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ADVANCEMENTS IN LIQUID DOSAGE FORMS: NANOTECHNOLOGY, ARTIFICIAL INTELLIGENCE, AND INNOVATIVE DELIVERY DEVICES

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ABSTRACT

This document provides an in-depth overview of liquid dosage forms (LDFs), including their classification, benefits, and drawbacks, as well as the revolutionary impact of modern technologies on their development and delivery. LDFs are classified as either monophasic (e.g., syrups, elixirs) or biphasic (e.g., suspensions, emulsions). While they offer advantages like ease of swallowing and flexible dosing, they face challenges such as taste issues and potential instability. The document highlights the crucial role of nanotechnology in creating Nanosuspensions and Nanoemulsions, which are designed to enhance the bioavailability and stability of poorly water-soluble drugs. Furthermore, it explores how Artificial Intelligence is accelerating development through predictive modeling and optimization. Finally, the article delves into advanced delivery devices, such as Pressurized Olfactory Devices (PODs) and Micro-Electro-Mechanical Systems (MEMS), and 3D printing for creating personalized liquid medications, all of which improve patient compliance and therapeutic outcomes.

KEYWORDS: Liquid Dosage Forms, Patient Compliance, pediatric patients.

INTRODUCTION

Liquid dosage forms are pharmaceutical preparations where an active drug is combined with non-active components such as solvents and additives to create a liquid medication. They are often classified into **monophasic** and **biphasic** formulations, with several dosage forms within each of these major groups. Monophasic liquids contain only one phase (e.g., syrups, elixirs, linctus's, etc.), while biphasic liquids are characterized by the presence of two distinct phases within the formulation (e.g., suspension, emulsion).

While liquid oral dosage forms offer advantages such as **dose flexibility** and **ease of swallowing** for children, they may require ingredients (excipients) that are not child-friendly, such as alcohol, artificial sweeteners, or certain preservatives, due to safety concerns or potential adverse effects.

Modern technological advancements, such as **Artificial Intelligence (AI)**, are transforming drug product development by converting scientific knowledge into new drug products. AI technologies integrate diverse data sources across various stages of the drug development pipeline to develop intelligent and efficient methods, boosting success rates by enabling faster, accurate, and more efficient drug discovery and development.

Figure 2: Classification of liquid oral dosage form.

ADVANTAGES OF LIQUID ORALS

1. **Ease of administration:** Oral specifics are simple to administer compared to other routes and are accessible for self-administration without technical outfit or professional backing.

1. **Accurate lozenge:** They allow for precise and accurate dosing, as specifics can be prepared in specific strengths and easily measured using calibrated bias such as hype, measuring mugs, or droppers.
1. **Self-drug:** Oral specifics are well-suited for self-medication, empowering patients to manage their health and treatment.
1. **Pain avoidance:** Oral drug delivery is effortless and non-invasive, a system preferred by many patients over painful routes like injections or intravenous infusions.
1. **Patient compliance:** The ease and convenience contribute to advanced patient compliance, as cases are more likely to cleave to their specified drug rules.
1. **Cost-effective:** Oral specifics are generally more cost-effective, often available in general forms, and their manufacturing and packaging are typically less complex and expensive.

DISADVANTAGES OF LIQUID ORALS

1. **Instability:** Liquids may lack the structural integrity of solid forms, making them more susceptible to damage and declination.
1. **Formulation challenges:** Developing controlled-release phrasings and ensuring patient compliance can be challenging.
1. **Taste issues:** The unwelcome taste of certain specifics in liquid form can be grueling, particularly for paediatric and senior cases.
1. **Excipient safety:** Liquid specifics may require excipients with unknown safety biographies, which could raise concerns.

MATERIALS AND METHODS

- *Note: This section combines "Nanotechnology in liquid dosage forms," "Artificial intelligence (AI)," and "Advanced drug delivery devices" to align with the journal's **Materials and Methods** requirements for describing new/modified procedures and technologies.*

NANOTECHNOLOGY IN LIQUID DOSAGE FORMS

Nanotechnology in liquid dosage forms, known as **Nano pharmaceuticals**, uses tiny particles to improve the delivery and effectiveness of drugs, especially poorly water-soluble compounds. Common types include **Nano suspensions, Nano emulsions, and lipid nanoparticles (LNPs)**, which can be administered orally, intravenously, or topically.

Key Types of Nanotech Liquid Formulations

- **Nano suspensions:** These are colloidal dispersions of **pure drug nanoparticles** (10 to 1000 nm) suspended in a liquid medium and stabilized by surfactants or polymers. The size reduction significantly increases the total surface area, which enhances the **dissolution rate, saturation solubility, and ultimately, the bioavailability** of poorly water-soluble drugs.
  - **Preparation:** Nano suspensions are typically produced using **top-down technologies** (disintegration) or **bottom-up technologies** (nanoprecipitation).
  - **Top-down technologies** (for industrial production) include **Media milling** (wet ball milling) and **High-Pressure Homogenization (HPH)**.
  - **Bottom-up technologies** (building from the molecular level) include **Anti-solvent precipitation**, **Emulsion solvent evaporation**, **Melt emulsification**, and **Flash Nanoprecipitation (FNP)**.**P)**.
  - **Applications:** Nano suspensions are used to improve the absorption of poorly soluble drugs (Oral), provide a high drug load for intravenous injection (Parenteral), and enhance penetration in the lungs (Pulmonary), eyes (Ocular), and skin (Dermal).
  - **Nano emulsions:** These are nanosized liquid dispersions of oil and water stabilized by surfactants, with a droplet size typically in the range of **20 to 500 nm**. Unlike microemulsions, nanoemulsions are **kinetically stable** and require energy input to form.
  - **Types:** They are categorized as **Oil-in-water (O/W)** (oil droplets in aqueous phase), **Water-in-oil (W/O)** (water droplets in oily phase), and **Multiple (W/O/W)** emulsions.
  - **Preparation:** They are prepared using **High-energy methods** (HPH, Micro fluidization, Ultra sonication) or **Low-energy methods** (Phase Inversion Temperature [PIT], Phase Inversion Composition [PIC], Spontaneous Emulsification).
  - **Advantages:** They offer **Enhanced Bioavailability**, **Increased Stability** (resisting creaming/flocculation), **Protection of Active Ingredients**, and potential for **Targeted Delivery**.
  - **Self-Emulsifying Drug Delivery Systems (SMEDDS/SNEDDS):** Lipid-based formulations that spontaneously form a fine emulsion or Nano emulsion upon contact with gastrointestinal fluids, significantly enhancing the absorption of hydrophobic drugs.
  - **In-Situ Gel-Forming Systems:** Liquid formulations that transform into a gel once administered, triggered by changes in \text{pH} or temperature, enabling prolonged and controlled release of medication.

ARTIFICIAL INTELLIGENCE (AI) IN FORMULATION

AI, leveraging **Machine Learning (ML)** and **Deep Learning** models, is accelerating development by reducing the reliance on traditional trial-and-error methods.

Predictive Modeling for Formulation Design

- **Solubility and Stability Prediction:** AI models, such as **Artificial Neural Networks (ANNs)**,

analyze large datasets to predict drug solubility in different solvent systems and forecast stability under various conditions.

- **Drug-Excipient Compatibility:** Platforms use ML and ANNs to predict the risk of incompatibility between a drug and its excipients, allowing formulators to select the most compatible and stable ingredients early in development.
- **Nanoparticle Design:** AI optimizes complex formulation parameters (e.g., surfactant concentration, energy input) in systems like nanoemulsions to achieve the desired particle size and stability.
- **Personalized Medicine:** AI algorithms analyze patient-specific data to design customized liquid therapies, such as developing dose prediction algorithms for immunosuppressant's in pediatric patients.

Manufacturing Process Optimization

AI works with **Process Analytical Technology (PAT)** to enable real-time monitoring and control.

- **Real-time Quality Control:** AI-integrated systems monitor processes (e.g., mixing, filling) to detect anomalies, ensuring each batch meets quality specifications and minimizing variation.
- **Automated and Continuous Manufacturing:** Robotics, powered by AI, perform high-precision tasks like mixing and filling in aseptic environments, boosting throughput and ensuring sterility.
- **Process Parameter Optimization:** AI uses reinforcement learning to dynamically adjust critical parameters (e.g., mixer rotor speed) in real-time for optimal quality results.

ADVANCED DRUG DELIVERY DEVICES

Innovations in devices improve targeting, precision, and patient compliance.

- **Pressurized Olfactory Devices (PODs):** These are nasal drug delivery systems that use propellant to deliver a targeted spray to the **upper nasal space (UNS)** or olfactory region.
- **Mechanism:** They overcome the limitations of traditional nasal sprays by creating a narrow, focused spray plume that displaces air and deposits medication directly onto the olfactory epithelium.
- **Advantage:** This enables **rapid, direct nose-to-brain delivery**, potentially bypassing the **blood-brain barrier (BBB)** for treating Central Nervous System (CNS) disorders.
- **Application:** Approved for the acute treatment of migraine (e.g., INP104-TRUDHESA).
- **Micro-Electro-Mechanical Systems (MEMS):** These miniaturized devices combine mechanical, electrical, and fluidic components on a microscopic scale, creating sophisticated drug delivery systems.
- **Components:** They consist of **micropumps** (e.g., piezoelectric, electrochemical), **micro reservoirs**, **microvalves**, and integrated **biosensors** that can trigger drug release in a "closed-loop" system.
- **Application:** Used for **implantable devices** for continuous delivery (e.g., insulin), **transdermal delivery** with hollow microneedles, and **localized chemotherapy**.
- **Advantage:** MEMS enable **ultra-precise, controlled dosing** in nanolitres to microliters and facilitate **targeted delivery**.
- **3D Printing for Liquid Encapsulation:** Additive manufacturing creates personalized dosage forms that can encapsulate liquid fills within a solid matrix.
- **Methods:** Common methods include **Extrusion-based printing** (e.g., Dual-head Fused Deposition Modelling [FDM] to print and fill a shell) and **Material jetting** (depositing liquid droplets).
- **Advantage:** This allows for **personalized dosing**, the creation of **polypills** (single tablets with multiple drugs), and customized, complex **release profiles** (pulsatile, sustained).d).

RESULTS AND DISCUSSION

The shift from traditional monophasic and biphasic oral liquids to advanced formulations is driven by the need to overcome challenges such as chemical instability, poor patient compliance (due to taste), and limited bioavailability of new drug compounds.

Impact of Nanotechnology: The discussion of Nano suspensions and Nano emulsions clearly illustrates that reducing particle size to the nanoscale is a highly effective strategy for solving the **bioavailability crisis** of poorly water-soluble drugs. The methods of preparation, especially the contrast between high-energy (HPH) and low-energy (PIT) methods for Nano emulsions, highlight the engineering complexity required to achieve stability in these kinetically-driven systems. Furthermore, the evolution of Lipid Nanoparticles (LNPs) from Solid Lipid Nanoparticles (SLNs) to Nanostructured Lipid Carriers (NLCs) demonstrates a continuous effort to improve drug loading and overcome issues like drug expulsion. The challenge of **physical stability** (aggregation, Ostwald ripening) in nanotech, however, remains a persistent concern that requires complex stabilizer optimization and solidification techniques.

Role of Artificial Intelligence: The integration of AI represents a fundamental change from empirical "trial-and-error" to a predictive, data-driven approach. The use of ANNs to predict **drug solubility** and **excipient compatibility** effectively streamlines the pre-formulation phase. In manufacturing, AI's ability to facilitate **real-time quality control** and **predictive maintenance** via PAT and IoT sensors addresses issues of batch-to-batch inconsistency inherent in complex liquid manufacturing processes. Crucially, AI's role in **Physiologically Based Pharmacokinetic (PBPK) modelling** allows for the simulation of ADME (Absorption, Distribution, Metabolism, and Excretion), making it a powerful tool for predicting optimal dosing for special populations, particularly **pediatric patients**,

who are often considered "therapeutic orphans" in clinical trials.

Revolution in Delivery Devices: Advanced devices like **PODs** and **MEMS** are transforming the administration of liquid drugs. The POD's success in targeting the olfactory region to **bypass the BBB** for rapid CNS delivery (e.g., DHE for migraine) is a significant clinical breakthrough. Similarly, MEMS devices, with their capability for ultra-precise dosing via micropumps and valves, are paving the way for truly **personalized medicine** through automated, implantable systems. Finally, 3D printing enables the creation of complex dosage forms like **polypills** with customized release profiles, directly tackling the issue of **patient non-adherence** to complex regimens.

CONCLUSION

The evolution of liquid dosage forms is defined by the strategic adoption of advanced technologies to overcome the stability, bioavailability, and administration challenges of traditional systems. **Nanotechnology** has fundamentally enhanced drug performance by improving the dissolution and absorption of poorly soluble drugs through particle size reduction and encapsulation. **Artificial Intelligence** has proven transformative by accelerating the drug development pipeline through predictive modeling, real-time quality control, and the creation of highly customized, personalized liquid therapeutics. Furthermore, innovative **advanced delivery devices** like **PODs**, **MEMS**, and **3D printing** are revolutionizing drug administration, enabling targeted delivery to the central nervous system and localized, precise dosing, thereby maximizing efficacy and improving patient compliance. The convergence of these technologies is shifting the pharmaceutical paradigm toward a new era of highly efficient and patient-centric liquid medication.

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