



ORAL TRANSMUCOSAL DRUG DELIVERY OF POLYSACCHARIDE POLYMERIC COMBINATION

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Abstract:

Oral route is one of the most preferred routes of drug administration due to its safety, ease of administration, and acceptability by patients. About 60% of conventional dosage forms are available as the oral solid dosage forms. Orally dissolving strips and films are useful in patients such as pediatrics, geriatrics, bedridden, and emetic patients and conditions such as sudden episodes of allergic attacks or coughing. Psychosis is a condition characterized by the hallucination, dementia etc. seizures. It requires quick management of in order to avoid the risk of permanent brain damage. Pharmacotherapy with anti-psychotic drugs remains the major treatment modality for psychosis. The formulation of anti-psychotic as an orally dissolving strip, required to be placed on the patient's tongue without swallowing for dose administration, would significantly facilitate dose administration, with subsequent improvement in patient compliance. Thus, the aim of this work was to design, develop and characterize mouth dissolving film of Anti-psychotic drugs. The backbone of an orally dissolving film is generally formed of a plasticizer and film forming polymer or a mixture of polymers that provide the necessary elasticity and shape to the film.

Keywords: Mouth Dissolving Films, Polysaccharide, Polymeric, Combination

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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 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 should not be confused with buccal films that are designed to remain on the cheek mucosa for a long time [8]. The fundamentals of a successful pharmaceutical formulation depend on the delivery of the medicament to the target site at therapeutically relevant level, with negligible or minimum discomfort and side effects to the patient. In this

respect, the route of drug administration has major influence. Among all the routes of drug administration, the oral route is the most common form of delivery of drugs because it has advantage of easy administration. But also has potential drawbacks like poor bioavailability due to first pass effect and tendency to produce rapid high and low plasma concentration of drug, due to this, the patient compliance occurs. Lurasidone is an atypical antipsychotic used to treat schizophrenia and depressive episodes associated with bipolar I disorder. Lurasidone is an atypical antipsychotic developed by Dainippon Sumitomo Pharma. Lurasidone is indicated for the treatment of schizophrenia in patients ≥ 13 years old. It is also indicated as a monotherapy 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-HT_{2A} (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 extrapyramidal side effects that are often associated with typical antipsychotics.

Material And Methods:

Physical Appearance: Colour, odour, taste and appearance was notified 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 upto 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 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 $40^{\circ}C \pm 2^{\circ}C / 75\% \pm 5\%$ RH for four weeks. The samples was analyze for physical and chemical incompatibilities and also by FTIR spectrophotometer.

Preparation of Calibration Curve: Calibration curve will prepare spectrophotometrically based on UV absorption at λ_{max} in PBS pH 6.8 for the quantitative estimation of the drug. Calibration curve was prepared spectrophotometrically based on UV absorption at λ_{max} 248 nm in PBS pH 6.8 for the quantitative estimation of the drug. 50 mg drug was accurately weighed and placed in a 50 ml volumetric flask to prepare a 1 mg/ml solution in 10ml methanol and 40ml PBS pH 6.8. 10 ml of this solution (1mg/ml) was added to 10 ml PBS pH 6.8 to yield a theoretical concentration of 100 μ g/ml. Diluents of 5 to 50 μ g/ml were prepared and measured at λ_{max} 248 nm. Calibration curve of drug lurasidone prepared was prepared using concentration vs 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 separately or 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 at $40^{\circ}C$ 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 \times 2.0 cm (4.0 cm²). It was dried for 24 hours at room temperature. The thin film was clear and bubble free and removed from the petri dish very carefully, where fast-dissolving films were prepared with different polymers and ratios by maintaining the concentration of the plasticizer and sweetener 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 \times 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 40 ml PBS pH 6.8 mixtures. The mixture was filtered through whatman filter paper. After suitable dilutions, the concentration of the drug was determine by uv method at 248 nm.

Surface pH: The film was placed in a petri dish and moistened with 0.5 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 \times 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

$$\% E = \{(L_s - L_o) / L_o\} \times 100$$
 Where, L_o = Original length
 L_s = Length of the film after elongation

The modulus of elasticity of films was calculated from the equation

$$F/A = EM \{(L_s - L_o) / L_o\}$$

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

EM = Modulus of elasticity

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:

$$\text{Water vapor transmission rate} = WL/S$$

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 Drug excipient compatibility study for 4 Weeks 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 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.

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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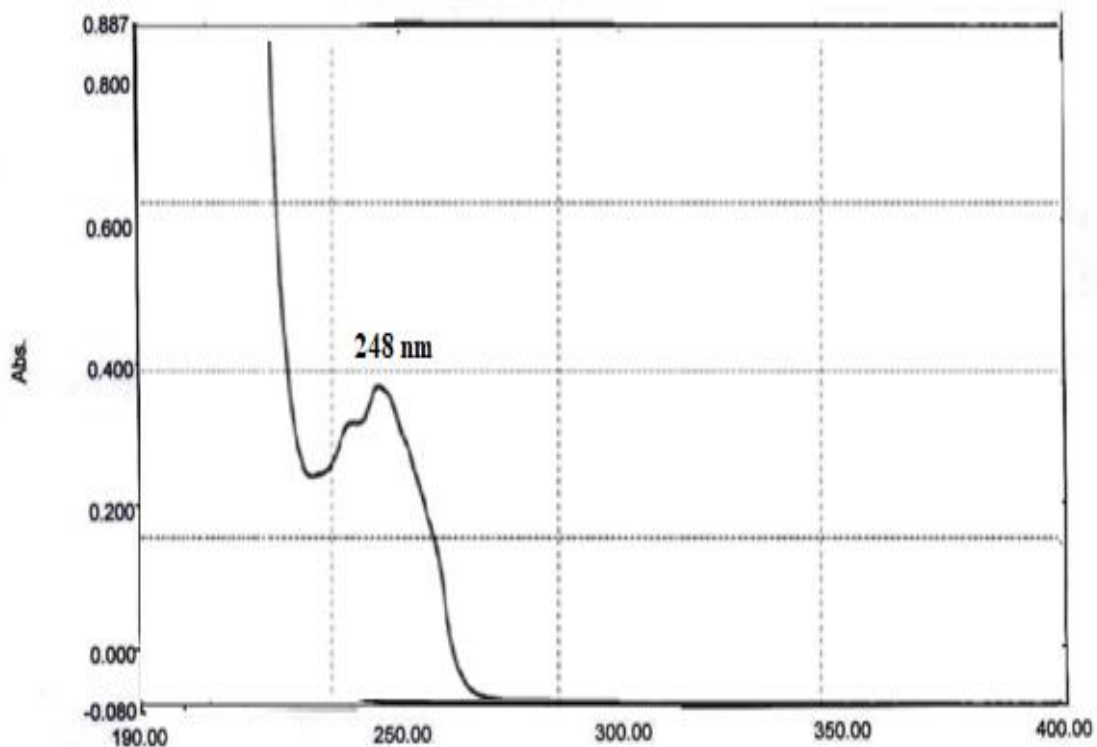


Figure 1: UV-Visible Scan of drug

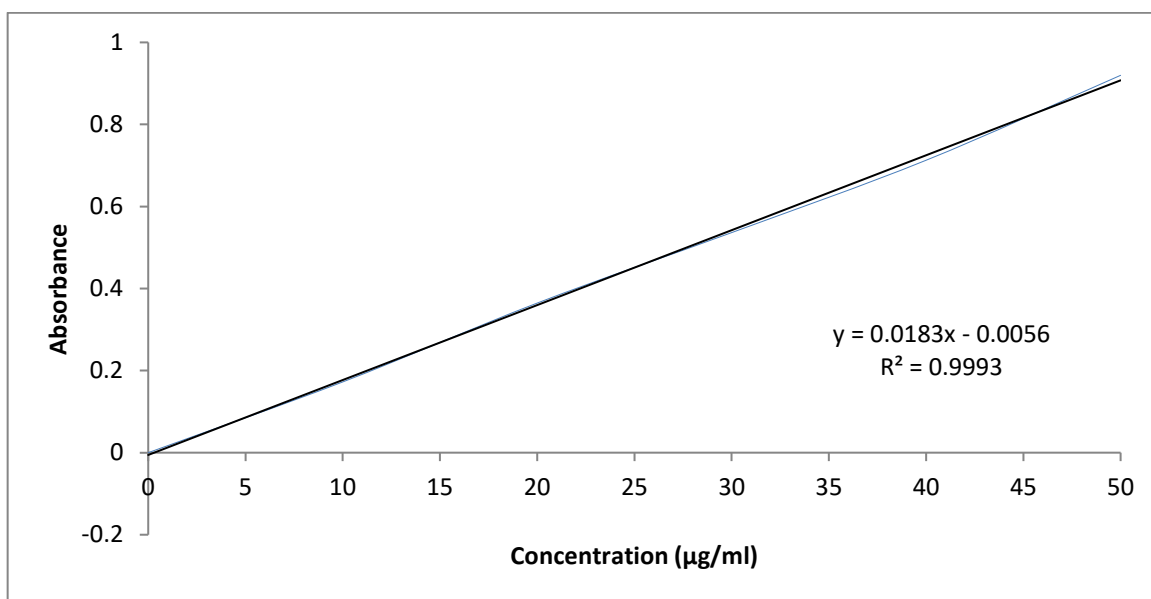


Figure 2: Calibration curve of drug in Ph 6.8 phosphate buffer

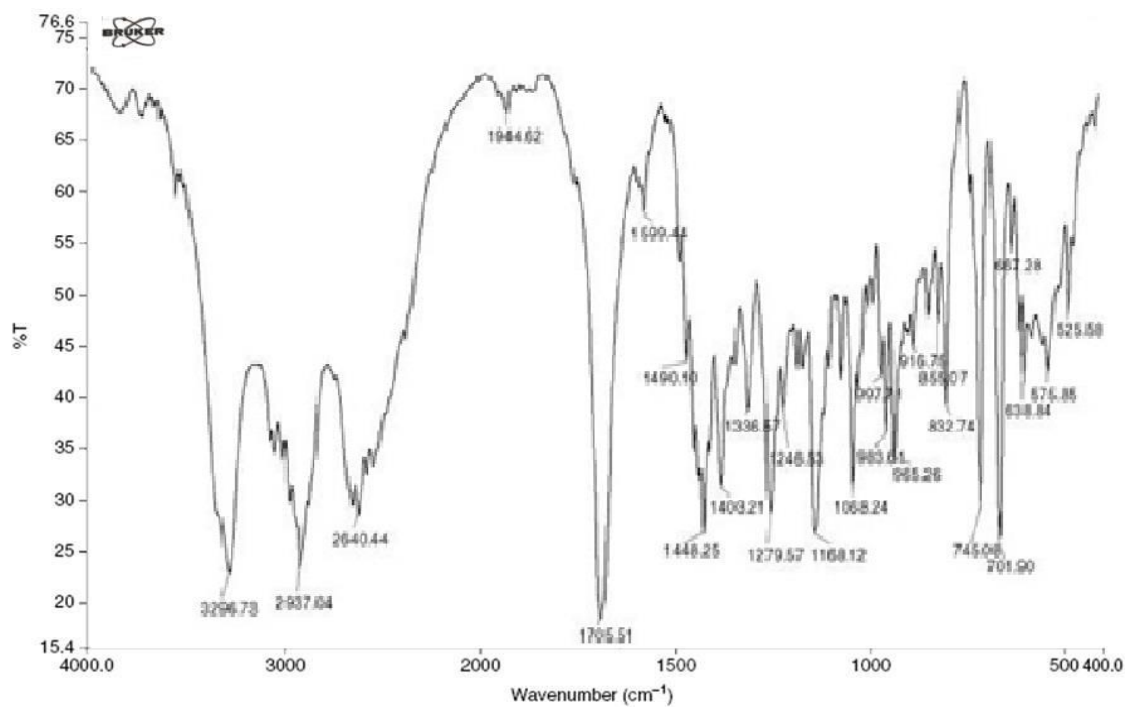


Figure 3: FTIR of drug

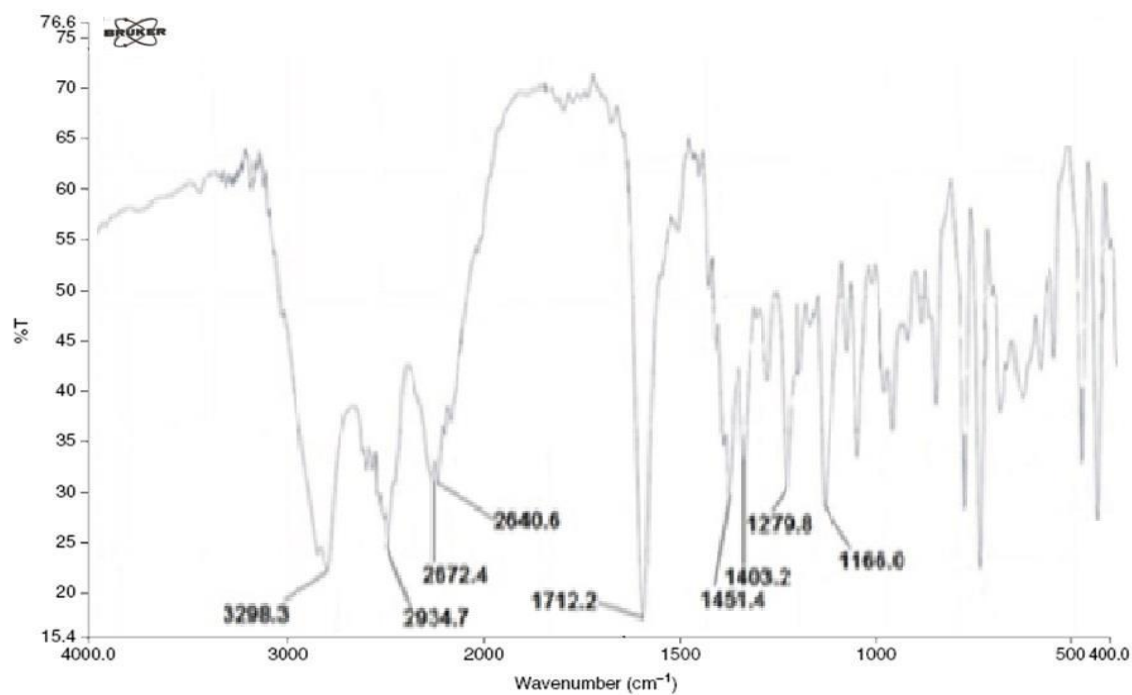


Figure 4: FTIR of drug and excipients

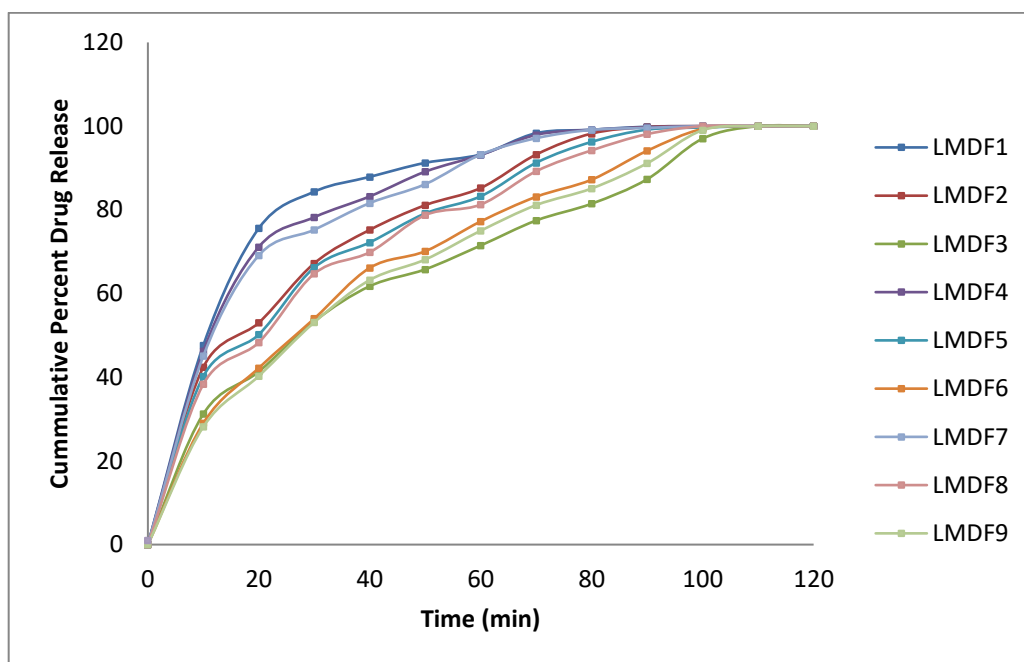


Figure 5: Zero-order plots of oral mouth dissolving films (LMDF10 – LMDF18)

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

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

| Formulation 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 |