Formulation and evaluation of orodispersible Enalapril maleate tablets: A comparative study on natural super disintegrants and synthetic super disintegrants

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Abstract
The aim of the present investigation is to formulate Enalapril maleate oral disintegrating tablet by using natural and synthetic super disintegrants. ODTs may also be used to deliver drugs to the oral cavity, for local action or, in some cases, absorption across the oral mucosa, thereby avoiding first-pass hepatic metabolism and potentially increasing the rate and extent of uptake, and reducing undesirable metabolites. The objectives of the research work is to formulate oral disintegrating tablets of Enalapril maleate by using different super disintegrates (Natural, Synthetic) in different ratio by direct compression technique and tablets were evaluated for precompressional and post compressional Parameters such as angle of repose, bulk density, tapped density, compressibility index, drug content and in-vitro drug release study, hardness, friability, wetting time and in vitro dispersion time. To study the physical characteristics of the individual drug and optimized formulations by FTIR spectroscopy. To evaluate various characteristics of the resulting tablets. Formulation CCS3, IH2 were subjected to stability Studies as per ICH guidelines at temperatures and humidity of 25±5ºC/60±5%RH; and 40±5ºC/75±5%RH. Tablets didn't reveal any appreciable changes in respect to hardness, disintegration time, drug content and dissolution profile.

Keywords: ODTs, Enalapril Maleate, Super Disintegrants, Sodium starch Glycolate, Ispaghula husk, Cross Povidone, MCC, Cross Carmellose Sodium

1. Introduction
1.1 Orally disintegrating tablets
The concept of Fast dissolving Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva [1]. The center for drug Evaluation and Research states an ODT to be: “A solid dosage form containing medicinal substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue.” These tablets are distinguished from conventional, sublingual tablets, lozenges and buccal tablets which require more than a minute to dissolve in the mouth. In the literature these are also called orally disintegrating, Orodisperse, Mouth dissolving, Quick dissolving, Fast-melt and rapidly disintegrating tablets and freeze-dried wafers [2].
Disintegration Mechanism of ODT drugs

1.2 Mechanism of Action Enalapril:
Enalapril, after hydrolysis to enalaprilate, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium.

2. Materials and Methods
Pre gelatinized Starch (SD Fine, Mumbai), MCC (PH-102), Lactose anhydrous, Crospovidone, Sodium starch Glycolate, Magnesium stearate, Lactose, Cross Carmellose Sodium, Sodium Saccharin, Orange Flavor, Aerosil, Glyceryl behanate.

2.1 Equipments
Analytical balance, pH meter, Friability tester, Hardness tester, Disintegration Tester, Dissolution apparatus (Vee-go), UV-Visible spectrophotometer (Analytical), Compression machine (sixteen stationary rotary) (Cadmach), Bulk Density Tester.

2.2 Methodology

2.2.1 Extraction of Natural polymer from Ispaghula husk:
For the extraction of mucilage, seeds of Plantago ovata were used. They were soaked in distilled water for 48 h and then boiled for 1 h for complete release of mucilage into water. The material was filtered by squeezing in a muslin cloth to remove marc. Then equal volume of acetone was added to filtrate to precipitate the mucilage. The mucilage was separated and dried in oven at a temperature less than 60°C, powdered (#60 mesh), weighed and stored in desiccator until further use.

2.2.2 Preparation of Mixed blends of drug and excipients
All the ingredients were weighed accordingly specified in the formulation (table-8) and mixed well except magnesium stearate. Then the blend was passed through sieve no 60 which was used for the evaluation of flow properties.

2.2.3 Compression of Tablets
To the mixed blend of powder and excipients finally add magnesium stearate and then mixed for 5 min. The mixed blend was compressed with twelve (12) station tablet punching machine using 7 mm flat punches. The working formula was given in Table.No.1

3. Results and discussions

3.1 Evaluation of Pre compressional parameters

Bulk density
Apparent bulk density was determined by pouring the blend into a graduated cylinder [3]. The bulk volume ($V_b$) and weight of the powder was determined. The results were given in table.no.2

\[
\text{Bulk density} = \frac{M}{V_b}
\]

Tapped density
The measuring cylinder containing a known mass of powder blend was tapped for a fixed number of times as per USP apparatus-II. The minimum volume occupied by the powder after tapping was measured. The results were given in table.no.2

\[
\text{Tapped density} = \frac{\text{weight}}{\text{tapped volume}}
\]

Compressibility index
Compressibility index is calculated as follows. The results were given in table.no.2.

\[
\text{Tapped density} = \frac{\text{Bulk density}}{\text{Tapped density} \times 100}
\]

The value below 15% indicates a powder with good flow characteristics whereas above 25% indicates poor flow ability [4].

Haussner’s ratio
It is an indirect index of ease of powder flow, it is calculated as follows.

\[
\text{Tapped density} / \text{Bulk density}
\]
Haussner’s ratio <1.25 indicates good flow properties, where as >1.5 indicates poor flowability. The results were given in table no.2.

**Angle of Repose**

Angle of repose was determined using funnel method. The blend was poured through funnel that can rise vertically until a maximum cone height (h) was obtained. Radius of the heap(r) was measured and angle of repose was calculated as follows [5]. The results were given in table 2.

\[ \theta = \tan^{-1} \frac{h}{r} \]

### 3.2 Evaluation of tablets

All the prepared tablets were evaluated for the following parameters as per the I.P guidelines.

**Weight variation**

Twenty tablets from each formulation were selected randomly and average weight was determined. Individual tablets were then weighed and compared with average weight [6,7]. The results were given in table no.3.

**Hardness test**

The force required to break a tablet in a diametric compression was determined by using Pfizer tablet hardness tester. The results were given in table no.3.

**Friability**

The weight of twenty tablets was noted and placed in the friabilator and then subjected to 100 revolutions at 25 rpm. Tablets were dedusted using a soft muslin cloth and reweighed [8,9]. The results were given in table no.3.

Percent friability = \[ \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100 \]

**Wetting time and Water absorption ratio**

A piece of paper folded twice was kept in a petri dish (internal diameter 6cms) containing 6ml of purified water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was weighed. Water absorption ratio, R was determined using the following equation [10]. The results were given in table no.3.

\[ R = \frac{W_a - W_b}{W_b} \times 100 \]

where W_a, W_b are the weights of tablets before and after wetting.

**In vitro dispersion time**

Tablet was added to 10ml of distilled water at 37± 0.5˚C, time required for complete dispersion of tablet was measured [11,12]. The results were given in table no.3.

**Drug content uniformity**

The drug content uniformity was determined by taking the powder equivalent to 10mg, then it was (n=3) dissolved in P6.8 phosphate. Required dilution (10µg/ml) was prepared and absorbance was taken against the blank at 206nm. The results were given in table no.3.

**In vitro disintegration time**

The disintegration was performed using an I.P 85 disintegration apparatus with distilled water at 37±0.5 °C. The time taken for disintegration of all formulations was noted in table 4.

**3.3 Dissolution studies**

Dissolution rate of Enalapril maleate from all formulations was performed using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with paddle. The dissolution fluid was 900 ml of P6.8 phosphate buffer with a speed of 50 rpm and temperature of 37±0.5˚C were used in each test. 5 ml of sample was withdrawn at different time intervals (2.5, 5, 10, 15 & 20 mins) and fresh medium was replaced to maintain sink conditions. The samples are analysed by using UV- Visible spectrophotometer at \( \lambda_{\text{max}} \) 205 nm. Dissolution studies were performed in triplicate and the results were shown in table no.5. We were plotted a graph by taking time on x-axis and % cumulative drug release on y-axis. The graphs were represented in fig. no. 1-4.

**3.4 Stability studies**

The stability studies were conducted for optimized formulations at 25˚C / 60%RH and 40˚C / 75% RH. For these formulations we were reconducting the wetting time, disintegration time and dissolution time [13,14].

**3.5 Characterization of Enalapril maleate tablets: FTIR studies**

The drug- excipients interaction was studied using FTIR. IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer using KBr pellet technique [15,16]. This spectra was scanned over the 3600 to 500 cm\(^{-1}\) range. The polymers should not show any change on the functional groups of enalparil maleate. The values were mentioned in the table 6. The IR spectra of pure drug and optimized formulations were showed in fig. no. 5-8.
Table 1: Formulation of oral disintegrating tablets of Enalapril maleate

| Ingredients                        | CCS1 | CCS2 | CCS3 | SSG1 | SSG2 | SSG3 | CP1 | CP2 | CP3 | IH1 | IH2 |
|------------------------------------|------|------|------|------|------|------|-----|-----|-----|-----|-----|
| Enalapril maleate                  | 10   | 10   | 10   | 10   | 10   | 10   | 10  | 10  | 10  | 10  | 10  |
| Lactose Anhydrous                  | 80   | 80   | 80   | 80   | 80   | 80   | 80  | 80  | 80  | 80  | 80  |
| MCC PH-102                         | 48.5 | 44   | 41   | 48.5 | 44   | 41   | 48.5| 44  | 41  | 48.5| 44  |
| Croscarmellose Sodium              | 4.5  | 9    | 12   | ---  | ---  | ---  | --- | --- | --- | --- | --- |
| Sodium Starch Glycollate           | ---  | ---  | ---  | 4.5  | 6    | 12   | --- | --- | --- | --- | --- |
| Crospovidone                       | ---  | ---  | ---  | ---  | 4.5  | 6    | 12  | --- | --- | --- | --- |
| Ispaghula Husk Powder              | ---  | ---  | ---  | ---  | ---  | ---  | 4.5 | 6   |     |     |     |
| Sodium Saccharin                   | 1.5  | 1.5  | 1.5  | 1.5  | 1.5  | 1.5  | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Orange flower                      | 1    | 1    | 1    | 1    | 1    | 1    | 1   | 1   | 1   | 1   | 1   |
| Aerosil                            | 3    | 3    | 3    | 3    | 3    | 3    | 3   | 3   | 3   | 3   | 3   |
| Magnesium Stearate                 | 1.5  | 1.5  | 1.5  | 1.5  | 1.5  | 1.5  | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Glycercyl Behenate                 | 1.5  | 1.5  | 1.5  | 1.5  | 1.5  | 1.5  | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Total Weight                       | 150  | 150  | 150  | 150  | 150  | 150  | 150 | 150 | 150 | 150 | 150 |

CSS - Croscarmellose Sodium; SSG - Sodium Starch Glycollate; CP – Crospovidone; IH - Ispaghula Husk Powder

Table 2: Evaluation of flow properties of the blend

| Formulations | Angle of repose | Bulk density | Tapped density | Carr’s index | Hausner’s ratio | Flow ability |
|--------------|-----------------|--------------|----------------|--------------|-----------------|--------------|
| CCS1         | 33              | 0.56         | 0.65           | 13.84        | 1.16            | Fair         |
| CCS2         | 32              | 0.57         | 0.64           | 13.62        | 1.1             | good         |
| CCS3         | 35              | 0.66         | 0.76           | 10.2         | 1.17            | Excellent    |
| SSG1         | 28              | 0.68         | 0.74           | 13.12        | 1.14            | good         |
| SSG2         | 32              | 0.54         | 0.62           | 12.14        | 1.12            | good         |
| SSG3         | 29              | 0.65         | 0.71           | 8.02         | 1.11            | good         |
| CP1          | 36              | 0.67         | 0.75           | 17.8         | 1.16            | Excellent    |
| CP2          | 35              | 0.54         | 0.65           | 11.25        | 1.19            | Excellent    |
| CP3          | 28              | 0.61         | 0.71           | 10.6         | 1.21            | Good         |
| IH1          | 38              | 0.59         | 0.63           | 7.8          | 1.09            | Good         |
| IH2          | 36              | 0.68         | 0.75           | 11.1         | 1.12            | Good         |

Table 3: Quality control tests for the oral disintegrating tablets of Enalapril maleate

| Formulations* | Average Weight* | Hardness *kg/cm² | Friability *% | Wetting time* | Water absorption ratio* |
|---------------|-----------------|------------------|--------------|---------------|------------------------|
| CCS1          | 149±0.12        | 3.6±0.11         | 0.48±0.16    | 11.12±0.21    | 39±0.14                |
| CCS2          | 150±0.21        | 3.6±0.24         | 0.56±0.17    | 10.13±0.34    | 28±0.15                |
| CCS3          | 151±1.8         | 3.5±0.49         | 0.57±0.17    | 8.55±0.15     | 34±0.24                |
| SSG1          | 149±0.25        | 3.9±0.11         | 0.31±0.16    | 16.87±0.16    | 38±0.16                |
| SSG2          | 148±0.54        | 3.8±0.14         | 0.46±0.19    | 14.76±0.19    | 40±0.14                |
| SSG3          | 150±0.01        | 3.9±0.17         | 0.41±0.24    | 15.41±0.13    | 38±0.18                |
| CP1           | 149±0.19        | 3.9±0.21         | 0.54±0.21    | 22.13±0.77    | 42±0.19                |
| CP2           | 148±0.71        | 3.7±0.15         | 0.52±0.27    | 20.14±0.14    | 44±0.28                |
| CP3           | 150±0.76        | 3.7±0.17         | 0.41±0.15    | 18.76±0.21    | 47±0.14                |
| IH1           | 147±0.16        | 3.8±0.2          | 0.31±0.16    | 13.12±0.13    | 51±0.13                |
| IH2           | 149±0.87        | 4.0±0.32         | 0.29±0.22    | 11.56±0.12    | 54±0.17                |

Table 4: Quality control tests for the oral disintegrating tablets of Enalapril maleate

| Formulations* | Disintegration time * (sec) | Drug content* (%) | Percentage Drug Dissolved After 10 min* | In vitro Disperstion time* (s) |
|---------------|-------------------------------|-------------------|----------------------------------------|-----------------------------|
| CCS1          | 14.25±0.45                    | 102.2±0.73        | 89.24±0.42                             | 15±0.22                     |
| CCS2          | 13.51±0.71                    | 98.97±0.12        | 91.21±0.31                             | 13±0.65                     |
| CCS3          | 10.64±0.61                    | 99.58±0.53        | 97.24±0.86                             | 11±0.72                     |
| SSG1          | 54.21±0.14                    | 97.25±0.62        | 87.24±0.68                             | 61±0.25                     |
| SSG2          | 56.85±0.32                    | 98.21±0.54        | 91.25±0.45                             | 59±0.36                     |
| SSG3          | 57.21±0.68                    | 98.56±0.41        | 91.35±0.76                             | 59±0.62                     |
| CP1           | 38.25±0.21                    | 94.95±0.25        | 84.91±0.13                             | 51±0.98                     |
| CP2           | 37.65±0.24                    | 96.78±0.61        | 88.24±0.95                             | 50±0.57                     |
| CP3           | 39.78±0.32                    | 98.8±0.32         | 95.42±0.42                             | 51±0.24                     |
| IH1           | 12.24±0.45                    | 98.25±0.23        | 97.21±0.68                             | 11±0.57                     |
| IH2           | 10.24±0.55                    | 99.6±0.4          | 98.21±0.9                              | 10±0.32                     |
Table 5: Dissolution profile of the oral disintegrating tablets of enalapril maleate

| Formulations | CCS1 | 0  | 2.5       | 5     | 10    | 15  | 20    |
|--------------|------|----|-----------|-------|-------|-----|-------|
|              |      | 0  | 37.6±0.26 | 60.2±0.35 | 79.2±0.92 | 91.2±0.24 | 98.4±0.31 |
|              |      | 0  | 41.2±0.12 | 62.2±0.95 | 81.5±0.7 | 89.3±0.89 | 97.2±0.71 |
| CCS2         |      | 0  | 50.2±0.21 | 71.2±0.31 | 85.4±0.12 | 91.7±0.21 | 99.1±0.11 |
| CCS3         |      | 0  | 44.2±1.16 | 59.2±0.24 | 78.4±0.12 | 89.9±0.1  | 95.2±0.21 |
| SSG1         |      | 0  | 43.2±0.14 | 60.2±0.1  | 75.2±0.21 | 88.7±0.31 | 96.2±0.14 |
| SSG2         |      | 0  | 43.8±2.3  | 69.3±0.35 | 78.9±0.26 | 91.3±0.32 | 94.2±0.12 |
| SSG3         |      | 0  | 39.8±1.26 | 67.2±0.54 | 79.2±0.11 | 90.4±0.12 | 93.1±0.78 |
| CP1          |      | 0  | 41.6±0.51 | 68.5±0.32 | 75.9±0.64 | 88.6±0.85 | 95.7±0.74 |
| CP2          |      | 0  | 43.7±2.5  | 60.3±0.12 | 75.4±0.46 | 88.6±1.3  | 97.2±0.2  |
| CP3          |      | 0  | 45.2±0.2  | 69.2±0.21 | 81.2±0.3  | 89.1±0.2  | 97.0±0.13 |
| IH1          |      | 0  | 49.1±0.74 | 70.2±0.1  | 85.2±0.3  | 91.4±0.6  | 99.7±0.1  |
| IH2          |      | 0  | 45.2±0.2  | 69.2±0.21 | 81.2±0.3  | 89.1±0.2  | 97.0±0.13 |

Fig 1: Comparative dissolution profile of Enalapril maleate tablets containing different concentrations of croscarmellose sodium as super disintegrant.

Fig 2: Comparative dissolution profile of Enalapril maleate tablets containing different concentrations of sodium starch glycinate as super disintegrant.
Fig 3: Comparative dissolution profile of Enalapril maleate tablets containing different concentrations of cross povidone as super disintegrant

Fig 4: Comparison of dissolution profiles of Enalapril maleate tablets containing different concentrations of Ispaghula husk powder as a natural super disintegrant

Fig 5: Comparison of dissolution profiles of optimized formulations CCS3 & IH2
FTIR Studies:

Fig 7: FTIR of enalapril maleate (pure drug)

Fig 8: FTIR of formulation CSS3
Fig 9: FTIR of formulation IH2

Table 6: FTIR values of Optimized Formulations

| Material                  | Peak      | Functional group       |
|---------------------------|-----------|------------------------|
| Pure API                  | 3274.34   | NH group               |
|                           | 1751.36   | C=O in esters          |
|                           | 1727.03   | C=O in acids           |
|                           | 1647.59   | C=O in amides          |
| Formulation CCS3 (Drug: CCS) | 3299.75   | NH group               |
|                           | 1751.26   | C=O in esters          |
|                           | 1727.02   | C=O in acids           |
|                           | 1647.23   | C=O in amides          |
| Formulation S2 (Drug: Isphagula husk) | 3298.54   | NH group               |
|                           | 1751.31   | C=O in esters          |
|                           | 1727.51   | C=O in acids           |
|                           | 1647.57   | C=O in amides          |

Stability analysis:

Table No 7: Stability Analysis of Optimized Formulations

| Formulation | No of days | Wetting time (s) 25˚C & 60%RH | Disintegration time (s) 25˚C & 60%RH | Wetting time (s) 40˚C & 75% RH | Disintegration time (s) 40˚C & 75% RH |
|-------------|------------|---------------------------------|------------------------------------|---------------------------------|-------------------------------------|
| CCS3        | 0          | 8.47±0.124                      | 10.68±0.226                        | 8.47±0.225                      | 10.68±0.146                         |
|             | 15         | 8.45±0.148                      | 10.65±0.446                        | 8.45±0.256                      | 10.61±0.228                         |
|             | 30         | 8.48±0.346                      | 10.66±0.424                        | 8.46±0.154                      | 10.59±0.446                         |
|             | 45         | 8.43±0.146                      | 10.64±0.568                        | 8.44±0.654                      | 10.62±0.356                         |
|             | 60         | 8.44±0.214                      | 10.62±0.146                        | 8.43±0.168                      | 10.64±0.186                         |
| IH2         | 0          | 11.56±0.146                     | 10.02±0.148                        | 11.56±0.983                     | 10.02±0.146                         |
|             | 15         | 11.54±0.566                     | 9.98±0.167                         | 11.53±0.156                     | 10.0±0.264                          |
|             | 30         | 11.50±0.354                     | 9.99±0.964                         | 11.51±0.256                     | 9.97±0.446                          |
|             | 45         | 11.51±0.446                     | 9.98±0.843                         | 11.54±0.140                     | 9.99±0.356                          |
|             | 60         | 11.49±0.176                     | 9.97±0.116                         | 11.50±0.146                     | 9.98±0.264                          |

Drug content:

| Formulation | No of days | Drug content 25˚C & 60%RH | Dissolution | Drug content 40˚C & 75% RH | Dissolution |
|-------------|------------|---------------------------|-------------|---------------------------|-------------|
| CCS3        | 0          | 99.08±0.86                | -           | 99.08±0.86                | -           |
|             | 15         | 98.12±0.56                | 98.75±0.23  | 98.06±0.36                | 97.86±0.28  |
|             | 30         | 98.74±0.24                | 98.36±0.52  | 98.12±0.16                | 97.56±0.34  |
|             | 45         | 98.38±0.328               | 97.54±0.442 | -                         | -           |
|             | 60         | 98.25±0.156               | -           | 98.6±0.86                 | -           |
| IH2         | 0          | 98.6±0.24                 | -           | 98.6±0.86                 | -           |
|             | 15         | 98.24±0.168               | 98.36±0.52  | 98.12±0.16                | 97.56±0.34  |
|             | 30         | 98.36±0.264               | 97.24±0.28  | -                         | -           |
|             | 45         | 98.14±0.188               | -           | 98.12±0.16                | 97.56±0.34  |
|             | 60         | 98.08±0.22                | -           | 98.6±0.86                 | -           |
4. Conclusion
The present work led to the development of orodispersible tablets of enalapril maleate by using different concentration of natural and synthetic superdisintegrants. The prepared oral disintegrating tablets of enalapril maleate were found to be good in appearance without cracking, lamination and chipping. The promising formula (CCS3, IH2) have showed fast disintegration and displayed in vitro dispersion time of 11 s and 10.5’s. The dissolution rates of the optimized formulations (CCS3, IH2) were found to be good. Among the promising ODT formulation CCS3, IH2 the formula IH2 was found to be superior when compared to formulation CCS3 since formulation CCS3 used natural disintegrant (i.e 6%w/w iaphagula husk ) at a lower concentration than the formulation CCS3 (8%w/w eros carnemellose sodium) , and hence it is found to be more cost effective. The FTIR studies were also showed the there was no interaction between drug and polymer. The stability study was done for 3 months all parameters such as wetting time, disintegration time, drug content and in-vitro dissolution studied at the end of every month, the results shows that no significant changes in that parameters.

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