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Research Article

Design and evaluation of three layer matrix tablet of Losartan potassium capped with Eudragit and HPMC combination

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ABSTRACT

In the present investigation concern the formulation and evaluation of trilayer matrix tablets of losartan potassium (LP). Losartan potassium is an angiotensin-II receptor antagonist drug used mainly to treat high blood pressure. The biological half-life and bioavailability of losartan is very poor. Therefore, by using trilayer matrix tablet, we can improve the bioavailability of losartan using combination of different polymers and improve the patient compliance by reducing the frequency of administration. In the trilayer matrix tablets by using polymeric matrix to control the release of an active ingredient is one of the simple ways of formulating dosage form, and has been widely studied for various drug molecules. Trilayer matrix tablets comprised of three layers, a middle layer containing drug capped with combination of different polymers. The powder blend prepared fortrilayer tablet formulations were subjected to FT-IR for any interaction. The tablets were prepared by direct compression method. The results showed that higher the concentration of HPMC in upper and lower layer were better in sustaining the release of the drug. The best sustained release profile in case of trilayer matrix tablets of losartan potassium was seen in F3 followed by F2, F6, F1, F5 and F4. The release data was fitted to various mathematical models such as Higuchi, first and zero order to evaluate kinetics and mechanism of drug release and it was observed that drug release was best fitted to Zero order and Higuchi model. All formulations were subjected for stability studies at different temperatures for 8 weeks and no significant change was observed.

Keywords: Trilayer Matrix Tablets; Losartan Potassium; Direct Compression Method; HPMC; Eudragit

INTRODUCTION

Modifying the rate and duration of drug release from dosageform may profoundly affect the clinical performance of the drug. Various methods have been designed and tested to achieve controlled release kinetics, such as film coating, multi-layering and using different polymer materials. Using a hydrophobic or hydrophilic polymer matrix to control the release of an active ingredient is one of the simple ways of formulating dosage form, and has been widely studied for various drug molecules. Various physicochemical properties of tablets such as hardness, friability, drug content, weight variation, swelling study and *in vitro* drug release profile was studied. In this study, we have prepared a new type of tablet, which has three-layered structure, using HPMC and eudragit, and evaluated the feasibility as a controlled release system. HPMC and eudragit were used as coating material on both sides of the central matrix containing the drug as losartan potassium. The slower swelling and dissolution of the HPMC may retard the release of the drug. As a model drug for the evaluation of the system, we have used LP.LP is an angiotensin II receptor antagonist drug used mainly to treat high blood pressure (hypertension) and introduced to the market first. Half-life of losartan is 1.5 - 2 h and bioavailability is 25 – 35%. The pKa value of LP is 4.9 and pH of LP in aqueous solution is 5 – 9. The recommended dosage of LP with high blood pressure (hypertension) is between 25 – 100mg/day. The biological half-life and bioavailability of losartan is very poor. Therefore, by using trilayer tablet, we can improve the bioavailability of losartan using different polymers and improve the patient compliance by reducing the frequency of administration (Parfitt K, 1999). Eudragit® L & S-100 are an anionic copolymer based on methacrylic acid and methyl methacrylate. We chose eudragit as the central hydrophobic matrix material containing drug molecules (McGinity JW *et al*., 1983). They have been extensively studied as a polymermaterial for controlled release and several oral drug delivery systems are already in the market (Genc L*et al.*, 1999). HPMC provides gel layer which may act as the rate controlling membrane. It is used as coating agent, controlled-release agent, modified-release agent, mucoadhesive, release-modifying agent, solubilizing agent, tablet binder, thickening agent and viscosi-

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ty increasing agent.HPMC swells in water many times to their original volume to form a gel when exposed to a neutral pH environment. HPMC polymers are effective at low concentrations (less than 10%) and show rapid gelation characteristics (Ranga RK et al., 1990).

MATERIALS AND METHOD

Losartan potassium was obtained from JB Chemical Co. (Ankleshwar, Gujarat, India). HPMC E-50LV was obtained fromLoba Chemical Pvt. Ltd. (Mumbai, India) and eudragit (L-100 and S-100) was provided by Evonik Rohm Pharma (Germany). While other excipients such as PVP, magesium stearate and talc were obtained fromLoba Chemicals Pvt. Ltd. (Mumbai, India). Sodium hydroxide and potassium dihydrogen phosphate were obtained from Sisco Research Laboratories Pvt. Ltd. (Mumbai).

Compatibility Studies

FT-IR studies

This was carried out to find out the compatibility between the drug losartan potassium and the polymers such as HPMC E-50LV, EudragitS-100, Eudragit L-100. A sample of 10 mgwith 400 mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into a pellet making disc and was compressed at a 10 kg/cm^2 using a hydraulic press. The pellet was kept onto the sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1} in Bruker FT-IR spectrophotometer. The spectra obtained were compared and interpreted for the functional group peaks.

Powder Properties

Angle of Repose (θ)

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using following formula (Lachman L *et al*., 2008; Carter SJ, 1986).

$$\theta = tan^{-1}\frac{h}{r}$$

h = height of pile, r = radius of pile

Bulk Density and Tapped Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by taking known mass of blend in measuring cylinder and it was tapped at fixed distance**.**LBD and TBD were calculated using the following formula(Lachman L *et al*., 2008; Aulton ME, 2009).

$$LBD\ (D_b) = \frac{M}{V_b} \quad TBD\ (D_t) = \frac{M}{V_t}$$

Where, M = Weight of the powder

V_b= Bulk volume of the packing

V_t= Tapped volume of the packing

Carr's Compressibility Index (Carr's consolidation index)

The compressibility index of the powder blend was determined from bulk density and tapped density. It was calculated by the formula given as below(Lachman L *et al*., 2008; Aulton ME, 2009).

$$Carr's\ index\ (\%) = \frac{TBD - LBD}{TBD} \times 100$$

Where, LBD = Loose Bulk Density

TBD = Tapped Bulk Density

Formulation of matrix tablets of losartan potassium

Trilayer matrix tablets were prepared in three stages by direct compression method. Tablets were formulated using 10.5 mm punch by rotary tablet compression machine (RimekMinipress-I, Ahmedabad). First stage was formulation of upper layer. The polymers were accurately weighed and mixed in mortar.Second stage was formulation of middle layer containing the drug. The drug, eudragit (L-100 & S-100), PVP, MCC, magnesium stearate and talc were accurately weighed and triturated in mortar. Third stage was formulation

Table 1: Formulation of trilayer matrix tablets of losartan potassium

Formulation Code	F1	F2	F3	F4	F5	F6
Ingredient	**Upper & Lower Layer**					
HPMC E-50LV	75	100	125	75	100	125
Eudragit L-100	75	50	25	-	-	-
Eudragit S-100	-	-	-	75	50	25
	Middle Layer					
Losartan Potassium	50	50	50	50	50	50
Eudragit L-100	20	20	20	-	-	-
Eudragit S-100	-	-	-	20	20	20
PVP	20	20	20	20	20	20
MCC	50	50	50	50	50	50
Mg. Sterate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total wt.	**450**	**450**	**450**	**450**	**450**	**450**

of lower layer which was same as upper layer. Powder mixture of all three layers were then placed in hot air ovan at 40°C to remove moisture.After drying first layer of polymer was filled in die cavity and precompressed. After that the contents of middle layer containing drug was placed over first precompressed layer in die and then again precompression was given to both layers. Then, filled the polymeric blend over precompressed layers and finally the full compression was givento formulate trilayer matrix tablet by using 10.5 mm punch. The prepared tablets were subjected to various characterizations (Sung In Hong*et al*., 2008; Krishnaiah YSR *et al*., 2004).Formulation of trilayer matrix tablets is given in Table 1.

Characterization of trilayer matrix tablet of losartan potassium

Weight Variation Test

To study weight variation, 20 tablets from each formulation were selected randomly and weighed using an electronic balance (OHAUS), and the test was performed according to the official method. The IP weight variation test is run by weighing 20 tablets individually, calculating the average weight and comparing the individually tablet weights to the average. The tablets meet the IP tests if no more than two tables are outside the percentage limit and if no tablets differ by more than two times the percentage limit. The deviation from average weight was reported. (Lachman L *et al*., 2008).

Hardness

From each formulations, the hardness of randomly selected six tablets was determined by Monsanto Hardness Tester. The lower plunger of tester is placed in contact with the tablet, and a zero reading was taken. The upper plunger of tester was then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring was compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture was recorded and values are reported inKg/cm^2(Lachman L *et al*., 2008).

Friability Test

Normally, six tablets from each batch selected randomly and weighed, then placed in Roche fribilator, which was then operated for 100 revolutions dropping the tablets from a distance of 6 inch with each revolution. The tablets are then dusted and reweighed. The friability was calculated as the percentage weight loss using the following formula**.** (Lachman L *et al*., 2008).As per IP, % friability of the tablet less than 1% considered as acceptable.

$$\%\ friability = \frac{W_i - W_f}{W_i} \times 100$$

Where, W_i and W_f are Initial and Final weight of tablets

Drug Content Estimation

Five tablets were weighed individually and powdered. Then, powder of tablets equivalent to 50 mg losartan potassium was weighed and dissolved in phosphate buffer pH6.8, the solution was filtered, diluted using phosphate bufeer pH 6.8 and then the drug content was analyzed using UV spectrometer at 204.6 nm (Lachman L *et al*., 2008).

Swelling and Erosion Studies

Swelling experiment was conducted on the prepared tablets using USP dissolution apparatus II at rotational speed of 50 rpm. The medium used was phosphate buffer pH 6.8. The volume of the medium was 900 ml. The temperature was maintained at 37°C. Swelling study was done upto 10 h. The tablets were removed using a small basket and swollen weight of each tablet was determined. The percentage of swelling was calculated according to the following formula, where S is the weight of the matrix after swelling and R is the weight of the eroded matrix.

$$\%\ \text{Swelling} = \frac{S}{R} \times 100$$

***In vitro* drug release profile**

In vitro drug release studies for developed matrix tablets were carried out by using USP XXIII dissolution apparatus II (Paddle type) [Electrolab (TDT-08L) Tablet Dissolution Tester] at 50 rpm. The drug release profile was studied in 900 ml of phosphate buffer pH 6.8 by maintaining at 37 ± 0.5 °C. Aliquots of 5 ml of dissolution medium were withdrawn atdifferent time intervals, filtered and replaced with fresh5 ml of dissolution medium. The amount of drug released was determined by UV spectrophotometer (Shimadzu UV 1800) at 204.6 nm.

Drug release kinetics

Different mathematical models are applied fordescribing the kinetics of the drug-release process frommatrix tablets and it was calculated using Microsoft® Office Excel.The kinetics of losartan potassium release from formulations was determined by finding the best fitof the dissolution data (drug-released fraction vs. time)to distinct models: zero-order, first-order andHiguchi (Higuchi T, 1963).

Stability studies

The purpose of stability testing is to provide evidence onhow the quality of a drug substance or drug product varies with time under theinfluence of a variety of environmental factors such as temperature, humidity and light.

The selected formulations were subjected to stability studies upto 8 weeks at different storage conditions. The tablets were sealed in airtight aluminium foil packets and stored at controlled room temperature condition (25±2°C and 60±5% RH) in a desiccator and at ac-

celerated condition (40±2°C and 75±5% RH) in stability chamber as per ICH guidelines.

RESULTS AND DISCUSSIONS

Compatibility studies

FT-IR Studies

The FT-IR spectrum of losartan potassium showed short bend of N-H group at 3480 cm^{-1}, absorption bend of O-H group at 3365 cm^{-1} and 3275 cm^{-1}, N=N group at 2258 cm^{-1} and CH2-Cl group at 1255 cm^{-1} and 1069 cm^{-1} in Fig.1 to 3. All these absorption bends of drug were also found in IR spectrum of all the formulation which indicate that there is no interaction between drug and polymer.

Powder properties

The bulk density, tapped density, Carr's consolidation index and angle ofrepose were determined and reported in the Table 3. The bulk density of middle layer was found to bewithin the range of 0.684-0.714 gm/cc, while tapped density was within the rangeof 0.746-0.795 gm/cc. The Carr's consolidation was found to be within the range of 5-15%. They can be said to have "excellent flow properties" as their Carr's index values are within the range of 5-15%. Losartan potassium was

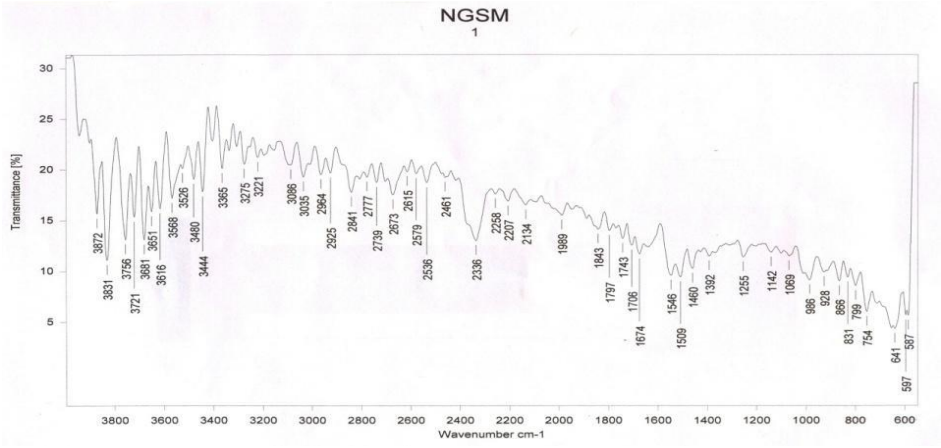

Figure 1: FT-IR spectrum of pure losartan potassium

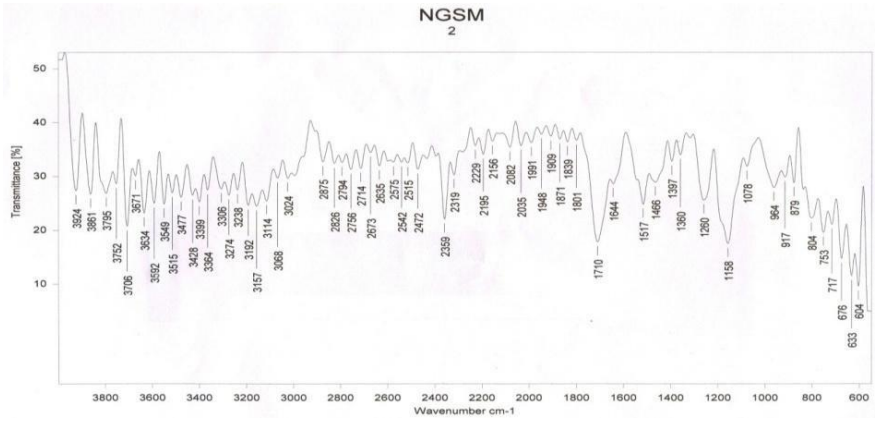

Figure 2: FT-IR spectrum of pure losartan potassium admixtured with eudragit L-100

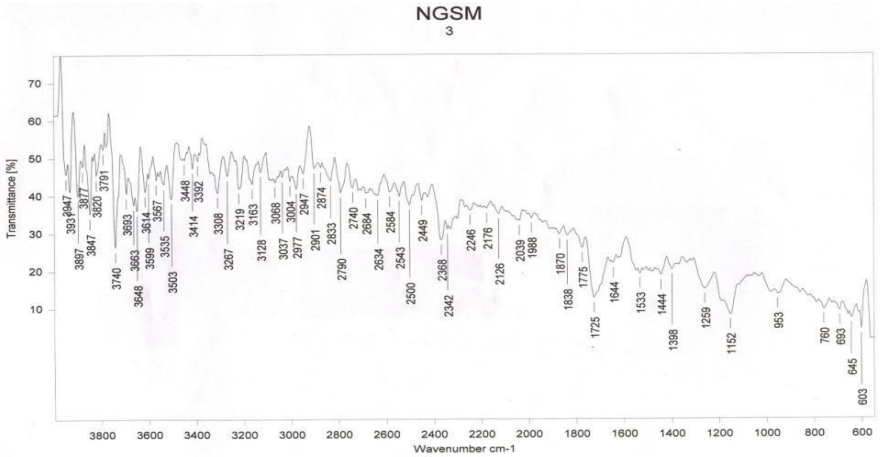

Figure 3: FT-IR spectrum of pure losartan potassium admixtured with eudragit S-100

Table 2: Powder properties of losartan potassium, powder blends of middle layer and polymers

Powder Properties	Losartan Potassium	Middle Layer containing Eudragit L-100	Middle Layer containing Eudragit S-100	HPMC E-50 LV + Eudragit L-100	HPMC E-50 LV + Eudragit L-100
Bulk density (gm/cc)	0.512±0.02	0.7050.14	0.714±0.56	0.684±0.78	0.695±0.02
Tapped Density (gm/cc)	0.629±0.17	0.767±0.20	0.795±0.93	0.746±0.82	0.781±0.048
Angle of Repose (°)	33.12±0.63	25.89±0.43	25.39±0.66	23.09±0.27	24.15±0.02
Carr's Index	19.49±0.51	8.29±0.91	8.35±0.94	7.62±0.58	7.28±0.33

Table 3: Characterization of trilayer matrix tablets of losartan potassium

Formulation Code	Hardness(Kg/cm^2)	Friability	Weight variation	Drug content
F1	7.6±0.73	0.76	444.3±2.34	99.06 ± 0.9832
F2	8.1±0.81	0.71	452.5±1.95	99.72 ± 0.8893
F3	8.3±0.11	0.68	449.2±1.12	100.2 ± 0.6673
F4	7.1±0.47	0.89	442±2.90	99.67 ± 0.5468
F5	7.4±0.019	0.91	447.5±1.23	98.95 ± 0.1612
F6	7.9±0.039	0.75	440.1±3.1	98.93 ± 0.9871

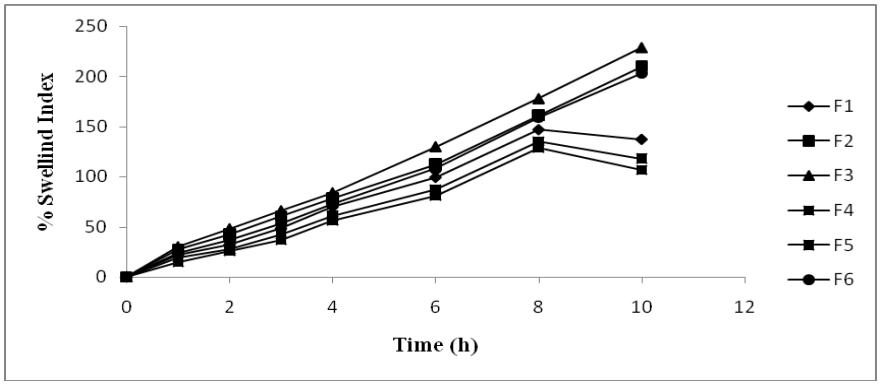

Figure 4: Swelling index of formulation F1-F6

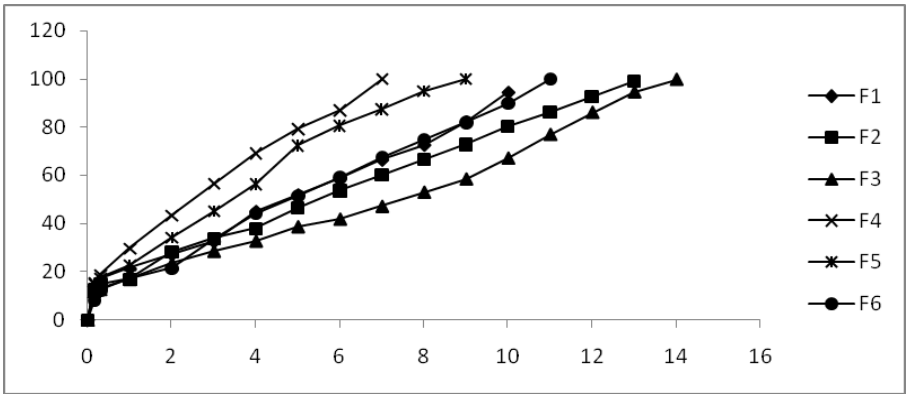

Figure 5: Comparative percentage release profile of F1-F6 formulation in phosphate buffer pH 6.8

found to have a bulk density of 0.512gm/cc and tapped density of 0.629 gm/cc. Flowability of losartan potassium was fair with an angle ofrepose of 33.12 and Carr's index value of 19.49 %.

Characterization of trilayer matrix tablets of losartan potassium

Sustained release tablets generally have hardness in the range of 7-10 kg/cm^2. In the case of trilayer tablets formulation, hardness of the tablets was found to be in the range of 7.1-8.3 kg/cm^2.The friability of all formulations was found to be less than 1.0 % and hence the tablets with lower friability may not break during handling on machines and or shipping. All the batches of tablets complied with the weight variation limits as per the Indian Pharmacopoeia i.e., ±5% limit. The drug content in different formulation was highly uniform and in

Table 4: Comparison of different orders of in vitro release of drug from trilayer matrix tablets of losartan potassium

Formulations Code	Zero-order	First-order	Higuchi model
F1	y = 8.175x + 9.938 R^2 = 0.983	y = -0.124x + 2.124 R^2 = 0.746	y = 26.81x - 3.463 R^2 = 0.948
F2	y = 6.961x + 10.29 R^2 = 0.99	y = -0.102x + 2.114 R^2 = 0.763	y = 26.36x - 5.592 R^2 = 0.962
F3	y = 6.334x + 7.090 R^2 = 0.982	y = -0.091x + 2.140 R^2 = 0.702	y = 24.41x - 7.505 R^2 = 0.913
F4	y = 13.00x + 12.91 R^2 = 0.973	y = -0.208x + 2.091 R^2 = 0.793	y = 36.38x - 2.522 R^2 = 0.987
F5	y = 10.69x + 11.69 R^2 = 0.977	y = -0.175x + 2.117 R^2 = 0.861	y = 33.70x - 4.667 R^2 = 0.972
F6	y = 8.502x + 6.833 R^2 = 0.993	y = -0.120x + 2.123 R^2 = 0.743	y = 29.31x - 8.761 R^2 = 0.957

the range of 98.93-100.2%. Characterization data is shown in Table 4.

Swelling Studies

In the alkaline medium pH 6.8, HPMC showed good swelling property. In trilayer tablets of losartan potassium, F3 showed highest degree of swelling index 229.63% whereasF4 showed least swelling with a swelling index of 129.21%. As the amount of HPMC was higher in formulation F3, so F3 showed good swelling index. Formulation F4 showed lower percentage of swelling index because of lower amount of HPMC as shown in the Figure 4.

***In vitro* drug release profile**

The release of losartan potassium from different formulations was carried out in phosphate buffer pH 6.8. The percentage of drug release was calculated and plotted againsttime and the release profiles were obtained (Figure 5).

The trilayer layer tablets sustained the drug release up to 10 h. The best sustained release profile was seen in F3, though F2, F6 and F1 were next in sequence.F3 has released least percentage of drug among all formulationsbecause of higher amount of HPMC E-50LV in F3 and it alo shown high degree of swelling (229.53%).The formulation F4 has the least release retardant property. It showed almost 99% drug release within 8 h which was because of lower amount of HPMC E-50LV. Rate of drug release from all the formulations is in the following order at the end of 14 h of *in vitro* dissolution studies. F3 (99.65% 14 h) > F2 (98.91% 13 h) > F6 (99.83% 11 h) > F1 (94.39% 10 h) > F5 (95.16% 8 h) > F4 (99.97% 7 h).

Drug release kinetics

In the present investigation drug release mechanism is best fitting to zero order and Higuchi model because regression coefficient was seen closest to 1 in these models which conforms diffusion assisted mechanism of release.Results are shown in Table 5.

Stability studies

The stability of the drug in the formulation was confirmed by UV scanning and no spectral change was observed. The drug content obtained for every 2 weeks showed that drug content did not differ from initial drug content by more than 3% indicating that the formulations are stable.

CONCLUSION

It was concluded thattrilayer matrix tablets of losartan potassium can be successfully prepared by direct compression techniques using different polymers combination.The drug release from all the formulations was found to be Zero order and best fitted to Higuchi's model confirming to be diffusion assisted mechan- ism. From *in vitro* drug release profile and drug release mechanism data, it was evident that formulation F3 is the best formulation among the all formulations. Stability study was carried out for all the formulations and revealed that there was no significant changes.

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