MEDDOCS Open Access Publisher

ISSN: 2578-8760

Journal of Nanomedicine

Open Access | Research Article

The role of α-lactose monohydrate as a grinding material during preparation process of ultra-high diluted successed medicinal products

D Kalliantas[1]*; M Kallianta[2]; K Kordatos[3]; Ch S Karagianni[1]

[1]Department of Materials Science and Engineering, School of Chemical Engineering, NTUA, GR15780 Athens, Greece

[2]School of Dentistry, National and Kapodistrian University of Athens, Greece

[3]Department of Chemical Sciences, School of Chemical Engineering, NTUA, GR15780, Athens, Greece

***Corresponding Author(s): D Kalliantas**

Department of Materials Science and Engineering, School of Chemical Engineering, National Technical University of Athens, 9 Heroon Polytechniou Str. Zografos Campus 15780, NTUA, GR15780 Athens, Greece

Tel: +302-1077-23-280, Fax: +302-1077-23-184;

Email: dimitris@kalliadas.com

Received: Mar 27, 2020

Accepted: May 26, 2020

Published Online: May 29, 2020

Journal: Journal of Nanomedicine

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Pharmacy; α-lactose monohydrate; Homeopathy; Trituration; Comminution.

Abstract

Objective: During manufacturing of ultra-high diluted successed solution medicinal products from solid origin source materials, the preparation process is close linked to the trituration in α-lactose monohydrate. The α-lactose monohydrate in these cases is used as friction substance and this process leads the solid source materials to become micro-nano particles as we have clearly shown in a previous study. The purpose of this study is to investigate any changes in the composition of the α-lactose monohydrate during this preparation process of these products, as well as, to exclude the chemical involvement of α-lactose monohydrate in the differentiation of properties of finished products.

Methods: The grinding followed was based on the standard approach for triturating of any solid raw starting material for making ultra-high diluted successed solution medicinal products according the guides of German Pharmacopoeia. For comparative reasons, we also used two diferent triturated in α-lactose monohydrate solid materials (sodium chloride, calcium carbonate) in addition to triturated α-lactose monohydrate and the results were analysed.

Results: The results showed that, during these preparations, the chemical and physical properties of α-lactose monohydrate remain unaltered after 360 min by hand trituration process.

Conclusion: α-Lactose monohydrate as trituration mean is quite safe for the final inorganic origin products and there are no molecular changes in its composition. The variations of the electrical conductivity and pH are closely intertwined with the kind of source material and not with α-lactose monohydrate itself.

Cite this article: Kalliantas D, Kallianta M, Kordatos K, Karagianni S. The role of α-lactose monohydrate as a grinding material during preparation process of ultra-high diluted successed medicinal products. J Nanomed. 2020; 3(1): 1024.

Introduction

Comminution (milling) of solid medicinal materials is one of the most important mechanical operations and it is a size reduction process of reducing large solid unit masses into small unit ones, coarse particles or fine particles. Fine drug particulates are especially desired in formulations designed for parenteral, respiratory and transdermal use [1]. Trituration is a form of comminution (reducing the particle size of a substance) as well as producing a homogeneous material by mixing component materials thoroughly. The reduction in size of large pieces of solid materials is achieved by applying compression, impact, friction and shear or a combination of these forces on them [2]. In Pharmacopoeia, although this method of triturating a solid substance in α-lactose monohydrate, is very old, it seems to be very effective, as it has been shown in our previous work [3,4]. It is a simple and effective way to convert solid particles into much smaller particles (micro- nano particles).

However, modern pharmacopoeia does not seem to use this methodology, i.e. the trituration of any solid medicinal substance in α-lactose monohydrate, to reduce the size so that, among other things, to become more easily absorbed by the living organism.

Lactose as a material is inert, has a safe toxicological profile, physical and chemical stability, is compatible with the drug substance and is readily available and inexpensive. In our present work, we will not deal with Pharmaceutical lactose particles' technologies or the solubility, dissolution and bioavailability of drugs nor e.g. with lactose as a carrier for inhalation, in systems of binary or ternary mixtures, as an excipient, as a filler-binder in direct compression of tablets or in the preparation of solid dosage forms (e.g. tablets, capsules) orally administered drugs, because this has been studied extensively by others [5-13].

This study focuses on whether the role of α-lactose monohydrate is neutral as a friction material when triturating a substance to produce final products of ultra-high diluted succussed solution for medical purposes used as remedies, i.e. whether α-lactose monohydrate has no change in nature and properties during the preparation of these products.

Materials and method

The materials used were:

Commercially manufactured α-lactose monohydrate DFM pharma GmbH & Co, KG, Gosh, Germany for pharmaceutical use as a mean for friction and dilution one during trituration.

Sodium chloride from Sigma -Aldrich GmbH Germany.

Calcium carbonate from Sigma -Aldrich GmbH Germany.

Distilled water further purified by filtering through a 200 nm syringe filter.

The required equipment was:

Hand mortar and pestle made from unglazed porcelain composition.

A porcelain scraper, a measuring tile,a timer, a balance (kern S72, version 4.07-centimeter accuracy 0.00 g).

SEM (SEM Quanta 200, FEI).

XRD (BRUKER D8 Advance).

FT-IR spectrometer (FTIR Jasco 4200 with ATR PRO 410-S, TGS detector).

Raman spectrometer (Renishaw in Via Raman microscope).

Electrical Conductivity meter (HACH Sension 7 μS/cm).

pH meter (pH ConSORT C532 version 2).

DLS- Zetasizer nano series (Nano ZS 173, Malvern instruments LTD) with i) Size ranging from 0.6nm to 6μm hydrodynamic diameter ii) Size ranging for Zeta potential from 3nm to 10μm. iii) He-Ne, 4.0mW, 633nm red laser iv) 173° detection optics - Backscatter detection.

All triturations were effectuated by hand both with dry and moisture free samples. One part of materials (α-lactose monohydrate, sodium chloride, calcium carbonate) as drug substance (raw starting material) and 9 parts of α-lactose monohydrate as solvent mean are taken. We followed trituration's method by hand as the one described in our previous works [3,14]. To investigate conductivity and pH changes, it was necessary to transform the solid samples into solutions. The solution preparation was effectuated from initial substance up to the last trituration step (6X), with 1 g substance from the previous trituration step in 99 mL distilled water, which was further purified by filtering through a 200 nm syringe filter prior to its use (18.2 g/100 mL of distilled water is the final solubility of lactose). In all case, the measurements were repeated three times. Here, we present the middle in size measurement of three taken in every trituration, so that, there is no any mismatch between the numerical and graphical results.

Results and discussion

SEM Analysis

The SEM examination allows the characterization of morphology and texture of the samples. Figure 1(a) shows the tomahawk shape of α-lactose monohydrate that used in our samples. In the same figure, in image (b), the α-lactose monohydrate particles have still a certain size and keep their shape, because of the addition of new quantity, but even so, it is clear that the particles' boundaries are smoother. This has also been observed previously [15]. In the images (d, f) presented in Figure 1, the gradual grain size change of our initial material images (c, e) in to 6X trituration can be observed. On the contrary, sodium chloride and calcium carbonate are completely ground and look like very small white dots firmly attached to the gray coarse particles of α-lactose monohydrate.

X-Ray diffraction analysis

In Figure 2, all the XRD patterns of α-lactose monohydrate present perfectly crystalized structures expressed in 1X (after 60 min trituration process) as well as in 6X (after 360 min trituration process) by the well-formed narrow and high in intensity peaks at 20°. All these peaks (20°) correspond to α-lactose monohydrate. The red peaks correspond to α-lactose monohydrate which is characterized by a high degree of crystallinity. The other corresponding materials (sodium chloride, calcium carbonate), although having a crystalline structure clearly imprinted on the initial spectra, these crystalline structures are not observed in the 1X and final 6X trituration steps due to their agglomeration with the larger crystals of α- lactose monohydrate, something which is evident in the SEM images (See Supplementary material Figures S 1-6).

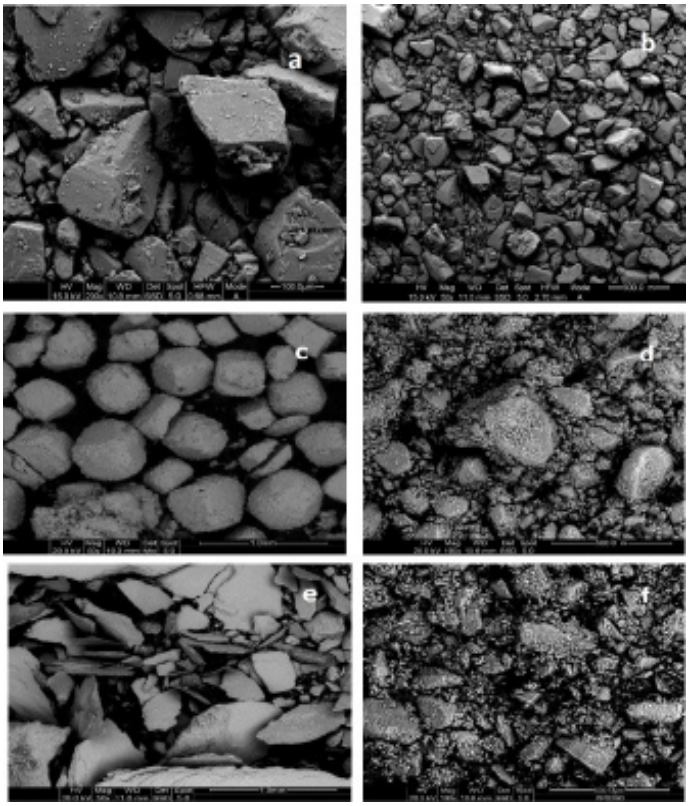

Figure 1: SEM images of (a) α-Lactose monohydrate source material, (b) 6X trituration step of α-Lactose monohydrate in a-lactose monohydrate, (c) Sodium chloride source material, (d) 6X trituration step of Sodium chloride in α-lactose monohydrate, (e) Calcium carbonate source material, (f) 6X trituration step of Calcium carbonate in α-lactose monohydrate

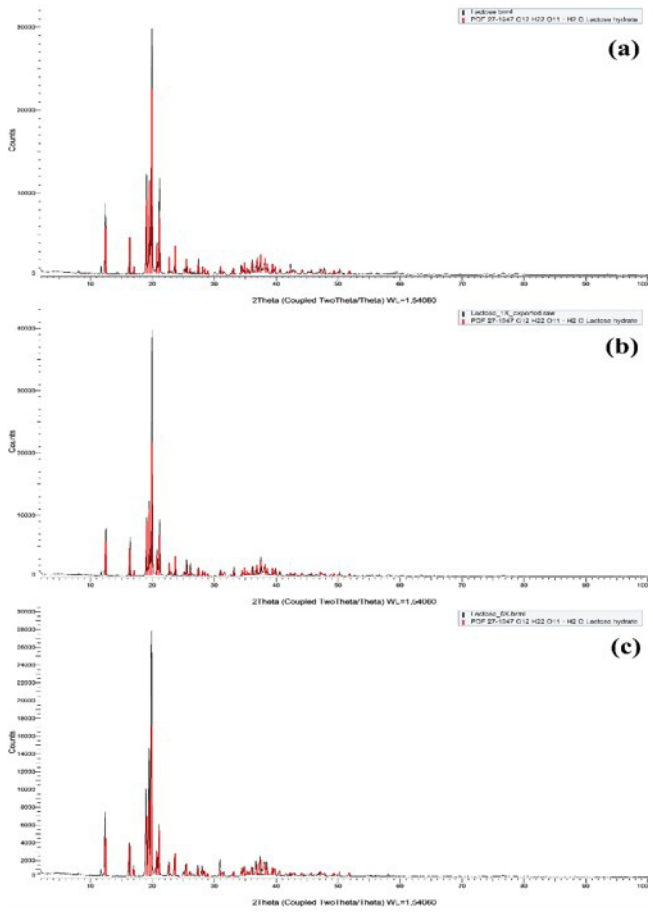

Figure 2: XRD spectra of Initial (a), 1X (b), 6X (c) α-lactose monohydrate samples

FT-IR analysis

Infrared spectroscopy has been used for gathering information on the chemical structure and functional groups of Initial, 1X and 6X samples. Comparing the FT-IR spectra of the initial raw starting materials (α-lactose monohydrate, sodium chloride, calcium carbonate) with the 1X and the final 6X triturated products, no changes or modifications to α-lactose monohydrate have been observed during trituration. Also, the wave numbers of the final 6X triturations in α-lactose monohydrate of inorganic RSM coincide, with small exclusions, with those of α-lactose monohydrate as friction and diluent mean. The graphs corresponding to 6X trituration present almost completely the same pattern as the one of α-lactose monohydrate, as it can be verified by comparing with that of the α-lactose monohydrate FTIR spectrum (See Supplementary material Fig. S7-12, Tables 1,2,3). More specifically, from the FTIR results is evident that in the spectrum of the initial sodium chloride sample, there is no any peak appearing because of the nature of the bonding in this salt (electrostatic, ionic Coulomb bond). On the contrary, in the spectrum of the same substance corresponding to the 6X trituration, all appeared peaks correspond to α-lactose monohydrate. Analogues results have been obtained for calcium carbonate because of its inorganic nature. The FT-IR spectrum of the initial sample demonstrates peaks corresponding to the bonding presented in the anion CO_3^{2-}. From the afore mentioned, it is evident that no changes take place for the examined substances during their trituration with α-lactose monohydrate. In Figure 3, the absolute similarity of the graphs of the1X (green line) and 6X (blue Line) trituration of α-lactose monohydrate in α-lactose monohydrate with the one of initial sample (red line) must be attributed mainly to the excess of α-lactose monohydrate present in the 1X and 6X triturated samples, because for every trituration nine new parts of this sugar are added.

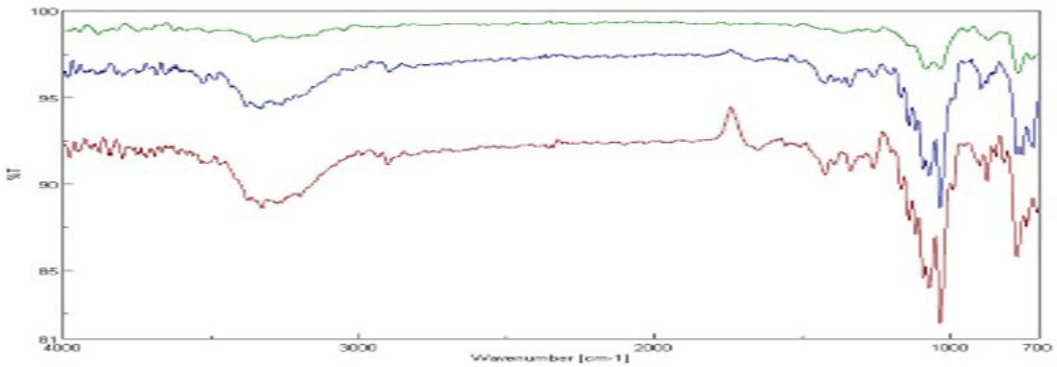

Figure 3: Concentrated FTIR spectra of Initial (red line), 1 X(green line),6X (blue line), α- lactose monohydrate samples

Raman analysis

The Raman pattern of α-lactose monohydrate has been known for a number of years.

In Figure 4, the picture of Raman spectra is evident, the difference in peaks in the interval 2000-2300 cm^{-1} is proportional and probably identical as the changes in the samples during the trituration.

According to literature, lactose has 129 Raman active vibration modes and 107 of them appear in the spectral window below 1500 cm^{-1} [16,17]. The same findings were also observed in the Raman spectra of the other two materials (sodium chloride, calcium carbonate) in 1X and 6X trituration steps (See Supplementary material Fig. S13-14). The results of our FTIR and Raman spectroscopy measurements lead to the same conclusions. Comparing the results presented here to those by others [18,19], the spectra are reasonably similar with this of α-lactose monohydrate.

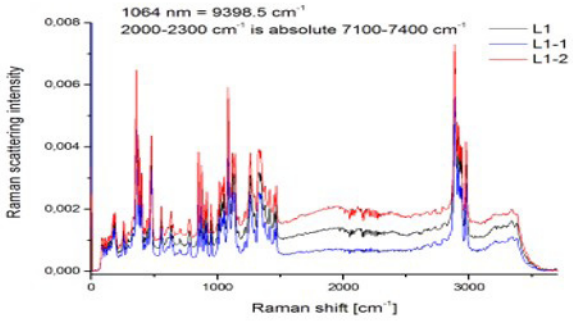

Figure 4: Raman spectra of Initial (L1),1X (L1-1),6X (L1-2) α-lactose monohydrate samples

Electrical conductivity – pH analysis

Three samples were measured from each trituration stage and the average of the findings are summarized in Figure 5. The electrical conductivity of the purified distilled water, which was used to prepare our samples, was 4.04 μS/cm. A remarkable variation in electrical conductivity is noticed, from the original raw starting materials up to the 6X trituration, which seems to depend on the material's kind. In materials where the initial of electrical conductivity is high, a remarkable decrease is observed at 6X trituration step (sodium chloride, calcium carbonate). Minor substantial changes in electrical conductivity and pH values between the α-lactose monohydrate and the various triturated steps are observed. These changes, 0.28% in Electrical Conductivity and 0.057 % in pH, for the case of α-lactose monohydrate can probably be attributed partly to the temperature difference during measurements. It is worth mentioning that for salts such as sodium chloride and calcium carbonate, the reduction of electrical conductivity is sufficiently impressive. A similar behavior is noticed for their corresponding pH values. A gradual reduction of the pH up to 4X, a small rise in 5X and a new impressive drop in 6X triturated step is observed. Generally speaking, α-lactose monohydrate is an organic molecule and so it is not dissociated i.e. it is not giving any ions. So, it is expected that its electrical conductivity is not high. After trituration (1X and 6X trituration) it ascertained, that the obtained solutions present even smaller values of electrical conductivity. Since no other modification took place, this diminution can be attributed only to the size diminution of lactose. Lactose is a disaccharide with no clear acid or alkali functional groups. According to the scientific literature, its pH value ranges from 4.5 to 7.5. In the case of our initial sample (no triturated α-lactose monohydrate), it was found to have a pH value of 4.60. After trituration, the 1X trituration solution had a pH value of 4.45 and the 6X trituration solution had a pH of 4.03, respectively. This reduction in pH value can be attributed to the reduction in lactose size during trituration, as no other substance was added or taken from the solution and no modification was observed from the characterization of the material. Finally, the mixing of α-lactose monohydrate and granular materials during trituration must be of essential importance for the quality and performance of the final products before turning them into solutions. The only reasonable explication for these changes seems to be the reduction in particle size since after grinding their size is on the micro-nanoscale. Thus, the raw starting materials have become micro-nanomaterials after the trituration process and their properties have been changed dramatically. Therefore, it is obvious, that the triturated mixture is a completely new/other material in comparison with the initial one with regard to its studied properties in the present work. To confirm the above, random samples were analyzed with Nanosizer from the 6x trituration step of sodium chloride and calcium carbonate and the results confirmed the reduction in particle size in the micro-nanoscale, something similar with that we observed in our previous study (Figures 6b, c) [3]. In contrast,the α-lactose monohydrate sample showed no peak on analysis with Nanosizer, due to its complete dissolution (Figure 6a). Chemically pure α-lactose monohydrate is rarely encountered. The α- and β- lactose anomers can transform from one to the other in solution, in a spontaneous process called mutarotation. Polymorphism and mutarotation both contribute to the complex chemistry of lactose, conferring on each form different chemical and physical properties. Another example of these complexity is, adding alcohol in lactose solution can decrease the solubility of lactose. This is common according the pharmacopoeia in ultra-high diluted succussed solution products for their long-term preservation requiring the addition of alcohol. Works in the research literature has been questionable. The impact of trituration, with the presence of α-lactose monohydrate seems to be quite great and interesting because of the variety of grain size which largely differentiate the properties of the materials before turning them into ultra-high diluted succussed solution products. In research studies, precautions must be taken to characterize the nature of the lactose sample under investigation. In addition to grinding, it is essential to give a certain time for mixing the materials with α-lactose monohydrate during trituration. The purpose of a mixing operation is that the whole process leads to an internal structure of desired quality. Mixing processes for α-lactose monohydrate and granular materials often ask to make a product with a degree of homogeneity suitable for the final use of the mixture. Also, in a similar work has been found that roller compaction did not cause changes in the chemical configuration of the lactose material through isomerization, but did affect the morphology of the α-lactose monohydrate, which enhanced the flowability of the powder [20]. Comminution, which are frequent processes in the drug and food industry, affect the moisture sorption properties of the final product in competing ways. As the ordinary commercial product of the α-lactose monohydrate is not always perfectly pure, for comminution uses as grinding mean it ought to be re-crystallized. It must be kept in a dry place, as it becomes musty when exposed to dampness. Moreover, the milling operation has been reported to trigger formation of amorphous material known to be more hygroscopic than crystalline powder [21]. This information is valuable for all persons which deal with the manufac-

ture of ultra-high diluted succussed solution products and are required to store 6X triturated raw starting materials in lactose (triturated mixtures) for future use in order to make these solution products.

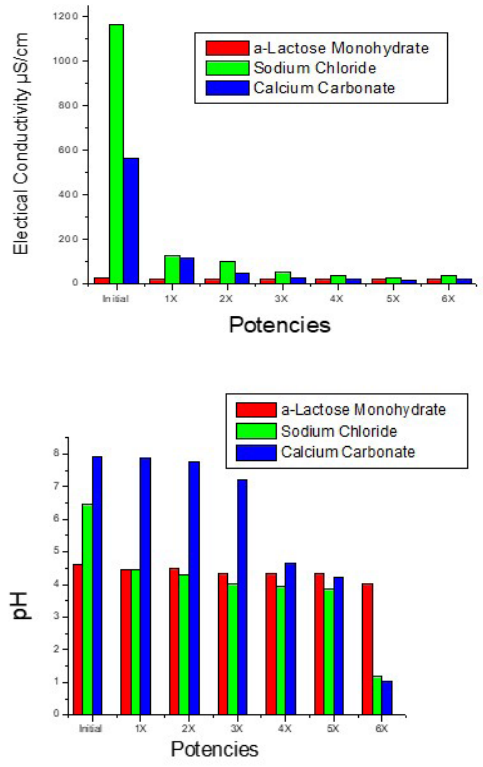

Figure 5: Changes of Electrical Conductivity and pH in α-Lactose monohydrate, Sodium chloride, Calcium carbonate samples

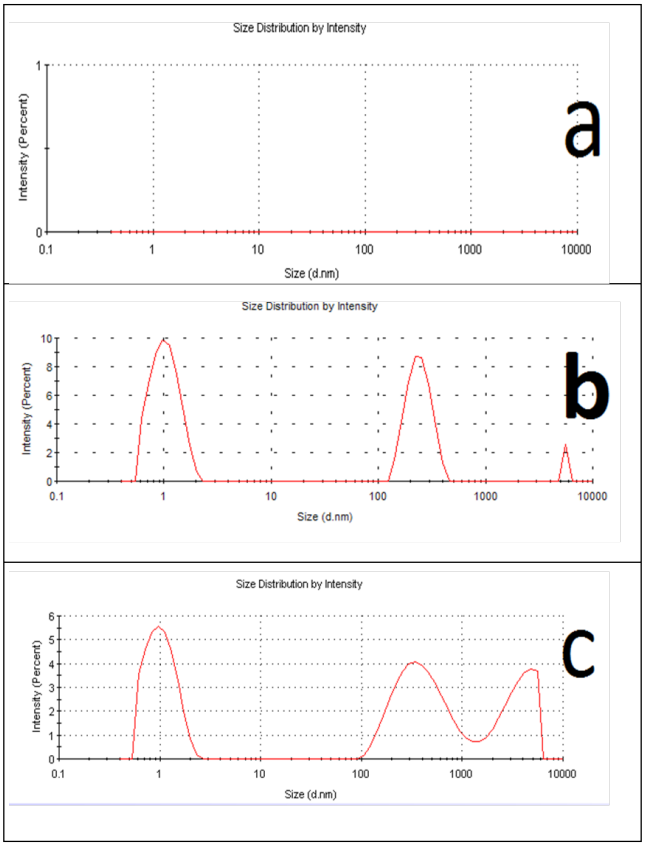

Figure 6: Size distribution by intensity for 6X trituration step in a-lactose monohydrate: a-Lactose monohydrate (a), Sodium chloride (b), Calcium carbonate (c)

Conclusion

From the aforementioned, it is obvious that α-lactose monohydrate, during the preparation process for ultra-high diluted succussed solution products: i) is and remains totally inert (i e it does not react with the substance during the trituration process, at least as far as compounds studied in the present work are concerned), ii) after 360 minutes of trituration process by hand as friction and the medium solvent are neutral and iii) contributes to a serious reduction in the size of the initial material particles and consequently to the property's modification due to their new micro-nano scale sizes.

Acknowledgments

The authors would like to thank Nopalia Natural Products company for supporting of this research.

References

1. Zhi Hui Loh, Asim Kumar Samanta, Paul Wan Sia Heng. Overview of milling techniques for improving the solubility of poorly water-soluble drugs, Asian journal of pharmaceutical sciences, 2015; 10: 255-274.
2. Patel RP, Baria AH, Patel NA. An overview of size reduction technologies in the field of pharmaceutical manufacturing, Asian Journal of Pharmaceutics 2008; 2: 216-220.
3. Kalliantas D, Kassalia ME, Georgiadou A, Karagianni Ch S. The physical features-size and granularity of solid materials are strongly affected by trituration in lactose, before turning them into homeopathic solutions, Materials Science and Engineering C. 2018; 93: 305-318.
4. Kalliantas D. The Chaos Theory of Disease, Kallianta A Publications, Eleusis, Greece 2008.
5. Prakash K, Jieun R, Hyeongmin K, Iksoo K, Jeong TK, et al. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability, Asian journal of pharmaceutical sciences. 2014; 9: 304-316.
6. Gabrielle Pilcer, Nathalie Wauthoz, Karim Amighi. Lactose characteristics and the generation of the aerosol, Advanced Drug Delivery Reviews 2012; 64: 233-256.
7. H. Steckel, N. Bolzen, Alternative sugars as potential carriers for dry powder inhalations, International Journal of Pharmaceutics. 2004; 270: 297-306.
8. G. Pilcer, K. Amighi. Formulation strategy and use of excipients in pulmonary drug delivery, International Journal of Pharmaceutics 2010; 392: 1-19.
9. Song Tao Wang, Jin Zhi Li, Xiao Lin, Yi Feng, Xiang Kou, et al. Novel coprocessed excipients composed of lactose, HPMC, and PVPP for tableting and its application International Journal of Pharmaceutics 2015; 486: 370-379.
10. Della Bella A, Müller M, Soldati L, Elviri L, Bettini R. Quantitative determination of micronization-induced changes in the solid state of lactose, International Journal of Pharmaceutics 2016; 505: 383-393.
11. Ziffels S, Steckel H. Influence of amorphous content on compaction behaviour of anhydrous a-lactose, International Journal of Pharmaceutics. 2010; 387: 71-78.
12. Masafumi Dohi, Wataru Momose, Kazunari Yamashita, Tadashi Hakomori, Shusaku Sato, et al. Application of Terahertz Attenuated Total Reflection Spectroscopy to Detect Changes in the Physical Properties of Lactose during the Lubrication Process Required for Drug Formulation Chem. Pharm. Bull. 2017; 65:

186-193.

13. Vikas Moolchandani, Larry L. Augsburger, Abhay Gupta, Mansoor Khan, et al. Characterization and selection of suitable grades of lactose as functional fillers for capsule filling: part 1, Drug Development and Industrial Pharmacy, 2015; 41:1452-1463.

14. Kalliantas D, Kassalia ME, Karagianni ChS, Trituration and Fractal Dimension in Homeopathic Pharmacopoeia, Pharmaceutica Analytica Acta. 2017; 8 :554.

15. Maria Badal Tejedora, Samaneh Pazesh Niklas Nordgren Michael Schuleit, Mark W. Rutlanda, Göran Alderborn, Anna Millqvist-Fureby Milling induced amorphisation and recrystallization of α-lactose monohydrate, International Journal of Pharmaceutics 2018; 537: 140-147.

16. Bronlund J, Paterson T. Moisture sorption isotherms for crystalline, amorphous and predominantly crystalline lactose powders, International Dairy Journal 2004; 14: 247-254.

17. Susi H, Jesse S. Laser-Raman spectra of lactose, Carbohydrate Research. 1974; 37: 351-354.

18. Murphy BM., Prescott SW, Larson I. Measurement of lactose crystallinity using Raman spectroscopy. J Pharm Biol Anal. 2005; 38: 186-190.

19. Kirk JH, Danna SE, Blatchford CG. Lactose: A definitive guide to polymorph determination International Journal of Pharmaceutics 2007; 334: 103-114.

20. Deeb Abu Fara, Iyad Rashid, Khouloud Alkhamis, Mahmoud Al-Omari, Chowdhry BZ, et al. Modification of α-lactose monohydrate as a direct compression excipient using roller compaction, Drug Development and Industrial Pharmacy, 2018; 44:2038-2047.

21. Listiohadi Y, Hourigan J, Sleigh R, Steele R. Properties of lactose and its caking behavior, Australian Journal of Dairy Technology 2005; 60: 33-52.