International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 993-1006 www.ijprajournal.com ISSN: 2456-4494

Formulation and Evaluation of Orally Dissolving Strips of Metaprolol Succinate

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Date of Submission: 15-05-2024 Date of Acceptance: 25-05-2024

ABSTRACT: Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility and most importantly, patient compliance. But the most evident draw back of oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of paediatric, geriatric, bedridden, nauseous patients. So, fast-dissolving drug delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for paediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Fast dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oro mucosal absorption or with formula modifications, will maintain the quick dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed.

The present study was aimed to formulate fast dissolving oral films of Metaprolol succinate to enhance bioavailability and avoid pre systemic metabolism. The key is to develop successful oral film by solvent casting method. Oral film was fabricated using sodiumcmc, sodium alginate and polyvinyl alcohol polymers. The prepared films were evaluated for Organoleptic evaluations, film weight, thickness, folding endurance, drug content uniformity of films, surface pH, disintegration time and in-vitro diffusion studies.

KEYWORDS:. Dissolution test apparatus – 11 (USP-TDT08L),Cyclo-mixer,UV-Visible spectrophotometer.

I. INTRODUCTION

Fast dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oro mucosal absorption or with formula modifications, will maintain the quick dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. They impart unique product differentiation, thus enabling use as line extensions for existing commercial products.

This novel drug delivery system can also be beneficial for meeting the current needs of the industry by improving solubility/stability, biological half life and bioavailability enhancement of drugs. Oral film includes various ingredients for its formulation which includes polymers, api, plasticizers, super disintegrating agents, sweeteners, flavors, colors, saliva stimulating agents, preservatives, surfactants etc but the most essential ingredients of oral films are polymers, plasticizers and super disintegrating agents.

A variety of polymers are available for preparation of fast dissolving oral films. The use of film forming polymers in oral films has attracted considerable attention in medical and nutraceutical applications. The selection of polymer, is one of the most important and critical parameter for successful development of the film formulation. The polymers can be used alone or in combination to obtain the desired film properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type and amount of polymer in the formulation. As the strip forming polymer is the most essential and major

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component of the film, at least 45%w/w of polymer should generally be present based on the total weight of dry film but typically 60 to 65%w/w of polymer is preferred to obtain desired properties.

Plasticizer is a vital ingredient of the fast dissolving films. It helps to improve the flexibility of the strip and reduces the brittleness of the films. It significantly improves the film forming properties by reducing the glass transition temperature.

ADVANTAGES:-

Fast dissolving oral films being an advanced evolution of fast dissolving drug delivery systems have some outstanding advantages over conventional dosage forms and orally disintegrating tablets. They are:

1. Improved patient compliance.
2. As fast dissolving thin oral films are flexible, they are easy to carry, store and handle, which is not the case with orally disintegrating tablets (fragile and brittle).
3. Precision in the administered dose is ensured from each of the strips as compared to drops or syrup formulations.
4. Water is not needed for administering, so problem encountered in swallowing of tablets or capsules can be evaded.
5. Patients suffering from emesis, dysphagia, motion sickness prefer this dosage form as they are unable to swallow large quantity of water.
6. Availability of larger surface area leads to fast disintegration and dissolution in the oral cavity.
7. As the oral mucosa is being highly vascularized, drugs directly enter the systemic circulation without undergoing first pass hepatic metabolism. It improved oral bioavailability of molecules.
8. These films can be manufactured through economically feasible non sophisticated procedures and uncomplicated equipment.

IDEAL CHARACTERISTICS FOR DRUGS THE TO BE SELECTED:-

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose upto 40 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

FORMULATION ASPECTS FOR ORAL DISSOLVING FILMS:

Formulation of ODFs involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolution, physical appearance, mouth feel etc. From the regulatory perspectives, all excipients used in the formulation of oral strips should be Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

A) Drug Category

It has the potential for delivering a variety of APIs. However since the size of the dosage form has limitation, high dose drugs are difficult to be incorporated in films. Less bitter, potent and highly lipophilic drug should be preferred for oral thin films.Various categories of drugs used such as antiemetic neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptics, anxiolytics, sedatives, hypnotics, diuretics, antiparkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, antialzheimers, expectorants.

B) Film Forming Polymers

Water-soluble polymers are used as film formers as they provide quick disintegration, good mouth feel, and mechanical strength to the films. The robustness of the strip depends on the type of polymer and its amount in the formulations.Variety of polymers are available for preparation of films of which pullulan, gelatin and hypromellose are most commonly used. Examples of water-soluble polymers include: Pullulan, Gelatin, guar gum, xanthan gum, Hydroxyl propyl methyl cellulose (HPMC), Modified starches, PVPK30, PVA etc.

Among this the Pullulan and HPMC are the best suitable polymers for the preparation of FDF. Pullulan is a neutral glucan (like Amylose, Dextran, Cellulose), with a chemical structure somewhat depending on carbon source, producing microorganism (different strains of Aureobasidium pullulans).HPMC is propylene glycol ether of methylcellulose. The low viscosity grades of HPMC are used for the preparation of MDF like
HPMC E3/E5/E6/E15.

C) Plasticizers

Plasticizer is a crucial ingredient of the mouth dissolving films. The selection of plasticizer depends upon its compatibility with the polymer and the type of solvent employed in the casting of film.

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It helps to improve the flexibility of the film and reduces the brittleness of the film. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. Typically the plasticizers are used in the concentration of 1 - 20%w/w of dry polymer weight. The Plasticizer should be volatile in nature. Examples include: Glycerol, Propylene glycol, Low molecular weight polyethylene glycols, Phthalate derivatives like dimethyl, diethyl, dibutyl derivatives, Citrate derivatives like triacetin acetyl citrate, etc.

D) Sweetening agents

Sweeteners have become an important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations.

Some suitable sweeteners include:
(1) Water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose, stevioside.
(2) Water soluble artificial sweetener: sodium or calcium saccharin salts, acesulfame-K etc.
3) Dipeptide based sweetener: aspartame

E) Cooling agents

Cooling agents monomethyl succinate can be added to improve the flavor strength and to enhance the mouth-feel effect of the product. Additional cooling agents like WS3, WS23 and Utracoll II can also be used in conjunction with flavors.

F) Flavoring agents

Perception for the flavor changes from individual to individual depending on the ethnicity and liking. Flavoring agents can be selected from synthetic flavor oils, oleo resins extract derived from various parts of the plants like leaves, fruits and flowers. The amount of flavor needed to mask the taste depends on the flavor type and its strength.

G)Coloring agents

Pigments such as titanium dioxide or FD&C approved coloring agents are incorporated (not exceeding concentration levels of 1%w/w) in oral strips when some of the formulation ingredients or drugs are present in insoluble or suspension form.

H) Surfactants

Surfactants are used as solubilizing or wetting or dispersing agents as a result that the film gets dissolved within seconds and release active agent immediately. Surfactants also improve the solubility of poorly soluble drugs in fast dissolving buccal films. E.g.: Polaxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, tweens and spans etc.

I) Stabilizing and thickening agents

The stabilizing and thickening agents are employed to improve the viscosity and consistency of dispersion or solution of the strip preparation solution or suspension before casting. Natural gums like xanthan gum, locust bean gum, carrageenan and cellulosic derivatives can be used.

MANUFACTURING METHODS FOR PRODUCTION OF OTF

Various approaches to manufacturing of Rapid dissolving films are classified as follows:

1.CASTING AND DRYING
a. Solvent casting
b. Semi solid casting

2.EXTRUSION
a. Hot melt extrusion
b. Solid dispersion

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3.ROLLING METHOD

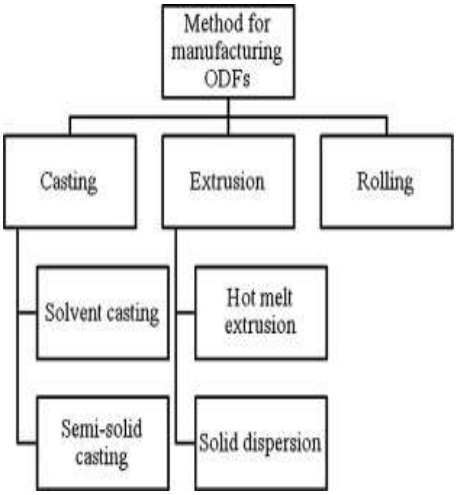

Fig.1 Method for manufacturing ODF

A) SOLVENT CASTING METHOD

The ODF are preferably formulated using the solvent casting method, where by the water soluble ingredients are dissolved to form a clear viscous solution. The API and the other agents are dissolved in smaller amount of the solution, and combined with the bulk. This mixture is added to the aqueous viscous solution. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size. The selection of solvent essentially depends on the API to be incorporated into the strip.

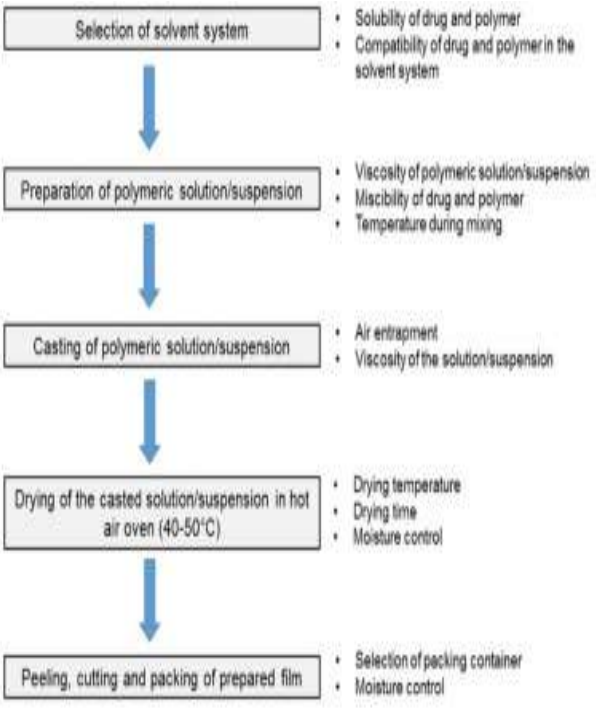

Fig. 2 Solvent casting method

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Advantages :

Great uniformity of thickness and great clarity than extrusion A typical relative standard deviation (RSD) for uniformity testing of an oral thin-film batch prepared by liquid casting is on the order of 1.2% RSD [19,20]. Film has fine gloss and freedom from defects such as die lines. Films have more flexibility and better physical properties. The preferred finished film thickness is typically 12-100 m, although various thickness are possible to meet API loading and dissolution needs.

Disadvantages :

The polymer must be soluble in a volatile solvent or water. A stable solution with a reasonable minimum solid content and viscosity should be formed. Formation of a homogenous film and release from the casting support must be possible.

B)SEMISOLID CASTING

In semisolid casting method firstly a solution of water soluble film forming polymer is prepared the resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted into the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

EXTRUSION

(a) Hot-Melt Extrusion

Hot-Melt Extrusion (HME) is commonly used to prepare granules, sustained-release tablets, transdermal and trans mucosal drug delivery system. It involves shaping a polymer into a film via the heating process rather than through the traditional solvent casting method. Melt extrusion is used as a manufacturing tool in the pharmaceutical industry since 1971. Since the turn of the century, many studies have been conducted on this process for the preparation of solid dispersion. Hot-Melt Extrusion method is used in the preparation of various dosage forms in the pharmaceutical industry such as preparation of sustained-release pellets. The drug carrier mix is filled in the hopper and is conveyed, mixed, and melted by the extruder. The die then shapes the melt in the required film form. Hot-Melt Extrusion include lower temperature and shorter residence time of the drug carrier mix (< 2 minutes), absence of organic solvents, continuous operation possibility, minimum product wastage, good control of operating parameters, and possibility scale up.

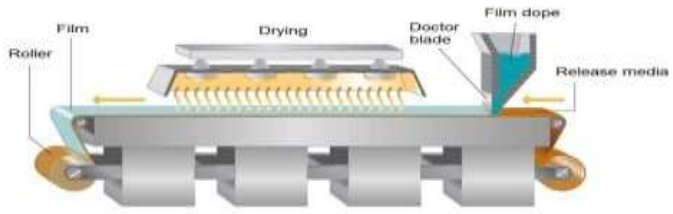

Fig.3 Hot melt extrusion

Advantages :

• No need to use solvent or water.
• Fewer processing steps
•Good dispersion mechanism for poorly soluble drugs.
•More uniform dispersion of the fine particles because of intense mixing and agitation.
• Less energy compared with high shear methods.

Disadvantages :

•Polymer stability problem
•Flow properties of the polymer are essential to processing.
•Limited number of available polymers.

(b) Solid dispersion Extrusion :

The term "solid dispersion" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. Drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70℃ without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic from of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.

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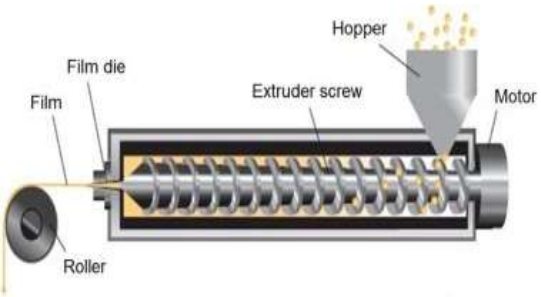

Fig. 4 Solid dispersion extruder

ROLLING METHOD

In this method the film is prepared by preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch which includes the film–forming polymer, polar solvent, and any other additives except a drug is added to the master batch feed tank. Then a pre-determined amount of the master batch is controllably fed via a first metering pump and control valve to either or both of the first and second mixers. The required amount of the drug is added to the desired mixer through an opening in each of each of the mixers. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan through the second metering pumps. The metering roller determines the thickness of the film and applies it to the application roller. The wet film is then dried using controlled bottom drying desirably in the absence of external air currents are heat on the top (exposed) surface of the film.

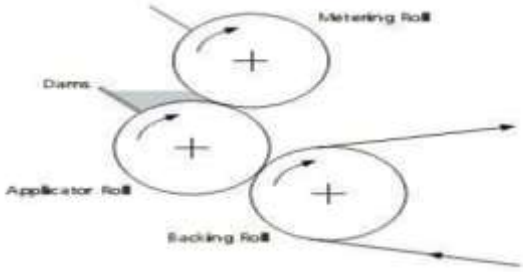

Fig.5 Roller

Techniques for solubility enhancement in oral film:-

Hydrotrophy :

Hydrotrophic effect means the increase in saturation solubility of a substance in water by the addition of either organic salts or nonelectrolytes which must be physiologically compatible for pharmaceutical application. These hydrotrophic substances are able to increase the number of hydrogen bridges in the water clusters. This makes the water more hydrophobic and thus it is a better solvent for non-polar drug.

Hydrotrophic agents like sodium acetate, sodium alginate, sodium benzoate, urea etc. are ionic organic salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotrophic salts" a phenomenon known as "Hydrotrophism".

Mechanism of hydrotrophy is by improving solubility which is closely related to complexation including a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs. Solubility enhancement in oral film can be done by this technique. During film preparation, organic salts or non- electrolytes are added in aqueous solution containing drug and after complete drug solubilisation, solution is transferred to polymer solution containing other excipients and further film is prepared by one of the techniques.

Advantages:

1. Hydrotrophy is suggested to be superior to other solubilisation method, such as miscibility, micellar solubilisation, co- solvency and salting in, because the solvent used in this technique is independent of

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pH, has high selectivity and does not require emulsification.
2. It only requires mixing the drug with the hydrotrope in water.
3. It does not require chemical modification of hydrophobic drugs or organic solvents.
4. The hydrotropes are known to self-assemble in solution.

Co-solvency:

Co-solvency is the best and easy method in oral film formulation. It is defined as the addition of a water miscible or partially miscible organic solvent (i.e. co-solvent to water) to increase solubility of a nonpolar drug. Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Weak electrolytes and non-polar molecules have poor water solubility and it can be enhanced by changing polarity of solvent which further change the solubility of drugs. Co- solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly called as solvent blending.

Most co- solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with water's hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting water's self- association, co- solvents reduce ability of water to squeeze out non- polar, hydrophobic compounds, thus increasing solubility.Examples of co-solvents used in this technique are polyethylene glycol, propylene glycol, ethanol or glycerol.

Advantages:
1. This is a simple and rapid process to solubilise drug in aqueous solution while formulating oral film.
2. High degree of increase in solubility appears as compared to other solubilisation techniques.
3. Toxicity problems do not appear.
4. Over complexing agents, it does not require identification of a suitable substance that will form the complex.

Micellar solubilisation:

Surfactants are compounds that have molecular structures with two distinct regions: A polar (hydrophilic) head group and a nonpolar (hydrophobic tail). Surfactants can lower surface tension and improve the solubility of lipophilic drug in formulation When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05-0.10% for most surfactants), micelle formation occurs, entrapping the drugs within the micelles . In film formulation, surfactant particles will form a micelle around insoluble drug particle in aqueous solution and enhance its solubility. Surfactants also act as permeation enhancers in oral film which can enhance permeability of dosage form. Surfactants used in oral film formulation are Sodium lauryl sulfate, tween 80, Sodium dodecyl sulfate, poloxamer 407 etc .

Solid dispersion:

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognised in 1961. The term refers to dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method or fusion – solvent method. Most commonly used hydrophilic carriers for solid dispersion are poloxamer 407, polyvinylpyrrolidone, polyethylene glycols, etc. Irbesartan solid dispersion was prepared by using polyvinylpyrrolidone as a hydrophilic carrier and mannitol as a solvent for evaporation.

Methodology:-

Determination Of λ_{max} Of Metaprolol Succinate:-

100mg of Metaprolol succinate was dissolved in few ml of phosphate buffer pH 6.8 diluted suitably to obtain the absorbance in the range of 0-1 and the solution was scanned at different wavelengths ranging from 200nm-400nm using UV-Visible Spectrophotometer to determine the λ_{max}

Preparation Of Phosphate Buffer pH 6.8:-

112ml of 0.2M sodium hydroxide(8gm in 1000ml water) was added to 250ml of 0.2M Potassium dihydrogen phosphate (27.218gm in 1000ml water) the volume was made upto 1000ml using distilled water to obtain Phosphate buffer pH 6.8.

Calibration Curve Of Metaprolol Succinate In Phosphate Buffer pH 6.8:-

100mg of Metaprolol succinate was dissolved in few ml of phosphate buffer pH6.8 and the volume was made upto 100ml with phosphate

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buffer from this primary stock solution 1ml was taken and make upto 100ml with phosphate buffer (stock II). From this 2,4,6,8,10µg/ml concentrations were prepared and their absorbances were determined.The absorbance of the volumetric solution was recorded at λ_{max} (222nm) of the drug and plotted graphically by taking concentration on X-axis and absorbance on Y-axis to give the standard graph of Metaprolol succinate.

Solubility Studies:-

Solubility of Metaprolol succinate and its formulations were determined in pH6.8 buffer. The buffer was prepared as described in USP. Metaprolol succinate (50mg) and its formulations were placed in a test tubes followed by solvent(5ml) addition and mixing for a total duration of 24 hrs. Intermittently, the test tubes were checked for complete solubility of drug and if required more amounts of drug or its formulations were added. After 24hrs the solution was filtered through 0.45µm filter and analyzed by UV spectroscopy at a wave length of 222nm and solubility determined.

Solubility ranges

TERMS	SOLUBILITY RANGES
Very Soluble	1 part in less than 1
Freely Soluble	1 part in l-10
Soluble	1 part in 10-30
Sparingly Soluble	1 part in 30-100
Slightly Soluble	1 part in 100-1000
Very Slightly Soluble	1 part in 1000-10000
Insoluble	1 part in more than 10000

PREPARATION OF ORAL DISSOLVING FILMS:-

Fast dissolving films were prepared by the solvent casting method. First of all film-forming polymers PVA, NaCMC, Naalginate were dissolved in distilled water and were allowed to stand for swelling. Plasticizer PEG 400 was added in a drop wise and stirred to obtain a homogenous solution.

The solution was kept for some time for the removal of bubbles and sodium saccharin imparts sweetness, Tween 80 as surfactant, CCS as disintegrant and vanillin imparts flavour then casted into the lubricated Petri-dishes (area of 63.585 cm2). Petri dishes were kept and maintained at room temperature for 48 hrs and an inverted funnel was placed over the petridish to prevent fast evaporation of the solvent or in hot air oven for 24h.

FORMULATION OF OTF

FORMULATION CODE	F1	F2	F3	F4	F5	F6
Metaprolol succinate	100mg	100mg	100mg	100mg	100mg	100mg
Na.CMC	200mg	300mg	---	---	---	---
Na.ALG	---	---	200mg	300mg	---	---
PVA	---	---	---	---	200mg	300mg
Tween 80	q.s	q.s	q.s	q.s	q.s	q.s
Citric acid	200mg	200mg	200mg	200mg	200mg	200mg
Sodium saccharin	30mg	30mg	30mg	30mg	30mg	30mg
PEG 400	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
CCS	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s

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EVALUATION OF ORAL THIN FILMS

1 General appearance

The physical appearance was checked with visual inspection of films and texture by feel or touch for transparency and opacity.

2 Weight Uniformity:

The cast film was cut at different places and the weight of each film was checked with the help of an electronic balance and the average weight was calculated.

3 Film thickness:

The thickness of three randomly selected films from every batch was determined using a standard Vernier Callipers and average values were reported.

4 Tackiness:

Six films were randomly selected. Each film was pressed against the finger tips and tackiness was recorded. Results were noted in qualitative terms as tack and non-tacky.

5 Folding endurance:

The folding endurance was determined by repeatedly folding one film at the same place till it broke or folded up which is considered satisfactory to reveal good film properties. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

6 Surface pH :

The surface pH of the films was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The 2cm X 2cm film was dissolved in 2ml of distilled water. The pH was measured by bringing the electrode in contact with the surface of the film and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate and average values were reported.

7 Percent moisture loss:

Films of area 2×2 cm are cut and weighed on electronic balance. Then the films are placed in desiccator containing fused anhydrous calcium chloride. The films should be kept for 72h in the desiccator. After 72h they are taken out and again weighed and the percentage moisture loss of films was measured by using the formula:

PML= Initial wt-Final wt/ Initial wt × 100

8 Drug content uniformity:

A otf is transferred into a graduated flask containing 100ml of phosphate buffer pH6.8. The solution was stirred for 1hr on magnetic stirrer. The solution was filtered and transferred and suitable dilutions with phosphate buffer were prepared and the absorbance was measured at 220nm and drug content was calculated.

9 Disintegration Time:

This test was done on randomly selected three films from each batch and average values were reported. 2ml of distilled water was placed in a Petridish and one film was added on the surface of the water and the time measured until the oral film was dissolved completely**.**

10 Dissolution studies:

The in vitro dissolution study is carried out in stimulated saliva solution pH 6.8 phosphate buffer using USP basket (Type II) apparatus at 37±0.5°C. Samples are withdrawn at regular time interval and analyzed by UV-Visible spectrophotometer. By this method cumulative drug release and cumulative percentage of drug retained were calculated. In-vitro drug dissolution was performed using USP basket apparatus. The studies were carried out at 37°C with stirring speed of 50 rpm in 900 mL of pH 6.8 phosphate buffer dissolution medium. 5 ml of samples were withdrawn at predetermined time intervals of 2, 4, 6, 8, 10 minutes and replaced with the same volume of buffer. The samples were collected and the absorbance was determined at 222 nm UVvisible spectrophotometer.

The results of in-vitro release data obtained for all formulations were fitted in two popular models of data treatments as follows: i. Zero-order kinetic model (cumulative percent drug released versus time) ii. First-order kinetic model (log cumulative percent drug remaining versus time).

II. RESULTS AND DISCUSSION

1. λ_{max} OF METAPROLOL SUCCINATE:-

Absorption maximum of Metaprolol succinate pure sample was found to be at 222 nm using UV visible spectrophotometer.

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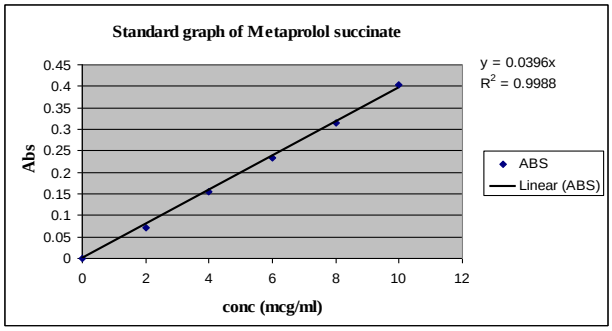
2 CONSTRUCTION OF CALIBRATION CURVE OF METAPROLOL SUCCINATE IN PHOSPHATE BUFFER PH -6.8

The data standard graph of Metaprolol succinate has shown good linearity over a concentration range of 0-10µg/ml with R^2 value of 0.998. The equation was Y=0.0396x. This was utilized in the estimation of Metaprolol succinate samples.

ABSORBANCE VALUES OF METAPROLOL SUCCINATE IN PHOSPHATE BUFFER PH -6.8

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE
1.	0	0
2.	2	0.072
3.	4	0.154
4.	6	0.234
5.	8	0.314
6.	10	0.403



Standard graph of Metaprolol succinate

3.SOLUBILITY STUDIES OF METAPROLOL SUCCINATE:-

Solubility of Metaprolol succinate and its formulations was determined in various solvents. It is freely soluble in water, sparingly soluble in ethanol, slightly soluble in dichloro methane and is more soluble in Phosphate buffer 6.8

4 EVALUATION PARAMETERS OF METAPROLOL SUCCINATE OTF:

The prepared films were evaluated for general appearance, weight uniformity, film thickness, tackiness, folding endurance, surface pH, Percent moisture loss, Drug content uniformity, Disintegration Time, Dissolution studies and the values were shown in table.All the films prepared were formed to be flexible, smooth, non sticky, transparent with no visible particulate matter. The surface ph was found to be in the range of 6.6 to 7.75 which is close to neutral pH.

Evaluation parameters of Metaprolol succinate OTF

Formulation code	Appearance	Weight variation	Folding endurance	Surface PH
F1	Transparent	25.09 ± 0.121	98.021 ± 1.56	7.2 ± 0.05
F2	Transparent	24.32 ± 0.53	99.00 ± 0.158	7.0 ± 0.15
F3	Transparent	22.33 ± 0.22	97.215 ± 2.99	6.7 ± 0.45
F4	Transparent	23.25 ± 0.529	98.77 ± 1.99	6.9 ± 0.11
F5	Transparent	21.12 ± 0.23	96.45 ± 3.02	6.7 ± 0.22
F6	Transparent	20.57 ± 0.40	95.03 ± 4.06	6.6 ± 0.06

International Journal of Pharmaceutical Research and Applications
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The film thickness was measured by using vernier calipers. As all the formulations contained different amount of polymer, hence the thickness was varied in range 0.1±0.06 to 0.8±0.090mm. The drug content for all films were evaluated and the values ranged from 98.96±0.132 to 98.05 ± 0.45 . No significant difference in the drug content among the films indicated good content uniformity.

The disintegration time for all formulations were evaluated and the values were ranged in 65±1.5 to 70±0.05. The disintegration time was found to increase with increase in the concentration of polymer. Films containing PVA and Sodium CMC were found to disintegrate faster than those with sodium alginate.

Evaluation Parameters of Metaprolol succinate OTF

Formulation code	Disintegration time	Film thickness	Drug content
F1	65 ± 0.94	0.1 ± 0.04	98.2 ± 0.74
F2	66 ± 0.68	0.3 ± 0.090	99.58 ± 0.02
F3	68 ± 1.01	0.4 ± 0.10	98.34 ± 0.98
F4	67 ± 0.99	0.5 ± 0.05	99.24 ± 0.04
F5	69 ± 1.29	0.6 ± 0.04	98.21 ± 0.08
F6	70 ± 0.58	0.8 ± 0.02	98.05 ± 0.45

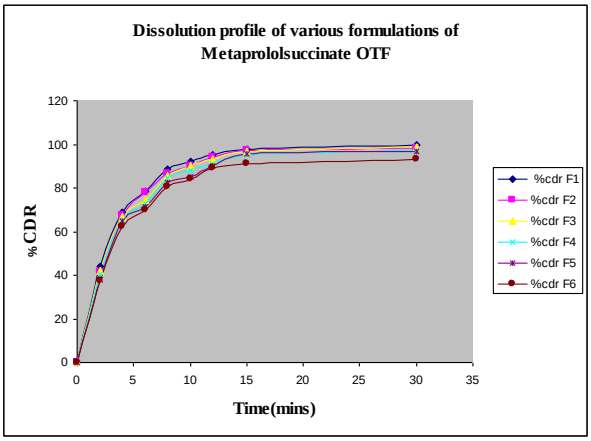
In-vitro Drug release studies:

It was observed that formulations containing Na cmc polymer, the drug release was found to be faster than PVA and Na.alginate. Among the formulations with increasing polymer concentration the drug release was found to be decreased due to increase in time required for wetting and dissolving drug molecules present in polymer matrices.

Formulations were fitted in two popular models of data treatments as follows: i. Zero-order kinetic model (cumulative percent drug released versus time) ii. First-order kinetic model (log cumulative percent drug remaining versus time).

In-vitro Dissolution profiles of Metaprolol succinate OTF

Time(min)	F1	F2	F3	F4	F5	F6
0	0±0	0±0	0±0	0±0	0±0	0±0
2	44.1±0.895	41.4±0.483	42.1±0.895	40.4 ±0.895	38.1± 0.8	37.4± 0.483
4	68.8± 0.570	67.5 ±0.623	66.8± 0.570	65.5 ±0.623	64.8 ±0.570	62.5 ±0.623
6	78.5± 0.995	77.8± 0.521	74.5 ±0.995	72.8 ±0.521	71.5 ±0.995	69.8 ±0.521
8	88.6± 0.924	86.5 ±0.321	85.6 ±0.924	84.5 ±0.321	82.6 ±0.924	80.5 ±0.321
10	92.1± 0.123	90.0± 0.115	90.1 ±0.123	88.0 ±0.115	85.1 ±0.123	84.0 ±0.115
12	95.3± 0.11	94.3± 0.125	93.3 ±0.11	91.3 ±0.125	90.3 ±0.11	89.3 ±0.125
15	97.8± 0.126	97.0± 0.1	96.8 ±0.126	95.0 ±0.1	95.8 ±0.126	91.0 ±0.1
30	99.8±0.15	98.4 ±0.14	98.8 ±0.15	97.4 ±0.14	96.8 ±0.15	93.4 ±0.14



International Journal of Pharmaceutical Research and Applications
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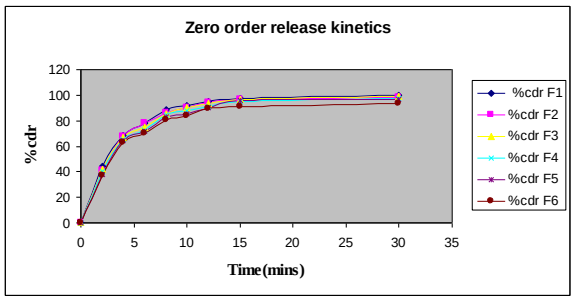
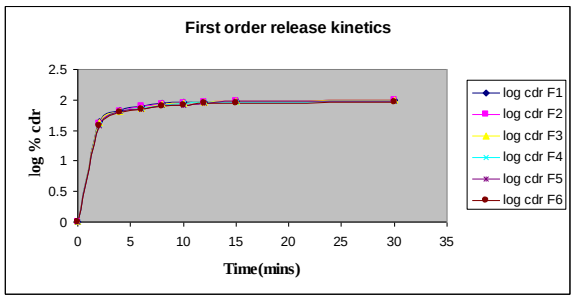
In-vitro Dissolution profiles of Metaprolol succinate OTF



Zero order release kinetics



First order release kinetics

III. SUMMARY

Fast dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oro mucosal absorption or with formula modifications, will maintain the quick dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed.

The present study was aimed to formulate fast dissolving oral films of Metaprolol succinate to enhance bioavailability and avoid pre systemic metabolism. The key is to develop successful oral film by solvent casting method. Oral film was fabricated using sodium cmc, sodium alginate and polyvinyl alcohol polymers. The prepared films were evaluated for Organoleptic evaluations, film weight, thickness, folding endurance, drug content uniformity of films, surface pH, disintegration time and in-vitro diffusion studies.

IV. CONCLUSION

Fast dissolving films of Metaprolol succinate were prepared by the solvent casting method using polymers PVA, NaCMC, Na alginate with varying concentrations 2%, 3%.

The prepared films were evaluated for general appearance, weight uniformity, film thickness, tackiness, folding endurance, surface pH, Percent moisture loss, Drug content uniformity, Disintegration Time, Dissolution studies and all the formulations were found to be in limits..All the films prepared were formed to be flexible, smooth, non sticky, transparent with no visible particulate matter. The surface ph was found to be in the range of 6.6 to 7.75 which is close to neutral pH.

Among six formulations, formulation with polymers sodium CMC and PVA showed rapid drug release compared to sodium alginate.

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