Laser Diffraction Estimation of Particle Size Distribution of Slightly Water-Soluble Drugs Coexisting with Additives: Application to Solid Dosage Forms[1)]

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Received November 7, 1991

A simple and quantitative evaluation method for particle size distribution ($f_x(r)$) of slightly water-soluble drugs dispersed in an aqueous medium together with other water-insoluble additives was developed using a laser diffraction method.

The particle size distribution function of the powder mixture, ($f(r)$), was assumed as $f(r)=\phi_x \cdot f_x(r)+\phi_a \cdot f_a(r)$, where ϕ is the volume fraction of each component dispersed in a measurement medium and $f_a(r)$ is the distribution function of another water-insoluble additive "a".

In order to calculate $f_x(r)$ from $f(r)$, it is necessary to know the density of drug and additive in the measurement medium, d_x and d_a, but this is difficult to determine since particles usually swell in the medium. Thus, a method was developed to use their relative value, δ_a ($=d_a/d_x$).

As a practical application, oxolinic acids (OA) of three sizes (OA-S (about 2 μm), OA-M (about 7 μm) and OA-L (about 24 μm)) were used as model drugs. δ_a values were determined for various additives using the mixture of OA-S and each additive. Then, using δ_as, $f_x(r)$ of OA-M or OA-L in the mixture containing OA-M or OA-L and additives was calculated from the $f(r)$ experimentally determined for the mixture. They agreed well with their original distributions.

The method was applied to some dosage forms, and the results obtained had good correlation with those from turbidity, wet sieving or dissolution test.

Keywords particle size distribution; slightly water-soluble drug; disintegrant; laser diffraction method; redispersion; solid dosage form; oxolinic acid

Introduction

The problem of low bioavailability in formulations of slightly water-soluble drugs made for oral administration is well recognized.[2)] Many pharmaceutical modifications have been studied to overcome this: such as pulverization, solubilization using surfactant or non-aqueous solvent, solid dispersion into water soluble polymers,[3)] dosage forms with rapid disintegration[4)] and so on.

The grinding of drugs into fine particles seems to be a practical and useful method.[5)] However, it is meaningless to use ground drugs unless there can be good redispersion from the dosage forms in the gastrointestinal (GI) tract. Ground drugs are usually mixed with additives and made to in the form of granules, tablets or capsules *via* kneading or mechanical compression of the mixture. These processes have a negative effect on the drug's later dispersion in the GI tract.[6)] Thus, the assurance of a good redispersion is very important in studies on the optimum formulation of slightly water-soluble drugs. This requires establishment of an *in vitro* evaluation method for drug dispersion into aqueous medium. Up to now, the dispersion of slightly water-soluble drugs has been estimated by means of the wet sieving method,[7)] membrane filter method,[8)] turbidity,[9)] microscopic observation[10)] or dissolution test using some special dissolution mediums such as surfactant solution or organic solvent.[11)] While these methods are very useful, measurement is slow with some, and others evaluate the dispersion only indirectly.

The laser diffraction method has been widely used lately[12)] for the evaluation of particle size distribution. The measurement procedure is very simple and rapid, however, its application has been limited to powder of one component and evaluation of drug redispersion from a dosage form has not yet been attempted.

In this paper, we propose a method using laser diffraction measurement to evaluate a drug's particle distribution in plural components. This was first applied to the powder mixture of oxolinic acid and typical pharmaceutical additives, and then dispersion of the drug from tablets was evaluated.

Experimental

Materials Oxolinic acid (OA) (Fig. 1) was purchased in the market (Bioindustria Co., Italy) and three types (OA-S, OA-M and OA-L with average particle sizes of 2.0, 7.1 and 23.7 μm respectively) were obtained as follows:

OA-M: Oxolinic acid purchased in the market was used as available.

OA-S: OA-M was milled using Jet Mill (LABOJET, Nihon Pneumatic Industrial Co., Ltd.).

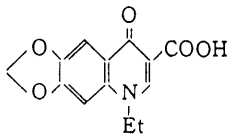

Fig. 1. Chemical Structure of Oxolinic Acid

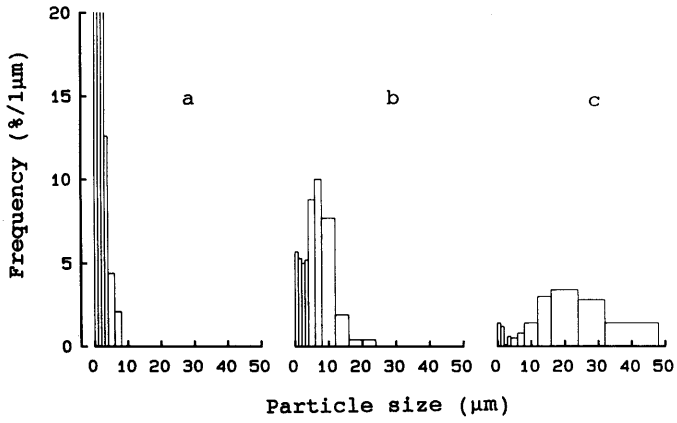

Fig. 2. Particle Size Distributions of OA Determined by CL Method
a, OA-S (average particle size; 2.0 μm); b, OA-M (7.1 μm); c, OA-L (23.7 μm).

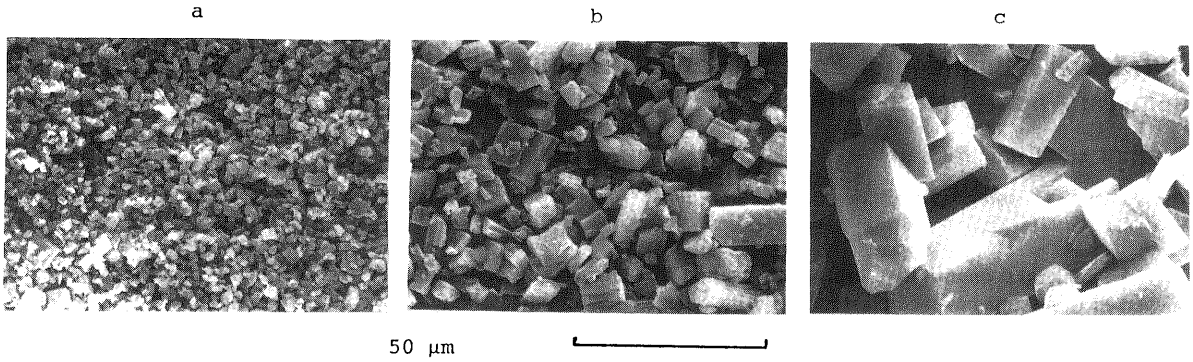

Fig. 3. Scanning Electron Micrographs of OA Powders
a, OA-S; b, OA-M; c, OA-L.

OA-L: OA-M was dissolved in hot *N*,*N*-dimethylformamide solution and recrystallized by cooling.

The particle size distributions estimated by laser diffraction (CL) method and scanning electron micrographs are shown in Figs. 2 and 3, respectively.

Cornstarch (Nihon-shokuhin-kako Co., Ltd., Japan, $\bar{r}$ (average particle radius measured by CL method in an aqueous medium) = 13.3 μm), low substituted hydroxypropylcellulose (abbreviated as L-HPC, grade LH-31, Shin-etsu Chemicals, Japan, $\bar{r}$ = 29.1 μm), carboxymethylcellulose calcium (ECG_{505}, Gotoku Chemical, Japan, $\bar{r}$ = 76.8 μm), croscarmellose sodium (AcDiSol, Asahi Chemical Co., Ltd., Japan, $\bar{r}$ = 76.0 μm), magnesium stearate (Nihon-yushi Co., Ltd., Japan, $\bar{r}$ = 8.8 μm) were purchased in the market and used without modification.

Preparation of Tablets One hundred grams of OA-S, 73 g of lactose and 20 g of disintegrant were mixed in a 500 ml beaker and kneaded well adding 6 g of binder dissolved in about 30 ml of 50% ethanol aqueous solution. The wet mass was sieved with 24 mesh screen and the resultant wet granules were dried at 45 °C for 4 h. After drying, 1 g of magnesium stearate was added. Then, the mixtures were compressed to tablets by an Autograph (Shimadzu, model IS-5000, tablet weight: 200 mg/tablet, diameter: 8 mm, surface: flat).

Determination of Particle Size Distribution Apparatus: A CILAS Laser Granulometer Model 715 by laser diffraction system (abbreviated CL, CILAS ALKATEL, France) was used.

Dispersion Medium: In the determination of OA powder, samples were dispersed into OA saturated 0.1% sodium lauryl sulfate (SLS) solution with a bath type sonicator (Sharp Co., UTA-152, Japan). Without SLS, they floated and did not disperse well. Water was used as dispersing medium in the physical mixture of dosage forms, since particle size distributions of OAs in the physical mixtures agreed well with the original OAs when determined by the following four media: 1) water, 2) OA saturated solution, 3) 0.1% SLS solution, 4) OA saturated 0.1% SLS solution. The disintegration test in JP XI (without disk) was applied to tablets for 10 min. About 10 ml of the disintegration medium was taken, and then CL measurement was performed immediately. Before sampling, the disintegration medium was agitated lightly with a glass bar so that the solid particles were dispersed uniformly. The measurement reproducibility was good.

Turbidity Absorbance of the suspension obtained by the disintegration method as above was determined at 600 nm. $A_{1\%}$, the absorbance of the suspension containing 1% of OA, was then calculated.

Membrane Filter Method[8] The suspension obtained by the disintegration method, was filtered under reduced pressure through a polycarbonate membrane filter (Nuclepore, pore size: 8 μm). The amount of filtrated OA was determined by ultraviolet (UV) absorbance at 340 nm after dissolving in an alkaline solution.

Dissolution Test The solubility of OA in water is about 5 μg/ml at 25 °C, however, in an alkaline solution OA is soluble due to its acidic property; for instance, the solubility in pH 8.4 buffer solution is about 110 μg/ml. A dissolution test was performed by the paddle method in JP XI (100 rpm, at 37 °C) using pH 8.4 buffer. Ten ml of test solution was taken out and filtrated with a millipore filter. Dissolved OA was assayed by the determination of absorbance at 340 nm after diluting the sample solution with 0.1 N NaOH.

Theory

Background of Calculation By CL method, the distribution functions of particles with r diameters are estimated on the basis of volume occupied by the particles. For the distribution functions $f_x(r)$, $f_1(r)$, $f_2(r)$, $\cdots$, $f_n(r)$, of a drug x and other water-insoluble additives 1, 2, $\cdots$, n, Eq. 1 is given for each component.

$$\int_0^\infty f_x(r)dr = \int_0^\infty f_1(r)dr = \int_0^\infty f_2(r)dr = \cdots = \int_0^\infty f_n(r)dr = 1 \tag{1}$$

When these powders are mixed with each other and there are no interactions between them, then the distribution function for the mixture, $f(r)$, can be expressed by:

$$f(r) = \phi_x \cdot f_x(r) + \sum \phi_i \cdot f_i(r) \tag{2}$$

$$\int_0^\infty f(r)dr = 1 \tag{3}$$

where ϕ means the volume fraction of powder dispersed in the measurement medium. ϕ is given by:

$$\phi_x = \frac{v_x}{v_x + \sum v_i}, \quad \phi_i = \frac{v_i}{v_x + \sum v_i}, \quad \phi_x + \sum \phi_i = 1 \tag{4}$$

where v means the volume of each powder in the medium. ϕ can be rewritten by means of weight fraction (w) of each powder.

$$\phi_x = \frac{w_x/d_x}{w_x/d_x + \sum w_i/d_i}, \quad \phi_i = \frac{w_i/d_i}{w_x/d_x + \sum w_i/d_i}, \quad w_x + \sum w_i = 1 \tag{5}$$

where d_x and d_i mean the densities of the drug and water-insoluble additive i in the dispersion medium, respectively. Substituting Eq. 5 into Eqs. 2, 6 is derived.

$$f(r) = \frac{1}{w_x/d_x + \sum w_i/d_i} \cdot ((w_x/d_x) \cdot f_x(r) + \sum (w_i/d_i) \cdot f_i(r))$$

$$= \frac{1}{w_x + \sum w_i/\delta_i} \cdot (w_x \cdot f_x(r) + \sum (w_i/\delta_i) \cdot f_i(r)) \tag{6}$$

where δ_i is defined by:

$$\delta_i = d_i/d_x \tag{7}$$

According to Eq. 6:

$$f_x(r) = \left(f(r) - \frac{\sum (w_i/\delta_i) \cdot f_i(r)}{w_x + \sum w_i/\delta_i} \right) \cdot \frac{w_x + \sum w_i/\delta_i}{w_x} \tag{8}$$

Equation 8 means that particle size distribution of the drug in the mixture, $f_x(r)$, can be calculated when δ_i and $f_i(r)$ of each additive are known.

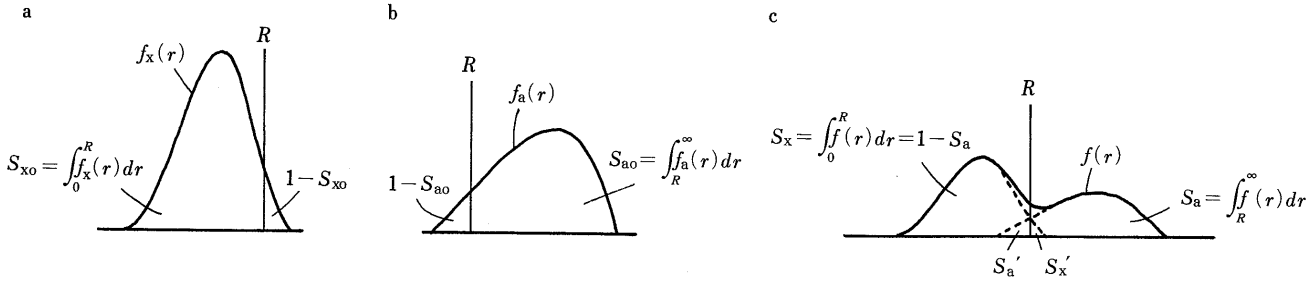

Fig. 4. Schematic Representation of the Distributions of Particle Size

R is an optional particle size and is defined for the calculation of the distribution function. a, OA particle; b, additive; c, mixed powder.

If there is only one kind of coexisting additive, Eq. 8 is rewritten as:

$$f_x(r)=\left(f(r)-\frac{w_a/\delta_a}{w_x+w_a/\delta_a}\cdot f_a(r)\right)\cdot\frac{w_x+w_a/\delta_a}{w_x} \tag{9}$$

In the case where multiple additives coexist with a drug, then $f_x(r)$ can be estimated by knowing w_i, $f_i(r)$ and δ_i of the individual additives. However, even in this case, it is not always necessary to know all of them, since the powder mixture itself can be regarded as one powder on the whole, then Eq. 8 can be rewritten as:

$$f_x(r)=\left(f(r)-\frac{w_m/\delta_m}{w_x+w_m/\delta_m}\cdot f_m(r)\right)\cdot\frac{w_x+w_m/\delta_m}{w_x} \tag{10}$$

where w_m, δ_m and $f_m(r)$ are w, δ and $f(r)$ of the powder mixture consisting of multiple components, respectively.

Thus, by knowing δ_a (or δ_m) value, $f_x(r)$ can be estimated since w_a (or w_m) and $f_a(r)$ (or $f_m(r)$) can be determined separately beforehand.

Estimation of δ If the distribution function of a drug and an additive are as shown in Fig. 4a and 4b, respectively, then that of the mixture is shown as Fig. 4c due to Eq. 2.

By denoting the fraction of the drug particles of with size less than R as S_{xo} $(=\int_0^R f_x(r)dr)$ and that of the additive with a size exceeding R as S_{ao} $(=\int_R^\infty f_a(r)dr)$, respectively, ϕ_x and ϕ_a are given geometrically as shown in Fig. 4c.

$$\phi_x=S_x-S_a'+S_x' \tag{11}$$

$$\phi_a=S_a-S_x'+S_a' \tag{12}$$

where S_x and S_a mean $\int_0^R f(r)dr$ and $\int_0^\infty f(r)dr$, respectively. If the distribution of each component is not changed by the mixing, S_x' and S_a' can be estimated using distribution functions of the drug and the additive as:

$$S_x'=\left\{\left(\int_0^\infty f_x(r)dr-S_{xo}\right)\Big/S_{xo}\right\}\cdot(S_x-S_a')$$

$$=(1-S_{xo})\cdot(S_x-S_a')/S_{xo} \tag{13}$$

$$S_a'=(1-S_{ao})\cdot(S_a-S_x')/S_{ao} \tag{14}$$

Substituting Eqs. 13 and 14 in 11 and 12, ϕ_x and ϕ_a are expressed by:

$$\phi_x=(S_{ao}-S_a)/(S_{xo}+S_{ao}-1) \tag{15}$$

$$\phi_a=(S_{xo}+S_a-1)/(S_{xo}+S_{ao}-1) \tag{16}$$

On the other hand, ϕ_x/ϕ_a can be expressed from Eqs. 5 and 7 as:

$$\phi_x/\phi_a=(w_x/d_x)/(w_a/d_a)=\delta_a\cdot(1-w_a)/w_a \tag{17}$$

Combining Eqs. 15, 16 and 17

$$(S_{ao}-S_a)/(S_{xo}+S_a-1)=\delta_a\cdot(1-w_a)/w_a \tag{18}$$

Equation 18 means that δ_a can be calculated by knowing S_{ao}, S_a and S_{xo} at R from the distribution function of the drug, the additive and the mixture, respectively. Using these δ_a values, $f_x(r)$ can be calculated from Eq. 9.

Results and Discussion

Examination of the Applicability of Eq. 18 To certify the propriety of the method described above, particle size distribution was determined first for the physical mixtures of the smallest OA (OA-S, all particles are less than 8 μm as shown in Figs. 2 and 3) and various insoluble additives at various mixing ratios. As a typical example, Fig. 5 shows particle size distribution of OA-S, the 1 : 1 physical mixture of OA-S and cornstarch, and cornstarch.

Here, since all particle sizes of OA-S are less than 8 μm, S_{xo} is equal to 1 when R is set as 8 μm. Then, Eq. 18 is rewritten as:

$$(S_{ao}-S_a)/S_a=\delta_a\cdot(1-w_a)/w_a \tag{19}$$

This equation means that the plotting of the left side value in Eq. 19 against $(1-w_a)/w_a$ has a linear relation and δ_a can be obtained by the slope of the line. Then, $f_x(r)$ in the mixture can be calculated using Eq. 9. When the additives are composed of multiple components, then Eq. 10 can be used by applying the above method to the additive mixture.

$(S_{ao}-S_a)/S_a$ was estimated from the distribution functions of the mixture $(f(r))$ and the additive $(f_a(r))$ setting R as 8 μm. Figure 6 represents the plot of $(S_{ao}-S_a)/S_a$ *vs.* $(1-w_a)/w_a$ for the physical mixtures of OA-S and 5 kinds of water-insoluble additives. All of them show good linearity passing through the origin of the coordinates. This suggests that the concept described in the theoretical section is reasonable.

As shown in Fig. 6 and Table I, δ_a values of the disintegrants obtained from the slopes were larger in the order cornstarch > AcDiSol > L-HPC > ECG_{505}. This suggests that disintegrants with low δ are less dense in the aqueous medium due to swelling.

Followin OA-S, the above method was applied to the physical mixture of the additives and OA-M or OA-L. Here, the value obtained from Fig. 6 was used as δ_a of each additive. The average particle sizes obtained are shown in Table II and some representative $f_x(r)$ are shown by

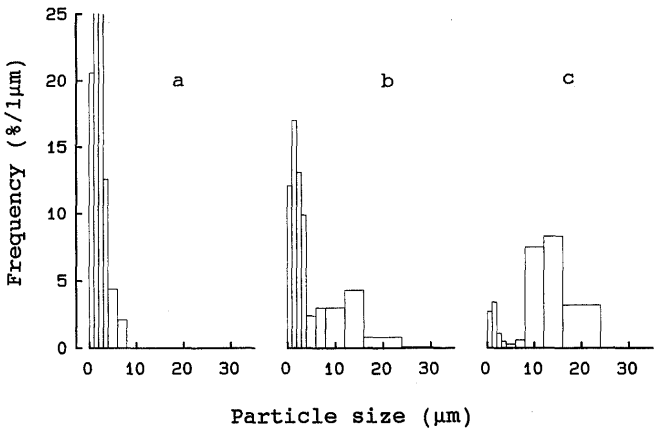

Fig. 5. Particle Size Distributions of OA-S, Cornstarch and Their 1 : 1 Mixture

a, OA-S alone; b, OA-S: cornstarch = 1 : 1; c, cornstarch.

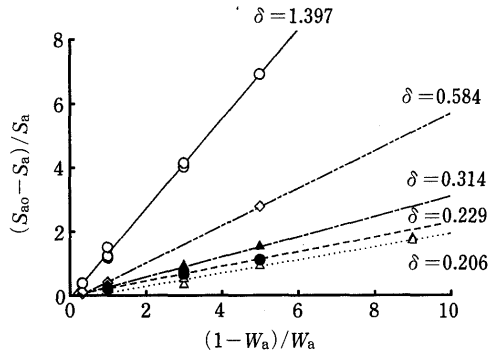

Fig. 6. Plotting of $(S_{a0}-S_a)/S_a$ against $(1-W_a)/W_a$ According to Eq. 19 for the Physical Mixture of OA-S and Various Additives

○, cornstarch; ●, L-HPC; △, ECG_{505}; ▲, AcDiSol; ◇, magnesium stearate.

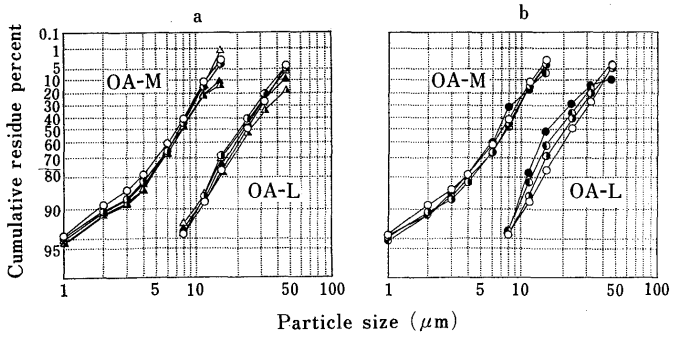

Fig. 7. Rosin–Rammler Plot of OA Particle Size Distribution in the Physical Mixture of OA and Additives

a: Influence of additive species. ○, OA alone; ◑, OA : L-HPC = 3 : 1; △, OA : ECG_{505} = 3 : 1; ▲, OA : AcDiSol = 3 : 1; ▲, OA : cornstarch = 3 : 1. b: Influence of mixing ratio (additive : cornstarch). ○, OA alone; ◑, OA : cornstarch = 3 : 1; ◐, OA : cornstarch = 1 : 1; ●, OA : cornstarch = 1 : 3.

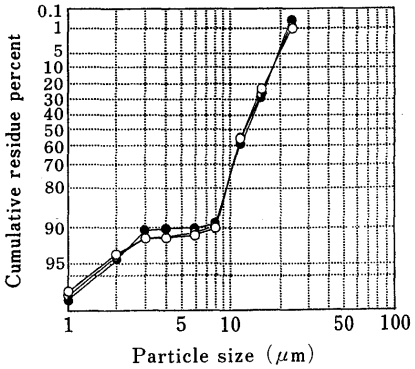

Fig. 8. Particle Size Distribution of the Placebo Mixture of Formulation No. 1 Plotted According to Rosin–Rammler

○, cornstarch alone; ◑, placebo mixture; ●, placebo tablet compressed at 0.5 t.

TABLE I. δ_a Values of Disintegrants

Disintegrants	δ_a
Cornstarch	1.397
L-HPC	0.229
ECG_{505}	0.206
AcDiSol	0.314

TABLE II. Average Particle Size of OA Determined by CL Method in the Physical Mixture of OA and Various Additives

Mixture	Mixing ratio	OA-M (μm)	OA-L (μm)
OA alone	—	7.1	23.7
OA : L-HPC	3 : 1	7.3	22.0
OA : ECG_{505}	3 : 1	7.8	25.4
OA : AcDiSol	3 : 1	7.7	22.4
OA : cornstarch	3 : 1	7.5	21.3
OA : cornstarch	1 : 1	7.8	19.5
OA : cornstarch	1 : 3	8.2	17.1

Rosin–Rammler plotting in Fig. 7.

As shown in Table II and Fig. 7, particle size distribution of the drugs (OA-M or OA-L) in the mixtures agreed well with that determined without any additives. The deviation increased as the weight fraction of additives increased as shown for cornstarch in Table II. In this method, the distribution function of OA was calculated by subtracting that function attributable to additives from the total distribution function of the mixture. Thus, the deviation seemed to increase with the increase of additive content.

Evaluation of OA Dispersion from the Solid Dosage Forms Redispersion of slightly water-soluble drugs from dosage forms can be evaluated as being the same as the physical mixtures using Eq. 10, if the following assumptions are satisfied:

(1) Additives redisperse completely from the dosage forms.

(2) Particle size distributions of additives, $f_a(r)$s, do not change during such manufacturing processes as kneading, granulation or tableting.

(3) Water-soluble additives dissolve completely and do not interfere with the measurement.

These assumptions, however, are not satisfied for many preparations; but they did, as a rule, seem true in formulations that showed rapid redispersion.

As examples, Fig. 8 shows the particle size distributions determined for corstarch and placebo mixture after dispersal in a disintegration medium, and placebo tablets of formulation No. 1 in Table III (20 mg of cornstarch, 6 mg of polyvinylpyrrolidone (PVP), 1 mg of magnesium stearate and 73 mg of lactose) after disintegration test. The distribution of the placebo tablets and placebo mixture

TABLE III. Average Particle Size of OA Dispersed from Tablets of Various Formulations after Disintegration Test in Water

Formulation No.		1	2	3	4	5	6	7	8
Disintegrant[a]		Cornstarch	L-HPC	ECG_{505}	AcDiSol	L-HPC	L-HPC	L-HPC	L-HPC
Binder[a]		PVP	PVP	PVP	PVP	—	HPC-SL	$TC5_{EW}$	PEG_{6000}
Hardness (kg)	(0.25)[b]	3.2	3.0	3.1	2.6		2.5	1.9	3.7
	(0.5)	5.3	5.6	6.0	5.6	2.8	5.1	4.4	6.1
	(0.75)	8.3	7.1	10.1	9.5	4.5	6.7	6.7	6.7
Disintegration time (min)	(0.25)	2.5	2.7	3.2	3.4	0.5	10.0	6.9	2.9
	(0.5)	2.3	3.0	3.8	2.4	0.3	6.6	5.2	4.3
	(0.75)	2.8	2.9	4.0	3.5	0.4	6.9	5.2	4.3
Average OA Particle size (μm)[c]	(0.25)	16.9	4.6	4.2	8.6	14.0	2.5	3.0	6.9
	(0.5)	23.0	6.3	6.5	13.3	24.6	3.0	3.8	14.7
	(0.75)	29.1	12.0	13.7	22.1	30.3	3.1	4.0	17.5

a) One tablet contains 100 mg of OA-S, 20 mg of disintegrant, 6 mg of binder, 1 mg of magnesium stearate and lactose (total weight is 200 mg). *b*) Figures in parentheses indicate compression forces (ton). *c*) Determined by CL method.

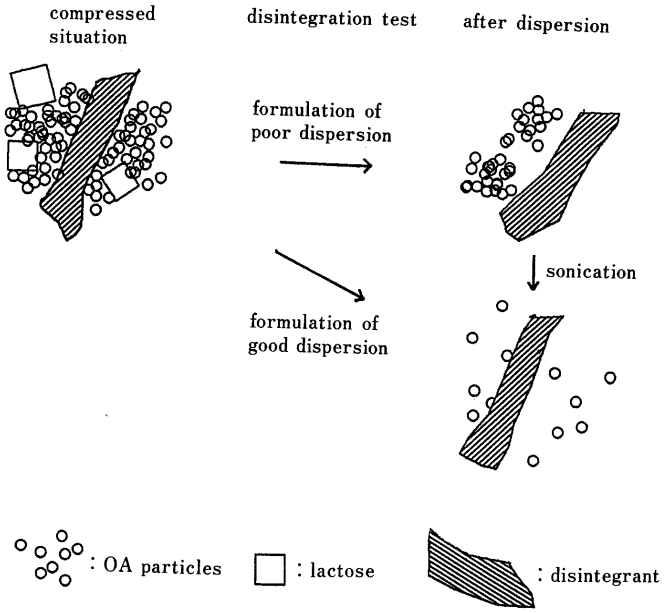

Fig. 9. Schematic Representation of Redispersion Processes of OA Particles from Dosage Forms

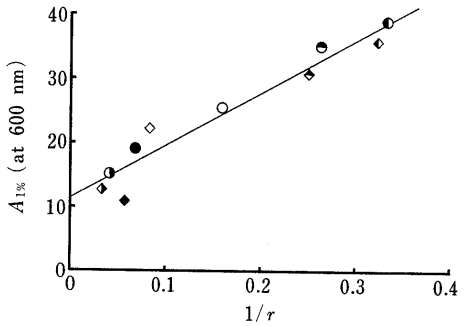

Fig. 10. Relationship between $A_{1\%}$ and Reciprocals of Particle Size Determined by CL Method

Tablets: formula no. 2, 5—8, compressed at 0.5, 0.75 t.

Formulation No.	2	5	6	7	8
(0.5 t)	○	◑	◐	◓	●
(0.75 t)	◇	◈	◈	◈	◆

agreed well with that of cornstarch which accounted for about 95% of the water-insoluble additives in the placebo tablets. This shows that cornstarch redispersed completely from the tablets and that the size distribution was not altered during the tableting process. This also held true for other disintegrants in Table II.

Microscopic observation after redispersion of the tablets by disintegration test, JP XI, revealed that the disintegrants of all the tablets in Table III (lactose and binders dissolve in aqueous medium and are not visualized) were completely separated from the OA particles and, so that OA particles alone agglomerated. Particle sizes of OA-S in the tablets determined by the CL method became constant within 10 min and were not changed further by the disintegration test, while they were reduced to about 2.5—3.5 μm, which is close to original OA-S, within 1 min when they were sonicated.

From these results, the redispersion process from dosage forms was speculated to be as schematically shown in Fig. 9.

In Table III the average particle sizes after the disintegration test are shown together with hardness and disintegration time for each formulation.

The particle sizes of OAs after redispersion from the tablets using PVP as a binder (No. 1—4) were increased with the increase of the compression force, although disintegration was rapid (within 3 min) in all the tablets. This suggests that the small grains passing through the screen of the auxiliary tube in the disintegration apparatus, JP XI, were not redispersed well. Formulations Nos. 6 and 7 showed good redispersion to individual particles although the disintegration was not rapid. The results coincided well with the actual observations.

The tablets prepared without binder (formulation No. 5) also showed poor redispersion. This might have been because the permeation of water into the fine grains of OA was not good due to the lack of hydrophilic binder.

In all cases, higher compression force resulted in worse redispersion, although disintegration time did not greatly change. The influence of the compression force could be observed more clearly by the CL evaluation than by disintegration test.

Comparison with Other Methods (1) Comparison with Turbidity Turbidity was often used as an index of particle size of dispersion.[9] $A_{1\%}$ can be related with $(1/r)$ as:

$$A_{1\%}=\tau/c=(3K/2d)(1/r) \quad (19)$$

where τ/c is specific turbidity and K is scattering coefficient.[13] Thus, $A_{1\%}$ was measured and plotted against the reciporocal of particle size determined by CL method for formulation Nos. 2, 5—8 in Table III. In all these

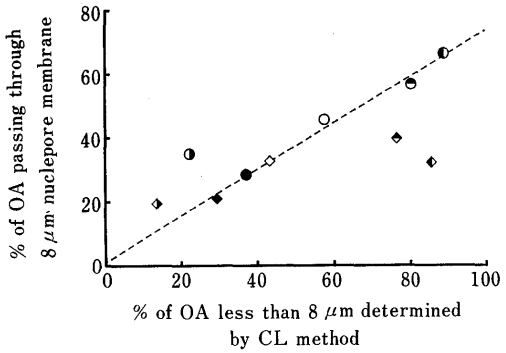

Fig. 11. Comparison of the CL Method and Membrane Filter Method
Symbols are the same as in Fig. 10.

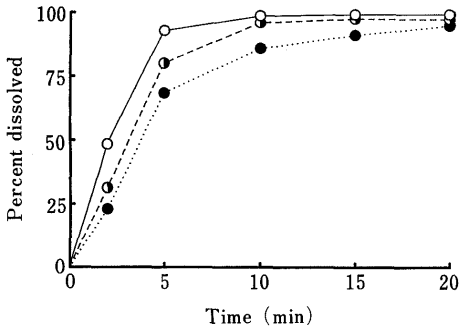

Fig. 12. Dissolution of OA from Tablets into pH 8.4 Buffer Solution
○, No. 2, compressed at 0.5 t, 6.3 μm[a]; ◑, No. 2, compressed at 0.75 t, 12.2 μm[a]; ●, No. 1, compressed at 0.75 t, 29.1 μm.[a] *a*) Table III.

formulations, L-HPC was used as disintegrant.

As shown in Fig. 10, fairly good linear relationship was observed between $A_{1\%}$ and $1/r$ (the regression coefficient, $r=0.967$). From Eq. 19, the regression line is presumed to pass through the origin of the coordinates, however, it took a positive value when $1/r$ was zero. This could be caused by other insoluble additives (L-HPC and magnesium stearate) coexisting with OA.

Evaluation using $A_{1\%}$ was simple and useful, however, it was an indirect method and could be applied only for the comparison of tablets prepared with the same kind and the same amount of insoluble additives since the absorbance is affected by insoluble additives (Fig. 10).

(2) Comparison with Membrane Filter Method The relation between the percent of OA particles passing through the polycarbonate membrane filter (pore size: 8 μm) and the proportion of OA less than 8 μm determined by CL method is plotted in Fig. 11. A linear relationship was observed between them, although the regression coefficient was not too good ($r=0.754$).

Conceptionally, fractionation by sieving determines the particle size directly, however, sieving is a very complicated process and the pores in the membrane are often closed by particles during filtration, leading to measurement error.

(3) Comaprison with Dissolution Test A dissolution test using a special dissolution medium has often been adopted to evaluate the dispersion of slightly water-soluble drugs.[10,11]

Figure 12 shows the dissolution percent of OA into a pH 8.4 solution from the three kinds of tablets having the same disintegration times (about 3 min) but showing varying degree of redispersion. As shown, the better the tablets redispersed, the more rapidly OA dissolved.

The dissolution test using an appropriate medium is useful means for determining the redispersion of slightly water-soluble drugs; however, selection of an appropriate dissolution medium is very difficult from a biopharmaceutical viewpoint. We need not worry about this, however, since water or an artificial GI medium can be used in the CL method.

To date, no overall method which can evaluate redispersion of slightly water-soluble drugs from dosage forms has yet been established; all known methods have the limitations.

This also holds true of our described method, since it is based on the assumption described in the preceding section. In some cases, the assumption may not be satisfied. For example, additives may not be separated completely from drug particles in some cases, or water-soluble additives may not dissolve completely. However, the more extensively drugs redisperse from the dosage forms, the more the assumption will be satisfied and the more exact the result will be. This technique should thus be effective for use at the time of formulation development in choosing the best redispersion.

In addition, evaluation implementing a combination of the CL method and an other means such as microscopic observation or dissolution test will provide more precise information on the nature of those formulations containing drugs which are rarely soluble.

References and Notes

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