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FORMULATION AND CHARACTERIZATION OF MOUTH DISINTEGRATING TABLET CONTAINING ANTIHYPERTENSIVE DRUG

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ABSTRACT

In this study mouth dissolving tablet of ramipril was prepared by direct compression method and simultaneously, the drug and excipient compatibility study was conducted to determine and select the best blend of drug and excipient formulation. Mouth dissolving tablet was formulated using different diluents like mannitol (DC), microcrystalline cellulose, with different superdisintegrants like sodium starch glycolate, crosspovidone. The six formulation were design and evaluated for powder parameter like Angle of repose, Bulk density, Tap density, Hausner's ratio, Car's index, after a satisfactory result of these preformulation parameter the tablet were prepared and subjected for evaluation like disintegration time, thickness, diameter, weight variation, friability and finally subjected for dissolution study. Finally the result were analyse and it was found that formulation 6shows better disintegration than other 5 formulation.

KEYWORDS: SSG:-sodium starch glycolate, MCC:-microcrystalline cellulose.

1. INTRODUCTION

Different types of dosage forms i.e tablets, capsules, suspensions, emulsions, syrups, aerosols etc. are available to treat various pathological and emergency conditions. The era belongs to morden technology and new advances have been made by the scientist in the field of drug delivery systems resulting in development of new dosage forms in order to enhance patient compliance. Solid dosage form have greater acceptance because of lack of pain, ease of self

administration, accuracy of dose and most important patient compliance; all these make the oral route most preferred route of administration. Dysphagia (Difficulty in swallowing) is the most common problem associated with frequent used of solid dosage form.[1] This problem is occurs all age group in patients. To overcome this problem it is the best attempt as per as MDT formulation is concern. Bitter drug can also be formulates as MDT by masking the taste of the drug by different method or else by incorporating the various flavouring/ sweetening agents.

Generally there are 3-4 superdisintegrants these are sodium starch glycolate, crosspovidone, crosscarmellose are used in the MDT these are play very important role during the disintegration of the tablet. Various methods are available in the preparation of MDT such as direct compression, mass extrusion, sublimation, lyophilisation, solvent evaporation. Each method has its own merit and demerit but the most useful is direct compression method because of its availability and simplicity.[4]

In the present study the MDT of ramipril were formulated by direct compression and with the help of different concentration of superdisintegrants and diluents.

Ramipril is an Angiotensin Converting Enzyme (ACE) blockers and used in the treatment of hypertension, it is inactive prodrug which is metabolized in liver by the liver esterase enzyme which convert inactive ramipril to active ramiprilat. the half life of ramiprilat is 4-16 hours, which may be extended in liver or kidney damage patients.[5] Ramipril is an unpleasant drug so, an attempt has been made to mask the unpleasant taste of the drug either by incorporating sweetner or else by incorporating the different flvouring agent which gives mouth a pleasant taste.

2. MATERIALS AND METHODS

Ramipril was procured from Ozone International, Mumbai. Other excipients like SSG, CP, mannitol, MCC, Magnesium Stearate, Talc, Flavor were gifted from alkem laboratories, taloja, Mumbai. All ingredients used were of analytical grade.

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied for preparation of MDT because of the availability of improved excipients especially superdisintegrants and sugar based excipients. In many orally disintegrating tablet technologies based on direct compression, the addition of

superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration. This is another approach to manufacture MDT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate. Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.[4]

Direct compression method involve the following two important steps.

1. All the ingridients were weighed accurately and passed through sieve no 40.
2. Ramipril was weighed accurately and mixed it with all other excipients with geometrical ratio in polythene bags.
3. Following parameter were adjusted.

1. Hardness:-3.5 to 4kg/cm^2
2. Thickness:-6mm

4. The blend were compressd using 6mm concave punch.

2.1. Preparation of ramipril mouth disintegrating tablet by direct compression

The accurately weighed amount of blend of powder (API and excipients) properly mixed in polythene bags for 15minutes and lubricants were added in to above mixture and finally the tablet is prepared in 6mm concave shape punch.

Table No-1(Formulation of Batches from F1 to f6)

Ingridients (mg)	F1	F2	F3	F4	F5	F6
Ramipril	2.5	2.5	2.5	2.5	2.5	2.5
Mannitol	104	84	80	84	80	92
M.C.C	10	22	22	22	22	10
Crospovidone	-	8	12	-	-	6
S.S.G	-	-	-	8	12	6
Talc	2	2	2	2	2	2
Mg-Stearate	1	1	1	1	1	1
Flavour	0.5	0.5	0.5	0.5	0.5	0.5

2.2. Preformulation parameter

Preformulation parameter of the tablet blend such as Angle of repose, Bulk density, Tapped density, Car's index, Hausner's ratio were studied successfully.

2.3. Evaluation parameter of powder blend

2.31. Bulk density

Apparent bulk density (g/ml) was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a large cylinder and measured the volume and weight of the powder bulk density was determined by following formula.[3]

bulkdensity=bulk mass/bulk volume

2.32. Tapped density

It was determined by placing a graduated cylinder, containing a known mass of powder on mechanical tapping apparatus, which was operated for fixed number of taps (around 100) until the powder blend volume reaches to minimum. weight of powder in a cylinder and this minimum volume was measured, the tapped density computed.[2]

Tapped density=bulk mass/tapped volume.

2.33. Angle of repose

angle of repose was measured by, glass funnel method in it funnel was secured with its tip at a given height (H) above a piece of graph paper place on a horizontal surface. Powder was allowed to pass through the funnel until the apex of the conical pile touches to the tip of the funnel. The angle of repose was calculate with the formula tan= H/R, where a is the angle of repose and R is the radius of the conical pile, H is a height of pile.[6]

tanø= H/R

2.34. Car's index

It decides the flow properties of granules or powder. It is an indirect method of measuring powder flow from bulk densities, it was developed by carr. It is calculated from the following formula.[10]

Carr's index={(tapped density-bulk density)/tapped density}100

2.35. Hausner's ratio

It is essential to determine the compressibility strength of powders. It was determined from the given equation.[2]

Hausner's ratio=gapped density/bulk density

2.36. Uniformity of weight (Weight Variation)

Twenty tablets was selected at a randomly and average weight was determined. Then individual tablets was weighed and the individual weight will compare with an average weight[10], it was found that all tablet of batches was passes this test.

2.37. Hardness

The tablet crushing load, which was the force required to break a tablet by compression in the radial direction, was determined by using a Monsanto hardness tester.[10]

2.38. Friability

Friability of tablets was measured by using Roche Friabilator. Friability was evaluated from the percentage weight loss of 20 tablets tumble in a friabilator at 100 rpm for 4 minutes. The tablet was dedusted, and the loss in weight cause by fracture or abrasion was recorded as the percentage weight loss. All formulation shows friability less than 1%.[11]

$F=(1-W/Wo)100$

Where,

W=weight of the tablet before test.

W=weight of tablet after test.

2.39. Disintegration Studies

In vitro disintegration time was performed by USP disintegration apparatus at 50 rpm. Phosphate buffer pH6.8 (600ml) is used as a disintegrating medium for this formulation. The temperature was maintained at 37 ± 2^0C. One tablet was placed in each of six basket tubes of apparatus and one disk was added in each tube over the tablet. The time taken for complete disintegration of tablet from stating up to the last small fragment (when no mass remaining in the apparatus) is noted.[7,8]

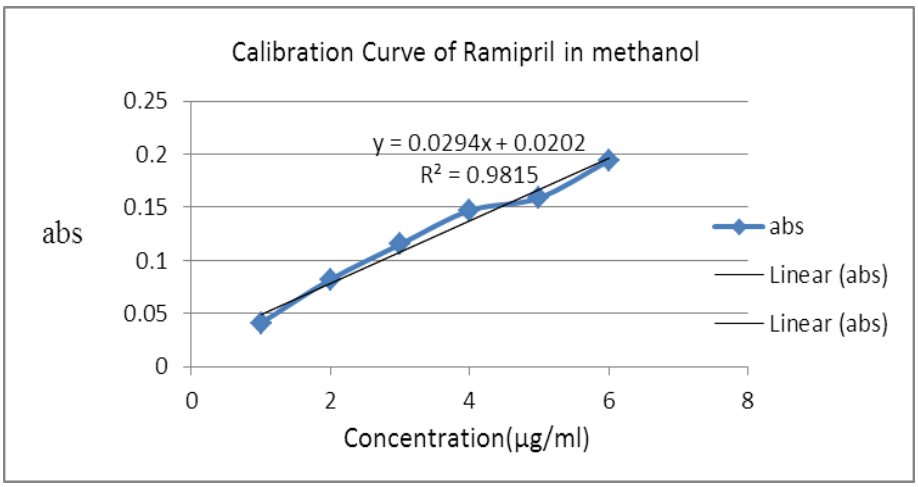
2.40. Dissolution Studies

For vitro Dissolution Studies dissolution apparatus USP type-2(paddle type) is used. In this method placed a 900ml of phosphate buffer solution of having pH6.8 in each of chamber of dissolution apparatus and maintained at 37 ± 2^0C temperature.[9] In a specified time interval (5,10,15,30,60,90). 1ml sample is withdrawn from each chamber of dissolution apparatus and each is replaced with same quantity of solution to maintained a sink conditions of solution.

The withdraw solution is filter through the what man filter paper and make up volume up to 10ml and analysed by UV-Spectrophotometrically at 217.3nm.

2.41. Calibration Curve of Ramipril

Standard calibration curve of Ramipril has been carried out in methanol 10mg of drug is dissolved in 5 ml of methanol and 5 ml of phosphate buffer (pH-6.8) to obtain stock solution of concentration of 100µg/ml. From this 1ml,2ml,3ml,4ml,5ml,6ml was withdrawn and diluted to 10ml to give the solutions of concentration 1-6µg/ml. Absorbance were checked at 217.3nm using UV-spectrophotometer and standard curve was plotted and values of slope, intercept and coefficient of correlation were calculated.[6]



(Fig. No:-1(Calibration Curve of Ramipril bu UV-Spectrophotometer At λ-217.3nm)

3. RESULTS

a. Pre compression Parameter

3.1. Bulk and tapped density

Densities i.e. bulk density and tapped densities were determined and bulk density was found in range of 0.52 to 0.56 gm/cm^3. And the tapped density was found in range of 0.56 to 0.67 gm/cm^3.the results were showed in tablet number-2.

3.2. Carr's Index

The carr's index of blend of powder was determined and it was found in between 5.3 to 22. Which was indicate a good flowability and result were tabulated in table number-2.

3.3. Angle of repose

The angle of repose directly gives an idea about flow properties of powder. The angle of repose of powder blend was determined and it was found in a range 30.41 to 35.75. the angle of repose below 40(θ^0) indicating a good flow properties.

3.4. Hausner's ratio

Hausner's ratio was determined and it was found in range of 1.17 to 1.23 gm/cm^3.

Table No-2 (Pre compression parameter of MDT Formulation)

Formulation Code	F1	F2	F3	F4	F5	F6
Bulk Density (gm/cm^3)	0.52	0.55	0.53	0.53	0.56	0.54
Tapped Density (gm/cm^3)	0.67	0.62	0.62	0.56	0.65	0.60
Carr's index(%)	22	11.29	16.12	5.3	13.84	6.66
Angle of Repose (θ)	32.21	35.37	32.10	35.37	30.41	31.38
Hausner's Ratio	1.23	1.17	1.20	1.05	1.20	1.12

b. Post Compression Parameter

3.5. Hardness

Hardness provides strength to resist the formulation from mechanical shocks. The hardness of tablet was determined and it was found in range of 3.25±0.2 to 3.85±0.1 kg/cm^2. The results were showed in table number-3.

3.6. Thickness

The reasons for carrying out this test to ensure that the tablets are producing are of uniform size, shape and thickness. thr result were presented in following table number-3.

3.7. Weight Variations

The weight variation test is performed and the results were tabulated in following table number-3.

3.8. Friability

The percentage friability of all formulations was found in range of 0.15 to 0.61. Further results were tabulated in table number-3.

3.9. Disintegration time

This test gives an idea about how much time is required for tablet formulation to dissolve completely in medium. The disintegration time was found in range 43 to 55 sec.

Table No-3(Post compression parameter).

Formulation code	F1	F2	F3	F4	F5	F6
Hardness (kg/cm^2)	3.75±0.1	3.45±0.12	3.50±0.01	3.65±0.5	3.85±0.1	3.25±0.9
Thickness (mm)	2.89±0.98	2.99±0.015	2.90±0.12	3±0.1	2.97±0.2	2.99±0.2
Weight Variations	109±1	106±2	109±1	106±1.2	106±1.2	106±2
Friability (%)	0.23	0.20	0.40	0.41	0.61	0.15
Disintegration Time(Sec.)	55	54	54	52	48	43

3.40. Disintegration Studies

In vitro disintegration study was done by USP dissolution apparatus. The disintegration time of following formulation was found between 43 to 55seconds and it was found that formulation F6 showed least disintegration time i.e. 43 seconds. The order for disintegration was found to be F6<F5<F4<F3<F2<F1 respectively.

3.41. Fourier Transforms Infrared Spectroscopy

IR Spectra is basically used for the detection of purity of compound, based on the peaks in a spectra its structure is determined. Aliphatic C-H of CH_3 and aro C-H streching the absorption peaks was found at 3100-2700. The C=O stretching was found at 1750 merged with C-N has undergone hydrogen bonding with the drug to give rise to adduct which is not a chemical product. This hydrogen bond can undergo cleavage during metabolic process. The same drug Ramipril is taken with Crospovidone and Sodium starch Glycolate and subjectedfor IR reading. It has shown presence of all the absorption peaks of the drugs along with C=O of carboxylic peak at 1750. Thus it is clear from this observations that tablet we prepared is containing –H bonding between drug and SSG. There is no interaction between the drug and superdisintegrants**.**

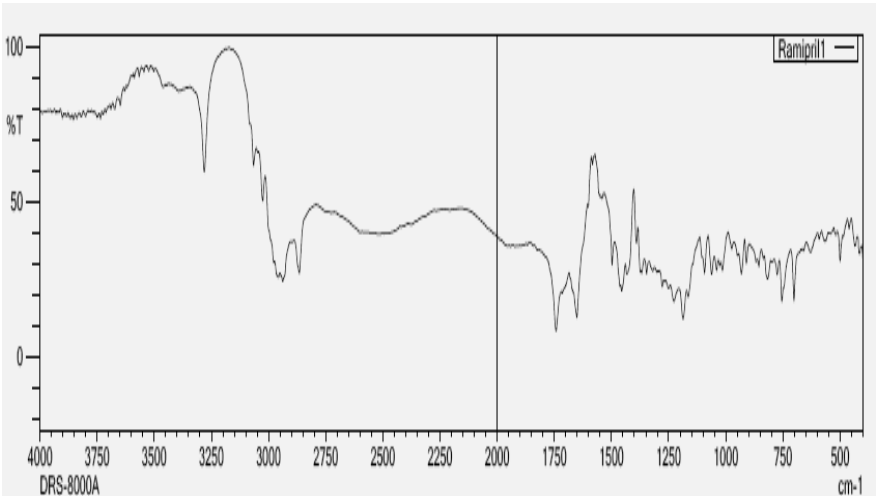


Fig No-2 FTIR Spectra of pure drug(Ramipril).

Table No-4(Characterstics Bands of Ramipril.)

Functional Group	Bandwidth
O-H Sterching	3600-3400
N-H Steching	3400-3200
Aro C-H Streching	3100-2900
Ali C-H Streching	2900-2700
C=O Sterching	1750
Ester Linkage	1630
C-N Streching	1300-1100
C-O-C Steching	1600-1400

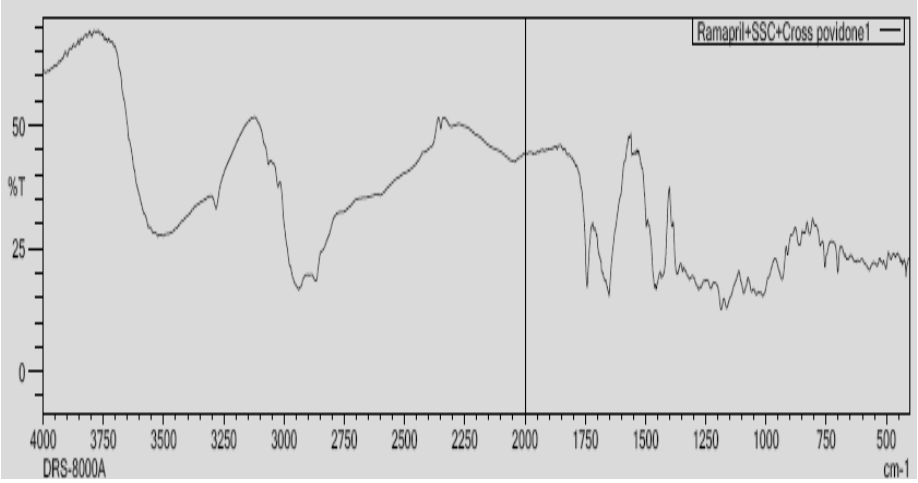


Fig. no-3(FTIR Spectra of Ramipril and superdintegrants)

3.42. Differential Scanning Colorimetry

Differential scanning colorimetry indicates the quantitative detection of all processes in which energy is required or produced i.e endothermic or exothermic. The thermograms of Ramipril, Crospovidone, Sodium Starch Glycolate, and mixture of all them presented in fig(4-5). Ramipril showed melting endotherm at 106.53^{o}C with enthalpy of fusion 21.81J/gm. The pure crospovidone showed melting endotherm at 165^{o}C with enthalpy of 77J/gm. The pure Sodium Starch Glycolate showed melting endotherm at 157^{o}C, were as the thermogram of mixture of all ingridients along with superdisntegrants was drawn and it was found that the the intensive peaks of Ramipril was absent, it might be due to the solubilization of drug in superdisintegrants. This indicates that the drug was completely dispersed in superdisintegrants.

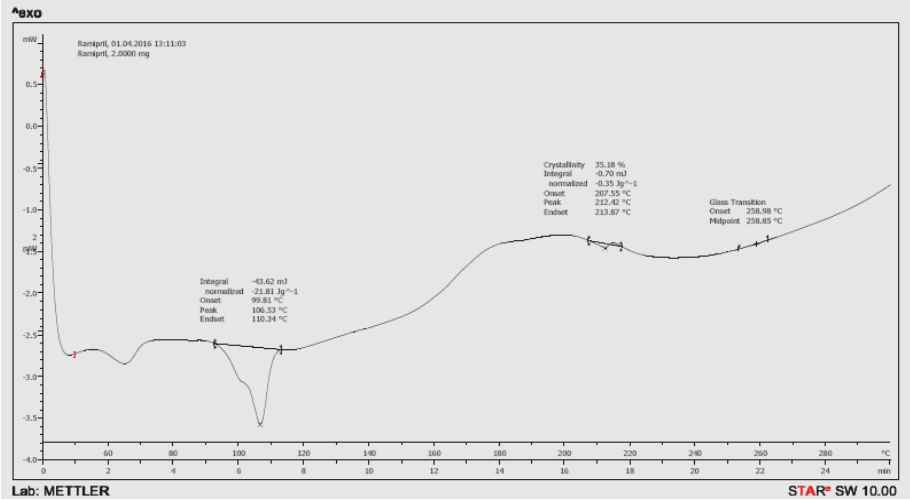


Fig. no-4(DSC Thermogram of Ramipril)

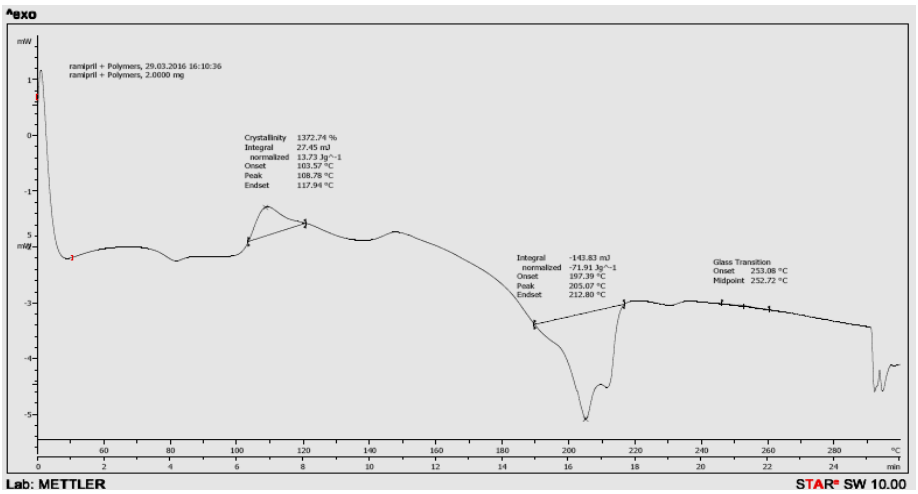


Fig. no-5(DSC Thermogram of Ramipril and mixture(SSG,CP)

3.43Dissolution Studies

Dissolution rate of any formulation is always depends upon its wetting time of that formulation we can also say it is directly proportional to dissolution rate of the formulation. Here F6 is having less disintegrating time than of other formulation. In vitro dissolution study of all formulation was done in all formulation formula F6 is shows a best results of in vitro dissolution study.6 batches of MDT were evaluated i.e. from F1 to F6 and F6 show a maximum % drug release at the end of dissolution study: USP type 2(paddle apparatus) was used at 100rpm at 37 ± 2^0C in 900ml of phosphate buffer pH6.8 as a dissolution medium .1ml sample is withdraw at a specific time interval same amount of solution is added into the dissolution chamber to maintained sink conditions. The withdraw solution is further diluted with 9ml of buffer solution having pH6.8 and this solution is further analysed by using UV-Spectrophotometer.

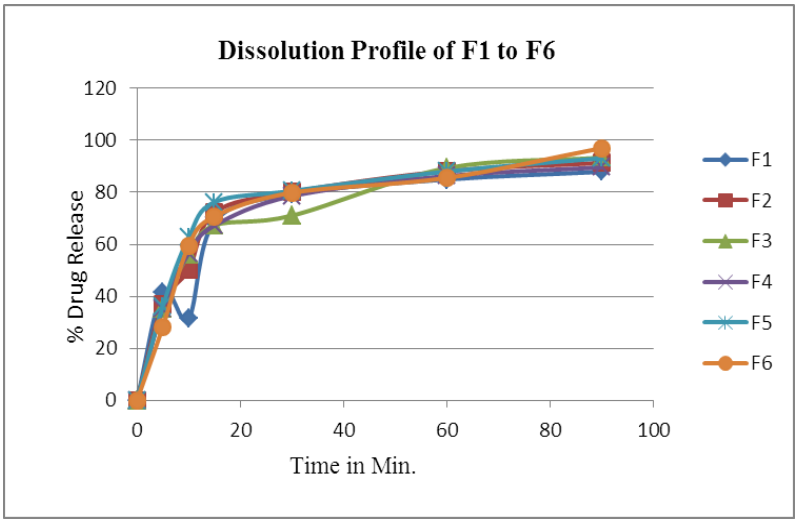


Fig.no-6(Dissolution profile of F1 to F6)

4. DISCUSSION

The present study was carried out to prepare Ramipril mouth disintegrating tablet that can be used to treat hypertension. The purpose of this study was to enhance patient compliance and provide rapid inset of action. Moreover mouth dissolving dosage form is very important for geriatric and pediatric patients who have difficulty in swallowing tablets or in situations where have no access of water.

For preparation of MDT various superdisintegrants like Crospovidone (4,8mg), sodium starch glycollate (4,8mg) are used in different concentration along with other additives used for preparation of MDT. The tablets were prepared by direct compression method. There are total 6 formulations were prepared and evaluated.

The formulations were evaluated for various preformulation properties such as angle of repose, bulk density, tapped density, percentage compressibility, flowability. It was found that all formulations had good flowability which indicates its suitability for direct compression.

Tablets were tested for evaluation parameter such as weight variations, hardness, content uniformity, in vitro-disintegration time, friability and dissolution study.

In all formulations thickness varies from 2.89 to 3.0 mm and hardness of optimized batch was found to be 3.25kg/cm^2. No variation in the hardness was found in optimized batch which clearly indicates that the blending was uniform.

The prepared tablet in optimized formulation possesses good mechanical strength with sufficient hardness. Friability was less than 1% in the entire batches. The entire tablet from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of 5% of the weight.

The in-vitro disintegration time for all the formulations varied from 43to 55sec. The rapid disintegration was seen in the formulation containing crospovidone and sodium starch glycolate. This is due to rapid uptake of water from the medium, swelling and burst effect. It was also noticed as the disintegrants concentrations was increased from the time taken for disintegration was reduced. It was found that the wetting time was rapid in crospovidone followed by sodium starch glycolate. The drug release was found to be more than 65% after 15 min.

Thus from result it was concluded that formulation (F6) of MDT tablets containing ramipril prepared by direct compression through incorporating various superdisintegrants in varying concentrations are very effective.

5. CONCLUSION

Mouth disintegrating tablet (MDT) of ramipril were successfully prepared by using direct compression method. MDT will surely enhance patient compliance, low dosing and rapid onset of action, increased bioavailability, good stability and its popularity in the near future. From this study, it can be concluded that direct compression method showed better disintegration and drug release.

The prepared tablets disintegrate within few seconds without need of water, there by enhance the absorption leading to its increased bioavailability.

MDT need to be formulated for geriatric, pediatric, bedridden, psychotics patients, for those patients who are busy in travelling, patients who are may not have access of water.

Among the various combinations of diluents and disintegrants used in the study, formulation (F6) that was formulated using crospovidone, sodium starch glycolate exhibit quicker disintegration of tablets than compared to other 5 formulations.

Due to this wide significance of MDT, this drug delivery system may lead to better patient compliance and ultimately in clinical output. Future might witness many more classes of drugs developed in the form of MDT.

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