DISSOLUTION OF OIL **SOFT GELATIN CAPSULES (SCG)** FROM FORMULATION TO ANALYTICAL DEVELOPMENT

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ABSTRACT

Quality by design has proven to be a cost-effective approach for the pharmaceutical development and manufacturing. In this regard, this article brings a case study of the application of the experimental design and the statistical treatment to evaluate the dissolution of soft gelatin capsules in the stages of product and analytical development.

INTRODUCTION

One of the most frequent issues in product development of soft gelatin capsules is dissolution performance. Gelatin is a protein containing terminal reactive amino o carboxylic groups which proceed to crosslinking reactions, leading to the formation of insoluble high molecular weight chains that decrease or limit the release of the fill content of the capsules to the dissolution media. The progress of this reaction will depend on the content of high molecular weight chains, the content of free groups to react in gelatin or the reactive impurities in excipients. In product formulation, some properties of the gelatin such as the gelatin type and the molecular weight have been identified to determine the dissolution of the product. In regards to the gelatin formulation, some relevant variables are the type and content of plasticizer.

Gelatin type. Due to the acid or basic hydrolysis, the aminoacid composition varies being the amino form for glutamine and aspargine in type A to glutamic and aspartic acid in type B [1]. These differences determine a different isoelectric point for each type, being in the basic range for type A (**from 8 to 9**) and in the acid range for type B (**from 4.8 to 5.5).** Besides the compatibility of gelatin with acid or basic APIs, it has been reported that at the isoelectric point the swelling is minimum and the gel strength is maximum, then these are important considerations to formulate gelatin for capsule applications as well as for evaluating the performance in the dissolution test, since in the most of the dissolution media (buffered solutions) both gelatins will be in their acid form [1].

Molecular weight. Commercial gelatins are highly heterogeneous in molecular weight distribution since they are commonly obtained by mixing different bloom fractions. In addition, it has been shown that the higher the molecular weight is, the higher the crosslinking potential will be, being this relation based on the content of macrogel molecules of the material.

Type and content of plasticizer. Plasticizers act as mechanical stabilizers, since they increase the elasticity and reduce the stress related to shrinkage of the shell during the encapsulation and the drying process. Selection criteria of the type and concentration of plasticizer in the shell is based on the features of the product (**fill content, size, shape, end use**) as well as the storage conditions. Most common plasticizers used in formulation of softgels are polyalcohols or mixtures and act as direct or indirect plasticizers whether they interact specifically to form the gelatin network or act as moisturizing agents. In each case, the migration process between the fill content, the shell and the environment will be different as well as some quality parameters of softgels such as disintegration, dissolution, hardness, mechanical resistance and clumping [2].

Besides the type and content of plasticizer, the ratio by weight of dry plasticizer to dry gelatin (**P/G**) is related to the mechanical properties and therefore the physical stability of the shell and it should be considered in regards to the size and intended use of the capsules [2]. Depending on this balance, a lack of plasticizer results in brittle capsules and an excess of plasticizer causes softening and clumping. Migration of plasticizer to the shell from the fill content or from the shell often leads to softening of the shell in stability conditions or crystallization of the fill content. Determining this balance allows to obtain the optimal mechanical properties of the shell as well as to guarantee the physicochemical stability of the fill content.

In addition to find the gelatin-plasticizer formulation that satisfies the critical quality attributes to the product such as dissolution, it is also important to consider the potential sources of reactive impurities in excipients such as peroxides or aldehydes in order to avoid cross-linking reactions promoted at stability conditions.

A case study for oil soft gelatin capsules was chosen to present some considerations in the product formulation as well as in the analytical development of this pharmaceutical dosage form.

For the product formulation, the effect of both gelatin type and content of plasticizer on disintegration times of the oil filled softgels was evaluated by means of a factorial design of two variables at two levels (22). **ANOVA** treatment of the results showed that the effect of the gelatin type is significant on disintegration times at 95% of confidence level. The corresponding contour plot (Fig.1) showed that the highest disintegration results were obtained for the type B gelatin at the highest level of plasticizer.

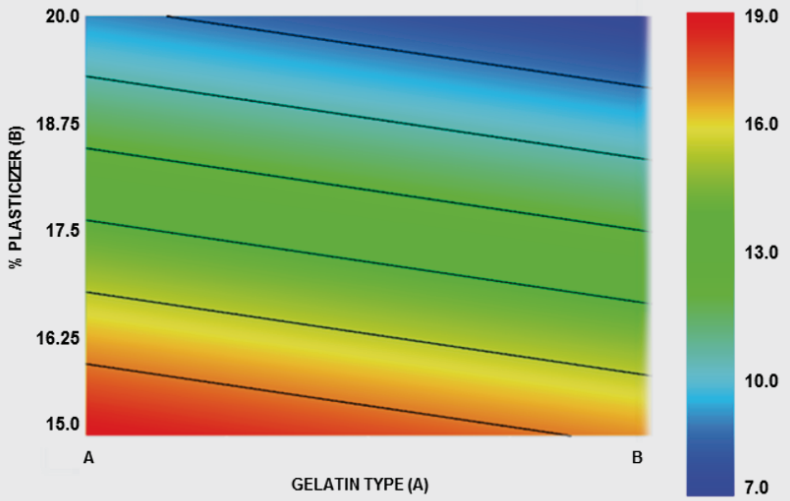

FIGURE 1

Contour plot of disintegration time of oil SGC using two levels for gelatin (type A and B) and for content of plasticizer.

For the analytical development, it was required to select the dissolution conditions, since the product is not compendial. First, the definition of the dissolution media was required. Since the fill content is oil and therefore a poorly soluble drug, the use of surfactant is critical in the in vitro drug release method development for the product.

In order to select the type and concentration of surfactant, the dissolution profiles were determined testing some recommended surfactants at different levels using Apparatus N.3 up to 60 min [4], as it is shown in the Figure 2.

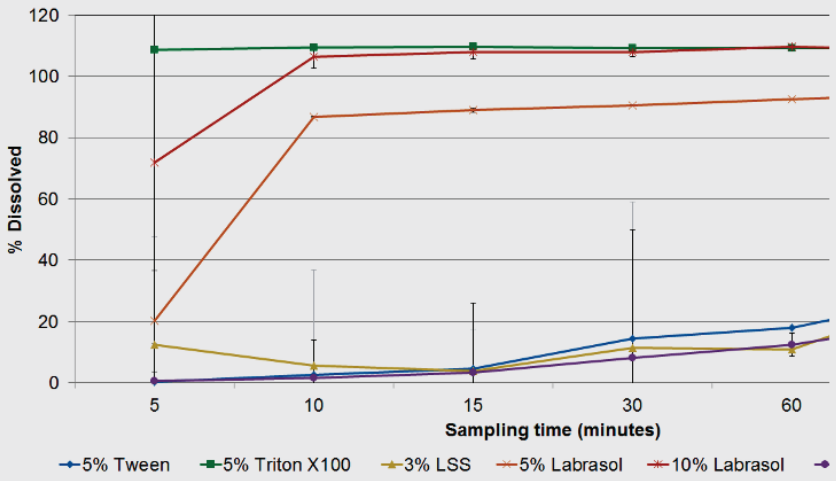

FIGURE 2

Dissolution profiles of oil SGC using different surfactants at recommended levels (app. USP N.3, 30 dips, 250 mL, mesh 40 top and below)

As it can be observed, the aqueous solution of Triton at 5% was selected since it showed the highest percentage of drug recovery from 5 to 60 min and is selective. The results obtained by means of this apparatus are accurate and precise, reaching values close to 100% and low values of RSD, as it is shown by the error bars in the figure.

As next step, the dissolution profile was determined in the apparatus N, 2 and N.3 using a sinker in both cases, as well as in the configuration open and closed of the apparatus N.4 using a modified flow-through cell designed for SGC. Results are shown in Figure 3.

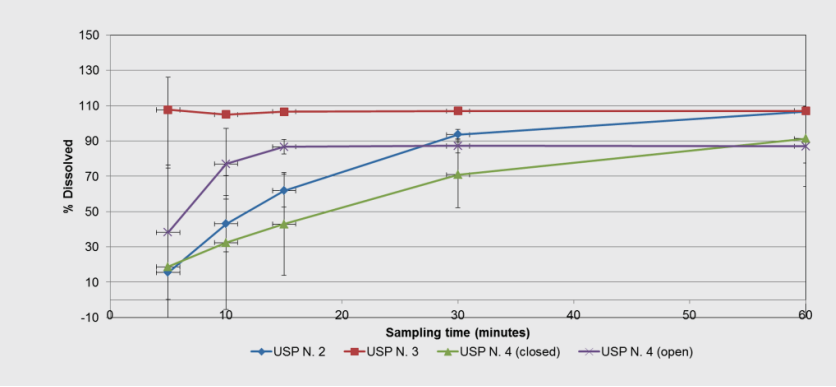

FIGURE 3

Dissolution profiles of oil SGC at different USP dissolution apparatus (surfactant Triton X100 5% water, 37 °C)

According to the FDA´s guidance for such kind of products tested on the apparatus N.4, the flow-through cell, some of the parameters that should be evaluated and optimized through experimental design are: the system mode, that is the closed system versus the open system, the size of the cell, the flow rate and the sample load in volume among others [3].

An experimental design was conducted to determine the analytical conditions for the dissolution test of an oil filled SGC product. The selected design was a fractional factorial design of five variables at two levels (flow type, flux, surfactant concentration, cell size and system mode). The dependent variable is the dissolution value Q at 60 min in each condition and the input variables are the concentration of surfactant and the flow rate. The cell size 22.6 mm was selected by technical reasons in regards to the capsule size. Figure 4 shows as example, the contour plots for laminar and turbulent flow using the 22.6 mm cell. It was possible to observe that in spite of the recovery was high at turbulent flow compared to the laminar flow, the last one was selected due to the high precision of its results, showing the lowest values of the relative standard deviation. In regards of the system mode, it was selected the closed system, since it showed a low variability compared to the open mode.

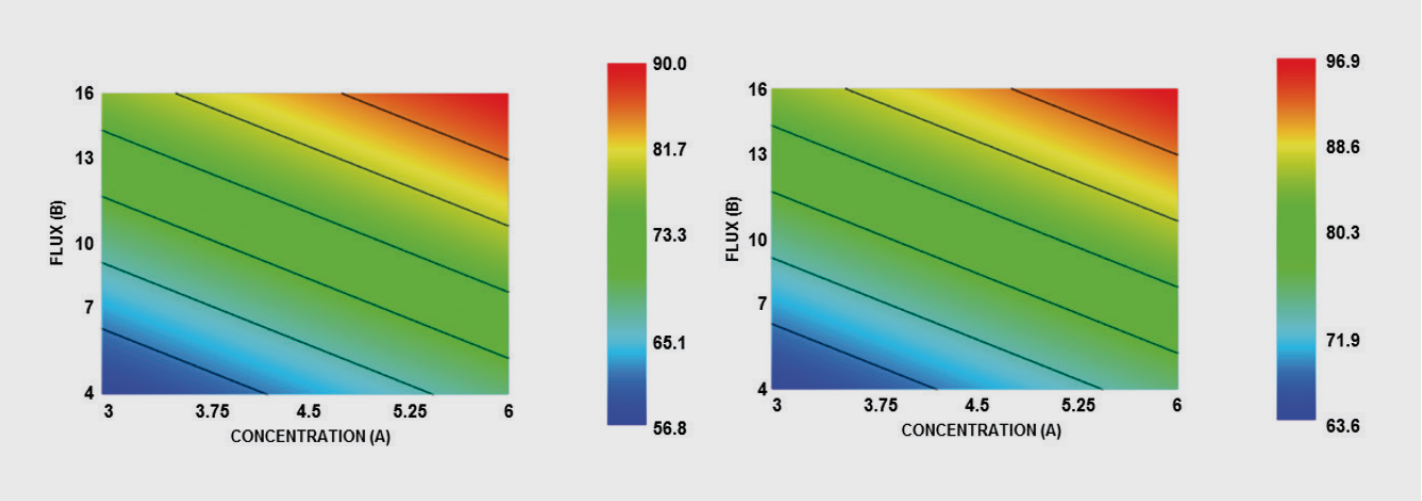

FIGURE 4 Contour plots for dissolution of oil SGC at App. N.4, closed system (surfactant Triton X100 water, 37 °C) a) laminar flow, b) turbulent flow

The results from the screening for the analytical method definition using the apparatus N.4 is to use the closed system, the laminar flow, the cell size 22.6 mm, and the surfactant concentration as well as the flux at their highest tested levels, 6% and 16 mL/min, respectively.

CONCLUSIONS

Some experimental designs were applied in a case study aimed to the product formulation as well as to the analytical development of a pharmaceutical oil filled soft gelatin capsule under the Quality by Design framework.

For the product formulation, it was defined that both the gelatin and the content of plasticizer had a significant effect on the disintegration times, obtaining the lowest values using the gelatin type B formulation at the highest level of plasticizer.
For the analytical development, it was shown that in such cases where the dissolution method is not specified in the monograph, the definition of the analytical method through an experimental design is required. It was shown for the particular of oil SGC that there are involved also some practical as well as statistical considerations to select the analytical conditions.

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