Original Research Article

Role of various natural, synthetic and semi-synthetic polymers on drug release kinetics of losartan potassium oral controlled release tablets

J. Jayasree[1], S. Sivaneswari[1,2], G. Hemalatha[1], N. Preethi[1], B. Mounika[1], S. Vasudeva Murthy[1]

[1]Department of Pharmaceutics, Jayamukhi College of Pharmacy, Warangal, Andhra Pradesh, India. [2]Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, Tirupati, Andhra Pradesh, India.

Abstract

Objective: The objective of the present work was to formulate and to characterize controlled release matrix tablets of losartan potassium in order to improve bioavailability and to minimize the frequency of administration and increase the patient compliance. **Materials and Methods:** Losartan potassium controlled release matrix tablets were prepared by direct compression technique by the use of different natural, synthetic and semisynthetic polymers such as gum copal, gum acacia, hydroxypropyl methyl cellulose K100 (HPMC K100), eudragit RL 100 and carboxy methyl ethyl cellulose (CMEC) individually and also in combination. Studies were carried out to study the influence of type of polymer on drug release rate. All the formulations were subjected to physiochemical characterization such as weight variation, hardness, thickness, friability, drug content, and swelling index. *In vitro* dissolution studies were carried out simulated gastric fluid (pH 1.2) for first 2 h and followed by simulated intestinal fluid (pH 6.8) up to 24 h, and obtained dissolution data were fitted to *in vitro* release kinetic equations in order to know the order of kinetics and mechanism of drug release. **Results and Discussion:** Results of physiochemical characterization of losartan potassium matrix tablets were within acceptable limits. Formulation containing HPMC K100 and CMEC achieved the desired drug release profile up to 24 h followed zero order kinetics, release pattern dominated by Korsmeyer — Peppas model and mechanism of drug release by nonfickian diffusion. The good correlation obtained from Hixson-Crowell model indicates that changes in surface area of the tablet also influences the drug release. **Conclusion:** Based on the results, losartan potassium controlled release matrix tablets prepared by employing HPMC K100 and CMEC can attain the desired drug release up to 24 h, which results in maintaining steady state concentration and improving bioavailability.

Key words: Carboxy methyl ethyl cellulose, eudragit RL 100, gum acacia, gum copal, hydroxypropyl methyl cellulose K100, losartan potassium

INTRODUCTION

Oral drug delivery continues to rise in popularity as formulation scientists look for ways to control drug release and improve patient convenience.[1] The development of controlled release drug delivery system has long been a major area of research in the pharmaceutical industry. Controlled release drug delivery designs involve the application of physical and polymer chemistry to dosage form design to produce well-characterized and reproducible units that control drug delivery into the body within the specification of the required drug delivery profile.[2] Losartan potassium is an angiotensin-receptor blocker (ARB) that may be used alone or with other agents to treat hypertension. Losartan and its longer acting metabolite, E-3174, lower blood pressure by antagonizing the renin-angiotensin-aldosterone system; they compete with angiotensin II for binding to the Type-I angiotensin II receptor subtype and prevents the blood pressure increasing effects of angiotensin II. Unlike angiotensin-converting enzyme inhibitors, ARBs do not have the adverse effect of dry cough. Losartan may be used to treat hypertension, isolated systolic hypertension, left ventricular hypertrophy, and diabetic nephropathy. It may also be used as an alternative agent for the treatment of systolic dysfunction, myocardial infarction, coronary artery disease, and heart failure, biological half-life is 2 h.[3] Daily total dose of 25-100 mg is recommended, the short biological half-life thus necessitating the frequent administration to maintain the therapeutic plasma concentration. Conventional dosage

Address for correspondence:
Ms.S.Sivaneswari,
Department of Pharmaceutics, Jayamukhi College of Pharmacy,
Warangal - 506 332, Andhra Pradesh, India.
E-mail: sivaneswariss@gmail.com

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form losartan potassium has a relatively poor pharmacokinetic profile. To reduce the frequency of administration and increase the bioavailability, the controlled release formulation is desirable for losartan potassium, which also improves patient compliance. The objective of the present study was to develop controlled release matrix tablets of LP using various natural (gum copal and gum acacia), synthetic (hydroxypropyl methyl cellulose K100 [HPMC K 100], Eudragit RL 100) and semi-synthetic (carboxy methyl ethyl cellulose [CMEC]) polymers with respect to *in vitro* drug release rate.

Hydrophilic polymers are widely used in the formulation of modified release dosage forms because of their flexibility to obtain a desirable drug release profile, cost-effectiveness and broad regulatory acceptance. HPMC is the first choice for formulation of hydrophilic matrix system, providing a robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost-effectiveness, and utilization of existing conventional equipments.[4] Eudragit, one of the most interesting acrylic polymers used as retardant of drug release, which is insoluble in water and digestive juices, but they swell which means that drugs embedded in their matrices can be released by diffusion and permeability of the drug is independent of pH of the gastrointestinal tract.[5] CMEC, a novel semi-synthetic polymer, which is a nongelling, hydrophobic used as a release retardant in controlled release tablets.[6,7] In recent years, researchers have become increasingly interest in the utilization of biopolymers due to their wide ranging advantages over synthetic polymers. Polysaccharide gums are the materials of choice because they are naturally abundant, bio-compatible, bio-degradable, and nonimmunogenic.[8] Until now, large numbers of natural and synthetic polymers were used in single or in combination as hydrophilic matrix excipients. Natural gums such as gum copal and gum acacia have also been examined as matrices for the controlled release of drugs. Gum copal is naturally hydrophobic resin isolated from the plant *Bursera bipinnata*, which is used as release retardant in the modified drug delivery systems.[9] Gum acacia is the dried gummy exudates obtained from the stems and branches of *Acacia Senegal,* family Leguminasae. It is a complex, loose aggregates of sugar and hemicelluloses, evaluated as a bioadhesive, used in the novel modified release tablets.[10] However, the use of hydrophilic matrices alone for extending the drug release for highly water soluble drugs is restricted due to the rapid diffusion of dissolved drug through the hydrophilic gel network. Hence in the present work, an attempt has been made to formulate the controlled release matrix tablets of losartan potassium and investigated for controlled drug delivery using hydrophilic (HPMC K100 and gum acacia) and hydrophobic(gum copal, eudragit RL 100 and CMEC) matrix substances. The novelty of the present work is to investigate the role novel semi-synthetic polymer (CEMC) and natural polymers (gum acacia and gum copal) in comparison with well-known release retarding agent HPMC K100 and eudragit RL 100 in order to control the losartan potassium release up to 24 h, which results in improved bioavailability. The above mentioned polymers were used individually, and probable synergistic effect of the polymers in combination also studied on retarding the drug release.

MATERIALS AND METHODS

Losartan potassium was obtained as a gift sample from Hetero drugs, Hyderabad. Gum copal, gum acacia, eudragit RL 100, HPMC K100, and CMEC were procured from commercial sources. All other reagents and chemicals used were of analytical grade.

Drug-excipient compatibility studies

In order to evaluate the compatibility of the drug and polymers used, Fourier transformer infrared (FT-IR) studies were carried out by potassium bromide pellet technique.

Preparation of losartan potassium matrix tablets

Matrix tablets of 100 mg losartan potassium were prepared by direct compression method based on composition shown in Table 1. All the ingredients such as drug, polymer and diluent except magnesium stearate were mixed geometrically in a mortar. The mixture were passed through No: 40 sieve and mixed in a polythene bag for 15 min. Later the powder blend were lubricated with magnesium stearate and compressed into tablets, in a rotary punching machine (Pankaj Industries, Maharashtra, India) and the total weight of the tablet is 300 mg.

Micromeritic properties

Before compression, the powder blend of all formulations were subjected to precompression parameters such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio.[11]

Table 1: Composition of losartan potassium matrix tablets

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Losartan potassium	100	100	100	100	100	100	100	100	100	100	100	100	100
Gum copal	100	—	—	—	—	50	50	50	—	—	—	—	—
Gum acacia	—	100	—	—	—	—	—	—	50	50	50	—	—
Eudragit RL100	—	—	100	—	—	50	—	—	50	—	—	—	50
HPMC K100	—	—	—	100	—	—	50	—	—	50	—	50	—
CMEC	—	—	—	—	100	—	—	50	—	—	50	50	50
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3	3
MCC	97	97	97	97	97	97	97	97	97	97	97	97	97

HPMC: Hydroxy propyl methyl cellulose, CMEC: Carboxy methyl ethyl cellulose, MCC: Micro crystalline cellulose

Characterization of losartan potassium matrix tablets

The tablets were evaluated for thickness, weight uniformity, crushing strength and friability test.[12]

Tablet thickness

The thickness of 10 tablets was determined using a Vernier caliper and then mean of these readings was taken as the mean tablet thickness.

Tablet weight uniformity

A total of 20 tablets was weighed individually, average weight was calculated and the individual tablet weights were compared with an average weight. The tablets meet the United States Pharmacopeia (USP) test if not more than two tablets are outside the percentage limit and if no tablets differs by more than two times the percentage limit.

Crushing strength

The crushing strengths of the tablets were determined individually with the Monsanto hardness tester. Three tablets were used, and the mean crushing strength was calculated and expressed in kg/cm^2.

Friability test

The friability of tablets was determined using Roche friabilator. Six tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W). The percentage of friability was then calculated by the following equation.

$$\%F = (1-W/W_0) \times 100$$

Percentage of Friability of tablets <1% are considered as acceptable.

Drug content

A total of 10 tablets was weighed and powdered. The quantity of powder equivalent to 100 mg of losartan potassium was dissolved in 100 ml of 0.1N HCl (pH1.2). Mechanical shaking was done to dissolve the powdered material in 0.1N HCl (pH1.2). Then the solution was filtered, diluted suitably and analyzed using an ultraviolet-visible spectrophotometer (Shimadzu, Japan) at 234 nm.[13]

Swelling index studies

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in 100 ml beaker of 0.1N HCl, the tablets were withdrawn at predetermined interval, blotted with tissue paper to remove the excess water and weighed on an analytical balance. Swelling index was calculated by using the following formula:[14]

$$\text{Swelling index} = ([\text{Wet weight of tablet} - \text{Dry weight of tablet}]/\text{Dry weight of tablet}) \times 100$$

In vitro drug release studies

Drug release were performed using USP Type I (basket) apparatus (Model TDT-08 L, Electro Lab, Mumbai, India) at 100 rpm in 900 ml of simulated gastric fluid (SGF pH 1.2) for first 2 h then in simulated intestinal fluid (SIF pH 6.8) for next 22 h, maintained at 37°C ± 0.5°C. Five milliliters of the dissolution samples were withdrawn at different time intervals and replaced with an equal volume of drug free dissolution fluid to maintain the sink conditions. The samples were suitably diluted and analyzed spectrophotometrically at 234 nm. The drug release profiles were shown in Figures 1 and 2.

Kinetic modeling of drug release

The results of *in vitro* release profile obtained for all the formulations were fitted to zero order, the first order, Higuchi and Korsmeyer — Peppas equation to assess the kinetic modeling of drug release.[15-18]

Zero order release would be predicted by the following equation,

$$A_t = A_0 - K_0 t$$

where, A_t - Drug release at Time "t", A_0 - Initial drug concentration, K_0 - Zero-order rate constant (h^{-1}).

First-order release would be predicted by the following equation:

$$\text{Log } C = \log C_0 - K_t/2.303$$

where, C - Amount of drug remained at time "t", C_0 - Initial amount of drug, K = First order rate constant (hr^{-1}).

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = (D\varepsilon/\tau\,[2A - \varepsilon Cs]\,Cst)^{1/2}$$

Where, Q - Amount of drug released at time "t", D - Diffusion coefficient of the drug in the matrix, A - Total amount of drug in unit volume of matrix, Cs - The solubility of the drug in the matrix.

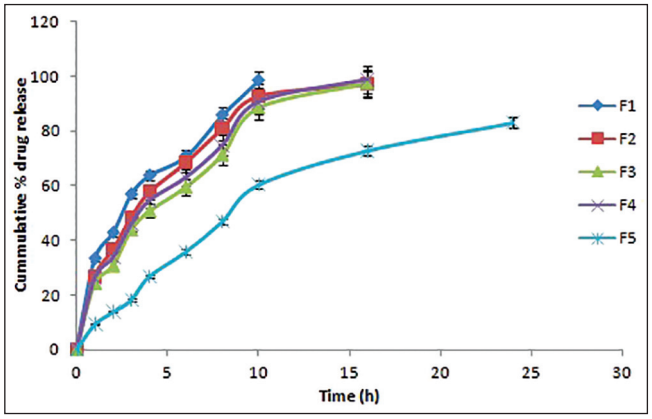

Figure 1: *In vitro* drug release profiles of formulations (F1-F5)

ε - Porosity of the matrix, τ - Tortuosity, t - Time (h) at which "q" amount of drug is released.

Above equation may be simplified if one assumes that "D", "Cs", and "A", are constant. Then equation becomes,

$$Q = Kt^{1/2}$$

To study the mechanism of drug release from the sustained release matrix tablets of cefixime, the release data were also fitted to the well-known exponential Korsmeyer equation Peppa's law equation, which is often used to describe the drug release behavior from polymeric systems.

$$M_t/M\alpha = Kt^n$$

Where, $M_t/M\alpha$ - The fraction of drug released at time "t".

K - Constant incorporating the structural and geometrical characteristics of the drug/polymer system.

n - Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides, and we get:

$$\text{Log } M_t/M\alpha = \text{Log } K + n \text{ Log } t$$

For Fickian release "n" = 0.5 while for anomalous (non-Fickian) transport "n" ranges between 0.5 and 1.0.

Accelerated stability studies

Accelerated stability studies[19] were performed at a temperature of 40°C ± 2°C and 75% ± 5% RH over a period of 1 month for optimized formulation F12. Sufficient number of tablets were packed in amber colored screw capped bottles and kept in modified stability chamber. At the end of 1 month period, physical appearance and post compression parameters such as weight variation, hardness, friability, drug content and *in vitro* release studies were performed to determine the drug release profiles.

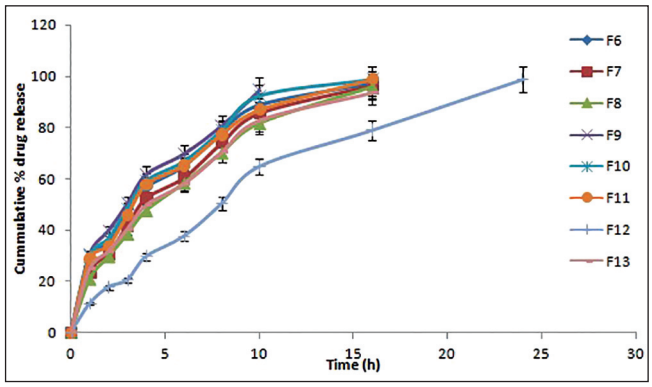

Figure 2: *In vitro* drug release profiles of formulations (F6-F13)

RESULTS AND DISCUSSION

Losartan potassium controlled release matrix tablets were prepared by direct compression using different natural, synthetic and semi-synthetic polymers such as gum copal, gum acacia, HPMC K100. Eudragit RL 100 and CMEC. The above polymers were used alone and also in combination to study synergistic effect of the polymers in controlling the release rate up to 24 h. Drug-excipient compatibility studies were performed for drug and physical mixtures. The drug excipient studies revealed that no interaction between drug and polymers. The FT-IR spectra of pure drug and physical mixture were shown in Figure 3.

Micromeritic properties

Initially, powder blend of all the formulations were evaluated for precompression parameters to know the flow property and compression characteristics. Bulk density and tapped density were found to be 0.32 ± 0.04−0.45 ± 0.04, and 0.32 ± 0.09−0.59 ± 0.04 respectively. The results of Carr's index, Hausner's ratio and angle of repose were found to be satisfactory in the range of 12.23 ± 0.61−15.60 ± 0.21, 1.11 ± 0.04−1.18 ± 0.08, 27.58 ± 0.15−29.69 ± 0.19 respectively which indicates the good flow ability of the powder blend and compression characteristics. The results were shown in Table 2.

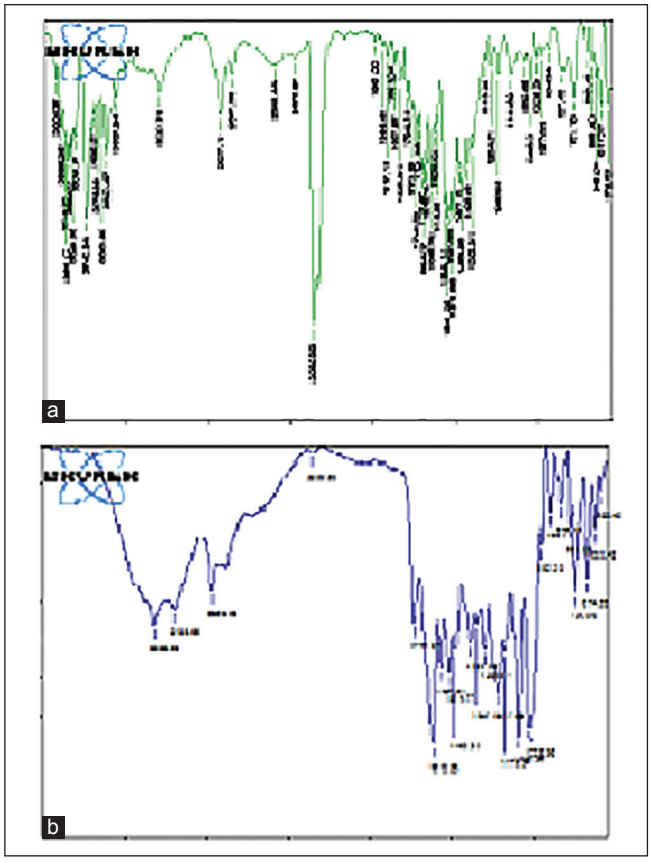

Figure 3: FT-IR graph of pure losartan potassium (a) and optimised formulation-F12 (b)

Physiochemical characterization

The prepared tablets were evaluated for physiochemical characterization such as hardness, thickness, average weight, friability and drug content found to be 8.3 ± 0.44−11.3 ± 0.57 kg/cm^2, 2.63 ± 0.25−2.90 ± 0.25 mm, 297 ± 0.57−305 ± 0.54 mg, 0.30% ± 0.01%−0.35% ± 0.01%, and 96.58% ± 0.80%−101.23% ± 0.88% respectively. Swelling index of the tablets was found to be 70.12% ± 0.54%−94.32% ± 0.63%. The results were shown in Table 3.

In vitro drug release studies

The *in vitro* drug release studies were conducted for 24 h. In formulations (F1-F5), the polymers such as gum copal, gum acacia, HPMC K100, Eudragit RL 100 and CMEC were used individually to retard the drug release. The drug release from formulations (F1-F5) were in the following manner, 98.6%, 96.95%, 97.6%, 98.8%, and 83.5% at the end of 10 (F1), 16 (F2, F3, F4), and 24 (F5) h. When the polymers were used individually, the drug was not sustained up to 24 h except formulation (F5). In the formulation (F5), a novel semi-synthetic polymer CMEC was used individually being hydrophobic in nature, it retarded the drug release, but only 83.5% drug released at the end of 24 h. In the formulation (F6-F8), gum copal used along with eudragit RL 100, HPMC K100 and CMEC individually. The drug release from formulation (F6-F8) was found to be 97.1, 96.3, and 95.8% respectively at the end of 16 h. In formulation (F9-F11), gum acacia used along with eudragit RL 100, HPMC K100 and CMEC individually. The drug release were in following manner 94.6%, 98.7%, and 98.8% at the end of 10 (F9), and 16 (F10, F11) h respectively. In formulation F12 and F13, synthetic polymers HPMC K100 and eudragit RL 100 were used in combination with semi-synthetic polymer CMEC individually. The drug release was found to be 98.7% and 93.4% at the end of 24 and 16 h. Formulation (F12) was shown desired release profile for controlled drug delivery up to 24 h. The slow release and desired release due to hydrophilic matrices present in the formulation starts swelling when comes contact with dissolution medium form the gel like network, hydrophobicity of CMEC retarding the drug release.[20] The *in vitro* drug release profiles were shown in Figures 1 and 2.

Release kinetics

To analyze the mechanism of drug release from losartan potassium controlled release matrix tablets, the *in vitro* dissolution data were fitted to various mathemathical models like zero order, first order, Highchi, Korsmeyer-Peppas and Hixson-Crowell models. The optimized formulation (F12) followed zero order kinetics (R^2 = 0.9473) indicating that the rate of drug release is independent of concentration, best fitted with Korsmeyer — Peppas model (R^2 = 0.782) and followed by nonfickian diffusion (n = 0.753). The linearity observed in Hixson-Crowell model (R^2 = 0.782) indicating that drug release also influenced by change in surface area of the tablets.

Table 2: Precompression parameters of the powder blend

Formulation code	Bulk density (g/cc)*	Tapped density*	Carr's index*	Hausner's ratio*	Angle of repose (θ)
F1	0.45±0.045	0.52±0.09	15.60±0.2	1.15±0.02	28.06±0.31
F2	0.48±0.045	0.50±0.07	12.23±0.6	1.11±0.04	27.58±0.15
F3	0.43±0.044	0.50±0.09	12.58±0.8	1.13±0.08	28.44±0.11
F4	0.45±0.045	0.52±0.04	15.19±0.1	1.15±0.06	28.36±0.13
F5	0.44±0.044	0.52±0.01	15.48±0.6	1.18±0.08	28.52±0.09
F6	0.45±0.045	0.51±0.04	13.48±0.8	1.13±0.09	29.32±0.19
F7	0.51±0.045	0.59±0.04	14.48±0.8	1.15±0.09	29.69±0.19
F8	0.32±0.045	0.37±0.04	14.36±0.8	1.16±0.09	25.58±0.19
F9	0.42±0.044	0.32±0.09	14.32±0.8	1.16±0.08	25.16±0.11
F10	0.44±0.041	0.50±0.09	12.58±0.8	1.13±0.08	28.44±0.11
F11	0.44±0.043	0.52±0.01	15.48±0.6	1.18±0.08	28.52±0.19
F12	0.45±0.045	0.50±0.07	12.23±0.6	1.11±0.04	27.58±0.15
F13	0.45±0.047	0.51±0.04	13.48±0.8	1.13±0.09	29.32±0.19

*All the values are expressed as mean ± SD, n = 3. SD: Standard deviation

Table 3: Physicochemical characterization of losartan potassium matrix tablets

Formulation code	Hardness (kg/cm^2)†	Thickness (mm)‡	Weight (mg)‡	Friability (%)	Drug content*(%)	Swelling index (%)
F1	8.3±0.44	2.84±0.17	302±1.48	0.32	96.25±1.37	70.13
F2	9.8±0.31	2.90±0.25	305±0.54	0.30	96.58±0.80	83.67
F3	10.8±0.40	2.80±0.80	299±0.41	0.36	99.32±2.47	81.87
F4	10.0±0.55	2.82±0.20	302±1.64	0.31	101.23±0.88	77.71
F5	11.3±0.57	2.68±0.66	297±1.14	0.34	99.54±1.25	94.32
F6	10.3±0.30	2.63±0.25	300±0.83	0.35	97.33±1.87	82.32
F7	10.9±0.57	2.85±0.40	302±0.67	0.32	96.68±1.99	84.12
F8	10.6±0.60	2.75±0.89	304±0.43	0.32	97.55±1.14	85.51
F9	9.3±0.40	2.65±0.40	297±0.57	0.34	97.56±1.14	72.67
F10	9.5±0.30	2.72±0.30	298±0.47	0.33	99.21±0.25	75.81
F11	10.5±0.32	2.65±0.32	299±0.37	0.35	98.33±1.27	79.31
F12	11.0±0.29	2.73±0.32	301±0.47	0.32	98.32±1.47	91.12
F13	10.7±0.43	2.82±0.41	301±0.37	0.35	99.05±0.25	87.21

†6 tablets, ‡20 tablets, *10 tablets. All the values are expressed as mean ± SD, n = 3. SD: Standard deviation

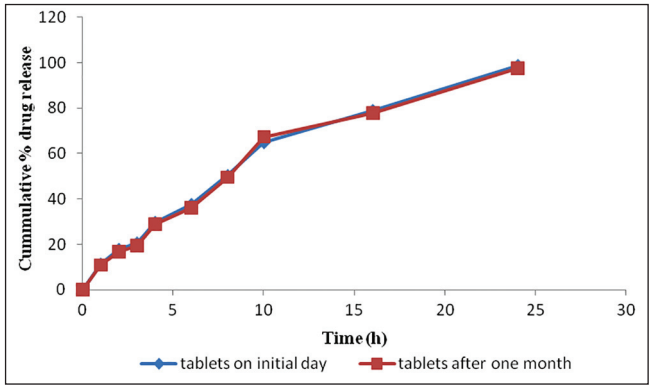

Figure 4: Stability study-*In vitro* release profile of formulation (F12)

Table 4: Stability studies data of formulation (F12)

Parameters	At initial day	After 1 month
Hardness (kg/cm^2)	11.0±0.29	10.9±0.15
Thickness (mm)	2.73±0.32	2.73±0.11
Weight variation (mg)	301±0.47	300±0.78
Drug content (%)	98.32±1.47	98.21±1.23

Accelerated stability studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic, and toxicological specifications. Formulation (F12) was kept for accelerated stability study at 40°C ± 2°C, and 75% ± 5% RH for 1 month in the modified stability chamber. After a period of 1 month, it was observed that surface was devoid of any change in color or appearance. It was also noted that surface was free of any kind of microbial or fungal growth. No changes in the smoothness of the tablets were noted. The drug content was found to be 98.92% indicates the no significant changes. The same drug release pattern was achieved after 1 month period indicates the stability of formulation. The *in vitro* release profiles were shown in Figure 4. The results were shown in Table 4.

CONCLUSION

In the present investigation, attempts were made to formulate losartan potassium controlled release tablets to provide effective drug release for 24 h. The formulation (F12) containing HPMC K100 and CMEC offered much slow release of losartan potassium compared with other formulations. Thus, the results of the current study clearly indicate a promising potential of the combined approach by using synthetic (HPMC K100) and novel semi-synthetic (CMEC) polymers for controlled delivery of losartan potassium to reduce the dosing frequency with improved patient compliance.

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