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Optimization of Ramipril as Oral Dosage Form by Solid Dispersion Technique using Box-Behnken Design for the Enhancement of Bioavailability

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ABSTRACT
Ramipril (RM) acts as an Angiotensin-converting enzyme (ACE) inhibitor which is used for the treatment of hypertension. The development of solid dosage form is significantly challenging due to the low aqueous solubility of the drug. The objective of the research work was to enhance the solubility and bioavailability of Ramipril (RM) by solid dispersion using Design of Expert (DOE). In present exertion solid dispersions (SDs) of RM were prepared by the screening of a mixture of polymers (PVP K 30, PEG 6000): surfactant (Poloxamer 188) using software Design of Expert (DOE) i.e. Box-Behnken Design (BBD). Two methods were adopted for the formulation and developments of solid dispersions are solvent evaporation method and the kneading method. The SDs was evaluated based on in-vivo formulation and post formulation study. The SDs showed a significantly high drug release rate as compared to conventionally prepared tablets due to increasing wet ability properties of drug dissolution rate. The dissolution rate of the marketed formulation was found to be 74.72% while the dissolution rate of optimized Ramipril-based formulation was found 96.86%. It was concluded that the solvent evaporation method of SDs enhanced solubility and bioavailability of Ramipril which may be a promising approach for the future.
Keywords: *Solid Dispersion, Ramipril (RM), Bioavailability, Box-Behnken Design (BBD), In-vivo methods*

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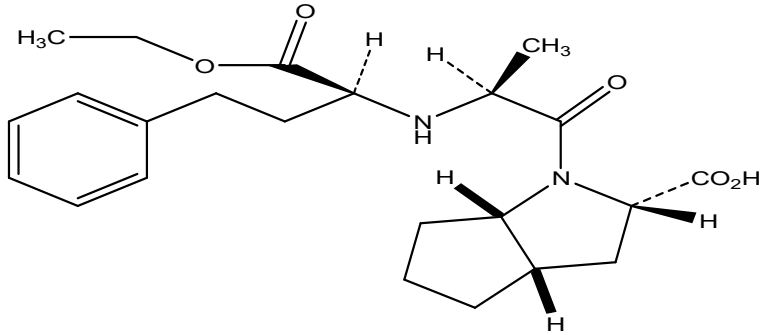
INTRODUCTION

Ramipril (RM) is a potent prodrug which kept under class II in Biopharmaceutical ClassificationSystem (BCS). RM is categorized as an ACE inhibitor and is mainly used in the treatment of hypertension, myocardial infarction, and heart failure [1]. RM (2S, 3aS, 6aS)-1-[(2S)-2-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl] amino} propanoyl]-octahydrocyclopenta [b] pyrrole-2-carboxylic acid) [1, 2] belongs to class of drug (Fig 1.1) called angiotensin converting enzyme (ACE) inhibitor administered orally (PO), and is effective in the treatment of hypertension, congestive heart failure and nephropathy.



(2*S*,3a*S*,6a*S*)-1-((*S*)-2-((*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanoyl)-octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid

Figure 1.1 Chemical structure of Ramipril

It is highly lipophilic poorly soluble in water and freely soluble in organic solvent like methanol with having their chemical formula $C_{23}H_{32}N_2O_5$. Based on the mechanism, it undergoes significant "first pass metabolism" and gets converted to its active metabolite ramiprilate by carboxylesterase enzyme and excrete out from the body through the kidney and completely inhibits angiotensin-converting enzyme (ACE) from converting angiotensin I to vasoconstrictor substance angiotensin II resulting in increased plasma renin activity and reduced aldosterone secretion [3]. It also increases bradykinin levels. A number of drugs with brand names were available in the market i.e. Delix, Altace, Tritace, Cardace, Acovil, Vesdil etc. contain ramipril (I) [4].

Third fourth (75%) metabolism of RM was carried out through hepatic metabolism while the rest (25%) was carried out by the liver.It has poor bioavailability [5] with 28% to 35% while active metabolite of RM (ramiprilate) bioavailability was observed 44% when it is orally administered. Formulation of RM as a solid dosage form is challenging due to its low aqueous solubility[6]. RM as the conventional method was previously reported by several research scientists. Among the various techniques of solubility enhancement like salt formation, inclusion complex, co-solvent, and pH adjustment, solid dispersion can be one of the promising technology for enhancement of the oral of poorly water-soluble drugs. To overcome the low bioavailability of lipophilic drugs, solid dispersions-based formulations are used to improve dissolution rate and bioavailability study [7, 8].

In addition, SDs were prepared by solvent evaporation and kneading technique using Box-Behnken Design (BBD) [9-11]. The main advantage of the solvent evaporation technique and kneading method is that the thermal decomposition of drug and polymers is evaded. Design of expert (DoE) software is a statistically method which determine relationship between the factors affecting the process and output of that process. DOE experiments are designed in such way that one or more factors (process variables) determinedly changed in an order to evaluate the changes with respect to response variables [10, 16, 17].

The hydrophilic carrier (i.e. PVP K-30, PEG 6000) and surfactant (Poloxamer 188) are used in the development of solid dispersion of Ramipril. These polymers are selected due to their hydrophilic nature and having potential to convert crystalline state of drug to amorphous state [7, 15, 21]. DOE approach was used in order to optimize drug polymer ratio as dependent variable while methods to prepare solid dispersion were selected as independent variable.

Thus, the main objective of the study is to validate the method of preparation for SDs of RM along with a suitable polymer ratio by using Box-Behnken Design. Another aim of the study is to find out the response of drugs through in vivo studies on rabbits.

MATERIAL AND METHODS

Materials

Ramipril as a gift sample was received from Akums drugs & Pharmaceuticals Ltd., Haridwar, India. Polyethylene Glycol 6000, Polyvinylpyrrolidone (PVP) K-30 are purchased from Titan Biotech, New Delhi, India while Poloxamer 188 was bought from Yarrow Chem., New Delhi, India. Solvent (Methanol, Ethanol) was purchased from Jiangsu Huaxi International., Jiangsu, China. HPLC Water from Rankem, Gurugram, Haryana while Acetonitrile (HPLC Grade) from Merck, New Delhi, India. Sodium percholate (HPLC Grade) was procured from Central Drug House, New Delhi, India. Orthophosphoric acid (HPLC Grade) from Fischer scientific, New Delhi, India, and Triethylamine (HPLC Grade) from S.D fine, Ambala, Haryana. All the chemicals used were analytical reagent grade.

Preparation of solid dispersions

Solid dispersions were prepared by kneading method using PVP K-30, PEG 6000, and Poloxamer 188 in drug: polymer ratio of 1:1, 1:2, and 1:3. The weighed quantities of drugs with respective polymers were placed in a mortar and then the mixture was kneaded using a gradient amount of ethanol to form a homogenous mixture. The formulations were dried in a hot air oven at 40-45ºC until it gets dried [11-13]. The dried samples were then pulverized and passed through 60 mesh sieve size. The formulations were stored in desiccators at room temperature for further use.

In addition, solid dispersions were prepared by an evaporation method using PVP K-30, PEG 6000, and Poloxamer 188 in a drug: polymer ratio of 1:1, 1:2, and 1:3. The weighed quantities of the drug and respective polymers were dissolved in 10 ml of solvent (ethanol) with a continuous stirring rate of 50 rpm on a magnetic stirrer. The solvent was then allowed to evaporate at 40ºC in a hot air oven for 30 min. The dried samples were then pulverized and passed through a sieve size 40 [11, 14-15]. The formulations were stored in desiccators at room temperature for further use.

Screening of variables by Box-Behnken design a statistical approach

The optimization of the concentration of the polymers is an important step to control and modulate the release pattern of drugs from the dispersion matrix. Three independent variables of varying concentrations of polymers were selected i.e. PVP K-30, PEG 6000, Poloxamer 188, and one dependent

variable (drug concentration i.e. 3mg, 4mg, and 5mg.) were chosen for screening response variable and calculated as given in table 1.1. The design generated by Box- Behnken Design (BBD) for the formulation is given in Table 1.2 [16, 17].

Table 1.1: Variables for optimization with their levels

Variables	Low level (-1)	Optimum level (0)	High level (+1)
PVP K-30	3 mg	4 mg	5 mg
PEG 6000	3 mg	4 mg	5 mg
Poloxamer 188	3 mg	4 mg	5 mg

Table 1.2: Design generated by Box- Behnken

Formulation	PVP K-30	PEG 6000	Poloxamer 188
1	-1	1	0
2	1	-1	0
3	0	0	0
4	-1	0	1
5	0	-1	-1
6	1	1	0
7	0	0	0
8	-1	0	-1
9	1	0	1
10	-1	-1	0
11	0	0	0
12	1	0	-1
13	0	0	0
14	0	0	0
15	0	-1	1
16	0	1	1
17	0	1	-1

Characterization of solid dispersions (SDs)

Phase Solubility studies

The equilibrium solubility of the purified RM and prepared RM SDs were carried out in Ultra-pure water (Millipore, USA) as per described Higuchi and Corner method. The solubility was performed by taking a sample equivalent to 10 mg in 10 ml distilled water (1mg/ml) and stirred for 24 hr. at 37ºC in a vertical wrist shaker (n=3) [18,19]. Then, supernatant samples were filtered through Whatman filter paper of 0.45µm (GE Healthcare, Germany) and assayed spectrophotometrically (Agilent technology, Germany) at the wavelength of 208 nm.

Evaluation of particle size

The vesicle size of the formulation was examined by microscope (Miotic, Hong Kong). It is useful in providing valuable morphological and functional information about the crystallinity and morphology of drugs. Microscopy of drug, excipients and solid dispersion was carried out at magnification power 10X. Particle size counts were carried on 500 particles of drug, excipients, and solid dispersion [20-22].

Fourier transform infrared studies (FTIR)

Infrared spectra were obtained using an FTIR spectrophotometer (Shimadzu, spectrum, USA). The Ramipril and solid dispersion of Ramipril were mixed with potassium bromide and covert in the form of a tablet. The scanning of the samples was obtained using a wave number range of 400 to 4000 cm^{-1}. After running spectra significant peaks which are related to the major functional group were identified and compared with the original spectra [20-22].

Differential Scanning Calorimeter (DSC)

DSC thermo grams were recorded for RM, polymer mixtures, and binary mixtures of RM with Poloxamer 188. The accurately weighed sample (2-5mg) was placed in aluminium (Al) pan with a reference of empty Aluminium (Al) pan. The nitrogen flow rate (35-40 ml/min) and scanning of samples were carried out in the range of temperature of 25-350°C for 20 min. Thermo gram was recorded and analyzed by observing the peak temperature and endothermic transition contours of samples. Thermo gram provides valuable information for changes in the crystalline structure of the drug and the formulation [18, 19, 20].

Dissolution studies

United States Pharmacopeia (USP) apparatus II (Mini Paddle) method (Lab India DS 8000, Mumbai, India) was adopted for the investigation of the release rate of RM SDs. Solid dispersions equivalent to 5 mg of Ramipril were filled into hard gelatine capsule and dissolution studies were conducted at 50 rpm in 500 ml medium (pH 1.2) of buffer media to mimic the physiological condition at 37±05°C. At a predetermined time interval, the aliquots of 2 ml were withdrawn with a calibrated pipette at a time interval of 10, 20, 30, 40, 50, and 60 minutes. The samples were filtered with Whatman filter paper (0.45 µm) and analyzed spectrophotometrically at 208 nm [19-22].

Drug Content Analysis

Drug content uniformity was determined by dissolving pure RM equivalent to 10 mg and dissolved in 1 ml methanol and volume was made up to 100 ml with a buffer of pH 1.2. A concentration level of 100µg/ml of this solution was prepared. The sample was filtered with Whatman filter paper (0.45 µm) and further dilution was carried out by taking 1 ml solution in a 10 ml volumetric flask and volume was adjusted with a buffer of pH 1.2. The drug concentration was analyzed at 208 nm using a UV spectrophotometer. The experiments were executed in triplicate and average values were reported [18, 20-22].

Comparison of solid dispersion with conventional formulation

Optimized formulation SD 1 was compared with the marketed product Cardiopril 5mg manufactured by Dr. Reddy. The dissolution was carried out in USP Apparatus II (mini paddle) at 50 rpm in a 500 ml buffer of pH 1.2 at 37^0C. At a predetermined time interval, the aliquots of 2 ml were withdrawn with a calibrated pipette at a time interval of 10, 20, 30, 40, 50, and 60 minutes. The samples were filtered with Whatman filter paper (0.45 µm) and analyzed spectrophotometrically at 208 nm [23, 24].

In vivo pharmacokinetic study

Adult rabbits (200-250 g/body weight) were taken for the experiment. The animals were kept on a standard laboratory diet under standard laboratory conditions, with the temperature at 25±2ºC and relative humidity (55± 5%). The formulation (saline water, solid dispersion, pure drug) was given by feeding sonde. The dose was calculated according to the weight of the rabbits (350 µg). The rabbits were anesthetized using Ketamine (Paksons Pharma Pvt. Ltd., India) by the subcutaneous route and 0.5 ml samples were withdrawn from the ear margin vein at 0.5, 1, 1.5, 2.5, 3.5, 4.5, and 5.5 hr. intervals using an insulin syringe (Becton Dickinson, Gurgaon, India). The plasma sample (0.5 ml) was taken in into centrifuged tube and acidified with orthophosphoric acid. 3 ml of solvent diethyl ether: dichloromethane (7:3 v/v) was added and samples were centrifuged at 2000 rpm [1, 25-27]. The organic layer was transferred to vials and evaporated at 70ºC. The sample residue was reconstituted using the mobile phase. The plasma concentration of the drug was determined with the help of a validated HPLC method (Agilent Technology, Germany).

RESULTS AND DISCUSSION

Ramipril is a second-generation ACE inhibitor used as an adjuvant in the treatment of hypertension which usually means high pressure in the arteries. Hypertension may cause difficulty in the heart to work, contributes to atherosclerosis, and increases the risk of congestive heart failure, heart disorder, kidney disorder, blindness, and stroke.

RM belongs to BCS class II with only 3.5 mg/ml solubility and exhibits poor bioavailability. With the application of the solid dispersion technique, it should be possible to improve the solubility behaviour of the drug.

The microscopic technique is used to examine the cellular structure of the sample which reveals the structure identification between pure drug and the formulation. It was examined that the drug (Fig. 1.2 A) was having a needle-shaped crystal structure with an irregular smooth surface while excipients (Fig. 1.2 B, C, D) had a spherical shape with a smooth surface. SDs have appeared as smooth scaly surfaces and homogeneously mixed mass. SDs was observed to have resembled morphology with pure drugs. It indicates that the drug was uniformly dispersed into the polymers. Microscopic images of drugs, excipients, and SDs suggested that individual properties were lost during formulation.

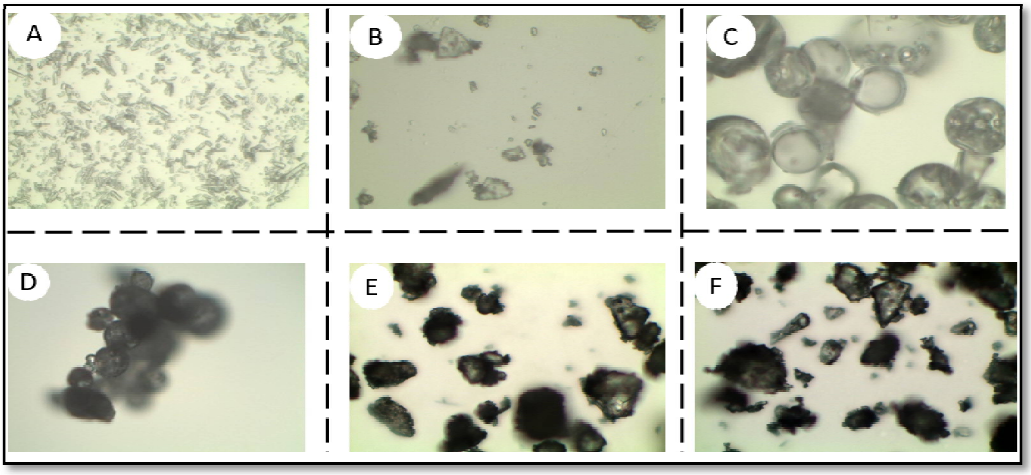


Figure 1.2: Microscopic images of drug and polymers. (A) Pure Ramipril, (B) PEG 6000, (C) PVP K-30, (D) Poloxamer 188, (E) Solid dispersion by solvent evaporation method, (F) Solid dispersion by kneading method

It was concluded that the average particles size of SDs prepared by a solvent evaporation method (Fig. 1.2 E) was less in comparison to SDs prepared by the kneading method (Fig. 1.2F). The reduction of particle size will increase the surface area of the drug and hence better solubility. The particle also had uniform distribution as shown in table no. 1.3.

Table 1.3: Particle size determination of drug, excipients and solid dispersion

Samples	Average particle size (Micron)
Ramipril (RM)	3.621
PEG 6000	3.576
PVP K-30	12.860
Poloxamer 188	4.535
SDs by solvent evaporation	2.123
SDs by Kneading method	3.140

Phase solubility studies were carried out by taking the excess drug in screwed capped vials containing various amounts of polymers in pH 1.2 buffer media. The vials were shaken in a wrist hand shaker at 37 °C for 48 hr. The samples were filtered with Whatman filter paper. The solubility of the drug was analyzed spectrophotometrically at 208 nm. Solubility of RM was increased in SDs prepared by a solvent evaporation method. The solubility of the drug was found to be 3.5 mg/ml. The solubility of SDs prepared by kneading method and solvent evaporation method was found to be 4.6 mg/ml and 7.3 mg/ml respectively. The SDs by solvent evaporation method was showing a good solubility profile. The possibility of high solubility contributed due to the increased wettability of drug particles in the formulation. The influence of polymer on the solubility of RM is presented in Figure 1.3 which shows the solubility of RM increases with the inclusion of polymer.

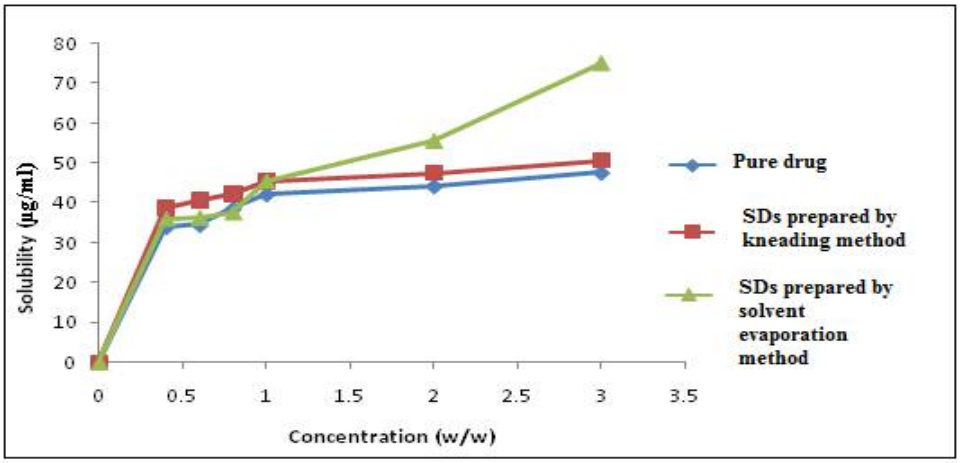


Figure 1.3: Phase solubility studies of pure and SDs prepared by kneading and solvent evaporation method

The FTIR spectrum provides information regarding chemical bonding, a characteristic functional group in drug and formulation. In this study, FTIR was applied to determine the possible interaction between RM and solid dispersion prepared by a solvent evaporation method. FTIR spectra of RM represent vibrational bonds with a characteristic peak at wavelength 3414 cm^{-1} for –NH and –OH. The NH group which is located at 3414 cm^{-1} in the spectra of Ramipril shifted to 3448 cm-1 in the solid dispersion. IR spectrum shows peaks of –CH aromatic stretching for RM and solid dispersion at 2866 cm-1 and 2873 cm-1. IR spectrum shows a peak for carboxylic acid for RM and solid dispersion at 1396 cm-1 and 1400 cm-1 respectively. The observed peak of Ramipril and solid dispersion when compared indicates that there was no chemical interaction. Since all the peaks of solid dispersion were in an acceptable range.

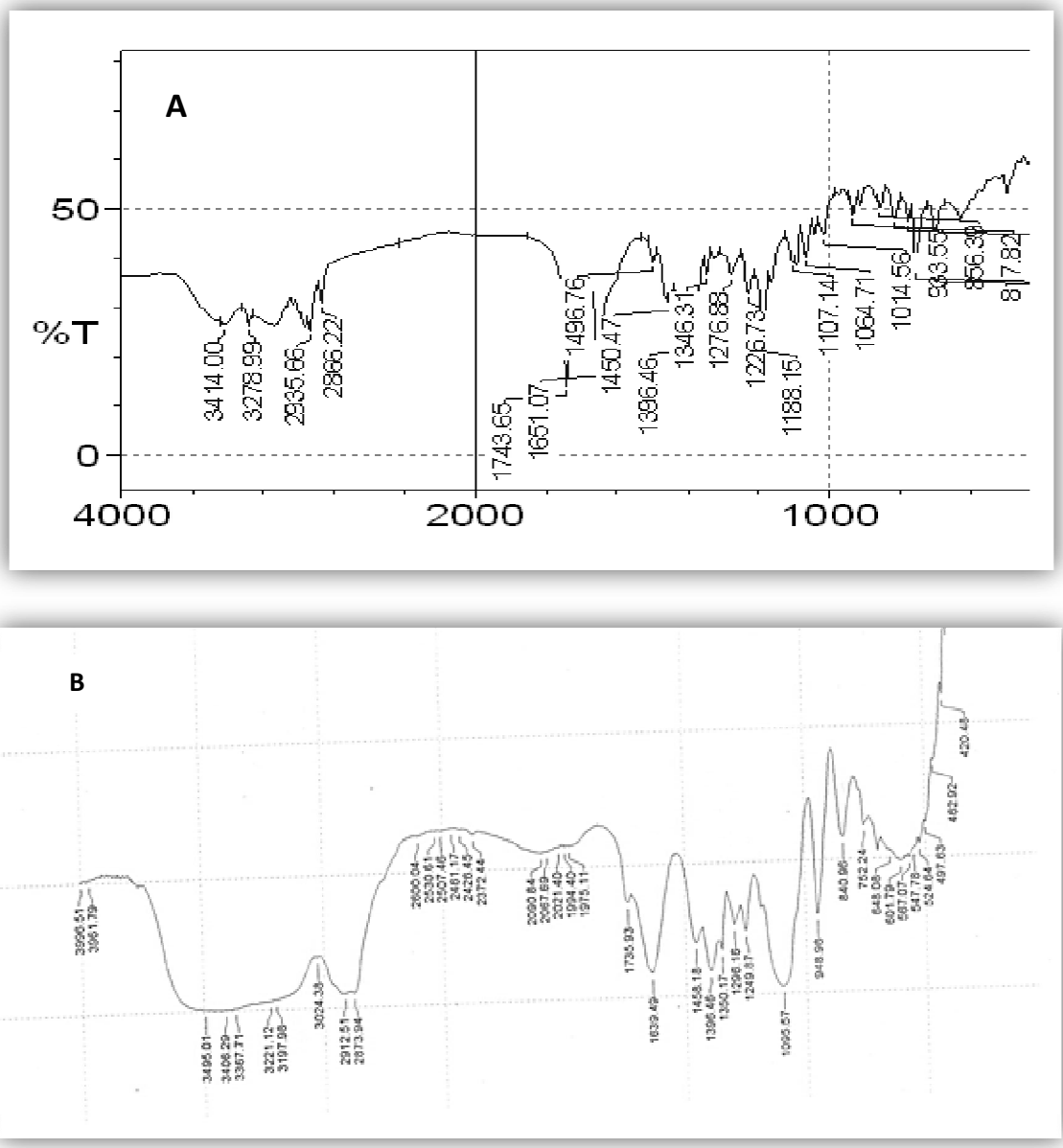


Figure 1.4: Fourier Transform infrared (FTIR) spectra of (a) pure Ramipril and (b) solid dispersion

Figure 1.4 shows the DSC curve of RM, pure excipients i.e. PEG 6000, PVP K-30, and Poloxamer 188, and optimized Solid Dispersion prepared by a solvent evaporation method. DSC of RM appeared with a sharp endothermic peak at 116.50ºC which corresponds to the melting point (Fig. 1.5 b). DSC curves of PEG 6000, PVP K-30 and Poloxamer 188 show one endothermic peak at 60 °C, 149 °C, and 52°C respectively which corresponds to their melting point (Fig. 1.5 c, d, and e). DSC curve of solid dispersion shows characteristic at endothermic peak at 100.5°C (Fig. 1.5 a). The drug peak shifted slightly toward the lower temperature this may be related to water loss.

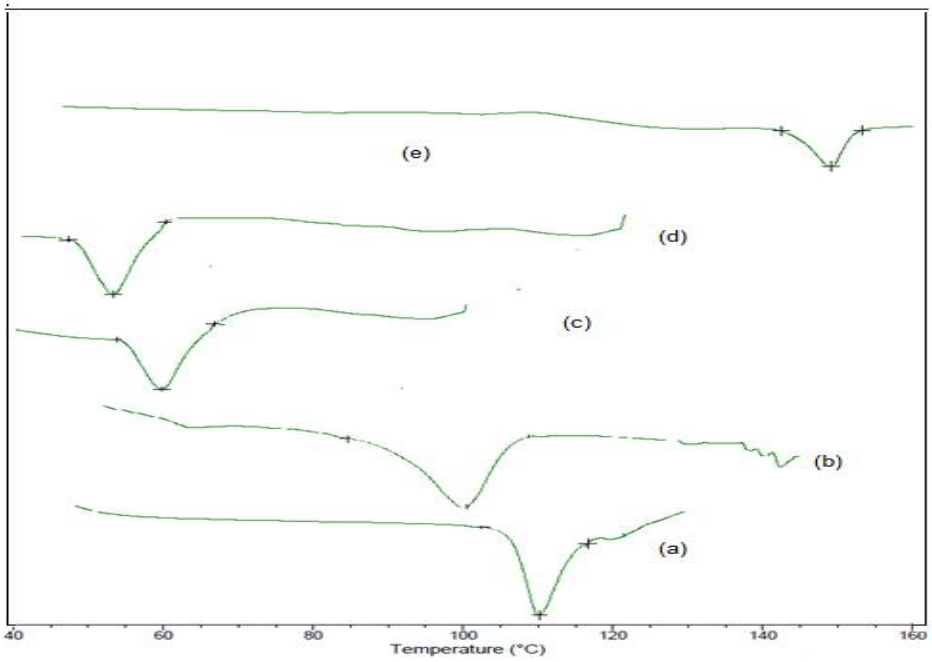
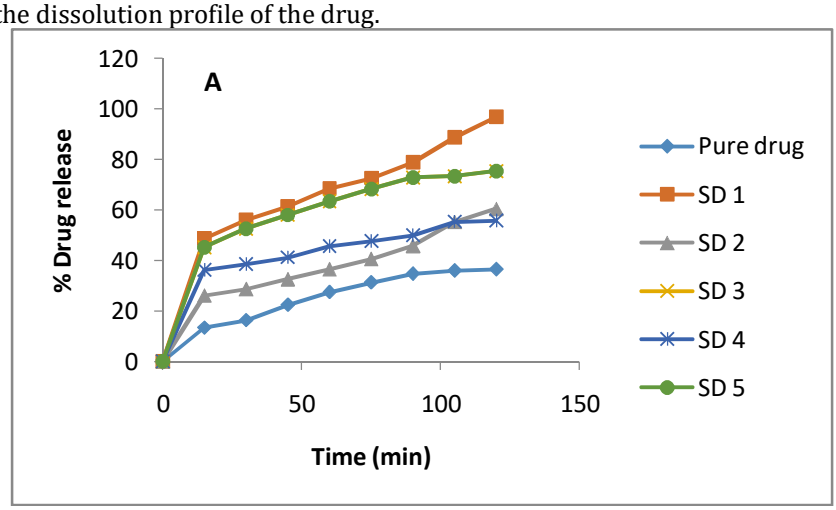


Figure 1.5: Differential scanning calorimetric (DSC) thermo gram of (a) Solid Dispersion, (b) Pure Ramipril, (c) PEG 6000, (d) Poloxamer 188 and (e) PVP K-30.

Solid dispersion was optimized by Box Behnken design and formulated by two methods that are solvent evaporation method and kneading method. SDs were prepared using polymers PEG 6000, PVP K-30 and Poloxamer 188 at different concentration ratios i.e. minimum (-1), maximum (+1), and optimum (0) levels. Solid dispersion prepared by solvent evaporation method is denoted as SD_1 while solid dispersion prepared by kneading method is denoted as SD_2. The result was supported by the surface response curve obtained by applying the Box-Behnken design. The effects of independent variables i.e. PEG 6000, PVP K-30, and Poloxamer 188 designated as X_1, X_2, and X_3 respectively on the dissolution of the drug as a dependent parameter was represented by surface response curves obtained by using Box- Behnken design, which signifies that effect of changing any of the variables at a time from its low level to its high level may alter the dissolution profile of the drug.



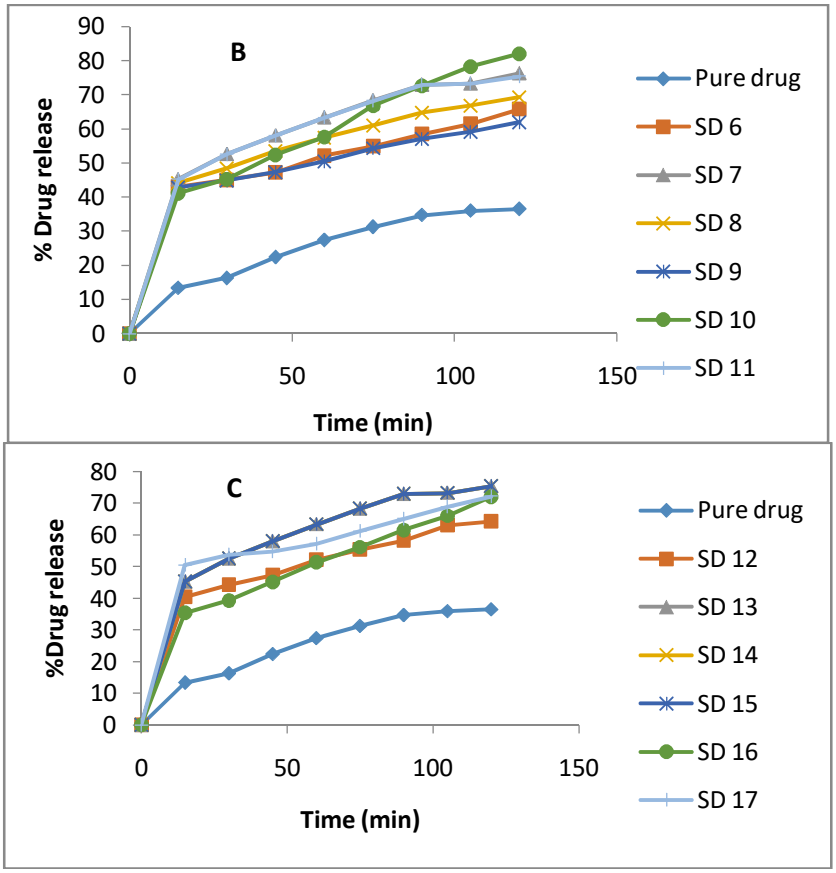


Figure 1.6: In vitro drug release profile of Ramipril from solid dispersion prepared by solvent evaporation method (a) pure drug and SD1-SD5, (b) pure drug and SD6-SD11(c) SD12-SD17

The dissolution of formulation SD_1 showed (Fig. 1.6) drug release between RM and formulation obtained by applying Box- Behnken design. It was concluded that formulation SD_1 showed 96% release in 120 minutes. Whereas formulation SD_2 showed (Fig. 1.6) drug release between RM and formulation obtained by applying Box- Behnken design. It was concluded that SD_2 showed 86% drug release in 120 minutes. Hence it is concluded that SD prepared by solvent evaporation method showed increased drug release profile.

From the surface response curves obtained by SD_1 (Fig. 1.7) and SD_2 (Fig. 1.8), it is concluded that dissolution was affected by changing the concentrations of PEG 6000 and Poloxamer 188. With the increase in the concentration of both PEG 6000 and Poloxamer 188 at their maximum levels the dissolution increases but dissolution was found to be maximum when Poloxamer188 was used in optimum and PEG 6000. According to the surface response curve PEG 6000 in concentration 5mg, PVP K30 in concentration 3mg, and Poloxamer 188 in concentration 4 mg showed an increased drug release profile in SD_1. So SD_1 prepared by solvent evaporation method is considered as optimized formulation and carried for further study. Hence it is concluded that the increase in dissolution rate was dependent on the ratio of PVP K-30, PEG 6000, and Poloxamer 188 and the method of preparation of solid dispersion.

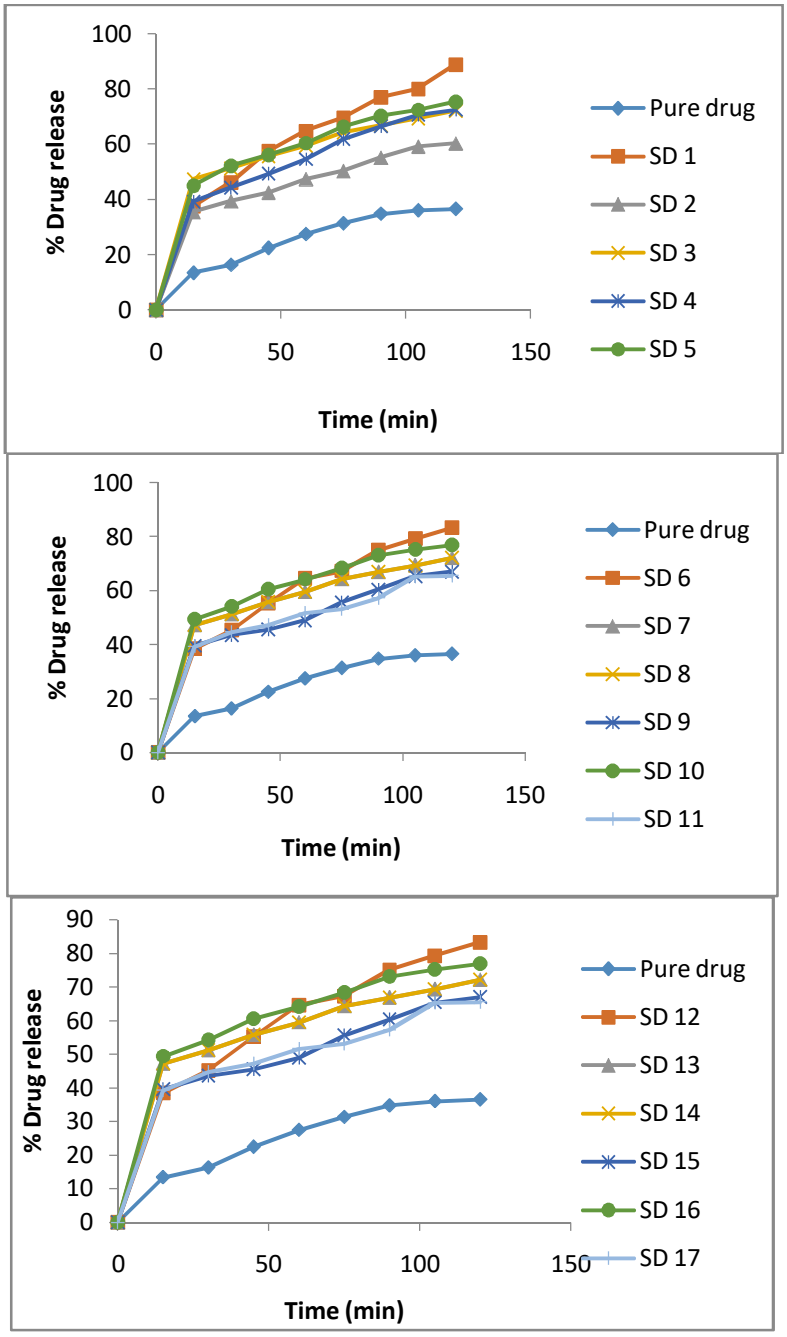


Figure 1.7: In vitro drug release profile of drug and Solid dispersion by kneading method (a) pure drug and SD1-SD4, (b) SD5-SD9 (c) SD10-SD17

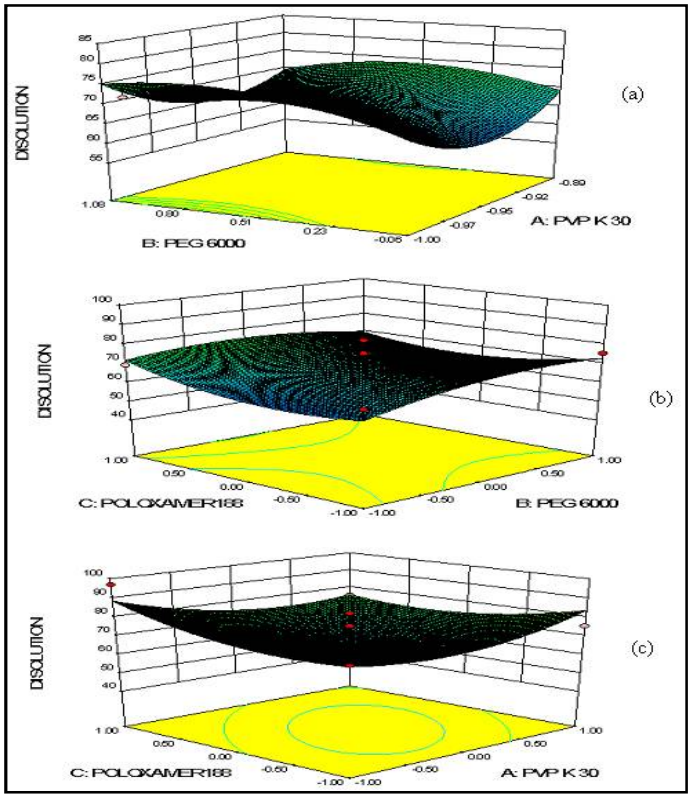


Figure 1.8 A: Response surface design by solvent evaporation method, (a) response between PVP K-30 and PEG 6000, (b) response between PEG 6000 and Poloxamer 188, (c) response between Poloxamer 188 and PVP K-30

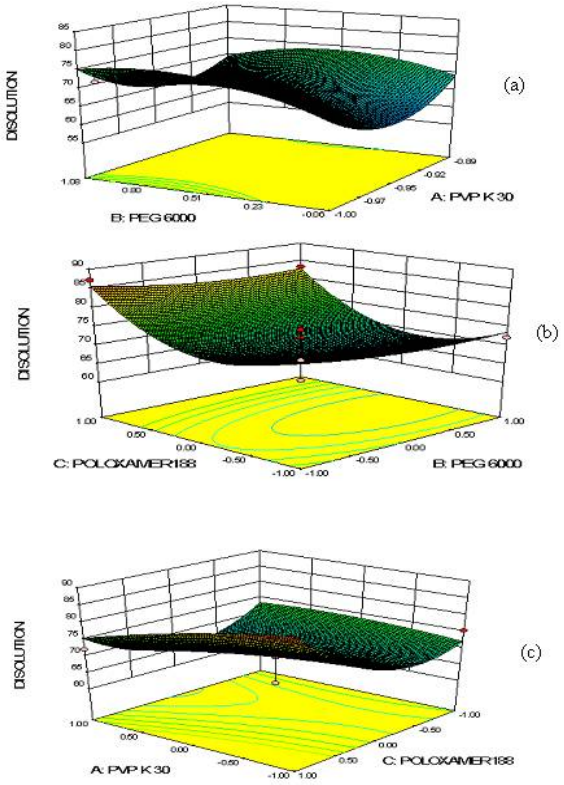


Figure 1.8 B: Response surface design by Kneading method (a) response between PVP K-30 and PEG 6000, (b) response between PEG 6000 and Poloxamer 188, (c) response between Poloxamer 188 and PVP K-30

The generalized polynomial equation is:

$$Y = X_0 + X_1A + X_2B + X_3C + X_{12}AB + X_{13}AC + X_{23}BC + X_{123}ABC$$

Quadratic equation obtained from experimental designwas figure outas

Y_1= +67.94-1.01A+1.95B+1.42C-1.71AB-5.35AC-3.04BC+6.98A^2-4.46B^2+5.89C^2(Eq. I)

Y_2= =+69.47-2.71A-1.66 B+4.36C+3.75AB-3.36AC+0.20BC-1.12A^2+1.60B^2+8.79C^2 (Eq. II)

Where A, B and C are concentration of PEG 6000, PVP K 30 and Poloxamer 188. Y_1 is denoted for solid dispersion by solvent evaporation method and Y_2 is denoted for solid dispersion by kneading method. X is denoted as dissolution coeffoicient.

3.1 Drug content analysis [18, 20-22]

Weighed equivalent quantity to 5mg of solid dispersion of RM was taken in a 25ml volumetric flask and volume was made up to the mark with 0.1N HCl solvent (200µg/ml). The stock (1ml) of aliquot was withdrawn in a 10ml volumetric flask and the volume was adjusted up to the mark with again 0.1N HCl solvent (20µg/ml). The absorbance of the solution was measured at 208 nm using 0.1N HCl as blank. The drug content of Ramipril was calculated using the calibration curve. The drug content of solid dispersion was in the range of 96-100%. Based on drug content the formulation SD1 showed a drug content of 99.05% (Fig 1.9).

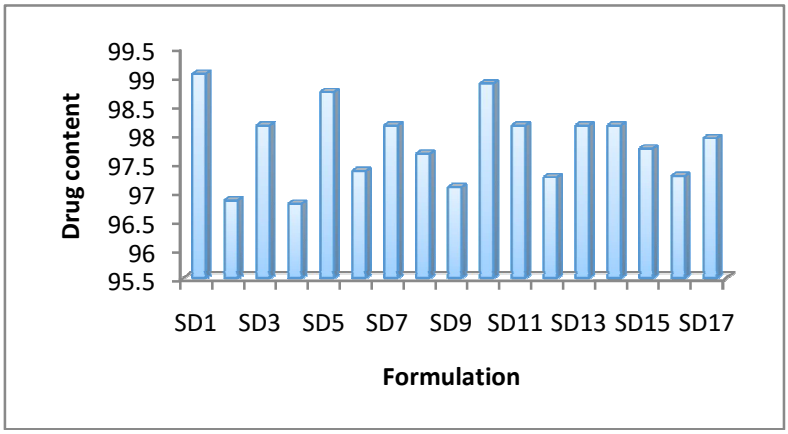


Figure 1.9: Drug content analysis of formulations

The data of release profile was studied by using zero-order, first-order, Higuchi's, Hixson Crowell, and Korsmeyer-Peppas model represented in Fig. 1.10.

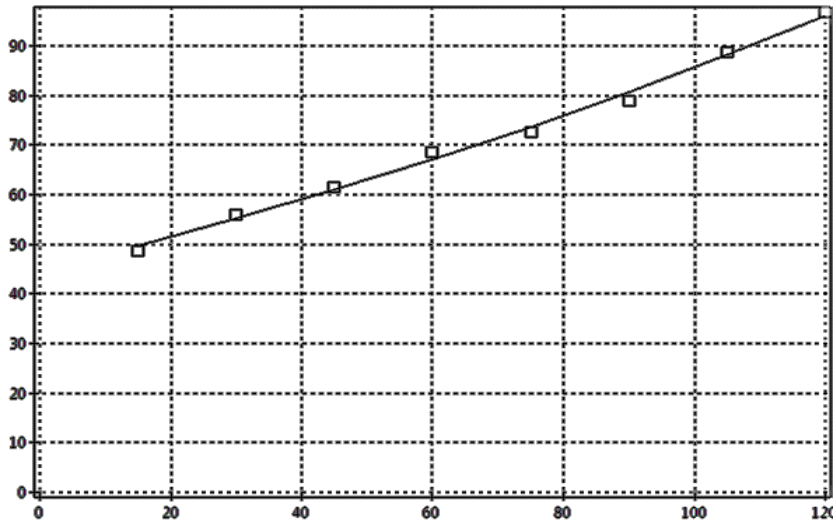


Figure 1.10: First order graph of optimized formulation

The kinetic release model clarifies the mechanism of drug release. The release profile fitted for the first order with a correlation coefficient R^2 =0.98. Dissolution studies were performed for optimized solid dispersion of RM and conventional formulation (Cardiopril). The result is shown in a graph in Fig. 1.11 for dissolution of RM and Cardiopril.

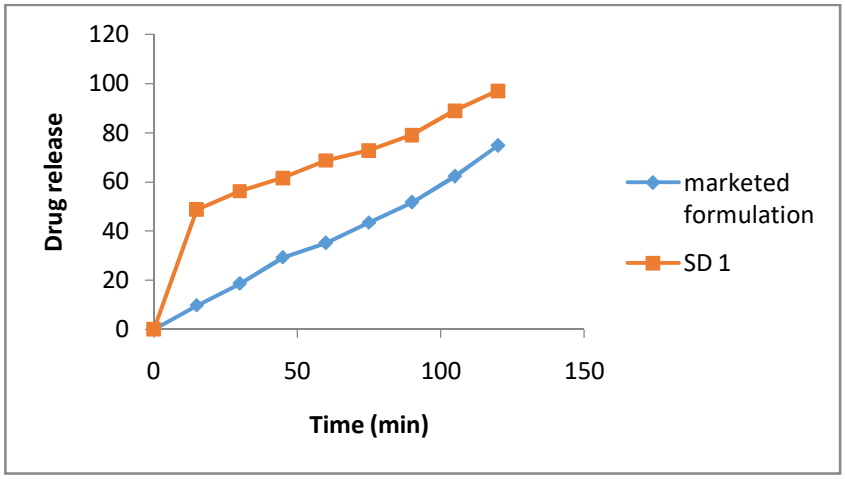


Figure 1.11: Comparison of optimized formulation with marketed product

The amount of drugs released from RM and Cardiopril was found to be 96.86% and 74.72% respectively in 120 minutes. The increase in wettability of the drug may be the reason for the 22.14% increase in the dissolution rate of RM as compare to Cardiopril. Dissolution efficiency i.e. the area under a dissolution curve is shown in table 1.4. Dissolution efficiency when plotted by using dissolution data for optimized formulation and Cardiopril it was found to be 35% and 65% for marketed product and solid dispersion respectively. Hence it is concluded that optimized solid dispersion can be considered to be suitable for the formulation.

Table 1.4: R^2 value of drug release kinetics of optimized batch

S. NO.	Model fitting	R^2 value
1.	Zero order	0.9702
2.	First order	0.9925
3.	Higuchi model	0.7770
4.	K-Peppas	0.9441
5.	Hixson-Crowell	0.9723

The in vivo studies were performed on 10 healthy rabbits by following oral administration of optimized formulation RM and marketed formulation. As can be seen in Table 1.5 &1.6, the mean peak concentration (C_{max}) for the optimized formulation was significantly increased by 2.75 fold compared to Cardiopril. It was found 2.0 mg/ml of Cardiopril while 5.5 mg/ml for optimized formulation. The AUC_{0-5} for Cardiopril was 7.5 hr. and 20.85 hr. for optimized formulation. $AUMC_{0-t}$ of Cardiopril and the optimized formulation were found to be 40.74 (mg/ml) hr^2 and 593.57 (mg/ml) hr^2 respectively which is 14.5 fold more than Cardiopril. MRT of Cardiopril was 5.43 hr. and the optimized formulation was 11.67hrs. The relative bioavailability of Cardiopril and the optimized formulation was 136% and 278% which is 2.04 times more than Cardiopril.

Table 1.5: List of dissolution parameter

S. No.	In-vitro release Parameters	Optimized formulation	Marketed product
(i)	**Dissolution efficiency (%)**	65	35
s(ii)	**T 25 (min)**	12.82	33.83
(iii)	**T 50 (min)**	30.89	81.52
(iv)	**T 90 (min)**	102.63	270.81

Table 1.6: Pharmacokinetic results of Ramipril and solid dispersion

Pharmacokinetic results of Ramipril and solid dispersion		
Parameters (units)	**Marketed product**	**Optimized solid dispersion**
t_{max} (hr.)	2.5	2.5
C_{max}(mg/ml)	2.0	5.5
AUC_{0-t} (mg h/ml)	7.5	20.85
$AUMC_{0-t}$[(mg/ml) hr^2]	40.74	593.57
MRT (hr.)	5.432	11.67
Bioavailability (%)	136	278

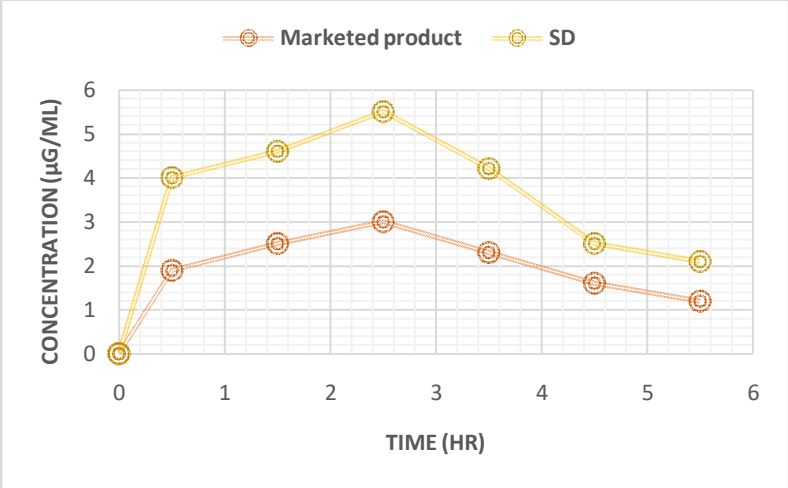


Figure 1.12: Plasma concentration of Cardiopril and optimized formulation after oral administration

The plasma concentration shown in Fig. 1.12 of optimized formulation and conventional marketed formulation, suggested that it has enhanced oral absorption as compare to Cardiopril. The enhancement of oral absorption and bioavailability solid dispersion of RM was possibly due to the presence of polymers in combination with a drug in the defined ratio which enhances the dissolution rate, wet ability, and solubility of the formulation that finally results in enhanced oral bioavailability. These

CONCLUSION

In this study, Box- Behnken design was applied to investigate the effect of polymer concentration on dissolution. RM solid dispersion was prepared by solvent evaporation method and kneading method. Box-Behnken design was generated for both the method which gives 17 formulations out of which formulation SD_1 prepared by solvent evaporation method showed highest dissolution rate. Further, the optimized formulation was carried for in vivo studies and comparison with the marketed formulation. All pharmacokinetics parameters revealed that optimized formulation had increased C_{max} and AUC compared with Cardiopril. Hence it is concluded that the solvent evaporation method could be an effective method for improving the oral bioavailability of RM.

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CONFLICT OF INTERESTS STATEMENt

The authors uphold that there is no conflict of interest.

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