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Enhancement of Dissolution Rate of Poorly Water Soluble Drug by Solid Dispersion Technique

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ABSTRACT

Solubility is a key parameter for the oral bioavailability of poorly water soluble drugs. Dissolution of drug is rate determining step for oral absorption of poorly water soluble drugs, which subsequently affect the *in-vivo* absorption of drug. Ramipril is a poorly water soluble drug and it also has poor bioavailability. Therefore, many strategies have been worked out to improve its aqueous solubility as well as its release rate from various solid dosage forms and also improve the flow property for easily compression. In the present study, the solid dispersion technique was evaluated for enhancement of solubility and dissolution rate. This study investigated the feasibility of quaternary solid dispersion of Ramipril with Poloxamer-188, HPMC and PVP K-30. In present study, synergism of three polymers i.e. Poloxamer-188, HPMC and PVP K-30 was evaluated for the enhancement of solubility and dissolution rate as well as Flowability and compressibility of Ramipril. The solid dispersions were characterized by FT-IR spectroscopy, differential scanning calorimetry and X-ray diffraction. The solubility and dissolution rate of solid dispersions were compared with untreated Ramipril.

Keywords: Ramipril, solid dispersion, dissolution.

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INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration, for example, parenteral[1].

More than 90% of drugs have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble[2]. After administering a drug orally, it firstly dissolves in gastric and or intestinal fluids, and then permeates the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agent's include[3].

(i) Enhancing solubility and dissolution rate of poorly water-soluble drugs and
(ii) Enhancing permeability of poorly permeable drugs.

Unfortunately, many of these potential drugs are abandoned in the early stages of development due to solubility concerns. It is therefore becoming increasingly more important that methods for overcoming solubility limitations be identified and applied commercially such that the potential therapeutic benefits of these active molecules can be realized.

Poorly water-soluble drugs are increasingly becoming a problem in terms of obtaining the satisfactory dissolution within the gastrointestinal tract that is necessary for good bioavailability. It is not only existing drugs that cause problems but it is the challenge of medicinal chemists to ensure that new drugs are not only active pharmacologically but have enough solubility to ensure fast enough dissolution at the site of administration, often gastrointestinal tract.

Dissolution of solid dosage forms in gastrointestinal fluids is a prerequisite to the delivery of the drug to the systemic circulation following oral administration. Dissolution depends in parts on the solubility of the drug substance in the surrounding medium. Surface area of drug particle is another parameter that influences drug dissolution, and in turn drug absorption, particle size is a determinant of surface area.

Solubilization is the process by which the apparent solubility of a poorly water soluble substance is increased. Solubilization techniques include addition of a co-solvent, salt formation, Prodrug design, Complexation, particle size reduction, and the use of surface active agents (Micellization). Use of solvate and hydrates, polymorphs, hydrotrophy, use of absorbents, pH adjustment, solubilizing vehicles, etc. are the some other physicochemical approaches to enhancing oral absorption of poorly water soluble drugs[4].

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs, there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the GIT may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability[5].

In 1961, Sekiguchi and Obi developed a practical method where by many of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome, which was termed as "Solid Dispersion"[6,7]. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion[8].

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly in amorphous particles (clusters) or in crystalline particles[9, 10]. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. They are described in Table 4. Moreover, certain combinations can be encountered, i.e. in the same sample; some molecules are present in clusters while some are molecularly dispersed.

Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions.

EXPERIMENTAL

A) MATERIALS

The drug, excipients, chemicals/reagents used for various experiments are enlisted as follows. All other chemicals and reagents used were of analytical reagent (AR) grade.

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Table: List of materials used

Sr. No.	Name of materials	Manufacturer/ supplier
1.	Ramipril	Chempro Pharma Pvt. Ltd., Mumbai.
2.	Hydroxyl propyl methylcellulose (HPMC)	Signet chemical corporation Pvt. Ltd Mumbai.
3.	Polyvinyl pyrrolidone K-30 (PVP)	Sandoz Pvt. Ltd. Mumbai.
4.	Poloxamer-188	Signet chemical corporation Pvt. Ltd Mumbai.
5.	Methanol	Merck Pvt. Ltd. Mumbai.
6.	Avicel (PH101)	Research-lab-Fine chemicals industries, Mumbai.
7.	Cross carmellose sodium	Loba cheme, Mumbai.
8.	Magnesium sterate	Signet chemical corporation Pvt. Ltd Mumbai.
9.	Talc	Loba Cheme, Mumbai.
10.	Concentrated hydrochloric acid	Rankem, Ranbaxy fine chemicals limited, New Delhi.

Table: List of apparatus/equipments/instruments used.

Sr. no.	**Equipments/ Instruments**	**Source**
1	UV –Visible Double Beam Spectrophotometer	Shimadzu UV-1700, Japan
2	Fourier Transform Infra-Red Spectrophotometer	Shimadzu, Model-8400S, Japan.

3	Hot-air Oven	Shital Scientific Industries
4	Dissolution Test Apparatus USP XXII (Type-II)	Electrolab Tablet dissolution tester USP TDT-06P
5	Electronic Weighing Balance (single pan)	Citizen, CY-104, Mumbai
6	Digital pH Meter	Hanna Instruments
7	Differential Scanning Calorimeter	DSC-60, Shimadzu, Japan
8	X-Ray Differactometer	Philips PW 1710, Holland
9	Roche Friability Tester	Lab Hosp, Mumbai
10	Stability Testing Chamber	Labtop Instruments and Engineering, Pvt. Ltd. Mumbai.
11	Tablet machine	Cadmach machinery co. Pvt. Mumbai

B) EXPERIMANTAL WORK

a. PREPARATION OF CALIBERATION CURVE[11]

Standard calibration curve of Ramipril in 0.1N Hydrochloric acid at λmax 258nm

Calibration curve of Ramipril was prepared in 0.1 N HCl at different dilutions. Different dilutions of concentration 2,4,6,8,10,12, 14&16µg/ml were prepared and their respective absorbance were taken by using double beam UV- Spectrophotometer. Using these absorbance, standard curve was prepared.

Y=0.003X - 0.0003

R^2=0.9993

Where,

Y is absorbance

X is concentration

R^2 is coefficient of regression.

Standard calibration curve of Ramiprilin Distilled water at λmax 258nm

Calibration curve of Ramipril was prepared in distilled water at different dilutions. Different dilutions of concentration 1-20µg/ml were prepared and their respective absorbance was taken by using double beam UV- Spectrophotometer. Using these absorbance, standard curve was prepared.

Y=0.015X + 0.0018

R^2=0.9984

Where,

Y is absorbance

X is concentration

R^2 is coefficient of regression.

b. FORMULATION OF SOLID DISPERSION OF RAMIPRIL[11,12,13]

Preparation of physical mixture

Physical mixtures containing binary, ternary, and quaternary systems were prepared according to the compositions presented in the table. The drug and the polymers were blended with mortar and pestle according to the geometric dilution method followed by sieving (<355 um).

Preparation of solid dispersion

Solid dispersions of Ramipril were prepared by solvent evaporation method. Ramipril together with polymers Poloxamer 188, HPMC and PVP K30 taken in weight ratio as given in table and then dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated with continuous stirring to obtain dry mass by adjusting the temperature to 40-45^{0}C.The final solid mass is crushed and pulverized using mortar and pestle, then passed through 44 mesh sieve. Prepared solid dispersion stored in desiccator until used for further studies.

Quaternary solid dispersion batches

In case of quaternary solid dispersions, applying 2^3 factorial design, Ramipril solid dispersions were prepared, the level of factors i.e. the amount of polymers **Pluronic F68, HPMC, PVP K30**, were studied at two levels.

Sr. no.	Formulation code	Ramipril (gm)	HPMC (gm)	PVP K30 (gm)	Poloxamer 188 (gm)
1	Q1	3	1	4	0.5
2	Q2	3	1	4	1
3	Q3	3	1	6	0.5
4	Q4	3	1	6	1
5	Q5	3	2	4	0.5
6	Q6	3	2	4	1
7	Q7	3	2	6	0.5
8	Q8	3	2	6	1

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Table 14: Formulation table for quaternary solid dispersions

Where,

Factor	Level	
	0	+1
HPMC	01	02
PVP K30	04	06
Poloxamer 188	0.5	01

c. SOLID-STATE CHARACTERIZATION OF SOLID DISPERSIONS

i. Drug and excipients interaction study (FTIR)[11]

Fourier transform infrared (FTIR) spectra of drug, polymer and granules were obtained on Shimadzu FTIR (Model-8400S, Japan). The spectra were scanned over the wave number range from 4000 – 400 cm^{-1}.

ii. Differential scanning calorimetry[11]

Thermograms of the samples were recorded using a differential scanning calorimetry (DSC-60, Shimadzu, Japan). Samples equivalent to approximately 2.4mg of the drug were loaded into aluminium pans and the lids were crimped using a Shimadzu crimper. The thermal behaviour of each sample was investigated under nitrogen at a heating rate of 10°C/min, covering temperature ranges of 25–300°C. The instrument was calibrated with an indium standard. Data analysis was conducted using the TA-60WS thermal analysis software.

iii. X- Ray diffraction analysis(XRD)[11]

The powder X-ray diffraction patterns of various samples were obtained using an X-ray diffractometer (Philips PW 1710, Holland). The 2θscan range was 10-70^0 and the scan rate was 1^0/min.

d. EVALUATION OF SOLID DISPERSIONS OF RAMIPRIL

The solid dispersions were evaluated by their micrometrics properties, such as bulk density, tapped density, Carr's compressibility index, Hausner's ratio and flow property.

i. Bulk density[14,15]

The bulk density was obtained by dividing the mass of a solid dispersion by the bulk volume in cm^3. The sample of about 5gmsolid dispersion was carefully introduced into a 25ml cylinder. The cylinder was dropped at 2 second intervals onto a hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then calculated by using equation given below

$$\rho_o = \frac{M}{V_o}$$

Where,

ρ_o = bulk density

M = weight of samples in grams

V_o = final volumes of solid dispersion in cm^3

ii. Tapped density[14,15]

The tapped density was obtained by dividing the mass of a solid dispersion by the tapped volume in cm^3. The sample of about 5gmof solid dispersion is carefully introduced into a 25ml cylinder. The cylinder was dropped at 2 second intervals onto a hard wood

surface 100 times from a height of one inch. The tapped density of each formulation was then calculated by using equation given below

$$\rho_t = \frac{M}{V_f}$$

Where,

ρ_t = tapped density

M = weight of samples in grams

V_f = final tapped volume of solid dispersion in cm^3

iii. Carr's index[14,15]

The percentage compressibility of solid dispersion was calculated according to equation given below

$$Percentage\ compressibility = \frac{\rho_t - \rho_o}{\rho_t} \times 100$$

Where,

ρ_o = bulk density

ρ_t = tapped density

Percentage compressibility	Flowability
5 –15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
> 40	Extremely Poor

Table 15: Relationship between percentage compressibility and Flowability

iv. Hausner's ratio[14,15]

The Hausner's ratio of a solid dispersion was calculated according to equation given below

$$Hausner's\ ratio = \frac{\rho_t}{\rho_o}$$

Where,

ρ_t= Tapped density

ρ_o = Bulk density

Hausner's ratio between1 to 1.2 shows good Flowability.

v. Angle of repose[14,15]

The Angle of repose (θ) i.e. flow property of the solid dispersion, which measures the resistance to particle flow, was calculated as

$$\tan\theta = 2H / D$$

Hence, $\theta = \tan^{-1} h/r$

Where,

2H / D is the surface area of the freestanding height of the solid dispersion heap that is formed after making the solid dispersion flow from the glass funnel.

Angle of repose (θ)	Flowability
< 20	Excellent
20 – 30	Good
30 – 34	Passable
> 40	Poor
33 – 38	Very Poor
> 40	Extremely Poor

Table 16: Relationship between Angle of repose (θ) and Flowability.

vi. Determination of drug content[12,16]

Weigh accurately solid dispersion equivalent to 5mg of Ramipril and transferred to 25ml volumetric flask and volume was made up to the mark with 0.1N HCl. From this 1ml was taken in 10ml volumetric flask and the volume is adjusted up to the mark with 0.1N HCl. The absorbance of the solution was measured at 258nm using appropriate blank. The drug content of Ramipril was calculated using calibration curve.

vii. Solubility study[11]

The solubility of the drug, physical mixtures, and solid dispersions were determined in distil water. Excess of samples were transferred to flask before adding distil water. The mixtures then placed in mechanical shaker maintained at 37°C for 48hr. The samples were filtered through 0.45µm filter and assayed by UV- spectrophotometry after suitable dilution.

viii. *In-vitro* dissolution studies[11]

In-vitro dissolution of Ramipril solid dispersion was studied in USP XXIII dissolution apparatus (Electro lab TDT, USP) employing a paddle stirrer. The dissolution medium was 0.1N HCl (pH 1.2) maintained at a temperature of 37±0.5°Cwith a paddle speed of 75rpm.The temperature of dissolution media was previously warmed to 37±0.5ºC and was maintained throughout the experiment. The powdered samples (sieved through a 355µm sieve) of pure drug, physical mixtures and solid dispersion mixtures equivalent to 25mg of Ramipril were fill in to the capsule and this capsule add to the dissolution vessels while stirring. 5ml of sample of dissolution medium were withdrawn at 0, 5, 10, 15, 20, 25, 30, 35, 40 and 45 min. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. These samples were immediately filtered through 0.45µm filters and analyzed for drug release by measuring the absorbance at 258nm after suitable dilution with 0.1N HCl. Percentage amount of Ramipril released was calculated and plotted against time.

Sr. no.	Parameter	Detail
1	Apparatus	USP Type II
2	Volume of medium	900 ml
3	Temperature	37 ± 0.5^{0}C
4	Paddle speed	75 rpm
5	Dissolution medium	0.1 N HCl (pH 1.2)
6	Aliquot withdrawn	5 ml

Table: Parameters of *in-vitro* dissolution test for solid dispersions

e. EVALUATION OF RAMIPRIL IR TABLET[17,18]

i. Weight variation

The weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weight to the average weight. The tablets meet the IP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Average weight of tablets(mg)	Maximum percentage difference allowed
80 or Less	10
80 - 250	7.5
More than 250	5

Table: Weight variation tolerances for uncoated tablets

ii. Friability

The laboratory friability tester is known as the Roche friabilator. Friabilator subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25rpm, dropping the tablets a distance of six inches with each revolution. Normally, a pre-weighed tablet sample is placed in the friabilator, which was then operated for 100 revolutions. The tablets are then de-dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable.

iii. Hardness

Tablet requires certain amount of strength or hardness to withstand mechanical shock of handling in manufacture, packaging and shipping. The hardness of the tablet was measured by Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and a zero reading was taken. The upper plunger is then forced against a spring by turning threaded bolt until the tablet fractures.

iv. Thickness

Thicknesses of the 10 tablets were measure by using Vernier calliper.

v. Disintegration test

The process of break-down of the tablet into smaller particles or granules is known as disintegration. The disintegration time was calculated by using tablet disintegration tester, at 37ºc ± 2ºc, containing 1L of 0.1N Hydrochloric acid as disintegrating medium.

vi. Drug content determination

5mg of Ramipril containing formulation (16.70mg) dissolved in 0.1N HCl to produced 100ml of solution. 2ml of solution was then diluted to 100ml, by using 0.1N HCl and then analyzed in Double beam spectrophotometer at 258nm. The IP limits for drug content was 95-105%.

vii. *In-vitro* dissolution

Dissolution was taken by using type-II apparatus of USP, (Electrolab TDT-06P, India) in 0.1N HCl (900ml) medium, at 75rpm, and at 37±0.5ºc. 5mg of Ramipril tablet was placed in dissolution media and 5ml of sample was withdrawn at time(min)

2,5,10,15,20,25,30,35,40,45 respectively and then analyzed with double beam spectro photometer at 258 nm.

viii. Accelerated stability study[11,19]

Stability studies of tablets were performed at 40±2°c and 75% RH for one month. Then the thickness, colour, hardness, release profile and drug content of tablets was determined and calculated.

RESULT AND DISCUSSION

a. PREPARATION OF CALIBERATION CURVE

i. Standard calibration curve of Ramipril in 0.1N Hydrochloric acid at λmax 258nm

Sr. no.	Concentration (µg/ml)	Mean absorbance at 258.0 nm
1	0	0
2	2	0.006
3	4	0.012
4	6	0.017
5	8	0.024
6	10	0.03
7	12	0.036
8	14	0.042
9	16	0.049

Table: Calibration curve for Ramipril in 0.1 N HCl

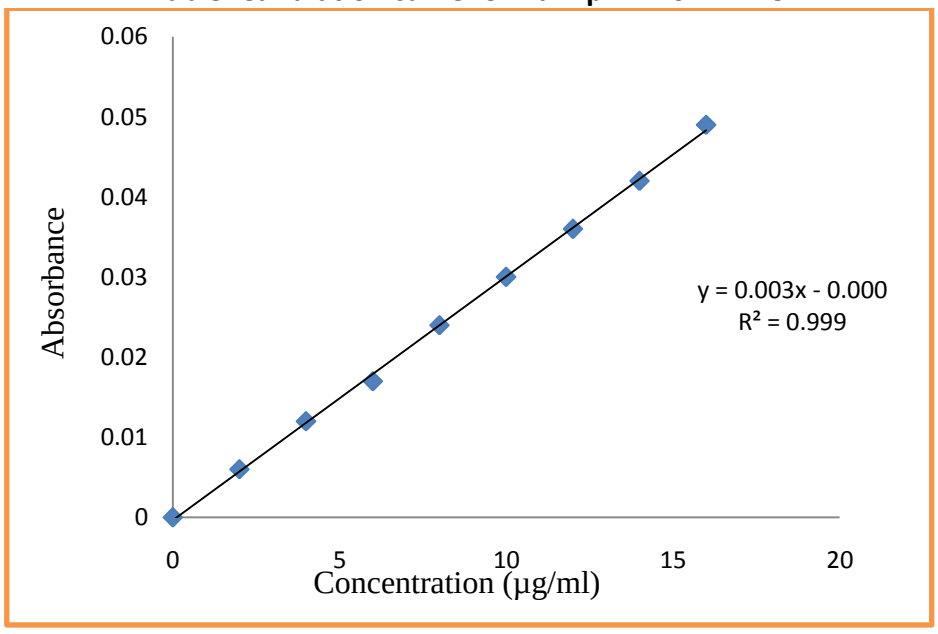

Figure: Standard calibration curve of Ramipril in0.1N HCl

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ii. Standard calibration curve of Ramipril in Distilled water at λmax 258nm

Sr. no.	Concentration (µg/ml)	Mean absorbance at 258.0 nm
1	0	0
2	2	0.03
3	4	0.06
4	6	0.1
5	8	0.12
6	10	0.15
7	12	0.18
8	14	0.21
9	16	0.24

Table: Calibration curve for Ramipril in distilled water

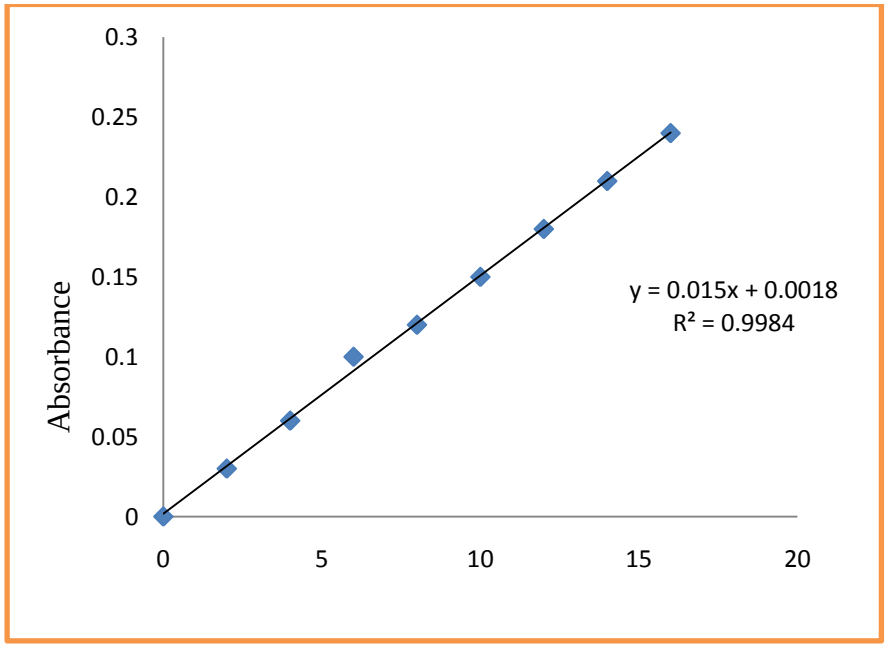

Figure: Standard calibration curve of Ramipril in distilled water

b. EVALUATION OF SOLID DISPERSION OF RAMIPRIL

i. Preparation of solid dispersion

The solid dispersion of Ramipril was prepared successfully by solvent evaporation method.

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c. SOLID-STATE CHARACTERIZATION OF SOLID DISPERSIONS

The solid state characterization of pure drug Ramipril and its optimized quaternary solid dispersion with HPMC, PVP K30 and Poloxamer 188 was done by using differential scanning calorimeter and X-ray diffraction analysis.

i. Drug and excipients interaction study (FTIR)

IR spectrum of Ramipril

IR spectrum of HPMC

IR spectrum of PVP K-30

IR spectrum of Poloxamer-188

IR spectrum of drug and all excipient

ii. Differential scanning calorimetry

DSC of pure drug Ramipril

DSC of optimized batch of solid dispersion of Ramipril

iii. X-ray diffraction analysis

XRD of pure drug Ramipril

XRD of optimized batch of solid dispersion of Ramipril.

d. EVALUATION OF SOLID DISPERSIONS OF RAMIPRIL

i. Micromeritic properties

The results of micromeritic properties of quaternary solid dispersion formulations were as below

Parameters / Formulation code	Bulk density (g/cm^3)*	Tapped density (g/cm^3)*	% Compressibility index	Hausner'sratio	Angle of repose
Q1	0.278±0.07	0.313±0.05	11.11	1.12	28°52'
Q2	0.244±0.05	0.278±0.03	12.19	1.14	26°34'
Q3	0.303±0.02	0.357±0.07	15.15	1.18	27°03'
Q4	0.263±0.03	0.303±0.04	15.38	1.18	29°32'
Q5	0.286±0.06	0.322±0.06	11.43	1.13	29°19'
Q6	0.27±0.09	0.303±0.09	10.81	1.12	26°08'
Q7	0.256±0.07	0.303±0.04	15.38	1.18	31°37'
Q8	0.303±0.04	0.345±0.08	12.12	1.14	27°27'

*mean ± standard deviation (n=3)

Table: Micromeritic studies of quaternary solid dispersion formulations

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ii. Determination of drug content

The results of drug content of quaternary solid dispersion formulations were as below

Sr. no.	Formulation code	Percent drug content*
1	Q1	97.83±0.57
2	Q2	101.17±0.73
3	Q3	98.67±0.39
4	Q4	99.5±0.64
5	Q5	100.66±0.59
6	Q6	99.67±0.82
7	Q7	96.17±0.57
8	Q8	99.17±0.94

*mean ± standard deviation (n=3)

Table: Percent drug content of quaternary solid dispersion formulations

iii. Solubility studies

The results of solubility study of quaternary solid dispersion formulations were as below

Sr. no.	Formulation code	Solubility (µg/ml)*
1	Q1	28.47±0.39
2	Q2	30.21±0.61
3	Q3	30.35±0.73
4	Q4	31.89±0.28
5	Q5	35.11±0.47
6	Q6	39.87±0.53
7	Q7	32.11±0.37
8	Q8	32.70±0.71

*mean ± standard deviation (n=3)

Table: Solubility (µg/ml) of quaternary solid dispersion formulations

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iv. *In-vitro* dissolution studies

The quaternary solid dispersions of Ramipril were prepared by solvent evaporation method and the results of their *in-vitro* dissolution profile were observed.

Cumulative percentage drug release*								
Time (min)	Formulation code							
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
0	0	0	0	0	0	0	0	0
5	25.38±0.37	33.6±0.56	29.4±0.50	31.32±0.59	33.54±0.57	39.42±0.63	30.42±0.73	33.66±0.37
10	55.44±0.89	68.34±0.43	59.16±0.45	75.12±0.87	70.26±0.48	74.12±0.34	66.72±0.67	67.86±0.64
15	73.02±0.61	87.48±0.49	75.6±0.82	87.6±0.64	83.04±0.89	92.1±0.84	83.34±0.43	77.28±0.43
20	81.48±0.29	91.38±0.95	91.92±0.31	92.7±0.35	94.74±0.61	93.36±0.43	93.12±0.76	94.02±0.76
25	90.78±0.42	95.34±0.36	94.14±0.56	94.92±0.54	96.06±0.26	95.52±0.76	95.22±0.43	96.36±0.67
30	94.74±0.63	97.08±0.44	96.18±0.74	97.08±0.21	97.74±0.62	97.86±0.45	97.02±0.58	98.58±0.56
35	98.22±0.83	99.66±0.89	98.22±0.38	98.82±0.68	98.82±0.93	99.12±0.73	98.88±0.51	99.54±0.70
40	99.06±0.81	100.38±0.22	99.84±0.21	99.24±0.72	99.3±0.89	100.08±0.37	99.72±0.46	100.62±0.59
45	100.5±0.66	101.34±0.19	100.86±0.77	100.1±0.13	100.2±0.95	100.6±0.81	100.26±0.91	100.86±0.72

*mean ± standard deviation (n=3)

Table: Cumulative percentage drug release of quaternary solid dispersions with HPMC, PVP K30 and Poloxamer 188

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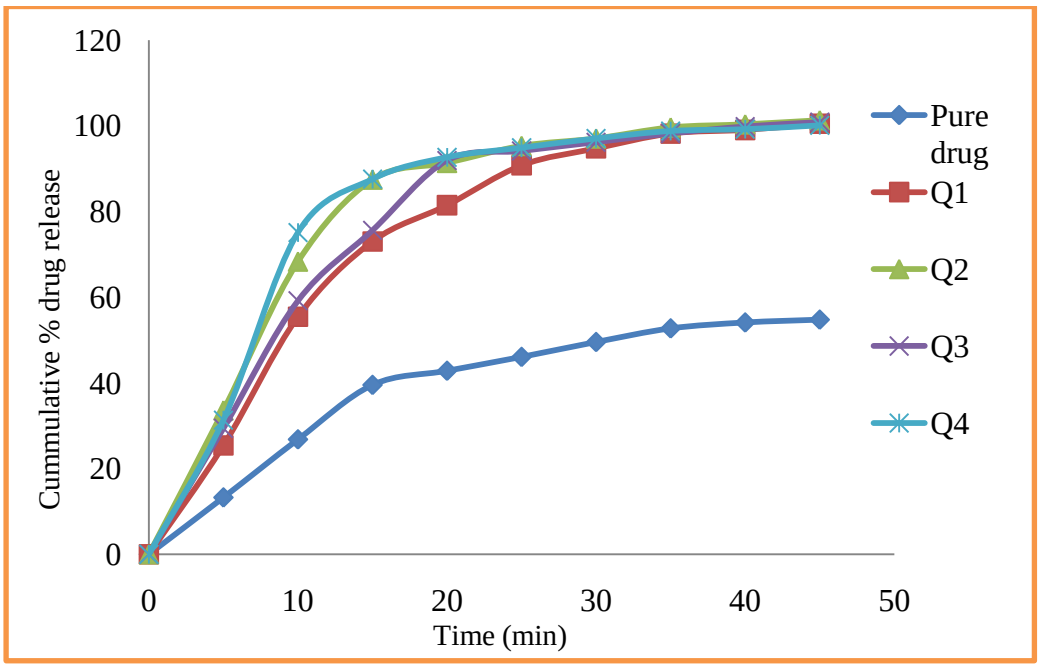

Figure: *In-vitro* dissolution profile of quaternary solid dispersion formulations (Q1-Q4)

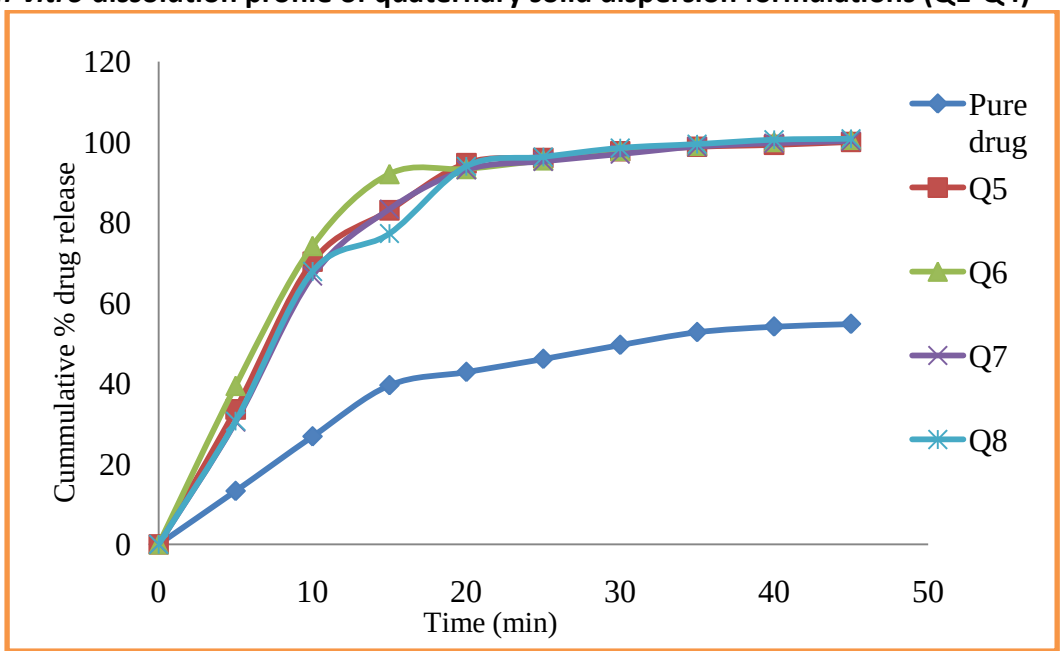

Figure: *In-vitro* dissolution profile of quaternary solid dispersion formulations (Q5-Q8)

e. FORMULATION AND EVALUATION OF RAMIPRIL IR TABLET[11,20]

i. Formulation of directly compressible 5mg Ramipril IR Tablet

Prepared Solid dispersion (16.70mg) equivalent to 5mg of Ramipril was mixed with cross carmellose sodium 2% (as super Disintegrants), magnesium stearate 1% (as lubricant) talc 1% (as glidants), and directly compressible excipients as Avicel pH 101 as diluents, triturated for 2 hours. The prepared mixture was then passed through a sieve no 80. The prepared granules were then compressed by using Cadmach Single station punching machine.

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Ingredients	Weight (mg)
Solid Dispersion (Formulation Q6)	16.7
Micro crystalline Cellulose (PH 101)	50.55
Cross carmellose sodium (2%)	1.4
Magnesium Stearate (1%)	0.7
Talc (1%)	0.7
Total weight	70

Table: Formula for 5mg Ramipril IR tablet

ii. Evaluation of Ramipril IRtablets

Parameters	Results
Thickness (mm)*	2.4 ±0.007
Weight Variation	< 10%(Passes IP Limits)
Friability(%w/w)*	0.39 ± 0.034(Passes IP Limits)
Hardness (kg/cm2)*	4.2±0.09
Disintegration Time (min)*	17 ± 0.89
Percent Drug Content*	98.97±0.07 (Passes IP Limits 95- 105%)

*mean ± standard deviation (n=3)

Table: Evaluation of Ramipril IR tablet

iii. *In-vitro* dissolution

Cumulative percentage drug release*		
Time(min)	Ramipril IR tablet	Marketed product (Ramichek)
0	0	0
5	16.20±0.02	10.8±0.08
10	35.40±0.03	22.2±0.06
15	54.60±0.06	41.4±0.01
20	82.80±0.02	54.6±0.04
25	88.20±0.03	67.8±0.03
30	95.4±0.09	79.2±0.04
35	98.4±0.05	83.4±0.08
40	100.2±0.04	85.8±0.01
45	100.8±0.10	88.2±0.04

*mean ± standard deviation (n=3)

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Table: Cumulative percentage drug releaseof prepared Ramipril IR tablet and marketed product (Ramichek)

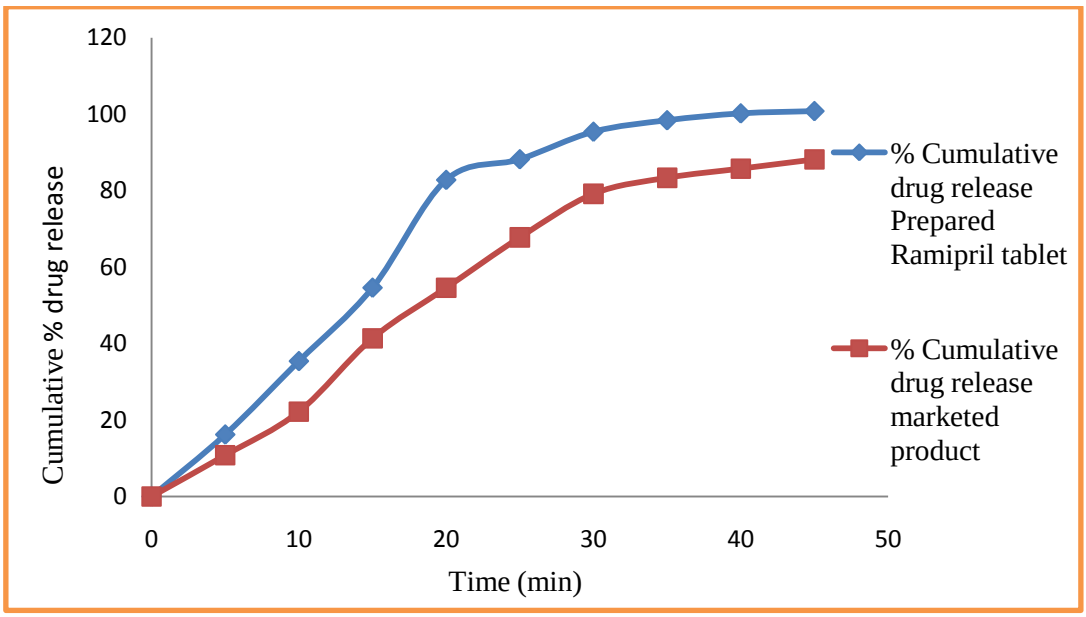

Figure: *In-vitro* dissolution profile of prepared Ramipril IR tablet and marketed product (Ramichek)

iv. Accelerated stability study

Stability studies of tablets were performed at 40±2°c and 75% RH for one month. Then the thickness, hardness, *in-vitro* release profile and drug content of tablets was determined and calculated. It indicates that irrespective of concentration of polymer, these formulations are able to retain their stability for a month.

Parameters	Evaluation of tablet	
	Before stability (0 Days)	After stability (30 Days)
Thickness (mm)*	2.4 ±0.007	2.4 ± 0.012
Hardness (kg/cm^2)*	4.2±0.09	4.1 ± 0.01
Disintegration Time (min)*	17 ± 0.89	17 ± 0.92
Percent Drug Content*	98.97±0.07	98.21 ± 0.03

*mean ± standard deviation (n=3)

Table: Evaluation of Ramipril tablet after stability study

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***In-vitro* dissolution profile**

Cumulative percentage drug release*		
Time(min)	**Before stability (0 Days)**	**After stability (30 Days)**
0	0	0
5	16.20±0.02	13.8±0.08
10	35.40±0.03	32.8±0.06
15	54.60±0.06	51.0±0.01
20	82.80±0.02	71.4±0.04
25	88.20±0.03	85.2±0.03
30	95.4±0.09	92.4±0.04
35	98.4±0.05	96.6±0.08
40	100.2±0.04	99.6±0.01
45	100.8±0.10	100.2±0.04

*mean ± standard deviation (n=3)

Table: *In-vitro* dissolution profile of Ramipril IR tablet after stability study

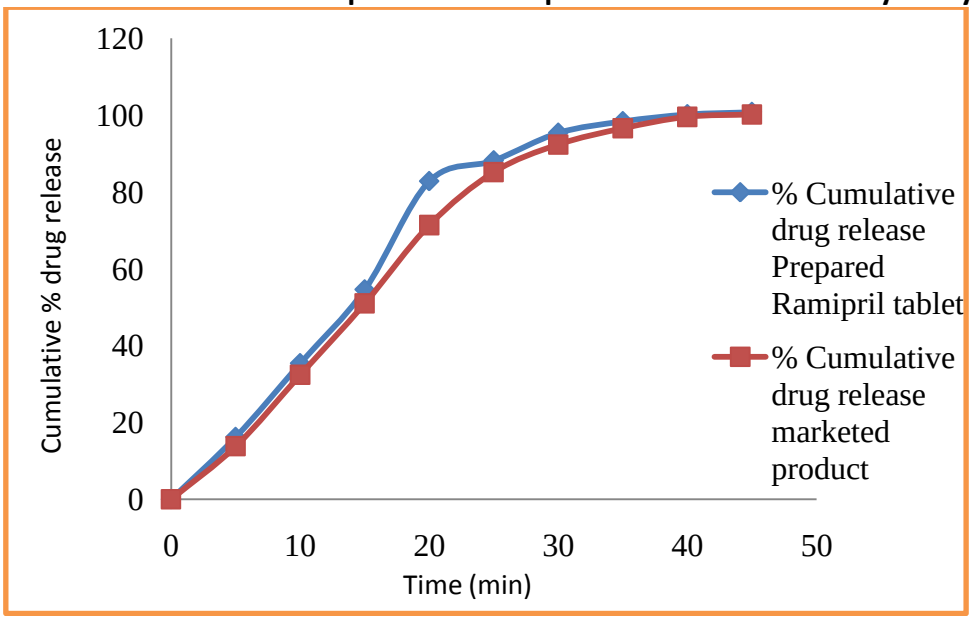

Figure: *In-vitro* dissolution profile of Ramipril IR tablet after stability study

SUMMRY AND CONCLUSION

Successful solubilization of Ramipril was achieved using solid dispersion technique. This study investigated the feasibility of quaternary solid dispersions of Ramipril with Poloxamer 188, HPMC, and PVP K30. In the present study synergism of three polymers i.e. Poloxamer

188, HPMC, and PVP K30 was evaluated for the enhancement of solubility and dissolution rate as well as Flowability, compressibility of Ramipril.

1. The poorly water soluble drug Ramipril used in the preparation of solid dispersions was characterized for preformulation and spectral analysis by UV spectroscopy and FTIR spectroscopy.
2. The physical characteristics and spectra of Ramipril were found to be identical with standard given in analytical profile of drug substance.
3. Solid dispersions were prepared using hydrophilic polymer. The hydrophilic carriers used were HPMC, PVP K30 and Poloxamer 188.
4. These hydrophilic polymers and Ramipril were check for compatibility by FTIR spectroscopy.
5. From the FTIR of all these polymers and drug Ramipril, it was evident that there was no probable interaction found between drug and polymers.
6. Further characterization of optimized formulation Q6 was done using, FTIR spectroscopy, differential scanning calorimetry, X-ray diffraction analysis. These studies also reveal no interaction between drug and polymers.
7. *In-vitro* dissolution profiles of solid dispersion formulations showed definite increase in the dissolution rate of all solid dispersion of Ramipril as compared to pure Ramipril.
8. Formulation Q6 containing Ramipril with HPMC, PVP K30 and poloxamer 188 in ratio 3:2:4:1 showed maximum dissolution rate i.e. more than 90% drug dissolved within 15 minutes.
9. Poloxamer 188 is a surfactant which can inhibit CYP3A4, an enzyme responsible for hepatic metabolism of many drugs including Ramipril.
10. This study investigated the effect of incorporation of Poloxamer 188 as quaternary and ternary component in solid dispersion of Ramipril, on dissolution rate of Ramipril.
11. Quaternary system comprising optimum proportion of drug with HPMC, PVP K30, Poloxamer 188 (03:02:04:01) enhanced the dissolution rate showing dissolution efficiency comparable to that obtained with marketed product of Ramipril.
12. The study thus presented a system capable of increasing the dissolution rate of Ramipril with potential for increasing oral bioavailability by inhibiting its pre-systemic metabolism as well.
13. The preparation process was simple, reproducible and the resultant solid dispersion has desired micromeritic properties.
14. Immediate release formulation is a solution to overcome the variable bioavailability problem of Ramipril.

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