Speed to Market

CASE STUDY

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Background

Common drug products for phase 1 clinical studies, often selected for their simplicity

- Blend in bottle
- Blend in capsule
- API in bottle
- API in capsule

DATA REQUIRED FOR EACH COMPARED TO A FORMULATED PRODUCT

DRUG PRODUCT	STABILITY	ASSAY	DOSE RECOVERY/ UNIFORMITY	DISSOLUTION
BLEND IN BOTTLE	X	X	X	
API IN BOTTLE	X	X	X	
BLEND IN CAPSULE	X	X	X	X
API IN CAPSULE	X	X	X	X
FORMULATED PRODUCT	X	X	X	X

APPROPRIATE FORMULATION DEVELOPMENT

Plan for success

Interactions with clinical development

- SAD and MAD
- Phase 2 - no need for bridging study
- Accelerate to Phase 3 with a commercially viable product

Look at key API attributes

- Compressibility
- Chemical and physical stability
- Form change
- Wettability and processability

Simplified QbD approach with small batches of prototypes

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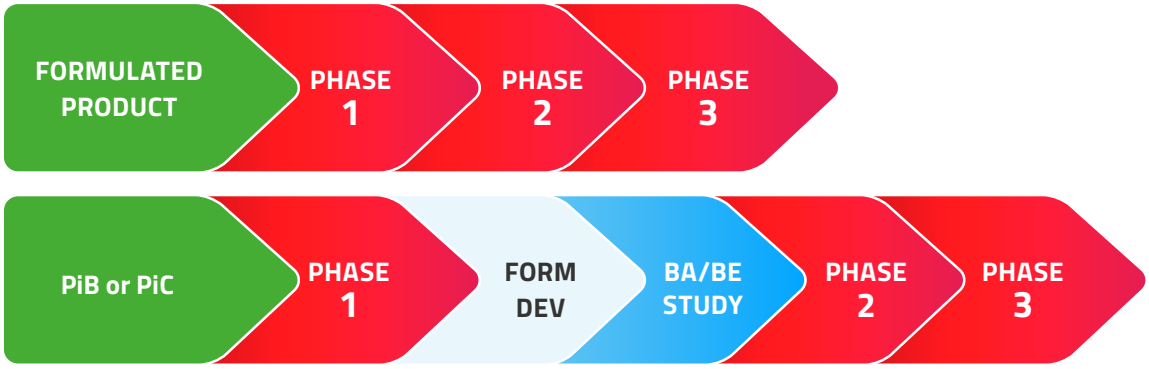
TIMELINE IMPLICATIONS



FASTER APPROACH

- Begin formulation and process development as soon as the API arrives.
- Proceed directly to prototype development using common, low risk excipients. This means skipping excipient compatibility studies for now.
- Make tablets using a wet or dry granulation process to avoid any potential issues down stream.
- Develop fit for purpose methods, i.e. clinical phase appropriate.
- Where possible, use automated processes, i.e. automated tablet preparation workstations, automated multi-dose dissolution apparatus, automated disintegration tester.
- Initiate stability studies using tablet prototypes.
- Maintain flexibility in GMP manufacturing schedules to accommodate project specific needs including delays in API delivery from the onset.
- Accelerate timelines for GMP preparations and release testing.

LATEST TURNAROUND TIME FROM RECEIPT OF API TO CLINICAL DOSING (EU) WAS 8 MONTHS

(4 TABLET STRENGTHS AND PLACEBOS)

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Example #1: API in Capsule

CAN YOU MAKE THIS EXISTING FORMULATION (API IN CAPSULE) WORK?

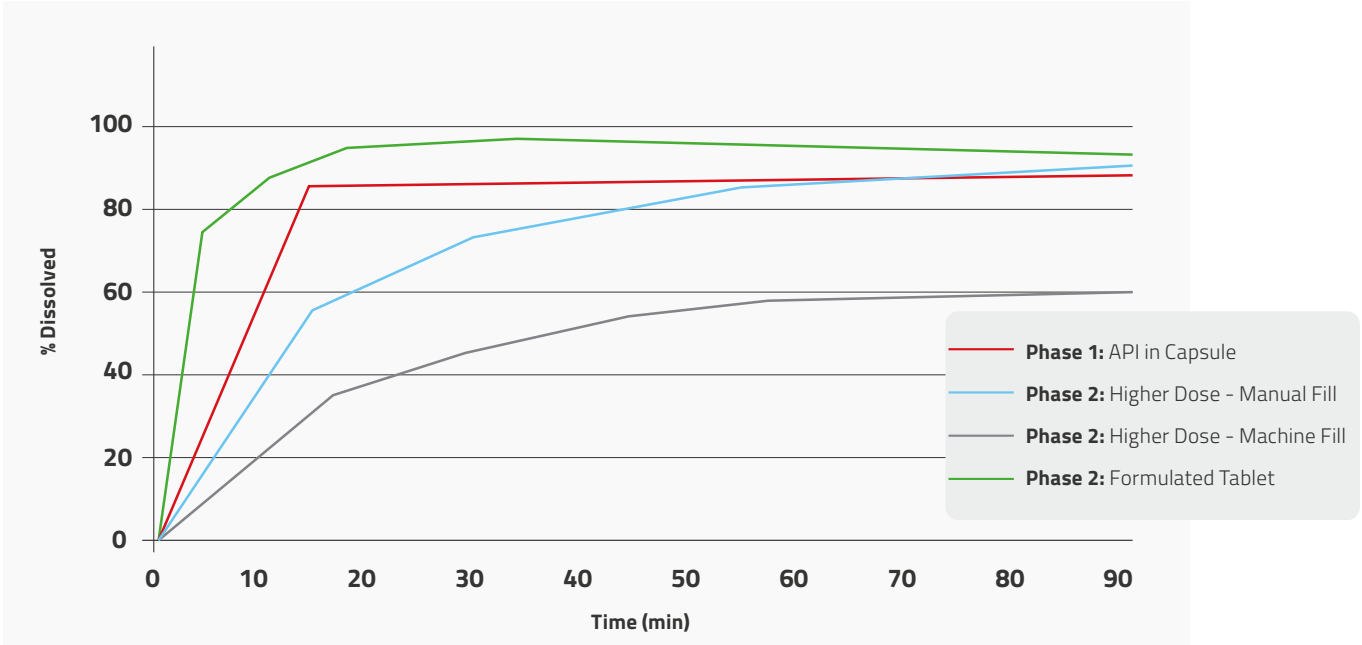
API CHARACTERISTICS

- Low solubility, high dose
- Concerns that plasma concentrations were plateauing at higher dose
- Targeting a higher dose for phase 2 studies
- Change in API vendor

THE FASTEST SOLUTION WOULD BE TO NOT CHANGE THE FORMULATION

#1

DISSOLUTION



THE RESULTS

- Successfully developed 3 strengths of a phase 2 tablet formulation
- Successfully transferred the formulation and process to GMP for CTM supply
- Met phase 2 clinical dosing date
- Initial development to clinical manufacturing in 10 weeks

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Example #2: Simple Blend in Capsule

- Accelerated phase 3 program
- Simple blend in capsule was developed years ago
- Low dose product
- Consistently demonstrating low recovery dissolution

#2

SOLUTIONS

- Developed dry granulation process with similar excipients
- Suitable as a tablet or capsule formulation
- Reduced risk of segregation
- Complete release demonstrated with optimized formulation
- Replaced filler with a simpler grade

KEY CONSIDERATIONS

- Use equipment representative of commercial scale equipment
- Identify edges of processing
- Identify the key attributes of the API that need to be addressed early in development
- Clearly set expectations on target product profile early with the project team

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Need to Move Fast? Start with a Tablet

- The drug development pathway is notorious for being long, complex, and costly. However, there are some innovative approaches that have successfully been used to save time when speed-to-clinic or speed-to-market is critical. One strategy that accelerates clinical drug product timelines is shown below.
- The drug candidate was only entering phase 1 clinical studies, and the associated timeline for clinical supply was so aggressive that the simplest solutions, for example, drug-in-bottle, initially appeared best. However, there was no time allotted later for dosage form development or subsequent BE/BA bridging studies, so the decision was made to pursue either a tablet or capsule from the onset. To avoid any potential stability issues, a tablet was selected.
- A traditional formulation and process development project for a solid oral dosage form typically starts with pre-formulation studies to characterize the API before moving to excipient compatibility studies, generating prototypes, and establishing lead and back-up formulations. These initial development milestones generally take at least 2-3 months to complete, but in this case that was too much time.
- Instead, the formulation team focused on key API attributes (chemical and physical stability of the API, and form changes), together with compressibility, wettability and processability. With this in mind, the team immediately devised a simplified QbD approach with small batches of prototypes that contained common, low risk excipients. This meant deferring excipient compatibility studies until later. The team also selected a dry granulation method of manufacture to improve powder flow properties and ensure acceptable content uniformity. In parallel, the analytical team started method development and validation activities.
- A commercially viable product was successfully accelerated through phases 1 and 2 and into phase 3 with this strategy. The scientific risk-based approach to tablet development reduced by one third (from 12 months to 8 months) the typical turnaround time from receipt of API to clinical dosing of four tablet strengths and placebos.

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