A quality by design (QbD) twin – screw extrusion wet granulation approach for processing water insoluble drugs

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In this study, a Quality by Design (QbD) approach was used to identify the effect of formulation parameters in a twin screw wet extrusion granulation process for the manufacturing of ibuprofen (IBU) granules with increased dissolution rates. A fractional factorial Design of Experiment (DoE) was used to investigate the effect of the excipient composition, binder amount and liquid to solid (L/S) ratio (independent variables) on drug dissolution rates, median particle size diameter and specific surface area (dependent variables). The intra-granular addition of the binder in inorganic/polymer blends processed with ethanol as granulating liquids facilitated the formation of granules at various particle sizes. DoE regression analysis showed that all formulation parameters affect the dependent variables significantly. The enhanced dissolution rates were attributed not only to the IBU particle size reduction and adsorption in the porous inorganic network but also to the high specific surface area of the produced granules. Dynamic vapour sorption showed increased water absorption for granules with small particle size distribution and high specific surface area.

**Key words:** wet granulation, DoE, QbD, dissolution rate, specific surface area, water sorption
1. Introduction

In the recent years twin–screw extrusion granulation (TSG) has attracted significant interest for the development of a variety of oral solid dosage forms such as granules, tablets or capsules in a continuous manufacturing manner. TSG approaches have been introduced as an alternative approach for the passage from batch processing to continuous manufacturing in the pharmaceutical industry. Although there are several reported studies, extrusion granulation is still in its infancy and further work is required to fully understand the technology (Schimdt et al., 2016). In a recent study, Thompson et al highlighted the influence of various processing and formulation parameters on the granulation process. According to Thompson et al., and Djuric et al., scaling up of extrusion granulation is not a straightforward exercise and the mechanisms within the process need to be better understood (Thompson, 2015; Djuric et al., 2009).

The two major extrusion granulation approaches are a) wet granulation where the granulating liquid, with or without the addition of binders, is pumped into the screw zones and b) hot melt granulation which uses a molten binder to effectively bind the drug and the polymers (Weatherley et al., 2013). Both process can effectively manufacture high quality granules for immediate or sustained drug release, however, both processes also present a number of drawbacks. For example, wet granulation requires a drying step for water removal that is time consuming while hot granulation uses relatively high barrel temperatures varying from 60-100°C.

An in-depth study was presented by Vercruysse et al., using a six-segmented fluid bed dryer of the ConsiGma™-25 system comprising of a continuous twin screw granulation and drying system (Vercruysse et al., 2015a). By running the system for 1 h the authors evaluated the effect of process outcomes, granule properties and tablet quality attributes. The torque and barrel wall temperatures were stabilized after 30 min performance while the tablet properties were adequate when comparing two ConsiGma systems (-1 and -25). Other studies have highlighted the impact of screw configuration on the particle size distribution, where conveying elements produced wide multimodal size distributions, while kneading elements have found to narrow the size of agglomerates (Vercruysse et al., 2015b; Meng et al., 2016). The delivery of the binder in the powder blend or in the granulating liquid has a tremendous effect on the obtained granule quality (Saleh et al., 2015; Batra et al., 2016). The incorporation of binders, which are blended in the powder mix, resulted in longer residence times and higher torque, but also produced narrower particle size distribution, spherical granules and better binder distribution. In contrast, Fonteyne et al. demonstrated that excellent binder distribution can be
obtained by both when the binder is added in the dry blend or when it is added within the granulation liquid (Fonteyne et al., 2014). In the case of melt granulation, low melting binders create stronger granules and the binder molecular weight appeared to have no effect in the process (Weatherley et al., 2013). More recently the use of a foamed binder solution led to the formation of more uniform wetted mass and larger granule growth (Rocca et al., 2015; Thompson et al., 2012).

Meier et al., (2016) showed that the feeder performance in conjunction to the screw design influences the granule quality for highly drug loaded formulations and the obtained granule particle size requires detailed knowledge of the feeding systems (Meier et al., 2016). The formulation composition is an aspect that clearly should be taken in account (Meier et al., 2015; Keen et al., 2015; Vanhoorne et al., 2016) where binary or ternary premix blends affect the granule quality as well as the drug dissolution rates.

In order to understand the granulation process and the mechanisms involved during material processing, in – line and off – line process analytical tools (PAT) have been implemented to provide valuable insights (Fonteyne et al., 2016; Monteyne et al., 2016a, 2016b; Kumar et al., 2014; Vercruysse et al., 2014; Chablani et al., 2011; Maniruzzaman et al., 2015; Kumar et al., 2014). Near infrared (NIR) probes were used to measure the granules moisture content in comparison to Karl Fisher and loss of drying moisture measurements. In addition, NIR was used to understand the mixing and distribution of granulating liquid. The coupling of Raman mapping with twin – screw granulation provides information of the polymorph transitions and allows mapping of the drug distribution in the granular agglomerates. Similarly, the binder mixing efficiency and distribution was identified through hyperspectral coherent anti-Stokes Raman scattering (CARS) microscopy. The use of high-speed camera enabled also the visualization of the particle size distribution and shape in real time.

The purpose of the current study was to investigate the effect of formulation parameters such as excipient composition ratio, binder amount and L/S ratio on the granule formation of a water insoluble drug when processed with organic granulating liquids. Dry blends of inorganic excipients such as anhydrous dicalcium phosphate with a low molecular weight hydroxypropylmethyl cellulose (HPMC) grade were processed for first time with ethanolic granulating liquid.
2. Materials and methods

2.1 Materials

Ibuprofen (IBU) was purchased from FarmaShino Pharmaceuticals Co. Ltd., (Nanjing, China) and dibasic calcium phosphate anhydrous (DCPA, Fujicalin®, DCPA) was kindly donated by Fuji Chemical Industries Co., Ltd. (Japan). Hydroxypropyl methylcellulose based polymer Pharmacoat 603 (HPMC) was kindly donated by Shin Etsu, Japan. Polyethylene glycol 2000 (PEG) and ethanol (95%, 190 proof) were purchased from Sigma Aldrich (Gillingham, UK). All solvents used were of analytical grade and used as received.

2.2 Twin screw granulation and DOE analysis

Extrusion granulation studies were conducted using a twin-screw extruder (EuroLab 16, Thermo Fisher, Duisburg, Germany) with a length/diameter (L/D) ratio of 40). A configuration with three kneading zones at 30°/40°/60°, 60° and 90° angles respectively was used for all the granulation trials. The IBU formulations were thoroughly mixed in a Turbula (TF2, Basel, Switzerland) mixer of 1 Kg batches for 10 min each, prior to the extrusion process. During granulation, dry blends of the drug, polymer, inorganic carrier and the binder PEG were fed into the extruder with a volumetric feeder (Brabender, Duisburg, Germany) at 1 kg/h feed rate while the screw rate was set at 100 rpm under ambient temperature. A peristaltic pump, plunged in close proximity to the extruder’s feeding opening, supplied the granulating liquid (ethanol) at a constant rate. The “as made” extruded granules were dried in an oven (Memmert UF30, UK) at 30°C for 2h then further micronized through a cutter mill (Retsch, Germany) with a 250 µm fitted mesh.

For the QbD approach a Design of Experiment (DoE) was introduced by using Fusion One software (DoE Fusion One™, California, USA). A response surface fractional factorial design (2^3+3=11) in randomized order with three centre points was designed with three independent and three dependant variables. The drug loading was kept constant (40%) where the DCPA/Polymer ratio (0.33 – 2.0), binder amount (5 – 12%) and L/S ratio (0.25 – 4.0) were set as independent variable. The drug release rate, the median particle size distribution (D50) and specific surface area (SSA) were defined as the dependant variables.

2.3 Particle size analysis

The particle size distribution of the extruded granules was determined using a Mastersizer 2000 laser diffraction analyser (Malvern Instruments, UK) with a dry powder sample dispersion accessory (Scirocco 2000). Samples were processed with a pressure at 0.5
bars and a vibration feed rate of 50% in triplicate. The software analysis provided the $d(10)$
d$(50)$ and $d(90)$ granular particle size values which are the geometric median particle size
particle diameters at 10 and 90% of the cumulative volume distribution, respectively.

2.4 Scanning electron microscopy (SEM)

SEM images of the extruded IBU granules were captured using a cold-cathode field-
emission gun scanning electron microscope (Hitachi SU8030 FEG-SEM, Tokyo, Japan) with
30 mm² Ultra-Dry window and Noran 7 software. The samples were glued using adhesive
carbon tape on sample tabs and coated with carbon (Edwards 306 high vacuum carbon
evaporation) prior to the analysis. The accelerating voltage was set at 8 kV.

2.5 X-ray powder diffraction (XRPD)

XRPD was used to determine the solid state of bulk materials, physical mixtures and
extruded granules using a Bruker D8 Advance (Karlsruhe, Germany) in theta-theta mode. For
the study purposes a Cu anode at 40 kV and 40 Ma, parallel beam Goebel mirror, 0.2 mm exit
slit, LynxEye Position Sensitive Detector with 3° opening (LynxIris at 6.5 mm) and sample
rotation at 15 rpm were used. Each sample was scanned from 2 to 60° $2\theta$ with a step size of
0.02° $2\theta$ and a counting time of 0.1 seconds per step; 176 channels active on the PSD making
a total counting time of 35.2 seconds per step. The positions of the diffraction peaks for both
the bulk, physical mixture and granulated products were identified using EVA phase analysis
software (Bruker, Karlsruhe, Germany). TOPAS V4.2 structural analysis software (Bruker,
Karlsruhe, Germany), was utilized to estimate the amount of amorphous content present in the
granules. Crystal structural data of for Ibuprofen was taken from the Cambridge structural
database (CSD) (REFCODE: JEKNOC10) and used as a standard alongside our granules.
TOPAS scales the peaks to the standard and redistributes the rest which allows us to estimate
the percentage amount of amorphous material present in the sample (Freer et al., 1993).

2.6 Differential scanning calorimetry (DSC) study

A Mettler-Toledo 823e (Greifensee, Switzerland) differential scanning calorimeter
(DSC) was used to conduct thermal analysis of the bulk materials, physical mixtures and
extruded granules. Typical samples of 3-5 mg were placed in sealed aluminium pans with
pierced lids. The samples were heated at 10°C/min from 0°C to 220°C under dry nitrogen
atmosphere and reheated at the same heating rate.
2.7 Dynamic vapour sorption (DVS) analysis

Moisture sorption and desorption of the IBU loaded granules were determined via an automated gravimetric dynamic vapour sorption (DVS) analyser, Advantage-1 (Surface Measurements Systems Ltd, UK). All samples were equilibrated at 0% RH for 5 min to record the dry and reference mass prior to the exposition of the samples to the following relative humidity (% RH) profile: 0 to 100% in 20% steps and the reverse for desorption at 25.0±0.1°C and 40±0.1°C. At each stage, prior to the change of the humidity, the sample mass allowed to reach equilibrium defined as \( \frac{dm}{dt}=0.002 \text{ mg/min} \) over 10 min, before the RH was changed. A total gas flow 200 sccm was maintained throughout the study. The amount of water uptake was calculated as percentage of weight change compared to the dry initial mass.

2.8 In vitro dissolution study

In vitro drug dissolution studies were carried out in 900 ml of both 0.1 M HCl (pH 1.2) and 0.2 M dihydrogen-sodium-orthophosphate (pH adjusted with NaOH to 6.8) for 2 hr using a Varian 705 DS dissolution paddle apparatus (Varian Inc. North Carolina, US) at 100 rpm. The dissolution bath and the vessels were equilibrated at 37 ± 0.5°C. Samples (5ml) were withdrawn at predetermined time intervals for HPLC assay. All dissolution studies were performed in triplicate.

2.9 HPLC analysis

The drug release was determined by HPLC analysis using an Agilent Technologies system 1200 series with a HYCHROME S50DS2-4889 (5 µm x 150 mm x 4mm) column. The mobile phase consisted of acetonitrile/water/phosphoric acid (65/35/0.2 v/v) while the flow rate and the wavelength were set at 1.5 ml/min and 214 nm. The calibration curve plotted with concentrations varying from 10 µg /ml to 50 µg/ml and 20 µl injection volumes. The IBU retention times varied from 2.5 – 3.0 min.

3. Results and discussion

3.1 Evaluation of extrusion granulation process

The QbD is well defined by regulatory authorities and involves “A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management”. However, we need to clarify that the current QbD approach is limited to the process
understanding and mainly to the effect of the formulation parameters on the extrusion granulation. The objectives included the formation of IBU granules with increased dissolution rates, uniform particle size distribution and excellent granule flowability.

One of the most important aspects in extrusion granulation is the appropriate selection of the drug carriers as different polymer grades (viscosity and substitution degree) are directly related to the quality of granules and the drug dissolution rates (Vanhoorne et al., 2016). Although HPMC grades with a higher molecular weight have been utilized for sustained release formulations before, in this study we used HPMC substitution type 2910 with a higher degree of hydroxypropyl substituents, which has a low molecular weight and low viscosity. Because HPMC is insoluble in primary alcohols, no swelling occurred and hence low torque values were observed. There is only one study by Djuric and Kleinebudde where inorganic excipients such as DCPA are used to study the scale up of wet granulation processing (Djuric and Kleinebudde, 2010). However, the authors used a low-quality grade of DCPA (Di-CaFos) with high cohesiveness and poor flowability. In this study, we introduced a spray-dried DCPA grade with excellent flowing properties, spherical shape, high surface area and porosity. As described above, for the purposes of the study the screw configuration consisted of three kneading blocks where disks offset at different angles varying at 30°, 60° and 90° (Fig.1). Previous work has shown that kneading elements narrow the particle size of the granules (Vercruysse et al., 2015b; Meng et al., 2016) and particularly the 90° configurations increase agglomeration resulting in fewer fines and small particles (Thompson and Sun, 2010).

The various PEG binder amounts were blended intra-granularly with the dry premix without being dissolved in the ethanolic granulating liquid to facilitate narrower granule size distribution with spherical shape and thus better flowability. In addition, DCPA has shown better granulating performance when processed with organic solvents. PEG was chosen as the binder due to its low molecular weight. PEG is extremely hydrophilic and hydrophilic binders have been shown to affect binder – polymer interactions (e.g. HPMC) and allow for faster dissolution rates (Tan et al., 2014). Finally, the screw speed and feed rate were kept constant at 100 rpm and 1Kg/h respectively, hence the process throughput, in order to reduce the number of granulation variables. There are contradictory reports related to the screw speed and throughput increase (Kumar et al., 2014; Vercruysse et al., 2012; Tan et al., 2011) on the obtained particle size distribution and the formation of large agglomerates. Thus, the effect of processing parameters would require a completely separate study and further experimentation. For the same reasons the IBU amount was kept at 40% for all formulations throughout the granulation process.
As shown in Table 1 the DoE the independent variables included the DCPA/Polymer ratio (A), the binder amount (B) and the liquid/solid (C) ratio on the granulation process while the drug dissolution rate, the median particle size (D50) and the specific surface area (SSA) were identified as the dependent variables. The software regression analysis (Table S1, Suppl. Material) showed that all independent variables have a significant effect on IBU dissolution rates (<0.05). A two-way interaction between A/B, A/C and B/C showed also significant effect on dissolution suggesting a complex granulation process. These results are quite different to a similar study conducted by Maniruzzaman et al., where deionized water was used as granulating liquid and only the excipients ratio influenced the drug dissolution rates. Similarly, DCPA/HPMC, PEG amount and L/S have a significant effect on the granule particle size distribution (p<0.05). The latter is in good agreement with other extrusion granulation studies (Maniruzzaman et al., 2015; Dhenge et al., 2012). Finally, the granule specific surface area was affected significantly by the DCPA/Polymer ratio and the binder (PEG %) amounts.

The contour plots in Fig. 2 show the response surface plots for the three dependent variables. The implementation and analysis of a response surface fractional factorial DoE with a reduced number of runs helped to identify the effects of the selected independent variables and identify those settings for granules of optimized quality.

3.2 Particle morphology and distribution

SEM analysis investigated the size and the morphology of the bulk materials and obtained granules. Fig. 3 shows needle shaped crystal morphology for bulk unprocessed IBU while all extruded formulations appear as granular agglomerates with almost spherical shape. For some extruded formulations, SEM images show the presence of minuscule particles varying for 10 – 50 μm. Furthermore, no drug crystals can be seen in the granules suggesting adsorption in the porous DCPA network (104 m²/g) and consequently particle size reduction of the drug substance through the granulation process. The average particle size of all extruded formulations (except F6) is much smaller compared to bulk IBU which supports this assumption. It is likely that IBU was partly dissolved by ethanol which facilitated its particle size reduction.

Additional investigations were conducted by using laser diffraction analysis to identify the particle size distribution of the various granules. As shown in Fig. 4 several of the granulated batches presented monomodal distribution while for most formulations the size distribution is bimodal. A careful observation of the laser diffraction analysis shows that
bimodal distributions are related to either an increased amount of fine or large agglomerates. Table 1 shows a wide variation for the d(50) particle size diameter of all DOE experiments ranging from 188.0 – 1033μm. The smaller particle size distributions correspond to higher SSA values, which can affect the granule hydration and consequently the IBU dissolution profiles. Furthermore, from Table 1 it can be observed that monomodal particle size distributions are affected by the DCPA/polymer (1:1) and binder amounts (8-12%). As shown in Table S2 (Suppl. Material) most of the granulated formulations presented excellent flowability which was attributed to the presence of DCPA and the obtained quality of the granules (Dhenge et al., 2012).

3.3 X-ray powder diffraction (XRPD)

X-ray analysis of the bulk materials and extruded granules was carried out to investigate the physical state of IBU during processing. Fig. 5 (inset) shows distinct intensity peaks corresponding to IBU at 6.03°, 12.09°, 16.48°, 17.55°, 18.75°, 20.02°, 22.13°, 24.47°, 24.99° 2θ position and PEG at 19.01° and 23.49° 2θ position, respectively (data not shown). The comparison of the physical mixtures and extruded granules diffractograms in Fig. 5 showed a decrease on the intensity of the diffractograms for all formulations. This indicates that a small fraction of IBU transformed from crystalline to amorphous during the granulation process. In order to obtain and identify the amount of amorphous content present, our data was fitted to a standard diffractogram taken from the Cambridge Structural Database (CSD). The amorphous content was then calculated from the redistributed amount which are not attributed to the crystalline material. This amorphous amount was found to be <5%. The usage of ethanol as granulating liquid and the application of high shear mixing due to the three zones of kneading elements facilitated the formation of a small amorphous IBU fraction. This is not uncommon and was also observed when aqueous granulating liquid or melt granulation were used for processing of IBU (Thompson, 2015). Extruded granules were further placed under accelerated stability conditions for six months and as expected, changes on IBU physical state were observed. As shown in Fig. S1 (Suppl. Material) a slight recrystallization of the amorphous fraction occurred at the end of the stability period. It has also been previously reported that IBU’s mobility in the presence of PEG (Zhu et al., 2010) affects the drug physical state.
3.4 DSC analysis

DSC thermal analysis was conducted to further investigate the IBU physical state in the extruded granules in comparison to the bulk substance. DSC scans were carried out for the bulk materials as well. Fig. 6a illustrates the thermal melting transitions of bulk PEG and IBU with endothermic peaks at 62.05°C ($\Delta H = 168.99$ J/g) and 77.79°C ($\Delta H = 92.42$ J/g) respectively. Due to its amorphous nature HPMC presented a glass transition peak at 152.69°C while no thermal event was detected for DCPA. Fig. 6b shows the thermal events for the physical mixtures where PEG presented decreased melting endotherms varying from 59.3 – 63.8°C while for IBU only negligible shifts at 77.5 – 78.5°C could be observed with melting peaks appeared broad. Further melting endotherm depression can be seen for the granulated formulations with PEG melting endotherms varying from 40.0 – 63.5°C and IBU from 69.5 – 75.3°C, respectively.

In both cases the thermal shifts are attributed to the PEG solubilizing capacity on IBU, which has been demonstrated in hot melt granulation studies. Weatherley et al., observed stronger depression of both PEG and IBU melting endotherms in melted granules due to the solubilisation of IBU in the melted polymer (Weatherley et al., 2013). As we didn't apply any thermal processing for the current extrusion granulation the depression of the melting endotherms is also attributed to a combination of factors such as a) the particle size reduction caused by the kneading elements (Niazi, 2007) and b) PEG reach domains in the granules due to the excellent mixing of the extrusion processing.

3.5 DVS analysis

The effect of controlled moisture on the physical solid state stability of the IBU granules manufactured via twin screw granulation process was studied using a DVS machine. The moisture absorption and desorption profiles of the manufactured granules assessed and monitored are depicted in Fig. 7. For this study, it is assumed that the amount of water uptake by various granules can be correlated to its solid-state stability via the dynamic vapour sorption analysis. The presence of hydrophilic components such as HPMC and PEG along with the inorganic DCPA, which promotes disintegration when used in oral solid dosage forms, may lead to an increased amount of water absorbed. As can be seen in Fig. 7, the vapour sorption isotherms indicates increased amount of water uptake upon increasing the relative humidity (RH) at two different conditions (ambient and 40°C). All formulations presented a mass increase from 1.1 – 3.0% at 60% RH at both 25°C and 40°C temperature settings. After
60% RH the water sorption accelerated and the mass of the granules was further increased up to 6 – 7.0% at 100% RH for all three granules batches. As expected the desorption segments of F2, F8 and F9 exhibited a reversible process projected by the event of a steady water loss. All three batches showed similar DVS profiles regardless the difference in formulation compositions and the changes in mass at any relative humidity values higher than 80% RH, dropped significantly.

The increase water sorption for the three granule batches was initially attributed to the composition of the formulations, which contain high amounts of hydrophilic carriers such as HPMC and PEG. However, as it can be seen in Fig. 7(d), unlike other two formulations (F8 and F9), F2 showed temperature independent mass gain as a function of water uptake. In both ambient and 40°C, F2 presented a significant mass gain when the relative humidity reached 100% RH. By examining the values of the dependent variables in Table 1 for the three batches carefully, it is noticed that F2 has a significant smaller particle size and higher SSA compared to the other two. Thus, the increased water sorption for F2 can be attributed to the impact of the physical properties such as particle size and SSA.

3.6 In vitro dissolution studies

One of the main targets of the extrusion granulation process was to enhance the dissolution rates of the water insoluble IBU. DCPA facilitates granule disintegration due to the rapid water uptake and HPMC has been reported to increase dissolution rates due to its hydrophilic nature. Fig. 8 shows the dissolution profiles of high IBU loaded granules (40% w/w) for extruded formulations with the highest dissolution rates in comparison to bulk substance in acidic medium (pH1.2). As it can be seen dissolution rates varied from 65 – 80% after 120min for the extruded granules while only 10% of bulk IBU was dissolved at the same time. As mentioned above all independent parameters have a significant effect on the granule dissolution rates. However, for the formulations with the best dissolution performance independent variables varied from 0.33 – 1.0 DCPA/HPMC ratios, 5 – 8% PEG amounts and 0.25 – 0.3 L/S ratios. Since X-ray analysis showed a small amorphous fraction of IBU in the granules the increase dissolution rates were attributed to the drug adsorption in the inorganic porous network and the subsequent particle size reduction mentioned above. In addition, faster dissolution rates were observed for granulated formulations with high specific surface area (>0.100m²/g), which is directly related to granule porosity. The phenomenon is not uncommon and dissolution properties have found to be significantly affected by porosity changes of the prepared granules (Weatherley et al., 2013; Le et al., 2011) which can result in faster hydration
rates and water sorption. This is in good agreement with the DVS analysis which showed higher water sorption for granules with high surface area and small particle size. The accelerated stability batches (Fig. S2, Suppl. Material) presented similar dissolution profiles after six months without any significant changes irrespectively of the IBU recrystallization as mentioned above.

4. Conclusions

A QbD study was designed to identify the effect of formulation independent variables such as DCPA/Polymer ratio, binder concentration and L/S ratio on the dissolution rate, median particle size and specific surface area (dependent variables) of wet extruded IBU granules. The DoE integration revealed that each dependent variable was significantly affected by the formulation parameters. Physicochemical characterizations showed that IBU crystallinity was slightly affected and a small fraction turned to amorphous state, despite the use of ethanolic granulating liquid. The extruded granules showed uniform particle size distribution, excellent flowability and fast dissolution rates in acidic media due to IBU particles size reduction, through the granulation process, the adsorption in the porous inorganic excipient and the high specific surface area of the obtained granules.

Acknowledgements

The authors would like to thank Fuji Chemical Industry Co., Ltd., Japan for the financial contribution.

5. References


Table 1: DoE of extrusion granulation with DCPA/Polymer ration, binder amount (%) and L/S ratio as independent variables and release (%), median particle size diameter $D(50)$ and specific surface area (m$^2$/g) as dependent variables

<table>
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<th>Run No.</th>
<th>DCPA/Polymer ratio</th>
<th>Binder (%)</th>
<th>L/S ratio</th>
<th>Release ($T_{120min}$) (%)</th>
<th>$D(50)$ ($\mu$m)</th>
<th>SSA (m$^2$/g)</th>
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<tr>
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Figures caption list

Fig. 1  Image of the twin – screw configuration used for the extrusion granulation process.

Fig. 2  Response surface plots of IBU release, specific surface area and particle size distribution dependent variables.

Fig. 3  SEM images of a) bulk IBU, b) F2 granules (DCPA/Polymer 1.0, Binder 8.0%, L/S ratio 0.30) and c) F10 granules (DCPA/Polymer 1.0, Binder 8.0%, L/S ratio 0.30).

Fig. 4  Laser diffraction particle size analysis of various extruded granules F2 (DCPA/Polymer 1.0, Binder 8.0%, L/S ratio 0.30), F9 (DCPA/Polymer 1.0, Binder 5.0%, L/S ratio 0.30) and F11 (DCPA/Polymer 1.0, Binder 12.0%, L/S ratio 0.25).

Fig. 5  XRPD diffractograms of bulk IBU (inset), physical mixture (red) and extruded granules (purple).

Fig. 6  DSC thermographs of a) bulk DCPA, HPMC, IBU and b) physical mixtures and extruded granules.

Fig. 7  DVS analysis of water sorption and desorption of F2 (DCPA/Polymer 1.0, Binder 8.0%, L/S ratio 0.30), F8 (DCPA/Polymer 0.33, Binder 5.0%, L/S ratio 0.25) and F9 (DCPA/Polymer 1.0, Binder 5.0%, L/S ratio 0.30) extruded granules.

Fig. 8  In vitro dissolution studies of bulk IBU and extruded granules (n=3, 37°C, 100 rpm).