AAPS PharmSciTech (2024) 25:174
https://doi.org/10.1208/s12249-024-02890-y

RESEARCH ARTICLE

An Advanced Twin-Screw Granulation Technology: The use of Non-Volatile Solvents with High Solubilizing Capacity

Siva Satyanarayana Kolipaka[1] · Laura Andrade Junqueira[2] · Steven Ross[3] · Vivek Garg[4] · Md Sadeque Hossein Mithu[3] · Saumil Bhatt[5] · Dennis Douroumis[1,2]

Received: 2 May 2024 / Accepted: 9 July 2024
© The Author(s) 2024

Abstract

Purpose Twin-screw wet granulation (TSWG) is a manufacturing process that offers several advantages for the processing of water-insoluble active pharmaceutical ingredients (APIs) and has been used for increasing the solubility and dissolution rates. Here we introduce a novel TSWG approach with reduced downstream processing steps by using non-volatile solvents as granulating binders.

Methods Herein, TSWG was carried out using Transcutol a non-volatile protic solvent as a granulating binder and dissolution enhancer of ibuprofen (IBU) blends with cellulose polymer grades (Pharmacoat® 603, Affinisol™, and AQOAT®).

Results The physicochemical characterisation of the produced granules showed excellent powder flow and the complete transformation of IBU into the amorphous state. Dissolution studies presented immediate release rates for all IBU formulations due to the high drug-polymer miscibility and the Transcutol solubilising capacity.

Conclusions Overall, the study demonstrated an innovative approach for the development of extruded granules by processing water-insoluble APIs with non-volatile solvents for enhanced dissolution rates at high drug loadings.

Keywords immediate release · non-volatile solvents · solubility enhancement · twin-screw wet granulation

Introduction

Twin screw granulation (TSG) is a process that aims to enlarge the particle size of powder blends usually comprising of an active pharmaceutical ingredient and polymer [1–3] in a continuous manner. As a result, it increases powder flowability, content uniformity, bulk density and porosity. TSG offers several advantages such as fewer or no scale-up steps, continuous productions at higher throughput, rapid technical transfer, less space requirement, cost-effectiveness, and improved manufacturing efficiency [4–6]. The applicability of TSG is widely recognised due to its major advantages for the continuous production of granules. Continuous granulation lines such as ConSigma and MODOCS for powder-to-tablet manufacturing have been investigated in depth on several occasions [7–14]. Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) are also encouraging the shift from conventional batch processing to continuous processing owing to its increased technical understanding of the processing during development [15]. Twin-screw granulation was first introduced for pharmaceutical research by Gamlen and Eardley in 1986 where a Raker Perkins MP50 (Multipurpose) granulator was used to produce paracetamol-based extruded granules with high drug loading [16].

The TSG flexibility allows for wet or melt granulation processing with the addition of a liquid (e.g., water, organic

✉ Laura Andrade Junqueira
laura.deandrade@hotmail.com

✉ Dennis Douroumis
D.Douroumis@gre.ac.uk

1 Centre for Research Innovation (CRI), University of Greenwich, Chatham Maritime Kent, Chatham ME4 4TB, UK

2 Delta Pharmaceutics Ltd., 1-3 Manor Road, Chatham, Kent ME4 6AG, UK

3 Custom Pharma Services, Conway St, Brighton and Hove, Hove BN3 3LW, UK

4 Wolfson Centre for Bulk Solids Handling Technology, Faculty of Engineering & Science, University of Greenwich, Central Avenue, Chatham ME4 4TB, UK

5 Cubi-Tech Extrusion Ltd., Unit 3, Neptune Close, Medway City Estate, Rochester, Kent ME2 4LU, UK

Published online: 31 July 2024

solvent) binder solution and the subsequent removal of the solvent or by using a molten binder (e.g., waxes, PEGs, lipids) [17–21]. The latter method counteracts the pitfalls of wet TSG, such as processing moisture-sensitive APIs, while facilitates faster processing times and lower energy consumption due to the omitted drying step [22–24]. Indeed, in wet-TSG, the selection of the binder liquid, binder amount, and liquid-to-solid ratio (L/S), among other critical material parameters, play a key role in the quality of the obtained granules [25–27]. Furthermore, the drying process must be carefully carried out to remove any residual solvents, which is usually conducted under elevated temperatures [28]. In melt-TSG, the binders are typically low melting point hydrophilic polymers, as the granulation process takes place near or just above their melting point to ensure that the binder is the only melted material [2, 29, 30].

Despite the numerous TSG studies, there are only a few related to increasing dissolution rates of water-insoluble APIs [25, 31–33], as in most cases, sustained release formulations are obtained [34–36]. Maniruzzaman *et al*. (2021) used TSG processing by introducing inorganic aluminometacilisates or dicalcium phosphate combined with hydrophilic polymers for enhanced dissolution of non-steroidal anti-inflammatory [33]. The granulation process was optimized by employing a Quality by Design approach, and parameters such as, inorganic/polymer ratio, L/S ratio and the binder amount were investigated. The use of inorganic excipients resulted in the formation of free-flowing powders with low loss of drying percentages, narrow particle size distribution, and increased dissolution rates of Ibuprofen (IBU). The selection of water or EtOH as the binder solution did not affect the granule quality and especially the IBU dissolution rates.

Steffens and Wagner (2020) exploited melt-TSG for the dissolution of carbamazepine formulated with three different water-soluble polymers: polyethylene glycol 6000 (PEG 6000), Kolliphor® P407, and Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) [31]. Interestingly, the CBZ loading varied from 80–90%, while the effect of polymer content varying from 10–20%, and the granulation temperature were found to have a significant impact on the produced granules. The higher processing temperatures resulted in the formation of CBZ type II and better dissolution rates were observed at low granulation temperatures. The dissolution rates were affected by the amount and nature of polymer, with PEG showing the highest dissolution rates followed by Poloxamer 407 and Soluplus. Similarly, a melt granulation process used by Forster and Lebo (2021) was used to increase dissolution rates of IBU through coprocessing with Glyceryl distearate (Precirol ATO 5®) which is known for its taste masking and enhanced dissolution properties [37]. A Design of Experiments (DoE) approach led to high drug-loaded granules with fast dissolution rates, depending on the particle size of the obtained granules. The IBU amounts varied from 20–40%, but the processing temperature was found to be the controlling factor of the granule particle size and hence the dissolution rates.

Sarabu *et al*. (2021) introduced a combined process based on previous studies where Gelucire® 48/16 and Neusilin® US2 acted as the solubilizer and porous surface adsorbent for Fenofibrate, a poorly water-soluble drug (logP 5.2) [32]. Screening studies showed a liner relationship for the solubility of Fenofibrate in the presence of Gelucire® 48/16. When formulation was co-processed with Gelucire and Neusilin, it was found that higher amounts of the latter resulted in decreased dissolution rates but improved storage stability. In contrast, higher Gelucire® 48/16 amounts showed even slower dissolution rates and tablets with a hard matrix.

Nevertheless, TSG is not fully exploited for the increase of dissolution rates of water insoluble APIs [38, 39]. The selection of appropriate powder excipients is restricted mostly to model hydrophilic polymers and drugs in order to simplify the TSG and identify optimal processing settings.

In this work we introduce a novel approach that utilises non-volatile solvents (or surfactants), with high solubilising capacity of water insoluble APIs, as granulating liquids co-processed with polymers that are highly miscible with the drug(s). The selected polymers served as drug carriers due to their high drug-polymer miscibility ($\Delta\delta$) which was less than 7 [40, 41]. A major advantage is that the technology offers less processing steps, as there is no need for drying processing (e.g., fluidize bed), making it cost-effective. Most importantly, it can be effectively used as a continuous TSWG platform for the solubility enhancement of water insoluble APIs. For the purposes of this study, IBU was granulated with cellulose derivatives using TSWG where a non-volatile solvent is introduced both as liquid binder and solubility enhancer.

Materials and Methods

Materials

Ibuprofen (IBU) was purchased from Farmasino Pharmaceuticals Co. Ltd. (Jiangsu, China). Pharmaceutical grade hydroxypropyl methylcellulose (METHOCEL K4M) was kindly donated by COLORCON (Dartford, Uk). Hydroxypropyl methylcellulose (Pharmacoat 603, Hypromellose 2910) and hypromellose acetate succinate (AQOAT- AS-LMP) were donated by Shin-Etsu (Tokyo, Japan) respectively. Caprylocaproyl macrogol-8 glyceride (Labrasol), Highly purified diethylene glycol monoethyl ether (Transcutol HP), Glycerol monocaprylocaprate (type I) (Labrafac WL1349) and Oleoyl macrogol-6 glyceride (Labrafil M

1944 CS) were kindly donated by Gattefosse (Saint-Priest, France). Tween 80 was purchased from Sigma-Aldrich (Gillingham, UK). The HPLC solvents were analytical grade and purchased from Fisher Chemicals (UK).

Continuous Twin-Screw Granulation

The IBU-polymer powder blends were placed in a Turbula TF2 mixer (Basel, Switzerland) for 10 min to ensure homogeneous mixing. For the continuous TSWG, each formulation was processed using a Eurolab 16mm twin-screw extruder (Thermo Fisher Scientific, Germany) and powders were fed with a DD Flexwall®18 feeder (Brabender Technology, Germany), while the solubilizer was pumped with a Watson-Marlow Ltd. (Cornwall, UK) peristaltic pump. The barrel temperature profile was set at 50 °C for all barrel zones and screw speed was maintained at 50 rpm for all the batches. The formulations are shown in Table I. The extruded granules were further milled using a cutting mill Retsch SM 100 (Haan, Germany) using a 250 µm sieve.

Thermal Analysis

The physical state of the bulk drug and the extruded granules were examined by differential scanning calorimetry (DSC). A DSC Mettler-Toledo 823e (Greifensee, Switzerland) was used to determine the melting point (T_{m}) and melting enthalpy (ΔH) of bulk IBU, physical mixtures, and extruded formulations. 2–5 mg of samples were placed in sealed aluminium pans with pierced lids. One single heating run from 10–220 °C was performed to analyse the thermal characteristics of bulk components, physical mixtures and extruded granules under a dry nitrogen atmosphere.

Powder X-ray Diffraction (XRPD)

XRPD was used to determine the solid-state of the bulk substance in the extrudate formulations. All formulations, including bulk IBU, physical mixtures and extruded granules were evaluated using Bruker D8 Advance in theta – theta mode, Cu anode at 40 kV and 40 Ma, parallel beam Goebel mirror,0.2 mm exit slit, LynxEYE position-sensitive detector with 3° opening and LynxIris at 6.5 mm, sample rotation at 15 RPM. The samples were scanned from 2 to 40° 2 theta with a step size of 0.02° 2-theta and a counting time of 0.2 s per step;176 channels active on the PSD making a total counting time of 35.2s per step.

Particle Size Morphology and Distribution

SEM was used to examine the surface morphology of the twin-screw extrudates. The samples were mounted on an aluminium stub using double-sided adhesive carbon type and placed in a low humidity chamber prior to analysis. Samples were sputter-coated with gold, and microscopy was performed using a Cambridge Instruments Stereo-Scan S360 (UK), SEM operating at an accelerating voltage of 20 kV.

The particle size distribution of the milled extruded granules of all formulations was measured by Laser Light Scattering technique with a dry powder sample dispersion accessory (Scirocco 2000). During the laser diffraction measurement, particles are passed through a focused laser beam. These particles scatter light at an angle that is inversely proportional to their size. The angular intensity of the scattered light is then measured by a series of photosensitive detectors. The number and positioning of these detectors in the Mastersizer 2000 have been optimized to achieve maximum resolution across a broad range of sizes.

Compressibility Index Measurement

Flowability of untreated and granulated samples was also examined from Carr's Index (CI) [42] was determined using a tap density meter (Qualtech, Manchester UK) at 1250 taps (616 US Pharmacopeia), bulk density and tapped density of powders). The CI was calculated from the bulk and tapped densities. Tapped density was determined by tapping the samples into a measuring cylinder using a tapping machine. The CI was calculated according to the following equation.

Table I Formulation Compositions for TSWG Processing of IBU Blends

Formulation	IBU (%, w/w)	K4M (%, w/w)	AQOAT (%, w/w)	PHAR603 (%, w/w)	Transcutol (%, w/w)
F1	40	55.0			5.0
F2	40		55.0		5.0
F3	40			55.0	5.0
F4	40	50.0			10.0
F5	40		50.0		10.0
F6	40			50.0	10.0

$$CI = \left[(\text{Tapped density} - \text{Bulk density})/\text{Tapped density}\right] \times 100$$

In vitro Drug Release Study

In vitro Drug Dissolution

In vitro drug release studies were carried out in 900 ml of pH 7.2 phosphate buffer medium acid for 2 h using a Varian 705 DS dissolution paddle apparatus (Varian Inc. North Carolina, US) at 50 rpm and 37 °C ± 0.5 °C. For the purposes of the study the milled granules were added directly in the dissolution baths. The granule amounts used for dissolution was 500mg for all formulations. At predetermined time intervals, samples were withdrawn for HPLC assay. All dissolution studies were performed in triplicates.

HPLC Analysis

The release of IBU was determined by using HPLC, Agilent Technologies system 1200 series. A HYCHROME S50DS2-4889 (5 µm × 150 mm x 4mm) column was used for the HPLC analysis of IBU. The wavelength was set at 214 nm. The mobile phase consisted of acetonitrile/water/phosphoric acid (65/35/0.2 v/v) and the flow rate was maintained at 1.5 ml/min and the retention time was 2–3 min (Gryckze *et al*., 2011; US Pharmacopeia, 2015). A calibration curve was prepared with concentrations varying from 10 µg/ml to 50 µg/ml and 20 µl injection volume.

Results and Discussion

Solubility Screening

The major objective of the study was to introduce the use of non-volatile solvents or surfactants as granulating liquids by combining their solubilization capacity for IBU. A great advantage of this approach is the absence of typical volatile solvents (e.g., ethanol) or water, which would result in less downstream processing and hence faster production times with high throughput. It is well known that existing continuous granulation lines, such as ConSigma and MODCOS, include a drying step (e.g., fluidized bed), which is time-consuming [43, 44]. Furthermore, the non-volatile solubilizer/surfactant will not only facilitate the granulation process but also enhance the API dissolution rates and potentially the bioavailability [45]. A key step of the proposed technology is the determination of API solubility in a range of solvents and surfactants that will later be selected as the granulating liquid. As shown in Table II, several water-dispersible surfactants and solvents were investigated for their solubilizing capacity on IBU.

Table II IBU Solubility in Various Solvents/Surfactants at 25 °C

Solubilizer/surfactant	IBU solubility (mg/g)
Tween 80	260 ± 1.2
Labrasol	280 ± 1.5
Labrafac WL1349	101 ± 0.5
Transcutol	398 ± 1.1
Labrafil M 1944 CS	92 ± 0.5
Capryol 90	70 ± 0.2

The experimental findings were similar to those found in literature [46] with Tween 80 < Labrasol < Transcutol showing increased IBU solubility in an ascending order. Transcutol is a powerful liquid solubiliser comprising of purified diethylene glycol monoethyl ether with low viscosity (20 cP) at ambient temperature. Hence, Transcutol was selected as the granulating liquid for all processed formulations.

Twin Screw Granulation

For the purposes of the TSG process, a range of hydrophilic cellulose derivatives were selected as polymeric carriers. These polymers have been previously used for the development of extruded amorphous dispersions and exhibit while present excellent milling effectiveness, rendering them suitable candidates for TSG [47–49]. The effect of the granulating liquid on the particle size distribution and API dissolution rates was investigated by varying the L/S ratio from 0.05 to 0.1. A successful granulating process should result in small fractions of fines where high L/S ratios have shown higher fractions of larger agglomerates (> 100µm). The screw configuration consisted of two kneading zones with 12 elements each at 30/60° staggered angles for higher energy intensive mixing. The use of kneading elements has been found to induce better particle agglomeration due to the increase of shear and compressive forces on the wetted blends [7]. Preliminary studies with conveying elements with different screw pitch were not satisfactory (data not shown). For this particular screw configuration, the feed rate was adjusted at 500 g/h in order to achieve higher torque within the extruder barrel. The measured torque varied from 18–20 Nm and 22–25 Nm for the 5–10% granulating liquid, respectively.

At first, granulation was conducted at ambient temperature but a large proportion of IBU still remained crystalline in the obtained granules. To further increase IBU amoprhicity it was decided to increase the barrel temperatures at the kneading zones but keep them below the drug's melting point. Thus, for all kneading zones the temperature was adjusted to 50 °C.

Effect of L/S Ratio on Particle Morphology and Distribution

The particle size and shape can influence important physical properties, manufacturing processability, and quality attributes, particularly dissolution rate and bioavailability of pharmaceutical ingredients. This depends on processing settings but also the nature of the polymeric carrier and its effect on the granule formation. As there were significant particle size differences of the "as made" granules produced by extrusion, we used a cutter mill and passed the extruded granules through a 250 µm mesh which reduced the particle size inconsistences.

SEM analysis was used to observe the surface morphology of the produced granules at the end of the milling process. As shown in Fig. 1, bulk IBU appears in the form of large elongated prismatic. However, it is evident that the morphology of the primary IBU particles has been changed during granulation. For all processed formulations, the granules appear to have a uniform size with irregular shape.

The particle size distribution was analysed by laser diffraction in order to identify the effect of polymers and the amount of granulating liquid. From Figs. 2 and 3, it can be seen that for Pharma 603 slighter larger granules (d50, 180 µm) with around 10% fines were observed at both transutol L/S ratios. The increase of the granulating liquid resulted in even larger granules (d50, 220 µm) and an increase of the 125–500 µm fractions by 11%.

To the contrary, K4M and AQOAT presented similar behaviour by forming larger granules towards the 125–500 µm fractions, particularly between 250–500 µm, when Transcutol increased at 10%. Hence, the higher L/S ratio led to reduced fines and larger particle sizes for K4M (d50, 260 µm) and AQOAT (d50, 280 µm). Overall, the suitable particle size fractions for tableting remained consistent and above 100 µm. By increasing Transcutol amount the granule growth increased due to efficient particle coalescence which minimised the content of ungranulated powder blends.

One of the TSG advantages is the improvement of the flowability and compactibility especially of APIs with poor flow. The flowability of bulk IBU is extremely poor due to its high cohesiveness, as it can be observed from the Carr's Index (CI) in Table III.

According to Carr's Index, a value between 5–15%, 12–16%, 18–21%, and 23–28% indicates excellent, good, fair, and poor flow properties of the powder, respectively[25]. The estimated CI values of the extruded granules are significantly lower than those of the bulk IBU, indicating excellent to good flowability. It can also be seen that granules prepared with 10% granulating liquid demonstrated lower CI values due to their larger particle size and the lower content of fines for each batch. Nevertheless, the TSG process appeared to be successful without causing any issues during downstream processing (milling). This is related to the selection of suitable polymers, the

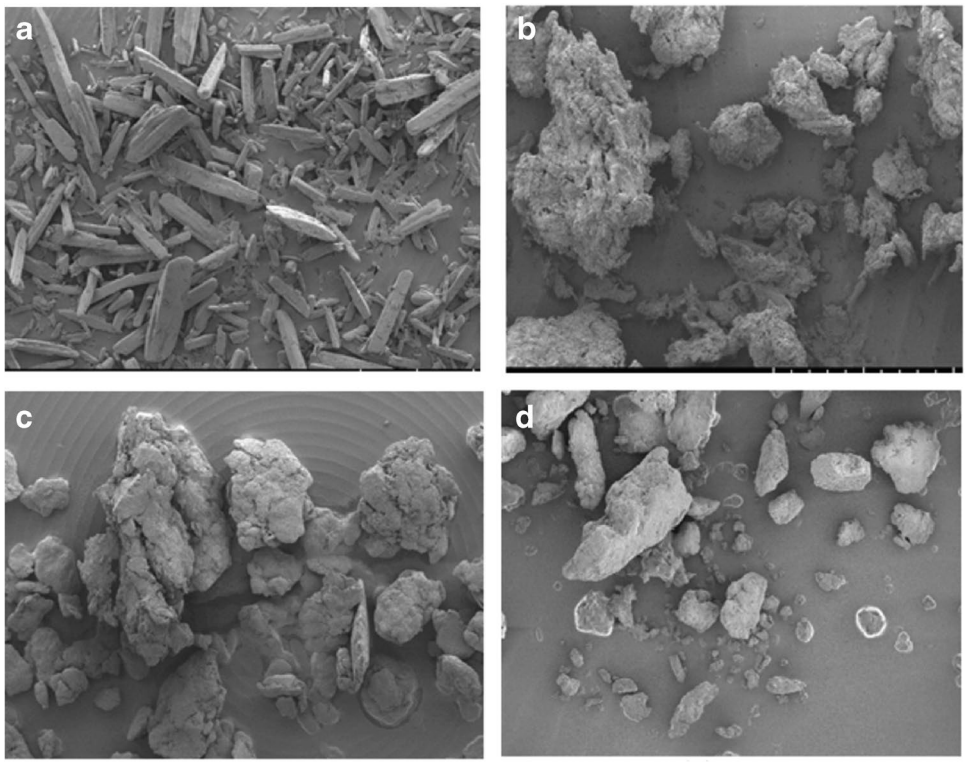

Fig. 1 SEM images of bulk and extruded formulations: **a** Bulk Ibuprofen, **b** IBU/K4M/Transcutol, **c** IBU/AQOAT/Transcutol, **d** IBU/Pharma 603/Transcutol granules

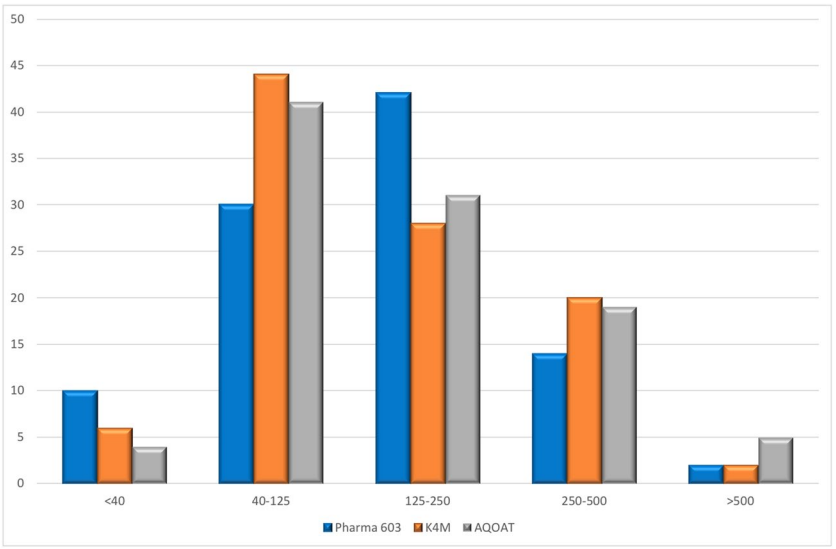

Fig. 2 Particle size distribution of IBU/Pharma 603 (blue bars), IBU/K4M (orange bars) and IBU/AQOAT (grey bars) at 5% Transcutol

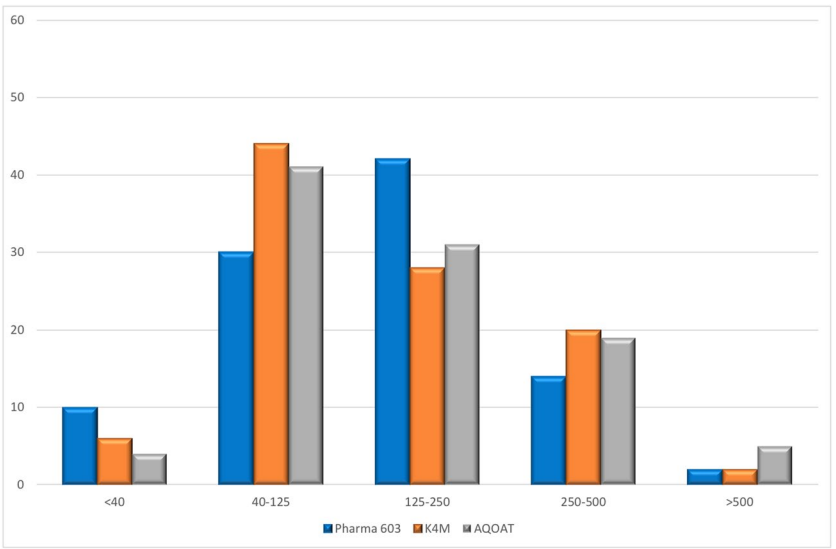

Fig. 3 Particle size distribution of IBU/Pharma 603 (blue bars), IBU/K4M (orange bars) and IBU/AQOAT (grey bars) at 10% Transcutol

granulating liquid, optimization of the critical processing parameters, and screw configuration [50].

X-ray Powder Diffraction (XRPD)

XRPD analysis was carried out for all batches including bulk IBU in order to identify the crystalline state of the granulated materials. As shown in Fig. 4, the XRPD pattern of IBU presented distant intensity peaks due to its crystalline structure at 2θ angles of 6.18°, 12.29°, 16.81°,17.75°, 18.82°, 19.15°, 20.26°, 22.13°, 24.31°, 24.62°, and 25.15°. Further analysis showed that IBU-polymer physical mixtures presented identical peaks at a lower intensity (Fig. S1, supplementary) indicating no alteration of IBU crystallinity.

However, Fig. 4 shows that IBU was transformed to a fully amorphous state in the extruded granules, as evidenced by the observed halo in the obtained diffractograms. The high shear mixing between the bulk drug and polymers during granulation resulted in the formation of amorphous IBU. It should be noted that TSWG process was conducted at a low processing temperature below the melting point of IBU or the glass transition of the polymer carriers.

Table III Carr's Index of Bulk IBU and Granulated Formulations

Formulation	Carr's Index
Bulk IBU	29.7
F1	12.7
F2	15.0
F3	10.5
F4	9.9
F5	6.6
F6	5.0

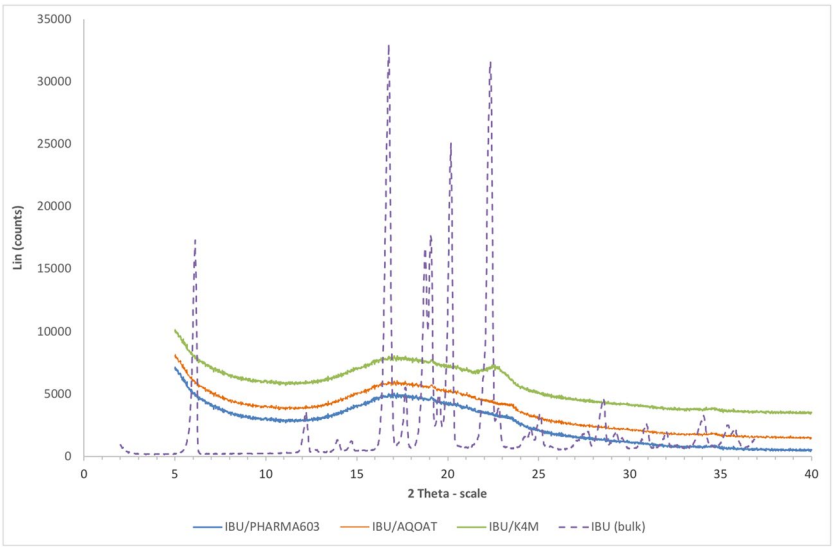

Fig. 4 X-ray diffractograms of extruded IBU granules with PHARM604, HMPC-K4M and AQOAT

Differential Scanning Calorimetry (DSC)

DSC carried out to further investigate the IBU physical state in the extruded granules in comparison to the bulk substance and physical blends. As shown in Fig. S2 (supplementary material) the IBU melting endotherms shifted at lower temperatures due to the interactions with polymers. This is a strong indication of the drug-polymer miscibility as IBU is a well known plasticiser for a range of polymers. It can also be seen that the shifts of melting endotherms vary depending on the degree of miscibility which increases in an ascending order for AQOAT (61.70 °C) < K4M (53.77 °C) < PHARM603 (27.64 °C).

However, in Fig. 5 the thermograms of the extruded granules showed the absence of any melting endotherms related to IBU melting point. However, it was not also possible to

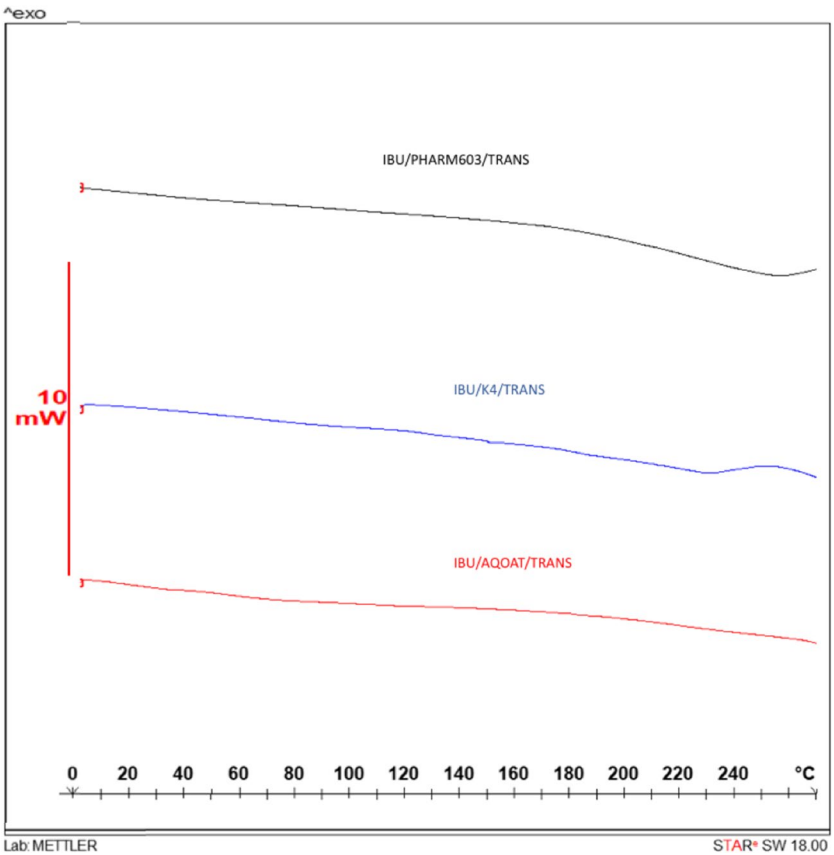

Fig. 5 DSC thermograms of extruded IBU granules with PHARM604, HMPC-K4M and AQOAT

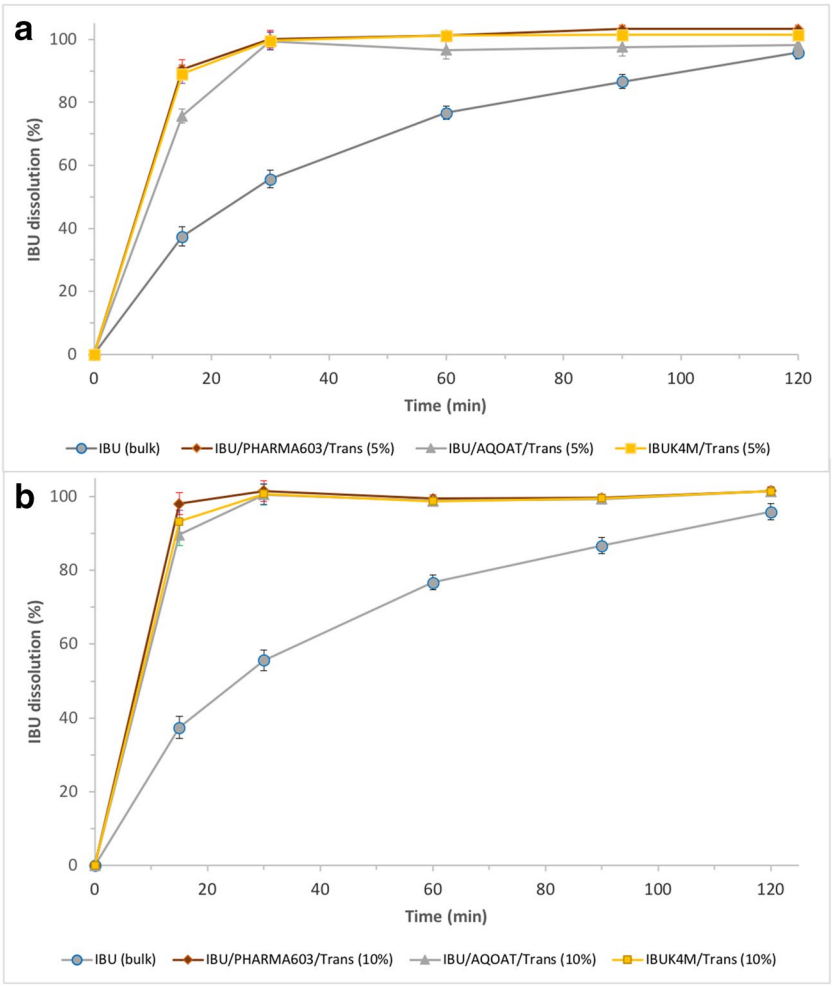

Fig. 6 IBU dissolution profiles from extruded granules of PHARM603, K4M and AQOAT. **a** with 5 of transcutol; **b** with 10% of transcutol

detect the new Tg for each amorphous dispersions due to the high IBU-polymer miscibility. The DSC findings were in good agreement with the X-ray analysis suggesting that the TSWG process resulted in the formation of amorphous IBU granules. This was attributed to the solubilising capacity of transcutol for IBU and the high IBU-polymer miscibility.

In vitro Dissolution Studies

The *in vitro* dissolution studies of extruded granules were carried out in alkaline media (pH 7.2) to investigate the effect of the formulation composition and the granulation process. At pH 7.2, the solubility increased significantly with the addition of polymer and solubilizer. From Fig. 6, it can be observed that for all formulations, IBU presented immediate release within the first 10 min, varying from 76 – 98%. The granules with 10% transcutol showed faster dissolution rates (93–98%), while those with 5% transcutol was slightly lower (63–90%). Among the three polymers, K4M and PHARM603 showed the fastest dissolution rates, while AQOAT rates were slower. The dissolution performance can be explained by the higher IBU miscibility for the three polymers, as was also shown in the DSC thermograms.

The improved dissolution profiles of granules containing the poorly water-soluble drug IBU are attributed to improved wettability with granulation and larger surface area of the granules compared to the bulk API. In addition, the effect of transcutol played a key role due to its high solubilizing capacity for IBU. It is worth mentioning that the extruded granules demonstrated the same dissolution profiles when using biorelevant media (pH 7.2) that we conducted for further investigation (data not shown).

Conclusions

In this study, TSWG was employed for producing IBU granules with miscible polymers for enhanced dissolution rates. IBU was effectively granulated with PHARM603, K4M,

and AQOAT at high loadings in the presence of transcutol, which acted both as a granulation binder and solubility enhancer. The granulation process was optimized to produce amorphous IBU with enhanced dissolution rates. This novel approach not only facilitates enhanced dissolution rates of water-insoluble APIs but also significantly reduces the downstream processing of TSWG, thereby shortening processing times as the granule drying step is not required. In addition, it could be used as platform technology for the optimization and continuous manufacturing of a wide range of water-insoluble drugs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1208/s12249-024-02890-y.

Author Contributions Siva Satyanarayana Kolipaka contributed to methodology, validation, formal analysis, investigation, data curation, writing – original draft, and writing – review & editing. Laura Andrade Junqueira was responsible for methodology, validation, formal analysis, investigation, data curation, writing – original draft, and writing – review & editing. Steven Ross was involved in methodology, validation, formal analysis, investigation, data curation, writing – original draft, and writing – review & editing. Vivek Garg contributed to methodology, validation, formal analysis, investigation, and data curation. Md Sadeque Hossein Mithu was responsible for methodology, validation, formal analysis, investigation, data curation, writing – original draft, and writing – review & editing. Saumil Bhatt contributed to conceptualization, methodology, formal analysis, resources, visualization, supervision, project administration, and funding acquisition. Dennis Douroumis was involved in conceptualization, methodology, formal analysis, resources, writing – original draft, writing – review & editing, visualization, supervision, project administration, and funding acquisition.

Funding This research received no external funding.

Data Availability Data will be made available on request.

Declarations

Conflict of Interest The authors declare no conflicts of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Nandi U, Trivedi V, Ross SA, Douroumis D. Advances in Twin-Screw Granulation Processing Pharmaceutics. 2021;13(5):624. https://doi.org/10.3390/pharmaceutics13050624.
2. Arce F, Schuman Y, Gawel J, Garmise R, Abebe A, Desai D. An Evaluation of Wet Granulation Process Selection for API Prone to Polymorphic Form Conversion in the Presence of Moisture and Heat. Pharm Res. 2024;41(3):595–607. https://doi.org/10.1007/s11095-024-03667-5.
3. Thakore SD, Reddy KV, Dantuluri AK, Patel D, Kumawat A, Sihorkar V, et al. Application of Twin-Screw Melt Granulation to Overcome the Poor Tabletability of a High Dose Drug. Pharm Res. 2022;39(12):3241–57. https://doi.org/10.1007/s11095-022-03369-w.
4. Cartwright J, Robertson J, D'Haene D, Burke MD, Hennenkamp JR. Twin screw wet granulation: Loss in weight feeding of a poorly flowing active pharmaceutical ingredient. Powder Technol. 2013;239:116–21. https://doi.org/10.1016/j.powtec.2012.04.034.
5. Keleb EI, Vermeire A, Vervaet C, Remon JP. Continuous twin screw extrusion for the wet granulation of lactose. Int J Pharm. 2002;239(1–2):69–80. https://doi.org/10.1016/s0378-5173(02)00052-2.
6. Portier C, Vervaet C, Vanhoorne V. Continuous Twin Screw Granulation: A Review of Recent Progress and Opportunities in Formulation and Equipment Design. Pharmaceutics. 2021;13(5):668. https://doi.org/10.3390/pharmaceutics13050668.
7. Vercruysse J, Burggraeve A, Fonteyne M, Cappuyns P, Delaet U, Van Assche I, et al. Impact of screw configuration on the particle size distribution of granules produced by twin screw granulation. Int J Pharm. 2015;479(1):171–80. https://doi.org/10.1016/j.ijpharm.2014.12.071.
8. Vercruysse J, Peeters E, Fonteyne M, Cappuyns P, Delaet U, Van Assche I, et al. Use of a continuous twin screw granulation and drying system during formulation development and process optimization. Eur J Pharm Biopharm. 2015;89:239–47. https://doi.org/10.1016/j.ejpb.2014.12.017.
9. Willecke N, Szepes A, Wunderlich M, Remon JP, Vervaet C, De Beer T. A novel approach to support formulation design on twin screw wet granulation technology: Understanding the impact of overarching excipient properties on drug product quality attributes. Int J Pharm. 2018;545(1–2):128–43. https://doi.org/10.1016/j.ijpharm.2018.04.017.
10. Fonteyne M, Soares S, Vercruysse J, Peeters E, Burggraeve A, Vervaet C, et al. Prediction of quality attributes of continuously produced granules using complementary pat tools. Eur J Pharm Biopharm. 2012;82(2):429–36. https://doi.org/10.1016/j.ejpb.2012.07.017.
11. Yu S, Reynolds GK, Huang Z, de Matas M, Salman AD. Granulation of increasingly hydrophobic formulations using a twin screw granulator. Int J Pharm. 2014;475(1–2):82–96. https://doi.org/10.1016/j.ijpharm.2014.08.015.
12. Grelier A, Zadravec M, Remmelgas J, Forgber T, Colacino F, Pilcer G, et al. Model-Guided Development of a Semi-Continuous Drying Process. Pharm Res. 2022;39(9):2005–16. https://doi.org/10.1007/s11095-022-03361-4.
13. Portier C, Pandelaere K, Delaet U, Vigh T, Di Pretoro G, De Beer T, Vervaet C, Vanhoorne V. Continuous twin screw granulation: A complex interplay between formulation properties, process settings and screw design. Int J Pharm. 2020;576: 119004.
14. Djuric D, Kleinebudde P. Continuous granulation with a twin-screw extruder: impact of material throughput. Pharm Dev Technol. 2010;15(5):518–25. https://doi.org/10.3109/10837450903397578.
15. Vervaet C, Remon JP. Continuous granulation in the pharmaceutical industry. Chem Eng Sci. 2005;60(14):3949–57. https://doi.org/10.1016/j.ces.2005.02.028.
16. Gamlen MJ, Eardley C. Continuous Extrusion Using a Raker Perkins MP50 (Multipurpose) Extruder. Drug Dev Ind Pharm. 1986;12:1701–13. https://doi.org/10.3109/03639048609042604.

17. Vandevivere L, Vangampelaere M, Portier C, de Backere C, Häusler O, De Beer T, et al. Identifying Critical Binder Attributes to Facilitate Binder Selection for Efficient Formulation Development in a Continuous Twin Screw Wet Granulation Process. Pharmaceutics. 2021;13(2):210. https://doi.org/10.3390/pharmaceutics13020210.
18. Vasanthavada M, Wang Y, Haefele T, Lakshman JP, Mone M, Tong W, Joshi YM, Serajuddin AT. Application of melt granulation technology using twin-screw extruder in development of high-dose modified-release tablet formulation. J Pharm Sci. 2011;100(5):1923–34. https://doi.org/10.1002/jps.22411.
19. Köster C, Pohl S, Kleinebudde P. Evaluation of Binders in Twin-Screw Wet Granulation. Pharmaceutics. 2021;13(2):241. https://doi.org/10.3390/pharmaceutics13020241.
20. Köster C, Kleinebudde P. Evaluation of binders in twin-screw wet granulation - Optimal combination of binder and disintegrant. Eur J Pharm Biopharm. 2023;186:55–64. https://doi.org/10.1016/j.ejpb.2023.03.003.
21. Nyavanandi D, Mandati P, Narala S, Alzahrani A, Kolimi P, Vemula SK, Repka MA. Twin Screw Melt Granulation: A Single Step Approach for Developing Self-Emulsifying Drug Delivery System for Lipophilic Drugs. Pharmaceutics. 2023;15(9):2267. https://doi.org/10.3390/pharmaceutics15092267.
22. Grymonpré W, Verstraete G, Vanhoorne V, Remon JP, De Beer T, Vervaet C. Downstream processing from melt granulation towards tablets: In-depth analysis of a continuous twin-screw melt granulation process using polymeric binders. Eur J Pharm Biopharm. 2018;124:43–54. https://doi.org/10.1016/j.ejpb.2017.12.005.
23. Schmidt A, de Waard H, Kleinebudde P, Krumme M. Continuous Single-Step Wet Granulation with Integrated in-Barrel-Drying. Pharm Res. 2018;35(8):167. https://doi.org/10.1007/s11095-018-2451-0.
24. Nyavanandi D, Narala S, Mandati P, Alzahrani A, Kolimi P, Almotairy A, et al. Twin Screw Melt Granulation: Alternative Approach for Improving Solubility and Permeability of a Non-steroidal Anti-inflammatory Drug Ibuprofen. AAPS PharmSciTech. 2023;24(1):47. https://doi.org/10.1208/s12249-023-02512-z.
25. Maniruzzaman M, Nair A, Renault M, Nandi U, Scoutaris N, Farnish R, et al. Continuous twin-screw granulation for enhancing the dissolution of poorly water soluble drug. Int J Pharm. 2015;496(1):52–62. https://doi.org/10.1016/j.ijpharm.2015.09.025.
26. Kumar A, Alakarjula M, Vanhoorne V, Toiviainen M, De Leersnyder F, Vercruysse J, et al. Linking granulation performance with residence time and granulation liquid distributions in twin-screw granulation: An experimental investigation. Eur J Pharm Sci. 2016;90:25–37. https://doi.org/10.1016/j.ejps.2015.12.021.
27. Miyazaki Y, Lenhart V, Kleinebudde P. Switch of tablet manufacturing from high shear granulation to twin-screw granulation using quality by design approach. Int J Pharm. 2020;579: 119139. https://doi.org/10.1016/j.ijpharm.2020.119139.
28. Willecke N, Szepes A, Wunderlich M, Remon JP, Vervaet C, De Beer T. Identifying overarching excipient properties towards an in-depth understanding of process and product performance for continuous twin-screw wet granulation. Int J Pharm. 2017;522(1–2):234–47. https://doi.org/10.1016/j.ijpharm.2017.02.028.
29. Verstraete G, Mertens P, Grymonpré W, Van Bockstal PJ, De Beer T, Boone MN, et al. A comparative study between melt granulation/compression and hot melt extrusion/injection molding for the manufacturing of oral sustained release thermoplastic polyurethane matrices. Int J Pharm. 2016;513(1–2):602–11. https://doi.org/10.1016/j.ijpharm.2016.09.072.
30. Batra A, Desai D, Serajuddin ATM. Investigating the Use of Polymeric Binders in Twin Screw Melt Granulation Process for Improving Compactibility of Drugs. J Pharm Sci. 2017;106(1):140–50. https://doi.org/10.1016/j.xphs.2016.07.014.
31. Steffens KE, Wagner KG. Dissolution enhancement of carbamazepine using twin-screw melt granulation. Eur J Pharm Biopharm. 2020;148:77–87. https://doi.org/10.1016/j.ejpb.2020.01.006.
32. Sarabu S, Kallakunta VR, Butreddy A, Janga KY, Ajjarapu S, Bandari S, et al. A One-Step Twin-Screw Melt Granulation with Gelucire 48/16 and Surface Adsorbent to Improve the Solubility of Poorly Soluble Drugs: Effect of Formulation Variables on Dissolution and Stability. AAPS PharmSciTech. 2021;22(3):79. https://doi.org/10.1208/s12249-021-01945-8.
33. Maniruzzaman M, Ross SA, Dey T, Nair A, Snowden MJ, Douroumis D. A quality by design (QbD) twin-Screw extrusion wet granulation approach for processing water insoluble drugs. Int J Pharm. 2017;526(1–2):496–505. https://doi.org/10.1016/j.ijpharm.2017.05.020.
34. Vanhoorne V, Vanbillemont B, Vercruysse J, De Leersnyder F, Gomes P, Beer TD. Development of a controlled release formulation by continuous twin screw granulation: Influence of process and formulation parameters. Int J Pharm. 2016;505(1–2):61–8. https://doi.org/10.1016/j.ijpharm.2016.03.058.
35. Monteyne T, Adriaensens P, Brouckaert D, Remon JP, Vervaet C, De Beer T. Stearic acid and high molecular weight PEO as matrix for the highly water soluble metoprolol tartrate in continuous twin-screw melt granulation. Int J Pharm. 2016;512(1):158–67. https://doi.org/10.1016/j.ijpharm.2016.07.035.
36. Vanhoorne V, Janssens L, Vercruysse J, De Beer T, Remon JP, Vervaet C. Continuous twin screw granulation of controlled release formulations with various HPMC grades. Int J Pharm. 2016;511(2):1048–57. https://doi.org/10.1016/j.ijpharm.2016.08.020.
37. Forster SP, Lebo DB. Continuous Melt Granulation for Taste-Masking of Ibuprofen. Pharmaceutics. 2021;13(6):863. https://doi.org/10.3390/pharmaceutics13060863.
38. Mamidi HK, Palekar S, Nukala PK, Mishra SM, Patki M, Fu Y, et al. Process optimization of twin-screw melt granulation of fenofibrate using design of experiment (DoE). Int J Pharm. 2021;593: 120101. https://doi.org/10.1016/j.ijpharm.2020.120101.
39. Ito A, Kleinebudde P. Influence of granulation temperature on particle size distribution of granules in twin-screw granulation (TSG). Pharm Dev Technol. 2019;24(7):874–82.
40. Hansen CM. The universality of the solubility parameter. Ind Eng Chem Res Dev. 1969;8:2–11. https://doi.org/10.1021/i360029a002.
41. Hoftyzer PJ, Krevelen DWV. Properties of polymers. Amsterdam, the Netherlands: Elsevier; 1976.
42. Carr RL. Evaluation flow properties of solids. Chem Eng. 1965;72:163–8.
43. Van Melkebeke B, Vervaet C, Remon JP. Validation of a continuous granulation process using a twin-screw extruder. Int J Pharm. 2008May 22;356(1–2):224–30. https://doi.org/10.1016/j.ijpharm.2008.01.012.
44. Kotamarthy L, Feng X, Alayoubi A, Kumar Bolla P, Ramachandran R, Ashraf M, et al. Switching from batch to continuous granulation: A case study of metoprolol succinate ER tablets. Int J Pharm. 2022;617: 121598. https://doi.org/10.1016/j.ijpharm.
45. Miyagawa Y, Sato H, Okabe T, Nishiyama T, Miyajima M, Sunada H. In vivo performance of wax matrix granules prepared by a twin-screw compounding extruder. Drug Dev Ind Pharm. 1999;25(4):429–35. https://doi.org/10.1081/ddc-100102192.
46. Syukri Y, Fitriani H, Pandapotan H, Nugroho BH. Formulation, Characterization and Stability of Ibuprofen-Loaded Self-Nano Emulsifying Drug Delivery System (SNEDDS). Indonesian J Pharm. 2019. https://doi.org/10.14499/indonesianjpharm30iss2pp105.
47. Douroumis D, Bouropoulos N, Fahr A. Physicochemical characterization of solid dispersions of three antiepileptic drugs prepared by solvent evaporation method. J Pharm Pharmacol. 2007;59(5):645–53. https://doi.org/10.1211/jpp.59.5.0004.
48. Maniruzzaman M, Islam MT, Halsey S, Amin D, Douroumis D. Novel Controlled Release Polymer-Lipid Formulations Processed by Hot Melt Extrusion. AAPS PharmSciTech. 2016;17(1):191–9. https://doi.org/10.1208/s12249-015-0470-2.

49. Scoutaris N, Ross SA, Douroumis D. 3D Printed "Starmix" Drug Loaded Dosage Forms for Paediatric Applications. Pharm Res. 2018;35(2):34. https://doi.org/10.1007/s11095-017-2284-2.
50. Kashani Rahimi S, Paul S, Sun CC, Zhang F. The role of the screw profile on granular structure and mixing efficiency of a high-dose hydrophobic drug formulation during twin screw wet granulation. Int J Pharm. 2020;575: 118958. https://doi.org/10.1016/j.ijpharm.2019.118958.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.