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VALIDATION OF TABLET FORMULATION

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ABSTRACT

The process validation as applied today is a passive control intervention on tablet manufacturing. In this contribution an active process validation of tablet formulation is proposed. This type of validation is based on the physics of compression. A tablet formula is validated when the stochastic weight variations do not determine unacceptable variations of tablet properties.

INTRODUCTION

Validation seems to have become the must frequently used word by those involved in pharmaceutical production. It is an essential part of the GMP and its application is now required for product registration by health authorities.
The quality of the pharmaceutical product must comply with the requirements of safety, efficacy and equivalence. Many pharmaceutical forms cannot be guaranteed individually because control procedures destroy them. In this case, each form possesses a probability of quality that can be increased to a maximum level by applying the Good Manufacturing Practices to the productive operations.

Several definitions were given to validation indication that the field is still in evolution, particularly for its application to pharmaceutical forms other than injectables.

FIP defines the validation process as the assessment by systematic means that a productive process is confiable and repeatable.

The FDA defines the process validation as "a documented program which provides a high degree of assurance that a specified process will consistently produce a product meeting its predetermined specifications and quality attributes".

These definitions indicate that validation is a bureaucratic procedure because the systematic means are primarily process observation, document collection and verification that the values of the variables controlling the process remain into predescripted limits for an optimal product. Practically, it is a certification that the instructions of production were strictly followed. Therefore, a process validation so considered is suffered by the producer and involves many risks due to the lack of respect of manufacturing instructions. In this situation, process validation plays the role of certifying that the GMP were applied. It is a passive control intervention, very different from monitoring. The assurance of product quality has not been reached. Only a certain quality level submitted to stochastic negative events for product requirements has been obtained. Effectively, in a flow-chart of development of a pharmaceutical form, the validation is indicated at the end of production procedures.

In this contribution we propose to examine the transformation of the passive validation to an active process, by identifying the variables of the manufacturing process that determine the product properties and by working with them in order to assure that the properties of the finished product will remain into the safety limits. This requires basing the validation on scientific knowledge able to give the true guarantee of the product quality.

It is evident that several difficulties exist for the application of active validation to all manufacturing procedures, because not all the pharmaceutical forms possess well defined, sensible and critical controlling variables. However, it is certain that the evolution of pharmaceutical technology can allow the overcoming of these obstacles, particularly if it is accompanied by an effort of the producer to exert a practical application of the obtained knowledge.

Controlling Variables in Tablet Production

Pharmaceutical forms obtained by compression possess interesting process variables on which the active process validation can be constructed.

These forms, although not so critical, contain enough variability capable to render the performance of one dosage form different from another. The critical step in tablet preparation is the compression phase and all the preceding manufacturing operations are done for its betterment. These considerations indicate that the validation of tablet production must be based on the compression step. The process variable that governs the properties of each tablet of the batch is the applied compression force. The properties of the tablet that cannot be tested without tablet destruction are dependent on it. Therefore, active validation of a tablet formula is founded on the scientific knowledge of the "physics of compression".

Weight, Compression Force and Tablet Properties Compression Force Definition

Compression force definition is essential for understanding of its role in the tablet manufacturing process.

In pharmaceutical tablet production the compression force is the resultant of the resistance given by the powder to the volume reduction effected by the punch movement. It is evident that when

the matrix is empty, no force can arise. Therefore the compression force depends on the quantity and quality of the powder into the die. The amount of powder in the die governs the effective contact surface between the punch and powder (active surface), while the quality of the powder is expressed by the yield value of the material. Thus, the compression force can be defined as the product between the active surface and the yield value. The active surface of a powder under pressure is difficult to measure, but can be evaluated from the ratio between the true volume and the height of the powder bed in the matrix. This relationship establishes the dependence of the compression force on the weight of the tablet. It is on this relationship that systems for automatic weight control during production are based.

The tablet weight is the first variable that is controlled during the production of a batch and suffers the randomness of the production events, such as filling of the die. The literature mentions an exponential relationship between compression force and the tablet weight. The fact that this relation is not linear introduces a practical problem for the weight control systems of the tablets based on force measurement: at symmetric values of weight variation around the mean weight value, there do not correspond symmetric values of the force.

Once it is established that the compression force at a certaion level of powder volume reduction depends on the amonut of material into the matrix, it remains to define the relationship existing between the compression force and the mechanical and biopharmaceutical properties of the tablets. These relationships are usually empirical. In general, there exists a logarithmic relationship between the force and the hardness, whereas the relationship between the force and disintegration time is exponential. The relationships found between the force and dissolution time are more complex. Situations in which the dissolution time increases with increasing compression force are described;

however, situations in which this time decreases with increasing force have also been reported. This relationship is here described by a sigmoidal curve, on the base of the consideration that the tablet dissolution times are distributed between a minimum value (in general the value of the uncompressed powder) and a maximum value (non disintegrating compact). The experimental data fit well this model, when the results are treated according to the Weibull distribution curve. Knowledge of these described relationships allows the interpolation of tablet properties at all compression force values.

Variation of Weight, Compression Force and Tablet Properties

We have now all the elements needed for affirmation of the importance of compression force in the tablet manufacturing process. It is this importance that justifies the choice of compression force as the main variable of the process. Its control and the knowledge of its influence are the scientific bases of the active validation process proposed.

This affirmation derives from the consideration that during the tablet manufacturing the main variability is due to the stochastic weight variations. According to the previous definition variations of compression force applied to the powder derive from the weight variations. Since the tablet properties are dependent on the compression force, the weight variations determine tablet property variations. The most disturbing consequence is that admitted weight variations can determine not admissible properties variations.

Some practical examples illustrate the central role of compression force in tablet manufacturing.

Figure 1 shows two relationships between weight and compression force at two different compression levels, obtained by varying the weight of the powder into the die without changing the position of punches, for each one of the compression levels. Each

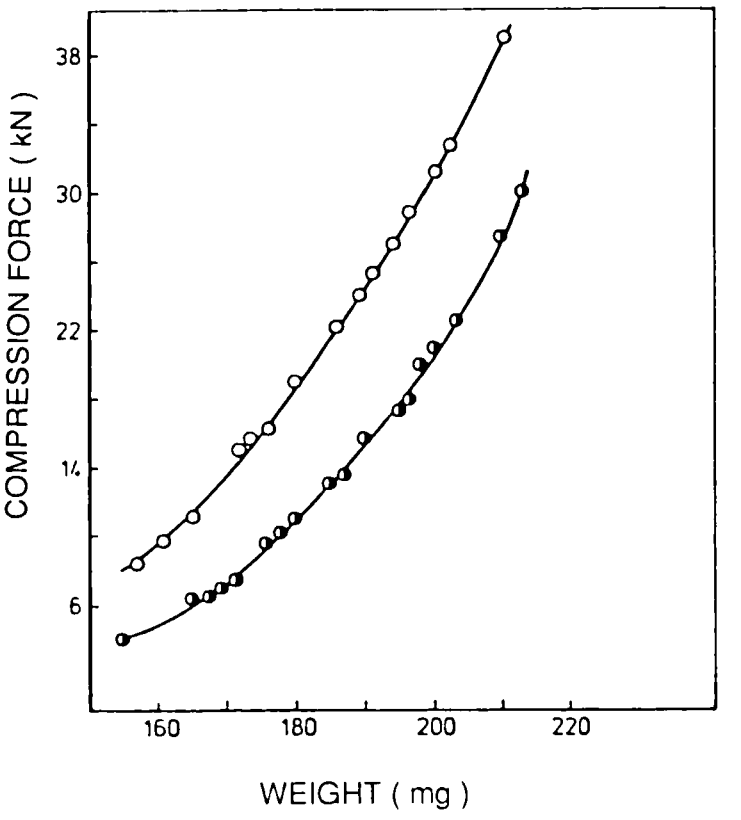

FIGURE 1

Relationship between weight and compression force for two series of tablets prepared at different compression levels (minimal distance between punches : o 161 10^{-2} mm ; o 192 10^{-2} mm). (adopted from reference No. 1)

relationship depends on the volume reduction level and becomes unique by substituting the apparent density of the powder bed the weight.

Figure 2 shows the relationship between weight and tensile strength of tablets obtained from different weights of powders compressed at three different values of volume reduction. Varying weights of powder determine different mechanical and biopharma-

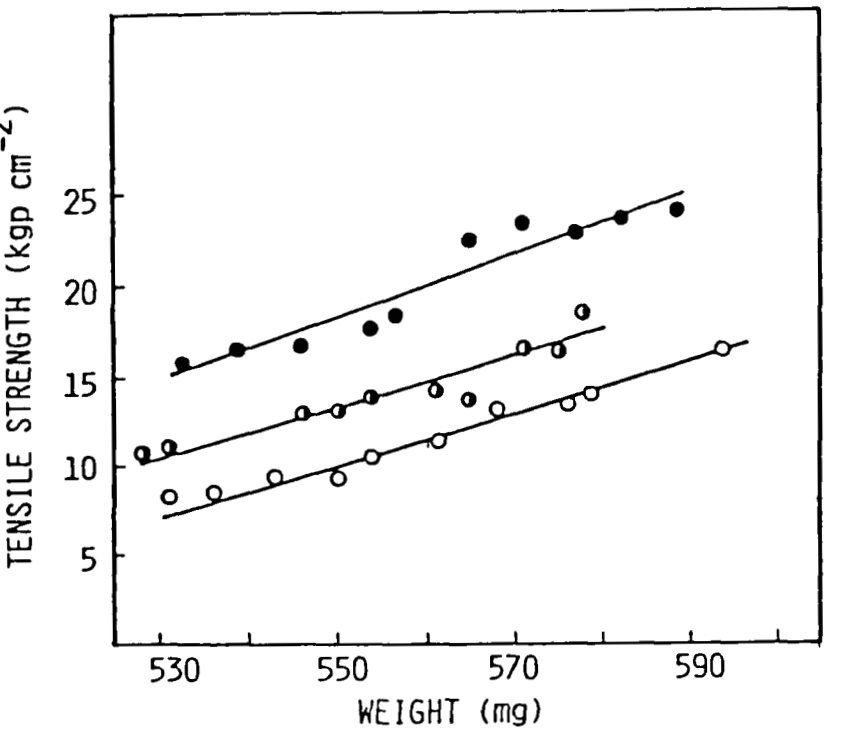

FIGURE 2

Relationship between weight and tensile strength for different amounts of powder compressed at three increasing values of volume reduction (o > o > o). (adopted from reference No. 2)

ceutical tablet properties, also if compressed at the same volume reduction (Figure 3). Again the relationship between the weight and properties is dependent on the value of volume reduction selected. However, if in the previous graphs the measured compression force is substituted for the corresponding weight, the three different curves become a unique curve (Figures 4 and 5).

On the other hand, when different weights of powder are compressed at the same compression force value, the obtained tablets show the same properties, independently of the different weight, provided that the properties have been normalized with

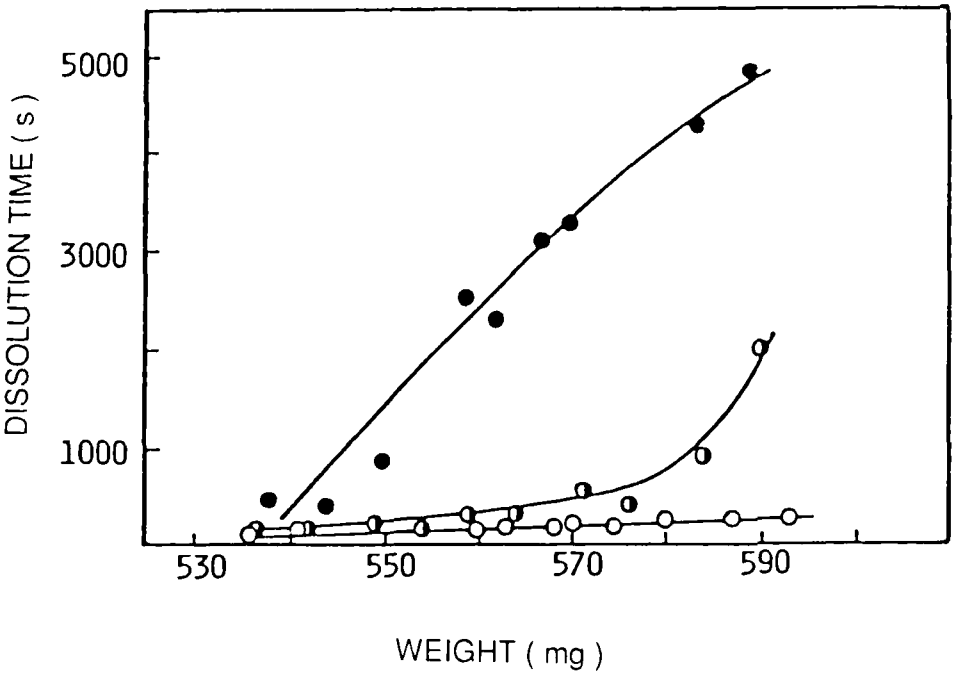

FIGURE 3

Relationship between weight and dissolution time (80% of drug dissolved) for different amounts of powder compressed at three increasing values of volume reduction (o > o > o). (adopted from reference No. 2).

respect to different dimensions of the tablets. This demonstrates that the compression force governs the properties of the tablets in a central manner (Figure 6).

Validation Procedure

We can see now how the tablet validation procedure develops, stressing that it is the tablet formulation that is validated and not the production apparatus.

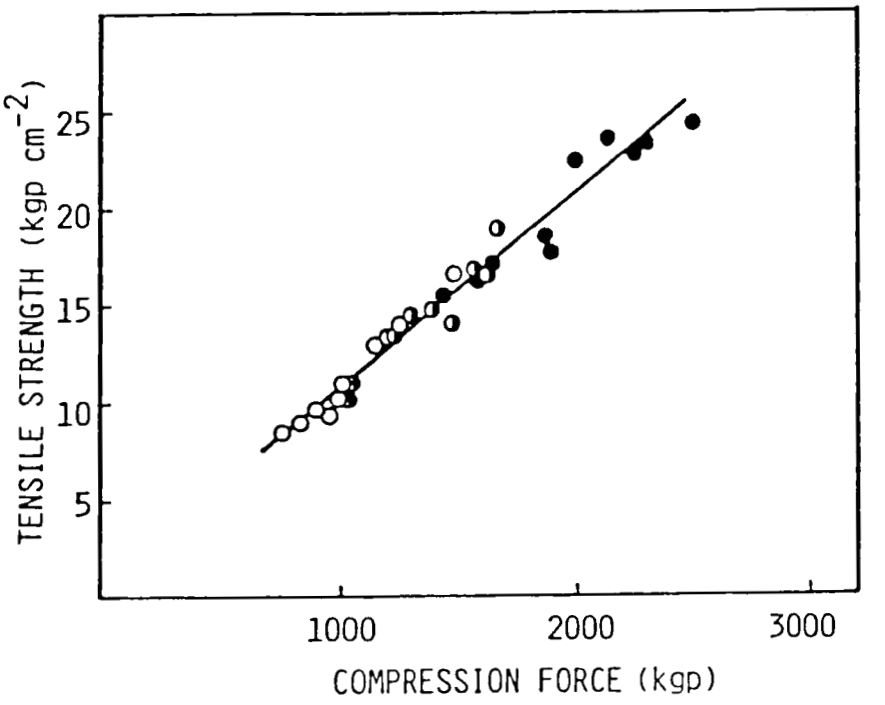

FIGURE 4

Relationship between compression force and tensile strength for different amounts of powder compressed at three increasing values of volume reduction (o > o > o). (adopted from reference No. 3).

The procedure is composed of three steps:

a) Sample preparation

Using an instrumented tabletting machine prepare a series of tablets (at least 20), varying the powder weight, without modifying the set of punches (volume reduction value), in a range between +- 20% of the mean weight. The series can be repeated at two other different volume reduction levels. On the tablets produced, measure compression force, weight, hardness and dissolution rate. Measure also the value of powder volume reduction (minimal distance between the upper and lower punches)

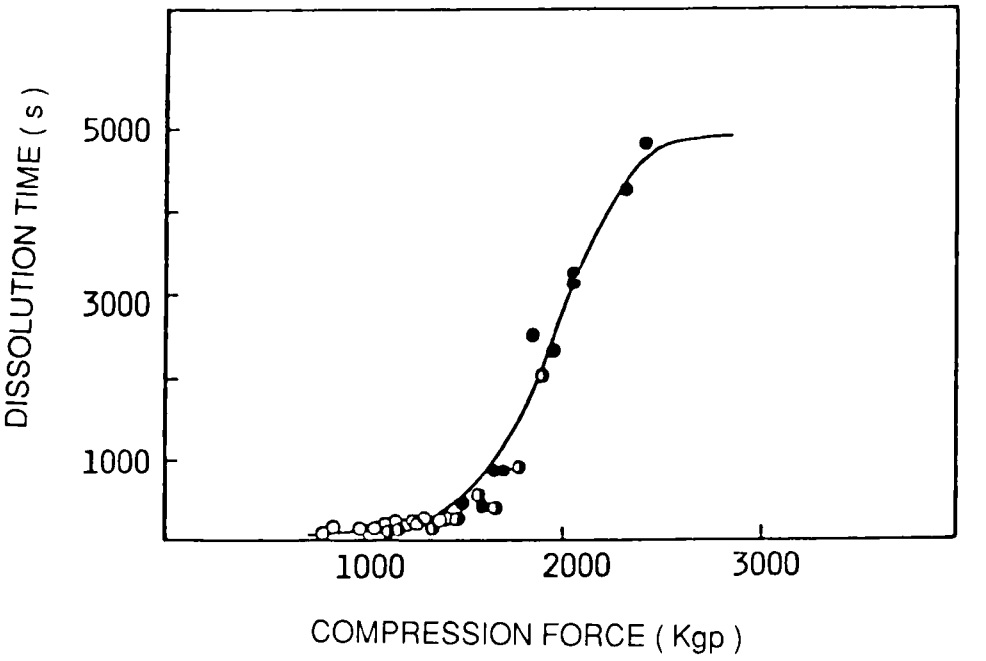

FIGURE 5

Relationship between compression force and dissolution time (80% of drug dissolved) for different amount of powder compressed at three increasing values of volume reduction (o > o > o). (adopted from reference No. 3)

b) Data treatment

Find the relationships between weight, compression force and tablet properties, for example fitting the logarithm of force versus weight/volume (apparent density), and the logarithm of force versus hardness and force versus dissolution time according to the Weibull distribution. The relationships determined allow the calculation for each tablet weight of the corresponding compression force, hardness and dissolution rate.

c) Prediction of the formula possibility (true validation)

The aim of this step is the determination of the possibility to have in the produced batch tablets exhibiting unacceptable properties.

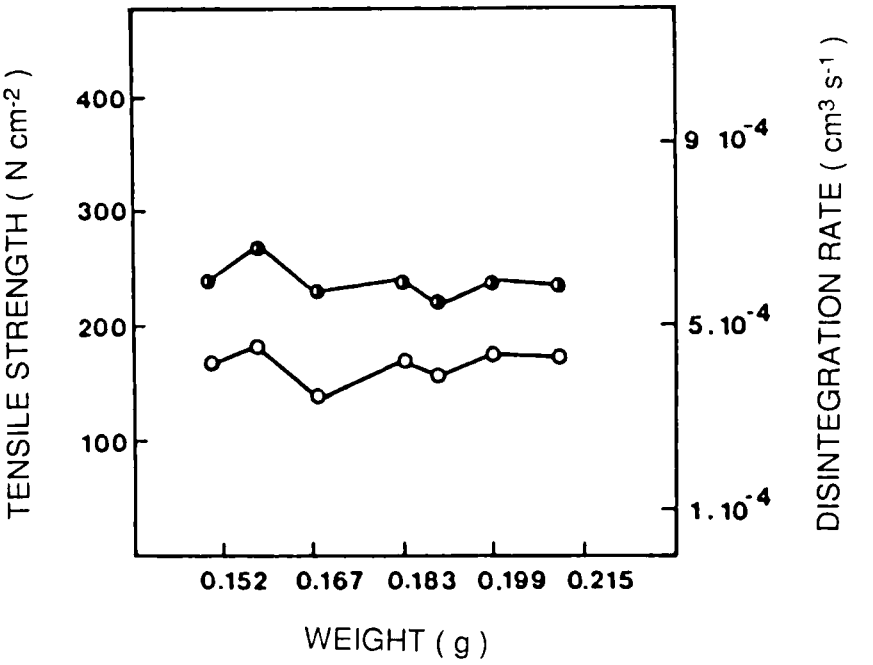

FIGURE 6

Weight, tensile strength and tablet disintegration rate for tablets prepared at same compression force (16.5 kN). (adopted from reference No. 1).

After the formula definition, the producer's choice is to use the compression force value with the mean weight of the powder in order to obtain the desired tablet quality. Generally this choice is a compromise between the mechanical and biopharmaceutical properties and determines the value of powder volume reduction. Once the weight limits around the mean weight are established, it is possible to calculate the corresponding limit values of compression force and from them the values of hardness and dissolution time. The probable composition of the batch in relation to the tablet quality, and in dependence of the possible weight variations, is then simulated. The results, possibly repeated for different force level on the mean tablet weight, show

the capability of the formula to bear the occasional weight variations.

CONCLUSIONS

A tablet formula is validated if the accepted stochastic weight variations during production keep the properties of the tablets of the batch within the prescribed values. This is an example of active validation, easy to accomplish for tablets because of the availability of a control variable such as compression force.

In this case to validate means to ascertain that the variations of compression force due to the weight variations do not determine unacceptable variations of tablet properties. The validation is now a guarantee attached to the formula, particularly for the possibility to monitoring the compression force for each tablet produced.

Finally, the presented procedure is an advanced validation concept because it works on the formula, in order to make it independent from the producing apparatus.

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