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Taste masked lipid pellets with enhanced release of hydrophobic active ingredient

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ABSTRACT

Solid lipid extrusion is a suitable technique to produce oral dosage forms with improved taste properties. The design of a lipid formulation for poorly water soluble drugs is a challenge because of the poor dissolution and potential bioavailability problems. In this study, solid lipid extrusion at room temperature was applied for the formulation development of the BCS Class II drug NXP 1210. Powdered hard fat (Witocan® 42/44 mikrofein), glycerol distearate (Precirol® ato 5) and glycerol trimyristate (Dynasan® 114) were investigated as lipid binders. Different amounts of polyvinylalcohol (PVA)–polyethyleneglycol (PEG)-graft copolymer (Kollicoat® IR) and crospovidone (Polyplasdone® Xl-10) were scrutinized as solubilizers. The dissolution profiles depicted a short lag time (about 2 min) and then fast and complete dissolution of NXP 1210 by increasing the amount of crospovidone. The initial release was more delayed with an increased amount of PVA–PEG-graft copolymer. Dissolution rate could also be influenced by changing the lipid binder from pure hard fat into a mixture of hard fat, glycerol distearate and glycerol trimyristate. The formulations are feasible for taste-masked granules or pellets containing poorly soluble drugs.

1. Introduction

Pellets are widely used in the pharmaceutical industry. They have a narrow size distribution, good flow properties and uniform packing (Reynolds, 1970). The gastrointestinal transit times are highly reproducible and potential local irritations may be reduced (Ghebre Sellassie, 1989). The risk of dose dumping is reduced to a minimum (Bechgaard and Hegermann Nielsen, 1978) and the spherical particles can be mixed with food or juices (Breitkreutz and Boos, 2007). One common pelletization technique is extrusion/spheronization. The mass is forced through the die plate forming cylindrical extrudates which are rounded to pellets in a spheronizer and, if necessary, dried afterwards. The standard pelletization aid in pharmaceutical applications is microcrystalline cellulose (MCC) (Dukic-Ott et al., 2009). Besides various other excipients, lipids are useful pelletization aids (Reitz and Kleinebudde, 2009; Krause et al., 2009). Breitkreutz et al. (2003) established the solid lipid extrusion without any solvents at room temperature using a ram extruder and hard fat. Drug loads of 80% are feasible. Thermal treatment of the drug-excipient blend is reduced to a minimum. Hence, the process is appropriate for thermosensitive substances. During process, the lipid with a low melting range softens to form solid extrudates which can be spheronized afterwards (Breitkreutz et al., 2003). The powdered hard fat quality Witocan 42/44® mikrofein offers these properties and is well suitable for this process. Lipid formulations are often associated with an improved absorption and bioavailability of a drug substance (Porter et al., 2007). A further special feature of lipids in pharmaceutical development is their taste-masking effect for bitter tasting drugs. Currently, various taste masking approaches are available. The most commonly used methods are film coating (Douroumis et al., 2011) and adding sugars, flavours or sweeteners (Ayenew et al., 2009). Granulation, spray drying (Bora et al., 2008), drug complexation by cyclodextrines (Ono et al., 2010; Woertz et al., 2010) ion change resins (Suthar and Patel, 2011) and other polymers are additional techniques to mask bad tasting drugs. Chemical approaches like prodrugs and different salt forms (Menegon et al., 2011) are often limited due to regulatory requirements. The co-rotating twin screw extruder was introduced as useful tool to produce lipid extrudates with taste masking properties in a continuous process (Michalk et al., 2008). Further, a mixture of theophylline, Witocan 42/44® mikrofein (powdered hard fat)

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and Dynasan® 114 (glycerol trimyristate) was extruded and further spheronized to pellets with sustained release matrix spheres in a solvent-free process (Reitz and Kleinebudde, 2009). It is also feasible to develop lipidic, immediate release pellets with high drug loads manufactured at room temperature (Krause et al., 2009). The addition of release modifiers to the lipid based matrix is also feasible (Windbergs et al., 2009; Gueres and Kleinebudde, 2011). However, it is still unknown whether this technique is applicable to design immediate release pellets, with incorporated lipophilic, poorly water soluble and/or poorly wettable drugs. NXP 1210 is an acidic, non-steroidal anti-inflammatory drug (Gilman et al., 1980). The lipophilic character is described by its log *P* value of 3 (Caron et al., 1997). The almost white crystalline powder melts between 104 and 107 °C. It is practically insoluble in water at 20 °C. The bitter tasting drug has a pK_a value of 4.89 with a dependence on the solvent (Ali, 1982).

The purpose of this study was to develop lipid based oral dosage forms (pellets) containing NXP 1210 as model drug with taste-masking properties but a fast and complete dissolution.

2. Materials and methods

2.1. Materials

NXP 1210 was used as received from NextPharma (Waltrop, Germany). Glycerol distearate (Precirol® ato 5) was supplied by Gattefossé (Weil am Rhein, Germany), glycerol trimyristate (Dynasan® 114) and powdered hard fat (Witocan® 42/44 mikrofein) were purchased from Sasol (Witten, Germany). The powdered lipids were desagglomerated using a sieve with a mesh size of 1000 μm. The following substances were investigated as solubilizers:

(a) Polyvinylalcohol (PVA)-polyethylenglycol (PEG)-graft copolymer (Kollicoat® IR, BASF Ludwigshafen, Germany)
(b) D-Mannitol, crospovidone, polyvinyl acetate and povidone (Ludiflash®, BASF Ludwigshafen, Germany)
(c) 6-o-α-D-Glucopyranosyl-d-sorbitol (GPS), and 1-o-α-D-glucopyranosyl-D-mannitol dehydrate (GPM, 1:1) (Galen IQ™ 720, BENEO-Palatinit, Mannheim, Germany)
(d) Crospovidone (Polyplasdone® XL-10, ISP Global Technologies, Köln, Germany).

Potassium dihydrogenphosphate (Grüssing, Filsum, Germany) and sodium hydroxide (AppliChem GmbH, Darmstadt, Germany) were used for preparing the buffer solution pH 7.5.

2.2. Methods

2.2.1. Compacted powder mixtures

NXP 1210 and the different solubilization aids were blended in a turbula mixer (T10B, W.A. Bachofen, Basel, Switzerland) for 20 min. The mixed powders were filled into the die of a Universal testing apparatus (H10KM, Hess, Sonsbeck, Germany). A punch of 12 mm diameter was used. The punch speed was set to 500 mm min^{-1} and the applied force to 5000 N. Flat faced compacts with a total mass of about 140 mg were produced.

2.2.2. Extrusion

The extrusion was performed with a co-rotating twin screw extruder (Mikro 27GL-28D, Leistritz, Nürnberg, Germany).

The different formulations were blended for 15 min at 25 rpm in a laboratory mixer (LM 40, Bohle, Ennigerloh, Germany). Afterwards, the powdered mixtures were filled into the gravimetric dosing device (KT20, K-Tron, Soder, Lenzhard, Switzerland). Extrusion was performed with a feeding rate of 30 g min^{-1} and a screw speed of 50 rpm at room temperature. Extrudates were manufactured with a die plate consisting of 23 holes and a thickness of 2.5 mm.

2.2.3. Spheronization

The lipid extrudates were stored for 24 h at 21 °C and a relative humidity of 40%. Batches of 300 g extrudates were spheronized with 1500 rpm for 15 min in a spheronizer (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) with a crosshatched rotor plate and a diameter of 300 mm. Compressed air (0.25 bar) was used to ensure a space between rotor plate and jacket.

2.2.4. Dissolution

For the dissolution experiments, a paddle apparatus (Erweka, Heusenstamm, Germany) was used in accordance to USP 33 Method 2. The dissolution tests were performed in 900 ml potassium dihydrogenphosphate buffer, pH 7.5 at 37 ± 0.5 °C. The buffer was sonicated for 20 min. Stirrer speed was set to 75 rpm. The drug release of NXP 1210 was measured by an UV–vis spectrometer at a wavelength of 295 nm (Lambda 2, Perkin-Elmer, Rodgau-Juegesheim, Germany) with flow-through cuvettes. Tanigawara et al. (1982) devised a function for calculating the mean dissolution time (MDT). This equation was modified for a drug release of 80%:

$$MDT_{80\%} = \int_{i=0\%}^{80\%} t_i \frac{dm_i}{m_{80\%}} \quad (2)$$

where $m_{80\%}$ is the concentration of 80% released drug related to infinite dissolution and m is the amount of drug dissolved at time t. Calculation of MDT 80% was made by linear trapezoidal integration of the dissolution profile. The MDT was calculated for 80% drug release to enable the comparison of all obtained dissolution curves even for formulations which did not release the drug completely within 120 min.

2.2.5. Contact angle measurements

Contact angles were determined with an optical contact angle meter (Drop shape analysis system DSA100, Krüss, Hamburg, Germany). A single drop of potassium dihydrogenphosphate buffer (0.8 μl) was placed on the top of a pellet. The mean value of eight measurements was determined for each sample.

2.2.6. Differential scanning calorimetry

A DSC-1 Star Systems calorimeter (Mettler-Toledo, Gießen, Germany) was used for thermoanalytical characterization. All samples with a weight of approximately 5 mg each were heated in sample pans in dublicate. First, the sample was transferred in a pre-heated chamber (50 °C). The temperature was held at 50 °C for 2 min and afterwards cooled down with a cooling rate of 20 K min^{-1}. In the second heat cycle, the sample was heated up to 110 °C with a heating rate of 2 K min^{-1}.

3. Results and discussion

3.1. Preliminary tests

Compacted binary mixtures of NXP 1210 (Section 2.2.1) and different excipients were dissolved in buffer solution to evaluate their applicability as solubilization aids.

No dissolution was found for pure NXP 1210. An increase in drug dissolution was observed for all investigated excipients (Fig. 1). The fastest dissolution rate without delayed release could be achieved by using crospovidone (Polyplasdone® XL-10). The drug dissolved completely within 20 min. Compacts of PVA–PEG-graft copolymer

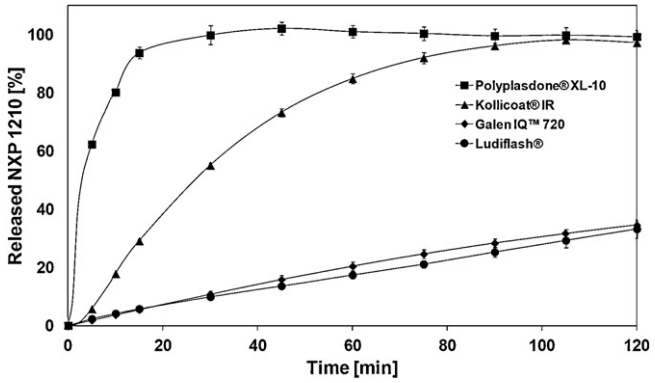

Fig. 1. Dissolution profiles of NXP 1210 compacts (binary mixtures), paddle apparatus Ph. Eur., potassium dihydrogenphosphate buffer pH 7.5, 75 rpm, 37 °C, $n = 3$, mean ± SD. Polyplasdone® XL-10: crospovidone, Kollicoat® IR: PVA–PEG-graft copolymer, Galen IQ™ 720: 6-O-α-D-glucopyranosyl-D-sorbitol and 1-O-α-D-glucopyranosyl-D-mannitol dehydrate, Ludiflash®: D-mannitol, crospovidone, polyvinyl acetate, povidone.

(Kollicoat® IR) and NXP 1210 dissolved more than 80% of the drug in 60 min with an initial delayed release. In contrast, GPS/GPM (Galen IQ™ 720) and the mixture of D-mannitol, crospovidone, polyvinyl acetate and povidone (Ludiflash®) exhibited a minor impact on dissolution characteristics of NXP 1210 with less than 20% drug release in 1 h. This fact together with a lack of a delayed release excluded these excipients as possible solubilization aids in a lipid based immediate release formulation. Based on these results, feasibility of PVA–PEG-graft copolymer and crospovidone as solubilization aids in the solid lipid extrusion at room temperature were investigated. In the extrusion experiments, a mixture of both solubilizers was investigated to combine a fast dissolution rate with an adequate delayed release.

3.2. Solid lipid extrusion with variations of hard fat and solubilizers

Hard fat is considered as essential excipient to ensure feasibility of the solid lipid extrusion at room temperature (Krause et al., 2009). The process is robust and a high drug load can be achieved. In the first extrusion trials, mixtures of pure hard fat, PVA–PEG-graft copolymer, crospovidone and NXP 1210 were processed (Table 1). The content of the lipid binder was varied depending on the amount of solubilizers. The NXP 1210 load was kept constant. A common screw set up with conveying elements was used to ensure the extrusion at room temperature (Fig. 2). The pitch size of the screw elements decreased from the powder feeder to the die of the extruder to enable a moderate pressure in the feed- and compression section and to arrange higher pressure at the die. The absence of kneeding elements should decrease high shear forces. Thompson and Sun (2009) described the low energy input of conveying elements in the extrusion process. Thermal stress of the formulation was reduced and an extrusion at room temperature was possible.

The fastest dissolution was obtained with 10% hard fat (Fig. 3) and 40% solubilizers. The dissolution rate decreased with decreased content of solubilizers (increased content of hard fat). All dissolution profiles exhibit a delayed release of NXP 1210 depending on the amount of lipid and solubilizers. However, no formulation released the drug completely after 2 h.

Table 1
Compositions of NXP 1210 with hard fat and mixture of solubilizers.

NXP 1210	50%	50%	50%	50%
Crospovidone	20%	15%	10%	5%
PVA–PEG-graft copolymer	20%	15%	10%	5%
Hard fat	10%	20%	30%	40%

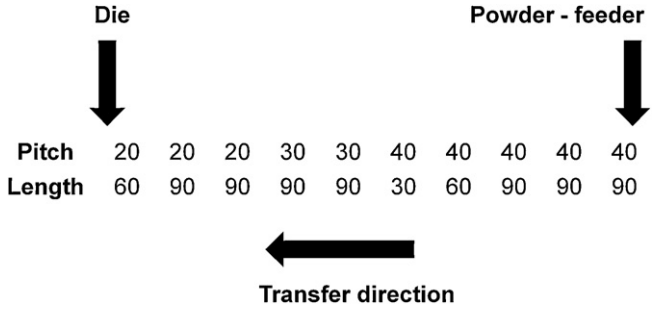

Fig. 2. Screw configuration for the solid lipid extrusion at room temperature. Extrusion was performed with a screw speed of 50 rpm and a feeding rate of 30 g min^{-1}.

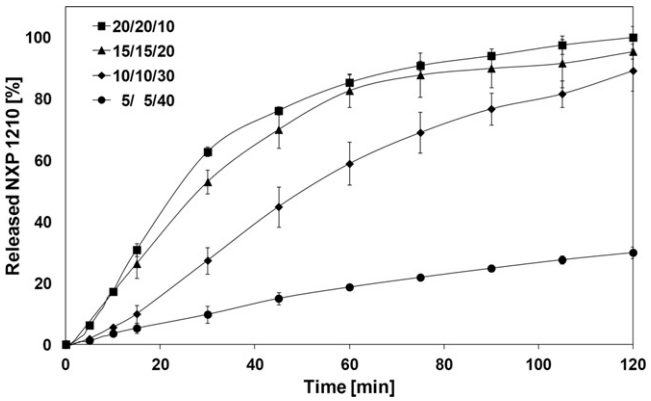

Fig. 3. Dissolution profiles of NXP 1210 extrudates (50% drug load) with variable amounts of excipients (compositions see Table 1): PVA–PEG-graft copolymer/crospovidone/hard fat, paddle apparatus Ph. Eur., 75 rpm, potassium dihydrogenphosphate buffer pH 7.5, 37 °C, $n = 3$, mean ± SD.

NXP 1210 has a partition coefficient between octanol and water (log P) of 3 (Caron et al., 1997) describing the lipophilic character of the drug and its high affinity to lipophilic systems. To exclude a potential interaction between hard fat and NXP 1210, different binary mixtures of hard fat with NXP 1210 were investigated with differential scanning calorimetry (Fig. 4). The higher the amount of hard fat, the lower the melting point of NXP 1210 in this mixture. This observation might be due to the solubility of NXP 1210 in hard fat and could be correlated with a decreased dissolution rate. Due to that fact, the total amount of lipid should kept as small as possible. Only 5% of drug substance is solubilized in molten hard fat by

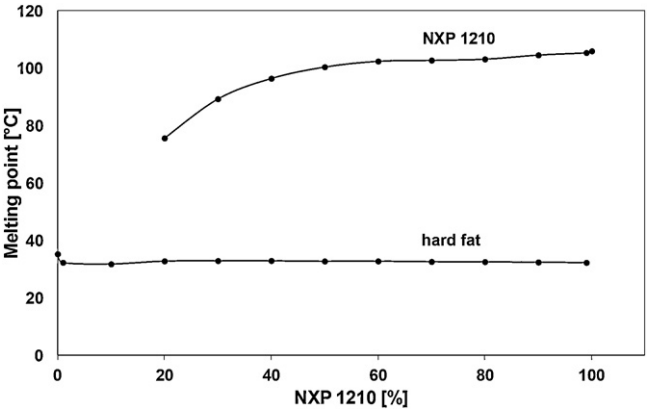

Fig. 4. Melting points of NXP 1210 and hard fat as pure substances and in binary mixtures determined in DSC measurements.

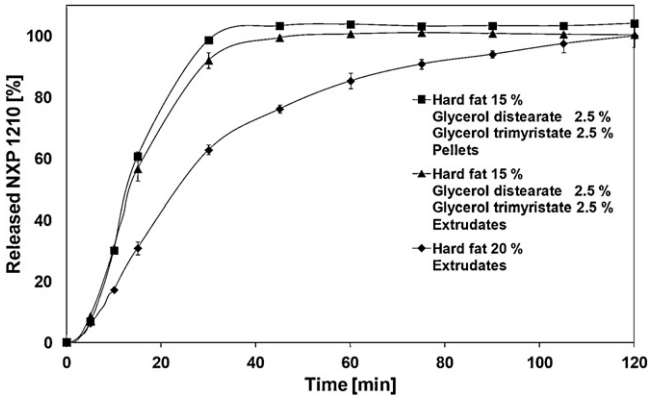

Fig. 5. Release of NXP 1210 (50%) from pellets and extrudates with different lipid binder, paddle apparatus 75 rpm, potassium dihydrogenphosphate buffer pH 7.5, 37 °C, $n = 3$, mean ± SD. All formulations included crospovidone (30%).

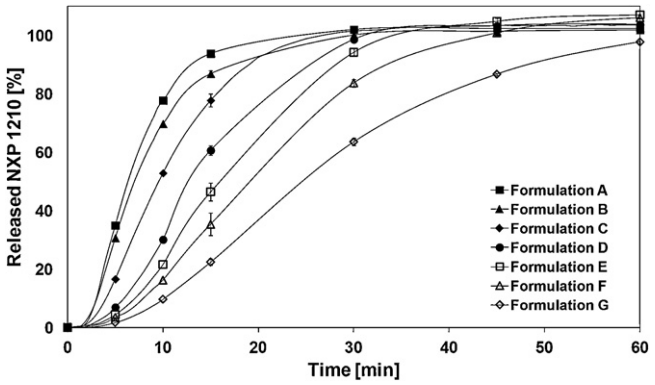

Fig. 6. Dissolution profiles of NXP 1210 pellets (50% drug load), each formulation included NXP 1210 50%, hard fat 15%, glycerol distearate 2.5%, glycerol trimyristate 2.5% with variable amounts of solubilizers (compositions see Table 2). Paddle apparatus Ph. Eur., 75 rpm, potassium dihydrogenphosphate buffer pH 7.5, 37 °C, $n = 3$, mean ± SD.

mixing at the ratio of 8:2, as indicated by thermoanalysis (differential scanning calorimetry). During extrusion, the hydrophobic binder just softens, but does not melt completely. Therefore, a melting of API in hard fat is negligible.

In conclusion, an extrusion at room temperature could be performed with all formulations. A good agreement between process performance and a fast dissolution profile with a corresponding delayed release was observed for the formulation containing 20% lipid binder.

3.3. Extrusion/spheronization-formulation improvement

For further investigations, a combination of hard fat (15%), glycerol distearate (2.5%) and glycerol trimyristate (2.5%) was used as lipid binder. This mixture was already successfully extruded with the hydrophilic salt sodium benzoate (80%) (Krause et al., 2009) and showed superior properties towards hard fat as extrusion aid only. Resulting pellets exhibited a small aspect ratio and adequate dissolution profiles.

In the first part of the present study, the lipid composition was blended with 50% NXP 1210 and 30% of a one to one mixture of PVA–PEG-graft copolymer and crospovidone. The extrusion was feasible at room temperature and the achieved extrudates had a smooth surface. Fig. 5 shows that the extrudates with hard fat as lipid binder released 80% of the drug within almost 50 min. The exchange of just hard fat (20%) as binder to a mixture of hard fat (15%) with glycerol distearate (2.5%) and glycerol trimyristate (2.5%) led to an increase in the dissolution rate. Within almost 30 min 80% of the drug was dissolved. A further improvement in the dissolution rate could be achieved by rounding the extrudates. Spheronization might increase the specific surface area and thereby lead to a slightly faster dissolution.

In the next step, formulations with different amounts of PVA–PEG-graft copolymer and crospovidone as solubilizer were extruded (Table 2) based on the results of the preliminary tests with compacts (Fig. 1). The total amount of solubilizers was kept constant. The aim was to achieve delayed release characteristics in the initial phase of the dissolution, but then a sufficient fast and complete drug release. Less than 5% drug release within 2 min was considered to indicate sufficient taste masking. All formulations were extruded at room temperature and afterwards spheronized. Increased dissolution of NXP 1210 pellets was obtained with an increased amount of crospovidone (Fig. 6). In comparison to the preliminary tests, all formulations showed a delayed release. A more delayed release was achieved with an increased amount of PVA–PEG-graft copolymer according to the preliminary tests. All formulations showed a delayed release indicating a taste-masking effect. The mean dissolution time 80% (MDT) decreased with a higher content of crospovidone (Fig. 7).

Dissolution behavior can depend on surface structure and wetting potential of the dosage form (Windbergs et al., 2009). Moreover, changes in the contact angle could also follow through alteration in the surface (Callies and Quéré, 2005). In this context impact of the variation in the amount of solubilizers on the contact angle was also investigated. A correlation could be drawn between the MDT 80% and the contact angle of the pellets (Fig. 8). Both, the mean dissolution time 80% and the contact angle decreased with an increased amount of crospovidone which corresponds to a lower amount of PVA–PEG-graft copolymer. Different affinities triggered by adhesion, solubility or mean particle size could affect the penetration of solubilizers into the lipophilic matrix. Hence, different

Table 2
Combination of NXP 1210 pellets with different amounts of solubilizers.

	A	B	C	D	E	F	G
PVA–PEG-graft copolymer	0%	5%	10%	15%	20%	25%	30%
Crospovidone	30%	25%	20%	15%	10%	5%	0%
Each formulation included							
NXP 1210	50%						
Glycerol distearate	2.5%						
Glycerol trimyristate	2.5%						
Hard fat	15%						

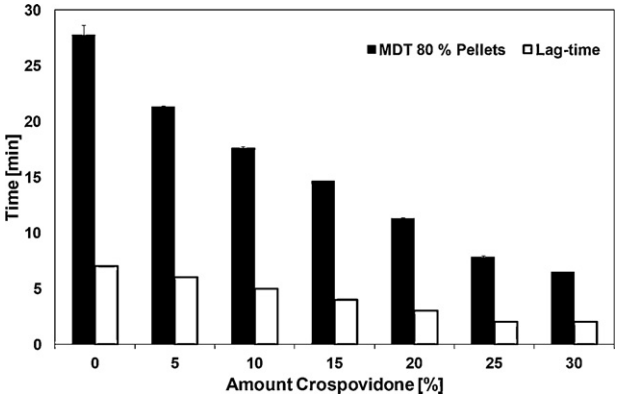

Fig. 7. Mean dissolution time 80% (MDT 80%) of lipid pellets (Table 2) and the corresponding lag-time (released NXP 1210 ≤ 5%), paddle apparatus Ph. Eur., 75 rpm, potassium dihydrogenphosphate buffer pH 7.5, 37 °C, $n = 3$, mean ± SD. A release of <5% NXP 1210 was defined as lag time.

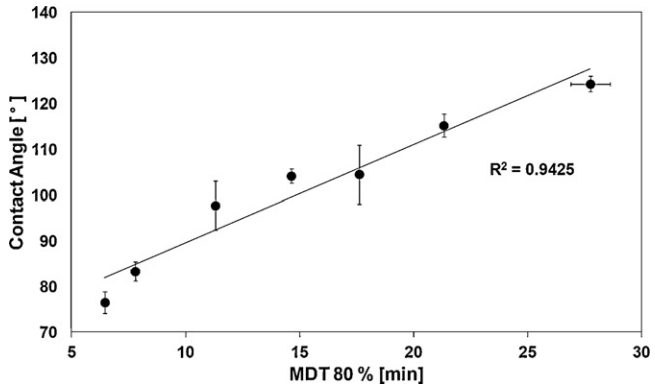

Fig. 8. Relationship of contact angle and mean dissolution time (80%) of NXP 1210 pellets (50% drug load) and different amounts of solubilizers (Table 2).

surface morphologies and properties might arise and therewith diverse contact angles could result.

4. Conclusion

In this study lipid based pellets of the poorly soluble drug NXP 1210 were successfully produced by the solid lipid extrusion/spheronisation at room temperature. An immediate release of the pellets could be combined with a delayed release at the beginning of the dissolution profile ensuring a taste-masking effect for the bitter tasting drug. Rate of dissolution and duration of the lag-time could be controlled by adapting type and amount of solubilizer. A correlation could be drawn between the contact angle and the mean dissolution time of the produced pellets. These results highlighted the applicability of the solid lipid extrusion at room temperature as promising technique to produce lipid based immediate release oral dosage forms with a taste-masking effect for poorly soluble drugs.

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