Formulation and Evaluation of Mouth Dissolving Film of Antipsychotic Drug Ulotaront

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ABSTRACT: This research explores the development and assessment of mouth dissolving films (MDFs) as a novel drug delivery system for antipsychotic therapies. MDFs present a convenient option, especially for individuals facing challenges in swallowing, such as children, elderly, and dysphagic patients. Utilizing the solvent casting technique, the films were formulated with a combination of polymers, plasticizers, and active pharmaceutical ingredients. The study examined key characteristics, including disintegration time, drug content uniformity, tensile strength, and in vitro drug release profiles. The findings confirmed that MDFs facilitate rapid drug release, circumvent first-pass metabolism, and enhance bioavailability, ultimately leading to improved therapeutic efficacy and patient compliance. This innovative approach underscores the potential of MDFs as an effective delivery system for antipsychotic drugs.

Keywords: Mouth Dissolving Film, Antipsychotic, Disintegration Time, FTIR Spectroscopy

INTRODUCTION: Mouth dissolving films represent an innovative oral solid dosage form that rapidly disintegrates and dissolves in the mouth without the need for water. These films are increasingly favored among pediatric and geriatric populations, as well as individuals with dysphagia, due to their ease of use and reduced risk of choking. Offering convenience and simplicity in administration, they enable faster therapeutic effects by facilitating drug absorption through the oral mucosa. This mechanism allows the medication to bypass first-pass metabolism, enhancing its systemic availability. [1,2]

Advantages of Mouth Dissolving Films
Mouth dissolving films offer several benefits over traditional oral dosage forms:

- Their thin and elegant design makes them visually appealing.
- Available in diverse shapes and sizes to suit different needs.
- Can be consumed without water, making them ideal for use during travel.
- Disintegrate and dissolve quickly on the tongue, eliminating the risk of choking.
- Provide precise and convenient dosing compared to liquid formulations.
- Enable localized action within the oral cavity for targeted treatment.
- Suitable for patients across all age groups, ensuring ease of administration.

Disadvantages of Mouth Dissolving Films

Despite their advantages, mouth dissolving films have certain limitations:

- They cannot accommodate high doses of active pharmaceutical ingredients.
- Taste masking is crucial for drugs with bitter flavors.

- Require specialized packaging and equipment for proper storage and handling.
- Manufacturing challenges include achieving uniformity in drug dosage and film thickness during production.

Method of Manufacture of Mouth Dissolving Films

Mouth dissolving films (MDFs) are generally manufactured using simple, cost-effective methods that ensure uniform drug distribution and desirable mechanical properties. The most commonly employed technique is the **solvent casting method**, although other methods like hot-melt extrusion and semi-solid casting are also used depending on the formulation needs.

Solvent Casting Method

The solvent casting technique is the most widely used approach for the preparation of mouth dissolving films. The general steps involved are:

- **Preparation of Polymer Solution:** A suitable film-forming polymer (such as hydroxypropyl methylcellulose, pullulan, or polyvinyl alcohol) is dissolved in an appropriate solvent, usually water or a hydro-alcoholic solution, to form a clear, viscous solution.
- **Addition of Plasticizer:** A plasticizer (like glycerin, propylene glycol, or polyethylene glycol) is added to the polymer solution to improve the flexibility and mechanical strength of the film.
- **Drug Incorporation:** The active pharmaceutical ingredient (API) is uniformly dispersed or dissolved in the polymeric solution. Other excipients such as sweeteners, flavoring agents, saliva-stimulating agents, and taste masking agents may also be included at this stage.
- **Casting of the Solution:** The resulting solution is cast onto a suitable flat surface, such as a teflon plate or glass mold, and spread evenly using a calibrated applicator or a spreader.
- **Drying:** The cast film is then dried under controlled conditions (such as in an oven or a drying chamber) at a specific temperature to evaporate the solvent and form a solid, flexible film.
- **Cutting and Packaging:** Once dried, the films are carefully peeled off, cut into uniform sizes containing the desired drug dose, and packaged to protect them from moisture and contamination.

Hot-Melt Extrusion Method

In this technique, the drug and polymers are mixed at an elevated temperature and forced through an extruder to form thin films. This method is solvent-free, reducing the risk of residual solvents, but requires careful temperature control to avoid degrading heat-sensitive drugs.

Semi-Solid Casting Metho

Here, a solution of water-soluble film-forming polymer is mixed with a solution of insoluble polymer and plasticizer to form a semi-solid mass. This mass is then cast into films and dried under appropriate conditions.

Key Considerations During Manufacture:

- Uniform distribution of the drug throughout the film matrix.
- Control of thickness and mechanical properties for ease of handling.
- Proper drying to avoid residual solvent traces.
- Maintaining stability and integrity of the drug and excipients.

What Is a Psychotic Disorder?

Psychotic disorders represent a group of severe mental health conditions that share a common feature: psychosis. Psychosis itself is not a specific illness but a cluster of symptoms in which an individual loses touch with reality. During a psychotic episode, disruptions occur in the person's thinking patterns and perception of reality, making it difficult for them to distinguish between what is real and what is not.

There is no universally strict definition of psychosis because it can appear differently in each individual. Mental health professionals typically rely on criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* to diagnose psychosis. Psychosis may involve one or more of the following abnormalities:

- **Delusions:** Strongly held false beliefs that are not grounded in reality and cannot easily be corrected.
- **Hallucinations:** Sensory experiences—such as hearing voices or seeing things—that are not perceived by others.
- **Disorganized Thinking or Speech:** Incoherent, illogical, or jumbled patterns of speaking or reasoning.
- **Disorganized Behavior:** Actions that are unpredictable, inappropriate, or lack purpose.
- **Negative Symptoms:** A reduction or absence of normal behaviors, such as reduced emotional expression, withdrawal from social interactions, or diminished speech output.

Types of Psychotic Disorders

Psychotic disorders impact a person's ability to think clearly, perceive reality accurately, and interact socially. Several recognized types include:

1. **Schizophrenia:** A chronic disorder marked by persistent delusions, hallucinations, disorganized speech, and cognitive impairment.
2. **Schizoaffective Disorder:** A condition combining symptoms of schizophrenia with significant mood disturbances, such as major depression or episodes of mania.
3. **Delusional Disorder:** Characterized by the presence of one or more persistent delusions without the broader psychotic symptoms typically seen in schizophrenia.
4. **Brief Psychotic Disorder:** A short-term psychotic episode, often stress-induced, lasting less than one month, with eventual full recovery.
5. **Substance-Induced Psychotic Disorder:** Psychosis triggered by the use of, or withdrawal from, substances like alcohol, drugs, or medications.
6. **Psychotic Disorder Due to a Medical Condition:** Psychosis resulting from an underlying physical health issue, such as a brain injury or a neurological disorder.
7. **Postpartum Psychosis:** A rare but severe psychiatric emergency that occurs shortly after childbirth, involving hallucinations, delusions, mood swings, and confusion.

MATERIALS AND METHODS:

Method of Analysis

Preparation of Reagents and Solutions

Preparation of 0.2 M Sodium Hydroxide Solution

A 0.2 M sodium hydroxide solution was prepared by accurately weighing 8 g of sodium hydroxide and diluting it to a total volume of 1000 ml using purified water.

Preparation of 0.2 M Potassium Dihydrogen Phosphate Solution
To create a 0.2 M solution of potassium dihydrogen phosphate, 27.22 g of the compound was weighed and dissolved in purified water, making up the volume to 1000 ml.

Preparation of pH 6.8 Phosphate Buffer
Phosphate buffer (pH 6.8) was prepared by combining 50 ml of the 0.2 M potassium dihydrogen phosphate solution with 22.4 ml of the 0.2 M sodium hydroxide solution. The mixture was then diluted with purified water to reach a total volume of 1000 ml.

Spectrophotometric Method Development for Ulotaront Estimation
A UV-Visible spectrophotometer (Shimadzu UV 1800, Japan) was used for quantitative analysis of Ulotaront in phosphate buffer (pH 6.8). This involved determining the absorption maximum (λmax) and constructing the standard calibration curve.

Determination of λmax for Ulotaront in Phosphate Buffer (pH 6.8)
A stock solution of Ulotaront was prepared by accurately weighing 100 mg of the substance and dissolving it in 100 ml of phosphate buffer (pH 6.8) to create a 1 mg/ml concentration. Subsequently, a 10 ml sample of this solution was transferred to a 100 ml volumetric flask and diluted further to obtain a concentration of 0.1 mg/ml (100 µg/ml). A 10 ppm solution was then prepared from the stock solution and scanned within a wavelength range of 200-400 nm using the spectrophotometer, with phosphate buffer (pH 6.8) as the blank. The λmax identified was utilized for preparing dilutions for the calibration curve.

Drug and Excipient Compatibility Study using DSC for Ulotaront Formulation
The compatibility study between Ulotaront and the excipients in its mouth dissolving film formulation was performed using DSC in a dry state. The analysis utilized the Differential Scanning Calorimetry instrument (Universal V4SA TA) at Ashian Labs, Mumbai. Thermograms were obtained for both the pure drug and the drug-polymer mixture, with scanning carried out at a rate of 1°C per minute over a temperature range of -100°C to 400°C under a nitrogen atmosphere. Any observable alterations in peak shape or appearance were critically examined to identify potential incompatibilities.

Drug and Excipient Compatibility Study
Ensuring the compatibility of the active pharmaceutical ingredient (API) with formulation excipients is a critical step in the development process. This verification guarantees that no undesirable interactions occur under experimental conditions, safeguarding the product's shelf life and maintaining formulation integrity. Compatibility studies were conducted using Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR).

RESULTS AND DISCUSSION

Method of Analysis of Ulotaront
Spectrophotometric Estimation of Ulotaront in Phosphate Buffer pH 6.8
A solution of Ulotaront in phosphate buffer (pH 6.8) at a concentration of 10 µg/ml exhibited maximum absorbance at 248 nm when scanned across a spectral range of 200–400 nm using a UV spectrophotometer (UV1800). Therefore, 248 nm was selected as the wavelength of maximum absorbance (λmax). A standard calibration curve for drug estimation was constructed using concentrations ranging from 2 to 22 µg/ml.

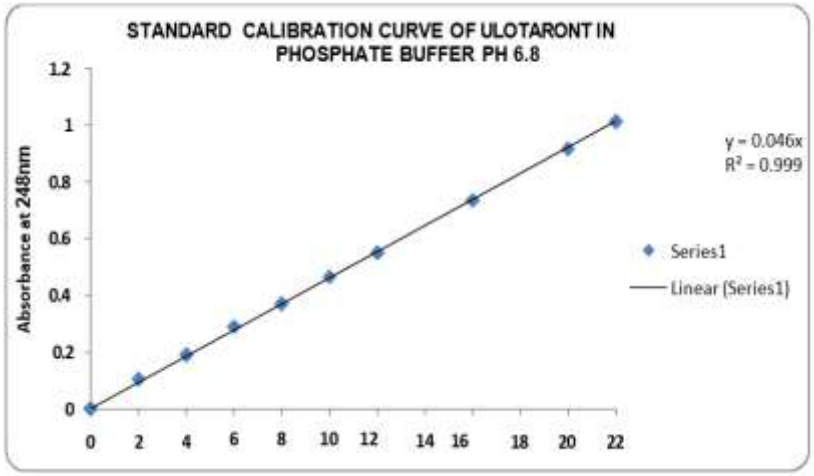

Figure 1: Calibration Curve for Estimation of Ulotaront

Table 1: Calibration Curve Data of Ulotaront in Phosphate Buffer pH 6.8

Sr. No	Concentration (µg/ml)	Absorbance			Average Absorbance ± SD
		1	2	3	
1	2	0.105	0.107	0.102	0.105 ± 0.003
2	4	0.189	0.192	0.194	0.192 ± 0.003
3	6	0.290	0.290	0.291	0.290± 0.001
4	8	0.371	0.374	0.372	0.372± 0.002
5	10	0.465	0.463	0.466	0.465± 0.003
6	12	0.55	0.552	0.551	0.551 ± 0.001
7	16	0.736	0.740	0.733	0.736 ± 0.004
8	20	0.919	0.917	0.916	0.917 ± 0.002
9	22	1.012	1.014	1.011	1.012 ± 0.002
Absorbance(y) = 0.046 * concentration(x)					
Correlation Coefficient (R^2) = 0.999					

Drug-Excipient Compatibility Study of Ulotaront Formulation Using the DSC Method

The compatibility of Ulotaront with the proposed excipients was evaluated through Differential Scanning Calorimetry (DSC). This analysis was conducted to identify any potential interactions between the drug and excipients. DSC thermograms were recorded for the pure drug as well as the combination of Ulotaront with excipients, providing insight into their thermal behavior.

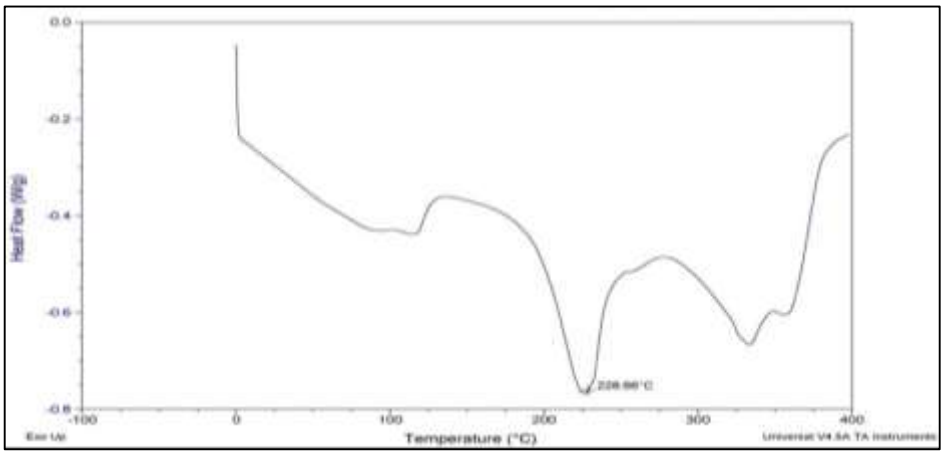

Figure 2: DSC Thermogram of Ulotaront Pure Drug

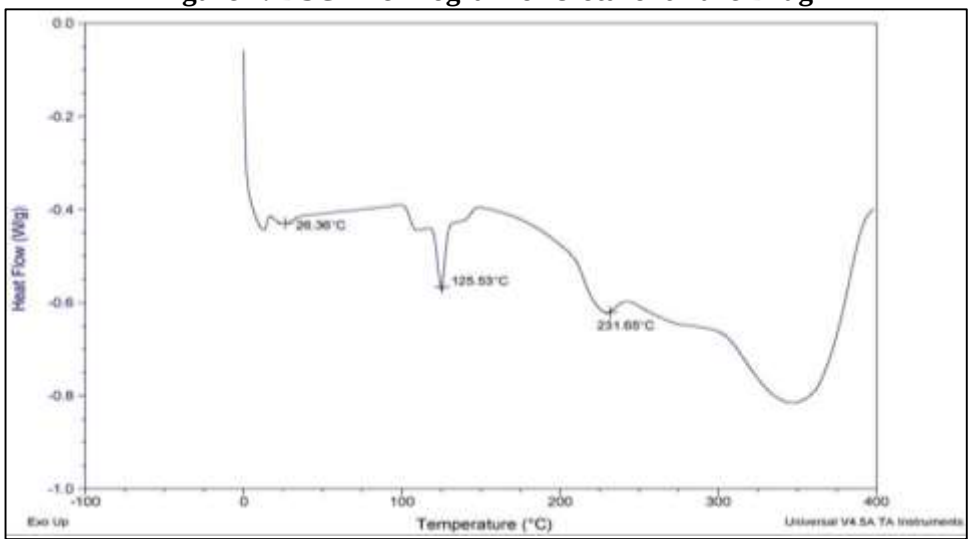

Figure 3: DSC Thermogram of Ulotaront Drug with Excipients

The DSC thermogram of the pure drug exhibited a sharp endothermic peak at 228.66°C, indicating its melting point. In the thermogram of the drug-excipient mixture, a slight shift in the endothermic peak was observed at 231.65°C. This minor variation can be attributed to the interaction with the polymers present in the formulation. However, the absence of any significant shift or the appearance of new peaks suggests that there is no incompatibility between the drug and the excipients.

Optimization of Ulotaront Mouth Dissolving Film using 32 Factorial Design

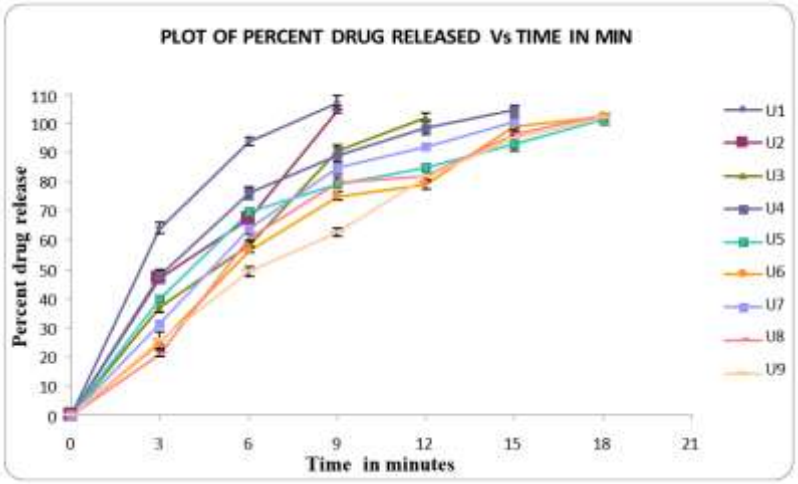

Figure 4: Comparative In vitro Drug Release of 32 Factorial Ulotaront MDF

CONCLUSION: The formulation and evaluation of mouth dissolving films (MDFs) containing the antipsychotic drug Ulotaront were successfully carried out in this study. Using the solvent casting technique, various film formulations were prepared by optimizing the concentration of polymers, plasticizers, and other excipients to achieve desirable film characteristics. The prepared films were evaluated for parameters including appearance, thickness, folding endurance, disintegration time, tensile strength, drug content uniformity, and in vitro drug release profiles.

Among the different formulations developed, the optimized batch exhibited rapid disintegration within seconds, uniform drug distribution, satisfactory mechanical strength, and a high percentage of drug release in a short period. Differential Scanning Calorimetry (DSC) analysis revealed only a slight shift in the drug's endothermic peak when combined with excipients, indicating no significant interaction or incompatibility.

The mouth dissolving film of Ulotaront developed in this study presents a patient-friendly dosage form, particularly advantageous for individuals with psychiatric conditions who may face difficulties in swallowing conventional tablets. The fast onset of action, ease of administration without the need for water, and improved patient compliance highlight the potential of this delivery system in clinical practice. Overall, the findings suggest that mouth dissolving films can serve as a promising platform for the effective and convenient delivery of Ulotaront in the treatment of psychotic disorders.

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CONFLICTS OF INTEREST: Authors have no conflicts of interest to declare.

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