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Research Article

FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILM

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Clopidogrel, solvent casting method, HPMC.

A B S T R A C T

Background: To prepare and evaluate oral fast dissolving film.
Material and Methods: Oral fast dissolving films were prepared by solvent casting method.
Results: The maximum drug release was found to be 52.05 % in formulation F3. The tensile strength of the film as the concentration of plasticizer (Propylene Glycol and Glycerin) was increased, the tensile strength of formulation was found to be decreased. The decrease in tensile strength may be due to weakening of bond linkage between the polymer chains.
Conclusion: The formulation F3 containing HPMC as a film forming polymer and Propylene glycol as a plasticizer was selected as an optimized formulation because it gave higher plasticity, good in-vitro drug release and less tensile strength etc. Hence, finally it was concluded that the prepared film containing Clopidogrel is considered as a potentially useful dosage form used as antiplatelet agent.

INTRODUCTION

The oral cavity has been the most prominent site of drug delivery for a long period of time. In1847, Sobrero found that nitroglycerine was absorbed from the oral cavity, since the various active substances have been investigated for local or systemic use. Recent developments in the formulation technology have presented viable dosage alternatives from the oral route for pediatrics, geriatric, bedridden, nauseous, or noncompliant patients. Buccal route of drug delivery is a good alternative, amongst the various routes of drug delivery [K. M. Maheshwari *et al*, 2014].

Buccal delivery is defined as drug administration through the mucosal membranes lining the cheeks and as an attractive route for systemic delivery of drug with relative permeable with a rich of blood supply. It has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. Drugs are absorbed into the systemic circulation through the deep lingual or facial vein, internal jugular vein, and braciocephalic vein which bypasses drugs. Avoid the hepatic first pass metabolism leading to high bioavailability amongst the various routes of drug delivery. [Ashish Gorle *et al*, 2015]. Mouth dissolving 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 oromucosal 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. [Arun Arya *et al*, 2010]. Further, these dosage forms are self administrable, pharmacoeconomic and have superior patient compliance. So we are proposed to do the buccal films for low bioavailability anti hypertensive drugs by decreasing its hepatic first pass metabolism [Radha Madhavi B *et al*, 2013].

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MATERIAL AND METHODS

Clopidogrel was received as gift samples from USV Pvt. Ltd, Govandi, Mumbai. Hydroxy Propyl Methyl Cellulose (HPMC), Glycerin, Propylene glycol, and Citric acid were purchased from Loba Chemicals (Mumbai, India). All other reagents and buffer solutions were of analytical grades.

Preparation of Buccal Films

Oral fast dissolving films were prepared by solvent casting method. HPMC was weighed accurately and added in 3 ml of distilled water. The contents in the beaker were stirred on magnetic stirrer for 15 min for swelling of polymer. Then Propylene glycol was added to the polymer solution. Clopidogrel was weighed and dissolved in 2 ml of distilled water. The drug solution was added to the polymer dispersion

and Citric acid was mixed thoroughly with the help of magnetic stirrer. Then the solution was subjected to sonication in a bath sonicator to remove the air bubbles. The mould containing polymeric solution of drug was kept for 24hours at room temperature for drying. After drying the films were removed by peeling from the moulds then cut into a square dimension of 2× 2 cm. Films were packed in aluminium foil and stored in air tight container to maintain their integrity and elasticity [MehrajUd Din Ganaie *et al*, 2014]. The compositions of the buccal films formulations are listed in following table:

Table 1 Formula for different batches of oral fast dissolving film of clopidogrel Containing HPMC

Ingredients (mg)	Formulation code		
	F1	F2	F3
Clopidogrel	75mg	75mg	75mg
HPMC	400mg	400mg	400mg
PG	-	-	0.4ml
PEG 400	-	0.4ml	-
Glycerine	0.4ml	-	-
Citric acid	10mg	10mg	10mg
Water	Upto 5ml	Upto 5ml	Upto 5ml

(Note: All solid ingredients are measured in milligram. Dose of drug per film is 75mg and Area of film is 2×2cm)

Characterization of Buccal Films

Weight Variation

For weight variation three films of every formulation were randomly selected and weighed individually on digital balance then average weight was calculated. [Y. Indira Muzib *et al*, 2011].

Thickness

The thickness of each film was measured using digital vernier calliper at different positions of the film and the average thickness was calculated. This is essential to ascertaining uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip. [MehrajUd Din Ganaie *et al*, 2014].

Surface pH Measurement

For determination of surface pH, three films of each formulation are allowed to swell for 2 h on the surface of an agar plate. The surface pH is to be measured by using a pH paper placed on the surface of this swollen patch. A mean of three readings is to be recorded. [Mitra Jelvehgari *et al*, 2015].

Folding Endurance

Three films of each formulation of required size are cut by using sharp blade. Folding endurance is to be determined by repeatedly folding the film at the same place, till it is broken. The number of times, the film could be folded at the same place without breaking gives the value of folding endurance. [Shinde Pramod *et al*, 2012].

RESULT

Evaluation of Buccal films of Clopidogrel

Swelling index

After determination of the original film weight and diameter, the samples are allowed to swell on the surface of agar plate kept in an incubator maintained at 37 ± 0.2ºC. Weight of the films (n=3) is determined at different time intervals (1-5 h). The percent swelling, % S is to be calculated using the following equation [N.G. Raghavendra Rao *et al*, 2013]

Percent swelling [% S]= [Xt–Xo/Xo]×100, eqn. (1)

Where,

Xt=The weight of the swollen film after time t,
Xo=The initial film weight at zero time

Tensile Strength

The Tensile strength value of the films directly characterizes the flexibility of films. Tensile Strength of films was performed using tensile tester (Instron 1121, Japan). One end of film strip of dimension 2x2cm was fixed between the two iron screens to give support to the film and another end was connected to the paper holder in which hook was inserted. A thread was tied to this hook, passed over the pulley and a small pan attached to the other end to hold the weight. A small pointer was attached to the thread, which travels over the scale affixed on the base plate. To determine tensile strength, the patch was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the patch was broken. The weights required to break the patch was considered as a tensile strength and it was calculated as kg/cm2 using following formula. [Sri K.V *et al*, 2013].

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Film width} \times \text{film thickness}} \quad \text{eqn. (2)}$$

Drug Content

Three film units of each formulation has to be taken in separate 100 ml volumetric flasks, 100 ml of solvent has to be added and continuously stirred for 24 h. The solutions have to be filtered, diluted suitably and analyzed at specified nm in UV spectrophotometer. The average of drug contents of three films has to be taken as final reading. [Elsheikh Tajelsir *et al*, 2016].

In -vitro Drug Release Studies

In-vitro dissolution of Amiloride Hydrochloride buccal film was carried out in USP paddle dissolution test apparatus using 500ml phosphate buffer pH 6.8 as the dissolution medium. The temperature was maintained at 37°C throughout the experiment. 5ml sample was withdrawn and the same quantity was replaced with phosphate buffer of pH 6.8. The cumulative percentage of drug released was determined using UV visible spectrophotometer at 361 nm. Sink conditions were maintained throughout the experiment. [Murthy P. N *et al*, 2013].

Table 2 Evaluation of Films

Formulation Code	Weight of films (mg)	Thickness of films (mm)	pH value	Folding endurance	Swelling index %	Tensile strength (kg/cm^2)	Drug content %
F1	21.5±0.16	0.06±0.01	6.3±0.01	107 ± 0.72	24.3±0.01	2.87±0.04	16.57
F2	23.0±0.26	0.09±0.03	6.7±0.05	110 ± 0.85	25.7±0.03	2.83±0.01	35.37
F3	**25.7±0.13**	**0.11±0.04**	**6.9±0.04**	**117 ± 0.45**	**28.1±0.02**	**2.73±0.00**	**52.05**

Values are expressed as mean ± S.D (n=3)

In-vitro Drug Release Studies

Table 3 Cumulative % drug release profile of formulation F1 to F3

Sr.No	Time (min)	% Drug release		
		F1	F2	F3
1	0	0	0	0
2	1	4.96	11.50	18.82
3	2	7.38	23.34	30.43
4	3	12.94	26.83	44.95
5	4	16.57	35.37	52.05

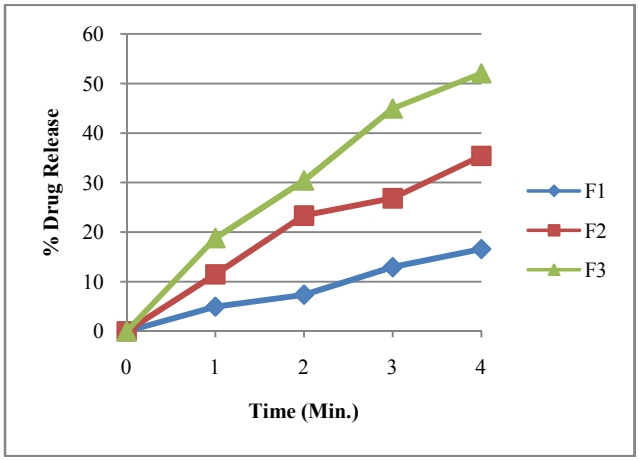

Fig 1 % Cumulative drug release profile of formulation F1 to F3

DISCUSSION

Three formulation of oral fast dissolving film were prepared using HPMC and as mucoadhesive polymers and evaluated for its mucoadhesive properties, release characteristics. In folding endurance test no films developed any visible cracks or breaks, thus showing good folding endurance. The surface pH of the films was determined in order to investigate the possibility of any side effects, in the oral cavity, showed that all the formulation have a similar pH with the buccal cavity which reflects absence of side effects like irritation, buccal damage. The tensile strength of the film as the concentration of plasticizer (Propylene Glycol and Glycerin) was increased, the tensile strength of formulation was found to be decreased and it shown higher plasticity. The decrease in tensile strength may be due to weakening of bond linkage between the polymer chains. The maximum drug release was found to be 52.05 % in formulation F3.

CONCLUSION

Clopidogrel inhibitor of ADP binding to its platelet receptor used as anticoagulant, antiplatelet agent.

The present study is an attempt to developed and formulate mouth fast disintegrate film of Clopidogrel with HPMC, Propylene glycol, PEG 400 and Glycerine within a minute in oral cavity, thereby reducing the time of onset of pharmacological action and to prevent the first pass metabolism of Clopidogrel.

The identification characteristics of drug like solubility, melting point λmax, were performed to find out the purity of drug .all parameter observed were satisfactory and were within the prescribed official limit. In film formulation HPMC as polymer glycerin, PEG 400 and Propylene glycol as plasticizer, by solvent casting method is used to formulate, film because of cost effective and due to reduced no of manufacturing steps.

The formulation F3 containing HPMC and Propylene glycol (HPMC 400 mg and glycerin 0.4 ml) show better and better to meet patient compliance result as compare to the formulation F1 and F2 containing HPMC and glycerin and PEG 400 (HPMC 400 mg and glycerin and PEG 400, 0.4 ml)

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