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FORMULATON AND EVALUATION OF RAMIPRIL IMMEDIATE RELEASE TABLETS

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ABSTARCT

The developments of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. In this research work Ramipril immediate tablets were prepared by using different concentrations of the super disintegrants. Immediate release tablets are those tablets which are designed to disintegrate and release their medicaments with no special rate controlling features, such as special coating and other techniques. Ramipril is poorly soluble in water hence the basic objective of this study was to produce immediate release Ramipril tablets containing disintegrant via wet granulation.

KEYWORDS

Ramipril, Super disintegrants, Immediate release tablets and Wet granulation.

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INTRODUCTION[1,2]

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and

equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights.

The developments of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of ineffective therapy.

Advantages of Immediate Release Drug Delivery System[3,4]

An immediate release pharmaceutical preparation offers:

- Improved compliance/added convenience
- Improved stability
- Suitable for controlled/sustained release actives
- Allows high drug loading
- Ability to provide advantages of liquid medication in the form of solid preparation.

Different types of super disintegrants are listed in Table No.1.

MATERIALS AND METHODOLOGY[5]

The materials required for the for the formulation of Ramipril immediate release tables are Ramipril, Starch, Lactose Anhydrous, Dicalicum Thiophosphate, Microcrystallaline cellulose, Magnesium Stearate, PVP K30, Sodium Starch Glycolate.

Precompression studies like Bulk density, Tapped density, True density, Angle of repose, Compressibility Index and Hausner's ratio are performed and the results are tabulated in the Table No.3.

Formulation procedure

The formula showed in the Table No.2.

Immediate release Ramipril were prepared through wet granulation method according to the composition shown in Table No.2. Various steps (sieving, dry mixing, binder solution preparation, granulation and subsequent drying) involved in wet granulation process:

Wet granulation Procedure

Granulation of Ramipril

Sieving

The active ingredient Ramipril was passed through the sieve#40 followed by the other ingredients were passed the same sieve.

Dry mixing

Ramipril, disintegrants, MCC were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug.

Preparation of binder solution

Weigh 22mg of PVP K-30 accurately and it is mixed with IPA to form a paste is used as binder solution and kept separately. Wet mass pass through 40# sieve and dry the granule for 2hrs in hot air oven at 45^{o}C. For, dried granules perform the micromeritic properties.

Lubrication and compression of tablets[6,7]

Magnesium stearate, Aerosil and talc were weighed and they were passed through sieve#20. Then mixed with dried granules of Ramipril separately in a polybag for 5minutes to get a uniform blend. Then the lubricated granules of Ramipril were added in the separate hopper double rotary punching machine and compressed into tablets using 7.5 caplet shape punches, at weight of 150mg each.

Pre-compression studies

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve#20) into a measuring cylinder and initial weight was

noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by

$$D_b = M/Vb$$

Where,
M is the mass of powder
Vb is the bulk volume of the powder.

Tapped Density

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

$$D_t = M/Vt$$

Where,
M is the mass of powder
Vt is the tapped volume of the powder.

Angle of Repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

$$\text{Tan } \theta = h/r$$

Therefore, $\theta = \text{Tan}^{-1} h/r$
Where,
θ = Angle of repose
h = height of the cone
r = Radius of the cone base.

Compressibility Index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

Carr's compressibility index (%)=$[(D_t-D_b)X100]/D_t$

Where,
D_t is the tapped density
D_b is the bulk density

Hauser's Ratio

Hausner's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = D_t/D_b$$

Where,
Dt is the tapped density,
Db is the bulk density.

Post compression studies

Tablet thickness test

Randomly 10 tablets were taken from each formulation trial batch and their thickness was measured using a Venire caliperse.

Weight Variation Test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Measurement of Tablet Hardness

The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test

It is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / Initial weight) X 100

RESULTS AND DISCUSSION

The flow properties and other derived properties evaluated and proved to be within limits showing good flow properties (Table No.2). The prepared

tablet formulations were evaluated for physical parameters and were proved to be within limits (Table No.3 and 4). *In vitro* drug release study results are among all formulations F6 formulation release of the drug immediately with in 25 mins (Table No.5).

Table No.1: Classification of super disintegrants

S.No	Structural (NF name)	Description	Trade name (manufacturer)
1	Modified starches (Sodium starch glycolate, NF)	Sodium carboxymethyl starch; the carboxymethyl groups induces hydrophilicity and cross-linking reduces solubility.	Explotab® (Edward Mendell Co.), Primojel® (Generichem Corp.), Tablo (Blanver, Brazil)
2	Modified cellulose (Croscarmellose, NF)	Sodium carboxymethyl cellulose which has been cross-linked to render the material insoluble.	AcDiSol® (FMC Corp.), Nymcel ZSX® (Nyma, Netherlands), Primellose® (Avebe, Netherlands) Solutab® (Blanver, Brazil)
3	Cross-linked poly-vinyl pyrrolidone (Cross povidine NF)	Cross-linked polyvinyl pyrrolidone; the high molecular weight and cross-linking render the material insoluble in water	Crospovidone M® (BASF Corp.), Kollidon CL® (BASF Corp.), Polyplasdone XL (ISP Corp.)

Table No.2: Formula for the preparation of immediate release tablets

S.No	Ingredients	Formulations								
		F1	F2	F3	F5	F10	F7	F8	F9	*F6
1	Ramipril	10	10	10	10	10	10	10	10	10
2	Microcrystalline Cellulose	34	30	33	30	32	45	125	--	--
3	Starch	95	--	--	50	50	50	--	--	125
4	Lactose Anhydrous	--	98	--	45	--	--	--	--	--
5	Di-calcium Phosphate	--	--	95	--	45	30	--	125	--
6	SSG	2	2.5	3	3.5	4	4.5	5	5.5	6
7	PVPK-30	4	4	4	4	4	4	4	4	4
8	IPA	QS	QS	QS	QS	QS	QS	QS	QS	QS
9	Magnesium stearate	2	2	2	2	2	2	2	2	2
10	Aerosil	3	3	3	3	3	3	3	3	3
Total wt of tablet		150	150	150	150	150	150	150	150	150

Table No.3: Pre-compression parameters for formulations F-1 to F-10

S.No	Formulation Code	Angle of repose (mean± SD)	Bulk Density (gm/cc) (mean± SD)	Tapped Density (gm/cc) (mean± SD)	Hausner ratio (mean± SD)	Compressibility Index (%) (mean± SD)
1	F-1	25.80±0.25	0.645±0.03	0.769±0.23	1.06±0.05	20.40±0.03
2	F-2	20.32±0.32	0.588±0.15	0.666±0.15	1.03±0.07	20.26±0.15
3	F-3	25.70±0.64	0.625±0.25	0.714±0.65	1.02±0.03	20.74±0.21
4	F-4	24.28±0.91	0.76±0.69	0.872±0.45	1.13±0.01	20.20±0.28
5	F-5	22.16±0.69	0.689±0.35	0.78±0.20	1.15±0.03	18.23±0.32
6	F-6*	20.34±0.25	0.555±0.16	0.625±0.89	1.11±0.05	17.50±0.35
7	F-7	26.59±0.32	0.714±0.75	0.833±0.64	1.15±0.07	13.00±0.39
8	F-8	25.26±0.64	0.748±0.42	0.868±0.78	1.14±0.03	12.26±0.45
9	F-9	25.12±0.72	0.749±0.16	0.868±0.82	1.13±0.06	12.44±0.52
10	F10	25.12±0.62	0.65±0.13	0.765±0.72	1.2±0.06	12.32±0.42

Table No.4: Evaluation of physical parameters for formulations F-1 to F-10

S.No	Formula	Weight Variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegration time (mins)	Assay (%)
1	F-1	502.6±0.13	3.97±0.03	5.02±0.11	0.28±0.04	9±0.25	98.62
2	F-2	504.1±0.45	3.52±0.31	5.13±0.07	0.29±0.02	14±0.32	99.68
3	F-3	497.2±0.16	3.31±0.23	5.48±0.14	0.22±0.05	22±0.59	101.08
4	F-4	501.0±0.21	3.27±0.08	5.52±0.16	0.29±0.01	13±0.33	100.36
5	F-5	505.7±0.17	3.60±0.16	5.44±0.04	0.20±0.03	20±0.50	99.02
6	F-6*	503.0±0.32	3.38±0.12	5.79±0.02	0.21±0.04	06±0.23	98.62
7	F-7	502.0±0.45	3.36±0.31	5.85±0.11	0.23±0.02	11±0.35	101.08
8	F-8	503.4±0.21	3.43±0.08	5.80±0.14	0.23±0.01	10±0.31	100.06
9	F-9	503.0±0.35	3.41±0.35	5.89±0.17	0.20±0.04	12±0.34	98.36
10	F10	501.0±0.21	3.27±0.08	5.52±0.16	0.29±0.01	21±0.40	101.08

Table No.5: Cumulative % drug release of Ramipril IR of formulations F1-F10

S.No	Formulations	Time							
		0	5min	10 min	15 min	20 min	25 min	30 min	45 min
1	F1	0	32.36	42.57	55.86	68.58	78.21	84.95	95.9
2	F2	0	26	38.14	51.62	65.5	75.12	78.8	87.07
3	F3	0	23.3	33.52	47.2	54.7	61.64	70.5	77.25
4	F4	0	25.62	37.75	49.9	64.73	78.98	88.61	98.24
5	F5	0	30.05	42.95	55.09	72.23	87.84	97.86	--
6	*F6	0	33.51	45.46	59.91	80.9	98.44	--	--
7	F7	0	36.6	50.08	67.42	89	96.31	--	--
8	F8	0	24.07	35.63	52.78	66.07	80.9	90.73	95.93
9	F9	0	21.57	34.29	43.53	53.75	60.1	66.65	74.74
10	F10	0	19.76	28.6	34.5	67.98	81.76	92.65	97.1

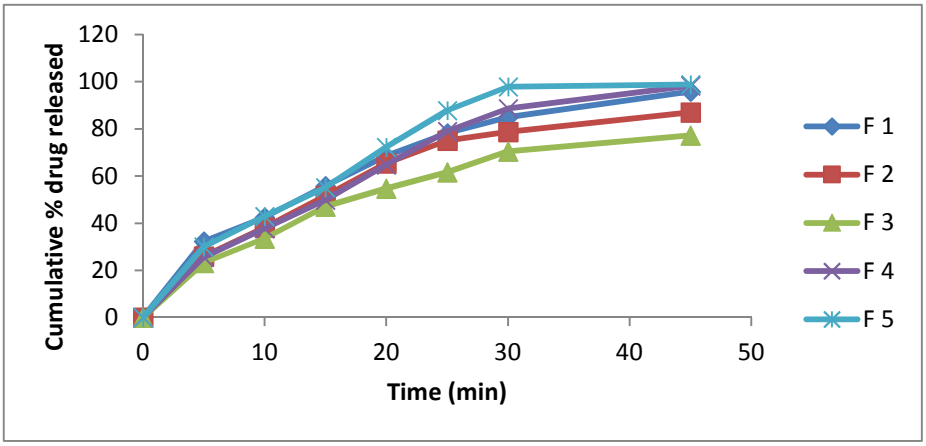

Figure No.1: *In vitro* dissolution profile of F_1 to F_5

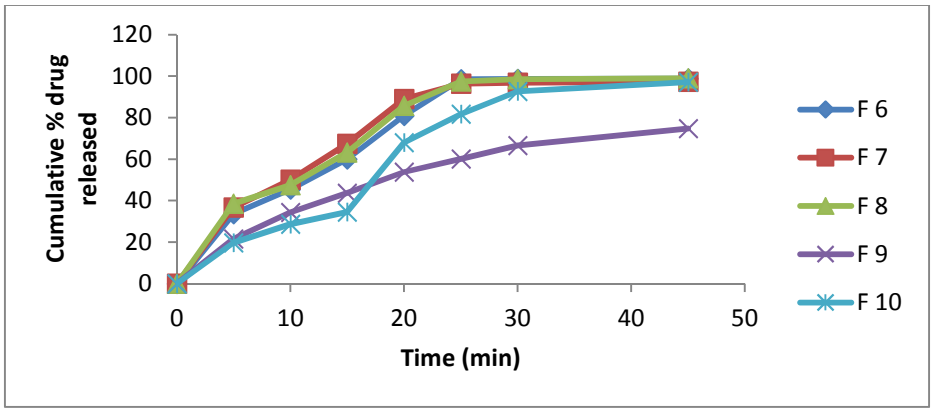

Figure No.2: *In vitro* dissolution profile of F_6 to F_{10}

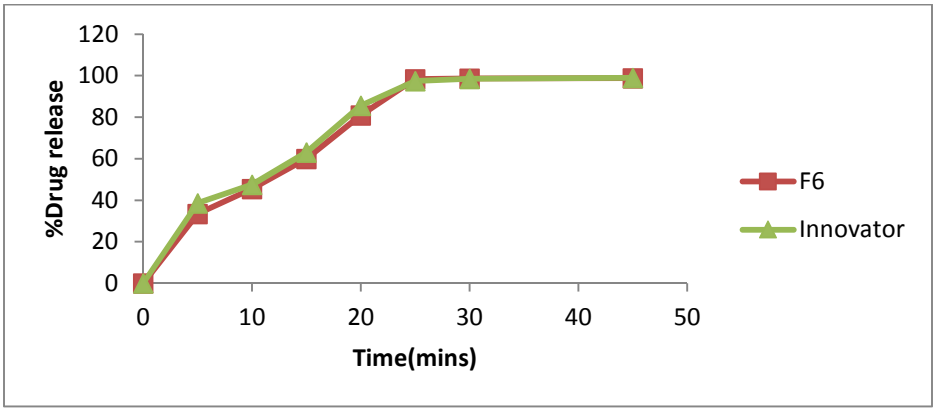

Figure No.3: Comparison *in vitro* drug release of optimized formulation and innovator

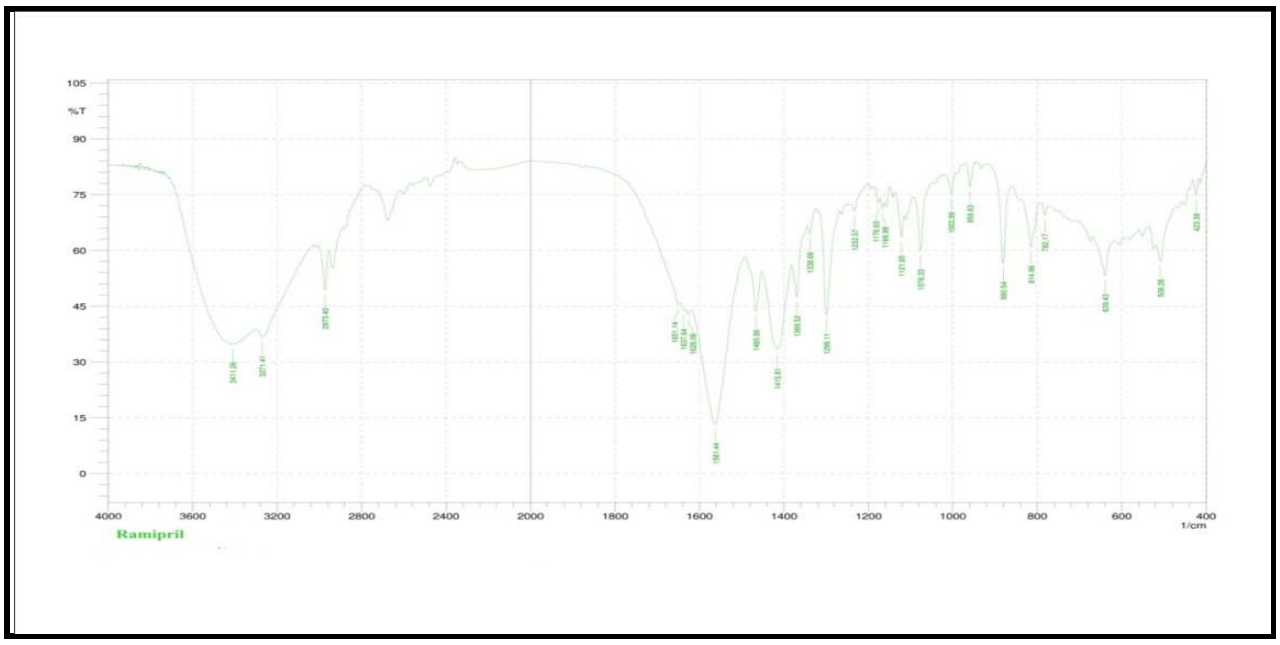

Figure No.4: FT-IR Study of Ramipril

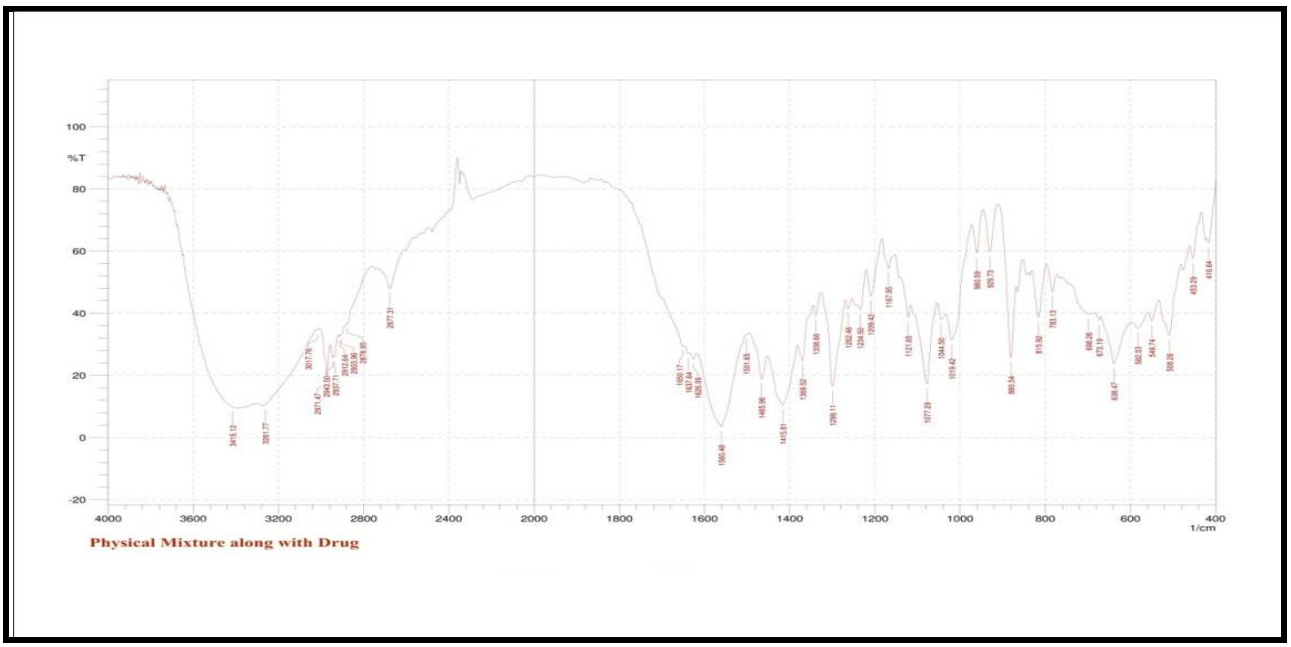

Figure No.5: Physical mixture along with drug

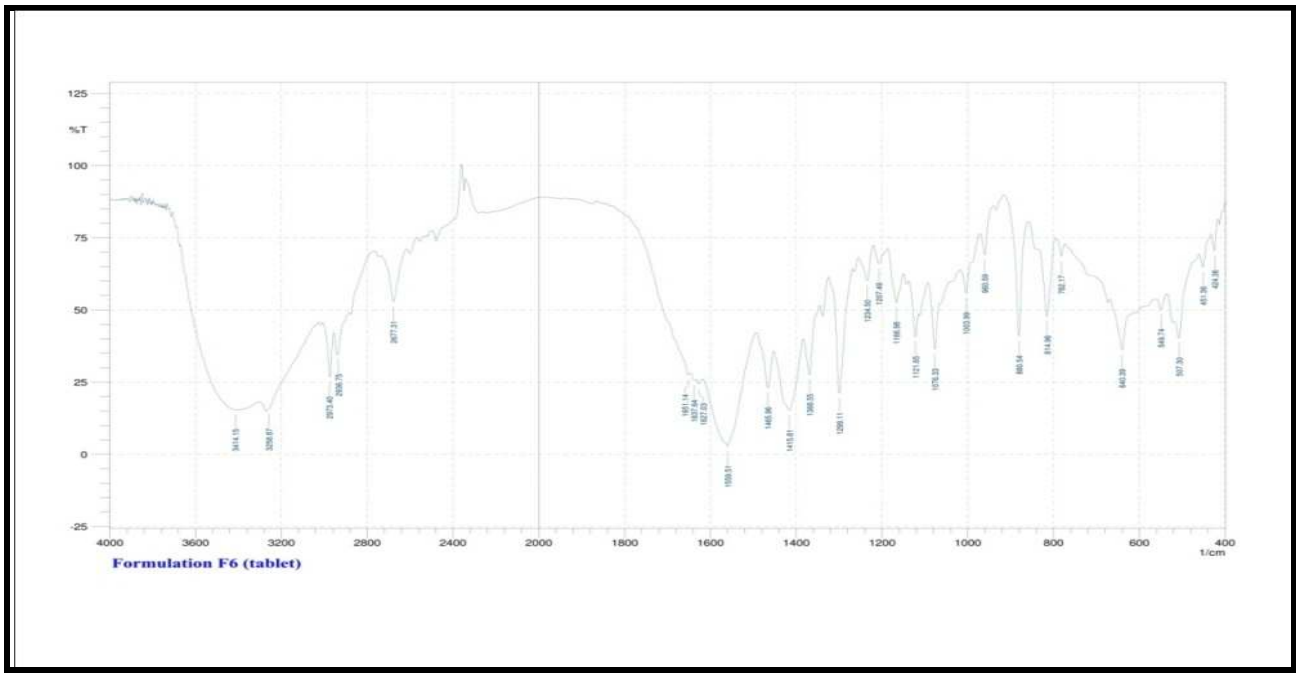

Figure No.6: FTIR of Optimized formulation of Ramipril and excipients

CONCLUSION

The Ramipril IR tablets were successfully prepared by wet granulation method. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index and drug content. The prepared granules were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability and drug content. The optimized formulation contains the average thickness of

2.98mm, average hardness of 5.2, average weight of 149mg, friability of 0.242 and 101.08% of drug content. In the 10 formulation, the optimized formulation was F6 formulation which releases the Ramipril immediately within an hour since the tablet disintegrated within 04 minutes. Those F6 formulation optimized tablets were selected for stability studies and they were kept in two different temperatures. The stability studies confirmed that there was no significant difference over a stability testing period.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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