EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 7
100-103
Year: 2020

EXPLORING DRY CO-GRINDING APPROACH AS A TOOL TO IMPROVE THE DISSOLUTION RATE OF POORLY SOLUBLE DRUG

Alaa Y. Bazeed[1]*, Ahmed Nouh[1], Ebtessam A. Essa[2] and Gamal M. El Maghraby[2]

[1]Department of Pharmaceutical Technology, Pharmacy College, Delta University for Science and Technology, International Costal Road, Gamasa, Aldekhlya, Egypt.
[2]Department of Pharmaceutical Technology, Pharmacy College, Tanta University, Egypt.

***Corresponding Author: Alaa Y. Bazeed**
Department of Pharmaceutical Technology, Pharmacy College, Delta University for Science and Technology, International Costal Road, Gamasa, Aldekhlya, Egypt.

Article Received on 10/05/2020 **Article Revised on 01/06/2020** **Article Accepted on 21/06/2020**

ABSTRACT
Nateglinide is a non-sulphonylurea which was approved for treatment of type II diabetes mellitus. It shows a pH dependent solubility that resulted in a variable and incomplete oral bioavailability, that may put the diabetic patient at risk. This work introduces dry co-grinding of the drug with inert carrier as a method for enhanced dissolution rate of nateglinide. Aerosil 200 was used as an inert excipient. Three formulations were prepared at different molar ratios (1:1, 1:2 and 1:3 drug to aerosil 200). Drug dissolution was monitored before and after processing. The developed formulations showed significant increase in drug dissolution compared to the unprocessed nateglinide. This study introduced the dry co-grinding process as a solvent free technique, which can be performed during the regular production process, as a promising tool to improve dissolution rate of poorly soluble drugs.

KEYWORDS: Nateglinide, Aerosil 200, colloidal silicon dioxide, co-processing.

INTRODUCTION
The dissolution of many drugs is the determining rate step for bioavailability and absorption after the drug oral administration. More than 40% of developed drugs and more than 70% of synthesized drugs suffer from poor dissolution rate and bioavailability. These new chemical interties are commonly classified under the Class II categories of the biopharmaceutical classification system i.e poorly soluble drugs with good permeability through the gastrointestinal tract. The dissolution problem of these drug is an obstacle in the way of developing effective drug product that can reach the market.[1] Different methods have been developed to improve dissolution rate and, consequently, the bioavailability of these drugs. These techniques can include microemulsification[2], solid dispersions[3], inclusion complex formation with cyclodextrines[4], salt formation[5], etc.

The aim of this research was to study the efficacy of colloidal silicon dioxide (Aerosil 200) on the dissolution rate of nateglinide using dry co-grinding approach. Aerosil 200 is an inert and safe excipient that is extensively used in pharmaceutical industry for enhancing powder flow properties during the manufacture of many solid dosage forms.[6] it is recognized as safe material by Food and Drug Administration. Due to its chemical structure (Fig.1a) it possesses the ability to form hydrogen bonding with many compounds via its silanol group.[7] Aerosil was previously employed as a co-crystal conformer to enhance dissolution rate of hydrochlorothiazide with a great success.[6] However, the authors used acetone assisted co-grinding approach. Though complete removal of the organic solvent is an essential step prior to further processing steps, however any residual traces may pose stability or safety issues. Therefore, dry co-processing has the advantage of being user friendly, solvent free technique which can be performed during the regular production process for solid forms.

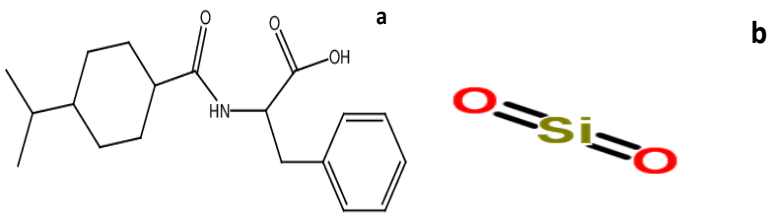

Figure 1. Chemical structure of (a) Nateglinide, (b) Aerosil 200.

Nateglinide (fig.1b), oral non-sulfonylurea antidiabetic agent used for type II diabetes mellitus, was used as model drug. It works by inhibiting of K-ATP channels with following stimulus of insulin secretion from the pancreatic β-cells.[8-10] Nateglinide expresses poor water solubility (8mg/L).[11, 12] Considering its acidic nature Being acidic in nature (Pka = 3.1), it is absorbed from the upper part of the GIT so it falls under the category of drugs with narrow absorption window. Considering this beside the acidic nature of the drug this will result in poor solubility and dissolution in the in the acidic environment of the upper GIT. Hence, low oral bioavailability. Increasing the dissolution rate via coprocessing with aerosil is expected to improve the oral bioavailability of nateglinide.

MATERIALS AND METHODS

Materials

Nateglinide was obtained from All Pro Corporation, China. Aerosil 200 was a gift sample from Sigma for Pharmaceutical Industries, Egypt. Methanol, hydrochloric acid as well as Sodium lauryl sulphate were purchased from El Nasr Pharmaceutical Chemicals Company.

UV-spectroscopy of nateglinide Methanol was used a solvent to prepare a stock solution of nateglinide at concentration of 1 mg/ml. From this stock solution, serial dilution of the drug (5 to 25 µg/ml) were prepared with 0.01 N HCl (pH 1.2) containing 0.5% w/v sodium lauryl sulphate. The calibration curve was plotted by measuring the absorbance value of the different prepared concentrations at 210nm using JENWAY UV-visible spectrophotometer. The calibration curve was constructed by plotting the absorbance as a function of concentration (Fig.2). The relationship was linear with R^2 value of 0.9997.

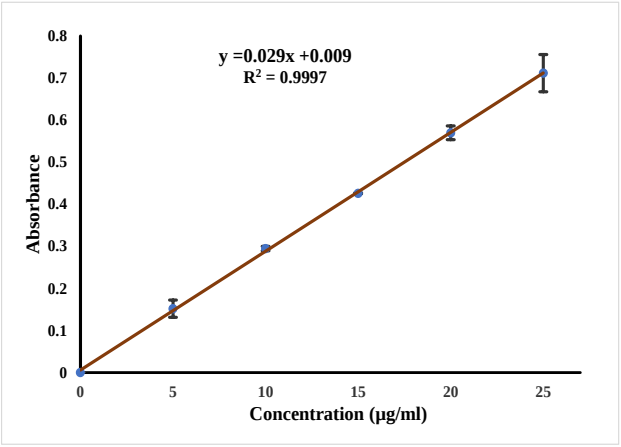

Figure 2. Standard calibration graph of nateglinide.

Preparation of drug/aerosil co-grounded mixtures.

Nateglinide/aerosil mixture were prepared by dry co-grinding method. Nateglinide and aerosil 200 were mixed in different molar ratios (1:1, 1:2 and 1:3, drug:aerosil, respectively) before using a mortar and pestle for 30 minutes. The prepared mixtures, if not used immediately, were stored in air-tight bottles till needed. The composition of the prepared formulations is presented as both molar and weight ratios in Table 1.

Table 1: The compositions of the tested formulations, together with dissolution parameters (percentage amount released after 5 minutes (Q5) and dissolution efficiency, DE).

Formulation	Nateglinide	Aerosil 200	Q5 (%)	Dissolution efficiency (%)
Pure nateglinide	1	0	47.3% ±1.5	64.6% ±2.1
Na (1:1)	1(1)	1(0.15)	65.5.8% ±3.4	78.3% ±4.4
N:a (1:2)	1(1)	2(0.3)	74% ±5.0	85%±1.5
N:a (1:3)	1(1)	3(0.45)	88% ±±2.3	93.3%±1.5

-values between brackets represents the weight ratio

In vitro dissolution studies

The dissolution studies employed the USP type II (paddle) method. The dissolution medium (1000 ml) comprised of 0.1 N HCl at 37 ± 10C containing 0.5% w/v sodium lauryl sulphate. The surfactant was added to maintain sink condition.[13] The paddle speed was adjusted to rotate at 50 rpm. An amount equivalent to 120 mg nateglinide from different co-processed mixture were added to the dissolution vessel, using unprocessed drug as control. Samples (5 ml) were collected from each dissolution vessel at appropriate time intervals (5, 10, 20, 30, 45 and 60 min), filtered through a 0.45 mm Millipore filter and assayed for drug content spectrophotometrically. The cumulative amount dissolved were computed and were plotted as a function of time to produce the dissolution profiles. The

dissolution parameters were extracted from these profiles and were used for comparison between different formulations. These parameters included the amount of drug dissolved in the first 5 minutes (Q5) and the dissolution efficiency (DE) which was calculated from the area under the dissolution curve for each sample relative to the corresponding area proposing 100% dissolution at the first time point [14].

Statistical analysis Statistical analysis employed the Kruskal Wallis test for comparison between formulations using SPSS 16.

RESULTS AND DISCUSSION

The effect of co-processing of nateglinide was evaluated in presence aerosil in comparison to unprocessed drug. The cumulative amount of drug released versus time plots were constructed and are presented in Fig.3. The dissolution parameters taken as percentage drug released after 5 minutes and dissolution efficiency are listed in Table 1. The dissolution profile of pure unprocessed nateglinide reflected its slow dissolution with a maximum of 48 % of the dose the first 5 minutes. The total amount released after 60 minutes was79% with an overall dissolution efficiency being 62% (Table 1). These dissolution parameters are in good agreement with previously published data by other researchers (Arafa et al., 2017). Co-processing the drug with aersoil as carrier developed products with significance ($P<0.05$) enhancement in dissolution pattern compared with the unprocessed drug. At the lower ratio of 1:1 (NA1), about 65.5.8% of the loaded drug was liberated after 5 minutes. The dissolution efficiency increased to 78.2%. The enhancement in dissolution parameters increased by increasing the molar ratio of aerosil. Formulations NA2 and NA3 showed Q5 of about 74% and 88% With an overalldissolution efficiencies were estimated to be 85% and 93.3%, respectively. These values were significantly higher than that recorded to unprocessed drug ($p < 0.01$). The obtained dissolution parameters are similar to those reported by El Gizawy and coworkers. [6] Knowing that the published work utilized acetone-based wet co-grinding of nateglanide with sucralose.

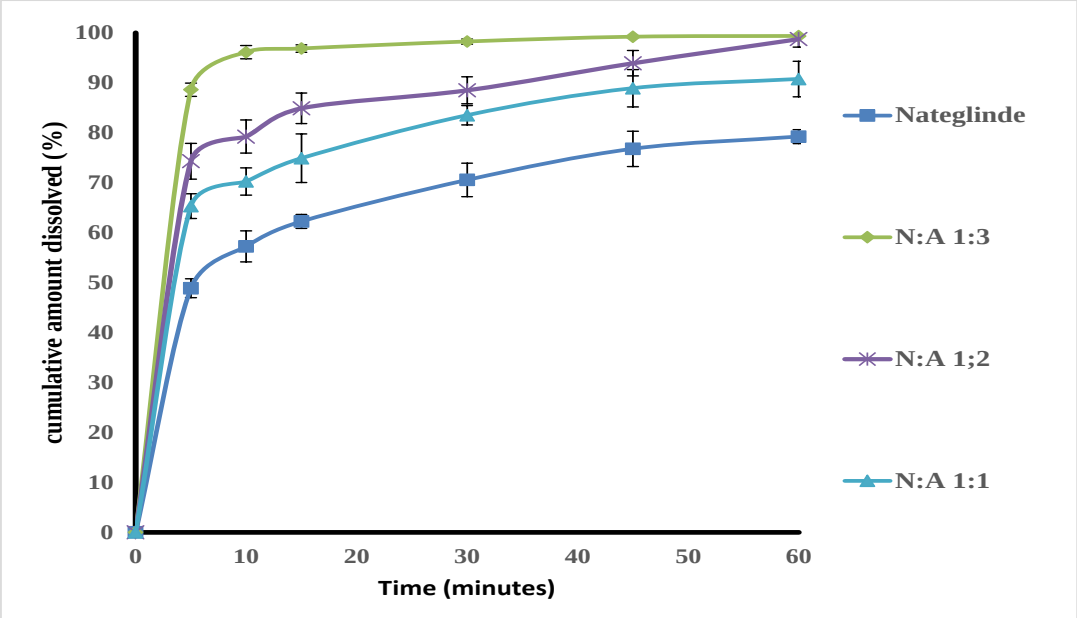

Figure 3. Dissolution profiles of the pure nateglinide the prepared Formulations as presented in details in table 1.

These data indicate that the co-grinding of nateglinide with aerosil may decreased the particle size of the drug due to the grinding process employing mortar and pestle. This is expected to increase the surface area of the drug with subsequent increased dissolution, as per Noyes-Whitny equation.[15] Adsorption of drug particles over aerosil, with its known huge surface are, is another expected scenario that would further increase the surface area. Additionally, there is a possible formation of newly hybrid crystalline species with weaker intermolecular bonds compared to pure drug. However, this requires further confirmation by physical state characterization.

CONCLUSION

Dry co-grinding of nateglinde with aerosil 200 produced product with improved dissolution rate Compared to pure drug. This solvent free technique provides a platform for employing co-grinding of drugs with other excipients in the dry state with high potential for improved dissolution rate.

REFERENCES

1. Merisko, E.L. Nanocrystals: Resolving pharmaceutical formulation issues associated with poorly water-soluble compounds. In: Marty, J.J. (Ed.), Particles. Marcel Dekker, Orlando; 2002.

2. He CX, He ZG, Gao JQ. Microemulsions as drug delivery systems to improve the solubility and the bioavailability of poorly water-soluble drugs. Expert Opin. Drug Deliv, 2010; 7: 445–60.
3. Essa EA, Balata GF. Preparation and characterization of domperidone solid dispersion. *Pak. J. Pharm. Sci*, 2012; 25(4): 783-91.
4. Kurkov SV, Loftsson T. Cyclodextrins Int. J. Pharm, 2013; 453: 167–80.
5. Naeem D, Osman M, El Maghraby G, Essa E. Salt and non-salt forming excipients to improve the dissolution of dexibuprofen; formulation of chewable tablets. EJBPS, 2020; 7: 01-11.
6. El-Gizawy SA, Osman MA, Arafa MF, EL-Maghraby GM. Aerosil as a novel co-crystal co-former for improving the dissolution rate of hydrochlorothiazide. Int J Pharm, 2015; 478: 773-5.
7. Ambike AA, Mahadik KR, Paradkar A. Spray-dried amorphous solid dispersions of simvastatin, a low tg drug: in vitro and in vivo evaluations. Pharm. Res, 2005; 22: 991–8.
8. Maggi G, Bruni M, Maietta A, Canobbio A, Cardini U. Technological approaches to improve the dissolution behavior of nateglinide, a lipophilic insoluble drug: Nanoparticles and co-mixing, Int. J. Pharm, 2013; 454: 562–7.
9. Sharma P.R, Lewis S.A., Design and in vitro/*in vivo* evaluation of extended release matrix tablets of nateglinide, J. Young Pharm, 2013; 5: 167-72.
10. Sahoo R.K, Biswas N, Guha A, Sahoo N, Kuotsu K. Development and in vitro/*in vivo* evaluation of controlled release provesicles of a nateglinide–maltodextrin complex, Acta Pharm. Sin. B, 2014; 4: 408–16.
11. Tang J, Sun J, He ZG, Self-emulsifying drug delivery systems: strategy for improving oral delivery of poorly soluble drugs, Curr. Drug Ther, 2007; 2: 85–93.
12. Remko M, Theoretical study of molecular structure, pKa, lipophilicity, solubility, absorption, and polar surface area of some hypoglycemic agents, J. Mol. Struc. Theochem, 2009 897: 73–82.
13. Arafa MF, El-Gizawy SA, Osman MA, EL-Maghraby GM. Cocrystallization for enhanced dissolution rate of nateglinide: In vitro and in vivo evaluation. J Drug Deliv Sci Tec, 2017; 38: 9-17.
14. Khan KA. The concept of dissolution efficiency. J. Pharm. Pharmacol, 1975; 27(1): 48–9.
15. Mosharraf M, Nystr€om C. The effect of particle size and shape on the surface specific dissolution rate of microsized practically insoluble drugs. Int J Pharm, 1995; 122: 35–47.