

RESEARCH ARTICLE

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF PERINDOPRIL ERBUMINE USING NATURAL SUPERDISINTEGRANT

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ABSTRACT:

Oral disintegrating tablets are emerging trend in Novel drug delivery system & received increasing demand & popularity due to ease of administration & better patient compliance. In recent years superdisintegrant have been employed to develop effectual mouth dissolving tablet & to overcome limitation of conventional tablets. In present study attempt was made to compare to disintegrating efficiency of natural superdisintegrants. Main aim of using *Ocimum basilicum* as natural superdisintegrant was to achieve quick onset of action, increases water uptake with short wetting time & decreasing disintegration time by cost effective direct compression method. 3 preliminary batches were prepared & these are evaluated for precompression parameter like angle of repose, Carr's index & post compression parameters like wetting time, water absorption ratio, in vitro disintegration. Hardness, friability of all formulations found within limit. Best formulation F2 batch had shown good hardness, friability, disintegration time, swelling time. Present study revealed that mucilage obtained from *Ocimum basilicum* was effective for their disintegrating property.

Keywords: Direct Compression, ODTs, Natural Superdisintegrant *Ocimum basilicum*

INTRODUCTION:

As tablets are most popular solid dosage form & as oral route of administration are more preferable, ODTs gain more increasing demand in recent years. Due to quick disintegration of ODTs in buccal mucosa it has been attracted a great deal of attention. Also these ODTs have been proved to be ideal for geriatric as well as periatic patients. Oral disintegrating tablets are also called porous tablets, fast disintegrating tablets, mouth dissolving tablets. Perindopril ter-butyl amine is an antihypertensive drug belongs to a group called Angiotensin Converting Enzyme (ACE) inhibitors¹. Inhibition of ACE results in decreased plasma Angiotensin II, leading to decreased vasoconstriction, increased plasma rennin activity and decreased aldosterone secretion. So that fall in blood pressure & also in workload of the heart takes place. As Perindopril tert-butyl amine is a pro-drug ultimately it is hydrolyzed with the help of esterases & forms active metabolite Perindoprilat. Perindopril is rapidly absorbed, reaching peak plasma concentration about 1 hour after a single oral dose whereas Perindoprilat reaches peak plasma concentrations in 2 to 6 hours. The Perindopril gives 70% bioavailability.^{2,3} As food reduces the conversion of Perindopril to Perindoprilat, presence of food does not show any effect. Mucilage was obtained from natural origin & used as natural superdisintegrant. Using these ODTs were prepared by direct compression method. Development of ODTs of Perindopril Erbumine by using natural superdisintegrant *Ocimum basilicum* is one of the important innovations. Due to swelling mechanism of superdisintegrant that tablet should disintegrate rapidly usually within matter of seconds when placed on tongue.

MATERIAL & METHOD:

Perindopril Erbumine (Hetero drugs Pvt Ltd), Manitol(Oswal chemicals). *Ocimum basilicum* (nursery). Magnesium stearate, microcrystalline cellulose, Talc was procured from Maple Biotech Pvt Ltd. All the chemicals

used were of Analytical grade & distilled water was used throughout the work.

Experimental

Direct Compression Method: Excipients like mannitol, talc, microcrystalline cellulose were passed through sieve. Magnesium stearate used for lubrication purpose.

Extraction of mucilage from *Ocimum Basilicum*⁴⁻⁷:

- 1) *Ocimum basilicum* plant was procured from the local nursery and the seeds were separated from same.
- 2) To it we added the alkali & heated it.
- 3) Rinsed it with water.
- 4) Soaked it for 6 to 7 hours. Separated out mucilage & discarded the seed coat & cotyledon.
- 5) As the mucilage contains the water it was dried until it became completely free from moisture.
- 6) It was Grind & used as dry powder.

Preformulation Studies:

Solubility Studies Solvents like distilled water & ethanol were used for solubility determination of Perindopril Erbumine.

Identification of Pure Drug FTIR spectroscopy was used for identification of pure drug.

Melting Point Determination Determination of melting point was done by capillary method.

Determination of λ_{max}

Preparation of Stock Solution: An accurately weighed 10 mg of Perindopril Erbumine was transferred in a 100ml volumetric flask. To the flask phosphate buffer was added in small proportion so as to dissolve Perindopril Erbumine. The volume was made up to 100ml with

phosphate buffer pH 6.8 to get a concentration of 100 μ g/ml

Determination of λ max: 20 μ g/ml solution of Perindopril Erbumine was prepared in diluent. The resulting solution was scanned in UV-Vis spectrophotometer from 400- 200nm to determine the λ max. The λ max of Perindopril Erbumine was found to be 215 nm.

Preparation of Calibration Curve for Perindopril Erbumine: Aliquots (0.2-2.0ml) from standard stock solution were pipetted out in series of ten 10 ml volumetric flask and the volume was made up with phosphate buffer. The absorbance was measured in triplicate at 215 nm against blank.

Fourier Transform Infrared Spectroscopy (FTIR): The drug was subjected to IR spectroscopy using FT-IR (SHIMADZU 8400S) and the KBr disk method.

Preparation of Batches of Orosoluble Tablets of Perindopril Erbumine:

Table 1: Formulation of Preliminary Batches Of fast disintegrating tablets of Perindopril erbumine

Ingredients	F ₁ (mg)	F ₂ (mg)	F ₃ (mg)
Perindopril erbumine	4	4	4
Mannitol	137	134.5	132
Mucilage	5	7.5	10
Microcrystalline cellulose	50	50	50
Magnesium stearate	2	2	2
Talc	2	2	2
Total	200	200	200

Evaluation of precompression parameters

Precompression Parameters:

1. 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.

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose

h is height of pile

r is radius of the base of pile

2. Bulk Density: Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

$$LBD = \text{Weight of the powder} \quad (a)$$

Volume of the packing

$$TBD = \text{Weight of the powder} \quad (b)$$

Tapped volume of packing

3. Carr's Compressibility Index: The compressibility index of the granules was determined by Carr's compressibility index.

For formulating orosoluble tablets Drug, mannitol. Magnesium stearate, talc, natural superdisintegrant (*Ocimum basilicum*) were used. Mannitol was used as diluents and imparts cooling sensation in Mouth. Microcrystalline cellulose was used as binder. The concentrations of *Ocimum basilicum* was varied between 2.5% to 5 %. All ingredients were passed through mesh 250 μ m for preparation of granules. The ingredients were mixed according to batches. Magnesium stearate and talc were added in a final step and mixed. This mixture was subjected for evaluation of pre compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio & after that it 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 prepared tablets were evaluated for wetting time, weight variation, thickness, friability, hardness and in-vitro disintegration time, In-vitro dissolution time.

$$\text{Carr's Index (\%)} = \text{TBD} - \text{LBD} / \text{TBD} \times 100 \quad (c)$$

4. Hausner's Ratio: It is determined by comparing tapped density to the bulk density by using following equation

$$\text{Hausner's ratio} = \text{tapped density} / \text{bulk density}.$$

Evaluation of Tablet properties:

Uniformity of Weight⁸ The test was performed according to specifications given in the Ph. Eur., 2004 on 20 tablets. The maximum acceptable limit is $\pm 7.5\%$ deviation of an individual mass from average mass.

Measurement of Tablet Friability⁹ Tablet friability was measured using the Roche Friabilator according to Ph. Eur, on ten tablets each. The friability was determined as the mass loss in percent according to Eq

$$F = (WA - WB) / WA \times 100$$

Where f—Friability, WA—Initial weight (g), WB—Final weight (g)

Tablets of friabilities under 1% are acceptable.

Measurement of Tablet hardness: The crushing strength of tablets was measured by a Monsanto Hardness Tester

Wetting Time¹⁰: A piece of tissue paper was folded twice and placed in small petri dish containing 6 ml of phosphate buffer (pH 6.8) the tablet was placed on it and the time required for complete wetting of tablet was recorded.

Water Absorption Ratio¹¹: 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. Water absorption ratio, R, was determined using following equation

$$R = (WA - WB) / WB * 100$$

Where, WB—Weight of tablet before water absorption, WA—Weight of tablet after water absorption

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)¹². 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 II apparatus. The dissolution medium was 900 ml of Phosphate buffer (pH 6.8). 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 & DISCUSSION:

Preformulation studies:

- **Solubility studies:** Perindopril was freely soluble in distilled water & ethanol after solubility determination.
- **Melting point determination:** After performing capillary method melting point of Perindopril found in range of 154-156°C.
- **Standard calibration curve of Perindopril Erbumine:**

λ_{max} was found to be at 215 nm, so the calibration curve of perindopril Erbumine was developed at this wavelength. The calibration curve showed linearity between 2-10 µg/ml concentration ranges. The standard calibration curve of

Perindopril Erbumine was determined in phosphate buffer pH 6.8 by plotting absorbance against concentration at 215 nm the r^2 value was found to be 0.998. The calibration curve is presented in as follows:

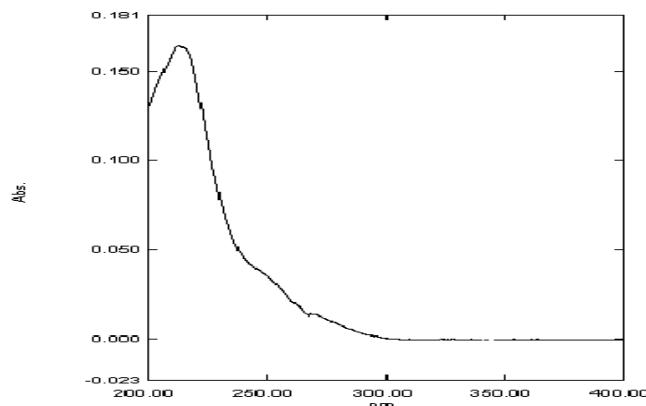


Figure 1: λ_{max} of Perindopril Erbumine

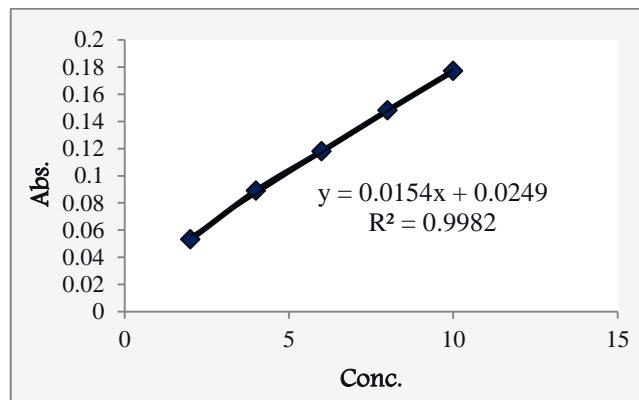


Figure 2: Calibration curve of Perindopril Erbumine

- **Identification of Pure Drug:** FT-IR spectroscopy was used to determine the functional group present in the pure drug sample. The characteristic peaks were observed at 2928cm⁻¹ corresponding to N-H stretching, 1730cm⁻¹, corresponding to C=O stretching, 1645cm⁻¹ corresponding to C=O stretching and 1568 cm⁻¹ corresponding to C=C stretching. IR SPECTRA of Perindopril as follows:

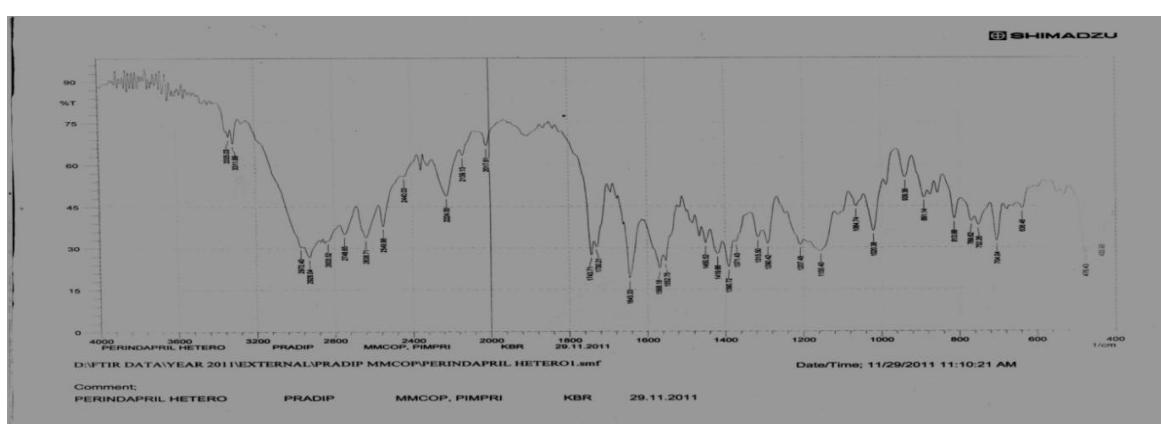


Figure 3: IR Spectra of Perindopril Erbumine

Evaluation of preliminary characteristics of Perindopril Erbumine:

The powder flow properties were analyzed. It was observed that all formulations showed good flow properties with Carr's index ranging from 11.66 to 19.04 and Hauser's ratio below 1.25 which indicated good compressibility and flowability.

Table 2: Evaluation of preliminary characteristics of Perindopril Erbumine

Sr no.	Formulation	Angle of repose	Bulk density	Tap density	Carr's index	Hauser's ratio
1.	F1	23.86	0.5	0.58	13.79	1.16
2.	F2	24.51	0.47	0.5	18.86	1.16
3.	F3	26.69	0.5	0.59	15.25	1.18

Evaluation of post compression parameters of preliminary batches of Perindopril:

The preliminary batches were evaluated for the post compression characteristics such as uniformity of weight, friability, hardness and In-Vitro Disintegration. The results of the evaluation are given in the following table.

Table 3: Evaluation of post compression parameters of preliminary batches of Perindopril

Batches	Weight variation	Hardness Kg/cm ²	%friability	Wetting time{min}	Water absorption ratio	In-vitro disintegration time	% drug release (Q _{5 min})
F1	Complies	3.7	0.65	1.25	65	60sec	100.56±1.84
F2	Complies	4.1	0.68	1.075	99.5	40sec	100.57±1.85
F3	Complies	4.4	0.71	2	57.5	77sec	100.64±0.70

In vitro disintegration time:

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 natural superdisintegrant showed disintegration time that was within 3 minutes. The basic principal that governs the action of superdisintegrant *Oscimum basilicum* is its extensive swelling which was found to increase with the increasing concentration of *oscimumbasilicum* above 3.75% as the contact of water with superdisintegrant led to formation of viscous plug. Due to increased viscosity with increased concentration of *oscimumbasilicum* it was observed that further uptake may be retarded and the tablets break into large particles instead of disintegrating into smaller particles.

% drug release:

Perindopril erbumine tablet test conditions for the dissolution rate studies were used according USP specifications using USP 24, type II apparatus. The dissolution medium was 900 ml of 0.1N Phosphate buffer. 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).

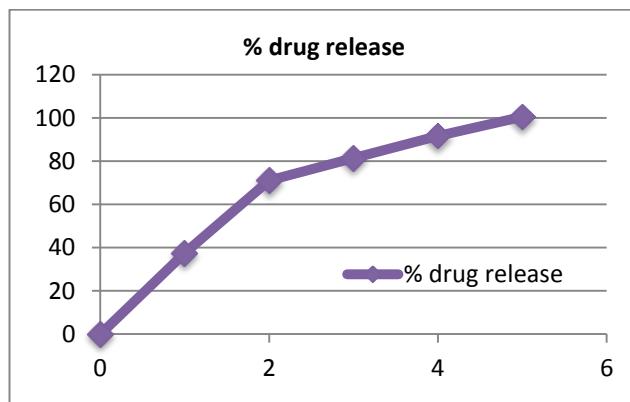


Figure 4: In-Vitro % Drug release of F1 Batch

{X- Axis: Time in min Y-Axis: % Drug release}

Table 4: In vitro % drug release

Batch	Time {min}					
	0	1	2	3	4	5
F ₁	0%	37.42%	71.07%	81.37%	91.69%	100.56%
F ₂	0%	41.80%	73.99%	84.30%	94.6%	100.57%
F ₃	0%	35.96%	60.84%	82.82%	85.84%	100.64%

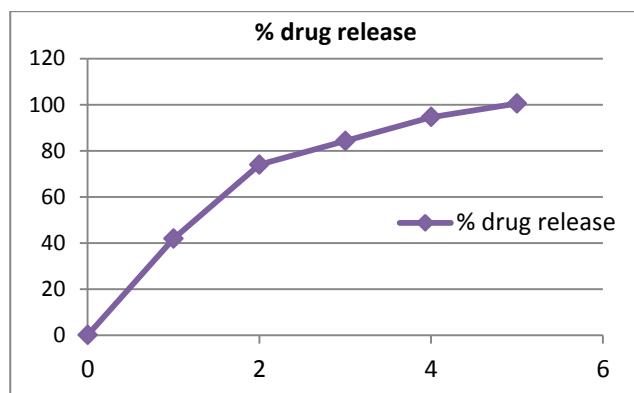


Figure 5: In-Vitro % Drug release of F₂ Batch
 {X- Axis: Time in min Y-Axis: % Drug release}

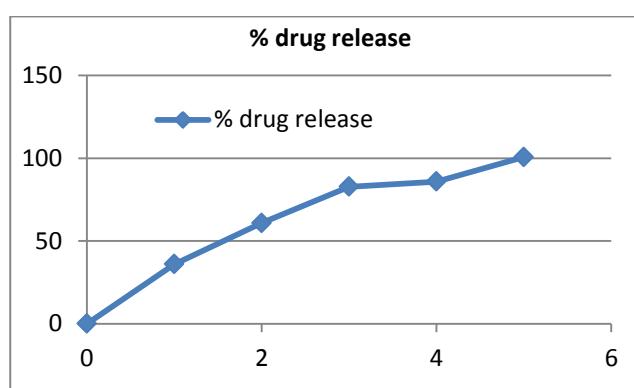


Figure 6: In-Vitro % Drug release of F₃ Batch
 {X- Axis: Time in min Y-Axis: % Drug release}

Wetting time:

Average Wetting time of all 3 batches was obtained & found in range of 1.44.. It was also observed that the batch

F2 showed the wetting time of seconds which was less as compared to other batches.

Water absorption ratio:

It was observed due to water uptake & swelling behavior of natural superdisintegrant. It was observed that with increase in water absorption ratio the disintegration of tablets was faster as compared to the tablets with low water absorption ratio. F2 batch has good water absorption ratio.

In vitro disintegration time:

This was carried out as mentioned above. It was observed that F2 batch has least in vitro disintegration time with good wetting time, good water absorption ratio

CONCLUSION:

The rapid disintegrating tablets have potential advantages as compared to conventional dosage forms. Because of increased patient demand. Good bioavailability & rapid onset of action, these are expected to become more popular in today's leading World. Choice of drug Perindopril was associated with its ACE property. Ocimum basilicum plant was procured from the local nursery and the seeds were separated from same. Isolated Ocimum basilicum seeds mucilage was characterized on the basis of its organoleptic properties; micromeritic Properties (Angle of Repose, Bulk Density, Tapped Density, Compressibility Index, Hauser's Ratio). Along with melting point and solubility determination was also performed. In the present investigational study, it was concluded that mucilage obtained from natural superdisintegrant *Ocimum basilicum* showed better disintegrating property. So it was concluded that better results were obtained with F2 batch. Thus it can be concluded that *Ocimum basilicum* may be explored as high functionality excipient for future applications.

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