Solid lipid microparticles containing liquid lipids as crystal modifiers: release behaviour in simulated fluids

Serena Bertoni*[1], Beatrice Albertini[1], Elena Simone[2], Stefano Sangiorgi[1] and Nadia Passerini[2]

[1] Alma Mater Studiorum – Università di Bologna, Dipartimento di Farmacia e BioTecnologie, Bologna. Email: serena.bertoni4@unibo.it

[2] Dipartimento di Scienza Applicata e Tecnologia (DISAT), Politecnico di Torino, Torino.

INTRODUCTION

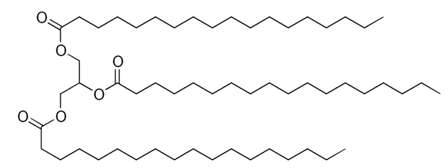
Triacylglycerol are important ingredient for formulating modified release solid oral dosage formulations. However, poor control over the structural modifications during storage and the resulting drug release instability are limiting factors for their widespread use[1]. A recent strategy involve the use of polymorphic modifiers, i.e. substances able to induce the conversion of the lipid into the most stable crystalline form, thereby avoiding further polymorphic transitions[2]. Tristearin (SSS) was selected as model solid triacylglycerol presenting three polymorphic forms, two metastable (α and β') and one stable (β)[3].

This study explores the influence of small amounts of four different liquid lipids acting as crystal modifiers on the structural and release properties of microparticles (MPs) based on tristearin.

METHODS

Microparticles were produced by **spray congealing** technology[4] using SSS alone or with addition of 5 % w/w of different liquid lipids: ethyl oleate (EO), isopropyl myristate (IM), oleic acid (OA) and medium chain triglycerides (MCT).

Caffeine (CAF) as model hydrophilic drug belonging to BCS Class I was loaded into the MPs at 30% w/w.



Tristearin (SSS, Dynasan®118)

RESULTS

1. Polymorphic transition

During production process, pure tristearin MPs crystallized in the metastable α-form. Liquid lipids act as polymorphic modifiers promoting the formation of the stable β-form within 24-48 hours from the production process (Figure 1).

Synchrotron-SAXS/WAXS showed that the polymorphic transition occurred at room temperature (25°C) directly from α to β (without passing through β') and that the additive did not affect the lamellar structure of SSS (Figure 2).

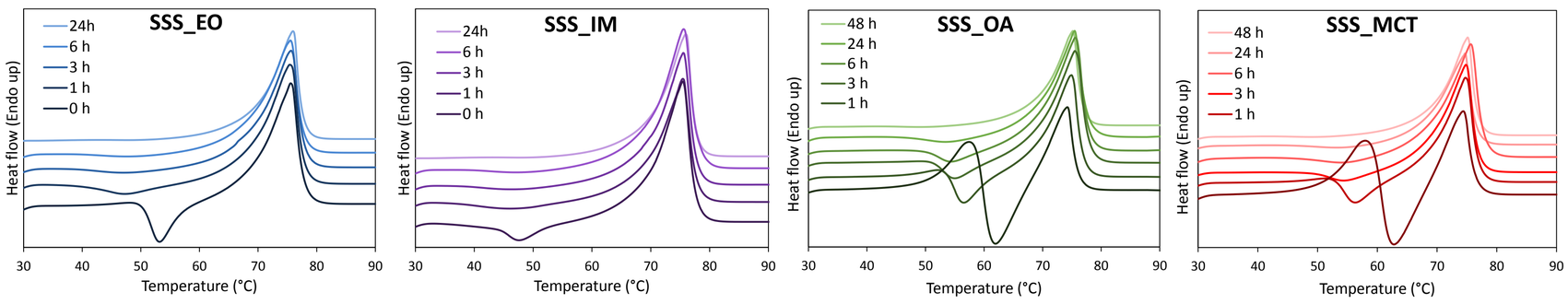


***Figure 1. DSC analysis** of MPs with 5% w/w of additives at various times after production*

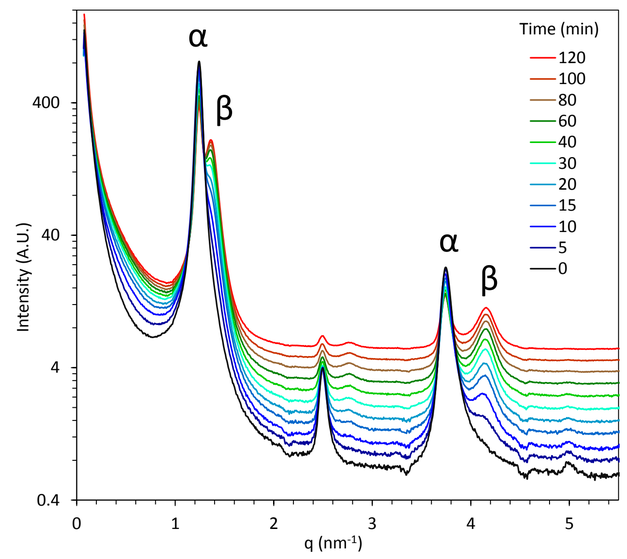


***Figure 2. Synchrotron SAXS/WAXS polymorphic transition** of MPs with 5% w/w of IM after cooling from the melt at isothermal conditions (25°C)*

2. Release behaviour

Release profiles of **MPs with pure SSS (without liquid lipids)** showed an initial burst release followed by a slow release phase (Figure 3). This profile fitted the Higuchi kinetic model that describes a diffusion mechanism-based profile.

MPs with liquid lipids showed linear release profiles without burst release and overall higher release rates (Figure 3). In water, formulations with EO, IM and MCT were capable of releasing drugs at a constant rate, or following zero-order kinetics (Table 1). CAF release rate from MPs containing OA followed the first-order release kinetics.

The release of CAF increased passing in fluid simulating the fasted gastric conditions (FaSSGF) and further enhanced in fasted state intestinal environment (FaSSIF). Beside the diffusion mechanism, the lipid degradation/digestion in intestinal environment can be an additional important mechanism facilitating drug release (Figure 4).

Sample	K × 10^{-3} (min^{-1})	R^2
SSS_EO	96	0.994
SSS_IM	111	0.997
SSS_MCT	98	0.994

Table 1. The coefficient of determinations (R2) and rate constants (K) of the formulations that exhibited zero-order release in water.

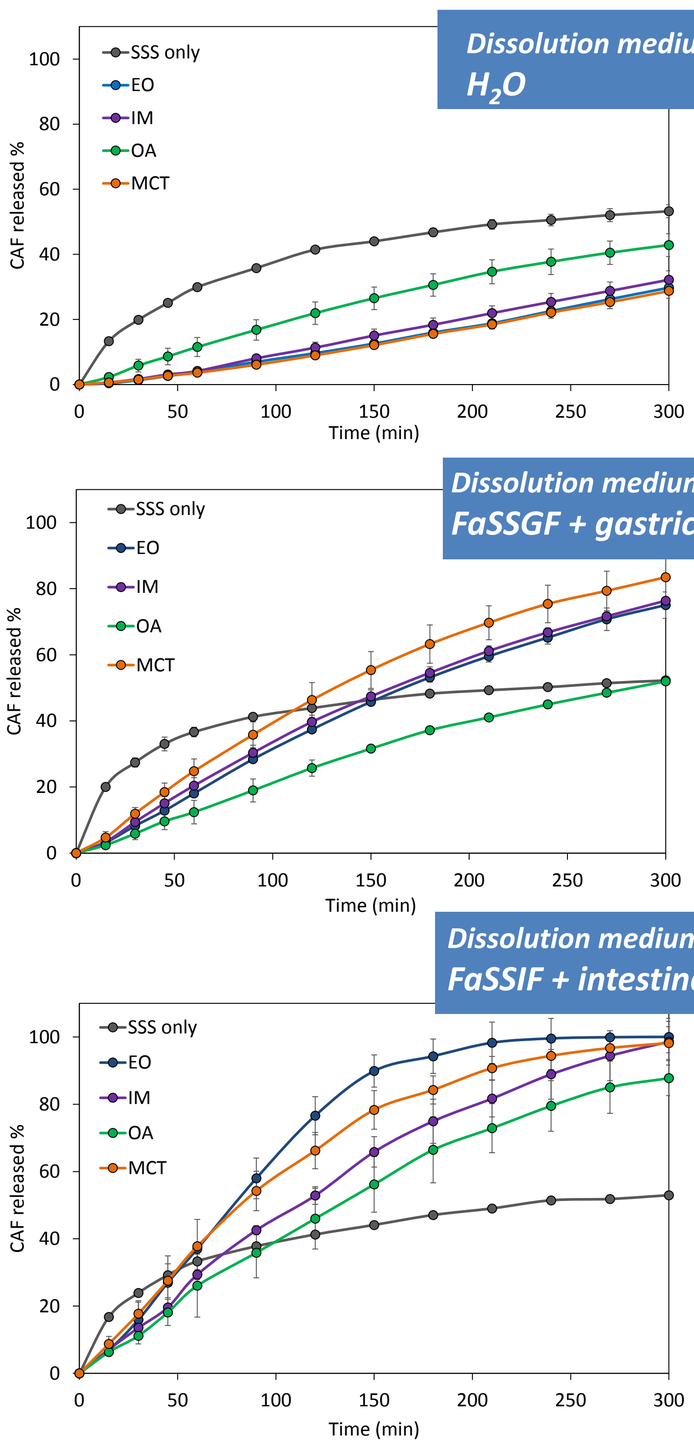


***Figure 3. Release studies** of MPs without or with 5% of additives containng 30% CAF in water, FaSSGF and FaSSIF.*

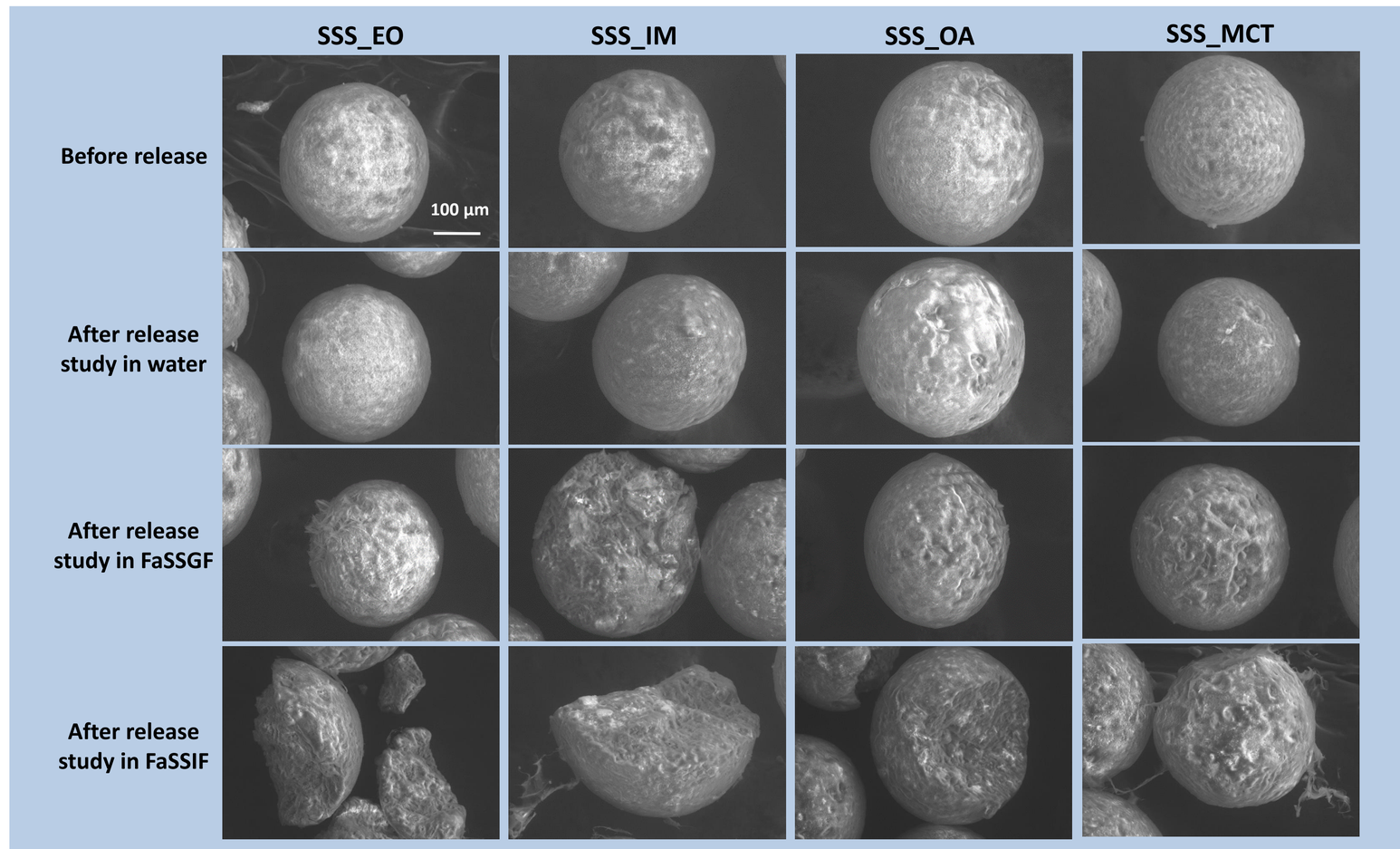


***Figure 4. SEM analysis** of MPs with 5% of additives and 30% CAF*

CONCLUSIONS

The addition of 5% w/w of selected LL (IM, ethyl oleate, oleic acid and MCT) allowed the complete conversion of the formulation into the stable polymorphic form within 1 week from production, concurrently with a controlled release of hydrophilic drugs in media simulating fasted state gastric and intestinal conditions.

This findings improve our knowledge on the use of crystal modifiers as strategy to face the challenging problem of drug release instability of solid lipid formulations.

References

1. Jannin, V.; Rosiaux, Y.; Doucet, J. Exploring the Possible Relationship between the Drug Release of Compritol®-Containing Tablets and Its Polymorph Forms Using Micro X-Ray Diffraction. *J. Controlled Release* **2015**, *197*, 158–164.
2. Bertoni, S.; Passerini, N.; Albertini, B. Liquid Lipids Act as Polymorphic Modifiers of Tristearin-Based Formulations Produced by Melting Technologies. *Pharmaceutics* **2021**, 13, 1089.
3. Chapman, D. The Polymorphism of Glycerides. *Chem. Rev*. **1962**, 62, 433–456.
4. Bertoni, S.; Albertini, B.; Passerini, N. Spray Congealing: An Emerging Technology to Prepare Solid Dispersions with Enhanced Oral Bioavailability of Poorly Water Soluble Drugs. *Molecules* **2019,** 24, 3471.