Development And Evaluation Of An Oral Liquid Dosage Form For Lumateperone, An Anti-Psychotic Drug

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Abstract

The novel antipsychotic drug lumateperone has demonstrated encouraging efficacy in treating a range of mental illnesses. However, some patient populations, such as those with dysphagia or paediatric patients, may experience difficulties with its current formulations, which are primarily in solid dose forms. The purpose of this study was to develop and assess an oral liquid dosage form of lumateperone in order to alleviate this limitation. In order to guarantee stability and improved bioavailability, solubility improvement techniques and compatibility tests were employed during the formulation process. To analyse formulation features, physicochemical characterisation was carried out, which involved assessments of viscosity, pH, and drug content uniformity. Studies on in vitro dissolution shed light on the kinetics of drug release and the effectiveness of the formulation.To determine long-term viability, stability evaluations under various storage settings were also conducted. The outcomes showed that lumateperone could be successfully developed into an oral liquid formulation that is stable, bioavailable, and has the desired physicochemical characteristics. Throughout the specified storage duration, the formulation showed stable and uniform drug release profiles. This study offers a practical and efficient lumateperone dosage option, marking a significant advancement in pharmaceutical technology. It may enhance treatment adherence and therapeutic outcomes, especially in patient populations for which solid dosage forms are unfeasible or difficult to administer.

Keywords: *Oral liquid dosage, Anti-psychotic drug, Formulation development, Evaluation, Liquid dosage form, Pharmaceutical formulation, Psychiatric medication, Drug delivery.*

1. INTRODUCTION

Screening investigations of novel chemical entities and formulation design and development often face the difficulty of solubilizing poorly soluble medicines.At the site of absorption, any medication that is to be absorbed needs to be there as an aqueous solution. Since permeability and solubility determine the drug's in vivo absorption, solubility augmentation methods can change or modify these properties.

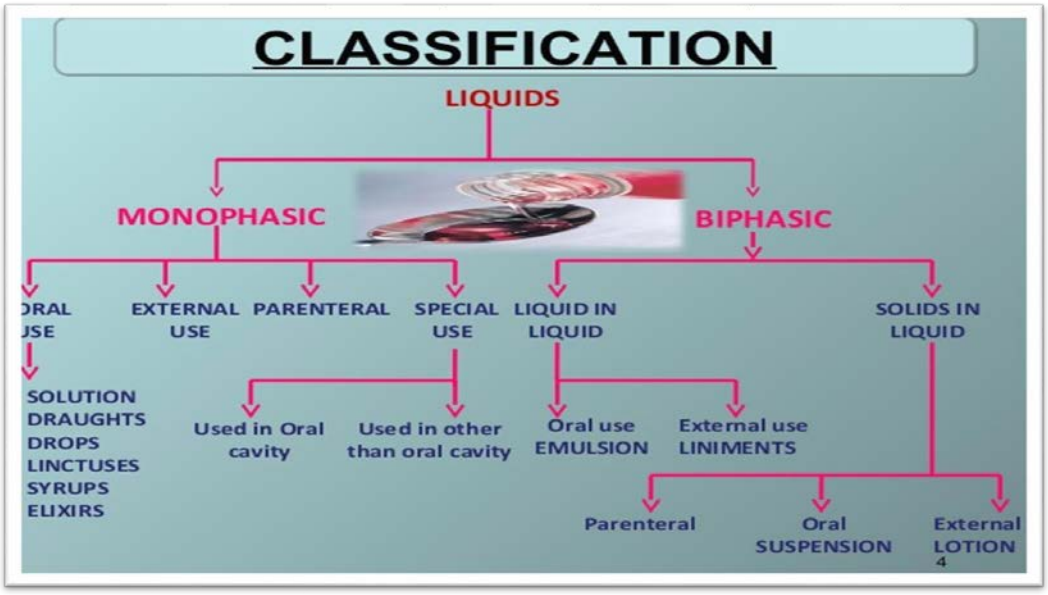
The maximum amount of a solute that may dissolve in a given volume of solvent or volume of solution at a given temperature is known as the solute's solubility. In qualitative terms, solubility can be described as the spontaneous interaction of two or more substances to generate a homogenous molecular dispersion. In quantitative terms, solubility is defined as the concentration of the solute in a saturated solution at a specific temperature.

A drug's solubility can be expressed in terms of volume fraction, molality, molarity, %, parts, and mole fraction. Enhancing solubility is a crucial factor to take into account when developing a formulation for a medicine that is taken orally but has low water solubility. One of the main obstacles to the oral delivery of novel pharmacological substances is the solubility of the molecule in aqueous media, which affects drug absorption, sufficient and repeatable bioavailability, and/or pharmacokinetic profile in humans. Compounds that are poorly or extremely poorly soluble are frequently referred to be insoluble.

Liquid dosage form

Liquid dose forms are intended to deliver fast therapeutic effects and/or maximise therapeutic response in a target group that has trouble swallowing pills and capsules. Commercial liquid dosage forms are first preformulated in the laboratory, then formed at the small-scale and finally at the pilot plant level before being produced on a large scale. One class of dosage forms that can be used parenterally, externally, or internally are liquid forms. Drugs can be suspended, dissolved in an aqueous or non-aqueous solvent, or incorporated into one of the two phases of an oil and water system to create liquid dosage forms.

Figure No 1. - Classification of liquid dosage forms



Mechanism of action

Lumateperone antagonises multiple dopamine receptors (D1, D2, and D4) with a reduced affinity while acting as a 5-HT2A receptor antagonist. Its suppression of serotonin transporter reuptake is modest. Without significant antimuscarinic or antihistaminergic actions, it exhibits extra off-target antagonism at alpha-1 receptors, reducing the side effects linked to other atypical antipsychotics.

Pharmacokinetics

Lumateperone has a terminal elimination half-life of eighteen hours and achieves maximal plasma concentrations in 1-2 hours after oral administration. Many different isoforms of glucuronosyltransferase (UGT) (UGT1A1, 1A4, and 2B15), aldo-keto reductase (AKR) (AKR1C1, 1B10, and 1C4), and cytochrome P450 (CYP) enzymes (CYP3A4, 2C8, and 1A2) are substrates of lumateperone.
No common CYP450 enzyme is significantly inhibited by lumedeperone. It isn't p-glycoprotein's substrate.

Drug interactions

Drug interactions might alter the way your prescriptions function or raise the possibility of severe side effects. Not every potential medication interaction is covered in this document. Make a list of everything you use, including over-the-counter and prescription medications as well as herbal remedies, and provide it to your chemist and physician. Before beginning, stopping, or altering the amount of any medication, get your doctor's approval. Metoclopramide is a substance that could interact with this medication.
Lumateperone's excretion from your body may be impacted by other medications, which could have an impact on the drug's effectiveness. Examples include St. John's wort, rifamycins (like rifabutin), and medications used to treat seizures (such phenytoin and carbamazepine), among others. If you take other medications that make you sleepy, like alcohol, marijuana (cannabis), opioid pain or cough relievers (like codeine, hydrocodone), muscle relaxants (like carisoprodol, cyclobenzaprine), antihistamines (like cetirizine, diphenhydramine) or medications for sleep or anxiety (like alprazolam, lorazepam, zolpidem), let your doctor or pharmacist know.

2. MATERIALS AND METHODS

Excipient grade selection

The generic product development used the same excipient types as were chosen for the oral liquid formulation. Based on formulation experience literature and knowledge of excipients that have been successfully utilised in approved goods, the excipient grade and supplier were chosen. In further formulation development investigations, the levels of excipients utilised in the formulation were examined.

Table No 1: Initial selection of excipient type, grade and supplier

S. No.	Ingredients	Grade	Manufacturer	Role
1	Lumateperone	--	MSN	Active pharmaceutical ingredient
2	Liquid sorbitol	Meritol	Tereos syral	Solvent
3	Propylene glycol	Macrogol 400 pH	Merck	Solvent
4	Edetate Disodium	--	Merck	Preservative
5	Methyl Paraben	--	Anipra chemicals	Preservative
6	Propyl Paraben	--	Anipra chemicals	Preservative
7	Citric Acid (Pharma grade)	--	Merck	pH modifier
8	Saccharin	--	Spectrum	Sweetener
9	Raspberry flavor	--	IIF India Ltd	Flavor

List of instruments

Sr. No.	Name of equipments	Make	Model
1	Remi stirrer	Remi	RQ-124A
2	Mechanical stirrer	Remi	RQ-1241
3	Halogen moister analyzer	Metler Toledo	HB43
4	Weighing balance (Range-0.02gm-151gm)	Metler Toledo	PB 153-S
5	Weighing balance (Range- 10mg-400gm)	Sartorius	BSA423S-CW
6	Weighing balance (Range- 10mg-600gm)	Sartorius	BSA623S-CW9
7	Weighing balance (Range-100mg-6000g)	Sartorius	BSA6202S-CW-9
8	Brookfield viscometer	Lab USA	DV III Ultra pro
9	UV Spectrometer	Shimadzu corp.	Spectral 210
10	FTIR spectrometer	Jascoinc	-
11	HPLC	Waters	E2695

Standardization of drug

Preformulation tests including visual organoleptic characteristics, particle size distribution, physico-mechanical characterization, and drug-excipient compatibility were performed on the drug sample.
The tests listed below were run for this study:
1. Features of the organoleptic
2. Distribution of particle sizes
3. Capturing physico-mechanical data
4.Compatibility study.

Organoleptic characteristics

We used descriptive vocabulary to describe and record the drug's colour, odour, and taste. This includes noting the drug's colour, flavour, and odour while using precise language. Early batch colour records are particularly helpful in determining suitable parameters for subsequent production. The majority of medications typically have distinct tastes and smells.

Physio-chemical characterization

1. Solubility Study - Tetrahydrofuran, alcohol, methylene chloride, and water were tested for API solubility. Excess API was placed in various beakers with the solvents to conduct solubility investigations. Regular shakes were performed on the mixes. Grade No. 41 Whattmann's filter paper was used to filter the solutions.
Spectrophotometric analysis is performed on the filtered solutions. Phase solubility testing was done on the API.

2. Melting Point - A substance's melting range, also known as its melting temperature, is the range of temperatures at which the substance starts to melt fully and starts to agglomerate. The capillary method was used to determine the API's melting point, and its results were compared to those that had been reported.

3. Differential Scanning Calorimetry (DSC): RCS-90 (-90°C to 450°C) cooling unit-equipped ATA instrument, Model Q200, was used for DSC investigations. Using a 2 mg sample in a T zero pan-Aluminum container and a T zero press to enclose it, DSC was carried out. Nitrogen gas was purged at a rate of 50 mL/min to maintain an inert atmosphere. The temperature range for the samples is 0 to 300°C, with a 10°C ramp.

4. Loss on Drying (LOD): LOD quantifies the percentage of water in a chemical. A Mettler Toledo halogen moisture analyzer operating at 1050C was used to do this.

Formulation development of oral liquid dosage from

1) Selection of vehicle
Literature survey revealed that is a propylene glycol very good vehicle and can be used in liquid formulation in a concentration of to make a required viscosity. it sis a water soluble and safe to use in liquid formulation to increase stability of formulation and viscosity.

2) Selection of sweeteners

As a liquid dosage form, the inhibition of bad odor because of drug and excipient. Literature survey revealed that liquid sorbitol and saccharin is a water soluble agent.

3) Selection of preservative

Literature survey revealed the use of Edetate disodium, Methyl paraben, Propyl paraben a common preservative in pharmaceutical dosage form. the selection of preservative done on the basis of solubility and compatibility criteria.

4) Selection of PH Modifier

Literature survey revealed that use of citric acid anhydrous a common pH modifier in pharmaceutical dosage form. the selection of pH modifier done on the basis of dosage form and route of administration.

Step in manufacturing process

Step 1: Dispensing the materials in the precisely stated quantity
Step 2: Prepare the ethylene dioxide solution and add it to the liquid sorbitol solution.
Use a 2-liter production vessel and fill it with 150 millilitres of filtered water. 7 grammes of edetate disodium filtered water should dissolve in 15 minutes while stirring. and mix for 15 minutes while swirling 250 g of liquid sorbitol.
Step 3: Saccharin solution preparation.
In 100 millilitres of water, dissolve 4 grammes of sucrose while stirring for 20 minutes. A beaker. Include this fix in Step 2.
Step 4: Lumateperone Preparation
To obtain a transparent solution, dissolve 42 grammes of lumateperone in 100 millilitres of diluent (ethanol:water 50:50 v/v) while stirring for 30 minutes. Add this mixture to the second stage while stirring.
Step 5: Berry taste addition
In step 2, add 0.05 g of raspberry flavour and stir for 10 minutes.
Step 6: Make a solution of propylene glycol, methyl paraben, and propyl paraben.
To make a solution, add 2.5 grammes of methyl paraben and 1 grammes of propyl paraben to 60 millilitres of propylene glycol and stir for 30 minutes. Then, add the solution to step 2 and stir for 10 minutes.
Step 7: Citric acid solution preparation
Pour 100 millilitres of filtered water and add 1.9 grammes of anhydrous citric acid. Stir for ten minutes.
Step 8: Modification of pH
Step 2 requires a gentle addition of the citric acid solution to reach pH 5.2 while stirring.

Step 9: Last-minute volume correction
To obtain the solution, use filtered water and increase the volume to one litre while stirring.
Step 10: Filtration
Run a 4.5 µ filter through the bulk solution.

3. RESULT AND DISCUSSION

This chapter relates with results and discussion of the experimental work carried out for the product development stage.

Identification of drug

Solubility Study

Table No 2: The solubility of Lumateperone in different media

Solvent	Solubility
Methylene chloride	Freely soluble
Tetrahydrofuran	Sparingly soluble
Alcohol	Very slightly soluble
Water	Insoluble

According to the data above, API is more soluble in acidic pH values but becomes less soluble in higher pH values. Therefore, the rate-limiting stage for absorption will be the dissolution.
Since the majority of medication candidates are weak acids or weak bases, the temperature, pka of the drug, and the medium's pH and ionic strength all affect how soluble these pharmaceuticals are.

Uv spectroscopy
The drug's UV spectrum is obtained by scanning at a medium scan rate between 200 and 400 nm. A qualitative comparison is made between the generated spectrum and the spectrum acquired from a reference standard. The wavelength used for analysis was 233 nm.

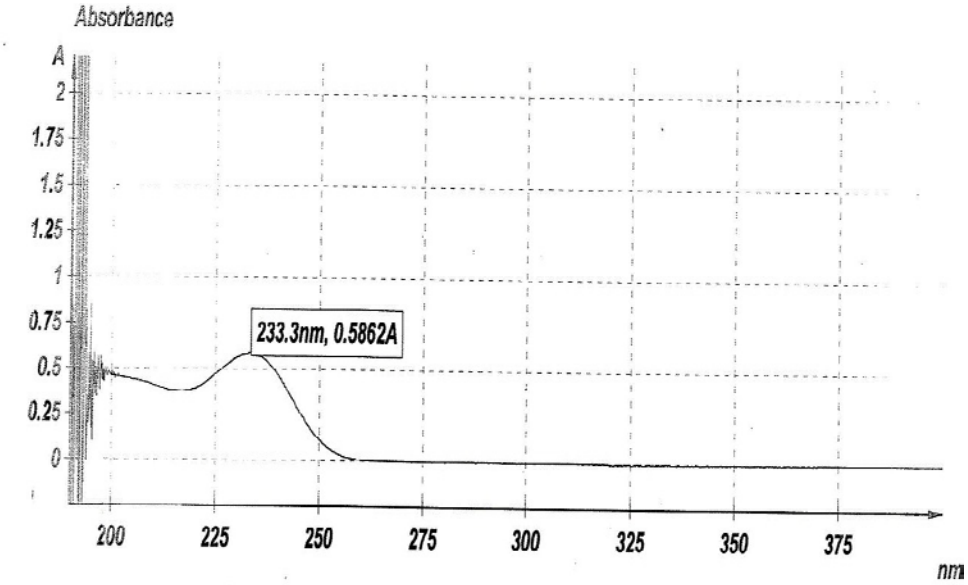


Figure No 1 : UV Spectrogram of Lumateperone

Particle size distribution

The laser diffraction technique is used by the particle size analyzer to do particle size analysis, wherein particles are sorted based on their diameter.

Table No 3 : PSD data of Drug Substance

Particle size (By Malvern)			
API B. No.	**D(10)**	**D(50)**	**D(90)**
LMT2305009	1.2 µm	6.3 µm	15.3 µm
LMT2308567	1.9 µm	6.8 µm	14.9 µm
LMT2401907	1.4 µm	5.9 µm	15.7 µm

Conclusion: From the above information it was observed that for

I) API Batch No. LMT2305009 D (90) indicates that 90% of the drug particles provided were smaller than 15.3 µm; D (50) indicates that 50% of the drug particles provided were smaller than 6.3 µm; and D (10) indicates that 10% of the drug particles provided were smaller than 1.2õm.

II) API Batch No. LMT2308567 D (90) indicates that 90% of the drug particles were under 14.9 µm, D (50) indicates that 50% of the drug particles were under 6.8 µm, and D (10) indicates that 10% of the drug particles were under 1.9 µm.

III) Batch No. LMT2401907 for the API 90% of the drug particles were less than 15.7 µm, 50% of the drug particles were smaller than 5.9 µm, and 10% of the drug particles were smaller than 1.4 µm, according to D (90), D (50), and D (10).

As a result, the API with the particle size distribution displayed above was used in this work. Therefore, we must utilise API with the same particle size distribution from development through production; otherwise, it may influence the API's homogeneity, flow characteristics, or dissolution pattern.

Conclusion:

1. It is discovered that every excipient to API ratio is compatible and falls well inside the original API standard.
2. No discernible increase or decrease in quantity is seen when compared to the initial samples.
3. Satisfactory compatibility results were obtained for the sample charged in open glass vials at the RT, 2-week, and 4-week sample time points.

Results of trial batch

Table no 4 : Evaluation of trial batch

Test	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Appearance	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution	Clear colorless solution
Clarity test	100	100	100	100	100	100	100	100
PH	5.0	5.2	5.4	4.9	5.0	5.5	5.4	5.3
Specific gravity	1.023	1.030	1.024	1.018	1.024	1.028	1.029	1.023
Viscosity	0.8	0.9	0.9	0.8	1.67	1.96	2.34	2.30
Assay	99.1	99.8	100.2	99.7	99.9	99.7	99.8	99.5
Preservative content Methyl paraben	98.9	99.1	98.7	98.4	99.7	99.4	99.5	99.8
Propyl paraben	99.2	98.3	99.6	99.9	98.5	98.3	98.7	98.9
Test of Sterility	sterile	sterile	sterile	sterile	sterile	sterile	sterile	sterile

4. CONCLUSION

1. In this work, we successfully developed Lumateperone Oral solution which matches with the standard specification of oral solution as per regulatory requirement and patient requirement.

2. Lumateperone was water insoluble vehicle solubility was found to be a very effective agent in improving the stability, solubility.

3. The fast onset of action for psychotic patient. so increased the bioavailability of Lumateperone compared with other dosage form of same drug by converting it into solution form.

4. The formulation were stable and robust at all time in testing and no crystal growth observed during bench top.

5. From the literature survey it has been concluded that it is widely used in the treatment of anti-psychotic drug & Lumateperone also used for psychotic patient.

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