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EXTRACTION, FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF NICOTINE FOR SMOKING CESSATION

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ABSTRACT

Objective: To produce oral films of nicotine in a laboratory setting to aid smokers in smoking cessation. Nicotine is a highly addictive drug and many people suffer from its addiction around the globe in the form of smoking. This problem is particularly pronounced in Pakistan and many smokers here do not have access to cessation medications. To prevent smokers from inhaling harmful chemicals like tar, carbon mono oxide and carcinogenic compounds produced from burning vegetable matter, pharmaceutical nicotine is used in the form of chewing gums, TDDS patches and oral films. The oral route is one of the most popular routes of drug administration because of its low cost, easy administration and a high rate of patient compliance. Many patients especially geriatric and paediatric ones have dysphagia or have some level of unease when swallowing hard gelatine capsules or solid tablets. This has led to the development of fast dissolving oral films. Fast dissolving oral thin-films are useful in patients such as paediatric, bedridden or developmentally disabled, geriatric patients, many of whom face difficulty in swallowing tablets or hard gelatine capsules. Oral fast dissolving films are a novel dosage form in which a thin film is prepared using hydrophilic polymers, which rapidly disintegrates or dissolves on the tongue or in the buccal cavity. Oral films are an alternative platform for molecules that undergo high first pass metabolism. **Method:** The method used here to prepare fast dissolving oral films is the solvent casting method. This method is fast, reliable, and extremely feasible in a laboratory setting. This simple method involves dissolving the ingredients to make a homogeneous solution and casting the said solution in a suitable container in order to produce oral films. **Results:** Using this method structurally sound films were obtained. These films were then tested; employing various parameters for this task. The results obtained hence thereof were sufficiently satisfying. **Conclusion:** The solvent casting method is a pragmatic and suitable approach to producing standard quality films in a laboratory. The concentrations of the polymer and the plasticizer may need to be adjusted according to the active pharmaceutical ingredient.

Key words: Hydrophilic polymers, Fast dissolving oral thin films, Patient compliance, Nicotine round films, Smoking cessation.

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INTRODUCTION

Fast dissolving oral film technology has been emerging out as a new drug delivery system that provides a very convenient mean of taking medications and supplements. Fast dissolving drug delivery systems were first developed in the late 1970s as alternative dosage forms as opposed to conventional dosage forms for paediatric and geriatric patients many of whom had trouble swallowing traditional oral solid-dosage forms. The oral cavity is an attractive route of administration for systemic drug delivery. The oral mucosa has rich vascularization and offers higher permeability to many drugs. It is a simple fact that after buccal and sublingual administration drug solutes are rapidly absorbed in to the reticulated vein and are then drained into the systemic circulation. The concept of Fast Dissolving Drug Delivery Systems emerged from the desire to provide patients with an

easy way of taking their medications. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and paediatrics, because of physiological changes associated with these groups of patients **[1]**. Dysphagia is associated with many medical conditions, including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy. This difficulty certainly discourages the use of tablets, capsules or any other dosage form that requires swallowing. Mouth dissolving films were 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 **[2]**. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects that allow gastrointestinal absorption to be achieved when swallowed **[3]**.In contrast to other existing, rapid dissolving dosage forms, which consist of liophilisates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets **[4]**.The instant bioavailability results from bypassing first pass metabolism. Therefore, they are generally designed for those drugs that have high first pass metabolism in order to achieve better bioavailability.

MATERIALSAND METHODS

The polymer used was HPMC (hydroxyl propyl methylcellulose), plasticizer used were commercial grade glycerine and PEG 400, which were purchased from a local pharmacy. The API used was nicotine extracted from cigarette tobacco in the laboratory.

The method used was the solvent casting method, which seemed the most pragmatic approach to making oral films in a laboratory setting. Other methods like the hot melt extrusion technique are too complex to be performed in a laboratory. For the extraction of nicotine from tobacco, the isolation of the alkaloidal drug using alkalis was done.

Extraction of Nicotine from Cigarettes

10 g of cigarette leaves were weighed and placed in a beaker and then 100 mlof NaOH solution was added. The reaction mixture was stirred for 15 minutes. The mixture was then filtered in a Buchner funnel using a glass wool and the leaves were pressed thoroughly. The leaves were transferred into another beaker and 30ml of distilled water was added while stirring. Both of the filtrates were collected and transferred to a separating funnel and the extraction process was started using 25ml of ether. This was repeated 3 times. All of the collected organic portion was transferred into a conical flask and dried using anhydrous potassium carbonate. The ether was evaporated and the resulting oil was treated with saturated picric acid and allowed to cool in an ice bath to produce precipitates of nicotine di picrate **[5]**.

Preparation of Oral Films

For the preparation of oral films, we tried various different approaches in order to produce structurally sound films with lasting flexibility. Various combinations of the polymer **[6]** and plasticizer ratios were used during experimentations to observe the effects of varying the concentration of the plasticizer and the polymer on the physical properties of the films thus produced **[7]**. Two different types of plasticizers were used. Six combinations labeled A to F were prepared with different concentrations and types of plasticizers. The concentration of the polymer was

changed as well. Altogether 3 films of each combination were prepared. The required amount of the polymer was dissolved in 20 ml of distilled water and stirred on a magnetic stirrer for 3 hours **[8]**. Then the API along with plasticizer was added and further stirring was done for 1 hour. After stirring a viscous homogeneous solution of the polymer along with the other ingredients was obtained as is important for formulation **[9]**. The solution was poured into petri dishes of a known diameter and allowed to dry at room temperature for 24 hours **[10]**. After drying the films were removed from the petri dishes and further dried on filter papers. Then they were cut into uniform squares. After cutting the films some of them were packed into a standard film container which acts a primary packaging material. This container was then packed into a regular secondary packaging.

Table 1: Formulation components of fast dissolving nicotine films.

Combination	Nicotine di picrate (mg)	HPMC (mg)	Glycerine (mg)	PEG 400 (ml)
A	1	600	1	0
B	1	1000	2	0
C	2	400	0.5	0
D	1	600	0	1
E	1	1000	0	0.5
F	1	400	0.5	0.5

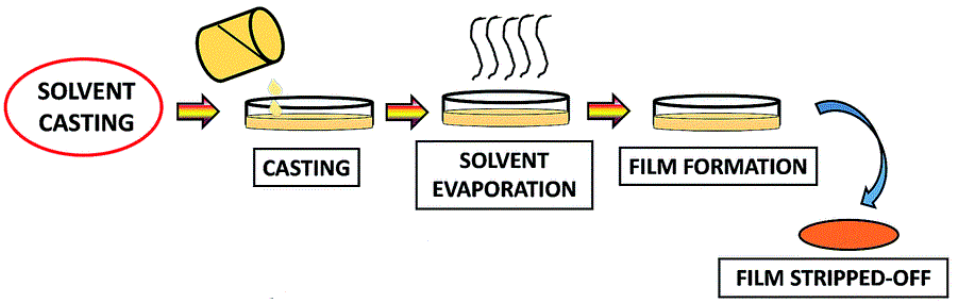

Figure 1: Schematic diagram of formulation steps.

Evaluation of the Films

Film Thickness

The thickness of the films was measured using a standard calibrated micrometre screw gauge at different strategic locations and the mean value was calculated **[11]**.

Dryness or Tack Test

This test was performed using a filter paper and the tendency of the film to adhere to it was observed **[12]**.

Tensile Strength

Tensile strength of the films was calculated using a hooked weight apparatus. This test was performed three times and mean value was calculated **[13]**.

Percentage Elongation

The same apparatus that was used to calculate the tensile strength of the films was also used to calculate the percentage elongation **[13]**.

Young's Modulus

The young's modulus was measured using the same apparatus as the above tests. This apparatus is also known as the young's modulus apparatus **[14]** and uses hooked weight to calculate the strain and stress values.

Folding Endurance

This test was performed manually by folding the films repeatedly using the same plane until they broke **[15]**. Folding endurance value is number of times the film is folded without breaking. Higher folding endurance value depicts the more mechanical strength of a film.

Disintegration Time

The films were placed in petri dish along with 10ml of water and the time taken for them to disintegrate was notes using a stopwatch **[16]**.

In-vitro Dissolution Time

The standard official paddle apparatus was used for conducting dissolution studies on films. Temperature was maintained at 37 ± 0.5 °C and rotation speed of 50 rpm was adjusted. Samples of drug dissolved were collected at pre-determined intervals and analysed by using a UV-spectrophotometer **[17**].

Surface pH

The pH value of a film was determined by putting the prepared film in petri dish and subsequently the film was made wet by using distilled water and the pH was noted by touching the film surface with a pH meter electrode.

Test for the Presence of the Drug in the Film

A standard test for the presence of the alkaloid (Hager's Test) was performed. An aqueous solution of the films was treated with saturated solution of picric acid and the result was observed.

RESULTS

Film Thickness and Mechanical Properties

The thickness of all the films was within acceptable limits. The results for this test and Tensile strength, elongation, folding endurance and other parameters are shown in T**able 2**.

Dryness or Tack Test

All of the films showed complete dryness after 36 hours of drying and did not adhere to a filter paper.

Texture, Appearance or Visual Inspection

All of the prepared films showed an acceptable texture and appearance as is normal for oral films.

Disintegration and Dissolution Times

Shown in tables 3 and 4 respectively. The disintegration time of the films fell within reasonable precision.

Other Tests

The surface pH of the films was within acceptable limits. Results are shown in Table 2. The pH of the films needs to between 6 and 8 so that it may not cause any corrosive harm to the oral mucosa. The contact angle was within a normal range as well. The films showed the presence of the active ingredient nicotine when yellow precipitates were seen.

DISCUSSION

Oral films disintegrate and dissolve to release the medication for oromucosal absorption or with formula modifications and maintain the quick-dissolving aspects that allow gastrointestinal absorption to be achieved immediately when swallowed. Oral films of nicotine were successfully prepared using HPMC by solvent casting method which is an easy, economical and reproducible method. It was confirmed that by increasing the polymer content made the films more thick as is to be expected and stated in previous studies. This also increased the tensile strength of the films. An increase in the amount of the plasticizers made the films more flexible and rubbery in texture thus making it sometimes difficult to be removed from the cast. It depends upon the type of plasticizer being used thus it should be noted that concentration of plasticizer should be such that it

does provide only the required flexibility to the formulation. The formulations containing PEG 400 showed better results of folding endurance as compared to those containing glycerine. Glycerine also induces some flexibility thus causing the films to collapse and making them difficult to be removed from the cast. Disintegration and dissolution are the most important parameters for orally fast dissolving films.

Table 2: Mechanical and physical properties of nicotine films.

Formulations	Thickness (mm)	% Elongation	Folding endurance	Tensile strength	Disintegration Time (sec)	Surface pH
A	0.243 ± 0.012	1.92 ± 0.82	93.66 ± 8.12	0.606 ± 0.61	45 ± 0.87	7.8
B	0.527 ± 0.020	2.74 ± 0.69	93.66 ± 8.12	2.18 ± 0.11	120 ± 1.67	8.1
C	0.312 ± 0.023	1.99 ± 0.67	93.66 ± 8.12	0.606 ± 0.61	40 ± 0.61	7.8
D	0.297 ± 0.014	2.21 ± 0.24	128.66 ± 5.87	0.709 ± 0.11	45 ± 0.87	7.6
E	0.527 ± 0.020	2.74 ± 0.69	128.66 ± 5.87	2.73± 0.11	116 ± 1.73	8.4
F	0.320 ± 0.018	3.9 ± 0.91	128.66 ± 5.87	2.40 ± 0.178	31± 0.97	7.4

Table 3: The dissolution profile of the film combinations.

Formulations	% drug release (2 min)	% drug release (10 min)	% drug release (20 min)
A	20.55 ± 3.89	87.38 ± 2.10	99.78 ± 1.47
B	27.21 ± 1.98	87.38 ± 2.10	99.78 ± 1.47
C	22.00 ± 2.98	87.38 ± 2.10	99.78 ± 1.47
D	20.55 ± 3.89	87.38 ± 2.10	99.78 ± 1.47
E	26.65 ± 1.89	87.38 ± 2.10	99.78 ± 1.47
F	20.55 ± 3.89	87.38 ± 2.10	99.78 ± 1.47

The disintegration time of the films fell within reasonable precision. Disintegration time of the films increased with an increase in the polymer content which is in confirmation with most of the previous studies. The films showed an average rate of drug release. On average 20 % of the drug was released in all tested films, however almost 99 % of the drug was released in all the formulations at 20 minutes. This could be due to the inaccuracy of the testing apparatus or due to the nature of the films because an official dissolution testing apparatus for oral films has not been designated yet.

CONCLUSION

From our present experimentation, it can be concluded that oral fast dissolving films of nicotine are acceptable as a regular dosage form. The films prepared by HPMC and PEG 400 had shown good mechanical strength, drug release, disintegration time and stability. Nicotine administered in the form of fast dissolving films has the potential to become a regular technique of combating withdrawal symptoms in smokers who are in the process of smoking cessation.

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