NOVEL ORAL DRUG DELIVERY: INNOVATING TO SIMPLIFY

In this article, Rashmi Nair, M Pharm, Senior Scientist, Formulation R&D, and Praveen Raheja, M Pharm, Principal Scientist, Formulation R&D, both of Dr. Reddy's Laboratories, Custom Pharmaceutical Services division, use case studies to illustrate their company's approach to simplifying existing oral drug delivery systems, including osmotic and matrix tablet technologies.

Drug delivery is a very important aspect for consideration during any drug development. The clinical and commercial success of a drug can be greatly affected by the route of administration as well as the drug delivery formulation. Given the advantages of oral drug delivery,[1] it has been an area of progressive evolution.[2,3]

The necessity to improve a drug's functional aspects like dosage regimen, *in vivo* drug stability, bioavailability, etc, has been the key driver of innovation in oral drug delivery. Some of these innovations brought complexity of product design and the manufacturing process. Various proprietary technologies have become the costly sophisticated solutions for oral drug delivery. Without undermining the importance of these drug delivery technologies, it is imperative to understand what creates a successful drug delivery system and evaluate whether existing drug delivery technologies can be simplified to suit conventional manufacturing. The following case studies for oral, controlled drug delivery of small molecules show that systematic science can simplify some of the sophisticated technologies.

APPROACH FOR SIMPLIFICATION

Defining the objective of product development with detailed enlisting of target product features is the first step. This should be followed by identifying what aspect of product or process requires simplification and possible alternatives that could be evaluated. Experimental design for testing the proposed alternative approach is the final stage. A typical step-plan for product development is depicted in Figure 1. Customised schemes of development are provided here with respective case studies.

CASE STUDY 1: OSMOTIC TABLETS SIMPLIFIED

The Osmotic Release Oral System (OROS) developed by ALZA Corporation (now J&J) in the 1990s is a commercially successful technology with various products incorporating it available in the market.[4] Merits of this technology have been validated with various drugs and therefore, for a formulator, it is probably the first choice when it comes to developing zero-order drug release for any product.

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Small laser drilled holes on the tablet surface provide precise drug release. However, there are limitations like the complexity of manufacturing requiring a different machine, a non-deformable tablet that remains as end product, and the technology associated cost. A development scheme for this case is depicted in Figure 2. Pseudoephedrine hydrochloride tablets 240 mg utilising OROS

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technology were taken as the target product. With immediate-release and extended-release components, it was a challenge to obtain zero-order drug release. Nevertheless, a matrix tablet was developed that was coated with extended-release coating and further coated with a drug layer. A successful bioequivalence study proved the validity of this work. Figure 3 depicts the approach summary.

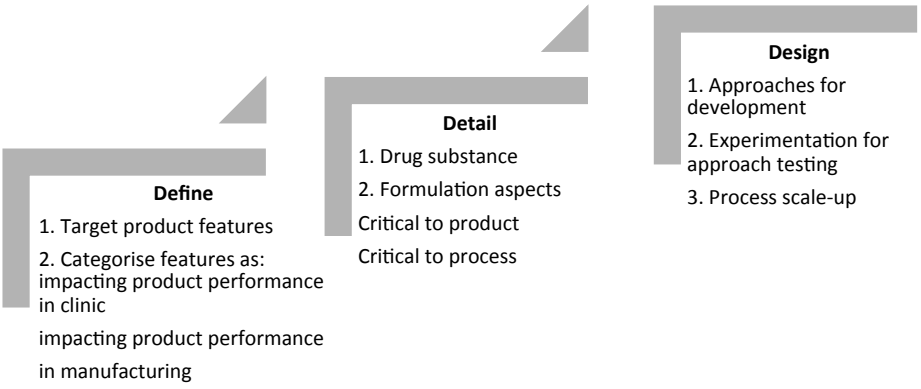


Figure 1: A typical step-plan for systematic product development.

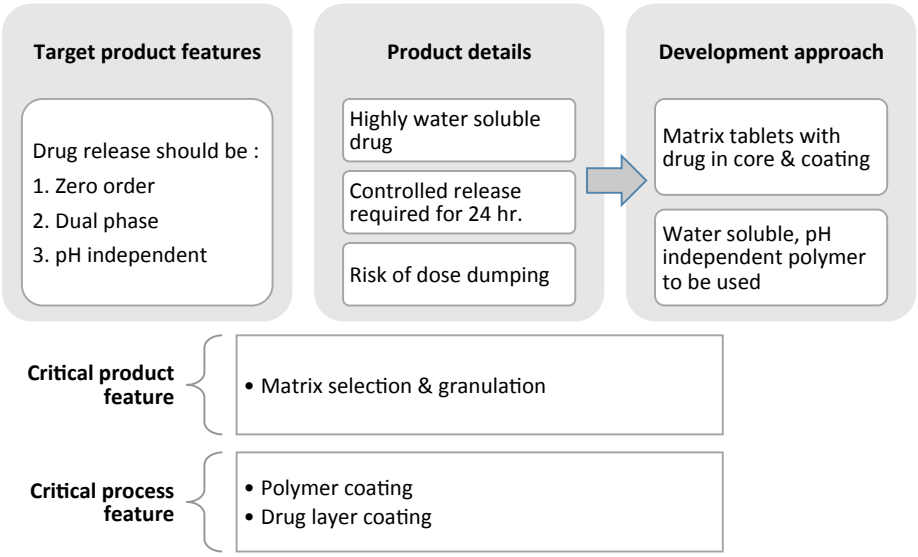


Figure 2: Scheme for development of matrix tablets.

CASE STUDY 2: MATRIX TABLETS MINIATURISED

A high-dose, highly water soluble drug required a compact dosage form. The marketed product was a large capsule with extended release pellets. This product was difficult to swallow and was not accepted well by patients. Mini matrix tablets were developed which resulted in product and process improvement. A mixture of high viscosity HPMC and carboxy methylcellulose salt were used in the matrix. The pelleting process took about 18 hours per batch manufacturing, whereas this approach simplified the process and reduced process time to less than six hours per batch. Humidity control was a critical consideration for extended-release coating of pellets. With this approach ambient conditions could be used and all process happened on conventional machines. The development scheme and approach summary are presented in Figures 4 and 5, respectively.

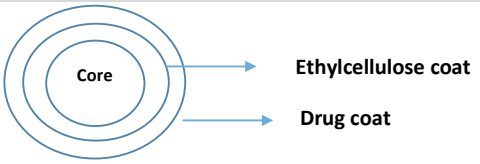
CASE STUDY 3: FLEXIBILITY BY DESIGN

A clinical study program for an NCE was conducted with a tablet dosage form. The study program required multiple, dose-ranging studies for monotherapy and additionally a fixed-dose combination.

Product design

75% drug in core

25% drug in drug coat



Performance testing (in-vitro)

Time (hr.)	% Drug release in dissolution study	
	SUDAFED 24	CPS product
1	27	27
2	29	28
6	47	48
12	76	78
18	96	94
24	103	99

Performance testing (in-vivo)

Mean linear plot for fed state bioequivalence study

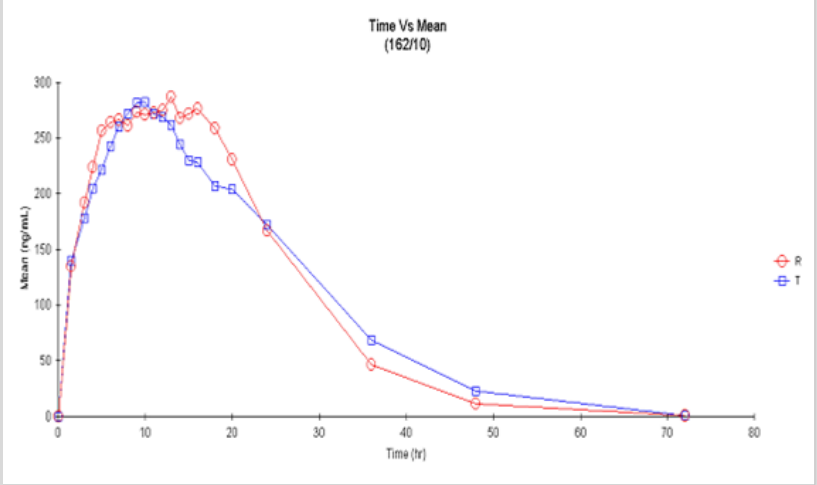


Figure 3: Summary of concept-to-product for matrix tablets.

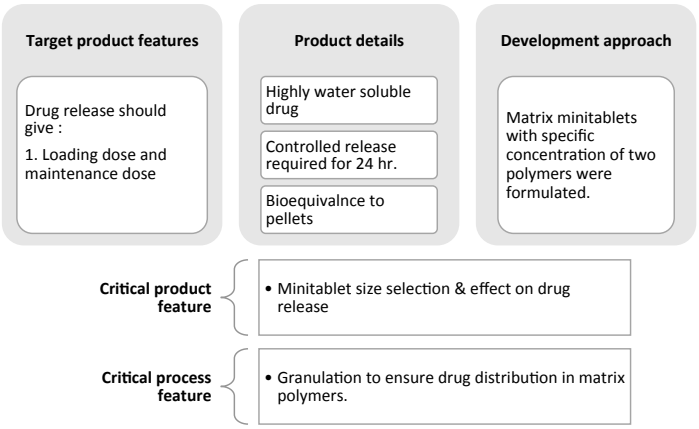
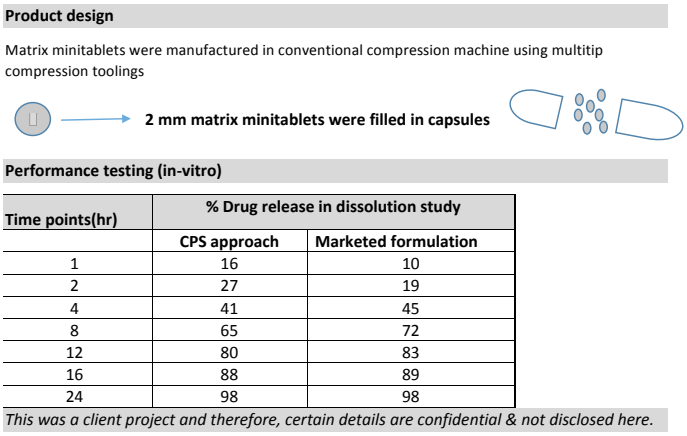


Figure 4: Scheme for development of matrix minitablets.



Time points(hr)	% Drug release in dissolution study	
	CPS approach	Marketed formulation
1	16	10
2	27	19
4	41	45
8	65	72
12	80	83
16	88	89
24	98	98

This was a client project and therefore, certain details are confidential & not disclosed here.

Figure 5: Summary of concept-to-product for matrix minitablets.

Different drug release profiles were required. A Wurster process for pellets was developed which allowed production of multiple drug release profiles from a single batch. This provided flexibility of adjusting the dose (by changing fill weights of pellets), tailoring different drug release profiles (by changing coating load) and making different permutations and combinations with the second drug for the fixed dose combination product.

CONCLUSION

In each of the above cases, the objective of the product development team was to design the best possible product utilising simple scientific principles and product experience. A thorough understanding of various aspects of a drug product, like the physicochemical properties, pharmacokinetics, target sites of absorption and action, excipients, manufacturing processes and critical product parameters, are essential to assess the development approach for a drug product holistically.

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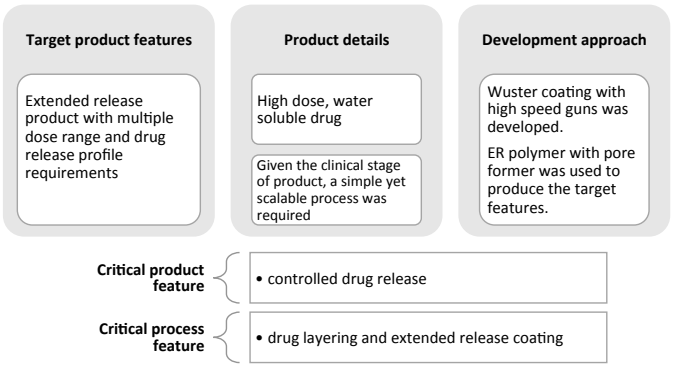
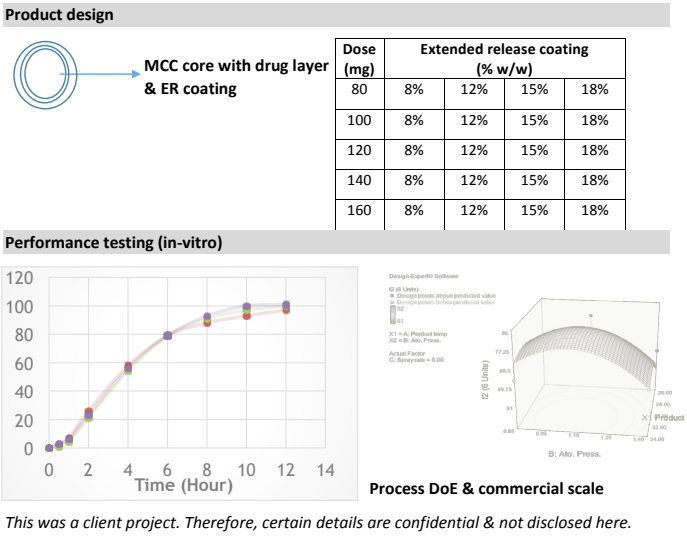


Figure 6: Scheme for development of extended release pellets.



Dose (mg)	Extended release coating (% w/w)			
80	8%	12%	15%	18%
100	8%	12%	15%	18%
120	8%	12%	15%	18%
140	8%	12%	15%	18%
160	8%	12%	15%	18%

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Figure 7: Summary of concept-to-product for extended release pellets.