

DESIGN AND EVALUATION OF A NEW FORMULATION OF ENALAPRIL MALEATE TABLET

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ABSTRACT

Enalapril maleate, one of the Angiotensin converting enzyme (ACE) inhibitor is effective in the treatment of hypertension. Enalapril maleate is selected for the present study. The aim of this study was to develop a new formulation of Enalapril maleate tablet and its comparative evaluation with other formulations of Enalapril maleate tablet that are listed in the local index of registered pharmaceutical products. To accomplish this task, a new formulation of Enalapril maleate tablet has been developed by direct compression method. All formulation tablets with 5mg potency were selected and the new formulation tablets were also developed with 5mg potency. For new formulation as well as for six available formulations of Enalapril maleate tablets, various pharmaceutical parameters namely weight variation, thickness, hardness test; friability test, disintegration test, dissolution test and pharmaceutical assay were performed in accordance with United States Pharmacopeias (USP). The results of all the above tests were within the specified limits as mentioned in USP, whereas hardness test results for two formulations were deviated from the specified limits. It is concluded that direct compression can be used as an alternate method for the manufacture of Enalapril maleate tablet.

Keywords: Direct compression, Enalapril maleate, comparative evaluation, pharmaceutical parameters.

INTRODUCTION

The oral route of drug administration is the most important method of administering drugs for systemic effects. Nevertheless, it is probable that at least 80% of all drugs to produce systemic effect are administered by oral route. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effects by the oral route. Of drugs that administered orally solid dosage forms represent the preferred class of product. Of the two oral solid dosage forms commonly employed, the tablets and the capsule, the tablet has a number of advantages. The following may be cited as the primary potential advantages of tablets.

1. They are unit dose form and they offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
2. Their cost is lowest of all oral dosage forms.
3. They are the lightest and most compact of all oral dosage forms.
4. They are in general the easiest and cheapest to package and ship of all oral dosage forms.
5. They have the best-combined properties of chemical, mechanical and microbiologic stability of all the forms.

Tablets are divided into two general classes, whether they are made by compression or moulding. Compressed and

moulded tablets are prepared for large scale and small scale production, respectively (Rudnic EM and Schwartz JB, 2005). The choice of tablet manufacturing method depends on the dose and the drug's physical properties, like compressibility and flow of the blend (Halbert, 1993). Direct compression is a process by which tablets are compressed directly from mixtures of the drug and excipients, without any preliminary treatment (British Pharmaceutical Codex, 1994 and Alderborn G, 2007). An active pharmaceutical ingredient (API), a diluent and a lubricant constitute a formula for direct compression (Martino *et al.*, 2004). The advent of direct compression was made possible by the commercial availability of directly compressible tablet vehicle that posses both fluidity and compressibility. Many common manufacturing problems are attributed to incorrect powder flow, including non-uniformity in blending, under or over dosage and inaccurate filling (Smewing J, 2002). The simplicity of the direct compression is obvious. It requires a new and critical approach to the selection of raw materials, flow properties of powder blends and effect of formulation variables on compressibility. Other advantages include economy and processing without moisture and heat. Although it is not well documented in the literature, it would seem obvious that fewer chemical stability problems would be encountered in tablet prepared by direct compression as compared to those made by wet granulation process. The primary cause of instability in tablet is moisture. Moisture plays a significant role not only in drug stability but in the compressibility characteristics of granulation. One other aspect of stability that warrants increasing attention is the

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effect of tablet aging on dissolution rates. Tablets prepared by granulation show variation in dissolution profile which is not commonly observed in tablets made by direct compression (Shangraw, 2008). The active drug particles are liberated after disintegration of tablets prepared by direct compression, resulting in comparatively faster dissolution (Gohel, 2005). This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms (Banker UV, 1994). Highly potent drugs with low flowability are not generally prepared by direct compression due to the limitation of this method (Jivraj *et al.*, 2000).

Direct compression formulations consist of three basic ingredients, an inert diluent to increase the bulk, a lubricant to improve flow of blend and the active ingredient. These ingredients are mixed in a blender (Prescott JK *et al.*, 1994). According to the survey conducted in 1993, direct compression seems to be the preferred manufacturing process for pharmaceutical tablets (Shangraw RF *et al.*, 1993). Many drugs likely Aspirin have been available in form that is suitable for tableting without any further processing (Kottke MK *et al.*, 2002). Other researchers also developed new formulations of tablets prepared by direct compression (Bhosale AV *et al.*, 2006 and Rangasamy M *et al.*, 2009).

Enalapril maleate is the maleate salt of enalapril, a derivative of two amino acid, L-alanine and L-proline. Enalapril maleate is angiotensin converting enzyme (ACE) inhibitor. It lowers blood pressure by reducing peripheral vascular resistance without relatively increasing cardiac output, rate or contractility. All grades of essential hypertension especially in patients with diabetes and other chronic renal diseases like glomerulosclerosis can be treated with Enalapril (Oates and Brown, 2008). It is also indicated in the treatment of heart failure. Hence, an attempt was made for preparation of a new formulation of Enalapril maleate tablet by direct compression with an aim of reducing the lag time and providing faster onset of action to reduce the blood pressure immediately.

MATERIALS AND METHODS

A new formulation of Enalapril maleate tablet was developed and evaluated for its pharmaceutical quality according to the procedure described in USP 31 (2008). Direct compression method was used for tablet preparation and the formulation ingredients and their percentages are listed in table 1. Various pharmaceutical parameters given in USP were studied for Enalapril maleate tablet formulations available in the local market as well as for new formulation. These parameters include appearance, weight, thickness, hardness, friability, disintegration, dissolution, content uniformity and assay.

Table 1: Formulation of new d.c.5mg Enalapril maleate tablet

Ingredients	Quantity/tablet	Percentage/tablet
Enalapril maleate	5mg	1.66%
Lactose DC	125 mg	41.66%
Avicel PH 101	125 mg	41.66%
Talc	20 mg	6.66%
Starch	25mg	8.33%

d.c. = directly compressed.

Reagents

Pure Enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$) powder, monobasic sodium phosphate (Merck), Phosphoric acid (Merck), acetonitrile (Merck). Different brands of Enalapril maleate were purchased from the market.

Weight variation test

For weight variation of individual tablets, the average tablet weight was determined by weighing 20 units or tablets individually using an analytical balance. The mean $\pm$ S.D. of each formulation is mentioned in table 2.

Thickness measurement

20 tablets were taken and their thickness was determined individually by vernier caliper. Mean and standard deviation were calculated (table-2).

Hardness determination

20 tablets were taken randomly and hardness was measured using Hardness Tester. The mean $\pm$ S.D of 20 tablets of each formulation is shown in table 2.

Friability testing

20 tablets were taken randomly and placed on a sieve. Loose dust was removed with the aid of air pressure or a soft brush. Tablet samples were weighed accurately and placed in Friabilator. After the given number of rotations (100 rotations/4 min) loose dust was removed from the tablets as before. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear (British Pharmacopoeia, 2004).

Disintegration test

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract (Block and Yu, 2001). Disintegration time was measured for 6 tablets by inserting disks using 900ml purified water at $37 \pm 2^\circ\text{C}$ in Disintegration Apparatus.

Dissolution test

Dissolution test was adopted from USP 31 (2008). In 900ml of distilled water, one tablet was operated at 50rpm for 30minutes; about 10ml of sample solution (test preparation) was withdrawn and filtered. Buffer solution

Table 2: Physical parameters of newly formulated Enalapril maleate.d.c.5 mg tablet and other available brands were assessed. Data average and standard deviation were calculated

Formulation	Weight of 20 tab in gm Mean (SD)	Thickness in mm Mean (SD)	Hardness in kg Mean (SD)
New formulated d.c.5 mg	0.2914(0.57)	1.84 (0.038)	6.48 (0.74)
Formulation 1	0.2277 (0.0021)	4.46 (0.035)	15.69 (0.92)
Formulation 2	0.1512 (0.0049)	2.79 (0.047)	5.69 (0.73)
Formulation 3	0.1312 (0.003)	3.4 (0.029)	2.35 (0.24)
Formulation 4	0.1404 (0.001)	3.29 (0.06)	5.3 (0.59)
Formulation 5	0.1421 (0.002)	2.5 (0.023)	2.26 (0.23)
Formulation 6	0.1305 (0.0025)	3.52 (0.035)	5.91 (0.94)

Table 3: Physical parameters of newly formulated Enalapril maleate.d.c.5 mg tablet and other available brands were assessed.

Formulations	Friability (%)	Disintegration time (min)	Dissolution test (n.l.t.80%)	Assay (90-110%)
New formulated d.c.5 mg	0.381	1.0	87.61	97.74
Formulation 1	0.168	3.5	90.97	97.95
Formulation 2	0.142	9.0	88.45	101.65
Formulation 3	0.145	1.0	80.55	99.05
Formulation 4	0.189	0.5	82.10	101.32
Formulation 5	0.507	0.5	82.19	98.90
Formulation 6	0.275	2.5	80.75	90.84

d.c. = directly compressed.

was prepared by dissolving 1.38gm of monobasic sodium phosphate in about 800ml of distilled water, adjusting the pH 2.2 with phosphoric acid and diluting with water to 1000ml. Mobile phase was prepared by mixing filtered and degassed buffer solution and acetonitrile (75:25). For standard preparation, an accurately weighed quantity of Enalapril maleate RS was dissolved in dissolution medium to obtain a solution having known concentration, about 0.11mg of Enalapril maleate per ml (USP 2004). Dissolved amount of Enalapril maleate tablet in dissolution medium was determined by using High Performance Liquid Chromatography (HPLC) equipped with 215nm detector.

Assay of Enalapril maleate using HPLC

The assay of different formulations of Enalapril maleate tablets was carried out using HPLC. Buffer solution was prepared by dissolving 2.76gm of monobasic sodium phosphate in about 1800ml of distilled water, adjusting the pH 2.2 with phosphoric acid and diluting with water to 1000ml. Mobile phase was prepared by mixing filtered and degassed buffer solution and acetonitrile (75:25). For sample preparation, one tablet (tablet strength is 5mg) was transferred into 50ml volumetric flask, 25ml of phosphate buffer was added to dissolve the tablet. Then add buffer solution to 50ml to obtain the concentration of 0.1mg of Enalapril maleate per ml Standard preparation was prepared according to USP. Equal volumes (about 100µl) of sample preparation and standard preparation

were injected separately into the chromatograph and chromatograms were recorded at 215nm.

RESULTS

A new Enalapril maleate formulation was developed by direct compression method (table 1) and was comparatively evaluated with six other formulations of Enalapril maleate tablets that are listed in local index of registered pharmaceutical products. All formulation tablets with 5mg potency were selected and the new formulation tablets were also developed with 5mg potency. Various pharmaceutical parameters namely weight variation, thickness, hardness test friability test, disintegration test, dissolution test and pharmaceutical assay were performed according to United State Pharmacopoeia USP 31 (2008). Results are shown in tables 2 and 3.

DISCUSSION

The present investigation was undertaken to design and evaluate newly formulated tablet of Enalapril maleate by the direct compression method comparing with the other available brands in the local market. The formulation ingredients of new formulation as shown in table 1, includes microcrystalline cellulose (Avicel PH 101) as filler, which showed excellent compressibility of the Enalapril maleate tablets. It is an effective lubricant

(Omray *et al.*, 1986) and also provides strength to the tablet (Hernier and Teleman, 1997). In oral solid dosage form, talc is used as lubricant and diluent (Dawoodbhai S *et al.*, 1990) but it is recommended to restrict its concentration to 5% as it can reduce the dissolution rate (Wang DP *et al.*, 1997 and Kottke MK *et al.*, 2002). The new formulation also contains talc.

Weight variation results for all formulations were in accordance with USP weight variation standards i.e. the weight of not more than two of the tablets out of twenty differs from the average weight by not more than $\pm 7.5\%$. Thickness of ten tablets for each formulation was measured and all the results were found in accordance with USP i.e., $\pm 5\%$ limit is allowed depending upon the size of the tablets. Hardness test for each formulation was performed. Hardness test result for new formulation and four available formulations were within specified limit, but for two formulations hardness of tablets was deviated from the specified limit. Minimum permitted hardness range for satisfactory tablets is 4 kg (Banker GS and Anderson, 2009). But two formulations have hardness less than the specified limit. Hardness of tablets should be within limit because if the tablets will be soft, with hardness range below limit, tablets will not withstand the handling during packing and shipping operations throughout their shelf life (Rudnic and Schwartz, 2005). Substantial alteration in the machine speed, a dirty or worn cam track, changes in particle size distribution of the granulation mix are the factors that may alter hardness of tablets. During the course of hardness testing, tablet size, shape and orientation in the tester can also affect the value of measured hardness for a given formulation.

Friability test results for Enalapril maleate tablet were within the specified limits i.e. friability % for all formulations were less than 1%. Similarly 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. Dissolution test performed for all seven formulations according to USP using High Performance Liquid Chromatography (HPLC). Out of seven samples 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. The use of HPLC in dissolution test protocol is more appreciated. It enables one to proceed with automation in an organized pattern. More over, it is cost effective and accurate system to handle the analysis of dissolution samples. Another advantage of HPLC is the requirement of far less volume of samples than other methods (Godwin W Fong, *et al.*, 1991). Pharmaceutical assay has been performed by HPLC for all the seven formulations as per USP recommended procedure. Results of assay for all formulations were within the USP limits. According to USP Enalapril maleate tablet contain not less than 90.0% and not more than 110.0% of the

labeled amount of $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$. All the above tests performed as per compliance of the Good laboratory practices.

As far as the pharmaceutical quality is concerned, new formulation of Enalapril maleate made by direct compression method can be compared with other formulations available in the local market because results for physical parameters as well as chemical assay are within USP limits for new formulation. 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 (Shangraw, 2008). Hence, many researchers are now developing new formulations using direct compression method (Yasmeen *et al.*, 2005 and Bushra *et al.*, 2008).

Many drugs are made and marketed by more than one pharmaceutical manufacturer. Bioequivalence and bioavailability studies show that the bioavailability of drugs from dosage forms is influenced by the method of manufacture and the final formulation of the drug (Shargel L *et al.*, 2005). Because of the plethora of drug products containing the same amount of active drug, physicians, pharmacists, other who prescribe dispense or purchase drugs must select the product that produce equivalent therapeutic effect. FDA has developed guidelines for these reasons and these requirements must be satisfied as a condition for marketing.

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