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Applicable of Polymers in the Formulation and Characterization of Amlodipine Besylate Oral Fast Dissolving Films

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Abstract : The purpose of the present work is to formulate and enhance the drug release of Amlodipine besylate by the incorporation of synthetic polymers in the oral dissolving films (ODF) for use in specific populations viz. geriatrics and patients experiencing difficulty in swallowing. The oral dissolving films loaded with Amlodipine besylate were prepared by solvent evaporation method using hydroxy propyl methyl cellulose-3cps and 5cps by adding suitable plasticizer PEG 400 and glycerin. The prepared oral dissolving films were evaluated for drug content, weight variation, thickness, pH, folding endurance, *In vitro* drug release and stability studies.The evaluation parameters of Amlodipine besylate were found to be satisfactory in terms of drug content, thickness and pH. Comparison of the dissolution profiles of Amlodipine besylate oral dissolving films in phosphate buffer (pH 6.8).Effective drug release was achieved for Amlodipine besylate by way of preparation of oral dissolving films by solvent evaporation method. AML5 showed the highest drug release at the 15 min time point. The AML5 oral dissolving film with higher amount of superdisintegrant Polyplasdone XL-10 and SSG showed fastest onset of drug release.
Keywords : Amlodipine oral dissolving films, solvent evaporation method and Dissolution rate.

Introduction

Amlodipine besylate is a long-acting calcium channel blocker dihydropyridine (DHP) class used as an antihypertensive and in the treatment of angina pectoris. The purpose of the study was to develop oral fast dissolving films of Amlodipine besylate (5mg). The films were prepared with various water soluble polymers, such as hydroxy propyl methyl cellulose-3cps& 5cps, Blanose, methyl cellulose and tamarind seed polyose by adding suitable plasticizer: PEG400 and glycerin. The films were investigated for *in-vitro* performance. In the absence of a drug (placebo film), the evaporation of organic solvent and water resulted in the polymers forming a circular film. The release profiles of drug from the films were investigated. The thickness of the film was controlled by adjusting the concentration of polymer. All the films were coded and prepared with different drug: polymer ratios. The films readily dissolved in the dissolution medium. The release of Amlodipine besylate from the films was 100% in 15mins in the dissolution medium of (pH 6.8 phosphate buffer) with the blanose polymeric drug film. The optimized formulation was compared with the pure drug and marketed formulation. The release profiles of films were analyzed by using UV- Visible spectrophotometer at 239nm. *In vitro* parameters like thickness, disintegration, folding endurance, assay and weight of the films were evaluated. Preformulation studies of Amlodipine besylate like compatibility studies with polymers, using FTIR, DSC and XRD studies were carried out. The drug and polymers were found to be compatible with each other. These

results strongly suggested that the water soluble polymers were suitable for the formulation of oral fast dissolving films of Amlodipine besylate.

Novel drug delivery system in the recent years was developed to enhance safety and efficacy of drug molecules by designing a suitable dosage form for administration[1]. The oral route is the most acceptable and preferred route for drug delivery, has its own merits and demerits[2]. There is a need for development of dosage form with better therapeutic efficacy and fewer side effects[3]. Various bioadhesive mucosal dosage forms include mucoadhesive tablets, gels, ointments, patches have been developed[4]. Recently, fast dissolving drug delivery systems has become one of the popular and acceptable drug delivery systems, because of their ease of administration and better patient compliance. This novel drug delivery system can also be beneficial for meeting the current needs of the industry for improved solubility, stability, biological half life and bioavailability enhancement of drugs[5]. Fast dissolving films (FDFs) have attracted interest as an excellent dosage form, not only for oral care, but also for patients with aphasia or dysphasia[6,7]. They can be taken with ease at any time by the patient without requiring any water for swallowing [8-10]. The oral strip technology delivery system consists of very thin oral strips which are postage stamp-sized rectangular shape polymeric films[11], which is placed on the patient's tongue or along the inside of the cheek. The hydration of the film by the saliva gets adhered onto the site of application. Then it disintegrates rapidly and dissolves to release the medication for absorption onto the oral mucosa as well as gastro intestinal tract producing faster onset of action[12]. These flexible films are suitable for oral, topical and enteral use where they can be applied to mucosal membrane areas of the mouth, rectum, vagina, nose and ear[13].

Experimental

Materials

Drug used in this study was purchased from Vijaya Scientifics limited, Hyderabad. HPMC (3cps and 5cps) was gifted from RA Chem Pharma Limited, Hyderabad. All the other materials and reagents used were of analytical grade.

Preparation of mouth dissolving films

The mouth dissolving film of AML using polymers were prepared by solvent evaporation method. An aqueous solution of the polymers was prepared in distilled water. AML was added to the aqueous polymeric solution. This was followed by addition of plasticizers like PEG 400 and glycerin. Citric acid was also mixed with it. Taste masking can be done by palatability evaluation studies by aspartame, which is known to be 200 times sweet than sucrose. The solution was casted on a Petridish and dried at room temperature for 24hrs. The film was carefully removed from the Petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose per strip.

Weight variation

The $4cm^2$ film was cut at three different places in the cast film. The weight of each film strip was taken and then weight variation was observed.

Thickness

The thickness of each fast dissolving film formulation(2×2 cm) was measured by using a micrometer screw gauge(Fscrow, China)(accuracy up to 0.001) at five points(centre and corners) on the film to ensure the uniformity of the film thickness. The mean thickness (mm) was calculated from the five points. Three samples of each FDFs formulation were measured.

Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

In vitro Disintegration

The *in vitro* disintegration time of the ODFs (2×2 cm) was determined using a disintegration tester (Electrolab ED-2L) with distilled water at 37± 0.5^0C. The disintegration time was defined as the time taken for ODF to completely disintegrate with no solid residue remains on the screen. This test was done in triplicates and the average value was taken as DT.

In vitro Dissolution Studies

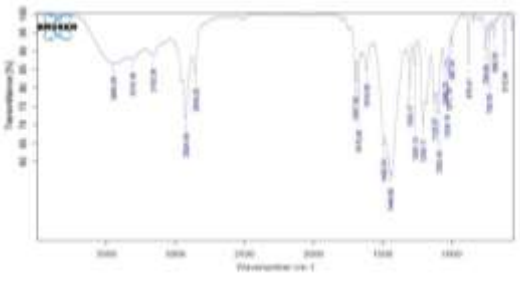
According to previous studies, dissolution studies were performed using USP 23 apparatus, paddle over disc method. As the paddle over disc apparatus was not available, USP apparatus 1 (basket) (Lab India Model No: DISSO-2000) was used for this study. Three hundred millilitres of phosphate buffer (pH 6.8), which is a prescribed media for amlodipine besylate was maintained at 37±5°C while the basket was set at 50 rpm. A film sample of $4cm^2$ was cut and taken into the basket. The five millilitres of dissolution samples were withdrawn at different time intervals, and the same amount was replaced with the fresh buffer. The withdrawn samples were filtered and analysed using a UV spectrophotometer at a wavelength of 239 nm. The percentage drug release was calculated. The relationship between time and percentage release was plotted to determine when the maximum amount of drug is released. The dissolution studies were carried out in triplicate (n=3).

Results and Discussion

Characterization

Compatibility studies by FTIR

When we observe the Fig.1&2 of FTIR spectra, the drug, exhibited the peaks at 3085.50 cm^{-1}, 3054.68 cm^{-1}, 3025.43 cm^{-1} for C–H aromatic stretching, 2925.98 cm^{-1} for CH_3, C–H stretching, asymmetry, 2233.93 cm^{-1} for C -N stretching and 1637.48 cm^{-1} for C =O. The same peaks of the drug were observed in the Fig.2, drug- polymer physical mixture, this indicates the absence of drug-polymer interaction.



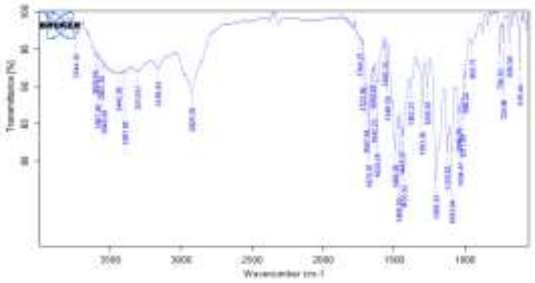


Fig.1:FT-IR spectrum of Amlodipine BesylateFig.2: FT-IR spectrum of oral thin film prepared by solvent evaporation method.

The FT-IR studies (Fig:1&2) all the spectra of drug and drug with polymer mixture at the same wave number, indicated no modifications or interaction between the drug and the excipients. From this it can be concluded that the drug has maintained its identity without losing its characteristic properties.

Differential Scanning Calorimetry

The DSC thermograms of pure drug and polymeric films are depicted in Fig.3&4. The DSC thermogram of AML was typical of a crystalline anhydrous substance, exhibiting a sharp endothermic peak at 195.9°C, corresponding to the melting point of the drug. AML polymeric thin film also exhibited an endothermic peak at 199.8°C similar to AML, indicating that there was no change in the crystallinity of AML after solvent evaporation.

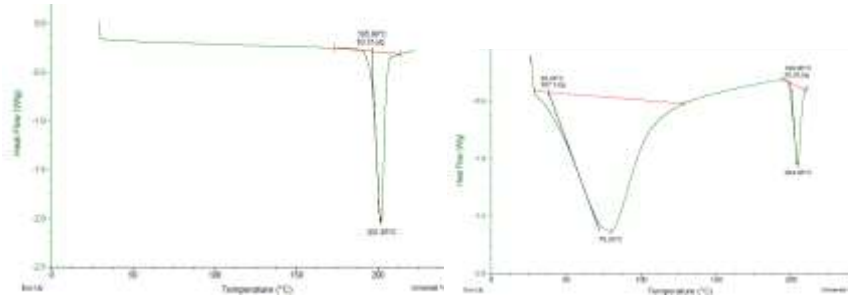


Fig.3:DSC thermogram of Amlodipine BesylateFig.4: DSC thermogram of physical mixture (AML5)

X-ray diffraction of film

To investigate the crystallographic properties of the observed particles in the drug loaded oral films X-ray diffraction was used. The X-ray Diffraction of the drug loaded film was recorded (Panalytical, Model-Xpert Pro).

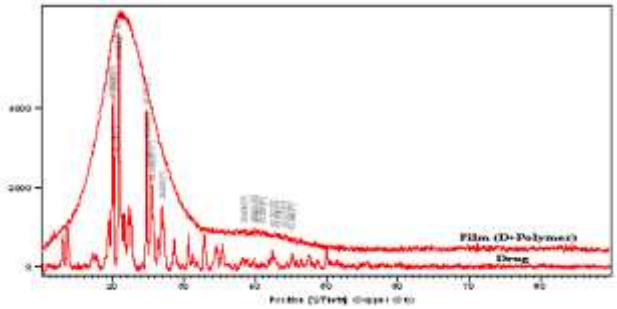


Fig.5: XRD of Drug and AML 15

The XRD results revealed that the Fig.5 showed the pure drug in sharp crystalline peaks. However, the crystalline peaks completely absent in the drug loaded film (AML5), this indicating that the drug present in the amorphous form in the film.

Variation of Mass

When manufacturing the oral films the film solutions were cast into sheets and then cut into smaller strips of 4cm^2(2cm ×2cm). Oral films were cut from different sheets and the variability between the sheets of the respective polymer was investigated. The variation of mass of HPMC 5cps oral thin films showed the highest variation in mass with an average mass of 293 mg. the film strips of HPMC 3cps exhibited an average mass of 277mg. Thus the mass was either lower or higher than the nominal value which can have consequences on the content uniformity. In conclusion, a homogenous distribution of pure drug and, if possible, prevention of recrystallization of pure drug reduces mass variation and enhance the content uniformity.

Film Thickness

The determination of film thickness is the most common method to characterize the produced oral thin films. The micrometer screw gauze method was used to determine the thickness of the AML polymeric oral thin films. The thickness of the films was determined by using the screw gauze. Oral thin films made from HPMC 5cps showed an average film thickness of 633µm and HPMC 3cps113µm.

pH value

The pH value was determined by dissolving one oral film in 2ml of distilled water and measuring the pH of the obtained solution. Differences were expected because various polymers were used. The pH value of AML polymeric oral films was measured by electrometric pH meter. The HPMC grades show the pH values of HPMC 5cps (7) and HPMC 3cps pH (7.5).

Folding endurance

Folding endurance was determined by repeatedly folding the film (2cm× 2cm) at the same place until it breaks at the place of folding. The an average folding endurance of AML polymeric thin films. The film strips of HPMC 5cps exhibited an average folding endurance of 17.3,HPMC 3cps 57.1.

***In Vitro* Dissolution studies**

Dissolution rate of AML and its polymeric films were determined in 500 ml of pH 6.8 phosphate buffer at 37°C with a stirrer rotation speed of 50 rpm using the USP I dissolution rate test apparatus employing the basket. A 5 ml aliquot of dissolution medium was withdrawn at different time intervals with the bulb pipette containing the prefilter. The samples were filtered through 0.45µm millipore filter. The samples were suitably diluted and assayed spectrophotometrically (Lab India) at 239 nm. Each test is repeated for three times. The percent of drug dissolved at various time intervals was calculated and plotted against time. The results are shown in Fig.6. The films AML2 and AML4 shows the slowest drug release at the 3 min time point. Compared to the AML pure drug, the film AML1 shows the drug release 99.8 % at the 45 min time point and AML3 showed the highest drug release 100.9 % at the 30 min time point.

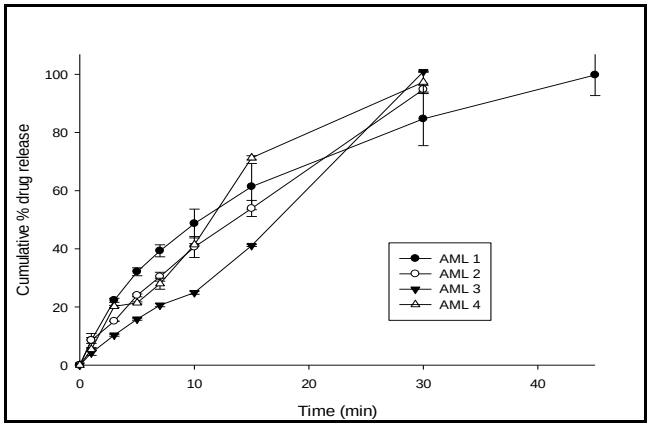


Fig.6: Comparative dissolution profiles of AML from pure AML and oral thin films of AML- HPMC-5cps containing varying concentrations of HPMC-5cps

The percent of drug dissolved at various time intervals was calculated and plotted against time. The results are shown in Fig.7.The films AML5, AML 6 and AML 8 shows the highest drug release at the 30 min time point. When the AML pure drug and AML 7 were compared, similar drug release was obtained at the 30 min time point.

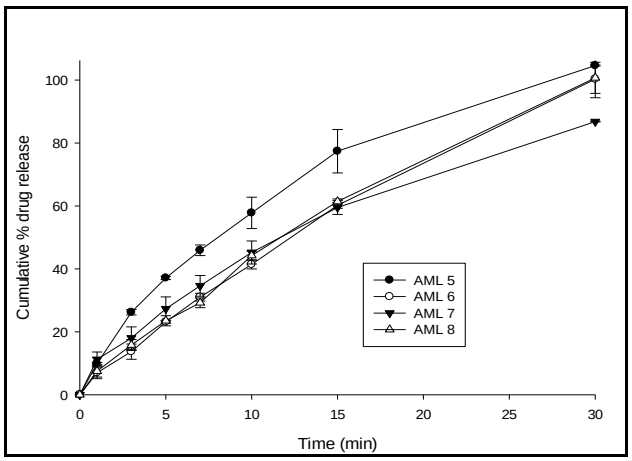


Fig.7: Comparative dissolution profiles of AML from pure AML and oral thin films of AML- HPMC-3cps containing varying concentrations of HPMC-3cps

Comparative Dissolution Profiles

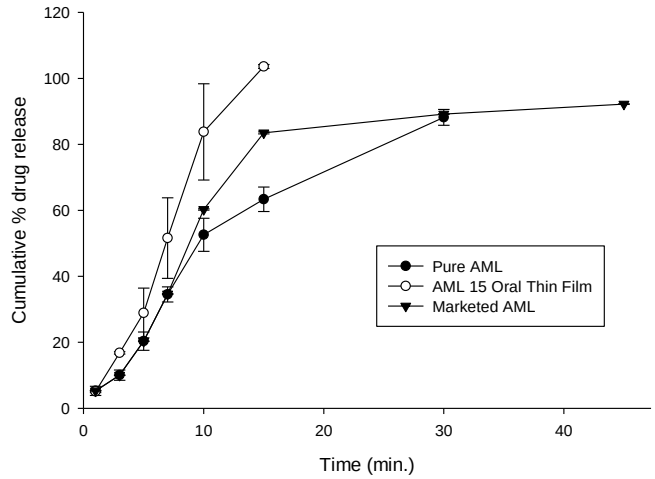


Fig.8: Comparative dissolution profiles of AML from pure AML, AML 5 and marketed AML branded formulation

Stability studies of promising oral thin films as per ICH guidelines

Hence, AML 5 was selected for stability studies and stored at 25°C/60 % RH and 40°C/75 % RH. The samples were withdrawn at 0, 3 and 6 months and subjected to drug content, dissolution and solid state analysis (DSC, XRD and FTIR studies).

The samples withdrawn from all the conditions (after 3 and 6 months) did not show the color change. The amounts of AML content (%) in the polymeric films stored under conditions according to ICH guidelines. Less than 5 % of the AML was lost during 6 months in the films stored at 25°C/60 % RH and 40°C/75 % RH. From the above results AML appeared to be stable in the storage conditions tested.

The comparative dissolution profiles of the freshly prepared AML 5 and the aged AML5stored at 25°C/ 60 % RH and 40°C/ 75 % RH for 6 months are shown in Fig.9. Reduced crystallinity and improved wettability are responsible for the faster dissolution rate. Therefore, it can be concluded that the AML- HPMC 5cps containing polymeric thin film (AML 5) is a fairly stable and promising film for improving the dissolution rate of the drug AML.

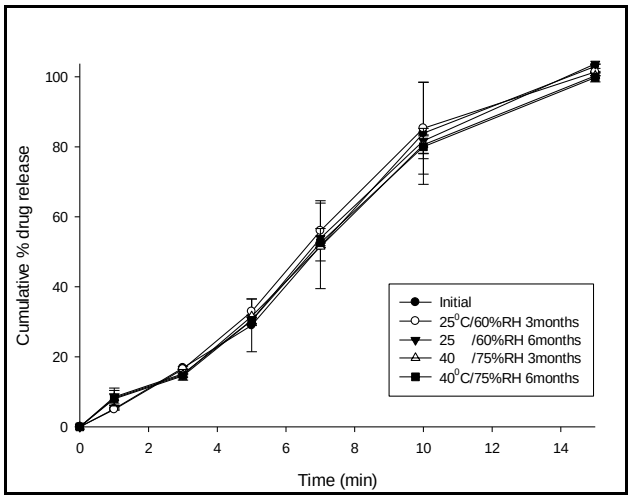


Fig.9:Comparative dissolution profiles of AML from oral thin films of AML 5 before and after stored at 25°C/ 60 % RH and 40°C/ 75 % RH for 6 months. (Mean ± S.D)

Conclusion

In conclusion, our studies showed that, hydrophilic polymers could be used as potential carriers in the dissolution rate enhancement of AML. The AML release from the pure drug and the oral thin films followed first order kinetics. The results demonstrated that the optimum AML: HPMC 5cps weight ratio is 1:6. Since, no drug carrier interaction in the oral thin films has been evidenced, increased dispersibility and reduced crystallinity of AML can account for the increased dissolution rate of the films. Oral thin films were prepared by solvent evaporation method. The advantages of the solvent evaporation method are ease of preparation avoidance of organic solvents or high temperatures. This technique is easy and more convenient and economical from a practical point of view.

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