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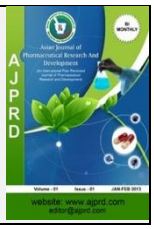

Open Access Research Article

Formulation, Optimised and Evaluation of Mouth dissolving film of Amoxapine

Anjudip Yadav*, ShailendraTripathi, Vandana Sharma, S. L. Soni, Deeksha Tiwari

Department of Pharmaceutics, Arya College of Pharmacy, Jaipur, Rajasthan, India

A B S T R A C T

Amoxapine is orally active, acts by decreasing the reuptake of norepinephrine and serotonin and used for depression. The research work was undertaken to formulate, optimize and evaluation of mouth dissolving film of amoxapine, so that rapid release of drug constituents and give faster action. Mouth dissolving film (MDF) is a better alternative compared to oral disintegrating tablet due to patient compliance. Amoxapinebelongs to Biopharmaceutics Classification System ClassII, means drug have low solubility. The problem is resolved by using Polomer188. MDF prepared by solvent casting method. For preparation of film, hydrophilic polymers were selected as film forming polymers. Different polymers were selected such as different grades of Hydroxyl Propyl Methyl Cellulosei.e. E5, E15, E50.Selection of plasticizer was also done and PEG-400 was found best giving better results. It was found that formulation contain desiredphysio-mechanical properties.

Keywords- Depression, Patient Compliance, BCS II, Polomer188, Solvent Casting

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***Address for Correspondence:**

Anjudip Yadav, Arya College of pharmacy, kukas, Jaipur, Rajasthan

1. INTRODUCTION:

Mouthdissolving thin film is widely used drug delivery system because of its various benefits. MDF when come in contact with saliva, it dissolves within a second, without the need of water. It increases patient compliance makes formulation suitable for paediatric and geriatric patients[9]. Most of the polymers used in MDFare amorphous inform, dispersion of drug in polymer matrix aids rapid dissolution[8]. Their advantages enhance the patient compliance and give faster action which makes pharmaceutical manufacturer invest money in change of the existing products in the market to MDF[1].Amoxapine is a potent, orally active inhibit norepinephrine and serotonin reuptake, use in the treatment of major depression[7]. It also has atypical anti-psychotic property and use in management of schizophrenia[6]. It may also be used in the treatment of depression accompanied by anxiety and agitation. Amoxapineis availablein tablets 25,50or 100 mg[8]. It is white to off-white powder, bitter. Amoxapine is practically insoluble in water and categorized to BCS class II (low soluble, high permeable). It is poor aqueous solubility and dissolution delay the rate of absorption[5]. Formulation of amoxapine MDF would improve aqueous solubilityby solid dispersion method along with fast dissolution of amoxapine in mouth itself resulting in faster drug absorption starting from oral cavity, itself leading to rapid management of depression[6]. The main challenges for preparation were taste masking and improving the aqueous solubility of the drug as medications that enter the oral cavity, it should have an acceptable taste[7]. One among the major problemthat prevents patient from adhering to a prescribed medication regimen is the unacceptable taste of active pharmaceutical ingredients (APIs) in this dosage form[2]. Taste plays an important role in the development of any oral formulation, with respect to patient compliance, and affect the market penetration of oral formulations, especially in manufacture for paediatricpatients[3].

Polomer188 increases the aqueous solubility of poorly soluble drugs by forming complexes by solid dispersion,

melting method. Theformed complex hides most of the hydrophobic functional group in its interior cavity, while the hydrophilic hydroxyl groups get exposed to aqueous the environment[4]. The bitter taste of substances can be reduced or even completely eliminatedby adding sweetening agent. In the present study,optimized batch of film forming polymer, plasticizer, Superdisintegrant and solubilizing agent was selected and further study for optimized batch was carried out based on result of evaluation[15].

MATERIALS AND METHODS:

2.1. **Material:** Amoxapine wassample obtained from Mehta Pharmaceutical Limited, Mumbai, India. HPMC E5 and E15 was obtained from Chem Dyes Corporation, India. Polomer 188 was brought from NavpadImpex, Mumbai, India. Sucrose sample was obtained from CDH Laboratories, Delhi, India.

2.2. **Drug-Excipient Compatibility Study:** FTIR spectra of pure drug sample, polymers used, and mix together was recorded on KBr disk method using FTIR Shimadzu 8400S Spectrophotometer with the IR solution software (Shimadzu, Japan) to show the compatibility between the drug and excipients. Thedrug and excipientwas blended in proportion by triturating with potassium bromide in a glass mortar with pestle and compressed into disks. FTIR spectra of all the samples were recorded from 4000 to 400 cm^{-1} using 20 scans with 4 cm^{-1} resolution.

2.3.Preparation of Solid Dispersion of Amoxapine and Polomer 188:Solid dispersion were prepared by melting method. The carrier was melted and then drug was added into melted carrier homogeneously. Then, it was allowed to cool down and solid mass was obtained. Later the solid mass was crushed. Dried complex was passed through sieve number 60.

2.4. Formulation of Amoxapine MDF: It was prepared by solvent casting[29]. Polymer solution was prepared by dissolving polymers, citric acid and sucrose in 5ml ethanol and 5ml chloroform. Other sideAmoxapine was dissolved 2 ml ethanol. Drug solution added to polymeric solution. And PEG 400, mixed and stirred well to form homogeneous mixture. Mixture solution was cast as film into glassPetri-dish and dried at room temperature. Placed an inverted funnel over the petri-dish for uniform solvent evaporation. The film was carefully removed from the petri-dish, checked for any imperfections and cut into the 2cm x 2cm in size. The film was stored in aluminium foil until further use.

2.4.1. Selection of solubility enhancer[18]: Drug is practically insoluble in phosphate buffer pH 6.8, solubility enhancer was required. Complexes of Amoxapine were formed using different solubility enhancement agent like PEG, Polomer188, β-Cyclodextrin. These complexes were prepared using fusion method and kneading method.

2.4.2. Selection of Film Forming Polymer: Film Forming polymer have characteristics of forming film and give mechanical strength to the formulation. Byusingdifferentfilmformingpolymer and in different concentrationslikeHPMCE5,HPMCE15,HPMCE50,placebo film was prepared by solvent casting method. Evaluation parameter like visual inspection, separability, folding endurance and disintegration time was checked for all placebo films to select suitable film forming polymer.

2.4.3.Selection of Plasticize-r: Plasticize-rs give the films improved flexibility and durability. Plasticize-rs like Glycerol and Polyethylene Glycol 400 (PEG-400) were utilized to select the best plasticizer for formulating the films. Depending on the stickiness and folding endurance the plasticize-r was selected.

2.4.4.Selection of Superdisintegrant: Superdisintegrant are the substances added to the formulation that facilitates the faster disintegration of the formulation[15]. Various superdisintegrantwere selected like Sodium starch glycolate, Croscarmellose sodium, Kyron T-314, Crospovidone.

2.4.5. Selection of Solubilizing agent: Solubilizing agents are used to solubilize the drug and give better dissolution results. Film was formulated using tween 80 as solubilizing agent.

2.5. Evaluation parameter of film:

Thickness: Thickness of film is directly proportional to drug uniformity and dose precision into film. Measurement of thickness of film can be done by using micrometre screw gauge or calibrated digital Vernier Calliper[21, 22].

Weight variation: It was calculated by weighing 10 random films and calculate the average of these three values was obtained[25].

Folding Endurance: Folding endurance of film was measured by folding the film at the same place, till it would be breaks down. The number of times the film was folded without breaking was calculated as it's folding endurance. It indicates the measure of the film brittleness and its mechanical ability to withstand folding[23].

Dryness test / Tack test: Tendency of the film to adhere to an accessory that has been pressed against its termed as tack.

Tensile strength: Maximum stress applied at which the film breaks is tensile strength[24]. It was calculated by applied load at rupture divided by the cross-sectional area of the film as given in the equation below:

Tensile strength =[Load at rupture × 100]/[Film thickness × film width]

Percent Elongation: When stress was applied on the film its stretches and was termed as strain. Strain was deformation of film divided by original dimension of the film. Generally, as plasticizer increases there be an increase in the elongation of the film[27].

Percentage Elongation = [Increase in length x 100] /[Original length

Surface pH: The formed MDFwere placed in petri-dish and moisture with O.5ml distilled water and kept for half second. The pH was recorded after bringing the electrode in contact with the surface of the formulation for 1min[26].

Uniformity of drug content:2×2 cm was cut and dissolved by homogenization in 100 ml of simulated saliva pH 6.8 for 30 minutes with continuous shaking. From this, 10 ml was

diluted to 50 ml simulated salivary fluid. Then, the sample was measured for absorbance using UV Spectrophotometer. The experiments were carried out in triplicate for the film of all formulations and average value were documented[24].

In vitro dissolution studies: For Mouth films dissolution is carried out using USP type II (Paddle apparatus) with 300 ml of simulated salivary fluid pH 6.8 as dissolution medium maintained at 37 ± 0.50°C and stirring the medium at 75 rpm. Samples are collected at every 1 minutes time interval, and replacing with the same quantity of fresh medium. Absorbance of the sample is determined by the UV spectrophotometer which will give the amount of drug present in the withdrawn samples. The % drug release is plotted against time[27].

Disintegration time:2×2 cm size of film is cut and placed in the petri-dish containing simulated salivary fluid (25 ml), the time at which film starts to disintegrate is considered as disintegration time[28].

RESULT AND DISCUSSION:

3.1.Drug Excipient Compatibility study:

FTIR spectrum of pure amoxapine drug showed characteristic peaks of aromatic C-N stretching at 1361 cm^{-1} and for aliphatic C-N 1027.6cm^{-1} respectively. Prominent N-H stretching vibrations peak at 3338.2 cm^{-1} andN-H band peaks at 1603.6 cm^{-1},1559.8cm^{-1}.Obtained spectrum thus confirms thepurity of the drug.FTIR spectrum of Polomer 188 characterized by absorption peaks at 2883 cm^{-1} (C-H stretch aliphatic), 1341 cm^{-1} (in-plane O-H bend) and 1099 cm^{-1} (C-O stretch), which were consistent in all binary systems with the drug. IR spectrum of amoxapine and polomer 188, bears the peaks corresponding to the peaksas well as that ofpolomer 188with no significant shift in the major peaks. FTIR spectrum of dry mix of amoxapineMDF shows all the prominent peaks of amoxapineindicating the maintenance of identity of the drug and thus the stability of the drug in film.

3.2. Selection of Solubility enhancer:

When the drug is complexes with poloxamer 188 in ratio 1:6, it showed maximum solubility. The drug was practically insoluble in its free-form, but later on after complexingwith poloxamer 188 it showed solubility 1.38 mg/ml.From the mentioned result, it was concluded that for formulating mouth dissolving film of Amoxapine with enhanced solubility, it was complexedwith poloxamer 188 for better results.

3.3. Selection of film forming polymer:

HPMC E5 as film forming polymer: Films prepared by solely HPMC E5 did not show satisfactory results as films were difficult to peel off from petridish.

HPMC E15 as film formingpolymer: Films formulated by HPMC E15 revealed satisfactory results, i.e.good separability, folding endurance and comparable disintegration time.

HPMC E50 as film formingpolymer: As HPMC E50 has higher molecular weight, films formulated by this showed good physical compactness but simultaneously it also increases the disintegration time compared to other grades of HPMC.

Combination of HPMC E5 and HPMC E15 as film formingpolymer: Films formulated by using these two grades showed better separability, folding endurance and disintegration time. FromtheabovementionedresultsasthecombinationofHPMCE 5andHPMC E15 showed better results, it was selected for further studies.

3.4. Selection of Plasticizer:

Films formulated with Glycerol as plasticizer: From the result of experiment, it is evident that films formulated by Glycerol were very sticky compared to other films formulated by PEG- 400. Due to stickiness, it was even difficult to separate out from the petridish at higher concentration. And it has low folding endurance at lower concentration.

Films formulated with PEG-400 asplasticizer: The results clearly describe that films formulated by PEG-400 as plasticizer gave films with better plasticity, good folding endurance, satisfactory disintegration time and no stickiness was observed which means separability from the petri-dish was very good. Considering the above parameters with same concentration; PEG-400 was selected for further study.

3.5. Selection of Superdisintegrant:

Films prepared using different superdisintegrant were not able to give satisfactory results in regarding disintegration time when compared with the above batches. Thus, it did not used for further studies.

3.6. Selection of Solubilizing Agent:

In batch B5 Tween 80 was used as solubilizing agent, but it didn't give satisfactory results as it was not able to peel off from the petriplate. As it was not able to separate the film form the petri-dish it was not selected for further study.

3.7. Evaluation Parameter of Film:

Peelability:The Peelability of all the above batches F1-F9 was found satisfactory.

Thickness: The thickness of mouth film was observed in the range of 0.12mm to 0.16mm, and it is observed that with increase in polymer concentration, increase the thickness of film.

Folding Endurance: The mouth films should have satisfactory folding endurance i.e. 295 to 315 and it is observed that as the plasticizer and polymer concentration increases the folding endurance also increases.

Surface pH:Acidic and alkaline pH may cause irritation to the mucous. The surface pH of mouth films ranged between 6.76±0.05 to 6.88±0.04. The results were found a close to neutral pH in all the batches, and this means that they have less potential to irritate the mucous.

% Drug content: The % drug content in all the formulations varied between ranges of 97.50±0.04 % to 99.58±0.03%. This indicates that the drug is dispersed uniformly throughout the polymeric films.

Tensile strength: Tensile strength of mouth film varied with different concentrations of polymer. Tensile strength of all the batches was in the range of 1.15±0.03 to 1.39±0.05.

Disintegration time: Disintegration time of films varied due to different concentrations of polymer. Disintegration time of all the batches was in the range of 20 to 58. It is evident from the results that as the polymer concentration increases the disintegration time for the film also increases.

CONCLUSION:

Marketed preparation of amoxapine have slow onset of action and undergoes first pass metabolism. Thus, to achieve fast onset of action and overcome the first pass metabolism, mouth film of amoxapine was formulated. Mouth film of Amoxapine was successfully prepared by solvent casting method having good disintegration time, appearance, folding endurance and % drug release.

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CONFLICT OF INTEREST:

The author declared that there is no conflict of interest.

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