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Formulation and Evaluation of Oral Thin Films of Amlodipine Besylate.

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Abstract: *The utmost accepted route of dispensation is oral route for the reason of low cost and improved patient compliance. Tablets and capsules are the highly prevalent dosage forms taken via oral route, however many pediatric & geriatric patients notice it problematic to consume and do not take their medicines as prescribed. To overcome these difficulties, several fast-dissolving oral thin film drug delivery systems are developed.*

This is convenient and uncomplicated to use compared to other delivery modes like orally disintegrating tablets. Oral fast dissolving film is comparatively a novel dosage form in which thin film is formulated employing hydrophilic polymers, which rapidly disintegrate or dissolves on tongue or in the buccal cavity. It is a substitute platform for molecules that go through high first pass metabolism.

The purpose of the current work was to prepare and evaluate oral thin films for sublingual dispension of Amlodipine besylate. Amlodipine besylate is a calcium channel blocker used in the medication of hypertension, angina and other heart diseases. Films were prepared using HPMC (15cps, 60cps), PVA, and HPC as different film-forming agents (3 and 4% (w/v)). Poly ethylene glycol 400 was used as plasticizer and SSG as disintegrant. Sodium saccharine was utilized to hide the unpleasant taste of the API. Films were formulated by solvent casting technique and estimated for weight variation, disintegration time, tensile strength, folding endurance. It can be decided after the analysis that the Amlodipine oral thin films for sub lingual dispension can be a potential innovative drug dosage form...

Keywords: Amlodipine Besylate, Oral thin film, Novel drug delivery system, first pass metabolism, hydrophilic polymers, HPMC, Solvent casting method

I. INTRODUCTION

Among the drug delivery routes, oral route is one of the most suitable, economical and favored route for drug administration.1

Fast dissolving oral thin films is an extreme thin film that uses a hydrophilic polymer that rapidly hydrates or adheres when placed on the tongue or in the buccal cavity.2

These films disintegrate or dissolve within seconds to discharge the active agent without drinking and chewing.3-5

As the mucosa is highly enhanced with blood supply, it offer fast absorption and immediate bioavailability of drugs.6

Buccal drug delivery is a significant route of drug administration, difficulties such as high first pass uptake and drug degradation in the gastrointestinal environment can be escaped by administering the drug through buccal route.23

Investigation in the oral drug delivery system has led to the advancement of dosage forms from simple conventional tablets/capsules to modified release tablets/capsules to oral disintegrating tablet to wafer to the recent development of fast dissolving oral thin films.7-9

The instant bioavailability results from avoiding first pass metabolism. So they are usually intended for the drugs having high first pass metabolism for attaining improved bioavailability.10,11

The European Pharmacopoeia describes them as “orodisperse” tablets, which are to be placed within the mouth where they disperse rapidly before swallowing. For the systemic drug delivery of active pharmaceutical ingredients (API) quick dissolving films are well proven and universally believed technology.12,13

An oral thin film are produced as an oversized sheet then cut into single dosage unit for packaging. Oral thin films are used for local action in mouth such as local anesthetic for toothaches, oral ulcer, cold sores or teething etc. Numerous

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drugs like cough remedies, antiasthamatics, antihistaminic, erectile dysfunction drugs, sore throat, gastrointestinal disorders, and nausea, pain and CNS drugs can be included in this dosage form.

Other purposes of oral thin films include the formulation of caffeine strips, multivitamins, sleeping aid and snoring aid etc.14-16

Figure 1: Formulation and Characterization of Oral Thin Films

2.1 Advantages17

i. Oral Thin Films have enriched the bioavailability of the drug which leads to faster action.

ii. Not like in the case of conventional dosage forms drugs in oral thin films bypasses the first pass action and hence the quantity of drug essential to be loaded is diminished.

iii. Matched to liquid dosage form oral thin films have increased stability. As the drug is loaded into an abuse resistant matrix oral thin films do not need unique packing.

iv. As competed to tablets Oral thin films are less friable.

v. Research has confirmed that, oral thin films have minor side-effects. Oral thin films have faster dissolution & disintegration due to greater surface area of oral cavity.

vi. Effortlessly portable.

Can be used to provide drugs in a non-invasive method for e.g., Transfer of Opioids through the Sublingual or buccal route to diminish the necessity of invasive means like parenteral injections.

Clinical Advantages17

i As oral thin films are delivered by oral route their administration is uncomplicated as it employs the oral route.

ii In pediatric and geriatric patients the threat of choking or suffocation is decreased.

iii Oral Thin Films are an effective substitute for patients with nausea.

iv Oral Thin Films do not required to be swallowed with water.

Market Advantages17

i This novel drug delivery system offers pharmaceutical companies with patents on the edge of termination to rise their profit sets.

ii OTFs discourage the ill use, manipulating and abuse related to some recommended drugs because the film is loaded with an precise amount of API.

iii The oral thin films market is presently in its emerging stages and restricted only to specific over the counter drugs accessible within the American, Japanese and EU Markets. Thus, researches and corporations have an excessive reach in formulating drugs that haven't been beforehand prepared into OTFs and evolving newer and inexpensive technologies.

iv.In India, per Indian demographics for 2017 roughly 13.39% of the population are senior citizens while 45.7% are children. Thus, Indian investors have a beneficial purchaser range and this technology is developing in our country

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2.2 Disadvantages17

i A major manufacturing trouble that challenges manufactures is that the drying time required for the OTFs. As thermolabile drugs disallow the use of hot air ovens and elevated temperatures, it takes each day for the films to dry at room temperature thereby decreasing the production amount.

ii As the films are highly hygroscopic and tend to fail stability in surroundings having high relative humidity.

iii In oral thin films it is hard to attain uniformity of dosage.

iv Drugs which are unstable at the buccal pH or irritate the mouth mucosa cannot be formulated into thin films.

v The co-administration of numerous drugs continues to be a task because the dissolution time is disturbed.

vi Drug with minimum dose requirement can only be dispensed.

vii Taste masking is required for bitter taste drugs.

viii Specific packaging is needed for OTFs, so as to protect it from water.

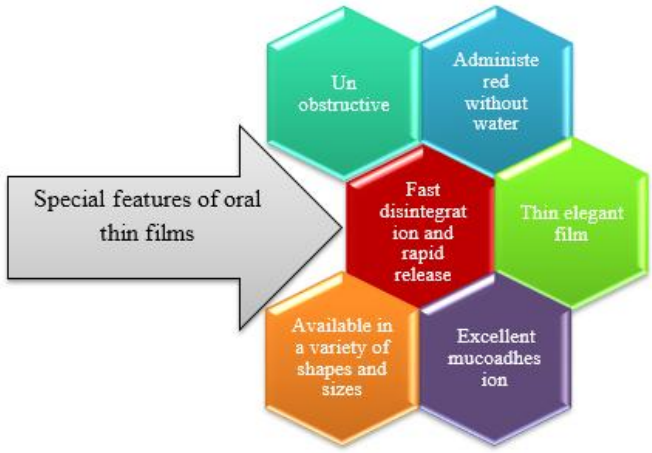

Figure 2: Special features of oral thin films

3. Drug Profile:

Hypertension is a health ailment in which the blood pressure is frequently rose which is usually signified as "high blood pressure"27. Amlodipine besylate belongs to the dihydropyridine (DHP) class of calcium channel blocker which has oral bioavailability of 64 – 90% and half-life of about 30 - 50 hours. It undergoes broad first pass metabolism. Hypertension is a disorder, which needs instant action. To attain this, drug was prepared into oral thin films for sublingual dispension so that the onset of action is quick. Oral thin films were formulated utilizing film forming polymers like HPMC, HPC and PVA, PEG 400 as plasticizer, Sodium starch glycolate (SSG) as Super disintegrant, Vanillin as flavoring agent and sodium saccharine as sweetening agent.28

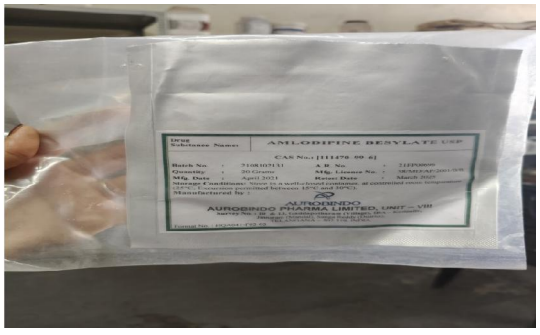

Figure 3: Amlodipine Besylate

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4. Standard Composition of Oral Fast Dissolving Film 18-19

Formulation of oral thin films of Amlodipine Besylate consists of following ingredients:

Table 1: Formulatory Ingredients and different batches of drug.

Ingredients (mg/film)	F1	F2	F3	F4	F5	F6	F7	F8
Amlodipine besylate	5	5	5	5	5	5	5	5
Hydroxy propyl methyl cellulose (60 cps)	3	4	-	-	-	-	-	-
Poly vinyl alcohol	-	-	3	4	-	-	-	-
Hydroxy propyl methyl cellulose (15cps)	-	-	-	-	3	4	-	-
Hydroxy propyl cellulose	-	-	-	-	-	-	3	4
Sodium starch glycolate	2	2	2	2	2	2	2	2
Poly ethylene glycol 400	20	20	20	20	20	20	20	20
Vaniline	1	1	1	1	1	1	1	1
Sodium saccharine	1	1	1	1	1	1	1	1
Water	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s

Figure 4: Formulation Ingredients.

5. Manufacturing Methodology:

Films were formulated by solvent casting technique . The quantified amount of polymer was balanced and dispersed in a required volume of water for overnight to acquire a even dispersion of 3% and 4% (w/v) solutions. Drug, sodium starch glycolate, vanillin, citric acid was dissolved in water.29 The drug mixture was poured to the polymer solution and mixed using laboratory stirrer for 1 hour. The resultant mixture was degassed to eliminate the bubbles developed. The bubble released mixture was transmitted on to a petri dish . It was dried for 24 hours at room temperature. The film was detached from the petri dish and viewed for any defects.30 Further findings were performed for the selected preparations. Films of area 2.25 cm2 (1.25 X 1.25) were cut and stored in a desiccator.

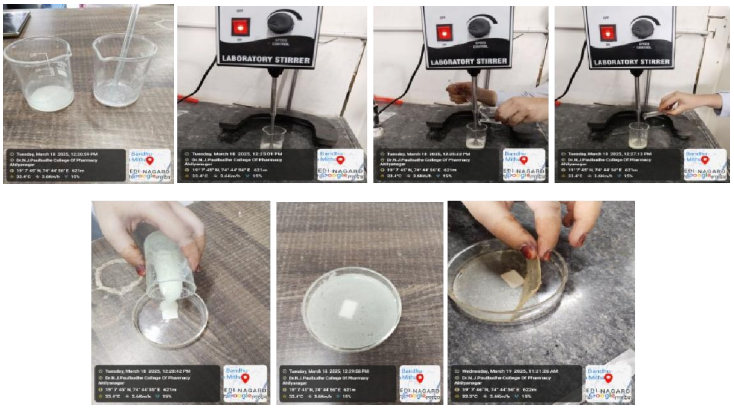

Figure 5: Procedure for formulating OTF's.

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6. Thin Layer Chromatography of Amlodipine Besylate:

Thin-layer chromatography (TLC) can be employed to isolate and identify amlodipine besylate, and it's frequently used in pharmaceutical analysis to determine its purity, stability, and quantification in different preparations.20

TLC Procedure:

• Stationary Phase:

Silica gel 60 F-254 plates are usually employed as the stationary phase due to their capability to successfully separate an extensive variety of compounds.

• Mobile Phase:

Mobile phase used is dichloroethane: methanol: ammonia solution (2.0:1.0:0.4 v/v). The exact solvent combination is selected to enhance the separation of amlodipine besylate from other constituents in the sample mixture.

• Detection:

Amlodipine besylate can be detected using several methods:22

• Ultraviolet (UV) Detection: The compound absorbs UV light, permitting for quantification at precise wavelengths, such as 244 nm or 326 nm.

• Fluorescence Detection: Amlodipine besylate can be made to fluoresce when combined with certain reagents, allotting for sensitive detection.

• Densitometry: TLC plates are scanned and analyzed densitometrically to measure the separated spots.

Figure 6: TLC Determination

7. Evaluation of Oral thin films:

7.1. Organoleptic evaluation:

The majority of people take products with sweet taste. Specific precise human taste panels are used for product estimation. For this purpose, in-vitro techniques of using taste sensors, specially designed equipment and drug release by improved pharmacopeial methods are used.16

Physical parameters	Appearance
Color	Yellow
Odor	Sweet
Taste	Vanilla

7.2. Weight uniformity:

Ten different randomly selected patches from each batch are weighted and the weight variation is calculated.

This was done by weighing for ten different patches of individual batch taking the uniform, size at random and calculating the average weight of it.21

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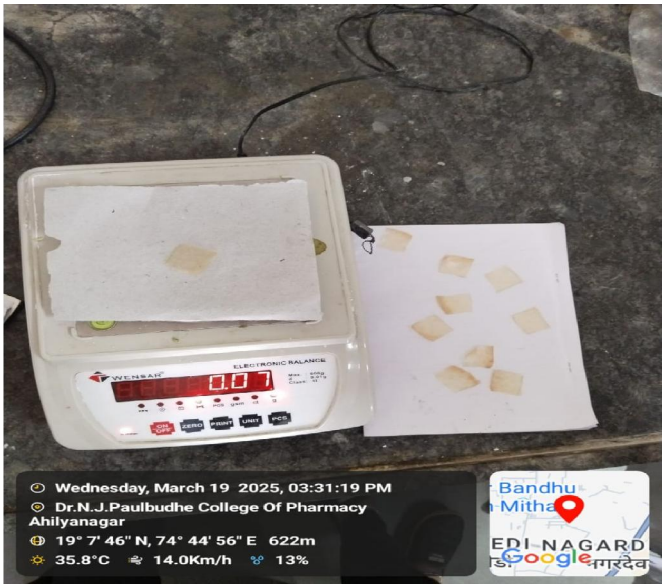

Figure 7: Weight variation test.

Table 3: Weight variation test of films.

NUMBER OF FILMS	WEIGHT
1	0.7
2	0.7
3	0.7
4	0.5
5	0.7
6	0.7
7	0.5
8	0.5
9	0.6
10	0.6
AVERAGE WEIGHT	=0.62

7.3. Dryness test/Tack test

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 are the eight phases of the film drying process that have been established. While these tests are usually designed to evaluate paint films, the majority of the inquiries may be exactly changed to measure pharmaceutical OTF. The tenacity with which the strip sticks to an accessory (a piece of paper) that has been pressed into contact with the strip is referred to as tack.25

7.4. Percent elongation

Strain occurs when tension is applied to a film (2 ×2 cm2) sample, which causes it to stretch. Strain is the deformation of a strip prior to it breaking due to stress. The Hounsfield universal testing machine is used to determine it. Strip elongation enlarges in general when the plasticizer content rises. It is calculated by the formula.24

$$\% \, Elongation = \frac{Increase \ in \ length \ of \ strip}{Initial \ length \ of \ strip} \times 100$$

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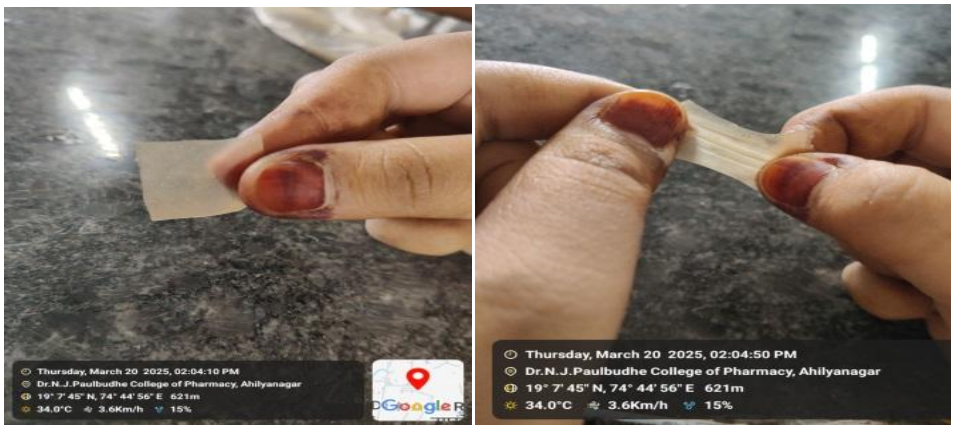

Figure 8: Percent elongation test.

7.5. Folding endurance

To check folding endurance, a strip of film is cut and folded frequently at the unchanged position until it ruptures. The rate of folding endurance is checked by the number of times the film could be folded at the same location without breaking. Standard folding endurance for film is between 100-150.15

Number of trials	Folding endurance
1	150
2	145
3	155
4	130
5	148

7.6. Swelling index

The examinations of the film's swelling index are carried out in simulated salivary fluid. The film sample is weighed and placed in a stainless-steel wire sieve that has been pre-weighed. In a mortar, the mesh containing the film is immersed in 50 ml of simulated salivary medium. At each interval, the weight of the film is calculated until it reaches a consistent weight. The following formula is used to determine the degree of swelling:

$$SI = \frac{wt - wo}{wo}$$

Where,

SI = swelling index

Wt = the film's weight at time "t" and Wo = weight of the film at t = 0. 15

Figure 9: Swelling index test.

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7.7. Surface pH test

Since the surface pH of a fast-dissolving strip can have adverse effects on the oral mucosa, it's essential to check the pH of the film. The pH of the film's surface must be 7 or nearby neutral. A mixed pH electrode can be used for this purpose. OTF was slightly wetted with water, and the pH was determined by placing an electrode on the surface of the oral film. This study should be carried out on minimum six films of each formulation, with the mean and standard deviation calculated. Another method for verifying the surface pH is to place the films on a 1.5 percent w/v agar gel, then place the pH paper on the film, and the change in color of the pH paper gives the surface pH of the film.24

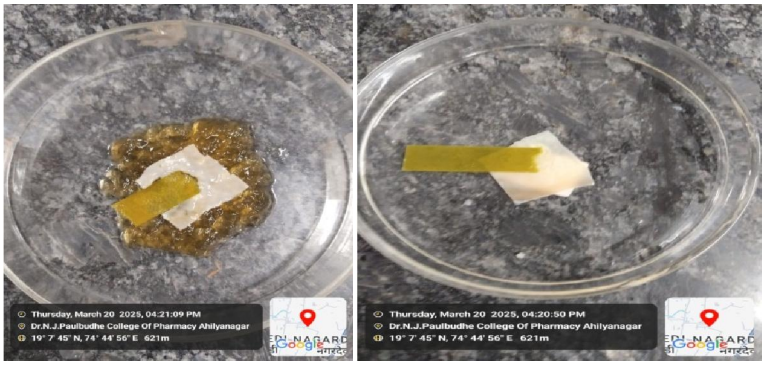

Figure 10: Surface pH test

Table 5: Surface pH test.

Methods	pH
1.Film wetted with water	5-6
2. Film placed on agar gel	6-7

7.8. Transparency

A basic UV spectrophotometer can be utilized to check the transparency of the films. Cut the film samples into rectangles and fix them on the spectrophotometer's inner side. Then, at 600 nm, verify the transmittance of the films. The films' transparency was determined as follows:

Transparency = (logT600) = − €c

b

Where,

T600 is the transmittance at 600 nm

b is the film thickness (mm)

c is concentration 15

Figure 11: Transparency test.

7.9. Moisture content

The manufactured film was initially weighed and then put in cadmium chloride desiccators. After 3 days the film was reweighed to obtain the percentage of moisture loss.15

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% Moisture content = $\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$

$= 0.9 - 0.85 \div 0.9 \times 100$

$= 5.5\%$

Figure 12: Moisture content test.

7.10. Disintegration test

When a film falls into contact with water or saliva, the disintegrating time (seconds) is calculated. Pharmacopeial disintegrating test apparatus may be utilized for this study. Standard disintegration time for film is 5-30 s.15

a. Slide frame method

A pipette was used to drop one drop of distilled water on the oral films. Then the films were clipped into slide frames and positioned on a petri dish surface. The time required for the film to dissolve and a hole to appear within it was measured.15

Figure 13: Disintegration by slide method.

b. Petri dish methods

2 ml of distilled water was poured in a petri dish and one film was placed on the surface of the water and the time calculated until the oral film dissolves completely was verified.15

Figure 14: Disintegration by Petri dish method.

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7.11. Stability study

The International Conference on Harmonization (ICH) guidelines must be obeyed when performing a stability study. The formulated preparation was wrapped in a unique manner. Initially, it was enfolded in a butter paper then above it an aluminum foil was wrapped and the packing should be placed in an aluminum pouch and make it heat sealed. Storage temperatures for formulations should be 30°C/60 percent relative humidity (RH) and 40°C/75 percent RH, respectively. The films were tested for drug content, disintegration time, and physical appearance after 3 months.24

8. Conclusion

Films combine the benefits of tablets (precise dosage, ease of application) and liquid dosage forms (easy swallowing, rapid bioavailability). As a result, several pharmaceutical companies are transitioning from tablets to fast-acting oral thin films.

Amlodipine Besylate buccal films were formulated by the solvent casting method. It is one of the best technique for the preparation of buccal films. The above mention composition is one of the suitable compositions for the preparation of Amlodipine buccal films. Fast dissolving buccal films have increased admiration since of improved patient compliance, fast drug delivery system, drug is straight absorbed into systemic circulation, first pass metabolism and deprivation in gastrointestinal tract can be escaped. Fast dissolving buccal films can be an advance option to enhance medicinal effectiveness of numerous API's in the upcoming.

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