Pharmaceutical Sciences 2024: Navigating the Future of Drug Discovery and Development
November 2024

DEVELOPMENT AND IN-VITRO CHARACTERIZATION OF SUSTAINED RELEASE LINEZOLID TABLETS: A NOVEL DRUG DELIVERY APPROACH

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Abstract

This study focuses on the development and evaluation of sustained-release tablets of linezolid to achieve the desired bioavailability and in-vivo release pattern. Preformulation studies examined the active pharmaceutical ingredient (API) for physical properties and solubility, along with weekly drug-excipient compatibility checks under specified temperature and humidity conditions, which confirmed stability with no changes in color or physical integrity. Linezolid tablets (300 mg) were prepared using fluidized bed processing, followed by formulation trials with varied ratios of ethyl cellulose (EC), PEG 6000, and magnesium stearate to optimize tablet characteristics and drug release profiles. The formulations were analyzed for particle size, bulk and tap density, moisture content, and weight variation, all of which were within acceptable ranges. Optimization through Trial 6 matched the release profile of the reference product, achieving a similarity factor of F2 = 0.828. Stability studies of this optimized formulation (Trial 6) conducted under different storage conditions (25°C/60% RH and 40°C/75% RH for 90 days) demonstrated stability in terms of physical appearance, moisture, drug content, and drug release. Kinetic analysis indicated a first-order release with Higuchi diffusion (R^2 = 0.9734), aligning the bioequivalence of the test formulation with the reference product. This validated approach supports the use of Trial 6 as a stable and bioequivalent sustained-release formulation for linezolid.

Keywords: Linezolid, sustained-release tablets, bioavailability, in-vivo release pattern preformulation studies, drug-excipient compatibility.

I. INTRODUCTION

Drug delivery systems have long played a critical role in treating acute and chronic illnesses, traditionally utilizing dosage forms such as tablets, injectables, capsules, and creams. These systems

aim to deliver therapeutic agents to the human body effectively and safely, with modern advances allowing for the enhancement of drug bioavailability and stability. An ideal drug delivery system is characterized by two primary requisites: it releases the drug at a rate matching the therapeutic needs of the body and targets specific areas within the body. The growing demand for precision in drug delivery has paved the way for modified release technologies, which provide increased efficacy, reduced toxicity, and fewer required doses. Conventional drug delivery methods, while effective for many drugs, pose limitations when dealing with agents that are unstable, toxic, or possess narrow therapeutic windows. For these cases, continuous or modified drug administration is essential to maintain consistent plasma levels. Modified release dosage forms, including delayed and extended-release types, address these challenges. Designed to release the drug either over an extended duration or at a specific location, these systems aim to improve therapeutic outcomes while enhancing patient compliance.

In delayed-release formulations, such as enteric-coated tablets, are structured to release the drug at a predetermined location, typically beyond the stomach. This approach not only protects the active ingredient from stomach acid but also mitigates gastric irritation. These systems utilize pH-sensitive polymers, which dissolve once the dosage form passes from the acidic stomach environment to the more neutral small intestine. Intestinal and colonic release systems are typical delayed-release types used in treating localized conditions like ulcerative colitis or for systemic absorption of specific drugs.

In contrast, extended-release forms are engineered for a prolonged therapeutic effect, gradually releasing the drug to reduce dosing frequency. By minimizing the peaks and troughs in plasma drug levels, extended-release formulations improve patient convenience and safety. They also allow a reduction in dosage frequency, making them more favorable for medications requiring consistent therapeutic levels over time, such as sustained-release formulations designed for conditions requiring extended drug action.

Controlled-release drug delivery systems (CRDDS) precisely regulate the rate of drug release to maintain steady therapeutic levels, minimize side effects, and enhance drug targeting through spatial and temporal control. This controlled release can be adapted to target specific disease sites, improve bioavailability, and reduce systemic side effects. The most advanced systems even adjust to physiological needs, ensuring that drug release aligns with therapeutic requirements.

Sustained-release dosage forms are integral to controlled release, extending the therapeutic effect by gradually releasing medication over an extended period. This reduces the frequency of dosing while achieving prolonged drug action, making them ideal for medications with shorter half-lives. The key factors affecting sustained release include drug stability, solubility, and biological half-life, with innovations continuously optimizing the efficacy and safety of these dosage forms.

In recent years, sustained and controlled-release systems have garnered research attention due to their potential for improved patient compliance and minimized adverse effects. These systems, such as polymer-based drug delivery, offer significant advantages over conventional methods by enhancing drug efficacy, reducing toxicity, and providing sustained therapeutic action.

II. LITRETURE REVIEW

Basling et al. (2022) developed and evaluated an immediate-release tablet of linezolid with effective taste-masking properties. The study involved optimizing several parameters, including swelling time, resin activation, drug-resin ratio, and stirring duration, to maximize taste-masking and drug-loading efficiency. The resultant Drug-Resin Complex (DRC) was thoroughly characterized through infrared spectroscopy, thermal analysis, and X-ray diffraction. Tablets were subsequently prepared via wet granulation, incorporating PVP K-30 as a binding agent, while alginic acid NF and crospovidone were tested as superdisintegrants. The optimal disintegration time was established at 55 seconds. Notably, tablets containing alginic acid exhibited a marginally longer disintegration time than those with crospovidone, which emerged as the most effective superdisintegrant for the DRC. Crospovidone-fortified tablets demonstrated rapid disintegration, short wetting time, and favourable friability profiles (Basling et al., 2022).

Jani and Patel et al. (2023) developed a sustained-release tablet formulation that combined linezolid with Aegle marmelos, a naturally occurring antibacterial. The gum derived from Aegle marmelos, valued in pharmaceutical formulations, was used as a plant-based excipient due to its biocompatibility, biodegradability, minimal side effects, and cost-effectiveness. The formulation incorporated Aegle marmelos fruit gum with HPMC K100M to create a matrix for controlled drug release, prepared using the wet granulation technique. These tablets underwent evaluation for weight variation, hardness, diameter, physical appearance, friability, thickness, and in vitro drug release, meeting all required physical standards. Dissolution testing confirmed sustained drug release over 10–12 hours. Additionally, various polymer combinations and fillers were assessed to fine-tune drug release profiles using a 3^2 factorial design. The final formulation, combining Aegle marmelos gum

with HPMC K100M, successfully controlled drug delivery and exhibited effective antibacterial activity, positioning it as a promising option in sustained-release linezolid formulations (Jani & Patel, 2023).

III. RESEARCH METHODOLOGY

In this study, the research methodology involves a series of steps that are carefully designed to prepare, evaluate, and optimize a multiple unit mini-tablet (MT) formulation for prolonged-release and fast-release drug delivery. The following details break down each step of the process:

The formulation is made using a variety of pharmaceutical excipients including:

Microcrystalline Cellulose (MCC): A binder that ensures the adhesion of powder particles.

Sodium Alginate, Ethyl Cellulose, and HPMC K15M: Polymers used to control drug release rates.

Starch: A disintegrant, facilitating fast drug release for some mini-tablets.

Magnesium Stearate and Talc: Lubricant and glidant, respectively, to improve the compressibility and flow of the mixture.

1. Weighing and Dispensing

All excipients and active pharmaceutical ingredients (API) are precisely weighed and dispensed according to the formulation design, ensuring accuracy in drug dosage.

2. Dry Mixing

The dry mixing process ensures that the API (Linezolid in this case) and other powdered excipients are uniformly distributed in the blend. A dry blender or mixer is used to create a homogenous mixture. This step is crucial for consistency in the tablet formulation.

3. Binder Solution Preparation

A binder solution is prepared by dissolving MCC in purified water or an appropriate solvent. The concentration and viscosity of the binder solution are carefully controlled to ensure optimal granulation in the following step.

4. Wet Granulation

In this step, the dry powder mixture is granulated by adding the binder solution while mixing. The gradual addition ensures the formation of uniform granules. The granules provide improved flow properties and help in achieving better tablet compressibility.

5. Drying of Wet Granules

The wet granules are dried using either a fluid bed dryer or tray dryer. The moisture content is reduced to a specified level (typically 1-3% loss on drying) to ensure stability and prevent degradation of the formulation during storage.

6. Sizing and Milling (if needed)

Post-drying, the granules are sized and milled to ensure uniform particle size distribution. This is an important step to achieve consistent tablet weights and avoid variability in tablet properties.

7. Blend Preparation

The dried granules are blended with additional excipients such as disintegrants and lubricants. This ensures the uniformity of the final tablet blend before compression.

8. Compression

The final blend is compressed into tablets using a tablet press machine. The pressure is controlled to form tablets of the desired size, shape, and hardness.

Pre-Compression Parameters

The research also focuses on analyzing several pre-compression parameters, including:

Angle of Repose: Measured to assess powder flowability. A lower angle indicates better flow properties.

Bulk Density and Tapped Density: These parameters reflect how tightly the powder particles pack together and are used to optimize compression processes.

Carr's Index: Calculated to assess the compressibility of the powder blend. It helps evaluate flow properties and predict the tablet's uniformity.

Hausner Ratio: A ratio of tapped density to bulk density, which further helps in understanding the flowability of the powdered material.

IV. RESULT AND DISCUSSIONS

The sustained-release Linezolid tablets (300 mg) were successfully formulated and characterized to meet the required bioavailability and in-vivo release patterns. The preformulation studies included evaluating the active pharmaceutical ingredient (API) for its physical properties and solubility, with no significant changes observed in the drug-excipient compatibility studies, confirming the stability of the combinations under the given storage conditions. Particle size distribution, bulk, and tapped density assessments for all formulations showed values within the expected ranges (0.64-0.67 gm/ml for bulk density and 0.68-0.71 gm/ml for tapped density). The moisture content was also found to be within acceptable limits at around 1.04%. By modifying the quantities and ratios of ethyl cellulose

(EC), PEG 6000, and magnesium stearate in various formulations, differences in the drug release profiles were observed. Formulation 6 (Trail 6) exhibited the closest drug release profile to the reference standard, with a similarity factor (F2) of 0.828. Stability studies conducted over 90 days at two storage conditions (25°C ± 2°C / 60%RH ± 5% and 40°C ± 2°C / 75%RH ± 5%) showed that the tablets remained stable with respect to physical appearance, moisture content, drug content, and drug release.

Table 1 : Formulation Table

S.No.	Ingredient	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1.	Linezolid	300	300	300	300	300	300	300	300	300
2.	MCC	15	14	15	15	14	15	15	14	15
3.	Starch	16	10	2	16	10	2	16	10	2
4.	HPMC.K15M	7	14	21	-	-	-	-	-	-
5.	Sodium Alginate	-	-	-	7	14	21	-	-	-
6.	Ethylcellulose	-	-	-	-	-	-	7	14	21
7.	Magneticstearate	1	1	1	1	1	1	1	1	1
8.	Talc	1	1	1	1	1	1	1	1	1
9.	Purifiedwater	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
10	Totalwt.	340	340	340	340	340	340	340	340	340

Table 2: Post-compression parameter:

Formulation No.	Wt. variatio	Thicknes s(mm)	Hardness (kg/Cm^2)	Disintegration Time (min)	%Friability
F1	340±0.23	3.1±0.12	5.0±1.2	8.31±1.2	0.17±0.009
F2	342±0.31	3.2±0.2	6.5±1.3	7.42±1	0.24±0.004
F3	341±0.22	3.3±0.22	6.4±1.28	8.22±1.19	0.26±0.005
F4	343±0.35	3.2±0.2	6.3±1.27	7.53±1.0	0.17±0.007

F5	344±0.25	3.4±0.34	5.3±1.21	7.61±1.1	0.22±0.009
F6	346±0.33	3.1±0.12	6.2±1.23	8.32±1.21	0.17±0.009
F7	342±0.24	3.3±0.23	5.4±1.22	8.21±1.18	0.2±0.013
F8	345±0.36	3.1±0.12	5.5±1.25	7.12±1	0.25±0.046
F9	341±0.32	3.3±0.22	6.0±1.29	8.11±1.12	0.18±0.004

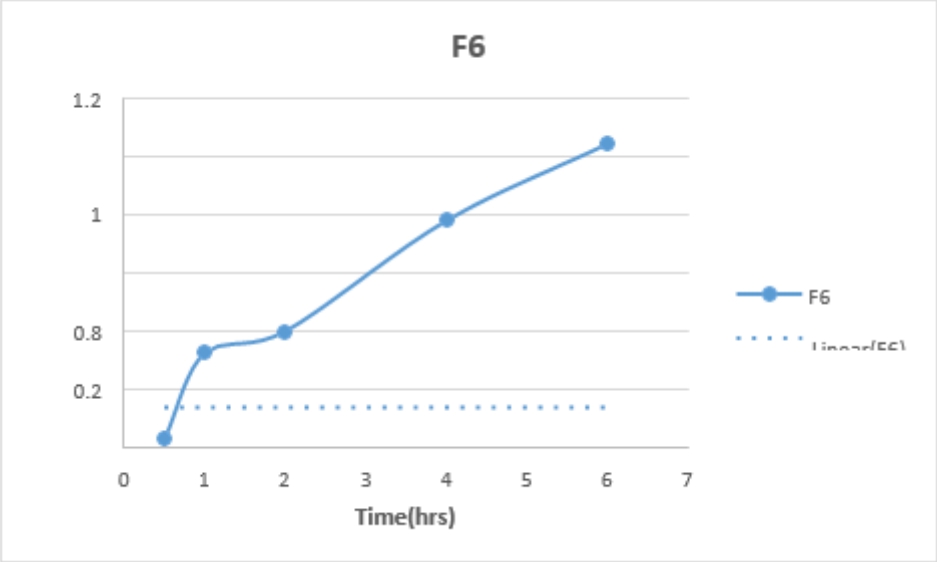

Figure: 1 Dissolution graph profile of optimized formulation F6

V. CONCLUSION

The optimized formulation F6 of sustained-release Linezolid tablets was developed using fluidized bed processing and exhibited favorable in-vitro and in-vivo release profiles. The drug release followed first-order kinetics with Higuchi diffusion (R^2 = 0.9734), making the formulation bioequivalent to the reference product. Stability studies confirmed the formulation's robustness, maintaining its quality over time under controlled environmental conditions. The development of these tablets demonstrates the potential for improved therapeutic efficacy and patient compliance through controlled drug release over a sustained period.

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