Characterization of USP XVIII Content Uniformity Plan

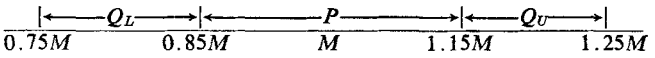
Keyphrases ☐ Tablets, content uniformity—probability equations, USP XVIII requirements ☐ Content uniformity, tablets—USP XVIII requirements, probability equations

Sir:

In our recent paper, "A Characterization of the Content Uniformity Plan" (1), a procedure was reported for determining the probabilities of tablets passing the USP XVII and NF XIII content uniformity sampling plans. At the time that paper was submitted, it was understood, based upon preliminary page proofs, that the same sampling plan would be effective in USP XVIII (2). However, the published 1970 volume contains a different requirement for tablet content uniformity which reads as follows:

> Tablets—The requirements are met if the content of each of not less than 9 of the tablets is within the limits of 85 percent and 115 percent of the average of the tolerances specified in the potency definition in the monograph, and if the content of none of the tablets falls outside the limits of **75** percent and 125 percent of that average.
>
> If the content of not more than 2 tablets falls ouside the limits of 85 percent and 115 percent, assay each of the remaining 20 tablets. The requirements are met if the content of each of the additional 20 tablets falls within the limits of 85 percent and 115 percent of the average of the tolerances specified in the potency definition in the individual monograph.

In the referenced paper, tables were presented showing the probability of meeting content uniformity requirements based upon certain combinations of four parameters of lot quality: γ_p, γ_y, δ_p, and δ_y. These tabled values were applicable to the content uniformity plans of USP XVII and NF XIII. The effect of the new sampling plan of USP XVIII on the reported probabilities of meeting content uniformity requirements has now been determined and may be developed by Scheme I.



Scheme I

In Scheme I, M represents the mean of the tolerances specified in a particular monograph. A lot of tablets meets the requirements of USP XVIII for tablet content uniformity if and only if one of the following events occurs:

1. 10 tablets have a drug content in the region P.
2. 9 tablets are in P and 1 in Q where $Q = Q_L + Q_U$.
3. 8 tablets are in P; 2 in Q from the first sample plus a second sample of 20, all 20 of which must be in P.

The probability that the lot meets requirements then becomes: Pr(lot passes) = Pr(event 1) + Pr(event 2) + Pr(event 3).

Letting p equal the proportion of single dosage units in P, q equal the proportion of units in Q, and $1 - p - q$ equal the proportion of units in neither, we can write the trinomial expression:

$$Pr(\text{Pass}) = \frac{10!}{10!0!0!}p^{10}q^0(1-p-q)^0 + \frac{10!}{9!1!0!}p^9q^1(1-p-q)^0 + \left[\frac{10!}{8!2!0!}p^8q^2(1-p-q)^0\right]\left[\frac{20!}{20!0!0!}p^{20}q^0(1-p-q)^0\right]$$
$$= p^{10} + 10p^9q + 45p^{28}q^2 \qquad \text{(Eq. 1)}$$

Lots are assumed to be of sufficient size to make the finite population correction factor negligible. Equation 1 may be evaluated for different values of p and q, where p is equal to $(1 - \pi)$ in *Reference 1*, and q is found as $Pr(0.75M, 0.85M) + Pr(1.15M, 1.25M)$ where:

$Pr(0.75M, 0.85M)$ = probability of a tablet potency failing in the region Q_L

$$= F\left[\frac{0.85 - (1+\delta_p)(1+\delta_y)}{\gamma_{py}}\right] - F\left[\frac{0.75 - (1+\delta_p)(1+\delta_y)}{\gamma_{py}}\right] \qquad \text{(Eq. 2)}$$

and, for region Q_U,

$$Pr(1.15M, 1.25M) = F\left[\frac{1.25 - (1+\delta_p)(1+\delta_y)}{\gamma_{py}}\right] - F\left[\frac{1.15 - (1+\delta_p)(1+\delta_y)}{\gamma_{py}}\right] \qquad \text{(Eq. 3)}$$

The trinomial expression (Eq. 1) was evaluated for the

Table I—Probability of Meeting USP XVIII Content Uniformity Requirement for Tablets when $\delta_p = \delta_y = 0$[a,b]

γ_p	γ_y 0.01	0.02	0.03	0.04	0.05
0.01	1.000 (1.000)	1.0000 (1.0000)	1.0000 (1.0000)	1.0000 (1.0000)	1.0000 (0.9975)
0.02		1.0000 (1.0000)	1.0000 (1.0000)	1.0000 (0.9998)	0.9998 (0.9936)
0.03			1.0000 (1.0000)	1.0000 (0.9983)	0.9989 (0.9786)
0.04				0.9994 (0.9861)	0.9938 (0.9331)
0.05					0.9729 (0.8322)

[a] When $\delta_p = \delta_y = 0$, the tables are symmetrical. [b] Probabilities for USP XVII and NF XIII are in parentheses.

Table II—Probability of Meeting USP XVIII Content Uniformity Requirements for Tablets[a]

γ_p	γ_y 0.01	0.03	0.05
	when $\delta_p = -0.04$, $\delta_y = 0.02$		
0.01	1.0000 (1.0000)	1.0000 (1.0000)	0.9999 (0.9954)
0.03	1.0000 (1.0000)	1.0000 (0.9997)	0.9979 (0.9663)
0.05	0.9996 (0.9896)	0.9966 (0.9539)	0.9600 (0.7871)
	when $\delta_p = 0.09$, $\delta_y = -0.08$		
0.01	1.0000 (1.0000)	1.0000 (1.0000)	0.9997 (0.9986)
0.03	1.0000 (1.0000)	1.0000 (1.0000)	0.9972 (0.9786)
0.05	1.0000 (0.9836)	0.9994 (0.9459)	0.9694 (0.7943)
	when $\delta_p = 0.07$, $\delta_y = -0.01$		
0.01	1.0000 (1.0000)	1.0000 (0.9986)	0.9447 (0.7794)
0.03	1.0000 (0.9996)	0.9947 (0.9560)	0.8734 (0.6310)
0.05	0.9708 (0.8593)	0.8994 (0.6823)	0.7052 (0.4063)

[a] Probabilites for NF XIII and USP XVII are in parentheses.

parameters given in Tables I and II of *Reference 1*. The results are shown here in Tables I and II. The probabilities for the NF XIII and USP XVII plans as previously reported are included in parentheses. (The new values are taken from tabled probabilities for all combinations of the four parameters where δ_p, δ_y go from -0.10 to 0.10 in steps of 0.01 and γ_p, γ_y go from 0 to 0.06 in steps of 0.005.)

As may be seen in Tables I and II, the probability of passing a lot, when the coefficients of variation increase, is greater for the new plan than for the old.

(1) C. B. Sampson, H. L. Breunig, J. P. Comer, and D. E. Broadlick, *J. Pharm. Sci.*, **59**, 1653(1970).

(2) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 930.

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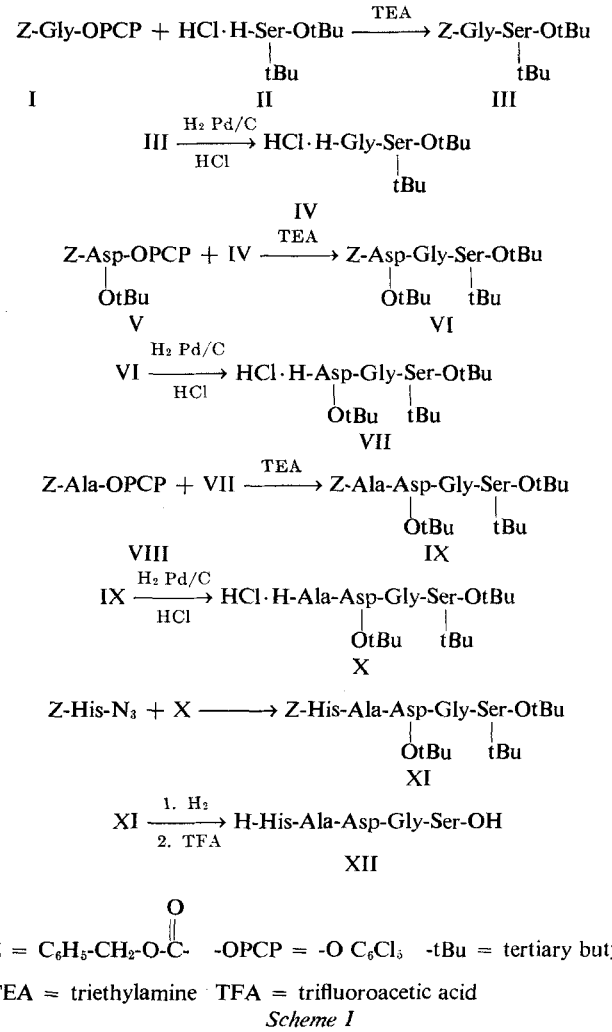
Enzyme-Active Sites: Importance of Aspartic Acid in Peptide Esterase Models

Keyphrases □ Peptide esterase models, catalytic activity—aspartic acid residue influence □ Proteolytic enzyme active sites—peptide catalytic activity determination



Scheme I

Sir:

Recent investigations point out that the serine proteinases, notably chymotrypsin and trypsin, require serine and histidine residues in some type of close steric relationship for their catalytic activity. While there are 246 amino acids in the total sequence of chymotrypsinogen, the inactive precursor of chymotrypsin, the suitable folding of this enzyme brings two histidines from positions 40 and 57 and one serine from position 195 close enough to act as the active center responsible for catalyzing the hydrolysis. Trypsin affords the same possibilities, where two histidines from positions 29 and 46 and a serine from position 183 act as the active site of the enzyme (1, 2).

One approach to studying the active sites of enzymes is the synthesis and evaluation of the catalytic activity of relatively simple peptides that embody as many known features of proteolytic enzymes as possible. A number of polymers and copolymers of histidine and serine (3) and small peptides incorporating histidine and serine were reported (4, 5). Photaki and Moschopedis (6) carried out the same type of studies with cysteine proteinases with peptides incorporating histidine and cysteine. A relatively more potent esterase model, L-histidyl-glycyl-L-aspartyl-L-seryl-L-phenylalanine, was reported recently (7). The catalytic coefficient (3) for this pentapeptide was 179 l. mole^{-1} min.$^{-1}$ compared with 147 l. mole^{-1} min.$^{-1}$ for L-seryl-γ-aminobutyryl-L-histidyl-γ-aminobutyryl-L-aspartic acid (5) and 10^4 l. mole^{-1} min.$^{-1}$ for α-chymotrypsin (3). Although the catalytic coefficient of these peptides, when compared with chymotrypsin, is considerably low, further evaluation is definitely warranted of a series of peptides where the molecule can be made more flexible. Moreover, the role played by individual amino acids in the peptide esterase models should be studied.

Among a number of peptides subjected to the catalytic activity determination, the peptides incorporating histidine and serine without aspartic acid showed very little or no catalytic activity. Examples are: L-histidyl-L-alanyl-glycyl-L-serine (catalytic coefficient 15 l. mole^{-1} min.$^{-1}$), L-histidyl-glycyl-L-tyrosyl-L-serine (catalytic coefficient 21 l. mole^{-1} min.$^{-1}$), and glycyl-L-histidyl-glycyl-L-serine (catalytic coefficient 17 l. mole^{-1} min.$^{-1}$).

In this communication, we report the importance of aspartic acid in the peptide esterase models. A comparative study of catalytic activity of peptides incorporating histidine and serine, differing only in the aspartic acid residue, was conducted. To provide more or less the same physicochemical environments, the comparison was made with the peptide incorporating glutamic acid instead of aspartic acid. The