Assessment of the feasibility of oral controlled release in an exploratory development setting

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Controlled release (CR) formulations have generally been considered as follow-ons to conventional immediate release formulations to manage the life cycle of a product. Although significant opportunities exist to use CR as an enabling technology for certain exploratory drug candidates, they have not been fully exploited. However, progress made in assessing CR feasibility based on the physicochemical and biopharmaceutical properties of the drug, together with advances made in understanding the various CR technologies and developing formulations in a fast and efficient manner, have increasingly made it possible to consider CR in an exploratory development setting.

Only a few years ago, controlled release (CR) was usually restricted to managing product life cycle, enhancing the proprietary position of marketed drugs and expanding and consolidating a product franchise. CR technologies were mostly licensed from small specialized drug-delivery companies. Although large pharmaceutical companies maintained internal CR formulation development (primarily as backup), the focus was on developing the next generation of new chemical entities (NCEs). Nowadays, CR is considered earlier in the development of drug candidates, primarily because it has been recognized that CR formulations represent a cost-effective way to progress candidates, compared with eliminating the deficiencies of a compound using discovery approaches. The rapid progress of drug candidates using the most appropriate formulation approach [from first-in-human (FIH) studies to clinical proof-of-concept (POC)] is particularly important when investigating a novel pharmacology (i.e. first-in-class).

The rationale for CR is the same for product enhancement and exploratory development (ED). There are two major reasons for pursuing CR formulations. First, the market expects once-daily dosing, so compounds with a short half-life, which require more-frequent dosing, might not be attractive to develop. Second, CR can sometimes minimize the undesirable side-effects related to high and rapidly increasing peak plasma levels. In product enhancement, improved product safety and efficacy, and the resulting expansion of market position are primary drivers. In ED, CR formulations could represent an attractive alternative to terminating the clinical development of a compound and starting again by identifying new candidates in the discovery phase.

In the past, CR development programs have been technically complex, requiring a large quantity of the drug substance and several iterations in the clinic to achieve and optimize the desired drug-release profile. It was not uncommon to develop three (or more) formulations with different release rates, obtained, for example, by selecting different polymer grades and levels in a matrix tablet formulation. The resource-intensive nature of CR formulations has been a major hurdle in exploring them in an ED setting and a source of major dilemma for project teams. Consider a drug candidate that has C_{max}-related

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GLOSSARY

Absorption rate constant (k_a). Rate constant characterizing drug absorption – generally first order or zero order.
Active pharmaceutical ingredient (API). Also referred to as 'active ingredient' or 'drug substance'. Any component that is intended to provide a pharmacological activity. Inactive Ingredients or excipients are components other than the API.
Asymmetric membrane technology (AMT). An osmotic drug delivery device that consists of a drug-containing core surrounded by an asymmetric membrane (i.e. with dense and porous regions). It provides prolonged release of drugs having good aqueous solubility by the osmotic pumping mechanism.
Caco-2. Human colonic adenocarcinoma cells that are used to determine intestinal permeability to assess the potential for oral dug absorption in humans.
Controlled release (CR). The science that deals with dosage forms intended to provide a therapeutic amount of drug to a specific site or location at the desired rate. Often used interchangeably with modified release (MR). MR dosage forms include both delayed release (i.e. those that release a drug at a time other than immediately after oral administration) and extended release (i.e. those that make the drug available over an extended period).
Cytochrome P450. A large group of enzymes present in the liver and small intestine. They play a major role in the metabolism and interactions of drugs.
Cytochrome P450 3A4 (CYP3A4). A member of the cytochrome P450 group, it is arguably the most important enzyme involved in the metabolism of xenobiotics. CYP3A4 is involved in the oxidation of the largest range of substrates of all the cytochromes, correspondingly, it is also present in the largest quantity of all the cytochromes in the liver.
Immediate release (IR). Dosage forms, such as solutions and conventional tablets and capsules, that allow the drug to dissolve in the GI tract with no intention of delaying or prolonging the dissolution or absorption of the drug.
Intestinal vascular access port (IVAP). A method for delivering drugs directly into the duodenum, jejunum, ileum or colon of a conscious beagle dog by using catheters, to assess regional drug absorption.
New chemical entity (NCE). A new drug that has not been previously approved by the FDA.
P-glycoprotein (P-gp). A 170 kDa transmembrane glycoprotein, normally expressed in the epithelial cells of the liver, kidney, intestine and the endothelial cells of the blood–brain barrier. It serves as an efflux pump and limits the exposure of a variety of chemicals including many drugs. P-glycoprotein substrates are generally moderately lipophilic, basic (or uncharged), and have a molecular weight between ~250 and 1900 Da.
Pharmacokinetics (PK). The study of the bodily absorption, distribution, metabolism and excretion of drugs.
Proof-of-concept (POC). Clinical studies aimed at validating the mechanism of action of the drug candidate and provide initial data on efficacy and safety.
Single pass intestinal perfusion (SPIP): An anesthetized rat model to evaluate intestinal permeability. For passively transported compounds, the effective permeability in the rat model correlates well with human intestinal permeability and the fraction of drug absorbed after oral administration.
Swellable core technology (SCT). An oral drug delivery platform that uses osmotic pressure and polymer swelling to deliver drugs with moderate-to-poor aqueous solubility over a prolonged duration. SCT formulations typically consist of a bilayer tablet core, containing the drug and a water-swellable composition. The core is coated with a semipermeable membrane that is laser-drilled on the drug side to provide a delivery port.

toxicity that limits the maximum dose that can be administered; or a drug with a short half-life that cannot provide adequate receptor occupancy over a 24 h period unless dosed very frequently. In these situations, a conventional tablet formulation might not be suitable to test the pharmacological hypothesis and achieve POC. If development teams choose to continue development with a suboptimal immediate release (IR) formulation, they run the risk of not testing the full potential of the drug candidate. In these situations, CR formulations represent an enabling technology for candidate progression.

These considerations have made it imperative to assess the feasibility of developing a CR formulation and selecting the most appropriate CR technology for a drug candidate. It is desirable to be able to rapidly develop CR formulations that have robust *in vitro* and predictable *in vivo* performances, thereby avoiding the need to develop multiple formulations or conduct several iterations in the clinic to identify the optimal drug-release profile. It is also important to manage expectations – a CR formulation might not be able to resolve all pharmaceutical issues and it is important to know when a CR formulation represents a reasonable likelihood of success and when it should be considered as a 'long-shot'. This review discusses CR feasibility assessment at the ED stage in the setting of a large pharmaceutical company with discovery and development operations. Considerations in late stage development, such as product and process robustness, ease of scale-up and commercialization and applicability of technologies to control the product quality, are not discussed.

CR feasibility assessment

Most pharmaceutical companies assess the 'developability' or 'drugability' of oral drug candidates to ensure that, in addition to potency and specificity, the candidate also has physicochemical properties that will result in good oral absorption and bioavailability [1–5] evaluated against specific criteria (e.g. Lipinski's Rule of Five) [6]. CR feasibility assessment is conducted in a similar manner, to evaluate the physicochemical and biopharmaceutical properties of the drug candidate in an effort to determine its suitability for CR formulation development. It can be carried out at any stage of development of a compound for which a CR dosage form is being considered. The assessment should address the degree of difficulty and the probability of success, provide an estimate of the resources and timelines required, recommend the CR technology and provide dosage-form development guidance.

The amount of information available on the drug candidate will depend on its stage of development. Most companies have a nomination document to recommend a drug candidate for development. This will usually include key attributes, such as chemistry, biology, pharmacology, safety and preclinical pharmacokinetics, including some basic biopharmaceutical characterization. This is a valuable source of general information about the candidate and its therapeutic objectives. The General Pharmaceutics profile [7] contains a more detailed physicochemical characterization of the compound and will generally include solid- and solution-state characterization, including the pH-solubility and pH-stability profiles, an analysis of absorption and the biopharmaceutical classification system (BCS) class of the drug candidate [8]. It should be noted that BCS is applicable only to IR dosage forms but some considerations and modifications have been proposed for CR dosage forms [9,10]. Other sources of information include the Investigator's Brochure and any

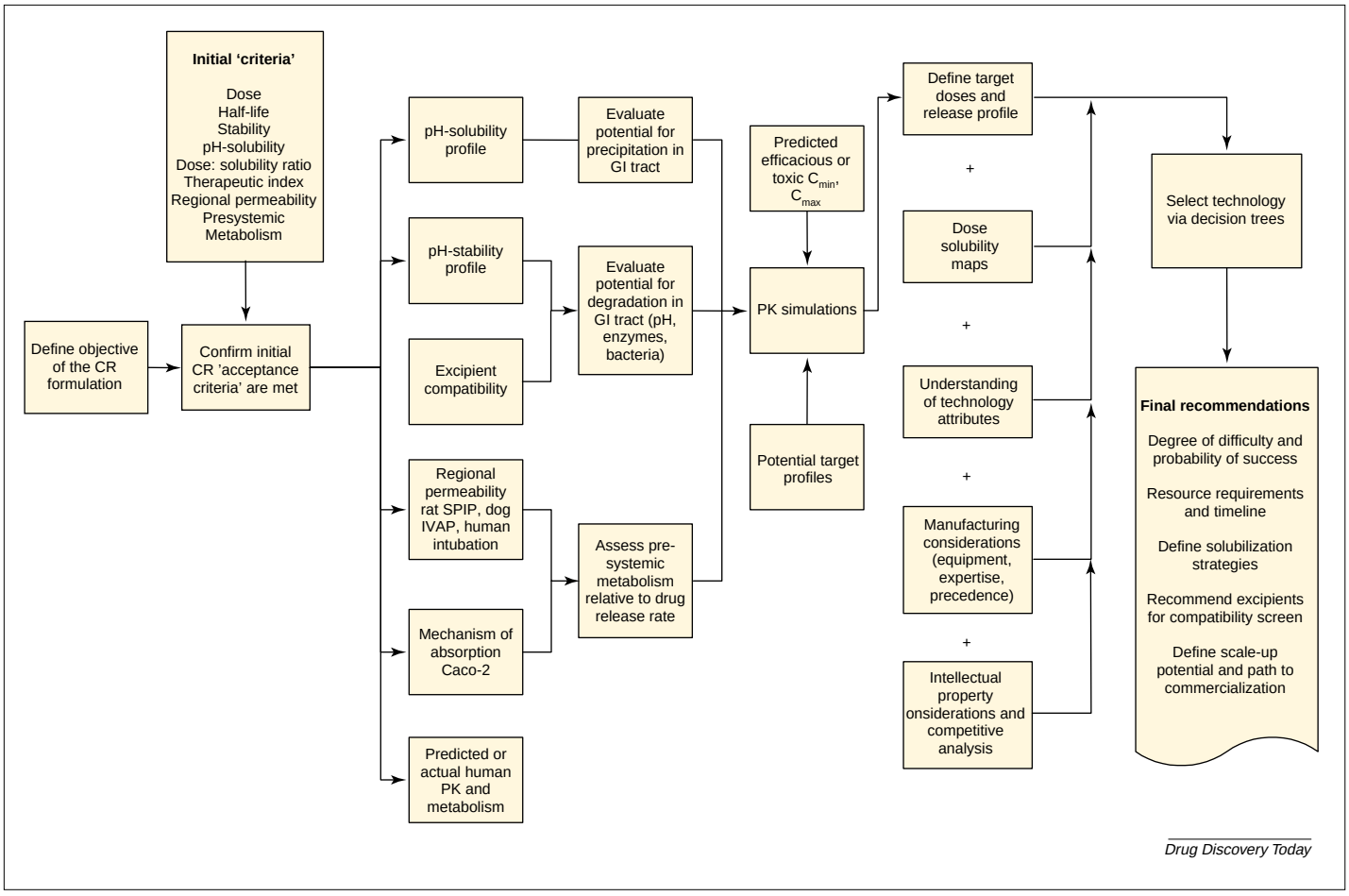

FIGURE 1

Controlled release feasibility assessment flow chart. Abbreviations: CR, controlled release; GI, gastrointestinal; IVAP, intestinal vascular access port; PK, pharmacokinetic; SPIP, single pass intestinal perfusion.

investigational new drug (IND) application that might have been submitted.

The flow chart in Figure 1 shows the steps in conducting a typical CR feasibility assessment. The components of the flow chart are discussed below.

CR objectives

Assessment starts by defining the objectives for a CR formulation. The key objectives could be to reduce the dosing frequency and thereby increase compliance, to increase the duration of effect or maintain a specific C_{min}, to decrease the systemic side effects by lowering the C_{max} or to improve therapy by reducing blood level fluctuations (i.e. by lowering the C_{max}:C_{min} ratio). These needs could translate to a CR dosage form with a 12–16 h delivery duration. However, if a CR formulation is needed to decrease side effects caused by local exposure of the drug to the upper gastrointestinal (GI) tract or to avoid degradation of acid-labile drugs, an appropriate delivery profile might consist of a time lag (~2 h) after oral administration followed by release over a 2–4 h duration. If CR is needed to blunt the peak plasma concentrations and reduce C_{max}-related side effects, the dosage form might have a 4–6 h delivery duration.

Initial criteria

The initial criteria (Table 1) are used to quickly assess the suitability of a drug candidate for CR development. They are classified into physicochemical, biopharmaceutical and pharmacokinetic (PK) or metabolism factors. It should be understood that the ranges given in Table 1 are empirical simple rules-of-thumb and they can be different depending on the properties of the drug candidate and prior experience in a company. Ideally, each drug candidate should be analyzed on a case-by-case basis because many of the factors are interrelated. Thus, for example, drug content uniformity is a complex function of the proportion of drug in the powder blend used to make the tablets, the properties of the inactive ingredients, such as particle size, and the processing variables, such as mixing time and whether or not the blend was granulated. Content uniformity not necessarily a development issue for doses <1 mg and it can sometimes be an issue even for doses >1 mg. Similarly, 250–300 mg represents a 'soft limit' because tablet size depends on the density of materials used in the formulation, and some tablet shapes are easier to swallow than others. The acceptable tablet size can also depend on the therapeutic area and the age

TABLE 1

Initial criteria in controlled release feasibility assessments

Physicochemical factors		Comments
Dose	<1 mg	Greater development complexity (potential drug content uniformity issue)
	10–250 mg	Average degree of difficulty
	>>250–300 mg	Could need more than one tablet to accommodate the drug load
Dose:solubility ratio (highest dose ÷ lowest solubility in the pH range 1–7.5)	<1 ml	Several technology options exist for CR development
	1–100 ml	Average degree of difficulty
	100–1000 ml	CR development will be challenging but feasible
	>1,000 ml	Need solubilization – CR development will be difficult
	>10,000 ml	CR development practically impossible
Stability	Generally stable as a solid or solution and with common CR excipients	Predict average degree of difficulty
	Compound shows or is predicted to have significant degradation	Predict higher degree of difficulty
Biopharm factors		
Absorption mechanism	Transcellular passive diffusion	Average degree of difficulty
	Other mechanisms including efflux	Performance could be difficult to predict
Regional permeability (colonic absorption)	Poor absorption, $P_{app,\ Caco\text{-}2}<10^{-6}$ cm/s, k_a <0.01 min^{-1}	CR formulations with prolonged delivery duration may not be feasible. Likely will not be bioequivalent to IR
	Moderate absorption, $P_{app,\ Caco\text{-}2}=10^{-6}$–$10^{-5}$ cm/s	CR development challenging but feasible. Might not be bioequivalent to IR
	Good absorption, $P_{app,\ Caco\text{-}2}>10^{-5}$ cm/s, k_a >0.01 min^{-1}	CR development should be feasible. Likely to be bioequivalent to IR
PK factors		
PK or PD half life	<1–2 h	Half life too short for CR development
	2–10 h	Acceptable half life
	>>10 h	Compound might not need CR for reducing dosing frequency
Metabolism and efflux	High presystemic or first pass metabolism	Relative BA of CR formulation might be low
	Compound is P-gp or CYP3A4 substrate	CR performance difficult to predict (depends on dose and K_m, V_{max})

of the patient population. Finally, formulation scientists can often find novel and creative solutions to many technical hurdles, and prior experience with similar compounds will impact positively on development time and the probability of success.

Challenges in CR formulation development

The major hurdles for oral CR development are the same as those for IR development: solubility, permeability, stability and metabolism. However, in the case of IR formulations, the drug is released and essentially absorbed in the upper GI tract. By contrast, CR formulations release the drug throughout the GI tract. Thus, in addition to GI transit of the CR dosage forms, the factors mentioned above must be considered as a function of position in the GI tract. Therefore, the solubility of the drug candidate over the entire physiological pH should be considered. Surfactants, such as bile, might not be available in the lower GI tract to solubilize the drug, which could be an important consideration for a CR dosage form that releases a portion of the drug in the lower GI tract. Also, regional permeability in the gut has to be taken into consideration. Prior to being systemically available, the drug might be metabolized by enzymes present in the gut wall or liver. The amount of drug metabolized depends on the concentration of drug, and, in some cases, high concentrations can saturate this metabolism. Because the concentration of drug released from CR dosage forms can be quite different to IR dosage forms, and because the local distribution of these metabolizing enzymes can vary along the GI tract, drug bioavailability could be different when released from a CR compared with IR dosage form.

Solubility

CR formulations are designed so that the drug-release rate from the formulation controls the rate of drug absorption. However, in some cases, absorption could be limited by the solubility or dissolution rate of the drug. Weakly basic drugs might be soluble in low gastric pH but can sometimes

precipitate at higher intestinal pH. Published information is limited on evaluating whether a drug can exist as a supersaturated solution, the potential for drug precipitation in the GI tract [11] and on modeling the impact of drug precipitation on absorption [12]. Also, in the case of many CR technologies, the release rate depends on the solubility of a drug. Thus, the solubility is an important consideration that influences the choice of CR technology.

Stability

The pH and enzyme stability profile can help in the assessment of drug stability in the GI tract. Preformulation studies, such as drug–excipient compatibility studies aimed at predicting the stability of drug in the presence of inactive ingredients used in formulations, are conducted in pharmaceutical development to help guide selection of formulation components [13]. These can be easily extended to include excipients commonly used in CR dosage forms. The binding of drug compounds to colon contents and the degradation of drugs by colonic microflora is not routinely studied but models have been developed to assess whether these factors could limit drug absorption from a CR formulation [14].

Permeability

Predicting human intestinal permeability using purely computational methods and *in vitro* and *in vivo* animal models is an active area of research, and several review articles are available on this topic [15–19]. Assessing and predicting drug absorption as a function of the position of the drug in the GI tract is important because this dictates whether long delivery duration, which might be needed for once-daily dosing, is feasible. Several factors can cause a decrease in colonic absorption, leading to poor bioavailability. These include solubility- or permeability-limited absorption, limitations due to insufficient water in the colon, and bacterial degradation or adsorption to fecal matter. There are several direct and predictive methods for assessing colonic absorption [20]. Human colonic permeability has been correlated to permeability in Caco-2 cells [21–23], to the absorption rate constant determined by rat single pass intestinal perfusion (SPIP) [24], to colonic dosing in beagle dogs via an intestinal vascular access port (IVAP) [25,26] and to colonoscopy-based methods [27]. Direct methods to determine colonic permeability include human intubation studies [28], PK scintigraphy studies using devices like the Enterion™ capsule (Phaeton Research) [29,30] and studies using a dosage form designed to release all or some portion of the drug in the colon [31,32].

Efflux and presystemic or first-pass metabolism

Efflux transporters, such as P-glycoprotein (P-gp) [33,34], located in intestinal enterocytes, and metabolizing enzymes, such as cytochrome P450 (CYP), especially the isoform CYP3A4, located in the liver and the gut wall, can influence the *in vivo* performance of CR formulations in two ways. First, these processes are dependent on the drug concentration, which will vary depending on whether the drug is released rapidly (from an IR formulation) or slowly (from a CR formulation). Second, P-gp synthesis and CYP3A4 activity varies as a function of position in the GI tract [35]. P-gp synthesis has been reported to increase from proximal to distal regions of the small intestine [36], so a decreasing absorption of drugs that are P-gp substrates can be expected during their transit through the small intestine. However, CYP3A4 expression decreases in the colon, so one might expect increased absorption of drugs that are CYP3A4 substrates in CR formulations, as seen in the case of oxybutynin chloride [37]. Food intake can also affect the presystemic clearance of drugs [38].

PK simulations

The use of PK simulations to design a CR dosage form [39–41] is a crucial component of CR feasibility assessments. In addition to custom-written computer programs, several simulation software programs are commercially available [e.g. Kinetica™ (Innaphase), Berkeley Madonna™ (University of California at Berkeley), and GastroPlus™ (Simulations Plus)]. The simulations should take into account the predicted efficacious or toxic plasma concentration, the therapeutic objectives of the drug and the potential delivery profiles to predict single-dose or steady state PK. The selection of CR technology is partly a result of what the simulations indicate regarding the projected performance of a formulation. The CR technology, in turn, influences what doses and delivery profile options are reasonable from a formulation standpoint, which will influence the simulations. Thus, PK simulations are best performed in collaboration with a formulation scientist. If information on colonic absorption is limited, simulations can be carried out assuming low, medium and high colonic absorption to explore the expected performance. Simulations also represent a valuable communication tool for project teams to describe what a CR dosage form could accomplish. In some cases, PK simulations can be used to provide examples in patent applications.

CR technology selection

There are a large number of CR technologies available to dosage form development scientists. Typical oral systems include: hydrophilic [42–44] and lipophilic [45] matrix tablets; osmotic systems, such as the asymmetric membrane technology (AMT) [46] or swellable core technology (SCT) [47]; and multiparticulates including those made by fluid-bed or melt-spray-congeal processes [48]. Drug release from hydrophilic matrix tablets is primarily controlled by diffusion through the matrix. AMT and SCT are examples of systems that use osmotic pressure and swellable polymers to pump out a solution or suspension of drug through one or more delivery ports. Multiparticulates control drug release by diffusion through a barrier membrane. In addition, several specialized technologies are available from drug delivery companies. It is suggested that each technology should be understood and characterized in great detail. In

addition, each technology should be profiled for preferred excipients, preferred manufacturing processes and critical process variables, and prior experience with the technology.

The factors influencing the selection of the CR technology include: match between the technology attributes and physicochemical and biopharmaceutical properties of the drug candidate (i.e. ability to achieve the desired dose and delivery duration target); ease of adapting to a pediatric formulation; and manufacturing factors, including prior experience with the technology, in-house processing expertise, the availability of commercial-scale equipment and the robustness of performance on scale-up.

In an ED setting, some additional factors to consider are: ease and speed of initial development and predictability of the *in vivo* performance; breadth of applicability (i.e. whether the technology is a 'platform technology' independent of the physicochemical properties of the drug); and dosing flexibility (i.e. whether the technology can deal with several doses and changing doses). Further factors are the intellectual property protection afforded [49–52], and initial capital investment required, to manufacture the dosage forms. It is also important to consider dosage form development complexity, the development time and the bulk required.

A particularly useful, although simplified, way of looking at technology selection is by using a dose–solubility map (Figure 2). Although it is obvious from the preceding discussion that the dose and solubility of the drug candidate are important factors in the selection of the CR technology, consideration of the dose:solubility ratio also has significant theoretical rationale because it represents the volume of fluid required to dissolve the dose and it is related to the mean dissolution time [53–55].

Rapid development of CR formulations

There are several unique aspects to developing CR formulations for ED candidates. The key considerations are:

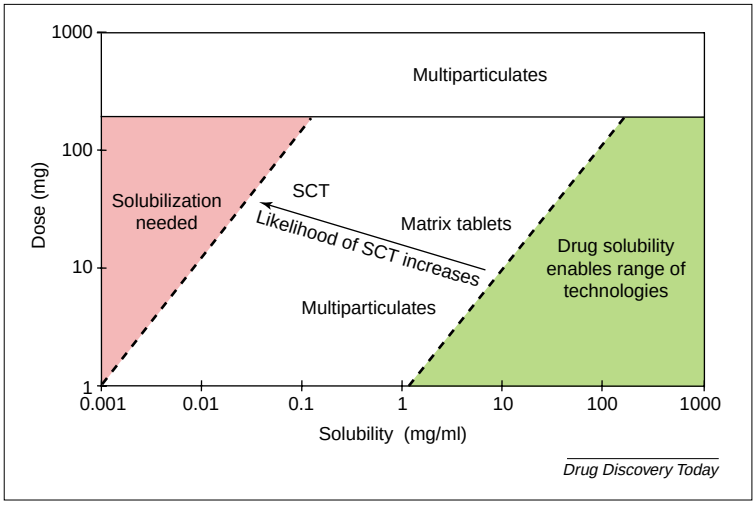

FIGURE 2

Example of a dose–solubility map to guide controlled release technology selection. Abbreviation: SCT, swellable core technology.

unknown pharmacology and unknown doses; limited supply of the drug substance; high candidate attrition frequently prompting a strategy of low initial investment in formulation technology; the desire to keep clinical studies ongoing to meet the major project milestones; and speed to reach POC. Some strategies for fast and efficient development of CR formulations in an ED setting are presented in Table 2.

Examples of CR feasibility assessments

Example 1: Drug A

CR was considered for Drug A because it has a short effective half-life of ~3 h. PK simulations indicated that to maintain the efficacious plasma concentrations of >5 μg/ml, high and frequent dosing of an IR tablet would be required (800 mg twice daily or 400 mg three times daily). The compound was a weak acid (pK_a of 3.9) with a solubility of 0.4 mg/ml at pH 1–3 and >100 mg/ml at pH 7. Based on structural similarity with a previous candidate, the chemical stability was predicted to be poor under acidic conditions. The permeability was good with a k_a of 0.017 min^{-1} in rat. Regional absorption studies were carried out using the intestinal vascular access port (IVAP) dog model. The data showed that compared with oral administration, the area under the curve (AUC) and C_{max} for colonic administration were 50% and 23%, respectively.

A CR formulation was not recommended for Drug A for the following reasons:

- High-dose PK simulations (assuming no decrease in bioavailability) indicated that a CR dose of 1.2 g would be required to maintain a C_{min} of 5 μg/ml. Even with a lower C_{min} target of 3.5 μg/ml, a dose of 875 mg would be needed.
- Reduced colonic permeability, as evident from the dog data, coupled with the need for a long delivery duration.
- Poor predicted chemical stability with excipients commonly used in CR formulations.

Example 2: Drug B

CR was needed for Drug B to reduce the high dosing frequency related to its short half-life (2.5–3.8 h) and to reduce C_{max}-related side-effects. The projected dose strengths were 3 and 10 mg. The compound was a weak base with a pK_a of 7.7. The solubility was >100 mg/ml at pH 4 and ~5 mg/ml at pH 7. It had excellent solid-state stability; solutions were most stable at pH 3 and showed no light sensitivity. The rat k_a of 0.01 min^{-1} indicated moderate absorption. The compound was classified as BCS Class III (high solubility, low permeability).

The dose–solubility map for Drug B indicated that an AMT dosage form would be suitable. The CR feasibility assessment recommended development of 3 and 10 mg strengths and AMT formulations with 12 and 24 h release duration. A lower bioavailability relative to an IR formulation would be expected for the longer duration formulation

TABLE 2

Strategies for fast and efficient development of CR formulations in an ED setting

Strategy	Comments
Complete a CR feasibility assessment before initiating a development project	Avoiding work on unsuitable candidate can save a year or more; CR might not be able to resolve all pharmaceutical issues and it is important to know when a CR formulation is likely to succeed
Work with the best estimates for dose and dosage strengths	Use multiple tablets to cover the desired dose range; consider multiparticulates to allow dose flexibility
Get the delivery duration right	Evaluate the drug candidate's pharmacology, assess colonic absorption using predictive methods or by regional absorption studies in humans to select the appropriate delivery duration; consider osmotic tablets with good *in vitro–in vivo* correlations
Conduct PK simulations	Valuable tool for communication to project teams; help selection of proper doses and delivery duration
Get the drug form and stability right	Strike a balance between waiting for extensive stability data and progressing prototype formulations to the clinic using 5°C storage and/or restrictive packaging; consider statistically designed excipient compatibility studies
Know CR technologies – guarantee *in vitro* and *in vivo* performance	Preserve institutional knowledge and prepare detailed development manuals for each CR technology; avoid situations where it is not clear if there was a dosage form failure
Establish development teams with production department	Manage team expectations; start dialog with colleagues in Manufacturing as early as deemed practical – especially if equipment and processes are novel

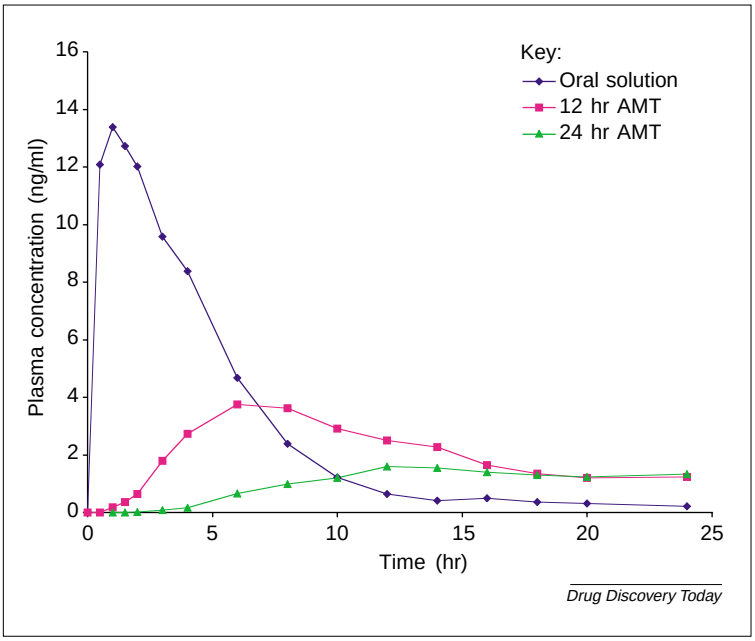

FIGURE 3

***In vivo* performance of controlled release formulations of Drug B.**
Abbreviation: AMT, asymmetric membrane technology.

because of the poor predicted colonic permeability. Other CR dosage forms such as hydrophilic matrix tablets are also feasible but would need to be buffered at the steep portion of the pH-solubility profile.

As recommended by the CR feasibility assessment, AMT formulations with 12 and 24 h delivery durations were developed for Drug B. Figure 3 shows the plasma concentration versus time profiles in humans. The performance was as expected with lower C_{max} and longer T_{max} using CR formulations. As predicted, the longer duration CR formulation had a lower exposure relative to the IR formulation but, when corrected for AUC, both formulations showed excellent *in vitro–in vivo* correlation.

Conclusions

CR formulations represent a cost-effective way of progressing some exploratory drug candidates. A framework is presented to assess the feasibility of developing CR formulations, which includes matching the physicochemical and biopharmaceutical properties of the drug to the desired target-release profile while considering the key attributes of various CR technologies. Included in the assessment is an evaluation of the degree of technical difficulty and the probability of success. The key properties of the drug candidate include the aqueous solubility and permeability along the length of the GI tract (particularly the colon). Advances in CR technologies have made it possible to deliver compounds with a wide range of physicochemical properties, and it is therefore possible to consider compounds that previously could not meet 'developability' criteria. Furthermore, with knowledge and experience, CR formulations can be developed in a fast and efficient manner and selection of the most appropriate CR technology is facilitated by the use of empirical dose–solubility maps. However, some key boundaries on the dose–solubility map will have to be further established based on growing experience. Streamlining the development of CR formulations will make it possible to rapidly progress drug candidates to POC.

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