Solid form change of carbamazepine during hot melt processing

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The aim was to study how hot melt (HM) process parameters affect the formation of carbamazepine containing Egalet® tablets and their functionality.

A fractional factorial 2^4 design of experiment (DoE) was composed, where the investigated factors were melting temperature (90, 115 and 140 °C), melting time (10, 25 and 40 min), drug loading (15, 30 and 50 % (w/w)) and molecular weight of the polymer (PEG 35 000, PEO 100 000 and 300 000). Hot melt processing was performed on injection molding system (HAAKE MiniJet, Thermo Scientific, Germany). Powder blend was placed into a barrel, heated into given temperature and for the time period described in the DoE, which after the molten mass was injected into a mould (height 6 mm, volume 50 mm^3, 25 °C). The polymorphic form of active pharmaceutical ingredient (API) was determined using X-ray diffractometer (X'Pert Powder, Pan Analytical, The Netherlands, a continuous 2θ scan, range of 2 to 40°, step size 0.0263 °2θ, scanspeed of 0.0673 °2θ/s). *In vitro* release behaviour of the Egalet® tablets were determined by paddle method (Vankel VK 7025 Dissolution tester, Agilent Technologies, USA, 900ml, 50 rpm, 37 °C, pH 1.2) using a wavelength of 269 nm (Cary UV-Vis specthrometer, Agilent Technologies, USA).

The results indicate that the HM process can induce polymorphic transition of API and the most crucial process parameters are melting temperature and molecular weight of the polymer. High process temperature and low molecular weight of the polymer induced polymorphic transition of API, which might be due to the dissolution of the API into rapidly melting polymer during the process and consequent recrystallization of API into metastable polymorphic form after the molten mass was injection molded and cooled down. Furthermore, the results indicate that the polymorphic transition can affect the release rate of the API.

Keywords: carbamazepine, solid form change, hot melt process, *in vitro* dissolution

1 Introduction

Hot melt (HM) processing, where active pharmaceutical ingredient (API) drug is either dispersed or dissolved into molten carrier, has emerged as a powerful processing alternative in solid dosage form production[1,2]. Thus it provides an attractive alternative for the traditional solid dispersion production methods, such as spray drying, coevaporation, coprecipitation and freeze-drying[3]. Despite the increased interest towards the method, the HM process can be still regarded as challenging and complicated alternative, since the relationship between actual process and *in vitro* release is not fully understood.

The aim of this work was to evaluate, how the hot melt process parameters affect to the formation of Egalet® tablets and their functionality in terms of carbamazepine release. A fractional factorial 2^4 design of experiment (DoE) was composed, where the investigated factors were melting temperature (90, 115 and 140 °C), melting time (10, 25 and 40 min), drug loading (15, 30 and 50 % (w/w)) and grade of the polymer (PEG 35 000, PEO 100 000 and 300 000). The detailed description of the design of experiment is presented in Table 1.

Table 1. Design of experiment, 2^4 fractional factorial design.

Formulation	Polymer grade	Temperature (°C)	Time (min)	API loading (% (w/w))
F1	35 000	90	10	15
F2	35 000	140	40	15
F3	35 000	140	10	50
F4	35 000	90	40	50
F5	100 000	115	25	30
F6	300 000	140	10	15
F7	300 000	90	40	15
F8	300 000	90	10	50
F9	300 000	140	40	50

2 Materials and methods

Carbamazepine (Hawkins Pharmaceuticals, Minneapolis, USA) was used as a model API and one polyethylene glycol (PEG 35 000, Sigma-Aldrich Chemie, GmbH, Taufkirchen, Germany) and two different grades of polyethylene oxides (PEO 100 000, Polyox WSR N-10, Dow Chemical Company, Midland, USA; PEO, 300 000 Polyox WSR N-750, Dow Chemical Company, Midland, USA) were used as polymers.

2.1 Powder blend preparation and hot melt processing

Powder blends consisting of API degrees of 15, 30 and 50 % (w/w) were mixed in a mortar using a card. Hot melt processing was performed by injection molding system (HAAKE MiniJet, Thermo Scientific, Germany). Powder blend was placed into a barrel, heated into given temperature and for the time period described in the DoE (Table 1), which after the molten mass was injected into a mould (height 6 mm, volume 50 mm^3, 25 °C). The injection pressure was adjusted according to polymer: 300 bars for PEG 35 000 and 800 bars for PEO 100 000 and 300 000.

2.2 Differential scanning calorimetry (DSC)

Behaviour of pure API during heating was determined by DSC (DSC 7, Perkin-Elmer, San Jose, USA). Instrument was calibrated with indium. Samples weighing approximately 4-6 mg were heated from 30 to 160 °C with a rate of 10°C/min.

2.3 X-ray powder diffraction (XRPD)

The polymorphic form of API was determined using X-ray diffractometer (X'Pert Powder, Pan Analytical, The Netherlands). Three replicate samples were measured and a continuous 2θ scan was performed in a range of 2º to 40° using CuKα radiation (λ = 1.5406 Å) with step size of 0.0263 °2θ and scan speed of 0.0673 °2θ/s.

2.4 Principal component analysis (PCA)

Principal component analysis was performed using SIMCA-P (Version 12.0, Umetrics AB, Umeå, Sweden) in order to identify and classify the Egalet® tablets containing different polymorphic forms of API. The data was pre-treated by standard normal variate (SNV) filter and centering. The predictive power of PCA model was cross-validated.

2.5 *In vitro* dissolution test

In vitro release behaviour of the Egalet® tablets was determined by paddle method (Vankel VK 7025 Dissolution tester, Agilent Technologies, USA, 900ml, 50 rpm, 37 °C, pH 1.2) using a wavelength of 269 nm (Cary UV-Vis specthrometer, Agilent Technologies, USA). Sample was taken every 3rd minute during the first 30 min, which after the sampling was performed in 5 min intervals up to 300 min.

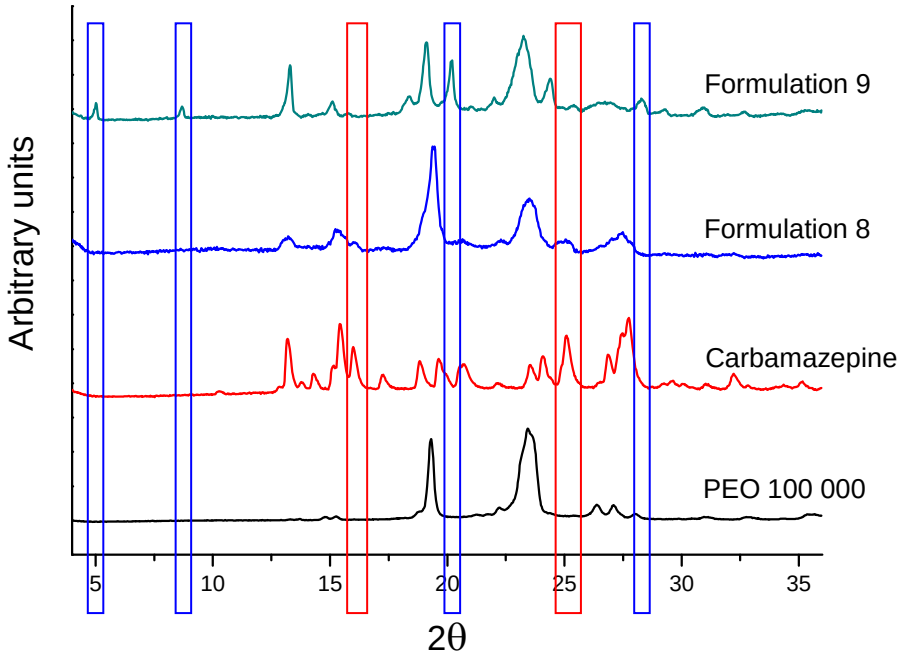

Figure 1. X-ray diffractograms of PEO 100 000, carbamazepine (untreated original form) and formulations F8 and F9. The distinctive reflections of the original polymorphic form are marked with red rectangle and for another polymorph with blue rectangle.

3 Results

3.1 Solid form transformation

The results suggested that another polymorphic form of API was present in some tablets, when the powder blend containing API and polymer was heat processed to produce Egalet® tablets. The diffractograms of PEO 100 000, untreated API, Egalet® tablet formulation F8 containing the original form of API and formulation F9 containing another polymorphic form are presented in Figure 1. The observed changes in the diffractogram of formulation 9 are suggesting presence of another polymorphic form.

PCA model was used in order to obtain an overview of the polymorphic transition during the hot melt process. Satisfying model was achieved by two principal components (PCs) (R^2X 0.95 and R^2Q 0.94), which of the first PC explained 0.86 % and the second 0.08 % of the variance. During model building data from 18.6 to 19.7 °2θ was removed, since it contained overlapping information and thus complicated the modeling. Additionally, F2 and F8 contain only two samples, since one observation from each formulation were discarded as outliers.

Loading plot, which indicates the importance of each variable in capturing the variance, is shown in Figure 2. The first PC captures the information arising from the presence of the polymer (Fig. 1). The second PC captures the information of the polymorphic form (Fig.1), i.e. high values indicate another polymorphic form and low values the original polymorphic form. Thus, in the score plot presented in Figure 3, the Egalet® tablet formulations 1, 2, 6, and 7 containing 15 % (w/w) API are mostly located at the right side of the origin where as formulations 3, 4, 8 and 9 containing 50 % (w/w) API can be found at the left side. Additionally formulations containing another polymorphic form can be located on the upper part of the score plot and formulations containing the original form are found in the lower part.

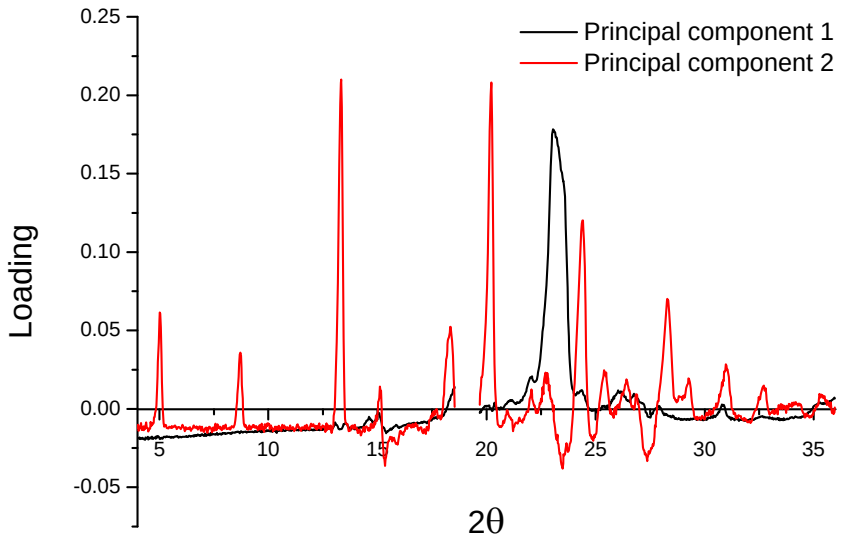

Figure 2. Loading plot of the PCA model.

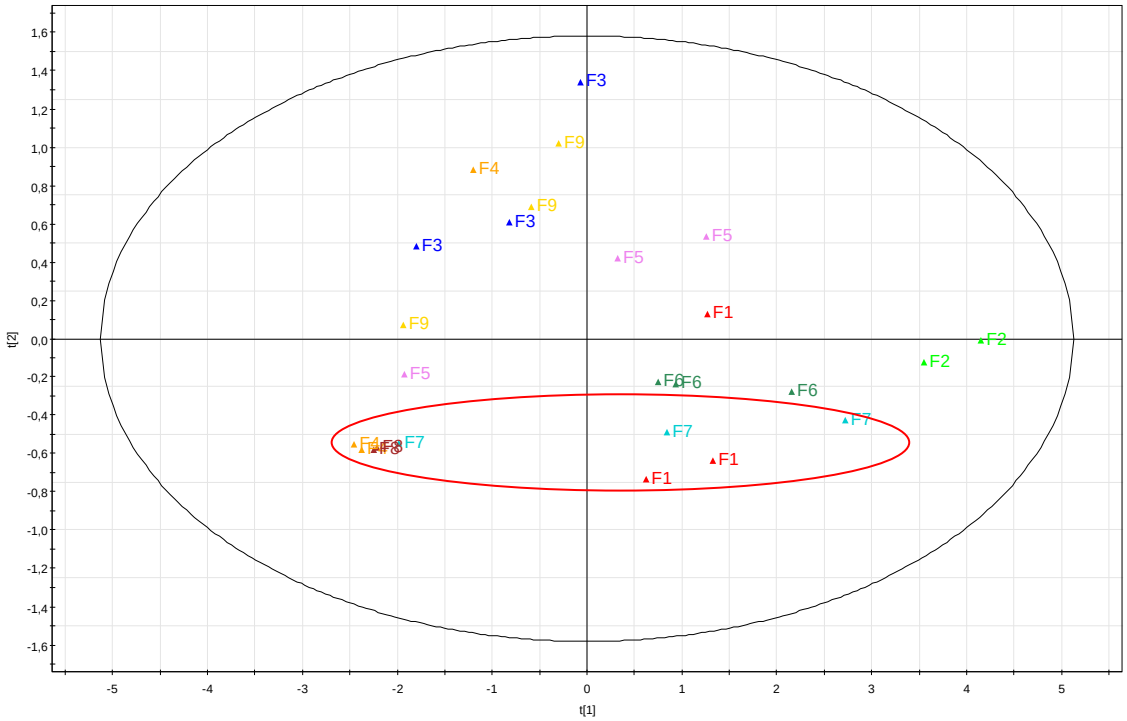

Figure 3. PCA score scatter plot: the first PC on X-axis captures the information on the presence of the polymer and the second PC on Y-axis the polymorphic form of the API. Black ellipse describes the 95 % confidence level according to *Hotelling's* T^2 and red ellipse designates Egalet® tablets consisting of the original polymorphic form of carbamazepine.

It can be concluded that Egalet® tablet formulations 2, 3, 5 and 9 consist all of another polymorphic form of carbamazepine, where as formulations 7 and 8 contain only the original form. Formulations 1 and 4 produce both original and another polymorphic form, which can be confirmed by the original XRPD data: one replicate of formulation 1 and 4 show distinctive reflections common to the new polymorphic form (results not shown). Formulation 6, which is located very close to the original form containing tablets in the score plot (Fig. 3), was an exception: although its diffractogram contained the reflections representing the another polymorphic form, it also had reflections corresponding to the original form (results not shown). It can be hypothesize that the API exists as a mixture of both forms in formulation 6.

2.2 *In vitro* release

The percentage of released amount of API is presented in Figure 4. As expected, the change in the polymer grade affects the release rate. PEG 35 000 containing formulations 1-4 have faster release rates than with PEO 100 000 and 300 000 containing formulations 5-9.

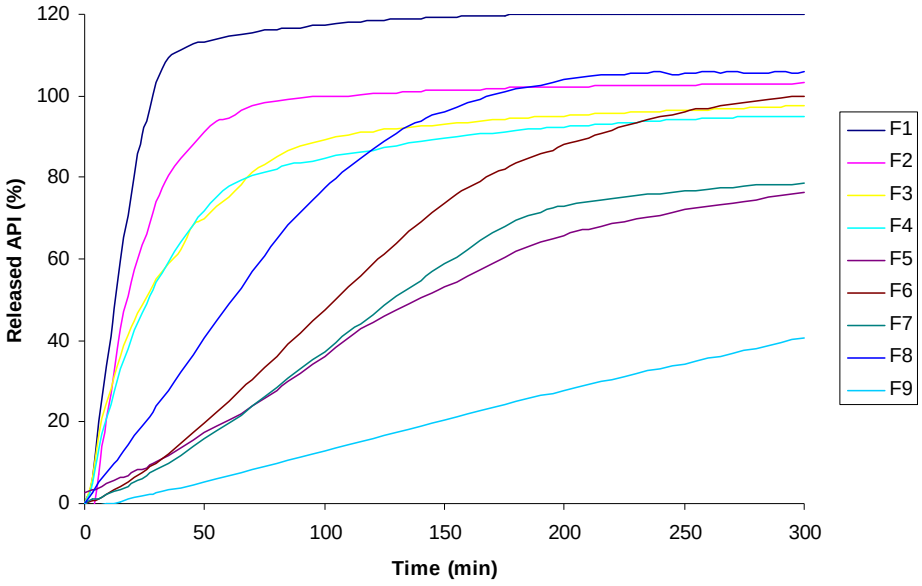

Figure 4. API release profiles of formulations F1-9 as a function of time. The formulation in question is indicated on the right side of the figure. (*n*=6)

Process induced polymorphic transition seems to decrease the release rate of carbamazepine. Egalet® tablet formulations 9 and 5 containing another polymorph form release their contents slower than formulations 7 and 8, which contain the original polymorph. The same trend is seen when PEG 35 000 is used as a polymer: formulations 3 and 4 release their contents slightly slower than the original form containing formulations 1 and 2. Formulation 6 is again an exception: in contrary to the observed trend the release rate of the formulation in question is slower than the original form containing formulation 7.

4 Discussion

The results indicate that by utilization of low melting temperature and high molecular weight polymer it is possible to maintain the original API form. This can be due that the high molecular weight polymer melts more slowly and/or the melting is incomplete, and thus the API has limited possibilities to dissolve into molten mass and consequently re-crystallizes into another polymorphic form. Although low molecular weight polymer melts faster and creates better environment for the API to dissolve into the polymer, the process is not always complete and thus a mixture of different solid forms can exist. This could be demonstrated with formulations F1 and F4, which exhibited, depending on the sample, either the original or new polymorph form of API.

Higher process temperatures produce the new polymorphic form in more robust manner, which indicates that sufficient heating is needed in order to melt the polymer, dissolve the API, create supersaturation and enable re-crystallization during cooling[1]. However, if the melting time is not long enough, the polymorphic form of the API can be a mixture of the original and another form regardless of the high melting temperature, as with the formulation 6.

The choice of the polymer has an impact on the release rate: the higher the molecular weight the slower the release rate. Additionally, the process induced solid form change can have

crucial effect. The release rate of another polymorphic form can differ from that of the original form. This is further complicated by the fact that the particle size of the recrystallized phase may differ from the original particles[1,4]. However, the degree of drug loading seems to be insignificant with the investigated range.

5 Conclusions

Melting temperature and the choice of polymer are crucial parameters, when carbamazepine is hot melt processed with polyethylene glycol or polyethylene oxides. Melting time can have some importance, but the role of drug loading degree seems to be insignificant with the investigated range.

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References

1. C. Bruce, K.A. Fegely, A.R. Rajabi-Siahboomi, J.W. McGinity: Crystal growth formation in melt extrudates. Int J Pharm 2007, 341:162-172

2. E. Verhoeven, T.R.M. De Beer, G. Van den Mooter, J.P. Remon, C. Vervaet: Influence of formulation and process parameters on the release characteristics of ethylcellulose sustained-release mini-matrices produced by hot-melt extrusion. Eur J Pharm Biopharm 2008, 69:312-319.

3. G.P. Andrews, O.A. Abudiak, D.S. Jones: Physicochemical characterization of hot melt extruded bicalutamide-polyvinylpyrrolidone solid dispersion. J Pharm Sci 2010, 99:1322-1335.

4. S. Šhehić, G. Betz, Š. Hadžidedić, S.K. El-Arini, H. Leuenberger: Investigation of intrinsic dissolution behavior of different carbamazepine samples. Int J Pharm 2010, 386:77-90.