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OPTIMIZATION OF PREBLENDING IN RANDOM MIXING

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Blending is a subject which is of importance pharmaceutically, and which has received a small to fair amount of attention in the pharmaceutical literature (1-4). The efficiency of a mix is judged by the standard deviation, s, of the assays of samples taken from various spots in the mixer and when s is plotted as a function of time, the following relation will hold in many cases:

$$\ln((s-s')/(s_0-s")) = -kt \qquad \text{Eq. 1}$$

where s' and s_0 are the standard deviation at infinite time and zero time respectively. The time, t_Q, to mix contains a fraction, X, of drug (denoted A in the following) and (1-X) of excipient (denoted B in the following). With this nomenclature, the premixing process consists of

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I mixing X of A with M of B to produce (X-M) of premix

II mixing the (X+M) of premix with the remaining (1-X-M) of B

The question which poses itself is what is the most advantageous value of M, i.e. for what value of M will the "mixing time" be the smallest.

To address this problem the following is to be noted. Akin to the relationships in segregation (5,6) it is assumed that the blending rate constant is a function of the value of the composition of a binary mixture by the relationship

$$k = 2\,(1-L)\,k_o \qquad \text{Eq. 5}$$

L is here the fraction of the most abundant component and k_o is the blending rate constant for a 1:1 mixture. It is also assumed that mixing I to a degree of 97.5% and then II to a degree of 97.5% results in a final blend which is $(0.975)^2 = 0.95 = 95\%$ mixed. It can readily be demonstrated (5) that on this basis pre-blending always produces a smaller blending time.

To achieve the blending scheme in I and II there are four distinct possibilities

A. M > X (i.e. B is the major component in I)

a. 1-X-M > X+M (i.e. B is major component in II)

b. 1-X-M < X+M (i.e. premix is major component in II)

B. M < X (i.e. A is the major component in I)

a. 1-X-M > X+M (i.e. B is major component in II)

b. 1-X-M < X+M (i.e. premix is major component in II)

It can readily be shown that B.b. is physically impossible (e.g. if X = 0.05 and M is smaller or equal to X, then it could be at most 0.05, i.e. X+M is 0.1 which cannot be larger than 1-X-M = 0.9). The three other cases will be treated consecutively below.

A.a. This domain is, as can be seen from rearrangement of the inequality A.a above, X < M < 0.5-X. The content of B in the premix is M/(m+X). From Eq. 4 it follows that the time, t_1, required to 97.5% blend the premix is

$$t_1 = 3.7/k \qquad \text{Eq. 6}$$

It follows from Eq. 5 that

$$k = 2\,(1-M/(M+X))\,k_o = 2\,k_o\,(X/(M+X)) \qquad \text{Eq. 7}$$

which inserted in Eq. 6 gives

$$t_1 = T\,(1 + (M/X)^{\ }) \qquad \text{Eq. 8}$$

$$\text{where } T = 3.7/(2\ k_o) \qquad \text{Eq. 9}$$

In II, B is the major component, and the fraction of B is (1-X-M) so that

$$k = 2\ (1-(1-X-M))\ k_o = 2\ k_o\ (X+M) \qquad \text{Eq. 10}$$

i.e. the time, t_2, required to 97.5% blend the premix with B is given by

$$t_2 = T\,(1/(X+M)^{\ }) \qquad \text{Eq. 11}$$

Hence the final blending time, $t = t_1 + t_2$ is given by

$$t = T\,(1 + (M/X) + (1/(M+X)^{\ }) \qquad \text{Eq. 12}$$

An extremum of this occurs when dt/dM is zero i.e.

$$dt/dM = 0 - T\,((1/X) - (1/(X+M)^2)^{\ }) \qquad \text{Eq. 13}$$

$$\text{i.e. when } X = (X+M)^2 \qquad \text{Eq. 14}$$

This has a root when

$$M = (X^{0.5}) - X \qquad \text{Eq. 15}$$

A completely analogous treatment leads to the following expressions for the situations A.b. and B.a:

A.b

$$t = T\,(1 + (M/X) + (1/(1-X-M)) \qquad \text{Eq. 16}$$

$$dt/dM = T(\,(1/X) + 1/(1-X-M)^2)\,) \qquad \text{Eq. 17}$$

Rearrangement of the inequality in A.b above shows that this applies to the domain $0.5 - X < M < 1-X$. The latter is dictated by the fact that M cannot be larger than the fraction of B, and when $M = 1-X$ the situation is no longer one of preblending but is straightforward blending. It is noted that dt/dM is positive for all values of X and M (recalling that these are positive). Hence t increases with increasing M in the domain.

In the domain given by B.a Eq. 18 and 19 below apply.

B.a

$$t = T\,(1 + (X/M) + (1/(X+M)) \qquad \text{Eq. 18}$$

$$dt/dM = -T\,((X/M) + (1/(X+M)^2)\,) \qquad \text{Eq. 19}$$

This domain is equivalent to $0 < M < X$, as can be seen from direct rearrangement of the inequality shown under B.a above. It is noted that dt/dM is negative for all values of X and M (recalling that X and M are positive), and that t, therefore, decreases with increasing M in the domain given by B.a.

The complete functional relationship for preblending (under the given assumptions) is therefore given by the equation system 12, 16 and 18. It is noted that Eq. 12 and 16 are equal with $X = M$, i.e. at the common point of the two domains. It is also

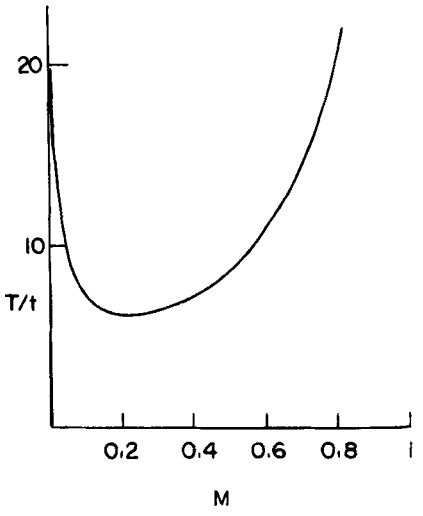

Fig. 1 t/T plotted as a function of M, according to Eq. 12, 16 and 18, for X = 0.1

noted that when 1-X-M = X+M, i.e. when M = (1-2x)/2, then the domains A.a and A.b are identical. Here Eq. 16 and 18 have the same value, so that t is the same by both expressions. Hence, the function presented by Eq. 14, 16 and 18 is continuous in the complete domain 0 < M < 1-X. In this domain it has ONE extremum, namely the minimum at M - $X^{0.5}$ - X. In reduced coordinates, the proper function to consider would be t/T. Values of this have been calculated for X = 0.1 as an example and are shown in Figure 1. It is noted here, that thepertinent intervals in the domain are bounded by the values M = 0, 0.1, 0.4 and 0.9.

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