Available online on 15.06.2020 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Formulation of Ramipril Tablets Containing Solid Dispersion Employing Selective Polymers to Enhance Dissolution Rate

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ABSTRACT

Objective: The present work based on formulation of Ramipril tablets containing solid dispersion employing selective polymers. The objective of the preparation is to prepare the solid dispersion of the Ramipril, which has more responsive value in terms of the dissolution rate.

Method: Solid dispersion complex was prepared with two different carriers PEG 6000 and PVP K30. Nine formulations were developed and each formulation were subjected to pre compression and post compression parameters.

Result and Discussion: Pre-compression and post compression parameters were studied which had shown good flow property and compiled the standard data. *In-vitro* dissolution studies shows more than 90 % drug release in phosphate buffer pH 6.8 in 30 min. Out of all formulation F4 showed 92.55±0.67 % drug release with in 30min which was the best result rest of the formulation.

Conclusion: Ramipril tablets were successfully prepared and evaluated. F4 formulation shows the greater dissolution rate in phosphate buffer pH 6.8 as compared to other formulations. When compared with marketed formulation it also shows better results. Therefore, Ramipril solid dispersion tablets enhanced the dissolution rate and can be more efficacious for improving oral bioavailability of Ramipril.

Keywords: Solid dispersion, Ramipril, Solvent Evaporation Technique.

Article Info: Received 22 March 2020; Review Completed 19 May 2020; Accepted 06 June 2020; Available online 15 June 2020

Cite this article as:

Kumar I, Verma S, Chaudhary A, Formulation of Ramipril Tablets Containing Solid Dispersion Employing Selective Polymers to Enhance Dissolution Rate, Journal of Drug Delivery and Therapeutics. 2020; 10(3-s):142-149
http://dx.doi.org/10.22270/jddt.v10i3-s.4109

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INTRODUCTION

One of the foremost difficult aspects pharmaceutical industries have long-faced is to boost the oral bioavailability of the poorly soluble medication. On an average 30-40% of newly discovered drug, candidates are poor water-soluble hence, it becomes necessary to enhance the solubility of the poorly water-soluble drugs.[1, 2]

Ramipril is an inhibitor of angiotensin converting enzyme and it is a pro drug. Liver is responsible for converting Ramipril to the Ramiprilet and in a less extent converted in kidneys. ACE is accountable for converting ATI to ATII and Ramiprilat is a potent and effective inhibitor of ACE. Angiotensin II is the key constituent of RAAS and it regulates blood pressure. For the treatment of hypertension, congestive heart failure and nephropathy, Ramipril is found to be useful.[3, 4]

Ramipril hinders the RAAS system by binding to and inhibiting ACE thereby preventing the conversion of angiotensin I to angiotensin II. Angiotensin 1 receptor mediates vasoconstriction, inflammation, fibrosis, and oxidative stress through a variety of signaling pathways. As plasma levels of angiotensin II fall, less activation of the G-protein coupled receptors angiotensin receptor I and angiotensin receptor II occurs. Angiotensin includes actions such as G_q coupling to the inositol tri-phosphate pathway, activation of phospholipases C, A_2, and D which contribute to eicosanoid production, activation of Ca^{2+}-dependent and MAP kinases, G_i and $G_{12/13}$, and eventual activation of the Jak/STAT pathway leading to cell growth and production of extracellular matrix components.

AT_2R acts in opposition to the effects of AT_1R by activating phosphotyrosine phosphatases, which inhibit MAP kinases, inhibiting Ca^{2+} channel opening, and stimulating cGMP and nitric oxide production leading to vasodilation.[5, 6]

According to the Bio pharmaceutics Classification System (BCS), Ramipril is a Class II having low solubility and high permeability. In the Present Study, formulation of Ramipril tablets containing solid dispersion employing selective

polymers were prepared to enhanced the dissolution rate that will leads to the increased bioavailability.

MATERIALS AND METHODS

Ramipril was obtained as a gift sample from SGPTC Pvt Ltd. Polymers like, PEG 6000, Cross caramellose sodium (CCS), Crospovidone (CP), Sodium starch glycolate (SSG) were procured from CDH Fine Chemicals New Delhi and all other chemicals were procured from SD Fine-chem. Ltd, Mumbai. The entire chemicals were used of Analytical Grade.

Pre-formulation studies

All the Preformulation studies like melting point, solubility study, and partition coefficient were carried out effectively.[7-9]

Estimation of Ramipril

Determination of λmax of Ramipril

A 10 µg/ml solution of Ramipril in methanol was scanned in the range of 200-400 nm. [10]

Preparation of standard curve of Ramipril in methanol

The standard stock solution of Ramipril (1mg/ml) was prepared in methanol. This solution was diluted with methanol, to obtain various dilutions from 2-20 µg/ml. Absorbance of these solutions was recorded at 210nm against methanol as blank using UV-visible spectrophotometer and standard curve was plotted against concentration. From the calibration curve intercept, slope, straight-line equation and correlation coefficient were obtained.

FTIR of Ramipril and Excipients

The samples were triturated and mixed well with potassium bromide in the ratio 1:100. Then the mixture was introduced in the sample holder and scanned to obtain the graphs in the range of 4000–400 cm^{-1}. The spectra of pure drug and drug with excipients were compared to check any incompatibility and physical changes. [11]

Preparation of Solid Dispersion

Freeze drying method was used for the preparation of solid dispersion. Accurately weighed drug, PEG6000, and PVP K30 in mM ratio of 1:1mM was dissolved in 1:1mM solution of methanol: water to get a clear solution. Both the solutions were mixed and were stirred for 24 hour at a controlled temperature (40 ± 1˚C) to remove the organic solvent. The obtained solution was filtered, gradually cooled down to room temperature, and then placed in a refrigerator at −20˚C. The fully frozen solution was dried in a vacuum freeze dryer, and the resulting solid complexes were collected. [12]

Evaluation of Solid Dispersion

Micromeretic properties

Micromeretics Properties like Bulk Density, tapped density, angle of repose, Carr's index and hausner ratio were evaluated. [13]

Solubility Study of Solid Dispersion Complex

Excess quantities of pure drug (20 mg) and its inclusion complexes were added to 5 ml of distilled water to obtain supersaturated solutions. The solutions were continuously stirred for 24h at 25˚C. After 24h each sample was centrifuged at 15000 rpm and supernatant was withdrawal. After that supernatant was filtered and filtrate was suitably diluted and determined spectrophotometrically at 210 nm.

Determination of Drug content

Drug: PEG6000 complex equivalent to 10 mg of drug was stirred for 60 minutes with 100 ml of methanol, then filtered and handled as 100µg / ml inventory solution. The level of 10µg / ml was prepared from this inventory solution and the medication content was determined using the methanol spectrophotometric calibration curve of pure medication at 210 nm using methanol as void. [14]

In-vitro dissolution studies of Solid Dispersion

Studies of drug release using USP apparatus II at 75 rpm were conducted in triplicate at 37 ± 0.5 ° C. Two dissolution media (Phosphate buffer pH 6.8 and 0.1N (HCl)) were used for the dissolution research. Dissolution studies were performed on pure drug (10 mg) and the complex containing an equivalent amount of the drug. At pre-specified time intervals, 0.25min, 0.5min, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24 hrs., samples (5 ml) were extracted and replaced with an equal volume of the same dissolution medium maintained at 37˚C and were analyzed spectrophotometrically at 210 nm. [14]

Formulation of Ramipril Solid Dispersion Tablets

The tablets were prepared in accordance with the formula provided in Table 5 by direct compression technique. All ingredients except magnesium stearate were carried through mesh #18. Stearate of magnesium was carried through mesh #22. Solid dispersion equal to 10 mg of drug and superdisintegrants were mixed by taking tiny portions of each in ascending order and blended into a mortar to obtain a uniform combination. The other ingredients were weighed and mixed in geometric order and tablets were compressed using a single punching machine with 8 mm round flat punches. [15]

Table 1: Composition of Ramipril Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug solid dispersion (equivalent to 10mg)	26	26	26	26	26	26	26	26	26
Cross caramellose sodium (CCS)	8	16	20	-	-	-	-	-	-
Menthol	15	15	15	15	15	15	15	15	15
Sodium starch glycolate (SSG)	-	-	-	-	-	-	8	16	20
Micro crystalline cellulose	132	124	120	132	124	120	132	124	120
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	3	3	3	3	3	3	3	3	3
Crospovidone (CP)	-	-	-	8	16	20	-	-	-
D-sorbitol	12	12	12	12	12	12	12	12	12

Evaluation of Tablets

Pre-compression studies like bulk density, tapped density, angle of repose, Carr's index and Hausner's ration were carried out successfully

Post Compression Studies

The prepared tablets were evaluated for post compression studies, which are as follows:

Weight variation

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The individual weight was then compared with the average value to find the deviation in weight.[16]

Hardness

The device measures the force needed to break the tablet when it reaches the tablet with the force produced by plungers. The tablet was positioned between two plungers; force was applied to the plungers and the crushing power was registered which only causes the tablet to break. From each formulation, the crushing force test was conducted on 5 tablets. [16]

Friability

Pre-weighed tablets (20) were placed in Roche friabilator and were subjected to 100 revolutions at 25rpm for 4 minutes at a height of 6 inches. The tablets were de-dusted and reweighed. It is calculated by the formula:

$$\text{Friability \%} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Thickness

The tablet thickness was determined using a caliper from Vernier. Five tablets were used and average values were calculated from each formulation type. [17]

In-vitro disintegration time

Place one tablet in each of the basket's six pipes. Add a disk to each tube and run the device using distilled water as the immersion liquid maintained at 37 ° ± 2 ° C. In the 0.1 N HCl maintained at 37 ° ± 2 ° C, the assembly should be raised and lowered between 30 cycles per minute. The time taken in seconds to disintegrate the tablet completely without any palpable mass left in the device was measured and registered. [17]

In-vitro dissolution studies

Using USP type-II devices (50 rpm), using 900ml of 0.1 N HCl and Phosphate Buffer pH 6.8 as a dissolution medium, dissolution rate was researched. The dissolution medium temperature has been maintained at 37 ± 0.5 ° C. At a predetermined time interval (5, 10, 15, 20, 25, 30 min) 5ml of the sample was removed and replaced by the fresh medium at every 5 min interval. The absorption of the filtered solution was assessed at 210 nm using a UV spectrophotometric technique and the drug concentration was determined from the normal calibration curve. [18]

RESULT AND DISCUSSION

Pre-Formulation

The selected drug Ramipril was subjected for investigation of physical characterization parameters such as: organoleptic properties, melting point, solubility, partition coefficient and were find with in the acceptance criteria as per IP.

Determination of absorption of Ramipril in methanol

The absorption maxima of Ramipril were obtained in methanol and it was found 210 nm. Calibration curve obtained from different concentration shows good regression value of 0.9925.

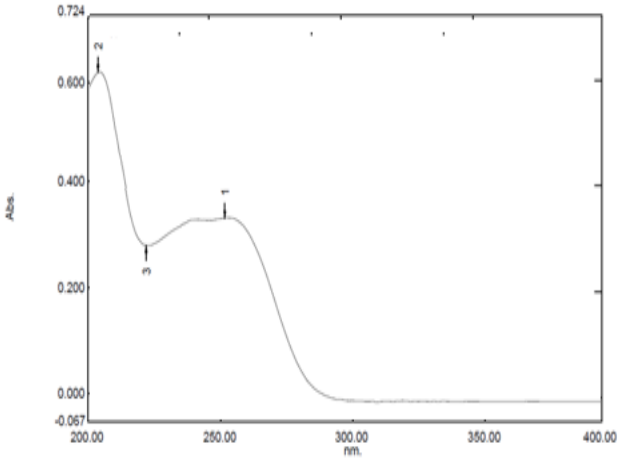


Figure 1: UV Spectrum of Ramipril in methanol

Table 2: Calibration curve of Ramipril in methanol

Concentration (µg/ml)	Absorbance (mean±SD)
2	0.149±0.001
4	0.256±0.001
6	0.373±0.001
8	0.486±0.002
10	0.58±0.007
12	0.671±0.008
14	0.743±0.006
16	0.824±0.007
18	0.901±0.008

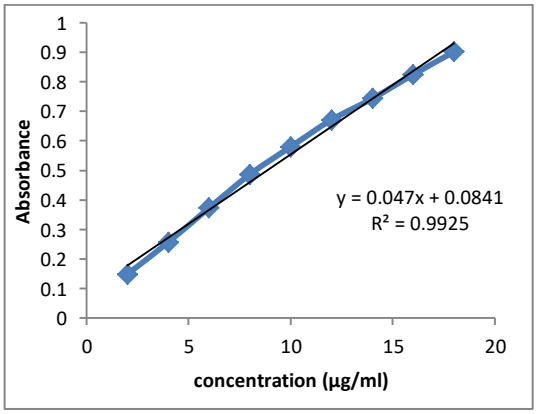


Figure 2: Standard calibration curve of Ramipril in methanol

FTIR of Ramipril and Excipients

In case of PEG 6000, the spectrum was characterized by the appearance of broad band at 3383 cm^{-1} which corresponds to the OH group. The band at 1232 cm^{-1} is for C–O stretching.

For the binary SD with PEG 6000, the spectrum is the sum of the spectra of the drug and polymer with the main bands being clear. This suggests absence of any interaction between the drug and PEG 6000 (Figure 3).

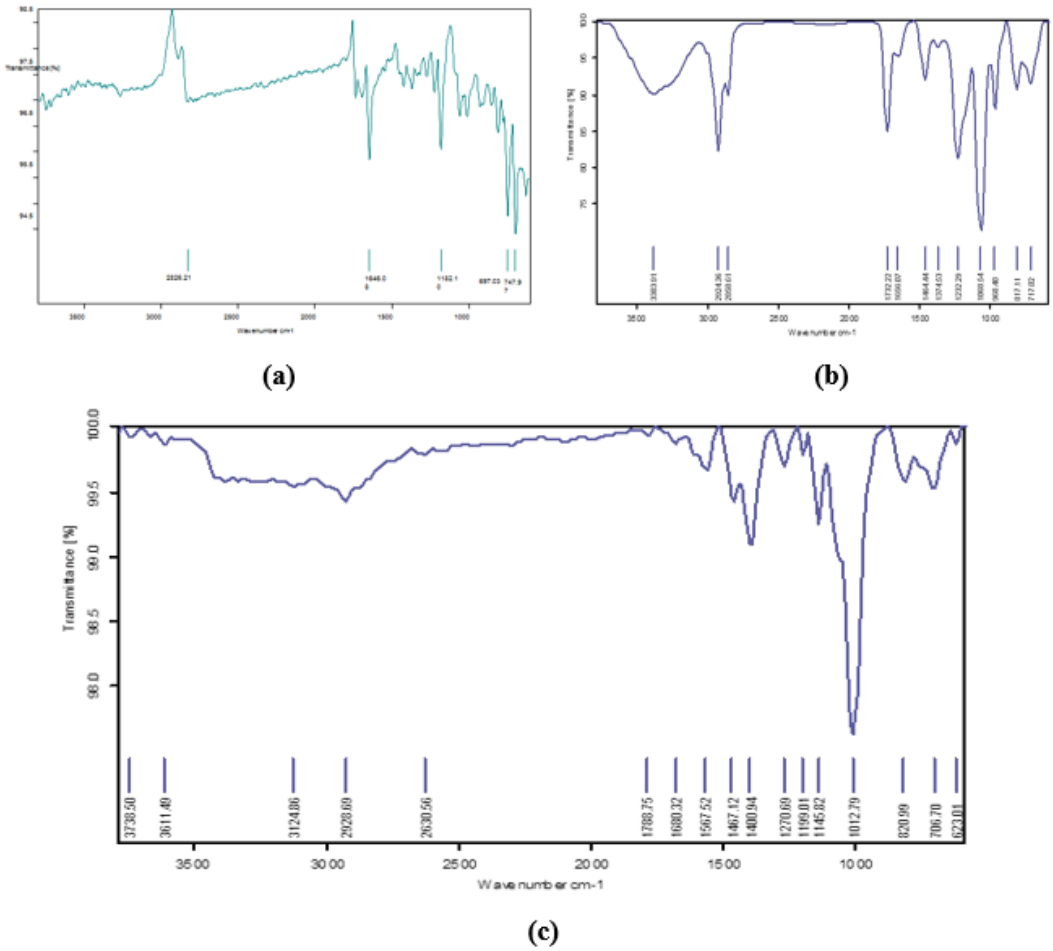


Figure 3: FTIR Spectrum of (a) pure drug (b) PEG6000 (c) Solid dispersion

Evaluation of solid dispersion

Micromeretic properties

After studying the flow properties it was found that angle of repose has value of 27.87°, which means powder will possess good flow property. The bulk density was found to be 0399 g/cm^3. Tapped density was observed as 0.477 g/cm^3. Carr's index was found to be 15.840 % indicates a good flow ability of the powder blend. Hausner's ratio was found to be 1.194. All the flow property parameters were studied thoroughly and all the properties compile the standard data, so we can say that solid dispersion show good flow property and data are shown in Table 3.

Table 3: Micrometrics properties of solid dispersion

Angle of Repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Hausner's ratio
27.87 ± 1.18	0.39 ± 0.01	0.47 ± 0.04	15.84 ± 0.80	1.19 ± 0.10

Mean ± SD; n = 3

Solubility study of the complex solid dispersion

After complexation with PEG6000 and PVP K30, Ramipril exhibits remarkable enhancement solubility, increasing from 0.025 mg/mL to 7.54 mg/mL and 1.50 mg/mL respectively. While both complexes show significant Ramipril solubilization, comparison of the solubility's of the two complexes indicates that the solubility of the PEG6000 complex is several times higher than that of the PVP K30 complex. These solubilization results demonstrate that PEG6000 is a more efficient solubilizer than PVP K30, thus, PEG6000 was selected for further formulation and evaluation studies.

Table 4: Solubility of Pure drug and solid dispersion Phosphate Buffer pH 6.8

Samples	Solubility (mg/ml)
Pure drug	0.025±0.006
PEG 6000-solid dispersion	7.54±0.021
PVP K30- solid dispersion	1.50±0.004

Determination of Drug content

The drug content of the complex formed was found to be 86.09 ± 0.535 %.

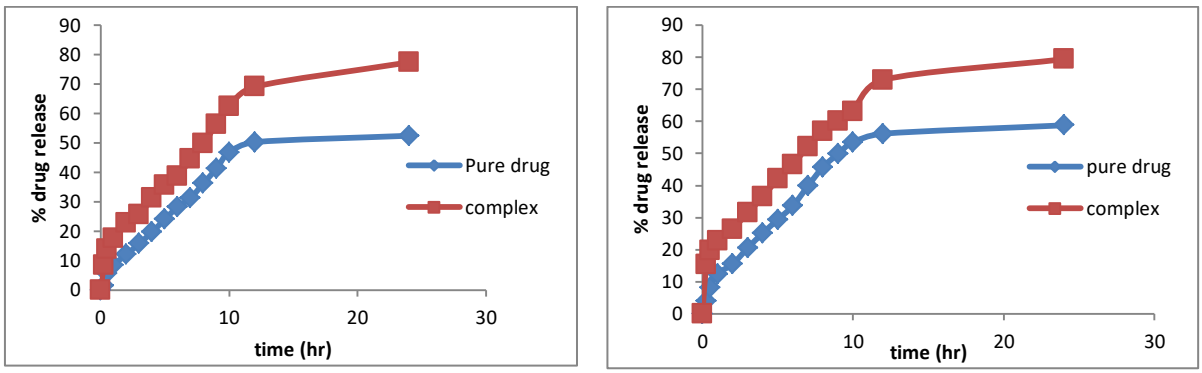
***In-vitro* dissolution studies**

Dissolution study shows that the dissolution rate of Ramipril has been enhanced largely. The drug release with PEG6000 was 77.42 ± 0.398 % in 0.1N HCl and of pure drug was 52.59 ± 0.481 % and the drug release with PEG6000 was 79.40 ± 0.292 % in phosphate buffer pH 6.8 (PBS 6.8) and of pure drug was 58.78 ± 0.382 %. Enhanced solubility and improved dissolution were obtained by solid dispersion in both PBS 6.8 and hydrochloric acid. Data are tabulated in Table 5.

Table 5: Percentage drug release of pure drug and Drug-PEG6000 solid dispersion complex in 0.1N HCl and phosphate buffer pH 6.8

Time (hrs)	0.1N HCl		Phosphate buffer pH 6.8	
	Pure Drug (%)	Complex (%)	Pure Drug (%)	Complex (%)
0	0	0	0	0
0.25	1.40±0.39	8.48±0.72	4.02±0.33	15.31±0.95
0.5	5.55±0.38	13.78±0.38	8.17±0.48	19.65±0.48
1	8.48±0.48	17.68±0.58	12.44±0.95	22.72±0.58
2	12.06±0.69	22.91±0.29	15.51±0.57	26.42±0.57
3	15.76±0.48	25.65±0.50	20.48±0.87	31.53±0.77
4	19.72±0.38	31.21±0.19	25.14±0.77	36.44±0.67
5	24.06±0.22	35.68±0.48	29.36±0.86	42.06±0.96
6	28.27±0.29	38.61±0.61	33.63±0.58	46.59±0.79
7	31.27±0.67	44.48±0.58	39.82±0.69	51.14±0.39
8	36.31±0.67	49.78±0.57	45.76±0.76	56.87±0.76
9	41.23±0.48	56.42±0.48	49.85±0.29	60.06±0.72
10	46.85±0.48	62.48±0.58	53.55±0.96	63.0±0.83
12	50.29±0.48	69.12±0.69	56.17±0.67	72.95±0.66
24	52.46±0.50	77.42±0.39	58.78±0.38	79.40±0.29

Mean ± SD; n = 3



(a) (b)

Figure 4: % drug release of drug and its complex in 0.1N HCl (left) and Phosphate buffer pH 6.8 (right)

Evaluation of tablets

Pre compression parameters

All the pre-compression parameters were studied thoroughly and all the properties compile the standard data, so we can say that solid dispersion show good flow property and data are shown in Table 6.

Table 6: Pre compression parameters of Ramipril solid dispersion powder blend

Formulation code	Angle of repose (˚C)	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)	Hausner's ratio
F1	29.40 ± 2.81	0.354 ±0.003	0.384±0.009	7.78±1.61	1.08±0.018
F2	23.21 ± 0.66	0.312±0.005	0.348±0.008	10.38±0.915	1.11±0.011
F3	20.93± 0.96	0.375± 0.014	0.446± 0.024	15.79±1.50	1.18±0.020
F4	20.15± 1.68	0.306± 0.012	0.337± 0.016	9.14± 0.959	1.10± 0.011
F5	23.17± 2.61	0.327± 0.001	0.398± 0.006	18.00± 1.82	1.21± 0.027
F6	27.46 ± 2.15	0.336± 0.005	0.385± 0.007	12.81± 1.21	1.14± 0.016
F7	25.96 ± 1.37	0.316 ± 0.008	0.361± 0.005	12.43± 1.15	1.14± 0.014
F8	27.08 ±2.50	0.321±0.002	0.353±0.005	9.17±1.54	1.10±0.018
F9	29.28±1.78	0.301±0.002	0.341±0.004	11.61±1.40	1.13±0.017

Mean ± SD; n = 3

Post Compression Parameters

All formulation were subjected to post evaluation parameters viz. hardness, thickness, friability, weight variation, disintegration time, drug content and *in-vitro* dissolution studies. Each formulation passes all the parameters (Table 7). *In-vitro* dissolution studies was done in 1N HCl and phosphate buffer pH 6.8 buffer solution. In dissolution studies formulation F4 shows best result in both the dissolution medium. In 0.1N HCl it shows 86.55±0.69 % and in phosphate buffer pH 6.8 dissolution release was 92.55±0.67 % in 30min (Table 8, 9). Therefore, we can say that phosphate buffer pH 6.8 shows better result as compared of 0.1N HCl. The best formulation F4 were than compared with marketed formulation and data is shown in Table 10.

Table 7: Post-compression parameters of Ramipril Tablets

Formulation code	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Disintegration time (sec)	Drug Content
F1	4.10±0.560	3.38±0.025	0.634 ± 0.073	59.57 ± 0.577	98.3±0.436
F2	4.01± 0.025	3.44±0.020	0.468 ± 0.094	58.35 ± 0.673	98.2±0.410
F3	4.04± 0.011	3.37± 0.025	0.580 ± 0.066	61.70 ± 0.608	99.6±0.071
F4	4.08±0.075	3.44± 0.040	0.345 ± 0.064	51.20 ± 0.779	99.2± 0.089
F5	4.42±0.015	3.29± 0.020	0.569 ± 0.101	70.10 ± 0.850	98.3±0.121
F6	4.41± 0.015	3.45± 0.020	0.452 ± 0.106	73.30 ± 0.557	97.4±0.520
F7	4.82± 0.015	2.99± 0.047	0.323 ± 0.072	59.90 ± 0.500	97.8± 0.520
F8	4.75±0.017	2.93±0.040	0.659 ± 0.129	72.06 ± 0.416	97.2±0.263
F9	4.03±0.015	2.87±0.020	0.655 ± 0.046	68.36 ± 0.416	96.3±0.473

Mean ± SD; n = 3

Table 8: Percentage drug release of Ramipril Tablets in 0.1N HCl

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	39.76±0.58	44.61±0.38	41.36±0.69	46.46±0.29	38.46±0.48	45.66±0.39	39.46±0.59	38.36±0.49	42.31±0.48
10	43.53±0.39	47.93±0.79	46.65±0.61	51.76±0.48	41.33±0.29	55.96±0.48	44.85±0.21	42.25±0.61	48.23±0.79
15	47.42±0.29	51.51±0.33	52.59±0.67	62.44±0.76	54.42±0.19	56.94±0.76	53.69±0.67	48.59±0.77	51.71±0.33
20	59.57±0.67	55.27±0.67	57.38±0.58	70.78±0.58	62.47±0.44	68.48±0.18	60.48±0.48	57.18±0.18	54.37±0.67
25	64.76±0.50	60±0.94	60.38±0.79	82.59±0.58	72.76±0.70	78.59±0.98	64.48±0.69	63.78±0.59	62.1±0.54
30	79.55±0.57	68±0.38	69.53±0.76	86.55±0.69	78.85±0.57	83.35±0.29	70.23±0.76	68.23±0.46	73.3±0.37

Mean ± SD; n = 3

Table 9: Percentage Drug Release of Ramipril Tablets in Phosphate Buffer pH 6.8

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	41.48±0.48	48.51±0.86	53.29±0.58	49.65±0.58	48.31±0.46	44.48±0.48	46.25±0.25	42.24±0.68	43.29±0.54
10	51.63±0.57	50.29±0.48	57.19±0.79	54.57±0.76	54.19±0.88	48.63±0.57	54.41±0.28	54.19±0.59	54.79±0.39
15	64.51±0.86	59.06±0.22	61.72±0.39	61.59±0.79	64.06±0.22	54.51±0.86	59.46±0.52	58.42±0.39	61.12±0.28
20	68.46±0.61	66.36±0.57	66.44±0.57	76.72±0.77	72.56±0.67	68.46±0.61	64.41±0.23	62.44±0.47	69.34±0.27
25	70.51±0.58	74.59±0.39	69.31±0.95	84.31±0.79	79.49±0.29	73.51±0.58	72.19±045	68.41±0.45	78.41±0.25
30	83.46±0.39	85.12±0.87	72.44±0.77	92.55±0.67	85.42±0.17	77.46±0.39	81.12±0.74	79.14±0.14	84.34±0.51

Mean ± SD; n = 3

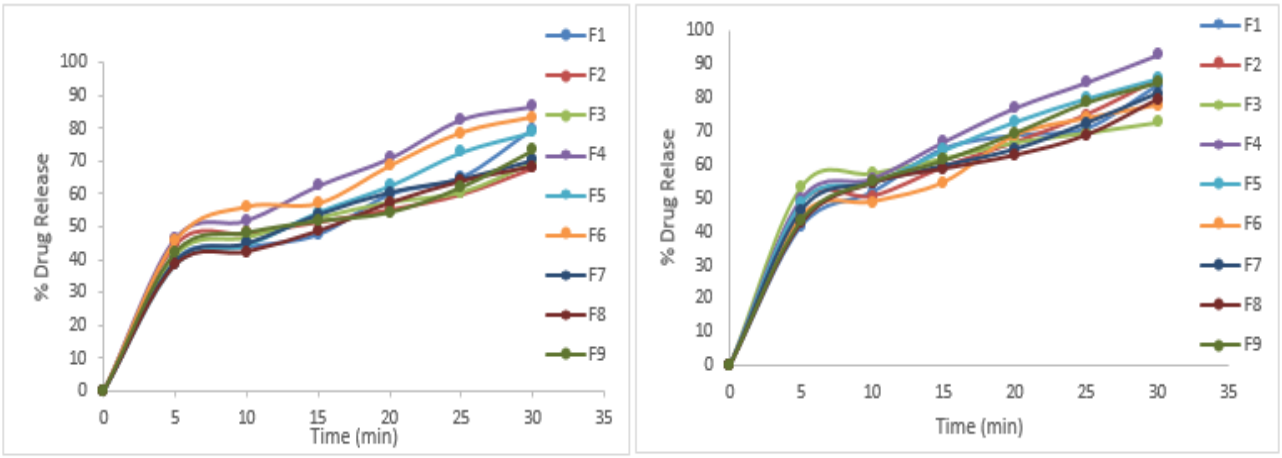


Figure 5: Percent drug release of all formulation (a) 0.1N HCl (b) Phosphate buffer pH 6.8

Table 10: Percentage drug release of optimized formulation (F4) with marketed formulation in phosphate buffer pH 6.8

Time (min)	Formulation F4	Marketed Formulation
0	0	0
5	49.65±0.58	48.74±0.72
10	54.57±0.76	55.53±0.48
15	66.59±0.79	63.46±0.77
20	79.72±0.77	77.36±0.29
25	90.31±0.79	84.82±0.57
30	92.45±0.67	88.45±0.98

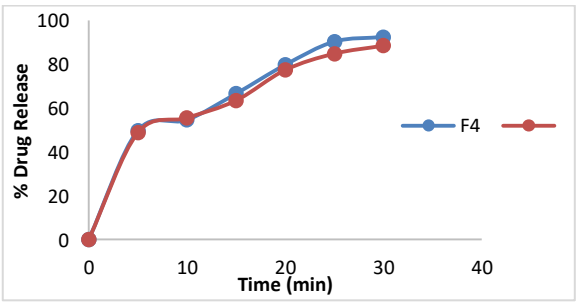


Figure 6: Percent drug release of optimized formulation (F4) with marketed formulation in phosphate buffer pH 6.8

CONCLUSION

The present work was based on the enhancement of the dissolution rate of Ramipril tablet by solid dispersion technique. Solid dispersion complex was prepared with two different carriers PEG 6000 and PVP K30. Phase solubility study of the PEG6000- complex had shown greater stability constant. FTIR studies of PEG 6000 with complex showed no interaction. The micromeretic properties of the solid dispersion was studied and showed good flow properties. Nine formulations were developed and pre-compression parameters were studied which had shown good flow property and compiled the standard data. In the post compression parameters, all formulation shows good results. Formulation F4 showed 92.55±0.67 % drug release in phosphate buffer pH 6.8 and 86.55±0.69 % in 0.1N HCl as compared to other formulation. The best formulation were compared with marketed formulation and shows greater result i.e. 92.45±0.67 % drug release in 30min. Therefore, Ramipril solid dispersion tablets have shown maximum drug release, and can be more efficacious for improving oral bioavailability of Ramipril.

CONFLICT OF INTEREST

The authors declare no conflict of interest

ACKNOWLEDGEMENT

The Author is highly grateful to the **Dr. R. K Abhilashi**, Chairman Abhilashi Group of Institutions, Mandi, India for providing necessary facilities to carry out the research.

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