DEVELOPMENT OF A PULSATILE DRUG DELIVERY SYSTEM BASED ON POLYVINYL ACETATE (KOLLICOAT® SR 30D) – SODIUM LAURYL SULFATE

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The Chemical Company

Purpose

Pulsatile systems are intended to release the active pharmaceutical ingredient promptly and quantitatively following a programmed lag phase.

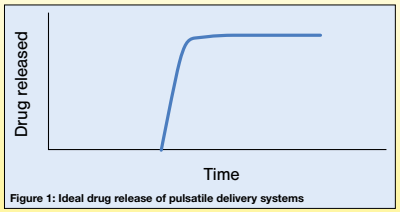

Figure 1: Ideal drug release of pulsatile delivery systems

Such systems are becoming increasingly interesting for treating chronopathologies; this is primarily due to circadian rhythms being extensively described for many diseases.

Chronic diseases with typical night or early-morning recurrence of symptoms are, for example, sleep disorders, bronchial asthma, rheumatic diseases and hypertension.

The goal is to synchronize drug delivery to the body's circadian rhythm, including disease states, to produce maximum health benefits and minimum harmful effects [1, 2].

Kollicoat® SR 30D, a 30% polyvinyl acetate dispersion, is commonly used for pH-independent sustained release formulations [3].

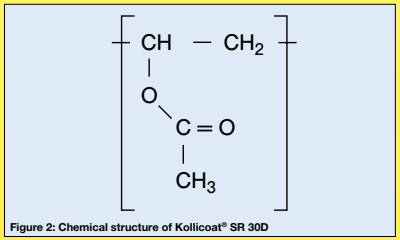

Figure 2: Chemical structure of Kollicoat® SR 30D

Interaction between Kollicoat® SR 30D and sodium lauryl sulfate is intended to modify the sustained release profile to a pulsatile one.

The idea was derived from the strong permeation-enhancing effect of high concentrations of sodium lauryl sulfate on polyvinyl acetate coatings. Pellets containing active ingredients should thus first be layered with sodium lauryl sulfate and then coated with Kollicoat® SR 30D. Kollicoat® IR proved to be an excellent binder for sodium lauryl sulfate.

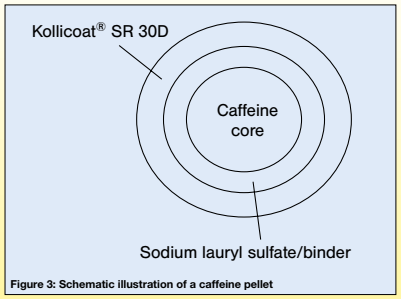

Figure 3: Schematic illustration of a caffeine pellet

When the pellets enter the gastro-intestinal tract, water needs some time to diffuse through the polyvinyl acetate coating and to dissolve the sodium lauryl sulfate layer. The dissolved sodium lauryl sulfate then exerts a strong effect on the the polyvinyl acetate coating, probably by partly disintegrating it.

Methods

Materials

Caffeine (BASF SE), Kollidon® CL-F (BASF SE), Avicel® PH 101 (FMC BioPolymer), GranuLac® 230 (Meggle); Kollicoat® IR (BASF SE), Kolliphor™ SLS Fine (BASF SE); Kollicoat® SR 30D (BASF SE), triethyl citrate (Jungbunzlauer), talc (Sigma Aldrich); Kollicoat® MAE 30DP (BASF SE), Kollisolv™ PG (BASF SE).

Experimental methods

Pellets (0.71 – 1.4 mm) comprising caffeine (20.0 %), GranuLac® 230 (38.5 %), Avicel® PH 101 (38.5 %), Kollidon® CL-F (3.0 %) were produced by wet extrusion and spheronization.

The composition of the coating formulations and process parameters are provided in the following tables.

Table 1: Sub-coating

Kollicoat® IR	8.0 %
Kolliphor™ SLS Fine	12.0 %
Water	80.0 %
Total	100.0 %
Solids content of the spray suspension	20.0 %
Polymer content of the dried film	40.0 %

Table 2: Top-coating

Kollicoat® SR 30D	50.79 %
Triethyl citrate	0.77 % (5 % rel. to polymer)
Talc	4.0 %
Water	44.44 %
Total	100.0 %
Solids content of the spray suspension	20.0 %
Polymer content of the dried film	76.2 %

Table 3: Enteric coating

Kollicoat® MAE 30DP	53.33 %
Kollisolv™ PG	4.0 % (25 % rel. to polymer)
Water	42.67 %
Total	100.0 %
Solids content of the spray suspension	20.0 %
Polymer content of the dried film	80.0 %

Table 4: Process parameters

Machine	**Aeromatic Strea (top spray)**
Batch size	0.5 kg
Inlet air temperature	60 °C
Product temperature	40 – 45 °C
Spraying rate	5 g/min
Spray pressure	1.4 bar
Nozzle diameter	0.8 mm

Dissolution tests were conducted with a USP apparatus 2 (paddle) operating at 50 rpm and using 900 mL dissolution medium (37 °C), hydrochloric acid (0.08 molar) and phosphate buffer pH 6.8.

Samples were taken automatically and measured by UV spectroscopy (273 nm).

RESULTS

Dissolution tests confirmed that the release characteristics of Kollicoat® SR 30D and pellets coated with sodium lauryl sulfate show a clear dependency on the thickness of the top coating and on the amount of sodium lauryl sulfate in the sub-coating.

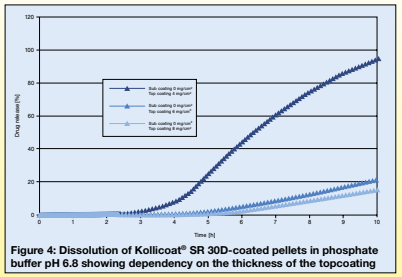

Figure 4: Dissolution of Kollicoat® SR 30D-coated pellets in phosphate buffer pH 6.8 showing dependency on the thickness of the topcoating

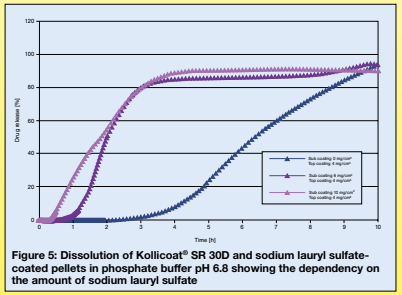

Figure 5: Dissolution of Kollicoat® SR 30D and sodium lauryl sulfate-coated pellets in phosphate buffer pH 6.8 showing the dependency on the amount of sodium lauryl sulfate

The higher the coating level of Kollicoat® SR 30D the slower the release rate and the thicker the sodium lauryl sulfate layer the quicker the onset of release and the release itself.

Best results were obtained with a sub-coating of 6 mg/cm² and a top coating of 6 mg/cm².

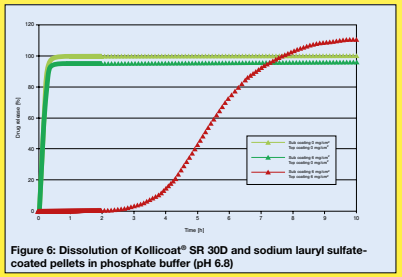

Figure 6: Dissolution of Kollicoat® SR 30D and sodium lauryl sulfate-coated pellets in phosphate buffer (pH 6.8)

Kollicoat® SR 30D and sodium lauryl sulfate-coated pellets released 20 % in phosphate buffer pH 6.8 for over 4 hours and then up to 80 % within the next 2 hours.

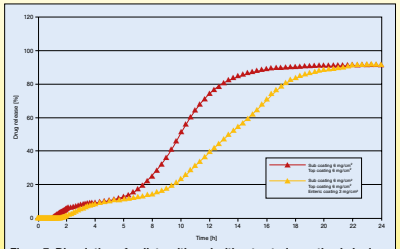

Figure7: Dissolution of pellets with and without enteric coating in hydrochloric acid (0.08 molar) over 2 hours and phosphate buffer pH 6.8 over the following 24 hours

Dissolution in hydrochloric acid (0.08 molar) followed by phosphate buffer pH 6.8 revealed a significantly increased lag time (about 20 % after 7 hours) which was further prolonged (about 20 % after 9 hours) by an additional enteric coating with Kollicoat® MAE 30DP.

Conclusion

- **The combination of Kollicoat® SR 30D (top coating) and sodium lauryl sulfate (sub-coating) is suitable for a pulsatile drug delivery system with a lag time of 3–9 hours.**
- **The lag time and speed of dissolution can be adjusted by the coating levels of sodium lauryl sulfate and Kollicoat® SR 30D.**
- **Increasing the amounts of sodium lauryl sulfate shortens the lag time and speeds up the dissolution rate.**

References

[1] Maroni, A. et al.: Oral pulsatile delivery: Rationale and chronopharmaceutical formulations. International Journal of Pharmaceutics 398 (1 – 8), March 2010

[2] Pallab, R. et al.: Multiparticulate formulation approach to pulsatile drug delivery: Current perspectives. Journal of Controlled Release 134 (74 – 80), August 2008

[3] Dashevsky, A. et al.: Physicochemical and release properties of pellets coated with Kollicoat® SR 30D, a new aqueous polyvinyl acetate dispersion for extended release. International Journal of Pharmaceuticals 290 (15 – 23), April 2004

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