수난용성 약물의 생물학적 이용률의 개선:나노현탁제제에의 마이크로파 건조의 적용(3)

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Improvement of Bioavailability of Water Insoluble Drugs (III)
- Microwave Drying Characteristics of Nanosuspensions -

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INTRODUCTION

The enhancement of bioavailability (BA) is an important factor for the design of dosage form formulation of insoluble drugs in particular. The theoretical background of improvement of bioavailability for insoluble drugs could be considered based on two equations; one is Noyes-Whitney Eq. on Dissolution rate, and the other Kelvin Eq. on solubility, which are indicating the relationship between the solubility of drug and the primary particle size of raw drug. The smaller the particle size is, the more the solubility is enhanced.

The possibility of improving the dissolution properties of water insoluble drugs based on the molecular interaction between drug and additives during pharmaceutical ultra-fine grinding process was presented at this session. Here, after the preparation of slurry nanoparticles of water insoluble drugs, the drying characteristics curve of slurry nanoparticles and the re-dispersion characteristics were compared and examined with the effects of drying methods such as microwave drying, freeze drying, reduced pressure drying, and conventional box drying and of drying and of formulation related with additives.

BASIC EQUATION PF MICROWAVE DRYING

A crucial fact to keep in mind at all times is that microwaves and dielectrics are not forms of heat but rather forms of energy that are manifested as heat through their interaction with materials. It is as if they cause materials to heat themselves (Schiffmann 1987). There are many mechanisms for this energy conversion and two mechanisms which are primarily interested in dielectric heating phenomena, those are ionic conduction and dipole rotation as shown in following Eqs. (1) and (2), respectively.

Power per unit volume for ionic conduction:

$$P_v = E^2 \square q \square n \square \mu \quad (1)$$

Power per unit volume for dipolar rotation:

$$P_v = k\, E^2 \square f \square \varepsilon' \square \tan \delta \quad (2)$$

where P_v is power per unit volume, E electrical field strength, f frequency, n ionic density, q electrical charge, δ dielectric loss angle, ε' dielectric constant, and μ mobility of ion.

EXPERIMENTAL

Materials : Biphenyl dimethyl dicarboxylate (DDB) as a model insoluble drug together with previous investigated samples was supplied from Dawoo Pharmaceutical Co. Ltd. (Busan, Korea). The various additives such as deoxycholic sodium DCNa, poloxamer 188, polysorbate 80, and PVP10 (Sigma Chemicals Co., Ltd., USA) were used. All the other chemicals were of analytical reagent grade and used without further purification (Table 2). (Table 1 was omitted

Formulation No. and grinding conditions : Table 3 is the summary of formulation No. and its

grinding experimental conditions. The numbering of formulation is named by the kind of additive, e.g. F1 of DCNa, F2 of poloxamer 188, F3 of polysorbate 80, F4 of PVP10, and F5 of combined additives. The number I, III, and V, No. of pot indicates the concentration of each additive as shown in this Table. The experimental conditions of planetary ball mill including the effective volume of mill and the material and size of grinding media ball are also shown in this Table.

Table 2. Summary on physico-chemical data of additives for each formulation

Additive	Molecular Formula	Molecular weight	Physical data			Functional category
			m.p.(°C)	ρ_p (g/cm^3)	Solubility in water	
DCNα	$C_{24}H_{39}NaO_4$	414.54	-	-	>333 g/l	Solubilizing
Poloxamer 188	$C_6H_{14}O_6$	7680~9510	52~57	1.06	Free soluble	Dispersing Wetting
Polysorbate 80	$C_{64}H_{124}O_{26}$	1845	-	1.08	Soluble	Dispersing Wetting
PVP10	$(C_2H_4O)_n$	2500~10000	150	1.18	Free soluble	Disintergrant Suspending
SLS	$C_{12}H_{25}NaO_4S$	288.38	204~207	1.07	Free soluble	Surfactant

Table 3. The summary of the components of each formulation and the experimental conditions.

Formulation No.	Formulation					Grinding media		
	Ingredient(g)	Additives(g)				V_B (ml)	d_{BL}(mm) M_L(g)	d_{BS}(mm) M_S(g)
	DDB	DCNa	Poloxamer	polysorbate 80	PVP10			
F1-Ⅰ	5	-	-	-	-	118	Φ10-395	Φ0.3-15
F1-Ⅲ	〃	0.5	-	-	-	〃	〃	〃
F1-Ⅴ	〃	2.0	-	-	-	〃	〃	〃
F2-Ⅰ	10	-	0.0275	-	-	〃	〃	〃
F2-Ⅲ	〃	-	0.275	-	-	〃	〃	〃
F2-Ⅴ	〃	-	2.75	-	-	〃	〃	〃
F3-Ⅰ	10	-	-	0.0275	-	〃	〃	〃
F3-Ⅲ	〃	-	-	0.275	-	〃	〃	〃
F3-Ⅴ	〃	-	-	2.75	-	〃	〃	〃
F4-Ⅰ	10	-	-	-	-	120	-	Φ1-281.4
F4-Ⅲ	〃	-	-	-	3.0	〃	-	〃
F4-Ⅴ	〃	-	-	-	9.0	〃	-	〃
F5-Ⅰ	10	0.5	-	2.75	3.0	120	-	Φ1-281.4
F5-Ⅲ	〃	-	2.75	2.75	3.0	〃	-	〃
F5-Ⅴ	〃	0.5	2.75	2.75	3.0	〃	-	〃

Equipment and methods : The grinding mill and its operating procedures are the same as previous paper (Choi et al. 2001), The dryers such as microwave oven for microwave heating, 15 ml vial for freeze drying (Labcon Co., Kansas, USA), DSR-01 for reduced pressure box dryer and DSB-02 for conventional box dryer (Dongsung, Korea). The microwave heating oven is a multimode microwave applicator with 700 W, 2.45 GHz microwave source for house cooking model (RE-C200M, Samsung Electronic Co., Ltd. Korea).

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.

Drying characteristics curve in microwave drying : Three ceramic dishes including 80 ml sample of each slurry sample recovered from grinding pot put on turntable of microwave oven. The mass of each slurry sample is measured in determined time interval. Here, 4 minutes in early drying step and 1 minute in final drying step.

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

RESULTS AND DISCUSSION

Characterization of nanoparticles : Fig. 1 shows the change of particle size, x10, x50, and x90 of DDB according to the increase of grinding time from 1 day to 4 days. The 10% diameter, median diameter, and 90% diameter in each formulation sample are also presented. The large change is occurred within one day. It is suggested from a few change of particle size in long time grinding that the grinding toward nanoparticle is very difficult and involved in various interdisciplinary academic fields. Here, Figs. 2 and 3 were omitted.

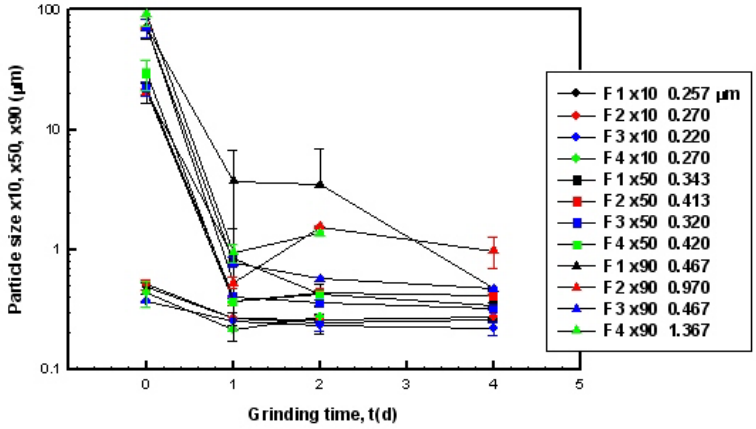
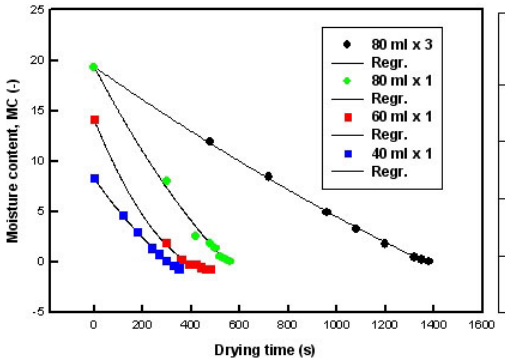


Fig. 1 Change of x_{10}, x_{50}, x_{90} of DDB with various grinding times for different formulation by planetary ball mill



Key	Drying time t_1(s)	R_{max}(g/s)	MC(-)
	t_2(s)	R_2(g/s)	MC_2(-)
●	480	0.059	11.895
	1380	0.025	0.006
●	300	0.144	8.019
	560	0.037	0.009
■	300	0.158	1.809
	360	0.102	0.222
■	120	0.116	4.617
	300	0.078	0.114

Fig. 4 Change of moisture content of DDB with microwave heating and drying time for different formulation by various drying conditions

Drying characteristics curve : Fig. 4 shows the change of moisture content of ground DDB sample with microwave heating and drying time for different formulation together with various drying conditions.

Drying method	Particle size	DDB	Formulation(additive)			
			F1 (DCNa)	F2 (Poloxamer)	F3 (Tween80)	F4 (PVP0)
MW	X_{10}	ND	ND	ND	ND	ND
	X_{50}	ND	**	ND	ND	ND
	X_{90}	ND	*	*	**	ND
FD	X_{10}	–	ND	–	–	ND
	X_{50}	–	**	–	–	ND
	X_{90}	–	*	–	–	ND
RP	X_{10}	–	–	ND	ND	ND
	X_{50}	–	–	*	ND	ND
	X_{90}	–	–	**	**	**
BD	X_{10}	–	–	ND	ND	ND
	X_{50}	–	–	*	ND	**
	X_{90}	–	–	**	**	**

Table 4. Summary on two sample t test for difference of means with the parametric method based on normal distribution test

ND : No difference of $p > 0.05$
* : $p < 0.05$
** : $p < 0.001$

MW : Microwave drying
FD : Freeze drying
RP : Reduced pressure drying
BD : Box drying

Here, the No. of drying dish was changed from 3 to one and the sample volume from 80 ml to 4ml and 40 ml. The smaller the No. of dish and volume are, the shorter the drying time is due to larger input energy per unit volume. In early drying stage, the constant drying rate period is considered to be observed, and at the final drying stage, the falling drying period is occurred. Moreover, it is suggested that the relative efficiency of microwave heating is improved with the increase of sample volume.

Re-dispersion characteristics: Table 4 shows the comparison on re-dispersion of two samples before and after various drying methods. The criteria are made based on two sample t test for difference of mean with the parametric method under assumption of normal distribution of sample. Here, ND indicates the no difference, $p > 0.05$.

CONCLUSIONS

The re-dispersion characteristics of two samples between the ground products dried by 4 methods such as microwave heating, freeze drying, reduced pressure drying, and conventional box drying, and the original slurry products prepared by a series of wet grinding experiments of water insoluble drug of DDB were examined with change of the particle size distribution and the following results were mainly obtained:

1. The pattern of particle size distribution of ground samples were changed with the species and addition amount of additives.

2. It was confirmed that the drying process of DDB slurry by the microwave heating including re-dispersion was more effective than other drying methods.

3. The nano-sized particle of DDB ground by wet grinding process was significantly enhanced higher than intact DDB.

ACKNOWLEDGEMENT

This study was carried out by financial support of Korea Science and Engineering Foundation, the International Joint Research Program between Korea and Japan, 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 Dr. S. Kato, Executive Committee Chairperson of MW2004 Symposium held in this summer for financial support to us.

REFERENCES : Omitted.