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Letter to the Editor

On the performance qualification of hypromellose capsules

Dear Sir,

Two papers recently published in the journal, "Performance qualification of a new hypromellose capsule. Part I. Comparative evaluation of physical, mechanical and processability quality attributes of Vcaps Plus®, Quali-V® and gelatin capsules" (Ku et al., 2010) and "Performance qualification of a new hypromellose capsule. Part II. Disintegration and dissolution comparison between two types of hypromellose capsules" (Ku et al., 2011), gave us some reason for concern. We should like to make the following comments on various aspects of the two reports.

In Part 1 the authors report that one reason for abandoning the use of Quali-V® hard shell capsules in their company was their lack of gloss, compared to gelatin capsules. It is correct that hydroxypropyl methylcellulose ("hypromellose", HPMC) films of whatever composition have a less glossy appearance than gelatin films. What would have been interesting to the reader would be the difference between glossiness of hypromellose shells 1, 2 and 3, but in neither part of the publication are we given any more details on this. Should we hence assume that there was no difference in glossiness i.e. shells 2 and 3 were equally dull? Glossiness can be quantified using a glossmeter, which measures specular reflection and reports the results in gloss units. As this report is written by the makers of hypromellose shells 2 and 3, reporting gloss units for the different shells would have added credit to their observations on the differences in glossiness between the types of capsule.

In Table 1 of this paper, the authors identify the manufacturers for hypromellose shells 1, 2 and 3. However, under Materials, Section 2.1, two further batches of shells are mentioned. For the second the trade mark LiCap® identifies the manufacturer (namely Capsugel), but there is no mention of the manufacturer for the "reference" hypromellose capsule batch. If the experiments reported in the papers were undertaken on an unbiased and scientific level, there is no reason for not naming the manufacturer.

There are a number of scientific issues related to how the authors have reported their experimental procedures. For example, under Section 2.3 readers are told that the capsules were "cut at the closure to expose the cross-section between the body and cap" but the tool used is not stated. The cleanliness of a cut depends on the tools used or their sharpness and handling, and if not correct or inappropriate can result in rough edges, ripping, smearing etc. It is also worth noting that storage of the capsule shells can lead to expansion or contraction resulting in a wider or narrower gap. As it is unlikely that the various capsule shell batches had been produced at the same time, storage effects cannot be ruled out when reporting such results, even if the capsules had been stored in their original unopened packages. Under Section 2.5, Table 2, results for the relative humidity of the storage air in desiccators are reported, but the method of determination is missing.

The authors report the methods for machineability testing under Section 2.7. They state that they have used a "Bosch H&K 400" machine. Such a machine does not exist. Robert Bosch produce a Bosch GKF 400 machine, while H&K refers to "Höfliger & Karg", a machine manufacturer no longer in existence. Was a modern Bosch GKF 400 or an old H&K 400 machine used? This will have had an influence on the capsule shell performance during opening and closing, plus while the modern GKF machines achieve tamping forces between 40 and 100 N only, the old H&K machines used much stronger springs enabling forces of 400–500 N to be applied, i.e. forming denser plugs, which will have had an effect on powder contamination in the gap between capsule cap and body, yet the tamping force has not been stated. It is also not clear why they used a dosing disk of 15 mm height for size 0 capsules, which will have resulted in under filling and hence larger variability of weight related to powder behaviour rather than capsule shell properties. The statement for the tamping pin settings is also dubious. In modern Bosch GKF machines, the graduations on the pin holders are in mm, being zero at the bottom of the powder bowl and ranging up to 30 mm at the top i.e. in the extreme, the tamping pins would be penetrating the dosing bores completely down to the bottom (zero setting), or their downward movement could be stopped, for example, at 10 mm above the 15 mm dosing disk. As has been shown previously (Podczeck, 2000) the pin setting has an important influence on the plug formation and while the first 3–4 pins should penetrate the dosing disk (pin 1 should have the deepest penetration, and any following pins less than the previous one to overcome fill weight variability due to inhomogeneous powder flow and bed height variations), the last tamping pin should be set so that it is flush with the upper surface of the dosing disk when at its lowest position to ensure a reproducible plug length. The authors state that they used settings of "19–17–12–12–9", without explaining what these numbers refer to, which under the assumption that they have indeed used a Bosch GKF 400 machine could mean that tamping pins 1 and 2 did not penetrate the dosing bores, whereas further tamping pins penetrated the dosing bores, the 5th pin by as much as 6 mm. The plug length might hence have shown considerable variability due to incorrect machine setting adding to variability in fill weight due to powder properties rather than capsule shells.

One could condone a bad description of the experimental procedures to some degree if the description of the results and their discussion were flawless. However, this is not the case. Under subheading 3.1 the results from the SEM studies are reported in Figs. 2 and 3 and a summary of the findings in Table 3. In this table it is claimed that shells 1 and 3 have a "rough edge", whereas only shell 2 (i.e. their own new shell) has a "clean edge". The properties of the edges can be seen in Fig. 3, and we find that in fact shell 1

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is the only shell with a clean edge, whereas the SEM pictures of shells 2 and 3 show some degree of roughness; notably shell 2 if one follows the gap from the yellow arrow mark upwards by about 30°, from which point onwards–upwards the gap is uneven and roughness of the edges is clearly visible. In Fig. 4 the equilibrium moisture content of shells 2 and 3 is compared. The first thing to note is that there are no error bars provided, which is not acceptable, especially as there is no indication of the number of replicates stated under Section 2.4. Also, without the knowledge of the moisture content of the capsules prior to the storage in the desiccators the plot has little meaning, because degree and kinetics of sorption and desorption of moisture depend on the moisture present in the samples.

In Section 3.4 the authors make the case that if capsules are weight-sorted after filling, then some capsules with fill weights within specification will be rejected due to the shell weight, while others with fill weights outside the specification will be accepted. Potentially, this might become a problem, but two counterarguments might be given here: (1) Assuming that due care has been given to the development of the powder formulation, larger variability of the capsule fill weight due to filling issues related to powder flow or lack of arching should not occur. As such, for a 250 mg fill weight as tested here, the maximum variation of the fill weight without the shell should be comparatively similar to that achieved on tablet presses i.e. less than 5% (i.e. ±12.5 mg). However, in recognising that empty shells add to the variability of the final product, Pharmacopoeias permit up to 10% variability for the chosen fill weight (i.e. ±25 mg). Only when considering the extreme value of 15% that the authors quote for shell 1 to have occurred (i.e. ±13.5 mg) would a fill weight outside Pharmacopoeial limits theoretically be possible. (2) However, the current standard practice is to use in-line systems to control the filling operation. Most of the latest automatic filling machines control capsule fill weights by using a balance connected to a computer system. The gross weight is measured and a mean empty capsule shell weight, determined according to a standard procedure, is subtracted. Samples are being taken continuously and there is a feedback mechanism to the machine. On dosator machines, for example, the feedback loop resets the position of the piston to adjust the weight to target value, while in Bosch tamp filling machines, the pressure in the tamping heads is adjusted to increase or decrease the amount of powder pushed into the dosing bores. As all the filling experiments in this paper were undertaken using size 0 capsules and a fill weight of 245 mg, similar studies under true manufacturing conditions should not therefore result in any significant differences between the capsule shells tested. The authors write "... shell 1 had been shown to have a relatively large weight variation, making it difficult to achieve weight uniformity, especially for low fill weight formulations where this effect of shell weight variability is exaggerated. As a consequence, formulations were necessarily diluted with more filler to have a higher fill weight to minimize the impact of shell weight variation on the total weight." This statement is dubious, as nowhere in the report have the authors used less than 245 mg of powder or smaller capsule sizes to compare these three types of shells. Did they try to under fill size 0 capsules even more by using, say 100 mg or 50 mg? Of course, when using smaller shell sizes and considerably smaller fill weights problems caused by shell variability might become more obvious, but the authors do not provide any data that could substantiate their claims. Assuming that a hypothetical inhalation product of 25 mg is to be filled into size 3 capsules, their own shell 2 with a weight variability of ±6 mg (see Table 4 in Part 1) would result in rejection of the final product due to excessive variability in weight. However, the vendor of shell 1 capsules can, as noted by the authors (2nd paragraph, Section 3.4), supply capsules that have been sorted for weight to ±2 mg, demonstrating that it is possible to fill even small amounts of powder into hard shell capsules thereby meeting the requirements of uniformity of mass without the need to dilute formulations.

The machineability trials lack consistency (i.e. not all three types of shells were studied on all three machines and machine speeds), but the main problem is the lack of repeats. These tests have been done with one batch of each type of shell only. Batch to batch variability could significantly affect the outcome of these tests. Furthermore, the authors failed to state the manufacturing date of the shell batches and how they had stored the capsules from purchase to use. Even in fully sealed bags the storage time and conditions will affect the machineability of the capsule shells, and it is hence unknown whether the differences reported in Tables 6–8 are due to the quality of the shells as such, or their age or storage conditions. The authors should have tested several batches of each type of shell and provide the data in Tables 6–8 with means and standard deviations. As it stands, the difference between 6.1 and 8.7% is not necessarily significant unless shown to occur consistently between batches of similar age and storage. What is even more disturbing is the anecdotal report from the floor operators. Such comments might be acceptable in commercial reports, but in a top scientific journal such as the *International Journal of Pharmaceutics* such comments should not be made and the authors should have stuck to factual evidence to make their claims. Why did they not provide photographic evidence of powder adherence to the shells after filling? Whether or not there are further improvements to shell 2 in the future remains to be seen and cannot be used as evidence for the quality of this product.

While it is unquestionable that the use of HPMC shells is important in the prevention of cross-linking and related problems in shell dissolution, Fig. 8 is unacceptable. It is very difficult to identify the time points at which samples have been taken, and a scientific report of dissolution data should show the mean and standard deviation.

In Part 2 there are also deficiencies. The Materials and Methods section lacks information. The authors seem to assume that the reader will have read part 1 of this publication first, but from our knowledge as teachers we know that many readers will not always follow the logic that experienced researchers would assume to be present. It would not have been too much trouble to repeat the details of the batches to ensure that readers have required details at hand. The authors list, however, the composition of each type of shell without giving a reference to the source from which they took the information and this is technically plagiarism. This is troublesome not only because of readers being unable to check the data, but especially because any reader without knowledge and experience in capsule shell manufacture will now be given the impression that HPMC shell 2 and gelatin shells are free of water. The authors should have considered the wide audience of the *International Journal of Pharmaceutics* and its aim not only to report on research but also to educate the young and inexperienced.

Under Section 2.2 they mention the excipients used in their formulations, without standard provision of manufacturers, grades, batch numbers, particle size distribution, shape, bulk densities, etc., but most importantly, without giving the actual % of composition in the various formulations. They also fail to provide details of the steps to manufacture the formulations. All these unknown factors will have had tremendous effects on the dissolution test results and hence what follows in this report is questionable.

The authors conducted a shell rupture time determination test (Section 2.3). They filled the capsule shells "loosely" with "180 mg diphenhydramine hydrochloride" and monitored "UV absorption of the dissolution medium". From this the reader might assume that the idea of this test is to detect the first amount of drug dissolved and released through an opening of the capsule shell. However, this is questionable, because theoretically water molecules are small enough to diffuse through a swollen, but still intact HPMC shell

(there are no literature reports that would disprove this hypothesis), dissolve some of this highly soluble drug substance, and the dissolved drug molecules might diffuse through an intact shell into the dissolution medium triggering a false signal due to the high sensitivity of the on-line system used. Also, the authors have not revealed how they managed to stop the capsules from floating (did they use a sinker?) in the dissolution medium, plus the description of the composition of the dissolution media is missing. For example, phosphate buffer pH 6.8 can be produced with different ionic strengths, which will have an important effect on the shell dissolution times (Tochio et al., 2002). The reader might assume that the buffer strengths used in this test are similar to those used in the dissolution tests, but this is not clear from the text.

It is always disappointing to see authors quoting references without trying to identify the origins of a methodology that has been used in these reports. This paper is another example of such inadequate use of secondary references. The ball bearing test should have been contributed to Boymønd et al. (1966) and in its modified form to Jones and Cole (1971) before extracting results from the paper by Chiwele et al. (2000). The authors present an "improved method to determine rupture/opening time of capsule shells" (see Introduction, last sentence); they would feel upset if in a few years time their method was attributed to other workers.

The authors claim that the ball bearing test has several disadvantages, for example, that the testing device does not resemble a conventional USP disintegration or dissolution tester and thus requires special equipment, and that the steel ball bearings will accelerate shell rupture due to their weight. Neither the USP disintegration nor the USP dissolution apparatuses are designed to enable easy determination of the time of first rupture of a capsule shell, and the USP monographs do not instruct the users to make an attempt to do so. The ball bearing test requires simple laboratory glass ware, a stirrer, a water bath and a strip of metal with preformed holes of defined dimensions. The ball bearing test was reported as a comparative, not an absolute test, and thus potential acceleration due to the weight of the steel ball bearings will cancel out. Similarly, their "improved" test can only be used as a comparative test method, because the physico-chemical properties of the drug used as tracer molecule will affect the shell dissolution results.

The authors report that "HPMC shell 1 tends to open up somewhat faster than HPMC shell 2", referring to Fig. 1. Fig. 1 shows the capsule rupture times as columns, their height being the mean value, and error bars, and while unfortunately no raw data are available to perform a numerical data analysis, it can be noted that, when comparing the two types of shells in each liquid tested, for three media (0.1 M HCl, pH 4.5 acetate, 1% SLS) the error bars of the two columns do not overlap at all, but they do overlap with each other but not across the mean values for pH 6.8 PBS-Na. In charts, in statistical terms a complete lack of overlap of error bars is usually seen for an error probability of $p < 0.001$, while the lack of overlap of error bars with the mean value of the other set of data corresponds to $p < 0.05$ (Adam, 1971). The hydration and dissolution time of the new HPMC shell 2 is thus not only "a little longer", but HPMC shell 1 ruptures significantly faster than their new HPMC shell. Fig. 1 implies that the rupture times of shell 2 are double of that of shell 1. In this context it is also not clear what the authors mean with a "more uniform HPMC film", but one might presume that they were thinking of their new HPMC shells to have a more homogeneous composition of the film due to the lack of gelling agent.

In Table 1 the authors list the solubility of the drugs tested in the dissolution studies in the test liquids they have used, and they also provide the dose per capsule. In the accompanying text they state that in some cases surfactants had been added to enhance solubility. The problem is, however, that for compounds 6–9 they did not test under sink conditions. Sink conditions are maintained as long as the dissolution of the complete dose of the drug does not result in more than 10% of the saturation solubility i.e. the sink ratio should be above 10. Dissolution results for compounds 8 and 9 will hence be particularly affected by the limited solubility of the drugs.

In Fig. 2 the authors compare the dissolution of compound 1 from the various hard shells and in the text they state that "for HPMC shell 1 capsules the dissolution profiles look like that of a controlled-release dosage form". Later in the text the authors contribute this to an interaction of the drug with the carrageenan in HPMC shell 1. We disagree with this explanation, as the amount of carrageenan in the shell is too small to form an effective diffusion barrier for the drug molecules. The authors filled their capsules manually (see Section 2.4) with formulations of their drugs of compositions that they did not disclose to the reader. In the Materials section the reader is informed that amongst others crospovidone has been added to some formulations. While crospovidone is reported to be chemically compatible with most organic and inorganic pharmaceutical excipients, it has been proposed that in aqueous media crospovidone could form molecular adducts due to the presence of some gelling enhancing compounds (Kibbe, 2009). As HPMC shell 1 contains potassium chloride and carrageenan as gelling agents it might hence be possible that such adducts were formed leading to increased gel formation of the excipient and thus slower release of the drug. More importantly, however, is that carrageenan can form an insoluble complex with a number of polymers similar in structure to crospovidone (Singh, 2009), which would explain the shell remnants shown in Fig. 3. These issues should have been considered when formulating the drug and should have been avoided. This also applies to the findings reported for compound 2 and clearly demonstrates that it is insufficient to consider drug properties only and to neglect the significant influence of excipients on drug release from solid dosage forms, as has been done in this study.

The data presented for compound 3 (Fig. 5) are unhelpful to the reader. Obviously, if there are any differences between the drug release profiles then these would have to occur in the first 15 min of the dissolution test, which consequently should have been repeated with more frequent sampling. That they have not found the same delayed drug release for compound 3 has nothing to do with a change in paddle speed — indeed this should have enhanced any differences — but is most likely due to the use of a different formulation with different excipients than used for compounds 1 and 2, but as the authors failed to disclose the excipients, a final judgement is not possible.

In Section 3.2.3 the authors discuss "trends" in data seen, where instead a thorough statistical data analysis should have been performed. For example, while the authors claim that at 15 min (Table 4) the amount of drug dissolved from HGC shells is less than that from HPMC shell 1; statistical comparison would have shown that in fact the degree of dissolution was similar. On the other hand, the amount dissolved from HPMC shells 1 and 2 is statistically highly significantly different ($p < 0.001$) which is much more than just a "trend".

The authors are very critical of the large variability in the dissolution times of shell 1 observed at 15 min for compound 6. Again, their discussion focuses on the properties of the shell alone and its interactions with phosphate buffer, while it might very well be possible that the formulation had a major influence on the findings. After all, the standard deviation for 15 min for HPMC shell 2 (potassium buffer) is also comparatively high. As it was known that HPMC shell 1 dissolution depends on the ionic strength of the phosphate buffer (Tochio et al., 2002) a more sensible choice of dissolution medium would have resulted in a more appropriate comparison of the dissolution properties of the capsules; there is no need to ban the use of potassium phosphate buffers as such. What the authors have not explained is the reason for this in comparison to HPMC

shell 1 and the large standard deviations obtained using shell 2 for compounds 8 and 9 (Figs. 9b and 10).

In Section 3.2.4 the authors attempt to justify the unusual, almost sigmoid-shaped appearance of the dissolution curve obtained for compound 8 using HPMC shell 2 (Fig. 8b) by calculating "initial rates of dissolution". They base their calculations on one data point at 15 min and one estimated point (i.e. the opening time obtained using a very different drug substance). However, the calculation of a rate requires a lot more data points and the experiments should hence have been carried out with more frequent sampling up to the 15 min time point. This could have confirmed the estimate of the opening time to be valid for this particular formulation and would have enabled the identification of the correct release law, which is essential when calculating rates. It is unlikely that the release law was zero order, which is what the authors have assumed by using a two-point approach.

1. Conclusion

In this letter we have pointed out the many pitfalls that can arise in the comparative testing of capsule shells and formulations. We hope that our comments will be of interest to readers of the *International Journal of Pharmaceutics* with a similar interest in the development of hard capsule formulations and desire to switch from the classical gelatin hard shell to a modern alternative.

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