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IMPROVED STANDARDS FOR THE DISINTEGRATION TEST OF SOLID PRODUCTS

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ABSTRACT

Means for an improved standardization of the static and dynamic design of disintegration equipment are discussed and tighter compendial specifications are suggested.

INTRODUCTION

The most common techniques for the disintegration test of tablets, coated tablets, and capsules are those described in USP XVIII (1) and BP 1973 (2): the specimen to be tested is contained in a vertical cylindrical tube which is closed at its bottom by a wire cloth and is periodically moved up and down through a liquid medium; the disappearance of larger particles from the wire cloth is taken as criterion of the completeness of disintegration. Similar methods are used in the compendia of e.g. Germany, Japan and Switzerland.

In an extension of the test, the same apparatus is proposed by NF XIII (3) for the control of drug release. Although this is now considered by many experts to be a "misuse", it has become common practice, particularly for slow-release products. In this application several cases have been observed in our company, where results obtained in different laboratories were not reproducible. It was found that equipment made by different manufacturers, although consistent with the compendial requirements, showed significant deviations in essential parameters. One consequence was to generally abandon this technique in the future, in favor of a more standardized dissolution-rate method. However, it is anticipated that similar problems may also arise in more critical cases of disintegration control which could be overcome by more definitive method specifications.

METHOD PARAMETERS IN USP AND BP

The most important mechanical feature of the test is the agitation caused by the liquid flow through the tubes. Unfortunately the compendia have chosen a hydrodynamical system in which the flow is not defined directly (like the forced flow achieved by a volumetric pump)but is governed by the kinetics of the periodic motion together with a large number of geometric dimensions (tubes, vessel, mounting rack, etc.). The volume of liquid displaced periodically by the diving tube is free to distribute between the lumen of the tube and the gap between tube and vessel. With the USP design, even the distribution between the six tubes is free and may be affected by small deviations in geometry. As a consequence, we have observed differences between 0 and 30 mm for the liquid levels within and around the tubes, during operation. For one single USP apparatus, level differences of more than 10 mm were found between the 6 tubes, due to loose or ill-centered support of the assembly.

With particular reference to the specifications in USP and BP, Fig. 1 shows the relevant dimensions, coded by letters a through o the numerical values of which are sum-

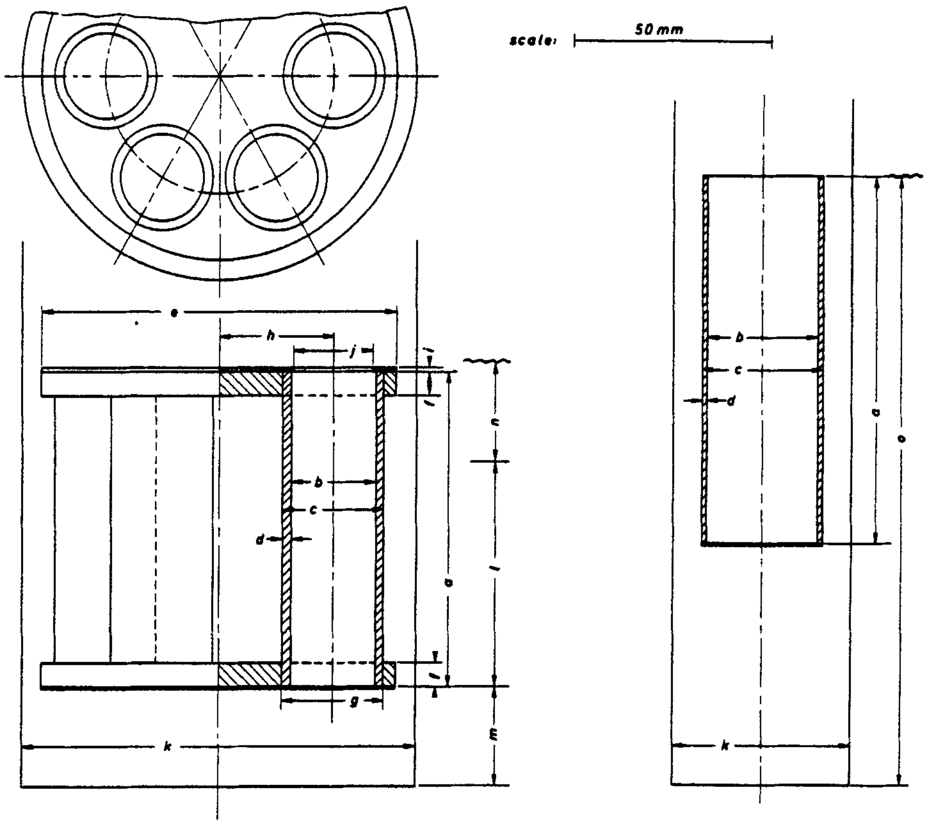

FIGURE 1

Scale drawing of vessel and basket-rack assembly used in USP (left) and of vessel and tube described in BP (right). For actual dimensions see text and Table 1.

marized in Table 1. The compilation immediately reveals several weak points. Sometimes, the specifications generate unnecessary critical borderline situations in which small deviations have a large influence on the result (e.g. the small gap between vessel and rack-assembly in USP). In other cases, primary manufacturing dimensions are not given directly but must be deduced from secondary quantities (e.g. the motion amplitude from the liquid level, in BP). Even critical dimensions are specified unreasonably wide, as "approximately", "about", or without limits. Important characteristics such as the motion profile or the vessel diameter are not mentioned at all.

In Table 1, suggestions for stricter specifications are presented which by themselves do not alter the actual features of the test but are expected to improve the inter-laboratory reproducibility. Comments on these proposals are given in the following paragraphs. As a general rule, tolerances are set forth as strict as is achievable without drastic increase in manufacturing expenditure.

Temperature

37.0° seems to be a good choice; however, in view of the influence of temperature on kinetic phenomena, it is desirable to narrow the limits to $\pm 0.5^{\circ}$. With modern laboratory equipment this will be no problem as long as the following points are observed: the surrounding water bath be well stirred; the vessel be immersed sufficiently deep and be closed

TABLE 1 (next page)

Actual specifications used in the USP and BP disintegration methods, and suggested modifications. Code letters refer to Fig. 1. All geometrical dimensions are given in mm. Unspecified quantities enclosed in [ ] .

code	apparatus parameter	USP XVIII official	USP XVIII modified	BP 1973 official	BP 1973 modified
	temperature (°C)	35 - 39	37.0 ± 0.5	36 - 38	37.0 ± 0.3
	frequency of motion (min^{-1})	28 - 32	30 ± 1	30	30 ± 1
l	amplitude of motion	50 - 60	55 ± 1	80-100 (from water level)	90 ± 1
	profile of motion	-	sinus or crankshaft with u = 51.5 ± 1	-	sinus or crankshaft with u = 51.5 ± 1
	number of tubes (specimens)	6 (1)	6 (1)	1 (5)	1 (5)
	material of tubes	glass	glass or plastic	glass or plastic	glass or plastic
a	length of tubes	77.5 ± 2.5	77.5 ± 0.2	80 - 100	90.0 ± 0.5
b	inner diameter of tubes	approx. 21.5	21.5 ± 0.2	about 28	28.0 ± 0.2
c	outer diameter of tubes	-	25.5 ± 0.5	30 - 31	30.0 ± 0.5
d	wall thickness	approx. 2	[2]	-	[1]
	bottom wire cloth	10-mesh No.23(.025 inch) W.&M. gauge	clear opening: 2.0 ± 0.1 wire diameter: 0.635	No. 1.70 sieve	clear opening: 1.70 ± .05 wire diameter: 0.80
	support for wire cloth	inner diam. not altered	inner tube diameter not altered	overall diam. of the basket not materially increased	inner diam. not altered, outer diam. by not more than 5 mm
k	diameter of vessel	1-liter beaker	100.0 ± 0.5	about 45	45.0 ± 0.5
m	distance wire/bottom (lowest point)	not less than 25	25.0 ± 1	-	30.0 ± 1
n	distance wire/level (highest point)	not less than 25	[25]	-	[30]
o	total liquid level (= l + m + n)	-	105 ± 2.5	not less than 150	150 ± 2.5
	volume of liquid (ml)	-	[825]	-	[240]
e	diameter	about 90	90.0 ± 0.2	rack assembly in USP	
f	thickness of plastic plates	6	6.0 ± 0.2		
g	diameter of holes in plastic plates	about 24	26.1 ± 0.2		
h	radial distance of hole centers	-	29.0 ± 0.5		
i	thickness of steel plate	1	1.0 ± 0.1		
j	diameter of holes in steel plate	about 20	21.5 ± 0.2		

by a heat-insulating cover (this also prevents evaporation which otherwise may become significant in prolonged tests); finally enough time be permitted for reaching temperature equilibrium. On the other hand a specification of ± 0.1° (as was proposed for the dissolution-rate test in the European Pharmacopoeia) would be unrealistic.

Frequency and Amplitude of Motion

30 strokes/min are required, with a tolerance corresponding to ± 6.7 % in USP and unspecified in BP. A limitation within ± 1/min would be meaningful and is easily achieved by proper selection of a suitable electrical drive with gear reduction. The amplitude should be stated intentionally, with limits of ± 0.5 or 1.0 mm, and not deduced indirectly from tube length and liquid level (as in BP).

Time Profile of Motion

Although of significant importance, this parameter is not mentioned at all (USP) or rather vaguely defined as "in a uniform manner" (BP). This would not exclude exotic profiles such as ramp or rectangular functions, but common drive mechanisms use a uniform rotation of an excenter which generates the periodic up-and-down motion of the pickup system (basket or rack-assembly), see Fig. 2. The resulting time profile is either a sinus or a crankshaft function, examples of which are shown in Fig. 3 and Table 2. The sinus profile is advantageous in that it is defined by one single parameter, the amplitude l=2p; in addition it shows better mechanical performance. On the other hand, most commercial apparatus seem to employ a circular-cam drive such as case B_2 in Fig. 2, which gives a crankshaft profile. It must be left open which of the two possibilities is more promising for future development. Details of the drive kinetics are presented in the APPENDIX.

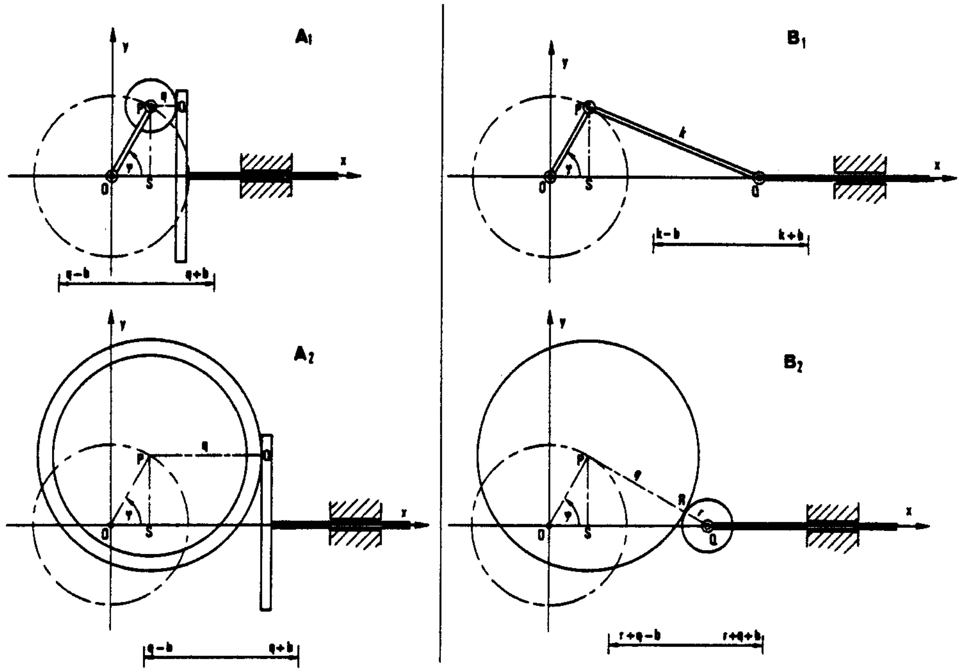

FIGURE 2

Drive mechanisms used in disintegration apparatus. The originally vertical displacement is shown along the horizontal x axis. Arrows indicate the total amplitude.

A: Sinus drives with small (A_1) or large (A_2) excenter roll.
B: Crankshaft drives as realized by crank OP and connecting rod PQ (B_1), or with excentric circular cam PR and pickup roll QR (B_2).

- O center of rotation and origin of the (x, y) coordinate system
- φ phase angle of rotation
- P excenter mid-point with radius OP = p, rotating with uniform speed on pivot O
- Q reference point of the pickup system
- S auxiliary point with displacement equal to excenter midpoint P

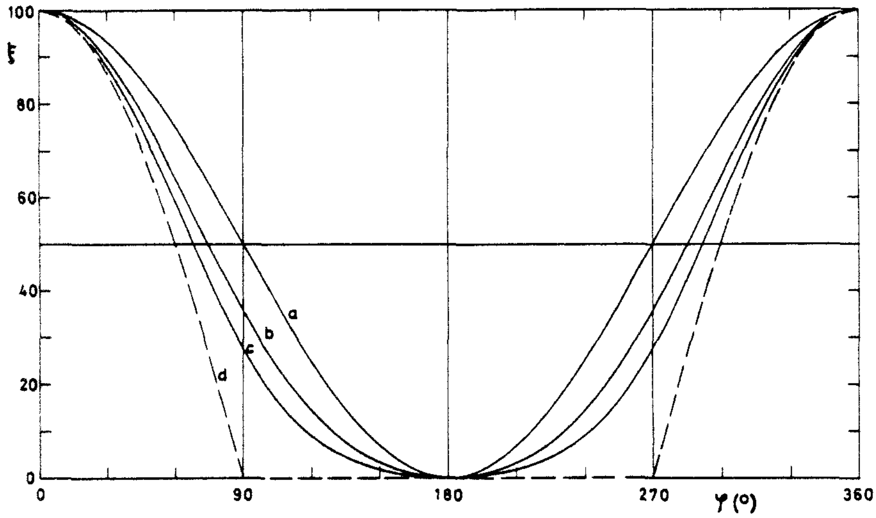

FIGURE 3

Motion profiles of USP disintegration apparatus. Numerical parameter values are given in Table 2; all amplitudes are normalized to 2p = 100.

a: sinus profile according to eq.(6a)

b and d: crankshaft profiles according to eq.(6b)

e: hypothetical borderline case of eq.(8)

TABLE 2

Geometrical characteristics of typical USP disintegration apparatus. All dimensions are expressed in mm. Code letters a through e correspond with Fig. 3.

	a	b	c	d	e
drive mechanism (according to Fig.2)	A_1	B_2	B_2	B_2	B_2
excentricity, p	25.0	27.0	25	27	27.5
amplitude, l = 2p	50.0	54.0	50	54	55.0
diameter of circular cam, q	-	41	55	35	27.5
diameter of pickup roll, r	-	9.5	9.5	1	0
crankshaft parameter, u	-	50.5	64.5	35	27.5
distance screen to bottom, m	25	20	7	-	-
rack diameter, e	92	90	96	?	-
inner tube diameter, b	22.0	21.0	20-23	?	-
outer tube diameter, c	26.0	25.0	25.0	?	-

a: ZT4, Sotax AG, Basel
b: Tablettenzerfall-Prüfgerät 1968, former J.R.Geigy AG, Basel
c: ZT3, former CIBA AG, Basel
d: I. Vanderkamp, Orange, N.J., (model before 1960)
e: hypothetical borderline case of eq.(8)

Number of Tubes and Specimens

Primarily, this is a statistical point and beyond the scope of this paper. It should be noted however, that with a similar total number of specimens (6 instead of 5) USP allows observation of all units individually, whereas only the slowest one is accounted for in BP. On the other hand, the USP design is more laborous; additional care is necessary to ensure identical conditions for all six units, and a rigid and well-centered support for the rack-assembly is required.

Tube Dimensions and Material

The tube dimensions ought to be specified in a logical sequence and according to their importance: first and with highest precision the inner diameter, followed by the outer diameter (the wall thickness is defined by the two diameters and must not be specified). It is not necessary to restrict the material to glass, since Perspex or similar plastics may be equally useful or even advantageous. On the other hand, glassware cylinders are also available with satisfactory precision (e.g. cylinders for interchangeable syringes).

Wire Cloth

The bottom wire cloth acts as the gauge for the judgment of disintegration but, at the same time, influences the flow of liquid through the tube. For optimum standardization, specification of the clear opening and the wire diameter in metric units is preferable to reference to industrial standard series of limited accessibility. The sieve support should be more strictly described, particularly with respect to the allowed alteration of the inner and outer areas.

Vessel and Rack Dimensions

The vessel diameter should be specified explicitly, also in the USP method. Here, the gap between vessel and rack-assembly has an area of only 2.5 cm^2 per unit, as compared with 3.6 cm^2 for the lumen of each tube. Hence the actual flow is more critically affected by the gap than the lumen. Note that a 1 mm deviation in the diameters of vessel and rack is equivalent to a 20 percent variation of the gap area and that ordinary glassware such as 1-liter beakers usually show variations at least of this size. In actual apparatus, rack diameters of 90, 92, and even 96 mm have been found! For ease of manufacture the holes in the plate should fit to the tubes (in the present description the holes are 24 mm but the tube diameter is 25.5 mm nominally).

Liquid Volume and Level

Neither of them is now explicitly specified in the compendia. The BP system of correlating the relevant parameters (tube length, liquid level, and motion amplitude) is highly abstract and also involves two critical situations at the end points ("at the highest position the gauze just breaks the surface of the water" and "at the lowest position the upper rim of the basket just remains clear of water"). Better instructions are given in USP and, from the characterization of the end points, the tablets are clearly supposed to be submersed throughout the motion.

For improved standards and ease of handling the relevant parameters should be specified in their logical sequence: motion amplitude, vessel diameter, minimum distance between bottom and wire cloth, and liquid level or volume. The critical endpoint conditions should be generally abandoned.

Guided Disks

Devices to prevent floating and/or stimulate the mechanical agitation on top of the specimen are used in all compendial methods. Their usefulness is not questioned here, but it should be kept in mind that they have an extreme influence on disintegration as well as release and should therefore be carefully standardized. A better discription of the USP guided disks is found in the Japanese pharmacopoeia (4).

CONCLUSIONS

With the improved standards suggested above, it should be possible to achieve worldwide reproducibility also in critical situations. It should however, be realized that the present methods suffer principally from two weak points: their design is complicated in that too many significant parameters have to be standardized, and the non-forced flow in these systems is too easily affected by small variations in geometry. A forced-flow method would avoid these problems and be advantageous for all testing of disintegration and dissolution: either in the form of a periodic forth-and-back flow as in the "Wechseldruck" method (5) or as the (uniform or pulsating) forward flow of the various "column" methods (6-9).

APPENDIX

With the notation shown in Fig. 2, the coordinates of the pivoting excenter are given by

$$x_P = OS = p \cos \varphi \quad (1a)$$

$$y_P = SP = p \sin \varphi \quad (1b)$$

where p is the excentricity OP. Depending on the construction, either a constant distance PQ or a variable SQ is added to x_P to give the total displacement x_Q of the pickup.

Case A: Sinus Motion

A circular roll (ball bearing) is pivoted such that its center point P describes a circle of radius OP = p. The roll radius PQ = q may be smaller (case A_1) or larger (case A_2) than the excentricity p. In any phase of the motion the plain foot of the pickup touches the outermost point Q of the roll, hence

$$x_Q = OS + PQ = p \cos\varphi + q \qquad (2)$$

This is a sinus profile with amplitude 2p, maximum displacement (q+p) at $\varphi = 0^o$, and minimum displacement (q-p) at 180^o.

Case B: Crankshaft Motion

This can be achieved in two different ways which are kinetically identical. In case B_1, a crank OP of length p is pivoted around O and is connected to the rod PQ of length u; the free end of the connecting rod is fixed to the pickup in point Q. In the alternative, B_2, a circular cam is pivoted as in case A; however, a pickup roll with radius QR = r moves along the x axis and touches the cam in a point R situated on the line PQ connecting the mid-points. In both cases the triangle PSQ is rectangular, which gives

$$SP^2 + SQ^2 = PQ^2$$

or

$$SQ = \sqrt{PQ^2 - SP^2} \qquad (3)$$

The distance PQ is given either by the length u of the connecting rod or the sum of the radii (q+r), hence all formulae derived for B_1 apply likewise for B_2 if the parameter u is replaced by (q+r). The individual size of q and r is kinetically irrelevant and may be defined from mechanical points. From Fig. 2, the total displacement of Q is

$$x_Q = OS + SQ \qquad (4)$$

and, by substituion from eqs.(1a), (3), and (1b)

$$x_Q = p \cos\varphi + \sqrt{u^2 - (p \sin\varphi)^2} \qquad (5)$$

This motion again is periodic with amplitude 2p, but the profile is "distorted" by the term under the root: as seen from Fig. 3 the upper inflection is more abrupt than the lower one.

The maximum displacement of Q is (p+u) at 0^{o} and the minimum is (u-p) at 180^{o}.

Special cases

For the further discussion it is convenient to use a transformed coordinate

$$\xi_Q = x_Q - x_Q(180^{o})$$

in which the minimum displacement at 180^{o} is set to zero. When applied to eqs.(2) and (5) this gives

$$\xi_Q = \begin{cases} p(1+\cos\varphi) & \text{sinus} \quad (6a) \\ p(1+\cos\varphi) + \sqrt{u^2 - (p\sin\varphi)^2} - u & \text{crankshaft} \quad (6b) \end{cases}$$

If in eq.(6b) the quantity u (or the corresponding sum q+r) is large in relation to p, the square-root term approaches u and eq.(6b) reduces to the simple sinus form of eq.(6a).

If in case B_2 the pickup roll degenerates to a sharp edge, as in example d of Table 2 and Fig. 3, then r=0 and the motion is described by eq.(6b) with u being replaced by q.

In a borderline situation of B_2, the pivot O may be localized on the circumference of the cam. This give q = p and

$$\xi_Q = p\cos\varphi + \sqrt{(p+r)^2 - (p\sin\varphi)^2} - r \qquad (7)$$

If, in addition, the pickup radius r vanishes, eq.(7) is further reduced to

$$\xi_Q = p\cos\varphi + \sqrt{p^2(1-\sin^2\varphi)}$$

$$= \begin{cases} 2p\cos\varphi & \varphi < 90^{o} \text{ or } \varphi > 270^{o} \\ 0 & 90^{o} \leq \varphi \leq 270^{o} \end{cases} \qquad (8)$$

This case is shown as e in Fig. 3 and Table 2.

With the cam drive B_2, any desired motion profile can be realized by use of an appropriate cam profile. In particular is a pure sinus motion obtained if the roll radius r is small and the cam profile obeys the equation of a cardioid or "Pascal" curve

$$q(\varphi) = s + p(1+\cos\varphi) \qquad (9)$$

Figure 4 shows examples of this cam profile, for a common amplitude 2p = 100, and with numerical values of 50, 75, and 100 for the parameter s. Note that the size of s is kinetically irrelevant in that is gives a constant contribution to the overall displacement ξ_Q; all three cams give the same motion and s may be chosen freely from mechanical considerations.

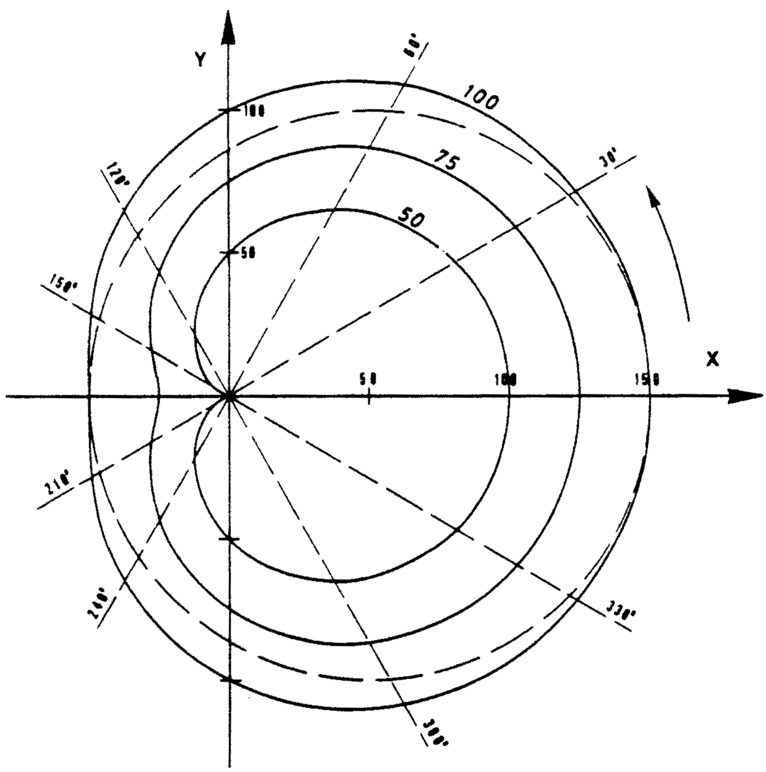

FIGURE 4

Cardioid cam profiles generating a sinus motion with amplitude 2p=100. Drive mechanism of type B_2 with infinitely small pickup roll, according to eq. (9).

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