Formulation and Development of Taste Masked Orally Disintegrating Tablets of Perindopril Erbumine by Direct Compression Method

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Abstract

The aim of current study was to formulate and evaluate taste masked orally disintegrating tablets of Perindopril Erbumine. Taste masking was done by using Eudragit E100 in the ratio of 1:3 (drug:polymer) by mass extrusion method. The preliminary batches were prepared by using different superdisintegrants like Ac-Di-Sol, Primogel, Tulsion-335 and Tulsion-339. From the preliminary study it was found that orodispensible tablets containing Ac-Di-Sol showed better disintegration time and it was considered for further studies. A 3^2 full factorial design was applied to optimize the formulations, nine batches were prepared and evaluated. It was observed from the evaluations that the batch A showed the best disintegration time and also completes drug release within five minutes. Hence it was concluded that orally disintegrating tablets of Perindopril Erbumine can be successfully formulated using Ac-Di-Sol.

Keywords: Perindopril erbumine; Taste masking; Ac-Di-Sol; Avicel PH101; 3^2 full factorial design

Introduction

Although various novel and advanced drug delivery systems have been introduced for therapeutic use, the popularity of oral dosage forms, particularly tablets have not been eclipsed, because tablets still have numerous advantages, besides others an economical production. However, one important drawback of tablets as a dosage form is the need to swallow. Dysphasia or general difficulties in swallowing of tablets may be a problem for geriatric, paediatric, or travelling patients, if the latter do not have access to water. Dysphasia is also pertinent with the number of medical conditions including strokes, Parkinson’s disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy hence resulting in higher incidence of non-compliance and ineffective therapy. Thus, the orally disintegrating drug delivery system (DDS) is fast dissolving / dispersing, and dissolves in the patient’s mouth within a matter of seconds without need of water or chewing. It may therefore be the best solution for patient suffering from dysphasia.

Perindopril ter-butyl amine belongs to a group called Angiotensin Converting Enzyme (ACE) inhibitors [1]. Inhibition of ACE results in decreased plasma Angiotensin II, leading to decreased vasoconstriction, increased plasma rennin activity and decreased aldosterone secretion. The overall effect of this is a drop in blood pressure and a decrease in the workload of the heart. Perindopril tert-butyl amine is a pro-drug that is hydrolyzed by esterases to the active metabolite Perindoprilat. Perindopril is rapidly absorbed, reaching peak plasma concentrations about 1 hour after a single oral dose. Perindoprilat reaches peak plasma concentrations in 2 to 6 hours. The bioavailability of Perindopril is about 70%. The presence of food does not affect the rate and extent of absorption of Perindopril; however, food reduces the conversion of Perindopril to Perindoprilat [2,3].

Therefore, the purpose of the present study was to develop a fast disintegrating tablet of Perindopril Erbumine by direct compression and to mask the bitter taste of Perindopril. Such tablet should disintegrate rapidly in the saliva without need of water and release the drug instantly for immediate therapeutic effect, and be of acceptable taste.

Material and Method

Perindopril Erbumine was generously gifted by Hetero drugs Pvt Ltd, Eudragit E100 was gifted by Evonick (Mumbai). Primogel, Ac-Di-Sol and Avicel (PH101) were procured from Maple Biotech Pvt Ltd, Tulsion 335 and Tulsion 339 were obtained from Thermax India Pvt Ltd. Manitol was obtained from Oswal chemicals. All other chemicals used were of analytical grade.

Determination of taste threshold value of bitterness for Perindopril Erbumine

The minimum concentration among a range of dilutions of a substance at which the volunteer just starts feeling the bitter taste is known as taste threshold concentration. The threshold bitterness concentration of Perindopril Erbumine was determined by a panel of 12 healthy human volunteers from whom the written consent were taken. The design of the experiment is shown in table 1. Different

| Sr no | Concentration µg/ml | 0 | 1 | 2 | 3 | 4 |
|-------|---------------------|---|---|---|---|---|
| 1     | 10                  |   |   |   |   |   |
| 2     | 50                  |   |   |   |   |   |
| 3     | 100                 |   | 12|   |   |   |
| 4     | 110                 |   | 3 |   |   |   |
| 5     | 120                 |   | 9 |   |   |   |
| 6     | 130                 |   | 12|   |   |   |
| 7     | 140                 |   | 12|   |   |   |
| 8     | 150                 |   | 12|   |   |   |

0=sweet, 1= acceptable, 2=slightly bitter, 3=bitter, 4=intensely bitter.

Table 1: Determination of taste threshold value of bitterness of perindopril erbumine.
concentrations of the drug sample ranging from 10 µg/ml to 150 µg/ml were prepared in phosphate buffer pH 6.8. The volunteers were administered with 10 ml of the test samples one at a time with an interval of ten minutes. The volunteers were told to keep the test solution in mouth for 30 seconds and later spit it out. The taste observed by the volunteers for each test sample was recorded. It was observed that 9 out of 12 volunteers felt bitterness after 30 seconds at concentration of 120µg/ml and three volunteers observed the bitter taste at 110 µg/ml. Therefore the concentration of 110 µg/ml was considered as the taste threshold concentration of Perindopril Erbumine [4-6].

Preparation of the taste masked granules

Physical mixtures of Perindopril Erbumine: Eudragit® E 100 was prepared in various ratios from 1:1 to 1:7. The recommended solvent for Eudragit® E 100 is ethanol and water respectively. A gel containing Perindopril erbumine and Eudragit® E 100 was prepared by the following method. Perindopril erbumine was mixed with different amount of powdered Eudragit® E100 then 10% ethanol was added to this mixture in a glass beaker and gel was prepared using a mechanical stirrer. The gel was manually extrudated through a syringe. The ethanol was evaporated, by keeping the extrudates overnight at room temperature. The solidified gel in the shape of strings was crushed and sieved through a sieve sized 255 μm to make the granules [7-9].

In-vitro Taste evaluation

The in-vitro taste evaluation was carried out to determine the drug release from the taste masked granules at the salivary pH [9-12]. It was determined by placing Perindopril Erbumine: Eudragit® E100 complex equivalent to 4 mg of Perindopril Erbumine in 10 ml of phosphate buffer and shaken for 30 seconds. The amount of drug released was then analysed at 215nm. The results of analysis are shown in table 2.

The prepared granules were subjected to thermal analysis, FTIR, X-Ray diffraction (XRD) studies.

Thermal analysis

Differential scanning calorimetry (DSC) was performed using a Mettlar TA 823 apparatus. The drug, the polymer, and the drug-polymer complex were subjected to the DSC study. Samples were heated at a scanning rate of 20 K/min from 40°C to 300°C under nitrogen.

Fourier Transform Infrared Spectroscopy (FTIR)

The drug, polymer and drug polymer complex were subjected to IR spectroscopy to check the drug polymer Interaction using FT-IR (SHIMADZU 8400 S) and the KBr disk method.

X-ray diffraction (XRD) studies

X-Ray Diffraction analysis was carried out to evaluate the degree of crystallinity. The pure perindopril erbumine, pure Eudragit® E 100, and the perindopril-erbumine-Eudragit® E 100 complex (1:3) were subjected to powder XRD at 2 angles between 5° and 50° in increments of 0.4°.

Preparation of preliminary batches of fast disintegrating tablets of Perindopril Erbumine

For the preliminary batches, Drug-Eudragit complex, Mannitol, Avicel (pH101), Superdisintegrants, Talc and Magnesium stearate were used. Mannitol was used as filler and also to impart cooling sensation in mouth. Avicel (pH101) was used as a binder because of its binding property. The concentration of Superdisintegrants such as Ac-Di-Sol, Primojel, Tulsion® 335 and Tulsion® 339 was between 2–5%. A control formulation was made without a disintegrant. All ingredients were

Taste threshold value | Absorbance noted | Drug: eudragit complex | % drug released in relation to taste threshold value
--- | --- | --- | ---
100µg/ml | 1.243 | 1:1 | 234.35%
 | 1:2 | 121.80%
 | 1:3 | 120.41%
 | 1:4 | 115.11%
 | 1:5 | 115.51%
 | 1:6 | 114.39%
 | 1:7 | 33.18%

Table 2: UV method for determination of the ratio for drug eudragit complex for taste masking.

| Ingredients | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) | F5 (mg) | F6 (mg) | F7 (mg) | F8 (mg) | F9 (mg) | F10 (mg) | F11 (mg) | F12 (mg) |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug: Polymer complex | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Mannitol | 129 | 127 | 124 | 129 | 127 | 124 | 129 | 127 | 124 | 129 | 127 | 124 |
| Avicel | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Ac-di-sol | 5 | 7 | 10 | | | | | | | | | |
| Primogel | | | 5 | 7 | 10 | | | | | | | |
| Tulsion 335 | | | | | | | | | | | | 5 |
| Tulsion 339 | | | | | | | | | | | | 5 |
| Mag- stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Total weight | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

Table 3: Formulation of preliminary batches of fast disintegrating tablets of perindopril erbumine.
passed through mesh 250 μm. The ingredients were mixed according to table 3. Magnesium stearate and talc were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr’s index and Hausner’s ratio [13,14]. The Blend was compressed on 8 mm (diameter) flat punches on a ‘Rimek mini press 16 station rotary compression machine. Each tablet weighing 200 mg corresponding to 4 mg of perindopril erbumine were obtained.

The tablets were evaluated for weight variation, thickness, friability, hardness and in-vitro disintegration time. In-vitro dissolution time was not evaluated for preliminary batches as improvement in disintegration time was of prime importance for this study.

**Full factorial design**

A 3<sup>rd</sup> randomized full factorial design was adopted to optimize the variables. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations [15-18]. Layout of full factorial design is shown in table 4. The amounts of binder, Avicel pH101(X<sub>1</sub>) and the amount of Ac-Di-Sol (X<sub>2</sub>) were selected as independent variables precompression parameters were evaluated and the observations are shown in table 5. The batches were formulated according to the formula given in table 6. The optimized batches were evaluated for content uniformity, disintegration time, wetting time, water absorption ratio and % drug release in 5 minutes (Q<sub>T5</sub>) Batches of factorial design is shown in table 7.

**Precompression parameters**

Angle of repose (θ): Angle of repose is defined as the maximum angle possible between the surface of a pile of the Powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

\[
\tan \theta = \frac{h}{r}
\]

\[
\theta = \tan^{-1} \left( \frac{h}{r} \right)
\]

Where, θ is the angle of repose

| Batch code | X<sub>1</sub> | X<sub>2</sub> |
|------------|------------|------------|
| A<sub>1</sub> | -1         | -1         |
| A<sub>2</sub> | -1         | 0          |
| A<sub>3</sub> | -1         | 1          |
| A<sub>4</sub> | 0          | -1         |
| A<sub>5</sub> | 0          | 0          |
| A<sub>6</sub> | 0          | 1          |
| A<sub>7</sub> | 1          | -1         |
| A<sub>8</sub> | 1          | 0          |
| A<sub>9</sub> | 1          | 1          |

**Table 4:** Full 3<sup>rd</sup> factorial layout.

| Sr.no | Formulation | Angle of repose | Bulk density | Tap density | Carr’s index | Hausner’s ratio |
|-------|-------------|-----------------|--------------|-------------|--------------|-----------------|
| 1     | A<sub>1</sub> | 25.27           | 0.55         | 0.58        | 12.00        | 1.13            |
| 2     | A<sub>2</sub> | 25.94           | 0.50         | 0.58        | 13.79        | 1.16            |
| 3     | A<sub>3</sub> | 25.27           | 0.58         | 0.62        | 10.77        | 1.07            |
| 4     | A<sub>4</sub> | 23.19           | 0.52         | 0.66        | 10.34        | 1.11            |
| 5     | A<sub>5</sub> | 24.10           | 0.50         | 0.62        | 13.79        | 1.16            |
| 6     | A<sub>6</sub> | 24.77           | 0.50         | 0.60        | 20.00        | 1.25            |
| 7     | A<sub>7</sub> | 27.82           | 0.52         | 0.58        | 16.80        | 1.20            |
| 8     | A<sub>8</sub> | 27.25           | 0.55         | 0.55        | 16.66        | 1.201           |
| 9     | A<sub>9</sub> | 27.89           | 0.50         | 0.58        | 16.66        | 1.20            |

**Table 5:** Evaluation of precompression parameters of optimization batches.

| Ingredients     | A<sub>1</sub> (mg) | A<sub>2</sub> (mg) | A<sub>3</sub> (mg) | A<sub>4</sub> (mg) | A<sub>5</sub> (mg) | A<sub>6</sub> (mg) | A<sub>7</sub> (mg) | A<sub>8</sub> (mg) | Control |
|-----------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------|
| Drug: Polymer complex | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Mannitol | 149 | 147 | 144 | 129 | 127 | 124 | 109 | 107 | 104 | 134 |
| Avicel (PH101) | 30 | 30 | 30 | 50 | 50 | 70 | 70 | 70 | 70 | 50 |
| Ac-di-sol | 5 | 7 | 10 | 5 | 7 | 10 | 5 | 7 | 10 |
| Mag- stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Total weight | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

**Table 6:** Formulation using 3<sup>rd</sup> full factorial design.
### Evaluation of Tablet Properties

**Weight variation**: The test was performed according to specifications given in the Ph. Eur., 2004 on 20 tablets. The maximum acceptable limit is ± 7.5% deviation of an individual mass from average mass [19].

**Measurement of tablet friability**: Tablet friability was measured using the Roche Friabilator according to Ph. Eur., on ten tablets each [20]. The friability was determined as the mass loss in percent according to Equation.

\[ F = \frac{W_A - W_B}{W_A} \times 100 \]

Where \( f \)-Friability, \( W_A \)-Initial weight (g), \( W_B \)-Final weight (g)

Tablets of friabilities under 1% are acceptable.

**Uniformity of drug content**: The test is mandatory for tablets with 10 mg or less weight of active ingredient [21]. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and the minimum concentration among a range of dilutions to a powdered equivalent to 4 mg of Perindopril was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of 0.1N HCl. The flasks were shaken to mix the contents thoroughly. The volume was made up to the mark with 0.1 N HCl and filtered. One ml of the filtrate was suitably diluted and Perindopril content was estimated at 215.0 nm using a double beam UV-visible spectrophotometer.

**Water absorption**: A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the paper and was allowed for complete wetting. The wetted tablet was then weighed Ratio [23]. Water absorption ratio, \( R \), was determined using following equation

\[ R = \frac{(W_A - W_B)}{W_A} \times 100 \]

Where, \( W_A \)-Weight of tablet before water absorption, \( W_B \)-Weight of tablet after water absorption.

#### In-vitro disintegration time

**In vitro disintegration time (DT) using petri dish method**: The in-vitro disintegration time of the orally disintegrating tablets was determined following the procedure described by Gohel et al (2004) [24]. 10 mL of water at 37°C was placed in a petri dish of 10 cm diameter. The tablet was then carefully positioned in the center of the petri dish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in replicates of three tablet (n=3) and mean were recorded.

**In vitro dissolution study**: Perindopril erbumine tablet test conditions for the dissolution rate studies were used according USP specifications using USP 24, type I apparatus. The dissolution medium was 900 ml of 0.1N HCl. The temperature of the dissolution medium and the rate of agitation were maintained at 37 ± 0.5°C and 50 rpm, respectively. Aliquots of 5.0 ml of the dissolution medium were withdrawn at specific time intervals and the volume replaced by fresh dissolution medium, pre-warmed to 37 ± 0.5°C. The drug concentration was determined spectrophotometrically at 215 nm using UV spectrophotometer (shimadzu 1800).

#### Result and Discussion

**Taste masking of perindopril erbumine by eudragit E100**

The results of the powder flow properties determination are summarised in table 7.

### Table 7: Evaluation of powder characteristics of preliminary batches.

| Sr.no | Formulation | Angle of repose | Bulk density | Tap density | Carr's index | Hausner’s ratio |
|-------|-------------|-----------------|--------------|-------------|--------------|----------------|
| 1     | F₁          | 23.19           | 0.52         | 0.66        | 13.79        | 1.16           |
| 2     | F₂          | 24.10           | 0.52         | 0.66        | 13.79        | 1.16           |
| 3     | F₃          | 24.77           | 0.52         | 0.66        | 13.79        | 1.16           |
| 4     | F₄          | 25.27           | 0.52         | 0.66        | 13.79        | 1.16           |
| 5     | F₅          | 25.97           | 0.52         | 0.66        | 13.79        | 1.16           |
| 6     | F₆          | 26.56           | 0.52         | 0.66        | 13.79        | 1.16           |
| 7     | F₇          | 29.19           | 0.48         | 0.54        | 12.01        | 1.13           |
| 8     | F₈          | 29.74           | 0.48         | 0.54        | 12.01        | 1.13           |
| 9     | F₉          | 29.93           | 0.48         | 0.54        | 12.01        | 1.13           |
| 10    | F₁₀         | 28.27           | 0.48         | 0.54        | 12.01        | 1.13           |
| 11    | F₁₁         | 27.89           | 0.48         | 0.54        | 12.01        | 1.13           |
| 12    | F₁₂         | 29.06           | 0.48         | 0.54        | 12.01        | 1.13           |

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substance at which the volunteers just start feeling the bitter taste is known as taste threshold concentration. Taste threshold bitterness concentration of Perindopril Erbumine was determined by panel of 12 volunteers and was found to be 110 µg/ml in order to mask the bitter taste of Perindopril Erbumine taste masked granules of Perindopril Erbumine by Eudragit E100. It was found that the amount of Perindopril Erbumine dissolved from the drug polymer complex within 30 seconds decreased with increased concentration of Eudragit E100. The drug: polymer complex that yielded drug release values just below the taste threshold concentration was considered optimum and was used for taste masking. It was observed that the Perindopril Erbumine complexed with Eudragit E100 in proportion of 1:3 showed D<sub>30s</sub> values below 100 µg/ml thus it was concluded that Eudragit E100 in proportion to 1:3 was optimum with respect to masking bitter taste of Perindopril Erbumine.

Characterization of perindopril erbumine-eudragit E100 complex

The DSC thermograms of Perindopril Erbumine, Eudragit E100 and Perindopril Erbumine:Eudragit E100 complex are shown in figures 1, 2 and 3 respectively.

The Dsc thermogram of Perindopril Erbumine shows endothermic peak at 154.38°C the thermogram of Perindopril Erbumine complex exhibits a peak at 154.06°C which indicates that there is very slight drug polymer interaction.

Perindopril erbumine, Eudragit E 100 and Perindopril erbumine: Eudragit E100 complex were also analysed using FTIR to check the changes in the IR spectra that might occur due to the slight drug polymer interaction as observed during the DSC studies. The IR spectra of Perindopril erbumine, Eudragit E100 and perindopril erbumine:Eudragit E100 complex are shown in figures 4, 5 and 6 respectively.

The spectrum of pure Perindopril Erbumine showed characteristic peaks at 2928, 1730, 1645, 1568 and 1392. The spectra of Perindopril Erbumine:Eudragit E100 complex showed the characteristic bands of both Perindopril Erbumine and Eudragit E100 with the exception of peak at 2928. This indicates the presence of interaction between drug and polymer.

The XRD diffraction pattern of Perindopril Erbumine shows sharp peak indicating that the drug is of crystalline nature while that of Eudragit E100 shows blunt peaks indicating its amorphous nature. When crystalline Perindopril Erbumine forms complex with amorphous Eudragit E100 the sharp peak of Perindopril Erbumine disappear. This indicates that the drug forms an apparent amorphous
state. The change in crystallinity may be the reason for improved dissolution rate of Perindopril Erbumine when complexed with Eudragit E100. The XRD patterns of Perindopril Erbumine, Eudragit E100 and perindopril erbumine:Eudragit E100 complex are shown in figures 7, 8 and 9 respectively.

**Preliminary trials**

**Characterization of powder flow properties:** The powder flow properties were analysed. It was observed that all formulations showed good flow properties with Carr’s index ranging from 10.34 to 18.51 and Hausner’s ratio below 1.25 which indicated good compressibility and flowability.

**Characterization of tablet properties of preliminary batches:** Orally disintegrating tablets were prepared by direct compression method. A total of twelve formulations and a control formulation (without superdisintegrant) were prepared using different superdisintegrants described above. All the formulations passed weight variation test. The hardness of all the tablets containing superdisintegrants was found in the range of 3.0-4.2 kg/cm². The hardness of control batch was found to be 4.5 kg/cm². Friability was found to be below 1% which was an indication of good resistance of tablets. The results of these evaluation and In-Vitro disintegration time are shown in table 8.

**In-vitro disintegration time**

Various reports have suggested the unsuitability of conventional disintegrating test apparatus when used for testing the disintegration time of orally disintegrating tablets. This is because of extreme operating conditions in the disintegration test apparatus which fail to provide significant discrimination among the orally disintegrating tablets. Furthermore the conventional disintegration test apparatus employs a relatively huge volume of test solution as compared to the volume of saliva present in human buccal cavity. Therefore the results obtained from conventional disintegration test apparatus do not reflect the actual disintegration time; hence in order to get a better response different method of testing the disintegration time was employed. The disintegration time was measured using a petri plate method as described above. It was found that tablets containing 2.5%, 3.75% and 5% of Ac-Di-Sol, 2.5% and 3.75% of Primogel, Tulsion-335 and Tulsion-339 showed disintegration time less than that of controlled tablet. However it was observed that tablets containing 5% of Primogel, Tulsion-335 and Tulsion-339 required more time to disintegrate than the controlled tablet.

The basic principal that governs the action of superdisintegrant Primogel is its extensive swelling which was found to increase with the increasing concentration of Primogel above 3.75% as the contact of water with Primogel led to formation of viscous plug. Due to increased viscosity with increased concentration of Primogel it was observed that further uptake may be retarded and the tablets break into large particles instead of disintegrating into smaller particles. This might be the reason for increased disintegration time with increased amount of Primogel.

Tulsion-335 and Tulsion-339 are swellable ion exchangers. Tulsion-335 is generally used as taste masking agent but owing to its swelling ability it was considered for the study to check its disintegrating efficiency as a superdisintegrant. It was observed that tablets containing Tulsion-335 and Tulsion-339 showed comparatively larger...
disintegration time compared to Ac-Di-Sol and Primogel. Furthermore, it was also observed that increased concentration of Tulsion-335 as well as Tulsion-339 above 3.75% caused a longer disintegration time than controlled tablets. This slow disintegration time may be due to the fact that these superdisintegrants have highly crosslinked structures as compared to other superdisintegrants which resulted into longer disintegration time.

It was observed that tablets containing 2.5%, 3.75% and 5% of Ac-Di-Sol showed lesser disintegration time when compared with the other superdisintegrants at the same concentration levels. Ac-Di-Sol swells to a larger extent when it comes in contact with water. The fibrous nature of Ac-Di-Sol allows intraparticulate as well as extraparticulate wicking of water at lower concentrations. Ac-Di-Sol is prepared by cross linking of sodium carboxymethyl cellulose, which greatly reduces its water solubility while permitting the material to swell and absorb water several times its mass without losing its fibrous structure. However it was observed that there was a prolongation in disintegration time with concentration of 5%. The reason behind this increased disintegration time may be because of increased viscosity and adhesiveness at higher concentration. As the disintegration time of all batches of tablets containing Ac-Di-Sol showed good disintegration time, it was considered as promising candidate for further studies.

Characterization of powder flow properties of optimized batches

The powder flow properties of the optimized batches were also studied and from the observations it was concluded that the optimized batches showed good powder flow properties with good compressibility.

Characterization of tablet properties of optimized batches

Orally disintegrating tablets were prepared by direct compression method. A total of nine optimized formulations were prepared using three different levels of concentration of Avicel PH101 and Ac-Di-Sol described above. All the formulations passed weight variation test and uniformity of content test. The hardness of all the tablets was found in the range of 3.4-4.2 kg/cm². Friability was found to be below 1% which was an indication of good resistance of tablets. It was found that with increase in concentration of Avicel PH101 the hardness of tablets increased. Smaller particle size of Avicel PH101 and strong hydrogen bonding between hydroxyl groups due to presence of large number of free hydroxyl groups and thus interaction force at contact points between particles may be a reason for the increased hardness.

Wetting time

Wetting time was determined for all the nine optimized formulations including the controlled batch it was observed that all formulations showed less wetting time as compared to control batch. It was also observed that the batch A₈ showed the wetting time of 63 ± 2 seconds which was less as compared to other batches. It was also observed that the batches containing 3.75% of Ac-Di-Sol showed better wetting time as compared to tablets containing 2.5% and 5% of Ac-Di-Sol.

Water absorption ratio

Water absorption being one of the important steps in disintegration process it was evaluated. It was observed that with increase in water absorption ration the disintegration of tablets was faster as compared to the tablets with low water absorption ratio. It was observed that the tablets containing 3.75% of Ac-Di-Sol showed highest water absorption ratio of 102.84 ± 0.752 which was the highest among all other batches.

In vitro disintegration time

In-vitro disintegration test was carried out using the method described above. It was observed that the disintegration time of all optimized batches was less as compared to the controlled batch. It was also observed that the disintegration time of batch A₅ was the least (50 ± 2 seconds). Thus it was observed that with lesser concentration of Avicel PH101 upto 15% and 3.75% of Ac-Di-Sol tablets with good wetting time, water absorption ratio and lesser disintegration time were obtained figure 10 shows the disintegration of optimized batch A₉.

In-vitro dissolution studies

The drug release of all optimized batches was found to be better than the controlled batch and marketed tablet. The control batch showed 100% drug release within 15 minutes where as marketed immediate release tablet of Perindopril Erbumine (Conpae 4) showed 100% drug

Table 8: Evaluation of post compression parameters of optimized batches.

| Batches | Weight variation Kg/cm² | Hardness | %Friability | Wetting time | Water absorption ratio | In-vitro disintegration time | % drug release (Q<sub>10</sub>) |
|---------|--------------------------|----------|-------------|--------------|------------------------|-----------------------------|-----------------------------|
| A₁      | Passes                   | 3.6      | 0.40        | 85±2         | 62.23±0.046            | 77±1.52                     | 100.90±1.85                 |
| A₂      | Passes                   | 3.5      | 0.55        | 63±2         | 102.84±0.752           | 50±2                       | 101.29±1.46                 |
| A₃      | Passes                   | 3.4      | 0.46        | 79±1.732     | 77.60±1.105            | 70±1.73                     | 100.40±0.74                 |
| A₄      | Passes                   | 3.4      | 0.35        | 85±1.527     | 68.80±0.732            | 72±2                       | 100.30±1.84                 |
| A₅      | Passes                   | 3.5      | 0.31        | 73±0.577     | 98.32±1.037            | 64±2                       | 99.35±0.70                  |
| A₆      | Passes                   | 3.5      | 0.36        | 109±2        | 63.40±1.173            | 97±1.52                     | 100.63±0.65                 |
| A₇      | Passes                   | 4.2      | 0.25        | 99±1.732     | 60.78±0.751            | 89±2                       | 90.82±3.03                  |
| A₈      | Passes                   | 4.0      | 0.25        | 84±2         | 63.83±0.594            | 74±1.52                     | 92.89±1.19                  |
| A₉      | Passes                   | 4.2      | 0.35        | 106±1.527    | 57.14±0.970            | 97±1.15                     | 88.90±2.4                   |
| Control | Passes                   | 3.8      | 0.40        | 143±0.711    | 51.75±0.242            | 138±0.33                    | 72.32±2.19                  |
release within 25 minutes. It was observed that as the concentration of Avicel PH101 increased the drug release was retarded and the formulations containing very high percentage of Avicel PH101 showed 100% drug release above 5 minutes whereas the batches containing lesser concentration of Avicel PH101 showed maximum drug release within 5 minutes. The graphs showing drug release are given in figures 11-15.

Development of polynomial equation

From the data of in vitro drug release of factorial formulation $A_1$ to $A_9$ polynomial equation for in-vitro drug release was derived using design expert 8.0 software. The polynomial equation for 3$^2$ factorial designs is

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where $Y$ is the dependent variable, $b_0$ is the arithmetic mean response of nine batches and $b_1$ is the estimated coefficient for factor $X_1$. The main effects $X_1$ and $X_2$ represent the average result of changing one factor at a time from its low value to high value. The interaction terms $X_1X_2$ shows how response changes when two factors are simultaneously changed. The polynomial terms $X_1^2$ and $X_2^2$ are included to investigate non linearity.

The % drug release within 5 minutes for the nine batches $A_1$ to $A_9$ showed wide variation from 88.90 to 100% drug release, thus the data clearly indicated that the % drug release in 5 minutes is strongly dependent on selected independent variables.

ANOVA showed that the F value of 26.98 implies significant model. There is only 1.07% chance that the ‘model F-value’ this large could occur due to noise. Values of prob F less than 0.0500 indicate model terms are significant. In this case the model terms $X_1$ and $X_1X_2$ are found to be significant. The $R^2$ value of 0.8752 indicates that the model is in reasonable agreement with the adjusted $R^2$ value.

The final equation relating to the response % drug release in 5 minutes ($Q_{T5}$) is given as follows

Coded factors: % drug release ($Q_{T5}$)=$100.53- 4.56\times X_1 -0.43\times X_2 -0.48\times X_1X_2 -4.35\times X_1^2 -1.12\times X_2^2$

Actual factors: % drug release ($Q_{T5}$)=$100.53-4.56\times \text{avicel PH101 concentration} -0.43\times \text{Ac-Di-Sol concentration} -0.48\times \text{avicel PH101 concentration} \times \text{Ac-Di-Sol concentration} -4.35\times \text{avicel PH101 concentration}^2 -1.12\times \text{Ac-Di-Sol concentration}^2$
It was found that the significance level of coefficient $b_{12}$ and $b_{22}$ were found to be $P=0.4521$ and $0.2507$ respectively, hence they were omitted from the full model to generate a reduced model. The final equation for the reduced model was found to be,

\[
Coded factors: \% \text{ drug release (Q}_{T5}^\circ)=99.78-4.56* X_1 -0.43*X_2 -4.35*X_1^2.
\]

**Actual factors:** $\% \text{ drug release (Q}_{T5}^\circ)=99.78-4.56* \text{ Avicel PH101 concentration}- 0.43*\text{ Ac-Di-Sol concentration}-4.35* \text{ Avicel PH101 concentration}^2$.

The negative signs of coefficients $X_1$ and $X_2$ indicate that as the concentration of binder (Avicel PH101) and superdisintegrant (Ac-Di-Sol) increases the in-vitro drug release decreases. It can also be observed that with increase in the concentrations of Avicel PH101 and Ac-Di-Sol the disintegration time increased.

Validity of the above equation was verified by designing 5 check point formulations ($B_1$ to $B_5$) and determining the in-vitro % drug release ($Q_{T5}^\circ$).

The In-Vitro drug release ($Q_{T5}^\circ$) predicted from the equation derived and those observed from the experimental results are summarized in table 9.

The observed values were in close agreement with the predicted values. This proved the validity of the model. The computer generated response surfaces and counter plots for the dependent variables are shown in figures 16 and 17 respectively (Table 10).

**Conclusion**

From the evaluations we found that Taste masked oro-dispersible tablet of Perindopril erbumine containing 15% Avicel PH101 and 3.75% Ac-Di-Sol gave the best disintegration time and also complete drug release within 5 minutes, it was thus concluded that Eudragit E100 can successfully mask the bitter taste of Perindopril Erbumine in

| Sr.no | Formulation | Weight variation | Friability % | Hardness Kg/cm² | In-vitro disintegration time (Sec) |
|-------|-------------|------------------|--------------|-----------------|-----------------------------------|
| 1     | F₁          | Passes           | 0.40         | 3.4             | 72                                |
| 2     | F₂          | Passes           | 0.55         | 3.5             | 84                                |
| 3     | F₃          | Passes           | 0.46         | 3.5             | 94                                |
| 4     | F₄          | Passes           | 0.35         | 4.0             | 82                                |
| 5     | F₅          | Passes           | 0.60         | 3.8             | 79                                |
| 6     | F₆          | Passes           | 0.55         | 3.5             | 152                               |
| 7     | F₇          | Passes           | 0.60         | 3.0             | 102                               |
| 8     | F₈          | Passes           | 0.35         | 3.6             | 117                               |
| 9     | F₉          | Passes           | 0.20         | 4.2             | 168                               |
| 10    | F₁₀         | Passes           | 0.55         | 3.4             | 81                                |
| 11    | F₁₁         | Passes           | 0.36         | 3.6             | 124                               |
| 12    | F₁₂         | Passes           | 0.31         | 3.8             | 173                               |
| 13    | Control     | Passes           | 0.40         | 3.8             | 138                               |

Table 9: Evaluation of preliminary batches of fast disintegrating tablets of perindopril erbumine.

| Sr.No | Formulation code | $X_1$ | $X_2$ | Predicted values | Observed values |
|-------|------------------|-------|-------|------------------|-----------------|
| 1     | B₁               | 0.00  | -1.00 | 99.870           | 100.058         |
| 2     | B₂               | -0.89 | 0.31  | 100.667          | 100.393         |
| 3     | B₃               | -0.77 | -0.17 | 100.857          | 100.423         |
| 4     | B₄               | 0.03  | -0.28 | 100.019          | 100.014         |
| 5     | B₅               | -0.01 | -0.45 | 100.120          | 100.307         |

Table 10: Summary of observed and predicted values of checkpoint batches.

![Figure 16: 3D response–surface showing effect of factorial variables on % drug release.](image)
the ratio of 1:3 and orally disintegrating tablets of Perindopril can thus be formed successfully by direct compression method.

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Figure 17: Contour plot showing effect of factorial variable on in-vitro % drug release.