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DEVELOPMENT AND EVALUATION OF EXTENDED-RELEASE TABLETS OF LOSARTAN POTASSIUM & ENALAPRIL MALEATE"

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ABSTRACT

The oral route of drug delivery is considered as the preferred and most patient convenience means of drug administration. Consequently, much effort is directed during drug discovery to identify orally active candidates that will provide reproducible and effective plasma concentration in vivo. The reality is that many compounds are either incompatibility or ineffectively absorbed after oral administration (bioavailability is an issue), or that the required during frequency is too short to enable once or twice daily administration (pharmacokinetic half-life in an issue). Conventional drug delivery systems have little or no control over drug release. This may result from constantly changing, unpredictable plasma concentrations. The rate and extent of drug absorption from conventional drugs may vary greatly depending on factors such as the pysico-chemical properties of drugs, presence of excipients the presence or absence of food, pH of the gastro-intestinal tract, and so on.

KEYWORDS: oral route, half-life, Conventional drug delivery systems, administration.

INTRODUCTION

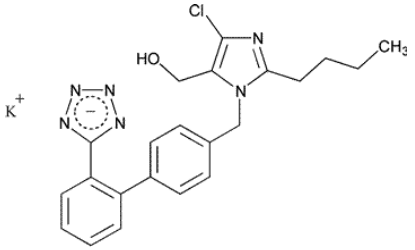
A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. Typically, the ingredients which comprise the tablet blend include the active pharmaceutical ingredients (API) together with various excipients which not only act as carrier for the drug compound, but which also enhance its therapeutic effect, or efficacy. Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia, Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet. All medicaments are available in the tablet form except where it is difficult to formulate or administer.[1]

The objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in the proper form, at or over the proper time and in the desired location and to have its chemical integrity protected to that point.[2]

BILAYER TABLETS: The bilayer tablet concept has long been utilized to developed sustained release formulations. Bilayer tablet has a fast-releasing layer and contain second layer to sustain the drug release. A fast-releasing granules lead to sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug release from the sustaining granules. Bilayer tablet consist of two layers of tablet in a single unit. This approach can be used for the treatment of various diseases which require not only single drug but also combination of drugs.[3,4]

Drug profile: Losartan Potassium

1. **Structural formula**



2. **Empirical Formula:** C22H22ClKN6O
3. **Molecular Weight:** 461.0g/mol
4. **IUPAC Name**: (2-butyl-4-chloro-1-{[2'-(1H-tetrazol-5-yl) biphenyl-4- yl Methyl}-1H-imidazol-

5-yl) methanol potassium salt
5. **Category:** Antihypertensive
6. **Class**: Angiotensin II Receptor Antagonist
7. **Dose:** Orally – 50 mg twice a day
8. **Description:** White to off- white crystalline powder
9. **Odour:** Odourless
10. **Melting Point:** 183-184˚C

11. **Solubility:**
Water: 400mg/ml
Organic solvent: Methanol: 400mg/ml

12. **Storage:** Keep away from Heat, Spark, and Flame
13. **Uses:** Hypertension, Congestive Heart Failure, Diabetic Neuropathy, Myocardial Infarction.
14. **Clinical Pharmacology:** Blocks vasoconstriction and aldosterone - secreting effects of angiotensin II at various receptor sites, including vascular smooth muscle and adrenal glands Also increases urinary flowand enhances excretion of chloride, magnesium, calcium, and phosphate.
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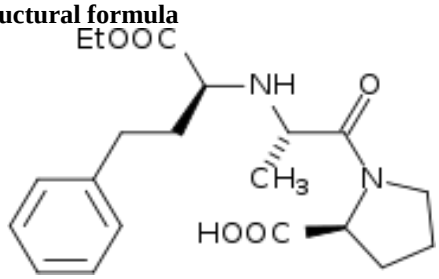
16 Adverse Effect: Hypotension, Hyperkalemia, Headache.

Enalapril Maleate

1. **Structural formula**



2. **Empirical Formula:** $C_{20}H_{28}N_2O_5$
3. **Molecular Weight:** 376.447 g/mol
4. **IUPAC Name**: (2S)-1-[(2S)-2-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}propanoyl]pyrrolidine-2-carboxylic acid.
5. **Category:** Antihypertensive.
6. **Class**: Angiotensin Converting Enzyme Antagonist.
7. **Description:** White to off- white powder.
8. **Odour:** Odourless.
9. **Melting Point:** 143 – 144.5 ˚C
10. **Solubility:**
Water: sparingly soluble
Organic solvent: Methanol: freely soluble
Ethanol: soluble
11. **Storage:** Keep away from Heat, Spark, and Flame
Uses: Hypertension, Congestive Heart Failure, Diabetic Neuropathy, Myocardial Infarction.

Clinical Pharmacology: Enalapril, after hydrolysis to enalaprilat, 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 decrease aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril maleate alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril maleate plus a thiazide diuretic, there was essentially no change in serum potassium.[5,6,7]

12. **Adverse Effect:** Hypotension, Hyperkalemia, Angiodema, Dysguesia.

Formulation of Table; For the Formulation of immediate release tablet, we will choose direct compression method.

Table 01: Formula for Tablet Preparation.

S. No.	Ingredient	Quantity
1	Enalapril Maleate	25 mg
2	Lactose	125 mg
3	Sodium Starch glyconate	50 mg
4	MCC	30 mg
5	Talc	18 mg
6	Magnesium stearate	02 mg
7	Color	qs
	Total Weight	250 mg

Table 2: Formula for Tablet Preparation.

S. No.	Ingredient	F 1	F 2	F 3	F 4	F 5	F 6
1	Losartan Potassium	75 mg	75 mg	75 mg	75 mg	75 mg	75 mg
2	Lactose	150 mg	160 mg	170 mg	150 mg	160 mg	170 mg
3	HPMC	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
4	MCC	30 mg	30 mg	30 mg	30 mg	20 mg	10 mg
5	Ethyl cellulose	30 mg	20 mg	10 mg	30 mg	30 mg	30 mg
6	Talc	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
7	Magnesium Stearate	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
8	Titaniumoxide	3 mg	3 mg	3mg	3mg	3mg	3mg
Total Weight		**300 mg**	**300 mg**	**300 mg**	**300 mg**	**300 mg**	**300 mg**

Evaluation of Bilayer Tablet

Weight Variation Test: Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated.[8,9]

Table 3: Weight variation of Tablets.

Average weight of tablet	Percentage weight variation
130 mg or less	10%
More than 130 mg and less than 324 mg	7.5%
324 mg or more	5%

Friability Test: Weighed amount of 20 de-dusted tablets were subjected to rotating drum of friability test apparatus. The drum rtated at a speed of 25 rpm. The apparatus was operated for 4 minutes and reweighed the tablets.[10]

Hardness Test: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using pfizer hardness tester. It was expressed in kg/cm^2. Ten tablets were randomly selected from each formulation and hardness of the same was determined. The average value was also calculated.[11]

Thickness Test: Control of physical dimension of the tablets such as sizes and thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. The dimensional specifications were measured using screw gauge. Twenty tablets were randomly selected from formulations and thickness was measured individually. It was expressed in millimeter and average was calculated.

Wetting time: A piece of tissue paper folded double was placed in a Petri dish containing 6 ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^0C. Wetting time corresponding to the time taken for the tablet to disintegrate when kept motionless on the tongue was calculated.[12]

Water absorption ratio: A piece of tissue paper folded twice was placed in a small petri dish (7.5cm) containing 7 mlwater. A tablet was put on the tissue paper & allow to wet completely. The wetted tablet was then weighed.

Disintegration Test: The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for FDT needs to be modified as disintegration is required without water thus the test should mimic disintegration in salivary contents. For this purpose a Petri dish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of Petri dish and time for tablet to completely disintegrate into fine particle was noted. (Table 4).

Sr. No.	Batch No.	Thickness (mm)	Weight variation (mg)	Friability (%)	Hardness (kg/cm^2)
1	B1	2.32	550 ± 5.12%	0.87	5.1
2	B2	2.43	550± 5.13%	0.58	5.2
3	B3	2.37	550 ± 5.14%	0.69	5.1
4	B4	2.34	550 ± 5.12%	0.79	5.0
5	B5	2.40	550 ± 5.13%	0.59	5.0
6	B6	2.36	550± 5.12%	0.65	5.0
Sr. No.	**Batch No.**	**Disintegration Test**		**Drug Content**	
		Layer 1	**Layer 2**	**Enalapril**	**Losartan**
1	B1	2 min	5 min	90.54	90.24

2	B2	2 min	8 min	91.22	92.12
3	B3	2 min	8 min	92.12	92.26
4	B4	2 min	6 min	93.55	93.56
5	B5	2 min	9 min	99.50	99.88
6	B6	2 min	7 min	95.26	94.89

In Process Quality Control

Table 5: In Process Quality Control.

For Immediate Release IPQC						
Sr. No.	**Batch No.**	**Angle of repose in degrees**	**Bulk density (g/ml)**	**Tapped density (g/ml)**	**Compressibility Index (%)**	**Hausnerratio**
1	B1	25.62	0.6682	0.6872	12.90%	1.028438

Table 06: Pre-compression parameters of all formulations.

For Sustain Release layer IPQC						
S. No.	**Batch No.**	**Angle of repose in degrees**	**Bulk density (g/ml)**	**Tapped density (g/ml)**	**Compressibility Index (%)**	**Hausner ratio**
1	B1	25.61	0.6681	0.6871	12.92%	1.028439
2	B2	25.07	0.6654	0.6954	10.77%	1.045086
3	B3	26.56	0.6645	0.6864	12.78%	1.032957
4	B4	26.70	0.6458	0.6874	10.87%	1.064416
5	B5	25.78	0.6445	0.6895	10.54%	1.069822
6	B6	24.89	0.6774	0.6875	11.7%	1.01491

Stability Studies: Stability studies of the selected formulated tablets were carried out by keeping the tablets at room temperature and at 40°C ± 2°C / 75 ± 5% RH (stability chamber) for 30days. The results are tabulated below. From the stability studies it was found that formulation was stable at room temperature and at 40°C ± 2°C / 75 ± 5% RH for a period of 30 days. There was no appreciable change in physical properties, drugrelease and drug content during the testing period.[13]

Table 07: Stability study Results.

Parameter	**Initial**	**At room temperature (After 30 days)**	**At 40°C ± 2°C / 75 ± 5% RH (stability chamber) (After30 days)**
Hardness(kg/cm^2)	2.1	2.1	2.0
Friability (%)	0.66	0.72	0.72
Drug Release (%)	93.63	94.44	94.21
Drug content (%)	99.88	99.10	97.75

Conclusion: Hypertension is one of the most common chronic diseases worldwide. However, many people have hypertension without awareness and treatment of the disease, indicating it is necessary to provide some basic knowledge and essential information of hypertension to our audience, upper primary pupils at early stage of their lifes to prepare them early in prevention or management of this disorder in their future life.

Many risk factors are related with hypertension. Avoiding the factors help to prevent hypertension, reduce symptoms and prolong lives. Complications of hypertension are major sources of mortality. Reducing blood pressure with medication or keeping it within normal range will prevent, attenuates or reduce these complications.

Treating hypertension in very old patients reduces stroke and heart failure with no effect on total mortality. The most reasonable strategy is the one associated with significant mortality reduction; thiazides as first-line drugs with a maximum of two drugs. The combinational therapy for hypertension is the need of disease to give patient better compliance.

In Bilayer tablet the benefit was that it gives both the immediate and Sustain release. Drug release from the first releasing layer leads to a sudden rise in the blood concentration. The time taken to achieve steady state plasma concentration is minimum. However the blood level is maintained in steady state, as the remaining drug is releasing slowly from the sustained layer.

In this bilayer tablet Enalapril Maleate gives immediate release and Losartan Potassium gives sustain release which maintains the blood serum level and give effect for a long time.

The Appearance oof Losartan Potassium and Enalapril Maleate was visually observed and found to be complies with the Standard limits.

- The Tapped Density of the drug of Losartan Potassium and Enalapril Maleate were found to be 0.6970 & 0.7492.
- The Bulk Density of the drug of Losartan Potassium and Enalapril Maleate were found to be 0.6173 & 0.6623
- The Angle of Repose of the drug of Losartan Potassium and Enalapril Maleate were found to be 28.89 & 33.02.
- The Carr's Index of the drug of Losartan Potassium and Enalapril Maleate was found to be 11.44 & 11.60
- The Hausner Ratio of the drug of Losartan Potassium and Enalapril Maleate was found to be 1.1291 & 1.312
- The Weight Variation of the tablet for B1, B2, B3, B4, B5, B6 was found to be 600 ± 5%, 605 ±5%, 603 ± 5%, 599 ± 5%, 600 ± 5%, 600± 5%
- The thickness of the tablet for B1, B2, B3, B4, B5, and B6 was found to be 2.32, 2.43, 2.37, 2.34, 2.40, 2.36
- The Friability of the tablet for B1, B2, B3, B4, B5, and B6 was found to be 0.87, 0.58, 0.69, 0.79,0.59, 0.65
- The Hardness of the tablet for B1, B2, B3, B4, B5, and B6 was found to be5.1, 5.2, 5.1, 5.0, 5.0, 5.0
- It can be concluded that Extended-release tablets of Losartan potassium & Enalapril can be performed by direct compression method.

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