Impacts of the High Moisture Wet Granulation and Novel Microwave Drying on the Textural Characteristics of Pharmaceutical Particles

Maha Al-Ali,1,3* Abdulqahar Alsamarrae,3 Kutaiba I Salih4, Selvakannan Pairsamy,2 and Rajarathinam Parthasarathy1

1Chemical and Environmental Engineering, School of Engineering, RMIT University, Melbourne, Australia
2Applied Chemistry, School of Science, RMIT University, Melbourne, Australia
3Chemical Engineering, Engineering College, Tikrit University, Iraq
4Samarra Drug Industry - Samarra - Iraq
*Corresponding author: E-mail address (basmala17@yahoo.com)

Abstract. Naproxen sodium is a common non-steroidal anti-inflammatory drug used as a painkiller or in the therapy of rheumatoid and arthritic diseases. Naproxen sodium is a dipole drug with high affinity towards the water. Therefore, this study aimed to investigate the impacts of high moisture content due to wet granulation, and drying processes on the textural properties of naproxen sodium powder. In the present work, a new formulation of naproxen sodium drug was prepared and moisturized to 50 wt% by wet granulation process. Microwave radiation was employed to dry the high moisturized wet granules of naproxen sodium powder. Powder X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), and scanning electron microscope (SEM) were used to characterize samples before and after wet granulation and drying. The results showed that the crystalline structure, the morphology, and the chemical groups of the dry drug powder are remarkably changed after wet granulation. Microwave drying also affected the textural properties of the dried particles with no significant change in the chemical structure.

Keywords: microwave drying; wet granulation, naproxen sodium; crystallinity; particle morphology; characterization.

1. Introduction
During various processes of producing pharmaceutical products - such as wet granulation, and crystallization, pharmaceutical powders are moisturized by water or organic solvents which produce compounds with different crystal lattices [1]. In the pharmaceutical manufactory, granules can be produced by dry granulation or wet granulation [2]. Wet granulation, the process which is used in the present study, is the common process of producing wet granules by adding a liquid-binder into the dry pharmaceutical powder [3, 4]. Wet granulation process can be performed by different methods such as fluid-bed technology [2], centrifugal non-vacuum mixing [5], or mechanical impeller with high shear mixer [4, 6], etc. Wet granulation is a process generally used to improve and enhance the drug tablets quality by changing fine particles into large and agglomerated granules according to the consistent distribution of the water within the dry pharmaceutical blend [2]. Various factors aid to increase the
content of the liquid in the pharmaceutical powders. For instance, the small size of water molecules and the nature of hydrogen bond help to fill the drug voids and create stable crystal structure [7]. Some excipients also tend to dissolve in water or other solvents during preparation processes [8]. On the other hand, the presence of the water in pharmaceutical powder has negative influences on the pharmaceuticals bioavailability and the mechanical and thermal properties [9]. For example, the high percentage of humidity in the prepared tablets can negatively affect the tablet hardness [10]. Therefore, removing the undesired amount of the water from pharmaceutical powders is very important. Dehydration of pharmaceutical products under ambient conditions does not remove the moisture entirely, thereby the incomplete dehydration affects the pharmaceutical formulations undesirably and produces different crystal forms of active drugs [11]. Therefore, drying is an essential process in the preparation of pharmaceutical solids as it dictates the textural properties and characteristics of the dried product significantly [8].

In this work, microwave radiation is used to dry naproxen sodium wet granules. In general, microwave radiation heating can be used to accelerate drying process, improve dried powder characteristics and enhance drug bioavailability and stability performance. Hui (2009) has accelerated the drying of the spheroidal particles contained lactose and microcrystalline cellulose by using the microwave. The dried spheroidal particles drug by microwaves had the large surface area and more pores with more misshaped in comparison to that obtained by hot air oven drying [12]. Loh et al. (2008) have investigated the stability of acetylsalicylic acid – loaded granules (composed of lactose, cross-linked polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate copolymer and acetylsalicylic acid) in microwave assisted drying. The results showed that the granule size and microstructure had more effects on the drying rate than the surface area and the stability of the dried particles was undesirably affected by increasing drying time [13]. In addition, Kniazeva (2008) has inspected the effect of microwaves on the dehydration of caffeine used in pharmaceutical industries, which exhibited that the metastable polymorph of the caffeine drug was formed at temperatures lower than that produced by conventional methods. Bohle company has improved a global roller with a microwave dryer to integrate the granulation and drying system [15]. However, Water et al. (2011) have reported that there was no significant difference in the formulation of stearic acid and ibuprofen drugs when microwave heating used in comparison to conventional heating.

As a result, wet granulation and drying processes can significantly change the structural characteristics and hence probably affect the bioavailability and the technological performance of the drug [13]. Thus, the present study focuses on the variations in the textural characteristics of naproxen sodium occurred due to wet granulation process at the high level of moisture content and the use of electromagnetic microwave drying to understand any undesirable changes that may occur which probably affect the active properties of the drug.

2. Methodology

2.1. Materials

Key materials used to in this work were the active pharmaceutical ingredient, naproxen Sodium powder, (S)-6-Methoxy-a-methyl-2-naphthaleneacetic acid, CAS: 26159-34-2; purity (Titration by HClO4): 98.0 - 102.0%, and the excipients, povidone powder, Polyvinylpyrrolidone, (CAS: 9003-39-8) and microcrystalline cellulose powder, (CAS: 9004-34-6). These chemicals were purchased from Sigma—Aldrich.

2.2. Method

In the present work, a new formulation of naproxen sodium dry drug powder was prepared from the materials and their compositions illustrated in Table 1. and moisturized by wet granulation process to 50 wt%. In wet granulation process, the dry drug powder was wetted and mixed manually to obtain wet granules containing 50 wt% water. Later was remixed at a speed of 500 rpm for 5 min by using a planetary centrifugal mixer (non-Vacuum Thinky-Mixer: ARE-310) to obtain a homogeneous distribution of wet granules of naproxen sodium [5]. A novel microwave radiation drying was employed to dry the prepared wet granules at 68 °C for 10 minutes using an accelerated microwave reaction system (CEM Corporation- MARS5, USA). Samples before and after wet granulation and
microwave drying processes were characterized using Fourier-transform infrared spectroscopy (FTIR), powder X-ray diffraction (XRD), and scanning electron microscope (SEM) to estimate and evaluate the changes occurred due to wet granulation and microwave drying on the texture properties of samples.

**Table 1.** Compositions of dry powder and wet granules of naproxen sodium formulation

| Materials                        | Dry drug powder (%) | 50% wet granules (%) |
|----------------------------------|---------------------|-----------------------|
| Naproxen-Sodium powder           | 50                  | 50                    |
| Polyvinylpyrrolidone powder      | 40                  | 40                    |
| Microcrystalline cellulose powder| 10                  | 10                    |
| Deionised water (binder liquid)  | ---                 | 100                   |

3. Results and discussion

Fig (1) which illustrates XRD patterns of dry drug powder, 50 wt% wet granules, and the dried granules by microwave, shows that the crystallinity of dry drug powder is changed after wet granulation and microwave drying. The peak of highest intensity at 12.9 degree in XRD pattern of the dry drug powder indicates the crystallinity of naproxen sodium. However, the addition of a large amount of water to the dry drug powder, throughout wet granulation process, makes remarkable changes in peaks intensities and positions. For example, the intensity of the peak at 12.9 degree is decreased, and its position shifted to 13.2 degree as well as neighboring by another peak at 13.85 degree with less intensity. These changes are due to the dispersion of naproxen sodium and/or the solubility of sodium salt in the water in the matrix, and forming new hydrated forms [5]. In addition, a new noteworthy peak at 19.45 degree appeared with high intensity which revealed the significant change occurred due to the addition of the water and possibly indicates the formation of new crystal forms of hydrated naproxen sodium [17]. Nevertheless, after drying by microwave, this high-intensity peak is missed in the dried particle pattern due to the removal of the water. Peaks at 21.7, 22.3, 22.8, 23.16 and 23.76 degrees in the dry drug powder are also transformed to a single peak at 23 degrees. Those peaks are changed again after drying as illustrated in the broadening peaks at 22.19 and 22.85 degrees. Contrary, the single peak at 26.91 degree is changed into two peaks at 26.43 and 26.83 degrees after adding the water to be absent after drying which state the dispersion of naproxen sodium with the matrix. These variations indicate the formation of new hydrated crystalline forms and changes in the amorphous structure of the wet granules [7] because naproxen sodium could diffuse consistently in the amorphous form [18]. These results were consistent with that reported by Kim and Rousseau [19] and Malaj [7] who have signposted that the temperature and relative humidity (moisture) can affect phase transformation of solids. During microwave drying, the rapid release of electromagnetic energy, which accelerated the heating process, improved naproxen sodium solubility in water [20]. Consequently, the resulted high solubility of naproxen sodium aids the distribution of the naproxen sodium within the matrix. Therefore, the crystal shape and size of the dried particles by microwave cannot return to be similar to dry drug powder before any process [5]. In summary, high moisturizing wet granulation process as well as microwave drying process affect the crystalline structure of the wet granules and dried particles and create different polymorphs.
It can be observed from Fig. 2 that the high level of moisture content (50 wt%) due to wet granulation process affect the pattern of the organic groups of the dry drug powder structure. After wet granulation to 50 wt%, a new strong, broad peak is formed between 3300 and 3500 cm\(^{-1}\) in the FT-IR spectrum which indicates the formation of the hydrogen bond (–OH radical peak) [21, 22]. The carboxylate group peak between 1500 and 1700 cm\(^{-1}\) is also changed due to the addition of the water. However, after microwave drying, the broad peak (3300-3500 cm\(^{-1}\)) is disappeared because of the removal of the water. Also, the carboxylate group peak changes again due to microwave drying to be similar to that of the dry drug powder, which indicates the removal of the water from the wet granules of drug powder.

SEM image in Fig 3A reveals that the morphology of dry drug powder comprised a combination of the non-uniform semi-rectangular particles of naproxen sodium and the spherical particles of povidone and flakes or needle-like particles of microcrystalline cellulose. The SEM image of the 50 wt% wet granules, as shown in Fig 3B, indicates the changes in their morphology to be more agglomerated and transformed into irregular flakes or needle-like aggregates due to the absorption and retention capacity of the excipients [8]. The high amount of water added to the dry drug powder assists to increase the solubility of naproxen sodium and the swelling of the microcrystalline cellulose and povidone which form different crystal forms and that can be noticed clearly from the changes occurred in the morphology of the wet granules [23]. On the other hand, the morphology of the dried particles extremely different from that of the wet granules and it is not exactly similar to those of dry drug powder particles, Fig 3C. The variation in the dry drug powder morphology is a result of adding the water thereby the formation of polymorphs or hydrated crystal forms which can not return as that in the original particles. Similarly, after drying polymer particles represented by microcrystalline cellulose.
cellulose and povidone tend to shrink which interpret the change in the morphology of the dried particles to that of the dry drug powder [5, 8].

![SEM images of A) dry drug powder, B) 50 wt% wet granules, and C) particles dried by microwave ~ 200 µm.](image)

**Figure 3.** SEM images of A) dry drug powder, B) 50 wt% wet granules, and C) particles dried by microwave ~ 200 µm.

It can be concluded that the addition of a high amount of water such as 50 wt% to the dry drug powder of naproxen sodium aided the variations in the structure and texture of the solid to form different hydrated polymorphs [5, 17]. Naproxen sodium drug is a dipole material with a strong affinity toward the water [24], which increases the solubility of the drug in water. The excipient materials represented by microcrystalline cellulose and povidone are polymers tend to swell when reacted with water which
interprets the formation of the large aggregates after wet granulation process. On the other hand, the nature of the water molecule in terms of the high polarity and the multidirectional property of hydrogen bond enhances filling the voids between particles with water to form more stable hydrated formulas [7]. This water property and its high dielectric constant (78.6) [25], also improves the interaction between the water and the electromagnetic waves which increase the radiation penetrability into the drug sample and hence accelerates drying process thereby have a rapid and effective removal of water [7].

4. Conclusion
A new formulation of naproxen sodium holding high moisture contents of 50 wt% due to wet granulation process was dried using novel microwave drying at a specific temperature. XRD, FTIR, and SEM instruments were employed to characterize the dry drug powder; the high moisturized wet granules and the dried particles by microwave to inspect the impacts of high moisturizing wet granulation and microwave drying processes on the drug particles shape, morphology, polymorphisms, and the chemical structure.

XRD results after wet granulation and microwave drying exposed the transformation of the crystal forms due to the addition and removal of the water. SEM images, compatible with XRD results, showed the impacts of the wet granulation and microwave drying from the variation occurred in the morphology of the wet granules and the dried particles. FTIR spectra result signposted that there were no significant changes in the chemical structure of the wet granules except the presence of –OH radical peak after adding the water which disappeared after microwave drying. As an overall result, in wet granulation process of naproxen sodium drug with 50 wt% moisture, some of the molecules of the sodium salt of naproxen sodium are dissolved in water which changed the morphology and crystallinity of the particle to the extent that it cannot return to its original morphology and the non-hydrated form. During drying, these particles particularly the polymer tended to shrink thereby leading to change in their morphology. In summary, wet granulation process had significant effects on the texture properties of naproxen sodium as well as microwave drying.

5. Acknowledgments
Authors would like to thank the facilities and the technical assistance of the Australian Microscopy & Microanalysis Research Facility at RMIT University, the laboratory of Applied Chemistry School and Chemical Engineering department at RMIT University.

References
[1] Kardum, J.P., A. Sander, and D. Skansi, Comparison of convective, vacuum, and microwave drying chloropropamide. 2001 Drying Technology, 19(1): p. 167-183.
[2] Šantl, M., et al., A compressibility and compactibility study of real tableting mixtures: The impact of wet and dry granulation versus a direct tableting mixture. 2011 International journal of pharmaceutics, 414(1): p. 131-139.
[3] Nordström, J. and G. Alderborn, The Granule Porosity Controls the Loss of Compactibility for Both Dry and Wet Processed Cellulose Granules but at Different Rate. 2015 Journal of pharmaceutical sciences, 104(6): p. 2029-2039.
[4] Briens, L. and R. Logan, The effect of the chopper on granules from wet high-shear granulation using a PMA-1 granulator. 2011 AAPS PharmSciTech, 12(4): p. 1358-1365.
[5] Al-Ali, M., S. Periasamy, and R. Parthasarathy, Novel drying of formulated naproxen sodium using microwave radiation: Characterization and energy comparison. 2018 Powder Technology, 334: p. 143-150.
[6] Nguyen, T.H., D.A. Morton, and K.P. Hapgood, Predicting Tablet Strength from the Wet Granulation Conditions via the Unified Compaction Curve. 2015 Procedia Engineering, 102: p. 517-526.
[7] Malaj, L., Impact of solid state properties of sodium naproxen hydrates on their technological performance. 2009, SCHOOL OF ADVANCED STUDIES-Doctorate course in Pharmaceutical sciences (XXI ciclo).
[8] Schrank, S., et al., Impact of drying on solid state modifications and drug distribution in ibuprofen-loaded calcium stearate pellets. 2014 *Molecular pharmaceutics*, 11(2): p. 599-609.

[9] Li, W., *Drying of Pharmaceutical Powders Using An Agitated Filter Dryer*. 2014, University of Leeds.

[10] Chowhan, Z., Moisture, hardness, disintegration and dissolution interrelationships in compressed tablets prepared by the wet granulation process. 1979 *Drug Development and Industrial Pharmacy*, 5(1): p. 41-62.

[11] Di Martino, P., et al., Physico chemical and technological properties of sodium naproxen granules prepared in a high shear mixer granulator. 2008 *Journal of pharmaceutical sciences*, 97(12): p. 5263-5273.

[12] HUI, L.Z., *Application of microwaves in pharmaceutical processes*. 2009.

[13] Loh, Z., et al., Microwave-assisted drying of pharmaceutical granules and its impact on drug stability. 2008 *International journal of pharmaceutics*, 359(1): p. 53-62.

[14] Kniazeva, S.M., *Microwave Assisted Polymorph Selection in Pharmaceutical Drugs*. 2008, WORCESTER POLYTECHNIC INSTITUTE.

[15] Vervaet, C. and J.P. Remon, Continuous granulation in the pharmaceutical industry. 2005 *Chemical Engineering Science*, 60(14): p. 3949-3957.

[16] Walters, R.H., et al., Next generation drying technologies for pharmaceutical applications. 2014 *Journal of pharmaceutical sciences*, 103(9): p. 2673-2695.

[17] Di Martino, P., et al., Physical characterization of naproxen sodium hydrate and anhydrate forms. 2001 *European journal of pharmaceutical sciences*, 14(4): p. 293-300.

[18] Arici, M., et al., Preparation of naproxen-ethyl cellulose microparticles by spray-drying technique and their application to textile materials. 2014 *Journal of microencapsulation*, 31(7): p. 654-666.

[19] Kim, Y.-s., Crystallization and Solid-state Transformation of Pseudopolymorphic Forms of Sodium Naproxen. 2005.

[20] Čerpnjak, K., et al., Characterization of naproxen-loaded solid SMEDDSs prepared by spray drying: The effect of the polysaccharide carrier and naproxen concentration. 2015 *International journal of pharmaceutics*, 485(1): p. 215-228.

[21] Kim, Y.B., I.Y. Park, and W.R. Lah, The crystal structure of naproxen sodium,(C14H13O3Na), a non-steroidal antiinflammatory agent. 1990 *Archives of Pharmacal Research*, 13(2): p. 166-173.

[22] Martino, P.D., et al., A new tetrahydrated form of sodium naproxen. 2007 *Journal of pharmaceutical sciences*, 96(1): p. 156-167.

[23] Al-Ali, M., P. Selvakannan, and R. Parthasarathy, Influences of novel microwave drying on dissolution of new formulated naproxen sodium. 2018 *RSC Advances*, 8(29): p. 16214-16222.

[24] Mohammad, F. and B. Ridwan, Medium Effect on Solvation Free Energy, Dipole Moment and Molecular Reactivity of Naproxen. 2015 *J Theor Comput Sci*, 2(134): p. 2.

[25] Komarov, V.V., *Handbook of dielectric and thermal properties of materials at microwave frequencies*. 2012: Artech house.