# Determining the formulation, processing and release of a sustained release softgel capsule

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## Introduction

Softgels are an attractive method of delivering a wide range of APIs to the human body. Due to the liquid/semisolid nature, potent and functional softgel fills can be employed to address many challenging topics facing the pharmaceutical industry. However, the ability to modify release of softgels, when compared to solid oral doses (tablets) is not yet fully matured. While enteric coatings are being widely utilized, for example, the prevention of "fish burps" in Omega 3 fatty acid softgels, the viable production of additional modifications to release, such as sustained release, to softgels is in its relative infancy1. The soft, flexible, and permeable nature of the gelatin capsule makes coating a challenge both from a formulation and from a processing perspective. In this work, a novel coating formulation using Kollicoat® SR 30 D, a polyvinyl acetate-based dispersion, is demonstrated as a simple and efficient coating of commercial softgels. Furthermore, novel imagery techniques are utilized in order to understand mechanistically how the coating works on a softgel.

## Methods

1 gram, Omacor® omega 3 fatty acid capsules were utilized in this study to test and evaluate parameters and formulations capable of effectively producing a sustained release coating. Sustained release coating formulations were prepared utilizing a blend of Kollicoat® SR 30 D, a polyvinyl acetate based 30% dispersion, Kollicoat® IR, a polyvinyl alcohol copolymer as an instant release coating and pore former, triethyl citrate as a plasticizer and purified water for dilution.

Various solids concentrations, coating weights, and processing parameters (Inlet Air temperature, exhaust air temperature, pan rotation speed, and spray rate) were tested on the Manesty XL Lab:01 pan coater. Batches were produced in 12 kg batches to closely mimic commercial coating mixing conditions.

Final coating formulation is listed in Table 1.

| Condition | Value |
|---|---|
| **Solids concentration** | 21% |
| **Triethyl Citrate (plasticizer) concentration** | 5% |
| **Ratio of SR/IR** | 7:3 |
| **Coating weight** | 15% w/w with capsules |

Table 1: Sustained release coating formulation parameters

Final coating conditions are listed in Table 2.

| Condition | Value |
|---|---|
| **Mass of capsules** | 12 kg |
| **Inlet air volume** | 70 ft3/min |
| **Inlet air temperature** | 50°C |
| **Bed temperature** | 32°C (approx.) |
| **Spray rate** | 7 g/min |

Table 2: Sustained release coating process parameters

Following formulation, A standard USP II dissolution apparatus was utilized to test sustained release coatings in both low pH conditions of the stomach as well as 6.8 pH of the GI tract. Dissolution was conducted at 37°C and 75 rpm; two hours of HCl buffer was utilized prior to moving to Phosphate buffer (6.8 pH) for the remainder of the studies.

Additional tests and analysis were performed using the Pion SDi2 in both visible and UV, with a monitored and reported release at 520nm.

Uncoated softgels were placed in the system and held in place using a metal pin. Both UV and Visible light spectrum were monitored in a circulating bath. 0.1 M HCl buffer, at 1.2 pH was utilized for stomach conditions, while 0.05 Sodium Phosphate buffer at pH 6.8 was used for intestinal conditions. pH shift was completed after 1 hour of stomach conditions. An image of the setup (courtesy of Pion) is shown in Figure 1.[2]

## Results and Discussion

In this study, it was found that for proper preparation and coating of a sustained release softgel, both the formulation and the manufacturing conditions are critical to performance. It was found specifically that a coating formulation of 15% w/w weight gain was required in order to achieve a homogeneous and adequate coating of the softgels to gain a consistant sustained release effect.

It is important to note that Kollicoat® SR 30 D, is not soluble in water, therefore, it is important to utilize a "pore former" which dissolves in water forming micro channels allowing water to penetrate into the coating and release drug. Further complicating this system, is that in a typical tablet based system, the pores would channel directly to the hydrophilic tablet core containing binders and disintigrants, thus allowing for drug release. However, in the case of a softgel, the pore channels only function to get to the gelatin softgel shell. Therefore, the pores must dissolve, then the gelatin, and finally drug release is possible.

Softgels, freshly coated with a blend of Kollicoat® SR 30 D and Kollicoat® IR as a pore former at a ratio of 7:3 was is shown in Figure 2. Triethyl citrate was utilized as a plasticizer due to its low tendency to evaporate during storage, an issue known to other plasticizers such as propylene glycol.

On the processing side, mixing in the pan was determined to be critical to adequate coating, while maintaining a relatively cool bed temperature of 36°C maximum was utilized to minimize the "spray drying" effect of the polymer coating. As previously noted, the sustained release coating itself is not soluble in water, consequently, after drug release and noted full dissolution of the gelatin capsule, the coating remains as a shell; this is shown in Figure 3.

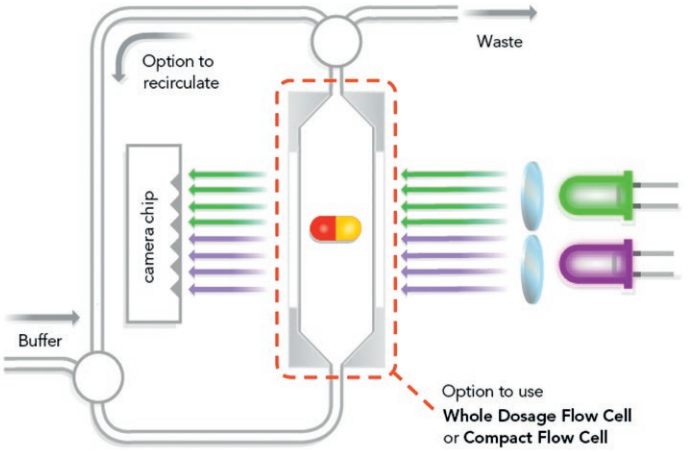



Figure 1: Setup of the SDi2 system; courtesy of Pion[2]

Figure 2: Sustained release softgels produced using Kollicoat® SR 30 D at a weight gain of 15% w/w.

Figure 3: Sustained release softgels after 1 hr. in acidic media; shells remain modulating the release of the contents as a function of pore former concentration.

This is further shown by observing dissolution characteristics. In Figure 4, T = 0, coated softgels are side by side with uncoated softgel on the lefthand side. At the start, nothing has been released from either formulation.

Further understanding this mechanism, the Pion SDi2 was utilized for constant monitoring.

First, in Figure 6, uncoated softgels are shown in a time lapse at 520 nm.

Utilizing the SDi2 imaging, the integrity of the uncoated softgel is clearly being dissolved prior to 15 minutes under acidic conditions. By thirty minutes, the shell is further dissolved and deformed, but after 60 minutes some elements of the gelatin remain.

Upon observing the sustained release coating, a completely different phenomenon is apparent; rather than slowly dissolve, the external portion of the softgel maintains shape and integrity throughout the experiment; again, noting that after 60 minutes, the continuous media was changed from stomach conditions to intestinal conditions. This is shown in Figure 7.

What is evident here is a slight swelling over time and the complete dissolution of the gelatin over the six-hour experiment (one-hour stomach, five hours intestinal conditions). The swelling and formation of the pores also results in bubbles forming intermittently on the surface of the softgel, this is evident in the images. The roughly 20% increase in volume was noted also by monitoring the width of the softgel over time visually using the software of the SDi2.

This work represents a first start in designing and understanding a functional, sustained release softgel capsule using an exterior coating. Future studies will compare and contrast an oil-based inner core with a hydrophilic (PEG) based inner core, which are expected to have contrasting release rates.

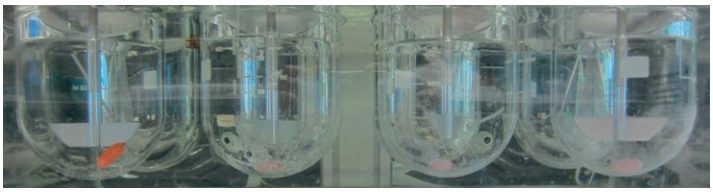


Figure 4: T = 0 mins, sustained release softgels and uncoated softgels; no drug has been released.

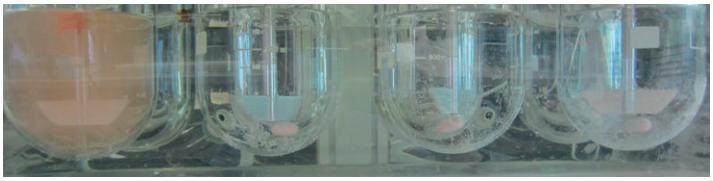
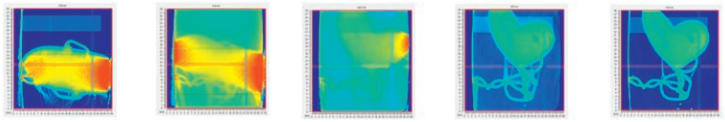
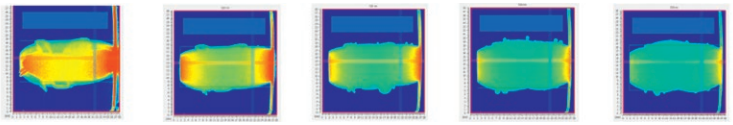


Figure 5: T = 60 mins under acidic conditions, sustained release softgels and uncoated softgels; oil has been fully released from the uncoated softgel, while primary integrity is apparent for the coated softgels.



T = 0 mins T = 15 mins T = 30 mins T = 45 mins T = 60 mins

Figure 6: Images snapshots from the video recording the dissolution of uncoated softgels utilizing the Pion SDi2 at 520 nm



T = 0 mins T = 60 mins T = 120 mins T = 240 mins T = 300 mins

Figure 7: Images snapshots from the video recording the dissolution of softgels coated with Kollicoat® SR 30 D utilizing the Pion SDi2 at 520 nm

## Conclusion

- Producing sustained release softgel formulations is possible through careful design of the coating formulation and care of the processing conditions; it is important to coat at bed temperatures at or less than 36°C to minimize spray drying of the coating formulation.
- It was found in this work that utilizing a 30% blend of pore forming, Kollicoat® IR combined with Kollicoat® SR 30 D produced adequate sustained release coatings of softgels in a traditional pan coater.
- Novel visualization tools such as the Pion SDi2 were utilized to understand the mechanism of dissolution; while it is clear traditional uncoated softgels loose structural integrity after 15 minutes in the stomach, the sustained release coated softgels retain structure throughout GI transit time.
- Future work will observe release rate differences between oil-filled capsules and hydrophilic, PEG based capsules containing applicable API.

## References

[1] Overcome Softgel Coating Challenges, Zhuang, K.; Romanski, F; Quiquero V.; Pharmaceutical Technology, 2014.

[2] Using the Pion SDi2 to characterize the swelling and drug release profiles of an extended release formulation of Metformin, Application note 307/16.

# Kollicoat® SR 30 D

## The aqueous polyvinyl acetate dispersion for pH-independent sustained release coatings

- ✓ Excellent film-forming properties
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- ✓ Insoluble matrix provides sustained release for solid oral doses
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