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Design Development and Evaluation of a Gastroretentive Floating Drug Delivery System of Dolutegravir for Enhanced Bioavailability

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Abstract:
The objective of this study was to formulate and evaluate a gastroretentive floating drug delivery system (GFDDS) for Dolutegravir, a potent integrase strand transfer inhibitor used in HIV therapy. Due to Dolutegravir's narrow absorption window and enhanced solubility in acidic conditions, a floating system was designed to prolong gastric residence and improve oral bioavailability. Various polymeric formulations (F1–F21) were developed using hydroxypropyl methylcellulose (HPMC) and glyceryl behenate in different drug-to-polymer ratios. The formulations were evaluated for pre-compression and post-compression characteristics including flow properties, hardness, friability, drug content, in vitro buoyancy, and dissolution profiles. The optimized formulation F7, demonstrated satisfactory physicochemical properties, floating lag time of less than one minute, and sustained buoyancy for over 12 hours. It showed a cumulative drug release of 94.32% over 12 hours, following Higuchi kinetics and non-Fickian diffusion, suggesting controlled release through a combination of diffusion and erosion. Comparative studies with marketed formulation (Tivicay) and pure drug indicated enhanced release kinetics and retention within the stomach. The compatibility between the drug and excipients was established using differential scanning calorimetry, while scanning electron microscopy revealed a consistent and homogeneous surface structure. The developed system showed significant promise as a gastroretentive platform for improving the therapeutic performance of Dolutegravir. The findings validate the potential of floating tablets as a strategy for antiretroviral drugs with limited absorption windows, thus enhancing patient compliance and therapeutic outcomes.

Key Words: *Dolutegravir, Gastroretentive Floating Drug Delivery System, Sustained Release, HPMC, Bioavailability*

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I. Introduction:

Oral administration remains the most widely adopted route for drug delivery due to its ease of use, non-invasive nature, and cost-effectiveness. Despite these advantages, challenges persist in achieving consistent therapeutic efficacy through this route, particularly when dealing with drugs that are unstable in the gastrointestinal (GI) environment or require site-specific absorption**.[1,2]** Many oral drugs suffer from limited bioavailability due to rapid gastric emptying, poor solubility at intestinal pH, enzymatic degradation, or extensive first-pass metabolism in the liver. These limitations become more pronounced in drugs with narrow absorption windows, where the therapeutic efficacy is closely tied to the site and duration of exposure within the upper gastrointestinal tract.**[3,4]**

To address these challenges, controlled and targeted drug delivery systems have been extensively explored. Among these, gastroretentive drug delivery systems (GRDDS) have gained significant attention. These systems are specifically engineered to remain buoyant or anchored in the stomach for extended periods, enabling localized and sustained release of the drug at its optimal site of absorption. Floating drug delivery systems (FDDS), a subclass of GRDDS, utilize polymers and gas-generating agents to reduce tablet density, allowing the formulation to float on gastric fluids. This approach enhances gastric retention time, reduces drug wastage in the lower intestines, and improves overall bioavailability.**[5-8]**

Dolutegravir, a potent HIV-1 integrase strand transfer inhibitor, is widely used in antiretroviral therapy. Its oral absorption is most efficient in the acidic environment of the stomach and proximal small intestine. However, conventional formulations may transit rapidly through the gastrointestinal tract, limiting the drug's absorption. Therefore, the development of a GRDDS for Dolutegravir offers a promising strategy to prolong

gastric residence, provide controlled release, and enhance therapeutic efficacy. The present research focuses on the design and evaluation of a floating matrix tablet of Dolutegravir using hydrophilic and lipophilic polymers, aimed at achieving prolonged drug release and improved bioavailability.**[9-15]**

II. Materials and Methods:

Dolutegravir was obtained as a gift sample from Lantec pharmaceuticals, Hyderabad for research purposes. Hydroxypropyl methylcellulose (HPMC) of varying viscosity grades, including HPMC K4M and K15M, was procured from Colorcon Asia Pvt. Ltd. Glyceryl behenate (Compritol® 888 ATO), a hydrophobic matrix-forming lipid, was sourced from Gattefossé India Pvt. Ltd. Citric acid anhydrous and sodium bicarbonate, used as gas-generating agents to facilitate buoyancy, were purchased from S.D. Fine-Chem Ltd., Mumbai. Microcrystalline cellulose (MCC) PH 102, serving as a diluent and flow aid, was obtained from FMC Biopolymer. All chemicals and reagents employed in the study were of analytical grade and utilized in their original form, without undergoing any additional purification processes.**[16,17]**

The optimized formulation (F7) of the gastroretentive floating tablet of Dolutegravir was composed of the following ingredients per tablet: 150 mg of Dolutegravir as the active pharmaceutical ingredient and 150 mg of Gelucire 43/01 (Hard Fat) as the primary polymer used for matrix formation. To facilitate buoyancy, 15 mg of citric acid and 30 mg of sodium bicarbonate were incorporated as gas-generating agents. Additionally, 50 mg of microcrystalline cellulose (MCC) PH 102 was included as a filler and to aid in compressibility. The total weight of each tablet was 395 mg. Floating tablets of Dolutegravir were developed by direct compression method. Appropriate quantities of Dolutegravir, polymer (HPMC), lipid (glyceryl behenate), gas-generating agents (citric acid and sodium bicarbonate), and MCC were accurately weighed and blended in a mortar and pestle to ensure uniform mixing. **[18,19]** The homogeneous powder blend was passed through a #40 mesh sieve and then compressed using a rotary tablet compression machine equipped with flat-faced punches. Tablet weight and hardness were maintained consistently across batches to ensure uniformity.To assess the flow characteristics and compaction behavior of the formulation prior to compression, key pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose were determined.**[20-25]**

After formulation, the prepared multi-unit granules were subjected to a series of post-compression evaluations to ensure their functional and pharmaceutical performance. Buoyancy characteristics were investigated using 0.1 N hydrochloric acid (pH 1.2) maintained at $37 \pm 0.5°C$ to simulate gastric conditions. Each formulation was tested for floating lag time, defined as the time taken for the dosage unit to rise to the surface, and total floating duration, which indicates how long the formulation remained buoyant on the medium.**[26-29]**

In vitro release profiling of the formulation was conducted utilizing a USP Type II (paddle) dissolution apparatus (Model: Disso 2000, LabIndia). A dissolution medium consisting of 900 mL of 0.1 N hydrochloric acid was used, maintained at $37 \pm 0.5°C$ to simulate physiological conditions, and stirred at 50 rpm. At defined time points, 5 mL aliquots were collected using a syringe fitted with a filter and promptly replenished with an equal volume of fresh medium to preserve sink conditions. The collected samples were suitably diluted and analyzed at 266 nm using a Cyberlab UV-Vis spectrophotometer to quantify the cumulative drug release.**[30,31]**

To understand the release mechanism, the drug release profiles were analyzed using different kinetic models such as zero-order, first-order, Higuchi, and the Korsmeyer-Peppas equation. Compatibility between the drug and excipients was assessed using Differential Scanning Calorimetry (DSC), which provided thermal behavior insights. **[33]**Additionally, the surface texture and internal architecture of the optimized formulations were studied through Scanning Electron Microscopy (SEM), aiding in the evaluation of matrix uniformity and porosity.**[33]**

III. Results and Discussion:

The present study aimed to formulate a gastroretentive floating drug delivery system (GFDDS) of Dolutegravir using various lipid-based polymers through different granulation techniques and evaluate their suitability based on physicochemical, in vitro buoyancy, and drug release characteristics. A total of 21 formulations (F1–F21) were prepared using three drug-to-polymer ratios (1:1, 1:1.5, and 1:2), and the optimized formulation was identified as F7.**[34-37]**

In the present study, the calibration curve of Dolutegravir was established at a wavelength of 266 nm using UV-Visible spectrophotometry in 0.1 N HCl as the medium. A series of standard solutions with concentrations ranging from 5 to 25 µg/mL were prepared and analyzed. The absorbance values were recorded and plotted against the respective concentrations, resulting in a linear regression curve with a high correlation coefficient ($R^2 = 0.999$), indicating excellent linearity. This calibration curve was used for the quantification of drug content and in vitro dissolution samples throughout the study. **(Fig-1) [38]**

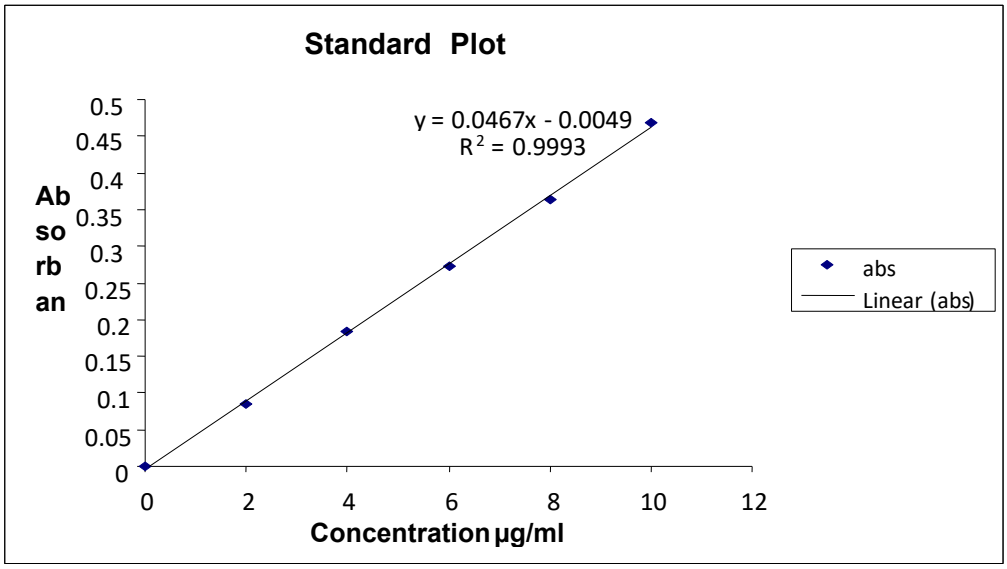

Figure-1: Calibration Curve of Dolutegravir at 266 nm.

Drug Content and Flow Properties: All formulations (F1–F21) were evaluated for drug content uniformity. The percentage of Dolutegravir in each formulation was within the acceptable range of ±5%, with F7 showing 98.64% content, indicating high accuracy and reproducibility in the formulation process. Flow properties, including Carr's index, Hausner ratio, and angle of repose, were assessed for the granules. While cellulose-based formulations exhibited superior flow characteristics, lipid-based formulations, including F7, maintained acceptable flowability, with F7 showing a Carr's index of 18.6%, Hausner ratio of 1.32, and angle of repose of 32.8°.**[39]**

In Vitro Buoyancy Behavior: The buoyancy of all formulations was tested in 0.1 N HCl. Formulation F7 showed an immediate floating onset (lag time = 0 min) and sustained floatation for more than 12 hours. Unlike cellulose-based systems (F1, F2, F8, F9, F15, F16), which exhibited measurable lag times due to hydrogel formation, lipid-based systems like F7 showed spontaneous buoyancy. Some lipid-based systems exhibited sedimentation issues; however, F7 remained buoyant throughout the test period without disintegration or sinkage.**[40]**

In Vitro Drug Release Studies: The release profile of Dolutegravir from all formulations was determined using USP Type II apparatus in 0.1 N HCl. Among the 1:1 ratio formulation, F7 exhibited the most controlled release profile, with 98.96% cumulative drug release over 12 hours. Formulations F1 and F2 released over 94% within 5–6 hours, while F3–F6 showed varied release durations between 4 and 10 hours. (Fig-2) The extended release from F7 was attributed to the hydrophobic matrix formed by Gelucire 43/01, which slowed down the drug diffusion and maintained buoyancy.**[41]**

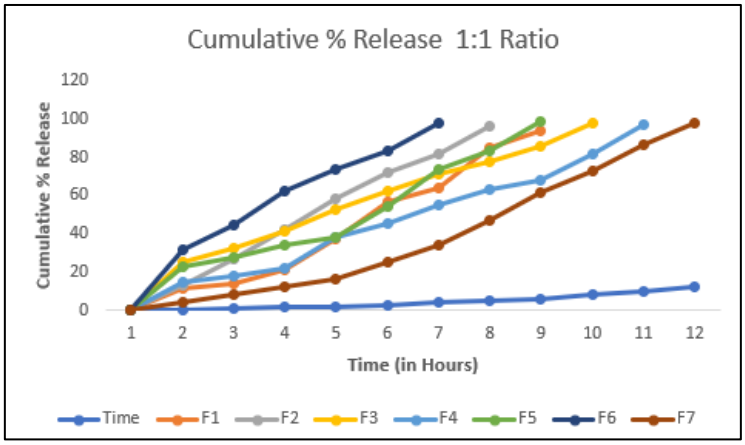

Figure-2: Comparative Dissolution profiles of Formulations F1-F7

The dissolution profile of F7 was compared against a single-unit GFDDS (drug: polymer 1:3), pure Dolutegravir, and the marketed formulation TIVICAY. The single-unit formulation released ~81% drug in 12 hours, whereas the pure drug and TIVICAY released over 93% and 97% within 30 minutes and 1 hour,

respectively. F7 demonstrated a more gradual and controlled release, making it preferable for sustained plasma levels.**(Fig-3) [42]**

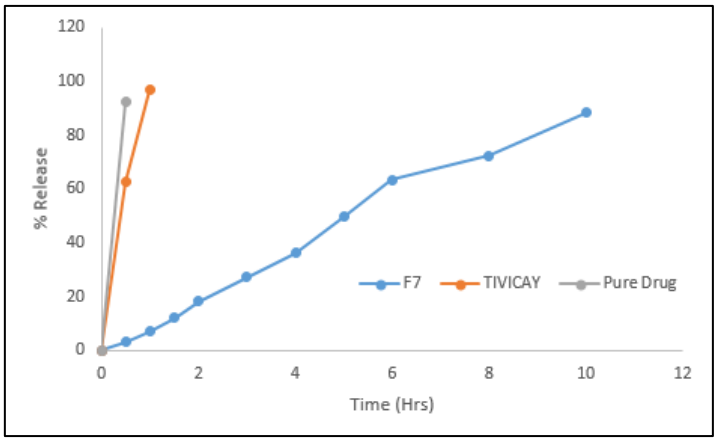

Figure-3: Comparative Dissolution Profiles of Formulations F7, TIVICAY and Pure Drug

Drug Release Kinetics: To elucidate the release mechanism, dissolution data were fitted into zero-order, first-order, Higuchi, erosion, and Korsmeyer-Peppas models. F7 exhibited a higher correlation coefficient (R^2 = 0.995) with the zero-order model, suggesting constant drug release over time. Additionally, the Peppas exponent (n > 1) indicated super case-II transport, pointing toward polymer swelling and erosion contributing to the controlled release mechanism. **[43]**

Drug-Polymer Compatibility (DSC & SEM Studies): To evaluate the interaction and compatibility between Dolutegravir and Gelucire 43/01, thermal and spectroscopic analyses were carried out using Differential Scanning Calorimetry (DSC) and Fourier-transform infrared (FTIR) spectroscopy. The DSC thermograms of the physical mixture and optimized formulation exhibited no significant shift in endothermic peaks compared to the pure drug, indicating no interaction. SEM images of the optimized formulation revealed uniform dispersion of lipid material and consistent surface morphology. Ageing studies confirmed the physical and thermal stability of the optimized system over time.**[44-46]**

IV. Conclusion:

A gastroretentive floating tablet of Dolutegravir was successfully formulated using Hard Fat (Gelucire 43/01) as the matrix-forming agent through melt granulation. The optimized formulation (F7) demonstrated immediate buoyancy, prolonged floating duration exceeding 12 hours, and a controlled drug release profile sustained over the same period. This system offers significant potential to enhance the oral bioavailability of Dolutegravir by retaining the drug in the upper gastrointestinal tract, where its absorption is most efficient. Compared to conventional formulations, this gastroretentive approach minimizes fluctuations in plasma drug levels and may contribute to improved therapeutic outcomes in antiretroviral therapy. The study confirms the suitability of lipid-based floating systems for drugs with limited solubility in intestinal pH and narrow absorption windows. Future research should include in vivo pharmacokinetic studies, long-term stability evaluation, and clinical validation. Additionally, this formulation concept may be extended to other antiretrovirals or similar drugs, offering a platform for targeted delivery and enhanced patient adherence.

Conflict of Interest: The Authors declare no conflict of interest.

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