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FORMULATE AND EVALUATE THE ORAL DISINTEGRATING FILMS OF SUMATRIPTAN TO IMPROVE THE BIOAVAILABILITY

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ABSTRACT

The main objective of the study was to formulate and evaluate oral thin film containing Sumatriptan succinate. The 4 and 5 % w/v HPMC, PVA, CMC films were prepared by solvent casting method. Compatibility of Sumatriptan with polymers was confirmed by FT-IR studies. films were evaluated for weight variation and thickness showed satisfactory results. Tensile strength and folding endurance of the films were increased with increase in the concentration of polymer due to increase in the elasticity nature of the polymer. Mouth dissolving time and disintegration time of the films were increased with increase in the concentration of the polymer, as more fluid is required to wet the film in the mouth. The presence of disintegrant showed a considerable effect on the disintegration time of the films. Content uniformity study showed that the drug is uniformly distributed in the film. No differences were observed in invitro dissolution of drug from the film I - VI as the film instantly gets wet by dissolution medium. Present study reveals that all the formulated films showed satisfactory film parameters. It can be concluded that, Oral thin film-containing Sumatriptan can be prepared by solvent casting method. 4% w/v of HPMC (FV) film exhibited required tensile strength, folding endurance and disintegration time. The drug release was about 98.5 % in 300 seconds.

Key words: oral thin film, Sumatriptan succinate, folding endurance

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INTRODUCTION

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing Mainly and parenterals are painful drug delivery, so most patient incompliance. Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance. So they formulate the fast dissolving tablets by using super disintigrant/s and hydrophilic ingredients. Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect.

Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarted, uncooperative, nauseated or on reduced liquid intake/diets have difficulties in swallowing these dosage forms. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and braciocephalic vein and then drained in to systemic circulation. Sublingual absorption is mostly rapid in action, but also short acting in duration. Nitroglycerine, for example, is an effective anti anginal drug but is extensively metabolized when taken orally (>90%). It is rapidly absorbed through the sublingual mucosa, and its peak plasma level is reached within 1-2 min. Because of its short biological half life (3-5 min.), however the blood concentration of nitroglycerine declines rapidly to a level below the therapeutic concentration within 10 15 min. In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The differences in permeability are generally based on the relative thickness, the blood supply, and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucous membranes, the extent of drug delivery is also affected by the physicochemical properties of the drug to be delivered. Sublingual products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia). Fast dissolving oral films (FDOFs) or Oral wafers or Oral strips (OS) or sublingual strips or oral thin films (OTF) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin [9]. FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething. OTFs also have an established shelf life of 2-3years, depending on the API but are extremely sensitive to environmental moisture. Oral thin 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. In contrast to other existing, rapid dissolving dosage forms, which consist of liophylisates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets (1-6).

MATERIALS AND METHODS

Preparation of Oral thin film (7-10)

Film was prepared by using specified polymer by solvent casting method. The specified amount of polymer was weighed and dissolved in specified amount of water for overnight to get a uniform dispersion of 4 % and 5 % (w/v) solution respectively. Drug, cross carmellose sodium, aspartame, citric acid were dissolved in specific amount of water in a beaker. The drug solution was added to the polymer solution and mixed using magnetic stirrer for 1 hour. The resulting solution was degassed so as to remove any bubbles formed. The bubble free solution was casted on to a petri dish of surface area 28.6 cm^2. It was dried for 24 hours at room temperature. The film was removed from the petri dish very carefully and observed for any imperfections. Film that was clear and bubble free was selected for further studies.

Film of area 2.25 cm^2 (1.25 X 1.25) was cut and stored in a butter paper cover with aluminum foil and stored in a desiccator.

Folding endurance

The folding endurance is expressed as the number of folds (number of times of film is folded at the same plain) required to break the specimen or develop visible cracks. This gives an indication of brittleness of the film. A small strip of 4 square cm was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was observed and the results are taken.

Disintegration time

Test was performed using disintegration test apparatus. 2.25 cm^2 film was placed in the basket, raised and lowered it in such a manner that the complete up and down movement at a rate equivalent to thirty times a minute. Time required by the film, when no traces of film remain above the gauze was noted. Test was performed in triplicate and the results are taken.

Mouth dissolving time

The mouth dissolving time was determined by placing the film manually into a beaker containing 50 ml of 6.8pH phosphate buffer. Time required by the film to dissolve was noted.

Content uniformity

The films were tested for content uniformity. Films of 2.25 cm^2 was cut, placed in 100 ml volumetric flask and dissolved in water, volume was made upto 100 ml with water. Solution was suitably diluted. The absorbance of the solution was measured at 282 nm.

***In vitro* Dissolution studies**

Dissolution study was carried out using USP type I (basket apparatus) with 500 ml of 6.8 pH Phosphate buffer as dissolution medium maintained at 37 $\pm 0.5^0$ C. Medium was stirred at 50 rpm for a period of 30 minutes. Samples were withdrawn at every 2 min interval up to 30 min, replacing the same amount with the fresh medium. Samples were suitable diluted with 6.8 pH and analyzed for drug content at 282 nm.

RESULTS AND DISCUSSION

Oral thin films containing Sumatriptan were prepared by casting method. The films of HPMC, CMC and PVA (low viscosity) were prepared with an objective to dissolve the film in the mouth. 4 and 5 % w/v each of HPMC, CMC and PVA films were exhibited desired mouth dissolving time and other film parameters, compared to 2 and 3 % w/v of HPMC, CMC and PVA films which were difficult to remove and having low strength and exhibited unacceptable mouth dissolving time. Hence 4 and 5 % w/v of HPMC, CMC and PVA films were used for the study. Propylene glycol (20 % w/w of polymer) was used as plasticizer and to enhance the tensile strength of film.2 % cross carmellose sodium is used as disintegrant to dissolve the films rapidly when comes in contact with saliva. 1 % w/w Sodium saccharine was used as a sweetener and 1 % w/w of aspartame was used as flavoring agent (Fig-1-4).

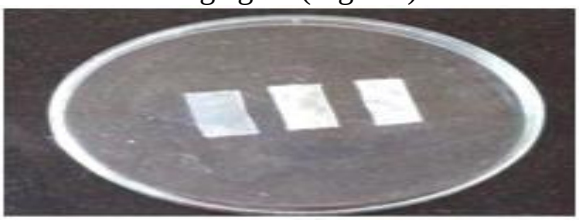

Fig-1 Oral thin film of HPMC

Fig-2 Oral thin film of Hydroxy propyl methyl cellulose

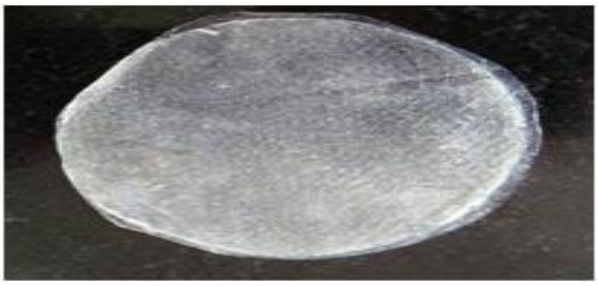

Fig-3 Oral thin film of Carboxy methyl cellulose

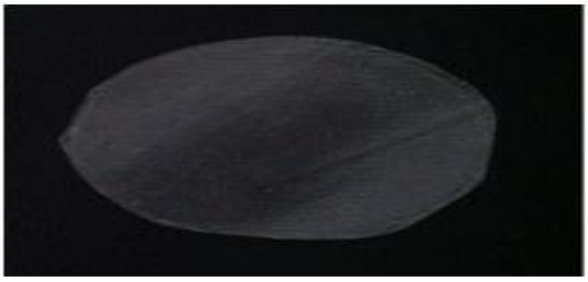

Fig-4 Oral thin film of Poly vinyl alcohol

The folding endurance was measured manually .A strip of film 4squre cm was cut and subjected for the folding endurance studies until it broke at the same place. Folding endurance increases with increase in polymer concentration. The no of times the film fold until it broke was reported in the fig-5.

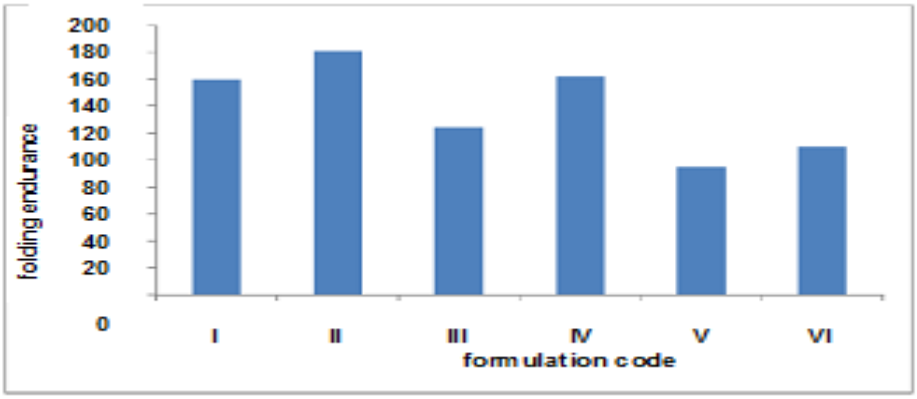

Fig-5 Folding endurance of oral thin films

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 500 ml of pH 6.8 phosphate buffer maintained at 37 ± 0.5^0C at 50 rpm. 5 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer maintained at 37 ± 0.5^0C. Sumatriptan in the samples was then determined spectrophotometrically at λmax of 282 nm. The results were expressed in table-1

Table-1 Comparative evaluation of *In vitro* dissolution profiles of oral thin Films

SNO	Time in sec	Cumulative % of drug release					
		FI	FII	FIII	FIV	FV	FVI
1	2	26 %	22.6%	22%	21%	45%	41%
2	4	53.3%	45.9%	49.3%	39.8%	77.3%	69.3%
3	6	78.3%	71%	69%	56%	98.5%	90.9%
4	8	93.2%	85.3%	80%	81%	98.5%	96.8%
5	10	96.3%	92%	92.4%	92.4%	98.5%	96.8%
6	12	97.3%	93.9%	94.5%	96%	98.5%	96.8%
7	14	98.4%	94.9%	97%	97.3%	98.5%	96.8%
8	16	98.6%	96.1%	97%	98%	98.5%	96.8%
9	18	98.6%	97.2%	97%	98%	98.5%	96.8%
10	20	98.6%	98	97%	98%	98.5%	96.8%

The stability studies of the optimized batch F5 was carried out at 40°C/75%RH, 25°C/60%RH and 25°C/40%RH. These films were found to be unacceptable. Films stored at 40°C/75%RH were highly unstable within 1 month storage. Films stored at 25°C/60%RH were unstable after 2 months period by developing color change (slight yellow) and becoming sticky in appearance. Films stored at 25°C/40%RH were found to be stable for 3 months. The batch was found be acceptable visually, mechanically, with slight change in in-vitro disintegration time 30sec. The above observations indicate that temperature and humidity plays a critical role in the stability of the rapidly dissolving films containing HPMC as the film forming polymer. Therefore, precautions would be required during packaging and selection of packaging container would play a crucial role for stability of the Oral thin films.

CONCLUSION

The main objective of the study was to formulate and evaluate oral thin film containing Sumatriptan succinate. The 4 and 5 % w/v HPMC, PVA, CMC films were prepared by solvent casting method. Compatibility of Sumatriptan with polymers was confirmed by FT-IR studies. films were evaluated for weight variation and thickness showed satisfactory results. Tensile strength and folding endurance of the films were increased with increase in the concentration of polymer due to increase in the elasticity nature of the polymer. Mouth dissolving time and disintegration time of the films were increased with increase in the concentration of the polymer, as more fluid is required to wet the film in the mouth. The presence of disintegrant showed a considerable effect on the disintegration time of the films. Content uniformity study showed that the drug is uniformly distributed in the film. No differences were observed in invitro dissolution of drug from the film I - VI as the film instantly gets wet by dissolution medium. Present study reveals that all the formulated films showed satisfactory film parameters. It can be concluded that, Oral thin film-containing Sumatriptan can be prepared by solvent casting method. 4% w/v of HPMC (FV) film exhibited required tensile strength, folding endurance and disintegration time. The drug release was about 98.5 % in 300 seconds. The accelerated stability studies of the optimized F5 formulation indicates that the formulated oral thin films were unaffected after 3 months storage under accelerated conditions as there were no signs of visually distinguishable changes in appearance, disintegration time and cumulative percentage of drug release. From the present investigation it can be concluded that oral thin film formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

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