China Petroleum Processing and Petrochemical Technology

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2861-2870

LAB SCALE STUDIES ON CONTINUOUS COOLING CRYSTALLIZATION OF ACTIVE PHARMACEUTICAL INGREDIENTS -DESVENLAFAXINE SUCCINATE

P.N.Baskaran[a], R.Ravi[a]*, K.Muthu[b]

[a] Biochemical Engineering Laboratory, Department of Chemical Engineering, Annamalai University, Chidambaram,608002, Tamil Nadu, India

[b] institute of Chemical Technology, Chennai, 600113, Tamil Nadu, India

***Corresponding author**

Email id:lect_ravi@yahoo.com

Highlights

- Production of pharma drug using continuous crystallization process
- Experiments with different parameters to achieve the desired crystal size distribution
- Dilution ratio, flow rate, and condenser coolant temperature are simultaneously optimized to get the desired particle size distribution

Abstract

Crystallization is recognized as a standard unit operation used to isolate and purify products in several pharmaceutical industries. It's one of the most critical separations involved in the purification of producing intermediates and active pharmaceutical ingredients (APIs). Crystallization processes in industry are attributed to the fact that crystallization acts as both a purification and isolation or separation step. Crystal products of particle size, shape, and high purity are produced in a single step. Crystallization processes have different advantages, but they are monitored to obtain the desired crystal size, shape, and product quality and to ensure a cost-effective and efficient crystallization process. The operating conditions of the crystallization process determine the crystal size distribution. This study performed continuous crystallization experiments using a laboratory pilot scale crystallizer. Effect of different process variables studied(such as solvent ratio, inlet feed flow rate, and the cooling temperature)on the particle size distribution of the product examined. From the results, it was observed that the PSD of D (10), D (50), and D (90) increased with the increase in solvent ratio and feed flow rate. However, the impact of condenser cooling temperature on the PSD was insignificant. The results also showed the favorable conditions to achieve the required PSD (more amount of lower dilution, i.e., the solvent ratio of 6) and higher feed flow rate, i.e., 90 ml/min).

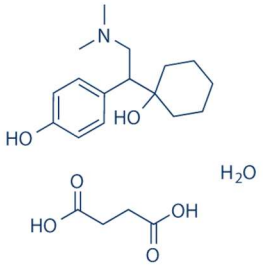
Keywords: Continuous crystallization, Desvenlafaxine succinate, Process variable, Particle size distribution (PSD), Particle shape.

1. Introduction

Crystallization is significant in producing a pharmaceutical product. Still, it is pretty complex because of several physicochemicals during the particle formation, as medicinal formulations have a diversified chemical nature [1]. Strict standards were set by regulatory agencies like the US Food

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2861-2870

and Drug Administration to regulate the efficacy and safety of the pharma product [2]. Crystallization operation is the mainstream in producing pharmaceutical products as this serves as both separation and purification stages. A pharmaceutical product with the desired specifications can be obtained in single or multiple steps [3]. Though the developments in the crystallization process have continued for quite a long, there is still a need for a deeper understanding of the crystallization process to produce the crystal of desired quality and to ensure a cost-effective and efficient process[4]. The main parameters that influence the crystal size, shape, and distribution are agitator type, speed of agitation, dilution factor, cooling pattern, and seeding mechanism in crystallization. The final product is formed by filtration followed by drying operations. In a pharmaceutical product, bioavailability, dissolution, and efficiency are related to particle size distribution, constantly desired to suit immediate release (IR), sustainable release (SR), Extended Release (ER), etc, to serve the market and patients' needs. Desvenlafaxine is a drug administered to treat major depressive disorders. It is an active metabolite of Venlafaxine. Desvenlafaxine inhibits the neuronal uptake of norepinephrine, serotonin, and dopamine to a lesser extent. Still, it has no monoamine oxidase inhibitory activity and low affinity for brain muscarinic, cholinergic, histaminergic, or alpha-adrenergic receptors[5-7]. *The molecular structure of Desvenlafaxine succinate is shown in Fig. 1.*



Molecular formula: $C_{20}H_{31}NO_6$

Molecular weight: 381.5 g/mol

Fig. 1. *Molecular structure of* Desvenlafaxine succinate.

It is approximately ten times more potent at inhibiting serotonin uptake than norepinephrine [8,9]. It works by blocking the "reuptake" transporters for key neurotransmitters affecting mood, thereby leaving more active neurotransmitters in the synapse[10, 11]. *Efficiency for Desvenlafaxine has been demonstrated, and no evidence of greater efficacy was observed with doses > 50 mg/day [12]. Crystallization and modeling determination of crystal dissolution constant under different operating conditions like cooling rate (°C/h), stirring rate (1/min), seeding temperature (°C), Quantity of seed (wt %), of APIs like fesoterodine fumarate have been reported in the literature [1].* Comparative studies on the Synthesis and structure of old and new Polymorphs of Desvenlafaxine have been reported in the literature *[13]*. Controlled cooling pattern temperature vs time experiments of the pharmaceutical crystallization process have been referred to in the literature [14]. However, to our understanding, no literature reports were available describing the continuous crystallization process of Desvenlafaxine succinate. Therefore, the main objective of the present work is to study the effects of process parameters, such as solvent dilution ratio, inlet feed flow rate, and condenser cooling temperature, on the crystallization process. Experiments are targeted towards achieving the desired particle size distribution(PSD) of Desvenlafaxine succinate.

2. Materials and methods

2.1. Materials

Desvenlafaxine Succinate (mol. wt. = 381.5 g/mol; density = 1.46 g/cm^3; boiling point = 403.8 °C, melting point = 127 °C), with 99.9% purity, was procured from Lupin Ltd. (Mumbai, India) and Acetone purchased from Sigma-Aldrich Chemicals (Bangalore, India).

2.2. Experimental procedure

Crystallization experiments are carried out in a 3-liter jacketed round bottom flask equipped with a mechanical stirrer. Hot oil is used to heat the contents in the reactor. An automatic cooling system with a PID controller fitted to the closed tank was employed for continuously monitoring and controlling the flow. The experimental setup is shown in Fig. 2.

In this experimental study, a hundred grams of the product of Desvenlafaxine succinate was used to prepare the feed solution. The mixture of Acetone and water(ratio of 88 % acetone and 22% water) was used as a solvent to prepare the solution. For continuous operation, three different dilution factors were considered. For 1st set of experiments, i.e., 6 volume ratio, a total of 600 ml solvent mixture; for 2ndset of experiments, i.e., 8 volume ratios; and for 3rdset of experiments, i.e., 10 volume ratio was used. The prepared solution was heated to around 75 °C till transparent. Then, the solutions were passed through the condenser under a controlled discharge rate to progress the crystallization process. The crystallization mass was filtered, and the cake was dried using a laboratory tray dryer at around 90 °C under vacuum. Obtained products from the crystallizer were analyzed for particle size distribution and shape.

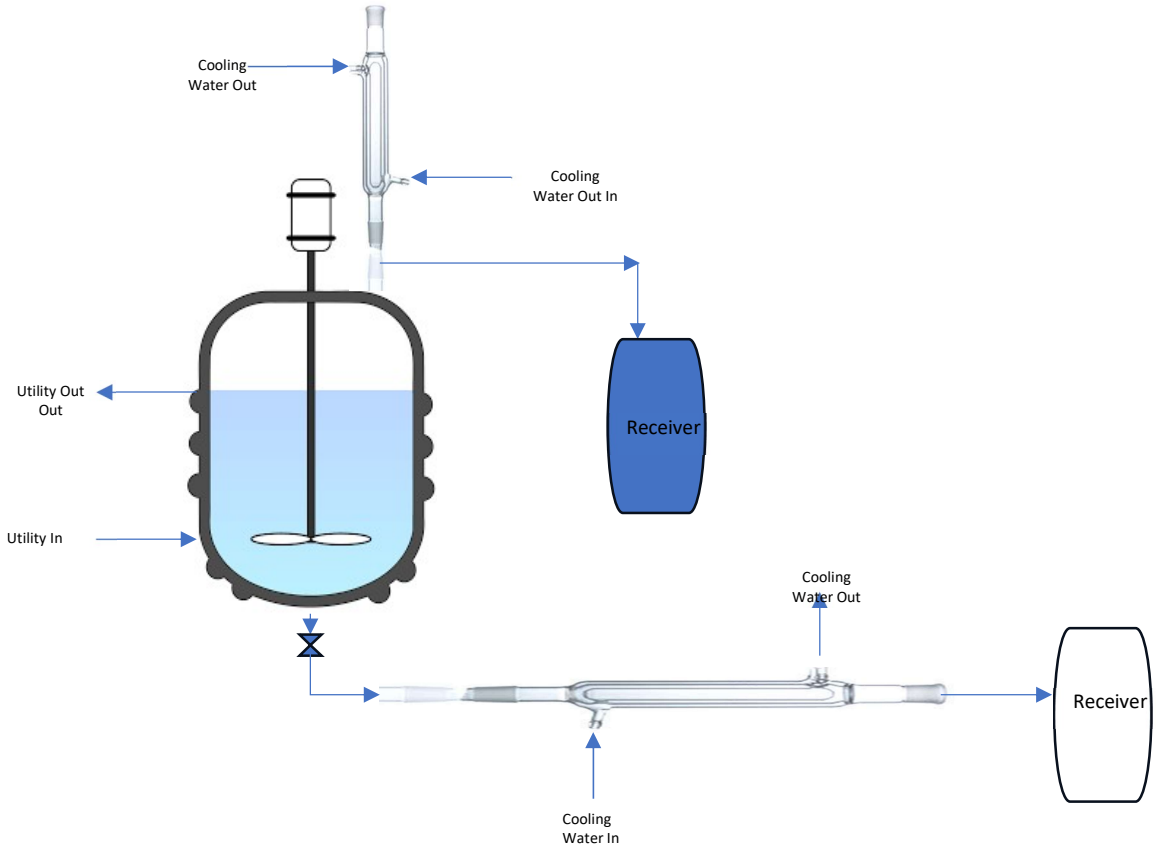


Fig. 2. Continuous crystallization experimental setup with heating and cooling provisions.

2.3. Analytical details

2.3.1. Particle size distribution (PSD) analysis

Malvern 3000 model instrument(United States) is used to analyze the particle size distribution of D (10), D (50), and D (90) with an auto-feeding system. Laser diffraction measures particle size distributions by measuring the angular variation with the intensity of light scattered as a laser beam passes through a dispersed particulate sample. Large particles scatter light at small angles relative to the laser beam, and small particles scatter light at large angles. The instrument measure D (10): The portion of particles with diameters smaller than this value is 10%. D (50): The parts of particles with diameters more minor and more significant than this value are 50%. Also known as the median diameter. D (90): The portion of particles with diameters below this value is 90%.The instrument detects the various particle sizes and gives the data of PSD. In the present study, the powdered sample was dispersed in liquid paraffin to estimate the PSD using the Malvern instrument.

2.3.2. Particle shape identification

A laboratory microscope (Olympus, CX21i, Japan) was used to identify the particle's shape. The powdered samples were placed on a glass slide, and then microscopic images were captured.

3. Results and Discussions

This study studied the effect of operating variables such as solvent ratio, inlet flow rate, and condenser cooling pattern on the particle size distribution of the crystallization product using a continuous crystallizer. The solvent ratio considered in the experimental study is 6-8, and the inlet flow rate was maintained in the range of 30-90 mL/min. Two different types of condenser cooling patterns, such as primary and secondary condenser, were considered to study their impact on the particle size distribution. The design of experiments to perform the continuous crystallization process is shown in Table 1. The obtained particle size distribution values in terms of D (10), D (50), and D (90) are shown in Table 2.

Table 1. Experimental planning of continuous crystallization process.

Exp. No.	Solvent ratio	Inlet Flow rate +/- 1 ml			Coolant temp. (°C)	
		Slow - 30 mL/min	Medium - 45 mL/min	High - 90 mL/min	Primary cooling	Secondary cooling
Base Sample	-	-	-	-	-	-
DIV 1	6	30			30	0
DIV 2	6		45		15	0
DIV 3	6			90	30	15
DIV 4	8	30			30	0

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2861-2870

DIV 5	8		45		15	0
DIV 6	8			90	30	15
DIV 7	10	30			30	0
DIV 8	10		45		15	0
DIV 9	10			90	30	15

Table 2. Particle size distribution of the pharma drug obtained at various experimental conditions.

Exp. No.	PSD (μm)		
	D (10)	D (50)	D (90)
Base Sample	3.64	16.1	60.3
DIV 1	3.05	15.5	74.6
DIV 2	3.25	18.5	92.8
DIV 3	4.11	37.1	141
DIV 4	5.55	38.7	89.7
DIV 5	5.14	37.5	99.5
DIV 6	6.18	50.2	121
DIV 7	3.83	24	91.7
DIV 8	5.93	40.6	95
DIV 9	6.13	47.6	114

3.1. Effect of solvent ratio on the particle size distribution

In the study, crystallization experiments were performed at three different solvent ratios to investigate the effect of solvent dilution volume in terms of solvent-to-pharma drug powder ratio (termed solvent ratio). The solvent ratio effect on the pharma drug particle size distribution is shown in Fig. 3.

From Fig. 3, it is observed that the PSD of D (50)and D(90)significantly increased with respect to the inlet feed flow rate from 30 ml/min (low flow rate) to 90 ml/min (high flow rate) under a fixed solvent ratio. In addition, as the solvent ratio increases, the PSD also increases at lower flow rates, whereas the PSD of D (90) decreases with the solvent ratio at higher flow rates, i.e., 90 ml/min. The data further shows that a lower solvent ratio and higher flow rate offer a maximum amount of D (90) PSD, which indicates that these conditions are more favorable for getting the required PSD.

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2861-2870

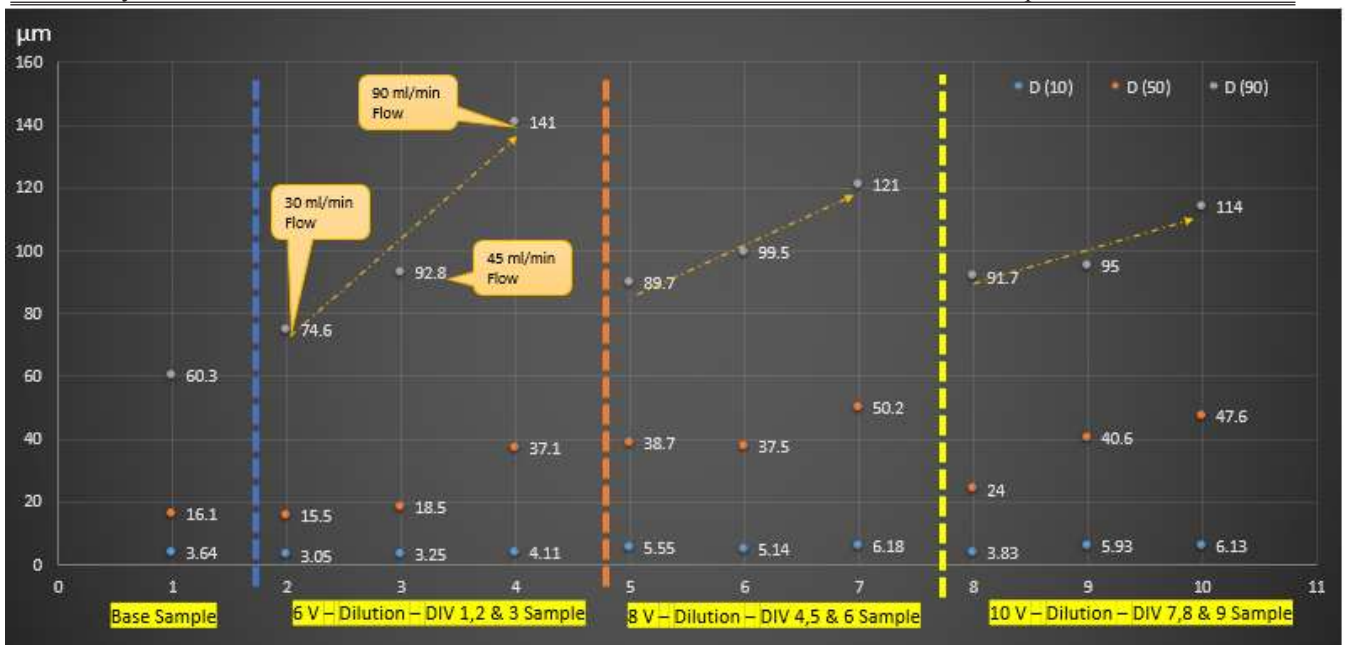
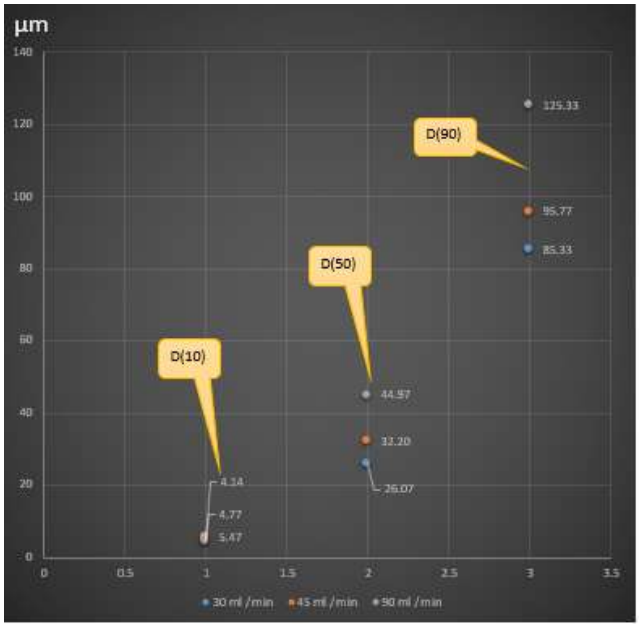


Fig. 3. The effect of solvent dilution ratio on the particle size distribution of the product.

3.2. Effect of feed inlet flow rate on the particle size distribution

Continuous crystallization experiments were performed at three different feed flow rates to investigate the effect of feed inlet flow rate on the particle size distribution of the pharma drug. The effect of feed flow rate on the particle size distribution of the pharma drug is shown in Fig. 4. From Fig. 4, it is observed that as the inlet feed rate increases, the PSD also increases for a fixed solvent ratio. In addition, the PSD of D (90) plays a significant role in obtaining better with the increase in feed flow rate.



Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2861-2870

Fig. 4. The effect of feed inlet flow rate on the particle size distribution of the product.

3.3. Comparison of the particle size distribution obtained from batch and continuous crystallization processes.

In the study, the particle size distribution of the batch crystallizer is compared with the continuous crystallizer. The resulting data is shown in Fig. 5. From the data, it is noticed that the PSD of D (10) and D (50) are almost comparable with the PSD of the batch, as well as continuous crystallization processes. However, the PSD of D (90) from the ongoing process is lower than that of batch process D (90). However, The PSDs of the continuous process are higher than those of the base or reference samples. The data further reveals that the continuous process is favorable over the batch process for large-scale production.

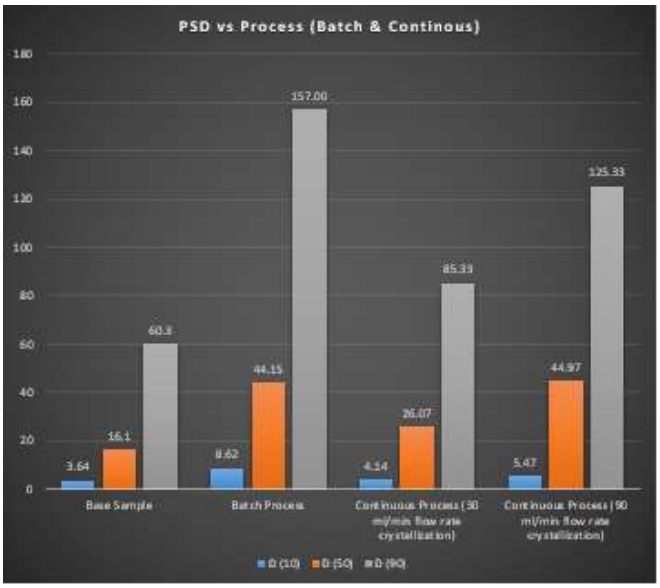


Fig. 5. Comparison of PSD of pharma drug obtained from batch and continuous crystallization processes.

3.4. Microscopic analysis of the prepared pharma drug

The shape of the pharma drug particles is observed using microscopic analysis. The obtained microscopic images of the pharma drug samples are shown in Fig. 6. From Fig. 6, it is observed that most of the particles are needle-shaped. In addition, a lower solvent ratio and higher flow rate are favorable conditions to achieve a number of D (90) crystals.

(a)

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2861-2870

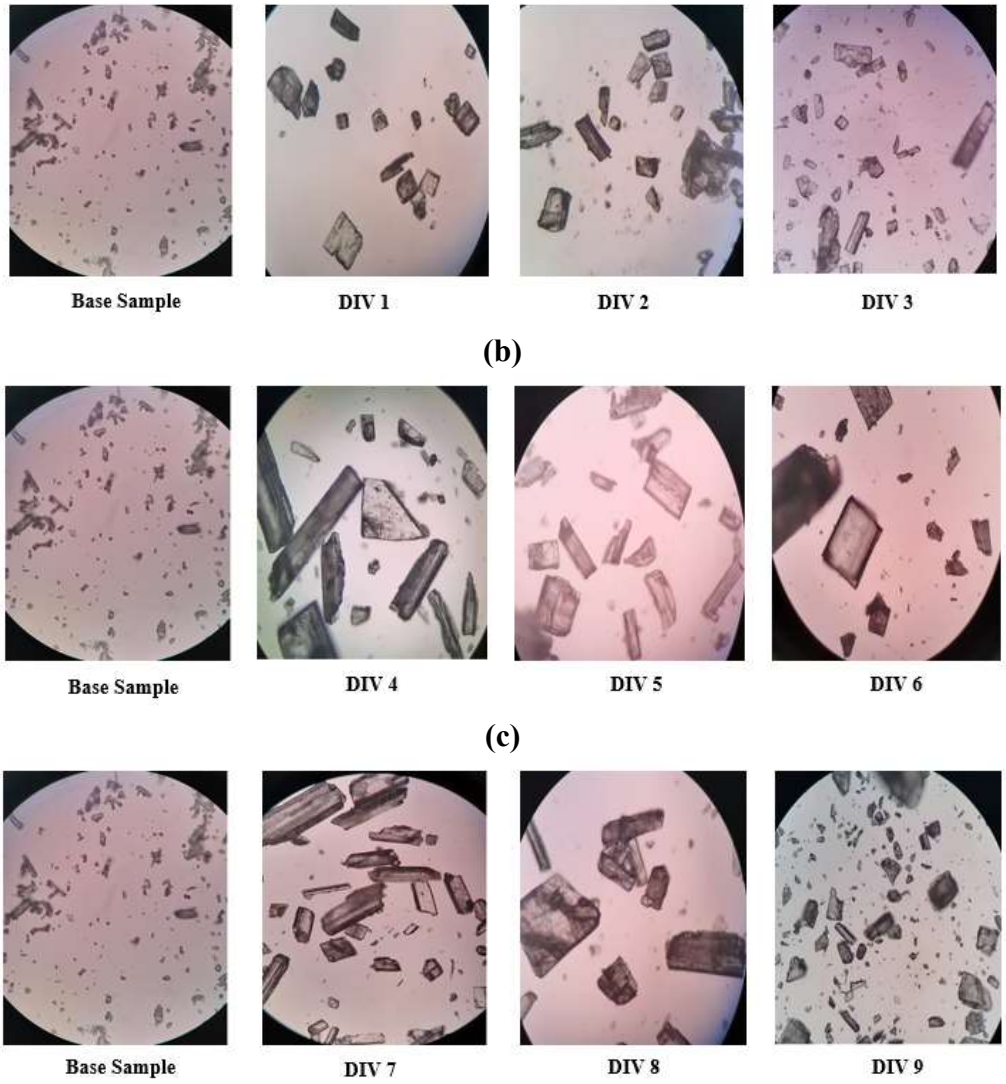


Fig. 6. Microscopic images of the pharma drug at different solvent ratios of (a) 6, (b) 8, and (c) 10 with respect to different feed flow rates.

4. Conclusions

In the study, continuous crystallization experiments were performed using a laboratory-scale crystallizer. The effect of process variables such as solvent ratio, inlet feed flow rate, and the cooling temperature on the particle size distribution of the product was examined. From the results, it was observed that the PSD of D (10), D (50), and D (90) increased with the increase in solvent ratio and feed flow rate. However, the impact of condenser cooling temperature on the PSD was insignificant. The results also show that the favorable conditions to achieve the required PSD (more D (90)) are lower dilution, i.e., the solvent ratio of 6, and higher feed flow rate, i.e., 90 ml/min.

References:

1. Marko Trampuzˇ a,b,⇑, Dušan Teslic' c, Blazˇ Likozar a,⇑ Crystallization of fesoterodine fumarate active pharmaceutical ingredient: Modelling of thermodynamic equilibrium, nucleation, growth, aggregation and dissolution kinetics and temperature cycling, Chemical Engineering Science 201 (2019) 97–111.
2. Formulation Development and Evaluation of Desvenlafaxine Microspheres Dipak P. Kardile1*, Pravin B. Awate1 , Madhuri S. Keskar1 ,Vishwas C. Bhagat1 , Rajkumar V. Shete1 , Dhanashree S. Kherade2 , Amruta D. Sonawane2 , Gayatri K. Jawale2 , Onkar P. Pawar1 , Adinath C. Bhusari1 .
3. US Food and Drug Administration. Guidance for industry: Regulatory classification of pharmaceutical co-crystals. Silver Spring: Center for Drug Evaluation and Research, US Food and Drug Administration; 2013 Apr.
4. Center for drug evaluation and research application number : 205583Orig1s000 summary review
5. Zhenguo Gao a,b, Sohrab Rohani a,*, Junbo Gong b, Jingkang Wang, Recent Developments in the Crystallization Process: Toward the Pharmaceutical Industry, Engineering 3 (2017) 343–353.
6. Development and evaluation of Desvenlafaxine loaded PLGA-chitosan nanoparticles for brain delivery - Gui-Feng Tong a 1, Nan Qin b 1, Li-Wei Sun c
7. Paroli F. Industrial crystallizers design and control. In: Chianese A, Kramer HJ, editors Industrial crystallization process monitoring and control. Weinheim: Wiley-VCH; 2012. p. 203–24.
8. *Lemke, Thomas L.; Williams, David A. (2012). Foye's Principles of Medicinal Chemistry. Lippincott Williams & Wilkins. p. 609.* ISBN 978-1-60913-345-0
9. The enantioselective pharmacokinetic study of desvenlafaxine sustained release tablet in Chinese healthy male volunteers after oral administration - Chen, Yin-xia; Du, Jiang-bo; Zhang, Yi-fan; Chen, Xiao-yan; Zhong, Da-fang
10. "Desvenlafaxine Succinate Monograph for Professionals." *Drugs.com. American Society of Health-System Pharmacists*. Retrieved 18 March 2019
11. *Coleman, Kristina A.; Xavier, Vanessa Y.; Palmer, Trish L.; Meaney, James V.; Radalj, Libby M.; Canny, Louise M. (2012).* "An indirect comparison of the efficacy and safety of desvenlafaxine and venlafaxine using placebo as the common comparator." *CNS Spectrums.* ***17*** *(3): 131–141.* doi:10.1017/S1092852912000648.
12. *Deecher, DC; Beyer, CE; Johnston, G; Bray, J; Shah, S; Abou-Gharbia, M; Andree, TH (August 2006*
13. "Desvenlafaxine succinate: A new serotonin and norepinephrine reuptake inhibitor" (PDF). *The Journal of Pharmacology and Experimental Therapeutics.* ***318*** *(2): 657–665.* doi:10.1124/jpet.106.103382. PMID 16675639. S2CID 15063064.
14. *Perry, Richard; Cassagnol, Manouchkathe (2009). "Desvenlafaxine: a new serotonin-norepinephrine reuptake inhibitor for the treatment of adults with major depressive disorder." Clinical Therapeutics. 31 Pt 1: 1374–1404.* doi:10.1016/j.clinthera.2009.07.012. ISSN 1879-114X. PMID 19698900

15. Sarkar, S.; Song, Z.; Griffin, S. R.; Takanti, N.; Vogt, A. D.; Ruggles, A.; Danzer, G. D.; Simpson, G. J. In Situ Crystal Growth Rate Distributions of Active Pharmaceutical Ingredients. Mol. Pharmaceutics 2020, 17 (3), 769−776.
16. *Thase ME, Kornstein SG, Germain JM, Jiang Q, Guico-Pabia C, Ninan PT (March 2009). "An integrated analysis of the efficacy of desvenlafaxine compared with placebo in patients with major depressive disorder." CNS Spectr.* ***14*** *(3): 144–54.* doi*:*10.1017/s1092852900020125.
17. Mahendra Khandpekar1 *, Jayanta Mheta2, Sanjay Patil2, Sonali Araj2, Pandurang Satpute3; Comparative studies on Synthesis and structure of old and new Polymorphs of Desvenlafaxine – An antidepressant drug;
18. Merve Öner a, Frederico C.C. Montes a, Tim Ståhlbergb, Stuart M. Stocks b, Johan Eriksson Bajtner b, Gürkan Sina,∗ ; Comprehensive evaluation of a data-driven control strategy: Experimental application to a pharmaceutical crystallization process