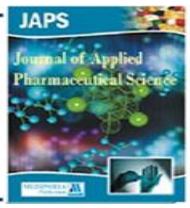
Journal of Applied Pharmaceutical Science 01 (09); 2011: 150-153

Journal of Applied Pharmaceutical Science

Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 06-10-2011
Revised on: 31-10-2011
Accepted on: 05-11-2011

Enhancement of dissolution rate of rapidly dissolving oral film of meclizine hydrochloride by complexation of Meclizine hydrochloride with β-cyclodextrine

Gupta M.M, Patel Mitul G and Madhulika Kedawat

Gupta M.M, Patel Mitul G
Dept. of Pharmaceutics, Jaipur college of Pharmacy, Sitapura, Jaipur, India.

Madhulika Kedawat
Dept. of Mathematics & Statistics, Banasthali University, Banasthali, Newai, Rajasthan.

For Correspondence
Gupta M.M
Dept. of Pharmaceutics, Jaipur college of Pharmacy, Sitapura, Jaipur, India.
Ph.No: +91-9414852269

ABSTRACT

Motion sickness is a very common disturbance of the inner ear that is caused by repeated motion such as from the swell of the sea, the movement of a car, the motion of a plane in turbulent air, etc. Most medications for motion sickness need to be taken at least 30 minutes prior exposure to the activity that can cause the problem. This project is based on the hypothesis that Mouth Dissolving Films (MDF) are rapidly dissolving dosage forms which when placed in the mouth release the drug immediately. These dosage forms would be preferred by pediatric and geriatric patients since these are not associated with fear of choking. The fast dissolving films prepared by solvent casting method with suitable appearance, mechanical strength, peelability and disintegration time were obtained using Methocel E-5 as a primary film former. Meclizine HCl, a poorly water soluble and bitter drug could be successfully incorporated in the fast dissolving films with the help of solubilizers such as β-Cyclodextrine and PEG-400.

Keywords: Meclizine HCl, Methocel E-5, β-Cyclodextrine, PEG-400, Solvent Casting Method, Motion Sickness, Mouth Dissolving Film (MDF).

INTRODUCTION

The peroral application is an effective and inexpensive way for drugs that can be absorbed in the gastrointestinal tract. The conventional dosage forms given by this route including tablets and capsules suffers from patient non-compliance due to difficulty in swallowing associated with their use. Moreover, the delay in onset of action by this route also calls for a delivery system which could provide a rapid onset and a quick relief (Arya, 2010). A film or strip can be defined as a dosage form that employs a water-dissolving polymer (generally a hydrocolloid, which may be a bioadhesive polymer), which allows the dosage form to quickly hydrate, adhere, and dissolve when placed on the tongue or in the oral cavity (i.e., buccal, palatal, gingival, lingual, or sublingual, etc.) to provide rapid local or systemic drug delivery. Drug release may be either quick (within seconds) or slower (within minutes) by varying the rate of dissolution of the films. These films are monolithic matrices and release the active ingredients multi-directionally when placed in the oral cavity. (Swarbrick, 2007).

FORMULATION DEVELOPMENT

A general composition contains the following excipients (Table-1). As polymers and plasticizers forms the main body of MDF, therefore, their properties greatly affect the characteristics of MDF.

Table 1: General Composition of Mouth Dissolving Film.

Components	Quantity (%)
Drug	1 - 25 %
Water-soluble polymers	40 - 50 %
Plasticizers	0 - 20 %
Fillers, colour, flavour etc.	0 - 40 %

Selection of Drug Candidate for MDF (Mouth Dissolving Film)

Drug should have sufficient water-solubility and intraoral absorption. In case of poorly soluble drugs, the solubility of drug should be enhanced by the use of water-soluble salts or complex. Even if the drug has little or no intra-oral absorption, rapid onset of action due to rapid dissolution within oral cavity and hence rapid absorption through GIT can be a driving force in the selection of MDF as dosage-forms (Borsadia et al, 2003).

Selection of Polymer

The polymers used should have good hydrophilicity, rapid disintegration, good mouth feel, and suitable mechanical properties. Along with its good solubility, the polymer should have sufficient mechanical, physicochemical and permeability properties. In order to remain intact against the internal and external stresses developed during storage and especially when exposed to environmental conditions, a film should have high mechanical strength with sufficient elongation and elasticity properties. These properties of films developed from the polymers are dominated by polymer chemistry, solvent effects, and additives such as plasticizer, sugars, and humectants (Ali et al, 2007).

Effect of Plasticizers

Plasticizers are the essential additives that are able to change hard and brittle films to more pliable and tougher form. Plasticizer is usually low molecular weight organic solvent. Most of the polymers used in film coating are either amorphous or have very little crystallinity. Most commonly employed plasticizers are glycerol, propylene glycol, sorbitol, and/or polyethylene glycol (Aulton et al, 1981).

Formulation Aspects of Mouth Dissolving Films

Various processes like Hot-melt extrusion, Solid dispersion extrusion, Rolling, Semi-solid casting, and Solvent casting are used to manufacture the films. The current preferred manufacturing process for producing films is solvent casting method. Solvent casting involves preparation of solution containing drug and film-forming excipients with volatile solvents followed by casting of a thin coat of solvent blend onto a moving, inert substrate.

Screening of the Components for Formulation of Blank Fast Dissolving Film

Various grades of water-soluble polymers, such as, various grades of HPMC and Polyethylene oxide were selected as primary film formers in order to obtain MDF with rapid disintegration, good mouth feel, and mechanical properties. Since the films formed were too fragile to be handled, mannitol was introduced in order to provide body to the films. Incorporation of mannitol in films results in white patches, therefore concentration of mannitol was adjusted as to produce little effect on appearance of the MDF. It is reported that, xylitol and sorbitol containing films have good characteristics (Nishimura et al, 2009). Xylitol was selected for the film formation due to its more negative heat of solution. The agents with more negative heat of solution are expected to give more cooling sensation in the mouth; xylitol therefore produces cooling sensation in the mouth. Aspartame was used as a sweetening agent. In order to achieve rapid disintegration, various disintegrating agents such as, Kollidon CL, sodium starch glycollate, Ac-di-sol were used at concentrations of 2% and 5%. Sodium starch glycollate was found to be an effective disintegrant at a concentration of 5%. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling, so it is preferable than other disintegrants. Effect of various film modifiers such as, guar gum, xanthan gum and glycerine was also studied. In addition, various surfactants were also tried as to improve the solubility of drug.

Drug Loaded MDF

Meclizine HCl is belong from BSC class II which is a poorly soluble drug. Initially the required dose was directly incorporated into the aqueous dispersion (Table 2). Water-soluble polymers in the aqueous dispersion solubilised the drug to a small extent only. To solubilise the drug completely, methanol was added. However, In-vitro dissolution studies showed that MDF formed doesn't release the drug completely. The problem was overcome later by forming 1:1 Meclizine HCl - β-CD complex.

Table 2: Composition of Various Drug Loaded Polymeric Films.

Components	Amount in milligram (mg)				
	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}
Meclizine HCl	11.8	11.8	11.8	11.8	11.8
Methocel E5	72.6	-	36.3	48.4	72.6
Polyox N80	-	72.6	36.3	24.2	-
Mannitol	9.6	9.6	9.6	9.6	9.6
Xylitol	4.8	4.8	4.8	4.8	4.8
Xanthan Gum	-	-	-	-	4.4
Aspartame	0.96	0.96	0.96	0.96	0.96
PEG400(ml)	0.5	0.5	0.5	0.5	0.5
Distilled Water(ml)	10	10	10	10	10

Methocel E5 and Polyox N80 were considered for further batches (F_{11}-F_{15}). Drug as well as other excipients such as, mannitol, xylitol, aspartame were incorporated so as to further improve the properties of MDF. The polymer ratio was decreased to 72.6% (F_{11}-F_{15}). In the presence of all the excipients, best films were formed with Methocel E3. Films with formula F_{14} were better in appearance, but had slower disintegration when compared with films of formula F_{11}. In order to obtain films with good appearance without compromising rate of disintegration Methocel E3 and

Polyox N80 were combined in varying ratios of 1:1, 1:2 and 2:1 (F_{16}-F_{18}) respectively. The presence of polyox improved the mechanical properties only slightly and resulted in films that were turbid and somewhat chalky in appearance. Methocel E-5 was therefore considered suitable polymer as it produces films with good appearance, excellent peelability, disintegration and acceptable mechanical properties. Formula F_{11} was therefore considered to produce most desirable films and considered for further study.

The *In-vitro* dissolution study of F_{11} formulations showed drug release of only up to 52.4% in 40 minutes. Since, this may be due to lower solubility of Meclizine HCl; therefore Meclizine HCl was complexed with β-cyclodextrine (β-CD) in order to improve its solubility. Meclizine HCl - β CD complex was added to F_{11}.

Complexation of Meclizine HCl with β-Cyclodextrine

Meclizine HCl was complexed with β-cyclodextrins in molar ratio 1:1 by kneading method. In kneading method, accurately weighed quantity of β-Cyclodextrine (1 gm.) was mixed with sufficient quantity of water to obtain a smooth and homogeneous paste. Weighed quantity of Meclizine HCl (1 gm.) along with various solubilising additives (citric acid, 0.61 gm.) was added slowly by grinding. The mixture was ground for 1 hour. During this process, appropriate quantity of water was added to maintain suitable consistency. Finally the paste was dried in oven at 40^0C for 48 hours. The complex was finally scrapped off from mortar and passed through sieve no. 100. Direct Complexation was done by stirring Meclizine HCl and β-Cyclodextrine in calculated amount of distilled water using a magnetic stirrer. The Meclizine HCl- β-CD complex as incorporated in the various batches (Table 3).

The optimized films (F_{20}) were finally casted using Mathis lab coater dried at a temperature of 60^0C for a period of 2 hours.

Table 3: Composition of Various Films Loaded with Meclizine HCl- β-CD Complex.

Components	Amount in milligram (mg)				
	F_{16}	F_{17}	F_{18}	F_{19}	F_{20}
Meclizine HCl - β-CD Complex (1:1)	24.7	20.6	20.6	21.8	22.3
Methocel E5	58.3	48.5	48.5	45.6	46.6
Mannitol	7.7	6.4	6.4	6.8	4.6
Xylitol	3.8	12.9	12.9	13.6	14.0
Aspartame	5.1	4.3	4.3	4.5	4.6
Sodium Starch Glycolate	7.0	7.0	-	7.0	7.0
Ac-di-sol	-	-	7.0	-	-
PEG400(ml)	1.0	1.0	1.0	1.0	1.0
Distilled Water(ml)	25	25	25	25	25

***In-Vitro* Dissolution Studies**

The dissolution studies were conducted using different media, such as, simulated saliva consisting of phosphate buffer saline solution (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8.00 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.8).

Each film sample (containing drug equivalent to 10mg) was then submerged into the dissolution media. The dissolution study was carried out using Dissolution apparatus USP type II rotating paddle method at 37^0C, at 50 rpm, using 900 ml phosphate buffer saline (pH6.8) as a dissolution medium. One side of each film (1.5cm diameter) was attached to glass slide with cyanoacrylate glue. The glass slide was put to bottom of the vessel so that patch remained on the upper side of the glass slide. Samples (5 ml) were withdrawn at 1, 2, 3, 4, 5, 10, 15, 20 and 30 minute time intervals, and analyzed spectrophotometrically at 226nm. An equal volume of fresh dissolution medium maintained at the same temperature was added after withdrawing sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally.

***In-vitro* Dissolution Studies of Meclizine HCl Film**

The release profile of Meclizine HCl from the films of formulae F_{11} and F_{15} in phosphate buffer saline solution is shown in Figure 1.

Table 4: *In-Vitro* Drug Release from Films, Formulae F_{11}, F_{12}, F_{13}, F_{14}, F_{15}.

Batch	Cumulative % Drug Release			
	5 min	10 min	20 min	30 min
F_{11}	74.23%	79.39%	81.27%	82.95%
F_{12}	76.44%	77.08%	80.83%	80.83%
F_{13}	78.54%	85.65%	85.00%	85.97%
F_{14}	70.87%	79.15%	79.11%	79.77%
F_{15}	75.20%	80.42%	83.41%	83.52%

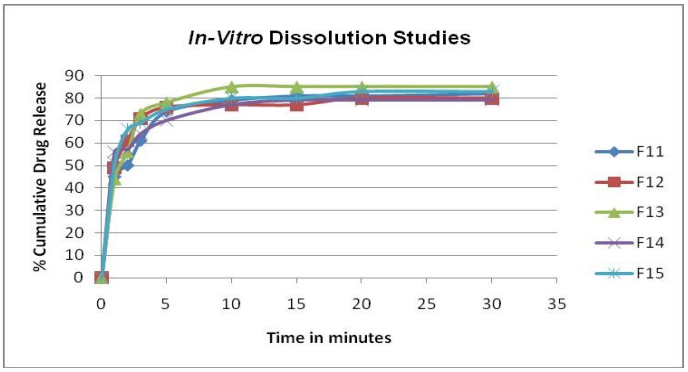


Fig 1: *In-Vitro* Drug Release from Films, Formulae F_{11}, F_{12}, F_{13}, F_{14}, F_{15}.

***In-Vitro* Dissolution Studies of β-Cyclodextrine Complex of Meclizine HCl Film**

The release profile of Meclizine HCl from the films of formulae F_{16} and F_{20} in phosphate buffer saline pH 6.8 is shown in Figure 2.

RESULT & DISCUSSION

Film of formula F_{15} to F_{20} showed an improvement in drug release over F_{11} to F_{15}. Batch F_{20} showed 98% drug release of in 30

minutes. F_{19} batch was then subjected to further modification to obtain films having faster disintegration and better appearance. Finally films of formula F_{20} were subjected to dissolution study. A release of around 80% was observed within 4 minutes. An overall release of 99% was obtained in 30 minutes. This proves the role of β-CD in improving drug dissolution.

Table 5: *In-Vitro* Drug Release from Films F_{16}, F_{17}, F_{18}, F_{19} and F_{20}.

Batch	Cumulative % Drug Release			
	5 min	10 min	20 min	30 min
F_{16}	80.56%	90.25%	91.95%	91.95%
F_{17}	81.92%	82.12%	82.93%	82.93%
F_{18}	78.67%	83.43%	87.97%	87.97%
F_{19}	81.23%	89.81%	90.77%	90.77%
F_{20}	90.45%	95.26.%	98.66%	98.66%

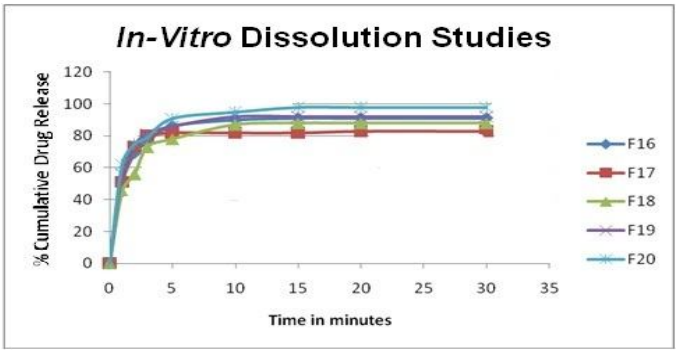


Fig 2: *In-Vitro* Drug Release from Films F_{16}, F_{17}, F_{18}, F_{19} and F_{20}.

CONCLUSION

The fast dissolving films with suitable appearance, mechanical strength, peelability and disintegration time were obtained using Methocel E-5 as a primary film former. Meclizine HCl, a poorly water soluble and bitter drug could be successfully incorporated in the fast dissolving films with the help of solubilizers such as β-Cyclodextrine and PEG-400. Methocel E-5 has good hydrophilicity, rapid disintegration, good mouth feel, and suitable mechanical properties along with its good solubility.

It has sufficient mechanical, physicochemical and permeability properties. A high % drug release (up to 80%) in Batch F_{20} within 4 minutes suggests rapid onset of action which is required for effective management of motion sickness. The fast dissolving films can be formulated for pediatric and geriatric patients, with the easily available components such as MethocelE5 and PEG-400. Meclizine HCl, a poorly water soluble and bitter drug can be successfully incorporated in the fast dissolving films with the help of solubilizers such as β-cyclodextrine and the bitter taste of the Meclizine HCl could successfully be masked in the films. In vitro evaluation of the films confirmed their potential as an innovative dosage form to improve delivery of Meclizine HCl.

REFERENCES

Arun Arya; Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form, International Journal of ChemTech Research: 2010; 2(1): 576-583.

Aulton, M.E., Abdul-Razzak, M.H., Hogan, J.E.; The mechanical properties of hydroxypropylmethylcellulose films derived from aqueous systems Part1: The influence of Plasticizers. Drug Dev Ind Pharm.:1981;7: 649-668.

Borsadia, S.B., Halloran, D.O., Osborne, J.L. Quickdissolving films-a novel approach to drug delivery. Drug Delivery Technology. :2003; 3(3) :3-7.

Dinge, A., Nagarsenker, M. Formulation and Evaluation of Fast Dissolving Films for Delivery of Triclosan to the Oral Cavity. AAPS Pharm Sci Tech. :2008; 9(2) : 349-56.

James Swarbrick**; '** Drug Delivery to the Oral Cavity Molecules to Market', published by foxit software company: 2007 :43-46.

Misao Nishimura; In vitro and in vivo characteristics of prochlorperazine oral disintegrating film, International Journal of Pharmaceutics :2009; 368: 98–102.

Prodduturi, S., Urman, K.L., Otaigbe, J.U., Repka, M.A. Stabilization of Hot- Melt Extrusion Formulations Containing Solid Solutions Using Polymer Blends. AAPS PharmSciTech. :2007; 8 (2):198-210.

Puri, R, Zielinski R.G; Dissolvable film. EP1757279, February :2007 ;28: 34-41.

S. Ali, A. Quadir, High molecular weight povidone polymer-based films for fast dissolving drug delivery applications, Drug Del. Technol. :2007; 7 (6) :36–43.

Yoshinori Itoh; Preparation of a fast dissolving oral thin film containing dexamethasone: A possible