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SMUFD, D/A ltr, 14 Feb 1972

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Pharazie 19: 276-79, 1964.

H. LAURENT:

A method for determining the particle size spectrum in pharmaceutical preparations.

In determining the quality of pharmaceutical preparations the size of the incorporated particles in an ointment or the particle size in suspensions is of great importance. During the production of preparations it is often necessary to examine, besides the nature of the manufactured preparations, the state of the intermediate products in this regard.

To my knowledge methods are seldom published for such examinations to satisfy the requirements of a routine business on a practical scale. The available instruments which of course make very exact results possible - besides high purchase prices should not necessarily give the most ideal conditions because of their handling and their specifity for the considerated use.

As examples of instruments for determining the particle sizes you should name the "Lanameter" of VEB Carl Zeiss, Jena [4], the particle size analysator TGZ 3 by Carl Zeiss Company, Oberkochen [3], and the electrical integrating instrument "Eltinor" of VEB Optical Company, Rathenow [1]. The named instruments provide on the one hand an exactness of measurements which are not absolutely necessary for these considerated objects, on the other hand they are not fully used in their various range of applications for the named examinations. The operating of the instruments for routine determinations takes also, to some extent, too much time.

Institutions, which only seldom have to determine the particle size spectrum of a substance - but not in regard to routine business - give up the purchase of such an expensive instrument.

RICHER + KLEIN [2] advice to make a microphotography of the substance - to be examined using at the same time the ocularmicrometer. The potography then can be determined according to quality conditions. The suggested method is relatively simple, but bears disadvantages which cannot be underestimated.

The photography shows only a very small part of the manufactured preparation which is only more diminished by the small depth of focus of the optical system - even with thin coating of the microscopical preparations. With relative inhomogeneity of ointments and suspensions in the microscopical field, microphotography can only give a rough synopsis, whose power of statement can only be qualified with caution. In ointments with small concentration of incorporated particles, a photo only shows very few particles. To compensate these faults, you would have to make either many photos or enrich the particles in a suitable way.

The named difficulties led in our laboratory to try out a method which allows to determine the particle size spectrum of optional preparations with sufficient exactness by relatively little instrument expense.

Methodology and results.

The following instruments are needed for the accomplishment of the determination: an efficient microscope, a strong microscope light, a Zeiss projection mirror, and a adapted projection sheet. Proved to be efficient is the bottom plate of a Zeiss standard camera with a 12V/100 Watt luminary and a mounted Zeiss microscope with slant tube. To keep the picture given by the mounted projection mirror free of distortions, a suitable slanted projection plate has to be used.

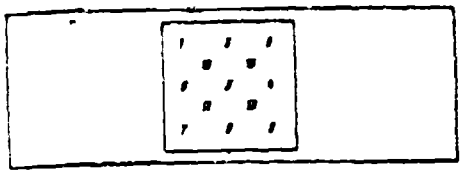


Fig. 1: Microscopical preparation with marked measurements. The numbers are made in the order followed by us.

We use a wooden projection plate to pin on it the proposed object with thumbtacks.

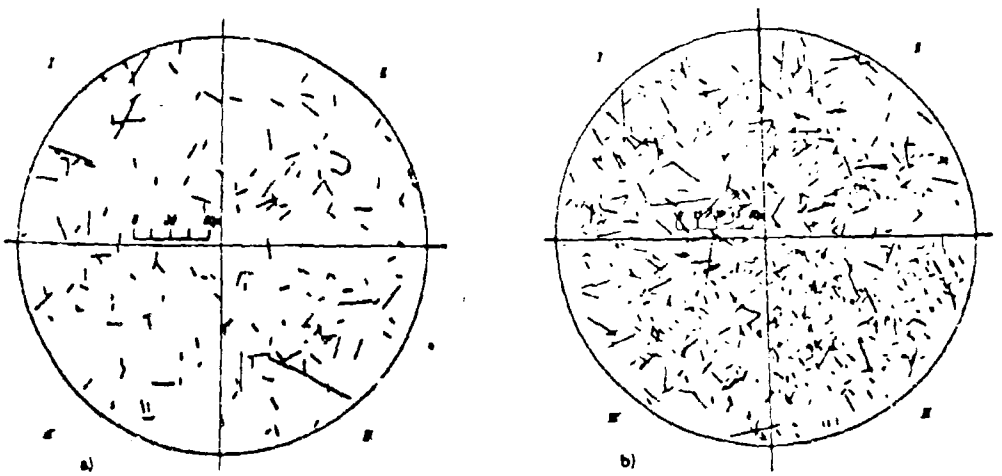
Since the projected picture is relatively dark, the measuring has to be done in a dark room where it is advisable to darken again the microscopical light and the microscope as much as possible.

To get a suitable unit of measurement for later valuation, we place an ocularmicrometer on the base of the field of vision of the chosen oculus. Since sometimes during the projection the line of grating of the ocularmicrometer is not clearly copied, you have to place a filter between the eyepiece and the ocular tube. The filter thickness differs from case to case and has to be adjusted to each optical system. The ocularmicrometer has to be gaged in the usual way with the help of a objectmicrometer. With the example of prednisolon-eye ointment and substances of prednisolon and oxytetracyclinhydrochloride we illustrate the determining of the particle size spectrum.

Relating to [2] we gaged the size groups from 0 to 30μ, 30 to 60μ, 60 to $<\mu$ in the prednisolon-eye ointment. The method of course allows further classification in smaller groups. So for example we ranged the size groups for the substances of prednisolon and oxytetraclinhydrochloride from 0 to 15μ, 15 to 30μ, 30 to 45μ, 45 to 60μ.

For the determining we make a suitable number of microscopical preparations of the substances to be examined in the following order. Fig. 1.

The production of preparations creates no problem in ointments. Powder has to be appropriatly suspended in a medium, in which the substance is practically not soluble (if necessary, paperchromatographic control). To avoid evaporation it is advisable with suspensions to frame the coverglass. Very suitable is agar since it is not affected by organic solutions. To move the preparation on the object table, you can use an object-guide, if the coverglass is big enough, it is even easy by hand. The preparation in suitable magnification will now be examined in the following order. For this you pin a paper on the projecting plate and copy with pencil the outlines of the projected picture and also the unit of measurement of the ocularmicrometer gage. It is appropriate with standard focus of the instrument to mark earlier on the copies with Indian ink the picture outlines and the picture graduates. (Fig. 2 a to c)



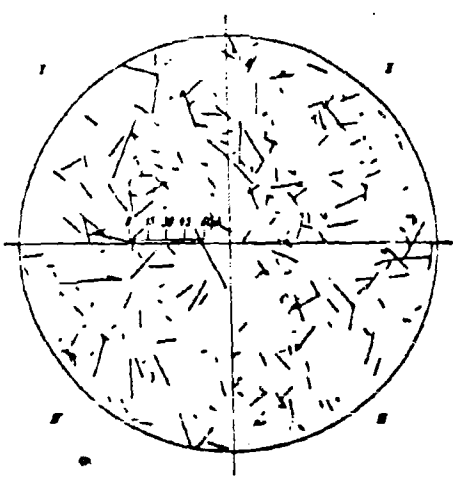


Fig. 2:

Copies with marked particle sizes

a. prednisolon-eye ointment preparation No. 2 (table 1)

b. prednisolon powder preparation No. 3 (table 2)

c. oxytetracyclinh drochloride preparation No. 2 (table 3)

magnification:

ocular 7x/objective 40, n.a. 0, 65/slant tube 1,5x

Table 1: Particle size spectrum of prednisolon-eye ointment.

	0–30 µ I	II	III	IV	(1) Insgesamt	%	30–60 µ I	II	III	IV	Insgesamt	%	60–90 µ I	II	III	IV	Insgesamt	%
(a) Präparat Nr. 1	38	38	58	41	173	96,60	—	—	2	—	2	1,14	—	—	—	—	—	—
(b) Präparat Nr. 2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]	—	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]	[illegible]
(c) Präparat Nr. 3	41	39	54	50	184	97,40	4	—	—	—	4	2,12	1	—	—	—	1	0,53
(d) Präparat Nr. 4	60	69	69	96	304	97,86	—	2	1	1	4	1,29	—	1	2	—	3	0,96

Sum and percentage of the individual size groups:
0 to 30µ, 818 = 97, 85 %, 30 to 60µ, 13 = 1,56 %, 60 to 90µ, 5 = 0,60 %

Table 1. Legend: (1) sum
(a) preparation No. 1
(b) preparation No. 2
(c) preparation No. 3
(d) preparation No. 4

Table 2: Particle size spectrum of prednisolon powder.

	0–15 µ I	II	III	IV	(1) Insgesamt	%	15–30 µ I	II	III	IV	Insgesamt	%
(a) Präparat Nr. 1	80	107	128	125	440	92,4	2	11	8	9	31	6,6
(b) Präparat Nr. 2	99	111	145	138	493	85,3	21	6	33	25	85	14,4
(c) Präparat Nr. 3	93	121	186	121	521	90,4	18	14	9	11	52	9,2
(d) Präparat Nr. 4	84	100	113	116	388	86,3	12	14	21	10	57	13,8

	30–45 µ I	II	III	IV	Insgesamt	%	45–60 µ I	II	III	IV	Insgesamt	%
(a) Präparat Nr. 1	1	3	2	—	6	1,3	—	—	—	—	—	—
(b) Präparat Nr. 2	—	—	1	—	1	0,2	—	—	—	—	—	—
(c) Präparat Nr. 3	—	1	—	2	3	0,6	1	—	—	—	1	0,17
(d) Präparat Nr. 4	1	—	3	—	4	0,9	—	—	—	—	—	—

Sum and percentage of the individual size groups:
0 to 15µ: 1329 = 88,4 %, 15 to 30µ: 222 = 10,7 %
30 to 45µ: 14 = 0,7 %, 45 to 60µ, 1 = 0,04 %

Table 2. Legend: (1) sum
(a) preparation No. 1
(b) preparation No. 2
(c) preparation No. 3
(d) preparation No. 4

Table 3: Particles size spectrum of oxytetracyclinhydrochloride

	0–15 I	II	III	IV	Insgesamt	%	15–30 I	II	III	IV	Insgesamt	%
(a) Präparat Nr. 1	60	70	87	88	305	83,9	51	14	10	8	83	14,7
(b) Präparat Nr. 2	31	60	49	45	187	73,4	18	16	12	12	58	21,6
(c) Präparat Nr. 3	33	33	48	40	153	78,4	12	13	11	7	43	21,2

	30–45 I	II	III	IV	Insgesamt	%	45–60 I	II	III	IV	Insgesamt	%
(a) Präparat Nr. 1	1	1	2	—	4	1,11	—	1	—	—	1	0,28
(b) Präparat Nr. 2	5	2	1	2	10	3,9[illegible]	1	—	—	2	3	1,15
(c) Präparat Nr. 3	1	2	2	—	5	2,6	1	1	—	—	2	0,98

Sum and percentage of the individual size groups:
0 to 15µ: 642 =78,5%, 15 to 30µ 151 =18,5%,
30 to 45µ: 19 =2,3%, 45 to 60µ: 6 =0,7%

Table 3: Legend

(1) sum
(a) Preparation No. 1
(b) preparation No. 2
(c) preparation No. 3

In the picture are now the graduates of the ocularmicrometer and according to sharp focus a number of particles clearly copied. With a sharp soft pencil you copy now the clearly printed particles in their full lenght with a pencil line. With the help of the fine adjustment you move the optical plane through the complete thickness of the preparation and mark all succesively appearing particles with a suitable line, with rectangular crystals for example the longest expansion is marked by the diagonales. After thoro examination of the unit of measurement you move the preparation according to fig. 1 and thus examine the complete thickness in equally divided places. Depending on concentration and size of the particles all 13 measuring marks of one or even several preparations can be made on one copy. Marking the particle size by a line avoids double counting and guaranties of getting every particle (fig. 2). With magnification of ocular 7x/objective 40-0,65/slant tube 1,5 a 2 mm long line signifies a particle size of nearly 3,3µ. With a sharp pencil you can copy then also a line of exactly 2 mm. Smaller particles can be copied in all cases by dots, or you chose a suitable larger magnification. After examining a suitable number of preparations you valuate the copy as follows.

With the projected graduates of the ocularmicrometer you measure the size groups which are to be counted with the points of dividers. With the gage dividers you count now the particles of the individual size groups in the four quadrants and tabularize them. Each counted particle will be crossed out - appropriatly each size group in a different color to avoid also double counting and omission.

From the received numbers you can calculate then the percentage of the individual size groups.

The table shows the results of prednisolon-eye ointment and crystalline prednisolon and oxytetracyclinhydrochloride. Each time we examined four or three preparations according to Fig. 1 and copied each preparation on a sheet. (fig. 2)

Conclusion: We described a method that permits with the help of a microscope and projection mirror to copy particle size spectrums of pharmaceutical preparations. This method bears the advantage that:

1. Double counting and omission are avoided.
2. A large number of particles can be copied in a short time.
3. The received drawings of the projected picture display a proof of the examined substance.

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Received August 12, 1963 Dr. H. Taubert
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