15th Annual Meeting

PSSRC Virtual 2021

Day 1: 16th June

Drug Release & Formulation and 3D Printing

15th Annual Meeting PSSRC Virtual 2021

Timetable

Time				Schedule		
UK/PT	CEST	FIN	NZ			
08:00	09:00	10:00	19:00	**Welcome and Introduction**		
Session 1: Drug Release Chair: Mohammed Al-Sharabi				**Presenter**	**Organisation**	**Presentation**
08:10	09:10	10:10	19:10	Mila Kovačević	University of Ljubljana	The influence of polymeric binder on flow and dissolution properties of SMEDDS loaded Syloid® 244FP-based granules
08:25	09:25	10:25	19:25	Erin Walsh	University of Strathclyde	Fine Tuning Dissolution Profiles via Surface Micro-Features
08:40	09:40	10:40	19:40	Fan Xie	KU Leuven	Development of a controlled-release carrier using mesoporous cellulose beads for poorly water-soluble drugs
08:55	09:55	10:55	19:55	Lise-Anne Lefol	University of Lille	Towards a better understanding of ibuprofen release from PLGA microparticles
09:10	10:10	11:10	20:10	Natalie Maclean	University of Strathclyde	The Role of Disintegration Mechanism in Physical Tablet Stability
09:25	10:25	11:25	20:25	**Break**		
Session 2: Formulation and 3D Printing Chair: Silke Henry				**Presenter**	**Organisation**	**Presentation**
09:35	10:35	11:35	20:35	Klemen Kreft	University of Ljubljana	Process parameters and tablet disintegration in Fused Deposition Modelling
09:50	10:50	11:50	20:50	Moaaz Abdelhamid	Research Center Pharmaceutical Engineering	New opportunities for pharmaceutical 3D-printing through advanced lipid-based excipients
10:05	11:05	12:05	21:05	Lena Hoffmann	Heinrich Heine University Düsseldorf	Hot melt extrusion and 3D printing of a thermolabile drug
10:20	11:20	12:20	21:20	Gerardo De León	Research Center Pharmaceutical Engineering	In-silico bitterness prediction: a practical tool for bitterants screening
10:35	11:35	12:35	21:35	Mitja Pohlen	University of Ljubljana	The potential of nanocrystalline cellulose – macroporous silica combination for the formulation of dry emulsion systems with improved flow properties: A DoE study
10:50	11:50	12:50	21:50	**Closing Remarks**		

Session 1:
Drug Release

The influence of polymeric binder on flow and dissolution properties of SMEDDS loaded Syloid® 244FP-based granules

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PURPOSE

Mesoporous carriers such as Syloid® 244FP are a convenient choice for solidification of self-microemulsifying drug delivery systems (SMEDDS) designed to improve the solubility of poorly water soluble drugs[1]. They are known for high liquid load capacity and ability to maintain characteristics of dry powders[2]. The aim of the present study was to investigate the influence of polymeric binders on granules quality attributes, with special attention given to flow properties and *in vitro* release profile of carvedilol, used as a model drug.

METHODS

SMEDDS granules were prepared manually by wet granulation method, followed by tray drying. Granulation dispersion containing microemulsion with SMEDDS/water ratio of 70/30 and vinylpyrrolidone-(co)polymer (PVP/VA 64, PVP K30 or K90) used as binder in concentration range 0-7.45 % w/w, was added dropwise to mesoporous Syloid® 244FP. Produced granules were evaluated for particle size distribution, flow properties and *in vitro* carvedilol release profile.

RESULTS

All produced granules showed median diameter from 600 to 800 nm and excellent flow properties (according to angle of repose criteria in Ph. Eur.). Neither concentration nor type of binder had a major influence on these properties. Therefore, granules with high and low binder concentration (1.85 and 7.45%), were chosen for *in vitro* dissolution testing. SMEDDS loaded granules with PVP K30 (low molecular weight) exhibited the fastest drug release, in contrast to ones with PVP K90 (high molecular weight), thus showing a negative influence of increasing molecular weight on release profile. Additionally, granules with higher binder amount showed slightly faster carvedilol release, in comparison to ones with lower polymer amount.

CONCLUSION

Incorporation of higher molecular weight binder (PVP K90) to SMEDDS loaded Syloid® 244FP-based granules resulted in slower *in vitro* carvedilol release profile, while higher binder concentration are related to faster drug release.

CHALLENGES

Loading of mesoporous carriers with lipid-based dispersions, such as granulation fluid with SMEDDS, frequently results in sticky powders with poor flow properties, inappropriate for further processing[2]. By incorporation of polymeric binders we were able to produce Syloid® 244FP-based SMEDDS granules with high carvedilol content as SMEDDS represented more than 60% of granules weight, at the same time keeping good flow properties. We believe these granules are suitable for further compaction and preparation of tablets with adequate mechanical characteristics.

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Fine tuning dissolution profiles via surface micro-features

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PURPOSE

The principle objective of this study is to produce pharmaceutical tablets with surface micro-features. These tablets are produced via Rapid Tooling Injection Moulding (RTIM). This technique is capable of producing accurate and precise dosage forms with an expanded formulation space compared to current additive manufacturing technologies. Tablets produced via this technique will be used to fine-tune dissolution profiles via modification of the tablet specific surface area (SSA).

METHODS

RTIM couples stereolithography (SLA) and injection moulding to combine the flexibility in tablet geometry from additive manufacture with the expanded formulation space of injection moulding. Previous studies have analysed the suitability of SLA for rapid tooling and the accuracy and precision of this technique was found to be very high when a scaling factor is applied to the print.[1] The accuracy and precision of the tablets produced is studied using dimensional and gravimetric analysis coupled with optical coherence tomography. Dissolution studies are conducted on a number of pharmaceutical formulations to better understand the impact that modifying the SSA has.

RESULTS

Tablets were able to be produced from a range of pharmaceutical polymers with high accuracy and precision. Three paracetamol-based formulations were produced and dissolution testing demonstrated that modification of the SSA can result in adjusted dissolution profiles however the polymer within the formulation has a significant impact on the extent of this. Of the formulations that underwent dissolution testing, the polyvinyl alcohol-based formulation proved to be the most sensitive to SSA modification.

CONCLUSION

The RTIM process has demonstrated an ability to produce tablets with surface micro features that are both accurate and precise. In addition to this, formulations that are typically challenging for additive manufacturing techniques were able to be processed via RTIM. Additionally, the drug release profile was adjusted by modifying the SSA of the tablet.

CHALLENGES

The main challenges associated with this research are in mapping out the limitations of this technique in terms of tablet geometry and formulation space.

ACKNOWLEDGEMENTS

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Development of a controlled-release carrier using mesoporous cellulose beads for poorly water-soluble drugs

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PURPOSE

Non-toxic and high porosity mesoporous cellulose beads will be designed to improve the bioavailability and solubility of poorly water-soluble drugs in the fluids of the gastrointestinal (GI) tract by changing the crystalline API to an amorphous state. Cellulose beads with functional groups can realize the release of drugs in different pH environments. The different kinds and amount of functional groups can be introduced to adjust properties of cellulose beads in order to improve the release of the poorly water-soluble drug.

METHODS

TEMPO oxidation of cellulose beads is generated using TEMPO/NaClO2/NaClO system to introduce -COO- into beads and increase the hydrophilicity and re-swelling capacity of beads. Periodate oxidation is used to convert cellulose beads to dialdehyde cellulose beads which makes it possible to dissolve in a neutral medium and under human body temperature. In addition, anions or cationic groups can be further introduced to realize drug release in different pH environments. Poorly water-soluble drugs with variable physicochemical properties are loaded in the freeze-dried cellulose beads by incipient wetness method. XRPD, FTIR, and DSC are used to investigate the physical state of API in the pore.

RESULTS

TEMPO-oxidized cellulose beads show the characteristics of shrinking in acidic medium and swelling in neutral medium. Dissolution experiments show that TEMPO cellulose beads can achieve the controlled release of model drugs in a neutral medium and the drug release rate can be controlled by adjusting the degree of oxidation. Periodate oxidized cellulose beads show good supersaturation maintenance ability, which improves the solubility of weakly basic model drugs in a neutral environment. The XRPD and DSC results show that the physical state of the drug in beads is partially amorphous.

CONCLUSION

So far, two kinds of oxidized cellulose beads with different groups have been successfully prepared, which have a good spherical shape and high drug-loading capacity, and the controlled release of model drugs with different properties has been studied. In conclusion, cellulose beads-based carriers show great potential for controlled drug release.

CHALLENGES

We found that the specific surface area of the periodate oxidized beads is only 20m^2/g, which is much smaller than that of unoxidized beads, but it still has a high drug-loading capacity. Therefore, figuring out where the drug is loaded is the challenge of our future work. In addition, how to maintain the stability of amorphous state is also an important point.

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Towards a better understanding of ibuprofen release from PLGA microparticles

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PURPOSE

To better understand the underlying mass transport mechanisms controlling drug release from poly(lactic-co-glycolic) acid (PLGA)-based microparticles. Despite their great practical importance, system optimization is generally highly cumbersome and unexpected formulation effects lead to long drug product development times. This can in great part be attributed to the potential complexity of the involved physico-chemical processes (Fredenberg et al., 2011). In particular, the role of polymer swelling (Tamani et al., 2019) is often neglected in the literature. Also, one of the key bottlenecks is the fact that usually only *ensembles* of microparticles are studied. In practice, however, each microparticle has its own composition, size and structure and releases the drug "in its own way".

METHODS

Ibuprofen-loaded PLGA microparticles were prepared using an oil-in-water emulsion-solvent evaporation technique: either in a "classical beaker set-up" or in a microfluidics device (to obtain more homogenous microparticle sizes). Different drug loadings were studied. Ibuprofen release was measured from single microparticles in phosphate buffer pH 7.4 at 37 °C. The initial drug content was determined as well as dynamic changes of the systems' size as a function of exposure time to the release medium using optical microscopy.

RESULTS

The investigated single microparticles prepared with the "standard beaker set-up" exhibited virtually no burst effect. An about "zero order release phase" started right from the beginning and lasted approximately 4 days. Subsequently, the release rate steeply increased, leading to complete drug exhaust after about 8 days. This behavior correlated well with only limited system swelling during the first 4 days, followed by substantial swelling afterwards. In contrast, single microparticles prepared using microfluidics showed very variable individual release and swelling patterns. This might be attributed to differences in the inner system structure.

CONCLUSION

PLGA microparticle swelling seems to play a key role for the control of drug release, the variability of single microparticle behavior being strongly affected by the preparation method. The latter might alter the inner system structure and, thus, the relative importance of the involved physico-chemical phenomena.

CHALLENGES

It is not straightforward to monitor structural changes within the microparticles upon exposure to the release medium, without artifact creation. For example, samples must be dried for scanning electron microscopy, and highly swollen polymer networks shrink.

ACKNOWLEDGEMENTS

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The role of disintegration mechanism in physical tablet stability

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PURPOSE

The objective of this work is to identify the links between storage conditions and physical tablet properties such as disintegration time, porosity, hardness and contact angle. Previously, the formulations used in this study were classified based on the performance-controlling mechanism[1]. By studying the role of disintegration mechanism, we can identify the key properties which are likely to affect the performance of a product after storage under different conditions.

METHODS

Placebo tablets were prepared by direct compression for 16 different formulations. Four different filler combinations (microcrystalline cellulose(MCC)/mannitol, MCC/lactose, MCC/dibasic calcium phosphate anhydrous (DCPA) and DCPA/lactose) were used with four different disintegrants (croscarmellose sodium (CCS), crospovidone (XPVP), low-substituted hydroxypropylcellulose (L-HPC) and sodium starch glycolate (SSG)). Tablets were stored for 2 and 4 weeks at 37ºC/30%RH, 37ºC/75%RH, 50ºC/75%RH, 70ºC/30%RH and 70ºC/75%RH. At each timepoint, the porosity, disintegration time, breaking force and initial contact angle[2] were measured.

RESULTS

The stability results show that generally, for all formulations an increase in humidity resulted in an increase in tablet porosity and a decrease in tensile strength. For tablets composed of MCC/mannitol and MCC/lactose, storage at high temperature generally resulted in an increase in initial contact angle. For MCC/DCPA and DCPA/lactose, changes in disintegration time were very low. For MCC/mannitol and MCC/lactose, the disintegration time changes appear to be influenced by the disintegrant choice, as well as filler-combination.

CONCLUSION

Generally, storage at accelerated humidity conditions results in increased tablet porosity and decreased tensile strength, likely due to premature swelling of some excipients after exposure to moisture. The effects of temperature vary based on the formulation, however tablets composed of MCC/mannitol and MCC/lactose generally show increases in initial contact angle after storage, indicating decreased wettability. Disintegration time was least affected for tablets composed of MCC/DCPA and DCPA/lactose, where initial disintegration times were already rapid.

CHALLENGES

The biggest challenge in this study is identifying the key property changes and inter-relationships which ultimately influence the tablet performance, and finding a method of modelling these changes.

ACKNOWLEDGEMENTS

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Session 2:
Formulation and 3D Printing

Process parameters and tablet disintegration in fused deposition modelling

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PURPOSE

Despite the growing importance of process parameters in fused deposition modelling (FDM), the field is still poorly explored. A DoE study was conducted to understand the process parameters of a custom made 3D printer and their influence on tablet disintegration. In a preliminary study, 10 settings in slicing tool Simplify3D were evaluated with further investigation into infill percentage, infill pattern, nozzle size and layer height.

METHODS

Fast soluble PVA filament of 1.75mm thickness was purchased from eSUN (eSUN, Shenzhen, China). Capsule shaped tablets of 18.0 x 8.0 mm dimensions were designed in SOLIDWORKS® 2018 (Dassault Systèmes, Waltham, USA). 3D printing was performed by a custom made FDM 3D printer. Printing temperature was set to 165 °C to reach adequate flow of the filament from the printer nozzle. Disintegration tests were performed in distilled water at 37.0 °C using a disintegration apparatus A. A design of experiment (DoE) study with infill percentage, infill pattern, nozzle size and layer height as factors was set up with statistical software Modde 11.0.1. A D-optimal study design was selected with 28 experimental runs.

RESULTS

In a DoE study, infill percentage, nozzle diameter and infill pattern showed significant influence on the disintegration time, infill percentage being the most relevant. Layer height enters into an interaction with the nozzle diameter. Based on the results, a summary-of-fit plot demonstrated a good model fit (R2=0.928), model predictability (Q2=0.847), model validity (0.792) and reproducibility (0.913). To analyse the reproducibility of the printing process, relative standard deviation (RSD) of mass and disintegration time were also evaluated. Both were influenced only by the infill pattern. Wiggle pattern provided the highest RSD of both responses, proving as the least suitable for the printing process. It appears that the infill pattern affects the uniformity of material deposition and layer fusion. This should be taken into account when selecting the optimal printing parameters. From mass uniformity standpoint, rectilinear infill pattern is the most optimal.

CONCLUSION

Infill percentage, nozzle diameter, layer height and infill pattern all influenced the disintegration time of 3D printed tablets. Since disintegration time and dissolution time can be related[1], findings could be used to accelerate or prolong drug release as desired. On the other hand, only infill pattern affected mass and disintegration time uniformity. This shows that the relevant printing process is robust enough to handle wide changes of the process parameters, which is advantageous for adoption of 3D printing in a pharmaceutical application.

CHALLENGES

To ensure constant mass of prepared tablets, the tablet size had to be adjusted for each combination of process parameters. The height of the tablet was therefore increased or decreased accordingly to maintain the mass of 300 mg. Length and width were fixed at all times.

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New opportunities for pharmaceutical 3D-printing through advanced lipid-based excipients

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PURPOSE

Recently, polyglycerol esters of fatty acids (PGFAs) were introduced as the next generation lipid-based excipients (LBEs) offering plenty of potentials for pharmaceutical applications[1]. The synthesis of this group of excipients typically yields a mixture of PGFA as the main component (>80% w/w) and two more species, namely free polyglycerins (PGs) and monoacid fractions (MAF). This study aims at investigating PGFAs, based on variations in their composition, as an advanced LBE for manufacturing lipid-based drug delivery systems via extrusion-based 3D-printing.

METHODS

PG6-C16 partial ester, a PGFA, was selected as raw material. Several blends composed of different ratios of its three components were prepared: either by adding PGs, MAF or both to the raw material. Filaments of the PG6-C16 partial ester and its blends were manufactured using solid lipid extrusion. A drug delivery matrix in the shape of a solid oral tablet was then 3D-printed using the produced filaments. Other conventional lipids had their extrudability and 3D-printability tested for comparison.

RESULTS

All LBEs tested were found extrudable, however, the printability was strongly influenced by the filament flexibility. The filaments of PG6-C16 partial ester were the most flexible, accordingly, easier to handle for 3D-printing than the other tested lipids. Varying the composition of PG6-C16 partial ester in terms of PGs and MAF showed improved performance in terms of extrudability and 3D-printability. The highest flexibility was found at the highest ratio of PGs and MAF (50 folds higher than that of PG6-C16 partial ester), driving a more efficient process. The filaments became spoolable during extrusion and less prone to breakage, which, in turn, allowed simultaneous 3D-printing of multiple tablets.

CONCLUSION

PG6-C16 partial ester was effectively extruded and 3D-printed via tuning its composition and performed better than the other conventional lipids. This approach is an essential step towards using LBEs as natural and biodegradable alternatives to polymer-based excipients, expanding the range of materials that can be used for 3D-printing of medicines.

CHALLENGES

The modification of the 3D-printer that is designed for polymers, to allow 3D-printing of lipids.

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Hot melt extrusion and 3D printing of a thermolabile drug

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PURPOSE

The aim of this study was to investigate the thermal degradation of the active pharmaceutical ingredient enalapril maleate during hot melt extrusion and 3D printing.

METHODS

Filaments containing the active ingredient enalapril maleate (Zhejiang Huahai Pharmaceutical Co., China) were extruded on a Leistritz ZSE12 HP-PH extruder (Leistritz, Germany) with the standard screw configuration and a 2 mm die diameter, and subsequently printed using a Fused Deposition Modelling (FDM) 3D printer (Prusa i3 Mk3, Prusa Research, Czech Republic). These filaments with 10 % drug loading were prepared using bPMMA (Eudragit E PO, Evonik, Germany) and polyethylene oxide polymers (POLYOX™ WSR N10, DuPont Nutrition & Biosciences, Germany) with the addition of anhydrous colloidal silica (Aerosil® 200 VV Pharma, Evonik, Germany). In addition to the drug-containing formulation, two drug-free formulations were also prepared. The extrusions were carried out at a screw speed of 35 rpm and a feed rate of 100 g/h. In addition, a venting port was installed. To investigate the degradation of the drug, DSC analyses of the powder mixture as well as the filament were performed using DSC (DSC 1, Mettler-Toledo, Germany). A Hitachi-VWR Elite LaChrom system consisting of L-2200 automatic sampler, L-2130 high pressure pump, L-2300 column oven and L-2400 UV detector was used for the chromatographic studies. The extruded filaments were printed into tablets on the 3D printer at a nozzle temperature of 190 °C and a bed temperature of 35 °C.

RESULTS

The filaments containing the active ingredient enalapril maleate and the two drug-free filaments showed a smooth surface and were flexible which would enable FDM printing. Filaments and 3D printed tablets thereof appeared orange, however the drug-free formulations appeared slightly yellow. During 3D printing it was observed that tablets strongly stuck to the print bed. DSC analyses show a new event for the filaments starting at about 165 °C. This is associated with the decomposition of enalapril maleate. Chromatographic investigations confirm that degradation of the active ingredient enalapril maleate took place during hot melt extrusion and 3D printing. The main degradation product has been identified as a diketopiperazine derivate, known as Impurity D (Imp-D, Ph. Eur.). When analysing the content of enalapril maleate in the bPMMA filaments over the entire extrusion process, it was observed that enalapril was approximately half degraded. When compared to the 3D printed tablet, only a small degradation of the active ingredient took place due to the 3D printing, but there was an increase in the content of the diketopiperazine derivate.

CONCLUSION AND CHALLENGES

Two drug-free formulations and one formulation containing the active ingredient enalapril maleate could be extruded and printed. The degradation of the drug could be confirmed through DSC and HPLC analyses. A colour change in the drug substance could also be observed visually by comparison with drug-free filaments.

In-silico bitterness prediction: a practical tool for bitterants screening

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PURPOSE

The function of TAS2Rs is not limited to bitter taste evaluation and food ingestion[1]. Pharmaceutical interest has grown on the latter topic, due to the potential therapeutic applications on targeting TAS2Rs and taste masking/evaluation. The already established methods for taste assessment *in vivo* come along with ethic, economic and time challenges[2]. *In vitro* methods are often economically and time expensive. Therefore, *in silico* tools improve the selection of substances to be screened, as well as the possible applications for drug design.

METHODS

An *in silico* ensemble predictor of bitter substances was built on an Anaconda 3 (version 2020.02 with Python 3.7.6 64 bit) environment with RDKit 2020.03.2.0. The training set used for the predictor was a set of 903 bitter substances and 1845 non-bitter substances, using as molecular descriptor Extended Connectivity Fingerprints (ECFP) created with GetMorganFingerprintAsBitVect() from RDKit, using a radius = 3 and ECFP length of 1024 bits. The ensemble consisted of three strong predictors: A support vector machine, an Adaboost with decision trees as weak learners and a Random Matrix Theory (RMT) based predictor. The ensemble was created using scikit-learn 0.23.1 and numpy 1.18.5. An external validation was performed using a set of 50 molecules external to the whole process.

RESULTS

The 5-fold cross-validation for the individual models was above 82%. As expected, the performance of the individual models was lower on an external set. The highest F-1 score obtained in the external validation by an individual model was the Adaboost model with 72%. The ensemble had 84% accuracy on the training set and 74% F-1 score on the external set.

CONCLUSION

The F-1 score on the external set, plus the latter reported accuracy, support the choice of the ensemble as a good performing model for bitterants prediction.

CHALLENGES

The analysis of the predictions of each individual model, also showed that any model was not able to successfully predict the non-bitter nature of 4 compounds, which indicates a probable overlap on the chemical space of a family of bitter compounds with non-bitter compounds. A deeper analysis of the chemical space of these 4 compounds could lead to an improvement on the predictive power of the model.

ACKNOWLEDGEMENTS

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The potential of nanocrystalline cellulose – macroporous silica combination for the formulation of dry emulsion systems with improved flow properties: A DoE study

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PURPOSE

The purpose of the study was to employ a new combination of two matrix materials, i.e. nanocrystalline cellulose (NCC) and macroporous silica (MS), for the production of dry emulsions powders with enhanced drug dissolution and flow properties, compared to the previously developed dry emulsion systems.

METHODS

A previously developed dry emulsion formulation was chosen as the starting point[1]. NCC and MS were characterised, included in the spray drying formulation (in combination and alone) and a DoE study was performed. NCC was added to stabilise liquid emulsion during spray drying and ease oil release from MS. MS was used to improve dry emulsion flow properties, mainly due to its particle size. Mercury intrusion porosimetry was employed to assess the formulation component effects on MS porosity. Energy-dispersive X-ray spectroscopy was used to determine the presence and spatial distribution of chemical elements and hence formulation components. Flow properties, as one of our main critical quality attributes, was assessed by Hausner ratio and avalanche testing. Finally, dissolution and release studies were performed.

RESULTS

Soluble matrix formers (mannitol, HPMC) were more efficient in encapsulating oil droplets compared to MS system, and NCC didn't have a significant effect on encapsulation efficiency. MS did strongly improve flow properties, as a consequence of particle size increase, however, MS did significantly deteriorate simvastatin release by entrapping it in the pores, not allowing its release. Addition of NCC on the other side impaired product flowability, due to the rod shape particles, however it did improve simvastatin release. The latter is likely a consequence of NCC covering a portion of the inner part of the pores, enabling easier oil desorption.

CONCLUSION

MS and NCC are biocompatible materials with great potential for producing dry emulsion systems. Each component has its own advantages regarding product characteristics. However, some disadvantages are still evident and the sole combination of MS and NCC does not solve them. Further combinations with other materials should be explored and tested in order to overcome them.

CHALLENGES

The biggest challenge we faced was improving the release of oil from MS, without affecting flow properties and *vice versa.* Another issue was the increased viscosity of NCC dispersion already at low concentrations.

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