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Design, characterization and Evaluation of mouth dissolving film (MDF) containing Enalapril maleate.

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Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. To avoid such difficulties, film like dosage forms were developed. The aim of this study was to formulate and optimized mouth dissolving film containing Enalapril maleate by 3 level 2 factor full factorial design using design expert® software. Mouth dissolving film was formulated by using solvent casting method. HPMC E15 and sodium starch glycolate concentrations were selected as independent variable. Enalapril maleate containing film of HPMC E15 was optimized by selecting the disintegration time and tensile strength as response which is evaluated by design expert® software. Disintegration time is important constraint for immediate release dosage form. Concentrations of HPMC E15 and sodium starch glycolate affect the disintegration of film and tensile strength. Desirability for Quadratic model was significant compare to other models. About 99.77 % of drug release was obtained from In vitro drug release study and follows korsmeyer peppas model. Films were characterized by using DSC Thickness, tensile strength, folding endurance test and evaluated for their physical and mechanical properties. Stability study of optimized film for two months reveals that formulation was stable for specified time period. From this study it was concluded that disintegration time was directly proportional to concentration of sodium starch glycolate and inversely proportional to concentration of HPMC E15.Concentration of Sodium starch glycolate directly proportional to tensile strength and inversely proportional to disintegration time.

Keywords: dissolving, release, film, HPMC, disintegration

Oral drug administration has been one of the most convenient and widely accepted routes of delivery for most therapeutic agents. Traditionally, oral dosage forms refer to tablets, capsules, and liquid preparations taken orally, swallowed, and transiting the gastrointestinal tract (GIT) for postbuccal absorption [48].However, some undesirable physiological properties of the GIT limit the feasibility of administration of some drug molecules

by this route. The mouth represents the initial portal of entry to the GIT and thus, most dosage forms placed in the mouth are expected to be swallowed, and transit the GIT either intact or when dissolved in saliva [21]. Quick-Dissolving Delivery Systems (QD) delivery systems undergo disintegration or dissolution in the saliva, generally within a few seconds to a minute, releasing the drug and inactive ingredients in the oral cavity. Other synonyms and definitions of QD delivery systems are loved with the saliva and transported along the GIT where the drug is subsequently absorbed. The technical advantages of these dosage forms include: ease of swallowing, administration without water anywhere and anytime, quick onset of action with some drugs, supervised administration, buccal or sublingual absorption, and local therapy of the oral mucosa [48]. Therapeutic benefits of the mouth dissolving dosage forms for patients may include: enhanced efficacy, improved convenience, and improved compliance. Pharmaceutical companies may benefit from these dosage forms due to product differentiation, life cycle management, reduction of development costs, and outsourcing. The following therapeutic categories have been reported to have market opportunities for QD delivery systems non opioid analgesics, opioid analgesics, migraine headache, cough and cold, allergy, gastrointestinal, cardiovascular, central nervous system, urology, and other categories [22].

Formulation of mouth dissolving film involves the application of aesthetic and performance characteristics such as, fast dissolving, physical appearance, mouth feel etc. All excipients should be Generally Regarded as Safe (i.e. GRAS listed) and should be approved for use in oral dosage forms according to FDA. 1.3.1. Active Pharmaceutical Ingredient Generally 5% w/w to 30% w/w of drugs or API is incorporated into the film. APIs can be milled, micronized or incorporated in the form of nanocrystals or particles depending upon the ultimate release profile desired. Before incorporating the API in the MDFs, the taste needs to be masked for bitter drugs. Several techniques were employed to enhance the taste and the simplest method involves the mixing and co processing of bitter tasting API with excipients with good taste which is called as obscuration technique[26]. The MDFs technology has the potential for delivery of variety of APIs. Water soluble APIs are present in the dissolved state in the MDFs or in the solid solution form; the water insoluble drugs are dispersed uniformly in the film. The distribution of water insoluble molecules in water miscible polymer becomes important from the large scale manufacture point of view. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the MDFs[53].

Advantages of mouth dissolving film

1. Oral dissolving films can be administered without water, anywhere, anytime [5].

2. Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity [26].

3. Oral dissolving films are flexible and portable in nature so they provide ease in transportation, during consumer handling and storage [53, 26].

4. Suitability for geriatric and pediatric patients, who experience difficulties in swallowing mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake ability or are nauseated.

5. Beneficial in cases such as motion sickness, acute pain, suede episodes of allergic attack or coughing, where an ultra-rapid onset of action required.

6. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

7. As compared to liquid formulations, precision in the administered dose is ensured from each strip of the film.

8. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.

9. Provide new business opportunity like product differentiation, product promotion, patent extension [2].

Disadvantages

1. High doses cannot be incorporated.

2. Dose uniformity is a technical challenge.

3. Special type of packing is required due to its moisture and temperature sensitivity [2].

Materials and methods

Characterization of Enalapril maleate [58]

1. Organoleptic Properties

The drug sample is observed for their color, odor and taste.

2. Melting Point Determination

Melting point of drug was determined by using melting point apparatus. (Omega scientific industries)

3. Characterization of Drug by FT-IR Spectrophotometer

The IR spectrum of drug is determined by using Fourier Transform Infra-Red spectrophotometer (Shimadzu IR Affinity 1). The drug sample is triturated uniformly with dried potassium bromide in 1:3 ratio (sample to KBr) then the IR spectra is determined by using diffuse reflectance spectroscopy. The scans were obtained at a resolution of 4000 to 400 cm^{-1}48

4. Characterization of Drug by Differential Scanning Calorimetry (DSC)

DSC curves were obtained by Mettler Star SW 9.01. Sample 1-4 mg was placed in aluminium pan press sealed with an aluminium cover. An empty sealed in the same way was used as reference. Thermo grams were measured by heating the sample from 35 to 300^0C at the rate of 10^0C /min, under a nitrogen flow of 10 mL /min.

Procedure for Preparation of Enalapril maleate mouth dissolving film

Mouth dissolving film of HPMC E15 was prepared by the solvent casting method. Aqueous solution of polymer and polyethylene glycol 400 in specific proportion in warm distilled water where prepared and was allowed to sonicate for 20 minutes and kept for 1 hour to remove all the air bubbles entrapped. This is aqueous solution A. Aqueous solution B was prepared by dissolving the Enalapril maleate, citric acid, and sodium starch glycolate in specific proportion, in distilled water. Both aqueous solutions A and B were mixed and stirred for 1 hour. Then the mixture solution was casted onto a plastic petri dish and it was dried at the room temperature for 24 hour. The film was carefully removed from the petri dish, checked for any imperfections, and cut according to the size required for testing (square film: 2 cm length, 2 cm width). The

samples were stored in a dessicator maintained at a temperature of 30 ±1^{0}C and relative humidity 60±5% until further analysis.

Evaluation of Enalapril maleate mouth dissolving film

1.Thickness of film

Film thickness was measured using Brookfield engineering labs, tensiometer. Thickness was measured at different 5 positions for each specimen having size 2×2 cm 2 and the average of the reading was recorded.

2. Folding endurance

Folding endurance is determined by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

3. Tensile strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the film by using the equation below Load at failure × 100 Tensile strength = Film thickness × Film width.

4. Percent elongation

When stress is applied, a film sample stretches and this is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally elongation of film increases as the plasticizer content increase. Increase in length of Film × 100 % elongation = Initial length of Film.

5. Surface pH test

The prepared mouth dissolving film was placed in a petri dish and moistened with 0.5 mL of distilled water and kept it for 30 seconds. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the film and allowing equilibration for 1 min. The average of three determinations for each film was done.

6. Assay/Content Uniformity

A film of about 2×2 cm^2 areas was dissolved in 100 mL of 0.1N HCL at 37°C. The content was passed through 0.4 µm membrane filter. The filtrate was assayed at 257 nm using UV- visible spectrophotometer.

7. In vitro Release Studies of mouth dissolving film

A drug is expected to release from the solid dosage forms (granules, tablets, capsules etc.) and immediately go into molecular solution. This process is called as dissolution. In-vitro release profiles of the mouth dissolving film were evaluated using rotating basket dissolution apparatus (Electrolab 08 L, Mumbai). 900 mL of simulated gastric fluid (pH 1.2) maintained at 37 ± 0.5 ^{0}C was used as dissolution media, and the basket was rotated at a constant speed of 50 rpm. (FIP guidelines, 2011) Film which having size of 2×2 cm^2 were cut and placed in the vessel. Aliquots of samples were withdrawn at the interval of 5 minutes. The samples withdrawn were filtered, diluted suitably and analyzed at 257 nm Spectrophotometrically for drug release. 10 mL of fresh dissolution media were added each time to maintain the sink conditions.

8. Stability study (effect of Temperature and Humidity)

Stability study was carried out on the optimized formulation. The formulation was wrapped in Aluminium foil and then placed in a stability chamber. It was stored at 40 ± 2^{0}C, 75% ± 6% relative humidity for 2 months. Films were evaluated for in vitro drug release and content uniformity after Zero, One, & Two months[25].

Results and discussion

Authentication of drug is performed by melting point, FTIR and UV spectroscopy. Excipients were authenticated by FTIR method. The nature of drug was found to be white to off-white crystalline powder. Hence, the organoleptic property complies with the reported literature[58]. Melting point of Enalapril maleate was found to be 143-144^{0}C. The reported melting point of Enalapril maleate is 143-144.5^{0}C. Hence, the experimental value complies with the reported values[58].

Solubility[58]. Enalapril maleate has been soluble in alcohol, freely soluble in dimethyl formamide and in methyl alcohol; slightly soluble in semipolar organic solvents, practically insoluble in nonpolar organic solvents and in dichloromethane.

Evaluation of mouth dissolving film containing Enalapril maleate

1. Thickness of film- Films of bathes F1 to F9 were evaluated for their thickness of area 2 cm^2. There was no statistically significant difference between the all formulated batches that is P>0.05. From this result it was conclude that as the concentration of film forming polymer increases the thickness of film also increases.

2. Folding endurance- Repeated folding of the film at the same place till the film breaks. The table no. showed that as the concentration of film forming polymer i.e. HPMC E15 increases the number folding the film was decreases. Concentration of HPMC E15 increases the brittleness of film.

3. Tensile strength- Tensile strength of films has batch no. F1 to F9. From this study it was concluded that as the concentration of films forming polymer HPMC E15 increases, the tensile strength of films was decreases. All results are statistically significant that is p> 0.05.

4. Percent elongation - When stress is applied, a film sample stretches and this is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally elongation of film increases as the plasticizer content increases.

5. Surface pH test- The prepared mouth dissolving film was subjected to determination of pH. F2 batch showing pH 6.7 which was acceptable limit.

6. Assay/Content Uniformity- A films containing Enalapril maleate was tested for their uniformity in drug content and it was found that all batches was showing content uniformity within given limit[58].

7. Disintegration test - The in vitro disintegration time was determined by a modified method. All 9 batches was subjected for disintegration test and result of this study was describes that disintegration time was increases with increasing concentration of HPMC E15. While decreases with decreasing concentration of sodium starch glycolate as superdisintegrants.

In-vitro Dissolution Studies

In-vitro dissolution studies of all the formulations were carried out using USP dissolution Apparatus I. The dissolution studies were carried out using simulated gastric fluid (pH 1.2). The data obtained in the in-vitro dissolution studies were grouped according to modes of data treatment as follows

1. Cumulative percent drug release v/s. Time (Zero-order).

2. Cumulative percent drug retained v/s. Square root of Time (Higuchi Matrix Model).

3. Log Cumulative percent drug retained v/s. Time (First-order).

4. Cumulative percent drug release in (mg) v/s. Time (Korsmeyer-Peppas Model)

The data obtained from dissolution was subjected to kinetic treatment for various models and from that the best fit model was selected. From the dissolution data, formulation F2 shows satisfactory result with drug release about 99.77±0.096%. The values of coefficient correlation (R^2) and release exponent (n) were calculated and that found to linear for Korsmeyer-peppas model of drug release.

Experimental Design and Data Analysis

1. Disintegration time a) Analysis of Variance for Experimental matrix (ANOVA) The aim of present work was to achieve optimized formulations determining the effects of some important factors and their interactions during the process preparation on mouth dissolving film physiochemical properties. Meanwhile the mouth dissolving film was being processed; the impact of different factors had been evaluated by making changes in their quantity. Finally, two of the most significant factors had been chosen as the independent variables. In the next step, for determining the low and high levels of each factor, some formulations were made, and the results. According to a 3 level 2 factorial design and considering these two variables, an experimental matrix was performed in which 9 experiments were performed given in TABLE 1. The disintegration time and Tensile strength was mentioned 9 formulations were obtained given in the TABLE 1.

   b) Analysis of Variance and Model Equations for disintegration time According to applied 3 levels 2 factorial experimental design including 9 experiments were performed to optimize the formulation of

Enalapril maleate containing film to get minimum disintegration time and moderate tensile strength in terms of responses. The obtained results were entered in design expert® software 7.1 and a model equation were obtained to get the fit result for disintegration time and tensile strength.

Stability study- (effect of Temperature and Humidity) Effect of temperature and humidity was studied at 40 ºC ± 2 ºC/75% ± 5 % RH maintained in environmental stability chamber for two month. An evaluation was done after 0, 1, and 2 month. The results were tabulated in TABLE 2. From the above tabulated results, it can be concluded that there was no significant changes in the optimized batch of Drug content & Drug release.

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TABLE: 1 HPMC and PEG400 effect on disintegration time

Sr. no.	HPMC E15 mg	PEG 400 mL	Disintegration time (Seconds)	Inference
1.	100	0.2	35	As conc. of HPMC E15 increases, disintegration time increases
2.	150	0.2	40	
3.	200	0.2	48	
4.	250	0.2	55	
5.	300	0.2	63	

TABLE: 2 HPMC and Sodium starch glycolate effect on disintegration time

Sr. no.	HPMC E15 mg	Sodium starch Glycolate (mg)	Disintegration time (Seconds)	Inference
1.	200	10	60	As conc. of HPMC E15 increases, disintegration time decreases
2.	200	20	57	
3.	200	30	52	
4.	200	40	48	
5.	200	50	40	