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Preformulation Considerations for Controlled Release Dosage Forms: Part I Selecting Candidates

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Abstract. The physical–chemical properties of interest for Controlled Release (CR) dosage form development presented are based on the author's experience. Part I addresses selection of the final form based on a logical progression of physical–chemical properties evaluation of candidate forms and elimination of forms with undesirable properties from further evaluation in order to simplify final form selection. Several candidate forms which could include salt, free base or acid, polymorphic and amorphic forms of a new chemical entity (NCE) or existing drug substance (DS) are prepared and evaluated for critical properties in a scheme relevant to manufacturing processes, predictive of problems, requiring small amounts of test materials and simple analytical tools. A stability indicating assay is not needed to initiate the evaluation. This process is applicable to CR and immediate release (IR) dosage form development. The critical properties evaluated are melting, crystallinity, solubilities in water, 0.1 N HCl, and SIF, hygrodymamics, i.e., moisture sorption and loss at extremes of RH, and LOD at typical wet granulation drying conditions, and processability, i.e., corrosivity, and filming and/or sticking upon compression.

KEY WORDS: candidate form selection; critical solubilities; hygrodynamics; logical selection.

INTRODUCTION

These papers present an overview of the physical–chemical properties relevant to the development of Controlled Release (CR) dosage forms. The overview is presented as a preformulation scheme using practical examples representing the experience of the author. Part I—Candidate Selection, describes the initial preformulation support phase in which candidate forms or a solo form are evaluated, from which optimal forms are identified, and a final form for continued development is selected. The selection process follows a logical path in which forms with undesirable properties are eliminated from further study reducing the number of candidates and simplifying selection of a final form for dosage form development.

Preformulation support is neither new nor novel to dosage form development. It is more frequently applied to immediate release (IR) dosage form development than to CR dosage form development, because most new chemical entities (NCEs) are developed as IR dosage forms, and CR is usually used in line extension to extend the life cycle of an existing drug substance (DS). However, CR dosage form development is applicable at any stage of development.

The term form applies to a specific NCE or DS salt, free base or free acid, polymorph or amorph. During the discovery phase, an NCE is usually synthesized in very small batch sizes, e.g., ≤5 g, and recovered by recrystallization as a salt form that is easily isolated, dependent upon experience and preference. In many pharmaceutical firms, the promotion of an NCE from discovery to development status results in the preparation of additional candidate forms that are evaluated for their physical–chemical properties in order to identify optimal forms from which a final form is selected for dosage form, preclinical, clinical and commercial development. This same tactic can be applied to any DS intended for line extension as a CR dosage form.

The very first scale up batch of an NCE is usually small in size, likely to be 25 to 50 g in size, and is intended to be shared for use in preformulation support and preclinical dose ranging studies. The number of forms that can be made is limited by the availability of the NCE and number of forms that are successfully prepared. Some laboratories engage in deliberate attempts to create new polymorphs. These experiments might be better suited for the next phase of development after selection of a final form and more DS is available. Also, accidental creation and discovery of polymorphic forms is more likely during the next phase of development. For these reasons polymorphism is discussed in Part II.

The primary objectives of preformulation support for CR and IR dosage forms are the same, to select an optimal form of an NCE or DS for development and provide adequate physical–chemical characterization of the candidate to facilitate dosage form development. In instances where chemistry, patents, or contracts limit the form to one form, that one form

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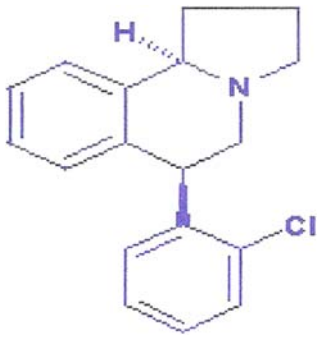

Fig. 1. Structure of McN-5707 (free base)

is evaluated to identify its physical–chemical properties and to identify its strengths and weaknesses.

The physical–chemical characterization of the forms should be quick and involve evaluations that are relevant to the expected dosage form manufacture, predictive of potential processing problems, require small amounts (5 to 7 g) of NCE or DS and easily available analytical tools, and not require a stability indicating assay.

The methods presented were derived and used to resolve problems that occurred previously. Simple analytical tools are used for much of the evaluation. X-ray powder diffraction (XRD) and DSC analysis are available from contract laboratories if not available in house. Chromatographic analysis is preferred for solubility measurements.

PROPOSED PREFORMULATION SCHEME

The applicability of the proposed preformulation scheme can be demonstrated with a review of the needs for CR dosage form development. CR can be created by reducing the rate of dissolution by increasing the particle size, creating matrices with waxes and polymers using heat or physical mixtures, applying cellulosic or pH sensitive polymers to tablets, particles or beads, formation of salts with ion exchange resins or salts such as pamoate and tannates which are practically insoluble in aqueous media. Controlled dissolution of more soluble salt forms can be created to deliver NCEs/DSs over 8, 12 and 24-h periods using osmotic pumps and pore forming systems. Pulsatile delivery systems that use pH sensitive polymers to release a DS at specific sites within the GI tract have created once daily dosing regimens for products that previously required two to three times a day dosing. Effective once a day dosing has also been achieved for a DS with an inherently long half-life originally formulated as an IR low dose two to four times a day dosage form by increasing the strength of the tablets 5- to 20-fold. GI residence times and absorption capabilities have been used to create CR by employing mucoadhesives and geometric forms to increase stomach residence times. And an apparently reverse CR tablet product is marketed in which a CR coat limits dissolution in the upper GI, and an IR core quickly releases the DS into the lower GI where there is limited absorption through the GI lumen.

The physical–chemical and pharmaceutical properties that are candidate form dependent and critical to the selection process are: melting behavior and crystallinity; processability, i.e., measuring the potential for filming and sticking on compression, and corrosivity (tablet press turret) at ambient room temperature and 83%RH; critical solubilities at ambient room temperature in water, hydrochloric acid, 0.1 N, and Simulated Intestinal Fluid, pH 6.8 (current) or 7.4 (previous USPs); hygrodynamics, weight change after drying at 49° or 50°C for 16 to 24 h; and storage for 1 week at ambient temperature and extremes of humidity, 11% RH and 83% RH, respectively. These properties are of interest to both CR and IR dosage form development.

CANDIDATE SELECTION

The 1977 publication, Pharmaceutical salts by Berge, Bighley and Monkhouse (1) is the primary source for identifying potential candidate salt forms for evaluation and selection of a form for development. It lists over 100 organic and inorganic anionic and cationic salts of drug substances (DSs) in marketed products at the time of publication. Several strategies might be employed based on the criteria for creating CR. One strategy could be to prepare salt forms that are poorly soluble or practically insoluble in water in the range pH 1.3 to 6.8 or 7.4. Another strategy would be to prepare a number of salts that include aliphatic, aromatic, sulfonic acid and inorganic salts and determine which have properties most applicable to the intended mechanism or delivery system. The number of salts prepared is dependent upon the availability of the NCE/DS and the success of salt formation trials. In exceptional cases more forms may be prepared until a form with optimal or nearly optimal properties is identified.

The term optimal form is used because of the impracticality of determining the best form. Optimal forms are the forms that comply best with the intended mechanism or delivery system and meet applicable patents and purity requirements for the NCE/DS. In some cases the NCE or DS form may be dictated by patent, contract or chemistry and there is only one form for evaluation. And in some cases, the

Table I. Melting, Crystallinity, Corrosivity Potential and Filming and Sticking on Compression Test Results for McN-5707 Candidate Forms

Candidate Form	Melting Range, °C	XRD Crystalline	Corrosivity Potential	Filming and Sticking
Free base	95–96	Yes	None	Slight
Hydrochloride	95–98	Yes	Very Severe	Omitted
Sulfate	190–193	Yes	Severe	Omitted
Phosphate hydrate	189–192	No	None	Slight
Fumarate	191–193	Yes	None	< Slight
Maleate	157–159	Yes	None	Slight
Tosylate	192–195	Yes	None	Omitted
2-Napsylate	141–144	Yes	None	Omitted

optimal form may have one or more undesirable properties. A complete description of the analytical methods has been omitted; however, they are available upon request.

PRACTICAL EXAMPLE OF CANDIDATE FORM SELECTION

McN-5707 (Fig. 1), has demonstrated antidepressant activity in animal models, a MW of 283. IR dosage form development anticipated a human dose based on animal pharmacology models of 100 to 400 mg per tablet three to four times a day and a much higher dose load for CR dosage form development. High aqueous solubility was identified as one of the critical criteria for optimal form selection.

Eight candidate forms, the free base, hydrochloride, fumarate, maleate, 2-napsylate, phosphate hydrate, sulfate and tosylate salts were prepared by the Chemical Development Department of McNeil Pharmaceutical in ~5 g batch sizes. The eight forms include inorganic, aliphatic, aromatic and sulfonic acid salts, all of which are listed in the 1977 article, Pharmaceutical salts (1).

Melting Behavior and Crystallinity. The melting ranges of all eight forms determined by the Chemical Development Department using a Hoover capillary melting apparatus are reported in Table I. All eight forms melt at temperatures ≥95°C. This temperature is higher than the temperatures that might be used to form a melt matrix and higher than temperatures that might be encountered in fluid bed coating and drying processes. Capillary melting data were used because they were reported by Chemical Development. However, Differential Scanning Calorimetry (DSC) would have been a better choice, possibly providing data regarding transitions and post melting behavior.

The crystallinity of all 8 forms was determined using X-ray powder diffraction (XRD). The XRD patterns of all but the phosphate hydrate were characteristic of crystalline compounds (Table I). This observation was noted despite an observed capillary melting range of 189–192°C. The cause of these differences was not investigated at the time of testing. XRD sample preparation may have affected the crystallinity of the phosphate hydrate.

Processability–Corrosivity Potential. Corrosivity testing (2) was performed on all eight candidates to determine the likelihood of tablet press turret rusting during manufacture during long compression runs or between runs in the absence of a complete equipment cleaning (Table I). The sulfate and hydrochloride forms exhibited severe corrosivity and were eliminated.

Table III. Weight Changes on Exposure to Typical Drying Temperatures and Extremes of Humidity

	Hygrodynamics, Weight Change %		
		1 week at 24°C	
Candidate Form	Drying 24 h at 49°C	11% RH	83% RH
Free base	−0.18	+2.60	0.0
Phosphate hydrate	+0.60	−0.70	+1.76
Fumarate	−0.03	+0.04	+0.03
Maleate	−0.11	+2.16	+0.04

+/− Signs added for clarity

Critical Solubilities. Solubilities were determined for six forms in water, 0.1 N hydrochloric acid and Simulated Intestinal Fluid (SIF, pH=7.4 at time of testing) at 25°C using an HPLC assay with UV detection. These media represent *in vivo* conditions within the GI tract, potential *in vitro* dissolution test media, preclinical and early clinical drug delivery systems.

The solubilities of the six forms are listed in rank order in Table II. The solubilities of all six candidates in SIF are very low, and the differences are negligible. The tosylate and 2-napsylate are appreciably less soluble than the four other forms and were eliminated from further consideration and testing. The observed 24.8 mg/mL solubility of the free base in 0.1 N hydrochloric acid is a result of *in situ* salt formation. Four forms remain for consideration and testing, the free base, phosphate hydrate, fumarate and maleate salts.

Processability—Filming and Sticking on Compression. The compression test measures the potential for filming and sticking to tooling during tablet compression. All five forms (Table I) exhibited slight or less slight filming/sticking behavior in this test. The problem is minor and could be corrected by one or more granulation techniques or avoided by using an alternative CR mechanism.

Hygrodynamics. These tests measure the gain and loss of weight on exposure to tray drying conditions, 49° or 50°C and to exposure at extremes of RH and ambient temperatures (Table III). The humidity test is predictive of hygroscopicity and tendencies to gain or lose water due to variations in environmental RH. The latter could affect potency and analytical test results for the DS or drug product. Incubation

Table II. Critical Solubilities of Six McN-5707 Forms in 0.1 N Hydrochloric Acid, Purified Water and SIF (pH 7.4) at 25°C

	Solubilities, Expressed as the Free Base Equivalent, mg/mL		
Candidate Form	0.1 N HCl	Water	SIF, pH 7.4
Free base	24.8	0.0038	0.0045
Phosphate hydrate	23.7	9.14	0.0093
Fumarate	12.7	1.75	0.0088
Maleate	8.63	3.16	0.0120
Tosylate	0.627	0.634	0.0067
2-Napsylate	0.647	0.630	0.0072

in a high RH chamber can also be used to desolvate a DS form.

The drying temperatures and humidity chamber conditions were based on institutional preferences and instrument availability. Another drying temperature might be more suitable than 49°–50°C for a specific application, and programmable vapor sorption apparatuses are available which expose a much smaller sample to ambient or controlled temperature and ramping relative humidity conditions while measuring sample mass.

The phosphate hydrate gained weight under all of the conditions of testing suggesting that it is hygroscopic, which would present as a problem for formulation and analyses. The fumarate salt behaved the best under these test conditions.

The amorphic phosphate hydrate salt appears to gain water during drying. The gain is probably the result of handling and not drying. The minor (<0.2%) changes observed on drying and exposures to humidity conditions are observed with other NCEs where there were no development difficulties. The other small losses observed with the free base, fumarate and maleate are not considered problematic. The leading candidates at this stage are the free base, fumarate, and maleate forms. They are the optimal forms.

Final Form Selection. The free base was selected for dosage form for development for these reasons.

(a) The free base is crystalline and has a sufficiently high melting range, 95 to 96°C.
(b) In near gastric simulating pH, it has higher solubility than the fumarate and maleate.
(c) The need for a solution dosage form in preclinical and clinical development such as pharmacokinetic and bioavailability testing could be met by *in situ* salt formation, as demonstrated by the solubility of the free base in 0.1 N hydrochloric acid.
(d) Finally, 1 mg of free base is equivalent to 1.41 mg of the fumarate or 1.41 mg of maleate salt. Dosage form size and the intended delivery system require that the minimal amount of the NCE be present in each CR dosage form. If 400 or 800 mg strength dosage forms were required for development, 565 or 1,130 mg of the fumarate or maleate salt would be required. The organization preferred developing the product with an NCE form having the lower MW, and lower total amount of NCE per dosage form.

CONCLUSIONS

The proposed systematic logical model for salt form selection met its established objectives.

- The proposed testing scheme of preformulation methods identified problematic physical–chemical properties of forms that could hinder dosage form development.
- The process of eliminating forms that had problematic properties from further consideration simplified the selection process.
- The proposed model reduced the number of final candidates to three forms, making selection of the final form for development easier.
- The evaluation process employed test methods that were relevant to mechanisms for creating CR and IR dosage forms.
- Analytical requirements were met with about 5 g of candidate forms, used simple apparatus, and were initiated without a stability indicating assay. Evaluation using DSC or vapor-sorption is available from contract laboratories if not available in house.

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