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DESIGHN AND EVALUATION OF A NEW FORMULATIONS OF ENALAPRIL MALEATE 20 MG TABLET IN A TIME EFFICIENT AND ON A LARGE INDUSTRIAL SCALE

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ABSTRACT

Objective: Aim of present study was to provide stable formulation of enalapril maleate 20 mg that can be manufactured simply, in a time efficient by using direct compression and on a large industrial scale.

Methods: Four Enalapril maleate formulations were prepared using three different lubricants consisting of Glyceryl monostearate, sodium stearyl fumarate and zinc stearate and the same stabilizer citric acid anhydrous. Tablets were prepared by employing direct compression technique and evaluated for post compression parameters such as determination of appearance, disintegration time, friability, dissolution, assay and related substances as well as stability and industrial difficulties during manufacturing like sticking. The tablets were packed in blister Aluminum/Aluminum. The four formulations were subjected to stability studies as per ICH guidelines at temperatures and humidity of 40 C° / 75% RH for six months. Formulation III and IV were kept for 12 months at the same conditions. Dissolution profile comparison between the best formula IV and Renitec 20 mg tablets, Merch Sharp& Dohme B.V., for specific post approval changes was achieved to assure similarity in drug release profile and signal bioequivalence.

Results: showed that formulation IV consisting of prosolv SMS 900, Lactopress anhydrous 250, aerosil, citric acid anhydrous and zinc stearate emerged as the best formulation.

Conclusion: thus our studies demonstrated the critical role of citric acid in protecting enalapril maleate and assured the inability of using glyceryl monostearate as lubricant.

Keywords: Enalapril maleate, Tablets, Direct compression, Stability.

INTRODUCTION

Enalapril maleate, an angiotensin converting enzyme inhibitor [1], known through U.S. Pat. No. 4,374,829 is useful in the treatment of essential and renovascular hypertension. It is highly susceptible to decomposition and undergoes autocyclization to form diketopiperazine. In addition enalapril maleate may form diacids via hydrolysis or may undergo oxidation resulting in discoloration when formulated into pharmaceutical dosage forms [2]. Through extensive comparative experiments using various combinations of excipients, it was demonstrated that the presence of microcrystalline cellulose, starch, and magnesium stearate all contributed to the decomposition of enalapril maleate. Further comparative experiments enabled the following additional conclusions:

The use of the dibasic calcium phosphate or tribasic calcium phosphate as filler also results in excessively rapid decomposition.

There is little or no decomposition caused by use of various water-soluble carbohydrates as fillers, including specifically lactose anhydrous, lactose monohydrate, compressible sugar, dextrates, dextrose, dextrin, mannitol and sorbitol.

The rat of decomposition is almost as high if magnesium stearate is replaced by calcium stearate. However, surprisingly, it was found that the rate of decomposition is substantially decreased, if any of stearic acid, zinc stearate or glyceryl monostearate is used as lubricant in place of magnesium stearate.

The inclusion of any starch, crosscarmellose sodium, crospovidone or sodium starch glycolate as disintegrant consistently gave higher rates of decomposition than when no disintegrant was used[3].

Warner-Lambert Company discloses a pharmaceutical composition containing from 1 to 70% by weight of an ACE inhibitor and about 1-90% by weight of the stabilizer which contains either ascorbic acid alone or at least 10% w\ w of ascorbic acid in combination with organic acids such as fumaric, maleic and citric acid as a cyclization and\or hydrolysis inhibitors with at least one lubricant and\or excipient [4].

A principal objective of patent U.S. Pat. No. 6,296,871 B1 is to provide a process for the preparation of a stable oral pharmaceutical composition in the form of tablets or capsules comprising enalapril maleate as the active ingredient and pharmaceutical excipients wherein at least one excipient is maleic acid or an edible desiccant as one of

The pharmaceutical excipient significantly reduces the rate of degradation of enalapril maleate in the formulation. Pharmaceutical excipients that may be used in the invention may include diluents such as microcrystalline cellulose, lubricants such as magnesium stearate, and disintegrants such as cross-linked carboxy methyl cellulose sodium, which have been reported to be incompatible with enalapril maleate in prior art references [5]. There is disclosed a stable pharmaceutical solid composition comprising enalapril as the sodium salt, which is made by the steps of:

Mixing enalapril maleate with a carrier, an alkaline sodium compound, and water.

Drying the wet mass, and;

Further processing the resultant dried mass into tablets.

When the water is added in the aforesaid process, an acid-base reaction occurs which converts the enalapril maleate into the more stable enalapril sodium salt. However a disadvantage of such processing is that the active ingredient does not retain its chemical identify as it is converted from enalapril maleate to enalapril sodium. But it provides excellent stability and great flexibility in the choice of excipients. Merch Sharp &Dome B.V. is one of many companies that prepare enalapril maleate tablets by this way[6].

In light of the foregoing**,** a principal object of the present work is to provide a process for the preparation of a stable formulation of

enalapril maleate, that can be manufactured simply, in a time efficient, by using direct compression and on a large industrial scale. We depended on above compatibility studies between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product, but we choose to use citric acid alone as a stabilizer.

MATERIALS AND METHODS

Enalapril maleate was purchased from zhejiang Huahai (India), Lactopress anhydrous 250 (ß-lactose anhydrous pharmaceutical grade conform USP/NF, Ph.Eur, JP) was purchased from DOMO (Germany), Prosolv SMCC 90 (silicified microcrystalline cellulose NF) was purchased from JRS pharma (Germany), aerosil 200 was purchased from WACKER (Germany), citric acid anhydrous was purchased from Weifang Ensign Industries (China), zinc stearate was purchased from Magnesia (Germany), crosscarmellose sodium was purchased from JRS pharma (Germany), glyceryl monostearate was purchased from Fin Organics Industries (India) and sodium stearyl fumarate was purchased from Rank (India).

Formulation of tablets

Enalapril formulations were prepared using three different lubricants consisting of glyceryl monostearate, sodium stearyl fumarate and zinc stearate. Tablets were prepared by employing direct compression technique and evaluated for post compression parameters such as determination of appearance, disintegration time, friability, dissolution, assay and related substances as well as stability and industrial difficulties like sticking. The ingredients of formulations are listed in table 1.

All the materials were passed through 1 mm screen prior to mixing and mixing was by using V-blender. Process of manufacturing of the formulations comprises the following ordered steps of:

Mixing Enalapril maleate with milled citric acid anhydrous.

Mixing last mixture geometrically with Lactopress anhydrous 250 (mixture 1).

Mixing aerosil and Prosolv, crosscarmellose formulation 3, (mixture 2).

Mixing (mixture 1) with (mixture 2) to get (mixture 3).

1- Lubricating (mixture 3) with glyceryl monostearate (formulation I), glyceryl monostearate and sodium stearyl fumarate (formulation II) and zinc stearate (formulation III and IV). The powder mixture was then compressed using a compression machine Cadmach CTX 37 into tablets of average weight 200 mg, upper punch is embossed with heart shape, die is scored and its diameter 8mm, thickness is 3.5-4.1 and at hardness 70 to 90 N. the tablets were packed in blister Aluminum/ Aluminum.

Table 1: ingredients of the four formulations

Ingredients	Quantity mg/tablet			
	Formulation I	**Formulation II**	**Formulation III**	**Formulation IV**
Enalaprila maleate	21.6 (overage* 8%)	21.6 (overage* 8%)	21.6 (overage* 8%)	21.6 (overage* 8%)
Prosolv SMCC 90	25	25	25	25
Lactopress anhydrous 250	123.4	122.4	140.5	141.5
Aerosil 200	2	2	2	2
Milled citric acid anhydrous	5	5	5	5
glyceryl monostearate	23	23	-	-
sodium stearyl fumarate	-	1	-	-
crosscarmellose sodium	-	-	1	-
zinc stearate	-	-	4	4
total	200	200	200	200

*Use of an overage of a drug substance to compensate for expected degradation during products shelf life because enalapril maleate decomposes easily.

Batch size

Pilot batch for solid dosage form is generally taken to be, at minimum, one-tenth that of full production or 100,000 tablets or capsules [7]. Our batch was 20 kg equal to 100,000 tablets of each formulation.

Stability Studies

The selected formulations were subjected for stability studies by keeping samples in their final packing in stability chamber (Binder, Germany). The formulations were stored at 40 C°/ 75% RH for six months as per ICH guidelines [8]. Formulation III and IV were kept for 12 months at the same conditions. The formulations were subjected to different tests such as appearance, disintegrating time, friability, dissolution, assay and related substances.

Hardness, thickness and diameter determination

20 tablets were taken randomly and hardness, thickness and diameter were measured using hardness tester (pharmatron Dr. Schleuniger).

Friability testing

20 tablets were taken randomly and placed on a sieve. Loose dust was removed with the aid of air pressure or soft brush. Tablets samples were weighed accurately and placed in friabilator (pharmatron Dr. Schleuniger). After the given number of rotations (100 rotations/4min) loose dust was removed from tablets as before. Finally tablets were weighed. The loose in weight indicates the ability of tablets to withstand this type of wear. A maximum loss of mass not greater than 1.0 per cent is considered acceptable for most products[9].

Disintegration test

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from gastrointestinal tract [10]. Disintegration time was measured for 6 tablets by inserting disks using 900 ml purified water at 37±2 C° in disintegration apparatus (pharmatron Dr. Schleuniger). The maximum time for most uncoated tablet is 30 minutes [11].

Dissolution test

Dissolution test was adopted from USP 34 (2011) by using dissolution apparatus (pharmatron Dr. Schleuniger). In 900 ml of medium, medium solution was prepared by mixing 250 ml of 0.2 M of monobasic potassium phosphate with 112 ml of 0.2 M of sodium hydroxide, diluting with water to 1000 ml and adjusting the pH 6.8 with phosphoric acid. Six tablets were operated at 50 rpm for 30 minutes; about 10 ml of each sample solution (test preparation) was withdrawn and filtered. Buffer solution was prepared by dissolving 1.38 g of monobasic sodium phosphate in about 800 ml of distilled water, adjusting the PH 2.2 with phosphoric acid and diluting with water to 1000 ml. mobile phase was prepared by mixing filtered and degassed buffer solution and acetonitrile (75:75). For standard preparation, an accurately weighed quantity of enalapril maleate RS was dissolved in dissolution medium to obtain solution having known concentration, about 0.022 mg of enalapril maleate per ml.

Dissolved amount of enalapril maleate tablet in dissolution medium was determined by using High Performance Liquid Chromatography (HPLC) equipped with 215 nm detector.

Chromatographic system: The liquid chromatography is equipped with a 215 nm detector and a 4.6 mm × 25 cm column that contains 5 µm packing L7. The column temperature is maintained at 50, and the flow rate is about 2 ml per minute.

The dissolution specification limit is 80% (Q) after 30 minutes(USP34).

Assay of Enalapril maleate using HPLC

Assay of enalapril maleate using HPLC (Shimadzo) was adopted from USP 34 (2011). The assay of different formulations of enalapril maleate tablets was carried out using HPLC, Buffer solution was prepared by dissolving 2.76 g of monobasic sodium phosphate in about 1800 of distilled water, adjusting the PH 2.2 with phosphoric acid and diluting with water to 2000 ml. Mobile phase was prepared by mixing filtered and degassed buffer solution and acetonitrile (75:25). For sample preparation, was by weighing and powdering 20 tablets of each formula. Average tablet weight was calculated. An accurately weighed portion (eq. to 20.0 mg of enalapril maleate) of the powder was transferred to a 100 ml volumetric flask, dissolved with mobile phase and diluted to volume with the mobile phase.

Standard preparation was prepared by dissolving an accurately weighed quantity of USP enalapril RS in mobile phase to obtain a solution having known concentration of about 0.2 mg per ml, equal volumes (about 20 µl) of sample preparation and standard preparation were injected separately into chromatograph and chromatograms were recorded at 215 nm. Same chromatographic system of dissolution test was applied in assay of Enalapril maleate. the relative standard deviation for replicated injections is not more than 2.0% for the enalapril peak, and responses for the enalaprilat peak agree within 5%.The assay specification limit is 90% -110% (USP 34).

Determination of Related compounds

Buffer solution, mobile phase, standard preparation, and chromatographic system proceed as directed in the Assay and test preparation used as Assay preparation. Enalapril diketopiperazine solution was prepared according to USP 34. All related compounds are set up to ≤5 % (USP 34)

Dissolution Profile Study

Dissolution profile comparison between the best formulation, formulation IV, and Renitec 20 mg tablets, Merch Sharp& Dohme B.V., for specific post approval changes was achieved to assure similarity in drug release profile and signal bioequivalence.

Renitec tablets are manufactured by wet granulation method and consist of lactose monohydrate, sodium bicarbonate, maize starch, pregelatinized maize starch, magnesium stearate and iron oxide E172. 12 individual values for every time point for each formulation and minimum of three time points (zero excluded) are taken. Dissolution measurements should be under exactly the same condition and same dissolution time points for both profiles. Only one measurement should be considered after 85% dissolution of both products**.** To allow use of mean data, the percent coefficient of variation at the earlier time points should not be more than 20 %, and at other time points should not be more 10% [7].

RESULTS AND DISCUSSION

Evaluation of Post Compression Parameter of Enalapril Maleate Tablets

The ingredients of formulations as shown in table 1 include anhydrous lactose DC as filler and binder, which is water soluble so the formulations may dissolve sufficiently rapidly in gastrointestinal fluids so as not to require use of a disintegrant. It has no decomposition effect on enalapril maleate and shows good compressibility so it is the optimal filler for tableting with enalapril maleate. Prosolv SMCC 90 is silicified microcrystalline cellulose composed of 98% microcrystalline cellulose and 2% colloidal silicon dioxide. It is ideally suited to direct compression formulations where it has advantages in both flow and compatibility. Citric acid anhydrous is used as a stabilizer to provide excellent stability in spite of the presence destabilizing excipients such as SMCC 90 and crosscarmellose sodium and thus provides greater flexibility in the choice of excipients for the formulation of enalapril maleate tablets. Aerosil 200 is colloidal silicon dioxide, it is used a glidant. Crosscarmellose sodium is a disintegrant. Glyceryl monostearate is lubricant and has no decomposition effect, it was used in high quantity in formulation I and II to get better lubrication, it has low melting point 55-60 C°[12]. Zinc stearate is lubricant and has no decomposition effect and sodium stearyl fumarate is also lubricant agent. Most of the pharmaceutical manufacturers are using wet granulation method for the formulation of Enalapril maleate tablets. Direct compression method can be adopted as alternative method because it is simple and economic, saving can occur in a number of areas including reduced processing, time and thus reduced labor costs, fewer manufacturing steps and pieces of equipments, less process validation and a lower consumption of power. The tablet quality is greatly improved when prepared by direct compression as this method does not require moisture and heat for processing [13]. Hence, our research was to develop new formulation using direct compression method.

The tablets of different formulations (I to IV) were evaluated for various parameters: appearance, disintegration test, friability, dissolution test, assay and related substances.

Physical parameters of the four formulated Enalapril maleate 20 mg tablets are shown in Table 2. Appearance test results for formulations III and IV were within the specification i.e. white heart shape scored tablets, but they were in formulation I and II out of specification, the tablets had white color with yellow spots, this was due to high used quantity of glyceryl monostearate which has pale yellow color. Disintegration test were conducted and results for all formulations were found within USP limits. As the maximum time for most uncoated tablets is 30 minutes [10]. Disintegration time for formulations I and II were relatively high 16-17 minutes this was also due to high used quantity of glyceryl monostearate which was used as lubricant. But it was relatively low in formulations III and IV about 6 minutes when glyceryl monostearate was replaced with zinc stearate. Friability test results for tablets were within the specified limits i.e. friability % for all formulations were less than 1%. Dissolution test performed for all four formulations according to USP using High Performance Liquid Chromatography (HPLC). Out of four formulations none has the dissolution less than the specified limit i.e. all samples has the dissolution not less than 80% of the labeled amount of enalapril maleate in 30 minutes. Results of assay for all formulations were within the USP limits. According to USP enalapril maleate tablet contain not less than 90% and not more than 110% of the labeled amount of $C_{20}H_{28}N_2O_5.C_4H_4O_4$. Related substances test performed for all four formulations according to USP and results for tablets were within the specified limits i.e. related substances % for all four formulations were less than 5%. All the above tests performed as per compliance of the Good Laboratory Practices. From the results, it could be concluded that the formulations III and IV were more preffered formulations because tablets had white color and lower disintegrating time but formulation IV was the best formulation because it had lesser component than formulations III i.e. crosscarmellose sodium had no improvement effect on disintegrating time. Results are shown in tablets 2, 3, 4 and 5. The tablets of different formulations (I to IV) were evaluated for their industrial facilities during manufacturing. Pilot batches, up to 20 kg, have been manufactured for each formulation and the results showed that in formulation I, there were problems in compression like sticking occurred after compression more than 7 kg, in addition to decreasing in dissolution rate also happened after compression about 7 kg. Glyceryl monostearate failed in lubrication after compression more than 7 kg. Decreasing in dissolution rate was due to low melting point of glyceryl monostearate 55-60 C°. In formulation II when we used 0.5 % sodium stearyl fumarate as assisted lubricant for preventing sticking to tooling, we faced same above problems. Using zinc stearate in formulation III and IV was the best choice to get good dissolution and compression over the entire batch.

Stability Studies

The stability studies revealed that there was no change in the various pharmaceutical parameters of the tablets namely appearance, disintegrating test, friability, dissolution test, assay and related substances. And There was no significant change occurred at any time during the six months. Indicating that the formulations were stable at the condition to which they were exposed. This is back to particular selection of excipients and stabilizing role of citric acid. Thus, we may conclude that the drug does not undergo degradation on storage. Formulation III and IV were kept for 12 months at the same

conditions, there was significant change in assay after 12 months in both formulations but assay and related substances were stayed within the specifications, so we recommend not to add overage while using last two formulations. Results are shown in tables 3, 4, 5 and 6.

Dissolution Profile Study

Dissolution Profile comparison between formulation IV and Renitec 20 mg tablets, Merch Sharp &Dohme B.V., for specific post approval changes was achieved to assure similarity in drug release profile and signal bioequivalence. Study showed that 85% of both products were dissolved in 15 minutes. This case of very rapidly dissolving products

and dissolution profile may be accepted as similar (FDA). The percent coefficient of variation at the earlier time point (5 minutes) was 14.98 for formulation IV and 8.89 for Renitec while it was 4.18 for formulation IV and 2.18 for Renitec at time point (10 minutes) and it was 3.83 for formulation IV and 2.52 for Renitec at time point (15 minutes). This allowed us to use the mean data. Results are shown in figure 1.

Table 2: Physical parameters of four formulated Enalapril maleate 20 mg tablets

Physical parameters	Limits	Reference
Appearance	white heart shape scored tablets	In house specification
Hardness	70 - 90 N	In house specification
thickness	3.5-4.1	In house specification
diameter	8mm ± 0.1	In house specification
Disintegration Time	Not more than 30 minutes	USP34
Friability	Not more than 1.0 %	BP 2011
Dissolution	80% (Q) after 30 minutes	USP34
Assay	90% -110%	USP34
Related substances	≤5 %	USP34

Table 3: stability studies results with initial values for formulation I

Appearance	Initial values	1 month	2 month	3 month	6 month
	White with yellow spots heart shape scored tablets	White with yellows spots heart shape scored tablets	White with yellow spots heart shape scored tablets	White with yellow spots heart shape scored tablets	White with yellow spots Heart shape scored tablets
Disintegration Time	18 min	17 min	18 min	18 min	18 min
Friability	0.20%	0.22%	0.24%	0.24%	0.23%
Dissolution	98.56%	99.62	99.00%	98.80%	98.50%
Assay	98.56%	102.30%	102.29%	100.89%	99.90%
Related substances	1.20%	1.29%	1.38%	1.10%	1.37%

RSD< 2% for all results

Table 4: stability studies results with initial values for formulation II

Appearance	Initial values	1 month	2 month	3 month	6 month
	White with yellow spots heart shape scored tablets	White with yellow spots heart shape scored tablets	White with yellow spots heart shape scored tablets	White with yellow spots heart shape scored tablets	White with yellow spots Heart shape scored tablets
Disintegration time	17 min	18 min	18 min	18 min	18 min
Friability	0.22%	0.21%	0.22%	0.22%	0.22%
Dissolution	98.02%	97.20%	99.16%	98.80%	97.50%
Assay	101.30%	98.28%	101.52%	97.60%	97.87%
Related,substances	1.39%	1.50%	1.74%	2.25%	2.00%

RSD< 2% for all results

Table 5: stability studies results initial values for formulation II

Appearance	Initial values	1 month	2 month	3 month	6 month	12 months
	white heart shape scored tablets	white heart shape scored tablets	white heart shape scored tablets	white heart shape scored tablets	white heart shape scored tablets	white heart shape scored tablets
Disintegration time	6 min	7 min	6 min	6 min	7 min	7 min
Friability	0.18%	0.19%	0.19%	0.18%	0.20%	0.20%
Dissolution	100.78%	99.00%	99.16%	98.30%	97.90%	98.10
Assay	104.47%	100.27%	101.50%	101.03%	100.27%	95.26%
Related, substances	1.30%	1.34%	1.49%	1.53%	1.47%	1.46%

RSD< 2% for all results

Table 6: stability studies results initial values for formulation IV

Appearance	Initial values	1 month	2 month	3 month	6 month	12months
	white heart shape scored tablets	white heart shape scored tablets	white heart shape scored tablets	white heart shape scored tablets	white heart shape scored tablets	white heart shape scored tablets
Disintegration time	6 min	7 min	7 min	7 min	7 min	7 min
Friability	0.17%	0.17%	0.16%	0.18 %	0.19%	0.19%
Dissolution	103.78%	100.00%	98.20%	98.98%	97.88%	97.90%
Assay	104.50%	102.27%	100.50%	99.41%	100.20%	95.12%
Related substances	1.23%	1.10%	1.53%	2.23%	2.20%	2.03%

RSD< 2% for all results

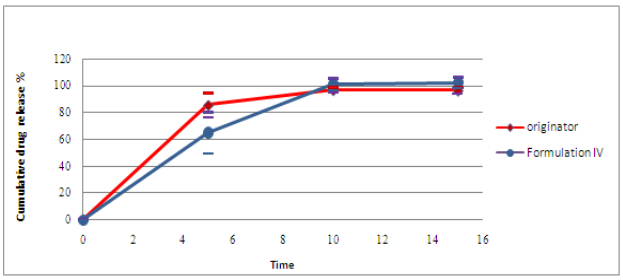

Fig. 1: Dissolution profile of Formulation IV and Originator Tablets.

CONCLUSION

The results of our investigation showed that formulation IV which is consisted of Prosolv SMCC 900, lactopress anhydrous, aerosil, citric acid and zinc stearate has the optimized formulation and provided stable formulation of enalapril maleate 20 mg that can be manufactured simply, in a time efficient and on a large industrial scale. Overall, the results assured that zinc stearate is preferred lubricant from the viewpoint of lubrication and stability while using direct compression method, and Inability of using glyceryl monostearate as lubricant although it has no decomposition effect on stability of enalapril maleat. Also, our study demonstrated the role of citric acid in protecting enalapril maleate without any assisted stabilizer.

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