15th Annual Meeting

PSSRC Virtual 2021

Day 2: 22nd September

Processing I, Amorphous & Stability I and Formulation & 3D Printing II

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 Details				**Processing I** Chair: Natalie MacLean					
				Presenter	**Organisation**	**Presentation**			
08:15	09:15	10:15	19:15	Anže Zidar	University of Ljubljana	Evaluation of Nanofiber Immunogenic and Immunomodulatory Properties In Vitro			
08:30	09:30	10:30	19:30	Mohammed Al-Sharabi	University of Cambridge	Investigating the impact of the preparation conditions and type of solvent on the liquid transport kinetics of ceramic powder compacts using terahertz pulsed imaging			
08:45	09:45	10:45	19:45	Luz Naranjo	Ghent University	Prediction of hopper discharge flow for a pharmaceutical powder using Discrete Element Method			
09:00	10:00	11:00	20:00	Carolina Corzo	RCPE	Solid state of lipid-based excipients: impact on their processability via spray-drying			
09:15	10:15	11:15	20:15	**Break**					
Session Details				**Parallel Session A: Amorphous & Stability I** Chair: Kārlis Bērziņš			**Parallel Session B: Formulation & 3D Printing II** Chair: Snezana Radivojev		
				Presenter	**Organisation**	**Presentation**	**Presenter**	**Organisation**	**Presentation**
09:35	10:35	11:35	20:35	Yixuan Wang	The University of Copenhagen	Effects of polymer addition on strongly and non strongly interacting binary co-amorphous systems	Sara Figueiredo	University of Lisbon	Paroxetine 3D-printable formulations for additive manufacture by Fused Deposition Modelling
09:50	10:50	11:50	20:50	Patrícia Nunes	University of Lisbon	Insights into the release mechanisms of amorphous solid dispersions: the role of drug-rich colloids	Michela Beretta	RCPE	Dual-combination DPI product performance: the importance of the carrier type, blending parameters and inhaler selection
10:05	11:05	12:05	21:05	Rong Di	The University of Copenhagen	Phase separation study based on finding the optimal mixing ratio of drug and co-former via detection of eutectic mixtures	Silke Henry	University of Ghent	Extrusion-based 3D printing of zolpidem tablets to aid in withdrawal therapy
10:20	11:20	12:20	21:20	Charline Henaff	Université de Lille	Solid state amorphization of riboflavin upon milling	J Macedo	University of Lisbon	Influence of different polymer:drug combinations on their processability by thermal processes and in the properties of 3D printed tablets
10:35	11:35	12:35	21:35	Nuno da Costa	University of Lisbon	Evaluation of the stability of amorphous forms of olanzapine during the production of granules, extrudates and pellets dosage forms	Please see parallel session A.		
10:50	11:50	12:50	21:50	**Closing Remarks**					

Session 1: Processing I

Evaluation of nanofiber immunogenic and immunomodulatory properties in-vitro

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PURPOSE

The purpose of this study is to develop a method to evaluate whether nanofibers induce immune responses or modulate their courses after application to damaged tissue. There is scarcely any research on this topic and methods are not standardized, which provides the basis for the present study. Furthermore, these methods will then be used to evaluate the impact of physical and chemical properties of nanofibers on their potential immunogenicity.

METHODS

The immune response to nanofibers, as well as their potential impact on pre-induced polyclonal T lymphocyte responses will be studied in new, appropriately adapted *in vitro* methods using human lymphocytes. MTS proliferation assay performed in microtiter plates lies at the core of this method, which enables us to determine potential immunogenic and/or immunomodulatory properties of nanofibers. It is based on metabolic activity of viable cells present in each well of a microtiter plate which is spectrophotometrically detected according to reduction rates of MTS tetrazolium salt to formazan.

Each nanofiber sample contained in a special cylindrical insert is tested in the presence or absence of phytohemagglutinin (PHA) a T lymphocyte activator to determine whether it modulates cell viability and/or proliferation. Two controls were included: negative control with only the lymphocytes, and positive control with PHA-activated cells, to reveal the effects of the nanofibers under both conditions.

To date, polycaprolactone and polyethylene oxide nanofibers have been prepared by electrospinning with various properties. The nanofibers were characterized in terms of their diameter, morphology, and pore size (using scanning electron microscopy), their polymer solid state (using differential scanning calorimetry), their mechanical properties (using atomic force microscopy), and their free surface energy/polarity (using the contact angle).

RESULTS

The initial results show that the sensitivity of this lymphocyte MTS assay is fit for purpose. However, the assay showed significant intraexperiment and interexperiment variability of the results obtained when using nanofibers without inserts. The inserts thus solved two problems: they standardized the test area, and they covered the nanofiber edges (which can have different properties to the rest of the sample). The polycaprolactone and polyethylene oxide nanofibers did not significantly induce and/or modulate lymphocyte proliferation. However, some small differences were observed in terms of the different nanofiber properties which will further be investigated. To sum up, the adapted MTS proliferation assay is suitable to determine whether different nanofibers can influence *in vitro* lymphocyte viability and polyclonal activation, and these results can be considered indicative of their *in vivo* potential immunomodulatory effects.

CONCLUSION

Initial findings indicate that our adapted MTS T lymphocyte proliferation assay is specific, robust, and sensitive. It will enable us to better understand *in vivo* immune processes since human PBMCs/lymphocytes are used for testing. This innovative approach thus provides a standardized method to assess potential immunogenicity of nanofibers which will allow investigations into the impact of specific nanofiber properties on their immunogenicity.

CHALLENGES

Future challenges include the definition of the influence on immunogenicity or immunomodulatory activity of nanofibers with different properties. Furthermore, other *in vitro* methods using additional human immune cells, like DCs, will be developed to provide a better perspective of the processes involved in the interactions of nanofibers with the immune system.

Investigating the impact of the preparation conditions and type of solvent on the liquid transport kinetics of ceramic powder compacts using terahertz pulsed imaging

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PURPOSE

The liquid penetration into ceramic powder compacts is an important phenomenon in many processes, such as tablet disintegration in the pharmaceutical field[1,2] as well as impregnation in the catalysis field.[3] The liquid transport is influenced by both the properties of the porous compact and the penetrating liquid. This study aimed at providing a better understanding of the effect of the preparation conditions and type of solvent on the liquid transport kinetics of ceramic powder compacts to enhance their design and performance.

METHODS

Terahertz pulsed imaging (TPI) was used to investigate the impact of the heating rate during sintering (firing) on the water penetration into α-alumina powder compacts that were prepared at different compaction forces. In this study, the TPI method was used for the first time to study the transport of a non-polar solvent, i.e. 1-octanol, into a range of α-alumina compacts and compare the transport results to those of water. For 1-octanol, it is possible to study the imbibition process as well as any changes in the sample structure behind the liquid front, such as the change in the effective refractive index of the sample and the fill fraction of solvent in the sample.

RESULTS

The TPI results reveal that the alumina samples fired at the largest heating rate of 200 °C h^{-1} have the largest water penetration rate compared to the heating rates of 100 °C h^{-1} and 150 °C h^{-1}. The TPI results also show that the transport process of 1-octanol in the alumina samples is slower compared to that of water at the same manufacturing conditions due to the larger viscosity of 1-octanol compared to that of water. It was also found that the effective refractive index of the sample, obtained through the analysis of the peak behind the liquid front, increases as a function of time upon the transport of 1-octanol into the sample due to the increase in the fill fraction of the solvent in the sample.

CONCLUSION

The results demonstrate the usefulness of the TPI method to quantitatively investigate the transport of polar and non-polar solvents into ceramic powder compacts that are prepared at different manufacturing conditions. The analysis of the liquid transport process can help formulation scientists in the pharmaceutical industry better understand the disintegration of tablets that contain ceramic materials.

CHALLENGES

It would be helpful to further explain the interaction between the polymeric binder in the unfired alumina compacts with the polar and non-polar solvents as well as to suggest further analyses of the sample structure using the terahertz reflection peak behind the 1-octanol front.

ACKNOWLEDGEMENTS

The authors would like to thank Johnson Matthey (JM) and EPSRC for their funding, Vincenzino Vivacqua for making the samples, and Natalie MacLean and Daniel Markl for conducting the contact angle measurements.

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Prediction of hopper discharge flow for a pharmaceutical powder using Discrete Element Method

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PURPOSE

Nowadays, the use of modelling tools, such as the Discrete Element Method (DEM), can play a key role in the development and implementation of manufacturing processes in the pharmaceutical industry. Indeed, it provides relevant insight into the manufacturing process and speeds up process development in terms of design, scale-up, and optimization with reduced experimental efforts[1].

Despite its benefits, DEM modelling remains underutilized due to the significant computational time required to simulate particle dynamics in the micron size range. This contribution aims to develop a predictive DEM model for hopper discharge of a pharmaceutical powder using scaled-up particles.

METHODS

The DEM methodology is exemplified by an application case of discharge dynamics in a quasi-three-dimensional hopper for a free flowing powder (SuperTab® 11SD spray-dried lactose monohydrate). The implementation stages include contact model selection (e.g., Hertz-Mindlin with JKR, Edinburgh-Elasto-Plastic-Adhesive). Subsequently, bulk calibration of DEM input parameters is performed by virtually replicating a ring shear cell test so that the assembly of scaled-up particles match the bulk behavior of the selected powder, and lastly, simplification of the system by using periodic boundary conditions is included.

RESULTS

The simulation runs performed during calibration helped the identification and selection of those DEM model parameters that adequately predict the behavior of the free flowing powder. The developed DEM hopper model allowed the visualization of flow profiles (e.g., mass flow), and highlighted key factors that affect its prediction such as ratio of hopper outlet to the selected scaled-up particle diameter. Additionally, a quantitative comparison with empirical correlations of the mass flow rate is implemented.

CONCLUSION

The implemented DEM model served as a preliminary basis in identifying strategies to reduce the computational burden during the modelling process, such as particle scale-up, the use of experimental design in the bulk calibration process, and system simplification. Furthermore, the results emphasized the relevance of DEM as a modeling tool to enhance process understanding in particle handling processes.

CHALLENGES

The DEM model developed included assumptions in terms of the selected particle representation (size, shape, size distribution) that need to be further revised for the selected application. In addition, experimental validation of predicted hopper discharge rate values is required.

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Solid state of lipid-based excipients: impact on their processability via spray-drying

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PURPOSE

Technical hurdles are commonly experienced when lipid-based excipients (LBEs) are spray-dried. The inability to yield a solid product has been associated to their low melting points. Comprehensive knowledge on the correlation between solid state and process boundaries can enhance processability. In this work, LBEs were screened in combination with ibuprofen (IBU) as model drug. Behenoyl polyoxyl-8 glycerides (BPG, Compritol®HD5 ATO), tripalmitin (PPP, Dynasan® 116) and triacylglycerol ester of behenic acid (PG3C22p, Witepsol® PMF123) were employed. Particle attributes were engineered for pulmonary delivery of IBU.

METHODS

Solid state interactions, temperature boundaries of spray-drying and API-loading were determined via binary phase diagrams. Tetrahydrofuran solutions of LBE:IBU were prepared, characterized and spray-dried. Mass and heat transfer rates and droplet drying kinetics were set constant for all LBE:IBU by controlling the outlet temperature (T_{out}) and initial droplet size. Yield was determined and particles characterized. Solid state of LBE was assessed via differential scanning calorimetry (DSC) and small and wide x-ray scattering (SWAXS).

RESULTS

Phase diagrams LBE:IBU evidenced eutectic interaction. The eutectic composition, having the least solid-liquid transitions at the eutectic temperature (T_{eu}), was selected for spray-drying. T_{eu} was found to be T_{BPG}=45.7, $T_{PG3C22p}$=60.5 and T_{PPP}=60.1°C at 70:30 LBE:IBU composition. T_{out} of spray-drying was engineered below T_{eu} to decrease the risk of melting. The combination of process parameters and inlet temperature (T_{in}=71°C) led to T_{out} of 32-35°C. Estimation of the initial droplet Sauter mean diameter yielded values of 8.931 to 9.012 µm. Despite the equal initial droplet size, analogous mass-heat transfer and $T_{out}<T_{eu}$, the outcome from each LBE:IBU was markedly different. Agglomeration and low yield were depicted by BPG (28.6%). PG3C22p and PPP, having the same T_{eu}, showed yields of 76.2 and 10.6%, respectively. PPP displayed agglomeration and general impairments, whereas PG3C22p yielded uniform particles. DSC and SWAXS analysis on the temperature profile of spray-drying revealed phase separation in BPG and a metastable polymorph in PPP. These events led to incomplete solidification inside the drying chamber. Monophasic crystallization and absence of polymorphism were observed in PG3C22p leading to higher yield. The median mass aerodynamic diameter (3.57 ± 0.11 µm) evidenced the inhalability of the particles.

CONCLUSION

The absence of processability of LBE via spray-drying is typically associated to their low melting points. However, it was demonstrated that, LBE having the same melting temperature and spray-dried at low T_{out}, resulted in entirely different yields and particle attributes. Multi-phasic crystallization and polymorphism negatively impact the yield associated to the formation of liquid fractions of long residence time in the drying chamber. The use of high melting LBE undergoing minimum solid state transitions, such as PG3C22p, can broaden the operational window of spray-drying leading to further possibilities of particle engineering.

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Parallel Session A: Amorphous & Stability I

Effects of polymer addition on strongly and non strongly interacting binary co amorphous systems

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PURPOSE

Co-amorphous systems have been developed as a promising option to address the poor water solubility challenge of many drug candidates. However, extreme supersaturation may occur in some co-amorphous cases, which is prone to result in precipitation, leading to the loss of the solubility advantage. In order to optimize the dissolution behaviour of co-amorphous systems, small amounts of polymers, potentially acting as precipitation inhibitor and/or release rate-modulator, can be added to the formulations [1]. The influences of polymer addition on both, strongly and non-strongly interacting co-amorphous systems are not well known and are investigated in this study.

METHODS

Carvedilol (CAR), L-aspartic acid (ASP), L- tryptophan (TRP) and hydroxypropyl methylcellulose (HPMC) were chosen as model drug, co-formers, and polymer, respectively. Spray drying and ball milling were used as preparation methods. The CAR to co-former molar ratios were 1:1 in all binary and ternary systems, and the weight fraction of HPMC was 10% of the total powder mass in ternary systems. The glass transition temperatures (Tgs) of all samples were determined by differential scanning calorimetry. FTIR spectra of all samples were scanned over a wavenumber range from 400 to 4000 cm^{-1} (64 scans, resolution 4 cm^{-1}). Non-sink powder dissolution tests of the systems with ASP and TRP were conducted at pH 7.2 and 6.8 in 0.1 M phosphate buffer, 37 °Crespectively.

RESULTS

Larger areas under the dissolution curves (AUCs) were achieved in ternary, polymer containing co-amorphous systems compared to the corresponding binary co-amorphous systems, which can be regarded as an improvement in dissolution behaviour. The FTIR spectra indicated that HPMC did not disturb the salt formation between CAR and ASP. On the other hand, the compounds in the co-amorphous CAR-TRP systems showed no specific or strong interactions with each other, and thus the addition of HPMC caused a decrease in the miscibility of CAR in TRP, due to the original CAR-TRP non-strong interaction being replaced by the newly formed stronger hydrogen bonds between CAR and polymer. As a result, CAR and TRP that exceeded the miscibility limit will potentially separate and crystallize.

(a) (b)

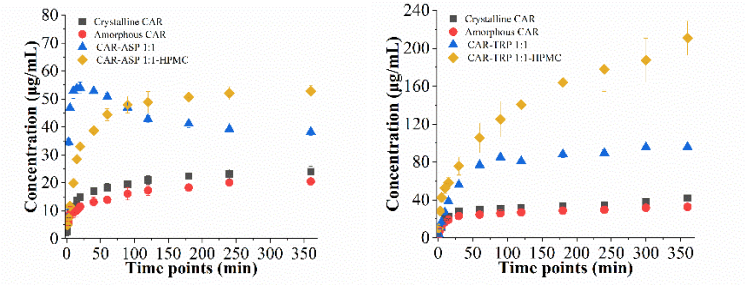

Figure 1 Powder dissolution profiles of crystalline CAR, amorphous CAR and the CAR in the strongly (a) and non-strongly (b) interaction binary and ternary systems.

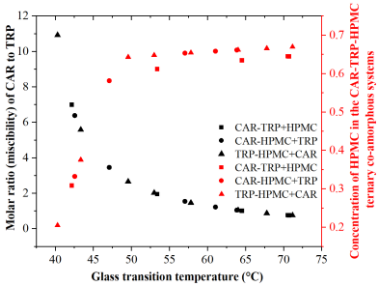

Figure 2 Molar ratio (miscibility) of CAR to TRP and the concentration of HPMC in the co-amorphous CAR-TRP-HPMC systems

CONCLUSION

A small amount of polymer can be added into co-amorphous binary systems to design ternary co-amorphous drug delivery systems with optimized dissolution characteristics. However, in the process of designing polymer containing ternary co-amorphous drug delivery systems, it is necessary to fully consider the effects of polymer on the original molecular interactions between drug and co-former.

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Insights into the release mechanisms of amorphous solid dispersions: the role of drug-rich colloids

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PURPOSE

This work aims to assess the influence of formulation and process parameters on the performance of ASDs made of itraconazole (ITZ), a BCS class-II drug, and different grades of Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS). The proposed study also intent to understand the underlying release mechanism(s) of API from these ASDs, as well as to describe their dissolution profile by means of differential equations.

METHODS

ASDs containing ITZ and HPMCAS were prepared by spray-drying varying the polymer's grade (L, M, H), the drug load (DL) (15-35%), the atomization ratio (R_{ATOM}) (0.3-1.2), and the outlet temperature (T_{OUT}) (30 – 60ºC), according to a design of experiments. The physical properties of the ASDs were evaluated by X-Ray Powder Diffraction (XRPD), Scanning Electron Microscopy (SEM) and Laser Diffraction (Sympatec). ASDs performance was determined by dissolution tests (USP Apparatus II) carried out in biorelevant dissolution media - a pH shift from FaSSGF (pH 1.6) to FaSSIF (pH 6.5). The free and total API in solution were separated by ultracentrifugation to allow its differentiation (HPLC). The size of drug-rich colloids was measured by Dynamic Light Scattering (DLS). The surface composition of dissolving particles was characterized by Raman microscopy to evaluate API and polymer release, and to identify any surface phenomena, such as API surface enrichment.

RESULTS

All ASDs were amorphous. The particle size was smaller for higher R_{ATOM} and the T_{OUT} affected the particles' morphology, ranging from shrivelled (T_{OUT}: 30ºC) to spherical particles (T_{OUT}: 60ºC). The API release changed from a diffusion-controlled mechanism in FaSSGF medium to a dissolution-controlled mechanism in FaSSIF.[1] In intestinal medium, the polymer rapidly dissolved and promoted an immediate release of the API, which attained concentrations above the solubility of the amorphous API, leading to drug-rich colloids formation.[2] However, after the pH-shift, the API % at the surface of dissolving particles drastically increased, suggesting that API and polymer were not releasing congruently and amorphous-amorphous phase separation (AAPS) has occurred at the surface of the particles.[3] After AAPS, the overall dissolution depended on the release rate and fraction of each component at the surface.[3] So, ASDs with low DL (i.e., high fraction of polymer at the surface) showed an enhanced dissolution compared to ASDs with high DL (35%), since the polymer released faster than the API. AAPS led to API surface enrichment, which limited the further polymer's dissolution.

CONCLUSION

All ASDs presented similar free API concentrations, thus what differentiates their performance is the ability to form colloids. ASDs with HPMCAS M and low DLs (15%) resulted in higher concentration of colloids, possibly due to the high amount of polymer that could be released until API surface enrichment occurred.

CHALLENGES

The polymer HPMCAS cannot be detected by the commonly applied detectors such as UV, so an HPLC method with an evaporative light scattering detector (ELSD) was developed to quantify HPMCAS release.

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Phase separation study based on finding the optimal mixing ratio of drug and co-former via detection of eutectic mixtures

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PURPOSE

To elucidate the fundamentals of phase separation and its role in physical stability of co-amorphous systems

METHODS

The eutectic behaviour of four different crystalline drug-drug mixtures; indomethacin-naproxen (IND-NAP), nifedipine-paracetamol (NIF-PAR), paracetamol-celecoxib (PAR-CCX), and indomethacin-paracetamol (IND- PAR) was studied by DSC. Furthermore, samples with different mixing ratios were prepared by melt quenching and the correlation of eutectic behaviour of the crystalline mixtures to physical stability of the co-amorphous systems upon storage of the respective co-amorphous systems is investigated by XRPD.

RESULTS

Results show that all the chosen systems can form eutectic systems (e.g. IND-PAR has eutectic point at 50:50 see Fig 1) and eutectic behaviour can be used to determine the optimal mixing ratio (e.g. the most stable mixing ratio of IND-NAP samples during storage is at eutectic point, see Fig 2) .

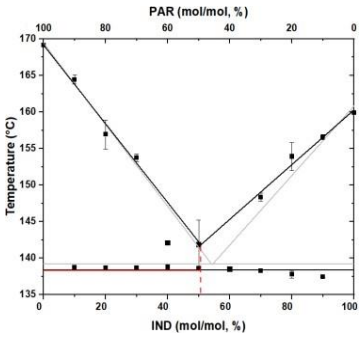

Figure 1. Phase diagrams of IND-PAR samples using experimentally determined data (black square) and theoretical data the Schröder–VanLaar equation (grey line).[1]

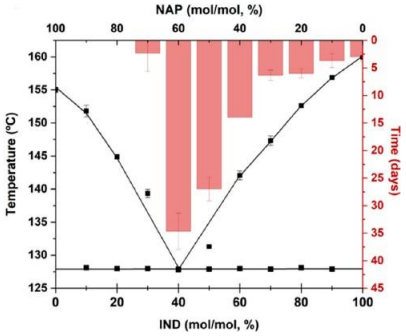

Figure 2.Time for the onset of crystallization (bar chart) for IND-NAP samples, and a comparison to their respective phase diagrams.[1]

CONCLUSION

Investigation of eutectic behaviour can be used as a potential basis for phase separation studies.
The IND-PAR system has previously been found to show phase separation upon storage.[2] Thus it is first chosen to be further investigated for its phase separation behaviour based on the optimal mixing ratio that was found in the eutectic behaviour study. Different IND to PAR molar ratios (below the optimal mixing ratio, at the optimal mixing ratio and above the optimal mixing ratio) will be stored at three different temperature conditions, which are 25 °C (below T_g), 40 °C (around T_g), and 70 °C (above T_g). The amorphous phase behaviour will be detected by mDSC and Raman microscopy during the storage.

CHALLENGES

During the investigation of eutectic behaviour, the liquid temperatures are hard to detect because of the overlap of the two melting peaks in the DSC graphs for some drug-drug mixtures. It is hard to find the best way to extrapolate the results to the mixing ratios that is not cover in the studies.

ACKNOWLEDGEMENTS

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Solid state amorphization of riboflavin upon milling

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PURPOSE

Mechanical milling is known to frequently modify the structural state of drugs by placing them in non- equilibrium situations[1]. It can either lead to an amorphization[2], either to a polymorphic transformation[3]. Such transformations can have a strong repercussion on both the physical stability and the bioavailability of drugs. The aim is to better understand the structural changes of riboflavin (free base) induced by a high energy milling process and their impact on drug release.

METHODS

1.1g riboflavin was milled using a high energy planetary mill (Pulverisette7,Fritsch). Milling was performed at room temperature using zirconium oxide milling jars (45mL) and 7 milling balls (⍰=15mm) at a rotation speed of 400 rpm. Milling was performed from 5 min to 12 hours. X- ray diffraction experiments were conducted with the Panalytical Xpert pro device (λ=1.5405Å) using Lindemann capillaries (Ø = 0.7 mm). DSC experiments were conducted with a Q20 calorimeter (TA instruments) using aluminium capsules or high pressure capsules with hermetic joint. Dissolution studies were conducted with an AT7 apparatus (Sotax) under sink conditions in HCl 0.1M.

RESULTS

After a milling process of 12 hours, the diffractogram of riboflavin showed no more Bragg peaks characteristic of the initial crystalline form I. Furthermore, the corresponding DSC scan revealed a glass transition and two recrystallisation peaks upon heating. The diffractograms of the recrystallized products showed significant differences with the one of crystalline form I revealing two new forms (form II and form III). Dissolution rates were compared for each form of riboflavin showing the quickest dissolution for the amorphous form and the slowest for the crystalline form III.

CONCLUSION

Riboflavin undergoes a solid state crystal-to-glass transformation upon mechanical milling. Milling appears to be a convenient and alternative process for the amorphization of this compound, since liquid riboflavin cannot be safely quenched due to severe degradation upon melting. Moreover, the recrystallisation of amorphous riboflavin upon heating has revealed two new polymorphic forms (II and III) of riboflavin which form a monotripic set with the most stable form I.

CHALLENGES

Riboflavin chemically degrades before it melts, rendering a thorough thermoanalysis difficult. Furthermore, not all polymeric forms of this drug have been described in the literature, although it is a widely used compound since decades.

ACKNOWLEDGEMENTS

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Evaluation of the stability of amorphous forms of olanzapine during the production of granules, extrudates and pellets dosage forms

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PURPOSE

The work developed aimed at the production of granules, extrudates and pellets dosage forms containing amorphous and co-amorphous systems of olanzapine, a BCS class II model drug. To produce the granules, extrudates and pellets different conditions were applied during processing (e.g. water content or drying temperature) and the stability of the systems was evaluated accordingly based on DSC, XRPD, FTIR and NIR characterization methods.

METHODS

Prior to the manufacture of the dosage forms, amorphous and co-amorphous olanzapine were prepared by quench cooling and solvent evaporation (using saccharin as co-former in a 1:1 molar ratio), respectively. After, amorphous and co-amorphous olanzapine were incorporated in formulations containing anhydrous dibasic calcium phosphate, microcrystalline cellulose and povidone.[1] Then, granules were prepared with demineralized water as the granulation liquid at 25 or 40% (w/w) and different drying temperatures (40, 65 or 90°C) were used to remove the water. To produce extrudates, wet masses (40% of water, w/w) were stored for 24 hours at room temperature (25±2°C). Extrusion was carried out by forcing the wet masses to pass through a die (L/D=4) in a universal testing machine. Spheronization was achieved in a radial plate spheronizer operating at 1000 rpm. Pellets were finally dried at 40, 65 or 90°C to remove the excess of water content.

RESULTS

Co-amorphization of olanzapine resulted in a powdered system which showed to be stable to the stress conditions applied in current experiments (moisture or temperature). This led to the production of granules, extrudates and pellets with the long-lasting enhanced solubility of the drug. Inversely, the utilization of pure amorphous olanzapine as feedstock material to produce the dosage forms resulted in a decrease in the amorphous fraction of the drug during processing, wherein a higher fraction of water and/or the increased drying temperature negatively impacted the fraction of the amorphous drug. Particularly, when samples containing amorphous olanzapine were stored for 24 hours, the full recrystallization of the drug was observed according to the differential scanning calorimetry and X-ray powder diffraction data.

CONCLUSION

The incorporation of saccharin as co-former in the preparation of co-amorphous systems has shown to stabilize the amorphous drug and enabled the manufacture of dosage forms, which otherwise would recrystallize and thus negatively impact the bioavailability of the drug.

CHALLENGES

The high cohesiveness of co-amorphous olanzapine hindered the preparation of pellets as these sticked together during processing.

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Parallel Session B: Formulation & 3D Printing II

Paroxetine 3D-printable formulations for additive manufacture by Fused Deposition Modelling

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PURPOSE

This work aims to report the preliminary development of formulations containing paroxetine (PRX) for the hot-melt extrusion (HME) coupled to fused deposition modelling-based 3D printing technology (FDM).

METHODS

3D-printed tablets containing PRX were prepared under distinct processing conditions by combining HME and FDM technologies. The polymeric formulations containing different ratios of paroxetine (PRX), hydroxypropylcellulose (HPC) and excipients (dicalcium dihydrate phosphate (CaP), magnesium stearate (MgSt) and triethylcitrate (TEC) were evaluated for the extrudability and printability upon the successful of the HME and FDM processes, respectively.

RESULTS

The formulation containing MC (MC:PRX; 60:40 ratio) was the only unable to be extruded into filaments (FIL), since it requires higher temperature (>180°C) and was thus excluded. The other polymers were successfully extruded by HME at temperatures of 140-160°C. Yet, these polymeric matrices generated non-printable FIL precluding FDM 3DP, due to surface irregularity and non-uniformity of diameter (closely related to the high viscosity of the formulation), thus preventing printer feeding. Mechanical properties of FIL proved to be inapt for 3DP since they were too brittle, rupturing inside the printing head, due to the forces applied by the extruding gear, which was ultimately responsible for blocking the printer. 3DP ability is directly influenced by the materials' properties and processing conditions may be enhanced by addition of adjuvants[1].First, a plasticizer (TEC; 15% w/w) was used to reduce the polymer Tg and allow gentler HME temperature (Polymer:PRX:TEC; 55:30:15 ratio). Though obtained at lower temperatures (130-150°C), FIL were unable to be printed into 3D-printed tablet (TAB) due to high ductility. Over-plasticization of the FIL caused permanent deformation along the printing head and feeding defects (mainly for SLP polymer so its use was discontinued). To address this issue, TEC was decreased and replaced by the same amount of a filler (CaP). In turn, a small quantity of MgSt was added (PRX (30% w/w), HPC (54% w/w) and excipients (CaP: MgSt: TEC; 10:1:5 ratio) to improve rheological properties of FIL. These HPC formulations were successfully extruded in PRX-loaded FIL apt to print TAB.

CONCLUSION

Fine tuning of formulations is proved crucial for optimal extrudability and printability.

CHALLENGES

The proper selection of the formulation and the suitable process setup were challenges during this work since both steps are crucial to assure that the filaments obtained have suitable properties to guarantee the success of both HME and FDM.

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Dual-combination DPI product performance: the importance of the carrier type, blending parameters and inhaler selection

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PURPOSE

Dry powder inhalers (DPIs) are one of the preferred delivery systems for inhaled active pharmaceutical ingredients (APIs). The performance of carrier-based DPI devices depends on several factors involved in the formation of a stable adhesive mixture and subsequent API detachment and deposition in the lung. In this study, we aimed at investigating how i) different carrier types, ii) blending parameters, and iii) aerosolization device type affected the DPI performance.

METHODS

Budesonide and formoterol fumarate dihydrate were selected as model APIs in the concentration of 1 wt% and 0.02 wt%, respectively. A total of 10 adhesive mixtures, comprising both APIs in α-lactose monohydrate (αLH) and mannitol (MAN), were prepared in a LabRAM I ResonantAcoustic® Mixer using different blending parameters: i) 30 s at three acceleration levels (i.e. 30, 45 and 60 g), and ii) 90 s at two acceleration levels (i.e. 30 and 60 g). The blend uniformity was quantified by high performance liquid chromatography and the aerodynamic performance of the three most uniform blends were tested using a capsule-based (Cyclohaler®) and a reservoir (Novolizer®) inhaler using a Next Generation Impactor.

RESULTS

Different blending homogeneities and dynamics were observed for the αLH- and MAN- based blends. For the αLH containing blends, a blending time of 30 s in combination with an acceleration of 60 g resulted in satisfactory homogeneity, whereas for MAN blends homogeneity (RSD<10%) was achieved following 90 s of blending at both acceleration rates. Analysis of the aerosolization behavior of those blends showed that a higher fine particle fraction was obtained for all the investigated blends, when the reservoir inhaler was used instead of the capsule-based one. Additionally, differences in the mass mean aerodynamic diameter were also visible. This resulted in distinct deposition patterns that could have an impact on the *in-vivo* performance of the formulations. Thus, *in-silico* models will be used in order to further investigate these potential changes.

CONCLUSION

This study highlights that the selection of a proper carrier type, blending process parameters and inhaler device are crucial for the design of an efficient DPI combination product.

CHALLENGES

The challenge of the study was to gather *in-vivo* data for the development of predictable *in-silico* models with the final aim of evaluating the impact of the DPI performance *in-vivo*.

Extrusion-based 3D printing of zolpidem tablets to aid in withdrawal therapy

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PURPOSE

Based on a survey conducted in 2011, 53% of the residents in 76 Belgian nursing homes use one or more benzodiazepine/Z-drugs and 50% utilize it chronically.(1) In general, BZD abuse is a major public health concern and an appropriate treatment of withdrawal symptoms is needed. (2) Different recommendations on the ideal phase-out schedule are available based on the patients' preference and needs. The development of a flexible dosing platform for zolpidem withdrawal focussing on the individual patient is highly desired and extrusion-based 3D printing provides an excellent platform to produce such flexible dosage forms.

METHODS

Thermal analysis of zolpidem hemitartrate (ZHT) was performed using DSC and TGA. XRD analysis of ZHT after heat treatment (10 min at 160 °C) was compared with the raw material. An immediate release polymer (Eudragit EPO, Kollidon VA64, Kollidon 12PF, Polyplasdone S-630U or Soluplus) blended with 30% (w/w) PEO N10 was processed using hot melt extrusion at different temperatures (100 to 180 °C). A suitable temperature for each blend was assessed and employed to produce filaments with a diameter of 1.75 ± 0.05 mm which were subjected to tensile testing. The stress/strain at break and tensile energy (area under the curve) were determined. Karl-Fischer (KF) analysis and Raman spectroscopy were performed on the extrudates. A temperature sweep (6.28 rad/sec) from 80 to 180°C was performed on raw materials within the linear viscoelastic region. Finally, an Eudragit EPO:PEO:ZHT (0.693:0.297:1) filament was extruded and 3D printed. Content uniformity (20 caplets) and drug dissolution (0.01M HCl) were assessed.

RESULTS

ZHT was thermally stable up to 190 °C after which degradation was initiated. When heated, crystalline ZHT converted from form A (hemihydrate) to form C (anhydrous). A suitable polymer matrix for ZHT should possess stable mechanical properties and provide a fast dissolution. The effect of processing temperature on extrudate quality was assessed. Poor quality extrudates with visual defects (fir tree) were obtained when the viscosity difference between the two polymers was above 10^5 Pa.s. Both polymers were evenly distributed in the extrudate as assessed by Raman spectroscopy but the resulting filament possessed poor mechanical properties. Filaments were produced at a suitable process temperature. The presence of PEO enabled printing for some but not all blends (e.g. Kollidon 12 PF, Polyplasdone S-630U were still too brittle). Treshold values for feedability were between 1.43 and 1.70% (strain at break), between 5.33 and 8.22 MPa (stress at break) and between 6.25 and 7.56 x 10^4 J/m³ (tensile energy). Blends containing Kollidon 12PF absorbed moisture to a high degree which could negatively impact the stability of the final formulation. Based on these considerations, an Eudragit EPO:PEO:ZHT blend (0.693:0.297:1) was extruded and printed. The resulting caplet possessed excellent content uniformity (103.10% ± 2.78%) and released 80% ZHT in 50 minutes.

CONCLUSION & CHALLENGES

A dosing platform for ZHT was developed with excellent stability in terms of mechanical properties and moisture absorption. The dissolution rate should however be enhanced in order to comply with the Ph.Eur. guidelines for immediate release dosage forms.

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Influence of different polymer:drug combinations on their processability by thermal processes and in the properties of 3D printed tablets

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PURPOSE

This work aimed to elucidate the influence of different polymers (HPC EF, PVA, HPMC-AS LG) and drugs (paracetamol, PAR; hydrochlorothiazide, HCT and celecoxib, CEL) in the production of solid dosage forms by fused deposition modelling (FDM) 3D printing. As both the preparation of filaments as feedstock material for printing by hot-melt extrusion (HME) and the printing process itself apply temperature and shear forces to the materials, polymers with different molecular weight and mechanical behaviour, and drugs with different melting temperatures and water solubility were selected.

METHODS

A design of experiments considering the 3 polymers, 3 drugs and 2 drug loads (10 and 30%) was elaborated, resulting in a total of 21 experiments [19 formulations; central point (HCT, PVA, 20% load) ran in triplicate]. Blends were processed via HME in a co rotating, fully intermeshing twin-screw extruder and filaments were fed into a Prusa i3 MK3S printer. Filaments and tablets were analysed for their dimensions, drug content and dissolution, and other properties, namely mechanical, thermal, diffractometric, and spectroscopic.

RESULTS

Polymers with lower molecular weight and glass transition temperature (T_g) allowed the HME processing in combination with the 3 drugs in study. On the other hand, the combination of HPMC-AS LG with HCT resulted in a brownish liquid out of the extruder die. Drugs with lower melting temperatures (PAR and CEL) presented a plasticizing effect on the polymers, with a superior effect from PAR. This higher plasticizing effect resulted in lower extrusion temperatures, which lead to the presence of crystalline PAR at higher drug loads, in opposite to CEL that amorphized for all formulations. Filaments of HPC EF:PAR presented a Young's modulus of 62.0 and 18.9 MPa for 10 and 30% PAR load, respectively, which hindered their printability as they were not able to work as a piston during the printing process. Generally, higher temperatures for printing were needed, which may result in a lower crystalline drug fraction for formulations with an initial low fraction of crystalline drug. The formulation with HPMC-AS LG and 30% CEL required that the cooling fan directed to the printing platform was turned off to allow the printing of a full tablet. With the fan turned on, the tablet tended to break easily between layers. Both filaments and tablets presented a drug content between 94.8 and 103.6% and no significant decrease was detected from filaments to tablets, suggesting that the dual thermal processing did not result in drug degradation. Nevertheless, yellowish and brownish coloration was observed for PVA- and HPMC-AS LG-based formulations, respectively. Drug release was highly influenced by the polymer and drug in use. Moreover, good reproducibility was obtained with the triplicated central point.

CONCLUSION

Overall, the study highlighted the need for an appropriate polymer and drug conjugation to allow their processing by HME and FDM 3D printing.

CHALLENGES

Quantification of crystalline drug was not possible with DSC due to interactions between materials during DSC heating (PAR) and drug melting (HCT) above degradation of polymers.

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