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Editorial

Special Issue on "Particulate Processes in the Formulation of Pharmaceuticals, Nutraceuticals and Bioactive Compounds"

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Introduction

Particulate processes are the basis of the production of solid dosage forms of medical and nutritional therapeutics. The expansion of solid dose pharmaceutical manufacturing is indicative of the advancements in drug delivery technologies, such as targeted drug delivery, controlled release and modifications to standard tablet and gelatin capsule dosage forms. The articles in this Special Issue "Particulate Processes in the Formulation of Pharmaceuticals, Nutraceuticals and Bioactive Compounds" (https://www.mdpi.com/journal/processes/special_issues/particulate_processes) present and review novel research work, highlighting developments in particulate processes that seek to improve the above-mentioned drug delivery technologies.

Comments on the Articles Presented in the Special Issue

Particulate processes form the cornerstone for the successful production of solid dosage forms of medical and nutritional therapeutic agents. The expansion of solid dose pharmaceutical manufacturing is indicative of the advancements in drug delivery technologies, such as targeted drug delivery, controlled release and modifications to standard tablet and gelatin capsule dosage forms. In 2018, among the 59 new drugs approved by the FDA, 24 were tablet form and 7 were capsule form products, and in 2021, about 50% of the approved new drugs were solid dosage forms [1]. Furthermore, the large number of poorly water-soluble drugs, as well as drugs with unpleasant organoleptic characteristics such as bitterness, have necessitated the development of modern particle engineering processes aiming to improve the solubility, permeability, targeting effectiveness and palatability of such drugs. The articles in this Special Issue highlight recent developments in particulate processes seeking to make a contribution to tackle the above issues. Equipment-based processes such as spray drying, nanomilling and continuous milling operations, hot-melt extrusion and electrospinning, together with theoretical and statistical investigations, have been employed to optimize the production variables and powder product characteristics of synthetic and natural origin drugs. Other methods such as complex coacervation that can be successful on a laboratory scale are difficult to realize on a large scale.

This Special Issue contains an article by Roy et al. [2], investigating the use of silicon dioxide as a guest particle in fast flow lactose (FFL) and microcrystalline cellulose (MCC) for dry coating by using a conical mill with a modified screen that permitted operation in both batch and continuous operation modes. After batch processing, particulates were completely covered with silicon dioxide. By increasing the SiO2/excipient mass ratio, the quality of coating was improved. These results demonstrated the potential use of conical mills for dry coating in the pharmaceutical industry and further defined processing time as a key parameter for the success of the process. Moreover, the outcome of their work has important implications in pharmaceutical formulation, as it provides a practical and feasible approach to improve the flowability, compressibility and thus the functionality of two widely used pharmaceutical excipients. As an extension of the above work, the

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physical stability of the tablet-form products was studied with a particular interest in the effects of environmental moisture [3,4]. A novel methodology was developed to determine moisture transport coefficients of microcrystalline cellulose tablets. Absolute permeability, moisture diffusion, moisture transfer and water vapor permeability coefficients were estimated for compressed tablets produced at different compression pressures. Average tablet porosity was found to be the principal parameter that determined the moisture transport coefficient. These findings may have further applicability, if they are used as a series of input parameters for modelling software such as COMSOL Multiphysics® to study the lamination, sticking and failure propensity of tablets due to moisture uptake.

A process that has found increasing application in industry is nanomilling, an effective process used to improve the aqueous solubility of poorly soluble drugs by increasing the specific surface area of drug particles. However, the produced nanosuspensions are thermodynamically unstable due to the large surface free energy, although this can be partly counteracted using polymeric stabilizers which provide short-term stability. For long-term stability solidification, for example by spray-drying, is required. For low melting temperature drugs, the selection of spray drying temperature is critical to avoid crystal aggregation or thermal decomposition. Fenofibrate was studied (m.p. 79–82 °C) for this purpose [5]. The drug's critical quality attributes and the spray drying temperature were defined by using together molecular simulations and QbD methodology.

Complex coacervation innovative methods were applied by other researchers [6] to encapsulate iron and chromium into novel nanoparticles for oral drug delivery. These nanoparticles were formulated using different molecular weight chitosan (CS) grades, dextran sulfate (DS) and whey protein isolate (WPI). Empty and loaded CS–DS nanoparticles were prepared via complex coacervation whilst whey protein nanocarriers were produced by a modified thermal processing method.

Taste masking is an important issue in the administration of pharmaceuticals and nutraceuticals since it affects the drug's palatability and consequently the compliance of patients to therapy. Panraksa et al. [7] employed ion-exchange resins for taste masking of the bitter antiulcer drug nizatidine (NZD). Polystyrene-based resin complexes with different resin/drug ratios were prepared. NZD–Dowex 1:5 was found to be the most promising formulation on the basis of percentage drug loading, particulate morphology, drug release and taste. NZD's bitter taste was effectively masked, as estimated by an electronic tongue and a human test panel.

Hot melt extrusion (HME), electrospinning and electrospraying, when used in conjunction with milling, are thermal processes that can deliver crystalline or amorphous particulate solids with a particle size ranging from a few up to about 100 microns. Therefore, the resulting product is suitable for further processing into tablet or capsule dosage form and offers the additional benefits of crystalline or amorphous solid dispersions. On the downside of these heat involving processes, the thermal treatment may cause changesor decomposition of the structure of the polymeric carriers that are used.

Partheniadis et al. [8] studied the impact of HME on the solid-state properties of methacrylic- and polyvinyl-based polymers. Overall, HME decreased the Tg but increased the electrostatic charge and surface free energy of the polymers. Additionally, HME reduced the work of compaction and material deformability but increased the elastic recovery (ER) and reduced the tablet strength (TS). Principal component analysis (PCA) organized the data of neat and extruded polymers into three principal components, explaining 72.45% of the variance. The main components included work of compaction, deformability and TS with positive loadings for compaction effectiveness, and ER with negative loading for compaction. Furthermore, application of hierarchical cluster analysis (HCA) assembled polymers with similar solid-state properties regardless of HME treatment into a major cluster comprised of neat and extruded Eudragit RSPO, Kollicoat IR, Kollidon SR, Soluplus and extruded Eudragit L100-55. In conclusion, PCA may be used to distinguish variables with similar or dissimilar effects, whereas HCA can be used to cluster polymers of similar

solid-state properties. Therefore, polymers can be suitably exchanged if such a need arises (e.g. shortage in supply).

Another area covered by the research articles exploits computational methods to provide numerical solutions and mathematical modeling of complex physical phenomena during mixing and compression [9,10]. The work of Hlosta et al. [10] is devoted to the selection of mechanical evaluation methods and a calibration procedure, leading to identification of relevant parameters for the application of a discrete element method (DEM) and virtual material creation. The most reproducible results were achieved by the pile formation and by the rotating drum methods of particulate's experimental characterization. However, it is always advisable to visually compare the slope between the calibration simulation and experimental curves. Furthermore, Hlosta et al. [11] applied DEM analysis to the study of the influence of particulate properties (shape, size and density) as well as the operating conditions (drum filling capacity, rotational speed and drum filling pattern) on the mixing process in rotary drums [11,12]. The optimal drum filling was 40–50% for spherical particles and 30–40% for sharp-edged particles. The relative standard deviation of the homogeneity index was 0.6% (ten simulation repetitions).

This Special Issue concludes with two very interesting review articles presenting extensive and critical accounts of the application of spray drying for improvement of tableting [13] and of the application of the contemporary electrospinning process for the fabrication of particulates in nanofiber form with exceptional drug solubility improvement [14].

Conflicts of Interest: The author declares no conflict of interest.

References

1. Available online: https://www.grandviewresearch.com/industry-analysis/oral-solid-dosage-osd-contract-manufacturing-market-report (accessed on 3 January 2023).
2. Roy, W.; Achouri, I.E.; Hudon, S.; Simard, J.-S.; Abatzoglou, N. A Continuous Conical-Mill Operation for Dry Coating of Pharmaceutical Powders: The Role of Processing Time. *Processes* **2022**, *10*, 540. [CrossRef]
3. Koumbogle, K.; Gitzhofer, F.; Abatzoglou, N. Moisture Transport Coefficients Determination on a Model Pharmaceutical Tablet. *Processes* **2022**, *10*, 254. [CrossRef]
4. Partheniadis, I.; Kopanelou, D.; Gamlen, M.; Nikolakakis, I. Monitoring the weight and dimensional expansion of pyridostigmine bromide tablets under dynamic vapor sorption and impact of deliquescence on tablet strength and drug release. *Int. J. Pharm.* **2021**, *609*, 121150. [CrossRef] [PubMed]
5. Ouranidis, A.; Gkampelis, N.; Markopoulou, C.; Nikolakakis, I.; Kachrimanis, K. Development of a Nanocrystal Formulation of a Low Melting Point API Following a Quality by Design Approach. *Processes* **2021**, *9*, 954. [CrossRef]
6. Patel, N.; Zariwala, M.G.; Hisham Al-Obaidi, H. Fabrication of Biopolymer Based Nanoparticles for the Entrapment of Chromium and Iron Supplements. *Processes* **2020**, *8*, 707. [CrossRef]
7. Panraksa, P.; Kasidech Boonsermsukcharoen, K.; Hwang, K.-M.; Park, E.-S.; Jantrawut, P. Taste Masking of Nizatidine Using Ion Exchange Resins. *Processes* **2019**, *7*, 779. [CrossRef]
8. Partheniadis, I.; Toskas, M.; Stavras, F.-M.; Georgios Menexes, G.; Nikolakakis, I. Impact of Hot-Melt-Extrusion on Solid-State Properties of Pharmaceutical Polymers and Classification Using Hierarchical Cluster Analysis. *Processes* **2020**, *8*, 1208. [CrossRef]
9. Partheniadis, I.; Terzi, V.; Nikolakakis, I. Finite Element Analysis and Modeling in Pharmaceutical Tableting. *Pharmaceutics* **2022**, *14*, 673. [CrossRef] [PubMed]
10. Hlosta, J.; Jezerská, L.; Rozbroj, J.; Žurovec, D.; Necas, J.; Zegzulka, J. DEM Investigation of the Influence of Particulate Properties and Operating Conditions on the Mixing Process in Rotary Drums: Part 1—Determination of the DEM Parameters and Calibration Process. *Processes* **2020**, *8*, 222. [CrossRef]
11. Hlosta, J.; Jezerská, L.; Rozbroj, J.; Žurovec, D.; Necas, J.; Zegzulka, J. DEM Investigation of the Influence of Particulate Properties and Operating Conditions on the Mixing Process in Rotary Drums: Part 2—Determination of the DEM Parameters and Calibration Process. *Processes* **2020**, *8*, 184. [CrossRef]
12. Nikolakakis, I.; Pilpel, N. Effect of Particle Shape on the Tensile Strength of Powders. *Powder Technol.* **1985**, *42*, 279–283. [CrossRef]

13. Al-Zoubi, N.; Gharaibeh, S.; Aljaberi, A.; Nikolakakis, I. Spray Drying for Direct Compression of Pharmaceuticals. *Processes* **2021**, *9*, 267. [CrossRef]
14. Partheniadis, I.; Nikolakakis, I.; Laidmäe, I.; Heinämäki, J. A Mini-Review: Needleless Electrospinning of Nanofibers for Pharmaceutical and Biomedical Applications. *Processes* **2020**, *8*, 673. [CrossRef]