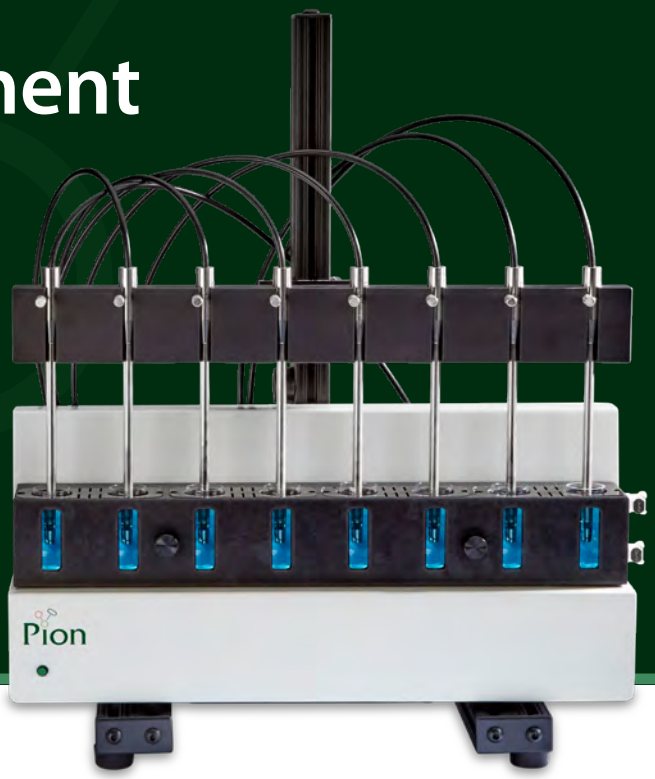
APPLICATION NOTE

Absorption-Driven Formulation Development

Using Absorption-Driven Development for Optimized Excipient Selection in Telmisartan Formulations



Pion's MicroFLUX™

Formulation development of poorly water-soluble active pharmaceutical ingredients (APIs) typically involves evaluating a range of excipients and formulation strategies to balance stability, compatibility, safety, manufacturability, and cost, without negatively impacting the *in vivo* performance.

The ability to predict *in vivo* performance earlier and throughout formulation development is therefore highly desirable. Even minor changes in formulation can significantly impact absorption behavior and invalidate earlier predictions. This challenge highlights the need for development tools that can capture formulation-dependent effects on absorption in a more dynamic and predictive manner.

USP guidelines emphasize dissolution testing as a primary *in vitro* surrogate for bioavailability assessment.[1,2] However, traditional dissolution methods do not provide a direct indication of drug absorption by permeation across biological membranes. In contrast, simultaneous dissolution–permeation approaches have been shown to provide improved prediction of *in vivo* performance.[3-6]

A growing body of evidence has further demonstrated the complex relationship between solubility and permeability, often referred to as the solubility–permeability interplay.[7] In many cases, formulation-driven increases in apparent solubility, such as those achieved through surfactants, cyclodextrins, or cosolvents, are accompanied by a corresponding decrease in permeability due to reductions in drug thermodynamic activity.[8-10] In contrast, formulations that generate supersaturation, including amorphous or lipid-based systems, do not alter the thermodynamic solubility of the API and therefore preserve intrinsic permeability.[11,12]

Amorphous solid dispersions (ASDs) represent a well-established strategy to enhance both dissolution and

oral bioavailability for poorly soluble compounds.[13] Electrospinning (ES) has emerged as an effective technique for ASD production, generating nano- and micro-fibrous materials from polymer–API solutions using electrostatic forces. Polymers used in ASDs are primarily intended to improve solubility through sustained supersaturation without altering equilibrium solubility, thereby providing a driving force for oral absorption and permeation across the intestinal membrane barriers.[14]

This application note describes how combined dissolution-permeation studies during formulation development yield better alignment between *in vitro* data and *in vivo* absorption behavior. A three-step process is used to systematically evaluate excipient effects on drug permeation, from the earliest stages of development through to final dosage form evaluation.

Step 1: Excipients are screened using the parallel artificial membrane permeability assay (PAMPA) to characterize API–excipient interactions and guide initial excipient selection for the formulations.

Step 2: The effect of individual excipients and formulation processes are evaluated using small-volume combined dissolution–permeation experiments performed with the MicroFLUX™ system.

Step 3: Biorelevant volumes are employed in large-scale dissolution–permeation studies using the MacroFLUX™ system to assess and compare the performance of final dosage forms.

The MicroFLUX™ and MacroFLUX™ systems are designed to simulate drug absorption by measuring the movement of compounds across a biomimetic lipid-coated artificial membrane, which separates a donor compartment (containing the sample) from an acceptor compartment (representing the bloodstream). The design allows for continuous, real-time measurement of drug concentration on either side of the membrane, enabling detailed assessment of drug dissolution, permeation, and the effects of different formulation strategies and excipients on absorption.

Case Study: Telmisartan

Telmisartan (TEL), an angiotensin II receptor antagonist with low solubility and high permeability according to the Biopharmaceutical Classification System (BCS), was used as a model drug in the study. The solubility of TEL is extremely low and pH-dependent (practically insoluble between pH 3 and 8).[15,16] Micardis®, the brand name formulation of TEL which contains the API in amorphous form, was selected as a reference product.[17] For complete details of the materials and methods used in this study, please refer to Kadar, *et al.*[18]

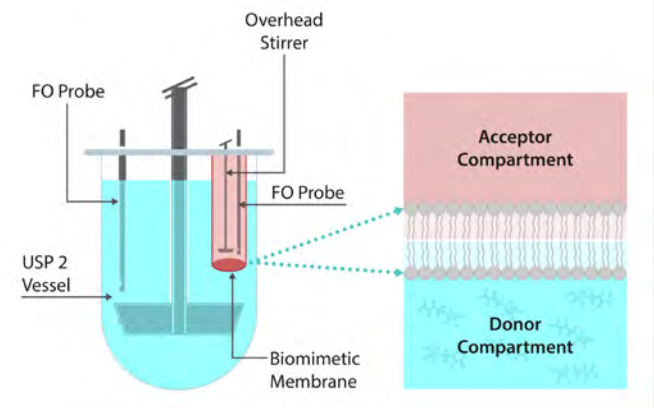


Figure 1. Schematic of the MacroFLUX™ system which is designed for simultaneous measurement of dissolution and absorption. Includes two fiber optic (FO) probes.

Step 1: Excipient Screening Using PAMPA

The initial stage of the workflow focused on excipient screening using PAMPA. Excipients present in commercially available TEL formulations, along with other commonly used formulation excipients, were evaluated to assess API–excipient interactions and their impact on membrane permeability.

As summarized in Table 1, inclusion of surfactants resulted in a statistically significant reduction in TEL permeability relative to the excipient-free control ($p < 0.05$). Reference permeability measurements obtained across different PAMPA plates showed low variability, confirming the robustness and reproducibility of the assay. Polymer-containing systems generally exhibited a modest, non-significant increase in permeability compared to neat TEL; however, formulations containing hydroxypropyl methylcellulose acetate succinate (HPMC-AS) produced a statistically significant enhancement in permeability.

Fillers demonstrated excipient-dependent effects on permeability. Sorbitol and lactose monohydrate were associated with a significant increase in TEL permeability, while mannitol had no measurable impact on permeability relative to the control.

In parallel with permeability testing, kinetic solubility

Table 1. Results of permeability measurements on the PAMPA platform

Type of additive	Additive	Additive concentration (µg/mL)	Pe (10^{-4} cm/sec)	SD	Reference API (Pe) (10^{-4} cm/sec)	SD	t-test (*p* value)
Surfactants/ complexing agents	**SDS**	**850**	**0.83**	**0.02**	**1.16**	**0.07**	**0.00**
	Tween 80	**0.45**	**0.86**	**0.02**	**1.16**	**0.07**	**0.00**
	HPβCD	1386	1.21	0.05	1.16	0.07	0.42
Polymers	HMPC 2910	212	1.22	0.06	1.16	0.07	0.60
	PVP K90	212	1.25	0.18	1.16	0.07	0.99
	PVP K30	212	1.31	0.15	1.11	0.07	0.06
	HPMC-AS	212	**1.28**	**0.10**	**1.11**	**0.07**	**0.01**
Fillers	**Sorbitol**	**667**	**1.42**	**0.10**	**1.11**	**0.07**	**0.00**
	Mannitol	667	1.23	0.20	1.11	0.07	0.41
	Lactose monohydrate	**667**	**1.39**	**0.06**	**1.16**	**0.07**	**0.02**

measurements were conducted. For poorly water-soluble compounds like TEL, thermodynamic solubility is extremely low (<1 µg/mL in fasted state simulated intestinal fluid – FaSSIF), making standard saturation shake-flask measurements impractical. Instead, kinetic solubility was assessed using *in situ* UV probes.[19] Surfactants such as Tween 80 and sodium dodecyl sulfate (SDS) significantly increased solubility while reducing permeability, while sorbitol decreased solubility and enhanced permeability. These trends are consistent with published reports on the solubility–permeability interplay.[10] Mannitol and the polymer excipients had no significant effect on kinetic solubility.

Based on the PAMPA permeability and kinetic solubility data, selected excipients, including both polyvinylpyrrolidone (PVP) grades, HPMC-AS, Tween 80, sorbitol, and mannitol, were used to prepare formulated samples as described in the following section.

Preparation of Amorphous Solid Dispersions by Electrospinning

Micardis® incorporates the API in an amorphous form to enhance oral bioavailability.[20] Consistent with this approach, an ASD–based formulation strategy with electrospinning as the manufacturing method was selected for ASD preparation. This technology enables the generation of amorphous solid dispersions through rapid solvent removal during fiber formation. Guided by the excipient interaction data obtained during PAMPA screening, electrospinning solutions containing TEL were prepared using a range of PVP polymers and HPMC-AS at equivalent concentrations, with or without Tween 80 surfactant.

Scanning electron microscopy confirmed uniform fibrous structures for PVP-based formulations, whereas HPMC-AS alone resulted in no fibers but the formation of spray-dried droplets instead. The addition of Tween 80 improved solution surface tension, enhancing fiber formation and process yield. All electrospun formulations including the spray-dried particles were confirmed to be amorphous by x-ray powder diffraction and were advanced to subsequent small-volume, combined dissolution-permeation studies.

Step 2: Small Volume Dissolution-Permeation Formulation Testing

Small-volume dissolution-permeation experiments were conducted using the MicroFLUX™ system (Figure 2). Donor dissolution media included a gastric-to-intestinal pH shift. All formulations exhibited complete dissolution in simulated gastric fluid (SGF) within the first 30 minutes and remained soluble during the intestinal stage (data not shown).

To assess excipient-specific effects on absorption, the ASD formulations were benchmarked against amorphous TEL alone. Because the donor concentration (loading dose) differed slightly between assays and the rate

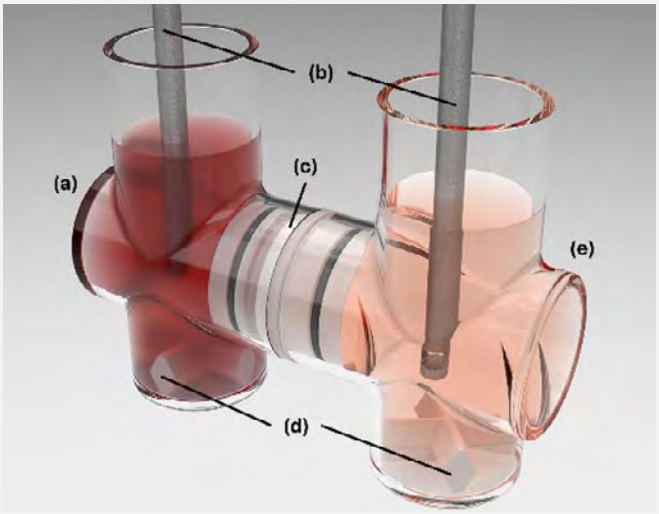


Figure 2. MicroFLUX diffusion cell pair with (a) donor compartment for collecting dissolution measurements, (b) fiber optic probes that transmit UV-Vis spectrometer data between the FLUX vessels and the Rainbow R6, (c) a lipid-coated, artificial membrane, (d) stir bars, and (e) an acceptor compartment for collecting permeation measurements.

of permeation (flux) is directly dependent on initial concentration, permeability was calculated to enable an accurate comparison of results.

Formulations containing Tween 80 consistently had significantly reduced permeation compared to surfactant-free systems (Table 2). Although Tween 80 increased electrospinning productivity by 100–200%, the reduction in permeability could negatively impact oral bioavailability. From a product quality perspective, PVP-based fibers were preferred over the beaded HPMC-AS particles, although polymer type had minimal effect on permeability. Consequently, only the surfactant-free PVP and surfactant-free HPMC-AS formulations were selected for advancement to the final dosage form stage.

Importantly, permeability trends observed in the MicroFLUX™ experiments were consistent with those identified during PAMPA screening and in rat intestinal permeability studies, supporting the predictive value of early excipient permeability assessment within absorption-driven formulation development.

Step 3: Large Volume Dissolution-Permeation Final Dosage Form Testing

Final dosage form tablets were prepared and evaluated using the MacroFLUX™ dissolution-permeation system. Both ASDs chosen for tableting (Tel_Na_HPMC-AS and Tel_Na_PVP) were mixed and pressed with mannitol and sorbitol fillers separately; as such, four different tablet versions were made by varying the polymer and the filler in the tablets as shown in Table 3.

Table 3. Composition of the final dosage form telmisartan tablets.

Ingredient	Composition (mg)	Composition (%)
Telmisartan	40	16.67
NaOH	3.6	1.5
Polymer (HPMC-AS/PVP)	2.4	1
Filler (Mannitol/Sorbitol)	191.6	79.83
Mg-stearate	2.4	1
Sum	**240**	**100**

Permeability measurements using the MacroFLUX™ were consistent with earlier screening results (Table 4). Polymers and mannitol produced slight, non-significant increases in TEL permeability, whereas sorbitol had a more pronounced enhancing effect. In most cases, the observed permeability reflected the combined, additive effects of the excipients.

An exception was the TEL_Na_HPMC-AS_mannitol

Table 2. Permeability data from small-scale dissolution-permeation assay of TEL-containing ASDs.

Formulation	Pe (10^{-4} cm/sec)	SD	t-test (*p* value) compared to amorphous
Tel_amorphous	1.19	0.09	—
Tel_Na_PVP	1.21	0.07	0.69
Tel_Na_HPMC-AS	1.21	0.06	0.68
Tel_Na_PVP + Tween 80	**0.74**	**0.12**	**0.01**
Tel_Na_HPMC-AS + Tween 80	**0.58**	**0.05**	**0.00**

Table 4. Permeability data from the large-scale dissolution-permeation assay of TEL-containing final dosage forms.

Formulation	P_e (10^{-4} cm/sec)	SD	t-test compared to amorphous (*p* value)	t-test compared to Micardis (*p* value)
Micardis	1.16	0.06	**0.01**	—
Tel_amorphous	1.03	0.03	—	**0.01**
Tel_Na_PVP _sorbitol	1.16	0.08	**0.05**	0.97
Tel_Na_PVP _mannitol	1.13	0.03	**0.02**	0.42
Tel_Na_HPMC-AS_sorbitol	1.15	0.07	**0.04**	0.93
Tel_Na_HPMC-AS_mannitol	1.07	0.05	0.21	0.09

formulation, where delayed tablet disintegration appeared to reduce permeability below expectations based on PAMPA data, suggesting potential interactions between the polymer and filler. Notably, the TEL_Na_PVP_sorbitol formulation showed permeability nearly identical to the brand product Micardis®, indicating that formulations with the same qualitative composition can reproduce similar absorption profiles. Modifying the filler alone, however, led to slight reductions in permeability relative to the reference product.

These results confirm that excipient choice, and particularly the filler identity, can meaningfully influence final dosage form absorption, and demonstrate that combined dissolution-permeation testing provides a predictive framework for optimizing permeability while maintaining bioequivalence.

Conclusion

This study demonstrates that absorption-driven formulation development provides a systematic framework for understanding how formulation decisions impact *in vitro* drug permeability and, ultimately, oral bioavailability. By considering not only dissolution and solubility but also membrane permeability at every stage of development, this approach enables more predictive, rational formulation design.

Early excipient screening using kinetic solubility and PAMPA successfully captured the solubility–permeability interplay of TEL across 10 excipients, guiding the selection of additives that enhanced absorption. Small-volume dissolution–permeation studies using the MicroFLUX system of ASDs highlighted that surfactants can significantly reduce drug permeability, potentially lowering oral bioavailability.

Large-volume dissolution–permeation testing using the MacroFLUX system of final dosage forms confirmed the early indications from PAMPA that sorbitol enhances TEL permeability relative to mannitol, a trend that is also reflected *in vivo*, where mannitol-containing products show lower C_{max} compared to sorbitol-containing formulations.[20] These findings underscore the importance of filler selection and demonstrate that permeability differences observed *in vitro* can meaningfully predict *in vivo* performance.

Overall, this study shows that incorporating permeability measurements from excipient screening to final dosage form evaluation offers a more informed and efficient pathway for formulation development. Absorption-driven formulation development leverages fast, cost-effective, combined dissolution-permeation screening tools to help developers optimize formulations while reducing reliance on late-stage clinical testing.

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