Polyvinyl alcohol: Revival of a long lost polymer

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Introduction

With target-oriented drug discovery and an increasing focus on specialized medicines, the manufacturing of final drug products is becoming more and more complex. The processing and formulation of active pharmaceutical ingredients (APIs) designed with a specific target and functionality in mind may present challenges during the development and manufacture of the final formulation. Aspects such as bioavailability of the API in the body, API stability, and low dosage formulations are frequent hurdles to be overcome when bringing a drug to the market.

It has been observed that approximately 60% of new chemical entities (NCEs) have solubility issues, compared to 39% of marketed APIs.[1] Sufficient solubility of the API is an important factor for the absorption of the API into the body and thus the API's therapeutic effect *in vivo*. Solubility may be increased by using specific solubility-enhancing techniques and excipients in pharmaceutical formulation. Controlled release of the API continues to be another area of major interest in the pharmaceutical sector, as it allows the performance of the final formulation to be adapted to the therapeutic need. Sustained release as a specific controlled-release drug delivery model makes 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.[2]

While novel solutions, excipients, and innovative technologies can open up new pathways to improved formulations, it is important to note that they may also induce hurdles to regulatory approval. Novel excipients require *in-vitro* and *in-vivo* safety assessments, as well as in-depth regulatory review. These additional assessments can result in unplanned costs and delays, and add a further dimension to the risk evaluations of taking the final drug product to market. However, *new* does not always mean *novel*. Using familiar materials in innovative ways can result in new solutions that offer the peace of mind and safety of tried and trusted excipients.

One of these familiar excipients, which shows great and not yet fully exploited potential for new formulation approaches, is polyvinyl alcohol (PVA; sometimes also referred to as PVOH in other sources). It is a synthetic polymer produced by the polymerization of vinyl acetate and partial hydrolysis of the resulting esterified polymer.

PVA is currently used very commonly in pharmaceutical products across the different classes of marketed new molecular entities, new formulations and new indications (Fig. 1). While PVA is predominantly applied in oral formulations, typically in tablet coatings, other marketed drug products that utilize the distinct features of the various commercially available PVA grades can also be found in ophthalmic, transdermal, and topical dosage forms, for instance (Fig. 2). This publication will focus on additional applications of PVA for sustained release and solubility enhancement that address the aforementioned challenges in pharmaceutical formulations.

Figure 1:

Overview of products containing PVA, sorted by product class [3]

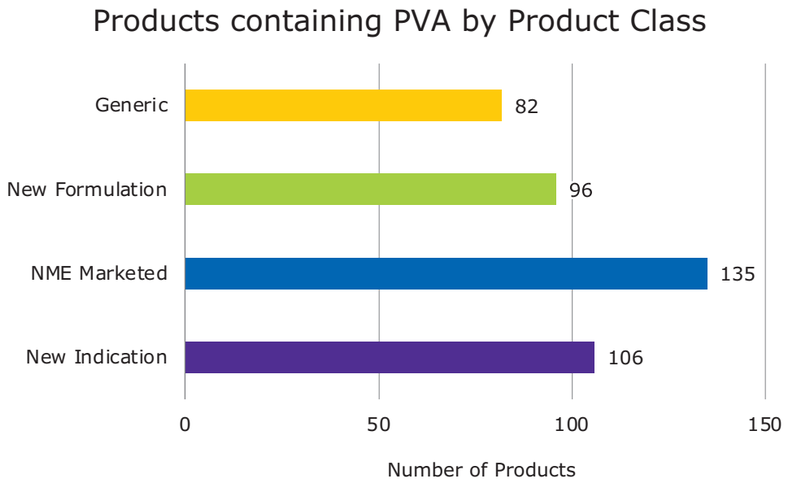
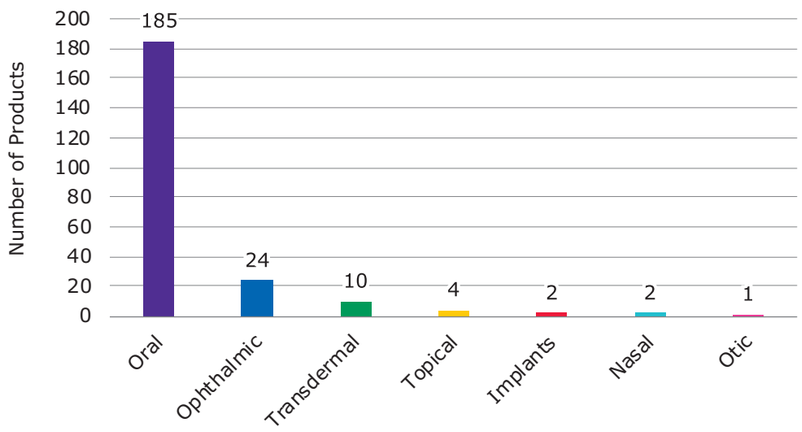


Figure 2:

Overview of products containing PVA, sorted by dosage form [3]



PVA Grade—Points to Consider

There are many points to consider when choosing the correct PVA grade. Typically, PVAs are classified according to their viscosity and degree of hydrolysis. The typical two-figure nomenclature for the different grades is thus made up of the viscosity of a 4% solution at 20°C (first figure) and the degree of hydrolysis of the polymer (saponification level; second figure). For example, PVA 5–88 indicates a PVA grade with a viscosity of 5 mPa·s that is 88% hydrolyzed. Both parameters have a substantial effect on the polymer's performance. For example, as hydrolysis increases, so do crystallinity, melting temperature, and mechanical strength, due to the high level of hydrogen bonding between chains. A lower hydrolysis grade has higher solubility in water and may show better compatibility with other excipients.

Viscosity, determined by the polymer chain length, also has a great influence on the performance of a formulation. As the chain length rises and with it the molecular weight (MW), the viscosity in solution also increases. However, while all PVAs are water-soluble, the dissolution time and the maximum amount in solution are strongly dependent on the PVA's MW. With increasing MW, the time required for dissolution increases while the maximum soluble amount decreases (Table 1). Viscosity is not only influenced by internal intrinsic factors but also by external conditions in the formulation, such as pH. For example, PVA solutions show a pH-induced viscosity shift in the presence of boric acid: up to a specific pH value, the viscosity of the PVA solution remains constant, but upon a further increase of the pH, the viscosity of the PVA solution begins to increase. As the molecular weight of the PVA rises, the viscosity shift occurs at lower pH values. The viscosity shift is also more distinct at higher concentrations of the PVA solution. For high-MW PVA grades, this shift tends to occur at lower pH than for low-MW grades (Fig. 3). Temperature can also have an effect on the viscosity of the PVA solution. As such, formulators can fine-tune formulations not only by selecting different PVAs for different applications, but also through the formulation conditions and additional excipients.

Table 1:

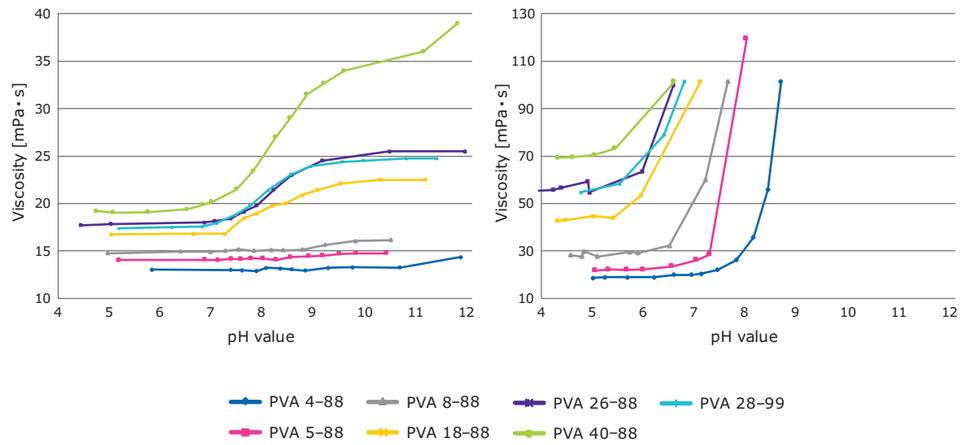
Aqueous solubility of PVA grades with varying molecular weight and degrees of hydrolysis at 4% and 10% and their respective maximum solubility*

	Dissolved at a Concentration of		
	4%	10%	max.*
PVA 4–88	✓	✓	33%
PVA 5–88	✓	✓	30%
PVA 8–88	✓	✓	25%
PVA 18–88	✓	✓	18%
PVA 26–88	✓	✓	15%
PVA 40–88	✓	✓	13%
PVA 28–99	✓	✓	15%

* Maximum solubility was defined as the concentration at which the mixture exceeded a viscosity of 10,000 mPa·s due to limited processability at this and higher viscosities.

Figure 3:

Influence of the pH on the viscosity of a 1.4% (left) and 4% (right) PVA solution; all concentrations in w/w



(Method description: NaOH is added dropwise and with continuous stirring to a solution of PVA and boric acid in water in a tempered glass beaker at 25 °C. For the 1.4% PVA solution, 0.07% boric acid was used. For the 4% PVA solution, 0.2% boric acid was added. The pH value of the solution is measured continuously using a pH meter equipped with a standard platinum pH-combination electrode with a ceramic diaphragm. The viscosity of the PVA solution at specific pH values is measured using a spindle viscometer.)

Another point to consider when choosing the PVA grade is the requirement of the pharmacopeias. When comparing the Ph. Eur. and JPE to the USP, the Ph. Eur. and JPE are more liberal, as the hydrolysis grade is stated as >72.2% or 78–96% and >97% respectively, compared to the USP's relatively narrow range of 85–89%. Of the PVA grades discussed above, only those with a hydrolysis grade of 85-89% fulfill the requirements of all three major pharmacopoeias.

PVA Safety

First discovered in 1924 by Herrmann and Haehnel [4, 5], PVA has been used in approved drug products for decades. As early as 1951, PVA was listed as a suitable polymer for coatings of pharmaceutical drug products in a pharmaceutical reference handbook.[6] PVA also has a long history of use in other applications such as the food and cosmetic industries. It is generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA)—a GRAS notice has been filed on the application of PVA in the solid oral coatings sector—and evaluations of PVA toxicity and safety by different authorities are available, as well as scientific publications on this topic. The acceptable daily intake (ADI) for humans is 50 mg/kg body weight as identified by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2003. To summarize, there is well-founded scientific evidence for the safety of PVA. [7–13] With regard to the application, additional parameter specifications should be considered to improve the safety profile—for instance, limiting the content of by-products such as residual solvents and crotonaldehyde, an irritant.

New Applications of PVA

PVA-based excipients have been characterized and introduced into the market for oral sustained release and solubility enhancement. These compendial grade PVAs surpass the requirements of all three major pharmacopeias (USP, Ph. Eur., and JPE) by having additional specified parameters relevant for their respective application. The following sections present experimental work that makes it possible to assess the potential of these compendial grade PVAs in their main applications.

PVA in Sustained Release

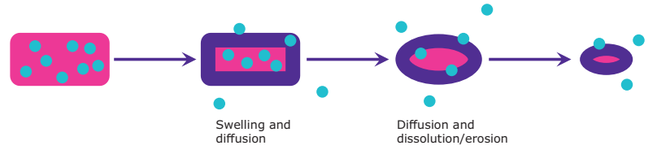
Sustained release technologies have been used in pharmaceutical formulations for many years. In fact, coatings as a first approach to modified release were presented to a scientific audience as early as the 19th century. In the 1950s and 1960s, matrix-controlled release systems were the topic of several scientific publications.[6] Today, a wide variety of approaches are available, all with the aim of altering the rate of release and/or place of liberation of the active ingredient compared to a conventional immediate-release formulation.[14] Typical release profiles are delayed, sustained, multiphasic/programmed, site-specific/targeted and triggered drug release. By modifying the drug release characteristics, significant therapeutic benefits can be achieved, such as improved efficacy of the therapeutic agent, reduced adverse effects, optimization of the dosing scheme and an overall improvement in patient compliance.

It is important to keep in mind that there is no one-size-fits-all solution for modified release formulations. When choosing the right approach, one must consider the API's properties, the required dose, needs regarding the release profile, clinical and market needs, the size of the dosage form, development time and cost, and the available equipment, in addition to other factors.

In the past few decades, many advances have been made in the area of formulation techniques, applicable materials, and especially in the understanding of the rational design and development of modified release formulations, including the API properties, pharmacokinetic profile and clinical needs. One major area of continued interest and research is the pharmacokinetic modeling of drug release profiles to predict the formulation's performance. While great progress has been made, there are still numerous challenges remaining in the modified release sector, such as finding a suitable material and/or technique to reliably achieve the desired release profile, prevent dose-dumping, and to facilitate the formulation of high-dose and low-solubility compounds.

Of the various possible modified release profiles, sustained release plays a major role in the pharmaceutical sector. Due to their simplicity, matrix systems—particularly monolithic matrix systems—are used extensively for sustained release formulations. The working principle of a hydrophilic matrix system is such that the API is homogeneously dispersed in a polymer-based matrix, where the polymer hydrates and swells upon contact with gastrointestinal medium. A gel layer is formed on the surface of the system and the API is then released via diffusion through the viscous gel layer and by matrix erosion. Another approach is the use of hydrophobic matrices, where the surrounding medium penetrates the dosage form, resulting in drug dissolution and diffusion through pores.

Sustained-release formulations: Matrix systems



Sustained-release formulations: Reservoir systems

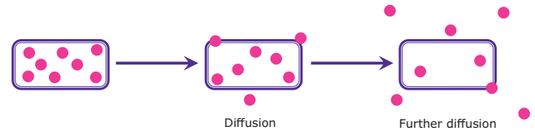


Figure 4:
Schematic comparison of the working principle for matrix- and reservoir-based sustained-release formulations

The difference in the drug release processes of the two matrix systems results in a different applicability: While the hydrophilic matrices can typically be applied to both insoluble and soluble APIs, the hydrophobic matrices are generally limited to soluble APIs, as the concentration gradient is too low for complete drug release of an insoluble API within the relevant timeframe.[2]

With sustained release matrix systems, there is generally a reduced risk of dose dumping compared to coated formulations: in the case of a single-unit dosage form where the only release rate-controlling material is present as a film coating on its surface, defects in the coating layer or the division of the tablet by the patient may compromise the intended modified release profile and result in an immediate release of the full amount of the active ingredient. Known as dose dumping, this can potentially result in serious adverse or toxic effects. With monolithic matrix systems, 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 sometimes even allowing for division of the tablet.

Several natural polymer and synthetic polymer excipients are available on the market for the sustained release application. The performance of the system can be fine-tuned by using different polymers or a combination of polymers as the matrix material. A few fixed combinations of excipients are available on the market, but the type and ratio of the excipients are typically determined on a case-by-case basis by the formulator, allowing for full flexibility depending on the active ingredient's properties and intended release profile. Common excipients for an oral sustained release formulation 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 a co-processed hypromellose (HPMC) and lactose excipient.

Probably the most commonly used excipients in this application are cellulose ethers, with semi-synthetic, non-ionic HPMC being the main representative. Upon contact with an aqueous medium, HPMC hydrates and releases the active ingredient through diffusion and erosion. The speed of these processes is dependent on the HPMC type selected.

Formulation with HPMC as the matrix excipient is relatively cost-effective and straightforward, making it a very popular excipient for oral sustained release formulations. However, being a semi-natural polymer, it also poses difficulties, such as batch-to-batch variations that can lead to varying performance of the final products [15, 16]; Quality by Design (QbD) processes can also be impacted.

As PVA is a fully-synthetic polymer, its physicochemical and functional characteristics can be tightly controlled, enabling robust and reproducible manufacturing processes, as well as reliable performance of the final products, batch by batch. Its suitability for sustained release formulations has been confirmed with formulations targeted at non-oral administration routes.[17–19]

The PVA-based Parteck® SRP 80 excipient was developed specifically for oral application. Its particle size is optimized to allow for easy handling and good reproducibility with respect to both sustained API release and direct compression manufacturability.

A formulation based on Parteck® SRP 80 and propranolol HCl as the model API with a drug load of 32.0% (w/w), as described in Table 2, demonstrated very good compressibility. As compression force increases, so does tablet hardness. At the same time, ejection forces remain constant over virtually the entire test interval, making Parteck® SRP 80 well-suited for high throughput direct compression processes (Fig. 5).

Evaluating tablet batches of different tablet hardnesses resulting from different compression forces, the formulation's *in-vitro* dissolution behavior was shown to be consistent irrespective of the tablet hardness, a prerequisite for robust manufacturing (Fig. 6).The effect of pH and ethanol on drug release was also investigated. In Fig. 7A, it is shown that a variation of medium pH value over a broad pH range does not have a significant effect on the drug dissolution profile. In media with different amounts of ethanol up to 40% (v/v), no dose dumping effect was observed (Fig. 7B). Thus it was shown that although the viscosity of a PVA solution is dependent on the outer pH (see Fig. 3), PVA itself is well-suited for use in oral modified release, as the dissolution profile is not affected by pH or alcohol (see Fig. 7). Stability studies under long-term and accelerated conditions, using both closed and opened containers, confirmed no change in the drug dissolution profile over a time period of 12 months (Fig. 8).

In summary, PVA-based Parteck® SRP 80 excipient was successfully used for sustained release solid oral formulations. Its very good compressibility makes it ideal for direct compression processes. Stability studies and dissolution testing in media of different pH and ethanol content confirmed the system's robustness.

Table 2:

Sustained-release formulation of propranolol HCl

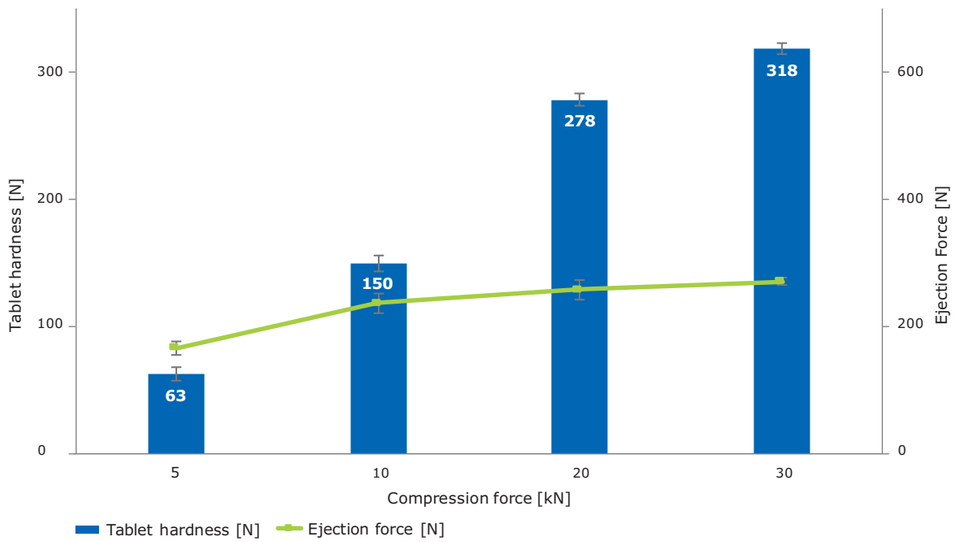
	Amount [mg]	Amount [%]	Function
Propranolol HCl	160.00	32.0	Model API
Parteck® SRP 80	167.5	33.5	Hydrophilic matrix polymer
Microcrystalline cellulose (MCC)	167.5	33.5	Binder/filler
Silicon dioxide, highly dispersed	2.50	0.50	Flow regulator
Parteck® LUB MST (Magnesium stearate)	2.50	0.50	Lubricant
Total	**500.00**	**100**	

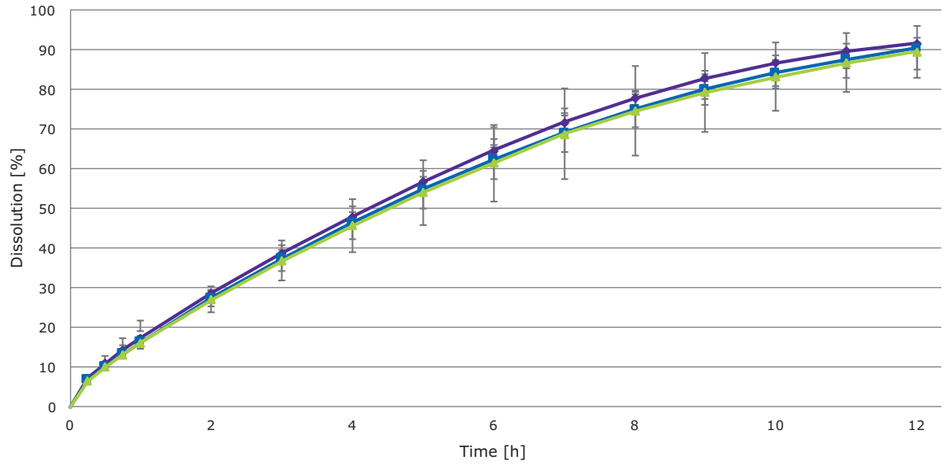
Manufacturing process

- Parteck® SRP 80 and MCC are pre-mixed for 10 minutes in a tumbling mixer.
- API and silicon dioxide are added, mixed again for 10 minutes and sieved over 800 µm mesh size to destroy agglomerates.
- Parteck® LUB MST is sieved through a 250 µm mesh sieve onto the mixture.
- All components are blended again for 5 minutes.
- **Direct compression** at 5, 10, 20 and 30 kN (500 mg tablets, Ø 11 mm, flat, facetted)
- Friability was measured according to the Ph. Eur./USP test method and was 0.7% for a compression force of 5 kN, and 0.0% for compression forces ≥ 10 kN.

Figure 5:

Effect of compression force on tablet hardness of a Parteck® SRP 80-based formulation with propranolol HCl as the model API and on the ejection forces during the tableting process



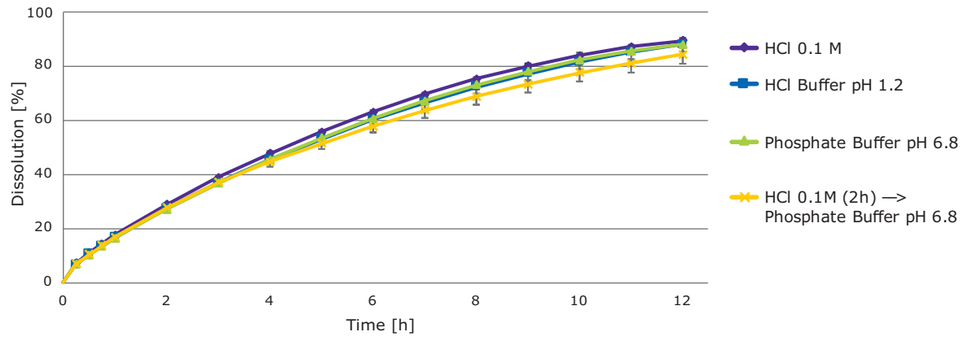


Dissolution procedure: USP Apparatus 2 (Paddle Apparatus), 900 mL phosphate buffer pH 6.8, 50 rpm, 37 °C, detection wavelength 214 nm; n = 3

Figure 6:

Dissolution profile of Parteck® SRP 80-based formulation with propranolol HCl as the model API prepared at different compression forces

A



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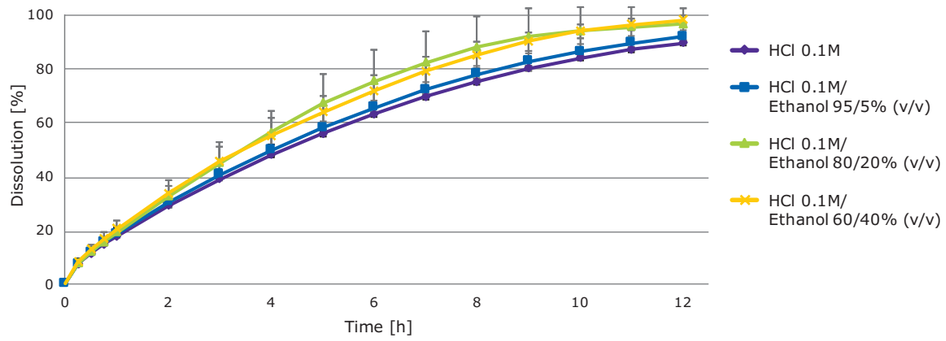


Dissolution procedure: USP Apparatus 2 (Paddle Apparatus), 900/1000 mL medium, 50 rpm, 37 °C, detection wavelength 214 nm; n = 3

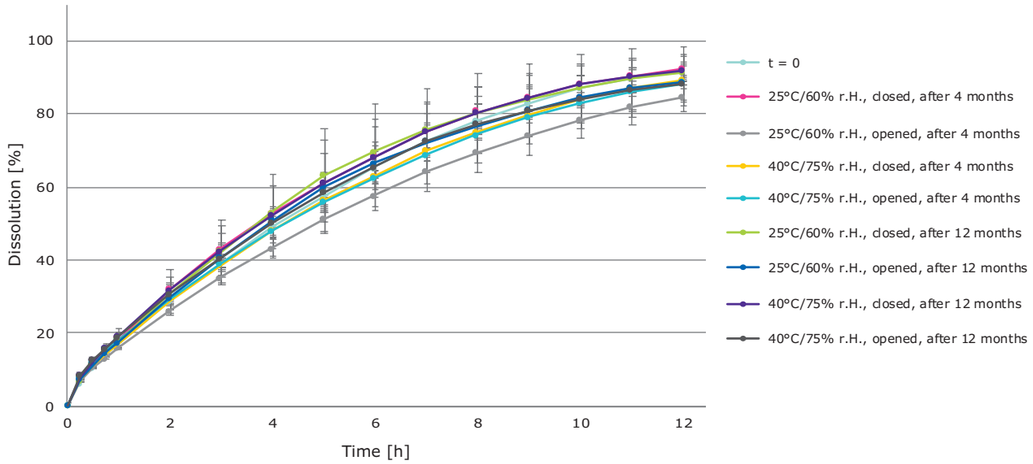
Samples used: tablets compressed at 20 kN

Figure 7:

Effect of media (A) pH and (B) ethanol content variation on the dissolution profile of a Parteck® SRP 80-based formulation with propranolol HCl as the model API

Figure 8:

Dissolution profiles of a Parteck® SRP 80-based formulation with propranolol HCl as the model API at t = 0, t = 4 months and t = 12 months of storage under long-term and accelerated conditions in both closed and opened containers



PVA for Solubility Enhancement

Poor aqueous solubility of the API is a critical challenge when developing a pharmaceutical formulation. Hot melt extrusion (HME) is one formulation technology that may be applied to increase drug solubility and thus improve bioavailability.

With this technology, the API is molecularly dispersed using elevated temperature and the mechanical force provided by the extruder screws. A solid dispersion is formed and fixed in a polymer matrix. The process is well-established in the plastics industry and was first used for pharmaceutical formulation in 1971.[20] In the following years, it was studied and refined further by various research groups.[21, 22]

The advantages of HME include enhanced solubility and bioavailability of the API and its ability to be used for both immediate and sustained release. The process is also suitable for continuous and solvent-free manufacturing. A number of final dosage forms are possible, manufactured either by direct shaping or by other downstream processing of the extrudate such as pelletizing and direct tablet compression.[23, 24]

When developing a HME formulation, the suitability of the API and excipients for the process must be considered, especially the degradation temperature, which acts as a limiting factor. Thermoplastic suitability of the polymer is a prerequisite for its use in HME. A high solubilization capacity of the polymer with respect to the API is also desirable, as this allows for high drug loadings.

Various polymers can be used in HME processes, with the most prominent examples being cellulose derivatives, polyacrylates and polymethacrylates, polyethylene glycols, and polyvinyl pyrrolidone.[25] Recently, PVA has been highlighted as another polymer well-suited to HME.[26, 27]

Parteck® MXP excipient is a PVA-based excipient specifically developed for use in HME. Considerations have been given to flowability, melt viscosity, thermostability, API compatibility, and the stability of the extrudate under stress conditions—all factors that are critical for solid dispersion systems manufactured via HME.

Nine different model APIs with low solubility were extruded with Parteck® MXP as the polymer, and the extrudate was assessed with respect to drug load and solubility enhancement. The model APIs were chosen to reflect the wide span of API melting temperatures as well as other physicochemical characteristics, including acidic, basic and neutral molecules. In all cases, a significant increase in API solubility was seen—from doubling to an over 150-fold increase compared to the solubility of the crystalline drug. With regard to drug load, seven of nine extrudes demonstrated a minimum API load of 30% (w/w), some going up as high as 55% (w/w); by contrast, many currently marketed drug products are limited to 10–15% (w/w). (Table 3)

Table 3:

Solubility enhancement and drug loads of selected model APIs with a wide span of physicochemical characteristics after extrusion with Parteck® MXP

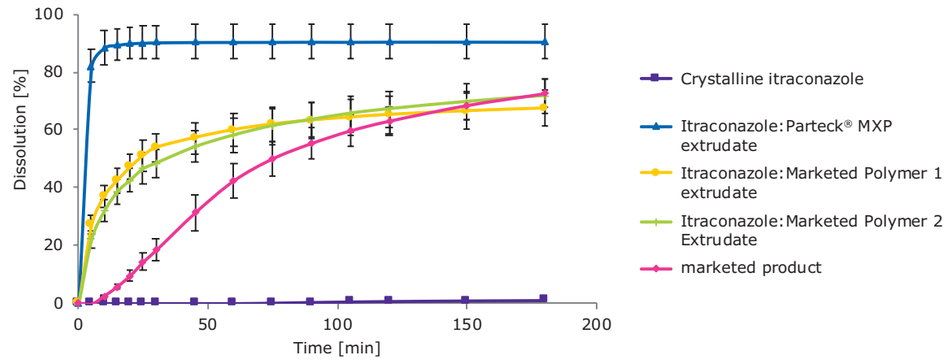
API	T_m of API [°C]	API Load Achieved* [%]	Solubility Enhancement (max.)
Ibuprofen**	78	30	2 x
Cinnarizine	118–122	< 20	10 x
Indomethacin	151	50	3 x
Ketoconazole	146	35	17 x
Naproxen	152	30	4 x
Atorvastatin	159–160	55	154 x
Itraconazole	166.5	30	80 x
Carbamazepine	204	30	2 x
Telmisartan**	260	15	35 x

*Maximum API load is defined as the maximum amount of API present in an amorphous state in the extrudate.
**Plasticizer is required to make the extrusion feasible or easier.

Using itraconazole as the model API, the extrudate and subsequent formulations were characterized further. Comparative dissolution demonstrated a 20% greater amount of dissolved API with Parteck® MXP compared to other marketed polymer extrudates of similar drug load and to a marketed, solid dispersion-based product at relevant (FDA-recommended) dissolution conditions (Fig. 9). As stability is a known issue of solid dispersion systems, stability testing was performed at low temperature, and under long-term and accelerated conditions. After storage for 12 months, dissolution, differential scanning chromatography, and high-performance liquid chromatography were employed to assess the effect of storage on the extrudate (see Fig. 10 for dissolution data). No recrystallization or degradation of the API was observed (data not shown).

Figure 9:

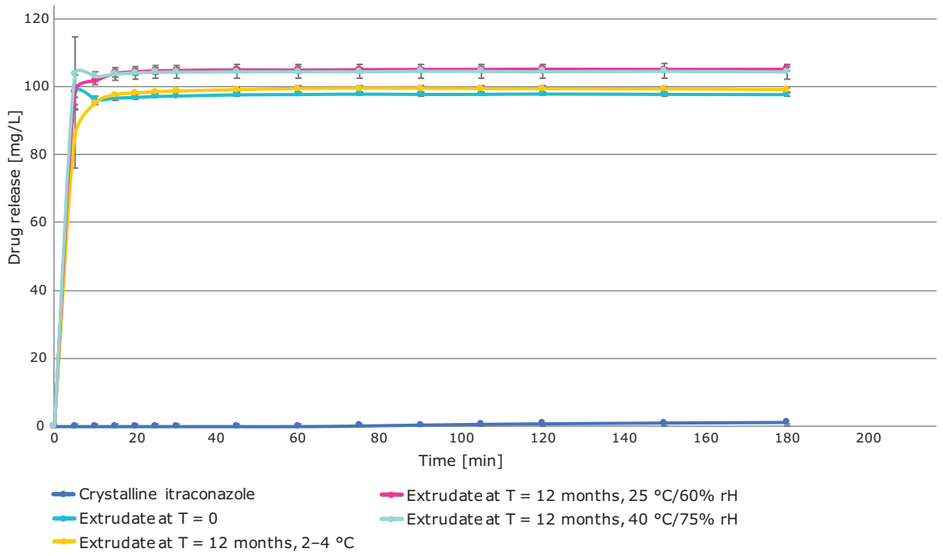
Comparative dissolution of itraconazole extrudates with different polymers as carrier, as well as a marketed, solid-dispersion based product of itraconazole



Dissolution procedure: FDA-recommended conditions for itraconazole, 900 mL SGF, 37 °C, 100 rpm, 100 mg itraconazole, 30% drug load; n = 3

Figure 10:

Dissolution profiles of Parteck® MXP-based formulation with itraconazole as the model API after 0 and 12 months of storage under cold, long-term and accelerated conditions

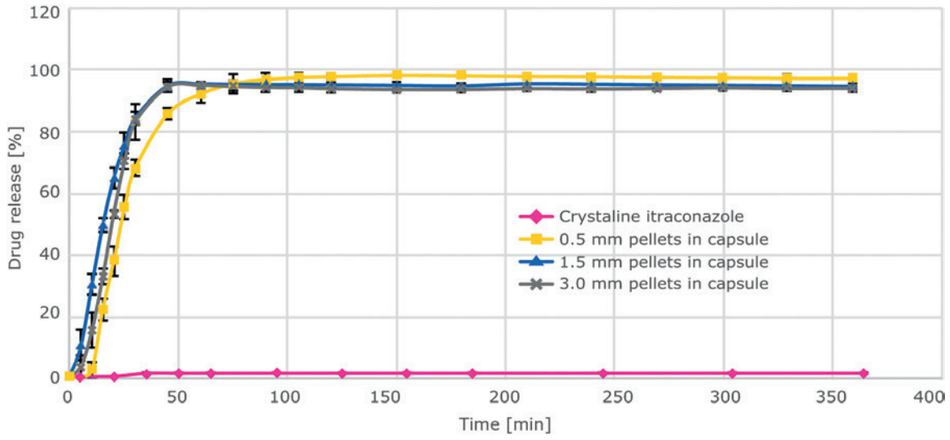


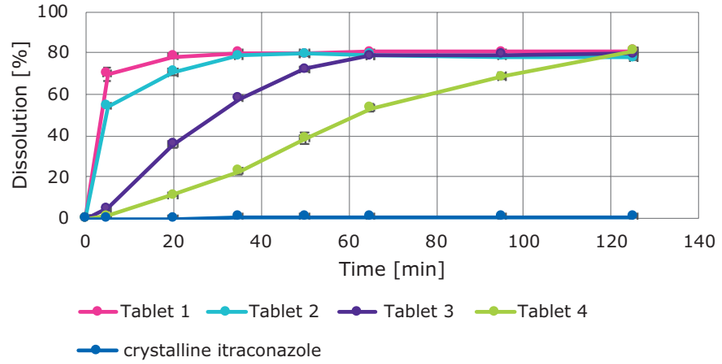
Dissolution procedure: FDA-recommended conditions for itraconazole, 900 mL SGF, 37 °C, 100 rpm, 100 mg itraconazole, 30% drug load; n = 3

Depending on the formulation, it is possible to apply Parteck® MXP excipient for both sustained and immediate release formulations, which makes it a very versatile excipient in HME. Again, using itraconazole as a model API, the extrudate was formulated into several different oral formulations: capsules, directly-compressed and directly-shaped tablets. For the capsules, the extrudate was pelletized and filled into capsules. Figure 11 shows that the dissolution profile corresponds to that of an immediate release formulation. In the case of compressed tablets formulated using milled extrudate, both immediate and sustained release profiles were achievable depending on the overall formulation (Fig. 12). Directly-shaped tablets demonstrated sustained release kinetics. In addition, it was shown that no significant changes of the release profile occur upon the addition of 10–40% ethanol (FDA requirement for sustained release formulations; Fig. 13).

Figure 11:

Dissolution from itraconazole-Parteck® MXP capsules: immediate release





Dissolution procedure: FDA-recommended conditions for itraconazole, 900 mL SGF, 37 °C, 100 rpm, 30% drug load; n = 3

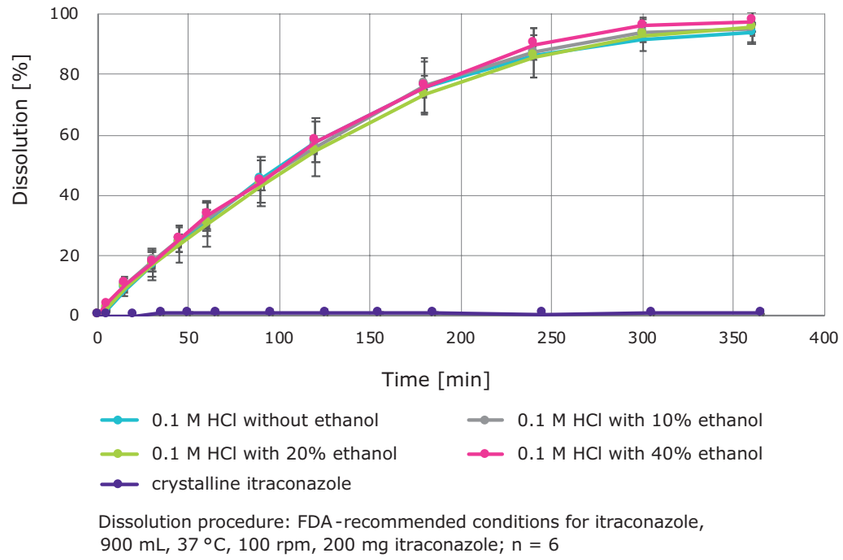
Figure 12:

Dissolution profile of compressed tablets: Sustained release and immediate release, depending on the tablet composition

	Tablet 1	Tablet 2	Tablet 3	Tablet 4
Extrudate [%]	50	50	50	60
Microcrystalline cellulose [%]	10	10	10	10
K_2CO_3 [%]	-	-	14.75	10
NaCl [%]	14.75	14.75	-	-
Magnesium stearate [%]	0.5	0.5	0.5	0.5
Lactose [%]	16.25	16.25	16.25	11
Silica [%]	1	1	1	1
Crospovidone [%]	7.5	7.5	7.5	7.5
Compressed force [kN]	15	10	10	10
T_{max} [min]	15	30	60	120

Table 14:

Formulation composition of compressed tablets based on a itraconazole-Parteck® MXP extrudate



Dissolution procedure: FDA-recommended conditions for itraconazole, 900 mL, 37 °C, 100 rpm, 200 mg itraconazole; n = 6

Figure 13:

Dissolution profile of directly-shaped tablets: sustained release and no dose dumping effect in up to 40% ethanol (FDA-recommended method for alcohol-induced dose dumping)

In summary, PVA is a thermostable polymer that is suitable for HME and can be used to improve the solubility of poorly water-soluble APIs by formulation of an amorphous solid dispersion. PVA-based Parteck® MXP excipient was successfully employed to manufacture stable amorphous solid dispersions using a wide range of model APIs, improving API solubility and allowing for a variety of downstream processing methods and release profiles.

Conclusion

Polyvinyl alcohol, a multi-compendial, pharmaceutical-grade polymer with a low risk profile, has been applied in the pharmaceutical sector for decades. Besides its established use in coatings for solid oral formulations, as well as in topical and ophthalmic formulations, this familiar excipient has other possible applications.

PVA's suitability for oral sustained release dosage forms was demonstrated, including benefits such as minimal susceptibility to pH-dependent or alcohol-induced dose dumping. A thermostable polymer, it was also successfully used in HME to formulate poorly water-soluble APIs into stable amorphous solid dispersions. A solubility enhancement of up to 150-fold compared to the crystalline API and high drug loading of up to 55% (w/w) were demonstrated.

Because of its fully synthetic nature, PVA is well-suited for QbD approaches. Synthetic polymers exhibit high batch-to-batch consistency and an additional specification outside of the compendia can be established with the final application in mind.

In conclusion, as a well-known polymer in the pharmaceutical sector, PVA is increasingly gaining momentum in new technologies for drug delivery. Recent publications indicate that PVA is suitable not only for the applications in HME and sustained release discussed above, but also for other technologies emerging in the pharmaceutical sector, such as microneedles for transdermal delivery and 3D printing.[28–31] The example of PVA clearly demonstrates that the exploration of new formulation technologies does not always necessitate the development of a new (and thus automatically novel) polymer, but that it is often worthwhile to first consider the polymers already on the shelves.

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Abbreviations

ADI	acceptable daily intake
API	active pharmaceutical ingredient
FDA	United States Food and Drug Administration
GRAS	generally recognized as safe
HME	hot melt extrusion
HPMC	hypromellose
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JPE	Japanese Pharmaceutical Excipients
MW	molecular weight
Ph. Eur.	European Pharmacopoeia
PVA	polyvinyl alcohol, sometimes also referred to as PVOH
QbD	Quality by Design
USP	United States Pharmacopeia

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