doi.org/10.36721/PJPS.2020.33.5.SUP.2231-2237.1

Design, Preparation and evaluation of various parameters of controlled release matrices of losartan potassium using polymers combination

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Abstract: Controlled release formulations are administered once a day and reduce frequency of dose and ensuring patient's compliance. In the current research controlled release matrices of losartan potassium formulated with polymeric combinations of ethocel grade 7 with carbopol 934P NF using different concentrations of polymers. In some polymeric tablets, Co-excipients like CMC, Starch, HPMC was added by replacing of 10% of filler in formulations at 10:5. Tablets were prepared by direct compression method and evaluated for physicochemical characteristics. USP Method-1 (rotating basket method) was used to carry out dissolution study in phosphate buffer pH 6.8. Drug release kinetics determined and comparison of dissolution patterns was done with reference tablets. The polymeric combinations well retarded drug release and drug was released by anamolous non-fickian diffusion mechanism. Dissolution profiles of tested tablets and reference tablets were found not similar. Drug release rate was increased by co-excipients. It was concluded from this research work that this polymeric combination can be used efficiently in designing of controlled release martices.

Keywords: Controlled release formulation, dissolution, combination, Losartan Potassium

INTRODUCTION

Losartan potassium belongs to angiotensin II receptor antagonistic as it blocks AT1 receptor and used for treatment of hypertension, delaying diabetic neuropathic progression and minimizes renal diseases. It is also effective in treating proteinuria and microalbuminuria. It has short half-life of 1.5 to 2.5 hours (El-Deen *et al.,* 2107). Oral route is the most preferable route for administration of tablet dosage forms (Madhuri *et al.,* 2017). Controlled release formulations have advantages over conventional drug delivery as controlled release formulations have predictable drug release kinetic and reduce drug fluctuation in plasma, reduce dosage frequency and reduce sides effects, weather oral or transdermal (Asija *et al.,* 2014, Rehman *et al*., 2019a and 2019b, Samiullah *et al*., 2020). Direct compression is simplest method for development of controlled release matrix tablets as it has few manufacturing step, few persons involved as manufacturing and least manufacturing cost of with high production rates (Rahman *et al.,* 2011). Direction method also requires less excipients for manufacturing (Manish and Abhay, 2012). Polymers has variety of uses like rate retarding agents, used as binder, filming coating agents and as rate retarding agents it can be added in matrix tablets (Bhowmik *et al.,* 2012). Previously polymeric substances like HPMC K4M, HPMC K100LV and HPMC K100M were added to develop Prazosin HCl directly compressed CR tablets (Sarkar *et al.,* 2016). Controlled release matrices of Enalapril Maleate were designed with different polymeric materials separately of in blended form such as, HPMC K100 and K15 as well HPC (Shah *et al.,* 2016). Losartan Potassium is a suitable candidate for designing controlled release matrices with combination of polymeric materials such as Ethocel grade 7 with carbopol 934P NF that might improve therapeutic outcome and avoid non-compliance issues.

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MATERIALS AND METHODS

Materials

Ethocel grade 7 (Dow Chemical Co., Midland USA), losartan potassium (Well & Well Pharma, Pakistan), carbopol 934P NF (Lubrizol, Wickliffe, OH, USA), Single punch machine (Erweka, Germany) was used for tablets compression and for sample analysis. Spectrophotometer (Shimadzu, Japan) and Dissolution apparatus pharma test of Hunburg Germany were used. The chemical were used as such without any purification process as all chemical were of analytical grade.

Methods

Formulation of Tablets

Pilot batches 100 of tablets were formulated in varying ratios of drug–to-polymer (10:3, 10:4 and 10:5) and

amount of drug was kept constant in all formulation while polymeric blend amount was changed in each ratio. In some selected formulation, co-excipients 10% of filler were added by replacing filler as shown in the table 1.

Tablet preparation

Tablets were prepared by directed compression method and all materials were weighed individually. Mixed formulation mixtures except lubricant with help of pestle and mortar geometrically and passed through sieve no 32. After initial mixing lubricant was added and passed twice through the same sieve and compressed into matrice with help of single punch tableting machine and hardness was kept constant at 5-10 kg/cm^2.

Flow properties

To prepare elegant tablets study of flow properties of formulation mixtures are very vital. Flow properties can be determined from flow parameters determined angle of repose was determined according to USP specifications (USP, 2007), and similarly Carr's index (Carr's, 1965) as well as Hausner's ratios was also checked (Hausner's, 1967).

Physical characteristic

Physical characteristics like thickness, diameter, friability, weight variation and hardness was determined according to standard procedures (Jan *et al.*, 2013).

Dissolution studies

Dissolution study was performed using USP-Method-I (rotating basket method). Phosphate buffer with pH of 6.8 was used as medium and temperature was kept constant at 37±0.5^{o}C. Rotation of baskets was kept constant at 100rpm. At specific time intervals samples of 5ml were collected in triplicate and replacement volume was added using same medium. Samples were filtered through membrane filter of 0.45µ to avoid any particulate material. The analysis of drug samples was done at 205nm (λmax) with spectrophotometer (Shimadzu, Japan) and cumulative drug release was calculated from analytical curve.

Drug content uniformity

Standard solution was prepared from reference powder (100mg) was added in the same buffer used in dissolution study and again 1ml was diluted to 100ml with same solution. Filtered and analyzed spectrophotometrically, in same way sample solution was also prepared from test tablets and analyzed spectrophotometrically (Shah, 2014).

Drug release kinetics

Kinetic models were used to study release of drug like Ist-order, Zero-order, Hixon Crowell's (Xu and Sunada, 1995), Higuchi model (Higuchi, 1963) and Power Law Kinetic (Ritger and Peppas, 1987) using Microsoft Excel.

Dissolution profiles comparisons

Drug release profiles of newly developed controlled release matrices were compared with reference tablets (Cardaktin®) drug release profile with difference factor (f_1) (Costa and Jose, 2001) and similarity factor (f_2) (Yuksel *et al*., 2000).

STATISTICAL ANALYSIS

For calculating mean with standard deviation, SPSS version 4 and for other calculations excel sheet was used.

RESULTS

Flow characteristics

Flow properties were assessed from results of flow parameters which indicated good to excellent flow properties. Results are given table. 2.

Physical tests

The prepared matrices were elegant in appearance and the results showed that physical tests complied the specification and all the results in table 3.

Content uniformity

Content uniformity was determined according to specified methods and results are given in table 4.

Drug release from matrices

It was found the combination of Ethocel 7 grade and Carbopol 934P NF well extended when used in different ratios with drug. Polymeric combinations of 7 Premium grade of Ethocel and Carbopol 934P NF extended over 24 hours in different ratios as 10:3 matrices release 68% of drug, 10:4 prolonged drug release rates (66%) while 10:5 release 63% of drug. When 7FP Premium grade of Ethocel was combined with Carbopol 934P NF also extended over 24 hours in different ratios as 10:3 matrices release 67% of drug and 10:4 prolonged drug release rates upto 65% while 10:5 release 62% of drug. The current study results are shown in fig. 1.

Co-excipients influence

When the co-excipients influence was checked in the formulation of 10:5 indicated that increase was observed in drug release. HPMC when added in the matrices increased release and was found 79.39 and 78.88% respectively. Similarly CMC enhanced 78.58 and 77.45% respective release rates in D: P 10:5 formulation and starch also increased the rates 76 and 75% in tablets at 10:5. These results are shown in fig.2.

Release kinetics

Release data of Losartan Potassium from various polymeric matrices were put into various kinetic models and results are given in the table 5 that showed that drug was released by anamolous diffusion mechanism.

Dissolution profiles comparison

Dissolution comparison showed that values of f_1 (37.85-52.43) and f_2 (13.18-20.13) did not found in the specified limits of f_1 (1-15) and f_2 (50-100) (Khan *et al.*, 2015; Costa and Jose, 2001; Shah *et al.*, 2012; Yuksel *et al*., 2000). The results as shown in table 6.

Table 1: Composition of Tablets

CR tablets without Co-excipients					
D:P	Drug (mg)	Polymeric blend (Ethocel 7 Premium + Carbopol 934P NF and Ethocel 7 FP Premium + Carbopol 934P NF) (mg)		Filler (mg)	Magnesium Stearate 0.5% (mg)
10:3	100	30		69	1.0
10:4	100	40		59	1.0
10:5	100	50		49	1.0
CR tablets with Co-excipients					
D:P	Drug (mg)	Polymeric blend (mg)	Filler (mg)	Lubricant (0.5%)	Co-excipient (10% of filler of HPMC or CMC or Starch)
10:5	100	50	44.1	1.0	4.9mg
Drug: Losartan Potassium Filler: Spray dried lactose					

Table 2: Flow Characteristics of formulations

Formulations	Angle of Repose	Carr's Index	Hausner's Ratio
	(Mean±SD, n=3)		
Ethocel 7P + Carbopol 934P NF (10:3)	30.53±0.21	11.69±0.52	1.12±1.42
Ethocel 7FP + Carbopol 934P NF (10:3)	31.32±0.15	12.72±0.19	1.13±1.50
Ethocel 7P + Carbopol 934P NF (10:4)	30.42±0.31	11.71±0.52	1.12±1.16
Ethocel 7FP + Carbopol 934P NF (10:4)	28.09±0.33	9.32±0.56	1.11±1.09
Ethocel 7P + Carbopol 934P NF (10:5)	31.16±0.55	12.76±0.03	1.10±0.31
Ethocel 7FP + Carbopol 934P NF (10:5)	30.69±0.30	11.68±0.52	1.12±0.60
Ethocel 7P + Carbopol 934P NF (10:5) with HPMC	29.05±0.15	10.86±0.18	1.11±0.27
Ethocel 7FP + Carbopol 934P NF (10:5) with HPMC	30.23±0.36	11.21±0.56	1.15±0.33
Ethocel 7P + Carbopol 934P NF (10:5) with CMC	30.31±1.45	11.27±0.54	1.14±0.47
Ethocel 7FP + Carbopol 934P NF (10:5) with CMC	30.62±0.20	11.84±0.23	1.15±0.29
Ethocel 7P + Carbopol 934P NF (10:5) with Starch	29.09±0.66	10.13±0.42	1.10±0.64
Ethocel 7FP + Carbopol 934P NF (10:5) with Starch	31.04±0.35	12.95±0.62	1.15±1.23

Table 3: Physical Characteristics of CR Tablets

Formulations	Thickness (mm, n=10)	Diameter (mm, n=10)	Friability (%, n=20)	Hardness (kg/cm^2, n=10)	Weight Variation (mg, n=20)
Ethocel 7P + Carbopol 934P NF (10:3)	2.5±0.11	8.0±0.22	0.15±0.78	8.5±0.15	201±0.12
Ethocel 7FP + Carbopol 934P NF (10:3)	2.4±0.05	8.0±0.33	0.13±0.16	9.3±0.19	200±0.25
Ethocel 7P + Carbopol 934P NF (10:4)	2.5±0.36	8.0±0.13	0.18±0.24	8.4±0.54	202±0.14
Ethocel 7FP + Carbopol 934P NF (10:4)	2.4±0.23	8.0±0.18	0.22±0.35	9.6±0.34	201±0.23
Ethocel 7P + Carbopol 934P NF (10:5)	2.5±0.47	8.0±0.25	0.11±0.16	8.5±0.62	201±0.17
Ethocel 7FP + Carbopol 934P NF (10:5)	2.4±0.35	8.0±0.32	0.20±0.21	9.7±0.55	200±0.53
Ethocel 7P + Carbopol P934 NF (10:5) with HPMC	2.5±0.11	8.0±0.34	0.09±0.05	8.6±0.29	201±0.06
Ethocel 7FP + Carbopol P934 NF (10:5) with HPMC	2.4±0.32	8.0±0.10	0.05±0.29	9.6±0.33	203±0.08
Ethocel 7P + Carbopol P934 NF (10:5) with CMC	2.5±0.18	8.0±0.28	0.04±0.33	8.4±0.72	198±0.24
Ethocel 7FP + Carbopol P934 NF (10:5) with CMC	2.4±0.14	8.0±0.16	0.03±0.28	8.5±0.31	202±0.32
Ethocel 7P + Carbopol P934 NF (10:5) with Starch	2.5±0.36	8.0±0.26	0.07±0.37	7.6±0.16	203±0.12
Ethocel 7FP + Carbopol P934 NF (10:5) with Starch	2.4±0.51	8.0±0.69	0.10±0.32	8.7±0.45	198±0.14

Tablet 4: Content uniformity test

Formulations	Content Uniformity (%, Mean of n=10)
Ethocel 7P + Carbopol 934P NF (10:3)	99.05
Ethocel 7FP + Carbopol 934P NF (10:3)	99.08
Ethocel 7P + Carbopol 934P NF (10:4)	99.34
Ethocel 7FP + Carbopol 934P NF (10:4)	98.76
Ethocel 7P + Carbopol 934P NF (10:5)	99.31
Ethocel 7FP + Carbopol 934P NF (10:5)	99.44
Ethocel 7P + Carbopol 934P NF (10:5) with HPMC	99.14
Ethocel 7FP + Carbopol 934P NF (10:5) with HPMC	99.03
Ethocel 7P + Carbopol 934P NF (10:5) with CMC	98.66
Ethocel 7FP + Carbopol 934P NF (10:5) with CMC	98.97
Ethocel 7P + Carbopol 934P NF (10:5) with Starch	98.55
Ethocel 7FP + Carbopol 934P NF (10:5) with Starch	98.76

Table 5: Drug Release Kinetics

Ist-order Kinetic		Zero-order Kinetic		Hixon Crowell's Erosion Model		Highuchi Diffusion Model		Power Law		
$k_1 \pm SD$	r^2	$k_2 \pm SD$	r^2	$k_3 \pm SD$	r^2	$k_4 \pm SD$	r^2	$k_5 \pm SD$	r^2	N
Losartan Potassium + Ethocel 7P + Carbopol 934P NF (10:3) Controlled Release Matrix Tablets										
-0.387±0.439	0.889	7.465±0.247	0.979	0.357±0.277	0.937	7.548±0.658	0.988	0.001±0.023	0.957	0.612
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:3) Controlled Release Matrix Tablets										
-0.393±0.774	0.879	8.468±0.346	0.985	0.279±0.213	0.898	7.565±0.467	0.989	0.002±0.135	0.927	0.579
Losartan Potassium + Ethocel 7P + Carbopol 934P NF (10:4) Controlled Release Matrix Tablets										
-0.387±0.545	0.858	7.687±0.322	0.992	0.243±0.265	0.864	6.676±0.654	0.992	0.003±0.042	0.923	0.698
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:4) Controlled Release Matrix Tablets										
-0.377±0.468	0.774	7.546±0.656	0.991	0.254±0.254	0.825	6.547±0.457	0.993	0.004±0.324	0.929	0.683
Losartan Potassium + Ethocel 7P + Carbopol 934P NF (10:5) Controlled Release Matrix Tablets										
-0.353±0.433	0.866	8.754±0.378	0.972	0.254±0.416	0.898	7.532±0.117	0.968	0.023±0.127	0.969	0.896
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:5) Controlled Release Matrix Tablets										
-0.154±.0.165	0.696	8.722±0.565	0.979	0.237±0.437	0.929	7.657±0.349	0.979	0.079±0.272	0.978	0.834
Losartan Potassium + Ethocel 7P + Carbopol 934P NF (10:5) Controlled Release Matrix Tablets with HPMC										
-0.448±0.132	0.434	4.232±0.281	0.882	0.265±0.130	0.785	4.632±0.376	0.894	0.016±0.092	0.982	0.721
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:5) Controlled Release Matrix Tablets with HPMC										
-0.276±0.245	0.889	4.321±0.375	0.992	0.291±0.238	0.968	5.041±0.382	0.991	0.013±0.022	0.981	0.793
Losartan Potassium + Ethocel 7P + Carbopol 934P NF (10:5) Controlled Release Matrix Tablets with CMC										
-0.451±0.521	0.884	6.723±0.226	0.990	0.246±0.765	0.903	6.624±0.154	0.993	0.024±0.035	0.978	0.728
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:5) Controlled Release Matrix Tablets with CMC										
-0.463±0.843	0.817	6.476±0.551	0.989	0. 257±0.339	0.923	4.834±0.547	0.991	0. 034±0.679	0.979	0.798
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:5) Controlled Release Matrix Tablets with Starch										
-0.391±0.0345	0.876	6.482±0.436	0.987	0.248±0.384	0.977	5.276±0.766	0.990	0.037±0.454	0.985	0.711
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:5) Controlled Release Matrix Tablets with Starch										
-0.382±.0.032	0.888	6.376±0.978	0.986	0.254±0.364	0.979	5.764±0.403	0.993	0.045±0.124	0.989	0.872

Table 6: Results of Dissolution Patterns Comparison

Test Formulation Versus Reference Cardaktin® Tablet	f_1 values	f_2 values
Losartan Potassium+ Ethocel 7P + Carbopol 934P NF (10:3) CR Matrix Tablet versus Cardaktin® Tablet	42.62	17.96
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:3) CR Matrix Tablet versus Cardaktin® Tablet	52.43	13.18
Losartan Potassium + Ethocel 7P + Carbopol 934P NF (10:4) CR Matrix Tablet versus Cardaktin® Tablet	37.85	19.95
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:4) CR Matrix Tablet versus Cardaktin® Tablet	41.38	17.39
Losartan Potassium + Ethocel 7P + Carbopol 934P NF (10:5) CR Matrix Tablet versus Cardaktin® Tablet	37.98	20.13
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:5) CR Matrix Tablet versus Cardaktin® Tablet	43.58	18,34
Losartan Potassium + Ethocel 7P + Carbopol 934P NF (10:5) with HPMC CR Matrix Tablet versus Cardaktin® Tablet	43.69	13.86
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:5) with HPMC CR Matrix Tablet versus Cardaktin® Tablet	44.75	13.97
Losartan Potassium + Ethocel 7P + Carbopol 934P NF (10:5) with CMC CR Matrix Tablet versus Cardaktin® Tablet	47.68	13.31
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:5) with CMC CR Matrix Tablet versus Cardaktin® Tablet	48.18	12.98
Losartan Potassium + Ethocel 7P + Carbopol 934P NF (10:5) with Starch CR Matrix Tablet versus Cardaktin® Tablet	46.23	14.28
Losartan Potassium + Ethocel 7FP + Carbopol 934P NF (10:5) with Starch CR Matrix Tablet versus Cardaktin® Tablet	46.55	13.58

DISSCUSION

Flow properties are very important for development of good tablet dosage forms. Flow properties were determined and angle of repose was checked and found 31.32±0.15 to 28.09±0.33. Carr's index was also determined and range of results was from 9.32±0.56 to 12.95±0.62. Flow parameter Hausner's ratios was also determined and was found from 1.10±0.31 to1.15±1.23. Formulations were added 0.5% of lubricant already to improve flow properties. These results are in similarity with the specifications given in official compendia USP (USP, 2007). Tablets physical characteristics were determined and it found within acceptable limits as adopted by authors (Shah *et al.,* 2011) and (Jan *et al.,* 2012). Content uniformity of controlled release matrices was found from 98.55% to 99.44%. These results are within standard range of USP for Losartan Potassium that is 90-110% (USP29-NF24, 2006). In dissolution study drug release extended for 24 hours that showed excellent drug

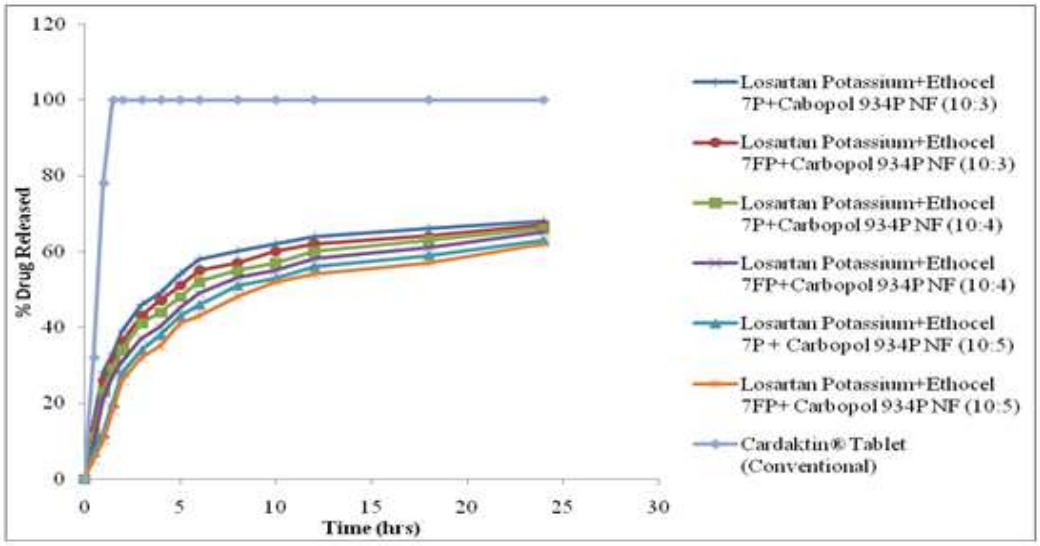

Fig. 1: CR Losartan Potassium Matrices release patterns as n=3 and mean±SD

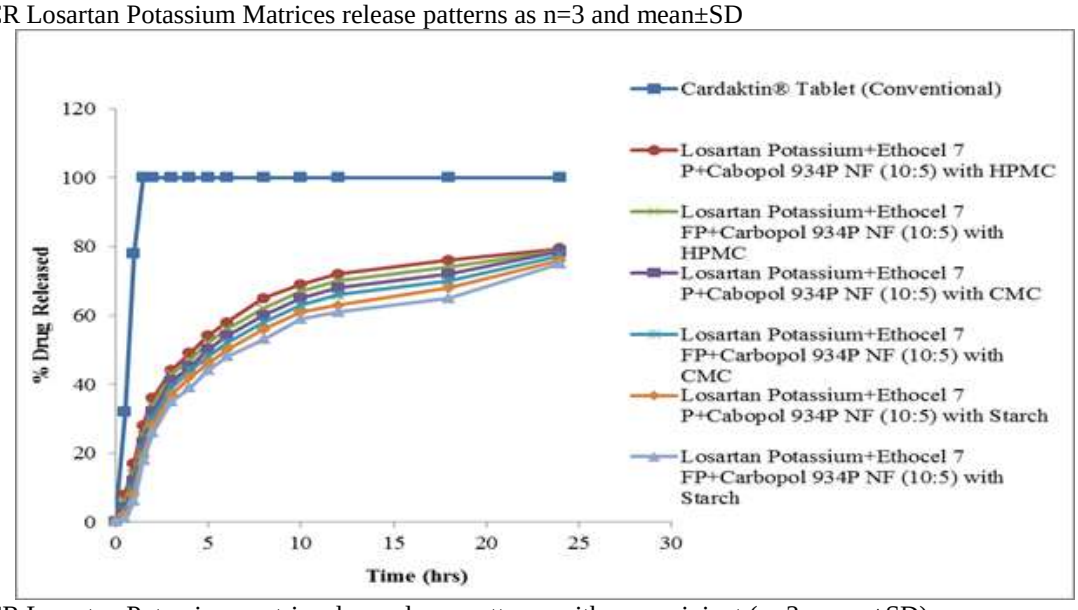

Fig. 2: CR Losartan Potassium matrice drug release patterns with co-excipient (n=3, mean±SD)

release from polymeric matrices. The results are in similarity with authors who found the ethocel of grade prolonged release rates (Shah *et al.*, 2011). As Carbopol has swelling capability when gets hydrated as well reduces pores sizes and retard the rate at which drug was released and conforms the results of authors (Rehman *et al.*, 2013) also found similar results with Carbopol when used as rate controlling agent. Co-excipient enhanced the drug release from polymeric tablets as these might acted as disintegrants when used in small amounts. This might be due to the reason that smaller amounts of these co-excipients enhanced the release of Losartan potassium acting as disintegrants and the results similar with authors finding (Jan *et al.*, 2012) and (Khan *et al.*, 2013) that increase drug rates was noted when used co-excipients in small quantities. The drug release mechanisms were obtained from power law kinetic model and the n were also calculated which is drug release exponent that ranged from 0.579 to 0.872 showed anamolous non-fickian diffusion kinetics. As n value is greater than 0.5 and less than 1 that indicating that drug is released by anamolous non-fickian diffusion (Ritger and Peppas, 1987). Authors (Ramzan *et al.*, 2015) also found that release of drug occurred by anamolous non-fickian diffusion form CR matrices. The dissolution profile was having no match with reference dissolution as the results were not with the acceptable limits (Costa and Jose, 2001; Yuksel *et al.*, 2000). It was noted that this polymeric combination well extended the drug release rates.

CONCLUSION

It was observed in this study that polymeric combination of ethocel grade 7 and carbopol 934P NF well extended

release rates as used in different concentrations. Drug from directly compressed CR matrice was released by anamolous non-fickian diffusion. Co-excipients increased the rates of drug release. There was no similarity in reference and tested formulations dissolution profiles. This combination of polymeric materials can be easily used in preparation of directly compressed tablets to control the drug release rate that might improve patient's compliance.

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