8. Useful in cases where a rapid onset of action required such as in motion sickness, sudden episodes of allergic attack or coughing, bronchitis or asthma.
9. An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tables.
10. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

1.8 Disadvantages of Orodissolving films

1. Drugs which are unstable at buccal pH cannot be administered.
2. Drugs which irritate the mucosa cannot be administered by this route.
3. Drug with small dose requirement can only be administered.
4. Taste masking most drugs have bitter taste, and need taste masking.

1.9 Composition of the Formulation –

A typical composition contains the following:
a) Drug – 5% to 30% w/w.
b) Water soluble polymer – 45%w/w
c) Plasticizers – 0-20%w/w
d) Sweetening agent- 3% to 6% w/w.
e) Saliva stimulating agent – 2 to 6% w/w
f) Fillers, Colors, flavor surfactant etc. q.s.

a) Drug:
The ideal characteristics of a drug to be selected –
1. The drug should have pleasant taste.
2. The drug to be incorporated should have low dose up to 40 mg.
3. The drugs with smaller and moderate molecular weight are preferable.
4. The drug should have good stability and solubility in water as well as in saliva.
5. It should be partially unionized at the pH of oral cavity.
6. It should have the ability to permeate oral mucosa.

b) Polymer
For the preparation of FDR the various polymers can be used in the film up to 40% w/w of the film content. The polymers are responsible for the strength of the film. The film should be tough to prevent damage during handling and transportation. The polymers can be use as single or in combination as per requirement. Polymers are – Hydroxyl Propyl methyl cellulose (HPMC), Hydroxy Propyl cellulose, starch and modified starch, Pullunan, pectin, Gelatin, carboxy, methyl cellulose, PVP+Cross linked PVP, Alginated, Poly vinyl Alcohol, Maltodextrose, and Polyox.

c) Plastisizer
The role of Plasticizer is beneficial for preparation FDF. Plasticizer helps to improve the flexibility of the film and reduces the brittleness of the film. The plasticizer should be compatible with polymer and solvent. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Propylene glycol (PG), Poly ethylene Glycol (PEG), Glycerol, Phthalate derivative like di-methyl, diethyl and dibutyl phthalate, citrate derivative such as tributyl, triethyl, acetyl, cirate, triacetin and castor oil are some of the commonly used plasticizer. Plasticizer may lead to film cracking, splitting and peeling of the film. It is also reported that the use of certain plasticizers may also affect the affect the absorption are of the drug. The plasticizer should be volatile in nature.

d) Flavors
Flavors include:
1. Both natural and artificial flavor such as artificial vanilla, cinnamon, and various fruit flavors; either individual or mixed.
2. Mints such as peppermint, menthol.
3. Essential oils such as thymol, eucalyptol and methyl salicylate.

e) Sweeteners
Sweeteners have become the important part of the formulation intended to be Disintegrated or dissolved in the oral cavity. Generally sweeteners are used in the Concentration of 3 to 6% w/w either alone or combination. Both nature sweeteners as well as artificial sweeteners are used in the formulation of these fast dissolving films. Polyhydric alcohols such as sorbitol, mannitol and isomalt can be used in combination as they additionally provide good mouth fell and cooling sensation. However it should be noted that the use of natural sugars in such preparation need to be restricted in people who are on diet or in the case of diabetic patients. Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparation. Saccharin cyclamate and aspartame is the first generation of the artificial sweeteners followed by acesulfame – K, Sucralose, alitame and neotame which fall under the second generation artificial sweetners. Acesulfame – K and sucralose.

f) Saliva Stimulating Agent
The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of good can be utilized as salivary stimulants. E.g. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. These agents are used along or in combination between 2 to 6% w/w of weight of the strip.

g) Coloring Agent
FDA approved coloring agents are used (not exceeding concentration levels of 1 percent; w/w) in the manufacturing of orally fast dissolving film E.g. Titanum dioxide.

2. Method of Preparation

1. Solvent casting.
2. Hot melt extrusion
3. Solid dispersion extrusion
4. Rolling

1. Solvent Casting Method –

In solvent casting method excipients are dissolved in water, then water soluble polymers and in last drug is added and stirred to form homogeneous solution. Finally solution is casted in to the Petri plate and dried.

Semisolid Casting –

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. In semisolid casting method gel mass is casted in to the films or ribbons using heat controlled drums. Gel mass is obtained by adding solution of film forming to a solution of acid insoluble polymer in ammonium or sodium hydroxide. Acid – insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4

2. Hot Melt Extrusion –

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then dried granular material in introduced into the extruder. The crew speed should set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3-4 min. The processing temperatures should be 800C (Zone 1), 1150C (Zone 2), 1000C (Zone 3) and 650C (zone The extrudate (T=650 C) then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion –

- Fewer operation units.
- Better content uniformity.
- An Anhydrous process.

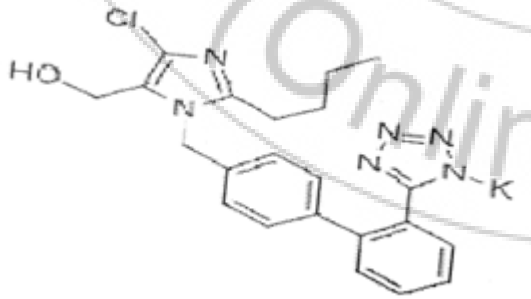
3. Solid dispersion Extrusion –

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

4. Rolling Method –

In rolling method a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers an cut in to desired shapes and sizes.

a) Drug Profile
b) Chemical Structure



c) Chemical Name – 2 Butyl -4-choro-1 {[2' – tetrazzol-5-yl) [bipheny]-4y) methl} – 1H-imidazol-5-methanol mono – potassium salt.
d) Empirical Formula – C22H22CIKN6O
e) Molecular Weight – 461.0
f) Category – Antihypertensive agent
g) Dose – 25 mg – 100mg
h) Solubility – In water – freely soluble
i) In ethanol – Low

5. Pharmacology

1. The main effect of angiotensin 2 vasoconstriction, aldosterone secretion and nor – epinephrine release from sympathetic nerve terminal.
2. Losartan is a specific and selective antagonist of angiotensine – 2 AT1 site.
3. It is able to block the contractile effect of angiotensine – 2in isolated strip of rabbit aorta, isolated guinea pig ileum.
4. Losartan causes an acute dose dependant blood pressure falls in renal hypertensive rat.

6. Pharmacokinetics:

Losartan is well absorbed rally but undergoes pre-systemic metabolism, forming an active metabolite E-3174. Both the losartan and its metabolites are 99% bound to plasma protein, primarily albumin. Volume of distribution is relatively low. Plasma half life is about 2 hrs. losartan is extensively metabolized in liver. Approximately 35% of oral route is excreted in urine.

a) Use – In all grades of hypertension.
b) Synonym – Hypromollose, Methocel, Hypromellosum.
c) Molecular weight – Approximately 10000 – 1500000.
d) Category – Bioadhesive material, coating agent, controlled release agent, dispersing agent, emulsifying agent, film forming agent, release modifying agent.
e) Description – It is an odorless, testless, white or creamy – white fibrous or granular powder.
f) Typical Properties :
   - PH – 5.0 – 8.0 for 2% w/v
   - Density (bulk) – 0.341 g/cm3
   - Density (tapped) - 0.557g/cm3
   - Melting Point – Browns at 190-200c
   - Specific gravity – 1.26
   - Solubility – Forming colloidal solution with cold water.

7. Glycerin

a) Synonym – Glycerol, Glycerolum, glycon g-100, optima, trihydroxypropane glycerol.
b) Chemical Name – Propane – 1, 2, 3 Triol.
c) Empirical Formula C3 H8 O3
d) Molecular Weight – 92.09
e) Category – Antimicrobial agent, cosolvant, emollient, humectants, plasticizer, sweetening agent.
f) Description – Racemic menthol is a mixture of equal parts of the (1R, 2S, 5R) and (1S, 2R, 5S) isomers of menthol. It is a free flowing crystalline powder, or colorless, prismatic or acicular shiny crystal, strong characteristic odor and taste.
g) Typical Properties – Boiling Point – 2120c
h) Melting Point -340c
i) Solubility – very soluble in ethanol (95%) chloroform, ether, liquid paraffin. Freely soluble in glacial acetic acid. Soluble in acetone and benzene.
j) Saccharin Sodium:
k) Synonym – Crystallose, saccharinum natricum, sodium o-benzosuifimide, sucaryl sodium.
l) Chemical name – 1, 2 Benzisothiazol – 3 (2H) One, 1, 1-dioxide, sodium salt.

m) Empirical Formula – C7H4NNa03s
n) Molecular weight – 217.24
o) Category – Sweetening agent
p) Description – it occurs as a white odorless or faintly aromatic, crystalline powder. It has intensively sweet taste.
q) Typical Properties :
- PH – 6.6
- Density (bulk) – 0.8-1. 1g/cm3
- Melting point – Decomposes on heating.

8. Ethanol

- Synonym – Ethanolum, ethyl alcohol, ethyl hydroxide, grain alcohol.
- Chemical name – Ethanol
- Empirical Formula – C2H6O.
- Molecular weight – 46.07
- Category – Antimicrobial Preservative, disinfectant solvent.
- Typical Properties –
- Boiling point – 78.15
- Flammability – Readily flammable burning with blue flame.
- Solubility – miscible with chloroform ether, glycerin, water.
- Specific gravity – 0.8119-0.8139 at 200c

2. Materials and Method

Losartan potassium, HPMC 15 CPS, Glycerin Polysorbate 80, Sodium saccharin, Menthol, Ethanol, Distilled water.

Method of preparation of Film:

The preparation of film was done by using solvent casting method. The polymer was dissolved in hot water. The drug and other excipients were dissolved in ethanol. This solution was added to the polymeric solution. Then the solution was mixed by using mixing device for 45 minutes with rotating speed 60-80 rpm. The entrapped air is removed by vacuum. The resulting solution was casted slowly and with continuous flow on glass plate. The plates were kept in a hot air oven at 60 for 24 hours. The dried film was gently separated from glass plate and cut into desired sizes of about 4 cm2.

Table 1: Different formulation batches F1 to F3 of orodissolving film

Batches	*F1*	*F2*	*F3*
Losartan Potassium	25 mg	25 mg	25 mg
HPMC 15 CPS	400 mg	400 mg	400 mg
Glycerin	60 mg	72 mg	84 mg
Polysorbate 80	40 mg	40 mg	40 mg
Sodium Saccharin	40 mg	40 mg	40 mg
Menthol	20 mg	20 mg	20 mg
Ethanol	1 ml	1 ml	1 ml
Dist. Water	9 ml	9 ml	9 ml

Evaluation test for mouth dissolving firm:

1. Mechanical Proprieties
- Thickness
- Dryness / tack test
- Tensile strength
- Percent Elongation
- Young's Modulus
- Tear resistance

Folding endurance
2. Organoleptic test
3. Swelling test
4. Surface pH test
5. Contact angle
6. Transparency
7. Assay / Content Uniformity
8. Disintegration test
9. In – Vitro Dissolution test

Thickness:
As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital vernier Calipers at different strategic locations.

Dryness Test / Tack Tests:
About eight stages of film drying process have been indentified and they are set – to touch, dust – free, tack – free (Surface dry), Dry – to touch, dry – hard, dry – through (dry – to – handle), dry-to-recoat and dry print – free. Although these tests are primarily used for paint films most of the studies can be adapted intricately to evaluate pharmaceutical OFDF. The details of evaluation of these parameters can be checked elsewhere and are beyond the scope of this review track is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study 30.

Tensile Strength:
Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross – sectional area of the strip as given in the equation below: 30Tensile Strength = Load at breakage.
Strip Thickness x Strip width

Percent Elongation:
When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increase as the plasticizer content increase
% Elongation = Increase is length x 100
/ Original length

Young's modulus:
Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as

follows: Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation 30.

Tear Resistance:

Tear resistance of plastic film or sheeting is a complex function of its ultimate to rupture. Basically very low rate of loading 51 mm (2 in) / min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton's (or pounds – force)

Transparency:

The transparency of the films can be determined using a simple UV spectrophotometer. Cut the film samples into rectangles and placed on the internal side of the spectrophomoter call. The determine transmittance of films at 600 nm. The transparency of the films was calculated as follows:

Transparency = (log T600) / b =

Where T 600 is the transmittance at 600 nm and b is the films thickness (mm) and c is concentration 33, 34.

Drug Content:

A film of size 2 x 2 cm2 is cut and put in 100 ml of breaker containing. This is then shaken in a mechanical shaker for 30 min to get homogeneous solution and filtered. The drug is determined spectroscopic ally after appropriate dilution. Limit of content uniformity is 85-115%

Disintegration test

It is determined by manually dipping the film in beaker containing 10ml distilled water. Time required to break or disintegrate the film is disintegration time.

Standard calibration curve

1. Preparation of phosphate buffer pH 6.8 – Place 50ml of 0.2 M Potassium dihydrogen phosphate in 200ml volumetric flask, add 22.4ml sodium hydroxide solution add water to make up the volume.
2. Preparation of stock solution :
3. Weigh accurately 10mg Losartan Potassium and transfer in to 100ml volumetric flask makeup the volume up to 100ml using phosphate buffer pH 6.8

Parameters

1. Beer's Lambert Rang – 2-20ug / ml.
2. Solvent – Phosphate buffer – pH 6.8.
3. Maximum wavelength – 254 nm.
4. RPM – 10

Table 2: Observation table of calibration curve

Sr. No.	*Concentration (g/ml)*	*Absorbance*
1	2	0.09
2	4	0.123
3	6	0.256
4	8	0.415
5	10	0.436
6	12	0.544
7	14	0.536
8	16	0.544
9	18	0.608
10	20	0.632
R2 = 0.96	Slope – 0.062	Intercept – 0.043

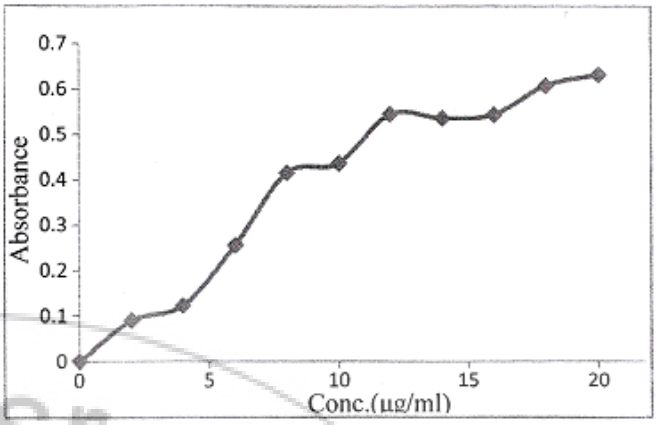


Figure: Calibration curve of Losartan Potassium

In Vitro drug Release:

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution is carried out in 900ml of PH 6.8 Phosphate buffer maintained at 37= 0.050c at 100 rpm. 10 ml of samples were taken at 2, 4, 6, 10, 15, 30, 45, 60 min which replaced with same volume of fresh PH 6.8 phosphate buffer. After appropriate dilution samples was then determined spectroscopic ally at 254 nm.

Table 3: Invitro drug release of formulation batches F1 to F3

Time (Min)	*% CDR*		
	F1	*F2*	*F3*
2	24.48	27.36	32.4
4	39.6	46.44	48.8
6	42.3	53.25	59.4
10	67.96	65.23	72.6
15	72.23	80.12	84.29
30	62.21	58.3	69.23
45	41.11	41.7	43.53
60	34.2	39.6	29.16

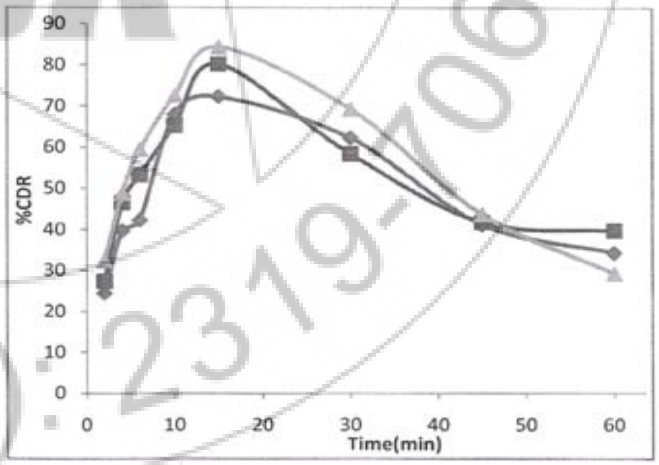


Figure 2: Invitro Drug release of Losartan Potassium

3. Result and Discussion

Table 3: Evaluation of orodissolving film formulation batches F1 to F3

Batches	F1	F2	F3
Thickness (nm)	0.09	0.1	0.09
% Elongation	5	10	25
Folding endurance	21	28	32
% Drug content	73.1	78.36	81.4
Disintegration time (sec.)	42	34.12	28.15
In vitro drug release	72.23	80.12	84.29

1. **Thickness -**
   The result shows that thickness of mouth dissolving film does not depend on the concentration of plasticizer.
2. **Percent elongation -**
   A result showed that as the concentration of plasticizer increases % elongation of orodissolving film also increases.
3. **Folding endurance -**
   As a result shows as the concentration of plasticizer increase folding endurance of orodissolving film also increases.
4. **Disintegration time -**
   As the concentration of plasticizer increases, disintegration time of orodissolving film decreases.
5. **Percent drug content-**
   As a result shows concentration of plasticizer increases percent drug content also increases.
6. **In vitro drug release -**
   As a result shows F3 formulation shows best release of drug .

4. Conclusion

The Losartan potassium orodissolving films were successfully prepared as orodissolving dosage form. In vitro dissolution studies showed fast release at 15 min. The formulation F3 showed fast drug release as compared to F1 & F2.

Order of release of Losartan potassium is as follows:
F3 > F2 > F1
Order of disintegration time is as follows:
F1 > F2 > F3

Thus, F3 formulation showed fast drug release 84.29% at the end of 15 min because glycerin also acts as cosolvant and enhances dissolution of Losartan potassium, so disintegrate rapidly and release is fast. Hence, as the concentration of plasticizer increases drug release increases.

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