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FORMULATION, OPTIMIZATION AND EVALUATION OF CONTROLLED RELEASE MICROSPHERES OF LOSARTAN POTASSIUM

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ABSTRACT

Objective: The aim of this study was to prepare losartan potassium loaded albumin microspheres. **Methods:** w/o emulsion thermal crosslinking method with different drug-to-polymer ratios {(1:1), (1:2), (1:3)}, using a 22-gauge hypodermic syringe into an external phase. A 3^2 full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio (X1) and stirring speed (X2), on dependent variables, encapsulation efficiency, particle size, and % drug release. **Result:** Nine F1, F2, F3, F4, F6, F7, F8 and F9, formulations prepared, F7 i.e., 1:3 (drug–polymer) ratio was selected as the optimized formulation based on particle size, encapsulation efficiency, and the release behavior. The microsphere formulations were able to sustain the release of drug in vitro more than 8 hrs Dissolution data obtained from in-vitro release studies fitted on zero order, first order, Higuchi, and Peppas model. The DRS spectrum revealed that the presence of excipient did not show any shift in the spectrum. The microspheres stored under variable storage condition were found to be stable both physically and chemically.

KEYWORDS: In vitro release, microspheres, encapsulation efficacy, losartan potassium, albumin.

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal

physiology offers more flexibility in dosage form design than most other routes.[1] This can be accredited to the numerous advantages of the oral route, such as, ease of ingestion, avoidance of pain, versatility and most importantly patient compliance, reduced risk of cross-infection, and needle stick injuries economical production methods, easy approvals from regulatory bodies and so on.[2] The important drawback of tablet and capsule dosage forms for pediatric and geriatric patients has been difficulty in swallowing and this problem leading to poor patient compliance.[3] A greater attention has been recently bestowed upon the development of sustained and controlled drug delivery systems. These dosage forms are very attractive for a variety of reasons. By now, for a large number of diseases, a large number of drugs are available. However, the effectiveness of these drugs is often limited because of the side-effects or need of invasive administration in a clinical setting.[4] These formulations are designed to deliver the drugs at a controlled and predetermined rate, thus maintaining their therapeutically effective concentrations in the systemic circulations for prolonged periods of time.[5]

Albumin

Albumin is the most abundant protein in the human blood plasma. It is hydrosoluble and presents a molecular weight of about 66 kDa. Characteristics like biodegradability, non-toxicity and non-immunogenicity, makes albumin a very promising material for biomedical/pharmaceutical applications, including drug delivery purposes. Albumin microspheres have proved to be a suitable carrier for drugs used in cancer treatment. This is mainly due to the fact that albumin is used by cancer cells as a source of nitrogen and energy, being taken up by tumor cells by a mechanism of fluid phase endocytosis, followed by lysosomal breakdown. With this mechanism, the drugs in the albumin microspheres are delivered on the specific site of action, minimizing systemic toxicity. Albumin microspheres, loaded with anti-cancer drugs, have shown to be efficient in breast cancer treatment.[6]

Microspheres

Microspheres are solid approximately spherical particles ranging from 1 to 100 mm in size to provide advantages over sustained release tablets, such as ready distribution over a large surface area, predictable and reproducible drug release kinetics, the delocalization of the total dose in GIT, reduced side effects of the drug, and the independent drug release rate on gastric transit time. Oral multi-unit dosage forms like microspheres have received much attention as modified/controlled drug delivery systems to attribute more uniformly in the gastro-intestinal

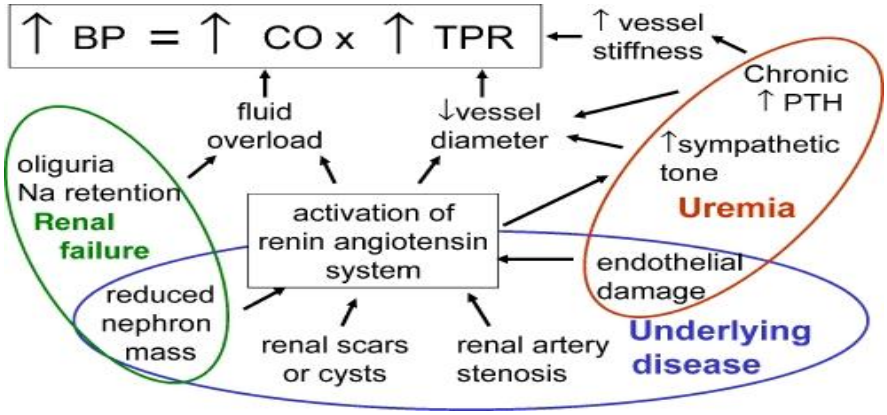
tract, thus resulting in more uniform drug absorption and reducing patient-to-patient variability. It has been reported that the selection of the proper microencapsulation technique and of the excipients, such as polymers as carriers, coaters, and emulsifiers, is very popular in the preparation of the modified release microspheres of the drug. Natural, biodegradable polymer-based microspheres as a drug carrier is widely used as they improve the safety and efficacy of drug delivery, drug targeting to specific cells or organs, and better patient compliance.[5]

Release mechanism of drug from microsphere

Polymer microspheres can be employed to deliver medication at a rate-controlled and sometimes targeted manner. Medication is released from a microsphere by drug leaching from the polymer or by degradation of the polymer matrix. Since the rate of drug release is controlled by these two factors.[7]

Hypertension

Hypertension is a leading cause of morbidity and mortality worldwide. Individuals with hypertension are at an increased risk for stroke, heart disease and kidney failure.[8] Hypertension is defined by a systolic blood pressure that is ≥140 mm Hg and a diastolic blood pressure that is ≥90 mm Hg . The World Health Organization ranks coronary heart disease and cerebrovascular diseases as the world's leading causes of death. Globally, according to the World Health Report 2002, about 62% of cerebrovascular disease and 49% of ischemic heart disease are attributable to suboptimal blood pressure (systolic >115 mm Hg), and hypertension is estimated to cause 7.1 million deaths, about 13% of the total. For the last several decades, hypertension has been ranked as one of the top 10 leading causes of worldwide disability-adjusted life years. According to the results of Kearney et al.[5] more than 25% of the world adult population (approx. 1 billion) has hypertension, and it was estimated that in 2025, 29% (1.56 billion) of the adult population will be hypertensive (an increase of the total number of hypertensive individuals by 60%).[9]



Interplay of different factors in the generation of hypertension in chronic kidney disease (B)P blood pressure, (CO) cardiac output, (TPR) total peripheral resistance, (PTH) parathyroid hormone, (Na) sodium).[10]

The angiotensin II receptor blockers (ARBs) ARBs inhibit the renin-angiotensin system and reduce cardiovascular mortality in adults. Losartan has the advantage of being available in suspension formulation, although not in Brazil. The use of ARBs can also be associated with a lower incidence of diabetes, and these agents can be used for long periods, as they are very well tolerated, due to their effects being similar to placebo.[11]

MATERIAL AND METHODS

Sr.no.	Materials	Grade
1.	Losartan potassium [LP]	L.R.
2.	Albumin	L.R.
3.	Light liquid Paraffin	L.R.
4.	Span 60	L.R.
5.	Petroleum Ether	L.R.
6.	Water	L.R.

(A) Preformulation Studies

1. Identification Tests

(a) IR Spectroscopy

Fourier transforms infrared (FTIR) study was carried out to check compatibility of the drug with polymers. The spectrum of a dried mixture of drug and potassium bromide was run to identify the drug.[12]

(b)Solubility Analysis

The solubility of Losartan potassium was checked in various solvents like water and methanol, ethanol, chloroform and ethyl acetate, ether and n-hexane. Studies revealed that

Lsartan potassium was found to be freely soluble in water and methanol. The International Bulletin of Drug Research., 1(2): 120-131 122 solubility was confirmed by analyzing the sample by quantitative determination by UV spectroscopy. Wavelength scan was done from 400-200 nm and maximum absorbance was found at 206nm.[13]

(c) Melting point Determination

Melting point determination of the obtained sample was done as it is a good first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range. Melting point of LP was determined by Open capillary method.[14]

(D) Compatibility study by FTIR

Fourier Transform Infrared Spectroscopy (FT-IR) FT-IR spectra's were recorded on a FTIR spectroscopy using the instrument Shimadzu FT-IR in the frequency range of 400-4000 cm-1 with the resolution of 4 cm-1 using potassium bromide discs method. The drug and selected excipient were stored at 40 ± 2oC and 75 ± 5 % RH for 1 month. Individual samples as well as the mixture of drug and excipients were ground, mixed thoroughly with potassium bromide for 3-5mins in a mortar and compressed into the disc by applying a pressure of 5 tons for 5 mins in a hydraulic press. The concentration of sample in potassium bromide should be in the range of 0.2% to 1%.The pellets were placed in the light path and spectrum was obtained and reviewed for evidence of any interactions.[15]

(B) Spectroscopic studies

1. Determination of λmax

A solution of LP containing the concentration 10 µg/ ml was prepared in pH 7.4 and UV spectrum was taken using Shimadzu (UV-1800) double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm.[13]

2. Construction of Calibration curve in 0.1N HCL pH 1.2 and 7.2 pH of buffer

i) Standard calibration of Losartan potassium in 0.1N Hcl

100mg of Losartan potassium was accurately weighed and dissolved in100ml of 0.1N HCL to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5ml were diluted in 10ml volumetric flask with phosphate buffer to give

concentrations in range of 5µg/ml to 25µg/ml respectively, absorbance was measured at 205nm.[16]

ii) Standard calibration of Losartan potassium in phosphate buffer of pH7.2: 100mg of Losartan potassium was accurately weighed and dissolved in100ml of pH 7.2 phosphate buffer to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 5µg/ml to 25µg/ml respectively, absorbance was measured at 224nm.[16]

(C) Optimization method for preparation of microspheres:

The ratio of the polymer to be used were optimized using 3^2 full factorial design.[17]

Batch code	Variable level in coded form	
	X_1	X_2
F_1	-1	-1
F_2	-1	0
F_3	-1	1
F_4	0	-1
F_5	0	0
F_6	0	1
F_7	1	-1
F_8	1	0
F_9	1	1

Translation of coded levels in actual units

Variable level	Low(-1)	Medium(0)	High(+1)
Drug- to- Polymer ratio(X_1)	**1:1**	**1:2**	**1:3**
Stirring Speed(X_2)rpm	**800**	**1000**	**1200**

Amount of drug in each formulation =100 mg

(D) Preparation of albumin microspheres

Albumin microspheres of LP were prepared by the w/o emulsion thermal cross-linking method with minor modification. 100ml of light paraffin oil was placed in a glass beaker and mixed with 0.4% w/v span 60 solution by stirring (800,1000,1200) and heating at 70°C for solubilization. The mixture was allowed to cool at room temperature. Add 10 ml of egg albumin aqueous solution of a different drug to polymer ratio ((1:1, 1:2 and 1:3) using a 22-gauge hypodermic syringe into an external phase. Light paraffin was stirred at different rpms

for 10 min with the help of a magnetic stirrer. A w/o emulsion was formed. The temperature of the oil bath was raised to 95°C. Spherical highest percentage yielding microspheres with moderate aggregation at (95°C) and stirring was continued until microspheres were completely dehydrated. Microspheres were then separated by decantation and washed six times with 20 ml of petroleum ether to remove traces of oil. Finally, microspheres were washed three times with 60 ml of distilled water and dried at room temperature for 24 h. After drying, a fine yellow free flowing powder was obtained that was stored in desiccators at room temperature. Different batches of microspheres were prepared using different drug to polymer ratio and different rpms. In each case, the other variables were kept constant. Average size of microspheres was determined by using a calibrated stage micrometer. A total of nine batches, each in triplicate, were prepared as per 32 factorial design.[5]

(E) EVALUATION OF MICROSPHEREs

Particle size analysis

Determination of average particle size of losartan potassium microspheres was carried out by optical microscopy, fitted with an ocular micrometer and a stage micrometer. The particle diameter of 100 microspheres was measured randomly by an optical microscope. The average particle size was determined by using the Edmondson's equation.[14]

$D_{mean} = \Sigma nd / \Sigma n$

Where n = no. of microspheres observed

D = mean size range

(F) Shape and surface morphology

The external morphology of microspheres was analyzed by scanning electron microscope (SEM). For scanning electron microscopy samples were prepared by lightly sprinkling microspheres powder on a double adhesive tape, which stuck to an aluminum stub. The stubs were then coated with gold to a thickness of (150–200 Å) using a fine coat ion sputter (JEOL, fine coat ion sputter JFC-1100). The microspheres were examined under scanning electron microscope (JEOL, JSM-6100 SEM, Japan).[18]

(G) Drug Entrapment Efficiency

Microspheres (50 mg) were crushed in a glass mortar and pestle, and the powdered microspheres were suspended in 50 ml phosphate buffer (pH 7.2). The resulting mixture was shaken by the magnetic stirrer for 24 h. The solution was filtered, and the filtrate was

analyzed for the drug content. The drug entrapment efficiency was calculated using the following formula.[17]

$$\text{DRUG ENTAPMENT EFFICACY} = \frac{\text{PRACTICAL DRUG CONTENT}}{\text{THEORTICAL YIELD}} \times 100$$

(H) In vitro dissolution test

The in vitro release was performed using USP method II (paddle). The dissolution media in the first set of experiments was 0.1N HCl for 2 hours, while in the second set 0.1NHCl was replaced with phosphate buffer of pH 7.2 for 6 hours. The volume of dissolution media in each vessel was 900 ml and the temperature was maintained at 37 ± 0.5°C during the study. The paddle speed was adjusted to 50 rpm. Samples of 5mL were withdrawn at different time intervals (1, 2, 3, 4, 6, 8, 10, and 12 hours). Each withdrawn sample was replaced by 5 ml at each time of dissolution media. The percentage drug release was determined using of UV-spectrophotometer where λmax was 205 nm in HCl and 224 nm in phosphate buffer respectively. A calibration curve was constructed and the concentration of losartan potassium was read from that curve.[20]

(I) Dependent-model method (Data analysis)

In order to describe the losartan potassium release kinetics from individual microsphere formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: zero order, first order, Higuchi, Korsmeyer Peppas. When these models are used and analyzed in the preparation, the rate constant obtained from these models is an apparent rate constant. The release of drugs from the sustained microsphere can be analysed by release kinetic theories. To study the kinetics of drug release from matrix system, the release data were fitted into Zero order as cumulative amount of drug release vs. time (Eqn.3), first order as log cumulative percentage of drug remaining vs. time (Eqn.4), Higuchi model as cumulative percent drug release vs. square root of time (Eqn.5). To describe the release behavior from the polymeric systems, data were fitted according to well-known exponential Korsmeyer – Peppas equation as log cumulative percent drug release vs log of time equation (Eqn.6).

(i) Zero order kinetics

$$Q_t = K_0 t \quad \text{.....Eqn.(3)}$$

Where,

Q= Amount of drug release in time t

K0 = Zero order rate constant expressed in unit of concentration /time

t = Release time

(ii) First order kinetics

Log Q=Log Q0-kt/2.303……Eqn.(4)

Where,

Q0= is the initial concentration of drug

k= is the first order rate constant, t =release time

(iii) Higuchi kinetics

Q=kt1/2……...…Eqn.(5)

Where,

k= Release rate constant

t=release time, Hence the release rate is proportional to the reciprocal of the square root of time.

(iv) Korsmeyer-Peppas

First 60% in vitro release data was fitted in equation of Korsmeyer et al. to determine the release behavior from controlled release polymer matrix system. The equation is also called as power law,

Mt /M∞ =Kt n …… Eqn.(6)

Where, Mt = amount of drug released at time t

M∞ = amount of drug released after infinite time

Mt /M∞ = fraction solute release

t = release time

K = kinetic constant incorporating structural and geometric characteristics of the polymer system

n = diffusional exponent that characterizes the mechanism of the release of traces.

The magnitude of the release exponent "n" indicates the release mechanism (i.e. Fickian diffusion, Non Fickian, supercase II release). For sustained release microsphere, values of n of near 0.5 indicate Fickian diffusion controlled drug release, and an n value of near 1.0 indicates erosion or relaxational control (case II relaxational release transport, non Fickian, zero order release). Values of n between 0.5 and 1 regarded as an indicator of both diffusion and erosion as overall release mechanism commonly called as anomalous release mechanism.[16]

(J) Stability studies

To assess long-term stability, the albumin microsphere formulations in triplicate were put in hard gelatin capsules and sealed in aluminum packaging coated inside with polyethylene. The studies were performed at 40°C/75% RH in the stability chamber for 3 months. At the end of storage period, the formulation was observed for physical appearance, drug content.[5]

RESULTS AND DISCUSSION

3.2 PREFORMULATION STUDY

3.2.1 Identification Test

3.2.1.1 I R Spectroscopy

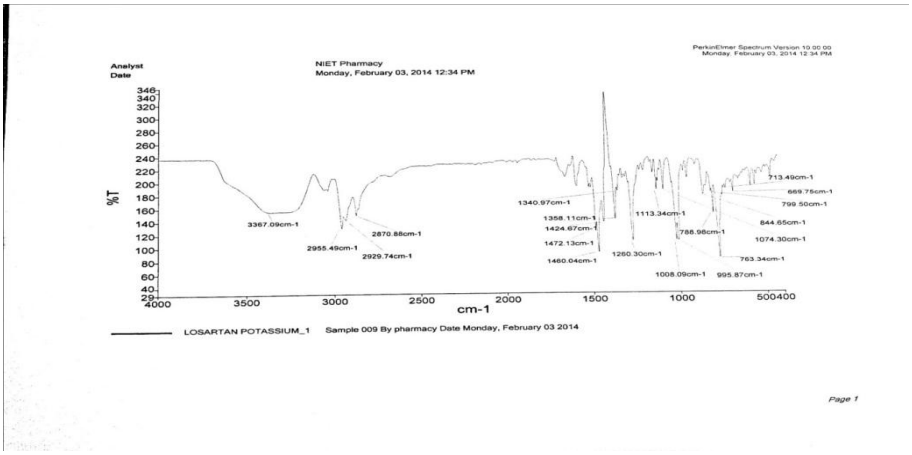


FIG.3.1: FT-IR SPECTRA OF PURE LOSARTAN POTASSIUM FOR IDENTIFICATION.

3.2.1.2 Solubility Analysis

Losartan potassium drug sample found to be freely soluble in water, methanol, ethanol, dichloromethane, and chloroform and it is also soluble into the dissolution medium. Preformulation solubility analysis was done to select a suitable solvent to dissolve and also to test solubility in dissolution medium.

3.2.1.3 Melting point determination

Melting point of drug sample was found to be 183.5 which were within the reported range 182-185. Melting point is a good first indication of purity of the sample since the presence of relatively small amount of impurity can be detective by a lowering as well as widening in the melting point range.

3.2.1.4 Compatibility study by I R spectroscopy: FT- IR spectroscopy was carried out to check the compatibility between drug and polymer. From the FT- IR spectra of the pure drug and the combination spectra of drug with polymer, it was observed that all the characteristics peaks of losartan potassium were present in the combination spectra as well thus indicating the compatibility with the polymer.

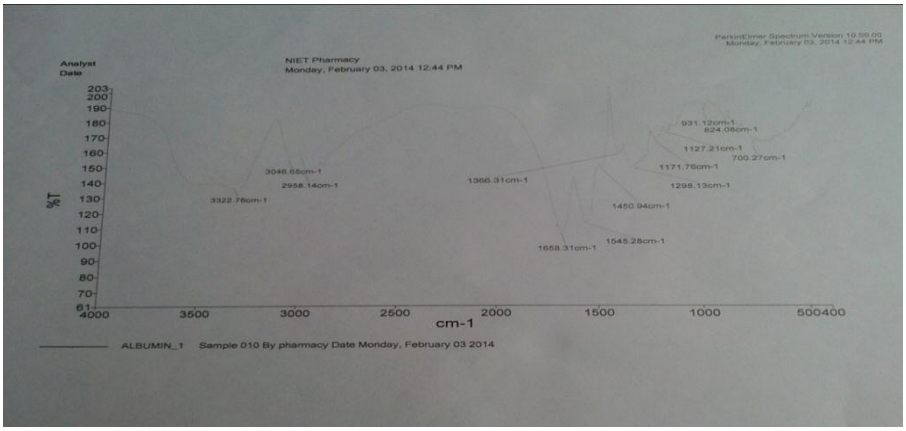


FIG.3.2 FT-IR SPECTRA OF ALBUMIN

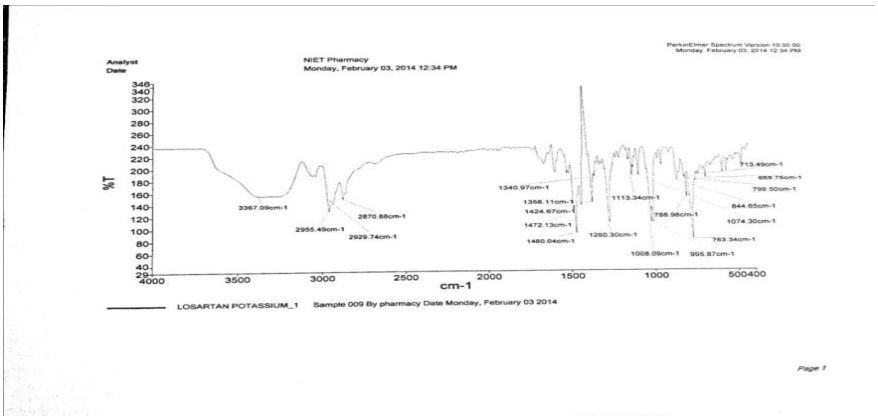


FIG. 3.3 FT-IR SPECTRA OF PURE LOSARTAN POTASSIUM

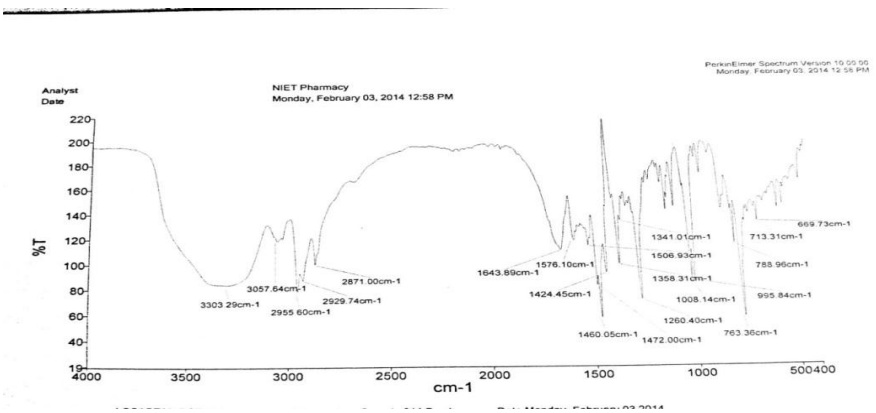


FIG. 3.4 FT-IR SPECTRA OF LOSARTAN POTASSIUM AND ALBUMIN

3.2.1.5 Spectroscopic studies

3.2.1.5.1 Determination of λ max (UV Spectroscopy)

Spectroscopic study was carried out in order to find out the λ max of losartan potassium in 0.1 N HCl and phosphate buffer pH 7.20.Solution of 10 µg/ml of losartan potassium in the test media when scanned for maximum absorption in the range of 200-400 nm exhibited sharp peak at 205 nm and 224 nm in 0.1 N HCl and phosphate buffer pH 7.2 respectively.

3.2.1.5.2 Construction of Calibration curve in 0.1N HCL pH 1.2 and 7.2 pH of buffer

The calibration curve was prepared in 0.1N HCL pH1.2 and pH7.2 with the below mentioned results.

3.2.1.5.2.1 Standard Calibration curve in 0.1 N HCL

The calibration curve of losartan potassium was prepared in 0.1 N HCL. Linear regression of the absorbance values resulted in r^2 values of 0.9857 in 0.1 N HCL.

- **Solvent :** 0.1 N HCL
- **Wavelength:** 205 nm.

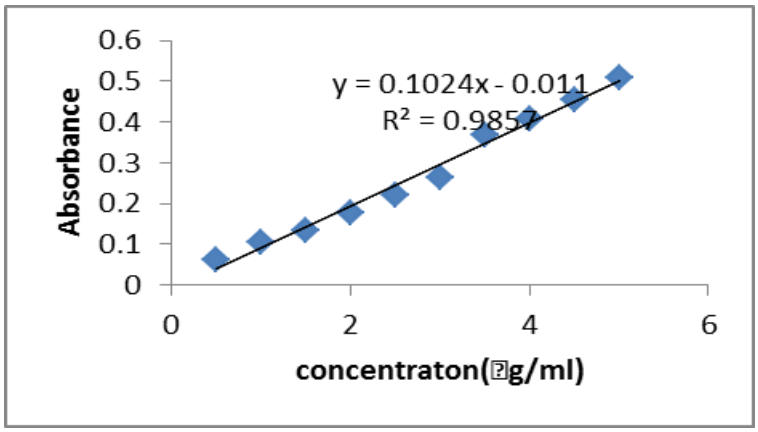


FIG. 3.5 STANDARD CALIBRATION CURVE OF LOSARTAN POTASSIUM IN 0.1 N HCL

3.2.1.5.2.2 Standard calibration curve in phosphate buffer pH 7.2

Table no. 3.2 shows the absorbance of standard solution of LP at λ max 224nm. Linear regression of the absorbance value resulted in r^2 values of 0.9996 in phosphate buffer pH 7.2.

- **Solvent:** pH 7.2 phosphate buffer.
- **Wavelength:** 224 nm

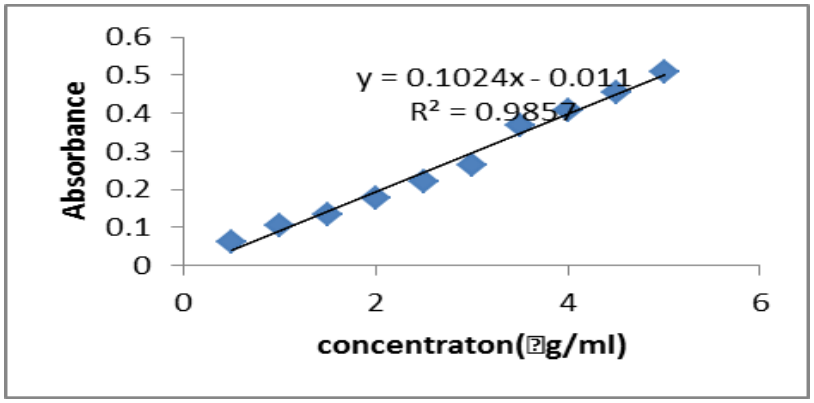


FIG.3.6 STANDARD CALIBRATION CURVE OF LOSARTAN POTASSIUM IN PH 7.2 BUFFER.

3.3 Optimization process

The concentration of polymer used was optimized by using 3^2 factorial design. On the basis of the factorial design, microsphere without drug were prepared using albumin at different amount with optimized stirring speed. It was observed that at high level of polymer yielded spherical shape microsphere.

3.4 Preparation of microsphere

Microsphere was successfully prepared by using the w/o emulsion thermal crosslinking method with minor modifications.

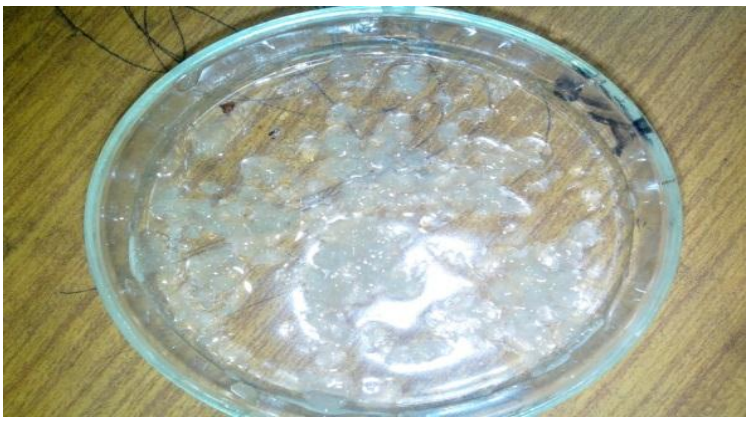


FIG.3.7 PREPARED MICROSPHERES

3.5. Evaluation of microsphere

3.5.1 Particle size Analysis

The average particle size of microsphere as determined by the optical microscopy by using ocular micrometer and stage micrometer as shown in (table no.9) and fig. The mean particle size of microsphere containing albumin was found to be 36.33±1.52, 47.49±0.52, 33.72±o.51,

56.41±0.46, 50.30±0.72, 48.49±0.65, 75.56±0.15, 68.05±0.05, 63.85±0.47 for formulation F_1 to F_9.As the drug to polymer ratio increased the particle size of microsphere is also increased. Stirring speed had a negative effect on the particle size (i.e., as the stirring speed increased, the particle size decreased).

TABLE 3.3: AVERAGE PARTICLE SIZE OF LOSARTAN POTASSIUM MICROSPHERE

Sr.no.	Formulation code	Average Particle Size(µm) Mean±SD
1.	F1	36.331±1.524
2.	F2	48.466±2.022
3.	F3	37.495±6.126
4.	F4	56.886±1.275
5.	F5	50.798±1.4786
6.	F6	49.06±1.581
7.	F7	76.266±1.331
8.	F8	69.548±2.642
9.	F9	60.126±6.844

(N= 3), Mean±SD

3.5.3 Shape and surface morphology

Shape and surface morphology was characterized by Scanning Electron Microscopy (SEM) Figure shows microsphere showing some morphological characteristics such as diameter, shape, and surface characteristics**:**

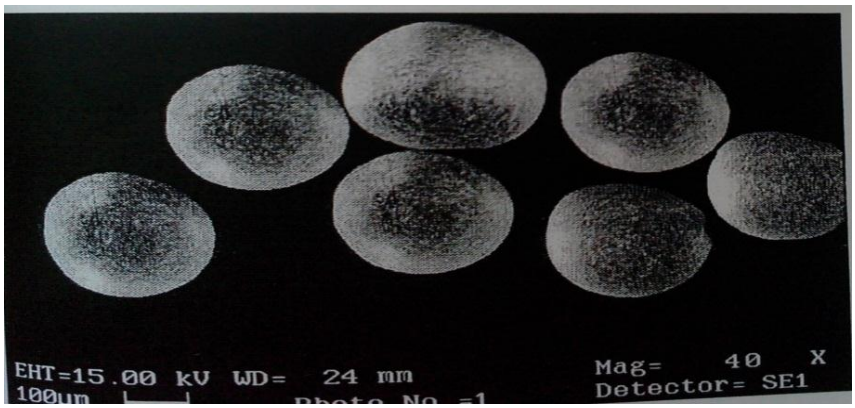


FIG.3.8 SEM PHOTO GRAPH FOR FORMULATION F7

PREPARED MICROSPHERE

3.5.5 Encapsulation efficiency

The drug entrapment efficiency is important variable for assessing the drug loading capacity of microspheres. This parameter is dependent on the process of preparation, physicochemical

properties of drug, and formulation variables. The drug entrapment efficiency varied from 41 % to 49%. Result of equation indicates the effect of X1 (drug-to-polymer ratio) is more significant than X2 (stirring speed). Moreover, stirring speed had a negative effect on drug entrapment efficiency (i.e., the stirring speed increased, the particle size decreased, and thus drug entrapment efficiency decreased). As the ratio of drug-to-polymer increased, encapsulation efficiency increased; this is due to the fact that higher ratio of drug-to-polymer would produce large size droplets with decreased surface area, such that diffusion of drug from such microsphere will be slow, resulting in higher encapsulation efficiency.

TABLE 3.6: DATA FOR ENCAPSULATION EFFICIENCY

Formulation code	% Encapsulation Efficiency Mean±SD
F1	42.224±0.06
F2	42.140±0.650
F3	41.425±0.124
F4	45.882±0.160
F5	45.05±0.014
F6	44.236±0.01
F7	48.919±0.199
F8	46.412±0.01
F9	46.35±0.015

(N=3) Mean±SD

3.5.6 In-Vitro Studies

In-vitro drug release study of F1to F9 formulation was carried out in o.1 N HCL for 2 hours followed by dissolution in phosphate buffer pH 7.20 for a period of 6 hrs. Initially, a burst effect within 2 hrs was observed predominantly in F1 to F9 formulation. Thereafter a period of slow release followed till 8 hrs. Various other factor that can affect the drug release from the microsphere include size of microsphere and its morphology, physical state of drug in polymer and type of polymer.

- **Apparatus:** paddle
- **Speed:** 50 rpm
- **Volume:** 900ml
- **Temperature:** 37±0.5^{0}C

TABLE 3.7: PERCENTAGE DRUG RELEASE OF FORMULATION (F1 TO F6)

Time (hrs)	F1 Mean±SD	F2 Mean±SD	F3 Mean±SD	F4 Mean±SD	F5 Mean±SD	F6 Mean±SD
1	6.268±0.024846	6.884±0.025403	7.177±0.025403412	11.235±0.050229	8.290±0.025403	7.819±0.078621
2	7.556±0.046014	7.895±0.025403	8.099±0.025403412	17.519±0.067211	8.993±0.091593	8.085±0.044
3	13.142±0.043981	14.187±0.049652	14.418±0.050229473	34.917±0.303541	20.089±0.1725	14.878±0.049652
4	13.409±0.198325	14.706±0.050229	14.734±0.172500242	39.465±0.049652	23.457±0.0855	15.627±0.131913
5	14.993±0.086002	15.310±0.049652	15.742±0.049652123	39.898±0.131913	26.423±0.099304	18.448±0.0865
6	15.742±0.349009	17.532±0.11547	17.786±0.099881597	41.798±0.099882	31.75±0.086	22.047±0.131804
7	16.404±0.049943	18.523±0.020785	18.995±0.099881597	48.103±0.050229	32.095±0.0865	28.554±0.173
8	17.440±0.099027	19.37±0.050229	20.147±0.049652123	50.233±0.0865	32.971±0.653821	30.8±0.086

(N=3) (Mean±SD)

3.5.7 Drug release kinetic

Dissolution data obtained from in-vitro release studies fitted on various mathematical models. The mathematical models were found to be on an average value. F1 formulation followed Peppas model and F2 followed Higuchi model of drug release.F3 to F9 formulation followed first order release.

TABLE 3.8: PERCENTAGE DRUG RELEASE OF FORMULATION (F7TO F9)

Time (hrs)	F7 Mean±SD	F8 Mean±SD	F9 Mean±SD
1	16.581±0.067211	15.362±0.188235	14.765±0.044
2	18.442±0.025403	16.479±0.088	17.167±2.487037
3	39.523±0.0865	34.168±0.0865	32.441±0.086
4	41.942±0.086	38.659±0.0865	37.364±0.173
5	47.873±0.050229	40.070±0.179584	41.683±0.173
6	53.486±0.099882	41.798±0.099882	44.216±0.099882
7	59.187±0.099882	54.84±0.131913	50.176±0.132459
8	60.137±0.131804	55.704±0.131913	54.466±0.173

(N=3) (Mean±SD)

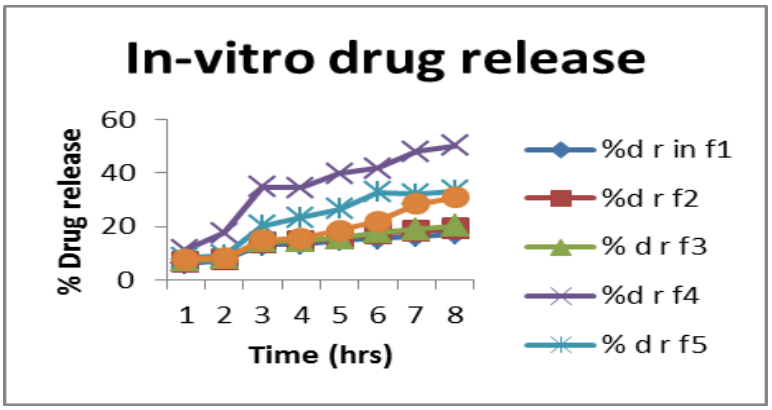


FIG.3.10 COMPARATIVE IN-VITRO RELEASE PROFILE LOSARTAN POTASSIUM MICROSPHERE FROM F1 - F6 FORMULATION.

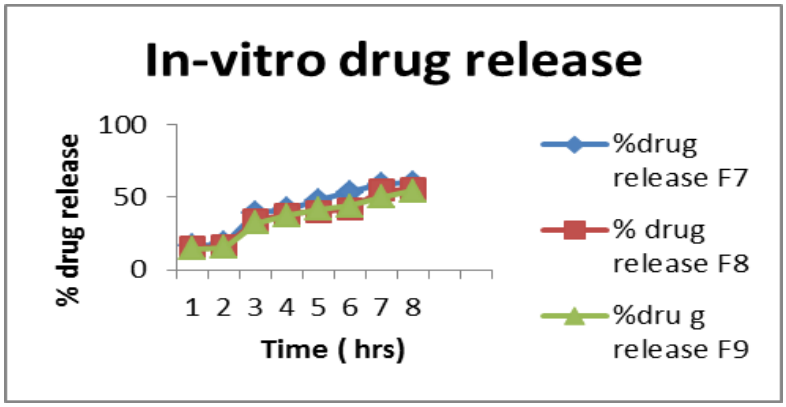


FIG.3.11 COMPARATIVE IN-VITRO RELEASE PROFILE LOSARTAN POTASSIUM MICROSPHERE FROM F7 – F9 FORMULATION.

3.5.7.1 Drug release kinetics

In order to obtain meaningful information for the release models, the dreg release profile fitted on various kinetic models.

TABLE 3.9: KINETIC MODEL TREATMENT OF DISSOLUTION PROFILES OF FORMULATIONS F1 –F9

Formulation Code	Zero Order r^2	First Order r^2	Higuchi Model r^2	Peppas and Kosmeyer r^2
F1	0.877	0.877	0.932	0.934
F2	0.899	0.898	0.939	0.928
F3	0.915	0.899	0.947	0.932
F4	0.905	0.991	0.949	0.946
F5	0.913	0.947	0.943	0.918
F6	0.967	0.971	0.925	0.919
F7	0.922	0.970	0.951	0.923
F8	0.924	0.954	0.933	0.914
F9	0.940	0.974	0.959	0.923

(N=3)Mean

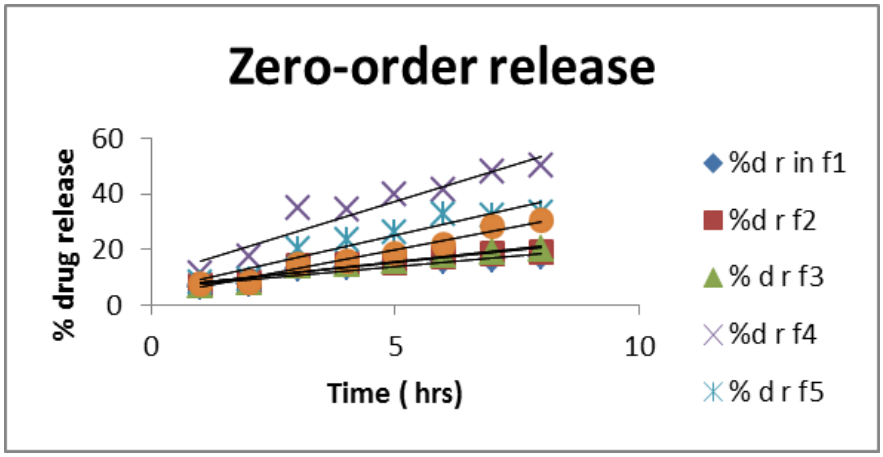


FIG.3.12 COMPARATIVE IN-VITRO ZERO-ORDER RELEASE PROFILE LOSARTAN POTASSIUM MICROSPHERE FROM F1 - F6 FORMULATION

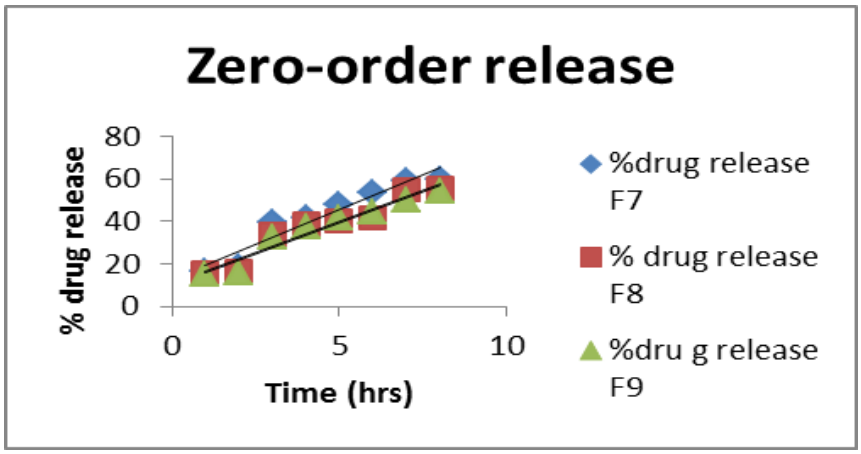


FIG. 3.13 COMPARATIVE IN-VITRO ZERO-ORDER RELEASE PROFILE LOSARTAN POTASSIUM MICROSPHERE FROM F7 – F9 FORMULATION.

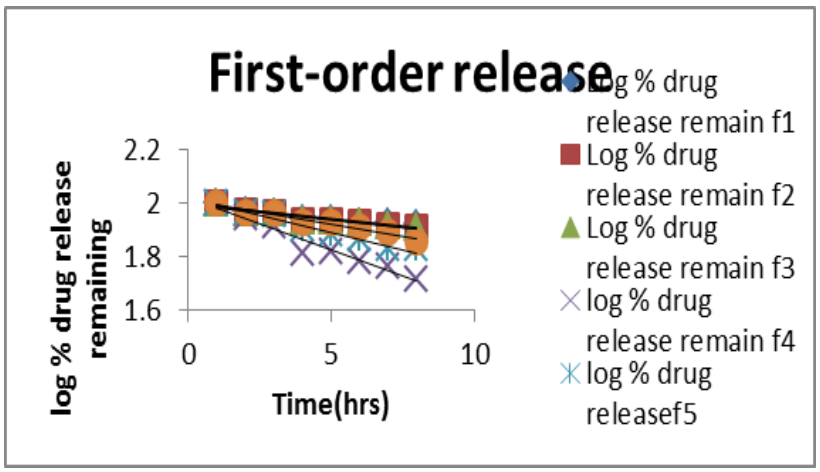


FIG.3.14 COMPARATIVE IN-VITRO FIRST-ORDER RELEASE PROFILE LOSARTAN POTASSIUM MICROSPHERE FROM F1 – F6 FORMULATION.

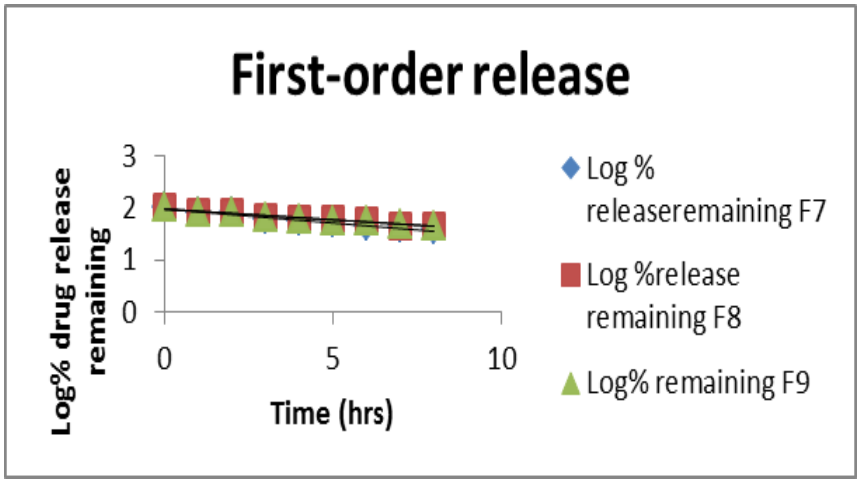


FIG.3.15 COMPARATIVE IN-VITRO FIRST-ORDER RELEASE PROFILE LOSARTAN POTASSIUM MICROSPHERE FROM F7 – F9 FORMULATION.

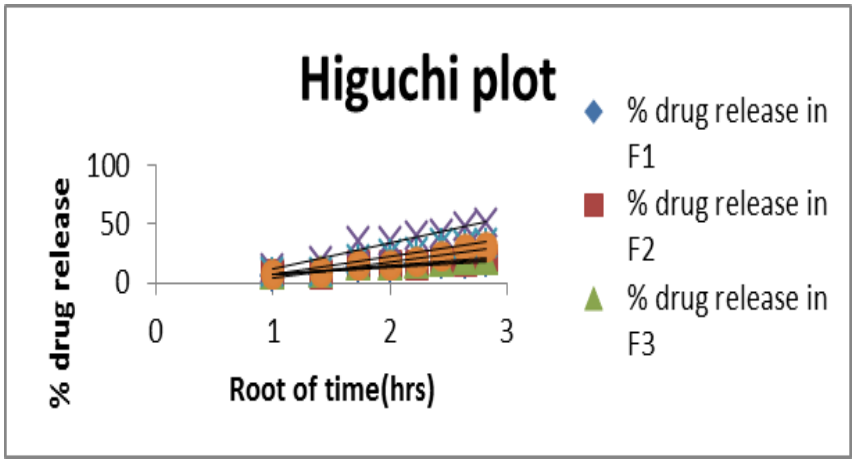


FIG.3.16 COMPARATIVE IN-VITRO HIGUCHI PLOT RELEASE PROFILE LOSARTAN POTASSIUM MICROSPHERE FROM F1 – F6 FORMULATION

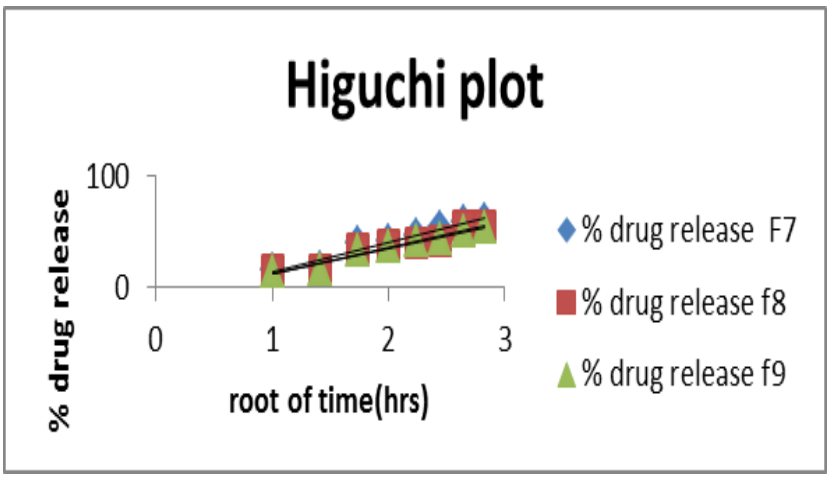


FIG.3.17 COMPARATIVE IN-VITRO HIGUCHI PLOT RELEASE PROFILE LOSARTAN POTASSIUM MICROSPHERE FROM F7 – F9 FORMULATION.

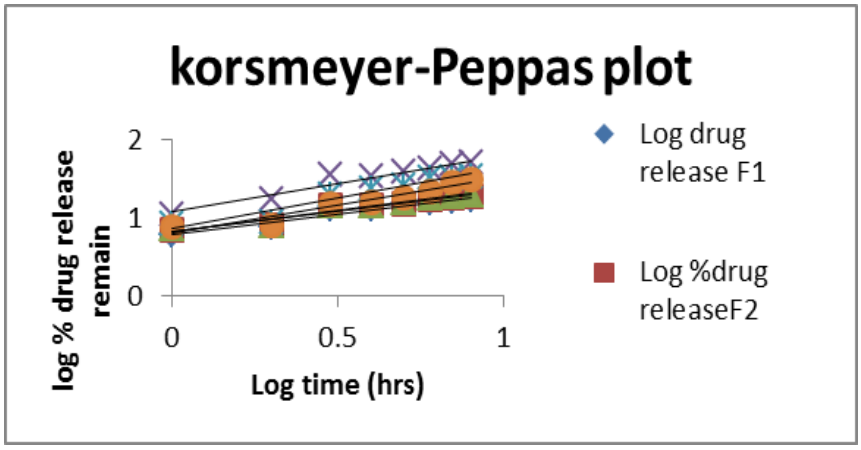


FIG.3.18 COMPARATIVE IN-VITRO PEPPAS PLOT RELEASE PROFILE LOSARTAN POTASSIUM MICROSPHERE FROM F1 – F6 FORMULATION.

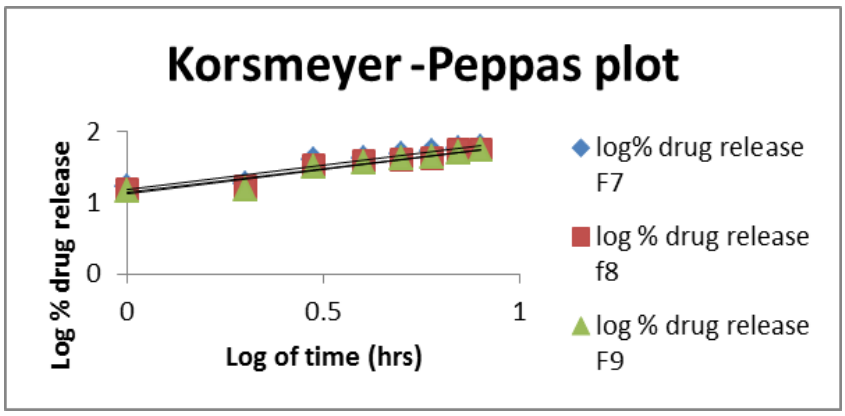


FIG.3.19 COMPARATIVE IN-VITRO PEPPAS PLOT RELEASE PROFILE LOSARTAN POTASSIUM MICROSPHERE FROM F7 – F9 FORMULATION.

3.5.8 Stability studies

3.5.9 The stability studies of F7 formulation was found stable at different temperature and humidity condition for 90 days. From the stability studies, it found that there was no significance change in the drug encapsulation efficiency and physical appearance of formulation. DRS spectra of microsphere saw that the formulation was physically and chemically stable.

TABLE 3.10 STABILITY STUDIES FOR % ENCAPSULATION EFFICIENCY AFTER 30 DAYS STORAGE

Formulation code	Time(days)	4^0±1 (Deep Freezer)	Room Temperature 25±2 ^{0}C	40±2 ^{0}C/75±5 % RH
F7	30	49.015	48.992	48.975

Diffuse Reflectance Spectroscopy

A shift in the DRS of the drug due to the presence of the excipient indicate physical absorption, whereas the appearance of new peak indicates chemisorption or formation of degraded product. Microsphere of LP using albumin are stable in terms of drug excipient compatibility.

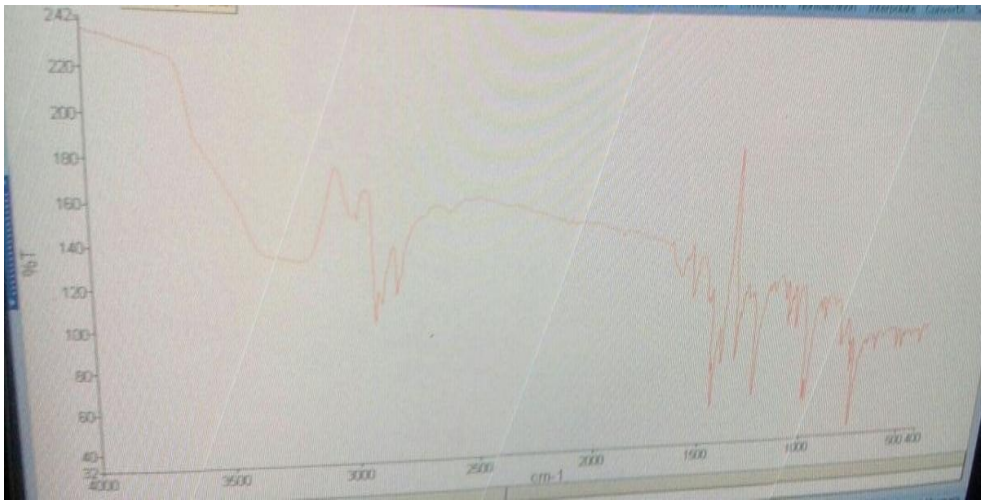


FIG.3.20 DRS SPECTRUM OF THE OPTIMIZED MICROSPHERE OF LOSARTAN POTASSIUM (FORMULATION F7).

TABLE 3.11 OBSERVATION TABLE OF VARIOUS FORMULATIONS FOR DEPENDENT VARIABLES

Formulation code	Particle size	Encapsulation efficiency	% drug release
F1	36.331±1.524	42.224±0.06	17.440±0.099027
F2	48.466±2.022	42.140±0.650	19.37±0.050229
F3	37.495±6.126	41.425±0.124	20.147±0.049652123
F4	56.886±1.275	45.882±0.160	50.233±0.0865
F5	50.798±1.4786	45.05±0.014	32.971±0.653821
F6	49.06±1.581	44.236±0.01	30.8±0.086
F7	76.266±1.331	48.919±0.199	60.137±0.131804
F8	69.548±2.642	46.412±0.01	55.704±0.131913
F9	60.126±6.844	46.35±0.015	54.466±0.173

CONCLUSION

The present study was a satisfactory attempt to formulate a sustained release microsphere of losartan potassium to improve its bioavailability and to controlled release of the drug. Stained release microspheres were containing losartan pota On the basic studies of particle size, SEM, encapsulation efficiency, drug release studies. It was concluded that formulation F7

was found the optimized formulation.The microspheres of best batch (F7) saw mean particle size of 76.266±1.331µm and entrapment efficiency of 48.919±0.199%. The % release was fond 60.137±0.131and release was found sustained.The stability studies of F7 formulation was found stable at different temperature and humidity condition for 90 days. From the stability studies, it found that there was no significance change in the drug encapsulation efficiency and physical appearance of formulation. DRS spectra of microsphere saw that the formulation was physically and chemically stable.

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