

Research Article

Segregation Leading to Drop in Thiamine Content during Solid-Solid Mixing

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Abstract

Purpose: The study aims at solving drop in assay value of thiamine hydrochloride in freshly made Vitamin B Complex tablet formulation despite incorporation of 15% over the label claim. Unaccounted results are always a matter of concern in the pharmaceutical industry. The study also aims at identifying a general procedure for the determination of optimum mixing time and suitable mixing machines for low strength active ingredients incorporated with dried granules in a similarly manner.

Methods: Rigorous evaluation of the entire manufacturing procedure pointed to a possible segregation as the cause. Three types of mixing machines representing convective, diffusion and shear mixing were investigated. Graphs were drawn using standard deviation (S), variance (S^2) and Lacey Mixing Index derived mixing scales – $\ln(S^2/S_0^2)$ of the thiamine content against accumulated mixing times.

Results: According to the curves obtained optimum mixing was found to be around 5 minutes for all three types of machines. The

drum mixer showed the lowest variance indicating best homogeneity of the blend.

Conclusion: The arbitrarily perceived safe mixing for 15 minutes had been counterproductive leading to segregation of thiamine. Reducing both the mixing time and the 15% overage of thiamine can still improve the assay towards the expected theoretical value.

Keywords: Solids mixing, Segregation, Lacey Mixing Index, Pharmaceutical formula, Polymorphism.

Introduction

The importance of solids mixing has not yet being identified due to insufficient knowledge on fundamentals of mixing. Even chemical engineers find it difficult to identify mixing problems and find solutions. There are no standards and codes available in mixing especially in solids mixing. Further, the mixing machine manuals have very little instructions on the subject. Industrialists have resorted to over addition of ingredients to



overcome mixing problems as in the present case under investigation.

The study was undertaken to find a systematic solution to the problem of comparatively low assay values of thiamine hydrochloride (TMH) in freshly made Vitamin B Complex tablet blends. The main focus of the study was to find out the optimum mixing time. The experiments were based on three mixing machines which operated on convective, diffusion and shear types of mixing.(1) Optimum mixing time for each mixer and the machine that gives minimum segregation were to be determined.

Problems in solids mixing

Unlike other mixing systems such as solid-liquid, liquid-liquid and gas-liquid where tendency to separate will start once agitation is stopped, in the case of solid-solid mixing the segregation is caused by agitation.(2) There are many factors that have a tendency for the particles to separate such as the particle size, density, shape and surface features and charges. The heavier, smaller, smoother and spherical particles tend to sink through lighter, larger and jagged particles.(3) Therefore segregation is possible due to transfer in to powder filling machines, in the tablet and capsule filling machine hoppers, vibration during transport, unloading from mixing machines and even during sampling of solid mixtures.(3)

Segregation occurs when differences in particulate properties cause preferential movement of particles to a certain region of the mixture. Particles with a size greater than 75 μm tend to segregate readily. When the size is reduced below 75 μm segregation is reduced but is still detectable whereas sizes below 10 μm shows no appreciable segregation.(4) Segregation can be reduced

by having the same particle size of mixture components or by adding a small percent of moisture. Both these are not possible in the Vitamin B Complex tablet formulation. Free flowing powder is a process requirement in most tableting operations with the accompanying potential for segregation. Hence the aim should be to suppress and minimize it rather than to eliminate it.(4)

Ideal mixture and the pharmaceutical formula

Casually it may be said that a mixture is well mixed when it is good enough for the purpose. For example compared to the pharmaceuticals, the food industry may survive with a lesser degree of homogeneous mixing than in the pharmaceutical industry. A coloring agent may be considered well mixed when the eye can no longer detect color variations in the bulk material. Inspection under magnification could well mean that the previously satisfactory mixture becomes unsatisfactory. Only a scientific approach to the problem can identify the parameters for a well-mixed, multi component solid bulk product.

The pharmaceutical formula expresses the theoretical amounts of all the raw materials per unit dose and it is possible to achieve this only in pharmaceutical liquid solutions down to every drop. Ideally it may be said that each of these tablets weighing 175 mg should represent all the constituent raw materials in the same proportion as in the batch manufacturing formula, in this case 350 kg. The significance of the pharmaceutical formula is that it shows how much of each ingredient in the formula including preservatives, antioxidants, artificial sweeteners, coloring agents and such other less desirable ingredients are ingested by a patient each time a unit dose is consumed.

Unit dose represents the unit therapeutic intervention. It may require just one such unit for an entire life time such as BCG vaccine (5) or Vermox tablets each containing 500 mg of mebendazole per de-worming event.(6) In the other extreme is the daily life long hormone replacement therapy as in the case of thyroxine tablets. It is a ready reference to officially approved daily intake limits of each of these ingredients. In the industry usually the pharmaceutical formula quantities are listed next to batch manufacturing formula of the standard operating procedure document.(7) Optimum mixing, not excessive mixing that facilitates representation of the ideal pharmaceutical formula.

The heavier batch manufacturing formula in reality is an expansion of the lighter pharmaceutical formula although it appears that the latter is a small division of the former in the manufacturing environment. Regular analysis of pharmaceutical preparations by the quality assurance and regulatory authorities is based on the pharmaceutical formula. The single most significant unit operation in this regard is mixing.

Mixing in the pharmaceutical industry

Some of the numerous terms associated with pharmaceutical mixing operations, extemporaneous and industrial scale combined include, mixing by doubling up, fusion, levigation, homogenizing, emulsification, shake well or gently or roll between hands before use, axial, tangential and radial mixing, molecular diffusion, laminar mixing and turbulent mixing, convective, diffusion and shear mixing.(8),(9) Even the modern horizontal mixers currently in use still need manual transfer of material, technically termed 'bulk transport', from one point of the container to the other to achieve homogeneous mixing. The active ingredient

content to be mixed may range from microgram quantities such as in trace elements or hormone preparations to over 98% by weight as in the case of certain high strength tablets such as sulfonamides and calcium lactate.

For very low strength active ingredients such as thyroxine, a method of incorporation used in practice in order to achieve homogeneity is to dissolve the substance in organic solvents, spread it over the powder mix to be followed by blending. Current awareness however points to the fact that the existence of polymorphism in thyroxine may lead to differences in solubility.(10) During the above process they may undergo changes from more soluble form to a less soluble form as the substance re-crystallizes during solvent evaporation with implications in bioavailability. A famous example is the therapeutic failure of ritonavir for HIV formulated as capsules by dissolving in a hydro-alcoholic medium. The polymorph I had been converted to polymorph II with 50% less solubility.(11) This method really belongs to a step in the stringently controlled active ingredient recovery process from the final stages of its synthetic pathway and should not be entertained in the formulation industry involving active ingredients known to exhibit polymorphism.

The effectiveness of the drug product depends on the content of active ingredient in the unit dose. Most pharmaceutical operations are based on batch processing. Attempt to adopt continuous processing for the pharmaceutical industry as practiced in the case of municipal water purification for public use has made little progress.(12)

What is envisaged in mixing is the 'relative motion' of the particles to each other. Under

certain circumstances the entire bulk could be in circular motion while the constituents remain adjacent to each other without relative motion. There is motion but no mixing and it is observed mostly in semi-solid preparations. Two or more substances including the active ingredient have to be mixed to form a uniform composition without causing a chemical change. When diluents and other excipients are not mixed well the tablet or the capsule blend does not have a favorable content uniformity so that some tablets or capsules made from such a blend may not have enough active ingredients. One has to ensure that the required amount of drug is found in each dose unit however small that may be. For example oral contraceptive tablet 'gross weight' may be as little as 60 mg and despite extremely high dilution, the declared active ingredient content should be present in the tablet.

The vitamins other than TMH in the Vitamin B Complex tablet blend under consideration here are incorporated during initial dry mixing stage together with fillers. They have the advantage of undergoing wet mixing so that their homogeneity is ensured as a result of binding with the granules. By incorporating TMH with the dried granules any possible deleterious effects due to oxygen, heat and moisture are minimized.

Degree of mixing

The study focuses on the establishment of a mathematical approach to determine the optimum mixing time beyond which segregation sets in for a given mixer. In expressing the degree of mixing of solids the statistical variation in composition among samples withdrawn at any accumulated time from the mix is used. These are the standard deviation (S) or the variance (S^2).⁽¹³⁾

When a material is partly mixed, then the degree of mixing can be represented by some term M. Term M is defined by the following expression,

$M = (\text{How much mixing has occurred}) / (\text{How much mixing could occur})$ or

According to Lacey Mixing Index, $M = (S_0^2 - S^2) / (S_0^2 - S_r^2)$ Equation A, where,

S_0 is the value of S for the unmixed material and S_r is the value of S for the completely mixed material.⁽¹⁴⁾ This can be expressed as follows.

When S_0^2 is much greater than S_r^2 the above Equation A can be rewritten as

$M = 1 - (S^2 / S_0^2)$ Equation B

Since the variance S^2 exponentially varies against time in any mixing mechanism, the velocity equation is expressed as,

$\ln(1 - M) = -kt$ Equation C,

in which k is a constant depending on the nature of the particles and physical action of the mixer.⁽¹⁵⁾ They include total volume of the material, speed of the machine, the particle size, density and volume of each component.

From Equations B and C,

$-\ln(S^2 / S_0^2) = kt$ Equation D.

If we plot a graph of $-\ln(S^2 / S_0^2)$ vs. t, it will result in a curve with distinct positive and negative gradients. First part of the graph which is a near straight line with a positive gradient shows increasing mixing of the materials and the second part with a negative gradient shows segregation of material following optimum mixing.

Methods

The study is based on the Vitamin B Complex tablet blend with batch sizes of 350 Kg (2,000,000 tablets) in the 650 L capacity double cone mixer (Fuji Paudal C. Ltd.,

Model CM300, Tokyo, Japan) and 87.5 Kg (500,000 tablets) each for the 200 L drum mixer (Nishida Doko Co. Ltd., Model DM 200, Japan) and 100 L planetary mixer (Shinagawa Machinery Works Ltd., Model 250DM-QR, Japan). Granule drying was carried out in the 100 Kg capacity fluid bed drier (Freund Industrial Co. Ltd., Model FLO 120EX, Tokyo, Japan) and compression was carried out in 45 station tableting machine (Hata Iron Works Ltd., Model HT-AP45MS-U, Japan). Each tablet weighs 175 mg with a label claim of thiamine hydrochloride 5.0 mg but theoretically expected to contain 5.75 mg due to 15% overage. The sample analysis was carried out using High Performance Liquid Chromatography (Agilent Technologies, Model 1200, Infinity Series, Germany). The project was carried out at the State Pharmaceuticals Manufacturing Corporation, No. 11, Sir John Kotalawala Mawatha, Kandawala Estate, Ratmalana, Sri Lanka.

Granules were prepared by wet granulation process with the fillers and all vitamins excluding TMH in the wet stage. Approximately four fold triturate of TMH made with dried granules was fed in to the milling machine together with bulk dried granules as evenly as possible in the proportion of their respective weights ensuring that about 20-30 Kg of dried granules remained. This amount is fed alone in to the milling machine after all of TMH had been fed so as to wipe down all traces of TMH that may be adhering to the machine parts. The procedure adopted avoids the vitamin being exposed to heat, moisture and light.

The concentration of TMH in the samples drawn at accumulated mixing times was determined as a w/w percentage. Samples were drawn using 'manual sample thief' of sufficient length to draw samples including

those from the bottom of the double cone mixer, the tallest among all three mixers. The standard deviation (S), the variance (S^2) and variance based mixing scale – $\ln (S^2/S_0^2)$ were calculated for each accumulated mixing time. Optimum mixing time was determined by plotting two variance based graphs against time at which point the value of variance is at a minimum.

Calculations based on variance S^2 of thiamine in the blend

The variance S^2 , where S is the standard deviation represents variation of data. The smaller the value of S^2 greater is the homogeneity of the mixture. Optimum mixing of thiamine occurs at which time the S^2 of thiamine is the minimum. In order to obtain the point at which S^2 is lowest a graph consisting of S^2 is drawn against the mixing time t in which U shaped curves were obtained (Figure 1). A second graph was drawn – $\ln (S^2/S_0^2)$ vs. t that shows how segregation sets in the three machines following achieving the optimum homogeneity (Figure 2).

Samples were drawn from each of the three mixers using imaginary parallel vertical planes running through the containers. The large batch size of 350 Kg in the double cone mixer had 5 such planes and the 87.5 Kg batches of the other two blenders had three such planes. All the planes were at an even distance from each other, middle plane passing through the center of each mixer. Proportionately higher number of samples was drawn from the central planes from different depths since they cut across the largest width of the powder bed. The central plane represents the diameter of the mixer containers all of which could be considered as conical, cylindrical or hemispherical. At each accumulated mixing times of 0, 2, 5, 10, 15

and 20 minutes, fifteen samples were drawn from double cone mixer totaling 90 samples. Similarly 5 samples were drawn from each of the other two smaller mixers at each accumulated mixing time totaling 2 X 30 samples. Two graphs were constructed using the results of sample analysis for thiamine, the first is the graph of variance S^2 vs. time t and the second is based on $-\ln(S^2/S_0^2)$ vs. t as per Equation C discussed above (Figure 1 and

2). In Figure 1 coordinates for zero time (0 min, S^2) were ignored as they disproportionately stretch the curve along Y axis without conveying any useful information. The samples were analyzed for TMH assay using an in-house method of the Corporation adopted from a method used in the National Institute of Hygienic Sciences, Japan.

Figure 1: Curves for three mixing machines on thiamine content variance S^2 vs. accumulated mixing times t

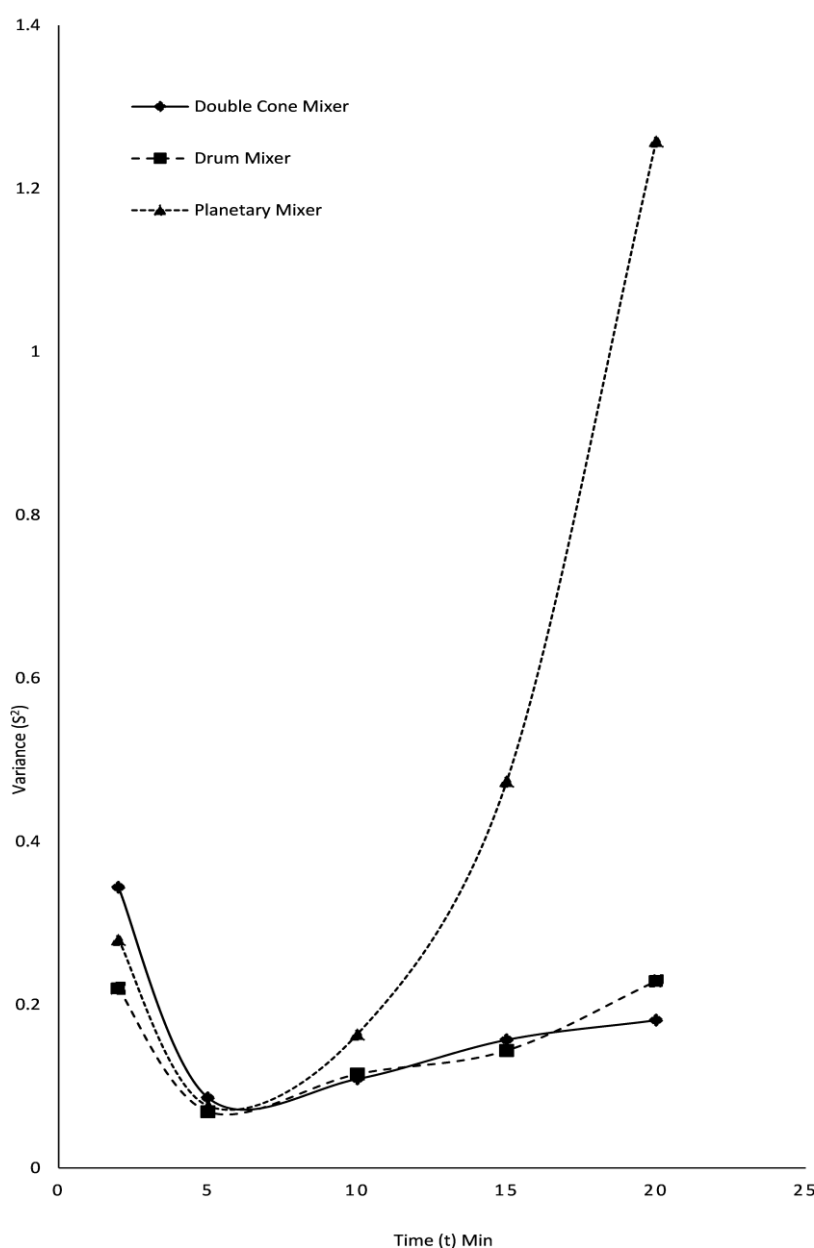
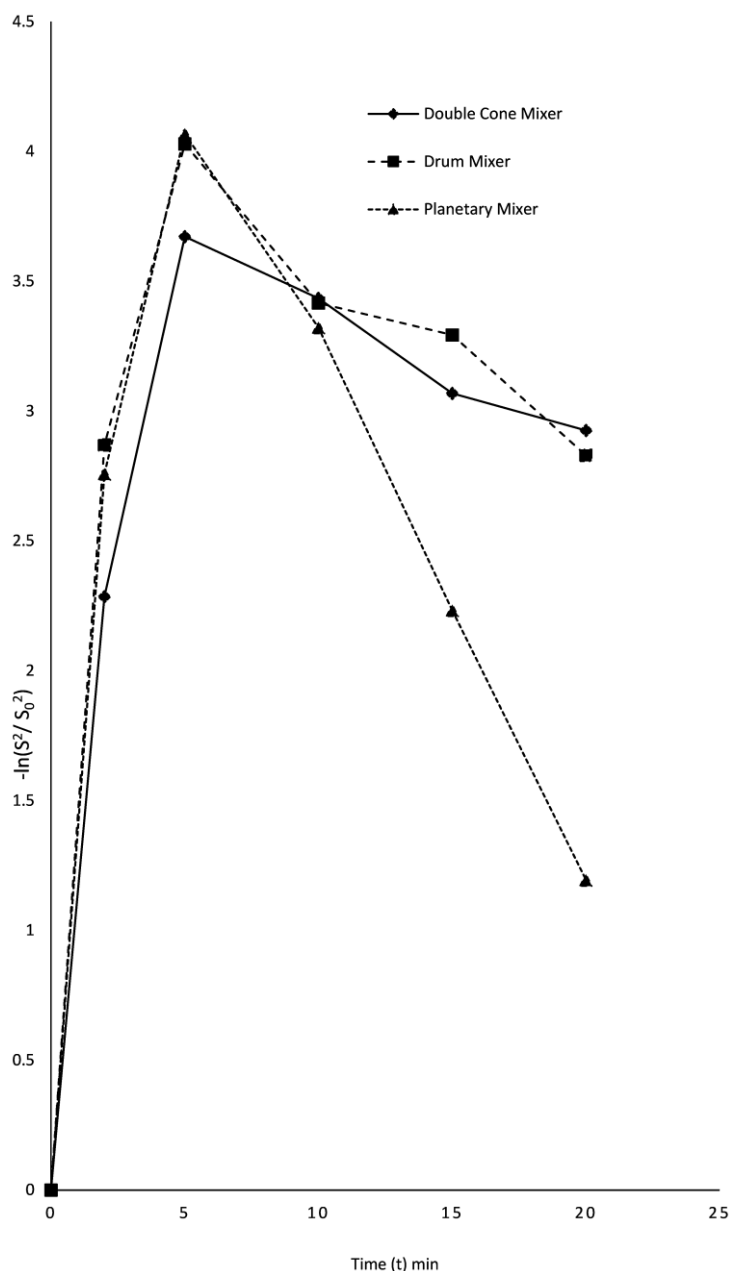


Figure 2: Curves for three mixing machines on thiamine content variance based values of $-\ln(S^2/S_0^2)$ vs. accumulated mixing times t



Results

The percentages of TMH detected in each sample from the three mixers were tabulated (Tables 1, 2 and 3). According to Figure 1 curves, it can be seen that minimum variance is achieved at the mixing time of 5 minutes for

all three types of mixers. This is an indication that for the solid blend under consideration deciding factor for optimum homogeneous mixing of TMH is the nature of the constituent particles rather than the mixer type or the mixing mechanism. Accumulated mixing time in excess of 5 minutes leads to

segregation of the vitamin. The lowest variance achieved is for the drum mixer (Figure 1).

Hence the 15 minutes mixing period adopted in the manufacturing process is far too long. Since the low end assay results of TMH in the tablets is due to segregation it is possible to reduce the overage of 15%. According to Figure 2, segregation will take place if the mixing will continue after the optimum mixing time. For a given material the best mixing time to achieve maximum homogeneity may depend on the particular

machine such as the drum mixer in this case. However given the machine capacities and acceptable degree of mixing, 650 L double cone mixer could be used provided mixing terminates at 5 minutes. Drum mixer may have to be considered as the machine of choice for low strength solid dosage forms where content variation determinations are official for the particular product. As the sharpest negative gradient past the optimum mixing time is for the planetary mixer this machine should be the least preferred for dry mixing operations of similar nature (Figure 2).

Table 1: Thiamine hydrochloride content in samples from double cone mixer at accumulated mixing times

Sample number	Thiamine hydrochloride percentage in the samples.					
	0 min.	2 min.	5 min.	10 min.	15 min.	20 min.
01	5.03	2.72	2.99	3.11	2.30	2.92
02	4.75	3.33	2.23	2.47	2.75	3.20
03	2.16	1.64	2.76	3.15	3.25	3.29
04	3.14	2.55	3.13	2.81	2.93	3.14
05	3.30	2.52	2.78	2.38	2.90	3.15
06	-	3.73	2.46	3.13	2.91	3.33
07	1.99	3.38	2.88	2.93	2.88	2.93
08	3.74	2.36	2.64	2.78	2.93	2.83
09	5.28	3.17	3.10	2.68	2.88	2.38
10	-	3.88	2.96	3.18	2.91	2.86
11	4.52	2.53	2.36	3.03	2.42	2.98
12	2.97	3.00	2.76	3.06	2.48	2.15
13	1.49	3.14	2.66	3.21	2.50	2.05
14	5.06	3.36	2.26	2.48	3.22	2.66
15	0.60	2.60	2.91	2.34	3.20	2.19
Variance (S^2)	3.381	0.344	0.086	0.109	0.157	0.181
	(S_0^2)					
$-\ln(S^2/S_0^2)$	-	2.285	3.672	3.434	3.068	2.925

Min, minute; S, standard deviation; S^2 , variance; S_0^2 , variance at 0 time.

Table 2: Thiamine hydrochloride content in samples from drum mixer at accumulated mixing times

Sample number	Thiamine hydrochloride percentage in the samples					
	0 min	2 min	5 min	10 min	15 min	20 min
01	1.64	3.15	2.87	3.11	2.30	2.38
02	0.87	2.38	2.14	3.15	3.25	3.29
03	3.02	3.22	2.58	2.78	2.94	2.33
04	5.28	2.50	2.54	2.68	2.87	2.86
05	5.00	3.44	2.61	2.34	3.20	3.33
Variance (S ²)	3.878 (S ₀ ²)	0.220	0.069	0.115	0.144	0.229
-ln(S ² /S ₀ ²)	0	2.869	4.029	3.416	3.293	2.829

Min, minutes; S, standard deviation; S², Variance; S₀², variance at 0 time.

Table 3: Thiamine hydrochloride content in samples from planetary mixer at accumulated mixing times.

Sample number	Thiamine hydrochloride percentage in the samples.					
	0 min	2 min	5 min	10 min	15 min	20 min
01	6.66	2.65	2.83	3.17	3.68	2.20
02	2.73	2.40	2.91	2.42	1.93	3.34
03	1.44	2.91	2.40	2.15	2.87	2.61
04	2.04	2.41	3.14	2.92	2.14	2.53
05	2.08	3.68	2.68	2.67	2.56	3.51
Variance (S ²)	4.417 (S ₀ ²)	0.280	0.076	0.164	0.474	1.258
-ln(S ² /S ₀ ²)	0	2.758	4.067	3.231	2.232	1.193

Min, minute; S, standard deviation; S², variance; S₀², variance at 0 time.

Discussion

The outcome of the project brings in to focus the validity of scientific approach to seemingly simple operation like mixing that is taken for granted in the pharmaceutical industry. Both favorable and unfavorable equipment and operating parameters can be identified by such experiments. Besides Lacey Mixing Index, Poole Mixing Index too can be used for these determinations.

A well designed sampling plan is a prerequisite for the reliable outcome of such a study. It is a unique feature in the solid-solid mixing that segregation could take place during agitation. During mixing, especially in triturate (dilution) preparation of small amounts of active ingredients with diluents like lactose, segregation could take place due to electrostatic charges when the container consists of plastic materials. Loss of active ingredient as a result of adherence to the

plastic surface could also take place.

The number of particles in the active ingredient is important for proper distribution and homogeneity of the final blend. The fineness of powder classification in the pharmacopoeia is important in this regard.(16) This is an analytical parameter often neglected in the industry. If the fineness does not comply fine milling of the material must be undertaken.

The article intend to highlight the requirement for the 'pharmaceutical formula' expressing the quantities of all ingredients present per unit dose in the master formula. Values displayed here are not visible in the commercial formula such as the overage added over and above the label claim of the active ingredient. Further the pharmaceutical formula is not a mere apportioned fraction of the batch formula to a unit dose. The changes to batch quantities following drying process for ingredients such as maize starch with 12-15% moisture and those with high degree of water of crystallization has to be accounted for. For diagnostic reagent tablets this requirement is of great significance.

It may be opportune here to mention few situations that warrant exact interpretation of a situation failing which the problem could never have been solved.

A smooth tableting operation carried out to required specification including that of the hardness had to be interrupted for a while to cleanup a seized tableting punch. On recommencing the operation it was found to the amazement that there was near total loss of tablet hardness with the prospect of terminating the manufacture of the rest of the batch. A thorough examination revealed an unusual mixing problem as the cause of

hardness failure. The powder feeding system of the machine has a built in power driven feeding chamber with rotating probes placed between the overhanging powder container and the die table to facilitate adjusting powder flow at a particular rate. It also cuts off the effects due to changes in powder head load influencing the tablet weight. While the machine was being cleaned this system had been in operation. The magnesium stearate in the portion of the blend held in the feed chamber had been over mixed as a result of continuous running of the powder chamber probes. The over mixed portion was removed and fresh material fed in to the machine with instant recovery of the hardness.

There had been a case of consistent unaccounted increase in assay value of a product, a situation opposite to that of the present study. This was identified due to heating up to 'boiling' of a solution by oversight whereas the recommendation is to 'warm' the solution. Once there was a mentholated tablet blend ready for compression. Overnight, the granule surface was found covered with loose white fluffy growth of fine menthol crystals that has separated from the mix. There was no agitation, yet a constituent has separated in a solid mixture. This was identified not due to solid mixing mechanisms but due to 'molecular diffusion' as a result of possible sublimation of menthol.

Incidentally there can be other unexpected surprises in pharmacy whenever the diligence is relaxed. Even the ingredient in focus here, thiamine hydrochloride in reality is a unique compound, a form of 'chloride hydrochloride'. Pharmacists are in a high risk profession where even inappropriate terms may lead to fatalities. This was the reason for

replacing the former term 'normal saline' with 'physiological saline'.

Conclusion

It is evident that solid-solid mixing has its own share of unique problems and demands the necessary attention of the pharmaceutical scientists. From the pilot scale to commercial scale up production a close tract must be kept on the degree of mixing and segregation.

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