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QUALITY ASSURANCE IN PHARMACEUTICAL POWDER PROCESSING: CURRENT DEVELOPMENTS

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ABSTRACT

Pharmacopoeial requirements relating to standardization of the physical performance of oral dosage forms containing powders are usually limited to tests on the final product.

Such tests are aimed at ensuring that all tablets or capsules have the correct, nominal, drug content and that the drug is released into solution within a specified time. Whilst dissolution or disintegration test to assess drug release can only be carried out on a finished dosage form, content uniformity tests currently carried out on tablets or capsules alone could also be usefully carried out earlier on component powders at different stages during processing. The aim of developing a quality assurance procedure for quantifying the homogeneity of powders prior to tablet compaction or encapsulation would be to pin-point more precisely the part of a process where content uniformity problems arise. Secondly, a good quality assurance procedure would provide full

mechanistic information about the behaviour of a given powder system, so that appropriate remedies could be applied.

Eleven different methods of testing homogeneity of powder mixes have been cited in pharmaceutically oriented literature and these will be reviewed in terms of their usefulness as routine quality assurance procedures for drug content uniformity. Of these 11 methods, 2 test methods were considered to be especially useful: one based on a flow test and the other on vibration analysis. This techniques has been validated using a complete vibration analysis and testing rig under conditions encountered during routine powder processing.

It would be desirable to see standard powder mixes tested on apparatus of the same design in different laboratories as a means of assessing the reproducibility of the proposed quality assurance method when used by different personnel.

INTRODUCTION

The advent of potent low-dose drugs has high lighted problems of producing tablets and capsules with a reproducibly high content uniformity.

Insufficient attention to particle or powder properties in a formulation, poor selection of processing equipment, inadequate mixing and lack of process control all contribute to drug segragation which is eventually manifested as a loss of content uniformity in a batch or batches of tablets or capsules.

Currently, the only content uniformity quality control procedure for most tablets and capsules which are the subject of official monographs is by analysis of mean drug content of 20 tablets which have been ground together (1). Train (2) realized that such an assay procedure could provide a satisfactory mean value, even though individual tablets showed large variations about the mean. The BP recognized the importance of this problem when in 1973 it introduced a requirement of individual tablet assays for

"microdose" preparations. As well as specific problems associated with interpretation of the data which such an assay provides (3), there are also more general problems such as the inability to detect batches where loss of homogeneity has occurred up until the testing of the finished product. Secondly, such late testing provides no information concerning the point of failure nor the mechanisms by which content uniformity has been lost.

In order to solve both specific and general problems associated with current pharmacopoeial testing, a simple reproducible and informative test is required by which tablet content uniformity under realistic processing conditions can be assessed. The test should be capable of being performed on powder mixes prior to processing into tablets or capsules and should reflect the actual homogeneity likely to be encountered when those finished dosage forms are actually produced. Such a model test system should also be capable of acting as either a pre-formulation/formulation tool which could be used to screen potential formulation at an early stage, or as an in-process quality assurance test prior to compaction or encapsulation.

It is clear from the criteria set out above that the test method of choice will subject powder mixes to conditions which reflect the most rigorous process conditions which the powder mix will meet during production. Powder systems which pass a suitably validated test procedure would then be considered to be physically stable, non-segragating and capable of producing tablets or capsules of a high uniformity.

However, there are almost as many test methods for assessing segregation tendency and physical stability of powder mixes as those carrying out research in this field. The test methods used can be divided into 5 main categories (see also table 1).

(1) Sieve methods, where the powder mixes are subjected to vibration, vacuum or rolling on test sieves for different lengths of time.

TABLE 1

Methods Used to Assess the Physical Stability or Segregation Tendency of Pharmaceutical Powder Mixes (4).

CATEGORY (1)

(a) De-agglomeration test (5)

A 5g sample of the powder mix is placed on a nest of four sieves of 2.0 cm diameter with a collector. Different sieve apertures are selected according to the mixture being analysed. Each sieve level is assayed for drug content following manual sieving. The experimentally determined concentrations are then related to the theoretical amounts which would be expected for an ordered mix; surface area ratios may also be used to assess ordered mix formation.

(b) Single vibrating sieve test (6,7)

In the method used by Stephenson and Thiel (6), sample weights varying from 0.125g to 4 g are assayed following vibration on a sieve with an aperture coarse enough to allow unbound or dislodged drug particles to pass through to the collector. Stephenson and Thiel (6) used a 100 m diameter sieve mesh was vibrated on a Russel Finex shaker for one hour.
Using the method devised by Malmqvist and Nystrom (7),the sieve is repeatedly tilted so as to cause powder to move back and forth across the sieve mesh.The oscillatory action was mechanised and a tapping function introduced at each end of the tilting cycle.A 5.00 g sample size and a 90 m sieve aperture diameter were used and the sieve was tilted 20 times before analysis of undersize and oversize drug content.This test produced lower removal forces than either that used by Stephenson and Thiel (7) or replacing the tilting mechanism with a sonic sifter when particles were sieved for 10 minutes.

(c) Single air-jet sieve test (7,8)

An air-jet sieve method has been used by Travers (8),in an analogous manner to that described above in method (b),although specific experimental details are not recorded.
Malmqvist and Nystrom (7) also used an air jet sieve tecnique in which the air stream was reduced to the minimum which would still produce an airtight seal at the sieve gasket.A sample size of 5.00 g and a 90 m diameter sieve mesh were used;the powder sample was sieved for 1 minute.

(d) Vabrating de-mixing test (9,19)

A sample from the powder mix is placed in a jar on a sieve shaker.Following vibration for different times up to 30 minutes,20 spot samples are removed and assayed for drug content and the percentage cv calculated.

CATEGORY (2)

(e) Jolting volumeter vibration test (11)

A modified jolting volumeter is used to subject a column of powder with a volume of approximately 250 cm^3 to vibration at a frequency of approximately 4 Hz.Following vibration,20 powder samples weighing 400 mg were analysed for drug content and the percentage cv calculated.

(f) Process model vibration test (12)

The powder sample is filled into a perpex holder which can be split into 20 sections for ease of spot sampling following vibration.The powder container is fixed to a vibration table which is made to vibrate in specific conditions within the frequency range 25-100 Hz and from 9.81 to 39.24 ms^{-2}(1-4g) accelaration.The range of accelaration and frequencies was

(continued)

TABLE 1 CONTINUED

chosen to reflect those found to occur during routine tablet production.Content uniformity of the powder following vibration is asessed from determinations of percentage cv.

(g) Process model random vibration test (13)

This test is essentially similar to that described above for test (9),except that here different random vibration conditions are used in place of combinations of specific frequencies and accelarations.

CATEGORY (3)

(h) Particle adhesion test (14,15)

A very small sample of powder is placed in a suitable holder in an ultracentrifuge tube.The holder may be a split sphere the two halves of which are seperated by a sieve mesh of appropriate aperture dimensions to allow dislodged fines through and to retain coarse excipient particles and intact ordered units.Using this method the non-adhering drug fraction is assessed by chemical assay of the collector hemisphere.Alternatively,the holder may be a plain brass plate into which fine holes have been drilled which are capable of retaining single ordered units;of the plate may have ordered units fixed to it by an epoxy resin adhesive.Using this method the drug fraction is assessed by microscopic examination of the ordered unit surface.A range of interparticle adhesion forces can be assessed by application different ultracentrifuge rotor speeds.

CATEGORY (4)

(i) Tableting homogeneity test (16)

Homogeneous mixtures were used to produce 200 mg tablets on a rotary press (Beta press,Manesty,UK) at a rate of either

42.500 tablets per hour or 50.000 tablets per hour.50 tablets were removed randomly after different times and assayed for drug content.

(j) Hopper vibration test (17)

Experimental details of this test are not recorded,although the method is based on vibration of a powder simple in the hopper of a single punch tablet machine for one hour.

CATEGORY (5)

(k) Powder flow test (18)

This test is based on the segration cell developed by Williams to study the segregation of coloured powders.In this test,the cell is reduced in size to a box 15.2 x 13.3 x 2.54 cm which holds appoximately 70 g of powder sample.Powder is poured into the box so that a "two-dimensional" heap is formed.The powder heap is immobilised by insertiion of a wedge and the front of the box removed and replaced by a sampling template.Samples are removed using a number 1 capsule dosator and assayed for drug content.

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(2) Vibration methods, where a powder mix is vibrated under known conditions, selected to reflect those known to occur during tablet production.

(3) Adhesion force methods, where an ultracentrifuge techniques is used to determine interparticle adhesion forces.

(4) Real-system methods, where the powder is subjected to normal process conditions with no modelling involved.

(5) Flow methods where the powder is allowed to flow into a heap in a sampling box.

Some of the test methods listed in Table 1 can be ruled out as having usefulness for the purposes of a quality assurance method for content uniformity. Thus, in category 1, none of the test methods have any relationship to either fundamental powder behaviour nor to any process environment. Many of the tests in this category were designed to monitor constituent segregation through breakdown of adhesive units rather than provide an analysis of complete powder mixing/de-mixing behaviour. For these reasons tests in category 1 are of little use for the purpose considered here. The category 3 tests were developed to produce accurate qualification of interparticle forces and could provide misleading data if used to predict intact powder systems. Category 4 tests are of little use for the purposes considered here since they use tableting machines as test instruments and therefore provide insufficient data too late in the process.

Of the remaining tests, (f) in category 2 and (k) in category 5 provide potentially the most useful information for the purposes considered here. The work reported below describes a single test combining a vibration and flow system which models the environment in which a powder is processed into a tablet. The model uses a relatively small mass of powder and is simple to use and analyse.

METHODS AND MATERIALS

The flow/vibration model is shown schematically in fig. 1. It consists of an interchangeable brass chute, of different lengths and widths. The angle of inclination of the chute to the horizontal could be changed between 25^{o} and 60^{o} using a goniometer-type mounting. The chute assembly is rigidly clamped to a vibration table and vibration conditions on the chute can be varied over a very wide range. In the present study, vibration was confined to a frequency of 50 Hz and an acceleration of 3 g (29.43 ms^{-2}) which represented the more rigorous vibration conditions found on rotary tablet machines in production. Powders were allowed to flow off the chute into a collecting tray fitted with a sampling matrix from

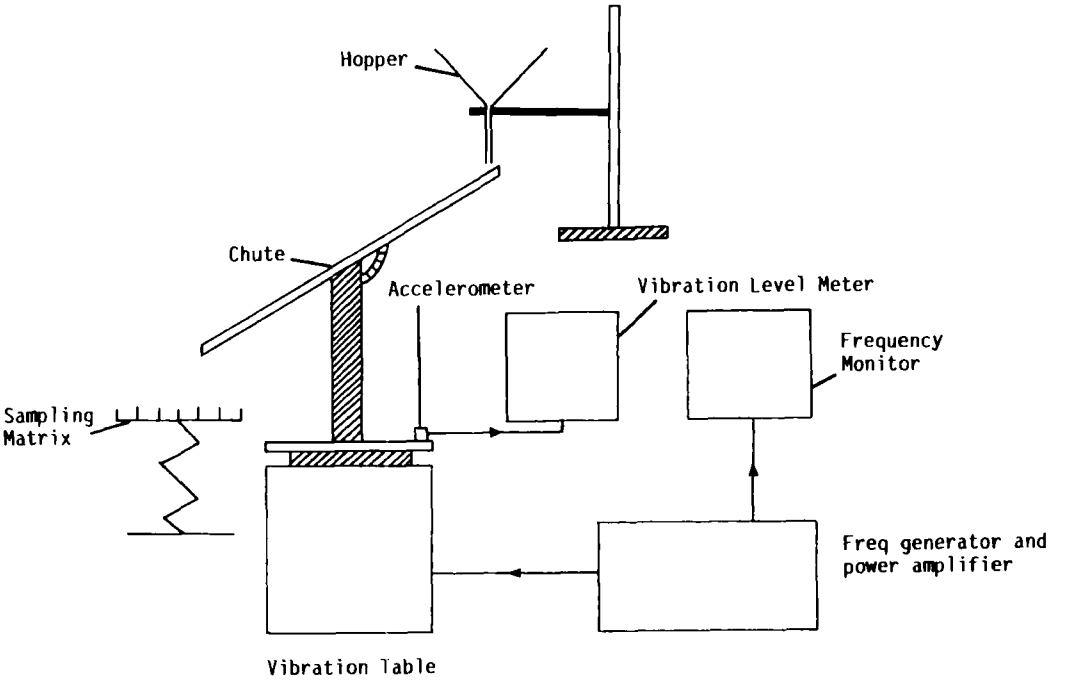

FIGURE 1

Schematic diagram of flow/vibration segregation model

which 20 samples, each of either 100 or 200 mg ± 1 mg, were removed for analysis of drug contents. The model drug used in these experiments was fine-particle potassium chloride which was assayed using atomic absorption spectrophotometry.

Simple binary systems consisting of Tabfine S 100I (Edward Mendell Co Inc, Route 52, Carmel, USA) and KCL; as well as more complex ternary and quaternary systems, also containing magnesium stearate, talc and colloidal silica were investigated using the flow vibration segration model. In all cases high powder homogenity, represented by a coefficient of variation (cv) less than 5%, was ensured prior to flow/vibration testing. In each test, appearance of coefficients of variation of drug content between the 20 spot samples, greater, than 5% was taken as an indication that the

physical stability of the system was likely to lead to content uniformity problems in full-scale production. The higher the cv % value, the more frequent and severe the appearance of content uniformity in production of tablets.

RESULTS

On 2 unvibrated chutes of different lengths, a binary mix containing potassium chloride and a sucrose-based tableting excipient Tabfine S 100I (Edward Mendell Co Inc, Carmel, USA) showed some segregation (fig. 2). Unsurprisingly, segregation was most pronounced on the longer chute, but on both chutes segregation was greatest at low chute angles and it was interesting to note that close to those hopper angles designed to produce mass flow, ie 50-60^{o}, that segregation was at its lowest. On vibrated chutes, segregation intensity increased slightly although again close to angles promoting mass flow, segregation intensity was lowest and little changed from the unvibrated systems (fig. 3). Chute length and a marginal effect on segregation intensity under these vibration conditions (fig. 3).

Addition of a ternary component, magnesium stearate, de-stabilized the binary mix at all chute angles, (fig. 4). It was considered that the reason for differences in segregation intensity for the same powder mixes poured off chutes at different angles, was not chute angle per se. Rather, it was considered that the role of chute angle was to change powder residence times on the chute which would therefore change the time over which powders were subjected to vibration. Changes in chute surface roughness were made to investigate the role of chute residence time. It was found that for a smooth-surfaced chute where residence times were uniformly low, that segregation remained consistently lower than for a rougher-surfaced chute where segregation was related to chute angle (fig. 5). In the case of talc added as a quaternary component, there was virtually no change in the poor homogeneity of the powder

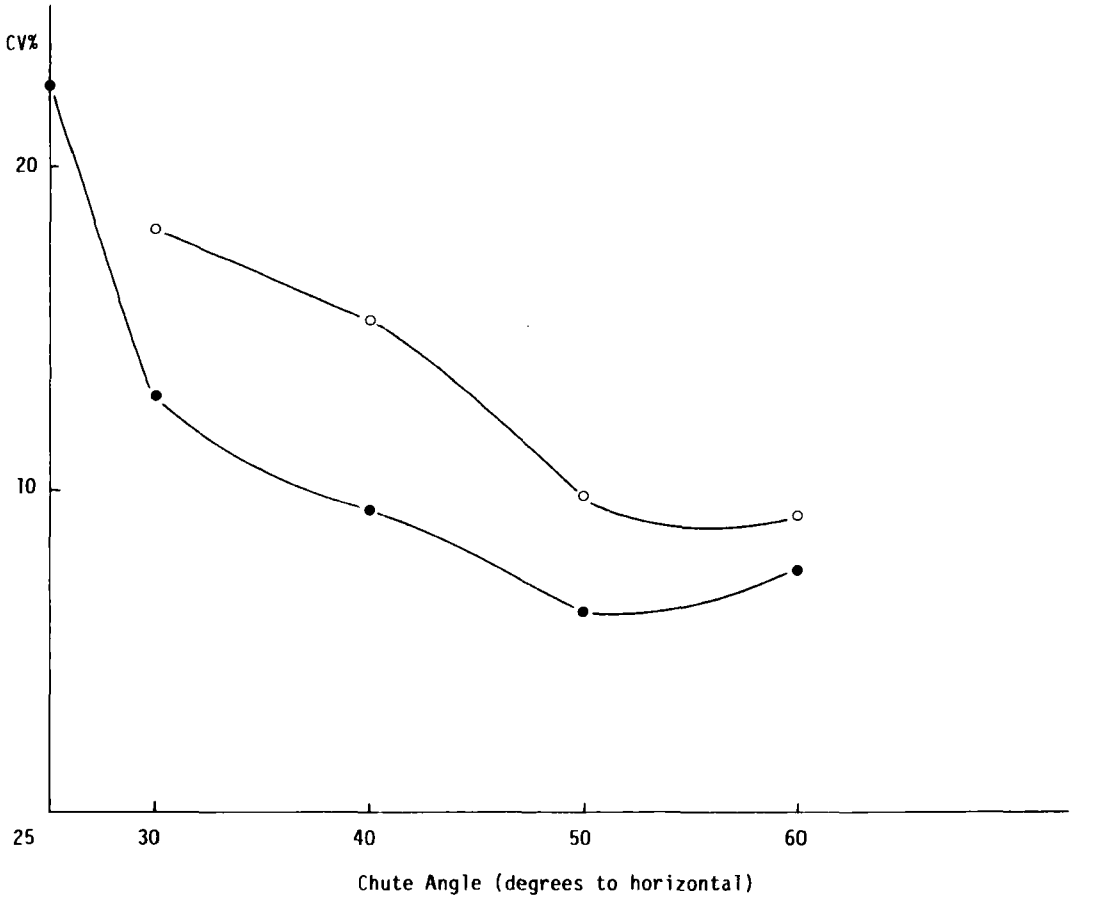

FIGURE 2

Segregation tendency of a binary mix of Tabfine S100I/ 1/2% potassium chloride following flow on non-vibrated chutes of different lengths: 0 - 12" chute; . - 9" chute

system in comparison with the ternary system (fig. 6). However, in the case of colloidal silicon dioxide added as a quaternary component, the flow/vibration model showed that this excipient re-stabilized the powder blend, producing lower homogeneities at all chute angles other than 25^{O}, (fig. 6).

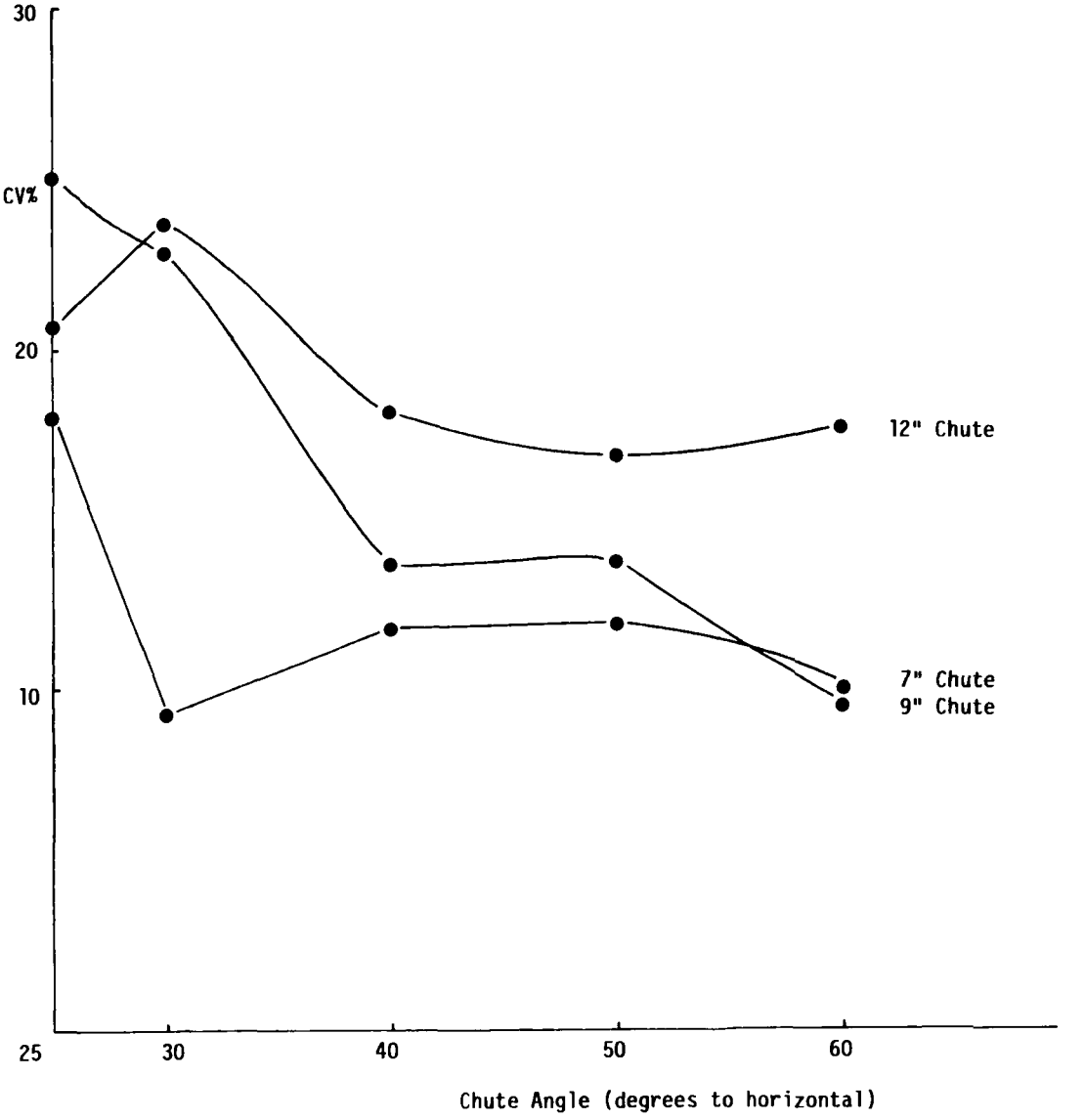

FIGURE 3

Segregation tendency of a binary mix of Tabfine S100I/ 1/2% KCl following flow on different length chutes under vibration at 50Hz and 29 ms^{-2}

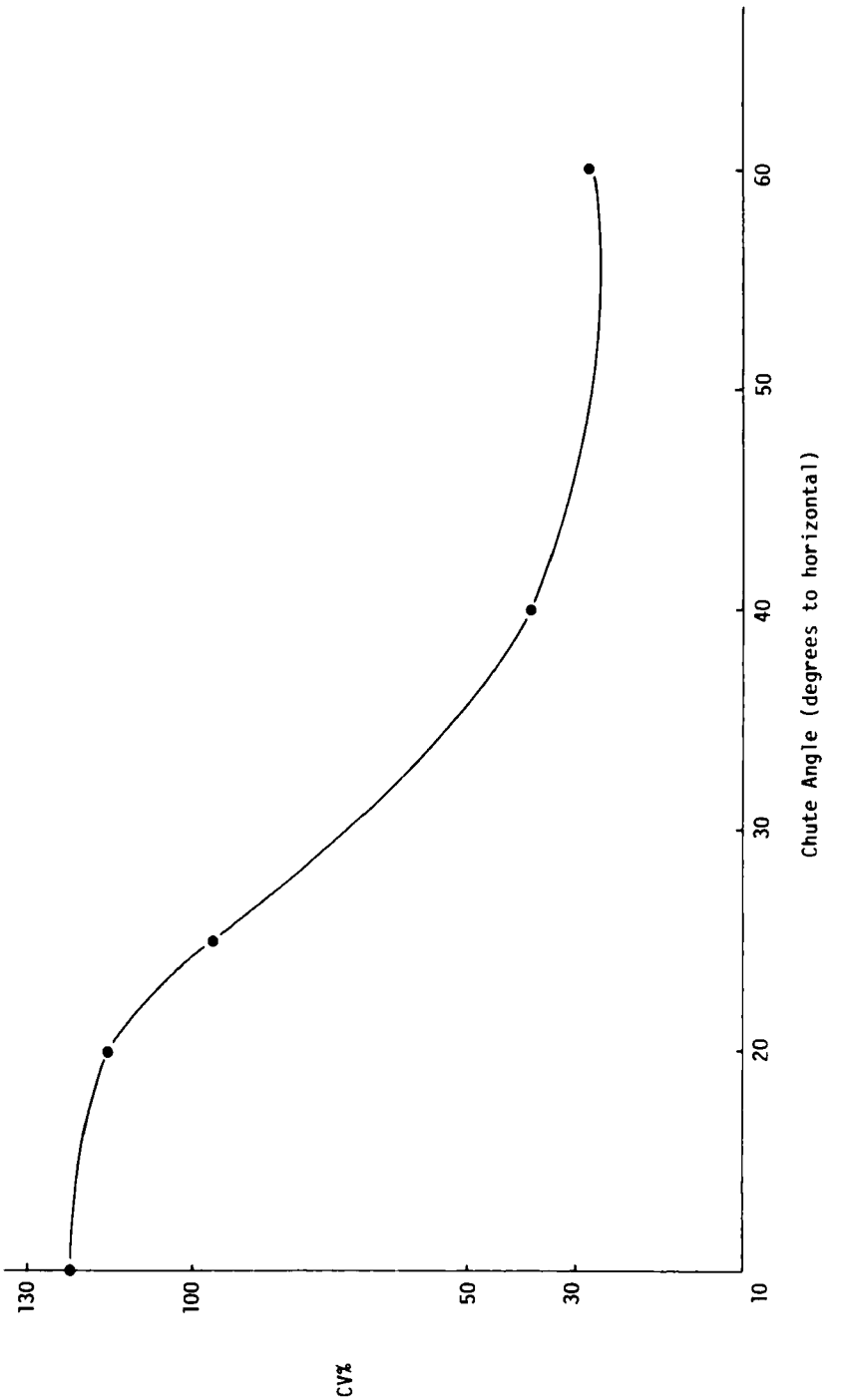

FIGURE 4

Segregation tendency of a ternary mix of Tabfine/KCl /Magnesium Stearate following flow on a non-vibrated chute at different angles

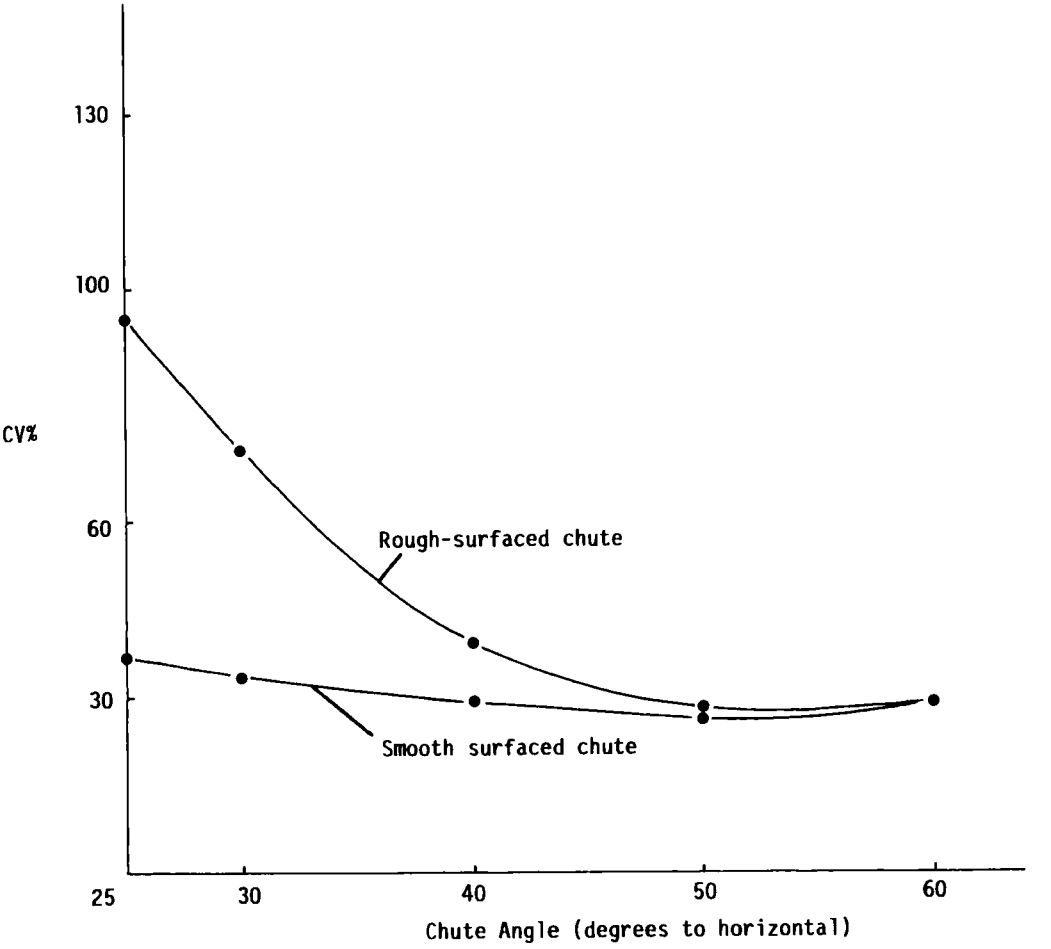

FIGURE 5

Segregation tendency of a ternary mix containing Tabfine/KCl / Magnesium Stearate following flow on chutes having different surface roughness

Changes in the order of addition of the quaternary component, colloidal silica, made little difference to the segregation behaviour of the drug component in this case. Thus, whether colloidal silica was pre-mixed with magnesium stearate and added to a binary mix of KCl and Tabfine or if colloidal silica was added to a ternary mix of magnesium stearate/KCl /Tabfine, appeared to have

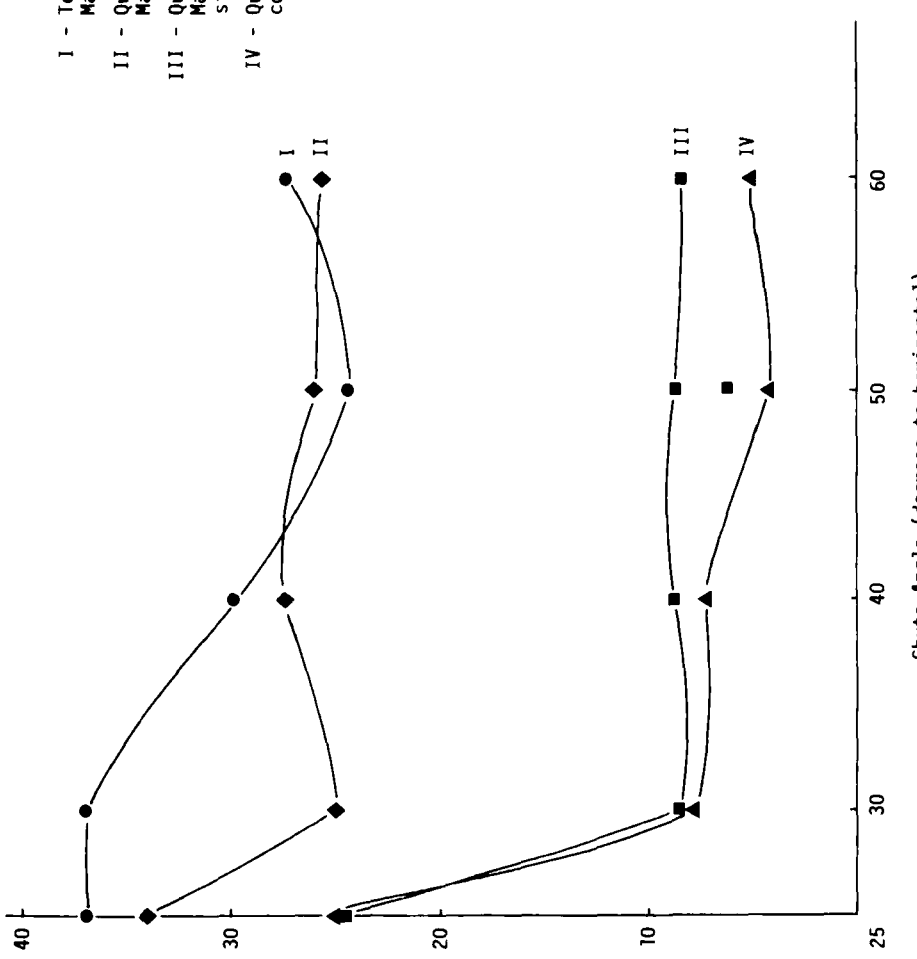

FIGURE 6

Segregation tendency of different ternary and quaternary mixes following flow on a vibrated chute at 30Hz, 29.4 ms^{-2}

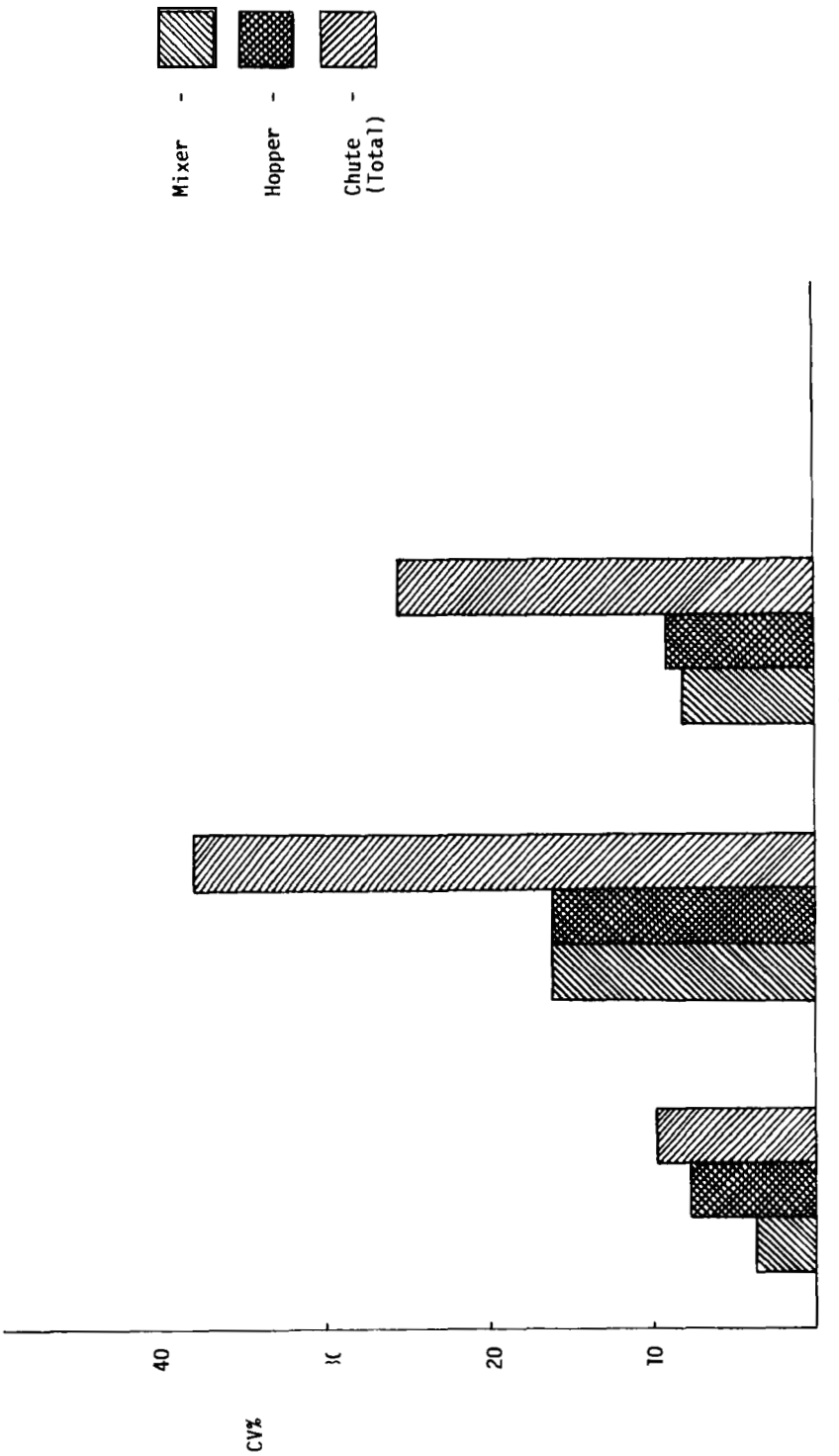

FIGURE 7

Histogram showing relationship between segregation and different stages of processing for 3 different mixes

no influence on the stability of the finished quaternary mix (fig. 6).

In binary (Tabfine/KCl), ternary (Tabfine/KCl/Mg Stearate) or quaternary (Tabfine/KCl/Mg Stearate/SiO_2) mixes, the main source of segregation occured during flow off the chute (fig. 7).

In all cases, powders sampled in the hopper prior to feeding on to the chute showed similar homogeneity to the same powders sampled in the mixer. Segregation was highest in the ternary mix because of the de-stabilizing effect of magnesium stearate on the drug/excipient binary adhesive units. The quaternary system was more stable and homogeneous than the ternary system, due to the re-stabilizing influence of colloidal silica.

DISCUSSION

The flow/vibration segregation test method has been used to separate different types of powder behaviour had identify those excipient/drug combinations and process conditional likely to lead to homogeneity problems in full-scale production. Because both flow and vibration conditions can be altered, a model can be produced which accurately mirrors specific production processes for a given formulation.

This test method has aleady been used by a number of international pharmaceutical companies as an aid to formulation development and problem solving and has proved to be capable of closely modelling production conditions using small powder samples in rigidly controlled test conditions.

We are currently continuing work to refine the test and to extend its application to quality assurance testing of a wide variety of powder mixes.

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