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# Release kinetics of highly porous floating tablets containing cilostazol

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ABSTRACT

This study focuses on developing a highly porous floating tablet containing cilostazol. The underlying release mechanism of cilostazol from porous and floating tablets in dissolution media containing surfactants was investigated. The tablets were prepared by compressing granules and excipients with a subliming agent, followed by sublimation under vacuum. The volatile material for the subliming agent was chosen based on its flow properties using conventional methods as well as the twisted blade method. Resultant tablets could float immediately and had significantly higher tensile strengths than conventional tablets of similar porosities, holding a promising potential for increasing gastroretentive properties. Fitting the release profiles to the Korsmeyer-Peppas equation indicated Super Case II, Case II and non-Fickian kinetics, which implied that the release was affected by both floating behavior and matrix erosion. Abrupt changes in release kinetic parameters and erosional behaviors were found between the tablets containing different amounts of HPMC, indicating the existence of an excipient percolation threshold. Neither the surfactant in the media nor the porosity affected the dominant release mechanism, which was matrix erosion. Understanding the dominant release mechanism and percolation threshold allows for tuning the formulation to obtain various release profiles.



## 1. Introduction

The gastroretentive drug delivery system refers to a dosage form that can prolong the gastric emptying time of a drug. One of the most practical and promising mechanisms in achieving gastroretention is flotation. It can prolong gastric retention time by causing the dosage form, which has a lower density than that of gastric fluid, to float. Previously, studies on novel floating dosage forms have shown promising results [1]. However, most of the dosage forms developed were gas-generating systems, which had inherent problems of either long floating lag time or short floating duration [2–4]. This was caused by the contradictory effects of the gas-generating agent and the swellable polymer on water diffusion into the matrix and on matrix integrity [5].

Some studies were successful in eliminating the floating lag time of their tablets. This was made possible by incorporating low-density excipients such as polypropylene foam powder [6,7], calcium silicate [8], and lipid materials [9] into the formulations. However, polypropylene foam powder is not yet approved by the FDA, and an excessive amount of calcium silicate or lipid material was required (3–10 times the weight of the drug), limiting the versatile use of these materials. Furthermore, it has been reported that the complexity of floating dosage forms (e.g., gas-generating agents) hinders the straightforward relationship between release kinetics and formulation variables [5].

Recently, a highly porous tablet was prepared by sublimation [10]. This floating tablet was novel in that it had no floating lag time while maintaining a long floating duration time. This was enabled by including volatile materials or subliming agents such as L-menthol or DL-camphor in the formulations, which generated pores after their sublimation. Consequently, the density of the tablet was sufficiently low to allow immediate buoyancy on dissolution media while maintaining physical integrity by excluding gas-generating agents in the formulation. This type of floating tablet has also eliminated potential health risks as the subliming agents can be removed from the tablet by sublimation. It was previously reported that the amount of residual subliming agent was well below the permissible dose set by regulatory agencies [11].

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However, volatile materials such as menthol or camphor are not commonly used in conventional sustained-release tablets. Accordingly, it is essential to assess the critical aspects of these excipients for successful scale-up and commercialization. Considering that these volatile materials are eliminated after sublimation, the most important aspect is their flow properties, as poor flow and agglomeration may lead to segregation and poor dose uniformity.

Cilostazol is a quinolinone derivative and inhibits phosphodiesterase type 3 (PDE-3), which is predominantly distributed to and regulates physiological responses in platelets. Clinically, it is well known as an anti-platelet agent that inhibits platelet aggregation. However, cilostazol has adverse effects such as severe headaches, assumed to be caused by high concentrations in the blood [12]. On the other hand, some studies show that the absorption site of cilostazol is limited to the upper part of the small intestine [13], which challenges a successful development of a sustained release dosage form. Therefore, cilostazol was chosen as a model drug for the proposed gastroretentive tablet in this study.

Another distinctive property of cilostazol is its low solubility [14]. However, only a few studies have investigated release kinetics of surfactant-mediated dissolution [15,16]. Further, previous studies of floating porous matrices have only focused on hydrophilic drugs or solid dispersions of hydrophobic drugs [10,11]. To our knowledge, this is the first study investigating release kinetics of a very hydrophobic drug from swellable and highly porous matrices, although there have been many studies covering release kinetics of floating tablets.

Recently, percolation theory was applied to pharmaceutical dosage forms, which has generated a considerable research interest [17–19]. One of the most important parameters in percolation theory is percolation threshold. It is a critical concentration point above which a infinite percolating cluster or a continuous phase may be formed. However, previous studies have only concentrated on identifying the percolation threshold of soluble drugs with different hydrophilicities, and there remains a need for investigating the percolation threshold of water insoluble drugs.

The purposes of this study were to prepare highly porous sustained-release cilostazol gastroretentive tablets by using the sublimation method and to investigate their release kinetics. Therefore, the effects of hydroxypropyl methylcellulose (HPMC) content, porosity, and surfactant concentration in dissolution media on release kinetics were observed. Excipient percolation threshold was also identified by comparing release kinetics and erosion profiles. In addition, suitable volatile material for a subliming agent was selected by comparing flow properties. Cilostazol was selected as a model drug not only because of its clinical necessity for a sustained release dosage form but also because of its insoluble property to identify the important factors in determining the release profile of a hydrophobic drug.

## 2. Materials and methods

### 2.1. Materials

Cilostazol (Hangzhou Pharma & Chem Co., Ltd., Hangzhou, China; solubility in water at 37 °C, 4.6 ± 0.3 μg/mL), hydroxypropyl cellulose (HPC) (Klucel® LF, Ashland, Inc., Covington, KY, USA), HPMC (Metolose® 65SH-4000, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan), L-menthol (Sigma-Aldrich, St. Louis, MO, USA), DL-camphor (Junsei chemical Co. Ltd., Tokyo, Japan), microcrystalline cellulose (MCC) (Avicel® PH 102, FMC BioPolymer, Philadelphia, PA, USA), magnesium stearate (Acros Organics, Geel, Belgium), ethanol (95%) (J.T. Baker Ltd., Phillipsburg, NJ, USA), and sodium lauryl sulfate (SLS, Sigma-Aldrich, St. Louis, MO, USA) were used in this study. All other ingredients, reagents, and solvents used in this study were of analytical grade.

### 2.2. Methods

#### 2.2.1. Particle size analysis of camphor, menthol and representative formulations

Volatile materials and their representative formulations (formulation A8-1 in Table 1 with either camphor or menthol) were analyzed for their particle size distribution using the laser diffraction particle sizing technique (Mastersizer 2000, Malvern Instruments Ltd., Malvern, UK). Camphor and menthol were provided from the manufacturers as large agglomerates or crystals, which were unsuitable for mixing and tableting. Therefore, menthol crystals were passed through a 500-μm aperture size stainless steel mesh screen by using an oscillating granulator (AR400, Erweka, Heusenstamm, Germany). On the contrary, camphor could not be sieved due to softening and adhesion to screen upon applying pressure, blocking the sieve aperture. Therefore, camphor was milled using a hammer mill (LM-05, Dalton Co. Ltd., Tokyo, Japan) at 12,000 rpm. Volume, weighted mean size (d[4,3]), surface-weighted mean size (d[3,2]), and size distribution width (span = (Dv0.9 − Dv0.1)/Dv0.5) were evaluated in this study [20].

#### 2.2.2. Flow properties of camphor, menthol and representative formulations

Compressibility index, Hausner ratio, and angle of repose for volatile materials and their representative formulations were identified as indicated in the USP38/NF33 general information for powder flow. Unsettled apparent volume ($V_0$), final tapped volume ($V_f$), tapped density ($\rho_{tapped}$), and bulk density ($\rho_{bulk}$) were used to calculate the following equations [21]:

$$\text{Compressibility index } (\%) = \frac{V_0 - V_f}{V_0} \times 100 = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \times 100 \quad (1)$$

$$\text{Hausner ratio} = \frac{V_0}{V_f} = \frac{\rho_{tapped}}{\rho_{bulk}} \quad (2)$$

Additionally, the twisted blade method using an automated powder rheometer (FT4, Freeman Technology Ltd., Tewkesbury, UK) was conducted to identify various parameters representing flow properties of sublimating agents. Briefly, a sample quantity of 160 mL was placed in a 50 mm inner diameter borosilicate cylindrical vessel. Before the actual measurement, the powder was 'preconditioned' by downward/upward rotating movement of the twisted blade in the powder bed to eliminate operator-to-operator deviation. After conditioning, the twisted blade with a 48 mm diameter was rotated and simultaneously moved axially into/out from the powder bed at predetermined velocities while forcing the powder sample to flow [22,23].

The parameters acquired using the twisted blade method were basic flow energy (mJ), specific energy (mJ/g), consolidation index and flow rate index. Basic flow energy corresponds to the total energy consumed in a standard downward rotating movement of the blade through the sample powder bed, forcing nearby particles to flow. Specific energy is the total energy consumed in the upward movement of the rotating blade through the sample powder bed divided by the powder sample mass. Consolidation index is the ratio of flow energy required for flowing consolidated powder samples (100 taps) to basic flow energy, as shown in Eq. (3):

$$\text{Consolidation index} = \frac{FE_{100\ Taps}}{Basic\ Flow\ Energy} \quad (3)$$