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FORMULATION AND EVALUATION OF SUBLINGUAL TABLET OF LOSARTAN POTASSIUM

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ABSTRACT:-

The objective of the current study was to develop and optimize a sublingual tablet of Losartan potassium, which is an effective drug in the treatment of hypertension. Owing to number of advantages dissociated with the quick onset of action and it by passes the liver. Sublingual tablets offer effective and easier way for management of Hypertension. The basic approach used in development of Sublingual tablet was the use of super disintegrates by direct compression method. Oral mucosal drug delivery is one of the promising method of systemic drug delivery which offers several advantages. The literal meaning sublingual is "under the tongue". Hence the method includes the administrating drug via mouth so that it is absorbed via blood vessels (systemic) present under the tongue. Sublingual tablet is tablet that dissolves or disintegrates in the oral cavity without need of drinking water. Sublingual tablet traditionally have been used as an effective method to improve the dissolution properties and bioavailability of water-soluble drugs. In the preformulation studies, Losartan potassium was characterized by its physiochemical properties such as melting point, solubility, partition coefficient, UV and FTIR studies. UV spectroscopic method was established for quantitative estimation of the drug and the absorbtion maxima were 234 nm. The tablets were formulated by using the direct compression technique. The post compression studies i.e. shape, size, weight variation, hardness, friability and wetting time determined the quality of the product.

Key words:-Sublingual, oral cavity, mucous, bioavailability, Gland, Losartan potassium, Systemic, Solubility.

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INTRODUCTION:-

Currently there is a high level of interest in the use of the oral cavity as a portal for drug entry to the systemic circulation. As a site for drug delivery the oral cavity offers advantages over the conventional gastrointestinal route and the parenteral and other alternative routes of drug administration. It provides direct entry into the systemic circulation thereby avoiding the hepatic first pass effect, ease of administration and the ability to terminate delivery when required. In addition the membranes that line the oral cavity are readily accessible and exhibit robustness and fast cellular recovery following local stress or damage. The oral cavity appears therefore to be a potential site for the delivery of drugs to the systemic circulation. However, this site is associated with limitations that restrict its use as a route for the systemic delivery of drugs. The low permeability of the membranes that line the oral cavity results in a low flux of drug; there appears to be the need to develop strategies which enhance drug penetration to improve bioavailability. The environment of the oral cavity and the continual secretion and swallowing of saliva are unique problems which need to be considered pre-formulation to ensure successful delivery of a drug via this route. This review highlights the advantages of systemically delivering drugs via the oral mucosa and discusses the membrane, drug, dosage form and environmental issues which limit its use as a site for systemic drug delivery. The oral

mucosa may be potential site for controlled or sustained drug delivery. Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance.

The target sites for local drug delivery in the oral cavity include the following: Buccal, Sublingual, Periodontal region, Tongue, Gum. Other desirable targeting sites adjacent to oral cavity include pharynx, larynx, adenoids and tonsils. Sublingual administration can offer an attractive alternative route of administration. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation bypassing enzyme degradation in the gut and liver. In addition, the thin sublingual mucosa (about 190 µm compared to 500–800 µm of the buccal mucosa) and the abundance of blood supply at the sublingual region allow excellent drug penetration (absorption) to achieve high plasma drug concentration with a rapid onset of action. A well-established example is nitroglycerin, which is used for the treatment of acute angina[1].

Overview of the oral mucosa:-

The anatomical and physiological properties of the oral mucosa have been extensively reviewed by several authors. The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue account for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells. The primary function of the oral epithelium is to protect the underlying tissue against potential harmful agents in the oral environment and from fluid loss. Beneath the epithelium are the basement membrane, lamina propia and submucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue. Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingiva (gums). The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity[2].

Sublingual delivery: Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarted, uncooperative, nauseated or on reduced liquid intake/diets have difficulties in swallowing these dosage forms. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth[3].

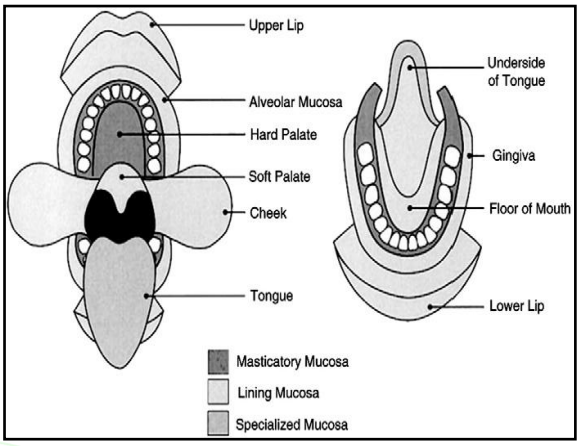

Fig.1:- Overview of Oral Mucosa

LITERATURE SURVEY:-

Talluri Manjula *et al.* (2016) made an attempt to develop and evaluate sublingual tablets of Zolpidem Tartrate used for the short-term treatment of insomnia. The tablet was prepared by direct compression technique using two classes of super disintegrates represented by Crospovidone and Sodium Starch Glycolate (SSG) and the efficiency of these super disintegrants in the tablets was compared with various tests like disintegration time, wetting time, water absorption ratio, *in-vitro* dissolution profile and stability study. *In-vitro* drug release from the formulations was studied using buffer pH 6.8.**Singh Baljinder** *et al.* (2015) made a new attempt to fabricate and evaluate the sublingual tablet of telmisartan using different superdisintegrants. Research work was done to improve the solubility ultimately bioavailability of Telmisartan by encapsulating it inside the cavity of β-cyclodextrin. Sublingual tablets (6 batches) using polymers like CP, SSG and CCS by employing direct compression method. The results of pre-compression parameters (Angle of repose, Carr's index and Hausner ratio) were in acceptable range as per the specifications given in IP.

El-Setouhy D.A.*et al.* (2015) prepared bioenhanced sublingual tablets (BESTs) of zolmitriptan using novel surfactant binder to enhance tablet disintegration and dissolution. Microencapsulated polysorbate 80 (SepitrapTM80) were included in the composition of BESTs to enhance the drug transport through the sublingual mucosa. The *in vivo* pharmacokinetic study using human volunteers showed a significant increase in the rate and extent of sublingual absorption with less variations of Tmax after sublingual administration of both BEST-5 and Zomig-ZMT ODT[4].

Novotna Stanislava *et al.* (2014) evaluated the efficacy and safety profile of fentanyl Ethypharm (FE) in relieving breakthrough pain (BTP) in opioid-treated

cancer patients. This newly developed galenic formulation with a higher early systemic exposure and a shorter T_{max} compared with oral trans mucosalfentanyl citrate makes a particularly suitable formulation for the management of BTP in opioid-treated cancer patients due to the rapid onset of action[5-6].

PRE-FORMULATION STUDIES:-

Physical Appearance

Physical appearance of drug was examined by its various organoleptic properties like color, state, odor and taste.

Melting Point Determination

The melting point of a solid is defined as the temperature at which the solid and liquid are in equilibrium at a total pressure of 1 atm. experimentally, melting point is actually as a range of temperature in which the first crystal starts to melt until the temperature at which the last crystal just disappears.

Solubility[7-8]

Qualitative Solubility of Losartan potassium in Different Solvents

The solubility was carried out in different solvents like methanol, phosphate buffer, and acetone. A pinch of Losartan potassium was added into separate test tubes, containing 5 ml of each solvent. The entire test tubes were shaken for 5-10 min. Then the solubility was visually determined.

Quantitative Solubility of Losartan potassium in Different Solvents

Pure Losartan potassium was added to 10 ml of phosphate buffer pH 6.8 in 25 ml volumetric flasks. The volumetric flasks was capped properly and shaken at temp. 37±2 °C in a temperature controlled water bath (Shaking water bath) for 48 hr. Resultant samples containing undissolved solid dispersions suspended in the volumetric flasks was filtered through Whatman filter paper, suitably diluted with phosphate buffer pH 6.8 and analyzed by UV spectrophotometer at 234 nm.

Table.1:- USP and BP Solubility criteria[9-10]

Terms	Approximate Volume of Solvent in Milliliters Per Gram of Solute
Very Soluble	< 1
Freely Soluble	1-10
Soluble	10-30
Sparingly	30-100
Slightly Soluble	100-1000
Very Slightly Soluble	1000-10000
Practically Insoluble or	>10000

Determination of Absorption Maxima (λ_{max})

A UV absorption maxima of the drug was determined by scanning (10 µg/ml) solution with phosphate buffer between 200-400 nm.

Partition Coefficient

Partition coefficient is a measurement of drug's lipophilicity and its ability to cross cell membrane. The partition coefficient of Losartan potassium was determined in n-octanol: phosphate buffer. 50 mg of drug was accurately weighed and added to 50 ml of n-octanol: phosphate buffer, in a separating funnel. The mixture was shaken until equilibrium was attained. Phases were separated in separating funnel and phosphate buffer was filtered through Whatman filter no. 41 and was accordingly The amount of Losartan potassium solublized in phosphate buffer was determined by measuring the absorbance at 234 nm using UV spectrophotometer. The partition coefficient was calculated and compared with literature value[6].

$$P_{o/w} = C_{organic} / C_{aqueous}$$

Preparation of Standard Curve[11-12]

Preparation of Phosphate Buffer 6.8

Dissolved 27.218g of Potassium dihydrogen phosphate in water and diluted with water upto 1000ml to make 0.2M Potassium Dihydrogen Phosphate.

Dissolved 8g of Potassium NaOH in water and made volume upto 1000ml to make 0.2M NaOH.

250 ml of 0.2 M potassium dihydrogen phosphate and 112 ml of 0.2N sodium hydroxide was placed in 1000 ml volumetric flask and then added distilled water to volume make up the mark.

Preparation of Calibration Curve in Phosphate Buffer pH 6.8

100 mg of Losartan Potassium was weighed accurately and dissolved in pH 6.8 phosphate buffer in a 100 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer. The concentration of this standard stock solution was 1000µg/ml. From this stock solution, aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml,1ml and 1.2ml were transferred to 10 ml volumetric flasks and volume was made up to 10 ml with phosphate buffer pH 6.8 and solution of varying concentration are 2, 4, 6, 0, 10 and 12µg/ml were obtained respectively. The absorbance of these solutions was measured at 234 nm against a blank phosphate buffer pH 6.8.

PREPARATION OF PRELIMINARY TRIAL BATCHES[13-14]

Preliminary trial batches containing selected inclusion complexes were prepared by direct compression method using single punch tablet machine to produce convex faced tablets weighed 80 mg using a set of die punch 8 mm.

Table.2:- Formulation of preliminary trial batches

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan potassium	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
β-cyclodextrin	40	40	40	40	40	40	40	40	40
MCC	20.5	18.5	16.5	20.5	18.5	16.5	20.5	18.5	16.5
SSG	2	4	6	-	-	-	1	2	3
CCS	-	-	-	2	4	6	1	2	3
Magnesium sterate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
PVP	1	1	1	1	1	1	1	1	1

Bulk density (ρb) = m/vb =m/π2rh[15-16]

Where; m = weight of powder or granules (gm),

Vb = Bulk Volume (cm^3),

π = 22/7 = 3.14,

r = Radius of Cylinder (cm),

h = Height reached by powder in cylinder (cm).

Tapped density (ρt) = m/vt =m/π2rh

Where; m = weight of powder or granules (gm),

v = Tapped Volume (cm^3),

π = 22/7 = 3.14,

r = Radius of Cylinder (cm),

h = Height reached by powder in cylinder after tapping (cm).

Carr's Index = (ρt – ρb/ρt) × 100

Where; ρt = tapped density,

ρb= bulk density.

Table.3:- Compressibility Index as an Indication of Powder Flow Properties

Carr's Index (%)	Type of Flow
5-12	Excellent
12-18	Good
18-21	Fair to Passable
23-35	Poor
33-38	Very Poor
>40	Extremely Poor

Hausner's Ratio (Hr) = Tapped density/ bulk density

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of Repose (θ)

calculated using the following equation.

$\theta = \tan^{-1} hr$

Where; h = Height of pile,

r = Radius of pile,

θ = Angle of repose.

Table.4:- Angle of Repose as an Indication of Powder Flow Properties

Angle of Repose (°C)	Type of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Table.5:-Weight Variation Limits for Tablets as Per IP

Average Weight of Tablets(mg)	Maximum % Deviation Allowed
80 or less	10
80-250	7.5
More then 250	5

MATHEMATICAL MODELING OF DRUG RELEASE PROFILE[17-20]

After doing the *in-vitro* dissolution study, the *in-vitro* dissolution data is fit into various experimental:

Zero-Order Model: This model has been used to measure the drug release from several modified dosage forms such as transdermal patches, matrix tablets with low solubility drugs and osmotic systems. Drug release can be described by equation:

$$Qt = Q_0 + Kat$$

Where; Qt = amount of drug dissolved in time t,

Q_0 = initial amount of drug in the solution,

Ka = zero order release constant expressed in terms of concentration per unit time.

First Order Model: This relationship has been used to describe the drug release from porous matrices

containing a water soluble drug. The release of drugs that follows the first order kinetics can be expressed by equation:

$$\textbf{Log C = Log C}_0 \textbf{ – Kt/2.303}$$

Where; C_0 = initial concentration of drug,

Kt = first order rate constant,

C = concentration of drug after time t.

Higuchi Model: It was the first mathematical model that has been used to describe the drug release from a matrix tablet. Higuchi model was based on certain hypothesis as described under mechanism of drug release from matrix systems. Model expression is given by equation:

$$\textbf{Ft = Q = A } \sqrt{\textbf{D (2Cs)*Cst}}$$

Where; Q = amount of drug release in time t per unit area A,

C = initial drug concentration,

CS = drug solubility in the matrix system,

D = diffusivity of drug molecules in matrix substance.

Korsemeyer-Peppas Model: This model describes the drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsemeyer-Peppas model.

$$\textbf{Mt/}\underset{\sim}{\textbf{M}}\textbf{ = Ktn}$$

Where; $Mt/\underset{\sim}{M}$ = fraction of drug release at time t,

K = release rate constant,

n = release exponent that characterizes different release mechanisms for different release mechanism for different geometrical shaped matrices.

Result:-

PREFORMULATION STUDIES:-

Physical Appearance and Melting Point

The Sample of Losartan potassium was analysed for various organoleptic, physicochemical and spectrophotometric methods. The sample possesses similar colour, odour, taste and texture as given in officials (Indian pharmacopoeia).

Table.6:- Organoleptic Character

Properties	Inference
Color	White to off-white
Taste	Bitter
State	Crystalline Powder
Odour	Odourless

Table.7:- Melting Point Determination

Method used	Experimental value	Literature value
Capillary fusion method	183 ˚C – 185˚C	183˚C - 184˚C

Solubility Studies:-

Table.8:- Solubility Profile of Losartan Potassium in Different Solvents

Solvents	Solubility (mg/ml)
Distilled water	0.80
Methanol	0.813
Acetone	0.309
Ethanol	0.785
Chloroform	0.281
Phosphate buffer, pH 6.8	0.701
Ether	0.680
Dichloromethane	0.411

Table.9:- λmax of Losartan potassium in Phosphate buffer 6.8

Method used	Experimental value	Literature value
UV Spectrophotometric	234nm	233.5nm

Table.10:- Partition Coefficient (log P) of Losartan potassium

Drug	Partition Coefficient
Losartan Potassium	5.19± 0.374

Infrared Spectroscopy:-

The FTIR Spectrum of Losartan potassium is shown in Fig 5.1. FTIR spectra verified the purity and authenticity of the procured sample.

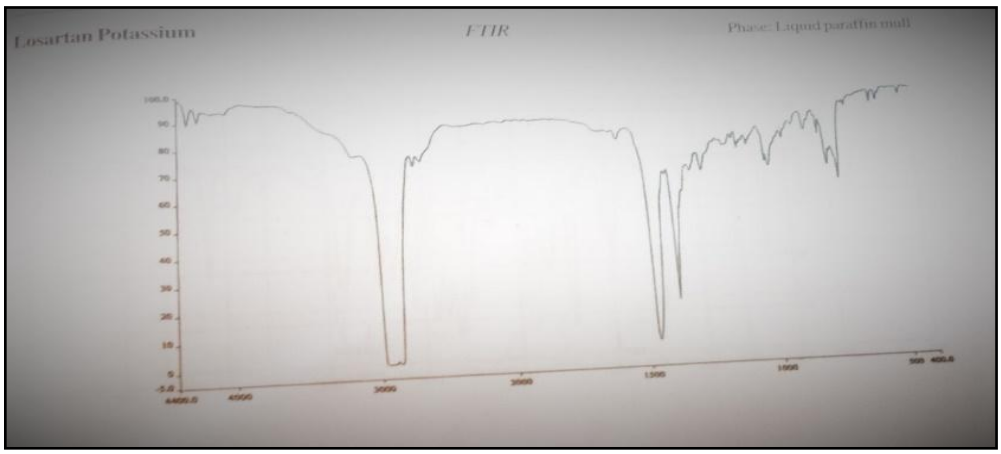

Fig.3:- IR Spectra of Losartan Potassium as per I.P. (2010)

Table.11:- Spectral Assignment of Losartan Potassium

Vibration Mode	Wave number (cm^{-1})
C-H stretching	3122.25
Distinct band sym CH3 group	2866.51
Stretching aromatic C-C ring	1693.69, 1516.69, 1462.93
Stretching O-H	2362.89
Stretching C-Cl	994.63

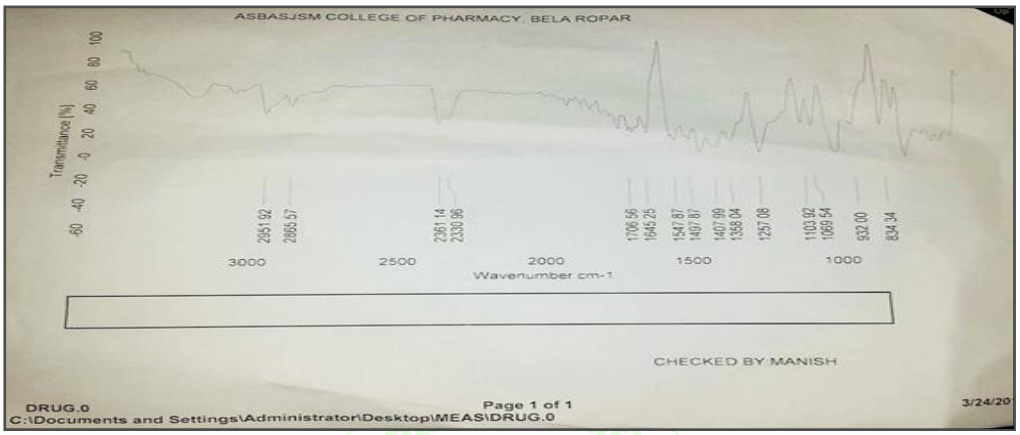

Fig.4:- FTIR Spectra of Losartan potassium (Pure Drug)

Drug Interactions Study

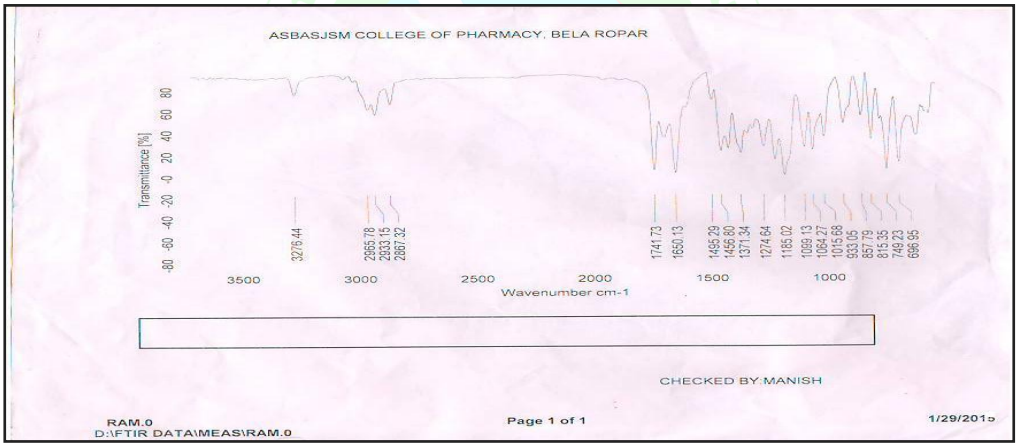

Fig.5:- FTIR Spectra of Losartan potassium and Cross carmellose sodium

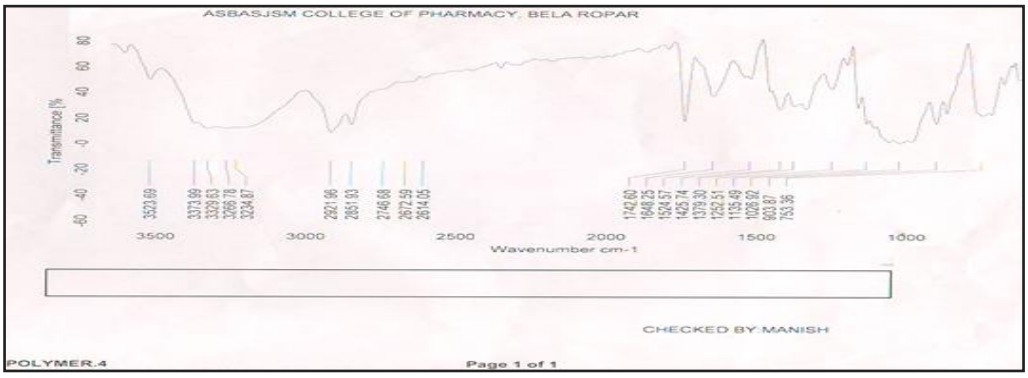

Fig.6:- FTIR Spectra of Losartan potassium and Sodium starch glycolate

PREPARATION OF CALIBRATION CURVES

The calibration curves of Losartan potassium were found to be linear in the concentration range of 0-20 µg/ml in phosphate buffer (pH 6.8).

Table.12:- Data for Measured Absorbance (234nm) in Phosphate Buffer pH 6.8

Conc.(µg/ml)	Absorbance1	Absorbance2	Absorbance3	Mean
0	0	0	0	0
2	0.113	0.141	0.147	0.133667
4	0.235	0.223	0.247	0.235
6	0.342	0.331	0.373	0.348667
8	0.431	0.428	0.441	0.433333
10	0.538	0.541	0.566	0.548333
12	0.633	0.631	0.652	0.638667
14	0.731	0.738	0.742	0.737
16	0.832	0.842	0.852	0.842
18	0.934	0.945	0.981	0.953333
20	1.059	1.061	1.071	1.063667

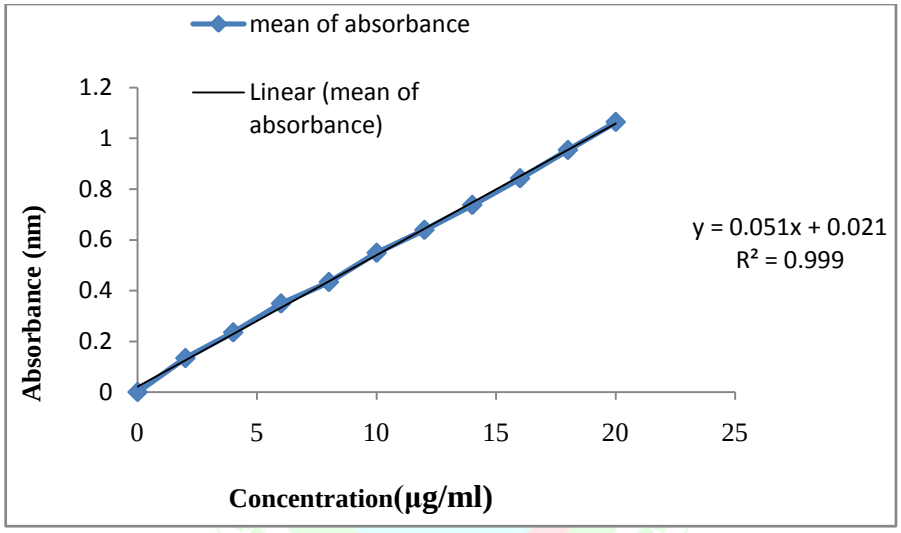

Fig.7:- Standard Curve of Losartan potassium in pH 6.8 Phosphate Buffer

CHARACTERIZATION OF TABLETS

The tablets were made for the final and stable formulations. Total 9 final formulations were formulated and designated as F1, F2, F3, F4, F5, F6, F7, F8 and F9.

Table.13:- Result of Pre-Compression Parameter of Formulations (F1-F9)

Batch No.	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Hausner's Ratio	Compressibility Index (%)	Angle of repose(θ)
F1	0.40±0.002	0.45±0.003	1.12±0.011	11.11±0.50	30.96±0.90
F2	0.355±0.002	0.45±0.002	0.78±0.013	21.11±0.54	30.14±0.87
F3	0.355±0.003	0.48±0.004	0.85±0.016	26.11±0.65	29.33±0.70
F4	0.42±0.001	0.53±0.002	1.22±0.017	24.52±0.63	30.37±0.66
F5	0.40±0.005	0.52±0.004	1.29±0.012	24.14±0.53	29.88±0.72
F6	0.42±0.002	0.53±0.003	1.26±0.011	24.52±0.50	28.86±0.54
F7	0.40±0.003	0.45±0.005	1.12±0.015	11.11±0.67	29.45±0.69
F8	0.45±0.001	0.52±0.001	1.15±0.014	24.52±0.54	30.14±0.78
F9	0.48±0.005	0.53±0.003	1.10±0.016	19.43±0.57	30.38±0.67

Data are expressed as mean ± SD (n=3)

Table.14:- Results of Post-Compression Parameters of Formulations (F1-F9)

Batch No.	Hardness (kg/cm^2)	Weight Variation (mg)	Friability (%)	Wetting Time(sec)	Disintegration-on Time(sec)	Drug content (%)
F1	2.3±0.056	81±2.7	0.90±0.002	40±0.03	48±1.56	92.01±0.005
F2	1.8±0.068	84±1.8	0.88±0.005	47±0.05	39±1.96	95.08±0.004
F3	2.2±0.063	82±3.9	0.62±0.002	39±0.02	27±1.62	93.43±0.003
F4	2.3±0.059	81±3.3	0.90±0.006	33±0.03	47±1.91	89.92±0.006
F5	1.7±0.071	79±2.6	0.72±0.004	36±0.06	35±1.35	89.96±0.004
F6	1.5±0.064	81±2.3	0.72±0.005	30±0.04	24±1.67	87.97±0.005
F7	1.8±0.069	82±4.2	0.70±0.003	29±0.03	42±1.86	89.78±0.003
F8	1.7±0.054	80±3.6	0.69±0.002	34±0.03	35±1.48	95.62±0.005
F9	1.5±0.064	79±4.3	0.67±0.004	39±0.03	39±1.54	92.33±0.002

Data are expressed as mean ± SD (n=3)

Table.15:- ***In-Vitro*** **Drug Release Profile of Preliminary Trial Batches (F1-F9)**

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	18.101	14.402	15.381	24.432	30.896	32.404	30.973	26.453	17.527
2	36.238	35.356	38.057	31.634	32.727	43.926	34.358	32.429	35.259
3	42.95	37.871	42.499	40.385	44.399	48.978	42.776	44.443	42.117
4	52.19	43.778	47.619	46.001	49.915	55.81	47.529	47.268	51.33
5	53.612	47.784	61.007	51.785	56.856	61.032	51.966	50.428	54.272
6	64.224	68.392	66.002	55.496	68.398	64.818	67.581	59.5	62.977
7	67.859	74.258	80.063	64.948	77.982	68.456	72.02	65.285	66.607
8	72.861	77.395	80.951	68.003	79.976	79.256	76.769	67.138	74.318
9	80.76	78.931	81.679	82.529	84.771	87.586	83.829	73.74	82.236
10	85.344	89.025	90.919	85.663	88.267	98.469	86.601	77.654	93.941

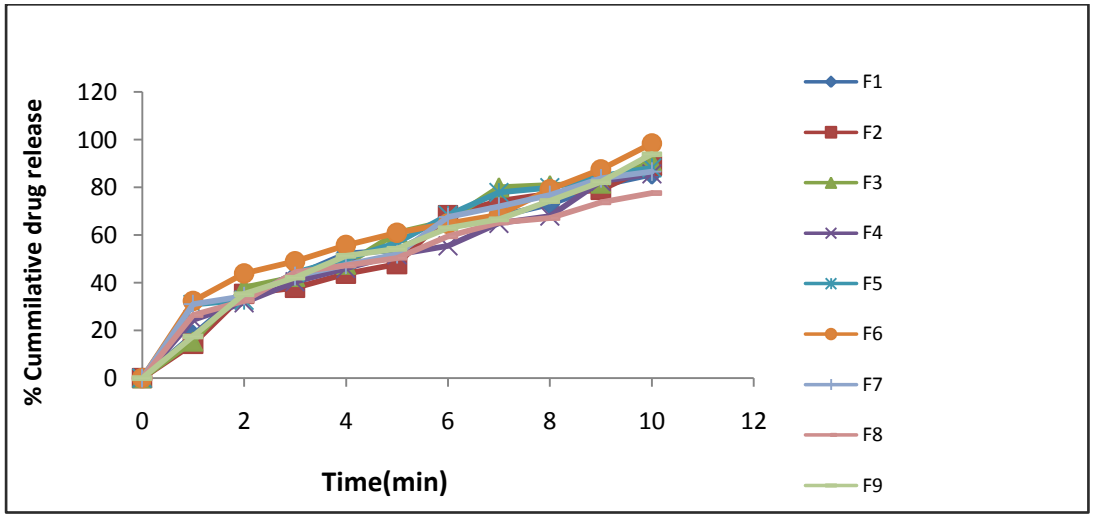

Fig.8:- *In-Vitro* Drug Release Profile of Preliminary Trial Batches (F1-F9)

MATHEMATICAL MODELING OF DRUG RELEASE PROFILES

Table.16:- Zero Order Release Kinetics Data of Formulations (F1-F9)

Time	% Cumulative Drug Released								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	18.101	14.402	15.381	24.432	30.896	32.404	30.973	26.453	17.527
2	36.238	35.356	38.057	31.634	32.727	43.926	34.358	32.429	35.259
3	42.95	37.871	42.499	40.385	44.399	48.978	42.776	44.443	42.117
4	52.19	43.778	47.619	46.001	49.915	55.81	47.529	47.268	51.33
5	53.612	47.784	61.007	51.785	56.856	61.032	51.966	50.428	54.272
6	64.224	68.392	66.002	55.496	68.398	64.818	67.581	59.5	62.977
7	67.859	74.258	80.063	64.948	77.982	68.456	72.02	65.285	66.607
8	72.861	77.395	80.951	68.003	79.976	79.256	76.769	67.138	74.318
9	80.76	78.931	81.679	82.529	84.771	87.586	83.829	73.74	82.236
10	85.344	89.025	90.919	85.663	88.267	98.469	86.601	77.654	93.941

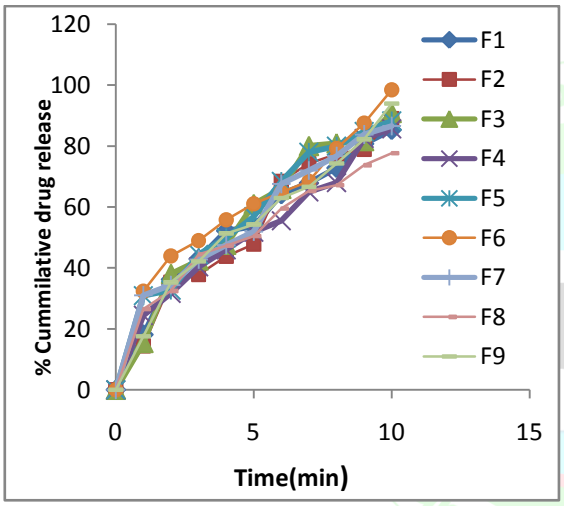

Fig.9:- Zero Order Release Kinetics of Formulations (F1-F9)

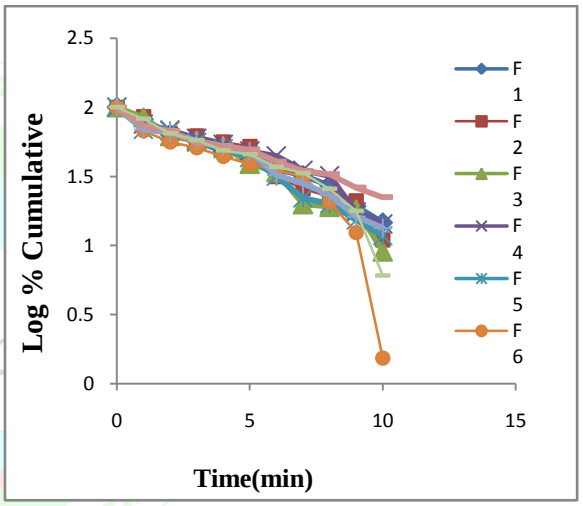

Fig.10:- First Order Release Kinetics of Formulations (F1-F9)

Table.17:- First Order Release Kinetics Data of Formulations (F1-F9)

Time	Log % Cumulative Drug Retained								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	2	2	2	2	2	2	2	2	2
1	1.9132	1.9324	1.9274	1.8783	1.8395	1.8299	1.8390	1.8665	1.9163
2	1.8045	1.8105	1.7919	1.8348	1.8278	1.7487	1.8171	1.8297	1.8111
3	1.7562	1.7932	1.7596	1.7753	1.7450	1.7077	1.7575	1.7447	1.7625
4	1.6795	1.7499	1.7191	1.7323	1.6997	1.6453	1.7199	1.7220	1.6872
5	1.6664	1.7178	1.5909	1.6831	1.6349	1.5907	1.6815	1.6952	1.6601
6	1.5535	1.4998	1.5314	1.6484	1.4997	1.5463	1.5108	1.6074	1.5684
7	1.5070	1.4106	1.2996	1.5447	1.3427	1.4989	1.4468	1.5405	1.5236
8	1.4335	1.3542	1.2798	1.5051	1.3015	1.3168	1.3660	1.5166	1.4096
9	1.2842	1.3236	1.2629	1.2423	1.1826	1.0939	1.2087	1.4192	1.2495
10	1.1660	1.0404	0.9581	1.1564	1.0694	0.1849	1.1270	1.3492	0.7824

Table.18:- Higuchi Release Kinetics Data of Formulations (F1-F9)

Square Root of Time	% Cumulative Drug Released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	18.101	14.402	15.381	24.432	30.896	32.404	30.973	26.453	17.527
1.41421	36.238	35.356	38.057	31.634	32.727	43.926	34.358	32.429	35.259
1.73205	42.95	37.871	42.499	40.385	44.399	48.978	42.776	44.443	42.117
2	52.19	43.778	47.619	46.001	49.915	55.81	47.529	47.268	51.33
2.23607	53.612	47.784	61.007	51.785	56.856	61.032	51.966	50.428	54.272
2.44949	64.224	68.392	66.002	55.496	68.398	64.818	67.581	59.5	62.977
2.64575	67.859	74.258	80.063	64.948	77.982	68.456	72.02	65.285	66.607
2.82843	72.861	77.395	80.951	68.003	79.976	79.256	76.769	67.138	74.318
3	80.76	78.931	81.679	82.529	84.771	87.586	83.829	73.74	82.236
3.16228	85.344	89.025	90.919	85.663	88.267	98.469	86.601	77.654	93.941

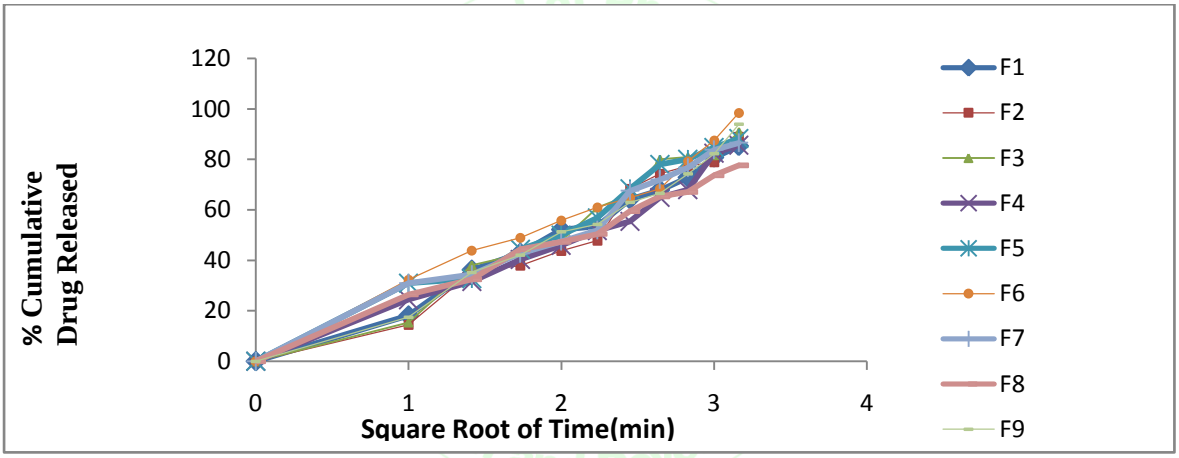

Fig.11:- Higuchi Release Kinetics of Formulations (F1-F9)

Table.19:- Korsmeyer-Peppas Release Kinetics Data of Formulations (F1-F9)

Log of Time	Log % Cumulative Drug Released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0	1.2577	1.15842	1.18698	1.38796	1.4899	1.5106	1.49098	1.42247	1.24371
0.30103	1.55916	1.54846	1.58043	1.50015	1.51491	1.64272	1.53603	1.51093	1.54727
0.47712	1.63296	1.57831	1.62838	1.60622	1.64737	1.69	1.6312	1.6478	1.62446
0.60206	1.71759	1.64126	1.67778	1.66277	1.69823	1.74671	1.67696	1.67457	1.71037
0.69897	1.72926	1.67928	1.78538	1.7142	1.75478	1.78556	1.71572	1.70267	1.73458
0.77815	1.8077	1.83501	1.81956	1.74426	1.83504	1.8117	1.82982	1.77452	1.79918
0.8451	1.83161	1.87074	1.90343	1.81257	1.89199	1.83541	1.85745	1.81481	1.82352
0.90309	1.8625	1.88871	1.90822	1.83253	1.90296	1.89903	1.88519	1.82697	1.87109
0.95424	1.9072	1.89725	1.91211	1.91661	1.92825	1.94243	1.92339	1.8677	1.91506
1	1.93117	1.94951	1.95865	1.93279	1.9458	1.9933	1.93752	1.89016	1.97286

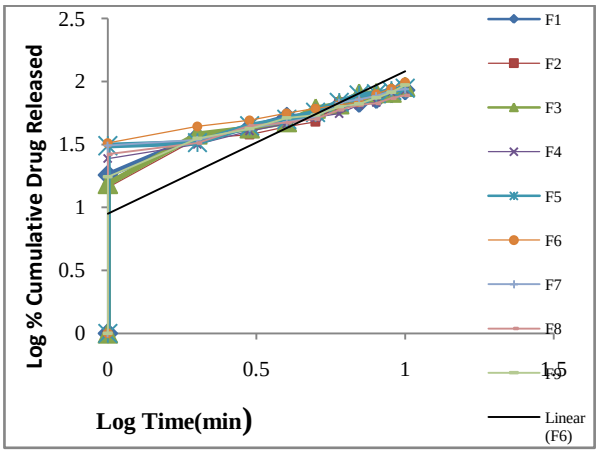

Fig.12:- Korsmeyer-Peppas Release Kinetics of Formulations (F1-F9)

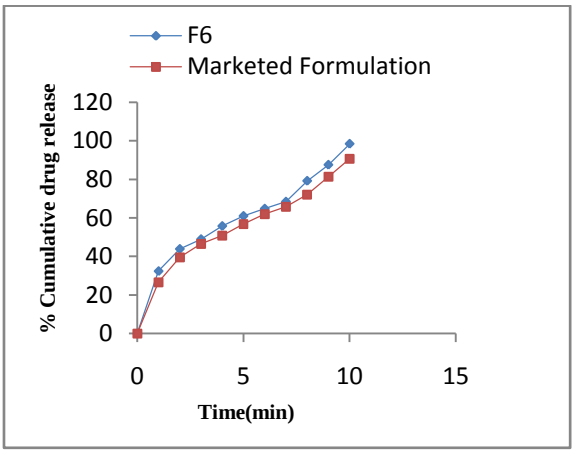

Fig.13:- *In-Vitro* Drug Release Curve for F6 and Marketed Tablet

COMPARISON WITH MARKETED PREPARATION

Table:- Post Compression Results of F6 and Marketed Tablet

Parameters	Marketed Preparation	F6
Avg. Weight (mg)	100.1±1.72	81±2.3
Hardness (kg/sq.cm)	1.6±0.57	1.5±0.06
Wetting Time (sec)	37±0.03	30±0.04
Friability (%)	0.60±0.008	0.72±0.0
Disintegration Time (sec)	24±1.91	24±1.67

Table.20:- *In-Vitro* Drug Release Profile of Losartan potassium from Marketed Tablet and F6

Time	% Cumulative Drug Released	
	Marketed Formulation	F6
0	0	0
1	26.608	32.404
2	39.504	43.926
3	46.51	48.978
4	50.921	55.81
5	56.884	61.032
6	62.047	64.818
7	65.776	68.456
8	72.116	79.256
9	81.44	87.586
10	90.728	98.469

DISCUSSION

β-cyclodextrin was used as solublizing and sweetening agent. Addition of PVP as binder, effect as decresed friability and increased hardness of the tablets. CCS and SSG as superdisintegrants decreased the disintegration time as its concentration was increased from F1 to F9. Pre-compression results showed the better flow properties of powder blend showed in Table: 4.11. The drug content of all the formulations was found to be between 87.9-95.6% which was within the acceptable limits. Tablets with lower friability (0.62%) may not break during handling on machines.

In-vitro release studies were carried out using tablet dissolution test apparatus paddle method at 37±0.5°C, taking 500 ml of pH 6.8 phosphate buffer as dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Aliquots of 5 ml were withdrawn after 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 min and analyzed spectrophotometrically at 234 nm.

Formulation F6 prepared by direct compression showed release 98.46% drug at the end of 10 min. The *in-vitro* dissolution profile (Fig.5.7) indicated faster and maximum drug release from formulation F6. The rapid drug dissolution might be due to easy breakdown of particles due to CCS and rapid absorption of drugs into the dissolution medium. Slope values signify that the release rate follows first order kinetics. Comparison with marketed preparation showed better results of F6 in *in-vitro* dissolution profile.

STABILITY STUDY

The stability method can be defined as validated quantitative analytical method that can detect the change with time in the chemical, physical or microbiological properties of the drug substance and drug product, and that are so specific that the content of active ingredients, degradation can be accurately measured without interference.

Test design

The product was properly filled in aluminum foil and was stored according to storage conditions.

Table. 21:- Storage Conditions and Period for Stability Studies

Formulation Code	Storage Condition/Period
F6	Accelerated, 2 months

Testing Plan

Formulation F6 was put in aluminum foil and was stored at the following storage conditions.

Table.22.:- Storage Conditions and Sampling Intervals for Stability Studies

Storage Conditions	Sampling Intervals
Accelerated (40 °C/75 % RH)	0, 15, 30, 45 and 60 days.

Table.23:- Post Compression Parameters After Stability Studies

Days	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (sec)	%Drug Content
0	81±2.3	1.5±0.064	0.72±0.005	24±1.67	87.97±0.005
15	81±2.1	1.5±0.028	0.73±0.004	27±1.56	87.92±0.002
30	81±1.91	1.46±0.074	0.75±0.006	26±1.59	87.92±0.005
45	80.9±1.95	1.46±0.04	0.74±0.002	24±1.72	87.91±0.003
60	80.9±2.06	1.5±0.048	0.75±0.005	25±1.65	87.89±0.004

Data are expressed as mean ± SD (n=3)

Table.24:- Comparison of *in-vitro* Drug Release Before and After Storage

Time	% Cumulative Drug Released	
	F6	**After Stability**
0	0	0
1	32.404	28.561
2	43.926	38.98
3	48.978	46.922
4	55.81	52.211
5	61.032	57.662
6	64.818	63.043
7	68.456	65.311
8	79.256	76.049
9	87.586	83.921
10	98.469	95.031

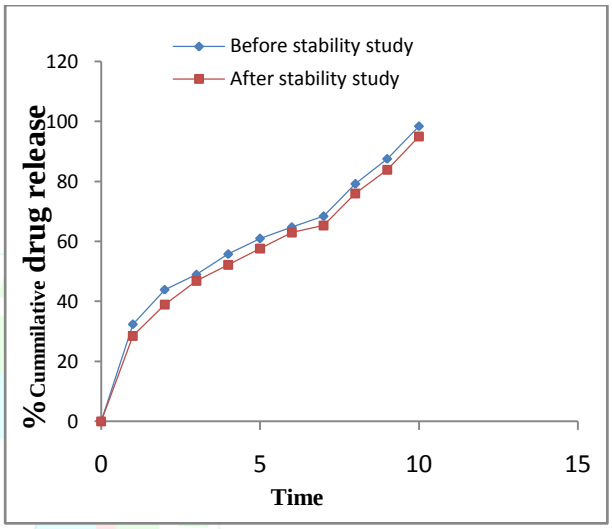

Fig.14:- Comparison of Drug Release Before and After Stability Studies

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