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Research Article

FORMULATION AND EVALUATION OF LOSARTAN MICROSPHERES

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ABSTRACT

Present investigation describes preparation of microspheres by solvent evaporation followed by in vitro characterization of microspheres to evaluate the effect of method of preparation on physical properties and drug release profile of microspheres. The microspheres were found to be discrete, spherical with free flowing properties. The particle size distribution, entrapment efficiency and their release profiles were investigated. The yield was found to be maximum in case of solvent evaporation method. The microspheres formulation prepared by solvent evaporation method the drug carrier interactions were investigated in solid state by Fourier Transform Infrared (FT-IR) spectroscopy study. In vitro drug release rate for a microsphere was found to be sustained over 24 hours. Hence, it can be concluded that the Formulation prepared by solvent evaporation method, has potential to deliver Losartan Potassium in a controlled manner in a regular fashion over extended period of time in Comparison to all other formulations and can be adopted for a successful oral delivery of Losartan potassium for safe management of hypertension.

Keywords: Losartan, Solvent evaporation, HPMC, and Carbopol.

INTRODUCTION

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. More precisely, sustained drug delivery can be defined as "Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

The efficiency of any drug therapy can be described by achieving desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period. This goal can be achieved on the basis of proper design of the dosage regimen.

Microspheres have potential to deliver drug in a controlled fashion. Losartan potassium is an effective antihypertensive drug but is extensively bound to plasma proteins and also causes gastrointestinal disorders, neutropenia, acute hepatotoxicity, migraine and pancreatitis. It maytherefore be more desirable to deliver this drug in a sustained release dosage form. The present study was focused on development of sustained release Losartan microspheres using solvent evaporation method and to study the effect of method of preparation on physical properties and drug release profile of Lorsatan potassium microspheres[1].

The purpose of this work is to develop multiparticulate sustained release drug delivery system of Losartan potassium, a low soluble drug, to improve the bioavailability with reduction in dosing frequency along with good patient compliance. A sustained release system is designed to release the drug at a predetermined rate in order to maintain a constant drug concentration for a specified period of time with minimum side effects[2]. The microspheres are prepared by incorporating

varying concentrations of Sodium alginate, Hpmc K15,K 100 and Carbopol 934P.

As sodium alginate is non-toxic, biocompatible and biodegradable biopolymer[3], it forms a bioadhesive and stable gel with divalent cations such as Ca2+, Sr2+, and Ba2+[4]. HPMC is a non-ionic, swellable polymer. These are rate controlling systems which are widely used in sustained drug delivery to obtain a desirable drug release profile and cost effectiveness because of their flexibility. Carbopol is a polymer consisting of acrylic acid cross-linked with either polyalkenyl ether or divinyl glycol[5]. It readily absorbs water, gets hydrated and swell. In addition to its hydrophilic nature and cross-linked structure, carbopol, an anionic polymer, is a potential candidate for use in sustained release drug delivery. Hence the uses of these polymers in this study were proven to be safe based on biocompatibility, safety and cost effectiveness.

Present work includes the development of multi-particulate dosage form because it offers several advantages like improving patient compliance by decreasing dosing frequency, less inter and intra subject variability[7] , reduced risk of local irritation, no risk of dose dumping[8]. Microspheres can provide sustained release properties with more uniform distribution of drugs within gastrointestinal tract[9,10]. Hence the bioavailability of beads can be enhanced.

MATERIALS AND METHODS

Materials: Losartan Potassium was obtained as a gift sample from, MSN Libratory Private Limited, Hyderabad, India. HPMC K15, K100 was obtained from Colorcon India Pvt.Ltd Sodium alginate, Carbopol 934P, Span-80 were obtained from SD Fine –Chem Private Limited, Mumbai, India. All other ingredients, reagents and solvents were of analytical grade.

METHOD

The microspheres were prepared by solvent evaporation method .The drug and polymers were dissolved in dichloromethane and methanol. This solution was dispersed in 100 ml of liquid paraffin light containing 0.5ml Span 80 in a 250 ml beaker. The dispersion was stirred at 800-1000 rpm for 90 min. After the stirring time, microspheres were centrifuged, washed several times with n-hexane, ether and finally with acetone. The microspheres were dried at 50˚C and stored in desiccator. Total 17 batches were prepared with different drug**:** polymer ratios using combinations of HPMC/CARBOPOL. For all batches rpm was maintained at 800-1000 and temperature was maintained at 15ºC. Total seventeen formulations were prepared with different drug polymer ratio. These seventeen formulations were included in the optimization study and evaluated.

Table 1: various formulations of Losartan potassium microspheres

Formulation	Losartan potassium (mg)	HPMC K4M (mg)	HPMC K15M (mg)	HPMC K100M (mg)	CARBOPOL 934 (mg)	RATIO	Liquid paraffin (ml)	Span 80 %	Methanol, Dichloro-methane
F1	500	500	-	-	-	1:1	100	0.5	20
F2	500	750	-	-	-	1:1.5	100	0.5	20
F3	500	1000	-	-	-	1:2	100	0.5	20
F4	500	-	500	-	-	1:1	100	0.5	20
F5	500	-	750	-	-	1:1.5	100	0.5	20
F6	500	-	1000	-	-	1:2	100	0.5	20
F7	500	-	-	500	-	1:1	100	0.5	20
F8	500	-	-	750	-	1:1.5	100	0.5	20
F9	500	-	-	1000	-	1:2	100	0.5	20
F10	500	250	250	-	-	1:1	100	0.5	20
F11	500	375	375	-	-	1:1.5	100	0.5	20
F12	500	500	500	-	-	1:2	100	0.5	20
F13	500	-	-	250	250	1:1	100	0.5	25
F14	500	-	-	375	375	1:1.5	100	0.5	25
F15	500	-	-	500	500	1:2	100	0.5	25
F16	500	-	-	250	500	1:1.5	100	0.5	25
F17	500	-	-	250	750	1:2	100	0.5	25

EVALUATION PARAMETERS

The prepared microspheres were evaluated for particle size, drug content, entrapment efficiency, invitro dissolution studies and stability studies.

Particle size analysis

The particle size of microsphere was determined using optical microscopy method. Particle size of all the batches of the formulated beads in a sample was measured with an optical micrometer fitted with a calibrated eye piece. Calibration of the microscope was done prior to particle size measurement of the beads[14]. Approximately 625 particles were counted for particle size using a calibrated optical microscope. All readings are average of three trials ± SD.

Scanning electron microscopy analysis (SEM)

The shape and surface characteristics were determined by scanning electron microscopy (model-JSM, 35CF, jeol, Japan) using gold sputter technique. The particles were vacuum dried, coated to 200 Ao thicknesses with gold palladium using prior to microscopy. A working distance of 20nm, a tilt of zero-degree and accelerating voltage of 15kv were the operating parameters. Photographs were taken within a range of 50-500 magnifications.

Drug entrapment efficiency

Drug entrapment efficiency of Losartan Potassium microspheres was performed by accurately weighing 100mg of drug equivalent microspheres and suspended in 100 ml of 6.8 pH phosphate buffer and it was kept on a side for 24 hours. Then, it was stirred for 15 mins and filtered. After suitable dilution, Losartan Potassium in the filtrate was analyzed spectrophotometrically at 205nm using U.V.Spectrophotometer.

Losartan Potassium drug content

Equivalent weight of microspheres was weighed and dissolved in 5ml of water and methanol mixture in a standard flask Shake for 30min and then make up with 6.8 pH phosphate buffer and then centrifuge it. From that take 5ml of solution in 50 ml standard flask make up with 6.8 PH phosphate buffer. Generally, the drug content in any formulation should fall within the limit of 90 – 110%.Then solution was filtered and the drug content was estimated at205 nm spectrophotometrically after suitable dilution.

In vitro drug release studies

Losartan Potassium

In vitro drug release from Losartan Potassium was performed using USP Apparatus I in 900 mL of buffer pH 1.2 for 2hrs and pH 6.8 for remaining time period stirred at 37 °C and 50 rpm maintaining sink conditions. The accurately weighed Losartan Potassium microspheres were enclosed in a sieve, placed in the basket, and processed for dissolution testing. All the Losartan Potassium microspheres stayed in the basket during 24-h dissolution testing (i.e., no particles diffused out of the sieve). Dissolution samples (5 mL) were withdrawn at regular intervals (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22 and 24h) using an auto sampler with replacement of equal volumes of fresh medium. The samples were filtered through a 0.45-µm filter and analyzed spectrophotometrically at 205 nm in triplicate. Drug concentration was calculated using a calibration curve.

Stability Study

Stability studies were carried out at accelerated condition (25º C ±2º C at 60% RH ±5% RH), (30º C ±2º C at 65% RH ±5% RH) and (40˚ C ±2˚ C at 75% RH ±5% RH) for the optimized formulation F18. The beads were stored at (25º C ±2º C at 60% RH ±5% RH), (30º C ±2º C at 65% RH ±5% RH) and (40˚ C ±2˚ C at 75% RH ±5% RH) for accelerated temperature in closed high density polyethylene bottles for 3 months. The samples were withdrawn after predetermined period of 1 month, 2 month and 3 month. The samples were analyzed for its drug content and *In-Vitro* drug release.

DRUG RELEASE KINETICS

Zero order release rate kinetics

To study the zero order release kinetics the release rate data are fitted to the following equation

F=K0t Here,

F is the fraction of drug release

K0 is the rate constant

T is the release time

First order model

This model has also been used to describe absorption and/elimination of drug, the release of the drug which followed first order kinetic can be expressed by the equation

Log C=log c0-kt/2.303

Where, Co is the initial concentration of drug

K is the first order rate constant

t = is the time

Higuchi release model

To study the higuchi release kinetics, the release rate data was fitted to the following equation

$$F = KH.t1/2$$

Where, F is the amount of the drug release
Kh is the release time t is the release time

Korsmeyer and peppas model

The release rate date were fitted to the following equation,

Mt/M8 =KM.tn

Where, Mt/M8 is the fraction of drug release
KM is the release constant
t is the release time.

RESULTS AND DISCUSSION

Evaluation parameters of microspheres

The various parameters in the production of microspheres were evaluated and reported in Table 2 and 3. The angle of repose was found to be between 23.3 to 29.1. The bulk density and tapped density was found to be between 0.94 to 1.04 and 1.03 to 1.16. The Car's index and Hausner's ratio was found to be between 7 to 11.4 and 1.07 to 1.114. The entrapment efficiency was found in the range of 75.69±1.91 to 92.02±1.07. The drug content is in the range of 96.89±2.1 to 99.92±2.67.

Table 2: Micrometric properties of LP

Formulation code	Angle of repose	Bulk density	Tapped density	Car's index	Hausner's ratio
F1	25.43±0.1	1.041±0.3	1.16±0.1	11.4±0.320	1.114±0.015
F2	26.46±0.2	1.02±0.4	1.12±0.2	9±0.208	1.09±0.015
F3	23.31±0.1	1.01±0.2	1.11±0.1	9±0.320	1.09±0.013
F4	26.89±0.17	1.02±0.28	1.11±0.21	8±0.342	1.08±0.016
F5	29.14±0.1	0.96±0.24	1.03±0.27	7±0.401	1.07±0.019
F6	28.14±0.2	0.95±0.24	1.03±0.27	9.5±0.210	1.095±0.012
F7	29.1±0.1	0.94±0.2	1.03±0.2	9±0.237	1.095±0.015
F8	28.2±0.1	0.96±0.2	1.04±0.2	8±0.238	1.08±0.018
F9	27.1±0.4	1.041±0.3	1.16±0.1	11.4±0.342	1.114±0.016
F10	25.1±0.4	1.02±0.4	1.12±0.2	9±0.282	1.08±0.018
F11	29.14±0.1	0.96±0.24	1.03±0.27	7±0.313	1.07±0.015
F12	28.14±0.2	0.95±0.24	1.03±0.27	9.5±0.196	1.095±0.011
F13	29.1±0.1	0.94±0.2	1.03±0.2	9±0.254	1.095±0.016
F14	28.2±0.1	0.96±0.2	1.04±0.2	8±0.195	1.08±0.010
F15	25.1±0.4	1.041±0.3	1.16±0.1	11.4±0.156	1.114±0.019
F16	25.1±0.4	1.02±0.4	1.17±0.3	9±0.164	1.09±0.016
F17	24.1±0.4	0.852±0.4	1.12±0.2	9±0.188	1.09±0.013

Table 3: Particle size, Drug Entrapment Efficiency

Formulation code	% Yield	Entrapment Efficiency	Drug Content
F1	93.70±1.28	87.04±1.92	98.56±0.63
F2	87.82±2.01	78.68±2.1	98.48±0.91
F3	92.70±1.19	85.04±1.87	97.59±1.97
F4	85.95±1.98	76.87±1.91	98.64±2.01
F5	94.82±2.16	88.35±2.67	98.46±3.22
F6	86.90±3.05	75.69±1.91	98.78±1.4
F7	93.25±1.37	86.98±2.08	99.11±2.1
F8	85.82±2.01	76.68±2.1	97.46±2.4
F9	93.70±1.28	87.04±1.92	98.95±1.8
F10	87.82±2.01	78.68±2.1	97.65±1.6
F11	85.95±1.98	76.87±1.91	96.89±2.1
F12	94.82±2.16	88.35±2.67	98.28±1.7
F13	86.90±2.45	75.72±1.94	98.73±1.9
F14	93.55±1.37	86.68±2.08	97.89±1.92
F15	85.35±1.98	76.84±1.98	98.48±2.08
F16	86.27±2.05	76.68±2.12	99.24±1.91
F17	98.70±1.87	92.02±1.07	99.92±2.67

Dissolution Studies

All the 17 formulations of Losartan potassium microspheres are subjected to dissolution studies. Dissolution is carried out in USP type 1 apparatus at 100 rpm in the volume of 900ml dissolution media (ph 6.8 phosphate buffer) for 24hours. The results are shown in Table 4 to 6 and Figures 1 to 4. Formulations F1, F2, F3 containing HPMC K4M (1:1,1:1.5,1:2) shows percentage drug release of 99.8% , 98.9% , 99.8% in 8 hrs. Formulations F4, F5, F6 (1:1,1:1.5,1:2) which contained HPMC K15M shows percentage drug release of 98.5% , 99.8% , 99.5% in 8hrs respectively. Formulations F7, F8, F9 which contained HPMC K100M (1:1,1:1.5,1:2) shows percentage drug release of 99.8% , 99.29% , 98.9% in 14 hrs respectively . Formulation F10 , F11, F12 containing HPMC K4M + HPMC K15M (1:1,1:1.5,1:2) shows percentage drug release of 98.25%, 97.92% 98.99%. Formulation F13, F14, F15, F16, F17 containing HPMC K100M+CARBOPOL 934p (1:1, 1:1.5, 1:2) shows percentage drug release of 97.29%, 98.29% in 16hrs. Formulation F17 containing HPMC K100M+CARBOPOL 934p shows percentage drug release of 97.43% in 24 hrs. It has been observed that the dissolution rate was found to decrease linearly with increasing concentration of carbopol 934p.

The graph indicates F17 formulation shows better drug release when compared with other formulations, and followed by the zero order kinetics. The mechanism of release F17 formulation as shown in fig 4-8, and it fits into Korsmeyer Peppas non fickian diffusion.

Table 4: Invitro drug release data of F1-F6 Formulations

S NO.	Time(hr)	F1	F2	F3	F4	F5	F6
1	1	58.6±0.6	48.7±0.5	30.6±0.7	35.7±0.7	26.81±0.6	19.7±0.6
2	2	69.7±0.9	60.6±0.3	38.9±0.3	49.6±0.2	35.4±1.3	31.5±0.3
3	3	79.3±0.4	68.7±0.2	43.8±0.5	50.7±0.1	47.8±0.5	42.6±0.6
4	4	87.6±1.1	75.8±1.9	50.6±0.2	61.3±0.8	59.4±0.2	53.6±1.5
5	5	99.8±0.6	84.9±0.5	64.9±0.3	75.4±0.2	67.8±0.3	61.8±0.2
6	6		98.9±0.2	68.6±0.4	85.6±0.5	83.6±0.9	80.7±0.5
7	7			70.3±0.6	98.5±0.9	99.8±0.7	91.7±0.5
8	8			99.8±1.5			99.5±0.6
9	9						
10	10						

Table 5: Invitro drug release data of formulations F7-F12

S NO.	Time	F7	F8	F9	F10	F11	F12
1	1	40.9±0.4	32.6±1.97	20.9±1.5	21.7±1.5	10.8±0.6	10.94±1.25
2	2	52.3±1.3	46.8±1.92	28.9±2.1	31.3±2.24	15.30±0.89	21.6±2.23
3	3	59.4±0.6	50.6±2.67	40.7±2.8	36.8±2.89	21.6±1.23	30.1±1.09
4	4	67.8±1.5	61.2±1.5	48.3±1.29	43.4±1.25	31.45±1.28	42.6±1.56
5	5	76.8±1.8	70.6±2.1	55.6±1.86	58.9±1.9	34.8±2.25	49.8±2.04
6	6	85.9±1.9	79.6±2.08	68.7±1.32	71.8±2.68	51.3±2.28	59.3±2.87
7	7	99.8±2.1	84.6±0.6	74.3±2.65	79.4±1.92	58.9±1.25	68.7±3.25
8	8		91.9±1.9	81.56±3.25	83.6±2.05	67.4±1.56	87.6±3.65
9	9		99.29±1.5	85.45±1.89	87.25±1.09	73.25±1.98	93.45±1.56
10	10			92.1±1.25	98.25±3.01	82.45±2.36	98.99±1.28
11	12			98.9±2.08		90.99±2.67	
12	14					97.92±1.56	
13	16						

Table 6: Invitro drug release data of F13-F17 formulations

S NO.	Time	F13	F14	F15	F16	F17
1	1	63.5±1.98	58.95±1.02	49.89±1.63	29.5±2.06	8.96±1.56
2	2	72.5±2.25	64.95±1.56	58.45±1.95	38.59±2.65	12.25±1.26
3	3	87.5±1.65	70.25±2.56	64.54±2.65	42.53±2.28	17.85±2.25
4	4	92.5±0.89	79.23±2.86	71.23±1.23	54.55±2.23	22.58±1.8
5	5	99.89±1.089	83.45±3.24	77.32±1.56	62.23±2.45	29.89±3.25
6	6		87.85±2.56	85.25±2.65	69.45±3.25	36.53±1.96
7	7		92.45±2.87	89.95±3.25	72.55±1.56	40.23±2.89
8	8		97.29±2.92	94.95±3.56	79.88±1.98	42.25±2.25
9	9			98.29±3.85	85.23±1.56	47.25±1.68
10	10				89.99±2.56	54.55±2.36
11	12				94.88±2.87	62.89±3.25
12	14				99.83±2.96	70.12±2.89
13	16					79.89±1.5
14	18					88.93±1.65
15	22					94.35±1.95
16	24					97.43±2.65

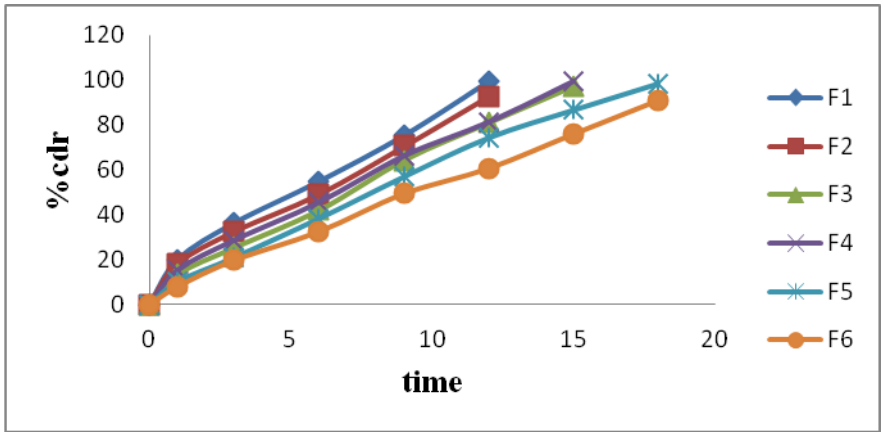

Fig. 1: Dissolution profile of F1 –F6

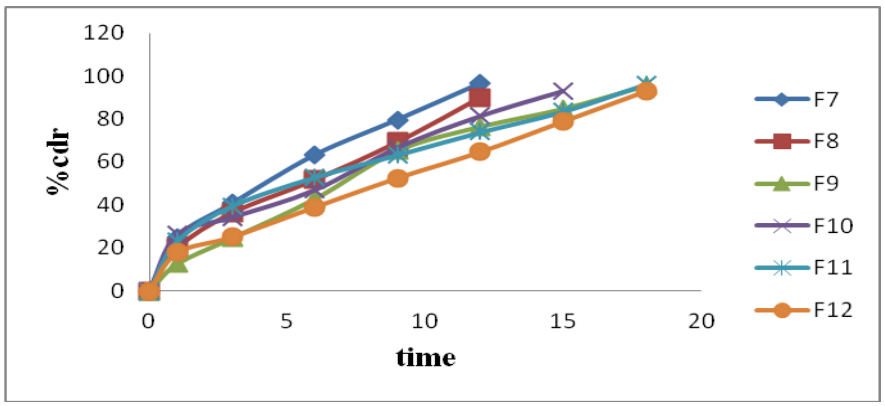

Fig. 2: In vitro dissolution profile of F7 –F12

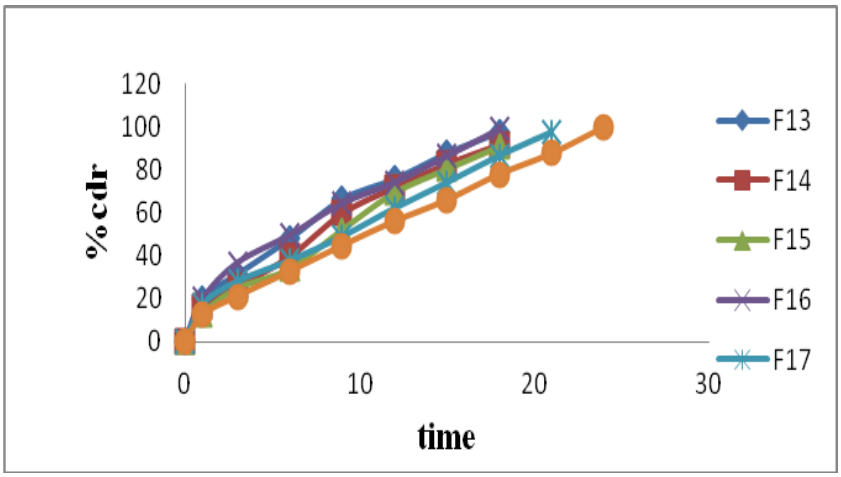

Fig. 3: In vitro dissolution profile of F13 –F17

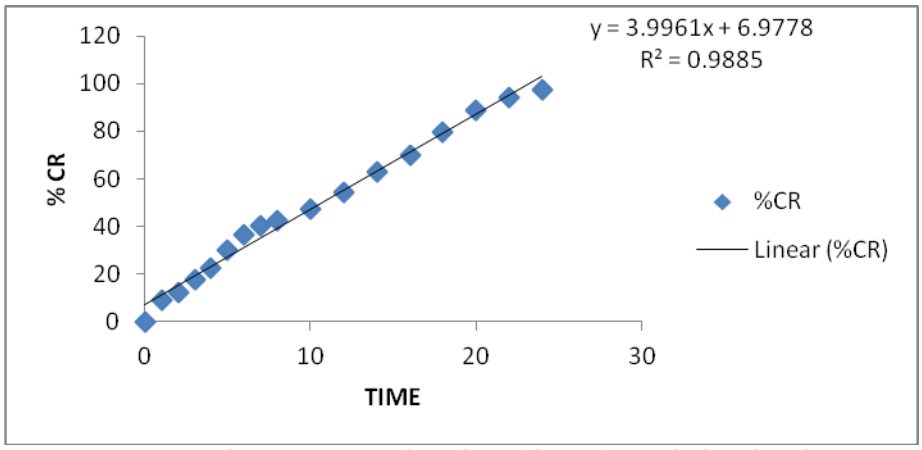

Fig. 4: Zero order plot of best formulation (F17)

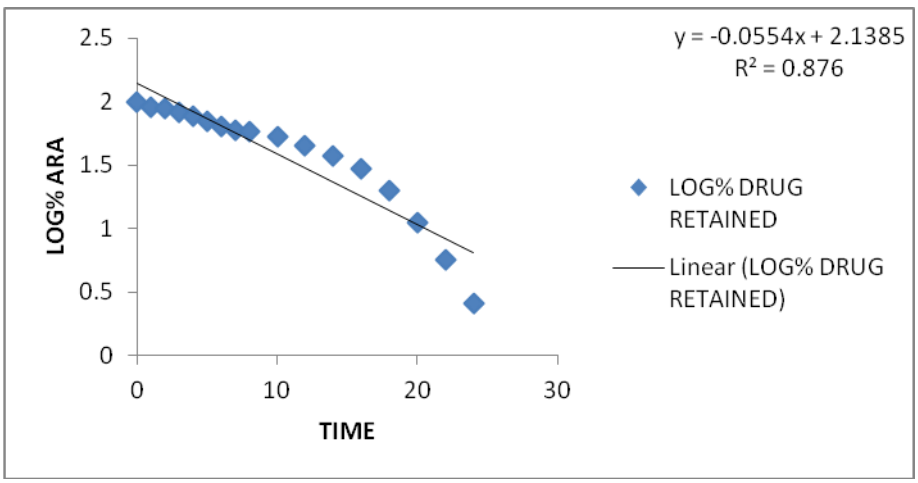

Fig. 5: First order plot of best formulation (F17)

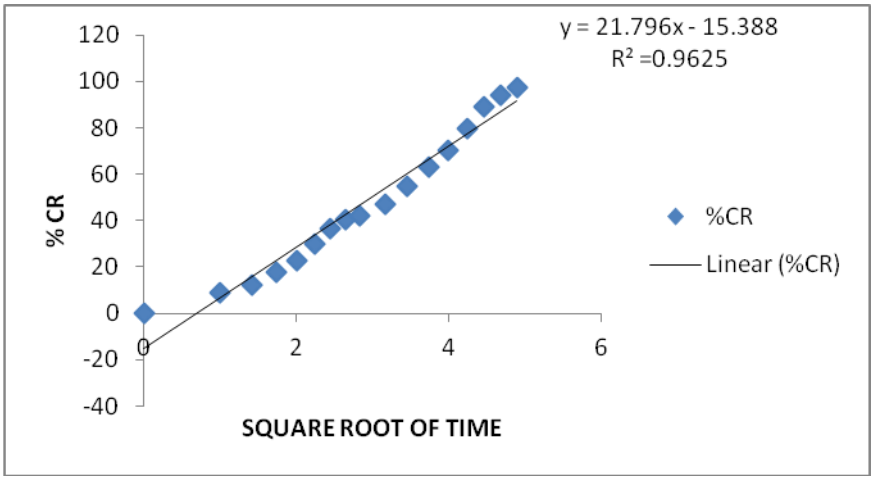

Fig. 6: Higuchi plot of best formulation (F17)

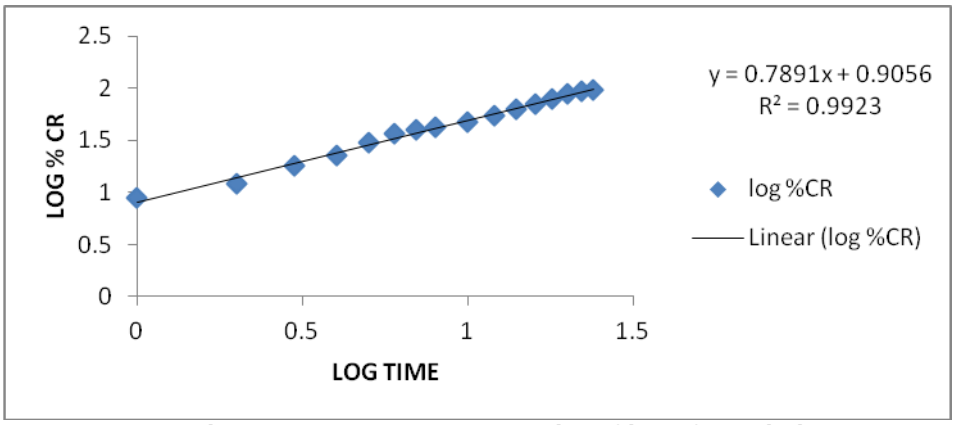

Fig. 7: Koresmeyer peppas plot of best formulation

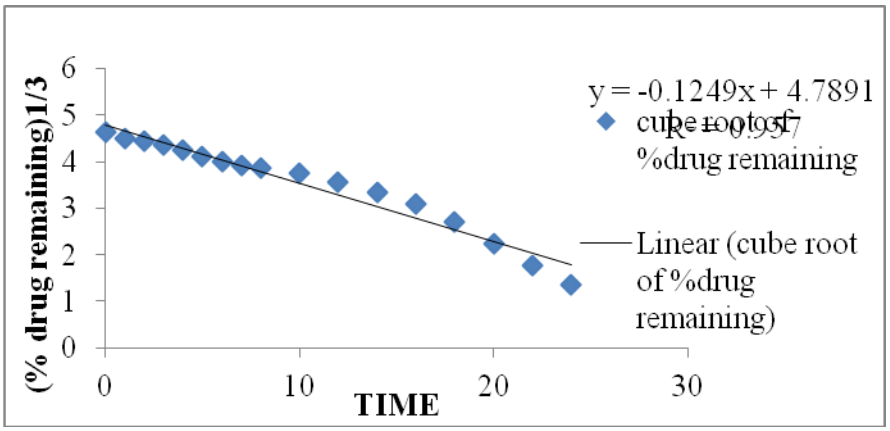

Fig. 8: Hixson plot of best formulation

CONCLUSION

The concept of formulating microspheres containing LP offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. Microspheres of LP were prepared successfully by solvent evaporation method using the different concentration of polymers, especially by means of improving the oral bioavailability of the drug. It would be faster and more economical to alter beneficially the properties of the existing drugs than developing new drug entities. Hence this formulation will be a boon to novel drug dosage forms.

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