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FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF FAST DISSOLVING TABLETS OF RAMIPRIL SOLID DISPERSION

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Abstract:

Ramipril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor which is metabolized to Ramiprilat in the liver and, to a lesser extent, kidneys.The poor solubility and wett ability of Ramipril leads to poor dissolution and variations in bioavailability.Solid dispersion of Ramipril was prepared using Hydroxy propyl β-cyclodextrin to improve water solubility. Prepared solid dispersion was shown improved solubility in water of 97.5 µg/ml. Fast dissolving tablets of Ramipril solid dispersion was prepared and evaluated for various tablet properties. Formulation (F6) was shown excellent in vitro disintegration time 100 seconds, wetting time 65.45 seconds and more than 90% drug release in 30 minutes as compared to other formulation. Prepared formulation may improve bioavailability and fast onset of action.

Keywords: *Ramipril, FDT, Cross povidone, Crosscarmellose.*

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INTRODUCTION:

Hypertension is a major health problem throughout the world because of its high prevalence and its association with increased risk of cardiovascular disease [2]. Ramipril is anti-hypertensive agent**.** It inhibits the angiotensin receptors and controls the hypertension**.** Ramipril undergoes extensive first pass metabolism when administered orally with low oral bioavailability and has half-life **(**~24 hours**) [3].** generally geriatric, pediatric and bedridden patient experience difficulties in swallowing the conventional oral dosage form. To overcome this problem a novel formulation was developed i.e. oral fast dissolving tablets. Orally disintegrating tablets are available in the market which disintegrates in one to two minutes, whereas Fast dissolving tablets are capable to disintegrate within few seconds**.** Initially Fast dissolving tablets were introduced in the market as personal care and breathe freshener products; later their importance for therapeutic benefits was observed [1]. To formulate fast dissolving tablet of Ramipril, using solid dispersion technique and fast disintegrating polymer for the increases of solubility and bioavailability is the major concern of this research work**.**

MATERIALS AND METHODS:

Ramipril were kindly supplied by Macleod Pharma (Mumbai, India), Croscarmellose and Crospovidone was supplied by Research Lab Fine Chemicals (Mumbai, India). All the products and materials used in this study comply with the pharmaceutical and analytical standards, respectively.All the research work was carried out at K. B. H. S. S. Trust Institute of pharmacy, Malegaon, Maharashtra during year 2017-2018.

Preformulation Studies:

Melting point:

Melting point of Ramipril was determined by taking a small amount of sample in a capillary tube closed at one end and placed in Thiele's melting point apparatus. The melting point was noted. [4]

FTIR Spectrum: Ramipril was subjected to FT-IR (Fourier transform Infrared spectrometer) study for characterization purpose. Ramipril was mixed with potassium bromide (KBr) in 1:100 proportions and spectrum was obtained in range of 400-4000 cm-1. Potassium bromide was used as a blank while running spectrum [5].

UV Spectrum: The Ramipril was subjected to UV spectroscopic analysis (Lab India; 3000+) to find out the wavelength (λ max) at which it shows maximum absorbance. Ramipril was accurately weighed and dissolved in solvent phosphate buffer pH 6.8 to obtain stock solution of 1000 µg/ml. This solution was then suitably diluted with same solvent to get solution of concentration 100 µg/ml and further diluted to10 µg/ml. Then the UV spectrum of this concentration was recorded over the wavelength range 200-400 nm [5].

Calibration Curve by U.V Spectroscopic Method

Preparation of stock solution of Ramipril in phosphate buffer pH 6.8

Preparation of phosphate buffer pH 6.8:

Weighed quantity of Potassium dihydrogen phosphate (KH_2PO_4), 2.722 g was dissolved in 100 ml distilled water (DW) and mixed properly. In another 100 ml of volumetric flask, solution of 0.2 M sodium hydroxide was prepared, by dissolving 0.8g NaOH in 100 ml DW. 50 ml of potassium dihydrogen phosphate was taken in 200 ml volumetric flask and specified volume of 0.2 N NaOH (22.4 ml), was added in it and the volume was adjusted with DW to 200 ml [4].

Standard stock solution of Ramipril:

About 10 mg of drug was accurately weighed and transferred to calibrated 10 ml volumetric flask. It was dissolved in phosphate buffer pH 6.8 and volume was made up to 10 ml with phosphate buffer pH 6.8 to obtain a final concentration of 1000 µg/ml.

Working stock solution: This standard stock solution was further diluted to get a working standard solution 100 µg/ml, by pipetting out 1ml from standard stock and diluting it up to 10 ml with phosphate buffer pH 6.8. A series of Ramipril dilutions were made from working standard solution, by pipetting out 0.4, 0.8, 1.2, 1.6, and 2.0 ml respectively into separate 10 ml volumetric flasks and diluting to volume with phosphate buffer pH 6.8 to produce the concentrations ranging from 4-20µg/ml.

Drug-Polymers compatibility studies:

A compatibility study for Ramipril was carried out with potential formulation excipients to determine possibility of any drug-excipients interaction/incompatibility. FTIR Spectrum of Ramipril, cross povidone, cross carmellose, Sodium Lauryl Sulphate, Polyviny Pyrrolidone K-30, Saccharine, Maize starch, Magnesium Stearate, Talc separate and physical mixture was taken. These samples were subjected to compatibility studies and stored for 30 days at elevated temperature and humidity conditions of 40 ± 2 °C / 75 ± 5 % RH. FTIR spectrum of these stored samples was then obtained after 30 days [5].

Preparation of Ramipril solid dispersion by Kneading Method:

A mixture of Ramipril and ß-cyclodextrin (1:1, 1:2, 1:3, 1:4, and 1:5 mol/mol) was wetted with a mixture of methanol and water (1:1) thoroughly for 30 min in a glass mortar by kneading method. The paste formed was dried under vacuum for 24 h, dried powder was scrapped, crushed, pulverized, passed through sieve no 100 (ASTM-100, 150 µm) and stored in desiccators for further studies. The prepared solid dispersions were evaluated for their physicochemical parameters such as yield, angle of repose, bulk density, compressibility, moisture uptake, drug content and *in vitro* dissolution studies [6].

Evaluation of Solid Dispersion

Total Ramipril content:

Total Ramipril content was determined using standard curve of Ramipril. Each sample of solid dispersion was accurately weighed (10mg) and solubilized in sufficient methanol to make up the volume up to 10 ml. Solutions were suitably diluted with methanol and analyzed by UV spectrophotometer at 221nm. Experiments were performed in triplicate [14].

Solubility:

Procedure: 25mg of sample was accurately weighed and transferred to 25ml volumetric flask and volume was made up to the mark with methanol. From this 1ml was taken in 10ml volumetric flask and the volume is adjusted up to the mark with same solvent. The absorbance of the solution was measured at 221nm using appropriate blank. The drug content of Ramipril was calculated using calibration curve [15].

Moisture Uptake study:

Moisture uptake study is important to check hygroscopic nature of the prepared solid dispersion no significance change in moisture content was observed after subjecting them to accelerated condition of temperature and humidity. In optimized solid dispersion NMT 3% weight gain was observed than initial weight [15].

5. Formulation and Development of fast dissolving tablets:

Formulations of Ramipril solid dispersion (1:1) was used to prepare its fast dissolving tablets. Fast disintegrating agents Croscarmellose, Cross povidone were used at varying concentrations. Sodium Lauryl sulphate was used as surfactant to study the effect of surfactant on disinteration time. Polyvinyl Pyrrolidone (PVP) K-30 was used as binder. Talc and Magnesium stearate were used as Lubricant and flow promoter. Saccharin was used as sweetner.

Table no. 1: Composition of Ramipril fast dissolving tablets:

Sr. No.	Name of Ingredients	Number of Formulation (Quantity in %)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Ramipril solid dispersion	20.2	20.2	20.2	20.2	20.2	20.2	20.2	20.2	20.2
2	Croscarmellose	6	12	18	-	-	-	-	-	-
3	Cross povidone	-	-	-	6	12	18	18	18	18
4	Sodium Lauryl sulphate	-	-	-	-	-	-	1	2	3
5	PVP K-30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
6	Saccharine	15	15	15	15	15	15	15	15	15
7	Magnesium Stearate	3	3	3	3	3	3	3	3	3
8	Talc	3	3	3	3	3	3	3	3	3

Evaluation of fast dissolving Tablets of Ramipril solid dispersion:

Physical Appearance: The thickness of tablet as a dimensional variable was evaluated. The tablet thickness was controlled within average value. The color, Odour and any other flaws like chips, cracks, surface texture, etc. are other important morphological characteristics were observed [7].

Weight Variation: Tablet weighing 150 mg or more, not more than two tablets differ from the average weight by 10 % deviation. The percent deviation in weight variation from average value for all formulation of design batches were within limit. The weight variation within limits indicates uniformity in tablet compression and consequently content of drug in a unit. 20 tablets were taken and average weight of the tablet was determined. The tablets were weighed individually and the weight variation was determined. [7].

Hardness: Tablet hardness is defined as force required to crushing the tablet in diametric compression test. The hardness was measured with Pfizer hardness tester. The tablets were placed diametrically between two plungers and the lower plunger is kept in contact of tablet to read as zero. The upper plunger is forced against a spring by turning the screw until tablet fractures [7].

Friability: Twenty tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which revolves at 25 rpm for 4 minutes dropping the tablets through a distance of 6 inch with each revolution. This process was repeated for all formulations and the percentage friability was calculated. [8].

Drug Content: From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to 200 mg was transferred to 250 ml volumetric flask. 50 ml of pH 6.8 phosphate buffer was added and then the solution was subjected to Sonication for a period of about 30 min. The solution was made up to 250 ml with 6.8 phosphate buffer.The solution was filtered and suitable dilutions were prepared with pH 6.8 phosphate buffer and then drug content was estimated by recording the absorbance at 221 nm by using UV-visible spectrophotometer [9].

***In vitro* Dissolution test in pH 6.8 phosphate buffer**

The volume of media was kept 900 ml to maintain sink condition. The apparatus for dissolution used was USP-II (Paddle) at 50 rpm. Aliquots were withdrawn at 5 mint intervals from a zone midway between the surface of dissolution medium and top of the rotating paddle not less than 1 cm apart from the suitable replacements with fresh medium was also made. Each sample solution was filtered through Whatman no. 41 filter paper. The absorbance was measured at 221 nm using spectrophotometer.

RESULTS AND DISCUSSION:

FTIR Spectrum:

For characterization of pure Ramipril FTIR studies were carried out. FTIR spectrum of Ramipril shown in figure 1 was complied as per Indian Pharmacopieal standards and was shown functional groups C-H (Stretch) at 2933.73 cm^{-1}, C=O (ester) at 1741.72 cm^{-1},C=O(amide) at 1460.82 cm^{-1} ,CH3(bend) at 1375 cm^{-1} and C-O at 1184.29 cm^{-1}.

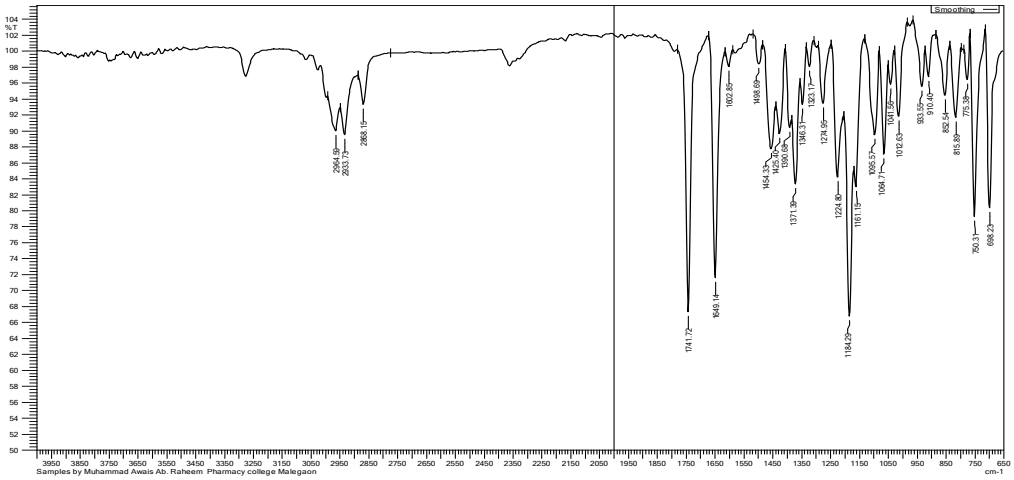

Figure1: FTIR Spectrum of Ramipril (pure drug)

UV- Visible Spectrum of Ramipril:

Ramipril was shown absorbance at 221nm (λ max) in phosphate buffer solution pH 6.8 shown in Figure 2.

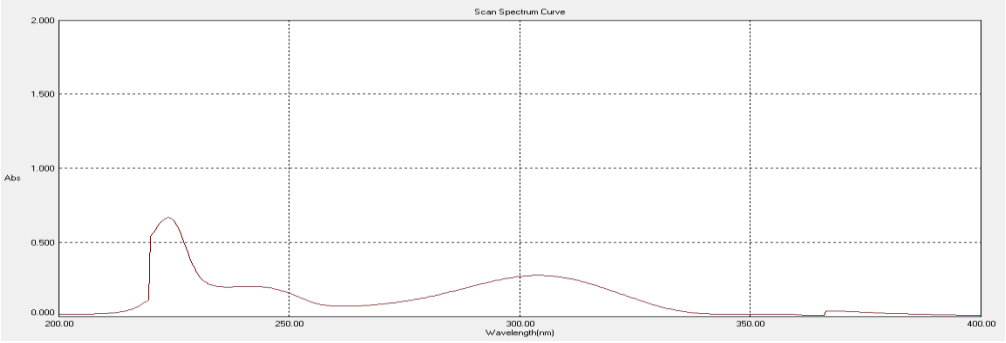

Figure 2: UV spectrum of Ramipril in Phosphate buffer pH 6.8

Calibration Curve by UV Spectroscopic Method:

1. Calibration curve in phosphate buffer pH 6.8:

A linear relationship was obtained in Beer-Lamberts plot of Ramipril.

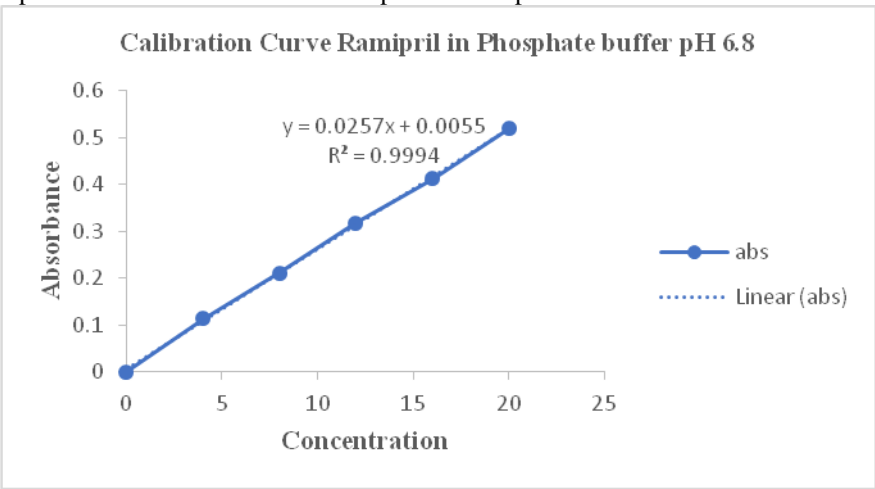

Figure 3: Calibration Curve of Ramipril in Phosphate buffer pH 6.8

Drug-Polymers compatibility study:

The Drug-excipients interaction study had shown no interaction between Ramipril and selected polymers as there was no significant shift of peaks in FTIR spectrum shown in figure no 4,5 Also, the characteristic peaks of drug Ramipril were observed in IR spectrum of drug-excipients and in physical mixture sample. From these FTIR spectra, it was concluded that the selected excipients were compatible with drug Ramipril.

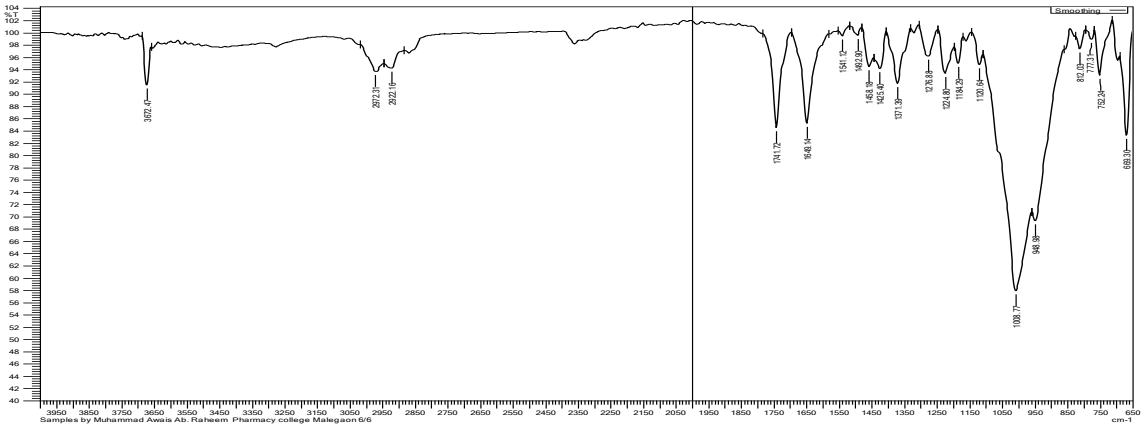

Figure: 4. IR Spectrum of Ramipril, Cross povidone, SLS, PVP K-30, Maize starch, Magnesium Stearate, Talc and sachharin

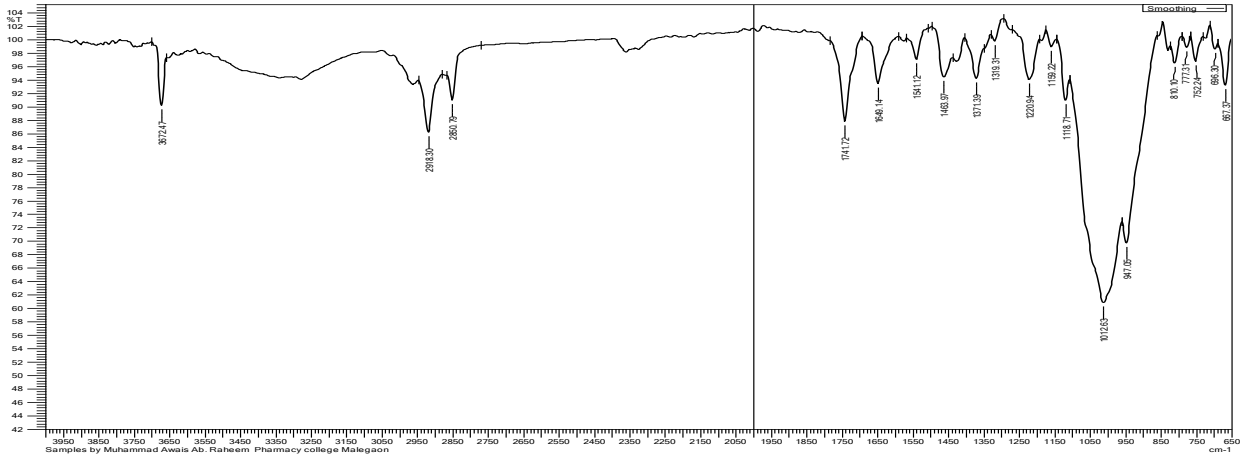

Figure: 5. IR Spectrum of Ramipril**,** Croscarmellose, SLS, PVP K-30, Maize starch, Magnesium Stearate, Talc and sachharin

Table No.02 Evaluation of Ramipril Solid Dispersion

Sr. No.	Parameter	Observation
1	Total Ramipril content	8.8 µg/ml
2	Solubility of Ramipril	72.6µg/ml
3	Solubility of Ramipril solid dispersion	97.50 µg/ml
4	Moisture Uptake study	4.0 to 4.5 **%**

5. Evaluation of fast dissolving tablets of Ramipril solid dispersion

Prepared tablets of Ramipril solid dispersion were evaluated for Weight variation, Hardness, Friability, Drug content, disintegration time, wetting time and drug release parameters.

Table No. 03: Evaluation of physicochemical parameters of Fast dissolving Ramipril solid dispersion Tablets.

Formulation	Weight variation mg±SD	Hardness (Kg/cm2) ±SD	Friability (%)	Drug content (%)
F1	150.00± 0.153	3.4±0.2	0.2811±0.2	96.26± 0.230
F2	149.35± 1.758	3.3±0.26	0.1696±0.5	99.85± 3.602
F3	151.65± 1.094	3.2± 0.25	0.3251±0.3	94.62±5.445
F4	149.95 ± 2.064	2.6± 0.2	0.1801±0.21	97.98±1.876
F5	149.5± 2.212	3.0± 0.26	0.3032±0.25	98.67±0.933
F6	151.12± 2.111	2.9± 0.26	0.4032±0.26	96.95±1.876
F7	148.00± 2.145	3.4± 0.26	0.4102±0.29	93.25±3.876
F8	149.99± 1.452	3.0± 0.26	0.4703±0.31	98.98±1.876
F9	150.15± 1.254	3.2± 0.26	0.4302±0.19	97.00±2.82

All values are mean ± SD, n=3

Weight variation

The weight variation of the formulation F1 to F9 ranged from 148.5 to 151.25 mg and percentage deviation ranged from 1.09 to 2.145 **%.** The percentage deviations of the tablets have to be specific, and they should not differ ± 5**%** according to IP specification**.**

Hardness and Friability

The Hardness of the formulation F1 to F9 ranged from 2.6 to 3.4 Kg/cm^2**.** However, hardness alone cannot be considered as absolute indicator of the tablet strength**.** Hence another parameter measured was the friability of the tablets**.** The friability of the tablets was found to be less than 1 **%** which was considered within the limit **[**USP**].** The measure of these two parameters gives the strength of the tablets during handling, packaging, shipping etc**.**

Drug content: The uniformity in the drug content is an important measure**.** It gives the percentage of drug present per unit dosage form**.** The content uniformity was found within 93.25 to 99.85 **%** of the 150 mg of Ramipril solid dispersion**.** Hence the tablets prepared showed good content uniformity**.**

Disintegration Time and Wetting time: Formulation (F6) was shown excellent in vitro disintegration time 100 seconds, wetting time 65.45 seconds and more than 90% drug release in 30 minutes as compared to other formulation

Table No. 4. Disintegration and Wetting time of Fast dissolving tablets of Ramipril solid dispersion

Batches	Parameter	
	Disintegration time (sec)	Wetting time (sec)
1	75.00 ± 2.00	68.00 ± .1145
2	80.00 ± 3.00	75.00 ± 2.00
3	80.00 ± 0.48	55.45 ± 3.56
4	125.00 ± 1.02	98.33 ± 2.12
5	105.00 ± 2.08	61.33 ± 2.89
6	100.00 ± 1.00	65.45 ± 0.67
7	75.00 ± 2.45	64.78 ± 0.58
8	80.00 ± 2.58	75.55 ± 2.65
9	83.00 ± 2.45	76.0 ± 2.52

***In- vitro* drug release studies:** Fast dissolving tablets of Ramipril solid dispersion (F6) was shown best results in terms of percent drug release. Formulation F6 was released more than 50% drug in 10 mints as compared to other formulation. Also, F6 was released more than 90% drug in 30 mints as compared to other formulations. Formulation F6 was found best formulation among developed formulation. when the data were plotted according to zero order equation and first order equation showed correlation coefficient values between 0.9602 **-**0.9960 and 0.8578 **-** 0.9935respectively**.** Hence, the results revealed that all the fast dissolving tablets formulation released the drug by Zero order kinetics as R^2 close to 1.0

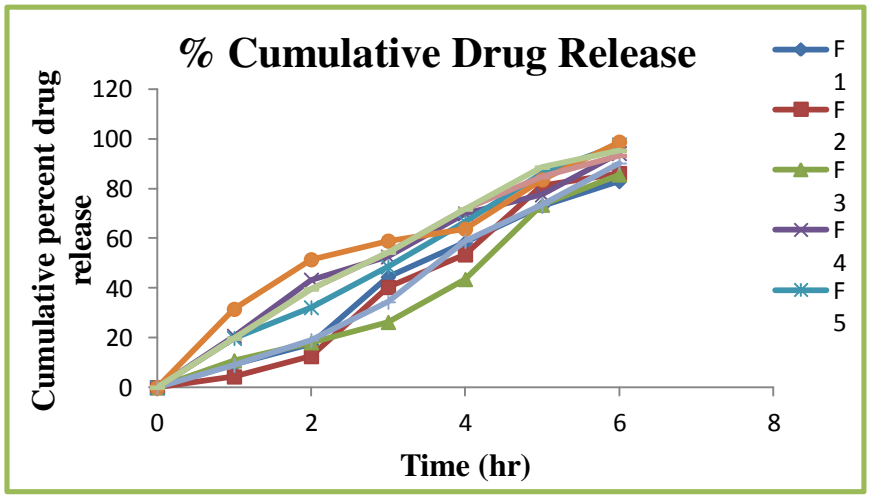

Fig 6:%Cumulative Drug Release of All Batches of Ramipril solid dispersion

CONCLUSION:

Ramipril and excipients used in the study were compatile and formed stable formulations. Solid dispersion containing Ramipril and Hydroxy propyl β-Cyclodextrin in the ratio of 1:1was shown better solubility than other solid dispersions.

Fast dissolving tablets of Ramipril solid dispersion (F6) was shown best results in terms of percent drug release, wetting time and disintegration time. Thus prepared Fast dissolving tablets of Ramipril solid dispersion can provide quick onset of action and better bioavailability than conventional Ramipril tablets.

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REFERENCES:

1. Bhowmik D., Chiranjib B., Krishnakanth, Pankaj, R. and Margret C.(2009) 'Fast Dissolving Tablet: An Overview'. Journal of Chemical and Pharmaceutical Research, 2009, 1(1): 163-177
2. Arun Chockalingam, MS PhD FACC,[1] Norman R Campbell, MD FRCP(C),[2] and J George Fodor, MD PhD FRCP(C)[3]Worldwide epidemic of hypertension, Can J Cardiol. 2006 May; 22(7): 553–555.
3. Reinhard H.A. Becker MD Bernard SchölkensMD, Ramipril: Review of pharmacology, The American Journal of Cardiology, 59, 10, 1987, 3-11
4. Pavia D. L., Lampman G. M. and Kriz G. S., "Introduction to Spectroscopy: A Guide for Students of Organic Chemistry", Hartcourt College publishers 3rd ed., (2001); p. 13-166.
5. Sharma Y. R., "Infrared spectroscopy and Mass Spectroscopy: Elementary Organic Chemistry", S. Chand & Company Ltd, New Delhi, (2005); p. 65-281.
6. Ladan Akbarpour Nikghalb , Gurinder Singh , Gaurav Singh and Kimia Fazaeli Kahkeshan, Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs Journal of Applied Pharmaceutical Science Vol. 2 (10), pp. 170-175, October, 2012
7. Lachman L., Liberman H.A. and Kanig, J.L., "The Theory and Practice of Industrial Pharmacy", IIIrd ed., Varghese Publishing House, Mumbai,1990; p. 293.
8. United States Pharmacopoeia 27/ NF 22, The Official Compendia of Standards, Asian edition, USP Convention, 2004; p. 1074, 3371-75.
9. Indian pharmacopoeia. (2014) Government of India, Ministry of Health and Family Welfare, Ghaziabad, Vol. 3. New Delhi, the Indian Pharmacopoeia Commission Publisher. P.n. 1735-1736
10. Aftab Modi, Pralhad Tayade.,Enhancement of dissolution profile of solid dispersion (kneading technique). AAPS PharmSciTech, 2006
11. Sunil Kumar Batra, Satish Sardana, a review on delivery of antihypertensive drugs through sublingual route.IJPSR (2017), Volume 8
12. VijayaLakshmi P. and Kusum D.V., Development of Extended Zero-Order Release Gliclazide Tablets by Central Composite Design, Drug Development and Industrial Pharmacy. 2008; p. 34:33-45.
13. Venkatesh D. P. and Rao Geetha C. G., "Formulation of taste masked oro-dispersible tablets of Ambroxol Hydrochloride", Asian Journal of Pharmaceutics. October-December 2008; 261-264.
14. Jagdale S, Dangat S, Kuchekar B.,Improvement of dissolution rate of Ramipril by solid dispersion technique and development of buccal patch. Int. J. Pharm. Sci. 2012 Aug; 4:309-318.
15. Chandrakant DS, Danki LS, Sayeed A, Mallikarjun B.,Preparation and evaluation of inclusion complexes of water insoluble drurg. International Journal of Research in Pharmaceutical and Biomedical Sciences ISSN: 2229-370.s