Mechanistic Evaluation of Monoterpene Release from Nanocarriers: An Assessment of Kinetic Models

Soroor Sadegh Malvajerd
Nano Drug Delivery Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

Kermanshah University of Medical Sciences

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Introduction

Monoterpenes constitute an important group of natural terpenoids made up of two isoprene units ($C_{10}H_{16}$) and are abundantly distributed in the essential oils of many aromatic plants. Their notable lipophilic nature, volatility, and ability to penetrate cellular membranes allow them to interact effectively with intracellular targets, resulting in a wide range of therapeutic effects. Owing to these characteristics, monoterpenes have gained extensive scientific interest for their broad pharmacological activities, including anti-inflammatory, antimicrobial, anticancer, and neuroprotective properties. Despite therapeutic potentials, their clinical translation has been hampered by inherent limitations such as low water solubility, instability, limited bioavailability, high volatility, and sensitivity to light, heat, and oxygen. To overcome these barriers, nanotechnology-based drug delivery systems have emerged as a promising strategy to improve the stability, solubility, and targeted delivery of monoterpenes. These formulations not only enhance pharmacokinetic performance but also allow controlled and sustained release. However, while numerous studies have reported on the encapsulation efficiency, stability, and biological performance of nanoformulated monoterpenes, relatively few have addressed the fundamental mechanisms governing their release from nanocarriers. The release kinetics of monoterpenes are crucial because they determine drug availability at the target site and ultimately dictate pharmacological outcomes. Drug release behavior represents a critical determinant of reproducibilityand quality control in nanocarrier-based systems, forming the scientific basis for their rational development.

Methods

A comprehensive literature survey was conducted to identify studies reporting the release kinetics of monoterpenes from nanocarrier-based delivery systems. Eligible datasets were selected following a rigorous screening process, emphasizing studies that evaluated release behavior under physiologically relevant conditions. The final dataset integrates a broad spectrum of monoterpenes—including carvacrol, cineole, linalool, thymol, α-pinene,limonene, sabinene, citral, and geraniol—

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encapsulated within diverse nanocarrier architectures such as chitosan, polymeric nanoparticles, dextrin matrices, liposomes, niosomes, Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), invasomes, and zein-based nanoparticles. The selected datasets were subsequently subjected to cross-comparative kinetic modeling using multiple classical release models, which details the physicochemical characteristics and experimental conditions associated with each formulation. Hese datasets were subsequently subjected to statistical and kinetic modeling analyses. To describe and analyze the release kinetics, eight classical mathematical models—such as zero-order, firstorder, Higuchi, and Hixson–Crowell Each model is presented with its corresponding equation, assumptions, and key parameters. Regression analyses were conducted to identify the most appropriate fitting model. To evaluate model performance, classical statistical parameters were calculated, including the sum of squares due to regression (SSR), the sum of squares due to errors (SSE), the total sum of squares (SST), and the coefficient of determination (R2). In this context, SSE serves as a key indicator of model accuracy, defined as the cumulative squared difference between experimentally observed and model-predicted values. A lower SSE indicates a closer agreement between predicted and actual data, thereby reflecting superior goodness-of-fit. Since SSE alone does not fully capture model performance, it was interpreted in conjunction with SSR, SST, and R2 to provide a more comprehensive assessment of the release kinetics. URFI computation proceeds through three sequential stages: extraction of kinetic performance metrics, robust percentilebased normalization, and weighted composite scoring. Across each dataset, URFI is calculated and ranked.

Results

A total of 30 datasets compiled from peer-reviewed publications were analyzed, each describing the release behavior of distinct monoterpenes from nanocarrier-based formulations. To ensure data reliability, only studies indexed in reputable scientific databases were included. Table I provides a comprehensive summary of formulation and experimental parameters for each dataset, including the type of monoterpene, nanocarrier system, particle size, and total duration of release testing. Nanoemulsions and polymeric nanoparticles were the most frequently utilized carrier systems, followed by SLNs and liposomes. Most formulations exhibited particle sizes within the 100–250 nm range, with predominantly spherical morphology. Release studies were typically performed in aqueous or buffer media with pH values in the range of 6.8–7.4, while the temperature was controlled within the range of 25–40°C. Considerable variability in release duration was observed, spanning from less than 24 h to more than 30 days, reflecting differences in formulation composition, stability, and experimental design. To further facilitate comparison, we applied the URFI, a composite measure integrating variance-based and error-based metrics into a single score. Higher URFI values corresponded to models with desirable characteristics: R2 values approaching unity, low SSE and error percentages, and high proportions of data points falling within acceptable error thresholds. The URFI results and the best-fitting release model identified for each dataset. While no single kinetic model provided a universal description of release behavior, the Weibull and Korsmeyer–Peppas models emerged as the most frequently superior, capturing both immediate and sustained release dynamics across a broad range of nanocarrier systems and monoterpenes.

Conclusions

This study provides the first systematic evaluation of monoterpene release from nanocarriers using a unified statistical framework. By extracting and analyzing 30 datasets from peer-reviewed studies, we compared eight classical kinetic models and introduced the URFI as a composite metric that integrates multiple goodness-of-fit and errorbased parameters. This approach enabled reproducible and transparent model comparisons, overcoming limitations of conventional single-metric evaluations. Our findings highlight the Weibull model as the predominant descriptor of release kinetics across diverse nanocarrier systems, including liposomes, SLNs, and polymeric matrices. Its empirical flexibility, particularly through the shape parameter (β), allowed it to capture biphasic release behaviors and bridge. empirical fitting with mechanistic interpretation. Nevertheless, formulation-specific deviations emphasized the importance of complementary models such as Korsmeyer–Peppas and Higuchi, especially in hydrophilic or swelling-dominated systems.