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White Paper

Poloxamer: a simple and powerful solution for accelerating dissolution

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Oral administration is the most commonly employed route for drug delivery. It is cost-effective and convenient for the patient, leading to high patient compliance. In order for the API to exert a physiological effect it must pass from the gastrointestinal (GI) tract and into the systemic circulation. The bioavailability of a drug therefore relies on its ability to overcome the barriers preventing this process, particularly passage through the intestinal membrane. To be successful, the drug must permeate through the cell membrane and must also be in solution. These two parameters led to the Biopharmaceutics Classification System, a system which groups drugs into various classes, based on solubility and permeability.[1]

Molecules with low solubility are at risk of not being absorbed from the gastrointestinal tract and so formulators have developed a toolkit of enabling formulation techniques to overcome this problem. These techniques include solid-state modification, formulation with lipids, or complexation with cyclodextrins. Unfortunately, these approaches can be highly complex and require significant resources to develop. An alternative approach is to increase absorption in the gastrointestinal tract by accelerating the rate at which the molecule goes into solution, called the dissolution rate. This white paper will introduce the concept of dissolution and discuss how poloxamers are a simple yet powerful formulation approach that can enhance dissolution rate, while minimizing resource requirements.

Solubility versus Dissolution

Solubility is the ability of a solute to dissolve in a solvent, forming a homogenous mixture. The process of solvation can be broken down in to three steps (Figure 1). First, a solute molecule must be separated from the solid state by breaking any solute-solute bonds. Second, a gap must be created within the solvent, a process known as cavitation. Finally, the solute molecule is incorporated within the solvent. The entire process of solvation is a function of the energy costs associated with each individual step.

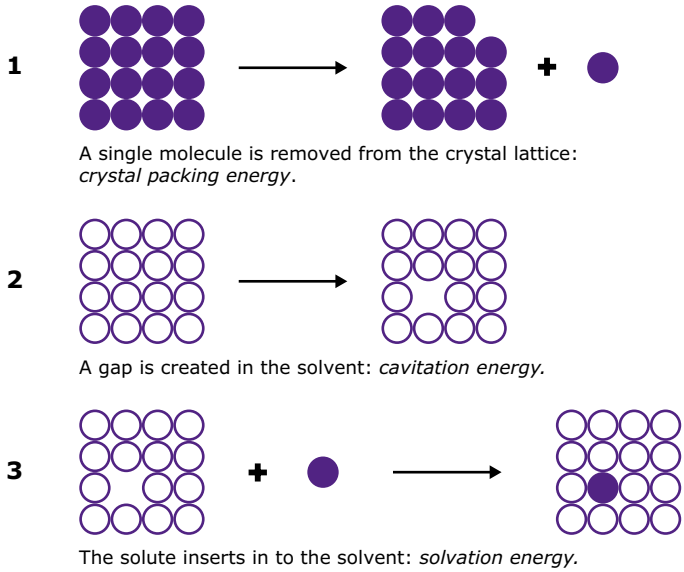

Figure 1.

Three steps of solvation.

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Equilibrium solubility is the point at which the dissolution rate is equal to the precipitation rate and represents the maximum amount of substance that can be dissolved in a stable equilibrium. An equilibrium measurement is a thermodynamic value and does not take in to account the rate at which the system reaches equilibrium. As such, these measurements can often be misleading, for example if a compound had acceptable equilibrium solubility but a poor dissolution rate, it may not reach the expected concentration levels in the GI tract before being cleared out of the body which is why absorption may not reach expected levels.

The process of dissolution is depicted in Figure 2. For a drug particle to dissolve, a concentration gradient must be present between the drug in free solution (C) and the drug concentration on the surface of the dissolving solid (Cs), separated by a layer of unstirred solvent (h). The presence of this gradient allows diffusion of the dissolving solid through the unstirred layer and into solution. The rate of dissolution, therefore, is equal to the rate of diffusion through the unstirred solvent layer.

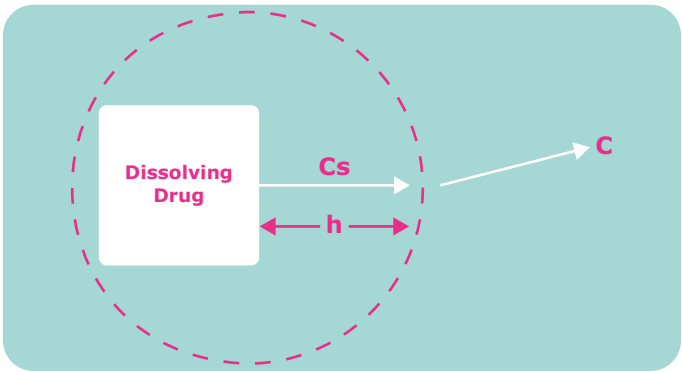


Figure 2.

The process of dissolution. A drug molecule must break from the solid bulk and dissolve through the unstirred water boundary, h, before passing into solution.

The rate of dissolution is described by the Noyes Whitney Equation, and is related to the solubility (C_s), the width of the diffusion layer (h), the surface area of the solid (A), and the diffusion rate of the drug (D).[2]

$$Dissolution\ Rate = \frac{DAC_s}{h}$$

In the laboratory setting, the width of the diffusion layer, h, can be improved by an increased stirring speed. However, this is not an option in the gastrointestinal tract. Therefore, to improve the dissolution rate without altering the solubility, both the surface area of the solid and the diffusion rate can be adjusted.

For surface area, the particle size of the solid can be reduced using techniques such as micronizing or even nanosizing. To improve the diffusion rate, the dissolution environment can be made more favorable by inclusion of co-solvents such as surfactants.

The Developability Classification System

The important distinction between solubility and dissolution was highlighted in the recently proposed Developability Classification System (DCS). Expanding upon the BCS, the DCS introduced key modifications to improve applicability to formulation development.[3] For example, biorelevant media was introduced to provide a more reliable assessment of in vivo solubility, and the BCS Class II was further divided into two sub-categories: DCS Class IIa and DCS Class IIb. Another modification was the shift in dose solubility ratio, resulting in a lower threshold for a molecule to be considered “soluble”.

As a result, the appearance of the DCS is different than the BCS, with the cut-off between DCS Class I and III and DCS Class IIa/b and IV appearing at a dose-solubility ratio of 500, as opposed to 250 in the BCS (Figure 3). Furthermore, the BCS II portion of the graph is split into two sections in the DCS to represent DCS Class IIa and IIb. This line, which separates the two sub-categories, is the solubility-limited absorbable dose (SLAD) line. It uses a ratio of solubility and permeability to determine if an increase in dissolution rate will have a measurable impact on overall absorption. Based on this ratio, a drug molecule is placed either above or below the SLAD line. Molecules above the line are dissolution rate limited (DCS Class IIa). Theoretically, if the maximum solubility is reached in a shorter period, absorption of the molecule can be enhanced; development should therefore focus on the dissolution rate. Molecules below the SLAD line (DCS Class IIb) have such a low solubility that no matter how quickly the drug gets into solution, there will not be a measurable impact on absorption. The fundamental challenge with DCS Class IIb molecules is therefore solubility.

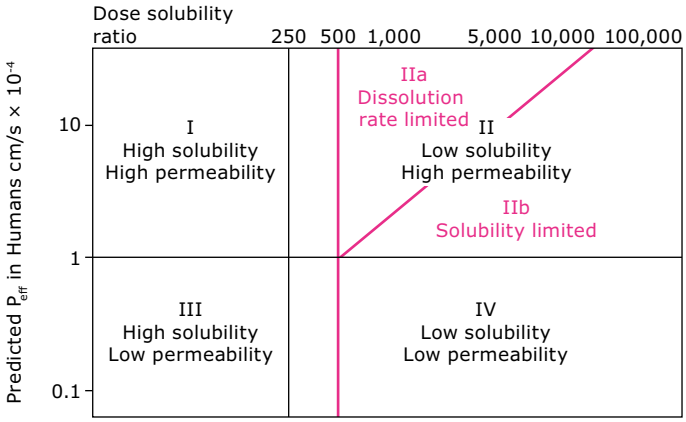


Figure 3.

The DCS is a modified version of the BCS, modifications in the DCS are shown in magenta.

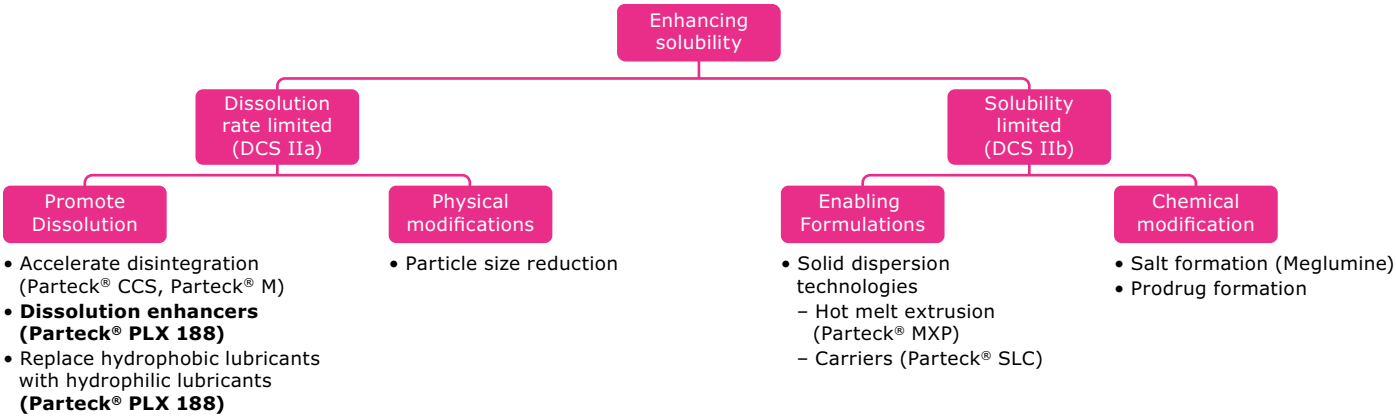


Figure 4.

Selection of formulation strategy for poorly soluble molecules can be guided by the DCS class of the molecule.

The value of having two new classifications to guide development of solubility enhanced formulations is clear. A more granular understanding of the root causes of solubility limitations – whether driven by dissolution rate or intrinsic solubility – can be used to guide design of optimized formulations rather than relying on trial and error. Figure 4 provides a workflow for selecting the best formulation strategy based the DCS class of a molecule.

Parteck® PLX 188 Excipient for Dissolution Enhancement

Parteck® PLX 188 excipient is an amphiphilic block co-polymer of poly(ethylene oxide) and poly(propylene oxide), which is especially suited for for solid dosage forms (Figure 5). Due to the amphiphilic nature of the poloxamer Parteck® PLX 188 excipient is ideally suited to act as a surfactant to enhance diffusion and subsequent dissolution rate of DCS Class IIa molecules. Parteck® PLX 188 excipient also conforms to the United States-NF and European Pharmacopeia and exceeds the regulatory requirements for specified formaldehyde content. As an Emprove® Essential qualified product, Parteck® PLX 188 excipient also comes with an extensive array of quality and regulatory documentation that can assist in the filing of applications to regulatory authorities and for internal risk assessments and Quality by Design (QBD) approaches.

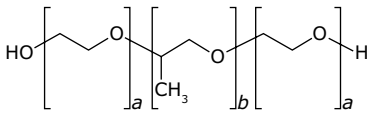


Figure 5.

Structure of poloxamer.

From a formulation perspective, Parteck® PLX excipient, due to favorable physical properties, is compatible with direct compression processes and simply needs to be incorporated into the tablet blend to enhance dissolution.

Parameter	Typical values
Particle size (D10) [µm]	~20
Particle size (D50) [µm]	~60
Particle size (D90) [µm]	~130
Molar mass [mol/g]	7,680–9,510
Angle of Repose [°]	49
Bulk density [g/mL]	0.47
Tapped density [g/mL]	0.63

Table 1.

Physical properties of Parteck® PLX 188 excipient.

Typical technical data for general characterization. Specification available at MerckMillipore.com.

An exemplary tablet blend consisting of poloxamer and standard excipients is shown in Table 2. For dissolution enhancement usually 2–10% of Parteck® PLX 188 excipient is required. However, even at concentrations as high as 30% effective tablets are obtained via direct compression (Figure 6).

Compound	Function	Amount
API	Active ingredient	<40%
DC Mannitol	Filler	45–95%
Parteck® PLX 188*	Dissolution Enhancer	1–15%
Crosscarmellose sodium (CCS)	Disintegrant	3–5%
Magnesium stearate	Lubricant	0.5–1.0%

Table 2.

Exemplary tablet composition when using Parteck® PLX 188 excipient.

*For use as a hydrophilic lubricant, Parteck® PLX 188 should be used in concentrations of 2–5%.

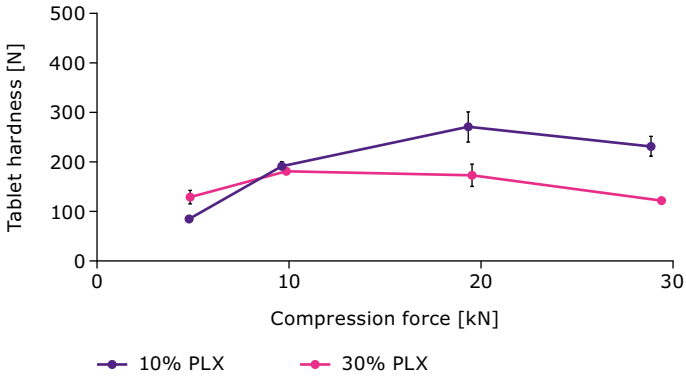
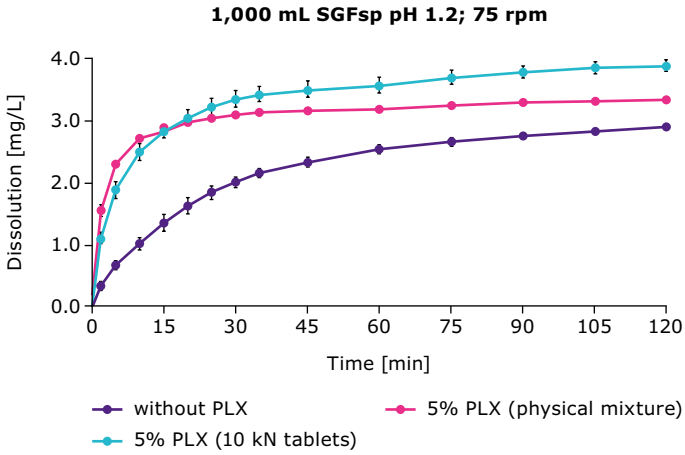


Figure 6.

Tablet hardness after direct compression when using 10% and 30% Parteck® PLX 188 excipient.

Dissolution enhancement with Parteck® PLX 188 excipient is quick, easy, and efficient using simple and effective direct compression processes. Once tablets containing Parteck® PLX 188 excipient contact aqueous media, for example in the GI tract, the polymer is dissolved and interacts with both the media and the molecule. Here, the amphiphilic structure of the polymer is important. The hydrophilic component of the polymer can interact with water, while the hydrophobic component of the polymer interacts with the molecule. This surfactant effect facilitates contact between the molecule and the media, thus accelerating dissolution. Figure 7 shows how Parteck® PLX 188 excipient can be used to enhance dissolution of the DCS Class IIa molecule itraconazole.



Compound	Content [%]
Parteck® PLX 188	5
Itraconazole	20
Parteck® M 200 DC mannitol	69
Crosscarmellose sodium (CCS)	5
Magnesium stearate	1

Figure 7.

Dissolution of itraconazole, a DCS Class IIa molecule, formulated with Parteck® PLX 188 excipient.

Parteck® PLX 188 Excipient Lubrication Effect

One additional benefit of Parteck® PLX 188 excipient is its dual functionality as a hydrophilic lubricant. In tablet production, lubricants are required to preserve tooling, prevent the tablets from sticking to the punches, and reduce ejection force. Magnesium stearate is the standard lubricant due to its good lubrication efficacy and attractive low price. However, it has several disadvantages, one being that higher amount of lubricant or excessive mixing can result in particle coating. In combination with plastic-deforming binders like microcrystalline cellulose, this particle coating can reduce the mechanical strength of tablets. Furthermore, the use of hydrophobic lubricants like magnesium stearate can also lead to a further reduction in dissolution rate due to strong interactions between the excipient and the molecule. Replacing magnesium stearate with Parteck® PLX 188 excipient can avoid this issue and enhance dissolution rate.

Figure 8 shows the ejection force when directly compressed tablets contained various concentrations of Parteck® PLX 188 excipient.

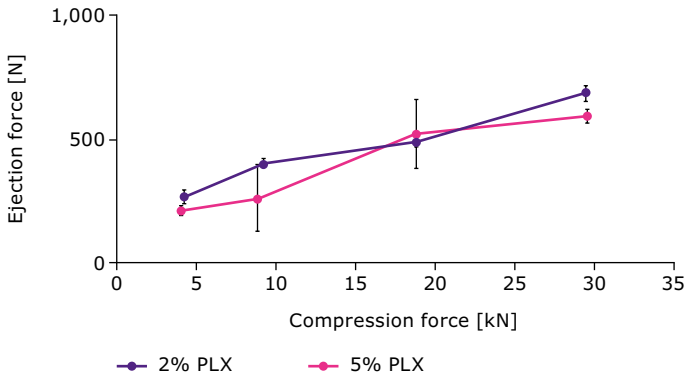


Figure 8.

Lubrication effect of Parteck® PLX excipient.

Parteck® PLX 188 excipient also has additional advantages compared to alternative hydrophilic lubricants due to the dissolution enhancement effects described previously. Figure 9 shows the dissolution rate of a tablet containing Parteck® PLX 188 excipient compared to one containing sodium stearyl fumarate.

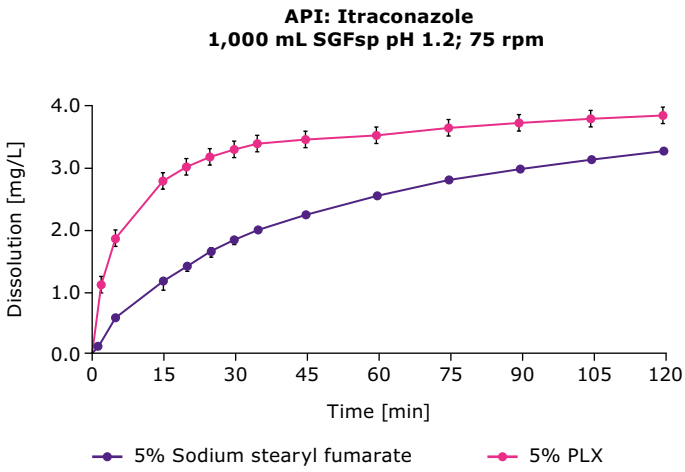


Figure 9.

Comparison of the lubricant's effect on the dissolution profile of a sample itraconazole formulation.

Conclusion

Absorption of molecules from the gastrointestinal tract is an essential consideration when developing orally delivered medications. Solubility, the concentration of drug in solution, is essential for this to occur and it is important to also consider the dissolution rate of the molecule. For DCS Class IIa molecules, defined as having a slow dissolution rate, simple yet effective formulations can be developed. Parteck® PLX 188 excipient should be considered for these challenging molecules to increase dissolution rate, provide hydrophilic lubrication, and enable simple and cost-effective manufacturing processes.

Reference

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Lit. No. MK_WP9214EN
03/2022