FABRICATION AND EVALUATION OF TIZANIDINE HYDROCHLORIDE FAST DISSOLVING FILMS

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ABSTRACT

Tizanidine Hydrochloride is widely used in the treatment of multiple sclerosis spastic diplegia back pain or certain injuries to the spine or CNS. **Objective:** The present work aimed at preparing quick release films of tizanidine HCl with the purpose of developing a dosage form for a very quick onset of action, which is beneficial in managing spasms and increased muscle tone, aiding in the enhancement of bioavailability, and is very convenient for administration, without the problem of swallowing and using water. **Methods:** The films of tizanidine hydrochloride were prepared by using polymers such as hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA), as either single polymer or in combination of two, by a solvent casting method. The concentration of Sodium alginate, Glycerol, Tween 80 were kept constant in all formulations. They were evaluated for physical characteristics such as uniformity of weight, thickness, folding endurance, drug content uniformity, surface pH, percentage elongation, and tensile strength, and gave satisfactory results. The formulations were subjected to disintegration, *in vitro* drug release tests. **Results:** A marked increase in the dissolution rate was exhibited by fast-dissolving films of Tizanidine hydrochloride containing HPMC as a polymer, when compared to conventional tablets. The formulation 'F3' was found to be optimized formulation. **Conclusions**: Fast dissolving films of tizanidine hydrochloride can be considered suitable for clinical use to relieve diplegia, back pain and injuries of spine, where a quicker onset of action for a dosage form is desirable along with the convenience of administration.

Keywords: Mouth Dissolving Film, Tizanidine Hydrochloride, Sodium Alginate, Solvent Casting.

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INTRODUCTION

Mouth dissolving films offers an attractive route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage. Also large surface area of absorption, easy ingestion & swallowing, pain avoidance make the oral mucosa a very attractive and feasible site for systemic drug delivery [1]. The delivery system consists of a very thin oral strip, which is simply based on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto site of application. It then disintegrates and dissolves to release the medication [2]. These systems either dissolve or disintegrate generally within a minute, without needing water or chewing.

An important benefit is the accurate dosing as compared to liquid dosage forms, mostly used with paediatric patients or in case of dysphagia [3]. These ODFs contain film-forming polymers such as

hydroxypropylmethyl cellulose (HPMC), hydro-xypropyl cellulose (HPC), pullulan, carboxymethyl cellulose (CMC), pectin, starch, polyvinyl acetate (PVA), and sodium alginate. Additional ingredients that are incorporated include plasticizers, sweetening and flavoring agents, coloring agents, saliva-stimulating agents, and thickening agents. Suitable uses for rapidly dissolving films are nicotine-replacement transdermal delivery, and as antiulcer and antihistamine drugs. Antipsychotic and sleeping-disorder drugs also are potential candidates for prescription products [3].

Over the past few decades, tendency toward innovative drug delivery systems has majorly increased attempts to ensure efficacy, safety and patient acceptability. As discovery and development of new chemical agents is a complex, expensive and time-consuming process, so recent trends are shifting toward designing and developing innovative drug delivery systems for existing drugs. Out of those,

drug delivery system being very eminent among pediatrics and geriatrics is orally disintegrating films (ODFs). These fast disintegrating films have superiority over fast disintegrating tablets as the latter are associated with the risks of choking and friability. This drug delivery system has numerous advantages over conventional fast disintegrating tablets as they can be used for dysphasic and schizophrenic patients and are taken without water due to their ability to disintegrate within a few seconds releasing medication in mouth [4].

Several films are designed to be dissolved quickly in the oral cavity for the absorption of a drug in the gastrointestinal cavity (oral and oral soluble, or orodispersible films), some are prepared to deliver a drug at the site of administration (e.g., buccal, sublingual and ophthalmic thin films). Drugs with high mucosal permeability have been known to be suitable for buccal and sublingual delivery with films [1].

Tizanidine is a centrally acting α_2 adrenergic agonist used as a muscle relaxant. It is used to treat the spasms, cramping and tightness of muscle caused by medical problems such as multiple sclerosis, ALS, spastic deplegia, back pain or certain other injuries to the spine or central nervous system. It is also prescribed off-label for migraine headaches, sleep aid, and as an anticonvulsant. It is also prescribed for some symptoms of fibromyalgia [5, 6].

Tizanidine hydrochloride is metabolized by first pass metabolism so in mouth dissolving film avoid the first pass metabolism of drug and the patient compliance increases. The objectives of this study were:

1. Rapid dissolution and absorption of drug, which may produce rapid onset of action.
2. To minimize first pass effect of drug.
3. Easily treat the multiple sclerosis.
4. Improve oral absorption and bioavailability.

METHODOLOGY

Tizanidine HCl, Polyvinyl alcohol, Hydroxy propyl methyl cellulose, Glycerol, Tween 80, Menthol, Colour, Water.

Preparation of Films

In this method firstly water-soluble ingredients (PVA, glycerol) and HPMC are mixed in water to form a viscous solution

⇓

API and remaining ingredients (tween 80, menthol, food grade green color) are dissolved.

⇓

Both the solutions are combined by using high shear process

⇓

Vacuum is used to remove the air entrapment

⇓

The solution thus formed is then cast as a film and pour the solution in a glass mould and allow the solution to dry in oven at 45˚- 50˚C
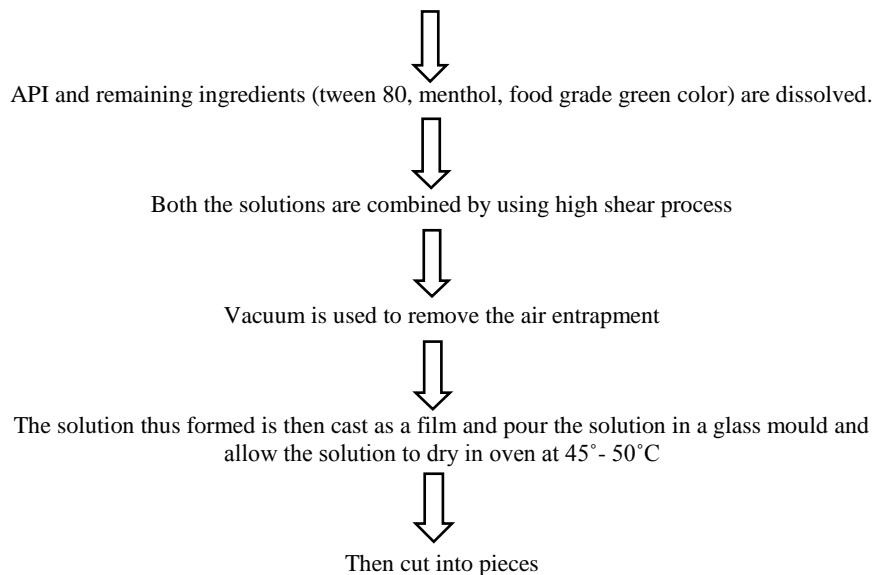
⇓

Then cut into pieces

Figure 1: Casting of films

EVALUATION OF FILMS

Appearance, Shape and Thickness
The formulated films of Tizanidine hydrochloride were checked for their appearance, shape and thickness. The thickness of randomly selected 5 test films was determined at five different places using a micrometer and mean value was calculated [7].

Surface pH
The surface pH of films was determined by placing film in petridish and moistened with few drops of distilled water and allowed to moisten for 1 hrs. After that bring an electrode of pH meter in contact with surface of film and pH were noted [8].

Dryness/Tack Test
About eight stages of film drying process have been identified and they are set-to touch, dust-free, tack-free (surface dry), dry-to-touch, dry-hard, dry through (dry to-handle), dry-to-recoat and dry print-free. Although these tests are primarily used for paint films, most of the studies can be adapted intricately to evaluate pharmaceutical orally fast dissolving film. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip.

Tensile Strength
Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. The instrument was designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. Three strips of patch were cut having 2 cm length and 2cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation. The rate of change of stress was kept constant with the increment of 0.5g per 2minutes. The tensile strength was calculated by using following formula.

Tensile strength = Load at breakage/ Strip thickness × Strip Width [7]

Folding Endurance
It was determined by repeatedly folding one film at the same place till it broke. The number of times that film can be folded at the same place without breaking gives the value of the folding endurance [8].

Percent Elongation
When stress is applied, a sample strip stretches, and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally, elongation of strip increases as the plasticizer concentration increases. The percent elongation at break was measured by formula given below.

% Elongation = (Increase in length/Original length) ×100 [9]

Assay/ Content Uniformity
Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85−115%. The films were tested for content uniformity. Films of size two square inches was cut, placed in 100 ml volumetric flask and dissolved in methanol, volume was made upto 100 ml with methanol. Solution was suitably diluted. The absorbance of the solution was measured at 228 nm.

Drug Content
The films (area 2x2 cm^2) was placed in beaker and to this add sufficient volume of phosphate buffer pH 6.8 and dissolved the film with the help of magnetic stirrer. Filter this solution and transferred into 100ml volumetric flask make up final volume (100ml) with phosphate buffer pH 6.8 solution. The absorbance of solution was measured at lambda max 237 nm using UV spectrophotometer (LABINDIA 3000+ UV-VIS spectrophotometer). The experiment was performed in triplicate [7].

Disintegration Time
In-vitro disintegration time was determined by placing the film (area 2x2 cm^2) in beaker containing 10 ml of phosphate buffer pH 6.8 and swirling at interval of 5 sec. The time at which films start to disintegrate considered as disintegration time [8].

In-vitro Dissolution Study
The *in-vitro* drug release study was carried out using USP dissolution test apparatus (USP type II) at temperature 37±0.5ºc and 50 rpm. The phosphate buffer pH 6.8 was used as the medium. During study 5ml of test sample was withdraw at 15sec. intervals and the absorbance of sample taken at lambda max with the help of UV spectrophotometer (LABINDIA 3000+ UV-VIS spectrophotometer). The values were transformed into concentration using standard calibration curve [9].

RESULTS

Appearance, Shape and Thickness
The appearance of the prepared fast dissolving films was smooth and even because the films were casted on a smooth and plane surface. The films can be cut into any shape in this project the films were cut into rectangular to square shape having an area of 6 centimeter square. The thickness of the films was measured with the help of a Vernier caliper and was found to be of a size of 0.5 mm (ranges from 0.2mm-0.7mm). The appearance, shape and thickness of all the films were same because all of them were prepared by using the same chemical ingredients, equipment and the casting material.

Surface pH
The surface pH of the films was estimated by using the pH meter the films were dissolved in water (100 ml) then one film was added into that water and was

allowed to dissolve, after that the pH was checked and was found to be 6.5 that was more near to the neutral pH.

Dryness/Tack Test

The strips were properly dried and were not sticky on contact with the hands.

Folding Endurance

The films were folded again and again from the same place and after an average of 95 folds the films were breaking from that specific point so the folding endurance was estimated to be 95.

Table 1: Parameters of tizanidine fast dissolving films.

PARAMETERS	OUTCOMES
Thickness	0.5 mm
Folding endurance	92
surface pH	6.5
Tensile strength	1.5 kg/mm^2
Content uniformity	6 mg every film
in-vitro dissolution	99%
Disintegration time	20 seconds
Percent elongation	4 stretches

Percent Elongation

Percent elongation is basically the point at which the shape of the films is changed (deformed) before the films break (the point before the plastic limit of the films). The percent elongation of the films was found to be an average of 4 stretches it means that after 4 times stretching the films the films were deformed.

Assay/ Content Uniformity

When the assay of tizanidine was performed the estimated quantity of tizanidine in each film was 6mg.

Disintegration Time

The average disintegration time of the fast dissolving films in the mouth was estimated to be 5-30 seconds

and when calculated by placing the film into the mouth was found to be 20 seconds approximately. The disintegration time of the films is small because the films are designed to be fast dissolving into the mouth in order to have the immediate desired pain-relieving effect of tizanidine.

***In-vitro* Dissolution Study**

The *in-vitro* dissolution study was performed by using USP paddle apparatus**,** for the purpose of dissolution the medium prepared was phosphate buffer because the environment of our mouth is slightly basic (8-6.8). The temperature was set to be 37 ℃ and the revolutions were 50 revolutions per minute.

Samples were taken from the apparatus from buffer solution and were checked by using UV spectrophotometer under UV spectrophotometer. The highest percent of the drug was releases in first few seconds.

DISCUSSION

The appearance of the prepared fast dissolving films was smooth and even because the films were casted on a smooth and plane surface. The surface pH was checked and was found to be near to the neutral pH. The strips were properly dried and were not sticky on contact with the hands. The weight was applied by using the manual hardness tester used for tablets, and tensile strength was in range [**10, 11**]. The films were folded again and again from the same place and after an average of 95 folds the films were breaking from that specific point so the folding endurance was estimated to be 95. The percent elongation was found to be 4 stretches. The content is uniformly distributed throughout the films. The disintegration and dissolution studies showed normal results that are the disintegration was done within seconds and dissolution was 99%.

CONCLUSION

After performing above mentioned tests it is assumed that the films formed are stable and according to the predetermined standards the excipients and the drug showed compatibility with each other. So the formulation is safe and can be used.

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