INTRODUCTION

Oral route is the most preferred and acceptable route due to ease of ingestion, pain avoidance, versatility, and most importantly, the patient compliance.[1] About 60% of all dosage forms available are the oral solid-dosage form.[2]

Fast-dissolving drug-delivery systems came into existence in the late 1970s 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.[3]

This delivery system consists of a thin film, which is simply placed on the patient’s tongue, instantly wet by saliva; the film rapidly disintegrates and dissolves to release the medication, the quick dissolving aspects allow for gastrointestinal absorption.[4]

Lacidipine is chemically a 1,4-dihydropyridine derivative, which is pharmacologically a calcium channel blocker used as an antihypertensive drug. It works by blocking calcium channels in the arterial wall those are present in the muscle cell.[5] The chemical structure of lacidipine was shown in Figure 1. It is white to pale yellow crystalline, freely soluble in acetone, and sparingly soluble in absolute alcohol.[5]

The objective of this study was to prepare mouth dissolving film of lacidipine using suitable polymer like hydroxypropyl methylcellulose (HPMC) as a film forming polymer and different plasticizers such as polyethylene glycol 400 (PEG 400) and glycerol. Plasticizer is one of the vital ingredients of fast dissolving film. It helps to improve the flexibility of the strip and reduces the brittleness of the strip. To facilitate the incorporation of lacidipine in the films and also to improve its in vivo solubility, poloxamer 407 was used as a solubilizer which would be advantageous for the development of oral films. The prepared films were characterized for thickness, weight variation, folding endurance, drug content, disintegration time and in vitro drug release.

ABSTRACT

Background: Fast dissolving oral drug delivery system is solid dosage form which disintegrates or dissolves within second when placed in the mouth without need of water or chewing. In present investigation, an attempt has been made to develop oral fast dissolving film of calcium channel blocker lacidipine. Method: Five formulas were prepared by solvent casting method using HPMC (METOLOSE)* as a film forming polymer and evaluated for their physical characteristics such as thickness, weight variation, folding endurance, drug content, disintegration time and in vitro drug release. The compatibility of the drug in the formulation was confirmed by FTIR and DSC studies. Result and Conclusion: The optimized formula F1 showed minimum in vitro disintegration time of 25 second and highest dissolution rate 97.3% in 10 minutes with good mechanical properties. Based on overall results, the conclusion that lacidipine was successfully prepared as oral fast dissolving film with accepted properties.

KEY WORDS: Hydroxypropyl methylcellulose (METOLOSE)*, Lacidipine, Oral films, Solvent casting method

MATERIALS AND METHODS

Materials

Lacidipine was purchased from Hangzhou Hyper Chemical Ltd., China; HPMC (METOLOSE)* was obtained from Shin-Etsu Chemical Co., Ltd., Japan.
Poloxamer 407 (Actico, Jordan), citric acid was obtained from Mumbai, India. All other chemicals used were of analytical grade.

Methods
Calibration curve of lacidipine
The required quantity of drug was dissolved in tween solution (prepared by mixing 100 ml of water with 10 ml of polysorbate 20 and then diluted to 1000 ml) to get a stock solution 1 mg/ml. From the stock solution, serial dilutions were made to get 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml, and 30 µg/ml. The absorbance of these dilute solutions was measured at 284 nm using double-beam ultraviolet (UV)/visible spectrophotometer (Cary, Australia).

Preparation of fast dissolving oral films
The oral dissolving films of lacidipine using HPMC polymer as a film-forming agent were prepared by solvent casting method. PEG 400 and glycerol act as plasticizer, citric acid as saliva stimulating agent, and sodium saccharin as sweetening agent.

An accurate amount of polymer was soaked in 5 mL of water for overnight to get a uniform dispersion. PEG 400 or glycerol, poloxamer 407, sodium saccharin, citric acid, and mannitol were dissolved in sufficient amount of water then added to the polymeric solution. Lacidipine was dissolved in 5 ml of acetone and then added to the solution. The dispersion was stirred for 30 min on magnetic stirrer and was used after at least 24 h of rest to remove all the air bubbles entrapped, then was cast onto 6 cm diameter petri dish and was dried in the oven at 40°C for 24 h. The films were carefully removed from the Petri dish, checked for any imperfections and cut into the required size (2 cm × 2 cm) to deliver the equivalent dose per strip. The samples were stored in the desiccators until further analysis.[7] The composition of lacidipine films was demonstrated in Table 1.

Calculation of drug loaded in the film
Diameter of the Petri dish = 6 cm, diameter = radius/2 = 6/2 = 3 cm.

The area of circle is πr², so 3.14 × 3 × 3 = 28.26 cm². Now, the dose in (2 cm × 2 cm) film is 2 mg, Hence, 28.26/4 = 7.065 strips per Petri dish (approximately 7). Total drug load = 7 × 2 = 14 mg.

EVALUATION OF FAST DISSOLVING ORAL FILMS
Physical Appearance and Surface Texture
Physical appearance and surface texture was checked by visual inspection and surface texture was evaluated by touch or feel of the film.[8]

Weight Variation
The weight variation of the lacidipine oral film was done by weighing 20 films individually and the average weight was calculated. For the film to be accepted, the weight of not more than two films deviates from the average weight by no more than 7.5% and no film deviates by more than 15%.[9]

Drug Content
Film (2 cm × 2 cm) from each formulation was taken, cut into small pieces and was allowed to dissolve in a 100 ml of tween solution. The solution was filtered, diluted suitably and the absorbance of the solution was measured using UV-visible spectrophotometer at a wavelength of 284 nm.

Folding Endurance
The folding endurance is expressed as the number of folds required to break the specimen or to develop visible cracks. This gives the indication of brittleness of the film. It was measured manually for the prepared film for the area (2 cm × 2 cm). Film of specified area was subjected to this test by folding the film repeatedly at the same plane for several times till visible cracks developed.[10]

Thickness of Films
The thickness of three randomly selected films from every batch was determined using a standard Vernier caliper and average values were reported. The film thickness was measured at five points (center and four corners) on the film to ensure the uniformity of the film thickness. The mean thickness was calculated from the five points.[11]

In vitro Disintegration study
It can be performed by Petri dish method for oral films, 2 mL of distilled water was placed in a Petri dish, and one film was added on the surface of the water and the time measured until the oral film was dissolved completely. This test was done on randomly selected three films from each batch and average values were reported.[12]

In vitro Drug Dissolution
The dissolution rates of all formulations were measured using dissolution apparatus United States

Table 1: Composition of lacidipine fast dissolving oral films

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacidipine</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>HPMC (METOLOSE)</td>
<td>24</td>
<td>26</td>
<td>29</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>Glycerin</td>
<td>-</td>
<td>5.8</td>
<td>6.4</td>
<td>6.6</td>
<td>-</td>
</tr>
<tr>
<td>PEG 400</td>
<td>4.8</td>
<td>5.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Sodium saccharin</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Citric acid</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Mannitol</td>
<td>3</td>
<td>3</td>
<td>2.5</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Pharmacopeia (USP) Type II. The in vitro dissolution study is conducted in 500 ml of purified water with 1% w/v polysorbate 20 at 50 rpm solution and 37°C ± 0.5°C. 10 ml of samples was withdrawn at predetermined time intervals of 2, 5, 10, and 20 min filtered through syringe filter 0.45 µm and diluted as per need and replaced with fresh medium. Sink conditions were maintained throughout the study. The samples were collected and the absorbance was determined by UV-visible spectrophotometer at 284 nm. The study was conducted in triplicate.[13]

DRUG-POLYMER INTERACTION STUDIES

Differential Scanning Calorimetry (DSC)
Samples (3–5 mg) were placed in aluminum pan and heated in the DSC-60 (Shimadzu, Japan) at a constant rate of 10°C/min, in an atmosphere of nitrogen over a temperature range of 25–300°C. The DSC studies were performed on the pure drug, HPMC, and on physical mixture of lacidipine and HPMC at ratio (1:1).

Fourier-transform Infrared Spectroscopy (FTIR)
It was performed using the infrared spectrophotometer (Lambda 7600, Australia). Samples of 2–3 mg were mixed with about 100 mg of dry potassium bromide powder and compressed into transparent discs then scanned over a wave range of 4000-400 cm\(^{-1}\) in FTIR instrument. The IR spectra were performed on the pure drug, HPMC, and on physical mixture of lacidipine and HPMC at ratio (1:1).

Statistical Analysis
All the results were expressed as mean value ± standard deviation (SD). t-test was used to test for significance, at a 5% significance level. Statistical difference dealing (\(P < 0.05\)) was considered statistically significant.[14]

RESULTS AND DISCUSSION

The calibration curve of lacidipine in tween solution was found to be linear in the concentration range 10–30 μg/ml. The Beer’s law was verified from the calibration curve by plotting a graph of concentration versus absorbance, the plot shown in Figure 2. Regression analysis showed very good correlation, the results obtained which indicate that the curves obey Beer–Lambert’s law within the concentrations used.[15]

Physical Appearance and Surface Texture
The prepared films were homogenous, colorless, smooth surface, and transparent. The prepared films showed uniform distribution of the drug without uneven shape and air entrapments.

Weight Variation
The average weights for all the prepared formulas were uniform and comply with referred values. The uniformity of the weights of the films indicates good distribution of the drug, polymer, and plasticizer.

Drug Content
The drug content of lacidipine film was ranged from 87.54 ± 0.87 to 108.32 ± 0.79. The results of content uniformity indicated that drug has been uniformly distributed in the film.

Folding Endurance
Brittleness of the film was determined through the folding endurance. It measures the ability of the film to withstand rupture. Any formulated film has a folding endurance value, and a value more than 300 indicates acceptable results. All the prepared formulas except F3 and F5 showed good folding endurance value (>300) indicated that the films have good flexibility.[11,16] F3 and F5 contain glycerol as plasticizer in concentration 24% (w/w) and 20% (w/w), respectively, gave folding endurance value <300.

Thickness of the Films
All the prepared films had uniform thickness. The thickness of all the formulations ranged between 0.084 and 0.118 mm. In all the cases, the SD values are very low which suggests the prepared films were uniform in thickness. The results are given in Table 2.

Table 2 summarizes the average values of thickness, folding endurance, and disintegration time of films of all the formulation.

In vitro Disintegration Time
In vitro disintegration time of lacidipine film was ranged from 25 to 48 s. The FDA recommends a disintegration time of 30 s or less for orally disintegrating tablets based on the USP disintegration test. This can be explained as the higher concentration of the polymer; the thicker gel will produce on

![Chemical structure of lacidipine](6)

![Calibration curve of lacidipine in tween solution](2)
contact with the media, which requires longer time to disintegrate.[17,18]

**In vitro Drug Dissolution**

The release profiles of the strips are shown in Figure 3. In vitro drug release studies in tween solution show more than 85% release of lacidipine from all film formulations within 10 min with F1 showing a maximum percentage drug release of 97.3%. This could be attributed to the higher rate and extent of swelling of the larger proportion of the hydrophilic polymer HPMC (METOLOSE)®. The low viscosity polymers such as HPMC (METOLOSE)® shown good dissolution rates because the loosely bound polymer molecules in these films were readily eroded, allowing the easy dissolution of lacidipine on contact with the dissolution medium.[19]

There is no statistically significant difference (P > 0.05) between the prepared films, so the optimized formula F1 was selected depending on the amount of drug released in 10 min (97.3%) and the in vitro disintegration time (25 s).

**DSC**

The DSC thermogram of the drug in Figure 4 depicts a sharp endothermic peak at 186°C corresponding to the melting temperature Tg of lacidipine. Such sharp endothermic peak signifies that drug used was in pure crystalline state.[5] The DSC thermogram of HPMC as in Figure 5 as a major film former shows glass transition Tg at 56°C, while the DSC thermogram of physical mixture of lacidipine and HPMC (at ratio 1:1) as in Figure 6 shows a sharp peak of lacidipine at 184°C indicated that there was no interaction between the drug and excipients used in the film formulations.

**FTIR**

The FTIR spectrum of lacidipine was illustrated in Figure 7 shows characteristic absorption peaks at 3348.78, 2978.52 to 2808, 1702 to 1653.66, 1629.55, and 1292/cm-1, denoting stretching vibration of -NH of dihydropyridine ring, -CH-, -C=O, -C=C functional groups, and ester group, respectively.[13]

The FTIR spectrum of HPMC (METOLOSE)®, presented in Figure 8, shows characteristic peaks at 3500–3400/cm-1 due to OH vibrational stretching. The band at 1645/cm-1 indicated the presence of stretching vibration of C-O, while the peak at 1100–1000/cm-1 indicated stretching vibration of C-O-C group.[20]

The characteristic peaks of lacidipine and polymer were present in the physical mixture as in Figure 9.
thus indicating no significant evidence of chemical interaction between drug and HPMC which confirms the stability of drug.

**CONCLUSIONS**

In the present research work, an attempt has been made to prepare mouth dissolving films of lacidipine by solvent casting method using a film forming polymer HPMC (METOLOSE). The films prepared by HPMC had shown good mechanical strength, drug release, and disintegration time. Lacidipine, a poorly water-soluble drug could be successfully incorporated in the fast dissolving films with the help of surfactant such as poloxamer 407.

**REFERENCES**