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Formulation and Evaluation of Fast Disintegrating Mucoadhesive Oral Thin Film of Lidocaine

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ABSTRACT
Mucoadhesives are the dosage form which are been intended to adhere on desired tissue when comes in contact with mucin present there. Mucoadhesive film have been identified as alternative approach to conventional dosage forms because of their controlled action, reduced size and thickness also bypassing first pass metabolism and increasing bioavaibility of various drugs. Mucoadhesive film was formulated with objective of reducing pain associated with canker sore by incorporating API Lidocaine and other polymer to produce a desired effect. Formulation F6 with Lidocaine, maltodextrin, propylene glycol, xanthan gum and HPMC E15 was selected as optimized formulation based on folding endurance, appearance and transparency. Further evaluations such as weight variation, thickness uniformity, surface pH, moisture loss, moisture uptake, percent elongation, folding endurance, disintegration time and content uniformity was done on F6. A stability study of 1 month was been done and similar parametrical evaluations were been performed. The formulated film showed optimum and desired results with immediate disintegration within 5-6 seconds and content uniformity with average standard deviation of 97.93±1.08% and 97.51±1.306% on same day and after one month respectively. The other parameters of evaluations performed on same day closely resembles to that after one month stability studies. Thus, Mucoadhesive buccal film utilizing Lidocaine as a drug can be used to heal canker sore providing immediate action also covering the sore.

KEYWORDS Buccal Film, Mucoadhesive film, Lidocaine, Canker sore, HPMC, Stability study, immediate

I. INTRODUCTION

The oral consumption of the drug is most typically tailored and it's the supreme route of administration[1]. The mouth is vital not solely as a result of it's the route by that we tend to ingest the nutrients that we'd like, however conjointly plays a vital role within the body's immune system since most of the time is exposed to a range of antigens and pathogens[2]. Mucoadhesive drug delivery prolong the continuance of the dose type at the positioning of application or absorption. They create associate degree intimate contact of the drug dose type with the underlying absorption surface and so enhancing the therapeutic performance of the drug. In recent years, several such mucoadhesive drug delivery systems are developed for oral, buccal, nasal, body part and channel routes for each systemic and native effects[3]. Every pharma needs to make a unique oral drug dose form that has the augmented bioavailability, fast action and acceptable patient compliance so that they produce a quick dissolving pill by use of superdisintegrants and hydrophilic ingredients. Quick dissolving drug delivery system was initial developed within the late 1970 as another ancient dose forms for medical specialty and geriatric patients. WHO expertise problem in swallowing traditional oral dose form. however, this too have some drawbacks.

Fast dissolving oral films (FDOFs) are the foremost advanced type of oral solid dosage type thanks to additional flexibility and luxury. It improves the effectualness of API by dissolving with in minute in rima oris after it has the contact with saliva while with neither choking shaving nor requirement of water for administration. It provides fast absorption and instant bioavailability of medication due to high blood flow and porousness of oral membrane which is 4-1000 times larger than that of skin. FDOFs are helpful in patients like medical specialty, geriatrics, bedridden, nauseant, diarrhea, patients with unforeseen episode of allergic attacks or cutting for people who have active life-style. It's additionally helpful once the native action desired like anesthetic for toothaches, oral ulcers or cold sores. OTFs even have a longtime time period of 2 to 3 years reckoning on

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the API however it is very sensitive to environmental wetness[4].

This fast-disintegrating oral films are been designed for the treatment of canker sore. These sores are a benign non-contagious and non-infectious[5] mouth lesion that arouses because of varied reasons like heat generation, nutrient insufficiency or nutrient deficiencies, malnutrition, dental procedures, etc. These ulcers occur sporadically and heal fully between attacks. Within the majority of cases, the individual ulcers last upto 7–10 days, and ulceration episodes occur 3–6 times annually. It affects around two hundredth population generally[6]. Canker sores are the ulcers that destroys the structure on the membrane. It is synonymously known as aphthae, apotheosis and aphthous stomatitis. Canker sores are usually intermittent spherical or oval sores or ulcers within the mouth on regions wherever the skin is not firmly guaranteed to the underlying bone, for instance, inside the lips and cheeks or beneath the tongue. They will likewise influence the genital organ in males and females which is conjointly known as Recurrent aphthous stomatitis (RAS) are typically a minor aggravation, but they're connected with crucial medical problems in certain people. Signs and symptoms of canker sore don't seem to be detected ab initio however seen at latter times. These are caused because of infection of Candila albicans, deficiencies of vitamins and minerals and stress[7]. Various medicine is been employed for treating canker sore which has Topical strategies such as Covering agents (Orabase), Analgesics (Benzydamine hydrochloride), Anesthetics (Lidocaine), anti-inflammatory (Diclofenac), Antiseptics (Chlorhexidine), mild adrenal cortical steroid (Hydrocortisone), and systemic medicaments (Prednisolone, Montelukast, Clofazimine). principally such sores are caused by vitamin deficiency and so daily recommended dose is additionally prescribed with the same[8].

The main advantage of formulating lidocaine buccal film is that it will protect the sore, provide immediate relief from pain, targeted topical action, surpass dysphagia along with compensating polypharmacyconfusion[9]. Lidocaine is an anesthetic agent which block pain receptor and provides a soothing sensation. Also, there is minimal side effects seen in modifying the biological fluid which is advantageous as compared to large compartment models. There are some side effects to this governs with solubility and permeability which can be covered up by addition of permeation enhancers or surfactants. Similarly other drawbacks are the physiological conditions of oral cavity such as too much saliva secretion (dilution), too less saliva secretion (Dry mouth syndrome) food and fluid uptake and their nature may also hamper the drug release[10,11].

II. MATERIALS AND METHODS

The materials utilized in formulation are Lidocaine (Nischi lifesciences, Ahmedabad), Maltodextrin (Signet chemical co-corporation Pvt. Ltd., Mumbai), HPMC E15 (Thomas Baker Chemicals Pvt, Ltd.), Propylene Glycol (Thomas Baker Chemicals Pvt, Ltd.), Sodium hydroxide (Thomas Baker Chemicals Pvt, Ltd.), Potassium dihydrogen phosphate (Thomas Baker Chemicals Pvt, Ltd.), PVP (Thomas Baker Chemicals Pvt, Ltd.) and Xanthum Gum (Thomas Baker Chemicals Pvt, Ltd.). Here a main aim was of green chemistry so water was used as solvent.

Formulation of film:

The polymers were added as per the quantity mentioned in **table1**in 10 ml of water, stirred and soaked for 2 hrs. as depicted in **Figure1**. Propylene glycolwas added in the polymeric solution as a plasticizer under constant stirring on magnetic stirrer then the obtained viscous solution was kept overnight to ensure clear, bubble free solution. The clear bubble free solution was poured on a pretreated petri dish at room temperature and was allowed to dry at 60-75℃ temperature till a flexible film was formed. This dried film was removed carefully and checked for any imperfection or air bubbles. This placebo films were cut into 2×2 cm2 area and were packed properly in a foil and kept away from moisture in a desiccator.These polymers were analyzed with different concentrations to get an optimized film. Drug was been added in single optimized film (mentioned in bold), along with propylene glycol. These films were subjected for further various evaluations.

Evaluation parameters:

i. Physical Appearance and Texture:

This evaluation was done by organoleptic behavior such as color, odor, taste and texture. All the films were primarily optimized upon these criteria along with folding endurance[12].

ii. Weight Variation Test:

The weight of triplets of optimized batch of similar shape were considered and weighed using a digital weighing balance and mean was calculated.

iii. Thickness Uniformity:

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The thickness of film was evaluated using vernier caliper having range 0-10mm with resolution 0.001mm at different locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip[13].

iv. Surface pH:

The pH of optimized formulation was measured using pH (DIGITAL pH METER MK VI) meter. The pH meter was calibrated with pH buffer solution of 4 and 7. For the determination of surface pH of the patch a whole patch was cut and was allowed to swell by placing it in distilled water. The surface pH was then noted by bringing a glass electrode near the surface of the film.

v. Moisture Loss and Moisture Uptake:

The moisture uptake studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. This test was carried out by dissolving KCl in 50ml of water till the solution gets saturated. It was transferred into desiccator and this container was allowed to saturate. Drug free patches from formulation was selected and weighed. They were then placed in desiccator containing saturated solution of KCl for three hours, removed and reweighed. The percentage moisture absorption was calculated by using the formula.

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

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs., the films were reweighed and determined the percentage moisture content from the below mentioned formula

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

These were performed on a set of triplets.

vi. Percent Elongation

The triplet optimized films were observed by affixing film on a pulley system. This can be calculated using various formulae the simple one is given below

$$\text{Percent Elongation} = \frac{\text{Final length}}{\text{Initial Length}} \times 100$$

vii. Folding Endurance

This holds for a better property of a film and indicates its elasticity. When a film is continuously fold for 300 times or more at a same area until no cracks or breakage seen indicates the film is mechanically elastic and is good[12].

viii. Disintegration Time:

The disintegration test was performed on three films by placing in petri dish containing 6.8 pH phosphate buffer. This set up was placed over magnetic stirrer. The time is noted when the films swell and disintegrates is noted.

ix. Content Uniformity:

The three optimized lidocaine film (2×2cm2) was dissolved in 15mL of Ethanol and filtered to remove the polymers and other visible materials. This aliquot was observed for UV scan at 263nm[14].

x. Stability Studies

The same triplet film was kept in CHM-65 GMP Environmental stability chamber for a period of 1 month maintaining condition of temperature 40℃ and 75% RH.

III. RESULTS AND DISCUSSION

Formulation Aspects:

A thin buccal film containing Lidocaine for treating Canker Sore was been prepared using various combination and concentration of polymers as shown in **Table no.1**. Only a single film was been optimized among the ten formulation F1-F10. The observations of all ten films are been mentioned in **Table no.2**and **Table no.3**. As per the desired criteria of fast dissolving thin mucoadhesive film F6 served the purpose. The film was both transparent and easily peelable. The other film was translucent and sticked to the surface of plate. The selected film was considered as an optimized one and were prepared in triplets.

Evaluations:The physical appearance and texture were smooth and transparent which can be clearly seen **figure2**. The film was astringent in taste due to drug and odorless. Weight variation test, thickness uniformity, surface pH, Moisture loss and moisture uptake were compiled in **table 4**. While the percent elongation, folding endurance, disintegration time and content uniformity is also recorded in **table 5**. A one-month stability studies

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of all mentioned parameters were performed and not much significant difference was observed. Thediffusion study was not performed as the disintegration time of film was within 5-6 s and film was formulated on aim for providing localized effect. The pH of film was also similar to that of buccal cavity indicating it will cause no irritation when administered.

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Figure 1: Swelling of polymer in water

The polymers like HPMC E15 and Xanthum gum was allowed to swell for 2 hours so that water gets entrapped within it for making of smooth and consistent viscosity solution.

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TABLE NO. 1: Different batches of Buccal Film with different polymers and their concentrations.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Lidocaine (%)	2	2	2	2	2	**2**	2	2	2	2
HPMC E15 (%)	15	7.5	5	2	2	**2**	2	2	2	15
Maltodextrin (%)	50	50	50	1.5	1.5	**1.5**	1.5	1.5	5	-
PVP (%)	-	-	-	0.5	0.5	-	-	-	0.5	10
Xanthum gum (%)	-	-	-	-	0.007	**0.7**	0.07	0.7	-	-
Glycerin (ml)	2	2	2	2	2	**2**	2	2	2	0.2
Water (ml)	25	25	25	20	20	**20**	20	20	20	20

The formulation of given ingredients was taken on their percentage except glycerin and water which was added on basis of their volume. Water was only as solvent utilized as green chemistry approach was considered and all the polymer as well as the drug was completely water soluble.

TABLE NO. 2: Observations of Placebo Films formulation (F1-F5) that were deigned

OBSERVATIONS	**F1**	**F2**	**F3**	**F4**	**F5**
APPEARANCE	Solution of polymer was turbid. film was not removable, very sticky film.	Solution of polymer was turbid. film was not removable, very sticky film.	Solution of polymer was turbid, film was not removable, very sticky film.	Film formed was opaque	Film formed was hard
FOLDING ENDURANCE	Fragile	Too Fragile	Fragile	80	53
TRANSPARENCY	Translucent	Translucent	Opaque	Opaque	Dusty or opaque

The above table consists of observation of placebo from F1 to F5 on basis of appearance, folding endurance and transparency. These were the trials for optimizing a final batch.

TABLE NO. 3: Observations of Placebo Films formulation (F6-F10) that were deigned

OBSERVATIONS	**F6**	**F7**	**F8**	**F9**	**F10**
APPEARANCE	**Film formed, easily removable. Optimized film.**	Film formed was too thin	Film not formed	Film formed was dusty in appearance	Film formed, not mucoadhesive, thick film.
FOLDING ENDURANCE	**312**	131	-	204	10
TRANSPARENCY	**Transparent**	Translucent	Clear	Opaque	Opaque

The above table consists of observation of placebo from F6 to F10 on basis of appearance, folding endurance and transparency. These were the trials for optimizing a final batch.

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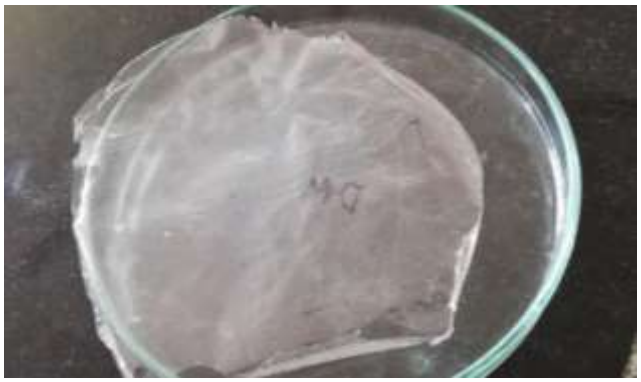

Figure 2: Optimized film of F6 formulation

Among all the 10 formulations F6 possess the required standards which was needed to optimize a film.

TABLE NO. 4: Evaluation of Weight Variation Test, Thickness Uniformity, Surface pH, Moisture Loss and Moisture Uptake on same day and after one month

Batch no.	Weight Variation		Thickness Uniformity		Surface pH		Moisture Loss		Moisture Uptake	
	DAY 1	DAY 31	DAY 1	DAY 31	DAY 1	DAY 31	DAY 1	DAY 31	DAY 1	DAY 31
B1	310 mg	303mg	0.26mm	0.28mm	6.4	6.5	1.25%	1.17 %	2.15%	2.51 %
B2	305 mg	306mg	0.28mm	0.25mm	6.6	6.4	1.48%	1.68 %	2.45%	1.89 %
B3	307 mg	307mg	0.30mm	0.30mm	6.5	6.5	1.70%	1.44 %	1.98%	2.12 %
Average with SD	307.3 ±2.552 mg	305.3 ± 1.52 mg	0.28± 0.041 mm	0.27 ± 0.02mm	6.5 ±0.053	6.46 ±0.053	1.47 ±1.26%	1.43 ± 0.173%	2.194 ±0.24 %	2.173 ± 0.2244%

These table contains observation of evaluation carried on F6 formulation. The evaluations are both on same day denoted as DAY1 and after 1 month denoted as DAY 31. The observation of DAY 1 and DAY 31with respectively are of parameters such as weight variation test (with SD of 2.552mg and 1.52 mg), Thickness Uniformity (with SD 0.041 and 0.02 mm), Surface pH (with SD 0.053 and 0.053), moisture loss (with SD 1.26 and 0.173%) and Moisture uptake (with SD 0.024 and 0.2244%). Where SD stands for Standard deviation. SD denotes standard deviation.

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TABLE 5: Evaluation of Percent Elongation, Folding Endurance, Disintegration Time and Content Uniformity on same day and after one month

Batch no.	Percent Elongation		Folding Endurance		Disintegration Time		Content Uniformity	
	DAY 1	DAY 31	DAY 1	DAY 31	DAY 1	DAY 31	DAY 1	DAY 31
B1	19.15	26.04	302	301	6 s	5 s	99.23%	95.55%
B2	23.12	18.13	305	308	5 s	5 s	96.31%	98.98%
B3	18.78	18.48	307	308	6 s	5 s	98.25%	98%
Average with SD	2.35 ± 1.84	20.88 ± 3.43	304 ±1.4	305.6 ±1.70	5 ±0.4	5 ±0.0	97.93 ±1.08%	97.51 ± 1.306 %

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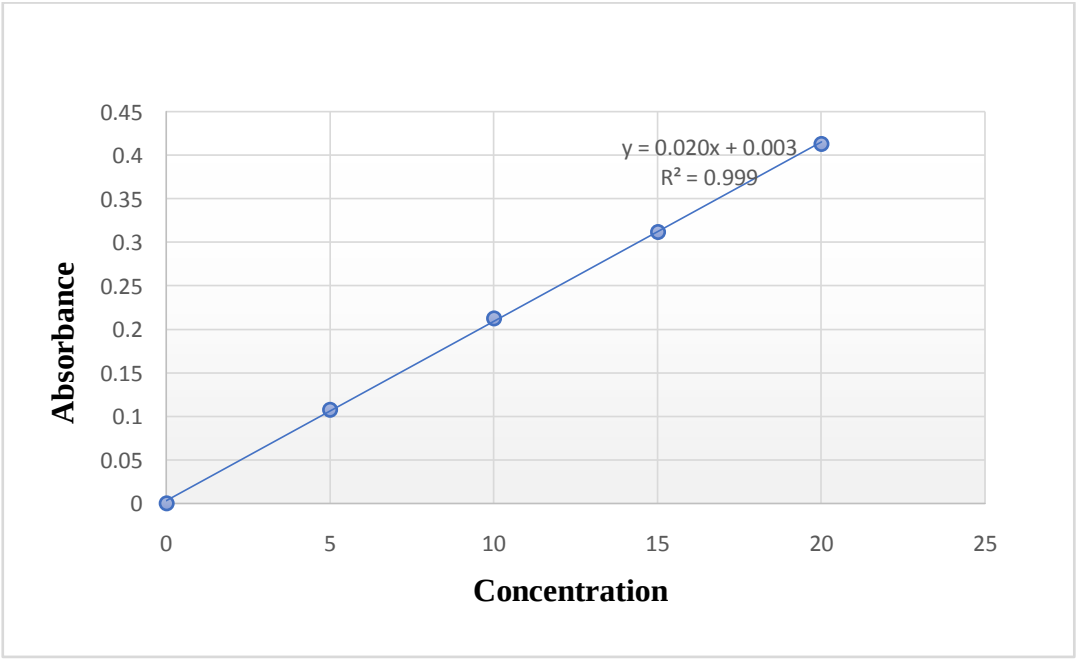

Figure 3: Calibration Curve of Lidocaine at 263nm

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The drug was dissolved in phosphate buffer pH 6.8 and linearity range was taken that was observed in UV spectroscopy at 263 nm taking phosphate buffer as blank. A concentration range of 5-30 ppm was taken on X-axis and observed Absorbance at Y-axis. Slope was derived and was further used in calculation of Drug content and Drug release. Slope of line is given by: **y = 0.0206x + 0.0032**

Table and Figure Tittles and Legends:

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