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FORMULATION DEVELOPMENT AND EVALUATION OF TASTE MASKED RAPIDLY DISSOLVING FILMS OF LAMOTRIGINE

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ABSTRACT

Rapidly dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages. An effort was made to formulate a rapid dissolving films containing lamotrigine using different viscosity grade of HPMC. The prepared films can be used in the treatment of epilepsy and bipolar disorder with a view to improve the onset of action, therapeutic efficacy, patient compliance and convenience. The effect of various viscosities of HPMC alone and in blend on various properties of film was investigated. Solvent casting method was used for the preparation of film. Prepared films were typically evaluated for its physical and mechanical properties, drug content, content uniformity, disintegration time, and *in vitro* dissolution. The drug-excipient compatibility study was performed using FTIR. Result of the evaluation study revealed that all the formulation showed reproducible quality. Hence lamotrigine can be safely incorporated into the film and used as antiepileptic whenever quick on set of action is desired.

KEYWORDS: Rapidly dissolving film, hydroxy propyl methylcellulose, lamotrigine, polacrilin potassium.

INTRODUCTION

In the present scenario though tablet and capsule are the most convenient and preferable route of drug administration, the pharmaceutical scientists have presented possible dosage alternatives for patients, particularly for pediatric and geriatric patients, who may have difficulty swallowing or chewing solid dosage forms.[1] Many of such patients are unwilling to take these solid preparations due to fear of choking.[2] Thus mouth-dissolving drug delivery is rapidly gaining interest in the pharmaceutical industry.

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 pediatric patients or in case of dysphagia. Moreover, these systems may offer superior clinical profiles with potential oral-mucosal absorption, thus increasing the drug bioavailability with respect to conventional oral administration. Rapid dissolving systems are mainly tablets, films and their rapid disintegrating properties are obtained through special process or formulation modifications. This fast-dissolving property is attributable to a rapid ingress of water into the polymer matrix resulting in its quick disintegration. Hence, the basic requirements to developing rapidly dissolving films include maximizing the porous structure of the polymer matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation.[3]

The purpose of the present study is to formulate rapidly dissolving films (RDFs) of lamotrigine, an anticonvulsant drug and to investigate the effect of various viscosities of hydroxy propyl methylcellulose (HPMC E3 and E5) alone and in blend on various properties of film. Lamotrigine (6-(2, 3-dichlorophenyl)-1, 2, 4-triazine-3, 5-diamine) is used in the treatment of epilepsy and bipolar disorder.[4] For quick onset of action and greater bioavailability, Rapid dissolving films of lamotrigine are formulated with polacrilin potassium (super dis-integrant) and low viscosity HPMC that disintegrates instantaneously, releasing the drug and dissolves or disperses in the saliva. Solvent casting is the most common and traditional method[3] used for the preparation of film. RDFs are typically evaluated for its physical and mechanical properties, drug content, content uniformity, disintegration time, and *in vitro* dissolution. The drug-excipient compatibility study was performed using FTIR.

MATERIALS AND METHODS

Materials

Lamotrigine was received as a gift sample from Glenmark Pharmaceuticals (Goa, India). HPMC E3 LV and HPMC E5 LV were received as gift samples from Colorcon Asia (Goa, India). PVP K-30 was obtained as a

gift sample from Alkem Lab (Daman, India). Polacrilin potassium was purchased from Central Drug House (New Delhi, India). Menthol and glycerol were purchased from S.D. Fine Chem (Mumbai, India). Sodium saccharine & Starch was purchased from Hi-Media Lab (Mumbai). Passion fruit flavor and lemon flavor were received as gift samples from Pentagon Trading Company (Ahmedabad, India).

METHODS

Preparation of the RDFs

RDFs of lamotrigine with various grades of HPMC were prepared using a solvent casting method.[3] All the ingredients are added one by one into the weighing bottle containing different ratio of dichloromethane and ethanol and lamotrigine was added to this non-aqueous polymeric solution. This step was followed by the addition of plasticizers such as glycerol. Sweeteners such as sodium saccharine and flavor were also added. The solution was cast on a 9-cm diameter glass Petri dish and dried at room temperature for 24 h. The film was carefully removed from the Petri dish, checked for imperfections and cut to the required size to deliver the equivalent dose (2 × 2 cm^2) per strip. The samples were stored in a desiccator at 30–35% relative humidity until further analysis. Film samples with air bubbles, cuts, or imperfections were excluded from the study. The formulation batches are described in Table 1.

Preliminary trials were undertaken for designing the RDF wherein the effects of various grades of HPMC namely E3 and E5 LV on the characteristics of the lamotrigine films were assessed. The initial trials were taken to evaluate the suitability of various grades of HPMC for the formation of RDF without addition of drug.

Table-1: formulation design

Ingredients	F_1	F_2	F_3	F_4	F_5
Lamotrigine (mg)	500	500	500	500	500
HPMC E3 (mg)	500	-	250	278	318
HPMC E5 (mg)	-	500	250	222	282
Starch (mg)	100	100	100	100	100
PVP K-30 (mg)	1.5	1.5	1.5	1.5	1.5
Polacrilin Potassium (mg)	56	56	56	56	56
Glycerol drops	8	8	8	8	8

EVALUATION

Film Thickness

The thickness of formulation patch of each type was measured using a micrometer screw gauge[5] and the average was determined.

Weight Variation

The individual weight of 2 X 2 cm^2 patch of each formulation was determined. The average weight was calculated.[6]

Taste evaluation

Taste acceptability was measured by putting a film sample of 4 cm^2 held in the mouth for 5–10 seconds, then spat out, and the bitterness level was recorded[7]. Volunteers were asked to gargle with distilled water between the drug and sample administration. The following scale was used:

+ = very bitter
++ = moderate to bitter
+++ = slightly bitter
++++ = tasteless or taste-masked.

Moisture Loss (Moisture Vapor Transmission)[8]

The percent moisture loss was determined by placing prepared film in desiccators containing anhydrous calcium chloride. After three days, the film was taken and reweighed. The percent moisture loss was calculated using following formula

$$\text{Moisture loss} = \frac{Wt - W0}{W0} X\ 100$$

Where W_0= initial weight Wt = final weight.

Measurement of Mechanical Properties[6]

The mechanical properties of the film gives an indication of the strength and elasticity of the film, reflected by the parameters - % elongation, tensile strength and folding endurance.

Percent Elongation

The prepared film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The elongation was determined by noting the distance travelled by pointer before break of film on the graph paper.[9] The percent elongation was calculated by using formula-

$$\text{Percent elongation} = \frac{L1}{L0} X\ 100$$

Where L_1= increase in the length, L_0 = Initial length.

Tensile Strength

Film strip of dimension 2 X 2 cm^2 and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 3 cm apart. A cardboard was attached on the surface of the clamp via a double sided tape to prevent the film from being cut by the grooves of the clamp. During measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks.[10] The force was measured when the films broke.

$$\text{Tensile strength} = \frac{\text{Force at Break}}{\text{Cross sectional area of the film}} X\ 100$$

Folding Endurance

This parameter was determined by repeatedly folding one film at the same place till it breaks or develops visible cracks. The number of times the film could be folded without breaking/cracking gave the folding endurance value.

pH value

The surface pH of the films was evaluated in order to investigate the possible side effects due to change in pH in vivo, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The pH of the film was determined after dissolving 2 x 2 cm^2 film in 4 ml of water, using a calibrated pH meter.[11]

Drug content and content uniformity

The drug content and content uniformity test were determined to ensure the uniform distribution of drug at different location of the prepared film. A three isolated cut films of $4cm^2$ area were taken from different location of the prepared film of each batch and suitably diluted in phosphate buffer pH 6.8. The samples were analyzed for the percent drug content using UV-visible spectrophotometer (UV-1700, Shimadzu, Japan) at 305.5 nm.[11]

In Vitro disintegration

Disintegration test was performed by placing the film of size 3×3 cm^2 in the glass Petri dish containing 20 ml of water. It was stirred at every 10 s time interval. The time required for the film to disintegrate completely was recorded and results are expressed as mean of 5 determinations.[11]

Dissolution

An isolated film of $4cm^2$ area was subjected to dissolution in 900ml phosphate buffer pH 6.8 at 37°c using USP dissolution apparatus Type-2 with a rotation speed of 50 rpm. Then the drug released at every interval of 5min was analyzed spectrophotometrically using UV-visible spectrophotometer (UV-1700, Shimadzu, Japan) at 305.5nm.

F T I R study

The molecular structures of the samples were recorded through FT-IR spectra using a FT-IR spectrometer (Shimadzu corporation, Japan).[12] IR spectra of lamotrigine, PVP K30, Polacrilin, Starch, blank polymer and drug loaded polymeric film were obtained separately at room temperature in kBr pellets between the range of 400-4000cm^{-1} with resolution 2cm^{-1}.

RESULT AND DISCUSSION

From the close photographs (figure-1) of the film, it was observed that the film seems to be uniform in thickness and without any imperfections or visible air bubble which is well supported by the results of thickness study as shown in the table-2. The photographs revealed a good smooth surface with uniform distribution of the excipients with significant rigidity.

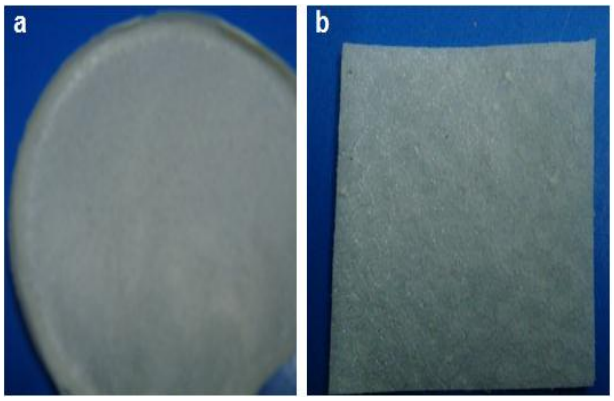


Figure-1: Photographs of Film, a; Formulation F5, b; Isolated cut film (closer view, 2X2 cm^2)

The weights of the isolated films are nearly equal and without any significant statistical variations (table-2). The amount of sweetener (Sodium saccharin) used was found to be just sufficient to make the film acceptable taste. The result of moisture loss and pH study were depicted in the table-2. The pH value was found to be close to neutral in all the formulations which means that they have less potential to irritate the buccal mucosa and therefore they should be fairly acceptable. The mechanical properties such as percent elongation, tensile strength and folding endurance of the film were examined and reported in table-3.

Table-2: Evaluation of different parameters of lamotrigine film

Formulation	Film Thickness (mm)	Average weight (mg)	Taste	pH value	% moisture loss
F_1	0.149 ± 0.002	76.31 ± **2.08**	+ + +	6.6 ± 0.14	1.29 ± 0.009
F_2	0.157 ± 0.002	74.31 ± **2.21**	+ + +	6.8 ± 0.15	1.17 ± 0.013
F_3	0.149 ± 0.001	75.31 ± **1.95**	+ + +	6.6 ± 0.19	1.31 ± 0.011
F_4	0.151 ± 0.002	75.31 ± **2.75**	+ + +	6.7 ± 0.11	1.27 ± 0.022
F_5	0.148 ± 0.001	74.31 ± **2.37**	+ + +	6.7 ± 0.18	1.23 ± 0.015

Table-3: Evaluation of different parameters of lamotrigine film

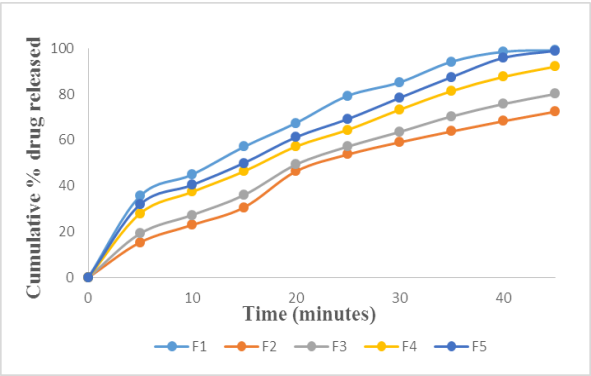
Formulation	Percent elongation	Tensile strength (Kg/mm^2)	Folding endurance	Percent drug content	Disintegration Time (Sec)
F_1	32.73±1.09	1.337±0.149	67	97.73±1.01	25
F_2	29.65±1.39	1.530±0.149	44	99.79±0.78	61
F_3	30.53±0.91	1.419±0.149	53	98.40±0.86	44
F_4	28.91±0.83	1.093±0.149	57	98.03±0.36	34
F_5	28.48±0.78	1.115±0.149	61	97.81±0.08	28

The content uniformity of isolated cut films of formulations were examined and the study revealed that the drug is thoroughly and evenly distributed in the entire formulation without any significant statistical differences. The drug content of all the formulations were found to be remaining within 97.73 ± 1.01 to 99.79 ± 0.78% as shown in the table-3.

The order of drug content was F2>F3>F4>F5>F1. The formulation containing high percentage of HPMC E5 shows high % drug content because of the fact that due to the high viscosity of the later prevents the escaping of drug towards the circumference of the film. Formulation F1 shows relatively lower drug content as the proportion of HPMC E3 was comparatively high.

The order of disintegration time of different formulation was found to F2>F3>F4>F5>F1.F2 took maximum time to disintegrate because the high viscosity matrix formed by HPMC E5 prevent the entry of dissolution fluid into the polymeric structure whereas F_1 showed a disintegration time of 25 seconds (Table-3) due to lesser viscosity and weaker matrix formed by it.

All the formulation shown good dissolution profile as more than 80% of the drug released into the dissolution medium with in 45 minute except the formulation (F_2) which contains only HPMC E5 as a rigidising polymer (figure-2). Dissolution of F_1 revealed a good release profile in which for almost all the drug was released in just 45 minute. The reason regarding this may be attributed to its low density of HPMC E3, whereas the dissolution of F_2 took 45 minutes in which just 70% of drug was released.



Comparing the spectra of pure drug and the formulation reveal that there were no differences in the position of absorption band (Figure-3). The absence of significant change in the IR spectra pattern of drug polymer indicated the absence of any interaction between the drug.

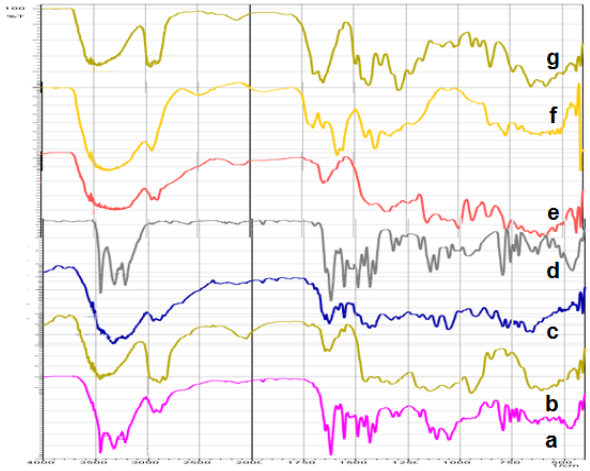


Figure-3: FTIR. a; Formulation-5, b; HPMC E5, c; HPMC E3, d; Lamotrigine, e; Starch, f; Polacrilin potassium, g; PVP K30

CONCLUSION

The present work describe a study on formulation and evaluation of first dissolving film of lamotrigine using different polymers such as HPMC E3,E5 in different proportion. Result of the evaluation study revealed that all the formulation showed reproducible quality. The study discovered that HPMC E3 is necessary to make the integrity of the film and prevent the fragile nature of the film and HPMC E5 attribute a good result to disintegration and dissolution as well. Thus amongst all the formulation F5 can be taken as the best formulation, showing a disintegration time of 28 second with a good integrity and dissolution profile as well. FT-IR study revealed that there was no interaction between the drug and the polymer occurred during preparation. Hence lamotrigine can be safely incorporated into the film and used as antiepileptic whenever quick on set of action is desired.

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