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RAMIPRIL: PREFORMULATION STUDY AND FORMULATION OF IMMEDIATE RELEASE GRANULES

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Abstract:

The objective of this work was to formulate and evaluate immediate release granules of ramipril with Preformulation study for the management of hypertension. Ramipril is an angiotensin converting enzyme (ACE) inhibitor drug used for severe hypertension and myocardial infarction. The poor solubility and wettability of ramipril leads to poor dissolution. In this study physicochemical property of ramipril was improved by using solid dispersion technique. Solid dispersion of ramipril was prepared with PEG 6000 polymer at three drug: polymer ratios (1:1), (1:2) and (1:3). The Preformulation study of ramipril included melting point, FTIR study, standard calibration curves and drug polymer interaction study. The immediate release granules of ramipril were prepared by wet granulation method by using different concentrations of superdisintegrant i.e croscarmellose sodium. The solid dispersion (1:3) showed maximum solubility. The immediate release granules formulation A4 showed maximum 96. Release in 30 minutes. So SD3 and A4 were selected as the best formulations.

Keywords: *Ramipril, Solid dispersion, Immediate release granules, Hypertension.*

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1.INTRODUCTION:

Hypertension is also called as high blood pressure. Blood pressure is the force of blood pushing up against the blood vessel walls. Hypertension cause very serious illnesses, such as heart failure, stroke, kidney failure, heart attack. The normal level for blood pressure is 120/80, Here 120 shows the systolic measurement and 80 show the diastolic measurement. Blood pressure of 139/89 is called prehypertension and blood pressure of 140/90 or above is called hypertension. **[1, 2]**

The angiotensin converting enzyme (ACE) inhibitors are one of the first choice drugs for all kind of hypertension like essential as well as Reno vascular hypertension. The ramipril is the long acting ACE inhibitor with extensive tissue distribution feature. The plasma $t_{1/2}$ of ramipril active metabolite ramiprilat is 8-18 hours. The bioavailability of ramipril is 60%. The other properties of ramipril are like molecular mass is 416.52 g/ml, pKa value is 3.17 and partition coefficient is 3.41. Ramipril shows hepatic biotransformation. It is a prodrug and is converted to the active metabolite ramiprilat by liver esterase enzymes. Ramipril is used to treat high blood pressure and symptomatic heart failure. The immediate release dosage forms are used to enhance the release rate of the active constituents. Immediate release dosage forms are disintegrate rapidly to release the drugs and provide fast onset of action. **[3, 4, 5]**

Hence immediate release granules of ramipril were developed, which provide rapid onset action because immediate release dosage forms reduce disintegration and dissolution timing. Ramipril is BCS class II drug so solubility of ramipril is very poor. Immediate release dosage forms are very useful for the delivery of poorly soluble drugs. **[6, 7, 8, 9]**

2. MATERIALS AND METHODS:

Ramipril was obtained as a gift sample from Ind-Swift Laboratories Ltd. All other material like PEG 6000, croscarmellose sodium (super-disintegrant), microcrystalline cellulose, lactose, magnesium stearate, talc were also of analytical grade.

2.1 PREFORMULATION STUDIES

Preformulation study is the first step done before the development of final dosage forms. In the Preformulation study investigation of physical and chemical properties of drug and excipients are done. The main objective of Preformulation study is to get data which is useful for the development of stable, effective and bioavailable dosage forms. **[10, 11]** Various Preformulation studies were preformed like-:

2.1.1 PHYSICAL APPEARANCE: Physical appearance of ramipril was examined by its various organoleptic properties like colour, state, odour and taste.

2.1.2 MELTING POINT DETERMINATION: The melting point of the ramipril was determined by capillary fusion method. A capillary sealed at one end was filled with small amount of drug and the capillary was kept inverted i.e sealed end downwards into the melting point apparatus. The temperature at which the solid drug converts into liquid was noted down with the thermometer provided.

2.1.3 ABSORPTION MAXIMA (λ_{max}) OF DRUG: UV absorption maxima of the drug was determined by scanning 20µg/ml solution with methanol, 0.1N HCI and phosphate buffer pH 6.8 between 200-400nm.

2.1.4 CALIBRATION CURVE OF RAMIPRIL

Calibration curve of Ramipril was prepared in methanol, distilled water and in different buffers i.e. 0.1N Hydrochloric acid, phosphate buffer pH 6.8.

In Methanol: - 50 mg of Ramipril was taken and dissolved in 100 ml of methanol. From this 50 ml of sample was taken and volume was made up 100 ml with methanol to get 250µg/ml stock solution. From this stock solution, 0.2,0.4,0.6,0.8,1 ml were withdrawn and transferred to 10 ml volumetric flasks and volume was made up to 10 ml with methanol to obtain different concentrations of 5,10,15,20 and 25 µg/ml. The absorbance was measured at 208 nm using methanol as blank.

In 0.1N Hydrochloric acid

Preparation of 0.1N hydrochloric acid: 0.1N hydrochloric acid was prepared by diluting 8.5ml of concentrated hydrochloric acid to 1000ml with distilled water.

50 mg of Ramipril was taken and dissolved in 100 ml of 0.1N hydrochloric acid. From this 50 ml of sample was taken and volume was made up 100 ml with 0.1N hydrochloric acid to get 250µg/ml stock solution. From this stock solution, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1 ml were withdrawn and transferred to 10 ml volumetric flasks and volume was made up to 10 ml with 0.1N HCI to obtain different concentrations of 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5 and 25 µg/ml. The absorbance was measured at 205.5 nm using 0.1N hydrochloric acid as blank.

In Phosphate Buffer pH 6.8

Preparation of phosphate buffer pH 6.8: Disodium hydrogen phosphate of 28.80g and potassium dihydrogen phosphate of 11.45g were dissolved in sufficient water to produce 1000ml.

50 mg of Ramipril was taken and dissolved in 100 ml of phosphate buffer. From this 50 ml of sample was taken and volume was made up 100 ml with

phosphate buffer to get 250µg/ml stock solution. From this stock solution, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1 ml were withdrawn and transferred to 10 ml volumetric flasks and volume was made up to 10 ml with phosphate buffer to obtain different concentrations of 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5 and 25µg/ml. The absorbance was measured at 208.5 nm using phosphate buffer pH 6.8 as blank.

In distilled water: - 50 mg of Ramipril was taken and dissolved in 5ml of methanol (as co-solvent) and made the volume 100 ml with distilled water. From this 50 ml of sample was taken and volume was made up 100ml with distilled water to get 250µg/ml stock solution. From this stock solution, 0.2, 0.4, 0.6, 0.8 and 1 ml were withdrawn and transferred to 10 ml volumetric flasks and volume was made up to 10 ml with water to obtain different concentrations of 5, 10, 15, 20 and 25 µg/ml. The absorbance was measured at 208.5 nm using water as blank.

2.1.5 FOURIER TRANSFORM INFRARED ANALYSIS (FTIR STUDY)

The IR spectrum of sample was carried out for qualitative compound identification. The IR spectra of ramipril was performed on Fourier transformed IR spectrophotometer (ALPHA – E). The sample was scanned at wavelength 4000cm^{-1} – 400 cm^{-1}.

2.1.6 DRUG POLYMER INTERACTION STUDIES

Compatibility study of drug and polymer was performed to ensure that drug is not interacting with the polymer used under experimental conditions (40^{0}C±2^{0}C and 75±5% RH) for 4 weeks. Desired quantity of drug with excipients were taken and mixed thoroughly and filled in dry vials. The vials were examined daily at regular interval for clumping, discoloration and liquefaction. **[12]**

2.1.7 PREPARATION OF SOLID DISPERSION BY USING FUSION (MELTING) METHOD

PEG 6000 was melted on a water bath at 70^{0}C, then mixed with the drug and triturated till cold. The prepared solid dispersions were passed through sieve no. 80 and stored in desiccator until used. **[13, 14, 15]**

Table No 1: Formulation of solid dispersions

Formulation codes	Drug (Ramipril)	Polymer (PEG 6000)	Ratio (D/P)
SD1	500 mg	500 mg	1:1
SD2	500 mg	1000mg	1:2
SD3	500mg	1500mg	1:3

2.1.7.1 Solubility studies of ramipril solid dispersion

The solubility studies of Ramipril solid dispersion were carried out in distilled water. Solid dispersion equivalent to 10 mg of Ramipril was shaken with 10 ml distilled water on magnetic stirrer for 24 hours at room temperature. Then, the solutions were filtered through Whatman filter paper. Filtered solution was diluted properly with distilled water. The diluted resultant suspension was then filtered through Whatman filter paper. Finally, the sample were analysed by UV spectrophotometer (SHIMADZU) at 208.5 nm.

2.1.7.2 Dissolution studies of solid dispersion

The in vitro dissolution of solid dispersion was carried out using USP Type I (Basket type) dissolution apparatus. 900 ml of a 0.1N HCI solution was used as dissolution medium and maintained at 37±0.5^{0}C. The medium was stirred as 75rpm. 10 ml of sample was taken at 5 minutes intervals for 40 minutes and were replaced with fresh dissolution medium. The collected samples were analysed after filtration at 205.5nm by using UV spectrophotometer against the blank. The drug release studies were carried out and percentage drug release was calculated.

2.1.8 PREPARATION OF IMMEDIATE RELEASE GRANULES

The granules were prepared by wet granulation method. Solid dispersion (1:3), croscarmellose sodium (CCS), microcrystalline cellulose (MCC), lactose monohydrate were weighed accurately and blended homogeneously for 15 minutes accordingly geometric dilution method. **[16, 17, 18]**

Polyvinyl pyrollidone (PVP) was dissolved in isopropyl alcohol and mixed with powder blend to get a coherent mass. Coherent mass was passed through sieve no. 22, and dried at 50^{0}C for 20 minutes. **[19]**

Table No 2: Composition of immediate release granules

Ingredients (mg)	A1	A2	A3	A4
Solid dispersion equivalent to 10 mg of the drug	40	40	40	40
Croscarmellose sodium (CCS)	2	3	4	5
Microcrystalline cellulose (MCC)	63	62	61	60
Lactose monohydrate	35	35	35	35
Magnesium stearate	5	5	5	5
Talc	5	5	5	5

2.1.9 EVALUATION PARAMETERS

EVALUATION OF BLENDS [20, 21]

- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio
- Angle of repose

EVALUATION OF GRANULES [22]

- % yield
- Drug content
- Dissolution study

2.1.9.1 EVALUATION OF BLENDS

Bulk density: Bulk density was determined by pouring weighed quantity of blend into graduated cylinder and measuring the height. Bulk density is the ratio of mass of tablet blend to bulk volume. The bulk density was calculated by using the formula.

Bulk density = m/Vb = m/л^{2}rh .....eq (1)

Here, m= weight of powder (gm)
Vb= Bulk volume (cm^3)
Л= 22/7 = 3.14
r= Radius of cylinder (cm)
h= Height reached by powder in cylinder (cm)

Tapped density: Accurately weighed amount of blend poured in graduated cylinder and height was measured. Then cylinder was allowed to 100 tap under its own weight onto a hard surface. The tapping was continued until no further change in height was noted. Here Vt was the tapped volume.

Tapped density = m/Vt = m/л^{2}rh .....eq (2)

Carr's index (compressibility index): Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as compressibility index. It is indirectly related to the relative flow rate. Compressibility index was determined by the given formula.

Carr's index = tapped density – bulk density/ tapped density * 100 .....eq (3)

Table No 3: Compressibility index of powder flow properties

Carr's index (%)	Type of flow
5-12	Excellent
12-18	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner's ratio: Hausner's ratio indicates the flow properties of powder and measured by the ratio of tapped density to bulk density. Hausner's ratio was determined by the given formula;

Hausner's ratio= Tapped density/bulk density .....eq (4)

Table No 4: Hausner's ratio of powder flow properties

Hausner's ratio	Type of flow
1-1.1	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.35-1.45	Poor
1.46-1.59	Very poor

Angle of repose (θ): The angle of repose of blend was determined by the funnel method. The accurately weighted blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the blend. The blend was allowed to flow through the funnel freely on the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following formula;

Angle of repose (tan θ) = h/r ……eq (5)

Here, h was the height and r was the radius of powder cone.

2.1.9.2 EVALUATION OF IMMEDIATE RELEASE GRANULES

Percentage yield:

The prepared granules were collected and weighed. The yield was calculated by dividing the measured weight by the total weight of components. The percentage yield of granules was calculated as follows;

% yield = weight of granules/ total weight of all components * 100 ……eq (6)

Drug content:

Accurately weighted granules were dissolved in a small quantity of methanol and then volume was made up to 100 ml with methanol. The solution was filtered through whatman filter paper and the absorbance was measured at 208nm.

***In- vitro* dissolution study for immediate release granules**

The in vitro dissolution was carried out using USP Type I (Basket type) dissolution apparatus under sink condition. 900 ml of a 0.1N HCI solution was used as dissolution medium and maintained at 37±0.5^{0}C. The medium was stirred as 75rpm. 10 ml of sample was taken at 5 minutes intervals for 30 minutes and were replaced with fresh dissolution medium. The collected samples were analysed after filtration at 205.5nm by using UV spectrophotometer against the blank. The drug release studies were carried out and percentage drug release was calculated.

3. RESULTS AND DISCUSSION

3.1 Preformulation studies

3.1.1 Physical appearance

The drug possesses similar colour, odour, state and taste as given in official's pharmacopoeia.

Table No 5: Organoleptic character of Ramipril

Physical parameters	Observations
Colour	White
Odour	Odourless
State	Crystalline powder
Taste	Bitter

3.1.2 Melting point determination

The melting point of procured sample was found to be 107-109^{0}C that is in concordant with the literature value. This verified the purity and authenticity of the procured sample.

Table No 6: Melting point of Ramipril

Drug	Literature value	Experimental value
Ramipril	109-112^{0}C	107-109^{0}C

3.1.3 Determination of absorption maxima

An absorption maximum (λmax) of the drug was observed to be at 208nm in methanol, 205.5nm in 0.1N HCI and 208.5nm in phosphate buffer pH 6.8 that is in concordant with the literature value. . Scan graphs are shown in Fig 1, Fig 2 and Fig 3.

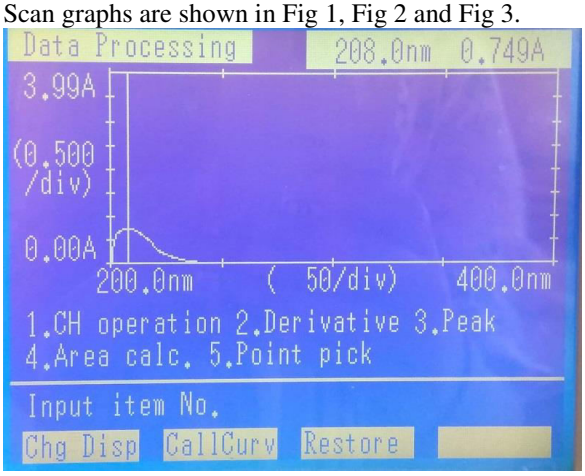

Fig 1: Absorption maxima of Ramipril in methanol

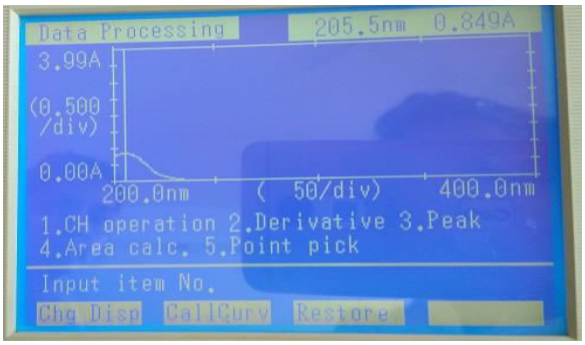

Fig 2: Absorption maxima of Ramipril in 0.1N HCI

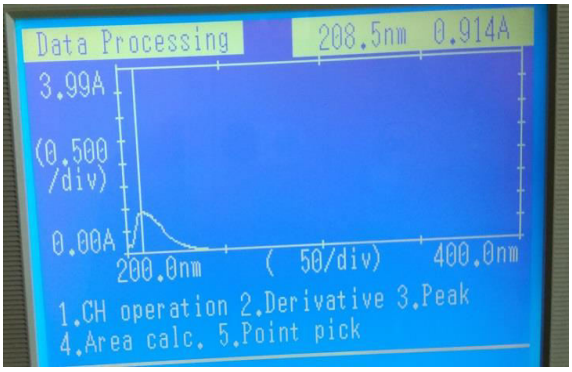

Fig 3: Absorption maxima of Ramipril in phosphate buffer pH 6.8

3.1.4 Calibration curve of ramipril

The calibration curves of ramipril in methanol, 0.1N HCI, phosphate buffer (pH 6.8) and distilled water were found to be linear in the concentration range of 2.5-25µg/ml. The calibration curves are represented as follows:

Table No 7: Calibration data of ramipril in methanol

Concentration (µg/ml)	Absorbance
5	0.162
10	0.345
15	0.584
20	0.749
25	0.962

The calibration curve of the drug in methanol follows Beer's lambert law. The calibration curve shown in Fig 2.

Table No 8: Statistical parameters related to calibration curve

Parameter	Values
Regression coefficient	0.9977
Intercept	0.0408
Equation of line	y= 0.0401x+ 0.0408

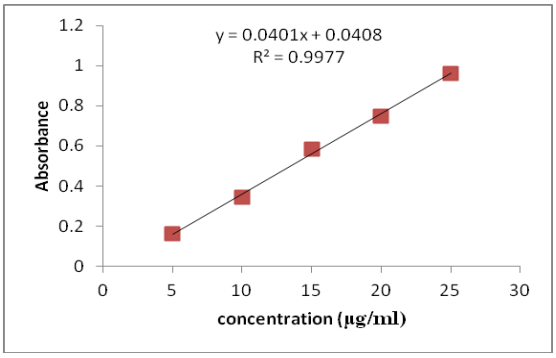

Fig 4: Calibration curve of Ramipril in methanol

Table No 9: Calibration data of ramipril in 0.1 N HCI

Concentration (µg/ml)	Absorbance
2.5	0.131
5	0.212
7.5	0.341
10	0.465
12.5	0.512
15	0.618
17.5	0.710
20	0.849
22.5	0.937
25	1.152

Table No 10: Statistical parameters related to calibration curve

Parameter	Values
Regression coefficient	0.994
Intercept	0.0218
Equation of line	y= 0.0407x + 0.0218

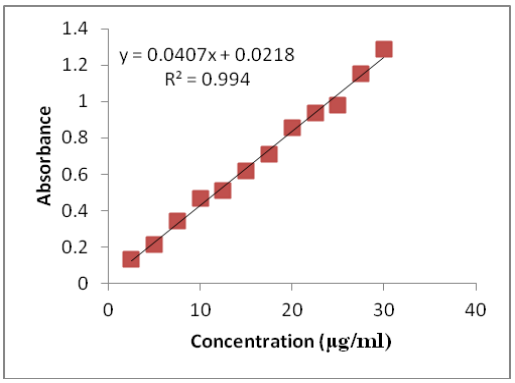

Fig 5: Calibration curve of Ramipril in 0.1N HCI

Table No 11: Calibration data of Ramipril in phosphate buffer pH 6.8

Concentration (µg/ml)	Absorbance
2.5	0.145
5	0.223
7.5	0.332
10	0.417
12.5	0.580
15	0.692
17.5	0.837
20	0.914
22.5	0.967
25	1.16

The calibration curve of the drug in phosphate buffer pH 6.8 follows Beer's lambert law. The calibration curve shown in Fig 4.

Table No 12: Statistical parameters related to calibration curve

Parameters	Values
Regression coefficient	0.9943
Intercept	0.004
Equation of line	y= 0.0453x + 0.004

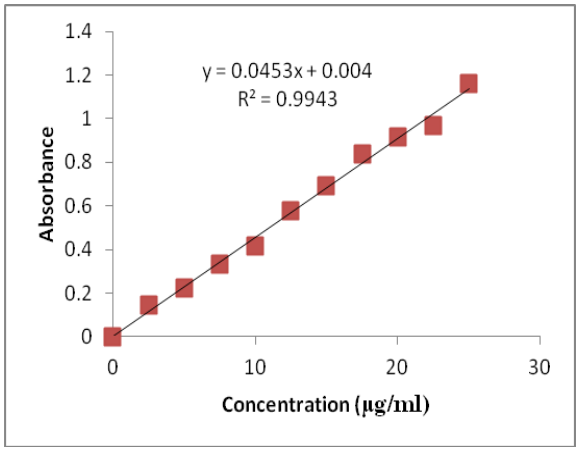

Fig 6: Calibration curve of Ramipril in phosphate buffer pH 6.8

Table No 13: Calibration data of Ramipril in distilled water

Concentration (µg/ml)	Absorbance
5	0.307
10	0.551
15	0.809
20	1.006
25	1.246

The calibration curve of the drug in distilled water follows Beer's lambert law. The calibration curve shown in Fig 5.

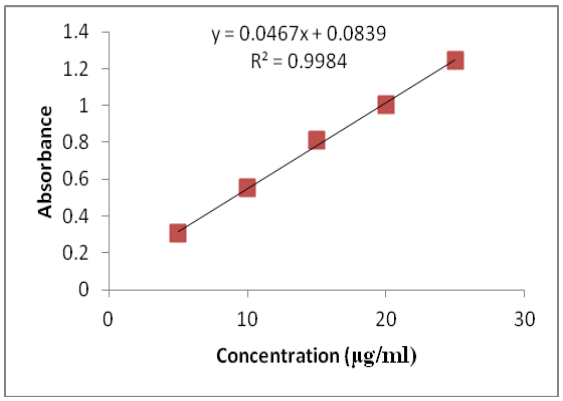

Fig 7: Calibration curve of Ramipril in distilled water

Table No 14: Statistical parameters related to calibration curve

Parameter	Values
Regression coefficient	0.9984
Intercept	0.0839
Equation of line	y = 0.0467x + 0.0839

3.1.5 FOURIER TRANSFORM INFRARED ANALYSIS (FTIR)

The characteristic peaks of Ramipril present at 3276.43 cm^{-1} (N-H), 2869.23 cm^{-1} (O-H), 1740.67 cm^{-1} (C=O), 1496.12 cm^{-1} (C=C). This further verified the authenticity of the drug. The FTIR spectra of Ramipril was shown in fig

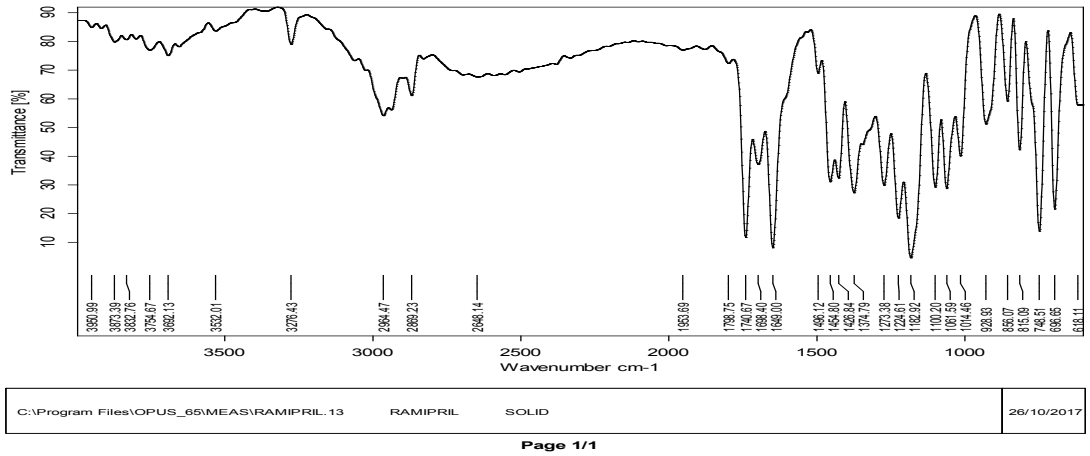

Fig 8: FTIR spectra of Ramipril

3.1.6 DRUG- EXCIPIENT INTERACTION STUDIES

During the drug – excipient compatibility studies no discoloration, liquefaction and clump formation was observed and the characteristic peaks of the drug in the IR spectrum were retained in the solid dispersion and mixture. This indicates that no incompatibility has taken place between drug and excipient

Table No 15: Drug- Excipient interaction study data

Mixture	Week 1 Physical changes	Week 2 Physical changes	Week 3 Physical changes	Week 4 Physical changes	IR peaks (cm^{-1})
Drug	---	---	---	---	(N-H) 3276.43 (O-H)2869.23 (C=O)1740.67 (C=C)1496.12
Drug + PEG 6000	---	---	---	---	(N-H) 3275.78 (O-H) 2868.34 (C=O) 1740.52 (C=C) 1497.45
Drug + CCS	---	---	---	---	(N-H)3275

					(O-H)2869.81 (C=O)1741.76 (C=C)1497
Drug + MCC	---	---	---	---	(N-H)3277.04 (O-H)2867.30 (C=O)1741.46 (C=C)1494.66
Drug + lactose	---	---	---	---	(N-H)3274.34 (O-H)2868.23 (C=O)1741.70 (C=C)1495.45
Drug + CCS+ MCC+ lactose	---	---	---	---	(N-H) 3272.54 (O-H) 2869.36 (C=O) 1740.27 (C=C) 1494.84

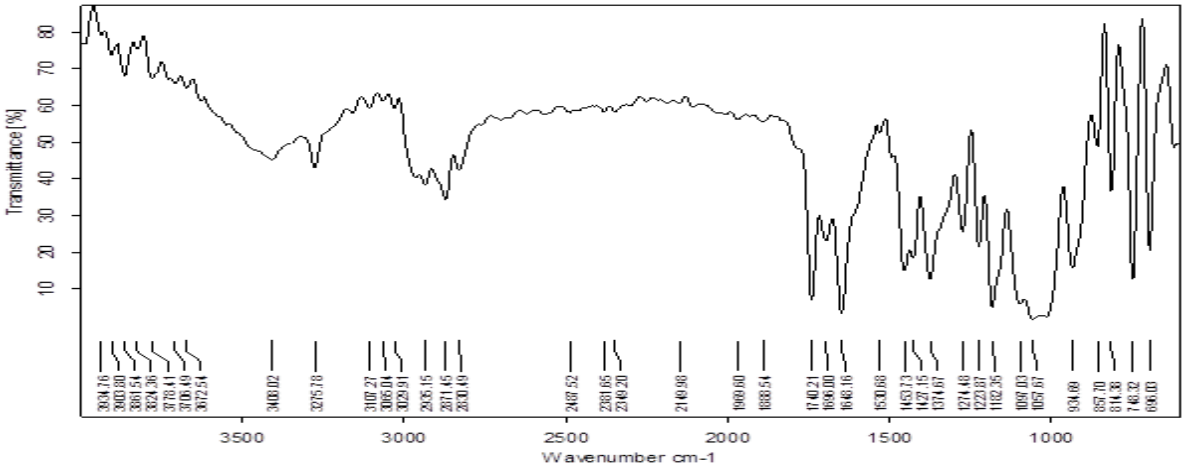

Fig 9: IR spectra of Ramipril + PEG 6000

IR SPECTRA OF RAMIPRIL + CCS

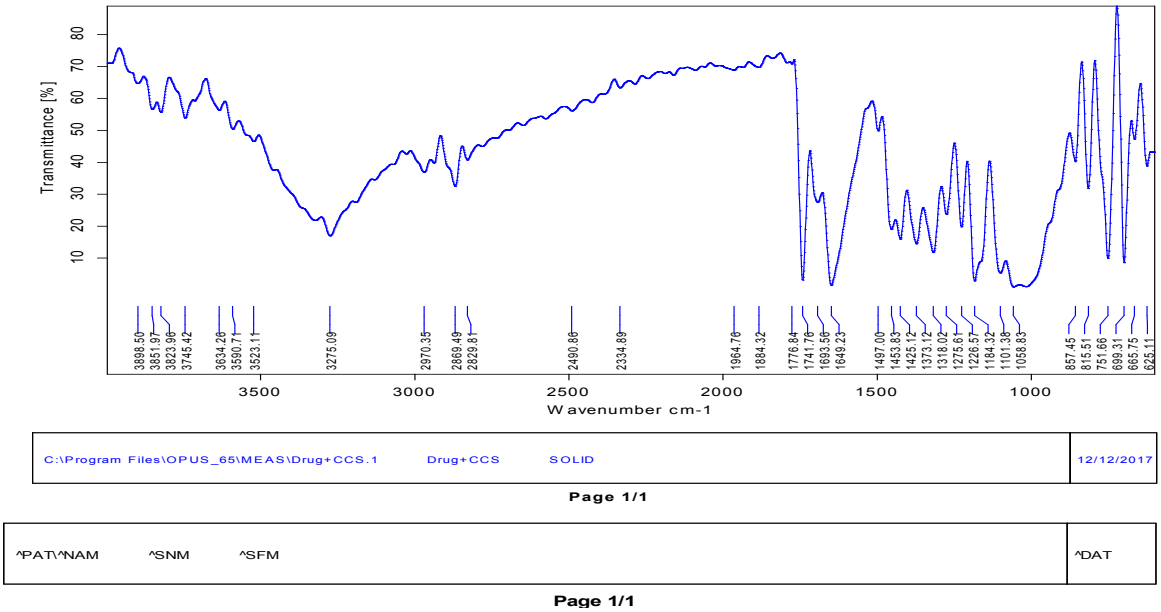

Fig 10: IR spectra of Ramipril + CCS

IR SPECTRA OF RAMIPRIL + MCC

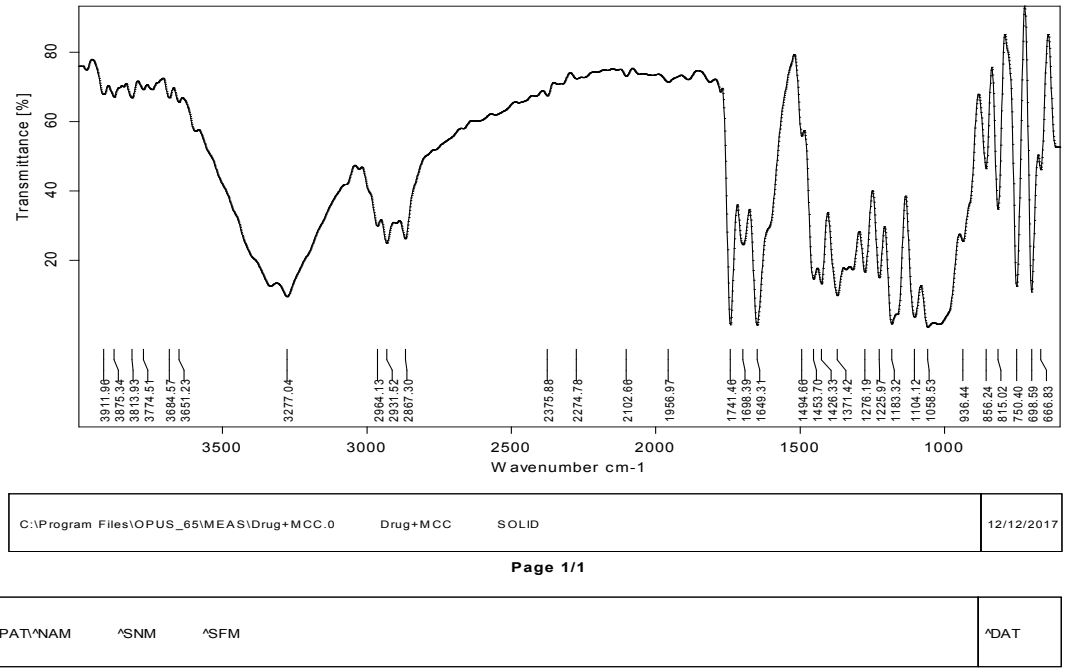

Fig 11: IR spectra of Ramipril + MCC

IR SPECTRA OF RAMIPRIL + LACTOSE

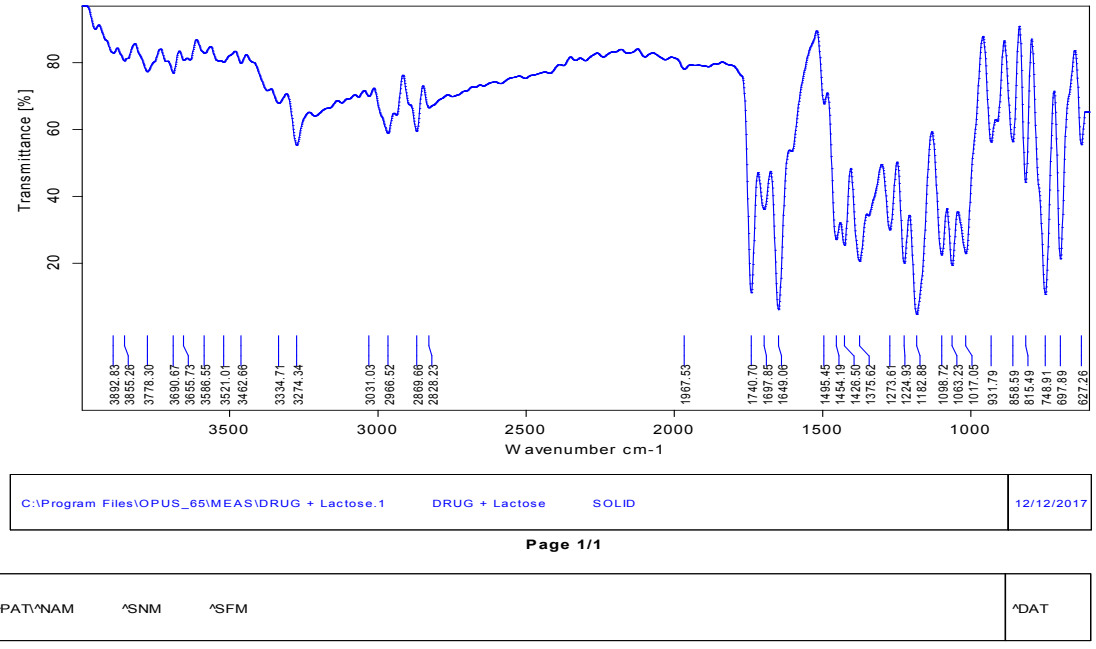

Fig 12: IR spectra of Ramipril + Lactose

IR SPECTRA OF RAMIPRIL + CCS+ MCC+ LACTOSE

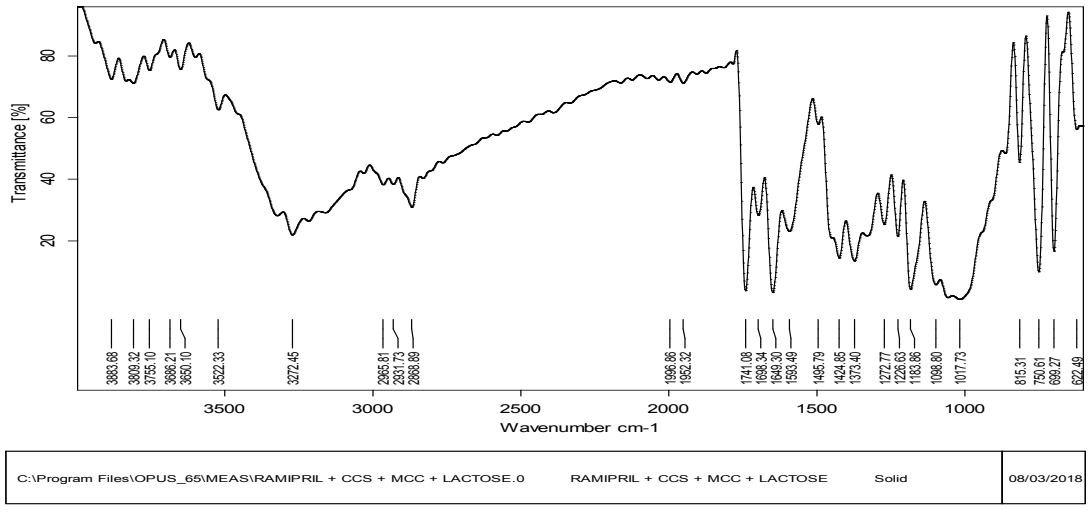

Fig 13: IR spectra of Ramipril + CCS + MCC + Lactose

3.1.7 SOLID DISPERSION BY USING MELTING METHOD

Solubility profile of pure drug and solid dispersions is shown in Table 16. It was found that the solubility of drug increased with the increase in concentration of the polymer SD3 (1:3) showed maximum solubility. This may be due to the wetting property and solubilisation effect of the polymer. Solid dispersion SD3 (1:3) also showed maximum drug release (96.77%) corresponding to 40 minutes. Hence this ratio was selected for the preparation of immediate release granules.

3.1.7.1 Table No 16: SOLUBILITY DATA OF SOLID DISPERSION PREPARED BY MELTING METHOD

Formulation code	Solubility (mg/ml)
Pure drug	0.039±0.0131
SD1	0.111±0.0108
SD2	0.253±0.0132
SD3	0.431±0.0152

Data are expressed as mean ± S.D (n=3)

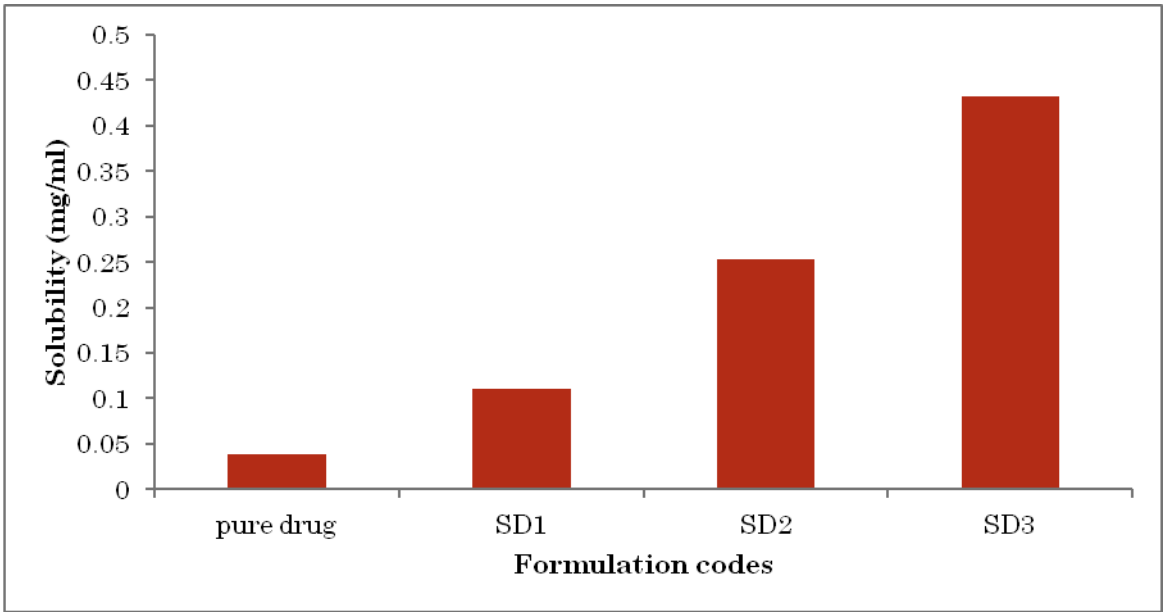

Fig 14: Solubility values of solid dispersion of different batches

3.1.7.2 Table No 17: Percentage drug release from solid dispersion

Time (minutes)	Pure drug	SD1 (1:1)	SD2 (1:2)	SD3 (1:3)
5	8.54 ± 0.18	15.71± 0.46	22.28± 0.67	26.65± 0.35
10	13.54± 0.39	24.09± 0.67	34.25± 0.75	37.42± 0.24
15	17.72± 0.49	32.04± 0.33	41.22± 0.54	49.16± 0.57
20	22.50± 0.54	41.21± 0.76	53.35± 0.62	61.70± 0.54
25	29.47± 0.37	48.59± 0.38	61.20± 0.37	69.90± 0.33
30	34.25± 0.49	56.54± 0.65	70.87± 0.29	77.45± 0.48
35	38.43± 0.57	62.51± 0.55	78.44± 0.46	86.40± 0.26
40	41.33± 0.27	68.87± 0.45	87.21± 0.44	96.77± 0.59

Data are expressed as mean ± S.D (n=3)

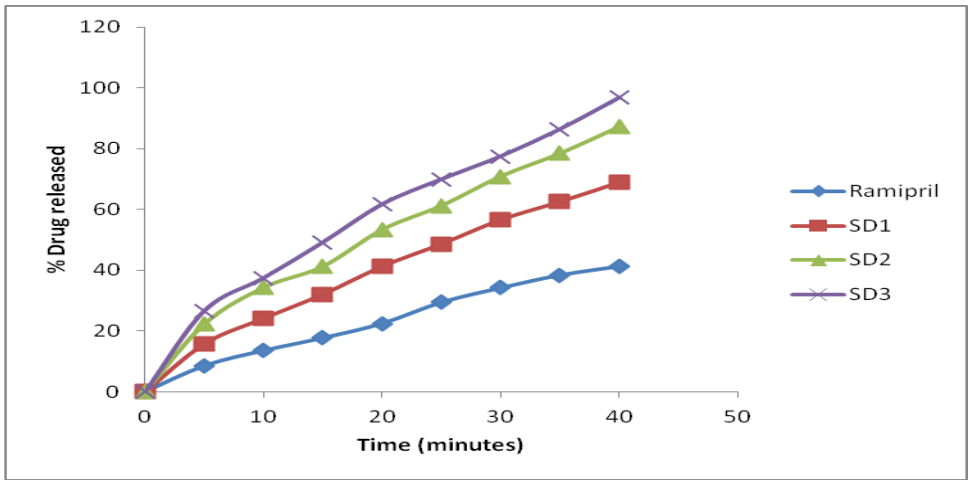

Fig 15: Percentage drug release from solid dispersion

3.1.8 EVALUATION OF POWDERS

Table No 18: EVALUATION PARAMETERS OF POWDER BLEND

Formulation codes	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio
A1	30.23±0.025	0.412±0.22	0.554±0.192	25.63±0.026	1.344±0.0243
A2	27.48±0.030	0.443±0.17	0.583±0.025	24.01±.030	1.316±.0233
A3	32.12±0.030	0.429±0.29	0.525±0.022	18.28±0.036	1.223±0.0152
A4	31.62±0.020	0.432±0.14	0.532±0.015	18.79±0.034	1.231±0.0123

Data are expressed as mean ± S.D (n=3)

3.1.8.1 EVALUATION OF IMMEDIATE RELEASE GRANULES

The percentage yield, percentage drug content and the dissolution efficiency was determined for all the formulations. The percentage yield for all the formulation was found to be from 81.20% to 93.21% as shown in Table 19.

Table No 19: PERCENTAGE YIELD

Formulation codes	% yield
A1	81.20±0.9
A2	89.80±0.8
A3	86.6±0.8
A4	93.21±0.5

Data are expressed as mean ± S.D (n=3)

The drug content for all the formulation was found to be from 86.58% to 96.86% as shown in Table 20.

Table No 20: DRUG CONTENT

Formulation codes	% DRUG CONTENT
A1	86.58±0.6
A2	89.32±0.2
A3	92.62±0.9
A4	96.86±0.4

Data are expressed as mean ± S.D (n=3)

.Table No 21: DISSOLUTION STUDIES OF IMMEDIATE RELEASE GRANULES

Time (min)	A1	A2	A3	A4
5	33.65±0.151	34.64±0.194	38.23±0.254	46.59±0.143
10	41.81±0.253	46.39±0.136	51.37±0.135	57.15±0.207
15	50.38±0.121	55.35±0.294	63.52±0.176	66.90±0.426
20	59.34±0.163	64.32±0.183	76.86±0.294	79.85±0.370
25	68.9±0.142	72.08±0.314	84.23±0.564	88.01±0.335
30	75.87±0.211	83.23±0.111	91.20±0.295	95.45±0.264

Data are expressed as mean ± S.D (n=3)

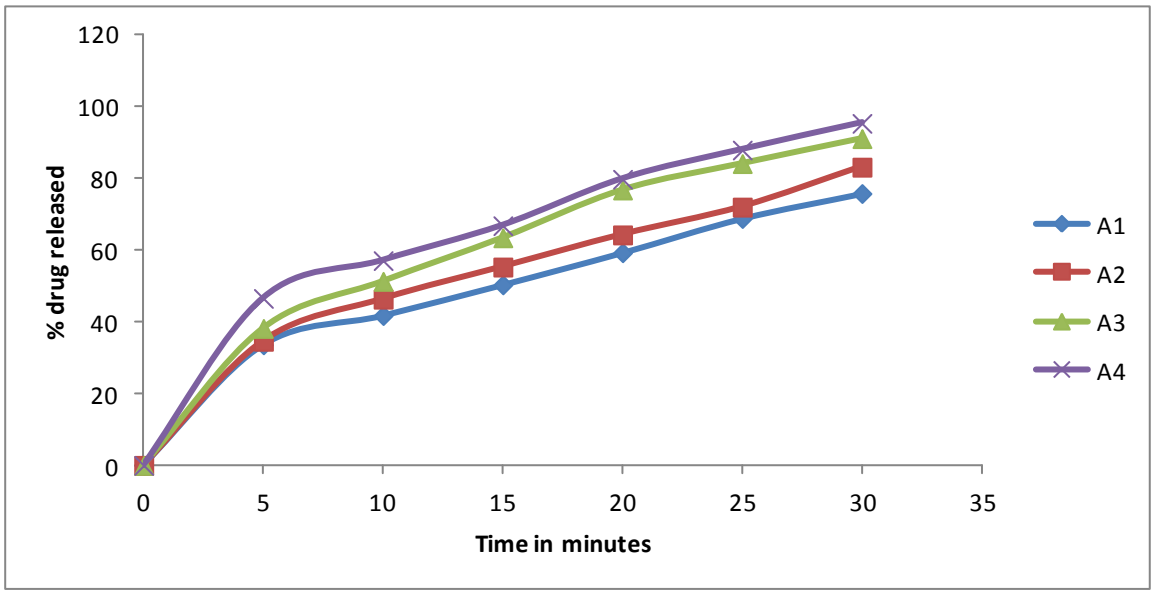

Fig 16*: In- vitro* drug release of Ramipril

The formulation code A4 showed maximum drug release (95.45%) corresponding to 30 minutes. There was an enhancement in the drug release as the concentration of superdisintegrant increased. Hence A4 formulation was the best formulation.

4. CONCLUSION:

From the present study it could be concluded that PEG 6000 had enhanced the dissolution rate of the drug in comparison with pure untreated drug. The croscarmellose sodium is suitable superdisintegrant for formulation of immediate release granules. All the evaluation parameters fulfilled the pharmacopeal requirements concerning angle of repose, bulk density, tapped density, carr's index, hausner's ratio, drug content and dissolution results. The formulation A4 showed best result and provide maximum release in 30 minutes. Hence this formulation is helpful for the management of mild to severe hypertension and myocardial infraction.

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