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Letter to the Editor

Filling hard gelatin capsules by the dosator nozzle system – Is it possible to predict where the powder goes?"

The transfer of powder into a capsule to provide a unit dose initially used the capsule shell as the measuring volume. The need to provide unit doses on an industrial scale necessitated the replacement of such systems with various procedures where a sample is removed from a bed of powder and transferred into the capsule body to provide the unit dose. As with industrial tablet production, the systems for selecting a sample of powder can be manufactured and adjusted with greater flexibility than a capsule shell. The various methods available to provide such a process are well described by Podczeck (2004). The ability to relate the properties of capsule formulations to their ability to be filled into capsules by the various manufacturing processes, has been the subject of several publications and the recent publications of Khawam (2011), Khawam and Schultz (2011), which claim to provide a theoretical insight and experimental support for their theoretical approach, are recent additions to these. There are certain problems with both theory and practice presented in these papers, which give me cause for concern, and before formulators rush to use the approach as an answer to their problems, I should like to outline my concerns.

First, I should like to consider the theoretical aspects of the work. The author claims that there are three settings that control the encapsulation process and illustrates these with the diagrams in Fig. 3. I cannot agree that these three dimensions are the only factors which govern the quantity of powder that can be removed from the powder bed in an industrial capsule filling machine of the dosator nozzle type. I agree that the height of the powder bed is vital but how can this be controlled and just what size of sample is removed is far from as simple as the author suggests, as I and my co-authors have shown in a series of publications on the topic (Jolliffe et al., 1982; Jolliffe and Newton, 1982, 1983; Tan and Newton, 1990a,b,c). While the author quotes the concept of the formation of a stable arch which we proposed (Jolliffe et al., 1980) to explain how a sample can be retained within a nozzle, even we realised that it was not the only factor involved in sampling and transfer. The author appears to be unaware of the reality of the machine, and the process. Their Fig. 3a represents an ideal situation. The nozzle is placed into the powder bed and a quantity of powder is confined within the dosator. Under ideal conditions, it should be possible to remove this volume of powder and if the bed is uniform in density, then a constant weight can be removed. We did in fact use such an approach to measure the bulk density of the powder beds in our capsule filling simulator (Jolliffe et al., 1982). The author suggests that it is always necessary to apply a compression force to the top of the powder bed to be able to remove a sample. It is clear from our work (Tan and Newton, 1990c) that this is not the case. A powder that could be sampled without applying compression was Microcrystalline Cellulose, one of the powders used by Khawam and Schultz (2011). What the quantity within the nozzle does represent is the maximum quantity that could be sampled. If the quantity of powder transferred is less than this, then there must be a loss of powder somewhere in the process. The possibility that the powder may not have the ability to from an arch across the bottom of the nozzle is one possibility. In this case, powder would be lost as the nozzle is removed from the bed. Dosator nozzle capsule filling machines were designed to apply a compression force to the powder within the nozzle and our original theoretical paper (Jolliffe et al., 1980) demonstrated the consequences of the application of a force at the top of the powder bed and the factors involved with providing a stable arch such that the powder would not fall from the nozzle when removed from the powder bed. Our subsequent papers however illustrated that it was not quite as simple as this and the quantity of powder removed was often less than that which was defined by the volume provided by the dosator dimensions. Increasing the amount of compression often resulted in a decrease in the amount of powder transferred (Jolliffe and Newton, 1982, 1983; Tan and Newton, 1990a,b,c). At the time we proposed that this was due to powder adhering to the wall of the nozzle, providing a reduced diameter and/or loss of powder behind the piston tip. In hindsight and looking at the theoretical approach of Khawam (2011), there may also be a further reason for the failure of the system to sample the quantity of powder available.

Khawam (2011) illustrates the two ways in which compression can be applied (Fig. 3b and c) and proposes equations to be able to quantify the amount of the powder which can be sampled, by relating to the heights of the powder bed and the piston. They also suggest how the height of the piston can be calculated for various stages of the process. The equations they propose for the calculations cannot be correct for they do not take into account the fact that the powder cannot be reduced in volume to the level they illustrate because to do so, the powder bed would have to have a greater density than the powder itself, which is clearly impossible. In our work we never used a compression ratio greater than 0.5. This would imply a reduction in volume in the nozzle of 50% of the original, which translates to a doubling of the density of the sample. For the system we studied, this would not exceed the apparent particle density of the powder within the nozzle. Even here, we often found that increasing the compression ratio lead to a reduction in capsule fill weight. The equations proposed by Khawam (2011) need to provide a limiting value beyond which further densification cannot occur. In terms of the dosage form itself, the whole objective of making capsules is not to provide a unit dose that is a tablet, but a powder structure that will readily disintegrate when swallowed.

What must also be considered is that the dosator nozzle system is not a 'stiff' machine, i.e., the piston movement is controlled only by the movement of the machine. The nozzle must be able to move into the bed and yet it must not touch the metal tray holding the powder bed. This provides a system, which cannot prevent that a loss of powder between the bottom of the feed hopper and the nozzle will occur. In addition, the system is fitted with a spring which

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as well as providing a mechanism to ensure that the piston returns to its position once the powder plug has been ejected, will also restrict the force that can be applied to the powder bed, to avoid damaging the piston. The forces that are applied are considerable less that those involved in the preparation of tablets as can be seen from the values obtained by studies involving instrumented capsule machines and simulated capsule filling systems (Armstrong, 2004). The compression of a long column of powder, such as in a capsule, is far more difficult than that of tablets, where the diameter or length is usually greater than the thickness. It would seem to me that, the loss of powder by coating of the nozzle and loss behind the piston are insufficient to account for major losses. A further source of powder loss is necessary, one which might also provide a possible reason why the equations of Khawam (2011) appear to give relationships between theoretical and experimental results. A solution is that the powder when subjected to compression is pushed out of the confines of the nozzle into the powder bed. This would allow the piston to move down into the nozzle, without further densification of the bed leaving the bed at some limiting density associated with the powder and the machine settings. The ability to predict how much powder can be lost by the application of increasing displacement is well beyond the current theoretical knowledge. Some experimental evaluation might give an empirical solution, but it would have to be done for each powder formulation and a wide range of machine settings of the position of nozzle and piston. Why would anyone want to provide a capsule fill weight that was less that 50% of the weight that was possible? From our studies of dosator nozzle filling, there appears to be an optimum setting of compression, and its value and range varies with the formulation. There is no attempt to feed the concept of an optimum setting into the theoretical approach presented by Khawam (2011).

My second concern with the papers is with several of the terminologies and some of the experimental procedures. Bulk powders are an unusual system in that they can exist in a wide range of configurations some of which have a degree of rigidity and yet in some circumstances, they can flow like a liquid. There are standard terms used to describe and define powders and their structures e.g. ASTM D 653, and bulk density is certainly one. There are also various standards and procedures available, for example, for measuring bulk density and defining the range available for bulk powders. These include standards provided by The American Society of Testing Materials (ASTM). I should have thought it is important in work with powders to use such standards, yet the authors do not use these procedures but invent their own and even then fail to describe them in an adequate manner to allow the experiments to be repeated. The standards for determination of bulk density by tapping all give the distance of fall, and how to determine the end point for the minimum and maximum tapped density. These values are used to calculate the Carr Index (ASTM D 6393-08). It is important that workers should use standard procedures to allow comparison of results. The authors refer to bulk density in the powder bed of the capsule machine but do not say which value this is or how it was measured and how it was maintained once a dosator nozzle had removed a sample. We are told measurements on the machine "were accurately achieved experimentally", but not provided with details about the callipers used and the level of accuracy they can provide.

In Khawam and Schultz (2011) the particle size distributions of the formulations are determined with sieves of differing mesh sizes but which mesh standard was used is not stated. Different standards have different mesh dimensions. One powder sample is shown to have 92.8% of particles less than 63 μm. This has very limited value and requires an alternative procedure to provide an improved characterisation of the range of particle sizes.

There is no description what so ever as to how the capsule filling was performed. This is totally unacceptable. The forming of the bed is critical as its method of reformation after a sample has been removed. It is not clear how nozzle piston heights were set and what procedures were used to arrive at the various stages at which the measurements were taken. Was the machine operated under manual or electrical control? It is particularly important to know how the nozzle insertion distance was set as this is probably the easiest way in which powder can be lost from the nozzle during piston compression. Some of the machine settings are totally inappropriate, both for assessment of 'powder flow factor' and capsule filling. It would not be possible for the piston to travel the distance set due to the quantity of powder within the nozzle (e.g. setting A9 would require a 7.5-fold densification of the sample). That piston heights associated with this setting cannot occur without the loss of powder from the confines of the nozzle was discussed earlier. The loss of powder from the nozzle also casts doubt on the values of "powder flow factor F and pre-densification factor $f_1(p)$" described by Khawam (2011). It is clear from the settings given in the paper by Khawam and Schultz (2011) (Tables 3, 4 and 9), that these values are associated with not only powder flow, powder compression and spring characteristics, but also with loss of powder from the dosator, which is very dependent on the machine and its settings. The use of a machine to measure fundamental properties is always fraught with problems.

We are not told how the capsule weights were determined and why only 7 were weighed when the EP requires 20 capsules and the USP requires 30 capsules. Tables 11 and 12 provide what I assume are supposed to be standard deviations for the piston height values based on 2 values. I am sure the computer might provide such values but they have no meaning whatsoever.

I find it very disappointing to find such poor science in the literature but am grateful to the authors for providing me with the opportunity to think again about some of the experiments my research students and I conducted some years ago, allowing me to identify alternative solutions to our findings.

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