution flask maintaining temperature at 37 ± 0.50C and 50 rpm. Samples were filtered through 0.45 membrane filter and then suitably diluted with the medium. The withdrawn samples were replaced every time with the same quantity of the fresh media. The collected samples were analyzed at 234 nm using dissolution medium as a blank. For each experiment three determinations were performed and the values were expressed as the mean ± SD.

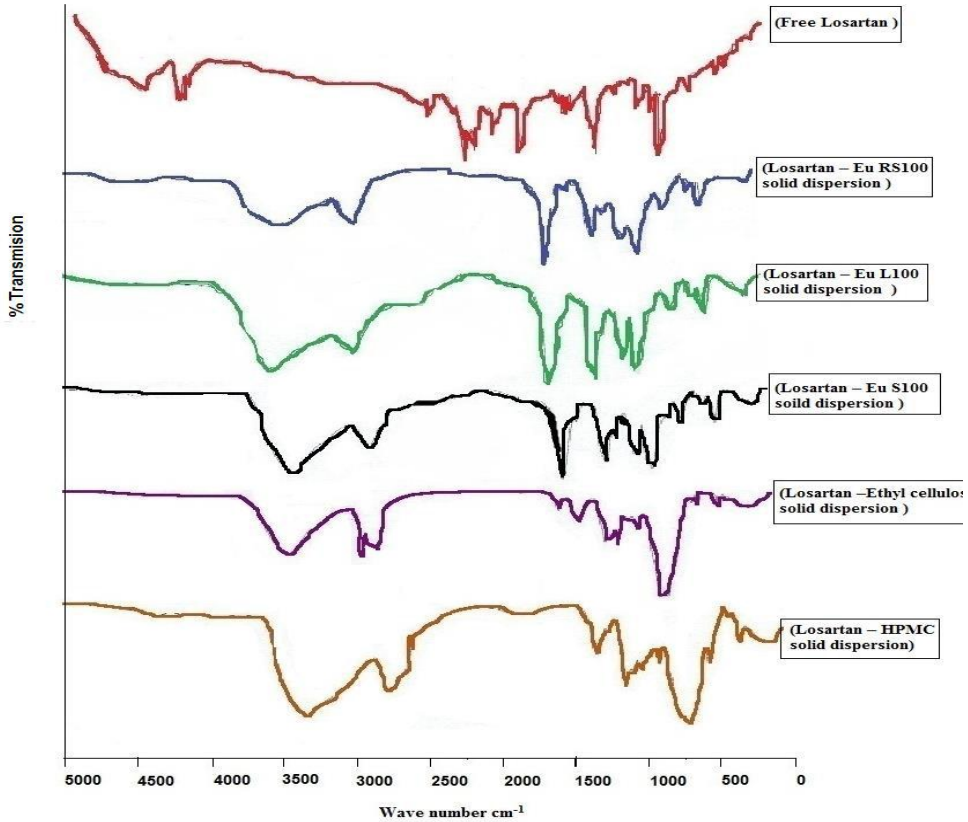


Fig.1: FTIR spectra of plain Losartan potassium and the proposed formulations.

5.1.2 DSC study

Further the compatibility between drug and the used polymers was detected by DSC study. Thermograms were obtained by using a differential scanning calorimeter (Fig.2). This study was performed to investigate the physical state of Losartan potassium in the proposed formulations and also to confirm the compatibility between the drug and polymers used. Pure Losartan potassium showed a single sharp endothermic melting peak at 87.59 0C, which was unaltered in the thermogram of different polymer composition formulations evidencing the absence of any interactions between the drug and chosen polymers.

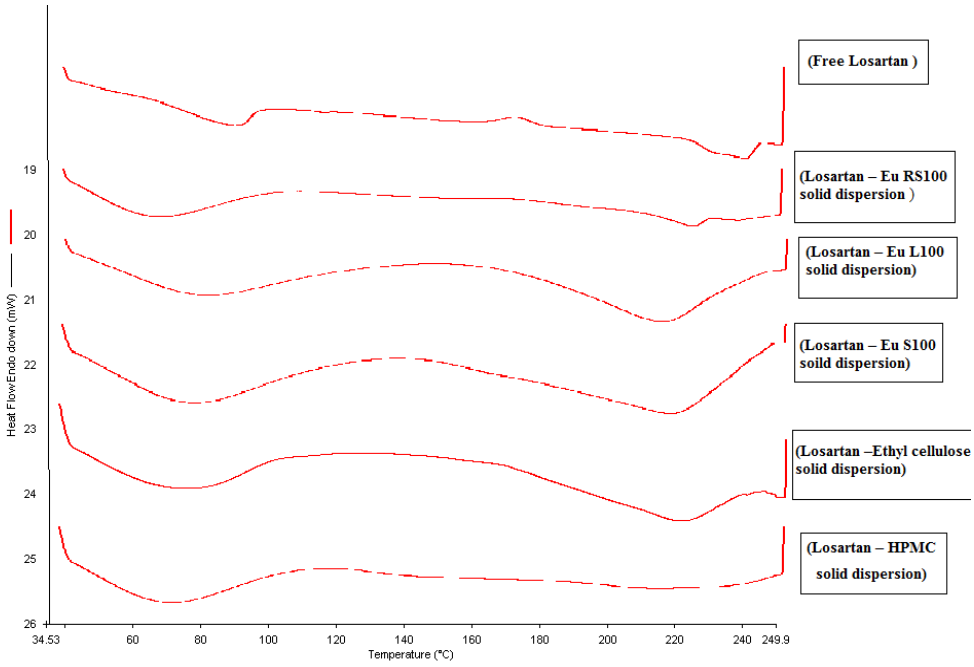


Fig. 2: DSC Thermogram of plain Losartan potassium and the proposed formulations.

5.2 Micromeritic properties

The micromeritic properties of the proposed formulations are presented in Table(2).

Table 2: Effect of different polymers on the micromeritic properties of Losartan potassium.

Polymer	Drug : polymer ratio	Angle of repose *	Hausner ratio*	Carr,s index*
Losartan	_____	40.20 ± 0.15	1.46 ± 0.17	31.40 ± 1.54
Eudragit RS100	1:1(F1)	34.39 ± 3.03	1.17 ±0.11	14.40±0.64
	1:2(F2)	33.19 ± 8.40	1.13 ±0.12	11.80±0.60
	1:3(F3)	32.60 ± 1.41	1.13± 0.10	11.09 ±0.46
Eudragit L100	1:1(F4)	38.74 ± 19.38	1.13±0.11	11.75±0.52
	1:2(F5)	31.18 ± 2.79	1.15 ±0.09	13.19±0.52
	1:3(F6)	34.56 ± 3.01	1.16 ± 0.08	13.64 ±0.46
Eudragit S100	1:1(F7)	34.84 ± 6.62	1.19 ±0.08	15.96±0.54
	1:2(F8)	31.68 ± 5.17	1.18 ±0.10	14.85±0.60
	1:3(F9)	31.60 ± 1.28	1.15 ±0.08	13.08 ±0.46
Ethyl cellulose	1:1(F10)	36.40 ± 3.38	1.16±0.10	13.47±0.55
	1:2(F11)	31.24 ± 1.10	1.16±0.14	13.53±0.78
	1:3(F12)	33.80 ± 1.15	1.13 ±0.09	10.79 ±0.43
HPMC	1:1(F13)	32.82 ± 2.54	1.18±0.13	15.28±0.77
	1:2(F14)	31.40 ± 5.7	1.13±0.11	11.53±0.56
	1:3(F15)	34.50 ± 2.41	1.15 ± 0.08	13.34 ±0.44
Physical mixture	(F16)	29.00 ±1.50	1.02 ± 0.15	9.0± 0.59

All values are expressed as mean ± SD, n =3

From the table, it is evident that by increasing the ratio of the polymer in the blend the micromeritic properties increase. Plain Losartan potassium exhibited angle of repose value of 40.20 ± 0.15 indicating poor flow property. It was further supported by high Carr's index (31.40 ± 1.54) and Hausner's ratio (1.46 ± 0.17). In all formulations prepared the ratio (1:3) drug to polymer showed the best micromeritic properties as follows: angle of repose ranged between29.0 ±1.50 (F16) and 38.74 ± 19.38 (F4), Carr's index ranged between 9.0± 0.59 (F16) and 15.96±0.54 (F7), while Hausner's ratio ratio ranged between 1.02 ± 0.15 (F16) and 1.19 ±0.08 (F7) indicating excellent and good flow properties. This is because the Hausner's ratio which reflects the interparticulate friction is less than 1.2. This reveals the spherical nature of the particles. Also the Carr's index which is a measure of potential compression bonds and their stability i.e the prepared formulations containing high percentage of the polymer are found to be with excellent compressibility.

5.3 Drug content estimation

The results of drug content estimation are presented in table (3). The drug content in the various formulations varied between 96.5 ±0.35 (F3) and 99.5 ±0. 25(F5). The low values in standard deviation indicate uniform drug content in all proposed formulations.

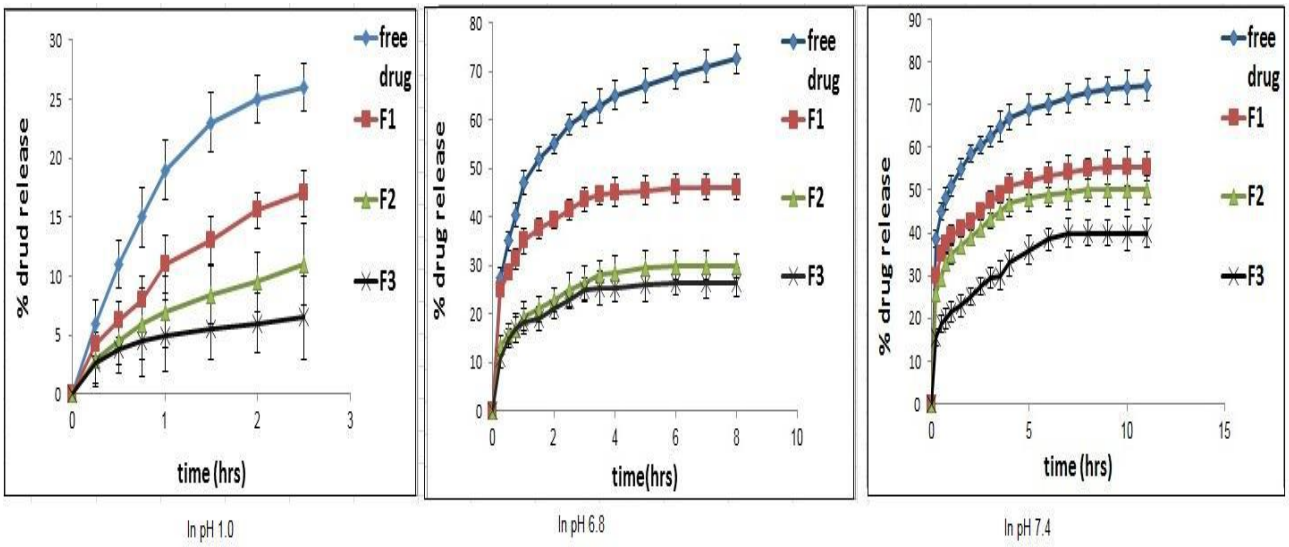
Table 3: Drug content in the proposed formulations.

Polymer	Formula (drug: polymer)	Drug content
Eudragit RS100	F1 (1:1)	98.5 ±0.30
	F2 (1:2)	97.0 ±0.45
	F3 (1:3)	96.5 ±0.35
Eudragit L100	F4 (1:1)	98.2 ±0.36
	F5 (1:2)	99.5 ± 0.25
	F6 (1:3)	98.0 ± 0.22
Eudragit S100	F7 (1:1)	99.0 ±0.36
	F8 (1:2)	96.5 ±0.37
	F9 (1:3)	98.0 ± 0.42
Ethyl cellulose	F10 (1:1)	97.0 ± 0.29
	F11 (1:2)	98.0 ±0.35
	F12 (1:3)	97.6 ±0.30
(HPMC) E5	F13 (1:1)	96.5 ±0.30
	F14 (1:2)	98.2 ±0.32
	F15 (1:3)	98.0 ±0.30

All values are expressed as mean ± SD, n =3

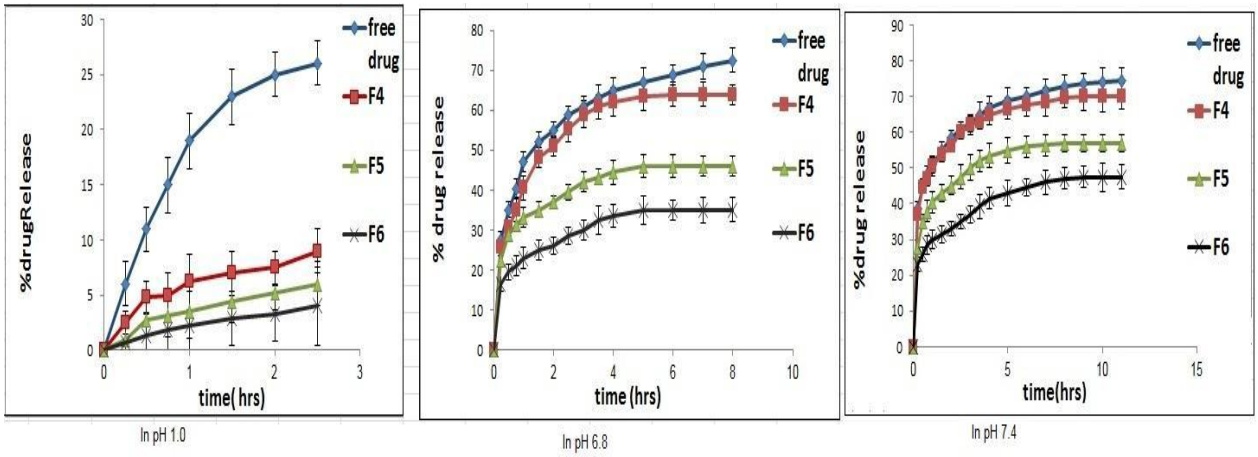
5.4 Drug release studies

The percentage drug released from formulations F1-F16 was observed for 12 hours in different pH media. Drug release in formulations F1-F16 indicates that by increasing the ratio of the polymer in each formulation is usually followed by a decrease in the amount of drug released at all pH values, accordingly the ratio (1:3) drug to polymer achieved significant reduction of Losartan release at the acidic pH while showed maximal release of the drug in the alkaline pH (Fig. 3-8).



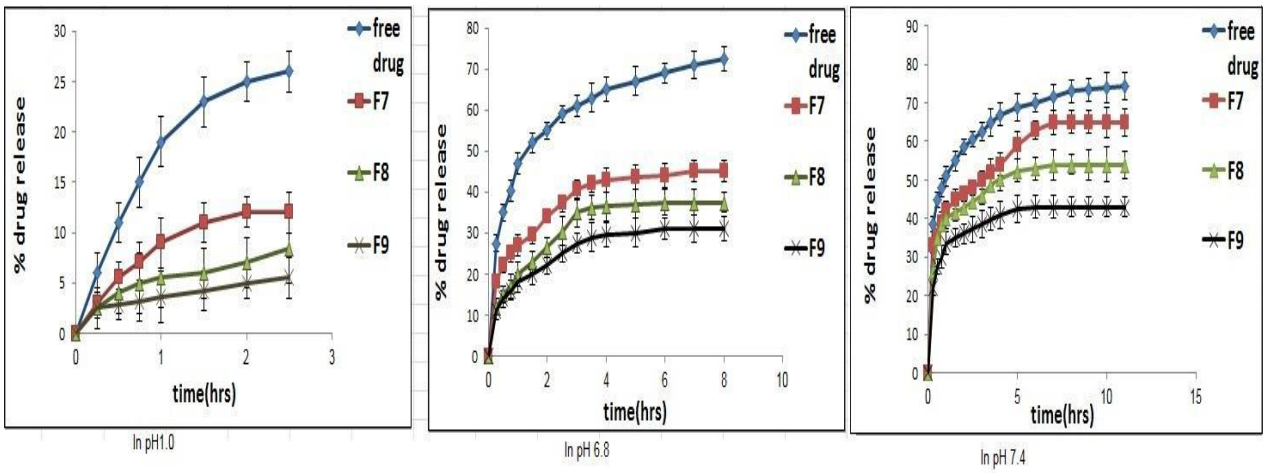
In pH 1.0 In pH 6.8 In pH 7.4

Figure3: Effect of different concentrations of Eudragit RS100 on the release of Losartan at different pH values.



In pH 1.0 In pH 6.8 In pH 7.4

Figure4: Effect of different concentrations of Eudragit L100 on the release of Losartan at different pH values.



In pH1.0 In pH 6.8 In pH 7.4

Figure5: Effect of different concentrations of Eudragit S100 on the release of Losartan at different pH values.

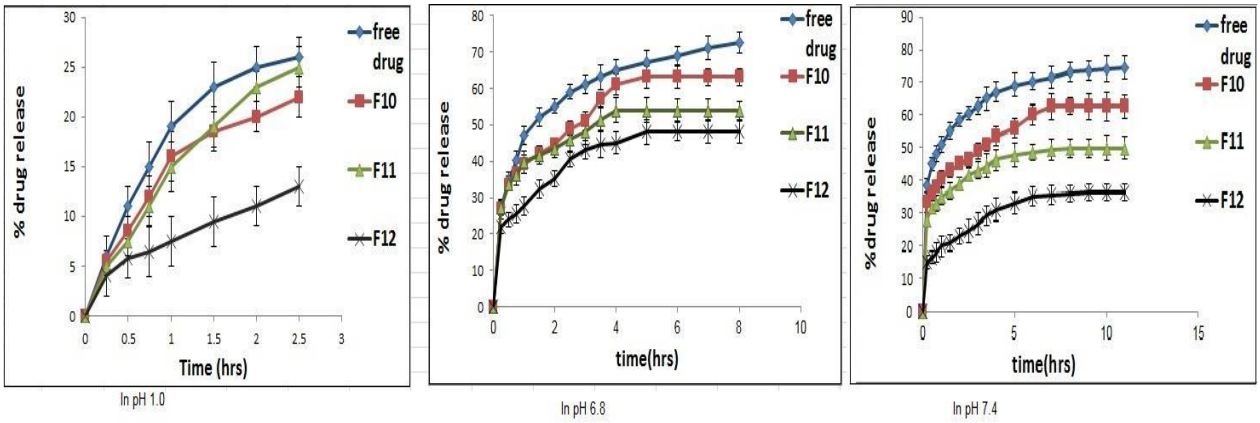


Figure6: Effect of different concentrations of Ethyl cellulose on the release of Losartan at different pH values.

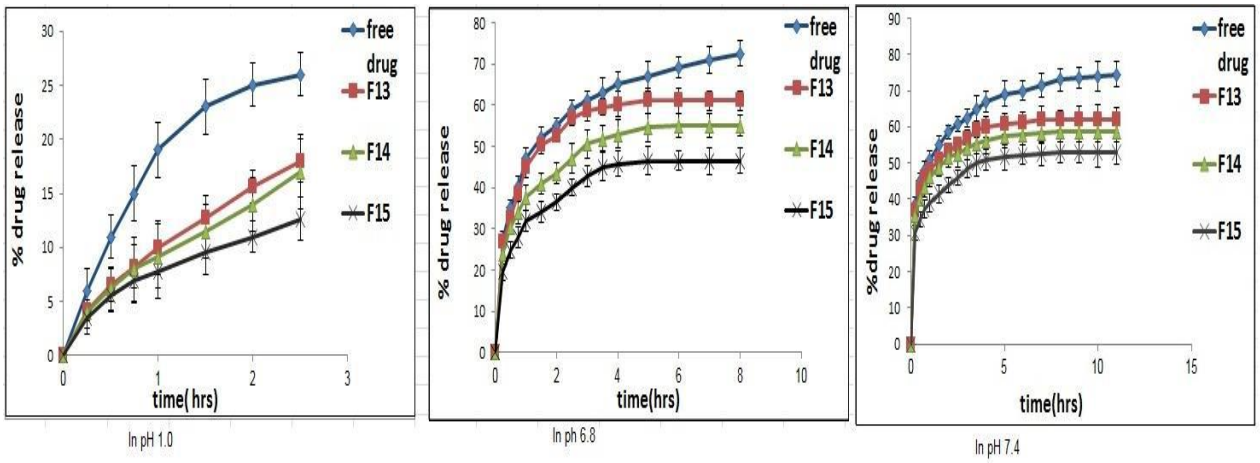


Figure7: Effect of different concentrations of HPMC on the release of Losartan at different pH values.

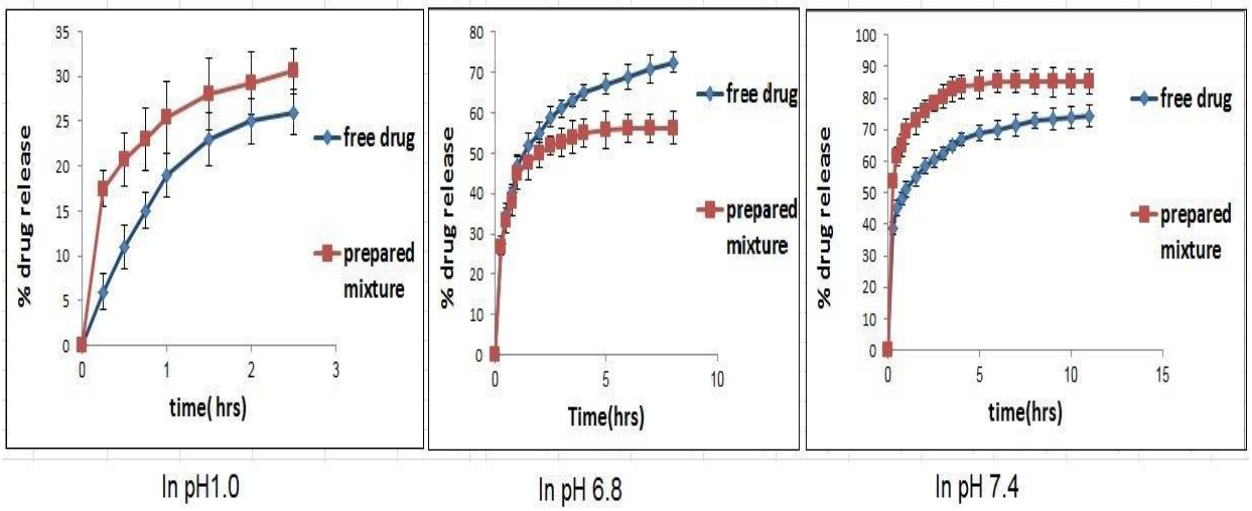


Figure8: Effect of mixing plain Losartan with solid dispersion on the release of Losartan at different pH values.

In case of Eudragit RS100, the sequence of Losartan release was as follows F1 > F2 > F3 at all pH values (Fig.3). At pH 7.4 about 45 % of the drug was released from F3 compared to about 50 % and 68 % from F1 and F2 respectively.

In case of Eudragit L100, the sequence of Losartan release was as follows F4 > F5 > F6 at all pH values (Fig.4). At pH 7.4 about 52 % of the drug was released from F6 compared to about 68 % and 70 % from F4 and F5 respectively.

In case of Eudragit S100, the sequence of Losartan release was as follows F7 > F8 > F9 at all pH values (Fig.5). Where about 45 % of the drug was released after 12 hours from F9 and about 56 % from F8 as well as 68 % from F7 at pH7.4.

In case of Ethyl cellulose, the sequence of Losartan release was as follows F10 > F11 > F12 at all pH values (Fig.6) the same sequence of drug release was obtained where about 38% of the drug released from F12 compared to 50% and 64% from F10 and F11 respectively after 12 hours.

In case of HPMC, the sequence of Losartan release was as follows F13 > F14 > F15 at all pH values (Fig.7) 50% of the drug was released from F15 after 12 hours at pH 7.4 compared to 57% and 64% from F14 and F13 respectively.

Figure 8 shows the drug release sequence from the prepared mixture (containing Losartan, F6 and F9), the amount of drug released at pH7.4 allover the release time.

The amount of the drug released was higher than from those obtained from each polymer individually about 95% of the drug released within 12 hours.

6. CONCLUSION

Results of the present study showed that Eudragit RS100, Eudragit L100, Eudragit S100, Ethyl cellulose as well as HPMC could be used as retardants for Losartan potassium in order to control drug release to meet the patient, s demand for the management of hypertension. This study offers an alternative way to obtain controlled release of losartan via formation of solid dispersions using different types of polymers in various drug to polymer ratios.

According to dissolution properties of Eudragit L100 at pH 6.8 and of Eudragit S100 at pH7.4, the drug release from the prepared mixture offers both immediate and sustained release of the drug and the % drug released was higher than that of separated formula, thus this combination offers better patient compliance.

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