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White Paper

New Opportunities for Oral Sustained Release Formulations with Polyvinyl Alcohol

Authors: Daniel Joseph Price, Gudrun Birk

Achieving the appropriate release kinetics for an active pharmaceutical ingredient (API) is essential to ensure success of the therapeutic. For example, for sustained release formulations, a consistent API dose over a prolonged period ensures that levels in the blood plasma remain within the therapeutic window. This is important, as the API levels must be maintained higher than the minimum effective concentration and below the maximum tolerated dose. The combined effect is a safe and efficacious dosage form, which provides a therapeutic effect while avoiding toxic side effects. For certain medications, sustained release can allow a larger amount of API to be taken in a single dose, which can reduce the number of total daily doses required. Ultimately, sustained release can combine a more optimized and safe dosage regime with patient convenience, leading to increased adherence.

Strategies for Sustained Release

There are two primary formulation strategies that can be applied to produce sustained release kinetics – functional coatings and matrix systems (Figure 1). Functional coatings are used to create a membrane around the tablet which controls the rate of API release related to the rate of dissolution of the coating layer, through which the drug will diffuse and dissolve. Such sustained release systems are also often referred to as reservoir systems. Flexibility can be provided in this approach, as the coating type, thickness and pores can be adjusted to modify the sustained release profile. However, there are several drawbacks to this approach, as well. The tablet coating process is an additional labor-intensive step, which increases process costs and production times. Furthermore, any inconsistency in the layer thickness or pores will introduce inconsistency in the sustained release profiles between different tablets. An additional concern is dose-dumping which is defined as the *"unintended, rapid release of the entire amount or a significant portion of the drug contained in a modified release form"*.[1] In the case of a single-unit dosage form where the release rate is controlled by a coating layer, defects in the layer or splitting or chewing of the tablet by the patient may compromise the intended modified release profile. The resultant high levels of the drug in the bloodstream can cause serious adverse or toxic side effects. Dose dumping can also occur due to pH variability in the gastrointestinal tract, e.g. induced by food intake, or if the medication is taken with alcohol.[2]

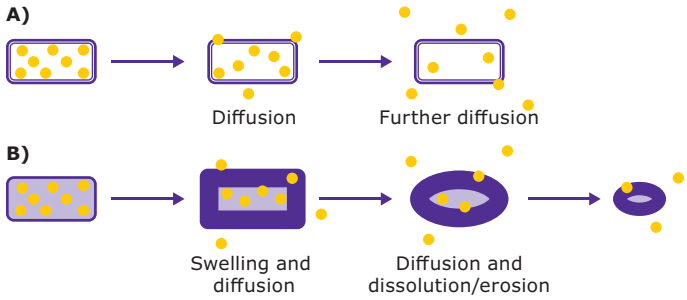

Figure 1.

Schematic depiction of the API release working principle from A) coated systems and B) hydrophilic matrix systems.

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In matrix-based sustained release formulations, the API is homogeneously dispersed within a polymer-based matrix. Depending on the rate-controlling polymer material properties, matrix systems are classified as hydrophilic and hydrophobic matrix systems, which show different release mechanisms. In hydrophilic matrix systems, the polymer hydrates and swells upon contact with gastrointestinal medium forming a gel layer on the surface of the system; the API is then released via diffusion through the viscous gel layer and by matrix erosion. Release kinetics can be adjusted with use of different polymer types, grades and quantity but are also dependent on API solubility. In contrast, hydrophobic matrix systems use polymers that are not water soluble and show no or only minimal swelling. The drug is dissolved by the outer liquid penetrating the matrix, with the porosity having a direct influence on the release kinetics.

With sustained release matrix systems, there is generally a reduced risk of dose dumping compared to coated formulations. The active ingredient is homogeneously mixed with the release-rate controlling material, making the release profile less sensitive to surface damage of the dosage form and even allowing for division of the tablet in some cases. The main drawback of this approach is the identification of the right matrix-forming material as release kinetics may be influenced by the test conditions such as pH value as well as API properties and, in the case of hydrophobic matrices, API content.[3]

Several naturally derived and synthetic polymers are available for oral sustained release formulations. These include cellulose ethers, polyethylene oxide, water-soluble natural gums of polysaccharides such as alginate, acrylic acid derivatives and methacrylates. Fixed combinations available on the market include a blend of polyvinyl acetate and povidone, as well as co-processed excipients based on hypromellose (HPMC) and a filler.

The most commonly used excipients for this application are cellulose-based polymers, with semi-synthetic, non-ionic HPMC being the main representative. Formulation with HPMC is relatively cost-effective and straightforward. However, the matrix system performance is dependent on polymer viscosity which in turn is directly related to the molecular weight of the material. Given that HPMC is a semi-natural polymer, batch-to-batch variations can lead to inconsistent performance of the final products. This inconsistency also poses a challenge to Quality by Design (QbD) implementation.

Advantages of Polyvinyl Alcohol for Sustained Release

Polyvinyl alcohol (PVA) is a synthetic polymer produced by the polymerization of vinyl acetate and partial hydrolysis of the resulting esterified polymer and is generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA). The polymer was first discovered in 1924[4] and has been used in approved drug products for decades. For example, PVA was listed as a suitable polymer for coatings of pharmaceutical drug products in a pharmaceutical reference handbook published in the 1950s.[5]

As a fully synthetic polymer, the physicochemical and functional characteristics of PVA can be tightly controlled, enabling robust and reproducible manufacturing processes and batch-to-batch consistency for reliable performance of the final products. Its suitability for sustained release formulations has been confirmed with formulations targeted at non-oral administration routes.[6,7,8]

This white paper describes the use of PVA-based Parteck® SRP 80, a functional excipient specifically developed for matrix-based sustained release oral solid dose formulations. With a mean particle size of 80 µm, Parteck® SRP 80 excipient is a PVA optimized for drug dissolution, easy handling, good flowability and good reproducibility with respect to both sustained API release and direct compression (DC) manufacturability (Table 1). Batch-to-batch consistency ensures consistent quality and enables use of QbD to further minimize risks in development and manufacture. Parteck® SRP 80 excipient is also compliant with Ph. Eur., USP, ChP and JPE monographs.

Parameter	
Bulk density	0.51–0.58 g/mL
Tapped density	0.70–0.77 g/mL
Angle of repose	32–37 °
Mean particle size (laser diffraction Dv50)	60–100 µm (target ~80 µm)
Mean particle size (laser diffraction Dv10)	15–30 µm
Mean particle size (laser diffraction Dv90)	160–220 µm
Surface (nitrogen adsorption BET)	0.3–0.5 m²/g
Pore volume (nitrogen adsorption BET)	not detectable
Loss on drying (3 h, 105 °C)	≤5.0%

Table 1.

Characteristics of Parteck® SRP 80 excipient.

Table 2 lists the components and ranges for a DC formulation that includes Parteck® SRP 80 excipient. To ensure consistent gel formation and release of the API, at least 20% of the polymer should be included; with the API incorporated in the range of 5 to 50%. Parteck® SRP 80 excipient has lubricating properties on its own; magnesium stearate can be added if additional lubrication is required. If needed, microcrystalline cellulose (MCC) can be added to further optimize tablet properties.

	Amount in % (w/w)
Active ingredient	5–50
Parteck® SRP 80 excipient	>20
Microcrystalline cellulose	0–60
Silicon dioxide, highly dispersed	0.25–1.50
Magnesium stearate	0.25–0.75
Total	**100**

Table 2.

General recommendation for DC formulation with Parteck® SRP 80 excipient.

Application Across Various Drug Models

Because sustained release properties are API-dependent, it can be difficult to identify one sustained release excipient that will work across a range of APIs.[3] Given this possible limitation, Parteck® SRP 80 excipient was evaluated as a sustained release matrix in direct compressible formulations of five different APIs to determine its application across different model compounds. The five drugs are shown in Figure 2 along with relevant formulation information (Table 3).

	Amount [%]	Amount [%]
API 1. Acetaminophen, Caffeine, Diltiazem HCl	22.5	
2. Propranolol HCl, Theophylline		32.0
Parteck® SRP 80 excipient	76.5	67.0
Silicon dioxide, highly dispersed	0.5	0.5
Parteck® LUB MST magnesium stearate	0.5	0.5
Total	**100.0**	**100.0**

Table 3.

Composition of model DC formulations.

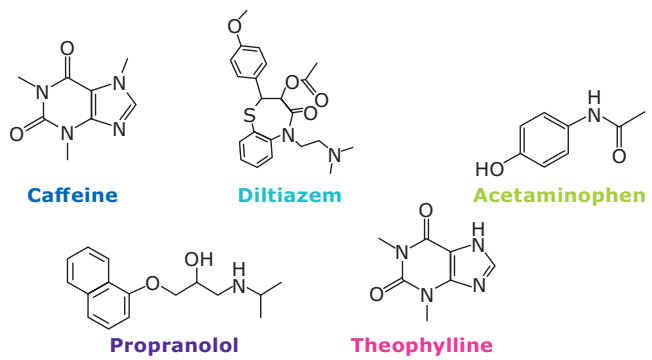

Figure 2.

Model APIs used for evaluation of Parteck® SRP 80 suitability for oral sustained release formulations.

Each formulation was compressed at 20 kN. Very good tablet hardness was achieved for all five drug models (Figure 3A) as well as reproducible sustained release profiles (Figure 3B), demonstrating the wide applicability of Parteck® SRP 80 excipient with a range of APIs.

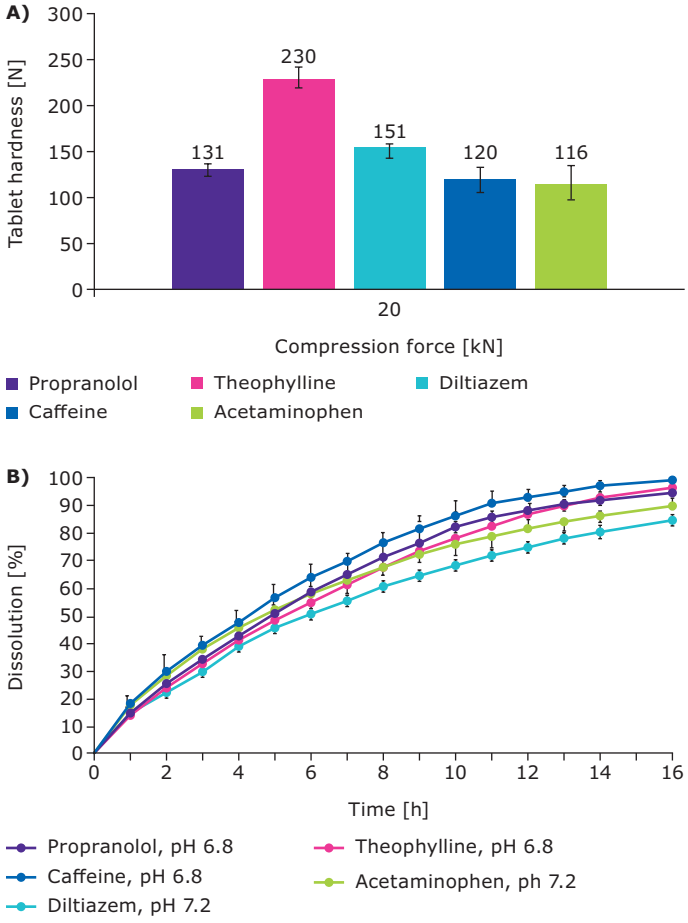

Figure 3.

Evaluation of A) tablet hardness and B) release kinetics for five APIs formulated with Parteck® SRP 80 excipient. (USP App. 2, 900 mL phosphate buffer pH 6.8/7.2, 50 rpm, 37 °C, n=3).

Protection Against Dose Dumping

Parteck® SRP 80 excipient was confirmed to not show dose dumping effects over a range of pH values and in the presence of alcohol. Figure 4A shows the sustained release profile of the propranolol formulation compressed at 20 kN, at both neutral and acidic pH values with no dose dumping. A similar study was conducted in presence of alcohol at 5, 10, 20 and 40%; similarly, no dose dumping was observed at any concentration (Figure 4B).

Flexible Modification of Release Profile

Formulations incorporating Parteck® SRP 80 excipient can be modified to fine-tune the release kinetics. For example, mannitol, a commonly used filler in solid oral formulations,[9] can be added to accelerate release. In the following study, different ratios of a directly compressible grade of mannitol and Parteck® SRP 80 excipient were included in the propranolol formulation (Table 4). API and silicon dioxide amounts were held constant while magnesium stearate was increased in the formulation as higher levels of mannitol required an increase in lubricant. Components were mixed for five minutes and compressed using different compression forces into 11 mm diameter tablets weighing 500 mg.

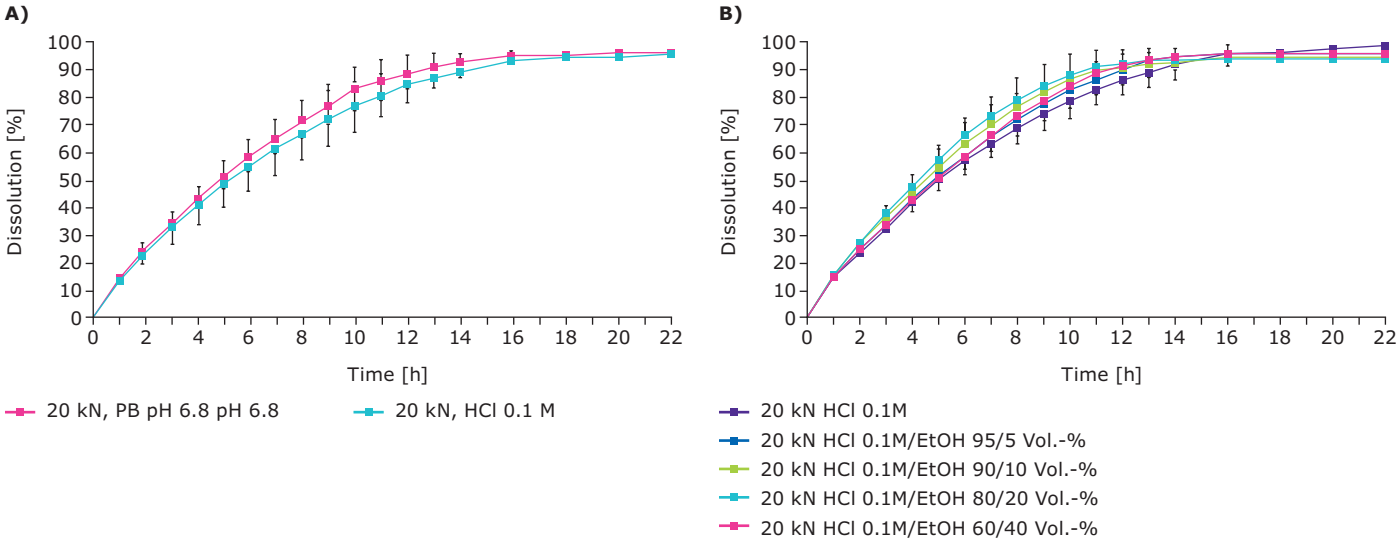

Figure 4.

Dissolution profile of propranolol-Parteck® SRP 80 formulation in A) media of different pH and B) varying alcohol concentrations (USP App. 2, 900 mL phosphate buffer pH 6.8/HCl 0.1 M/media composition as shown in graph, 50 rpm, 37 °C, n=3).

	Parteck® SRP 80/Parteck® M 200 ratio (w/w)			
	1/0 Amount [%]	1/1 Amount [%]	2/1 Amount [%]	1/2 Amount [%]
Propranolol HCl	32	32	32	32
Parteck® SRP 80 excipient	67	32.75	43.7	21.65
Parteck® M 200 DC mannitol	–	32.75	21.8	43.35
Silicon dioxide, highly dispersed	0.5	0.5	0.5	0.5
Parteck® LUB MST magnesium stearate	0.5	2	2	2.5*
Total	**100**	**100**	**100**	**100**

- Premix of Parteck® SRP 80 and filler
- Addition of other components (including API)
- Addition of lubricant
- Mixing for 5 min, 50 rpm after each step
- Compression of tablets (500 mg, 11 mm, 10/20/30 kN)

* More lubricant was needed due to high ejection force.

Table 4.

Composition of propranolol-Parteck® SRP 80 formulations with varying amounts of mannitol.

Figure 5 demonstrates that the release profile of propranolol can be modified by addition of mannitol to the direct compressible formulation. Very good tablet properties were achieved (A) and the release kinetics were effectively modified (B). The formulation that included only Parteck® SRP 80 excipient and no mannitol had the slowest release; a more rapid release was observed for the formulations with added mannitol.

Compatibility with Different Tableting Technologies

While direct compression offers several benefits for tableting including efficiency and suitability for water-sensitive APIs, granulation processes are widely used in solid formulation and manufacturing processes. As such, the suitability of Parteck® SRP 80 excipients for direct compression, as well as wet and dry granulation has been evaluated.

Direct Compression

Parteck® SRP 80 polyvinyl alcohol can be used in direct compression, requiring only a mixing step beforehand. In contrast, other excipients used for sustained release may first require granulation to improve flowability and compressibility of the mixture, adding process steps, time and costs. Alternative approaches to sustained release such as functional coatings or multiparticulate formulation require also additional process steps compared to DC (Figure 6). As a direct result of the reduced number of process steps and a corresponding increase in process efficiency, direct compression can provide a total cost reduction of up to 75%.[10]

A formulation using Parteck® SRP 80 excipient for sustained release of propranolol was developed to evaluate tableting performance, uniformity of tablets and tablet hardness (Table 5). The formulation was compressed on a single punch press at different compression forces.

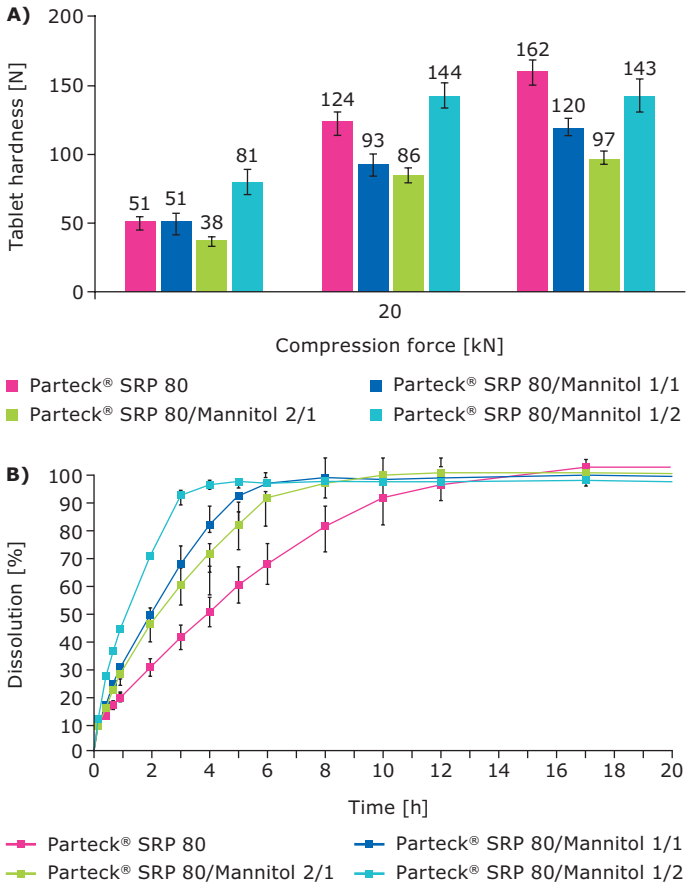

Figure 5.

A) Tablet hardness and B) dissolution profiles of propranolol-Parteck® SRP 80 formulations with varying amounts of incorporated mannitol (USP App. 2, 900 mL phosphate buffer pH 6.8, 50 rpm, 37 °C, n=3).

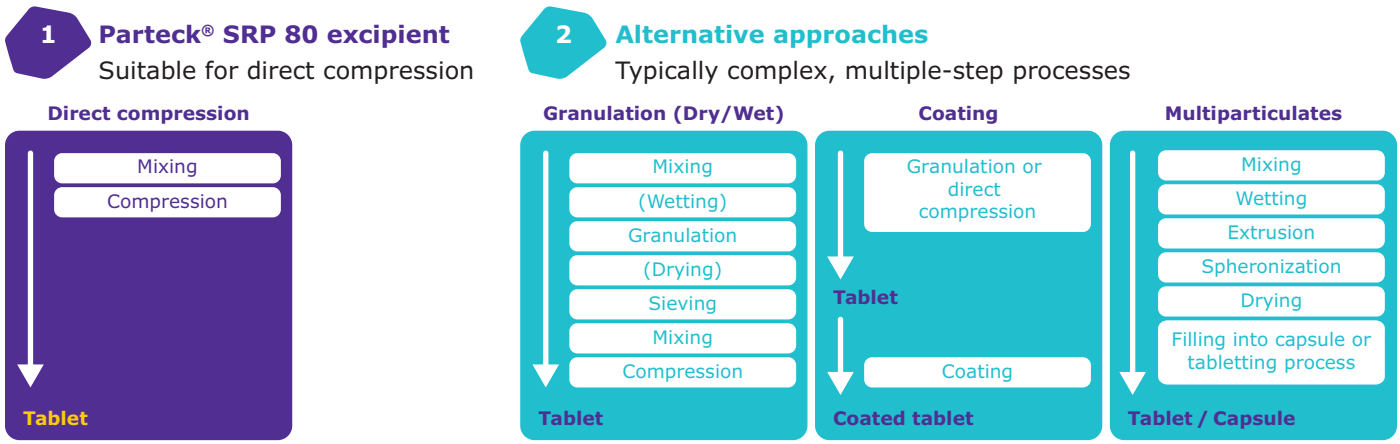

Figure 6.

Parteck® SPR 80 excipient offers a simpler direct compression process in comparison to alternative approaches commonly used for solid oral sustained release.

	Amount [%]	Amount [%]
Propranolol HCl	160.0	32.0
Parteck® SRP 80 excipient	335.0	67.0
Silicon dioxide, highly dispersed	2.5	0.5
Parteck® LUB MST magnesium stearate	2.5	0.5
Total	**500.0**	**100.0**

Table 5.

Composition of propranolol-Parteck® SRP 80 formulation.

Figure 7 shows the tablet hardness for the compressed tablets using compression forces of 10, 20 and 30 kN. Tablet hardnesses of approximately 60 N with the 10 kN compression, 130 N for 20 kN and 180 N for 30 kN were achieved along with a low ejection force. These results demonstrate the high compressibility and low ejection force over wide range of compression forces when using Parteck® SRP 80 excipient in a directly compressed formulation.

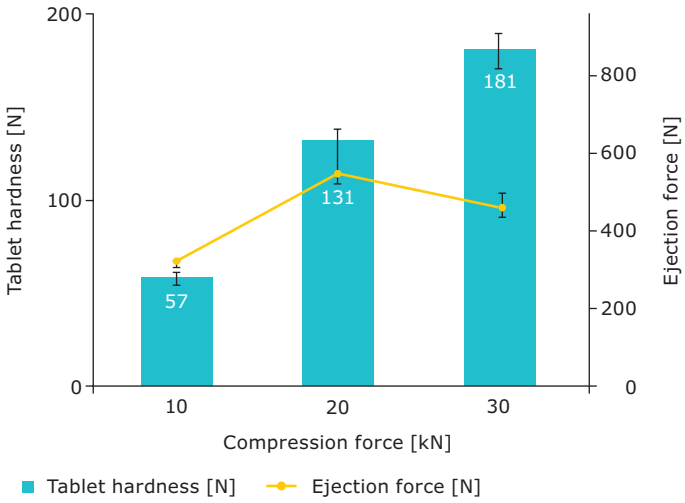

Figure 7.

Tablet hardness and ejection force of propranolol-Parteck® SRP 80 formulation at different compression forces.

In tablet formulation, content uniformity is a critical aspect and can be assessed using acceptance values provided in the pharmacopeia. Especially DC formulations can be prone to demixing effects, resulting in low content uniformity of the final dosage forms. This is why special emphasis was put on content uniformity evaluation of the propranolol-Parteck® SRP 80 DC formulations. Figure 8 shows that at all compression forces, an acceptance value of less than 2 was achieved, indicating that the tablets met the criteria of Ph. Eur.

Parameter	10 kN	20 kN	30 kN
Average weight [mg]	498.4	499.8	500.5
Standard deviation [mg]	4.0	2.4	2.3

AV <15 acc. to pharmacopoeia
AV = (M – X) + ks
M = X, k = 2.4 (n=10), s = standard dev.

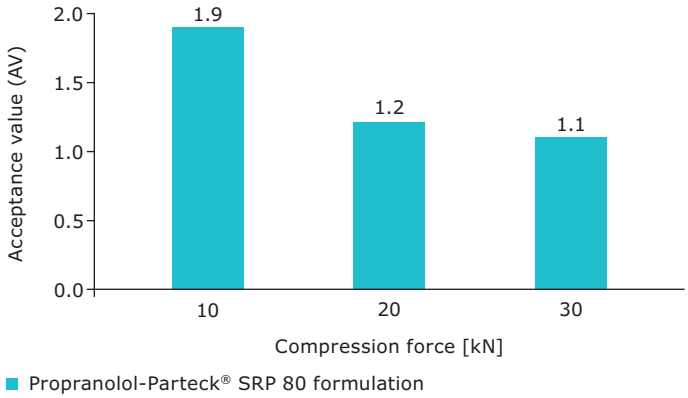

Figure 8.

Acceptance values of propranolol-Parteck® SRP 80 formulation at different compression forces.

Figure 9 shows the release performance of the propranolol formulations. Consistent *in vitro* release behavior for the tablets compressed at three different direct compression forces – 10, 20 and 30 kN – was observed, with the release sustained over 16 to 18 hours.

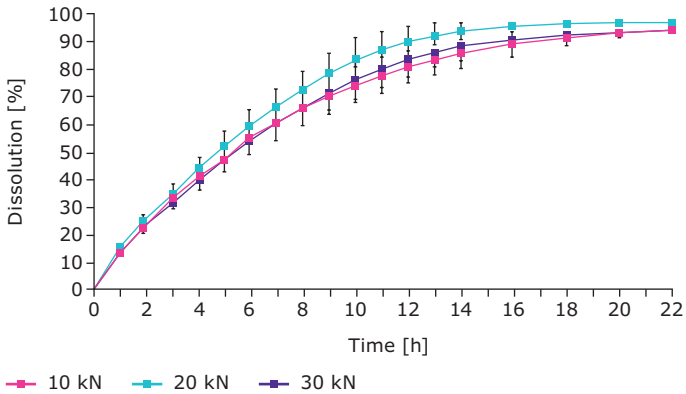

Figure 9.

Dissolution profile of propranolol-Parteck® SRP 80 formulation (USP App. 2, 900 mL phosphate buffer pH 6.8, 50 rpm, 37 °C, n=3).

Dry Granulation

In the process of dry granulation, granules are formed using compaction without the need for a binder solution, followed by size reduction to the desired particle size. Dry granulation is used to improve flow properties and prevent segregation of components. It is particularly suited for use in cases where direct compression processes reach their limits and to avoid API degradation induced by wet granulation. Dry granulation enables a shorter, more cost effective manufacturing process than wet granulation and because it does not use moisture, this technique is especially suitable for active ingredients that are sensitive to solvents or moisture.

Ascorbic acid was used as a model drug and formulated with Parteck® SRP 80 excipient in a dry granulation study. Roller compaction with a smooth roller surface was studied at a pressure of 75 bar (Table 6). Tablet hardness, while lower than that achieved with direct compression, was acceptable (Figure 9A) and dissolution performance was comparable to the tablets produced via direct compression (Figure 9B). Roller compaction can therefore also be applied if homogeneous distribution of the API is an issue or flowability is not compatible for direct compression.

Components	Amount	
	mg/tablet	% (w/w)
Internal phase		
Ascorbic acid	160	32
Parteck® SRP 80 excipient	335	67
External phase		
Silicon dioxide, highly dispersed	2.5	0.5
Parteck® LUB MST magnesium stearate	2.5	0.5
Total	**500**	**100**

- Roller compactor RCC 100x20, powtec Maschinen und Engineering GmbH, Remscheid, Germany
- Smooth roller surface, roller speed 3 rpm, compaction pressure adjusted by screw speed and roller gap; resulting compaction pressure 75 bar
- Integrated 1.25 mm oscillating sieve with 50 rpm, 75 bar

Table 6.

Composition of ascorbic acid-Parteck® SRP 80 formulation.

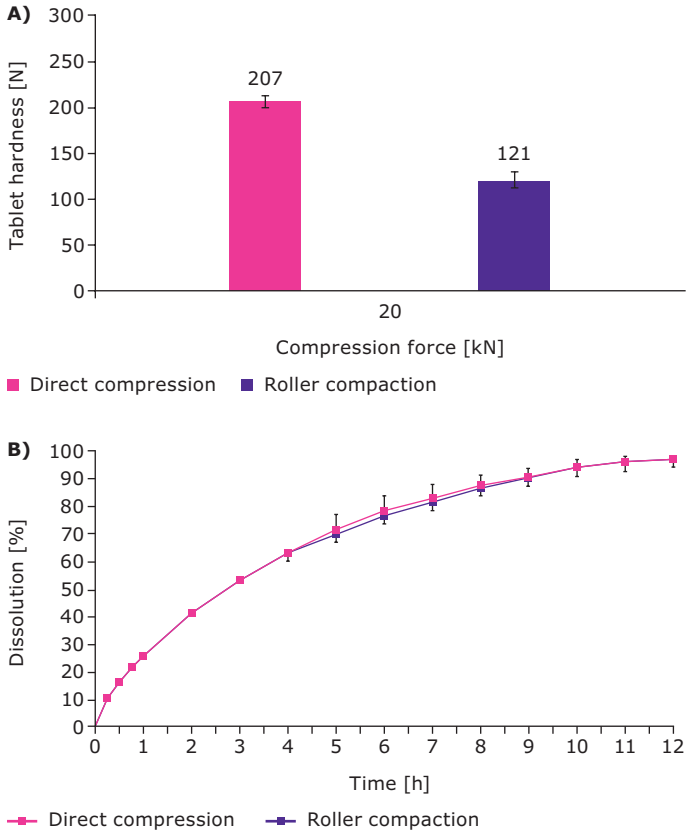

Figure 10.

Comparison of tablet hardness (A) and release kinetics (B) of ascorbic acid tablets produced via dry granulation or direct compression (USP App. 2, 900 mL phosphate buffer pH 2.7, 50 rpm, 37 °C, n=3).

Wet granulation

Wet granulation reduces undesirable powder characteristics via particle enlargement by agglomeration and improves content uniformity, flowability and compressibility. In wet granulation, a liquid binder is used to granulate the powder; the overall process includes blending, wetting, the wet mass stage, drying and sizing. The advantages of wet granulation include content uniformity, better compressibility of granules and the fact that a special grade of excipient is not required. The drawbacks include the fact that the process is not suitable for moisture- or heat-sensitive APIs, and that it usually is a relatively lengthy and costly process. Also, incompatibilities of formulation components may be aggravated when using wet granulation in comparison to other techniques.

Compatibility of Parteck® SRP 80 excipient (74.75%) in low shear, high shear and fluidized bed wet granulation was evaluated with ascorbic acid (25.25%). Varying amounts of water; magnesium stearate and silicon dioxide were also added to the final tableting mixture (Table 7).

Process parameters	Granulation process		
	Low shear (LS)	High shear (HS)	Fluidized bed (FB)
Granulation liquid	5/10/20/30% water	10/30/50% water	10% water/25% PVA 40–88 solution (4%)
Impeller speed [rpm]	139	150	n/a
Inlet temperature [°C]	n/a	n/a	70
Batch size [kg]	0.5	2	1

Table 7.

Process parameters of the three applied wet granulation technologies used to create tablets containing ascorbic acid and Parteck® SRP 80 excipient.

In-process photos reveal the challenges encountered during the wet granulation process with the model formulation, regardless of applied technology (Figure 11). All applied approaches (LS, HS and FB) produced a sticky product. Prior to drying and sieving, the resulting product was deemed not to be an acceptable powder.

Figure 11.

The stickiness of the resulting product proved to be a challenge in all applied wet granulation processes (exemplary pictures for HS and FB process as well as final granules).

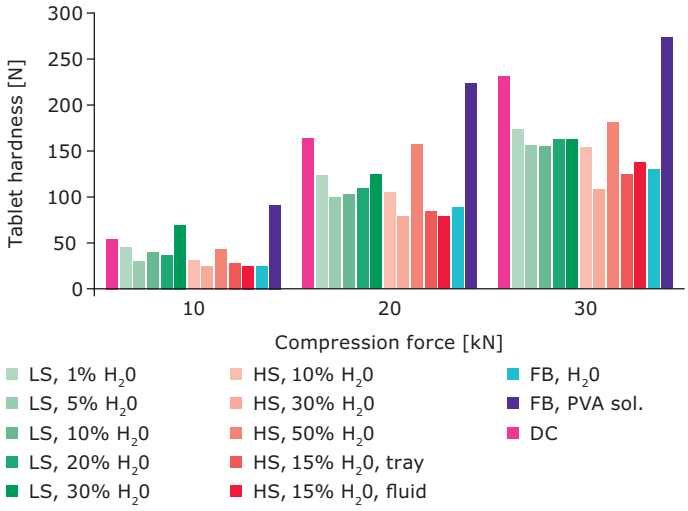

Figure 12.

Tablet hardness of wet granulated and directly compressed tablet formulations, comparing different processes and compression forces (LS – low shear, HS – high shear, FB – fluidized bed, DC – direct compression).

Figure 12 compares tablet hardness resulting from wet granulation and direct compression. Performance of the tablets produced via low and high shear processes was lower compared to the directly compressed tablets; higher hardness was achieved for the mixture processed via fluidized bed technology.

Overall, the wet granulation process was quite challenging and, in most cases, did not deliver an acceptable tablet robustness. Dissolution performance was, however, mostly comparable to that observed with tablets processed using direct compression, with a slight variation for granules produced with the fluidized bed (Figure 13).

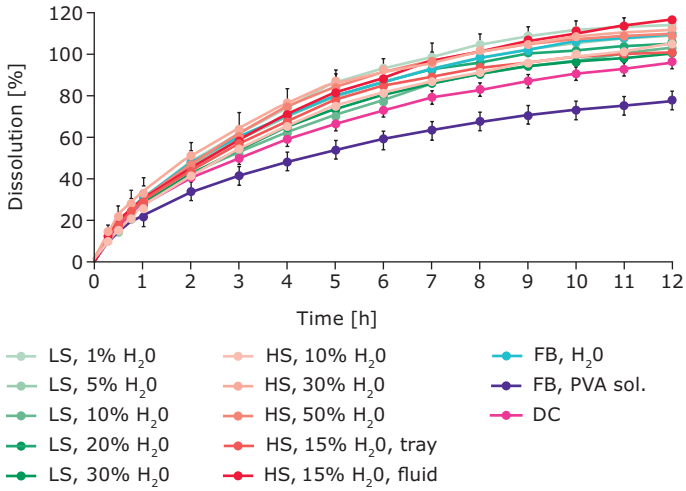

Figure 13.

Effect of used manufacturing process on product release profile (LS – low shear, HS – high shear, FB – fluidized bed, DC – direct compression); (USP App. 2, 900 mL phosphate buffer pH 2.7, 50 rpm, 37 °C, n=3).

Conclusion

The data summarized in this white paper confirm that PVA is well-suited for sustained release solid oral release formulations.

Parteck® SRP 80 PVA polymer enables release performance that is robust over a broad range of compression forces at different pH values and in presence of alcohol, reducing the risk of dose dumping. The data presented also confirm sustained release performance for several different APIs, demonstrating a broad application range; release profiles can also be modified as needed. Because of its fully synthetic nature, Parteck® SRP 80 excipient is well-suited for QbD approaches. Synthetic polymers exhibit high batch-to-batch consistency, and additional specifications outside of the compendia can be established with the final application in mind. It is also suitable for direct compression and can be used in dry granulation as alternative process. However, with good compressibility and performance in direct compression applications, there is no obvious advantage for use of more complex granulation processes, especially as lower tablet hardness was observed.

Sustained release formulations make it possible to address issues highly relevant to long-term therapy, such as dosing regime, convenience and patient compliance, as well as the efficacy-to-safety ratio. While novel excipients may enable these formulations, it is important to note that they may also create hurdles and delays in terms of regulatory approval. Novel excipients require comprehensive *in vitro* and *in vivo* safety assessments, as well as in-depth regulatory review. The advantages of Parteck® SRP 80 for formulation of oral sustained release dosage forms demonstrate that exploration of new formulation technologies does not always necessitate development of novel polymers. In many cases, it can be worthwhile to first consider proven, well-documented polymers such as polyvinyl alcohol.

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