Taste-masked pellets of sodium warfarin prepared by hot melt extrusion

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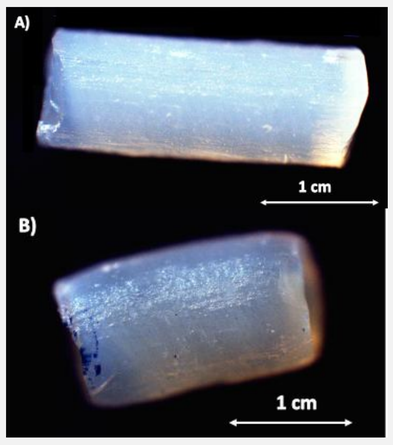


Fig. 1. 20% drug-loaded particle microscopy before (A) and after (B) 360 minutes of thermal treatment, magnification (40x)

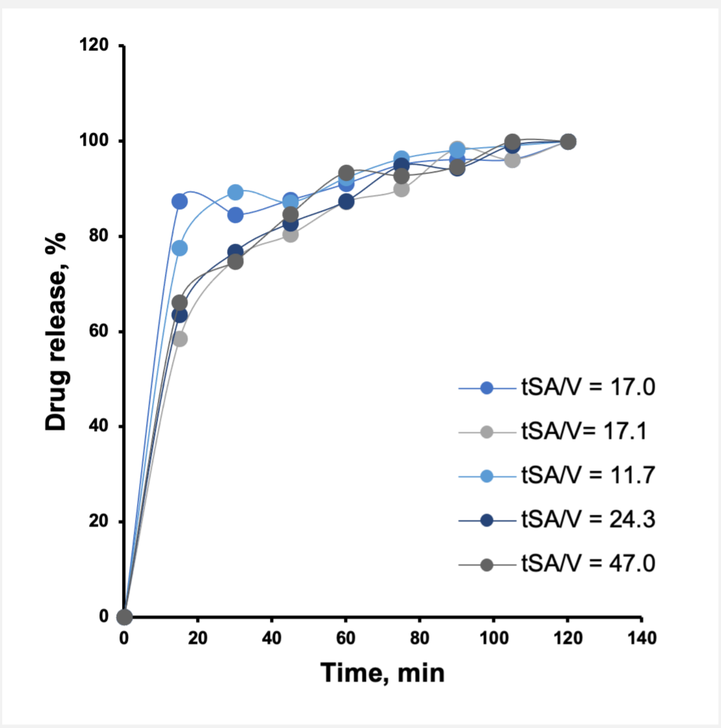


Fig. 2. The dissolution profile of 30 % drug-loaded filament particles

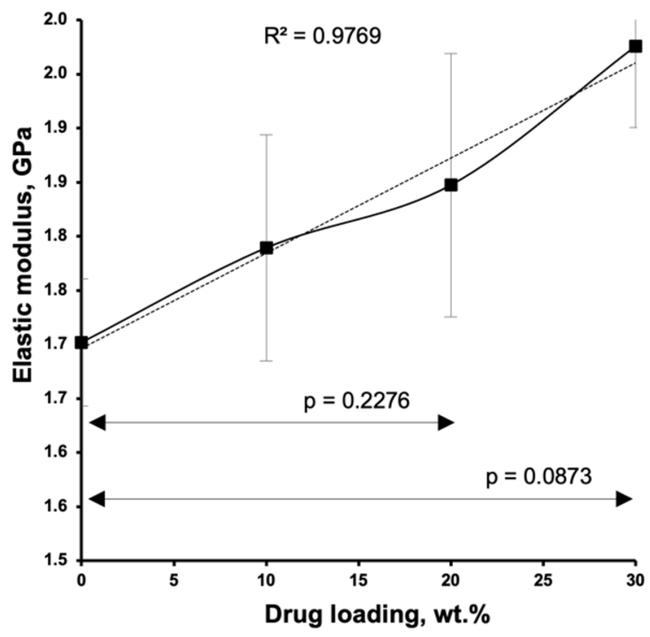


Fig. 3. Filament elastic modulus dependence of the WSC mass percentage (n = 5)

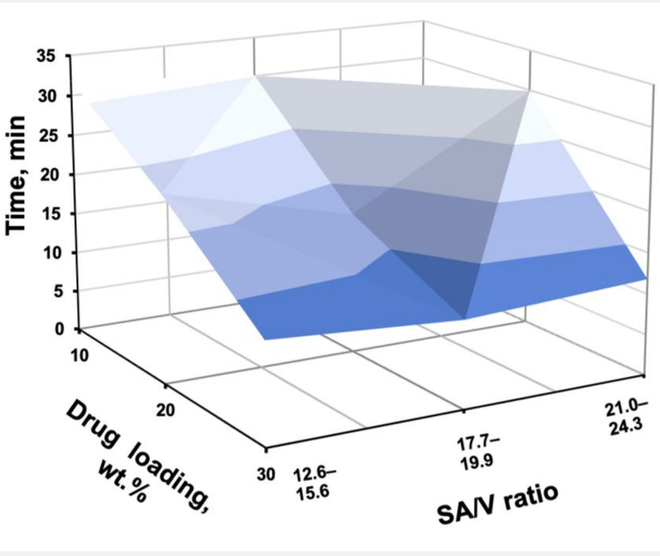


Fig. 4. The time needed to achieve 50 % of the drug release as a function of drug loading and surface area-to-volume ratio (SA/V, cm^2/cm^3)

Introduction

Warfarin, a coumarin derivative, is an indirect-acting anticoagulant and a vitamin K antagonist [1]. The main challenges and limitations of warfarin use include the risk of bleeding from improper dosing and its bitter taste [1].

This study investigated an alternative approach for personalising warfarin dosing by developing taste-masked multiple unit pellets (MUP) using hot melt extrusion (HME) and thermal treatment. The effects of varying drug loads (10, 20, and 30 wt. %) on the duration of post-processing thermal treatment to achieve the desired aspect ratio (AR) and drug release were examined.

Materials

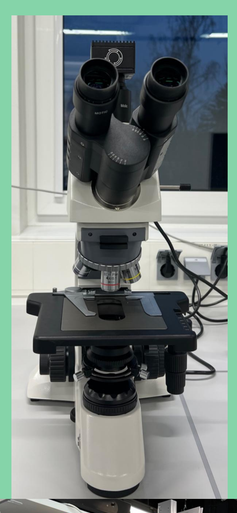
Warfarin sodium clathrate (WSC, Alchymars Icm SM Private Ltd., Tamil Nadu, India); Methyl methacrylate and diethylaminoethyl methacrylate copolymer (Kollicoat® Smartseal 100 P; BASF SE, Ludwigshafen, Germany); glass beads (60 mesh/250 µm); Hydrochloric acid, potassium phosphate monobasic, sodium phosphate dibasic dihydrate and phosphoric acid (pharmaceutical grade, used as received);

Methods

Hot melt extrusion (extruded 0, 10, 20, 30 wt% WSC in Kollicoat ® Smartseal 100 P using Thermo Fisher Pharma 11) Feeding rate 4.63 g/min, 150 rpm. Temperature in zones – 30, 70, 190, 190, 190, 190, 190 °C, torque – max 30 % of 6 N·m;

Elastic modulus measurement (Zwick Roell Z 2.5, grip to grip separation 100 mm, pre load 0.3 N, test speed 0.5 mm / min, measured at 23 °C and relative humidity of 26 %);

Optical microscopy (Motic, BA410E, equipped with 50 W halogen lamp, Motic EC-H Plan objective lenses.);



Manual cutting and dimension measurement using electronic calliper (1, 2, 3 and 4 mm microparticles);

Drug release (ATS Xtend™, Sotax AG, in 500 mL in PBS (pH = 6.8) and 0.1 M HCl at 100 rpm and 37 ± 0.5 °C. Concentration was measured spectrophotometrically (Shimadzu, UV-1900i);

Thermal treatment (Chemtron Strike 380. The bath temperature 80 °C, rotation of 20 rpm. Temperature inside of the glass beads near the polymer glass transition temperature 65 °C);

Results

Thermal treatment of the filament particles reduces their length and increases their diameter due to the elastic deformation of the polymer macromolecules. After cutting, the particles have sharp edges (**fig. 1 A**), but thermal treatment brings their aspect ratio (AR) closer to 1, visibly enhancing their smoothening (**fig. 1 B**).

The particle's surface area and volume were calculated based on the cylinder geometry. The total surface area (tSA) was then divided by the total volume (V) to obtain the total surface area-to-volume ratio (tSA/V). The highest dissolution rate in 0.1 M HCl is observed in samples with larger tSA/V ratios (**fig. 2**). After 60 minutes, drug release reaches at least 80% in all cases, indicating that this formulation is not a good fit for an immediate-release dosage form. No significant dissolution was observed in PBS.

The correlation between elastic modulus and drug loading for filament samples is nearly linear ($R^2 = 0.9769$) (**fig. 3**).

Figure 4 shows a clear correlation between drug loading and the time required to reach 50% drug release. However, no correlation is observed between the tSA/V ratio and the time necessary to reach 50% drug release.

Conclusion

As the drug loading in the filament increases, so does its elastic modulus, which limits the elastic deformation of polymer macromolecules. Decreased elasticity raises the thermal treatment duration required to achieve an AR of 1.

Higher drug loading enhances the dissolution rate, which shortens the time needed to reach 50% drug release. Such correlation for surface area-to-volume (tSA/V) ratio was not obtained.

After the cutting and thermal treatment, the particle edges become smoother, contributing to a more rounded particle shape, which should be beneficial for mouthfeel and medical compliance.

This concept is suitable for producing taste-masked MUP pellets, but further investigation is required.

Ref.

[1] Kovalenko L, Kukuls K, Berga M, Mohylyuk V. Taste-Masked Pellets of Warfarin Sodium: Formulation towards the Dose Personalisation. Pharmaceutics. 2024;16(5), 10.3390/pharmaceutics16050586.

Kaufelde P, Aniskevics A, Sevcenko J, Žogota M, Mohylyuk V. Taste-masked pellets of sodium warfarin prepared by hot melt extrusion, 5th European Conference on Pharmaceutics; 2025.03.24-25: Porto, Portugal.