Effect of Preparation Method on Release Behavior of Kollidon® SR Tablets Hot Melt Extrusion versus Direct Compression

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Abstract Summary

The suitability of preparing theophylline loaded Kollidon® SR tablets by hot melt extrusion was evaluated and compared to a direct compression method. All formulations showed good tabletting properties. Release of tablets prepared by melt extrusion was slower and fitted better to the mathematical kinetic model (Higuchi). Adjustment of release behavior by adding Kollidon® VA 64 is possible.

Introduction

To achieve controlled release of drugs matrix forming polymers such as Kollidon® SR can be employed. This product consists of approx. 80% polyvinyl acetate and 20% polvinylpyrrolidone. Due to the excellent powder properties of Kollidon® SR tablets can be prepared by direct compression and ensure controlled release of API (1). However, the particle size of the drug might require a further processing step such as granulation to enable compression. It could be shown that wet granulation led to an increase of drug release (2), whereas melt granulation enabled an extended release rate to be maintained (3). Therefore, this study was designed to investigate the application of melt extrusion of Kollidon® SR for the manufacturing of controlled release tablets and to compare the preparation method with direct compression. Furthermore, the possibility to generate a desired release pattern by incorporation of Kollidon® VA 64 as a release enhancer was evaluated.

Experimental Methods

• Materials:
Theophylline (BASF SE, Germany) was selected as a model drug. Kollidon® SR and Kollidon® VA 64 (BASF SE, Germany) were used as matrix material. Magnesium stearate was purchased from Bärlocher (Germany).

Formulations

Charge	1	2	3
Theophyllin	50%	50%	50%
Kollidon® SR	50%	40%	30%
Kollidon® VA 64	0%	10%	20%

Table 1

• Extrusion:
Melt extrusion was performed using a twin screw extruder (ZSK 25, Werner & Pfleiderer, Germany) with a screw diameter of 25 mm, a length to diameter ratio of 34 and 8 heating barrels. The extrusion parameters are displayed in table 2. The extruded formulations were milled and sieved through a 800 µm sieve.

• Tablet preparation:
For direct compression (DC) powder formulations were sieved through a 800 µm mesh and blended for 10 min at 42 rpm in a Turbula mixer (T2C, Willy A Bachofen AG, Germany). 0.5% magnesium stearate was added to the DC and extruded formulations prior compression followed by a further mixing step of 2 min at 42 rpm.

Extrusion parameter

Die pressure		63-70 [bar]
Power		1.6- 1.8 [kW]
Screw speed		197-199 [rpm]
Nozzle diameter		1.5 or 2 [mm]
Nozzles		2 or 3
Torque		8-8.9 [A]
Heating zone 1-2	Melting zone	135-141 [°C]
Heating zone 3-5	Mixing and kneading zone	138-146 [°C]
Heating zone 6	Degassing	141-143 [°C]
Heating zone 7-8	Discharging	148-163 [°C]

Table 2

• Compression:
The tablets were prepared on an instrumented single punch press (XP1, Korsch, Germany) applying 18 kN (12 mm punches with beveled edges). Compression profiles were recorded and analyzed using the software PMA 3 (Korsch, Berlin Germany).

• Tablets:
The tablets were characterized with respect to hardness, friability and drug release in accordance with the Ph. Eur.. For release testing, the tablets were first incubated in 0.08 mol HCl for 2h followed by 22 h in phosphate buffer pH 6.8. Drug release was determined by UV spectroscopy.

Results and Discussion

Investigation of the compression profiles of the extruded formulation showed a plastic deformation of 9.2 to 9.8 Nm and an elastic recovery ranging from 1.8 to 2.4 Nm. Increasing the Kollidon® VA 64 content, led to higher elastic recovery; a similar trend was observed for direct compression. Compared to direct compression lower plastic deformation and higher elasticity were found. This compression behavior results in lower tensile strength of the tablets prepared via melt extrusion. Furthermore, addition of Kollidon® VA 64 decreased the hardness of tablets (see figure 1). Friability of all formulations was below 0.1%.

Evaluation of the release behavior of tablets prepared by melt extrusion showed a continuous release over a 24 hours time period. Addition of 10% and 20% Kollidon® VA 64 accelerated the release rate within 24 hours from 58% to 76% and 94 %, respectively (see figure 2).

When compared to direct compression melt extrusion of the formulation prior compression reduced the initial release rate and the overall drug release within 24 hours (see figure 2 and 3). A better linear release enhancing effect was observed when Kollidon® VA 64 was added.

Drug release of diffusion controlled matrix tablets follows the Higuchi equation. Plotting the release data of the melt extruded formulations against the square root of time demonstrated an excellent correlation to the kinetic theory resulting in correlation coefficients of 0.99 (see figure 4). For tablets manufactured by direct compression the release rate slowed down over time leading to a minor deviation of the mathematical model (see figure 5).

Influence of process and composition on the tensile strength of tablets

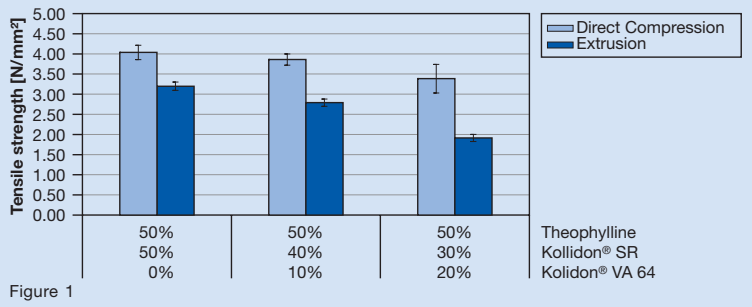

Figure 1

Release of theophylline from Kollidon® SR tablets prepared via melt extrusion.

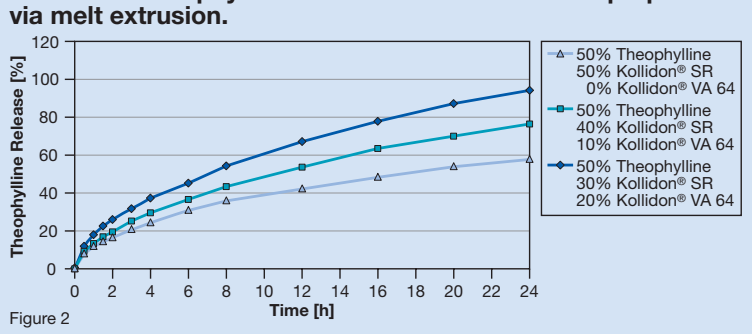

Figure 2

Release of theophylline from Kollidon® SR Tablets prepared via direct compression.

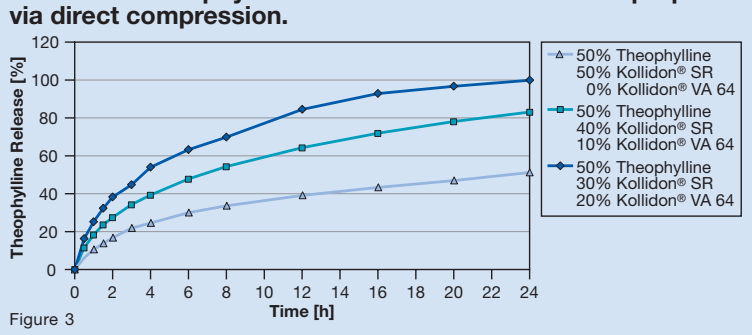

Figure 3

Release of theophylline from Kollidon® SR tablets prepared via melt extrusion.

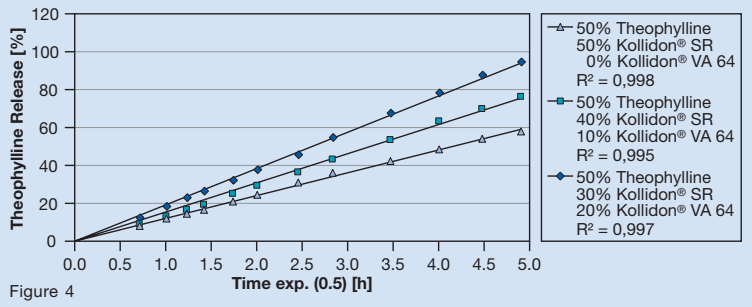

Figure 4

Release of theophylline from Kollidon® SR tablets prepared via direct compression.

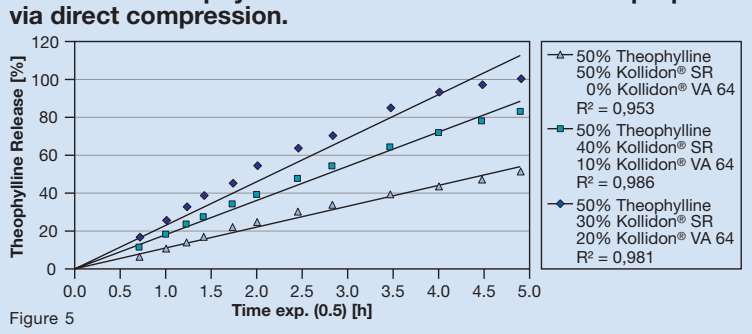

Figure 5

Conclusion

- **Controlled release formulations of Kollidon® SR tablets can be prepared by hot melt extrusion thus broadening the formulation techniques with respect to granulation.**
- **Desired release profiles can be obtained by addition of Kollidon® VA 64 acting as a release enhancer.**
- **Improved control of release rate and a better correlation to the Higuchi kinetics was observed for melt extruded formulations compared to direct compression.**

References

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[3] Melt granulation with Kollidon® SR for the manufacturing of sustained release tablets, CRS 2000, Paris

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