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SEGREGATION AND CONTINUED MIXING IN AN AUTOMATIC CAPSULE FILLING MACHINE

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ABSTRACT

During test production of an indomethacin 25 mg capsule preparation problems with single-dose variation and variation/reduction in dissolution rate were ascertained. The problems were identified as segregation and overmixing of the powder mixture, which contained magnesium stearate as lubricant. The problems were solved by removing the propeller mixer in the powder hopper and replacing the cylindric powder hopper with a cone-shaped hopper, which resulted in mass flow.

INTRODUCTION

When reading scientific literature you will often get the impression that all results are based on carefully planned experimental studies and well-defined

targets. This is also the case in basic-scientific studies and also often in formulation work; but in connection with a planned production and marketing of a product the conditions may be very different, especially because there will often be a tight time schedule. In this article the problems inherent in such a situation, i.e. in connection with upscaling of a capsule preparation, will be described, the symptoms being dose variation and variation in dissolution rate, which appeared during the batch analyses of the first production batches.

Description of Symptoms

The symptoms are as mentioned dose variations and variation in dissolution rate as seen in figure 1 and 2.

The problems were solved according to the known plan for problem-solving which includes the following points:

1. Description of the symptoms.
2. Analysis of the underlying problem.
3. Suggestions for solutions.
4. Determination of consequencies of the suggestions for solution.
5. Choice of solution.
6. Implementation of the solution.
7. Results.

These points have thus been incorporated into the framework of the article.

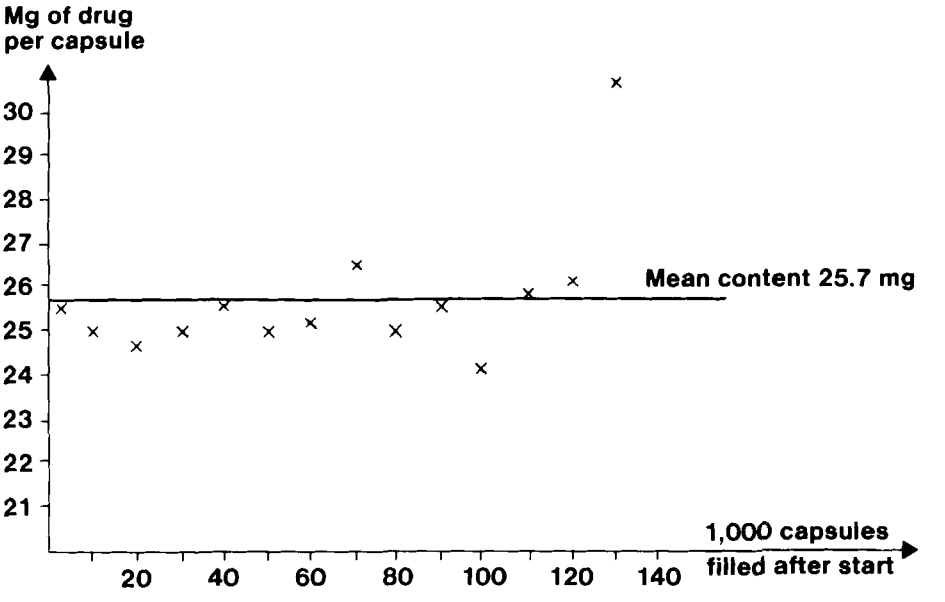

FIGURE 1

Single-dose Variation for Production Batch 133451.

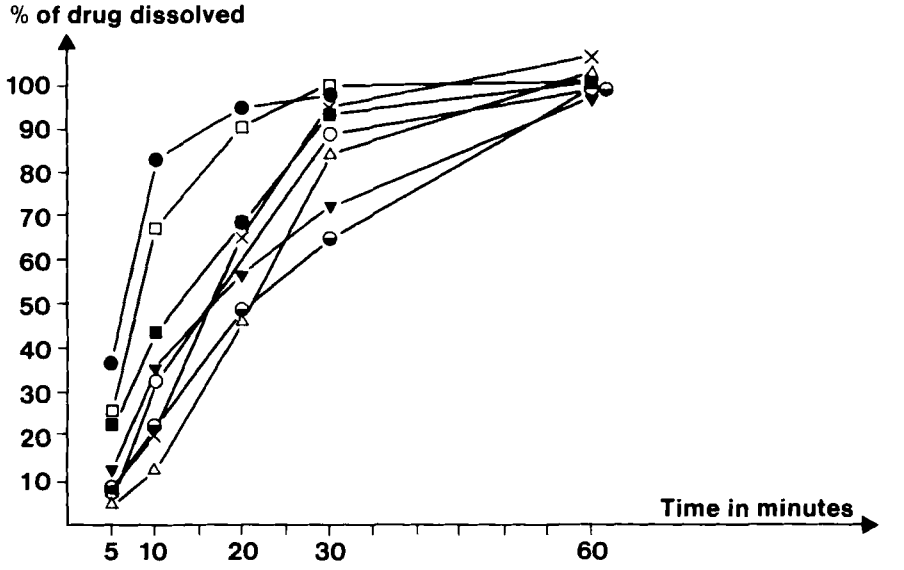

FIGURE 2

Variations in Dissolution Rate (Different Batches).

METHODS

Product Manufacture

The capsules were manufactured by mixing the constituents in a planet mixer. Magnesium stearate was added as single-dose agent followed by a short mixing period of five minutes. The powder mixture was filled on hard gelatine capsules, size 1 and 3, on a mG2-G 36/4 automatic capsule filling machine, in order to obtain a dose size of 25 mg indomethacin. Filling velocity 6-9,000 capsules/hour.

Dissolution Rate

It was determined by a beaker method with a magnetic stirrer [1] under application of 1,000 ml phosphate buffer solution pH 7.0 (± 0.1) at 37.0°C. At the stated periods 2.0 ml test solution was sample-taken, which was analyzed spectrophotometrically at 320 nm with respect to the concentration of indomethacin. During the test the capsules were floating on the surface of the liquid, centered by the rotation helix until the capsule shell disintegrated. Thereafter the capsule shell was moistened with the dissolution liquid, and the capsule with contents remained suspended in the liquid during the continued dissolution test. The method is thus sensitive to the hydrophobic conditions of the capsule content. One capsule per test was applied, and the results constituted an average of the dissolution rate of the six capsules. The uncertainty of the method is ± 5%.

Single-dose Determination

The contents in a capsule was weighed, and 13 ml phosphate buffer (2.890 g KH_2PO_4, 5.120 g $Na_2HPO_4,2H_2O$ and carbon dioxide-free water ad 1000.0 ml) was added. The mixture was shaken for five minutes, 13 ml methanol was added, and after another five minutes' shaking a mixture of phosphate buffer and methanol (1:1) v/v was added to 50.00 ml. 0.750 ml of the filtrated sample solution was diluted to 25.00 ml with phosphate buffer and methanol mixture (1:1) v/v and measured spectrophotometrically at 320 nm against blind and reference solutions manufactured according to the above description. The accuracy of the method is $\pm$ 2%.

Sample-taking

The dissolution test on the production batches was determined on representative samples.

Dissolution tests were also effected on capsules sample-taken during the filling process. Each sample contained 30 capsules, which were taken from the filling machine according to the indicated number of filled capsules, figure 4.

Single-dose analysis on capsules taken during the filling process was effected as stated above.

MATERIALS

The studies have been made on indomethacin capsules 25 mg, DAK, containing micronized indomethacin, lactose, siliciumdioxide, and magnesium stearate, all

pharmacopoeial quality in hard gelatine capsules (Cornisnap®). Batch size 150,000 pieces ~ 28.5 kg.

RESULTS OF DISCUSSION

Analysis of Symptoms

Dose variation may be caused by several factors. An obvious cause may be mass variation, but the indicated results have been rectified with respect to variations in the mass of the capsule content. Another possibility may be segregation, which may also be ascertained visually by inspection of the powder hopper during the filling process.

Several causes for the dose variations may be conceivable, but by effecting a test with a test batch, where the powder hopper and mixer are working uninterruptedly, i.e. without replenishing granulate or manual mixing, segregation was confirmed.

Variations in dissolution rate may have been caused by many factors. Variations in plug hardness, variations in disintegration times, bad formulation, variations in granulate handling by a problematic filling process and overmixing of a magnesium stearate-containing product were some conceivable possibilities. Tests with variation in plug hardness and disintegration time were easy to effect, but did not solve the problem.

Overmixing was also examined carefully. A test (1 kg scale-Erweka planet mixer) showed no changes in dissolution rate in case of continued mixing for up to four hours of powders without addition of magnesium stearate. After admixture of magnesium stearate reduced dissolution rate concurrently with increased mixing time was ascertained.

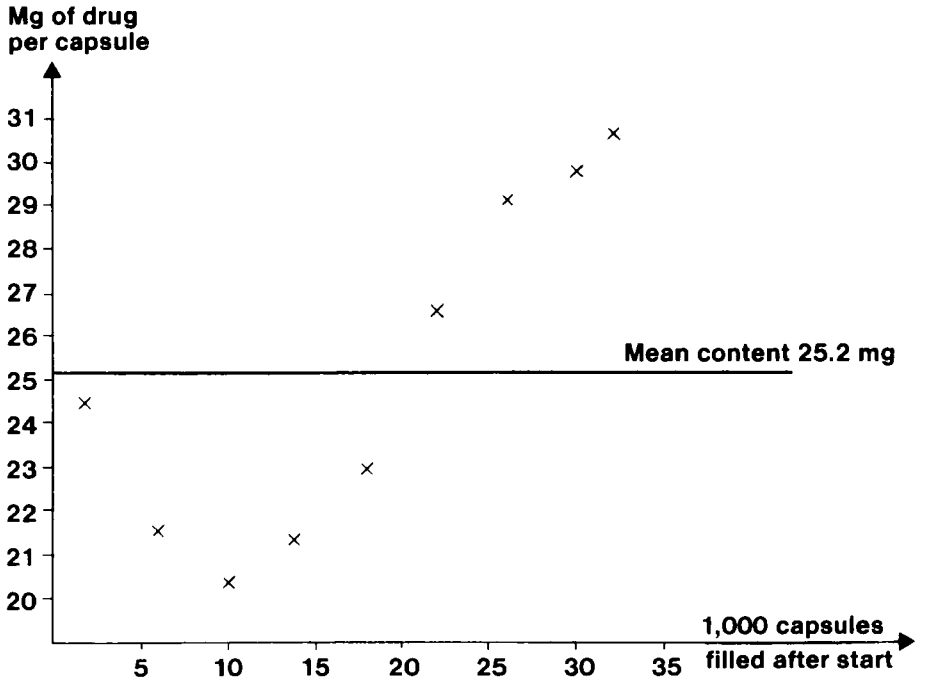

FIGURE 3
Single-dose Variation for a Test Batch.

This was re-examined in production scale by sample-taking prior to admixture of lubricant, after admixture (short optimum mixing time), and finally under the filling process itself. The results indicated that no changes in the dissolution rate were ascertained during the mixing process, but evidently during the filling process.

This may be explained by continuous influence or mixing in the capsule filling machine in connection with the use of magnesium stearate as lubricant.

Suggestions for Solution and Consequence of Those

Segregation in the applied capsule filling machine may be avoided by a change in the design of powder hop-

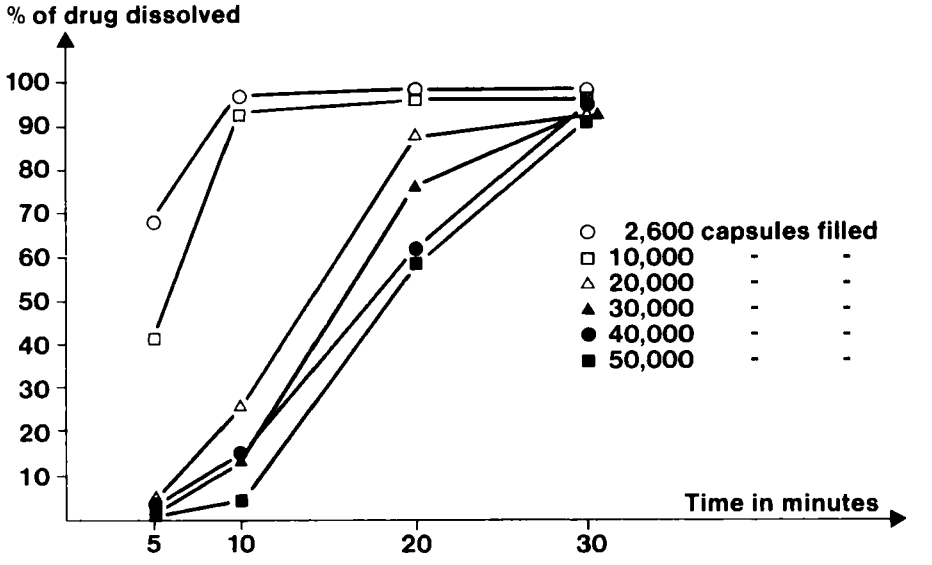

FIGURE 4

Dissolution Rate according to the Indicated Number of Filled Capsules.

per and mixer, so that mass flow of the granulate is obtained. A more simple and thus more economical solution would be to design an insert to the existing hopper, so that segregation may be avoided and the existing powder feeding system may still be utilized.

The problem with variation/reduction in dissolution rate as a result of a combination of continued mixing in the capsule filling machine and the use of magnesium stearate as lubricant entails several possibilities for a solution. Magnesium stearate is known to be sensitive towards mixing time in the tablet formulation [2, 3, 4]. Hardness, disintegration time, and dissolution rate are influenced substantially to a negative extent. Concurrently the mixing time is increas-

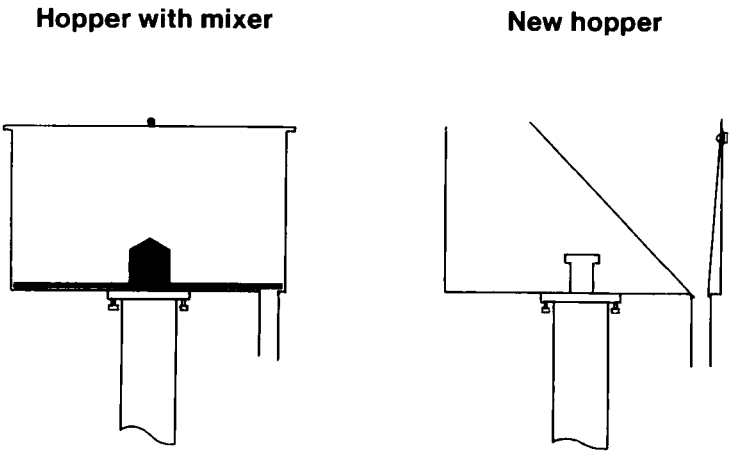

FIGURE 5

Cross Section of the Empty Powder Hopper. Leftward the Original Design with Mixer (Black) and Rightward the New Cone-shaped Insert.

ed as a result of a coating of the granulate constituents with a hydrophobic magnesium stearate coating. A change of the lubricant from magnesium stearate to sodium stearylfumerat has proved to be less sensitive to overmixing [5], but the re-formulation will require documentation on stability for the shelf-life of the preparation. This is a time-consuming and expensive process.

Another possibility for a solution might be to increase the number of dosators from 3 (max. 9,000 caps/h) to 6 or 12 (max. 30,000 caps/h) and thus increase the powder flow through the powder hopper and to reduce the contact time with the powder mixer. This would reduce overmixing, but would also be an unrealistic solution, as the delivery time for the mentioned extra dosators would postpone the marketing of the product.

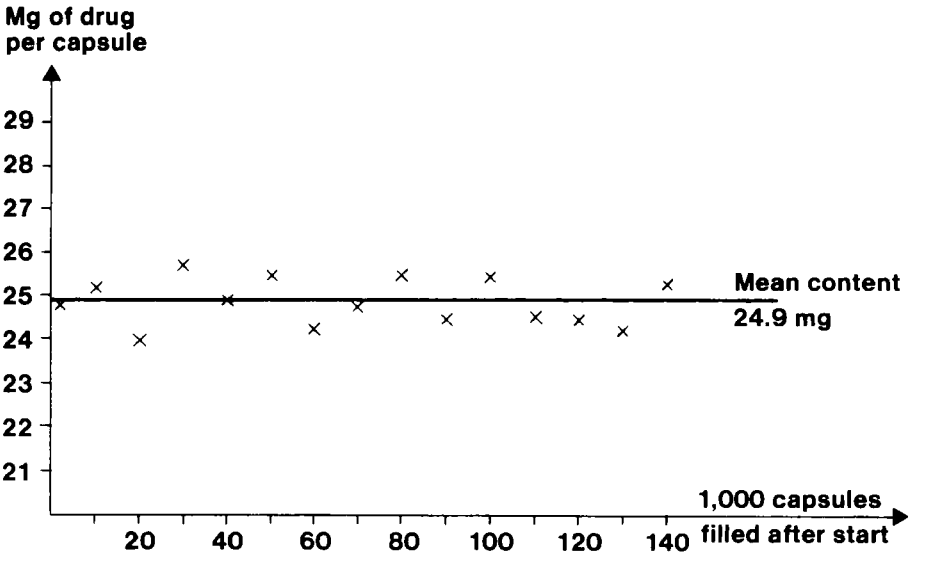

FIGURE 6

Single-dose Variation for Production Batch 221953. Filling Machine Equipped with New Hopper.

Alternatively a change of the capsule filling machine might solve the problem. Continued mixing is effected in the already mentioned powder hopper, but could also take place in the rotary powder hopper by the powder-depth controller and by the weir mixing device. It would be an obvious thing to hope that the main part of the continued mixing process was effected in the powder hopper, as the mixing would thus be avoided with the new hopper.

Choice of Solution

As the most simple, quickest, and most economical possibility for a solution for the mentioned problems it was chosen to remove the mixing blade and mount a

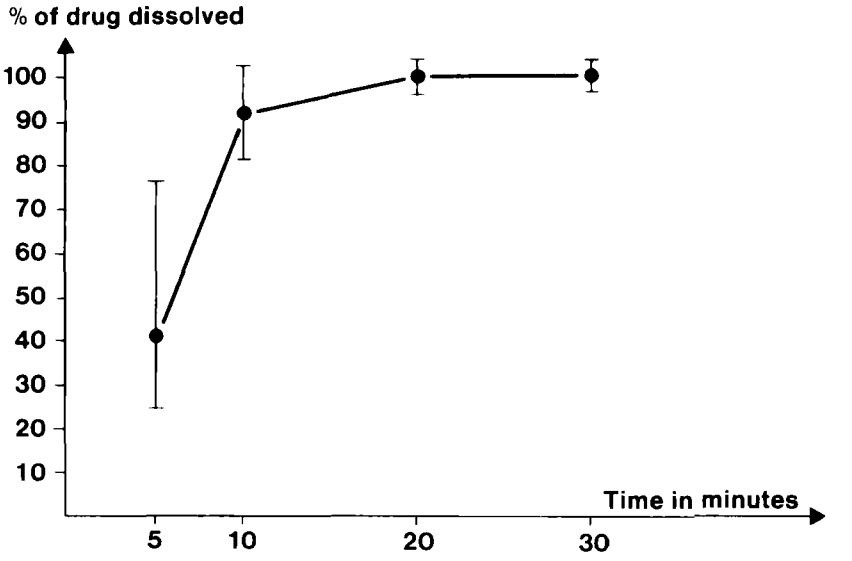

FIGURE 7

Dissolution Rate for 12 Production Batches. Filling Machine Equipped with New Powder Hopper. The Results Given as Mean Values with Range.

new powder hopper. If this could not solve the problems satisfactorily a re-formulation would be our second choice.

Implementation of Solution and Results

The outlined powder hopper was designed and mounted in the old powder hopper, and at the same time the mixing blade was dismounted. The reduced powder reserve volume did not present any problem, as a replenishing could easily be adapted in connection with weighing control of the filled capsules. The results will appear from figure 6 and 7, which indicate satisfactory single-dose variation and, as requested, a quicker dissolution rate of the pharmaceutical preparation.

CONCLUSION

It was considered to be proven that the original design of the powder hopper and the mixer on a mG2-G36/4 capsule filling machine (and maybe other makes) may result in segregation and overmixing of a magnesium stearate-containing preparation, which is filled on at a velocity of 6-9,000 capsules/hour. The physical design of hopper and mixer entails segregation, and the powder flow though the powder hopper is so slow that even at a rotation velocity of 1 rev./min. the mixing blade will result in overmixing in case of a sensitive powder mixture. The problems were solved by removing the mixing blade (minus overmixing and segregation) and mounting a cone-shaped hopper (minus segregation) in the original cylindric powder hopper.

REFERENCES

1. O. Wulff and T. Hansen, Medd. Nor. Farm. Selsk., 36, 1 (1974).
2. G.K. Bolhuis, C.F. Lerk, H.T. Zijlstra and A.H. de Boer, Pharm. Weekblad, 110, 317 (1975).
3. G.K. Bolhuis, A.J. Smallenbroek and C.F. Lerk, J. Pharm. Sci., 70, 1328 (1981).
4. C.F. Lerk, G.K. Bolhuis, A.J. Smallenbroek and K. Zuurman, Pharm. Acta Helv. 57, 282 (1982).
5. A.W. Hölzer and J. Sjögren, Int. J. Pharm., 2, 145 (1979).