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DESIGN AND EVALUATION OF CLOPIDOGREL BISULPHATE FAST DISINTEGRATING FILMS

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ABSTRACT

Clopidogrel bisulphate is an antihypertensive agent used in the management of hypertension and prophylaxis of angina pectoris and heart failure. Present work aimed at preparing quick onset of action which is beneficial in hypertension, aiding in the enhancement of bioavailabity and is very convenient for administration without the problem of swallowing and using water. The film were prepared by using polymers such as hydroxypropyl methyl cellulose (HPMC) and Maltodextrin, plasticizer such as PEG 400, by a solvent casting method. They were evaluated for physical characteristics such as thickness, uniformity of weight, folding endurance, drug content, surface pH, percentage elongation and tensile strength and give satisfactory results. The formulations were subjected to disintegration, in-vitro drug release test. The in vitro disintegration time of the optimized batch F4 was found to be 20 sec. The optimized batch was found to be stable for 1 month under specified stability conditions.

KEYWORDS: Clopidogrel bisulphate, Fast dissolving film, HPMC, Maltodextrin, Solvent casting method.

INTRODUCTION

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets. The most common complaint was tablet size, followed by surface form and taste. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water.[1,4]

So, fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues exploredfor the rapid drug releasing products, oral strip technology is gaining much attention.[5,6] 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 oromucosal and intragastric absorption.

A quick dissolving delivery system that disintegrate within 60 seconds when placed in the mouth without drinking or chewing The active ingredients are absorbed through mucous membranes in the mouth and GIT and enter the blood stream.[7]

MATERIALS AND METHOD

Clopidogrel bi sulphate was a kind gift sample from micro labs pvt ltd, bangalore, India. Maltodextrin from Viratlab (Mumbai), HPMC E15 from Research lab fine chem. Industries (Mumbai) Ethanol and all solvents used were analytical grade.

Preparation of Mouth Dissolving Film by Solvent Casting Method

The fast dissolving oral film of the Clopidogrelbisulphate by using HPMC E15 and Maltodextrin is prepared by solvent casting method. In this first aqueous solution of the HPMC E15 and Maltodextrin is prepared by dissolving the HPMC E15 and Maltodextrin in distilled water.

Clopidogrelbisulphate is added to the aqueous solution after that citric acid is added to the above solution followed by addition of the sweetener and plasticizer. The solution was casted on the casting surface (mould, Petri dish) and dried at room temperature for 10 hours or dried into a Hot air oven for 6 hrs. Then film removed from the surface and cut into the desired size (2x2) of equivalent dose ofClopidogrelbisulphate.

Table 1: Formulation of Oral Fast Dissolving Film.

Ingredients	F1	F2	F3	F4	F5	F6
Drug	75	75	75	75	75	75
Hpmc	400	400	400	400	400	400
Maltodextrin	50	100	50	100	50	100
Peg	50	50	60	60	70	70
Colour	q.s	q.s	q.s	q.s	q.s	q.s
Aspartame	50	50	50	50	50	50
Water	10	10	10	10	10	10

Evaluation of clopidogrel bisulphate film

Weight variation

The weight variation test is determined by measuring the weight of the individual film of 2 cm x2 cm area. For the measurement of the weight digital analytical balance was used. The weight of three films was measure and mean is taken.

Thickness

The thickness of strip was measured by digital verniercaliper 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.

Folding endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

Tensile strength

Tensile strength of films was determined using an apparatus fabricated in laboratory. A small film strip (2 × 2 cm2) was cut and fixed to assembly. The weight required to break the film was noted and simultaneously film elongation was measured with the help of pointer mounted on the assembly. Measurements were done in triplicate for each batch. The mechanical properties tensile strength and % elongation were calculated for the fast dissolving film from the above measurements. Tensile strength is the ratio of maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture to the cross sectional area of the fractured film as a mean of three measurements and described in the equation-

$$\frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{Strip width}}$$

Percent elongation

When stress is applied, a strip sample 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 content increases.

$$\frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

pH Value

The pH value can determine by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution. It is necessary that film should have nearly uniform pH value.

Drug content

For determination of the drug content of Clopidogrel bi sulphate oral film equivalent to dose of 2.5 mg was dissolved in 50 ml of pH 6.8 buffer .The solution was sonicated for 10 minutes and then filtered through Whatmann filter paper no. 41, to separate out the insoluble excipients. 1ml of filtrate was diluted to 100 ml with pH 6.8 buffer. The absorbance of resultant solution was measured using U. V. spectrophotometer at 248 nm and drug content was calculated.

Disintegration time

The disintegration for orally disintegrating tablets described in CDER guidance can be applied to oral film. Although, no official guidance is available for FDOF, this may be used as a qualitative guideline for quality control test or at development stage. But for the present work disintegration was measured by taking the 25 ml of distilled water in 50 ml beaker and individual film is dipped into that solution and disintegration time was recorded.

In Vitro Dissolution study

The in vitro release of drug from all formulations was determined using USP apparatus type II (Paddle method). The following conditions were followed to study the in-vitro dissolution study of Clopidogrel bisulphate Oral Film.200 ml of 6.8 phosphate buffer in a 500ml beaker was taken and is inserted in a 900ml dissolution beaker containing 50ml of water. Aliquots of dissolution medium of 5 ml were withdrawn at 1 min interval for 3 min. The volume withdrawn was replaced by fresh volume of dissolution medium. The filtered samples were analysed spectrophotometrically at 248nm and absorbance was noted. Cumulative percent drug release was calculated.

RESULTS AND DISCUSSION

Formulations	Surface PH	Thickness (mm)	Average Disintegration time in sec	Average weight	Folding endurance
F1	6.8	0.09	75	25	92
F2	6.9	0.1	97	31	110
F3	7	0.09	68	39	122
F4	6.9	0.1	123	35	129
F5	7.1	0.1	151	41	135
F6	7	0.11	231	43	145

The thickness of the film lies between 0.09 to 0.11 mm with uniformity in the thickness. It was observed that increase in the polymer concentration the thickness of film increases with 0.01 mm was shown in the figure-7Thickness of clopidogrel bisulphate films. The thickness was increased with increase in maltodextrin and HPMC

Surface pH

The Surface pH of all formulation observed between 6.9 to 7 It was observed from the figure-8 comparative disintegration profile of clopidogrel bisulphate films that after addition of the plasticizer the pH moves slightly towards basic pH. The pH between 6.9 to 7 indicates the pH of formulation near to pH of saliva.the observed ph indicate that the formulation is suitable for the development of fast release formulation.

Folding Endurance

The folding endurance of all batches observed between 90-155 .For the batches F4, F7, F9 the folding endurance observed 155,130,135 respectively. From the comparative folding endurance of clopidogrel bisulphate film, the evaluation of folding endurance it was concluded .that with increase in polymer concentration folding endurance decreases and with increase in plasticizer concentration folding endurance increases.

Percent Drug content

The percent drug content observed between 97 to 150%. The values ensure good uniformity in the drug content in Fast Dissolving oral Film of Clopidogrelbisulphate. The results indicate that the formulation has good content uniformity and the drug is distributed uniformly.

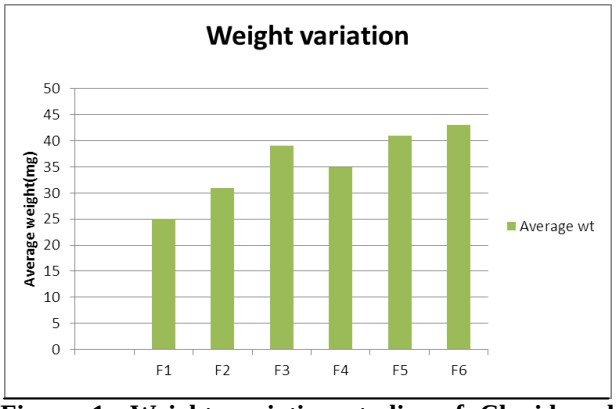


Figure 1: Weight variation studies of Clopidogrel bisulphate films.

Weight Variation

The weight variation of different fast disintegrating Clopidogrel bisulphate containing maltodextrin is given in figure-5. The weight of all batches observed between 25.15 to 41.60 mg with standard deviation less than 0.2% for all batches which indicates uniformity in the weight. The weight of the films was increased with increase in the weight of maltodextrin

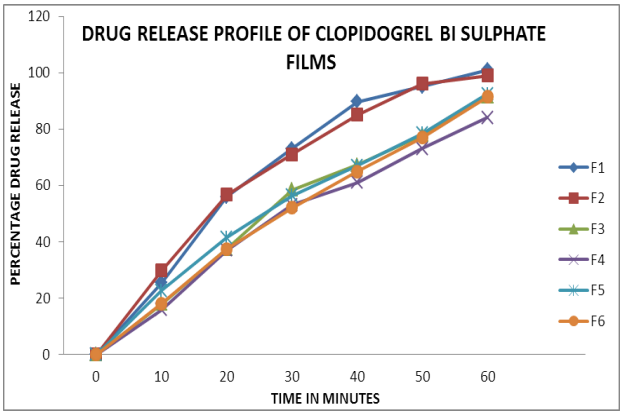
In Vitro Disintegration Time

The in vitro disintegration time for all batches measured between 45to 90 seconds from the clopidogrel bisulphate indicated faster disintegration time as compared to the fast dissolving tablet which have normal disintegration time 60 seconds in many reported literature.

The time required to disintegrate the film was increased with increase in maltodextrin and hpmc. It was assumed that the increased thickness and the quantity of maltodetrin resulted in increase in disintegration time. But all the formulation showed disintegration within the limits making it suitable for fast oral drug delivery.

Dissolution profile

The *in-vitro* drug release from film of all formulation was performed in triplicate using USP apparatus II (paddle method). Dissolution study was performed in pH 6.8 phosphate buffer. In case of F4 and F9 formulations about 99 % and 98.85 % of drug was released in 30 min. In case of F1, F7 formulation about 94.35 % and 94.2 % of drug released in 30 min.



This drug release pattern indicates that the increased concentration of polymer decreases drug release and increased concentration of plasticizer increases drug

release. The films containing high amount of PEG 400 as plsticizer showed high folding in durance the film resistance to break was increased with increase in plsticizer

CONCLUSION

The study revealed that clopidogrel bi sulphate fast dissolving strips can be made by solvent casting technique with enhanced dissolution rate, and hence better patient compliance and effective therapy.

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