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PREPARATION AND SOLUBILITY ENHANCEMENT OF SOLID DISPERSION OF POORLY SOLUBLE LISINOPRIL DRUG

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ABSTRACT
The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. Lisinopril is an angiotensin converting enzyme inhibitor (ACEI) used to treat hypertension, heart failure and myocardial infarction. It functions by inhibition of angiotensin converting enzyme as well as the renin angiotensin aldosterone system. It is characterized with poor solubility which limits its absorption and dissolution rate which delays onset of action. The objective of the present study was to enhance the dissolution characteristics of the model drug by increasing the solubility and release rate of Lisinopril through solid dispersions using polyethylene glycol and polyvinylpyrrolidone polymers by the solvent evaporation method. The compatibility analysis was carried out through Fourier Transform-Infrared Spectroscopy (FT-IR). The kinetic studies for drug release mechanisms were characterized through zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models. The dissolution analysis of solid dispersions showed exhibited more than 92.45% drug released. The optimized formulation was found to follow the Higuchi model of drug release kinetics with an R^2 value of 0.993. Solid dispersions containing PEG and PVP polymers prepared through the solvent evaporation method exhibited significant enhancement in the release profile compared to a pure drug, lisinopril.

KEYWORDS: Lisinopril, Bioavailability, Solvent evaporation method, Kinetic studies, Higuchi model.

INTRODUCTION
An oral route of drug administration is the most preferred route of drug delivery due to convenience and ease of ingestion. A solid dosage form is a comfortable and familiar means of taking medication. Hence, a patient compliance and drug treatment are usually more effective with orally administered medications than other routes of administration.[1] At least 40% of the new chemical molecules tested are drugs having poor aqueous solubility. Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization, and addition of solvent or surface-active agents. Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs.[2] Solid dispersion technology is one of the most promising and extensively performed approaches to improve the dissolution rate of insoluble compounds. Ease of scalability, its conversion to solid dosage forms such as capsules, tablets, taste masking strips and implants are some of the advantages offered by solid dispersion over other approaches.[3] Lisinopril is an angiotensin converting enzyme inhibitor (ACEI) used to treat hypertension, heart failure, and myocardial infarction with a molecular weight of 405.488g/mol, with an initial dose of 2.5mg once a day. Lisinopril and captopril are the only ACEIs that are not prodrugs. It functions by inhibition of angiotensin converting enzyme as well as the renin angiotensin aldosterone system. Lisinopril is an angiotensin converting enzyme inhibitor (ACEI), preventing the conversion of angiotensin I to angiotensin II. This action prevents myocyte hypertrophy and vascular smooth muscle cell proliferation seen in untreated patients. Increased levels of bradykinin also exhibit vasodilating effects for patients taking ACEIs. Lisinopril also inhibits renin's conversion of angiotensin to angiotensin I.[4,5] The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Lisinopril by preparing solid dispersions with polymers such as PEG and PVP. The prepared solid dispersions were evaluated for solubility study, drug content and *in vitro* dissolution rate studies.

MATERIALS AND METHODS
Materials
Lisinopril was a gift from Aurobindo Pharma Limited, HITEC City, Hyderabad, India. Polyethylene glycol was obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai,

India. Polyvinylpyrrolidone was procured from Central Drug House (P) Ltd. New Delhi. Ethanol, acetonitrile was procured from SD Fine Chemicals Ltd., Mumbai. All other solvents and chemicals used were of analytical grade.

Method

Preformulation study[6-8]

Solubility

Solubility study was conducted to determine the effect of different buffers on the drug. An excess amount of drug was dispersed in 5 ml of distilled water, methanol, acetone, phosphate buffer solution (pH 6.8 and 7.4), 0.1N HCl, in glass stoppered tubes respectively, all the glass tubes were closed with stopper and covered with cellophane membrane to avoid solvent loss. Tubes were kept in water bath shaker at 37°C for 24 hrs. As the samples attain equilibrium, they were subjected for centrifugation at 3000 RPM for about 5 minutes. After completion of centrifugation the samples get separated, then supernatant liquid is filtered through membrane filter and then analyzed by UV spectrophotometer at 252nm respectively.

Melting point determination

Melting point of lisinopril was determined by open capillary method.

Determination of partition coefficient

25 mg of lisinopril with aqueous phase and n-octanol was taken in three separating funnels. The separating funnels were shaken for 2 hrs in a wrist action shaker for equilibration. Two phases were separated and the amount of the drug in aqueous phase was analyzed spectrophotometrically. The partition coefficient of the drug in phases was calculated.

Determination of λmax

A solution of lisinopril containing the concentration 10µg/ml was prepared in distilled water and UV spectrum was taken using Shimadzu (UV-1800) double beam spectrophotometer. The solution was scanned in the range of 200- 400 nm.

Preparation of standard calibration curve of lisinopril

100mg of drug was accurately weighed and dissolved in 100ml distilled water in 100 ml volumetric flask, to make (1000µg/ml) standard stock solution (1). Then 10 ml stock solution (1) was taken in another 100 ml volumetric flask to make (100µg/ml) standard stock solution (2), then again 0.5, 1, 1.5, 2, 2.5 and 3.0 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 5, 10, 15, 20, 25 and 30µg/ml with distilled water. The absorbance of standard solution was determined using UV/VIS spectrophotometer (Shimadzu UV-1800) at 252nm. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which determined by least-square linear regression analysis.

Drug-excipient interaction studies by FTIR

Infra-red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tones pressure. It was scanned from 4000 to 150 cm-1 in a Shimadzu FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

Preparation of solid dispersions

Solid dispersions of lisinopril in PEG and PVP were prepared by solvent evaporation method. A 40 mg quantity of lisinopril and carrier were dissolved separately in 100 ml of absolute ethanol. The solution was stirred for 1 h and the solvent was allowed to evaporate at room temperature. The solid dispersions obtained were pulverized and sieved through 22mesh and then stored in screw cap vials at room temperature for further use. The same procedure was carried out for all the formulations. The prepared dispersions were then characterized.[9,10]

Table 1: Composition of solid dispersion preparation.

Ingredients	Formulation batches					
	F1	F2	F3	F4	F5	F6
Lisinopril (mg)	40	40	40	40	40	40
PEG (mg)	100	200	300	400	500	600
PVP (mg)	600	500	400	300	200	100
Ethanol (ml)	100	100	100	100	100	100

Characterization of solid dispersion[11,12]

Saturation solubility determination

The shake flask method was used for the determination of the solubility of prepared solid dispersions. The excessive quantity of prepared SDs was added in a glass stoppered flask containing 25 ml of solvent and flasks were shaken for 24 hr at 37±0.5 °C. After 24 hr, the solution was filtered, diluted appropriately and absorbance was taken at the λmax of a drug. Analysis of each sample was carried out in triplicate. The change in solubility value was compared with pure drug solubility.

Determination of percentage yield

The percentage yield of F1 to F6 formulations was calculated by using the following equation. Determination was carried out in triplicate.

$$\%\ Yield = \frac{Actual\ weight\ of\ solid\ dispersion}{Total\ weight\ of\ drug\ and\ carrier} \times 100$$

Estimation of drug content

The solid dispersion equivalent to 10 mg of drug was dissolved in 10 ml of phosphate buffer (7.4 pH), filtered, diluted, and drug content was determined using UV spectrophotometer at λmax of a drug against phosphate buffer (7.4 pH) as a blank. Analysis of each sample was carried out in triplicate.

Scanning electron microscopy

Scanning electron microscopy (SEM) was also conducted to characterize the surface morphology of the solid dispersion for which a drop of formulation system was mounted on clear glass stub, air dried and coated with Polaron E 5100 Sputter coater (Polaron,) and visualized under Scanning Electron Microscope (SEM Leo 430,).

Particle size determination

The mean size of the solid dispersion preparations were measured by laser diffraction analyzer (Malvern). Each sample was diluted with water until the appropriate concentration of particles was achieved and measured. All measurements were performed at 25°C.

In vitro dissolution studies

The in vitro dissolution data was obtained by using USP Type II (Paddle type) dissolution apparatus with a rotating speed of 100 rpm and the media used was 900 ml phosphate buffer pH 7.4 maintained at 37±0.5 °C. At specific time intervals i.e. 5, 10, 20, 30, 45, 60 and 90 min, a 5ml sample was pipetted, and an equal amount of fresh media was added. Pipetted samples were filtered, diluted, and analyzed by UV spectrophotometer at λmax of drug.

Kinetic modeling of *in -vitro* release rates of formulations

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

Zero-order kinetic model-cumulative percentage drug release versus time

First- order kinetic model-log cumulative percentage drug release remaining versus time

Higuchi's model-cumulative percentage drug released versus square root of time

Korsmeyer's equation/peppa's model-log cumulative percentage drug released versus log time.[13,14]

RESULTS AND DISCUSSION

The lisinopril is found to be soluble in distilled water, freely soluble in phosphate buffer (pH 7.4) and practically insoluble in ethanol and acetonitrile. The melting point of lisinopril was 160 ºC -165ºC and λ_{max} of lisinopril was found to be 252 nm by using U.V. spectrophotometer (Shimadzu UV-1800). The calibration curve of lisinopril was found to be linear in the concentration range of 5-30µg/ml at 252 nm Figure 1 & 2. The partition coefficient of lisinopril was found to 0.672 in octanol: water. FTIR Spectrophotometric method was developed to establish the compatibility of lisinopril complex and pure drug. Both the spectra were compared for confirmation of common peaks. Lisinopril showed no significant variation in height, intensity and position of peaks, suggesting that drug and recipients were compatible. Hence it can be determined that the drug is in free state and can be released easily Figure 3(A-C). The solubility of solid dispersions was determined and compared with that of pure drug solubility in phosphate buffer (pH 7.4). It was found to be an increase in solubility of all the prepared solid dispersions as shown in Table 2. The maximum increase in solubility was found in the F3 formulation that was prepared by solvent evaporation technique employing PVP and PEG as a carrier in the ratio of 4:3 with the drug. The percentage yield values were found to get decreased at the higher ratios of the carrier due to the difficulty during sieving. Percentage yield values are found to in the range of 88.78 to 95.46%. The yield was high in the F3 batch i.e. 95.46%. The drug content of all the prepared solid dispersions were estimated and found in the range of 85.26 to 92.64, Table 3. SEM photographs for optimized formulation F3 are shown in Figures 4. Solid dispersions appeared as uniform and homogeneously mixed mass with wrinkled surface. The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the polymer. The particle size of optimized formulation of solid dispersions F3 was given in Figure 5. The *In vitro* dissolution studies of pure drug and SDs were carried out in phosphate buffer pH 7.4 up to 90 min. The formulations F1 to F6 showed drug release from 86.14 to 92.45% drug release. F3 formulation showed maximum drug release i.e. 92.45% in 90 min which is 2 times greater than pure drug. This marked increase in dissolution and solubility can be attributed to the reduced, uniform particle size and hydrophilic nature of PVP Table 4 & Figure 6. F3 was found to be the best formulation so drug release kinetics was obtained from in vitro dissolution data and shown in Table 5. It was found to follow higuchi kinetic model with an R^2 of 0.993 as shown in Figure 7-9.

Table 2: Solubility of pure drug and prepared solid dispersions.

S. No.	Formulations	Solubility in phosphate buffer 7.4
1	Pure drug	20.45 mg/ml
2	F1	65.15 mg/ml
3	F2	48.25 mg/ml
4	F3	74.24 mg/ml
5	F4	59.16 mg/ml
6	F5	63.86 mg/ml
7	F6	60.94 mg/ml

Table 3: Percentage yield drug content and of all the prepared formulations.

S. No.	Formulation code	Percentage yield	Drug content (in %)
1	F1	93.45	88.26±0.97
2	F2	90.25	85.26±0.85
3	F3	95.46	92.64±1.36
4	F4	88.78	90.45±0.96
5	F5	92.85	88.79±1.08
6	F6	89.45	87.68±0.92

Table 4: *In-vitro* dissolution of all the prepared formulation.

Time in min	Cumulative % Drug Release					
	F1	F2	F3	F4	F5	F6
5	15.28	17.46	20.49	20.46	18.25	18.51
10	22.61	25.14	33.75	35.14	29.45	31.45
20	35.54	38.67	45.61	43.25	38.49	44.28
30	48.25	49.28	51.26	59.48	52.84	56.84
45	61.25	62.58	68.65	67.25	66.28	64.81
60	75.35	79.54	77.59	77.54	75.15	79.58
90	88.24	86.14	92.45	91.05	87.45	89.68

Table 5: Release kinetics study of F3 formulation.

Formulation	Model	Kinetic parameter values
F3	Zero Order	y = 0.815x + 25.41 R^2 = 0.950
	First Order	y = -0.011x + 1.980 R^2 = 0.980
	Higuchi	y = 9.827x + 0.526 R^2 = 0.993

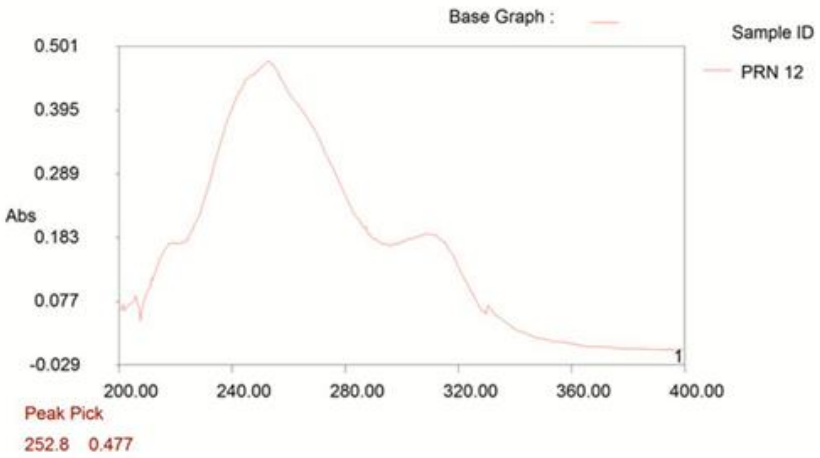


Figure 1 Wavelength maxima of lisinopril in distilled water.

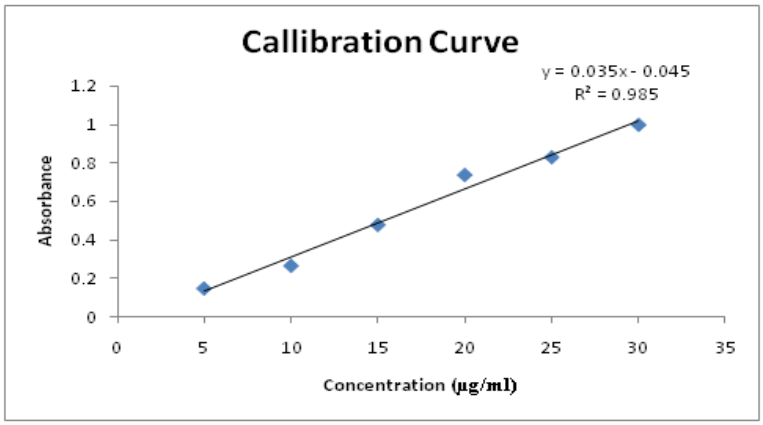
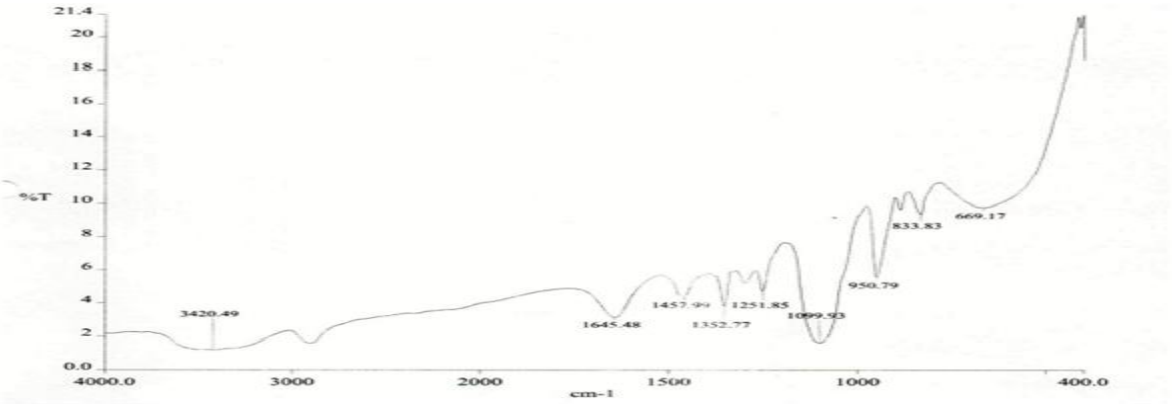
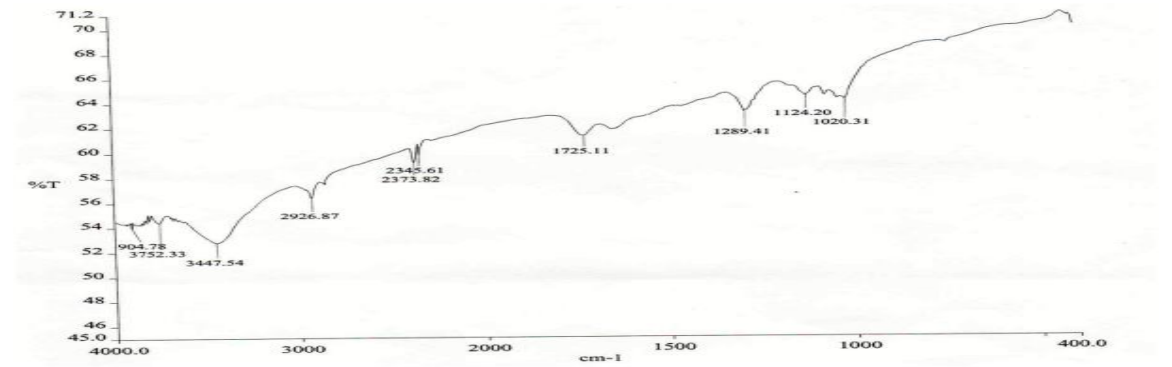


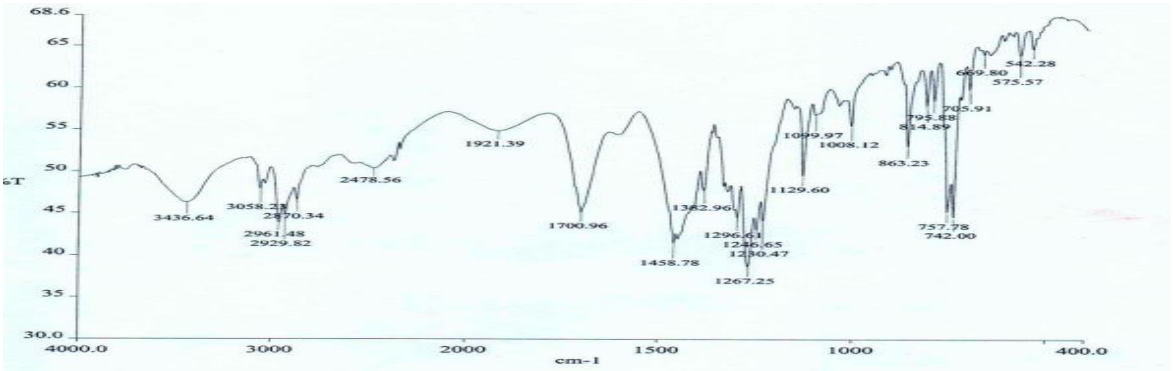
Figure 2 Calibration curve of lisinopril in distilled water.



(A)



(B)



(C)

Figure 3 FTIR spectra of (A) PEG, (B) PVP, (C) drug and excipient.

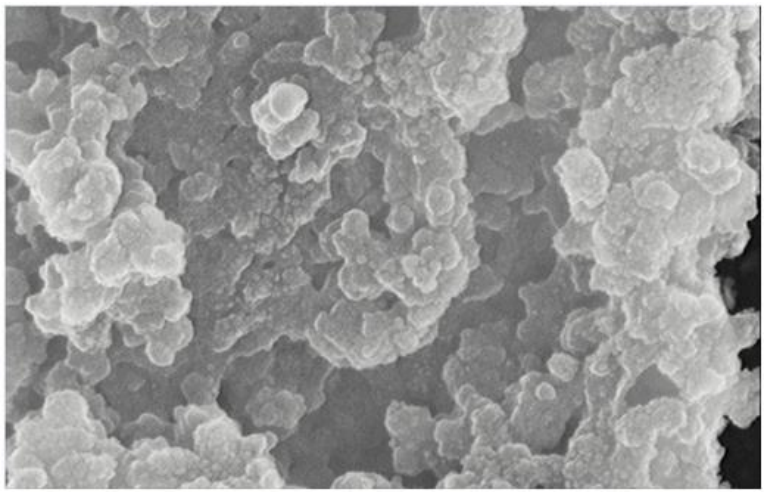


Figure 4 SEM of lisinopril optimized formulation F3.

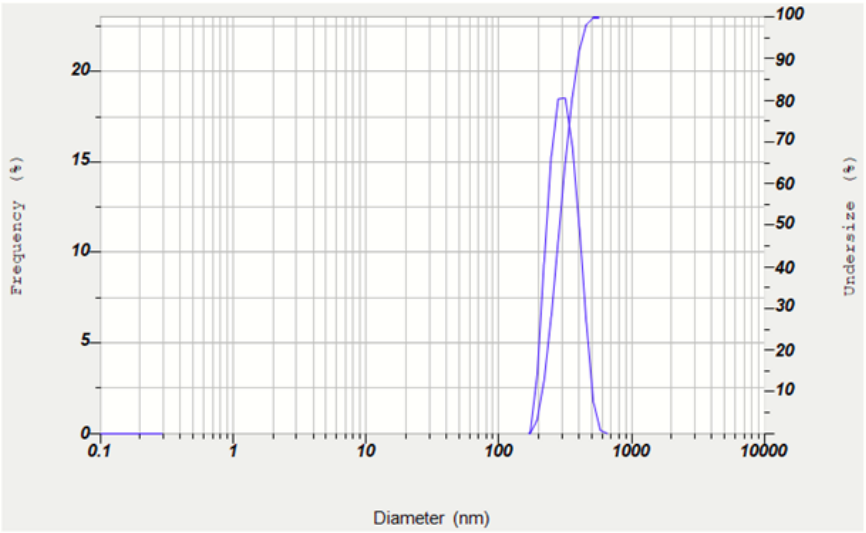


Figure 5 Particle size of optimized formulation of solid dispersions F3.

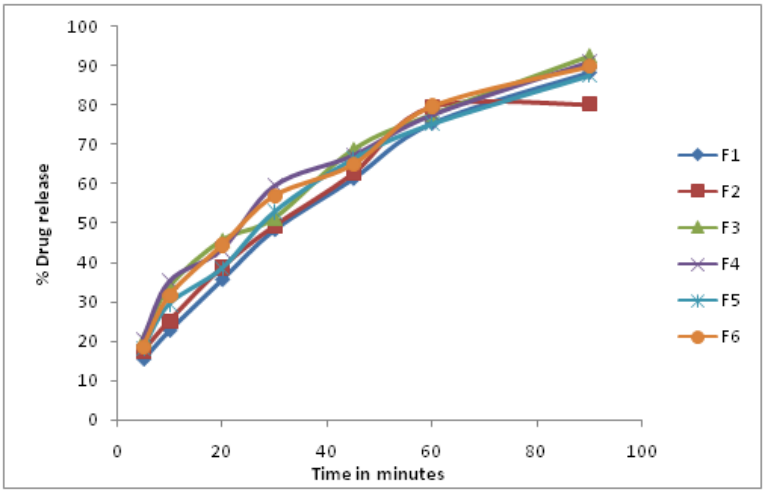


Figure 6 Cumulative drug releases of all the formulations.

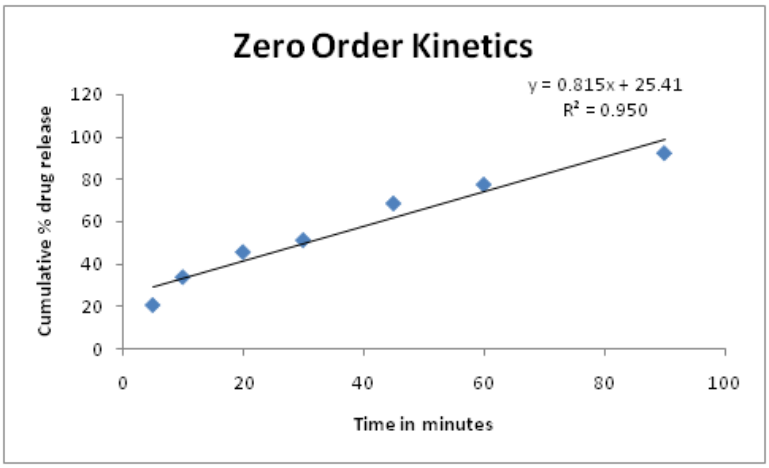


Figure 7 Zero order kinetic model.

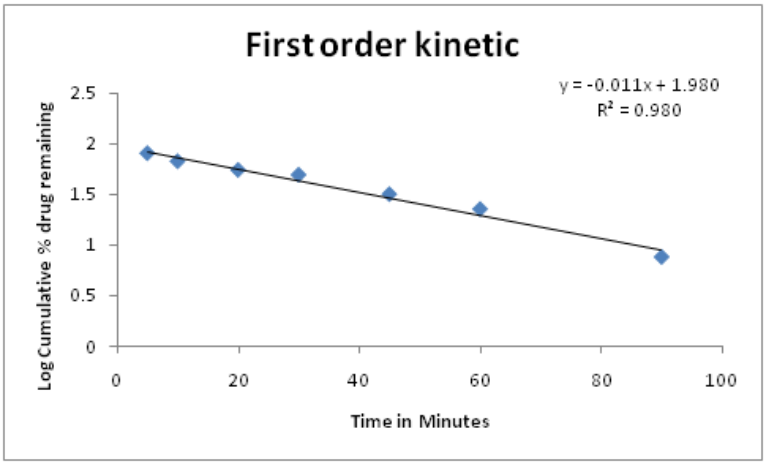


Figure 8 First order kinetic model.

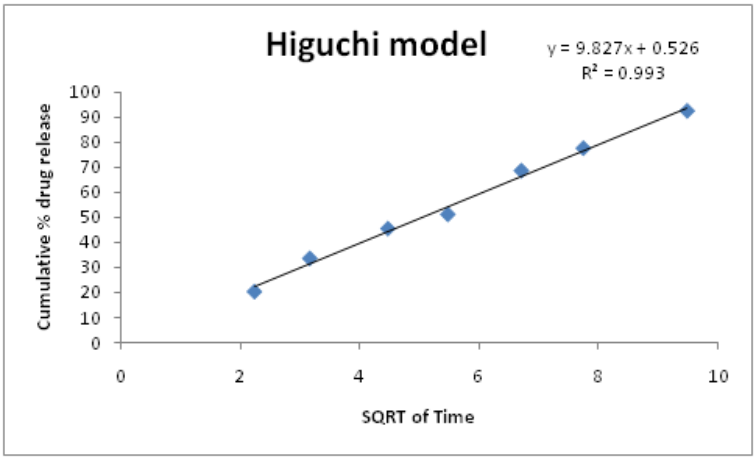


Figure 9 Higuchi kinetic model.

CONCLUSION

Finally, based on the above study, it was concluded that the solid dispersion technique was shown to be a successful approach for improving the dissolution rate of lisinopril. The nature and amount of the carrier used played an important role in the enhancement of the dissolution rate. The increased solubility and dissolution rate of lisinopril provided the rapid onset of action.

REFERENCES

1. Patil A, Kumar S. Formulation and evaluation of solid dispersions of an anthelmintic drug for enhancement of dissolution rate. JIPBS, 2017; 4(3): 71-74.
2. AppaRao B, Shivalingam MR, Kishore Reddy YV, Rao S, Rajesh K, Sunitha N. Formulation and Evaluation of Aceclofenac Solid Dispersions for Dissolution Rate Enhancement. International Journal

of Pharmaceutical Sciences and Drug Research, 2010; 2(2): 146-150.
3. Enose AA, Dasan P, Sivaramakrishanan H, Kakkar V. Formulation Characterization and Pharmacokinetic Evaluation of Telmisartan Solid Dispersions. J Mol Pharm Org Process Res., 2016; 4(1): 131.
4. Knutter I, Wollesky C, Kottra G, Hahn MG, Fischer W, Zebisch K, Neubert RH, Daniel H, Brandsch M: Transport of angiotensin-converting enzyme inhibitors by H+/peptide transporters revisited. J Pharmacol Exp Ther., 2008 Nov; 327(2): 432-41.
5. Song JC, White CM: Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. Clin Pharmacokinet, 2002; 41(3): 207-24.
6. Nagarajan K, Rao MG (2010) Formulation and dissolution studies of solid dispersions of nifedipine. Indian Journal of Novel Drug Delivery, 2: 96-98.
7. More CG, Dabhade PS (2015) Solubility and dissolution enhancement of gliclazide by solid dispersion technique, 2: 51-58.
8. Par KC, Lee BJ (2013) Current trends and future prospective of Solid dispersions containing poorly water soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics, 85: 799-813.
9. Sapkal SB, Adhao VS, Thenge RR, Darakhe RA, Shinde SA, Shrikhande VN. Formulation and characterization of solid dispersions of etoricoxib using natural polymers. Turkish Journal of Pharmaceutical Sciences, 2020 Feb; 17(1): 7.
10. Klecia MDS, Raquel MB, Fernanda GAV, Eduardo PA, Antonio CSL, Celso AC, et al. Development of solid dispersions of β-lapachone in PEG and PVP by the solvent evaporation method. Drug Dev Ind Pharm, 2018; 44: 750-6.
11. Deepak K, Narender S (2011) Enhancement of Dissolution profile of Gliclazide by Solid dispersion adsorbates. Lat Am J Pharm, 30: 2057-2060.
12. Dua K, Ramana MV, Sara UVS, Himaja M, Garg V, Agrawal A. Dissolution enhancement of aceclofenac through solid dispersions. Indian pharmacist, 2006; 70-72.
13. Subramanyam CVS. Textbook of Physical Pharmaceutics. 3rd ed. Vallabh Prakashan: Delhi, 2001; 181-234.
14. Brahmankar D M and Jaiswal S B. Biopharmaceutis and Pharmacokinetics: A Tretise, Vallabh Prakashan, New Delhi, 1st edition, 2006; 335-357.