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Design of Mouth Dissolving Films of Polysaccharide Polymeric Combination

Swapnil Salunkhe*[1], Dr. Shweta Shriwas[2], Dr. Rakesh Patel[3]
Research Scholar, Dr. A.P.J. Abdul Kalam University, Indore MP, India
Professor, School of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP, India
Professor & Principal, School of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore MP, India

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ABSTRACT:
The oral route is one of the most popular ways to administer drugs since it is patient-acceptable, safe, and easy to administer. Oral solid dose forms are available for about 60% of conventional dosage forms. For patients with illnesses including abrupt episodes of allergy reactions or coughing, as well as bedridden, emetic, pediatric, and geriatric patients, oral dissolving strips and films are helpful. Psychosis is a condition marked by convulsions, dementia, and hallucinations. In order to reduce the chance of irreversible brain injury, prompt care is necessary. The primary treatment approach for psychosis is still pharmacotherapy using anti-psychotic medications. Anti-psychotic medication formulation as an orally dissolving strip, which must be applied to the patient's tongue without swallowing in order to administer the dose, would greatly simplify dosage administration and increase patient compliance. Therefore, the objective of this effort was to design, create, and describe anti-psychotic medication mouth dissolving films. The core of an oral dissolving film is often composed of a plasticizer, a polymer that forms the film, or a combination of polymers that give the film the essential elasticity and shape.

Introduction

Psychosis is a clinical syndrome composed of several symptoms. Delusions, hallucinations, and thought disorder may be regarded as core clinical features. A “nosology” of psychosis would need to be based on the knowledge of the causes and pathophysiology of these “psychotic” symptoms. Psychosis is a clinical syndrome, not a nosological entity [1]. The term “psychosis” has been used for about 170 years, and has evolved to reflect the scientific and social contexts of the respective times. The term “psychosis” was soon used by others, and a long and intricate history of its meaning ensued. In today’s definition, the characteristic symptoms of psychosis are related to the degree of severity (with psychosis being the severe form of mental disorders), lack of insight, communication disorders, lack of comprehensibility of the symptoms, and reduced social adaptation [2]. The line between “disorder” and “normality” is an important aspect of such classification systems and symptom definitions, questions regarding the validity of the concepts of mental disorders come into play, as well as the quest for defining disease entities. This reflects etiopathological or pathophysiological insights, lending credibility to a

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concept of psychosis due to valid constructs [3].The signs and symptoms for the prodromal stage of psychotic illness and the eventual psychotic experience may be different. Early warning signs of this syndrome may include [4]. The cause of the syndrome can be different for every patient. "Psychosis is a heterogeneous psychiatric condition for which a multitude of risk and protective factors have been suggested," suggests a 2018 study [5]. Mouth dissolving films have been described as an alternative approach to conventional dosage forms. These drug delivery systems can be administered in various ways such as orally, buccally, sublingually, ocularly, and transdermally [6-7]. Mouth dissolving films or strips can be defined as follows: "These are drug delivery systems that they are quickly releasing the drug by dissolving or adhering in the mucosa with saliva within a few seconds due to it contains water-soluble polymers when it placed in the mouth cavity or on the tongue" [8]**.** These innovative dosage forms are taken orally but do not require water for ingestion and absorption as do conventional drugs. OTFs are not to be confused with buccal films, which are intended to stay on the mucosa of the cheek for an extended period of time [8].The delivery of the medication to the target site at a therapeutically relevant level, with negligible least discomfort and side effects to the patient, is one of the principles of a good pharmaceutical formulation. The method of drug administration has a significant impact in this regard. The oral route is the most often used method of medication delivery among all other routes because of its ease of administration. However, it also has some downsides, such as poor bioavailability because of first pass action and a propensity to produce fast high and low plasma concentrations of the medication; as a result, patient compliance occurs. An atypical antipsychotic called lurasidone is used to treat bipolar I disorder-related depressive episodes and schizophrenia. Lurasidone is an atypical antipsychotic developed by Dainippon Sumitomo Pharma. Lurasidone is indicated for the treatment of schizophrenia in patient's ≥13 year's old.3 It is also indicated as a mono therapy for the treatment of bipolar depression in patients ≥10 years old, or in combination with lithium or valproate for the treatment of bipolar depression in adults. Mouth dissolving film is now a days preferred route of drug administration due to patient compliance. Lurasidone is an atypical antipsychotic that is a D2 and 5-HT2A (mixed serotonin and dopamine activity) to improve cognition. It is thought that antagonism of serotonin receptors can improve negative symptoms of psychoses and reduce the extra pyramidal side effects that are often associated with typical antipsychotics.

Material and Methods:

Physical Appearance: Colour, odour, taste and appearance was notify by sensory organs and was found to be a yellow, odourless, crystalline powder

Melting Point: The required amount of drug will take in a capillary tube, and then the capillary tube will keep in a melting point apparatus.

Solubility Studies: The solubility study was done by incremental method of solvent. The fixed amount 10 mg of drug was kept in conical flask. Now the solvent was filled in burette up to desired scale. The solvent was continuously drop down into conical flask drop by drop with continuously stirrer and determined the amount of solvent need to dissolve the drug present in conical flask. Thus, we found the concentration of solution of solvent and drug to identify the solubility of drug [8].

Partition Co-efficient: The partition coefficient indicates the polar and non-polar nature of the drug. 10 mg of drug (lurasidone) was added in a mixture of distilled water (10 ml) and then n-octanol (10 ml) in a glass-stoppered test tube and shake for 2 hr. The aqueous phase will then separate using a separating funnel, and drug content was estimate by UV spectrophotometrically at 248 nm. The partition coefficient of drug calculated as follows

$Po/w = Co/C_{pH6.8}$ where, Po/w = partition coefficient of drug, Co= concentration of drug in n-octanol, $C_{pH6.8}$=concentration of drug in pH 6.8 phosphate buffer

FTIR of drug: KBr pellet technique will use for this study. In this, the sample and the KBr were taken in 1:300 ratios. The mixture of sample and KBr was triturated to make a fine powder and investigated the functional group wave number of drug and drug excipients mixture for determination of incompatibility study with FTIR spectrophotometer. The drug-excipient compatibility study was carry out for designing a chemically stable formulation for clinical and commercial development. The drug and the excipients

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was mix in the selected ratios using a mortar and pestle. The mixtures will transfer into glass vials and seal. The samples were kept at 40ºC±2ºC/75%±5% RH for four weeks. The samples was analyze for physical and chemical incompatibilities and also by FTIR spectrophotometer.

Preparation of Calibration Curve: The calibration curve will be used to prepare spectrophotometrically for the quantitative measurement of the medication using UV absorption at λmax in PBS pH 6.8. For the quantitative measurement of the medication, a calibration curve was created using spectrophotometry based on UV absorption at λmax 248 nm in PBS pH 6.8. A precise 50 mg medication was weighed and then put into a 50 ml volumetric flask together with 10 ml methanol and 40 ml PBS pH 6.8 to create a 1 mg/ml solution. A theoretical concentration of 100µg/ml was achieved by adding 10 ml of this solution (1 mg/ml) to 10 ml of PBS pH 6.8.At 248 nm, diluents ranging from 5 to 50 µg/ml were produced and tested. Lurasidone's calibration curve was created using concentration versus absorbance data.

Formulation of fast dissolving films: Casting solutions was prepared by using selected polymers. The required weighed quantities of polymers HPMC E15/ Xanthan gum (XG) were separatelyor in combination kept for swelling overnight in 5 ml distilled water and dissolved. The drug and aspartame as sweetener were added to the polymeric solution directly as given in Table 1 along with glycerol as a plasticizer and mixed thoroughly to form a homogenous mixture on magnetic stirrer. The entrapped air bubbles were removed by applying sonication process. The casting solution (10 ml) was poured into glass molds and dried at40°C in a vacuum oven for 24 h for solvent evaporation. The films were removed by peeling and cut into a square dimension of 2.0 cm × 2.0 cm (4.0cm^2). It was dried for 24 hours at room temperature. The transparent, bubble-free thin film was carefully removed from the petri plate, where quick-dissolving films were made using various polymers and ratios while keeping the plasticizer and sweetener concentrations constant [9].

Evaluation of mouth dissolving films

Weight variation: Mouths dissolving oral films will weigh on digital balance and average weight will determine for each film. It is desirable that films should have nearly constant weight. It is useful to make sure that a film contains the required amount of excipients and drug.

Thickness of Films: By using micrometer screw gauge the thickness of the film was measured at 5 totally different places; an average of 3 values was calculated by using screw gauge.

Folding endurance: The folding endurance was expressed as the number of folds (number of times the film is folded at the same place) requires to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 2.5 cm × 2.5 cm was subject to folding endurance by folding the film at the same place repeatedly several times until a visible crack was observed [9].

Drug content uniformity: The prepared oral thin films were dissolved in 10ml methanol and 40ml PBS pH 6.8 mixtures. The mixture was filtered through whatman filter paper. After suitable dilutions, the concentration of the drug was determined by uv method at 248 nm.

Surface pH: The film was placed in a petri dish and moistened with0.5 ml of distilled water and keep for 30 s. The pH of mixture was noticed by attaching the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min.

Tensile strength: The tensile strength is determined by the apparatus which has two clamps, the upper one is fixed and the lower is movable. The film sample (0.5×3 cm) is clamped between the two clamps. The force at tearing and elongation is determined. The percent elongation (%E) is calculated using the following equation

% E = {(Ls-Lo) / Lo} x 100 Where, Lo = Original length

Ls = Length of the film after elongation

The modulus of elasticity of films was calculated from the equation

F/A = EM {(Ls-Lo) / Lo}

Where F = Breaking load (N), A = Cross- sectional area of the film

EM = Modulus of elasticity

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Water vapor transmission rate: The water vapor transmission rate study, vials of equal diameter can be used as transmission cells. Cells are washed thoroughly and dried in an oven. One gm of calcium chloride is taken in the cell and the polymeric films (two cm2 area) are fixed over the brim with the help of an adhesive. The cells are accurately weighed and the initial weight is recorded. Films are then kept in a closed desiccator containing saturated solution of potassium chloride (80-90 % RH). The cells are taken out and weighed after 18, 36, 54 and 72 hours. From increase in weights, the amount of water vapor transmitted and the rate at which water vapor transmitted can be calculated by using the following formula:

Water vapor transmission rate = WL/S

Where, W = Water vapor transmitted in mg

L = Thickness of the film in mm, S = Exposed surface area in cm2

In vitro diffusion study: In vitro diffusion study was carried out by using Franz-diffusion cell apparatus with PBS pH 6.8 as a dissolution medium. The temperature was maintained at 37±0.5°C with 50 rotations per minute. 1 ml of aliquots was withdrawn at different time intervals and same amount of fresh dissolution medium was added to maintain sink condition. The aliquots were analyzed for drug content at λ max 248 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated and reported [10].

Results And Discussion

The absorption maximum of lurasidone in PBS pH 6.8 was found to be 248 nm. The data of calibration curves were linearly regressed, and the equation of the straight line for the standard curve as well as correlation coefficients was determined. The correlation coefficient for standard curves was found to be very near to one. Hence, drugs are following the Beer-Lambert Law in the range of 5-50 µg/ml.The melting point of the drug was found to be similar to the published in reference books. The solubility profile of drug lurasidone showed its hydrophobic nature and was insoluble in chloroform and water but freely soluble in methanol. The partition coefficient was found according to their solubility profile that was indicating the hydrophobic nature of the drug. The partition coefficient of drug in n-octanol: pH 6.8 phosphate buffer was 3.8 and Drugexcipientcompatibilitystudyfor4Weeks was done and there was no change in sample of drug and excipients. Lurasidone was studied for compatibility with excipients in different environmental conditions. No drug interaction was observed during the time period of storage, showing their compatibility with all ingredients **(Figure 1 – 2)**.

Mouth dissolving films of lurasidone were prepared by the solvent casting method on glass molds, using HPMC E15 / Xanthan gum, glycerin as plasticizer and aspartame as sweetener and distilled water as a solvent. The effect of the nature of polymers was studied by preparing various formulations of oral dispersible films. The characterization and evaluation of prepared fast dissolving films were done for various parameters like thickness of the films, drug content uniformity, folding endurance of the films, disintegration time, In-vitro dissolution and stability studies.

The Effect of polymer concentration was studied with different formulations prepared using HPMC E15, Xanthan gum, individually and in a combination of these polymers in different concentrations. The weight variations in the films were found to be uniform in all the prepared batches. The thickness of MDF1 to MDF9 was found and can be concluded that the uniformity was achieved during the formulation. The prepared oral films were studied for folding endurance by number of times, the film could be folded at the same place without breaking gave the value of folding endurance. Percentage of drug content for different formulations was calculated. Percentage of drug content of MDF7 was found to be 99.80% and was considered as best formulation compared to the other formulation. The formulations showed percentage drug content 86.12-99.80 %. From the results obtained from the above formulations. The pH of surface of oral films was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1 min. The average of three determinations for each of the formulation was taken. Surface pH of all films was found to be within the limits 6-7. The tensile strength of oral thin films were be in the range of 1.04 – 4.29 (Mpa). The in vitro drug release was observed that in formulations containing a single polymer, the drug release was found to be faster and films formed of HPMC E15 resulted in a fastest

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release of drug. Further, as the concentration of the polymer increased, the drug release was found to be decreased due to the increase in the time required for wetting and dissolving the drug molecules present in the polymer matrices. The results of the release kinetics study showed that all the formulations obeyed first order drug release profile more closely, i.e., the release rate depended upon the initial concentration of drug. The slope values of the Korsmeyer-Peppas plot showed that the mechanism was non-fickian or supercase II transport mechanism. The stability study of optimized formulation LMDF15 oral mouth dissolving film was showed upto 2 years and followed accelerated stability study test as per ICH guideline at room temperature.

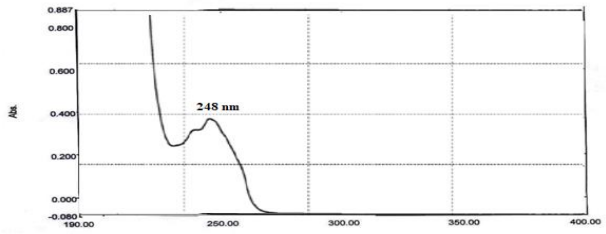

Figure 1: UV-Visible Scan ofdrug

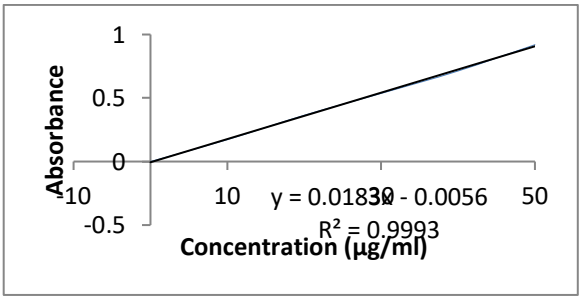

Figure 2: Calibration curve of drug in pH 6.8 phosphate buffer

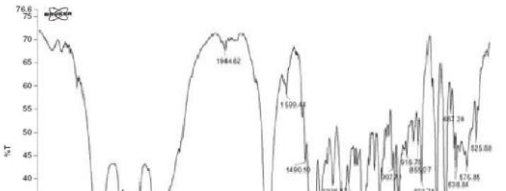

Figure 3: FTIR of drug

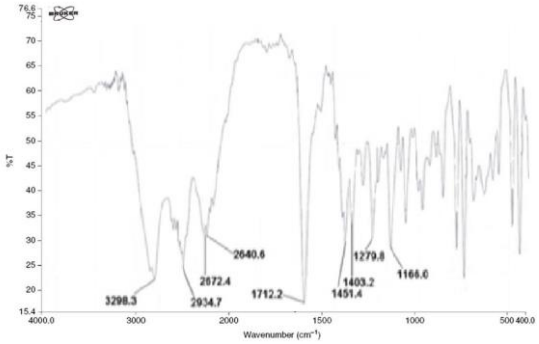

Figure 4: FTIR of drug and excipients

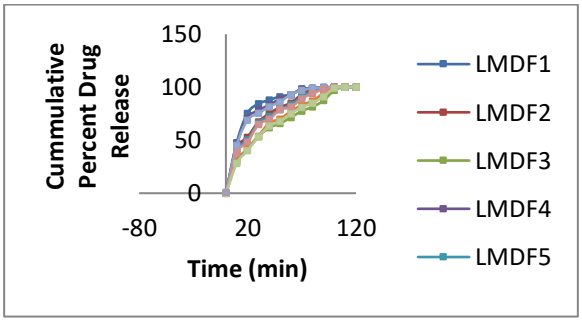

Figure 5: Zero-order plots oforal mouth dissolving films (LMDF10 – LMDF18)

Table 1: Formulation casting solution of mouth dissolving films

F. Code	Lurasidone (mg)	HPMC E15 (mg)	Xanthan gum (mg)	Sodium starch glycolate (mg)	Glycerol (ml)	Distilled Water qs (ml)
MDF1	30	50	0	10	0.5	10
MDF2	30	100	0	10	0.5	10
MDF3	30	150	0	10	0.5	10
MDF4	30	0	50	10	0.5	10
MDF5	30	0	100	10	0.5	10
MDF6	30	0	150	10	0.5	10
MDF7	30	25	25	10	0.5	10

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MDF8	30	50	50	10	0.5	10
MDF9	30	75	75	10	0.5	10

Table 2: Physical properties evaluation oforal mouth dissolving films (MDF1 – MDF9)

Form. Code	Weight of film (mg)	Thickness of film (µm)	Folding endurance	Drug content (%)	Water vapor transmission rate	Surface pH	Tensile strength (Mpa)
MDF1	37.24	98.1	98	86.11	18.18	6.28	2.04
MDF2	39.22	100.2	99	90.41	12.14	6.34	2.37
MDF3	40.8	102.1	93	93.12	22.22	6.25	2.12
MDF4	38.25	101.3	105	94.17	21.18	6.51	3.21
MDF5	38.9	105.2	92	91.17	28.14	6.44	2.03
MDF6	40.01	109.2	94	93.21	29.21	6.67	2.29
MDF7	37.16	99.3	112	99.19	21.22	6.71	3.29
MDF8	38.13	106.3	101	97.22	19.31	6.72	3.21
MDF9	36.11	110.2	98	99.51	23.11	6.81	3.19

Summary and Conclusion

Oral thin dissolving films or strips is based on as quickly releasing the drug by dissolving or adhering in the mucosa with saliva within a few seconds due to it contains water-soluble polymers when it placed in the mouth cavity or on the tongue. The oral transmucosal drug delivery bypasses first pass effect and avoids pre-systemic elimination in the GI tract. Lurasidone, has a need to formulate into buccal patches and the drug is suitable for psychotic effect. Lurasidone was used as a model drug candidate and nine fast-dissolving films formulations containing different polymer concentrations were prepared. The effect of the nature of polymers was studied by preparing various formulations of oral dispersible films. The various formulations containing a combination of polymers, release was found to be in terms of drug release The release rate depended upon the initial concentration of drug. The slope values of the Korsmeyer-Peppas plot showed that the mechanism was non-fickian or supercase II transport mechanism. Thus the oral thin films of lurasidone prepared by the solvent casting method on glass molds, using HPMC E15 and Xanthan gum in combinational study with Sodium starch glycolate as disintegrating agent, glycerin as plasticizer and aspartame as sweetener and distilled water as a solvent was valuable dosage form for the future aspects in the field of pharmaceutical sciences.

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