수난용성 약물의 생물학적 이용율의 개선: 나노 사이즈의 분쇄의 가능성(3)

최우식*, 황선환[1], 이동범[1]
부산대학교, [1]부산대학교 대학원 분체공학협동과정
(wschoi@pusan.ac.kr*)

Improvement of Bioavailability of Water Insoluble Drugs (III) Possibility of Nano-sized Comminution

Woo Sik Choi1*, Sun Hwan Hwang[1], Dong Beom Lee[1]
Department of Pharmaceutical Manufacturing, Pusan National University
[1]Interdisciplinary Program in Powder Technology, Graduate School, PNU
(wschoi@pusan.ac.kr*)

INTRODUCTION

Many attempts have been conducted to obtain a good bioavailability achieved by creating an amorphous product (Chow and Riegelman 1971, Chaumeil 1998). The amorphization of drug in co-grinding process has been recognized as one of the effective way to improve the dissolution behavior (Yamamoto et al. 1974, Nakai et al. 1984). It is well known that the pharmaceutical processing of a solid causes defects in the crystal lattice, which contribute to the disorder (Morita et al. 1984). A grinding process could induce defects in the crystalline network: these defects would improve the compression and dissolution (Pirttimaki et al. 1993). The amorphous and crystalline states are two extreme states of solid substances. In an amorphous product, molecules are in an irregular arrangement within the particles. The lack of long-range order that characterizes crystalline state confers with the particles on a good compression ability due to the plasticity and isotropy of force transmission through such a structure. However, amorphous states have been known as a high energy state, and their physical and chemical stability is poor (Piyarom et al. 1997).

A series of attempts to enhance the bioavailability of insoluble drugs have been made by the fine grinding technique using a planetary mill(Chung et al. 2003, Choi et al 2003). Here, the possibility of improving the dissolution properties of water insoluble drugs such as diphenyl hydrantoin (phenytoin) and biphenyl dimethyl dicarboxylate (DDB) based on the molecular interaction between drug and additives during pharmaceutical ultra-fine grinding process will be discussed with comparison to experimental data using practical mills such as high speed stirred ball mill and wet type jet mill.

EXPERIMENTAL

Materials: Dipheny hydrantoin (phenytoin) and biphenyl dimethyl dicarboxylate (DDB) were supplied from Tokyo Kasei Kogyo Co. Ltd. (Tokyo, Japan), and from Dawoo Pharmaceutical Co. Ltd. (Busan, Korea), respectively. The additives such as sodium lauryl sulfate (SLS, Taidong Chemical Co.), polyvinyl alcohol (PVA, Sigma Chemicals Co.), methylcellulose (MC, Sigma Chemicals Co.), D-mannitol (Yakuri Pure Chemical Co., Ltd. Kyoto, Japan), and ß-cyclodextrine (ß-CD, Wacker, Co. Ltd., UK) were used. All other chemicals were of analytical reagent grade and used without further purification.

Preparation method of ground products: A vertical type planetary mill (KVP-03, power 2.2 kW) was mainly used (Choi et al. 2001, Chung et al. 2003). The revolution speed of turntable was kept constant at 112 rpm in anti-clock direction in all runs. The inner volume and diameter of the pot of cylindrical shape were 372 ml and 74 mm, respectively. The pot was made of wear-resistant zirconia and the grinding balls of 1 mm, 2 mm, and 5 mm were also made of the same material. Both the pot and grinding balls were made by Nikkato Co., Ltd. (Osaka, Japan). The stainless ball and nylon-coated stainless ball were partly used as grinding media. As the standard operating conditions, the previously described procedures were used in this study as it was (Choi et al. 2001).

Particle size distribution (PSD): The particle size distribution of single ground sample and co-ground sample was measured with Mastersizer microplus of Malvern Instruments Ltd. (Spring Lane South, UK) on the basis of particle size analysis by the laser diffraction and scattering method. Prior to measurement, the sample was externally dispersed for 2 min. with an ultrasonic homogenizer, US-300T (Nihonseiki Co., Ltd. Osaka, Japan). The optimum value of refractive index for three sample drugs was experimentally determined to be 1.680.

Powder x-ray diffraction (PXRD): A Miniflex diffractometer (Rigaku, Tokyo, Japan) was employed. The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 30 kV; current, 15 mA; and scanning speed; 4°/ min.

In vitro apparent solubility and dissolution rate test: The solubility of phenytoin and DDB were determined by the chemical analysis described by the general testing method of Korean Pharmacopoeia.

RESULTS AND DISCUSSION

Experimental results by planetary ball mill

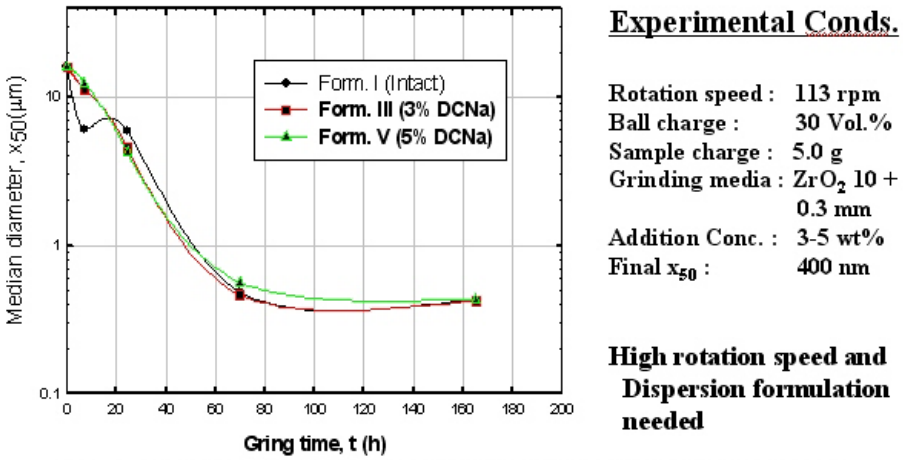

Fig. 1 Change of the median diameter of DDB with various grinding times for different additive concentration by planetary ball mill

Fig. 1 shows that the median diameter of DDB is varied with the progress of grinding time by planetary ball mill for different additive concentrations. The median diameter is near to 400 nm by long grinding time. It is considered to reflect that the extent of adverse grinding depends on the mechanical properties, the thermal properties of the drugs and the additives, and the molecular interaction between solid surfaces of the drugs and the additives.

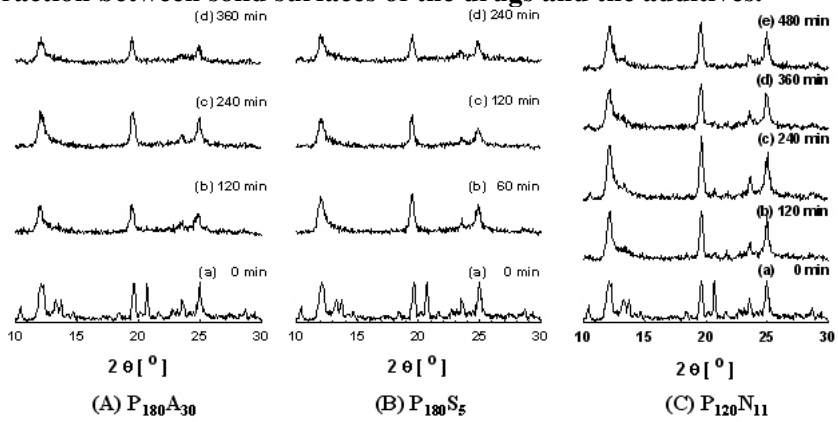

Fig. 2 Change in powder X-ray diffraction patterns of ground products by fine grinding mill of DDB

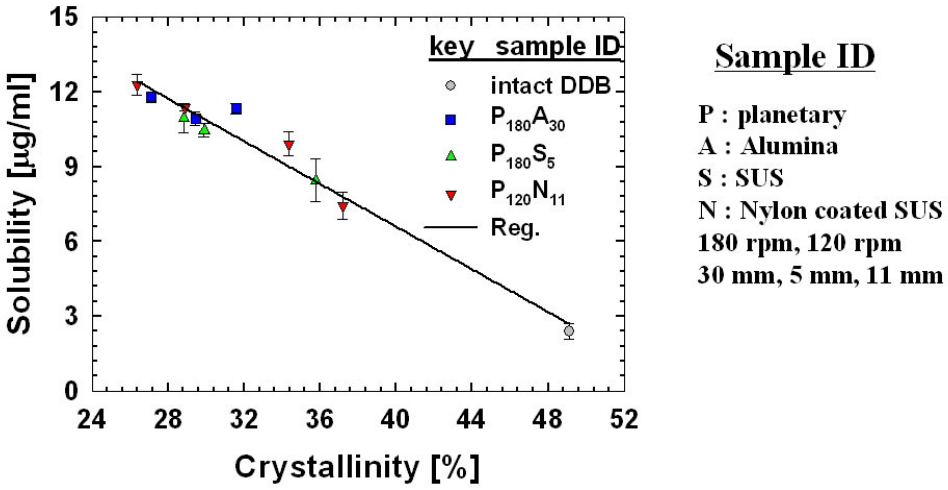

Fig. 3 Correlation between crystallinity and solubility of DDB

Fig. 2 shows typical examples of changes in the XRD patterns of DDB by dry grinding, where the samples ID are the same as shown in previous figures. The crystallinity of all the ground samples was changed from crystalline to partially amorphous forms. Here, the degree of crystallinity of ground products was calculated according to Herman's method.

Fig. 3 shows a typical example of the correlation observed between crystallinity and apparent solubility of DDB. The diagram indicates that these variables are correlated fairly well. It should note that we could not be discussed only the crystallinity effect without considering of the size effect separately. The amorphous state is important for enhancing of bioavailability.

Nano-sized grinding experimental data using practical mills :

Recently, according to the progress of ultrafine grinding technology, it is confirmed that the nano-sized particles could be produced by the combination of hardware and software of new grinding technologies. Furthermore, the grinding limit of particle size has been decreased below a few 100 nanometer range for various industrial fields.

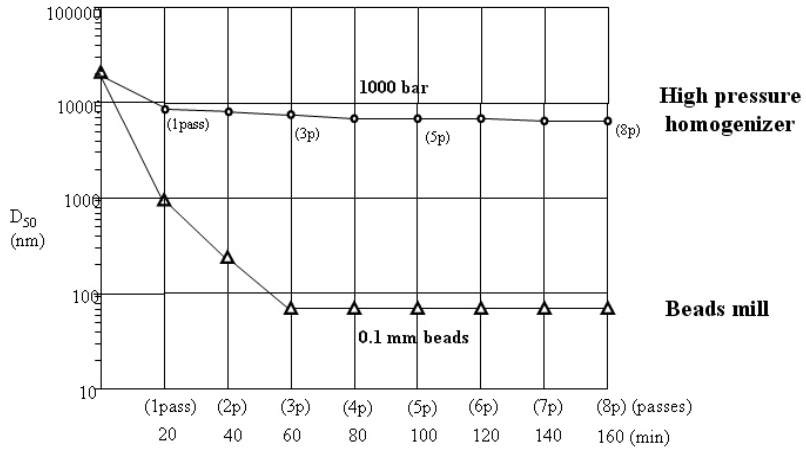

Fig. 4 Relationship between the median diameter and passing number for high pressure homogenizer or grinding time for beads mill.

Fig. 4 hows the comparison of nanoparticle formation of DDB by two types of mills, high pressure homogenizer and bead mill, based on largely different principles of particle breakage. This figure indicates the comparison of dispersing performance between meads mill and high pressure homogenizer. As shown in figure, the production of nanoparticle below 100 nm of median diameter could be possible by using the stirred media mill with beads size of 0.1 mm. Even in the case of drug materials, it is considered to be possible when the higher specific energy added with prevention of adverse grinding using a proper formulation.

CONCLUSIONS

From a series of grinding experiments of poorly water-soluble drugs, phenytoin and DDB, the following results were mainly obtained.

The pattern of particle size distribution of ground samples were changed with the species and addition amount of additives. Among investigated additives, SLS for UDCA, PVA for phenytoin, and ß-CD for DDB were most effective in the co-grinding. It was confirmed that the solubility data of ground samples could be improved by decreasing the particle size and the crystallinity of ground samples.

The applications of water insoluble drugs to nano-sized particles by top-down process was possible and useful for development of a novel dosage form formulation.

ACKNOWLEDGEMENT

This study was carried out by financial support of Korea Science and Engineering Foundation, No. 2000-6-217-01-2. The authors wish to express gratitude to the president of Daewoo Pharmaceutical Co., Ltd. for providing of sample DDB and Mr. Oomura of Yoshida Kikai Co., Ltd. (Nagoya, Japan) , Mr. Ueda of Shinmaru Enterprises Corp. (Osaka, Japan) and Mr. Ooshio of Sugino Machine Co. Ltd. (Toyama, Japan) for supporting of nano-sized grinding experiments.

REFERENCES

Chaumeil J.C. 1998. Micronization: A method of improving the bioavailability of poorly soluble drugs. *Meth. Find. Clin. Pharmacol*., 20:211-215.

Choi, W.S., Chung, H.Y., Yoon, B.Y., Kim, S.S. 2001. Applications of grinding kinetics analysis to fine grinding characteristics of some inorganic materials using a composite grinding media by planetary ball mill, *Powder Technology*, 115:209-214.

Chung, H.Y., Yonemochi, E., Saito, T., Terada, K., Tozuka, Y., Oguchi, T., Yamamoto, K., Chung, H.Y., Choi, W.S. 2003. Factors affecting the apparent solubility of ursodeoxycholic acid in the grinding process, *Int. J. Pharm.*, 255:49-56.

Chiou, W.L., Riegelman, S. 1971. Pharmaceutical applications of solid dispersion systems, J. *Pharm. Sci.,* 60:1281-1302.

Morita, M., Nakai, Y., Fukuoka, E., Nakajima, S. 1984. Physicochemical properties of crystalline lactose. II. Effect of crystallinity on mechanical and structural properties, *Chem*. *Pharm. Bull.*, 32:4076-4083.

Pirttimaki, J., Laine, E., Ketolainen, J., Paranen, P. 1993. Effect of grinding and compression on crystal structure of anhydrous caffeine, *Int. J. Pharm.*, 95:93-99.

Piyarom, S., Yonemochi, E., Oguchi, T., Yamamoto, K. 1997. Effects of grinding and humidification on transformation of conglomerate to racemic compound in optically active compounds, *J. Pharm. Pharmacol.,* 49:384-389.

Yamamoto, K., Nakano, M., Arita, T., Nakai, Y. 1974. Dissolution rate and bioavailability of griseofulvin a ground mixture with microsrystalline cellulose, *J. Pharmacokinet. Biopharm.,* 2:487-493.