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Spray-Drying, Solvent casting and Freeze-Drying techniques: a comparison study on their suitability on the enhancement of drugs dissolution rate

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Dear Editor, attached with this cover letter you'll find the manuscript entitled "Spray-Drying, Solvent casting and Freeze-Drying techniques: a comparison study on their suitability on the enhancement of drugs dissolution rate", by Laura Modica De Mohac, Roberto Caruana, Gennara Cavallaro, Gaetano Giammona, and Mariano Licciardi. We would appreciate if you will consider this manuscript for the publication in Pharmaceutical Research. The manuscript explore the potentialities of the three most common formulation methods used to prepare solid dispersions, such as spray-drying, solvent casting method, and freeze-drying, that have been compared in order to investigate their capability in increasing the drug dissolution profile. It the author's opinion that the proposed research strongly fulfill the scope of the Journal and may contribute to improve he knowledge in the field of pharmaceutical formulations.

All the authors above contributed individually to the study and manuscript production with the following roles: Laura Modica De Mohac, conceptualization, data curation and writing; Roberto Caruana, formal analysis; Gennara Cavallaro, software; Gaetano Giammona, funding acquisition; Mariano Licciardi, investigation, methodology, project administration, supervision, writing.

Sincerely

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Spray-Drying, Solvent casting and Freeze-Drying techniques: a comparison study on their suitability on the enhancement of drugs dissolution rate

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Abstract

Purpose: In this work, the three most common formulation methods used to prepare solid dispersion (SD) such as spray-drying, solvent casting method, and freeze-drying, have been compared in order to investigate their capability in increase the most drug dissolution profile.

Methods: Three formulation strategies have been used to prepare a mixture of Polyvinyl-Alcohol (PVA) and Maltodextrin (MDX) as SD loaded with three model poorly soluble drugs: Olanzapine, Dexamethasone and Triamcinolone acetonide. The formulations obtained have been analysed and compared in term of drugs particle size, drug-loading capacity, surface homogeneity, and dissolution profile enhancement. Physical-chemical characterization has been conducted on both drugs molecules and obtained formulations by thermal analysis and infrared spectroscopy.

Result: The polymers used were able to increase drugs saturation solubility. The formulation strategies effected the drugs particles size, and solvent casting method resulted to give more

homogeneity in particle size and distribution compared with the other. The best drug dissolution rate performance enhancement has been achieved by each sample prepared by the solvent casting method.

Conclusion: All the methods used were able to increase all drug dissolution rate but the solvent casting method gave a product with higher surface homogeneity, drug incorporation capability and reached the faster dissolution profile.

Keywords solid dispersion, spray-drying, freeze-drying, solvent casting method, dissolution rate

Abbreviation

Solid Dispersion (SD)

Polyvinyl-Alcohol (PVA)

Maltodextrin (MDX)

Active Pharmaceutical Ingredients (APIs)

Biopharmaceutical Classification Systems (BCS)

Hot Melt Extrusion (HME)

hydroxypropyl-methylcellulose (HPMC)

Polyvinylpyrrolidone (PVP)

Olanzapine (Olz)

Dexamethasone (Dsm)

Triamcinolone acetonide (Trm)

Dulbecco buffer phosphate (DPBS)

Potassium Bromide (KBr)

Dimethyl Sulfoxide (DMSO)

Scanning electron microscopy analysis (SEM)

Fourier transform infrared (FTIR)

Differential Scanning calorimetry (DSC)

Thermogravimetric analysis (TGA)

Melting point (Tm)

Glass transition (Tg)

Heat capacity (Δcp**)**

1. Introduction

Any drug delivery systems are composed of two components, the active pharmaceutical ingredients (APIs), which produces the physiological effects, and the excipients, that allows the administration and the distribution of the drug in the physiological environment. One of the methods generally accepted to classify API is according to their solubility and permeability through cellular membranes is the Biopharmaceutical Classification Systems (BCS), according to it API is, thus organized in four classes, from I to IV. The 40 % of the New Chemical Entity is hosted into the II and IV classes for oral administration, due to their high hydrophobicity.[1, 2] APIs with low solubility represent a significant challenge in the drug-delivery formulation and several pre-formulation strategies have been employed in order to overcome this issue[3, 4]. In particular, since five decades the most common methods is based on the formulation of SD[5–8]. A SD is a system where the drug is dispersed in a suitable polymer with high aqueous solubility and once the SD is exposed to an aqueous media the hydrophilic carrier dissolves, releasing the drug as very fine particles. Most recently, SD has been described as a delivery system whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability.[9, 10] According to Noyse and Whitney equation and Nernst-Brunner theory, the dissolution rate is directly proportional to the surface area of the drug and its increase by the decreasing of the particle size achieves enhancement of the dissolution rate.[11]

Preparation of SDs can be categorized into two general types; solvent methods, e.g. the solvent cast method or spray-drying and fusion or melting methods, including Hot Melt Extrusion (HME). In

the following sections, the most common methods are discussed chronologically in order to highlight technological development.

Solvent Casting Method. It is the oldest technology in SD formulation and was developed over a centuries ago, driven by the needs in the emerging photography industry.[12] The first reported use of the solvent cast method for pharmaceutical applications was in 1951, by Wolff and co-workers who produced pharmaceutical films of amylose.[13] Later, Saldanha and Kyu, studied the use of this technique using polycarbonate and polymethylmethacrylate.[14] Lee and co-workers used solvent casting to formulate heparin derivatives for medical devices (i.e. cardiopulmonary bypass circuits, heart-lung oxygenators, and kidney dialyzers).[15] Law and co-workers first prepared PEG–amorphous Ritonavir SD with different drug loadings. Their work highlighted the enhanced drug bioavailability advantage of SDs.[16]

Spray Drying. It is particularly suitable for the production of SD as the short residence time of the drug in the heating chamber limits the conversion of the drug from the amorphous to crystalline state. It is also suitable for thermo-labile drugs.[17–19] Spray drying has been used by several researchers such as Beak and co-workers in 2012, who produced ASD containing dutasteride and various excipients including Eudragit, hydroxypropyl-β-cyclodextrin, hydroxypropyl-methylcellulose (HPMC) and Polyvinylpyrrolidone (PVP). Mahmah and co-workers demonstrated the enhancement of felodipine dissolution rate by using spray-drying and HME methods, using PVP and HPMC as polymeric carriers.[19],[20] Most recently, Spray-Drying has been recently used from Modica de Mohac and co-workers to improve the permeation of an anti-cancer drug named Irinotecan.[21]

Freeze-Drying. In this process, water is firstly frozen and then removed from the sample by sublimation and then by desorption, causing the creation of porous materials.[22] Pharmaceutical companies often use freeze-drying to increase the shelf life of products, increasing sample stability.[23, 24] More than 150 biopharmaceutical products FDA approved available on the market

are made from freeze-drying.[25, 26] Freeze-drying has been often used to produce SD to increase both drug solubility and stability such as lovastatin, Δ9-tetrahydrocannabinol, and glyburide.[27–29] The purpose of this research work is to compare of above described methods, as they are the most common used formulation methods to prepare drug loaded SD, and investigate the pharmaceutical advantages that may be achieved in terms of faster drug release profile, surface homogeneity, drug incorporation capability and faster dissolution profile of three different model active molecules, olanzapine, dexamethasone and triamcinolone acetonide.

2. Experimental part

2.1 Materials

Olanzapine (Olz, molecular weight, Mw 312.43 g/mol), Dexamethasone (Dsm, Mw 392.46 g/mol), Triamcinolone acetonide (Trm, Mw 434.50 g/mol), Maltodextrin (MDX, Mw 34000 g/mol), Polyvinylalcohol (PVA, Mw 44.053 g/mol) were purchased from Merck KGaA (Darmstadt, Germany). Ethanol, Dulbecco buffer phosphate (DPBS), chloride acid, potassium bromide (KBr), dimethyl sulfoxide (DMSO), sodium chloride and sodium hydroxide were obtained from Merck KGaA (Darmstadt, Germany). The water used was produced with Milli-Q ® (Millipore).

2.2 Samples preparation

A 10% w/v solution of PVA:MDX (50:50 weight ratio) mixture was prepared. The polymers were added to 20 mL of water and stirred overnight and then heated for 40 minutes in ultrasonic bath. Proper amounts of the polymers solution was processed by using one of the three different formulation methods. Five mL has been put in a Petri dish of 5 cm diameter and water evaporated under a laminar flow of 0.45 ml/min for 24 hours. 5 mL has been passed through the freeze-drying in which after freezing the sample has been put in the shelf with a temperature of 30 °C and under vacuum condition. 7 mL has been then passed through the Spray-Drying process with an inlet temperature (Tinl) of 120°C, 20% pump and 100% aspiration.

Each drug has been then added to the polymers solution and subjected to the same procedures. A small amount of each polymers solution containing the drug has been withdrawn and tested in order to evaluate polymers influence of drugs solubility.

2.3 Drugs dissolution test

The aqueous solubility of Olz, Dsm, and Trm was investigated in the presence of PVA and MDX. Excess amounts of each drugs powders were dispersed in aqueous polymer solutions for 72 h and stirred with 150 rpm at 37°C using a shaking incubator. The polymer solutions were then filtered through a 0.22 mm Millex-GP filter (Merck Millipore, UK) and the concentration of them was determined spectrophotometrically at specific wavelength after calibration curves of each drug have been performed. The wavelength was: 253 nm Olz, 242 nm Dsm and 241 nm Trm.

2.4 Scanning electron microscopy analysis (SEM)

SEM images were recorded on freshly prepared samples to investigate their surface aspects, morphology and size, by using a Phenom ProXSEM. Each sample was deposited onto a carbon-coated steel stub and dried under vacuum (0.1 Torr) before analysis.

2.5 Fourier transform infrared (FTIR)

Samples were prepared by compression of the thin circular tablet using as 1:99 drug:KBr ratio. Samples were placed on the holder and nitrogen gas was used to reduce carbon dioxide peak and spectra were collected using a JASCO FTIR-6000 spectrometer, from 2θ 4000 to 300 cm-1 with 128 scans (same as background) at a resolution of 2 cm-1 for each sample. Spectra were recorded in triplicate.

2.6 Differential Scanning calorimetry (DSC) and Thermogravimetric analysis (TGA)

DSC studies were performed using a LABSYS evo STA (simultaneous thermal analysis) TGA-DSC. DSC studies were carried out at heating rates of 7°C/min. Experiments were performed between 30°C and 500°C and alumina crucibles were used in all experiments. Nitrogen purge gas was used with a flow rate of 5 mL/min. Measurements were repeated at least in triplicate. TGA studies were carried out to measure the water content of the prepared sample with the same instruments.

2.7 Drug-loading evaluation

Drug-loading of prepared formulations were determined after weighing 2 mg of each sample and dissolving it in DMSO. DMSO has been chosen because resulted to be the best solvent for the drug. The dispersions were agitated by Shake incubator for 3 days at room temperature. Then, 1 mL of solution was withdrawn and filtered with a 0.45 mm syringe filters with cellulose acetate membrane (VWR International, USA). The drug loading of each sample was determined spectrophotometrically. UV–VIS spectra were recorded on a 2401 PC Shimadzu Recording Spectrophotometer UV, in the 600–200 nm spectral range. A calibration curve was used for quantification of each drug, performed in the concentration range of 0.1-0.0001 mg/ml from a standard solution of each drug in DMSO (R=0.999) and spectra were recorded at the wavelength of 253 nm Olz, 242 nm Dsm and 241 nm Trm respectively. Each measurement was performed in triplicate.

2.7 In vitro release studies

In vitro drug release studies were carried out by using the basket apparatus method, reproduced appropriately. Each experiment was repeated in triplicate and simulated intestinal condition was obtained according to the European Pharmacopeia (European Pharmacopeia 7.6, 2012). The intestinal environment was mimed by using DPBS at pH 6.8. Twenty mg of each formulation was added to 100mL of dissolution medium and stirred at 100 rpm at 37°±1 °C. At predetermined time

intervals, 1 mL of solution was withdrawn and filtered through a 0.45 µm cellulose acetate membrane syringe filter and replaced with the same amount of fresh buffer. Subsequently, the filtrate was analyzed spectrophotometrically at a specific wavelength for each drug and drug amount calculated according to a calibration curve. Each release study was performed in triplicate.

3. Results

3.1 Effect of polymeric excipients on drug solubility

Three different methods to produce SDs have been investigated by using three different model drugs as reassumed in Table I. In order to evaluate which of the used preparation method (Spray-Drying, Solvent-Cast and Freeze-drying) has achieved the goal of improving drug dissolution rate in the aqueous environment, many parameters has been evaluated.

Table I: Summary of prepared SD formulations and composition.

Sample Name	**Drug**	**Methods**	**Composition**
A1	Olz	Spray-Drying	All the formulations contain a 10% w/w drug loading and the polymeric matrix formed by PVA:MDX with a weight ratio of 50:50.
A2	Olz	Solvent-Cast	
A3	Olz	Freeze-drying	
B1	Dsm	Spray-Drying	
B2	Dsm	Solvent-Cast	
B3	Dsm	Freeze-drying	
C1	Trm	Spray-Drying	
C2	Trm	Solvent-Cast	
C3	Trm	Freeze-drying	

In principal, polymers effect (PVA and MDX with a weight ratio of 50:50) on drug solubility has been evaluated in order to predict the drug behavior in the physiological environment. The experiment shown an improvement of water solubility for each drug for more than 100%, as shown in Table II.

Table II. Drugs solubility expressed as g/mL in water and in polymers solution (PVA and MDX with a weight ratio of 50:50).

	Drug solubility in Water g/mL	Drug solubility in polymers solution
Olz	0.002385 ± 1.35	0.099117 ± 0.0253
Dsm	0.000816 ± 0.8614	0.455442 ± 1.7249
Trm	0.001301 ± 0.3598	0.199201 ± 3.42

3.2 Characterization of SDs

SEM has been used to evaluate the surface homogeneity and morphology of each sample. Has been possible to notice that the shape and surface morphology of SD samples prepared by Spray-Drying were reproducible due to the use of the same polymers-based composition, even if loading different drug molecules. However, spray-dried microparticles showed a not homogeneous size, with diameter values ranging from 7 to 30 μm (see SEM images A1, B1 and C1 of Figure 1). Similarly, freeze-drying sample (see SEM images A3, B3 and C3 of Figure 1) showed a reproducible surface morphology, with porous of about 1μm. Differently, surface analysis of the pharmaceutical films, obtained by solvent casting method (see SEM images A2, B2 and C2 of Figure 1), showed the presence of spherical drug aggregates having diameter and abundance per unit area different for each loaded drug. In particular, films containing Dsm (image B2 of Figure 1) and Trm (image C2 of Figure 1) showed a homogeneous distribution of drug aggregates in the pharmaceutical films, with a diameter of 5 μm for B2 and 10μm for C2 respectively. Olz containing pharmaceutical films (image A2 of Figure 1), instead showed a non-homogeneous distribution of drug aggregates, with diameter ranging between 2-15μm.

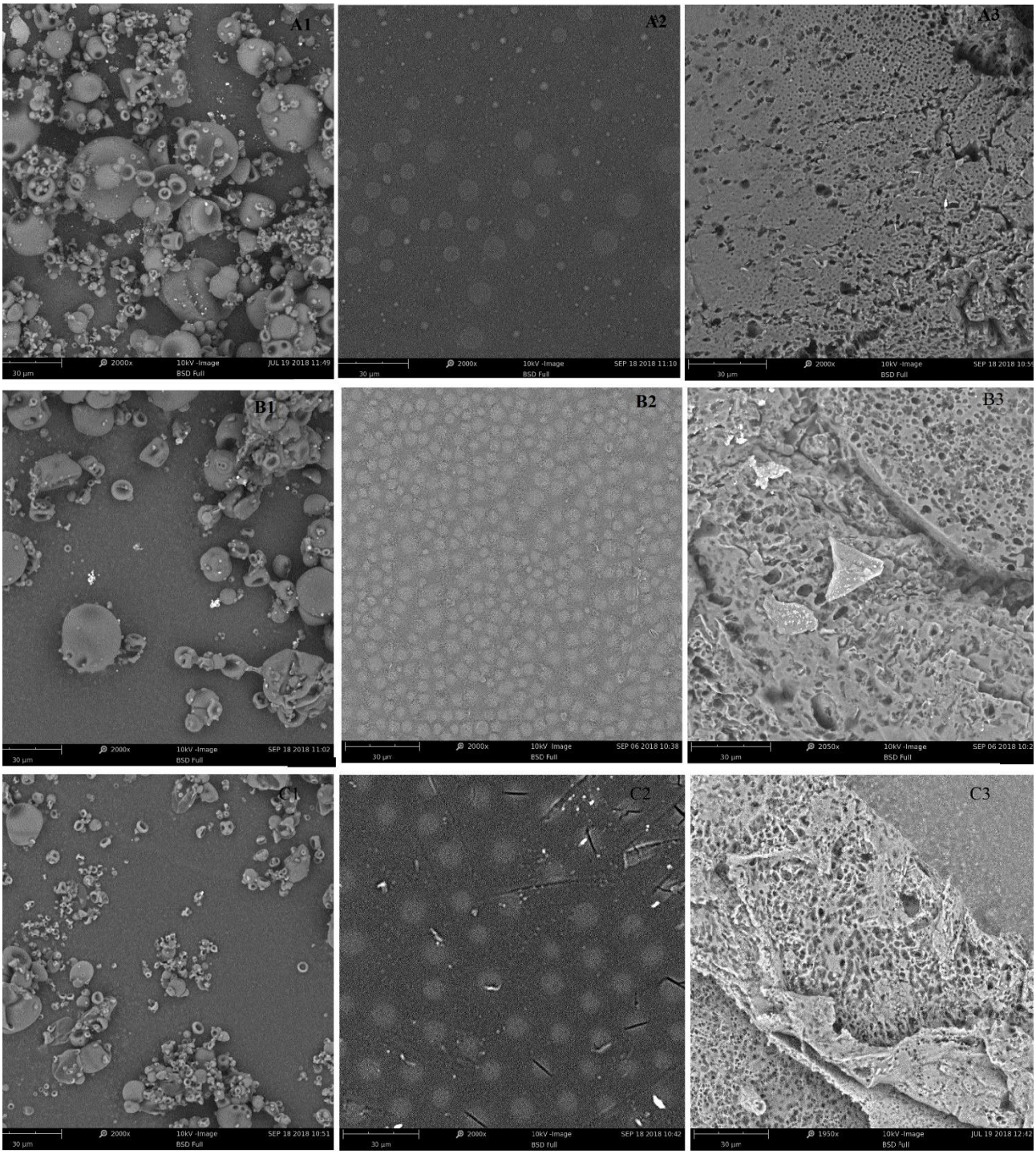

Figure 1. SEM images of all SD samples loading Olz (samples A), Dsm (samples B) and Trm (samples C) respectively, recorded at 2000x magnitude. From the left side, the sample prepared by Spray-Drying (images A1, B1 and C1), in the centre the one prepared by solvent casting method (images A2, B2 and C2) and on the right side the samples produced by Freeze-Drying (images A3, B3 and C3).

The chemical-physical characterization of each drug in the formulation has been evaluated by FTIR analysis (Figure 2). Drugs as pure crystalline materials have been analyzed in order to identify the presence of drug-excipient possible interactions between specific chemical groups in their structures. Table III summarised the pick assignation of each pure drug and the respective peaks highlighted in each formulation. The identified peaks found relevant correspondence in literature.[30–32] and no abnormal chemical interaction were detected, as also confirmed by thermal analysis.

Table III. FTIR peaks assignation for each drug molecule and SD formulation.

FTIR peaks assignation				
Olz cm-1	A1 cm-1	A2 cm-1	A3 cm-1	
3221	3221		3221	NH stretching
3078-3060		2931	2936	CH aromatic ring stretching
2931	2939			CH3 methyl stretching
1584-1558	1584	1586-1561	1582	C=C asymmetric aromatic stretching
1470-1446-1412	1415		1418	C=C aromatic ring stretching
1289-1223				CN bonding
Trm cm-1	C1 cm-1	C2 cm-1	C3 cm-1	
3464-3397	3375			OH alcohol vibration H bond
1707-1662	1715-1654	1704-1659	1718-1660	CH Stretching
1456			1454	CH3 methyl
1375-1302-1278	1375		1375	COC acid alcohol
1057-1080	1078	1080	1080	CF stretching
Dsm cm-1	B1 cm-1	B2 cm-1	B3 cm-1	
3407			3407	OH alcohol vibration H bond
2981-2953-2932-2866	2936-2862	2932		CH3 methyl
1704-1659	1705	1662	1655	CO stretching carbonyl
1617-1603-1436	1616-1602	1620-1603-1425	1620-1610	C=C stretching aromatic ring
1268	1268	1254	1268	CF stretching

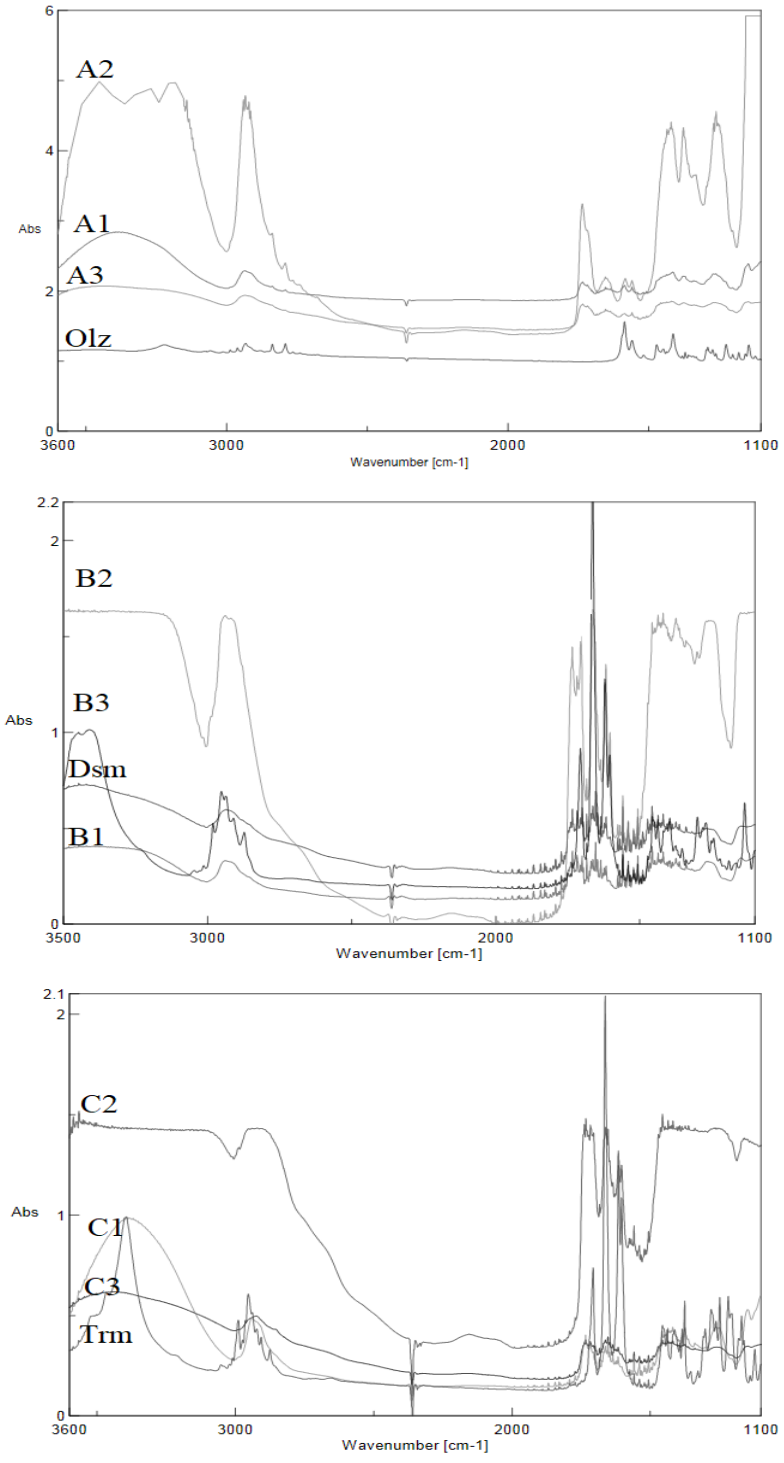

Figure 2. FTIR spectra of: from the top, Olz and formulations A1, A2 and A3; Dsm and formulations B1, B2 and B3; Trm and formulations C1, C2 and C3.

Table IV reported the thermal analysis properties such as melting point (Tm), glass transition (Tg), heat capacity (Δcp**)** and water content of pure drugs and of each SD sample prepared. It is possible

to notice that all used the formulation strategies did not cause drug amorphization over time. This founding let classifying each prepared formulation as SD of the second generation according to Meng and co-workers and Modica de Mohac and co-workers classification where drugs are dispersed as crystal in an amorphous carrier matrix[33, 34].

Table IV. Thermal analysis data from each drug loaded formulation and of pure drugs.

Sample name	Water %	Tm/Tg (°C)	Δcp (J/g)
A1	0.24	193 ± 0.95	10.116
A2	0.60	191 ± 0.87	11.438
A3	0.17	192 ±1.21	14.93
Olz	0.02	193 ± 1.35	15.80
B1	4.95	271 ± 0.23	4.95
B2	1.49	267 ± 0.52	1.71
B3	2.82	265 ± 0.78	1.82
Dsm	0.06	267 ± 0.95	18.5
C1	1.74	292 ±1.35	2.11
C2	0.64	298 ±2.09	9.13
C3	2.95	290 ± 0.64	1.29
Trm	0.16	292 ± 0.24	10.01

3.3 Drug loading and release studies

Each SD formulation was prepared with a starting drug amount of 10% weight. As expected, a correspondent drug loading value has been obtained from formulation prepared by the solvent casting and freeze drying techniques, while lower drug loading has been detected in all formulation prepared by spray-drying (samples A1, B1 and C1). The drug content for each formulation has been summarized in Table V. Actually, results suggest that solvent-casting method allowed the higher

and coherent drug loading, while freeze-drying, but even more, spray-drying gained a significant drug lost during the formulation processes.

According to the drug loading, each formulation has been evaluated in terms of drug release profiles. The dissolution rate of each formulation has been compared with the dissolution rate of the pure drugs in buffer solution. In general, each tested formulation achieved a faster drugs dissolution profile respect the pure drugs. Moreover is it possible to notice that even if all the formulation strategies showed the 70% of drug release after 60 minutes, the solvent casting method was the only method that achieved the 50% of release after 5 minutes and the reaching of the 100% after just 120 minutes, as shown in the graphs of Figure 3. It is possible to suppose that in pharmaceutical films prepared by solvent casting, drug molecules are more readily soluble since they are more accessible to the aqueous solvent, being placed more on the surface of the SD, than the other formulations.

Table V. Drug loading values for all SD formulations prepared by spry drying (samples A1, B1 and C1), solvent casting (samples A2, B2 and C2) and freeze drying (samples A3, B3 and C3) respectively.

Sample name	Drug Loading
A3	9.20± 0.2
A2	9.89+2.56
A1	5.96 ±1.37
B3	8.54 ± 1.95
B2	9.12 ± 0.98
B1	5.23 ± 1.49
C3	7.56 ± 2.6
C2	9.74 ±0.81
C1	8.39±1.79

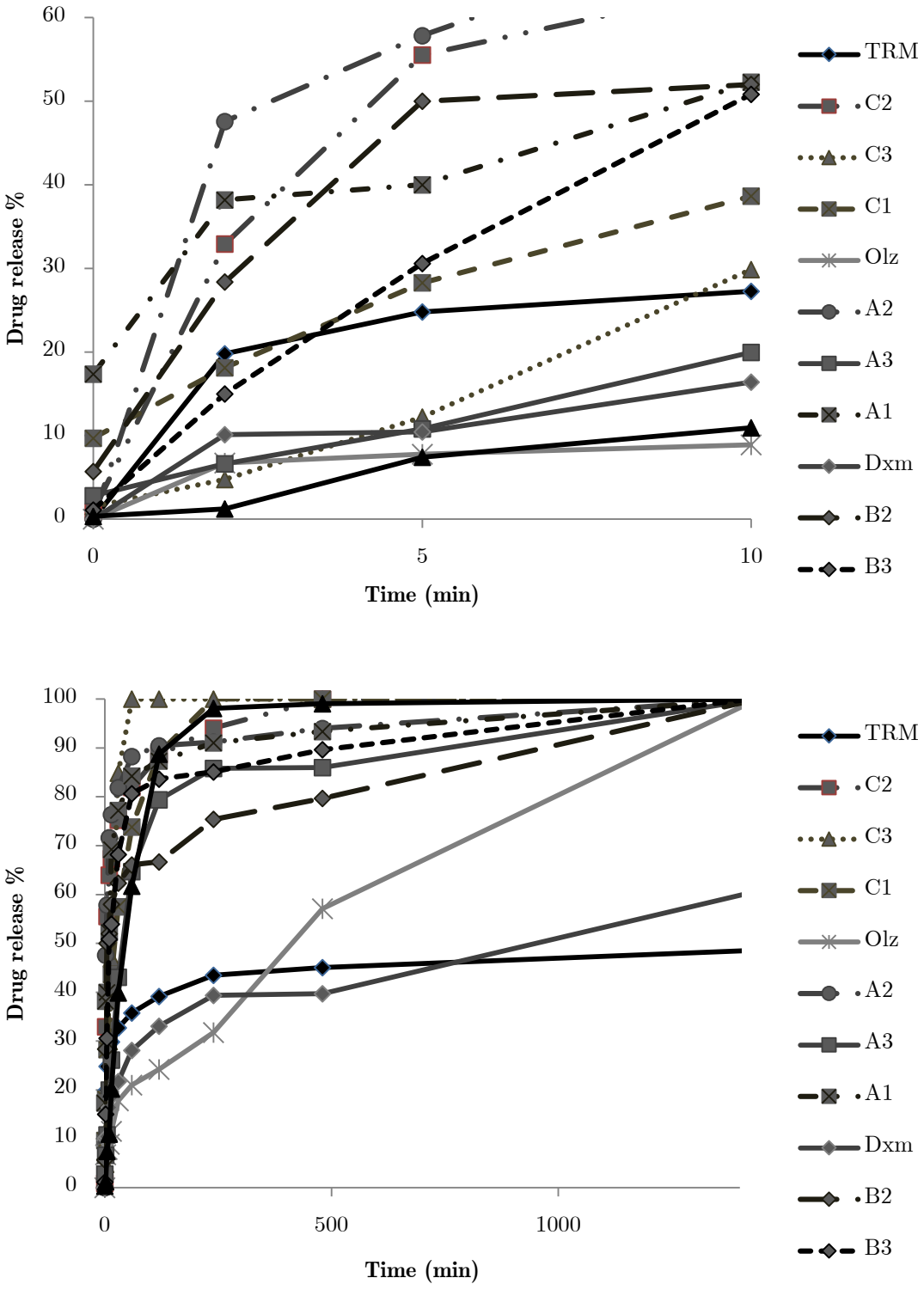

Figure 3. Drug release profiles expressed drug released percentage for each SD formulation: top graph in the first 10 minutes; graph below, up to 24 hours.

Discussion

The aim of this piece of work was to investigate the pharmaceutical advantages of the methods described above in terms of achivineg faster drug release profile, surface homogeneity and drug incorporation capability on three different active molecules Olz, Dsm and Trm. At first the effect of the polymers mixture on each drug saturation solubility has been evaluated. The experiment showed an improvement of all drugs water solubility of more than 100%. This finding has been related to the potential action of PVA and MDX as stabilizers or emulsifiers, they in fact, might have decreased the surface tensions of the aqueous solutions or generated adsorption onto colloid whit steric interactions that may be repulsive, stabilizing the system, although attractive interactions, increasing the solubility of the adsorbed molecules[35–37]. As in pharmaceutical research has always been highlighted the importance of particle size on the final dissolution performance of the drug delivery systems, the SEM analysis has been used for the purpose to understand which methods were able to allow best reproducibility in term of shape and surface morphology. It has possible to conclude that while freeze-drying and solvent-casting method allowed to obtain a good reliability in term of shape and surface morphology, spray-drying need further optimization, depending by various experimental variables in the samples preparation, as expected from previous work[21]. Physical-chemical characterization has been conducted to evaluate both the absence of physical or chemical interactions and the drugs solid state morphology. From the FTIR spectra no drugs-polymers interactions were detectable and drugs main absorbance peaks were easily identified. Each drug internal morphology has been then studied by DSC analysis. The data showed that all the drugs remained in their crystalline state due to detection of drugs typical Tm. This allowed to conclude that the formulation processes did not effected drugs morphology during operation steps, while both polymers were maintained in their amorphous conformation. Such drugs-polymers morphological structure is referred in literature as a second generation SD in which carriers, generally polymeric, are in the amorphous state while the drug is dispersed molecularly within the inert matrix as crystalline[34, 38]. Then, dissolution studies have been conducted as the main aim of

the present work was to evaluate which method was more suitable in increasing all drugs dissolution rate performances. Overall, each formulation strategies showed to achieve a faster drug dissolution profile compared to the pure drugs themselves. This is coherent with the funding that the selected polymers, used as excipients for all the formulation, increase the solubility of each drug in aqueous environment. However, in term of release, the solvent casting method was able to achieved the release of more than 50% of each drug in 5 minutes compared with pure drugs and SDs prepared by freeze-drying and spray-drying. It was, then, possible to suppose that in pharmaceutical films prepared by solvent casting, the drugs molecules were more readily soluble since they have been being placed on the surface of the SD respect to the other formulations, where the drugs were internalised.

Conclusions

More than 40% of commercialized drugs are poorly soluble drugs and SD has been proposed since decades as dosage form capable to increase those drugs dissolution profiles. As SDs could be produced by several formulation strategies, in this work the three most common used, spray-drying, solvent casting and freeze-drying, have been compared. In particular, the observed parameters were surface homogeneity, drug incorporation capability, drug stability over the formulations process and drug dissolution/release rate enhancement. It has been shown that freeze-drying and solvent-casting method allowed to obtain more homogenous and reproducible surface morphology and porous/particles size, while spray-drying did not show reproducible particle either in size or shape. Moreover, spray-drying caused loss of drug during the production process, while the other two methods allowed the best drug loading results. All the methods were able to maintain each drug in their original crystalline morphology. According to the dissolution rate enhancement, all the method allowed an increase in the dissolution rate, and this was in part attributed to the emulsifier properties of the PVA/MDX mixture. In particular, solvent-casting generated the faster drug dissolution/release rate, for all the used model drugs. These results suggest that solvent casting still

represents the most efficient and repeatable production method for solid dosage forms, such as SD, even if further investigations, to let the method industrially scalable and much innovative, are needed.

References

1. Dahan A, Miller JM, Amidon GL. Prediction of solubility and permeability class membership: provisional BCS classification of the world's top oral drugs. *AAPS J*. 2009;11(4):740-746. doi:10.1208/s12248-009-9144-x.
2. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. *Acta Pharm Sin B*. 2015;5(5):442-453. doi:10.1016/j.apsb.2015.07.003.
3. Samie A, Desiraju GR, Banik M. Salts and Cocrystals of the Antidiabetic Drugs Gliclazide, Tolbutamide, and Glipizide: Solubility Enhancements through Drug–Coformer Interactions. *Cryst Growth Des*. 2017;17(5):2406-2417. doi:10.1021/acs.cgd.6b01804.
4. Campardelli R, Oleandro E, Scognamiglio M, Della Porta G, Reverchon E. Palmitoylethanolamide sub-micronization using fast precipitation followed by supercritical fluids extraction. *Powder Technol*. 2017;305:217-225. doi:10.1016/j.powtec.2016.09.084.
5. Modica de Mohac L, de Fátima Pina M, Raimi-Abraham BT. Solid microcrystalline dispersion films as a new strategy to improve the dissolution rate of poorly water soluble drugs: A case study using olanzapine. *Int J Pharm*. 2016;508(1-2):42-50. doi:10.1016/j.ijpharm.2016.05.012.
6. Marano S, Barker SA, Raimi-Abraham BT, Missaghi S, Rajabi-Siahboomi A, Craig DQM. Development of micro-fibrous solid dispersions of poorly water-soluble drugs in sucrose using temperature-controlled centrifugal spinning. *Eur J Pharm Biopharm*. 2016;103:84-94. doi:10.1016/j.ejpb.2016.03.021.
7. Pina MF, Zhao M, Pinto JF, Sousa JJ, Craig DQM. The influence of drug physical state on the dissolution enhancement of solid dispersions prepared via hot-melt extrusion: A case

study using olanzapine. *J Pharm Sci*. 2014;103:1214-1223. doi:10.1002/jps.23894.

8. Marano S, Barker SA, Raimi-Abraham BT, Missaghi S, Rajabi-Siahboomi A, Aliev AE, et al. Microfibrous Solid Dispersions of Poorly Water-Soluble Drugs Produced via Centrifugal Spinning: Unexpected Dissolution Behavior on Recrystallization. *Mol Pharm*. 2017;14(5):1666-1680. doi:10.1021/acs.molpharmaceut.6b01126.
9. Sinko PJ. Martin's physical pharmacy and pharmaceutical sciences Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical sciences. *Martin's Phys Pharm Pharm Sci*. 2011:182-196.
10. Mogal S a., Gurjar PN, Yamgar DS, Kamod a. C. Solid dispersion technique for improving solubility of some poorly soluble drugs. *Der Pharm Lett*. 2012;4(5):1574-1586.
11. Goldberg a H, Gibaldi M, Kanig JL, Mayersohn M. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. IV. Chloramphenicol--urea system. *J Pharm Sci*. 1966;55(6):581-583. doi:10.1002/jps.2600540810.
12. Douglas Collins. The Story of Kodak. 1990.
13. Saldanha JM, Kyu T. Influence of Solvent Casting on the Evolution of Phase Morphology of PC/PMMA Blends. *Macromolecules*. 1987;20(11):2840-2847. doi:10.1021/ma00177a033.
14. Lee Y, Moon HT, Byun Y. Preparation of Slightly Hydrophobic Heparin Derivatives which Can Be Used for Solvent Casting in Polymeric Formulation. *Thromb Res*. 1998;92(4):149-156. doi:10.1016/S0049-3848(98)00124-8.
15. Law D, Schmitt EA, Marsh KC, Everitt EA, Wang W, Fort JJ, et al. Ritonavir – PEG 8000 Amorphous Solid Dispersions: In Vitro and In Vivo Evaluations. *J Pharm Sci*. 2004;93(3):563-570.
16. Takeuchi I, Taniguchi Y, Tamura Y, Ochiai K, Makino K. Effects of l -leucine on PLGA microparticles for pulmonary administration prepared using spray drying: Fine particle fraction and phagocytotic ratio of alveolar macrophages. *Colloids Surfaces A Physicochem*

Eng Asp. 2018;537(October 2017):411-417. doi:10.1016/j.colsurfa.2017.10.047.

17. Wlodarski K, Tajber L, Sawicki W. Physicochemical properties of direct compression tablets with spray dried and ball milled solid dispersions of tadalafil in PVP-VA. *Eur J Pharm Biopharm*. 2016;109:14-23. doi:10.1016/j.ejpb.2016.09.011.
18. Ogawa N, Hiramatsu T, Suzuki R, Okamoto R, Shibagaki K, Fujita K, et al. Improvement in the water solubility of drugs with a solid dispersion system by spray drying and hot-melt extrusion with using the amphiphilic polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and D-mannitol. *Eur J Pharm Sci*. 2018;111(June 2017):205-214. doi:10.1016/j.ejps.2017.09.014.
19. Beak I-H, Kim M-S. Improved Supersaturation and Oral Absorption of Dutasteride by Amorphous Solid Dispersions. *Chem Pharm Bull*. 2012;60(11):1468-1473. doi:10.1248/cpb.c12-00563.
20. Mahmah O, Tabbakh R, Kelly A, Paradkar A. A comparative study of the effect of spray drying and hot-melt extrusion on the properties of amorphous solid dispersions containing felodipine. *J Pharm Pharmacol*. 2014;66(2):275-284. doi:10.1111/jphp.12099.
21. Modica De Mohac L, Caruana R, Pavia FC, Cavallaro G, Giammona G, Licciardi M. Multicomponent solid dispersion as a formulation strategy to improve drug permeation: A case study on the anti-colorectal cancer irinotecan. *J Drug Deliv Sci Technol*. 2019;52:346-354. doi:10.1016/j.jddst.2019.04.040.
22. Nireesha GR, Divya L, Sowmya C, Venkateshan N, Babu MN, Lavakumar V. Lyophilization / Freeze Drying. 2013;3(4):87-98.
23. Shivanand A, Mukhopadhayaya S. A Review on Lyophilization : A Technique to Improve Stability of Hygroscopic , Thermolabile Substances. 2017;5(11).
24. Emami F, Vatanara A, Park EJ, Na DH. Drying technologies for the stability and bioavailability of biopharmaceuticals. *Pharmaceutics*. 2018;10(3):1-22. doi:10.3390/pharmaceutics10030131.

25. Zhong H, Chan G, Hu Y, Hu H, Ouyang D. A Comprehensive Map of FDA-Approved Pharmaceutical Products. *Pharmaceutics*. 2018;10(4):263. doi:10.3390/pharmaceutics10040263.

26. Allen L V, Nicholas G, Ansel HC. Book reviews. *Anticancer Res*. 2013;33(5):2345. http://www.ncbi.nlm.nih.gov/pubmed/23645785.

27. van Drooge D-J, Hinrichs WLJ, Dickhoff BHJ, Elli MN, Visser MR, Zijlstra GS, et al. Spray freeze drying to produce a stable Δ9-tetrahydrocannabinol containing inulin-based solid dispersion powder suitable for inhalation. *Eur J Pharm Sci*. 2005;26(2):231-240. doi:10.1016/j.ejps.2005.06.007.

28. Betageri G. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. *Int J Pharm*. 1995;126(1-2):155-160. doi:10.1016/0378-5173(95)04114-1.

29. Naik JB, Mokale VJ. Preparation of Freeze-dried Solid Dispersion Powder using Mannitol to Enhance Solubility of Lovastatin and Development of Sustained Release Tablet Dosage Form. 2014;1(1):11-26.

30. Shin S-C, Kim J-Y, Oh I-J. Mucoadhesive and Physicochemical Characterization of Carbopol-Poloxamer Gels Containing Triamcinolone Acetonide. *Drug Dev Ind Pharm*. 2000;26(3):307-312. doi:10.1081/DDC-100100358.

31. Hiriyanna SH, Basavaiah K, Goud P, Dhayanithi V, Raju K, Pati HP. Identification and characterization of olanzapine degradation products under oxidative stress conditions. *Acta Chromatogr*. 2008;20(1):81-93. doi:10.1556/AChrom.20.2008.1.7.

32. Rodrigues LB, Leite HF, Yoshida MI, Saliba JB, Junior ASC, Faraco AAG. In vitro release and characterization of chitosan films as dexamethasone carrier. *Int J Pharm*. 2009;368(1-2):1-6. doi:10.1016/j.ijpharm.2008.09.047.

33. Meng F, Gala U, Chauhan H. Classification of solid dispersions: correlation to (i) stability and solubility (ii) preparation and characterization techniques. *Drug Dev Ind Pharm*. 2015;41(9):1401-1415. doi:10.3109/03639045.2015.1018274.

34. Modica de Mohac L, Keating A, de Fátima Pina M, Raimi-Abraham B. Engineering of Nanofibrous Amorphous and Crystalline Solid Dispersions for Oral Drug Delivery. *Pharmaceutics*. 2018;11(1):7. doi:10.3390/pharmaceutics11010007.

35. Takeuchi H, Kojima H, Yamamoto H, Kawashima Y. Polymer coating of liposomes with a modified polyvinyl alcohol and their systemic circulation and RES uptake in rats. *J Control Release*. 2000;68(2):195-205. doi:10.1016/S0168-3659(00)00260-1.

36. Shogren R, Biresaw G. Surface properties of water soluble maltodextrin, starch acetates and starch acetates/alkenylsuccinates. *Colloids Surfaces A Physicochem Eng Asp*. 2007;298(3):170-176. doi:10.1016/j.colsurfa.2006.10.070.

37. Agama-Acevedo E, Bello-Perez LA. Starch as an emulsions stability: the case of octenyl succinic anhydride (OSA) starch. *Curr Opin Food Sci*. 2017;13:78-83. doi:10.1016/j.cofs.2017.02.014.

38. van Drooge DJ, Braeckmans K, Hinrichs WLJ, Remaut K, De Smedt SC, Frijlink HW. Characterization of the Mode of Incorporation of Lipophilic Compounds in Solid Dispersions at the Nanoscale Using Fluorescence Resonance Energy Transfer (FRET). *Macromol Rapid Commun*. 2006;27(14):1149-1155. doi:10.1002/marc.200600177.