Formulation and i*n vitro* evaluation of directly compressed controlled release tablets designed from the Co-precipitates

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Abstract: Controlled release dosage forms provide sustained therapeutics effects for prolonged period of time and improve patient compliance. In present study, controlled release co-precipitates of Metoprolol Tartrate and Losartan Potassium were prepared by solvent evaporation method using polymers such as Eudragit RL 100 and Carbopol 974PNF and controlled release tablets were directly compressed into tablets. *In-vitro* dissolution of controlled release co-precipitates were performed by USP Method-II (paddle method) and tablets were evaluated by USP Method-I (rotating basket method) in phosphate buffer (PH 6.8) using pharma test dissolution apparatus. The temperature was maintained constant at 37±1.0 ^{0}C and the rotation speed of paddle and basket was kept constant at 100rpm. Drug release mechanisms were determined by applying Power Law kinetic model. The difference and similarity of dissolution profiles test formulations with reference standards were also determined by applying difference factor (f_1) and similarity factor (f_2). The results showed that the controlled release co-precipitates with polymer Eudragit RL 100 of both the drug extended the drug release rates for 10 hours and those having polymer Carbopol 974P NF extended the drug release rates for 12 hours. The controlled release tablets prepared from controlled release co-precipitates extended the drugs release up to 24 hours with both the polymers. The drug was released by all tests anomalous non fickian mechanism except F1 and F5 do not follow Power Law. The f_1 and f_2 values obtained were not in acceptable limits except F15 whose values were in acceptable limits. It is concluded from the present study that polymers (Eudragit RL 100 and Carbopol 974P NF) can be efficiently used in development of controlled release dosage forms having predictable kinetics.

Keywords: Metoprolol tartrate, losartan potassium, dissolution, controlled release, Eudragit RL 100, Carbopol 974 P NF

INTRODUCTION

Drugs administration by oral route is most preferred and tablets are orally administered dosage form and preferred both by physicians and patients. Treatment of chronic disorders need long term therapy and conventional dosage forms are given in multiple doses. As compared to conventional dosage forms, controlled release tablets have advantages such as maintaining constant plasma drug level, reduced dosing frequency and improved patient compliance (Kar *et al.,* 2009).Controlled release co-precipitates of Morphine have been developed and studied to achieve predictable drug delivery by authors (Alvarez-Fuentes *et al.,* 1994). The physicochemical improvement of Ibuprofen has investigated by co-precipitation using PVP and agar (Maghsoodi and Kiafar 2013). Extended release co-precipitates of Ibuprofen using Carbopol 934P NF were prepared and *in-vitro* release was conducted by authors (Khan and Jiabi, 2000a). In development of controlled release dosage forms, bio functional polymers are extensively used (Akhlaq *et al.,* 2014; Jan *et al.,* 2011, 2012 and 2013a&b*;* Khan *et al.,* 2013 and Shah *et al.,* 2011 & 2012). Carbopol is used in the development of controlled release dosage form as rate controlling agent and is high molecular weight polymers formed from chemically cross-linking of acrylic acid with either polyalkenyl alcohols or divinyl glycol (Tabandeh and Mortazavi, 2014).Carbopol 974 NF is crossed-linked polymer of acrylic acid and is having high molecular weight and is a synthetic polymer. Carbopol 974 NF is hydrophilic and has the ability to absorb water, swells and cross-linked configuration makes it suitability for development of controlled release dosage forms (Rehman *et al.,* 2013; Khan and Jiabi 1998b). Eudragit RL 100 is used in the designing of controlled release dosage form and is copolymer of ethyl acrylate, methyl methacrylate and low quantity of methyl acrylic acid ester with quaternary ammonium groups. It is insoluble, having pH independent swelling and suitable for matrix structures (Sonje and Chandra, 2013). Metoprolol Tartrate is having short half-life 3-4 hours and is cardio selective β-blocker used in cardiac diseases such as hypertension, angina pectoris and myocardial infarction (Naikkhanvte *et al.,* 2012). Losartan Potassium is angiotensin-II receptor antagonist having short half-life of 1.5-2.5 hours (Raju *et al.,* 2010). Controlled release matrix tablets preparation by direct compression is a simple manufacturing method, economical process and easier to scale up (Khan *et al.,* 2013). In present study the main objective was to develop

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controlled release co-precipitates of Metoprolol Tartrate and Losartan Potassium, direct compression into controlled release tablets, *in vitro* evaluation, investigation of release mechanism and dissolution profiles comparison with reference formulations. The development of controlled release Co-precipitated and the controlled release tablets might extend the drug release rates up to 24 and this might reduce the dosage frequency of the selected drugs and ensure compliance of the patient as compare to conventional tablets.

MATERIALS AND METHODS

Materials

Metoprolol Tartrate and Losartan Potassium were gifted by (Well and Well Pharma, Islamabad, Pakistan), Eudragit RL 100 (Rohm GMBH, Germany), Carbopol 974P NF (Lubrizol, Wickliffe, OH, USA), Single Punch Tableting Machine (Erweka, AR 400, Germany), Pharma Test Dissolution Apparatus (Pharma Test, PTWS-11/P, Hunburg, Germany) and UV-Visible double beam spectrophotometer (Shimadzu 1601, Japan)

Methods

Formulation of controlled release co-precipitates

Controlled release co-precipitate of Metoprolol Tartrate and Losartan Potassium with polymer (Eudragit RL 100) was formulated at drug-to-polymer ratios of 10:1, 10:2, 10:3and 10:4 as given in the table 1. The formulations with polymer Carbopol 934 NF are givenin table 2 at various drug-to-polymer ratios.

Table 1: Formulations of Metoprolol Tartrate and Losartan Potassium and Eudragit RL100 Controlled Release Co-precipitates

Co-precipitates of Metoprolol Tartrate –Eudragit RL 100		
Formulations	Drug (gm)	Polymer (gm)
F1	3.0	0.3
F2	3.0	0.6
F3	3.0	0.9
F4	3.0	1.2
Co-precipitates of Losartan Potassium –Eudragit RL 100		
Formulations	Drug (gm)	Polymer (gm)
F5	3.0	0.3
F6	3.0	0.6
F7	3.0	0.9
F8	3.0	1.2

Preparation

The controlled release co-precipitate was prepared by solvent evaporation method (Khan and Jiabi, 2000). Metoprolol Tartrate, Losartan Potassium, Eudragit RL 100 and Carbopol 934P NF were weighed using analytical balance (Shimadzu; AX 200, Japan) according to the respective drug-to-polymer ratios. The controlled release co-precipitates were prepared by solvent evaporation method. The drug and polymer were separately dissolved in small amounts ethanol for each formulation. Sucrose fatty acid ester solution 25% (w/v) aqueous solution of 450ml and temperature was maintained at 5^{o}C was incorporated into the respective alcohol solutions. The mixtures were stirred at 500rpm for 20 minutes using constant velocity stirrer (Velp Scientica, Germany) and passed the co-precipitate through membrane filter (0.45µ) and placed at 60^{o}C for drying to attain constant weight. The dried co-precipitates were through sieve No.20 and labeled the containers and stored in desiccator.

Tablet 2: Formulations of Metoprolol Tartrate and Losartan Potassium and Carbopol 974P NF Controlled Release Co-precipitates

Co-precipitates of Metoprolol Tartrate – Carbopol 974P NF		
Formulations	Drug (gm)	Polymer (gm)
F9	4.0	0.4
F10	4.0	0.8
F11	4.0	1.2
Co-precipitates of Losartan Potassium – Carbopol 974P NF		
Formulations	Drug (gm)	Polymer (gm)
F12	4.0	0.4
F13	4.0	0.8
F14	4.0	1.2

Table 3: Drug release Mechanism of Controlled Release Co-precipitates

Power Law Kinetic Model			
Formulations#	r^2	K±SD	n
F1	0.938	0.004±0.011	0.460
F2#	0.964	0.022±0.064	0.539
F3#	0.949	0.059±0.180	0.586
F4#	0.933	0.415±1.343	0.684
F5#	0.944	0.005±0.016	0.478
F6#	0.934	0.035±.0109	0.547
F7#	0.924	0.196±0.635	0.643
F8#	0.912	0.956±3.204	0.746
F9#	0.967	0.016±0.041	0.515
F10#	0.973	0.266±0.602	0.678
F11	0.981	0.126±3.100	0.815
F12	0.982	0.025±0.062	0.572
F13	0.971	0.123±0.314	0.652
F14	0.965	0.441±1.228	0.727

Preparation of tablets from co-precipitates

The controlled release co-precipitates of Metoprolol Tartrate (equivalent to 200mg of Metoprolol Tartrate) and the controlled release co-precipitates Losartan Potassium (equivalent to 100mg of Losartan Potassium) were weighed using analytical balance (Shimadzu; AX 200, Japan). The various formulations of controlled release co-precipitates of both the drug were prepared directly compression into controlled release tablets using single punch tablets compression machine (Erweka, AR 400, Germany) and tablets formulations (F15-F28) were

obtained. The hardness was kept constant ranged from 7-10kg/cm^2.

In-vitro evaluation

In-vitro dissolution studies of controlled release co-precipitates equivalent to 200mg of Metoprolol Tartrate (200mg Metoprolol Tartrate powder was taken as control) and 100mg controlled release co-precipitate of Losartan Potassium (100mg Losartan Potassium powder was used as control) were conducted by using USP Method II (Paddle method) in Pharma Test dissolution apparatus (PTWS-11/P, Hunburg, Germany). Controlled release tablets developed from the co-precipitates of both drugs and their respective reference standard tablets were evaluated according to USP Method I (rotating basket method). Phosphate buffer (PH 6.8) was used as a dissolution medium and each flask was filled up to 900ml of 8 stations of the dissolution apparatus. The temperature of the dissolution mediums were maintained at 37±0.5°C and rotation speed of basket was kept constant at 100rpm. Samples of 5ml were collected and filtered using membrane filter (0.45µ). Replacement volume (5ml) was added to each flask with from same dissolution medium. The samples of Metoprolol Tartrate were analyzed at λ_{max} 275nm and Losartan Potassium at 205nm (λ_{max}) using UV-Visible Double beam Spectrophotometer (Shimadzu 1610, Japan). The studies were performed in triplicate and the values of mean absorbances were incorporated analytical curves of and percent drug release was determined.

Drug release kinetics

In order to determine drug release kinetics, Power Law was applied to the cumulative drug release data for the formulations.

Power Law equation; $M_t / M_\infty = K\, t^{n}$ Eq.1

M_t / M_∞ show the fraction of drug released at time t and K_5 indicates the rate constant. Where, n shows the release exponent, when n value is 0.5 representing quasi-fickian diffusion, when n value is >0.5 representing anomalous non fickian release mechanism and n value is = to 1 indicates non fickian zero order release kinetics (Ritger and Peppas, 1987).

Dissolution profiles difference and equivalency

In order to determine the dissolution profile comparison, difference factor (f_1) and similarity factor (f_2) were applied to the drug release data. Metoprolol Tartrate powder (control) and Losartan Potassium powder (control) were used as reference standard for comparison of respective controlled release co-precipitates. Mepressor® SR tablets (200mg Metoprolol Tartrate sustained release tablets) were used as reference standard for comparison with the controlled release tablets of Metoprolol Tartrate prepared from controlled release co-precipitates of Metoprolol Tartrate and Cardaktin® tablet (100mg Losartan Potassium immediate release tablets as available in local market) were used as reference standard for comparison with controlled release tablets designed from controlled release co-precipitates of Losartan Potassium.

$$f1 = \left\{ \frac{\sum_{t-1}^{n} |R_t - T_t|}{\sum_{t-1}^{n} R_t} \right\} * 100 \qquad \text{Eq. 2}$$

$$f_2 = 50\text{Log}\ \{[1+1/n\ W_t \textstyle\sum_{t=1}^{n} (R_t\text{-}T_t)^2]^{-0.5} \times 100\} \qquad \text{Eq.3}$$

Where n represents the number of pull points, Wt shows an optional weight factor, R_t indicates the reference dissolution profile after time t and T_t shows the test formulation dissolution profile at the same time point (Costa and Jose, 2001; Yuksel *et al*., 2000).

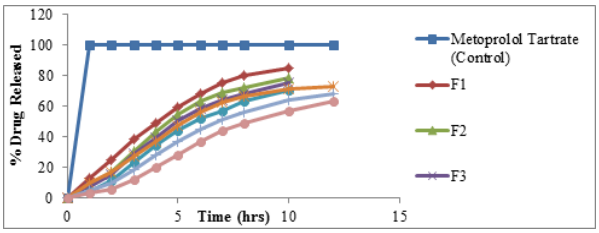

Fig. 1: Drug Release Patterns of Formulations (F1, F2, F3, F4, F9, F10 and F11) and Reference Standard

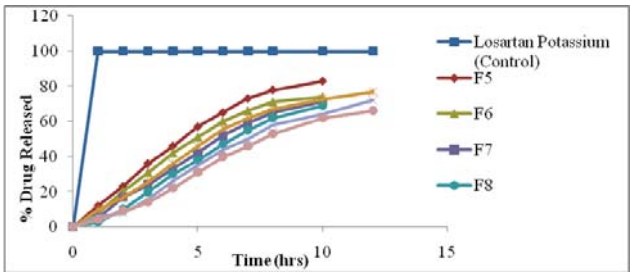

Fig. 2: Drug release Patterns of Formulations (F5, F6, F7, F8, F12, F13 and F14) and Reference Standard

RESULTS

Drug release

The drug release from controlled co-precipitate of Metoprolol Tartrate and Losartan Potassium and the tablets developed from co-precipitates are given in figs. 1, 2, 3 and 4. The controlled release co-precipitate of Metoprolol Tartrate and Eudragit RL 100 extended the drug release rates at different formulations (F1, F2, F3 and F4) released 85, 78, 75 and 70% of the drug respectively within 10 hours. The controlled release co-precipitate of Losartan Potassium and Eudragit RL 100 extended the drug release rates at different formulations (F5, F6, F7 and F8) released 83, 74, 71 and 69% of the drug respectively within 12 hours. The co-precipitates based on polymer; Carbopol 974P NF also extended the drug release rates. The formulations (F9, F10, F11, F12, F13 and F14) released 73, 78, 83, 77, 72 and 66% of the drug within 12 hours respectively. Metoprolol Tartrate

powder (control) and Losartan Potassium powder (control), each released 100% of the drug in 1 hour. The drug release was extended when the co-precipitates were compressed into tablets and the drug release of different tablets was extended for 24 hours. The tablets formulations developed from controlled release co-precipitates (F15, F16, F17, F18, F19, F20, F21, F22, F23, F24, F6, F27 and F28) released 96, 92, 89, 85, 98, 95, 93, 87, 88, 84, 82, 89, 87, and 81% in 24 hours. The reference standard Mepressor® SR tablets (containing 200mg Metoprolol Tartrate) released 100% of the drug in 12 hours and reference standard Cardaktin® tablets (containing 100mg Losartan Potassium) released 100% of the drug in 1hour.

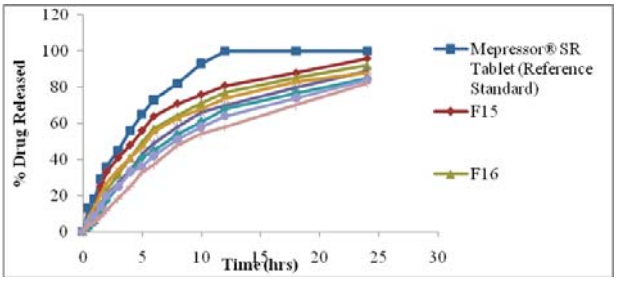

Fig. 3: Drug Release Patterns of Formulations (F15, F16, F18, F23, F9, F24 and F25) and Reference Standard

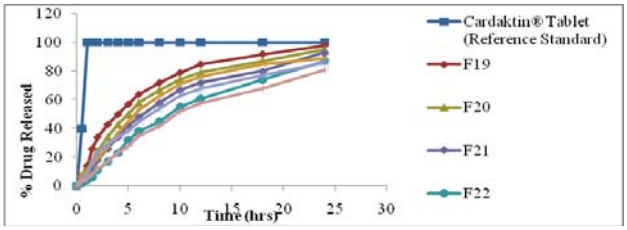

Fig. 4: Drug Release Patterns of Formulations (F19, F20, F21, F22, F26, F27 and F28) and Reference Standard

Drug release kinetics

The cumulative percent *in-vitro* drug release data was fitted in the Power Law kinetic model, in order to determine the drug release mechanism. The r^2 (co-efficient of determination) of all the test formulations ranged from 0.843 to 0.989 and rate constant values ranged from 0.004±0.011to1.133±2.705. The r^2 values of reference standards; Mepressor® SR tablets and Cardaktin® tablets were 0.976 and 0.500 respectively. The rate constant respective values of reference standards; Mepressor SR® tablets and Cardaktin® tablets were 0.005±0.012 and 0.001±1.310. The n (drug release exponent) values of different formulations show the drug release mechanisms. The n values of test formulations F1 and F5 were 0.460 and 0.478, indicating that these formulations do not follow Power Law and rest of the test formulations n values ranged from 0.515 to 0.993 and released the drug by anomalous non fickian diffusion. The respective n values of reference standards; Mepressor® SR tablets and Cardaktin tablets were 0.519 and 0.125 indicating that the Mepressor® SR tablets release the drug by anomalous non fickian diffusion and Cardaktin® tablets do not follow the Power Law. The results are given in tables 3 and 4.

Table 4: Drug release mechanism of controlled release tablets

Power Law Kinetic Model			
	r^2	K ±SD	n
F15	0.938	01.00±0.272	0.687
F16#	0.988	0.230±0538	0.776
F17#	0.961	0.962±2.252	0.865
F18#	0.981	3.056±7.539	0.980
F19#	0.944	0.053±0.146	0657
F20#	0.984	0.109±0.259	0.731
F21#	0.977	1.133±2.705	0.897
F22#	0.989	3.983±9.249	0.993
F23#	0.945	0.034±0.090	0.614
F24#	0.942	0.192±0.534	0.711
F25	0.934	0.919±2.667	0.826
F26	0.888	0.049±0.163	0.615
F27	0.869	0.177±0.601	0.663
F28	0.843	0.920±3.195	0.748
Mepressor® SR tablets	0.884	0.004±0.0143	0.519
Cardaktin® tablets	0.501	0.001±5.682	0.125

Difference and similarity of dissolution profiles

The controlled release co-precipitates of Metoprolol Tartrate dissolution profiles were compared with Metoprolol powder (control) taken as reference standard and similarly Losartan Potassium powder (control) was taken as reference standard for the dissolution profiles comparison of controlled release co-precipitates of Losartan potassium using difference factor (f_1) and similarity factor (f_2). The results showed that both Metoprolol Tartrate and Losartan Potassium controlled release co-precipitates dissolution profiles were not similar with their respective reference standards. Test controlled release matrix tablets developed from metoprolol controlled release co-precipitates dissolution profiles were compared reference standard Mepressor® SR tablets dissolution profile and Cardaktin® tablets were used as reference standard for comparison of dissolution profiles of the test controlled release tablets of Losartan Potassium developed from Losartan Potassium Controlled release co-precipitates applying f_1 and f_2. The results showed that f_1 values of tablet formulation (F15) is 13.95 and occur in acceptable range of f_1 (1-15) showed difference from dissolution profile of the reference standard. The f_2 value of F15 is 50.3 which showed similarity with reference standard dissolution profile as the f_2 acceptable range is from 50-100. Rest of test tablets

dissolution profiles do not occur within the acceptable range of either f_1 or f_2. The results are given in table 5 and 6.

DISCUSSION

Controlled co-precipitates and controlled release tablets developed by directly compression of controlled release co-precipitates based on polymer Eudragit RL 100 extended the drug release rates up to 10 hours and 24 hours respectively. This might be due to the reason that Eudragit RL100 is hydrophobic in nature and act as retardant to the solvent molecules penetration and extend the drug release rates. These results are in confirmations with authors (Karthikeyini *et al.,* 2009) that Eudragit RL 100 extended the drug release rate due to the fact that the polymer hydrophobic nature and presence of its layer on tablet surface prevent the solvent into the system. The increase in polymer concentration has also effect on the drug release rates as increase in polymer concentration in more extended the drug release rates. The n (drug release exponent) values of power law indicates drug release mechanisms (n= 0.5; indicates quasi fickian diffusion, n> 0.5; indicates anomalous non fickian diffusion, when n= 1; indicates non fickian zero order kinetics) (Ritger and Peppas, 1987).

The n values of controlled release co-precipitates (F1 and F5) are 0.460 and 0.478 which shows that these formulations do not follow the Power Law while the rest (F2-F4, F6-F8 and F15-F22) of controlled release co-precipitates and controlled release directly compressed tablets based on Eudragit RL 100 released the drug by anomalous non fickian diffusion as the n values of these formulations ranged from 0.515- 0.993. These findings

Table 5: Difference Factor (f_1) and Similarity Factor (f_2) of Reference Standard versus Controlled release Co-precipitates

Formulations#	f_1 values	f_2 values
Metoprolol Tartrate (control) vs F1	45.33	18.52
Metoprolol Tartrate (control) vs F2#	51.66	16.27
Metoprolol Tartrate (control) vs F3#	56.00	14.95
Metoprolol Tartrate (control) vs F4#	59.98	13.71
Losartan Potassium (control) vs F5#	47.44	14.16
Losartan Potassium (control) vs F6#	52.60	14.96
Losartan Potassium (control) vs F7#	56.30	13.63
Losartan Potassium (control) vs F8#	59.30	12.63
Metoprolol Tartrate (control) vs F9#	54.90	14.41
Metoprolol Tartrate (control) vs F10#	68.80	12.08
Metoprolol Tartrate (control) vs F11	68.10	10.26
Losartan Potassium (control) vs F12	54.70	11.49
Losartan Potassium (control) vs F13	59.90	12.62
Losartan Potassium (control) vs F14	64.60	11.25

Table 6: Difference Factor (f_1) and Similarity Factor (f_2) of Reference Standard versus Test Controlled Release Tablets

Reference Standard vs Test Formulations#	f_1 values	f_2 values
Mepressor®SR Tablets vs F15	13.95	50.03
Mepressor® SR Tablets vs F16#	23.45	40.72
Mepressor® SR Tablets vs F17#	30.98	34.61
Mepressor® SR Tablets vs F18#	37.28	30.77
Cardaktin® Tablets vs F19#	44.53	13.85
Cardaktin® Tablets vs F20#	50.38	11.83
Cardaktin® Tablets vs F21#	57.00	09.80
Cardaktin® Tablets vsF22#	62.46	08.41
Mepressor® SR tablets vs F23#	20.24	42.58
Mepressor® SR tablets vs F24#	29.25	36.40
Mepressor® SR tablets vsF25	36.29	31.06
Cardaktin® Tablets vs F26	52.50	12.79
Cardaktin® Tablets vs F27	54.15	11.32
Cardaktin® Tablets vs F28	59.00	09.92

are in confirmation with authors (Kar *et al.,* 2009) that the controlled release matrix tablets of Zidovudine using Eudragit RL 100 release the drug by anomalous non fickian drug release mechanism. The controlled release co-precipitates and its directly compressed controlled tablets with Carbopol 974P NF extended the drugs release rates up to 12 hour and 24 hours respectively. The drugs were released from the Carbopol 974 NF controlled release formulations by anomalous non fickian diffusion mechanism. It was observed that with increase in concentration more retardation to drugs release occurred and this might be due to the fact that as solvent penetrates into the controlled release formulation might close up the microspores in the swollen formulations and linearity of drug release curves. These results are in confirmation with findings of authors (Rehman *et al.,* 2013; Khan and Jiabi 1998) that Carbopol 974P NF based controlled matrix tablets swell as results of water intake and the creates closing up of micropores which causes slow release of drug and extend the drug release rates and drug release mechanism shifts towards swelling controlled mechanism. The f_1 and f_2 values of test formulation (F5) after comparison with reference standard (Mepressor® SR tablets) were 13.95 and 50.03 indicating that F5 is having similarity in dissolution profile with the reference dissolution profile. The f_1 and f_2 values rest of the test formulations dissolution when compared with dissolution profiles of respective reference standards ranged from 20.24 to 68.80 and 8.41-42.58 indicating that f_1 and f_2 values were not in acceptable limits of f_1 ranging from 1-15 and f_2 values ranging from 50-100 (Costa and Jose, 2001; Yuksel *et al*., 2000).

CONCLUSION

It is concluded from the present study that both polymers (Eudragit RL 100 and Carbopol 974P NF) extended the drug release rates either in case of controlled release co-precipitates of the drugs (Metoprolol Tartrate and Losartan Potassium) or controlled release tablets developed from direct compression of the controlled release co-precipitates. All the formulations released the drugs by anomalous non fickian diffusion mechanism except F1 and F5 which do not follow Power Law. The dissolution profiles comparison of the test formulations showed that f_1 and f_2 values were not in acceptable limits except formulation F5 which shows similarity with respective reference standard. The polymers; Eudragit RL 100 and Carbopol 974P can be proficiently incorporated in the designing and preparation of oral controlled release dosage form with reproducibility and predictability of the drug release kinetics.

ACKNOWLEDGEMENT

The authors are thankful to Gomal University DI Khan and HEC for providing research facilities.

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