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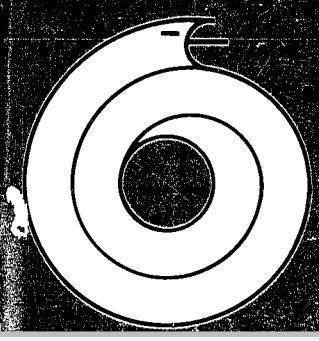

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Research Papers

An integrated approach to the selection of optimal salt form for a new drug candidate

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Abstract

A general method was developed to select the optimal salt form for BMS-180431, a novel HMG-CoA reductase inhibitor and a candidate for oral dosage form development, in an expeditious manner at the onset of the drug development process. The physicochemical properties such as hygroscopicity, physical stability of crystal forms at different humidity conditions, aqueous solubility, and chemical stability of seven salts, e.g., sodium, potassium, calcium, zinc, magnesium, arginine and lysine, were studied using a multi-tier approach. The progression of studies among different tiers was such that the least time-consuming experiments were conducted earlier, thus saving time and effort. A 'go/no go' decision was made after each tier of testing the salts, thus avoiding generation of extensive data on all available salt forms. The hygroscopicities of all BMS-180431 salts were evaluated at tier 1 and four salts (sodium, potassium, calcium and zinc) were dropped from consideration due to excessive moisture uptake within the expected humidity range of pharmaceutical manufacturing plants (30–50% R.H. at ambient temperature). The remaining three salts were subjected to the tier 2 evaluation for any change in their crystal structures with respect to humidity and the determination of their aqueous solubilities in the gastrointestinal pH range. The magnesium salt was dropped from further consideration due to humidity-dependent changes in its crystal structure and low solubility in water (3.7 mg/ml at room temperature). Arginine and lysine salts, which were resistant to any change in their crystalline structures under extremes of humidity conditions (6 and 75% R.H.) and had high aqueous solubilities (> 200 mg/ml), were elevated to tier 3 for the determination of their chemical stability. Based on solid state stability of these two salts under accelerated conditions (temperature, humidity, and presence of excipients), consideration of ease of synthesis, ease of analysis, potential impurities, etc., and input from the marketing group with respect to its preference of counter ion species, the arginine salt was selected for further development. The number of tiers necessary to reach a decision on the optimal salt form of a compound may depend on the physicochemical properties studied and the number of salts available. This salt selection process can be completed within 4–6 weeks and be easily adopted in the drug development program.

Key words: Salt selection; HMG-CoA reductase inhibitor; BMS-180431; Hygroscopicity; Arginine salt; Lysine salt

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1. Introduction

Berge et al. (1977) reviewed various advantages of using salt forms of drugs in pharmaceutical formulations, which include improved dissolution rate and bioavailability of poorly water-soluble compounds. For some drugs, preparation of stable salts may not be feasible, and free acid or base forms may be preferred (Serajuddin et al., 1986). In selecting the optimum chemical form of a new drug candidate, one must, therefore, take into consideration all physicochemical properties which would influence its physical and chemical stability, processability under manufacturing conditions, dissolution rate, and bioavailability. Such a selection of chemical form must be done at the initial stage of drug development. Changing the chemical form in the middle of a developmental program may require repeating most of the biological, toxicological, formulation, and stability tests performed. On the other hand, continuing the development of a nonoptimal chemical form may lead to increased developmental and production costs and even product failure.

Although the importance of using the optimal salt form of a compound in dosage form design is well-recognized (Berge et al., 1977; Hirsch et al., 1978), there is no generally accepted procedure of selecting such a form during the drug development process. More often than not, the medicinal chemists select salt forms on a practical basis, such as previous experience with the salt type, ease of synthesis, percent yield, etc. (Berge et al., 1977). It is, therefore, desirable that a procedure be developed for the selection of salt or other chemical form of a drug candidate expeditiously at the outset of the developmental program. We have developed an integrated approach which was successfully applied to the selection of the optimal salt forms of several compounds. Its application in the selection of the salt form of BMS-180431, a new HMG-CoA reductase inhibitor which is a candidate for the development as a solid dosage form, is described in this paper.

2. Development of salt selection strategy

Gould (1986) described a salt selection process based on melting point, solubility, stability, wettability, etc., of various salt forms. However, in the absence of clear go/no go decisions at any particular stage of the salt selection process, this approach would lead to the generation of extensive physicochemical data on all salt forms synthesized. Gould concluded that "the balance required in assessing the correct salt form to progress into drug development makes it a difficult semiempirical exercise." A more rational approach is, therefore, required to select the appropriate salt form expeditiously during drug development. In the present method the physicochemical tests were conducted at different tiers and a go/no go decision was made after each tier of testing the salts, thus avoiding generation of extensive data on each salt form synthesized. The studies were planned such that the least time-consuming experiments which could still give a go/no go decision were conducted at tier 1. Progressively more time-consuming and labor-intensive experiments were conducted at tier 2, tier 3, etc. In this way, many different salt forms could be screened with the minimum of experimental effort.

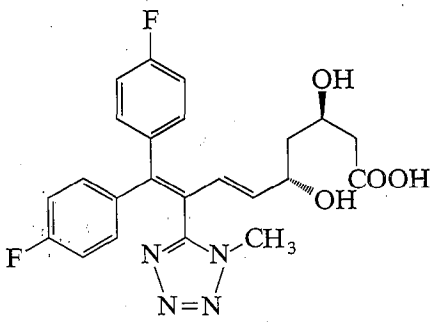
Based on the review of literature (Berge et al., 1977; Hirsch et el., 1978; Gould, 1986; Serajuddin et al., 1986) and our experience in product development, we identified low hygroscopicity, integrity of crystal form at different storage conditions, aqueous solubility, and chemical stability as primary criteria for the selection of BMS-180431 salts, and set limits for the acceptability of these criteria. All salt forms of the compound which were found to be crystalline were tested at tier 1 for their hygroscopicity. A high degree of moisture sorption or desorption by the salts under expected ambient humidity conditions of pharmaceutical manufacturing plants may create handling and manufacturing difficulties, such as change in potency of the drug substance, change

in the true density, variation in flow behavior, etc. There may be batch-to-batch variability in the potency of dosage forms if care is not taken to ensure that the bulk drug substance maintained its declared potency prior to batching. The change in moisture content may also affect the physical and chemical stability of salts. Therefore, at the end of tier 1, all salt forms with excessive moisture sorption/desorption behavior were dropped from further consideration.

The salts which were considered to have acceptable hygroscopicity were then screened in tier 2 for changes in crystal structure under extremes of humidity conditions by using combinations of powder X-ray diffraction and thermal analysis techniques. This would indicate any propensity for pseudopolymorphic and solution-mediated polymorphic changes which might occur during manufacturing or accelerated stability testing of the bulk material or the solid dosage form. At this stage, the salts were also screened for their aqueous solubilities to determine if there is any potential dissolution and bioavailability problems and whether the formulation of a solution dosage form, if required, is feasible. The go/no go decision would depend on the consideration of both the physical stability of crystalline structure at different humidity conditions as well as the solubility. The criteria for the selection of salts at tier 2 may depend on the judgment of the drug development scientists in consideration of the type of dosage form and the expected dose of the compound. A salt with lower solubility which can still provide good dissolution rate in the judgment of a formulation scientist could be selected over a salt which is highly soluble but prone to crystalline changes. On the other hand, if the solubility is not acceptable in consideration of the dissolution rate or if a solution with high drug concentration is required for oral or parenteral use, another salt with some propensity for changes in crystal properties under extremes of humidity may be considered.

Finally, at tier 3, the selected salts were subjected to accelerated thermal stability and photostability screening. Since the stability testing of salts required much time and effort, placing this at tier 3 limited the number of salts on which such tests were conducted and avoided generation of unnecessary data with other salt forms. Compatibility screening with selected excipients may also be conducted at this stage.

In the above scheme, the number of salt forms available and the physicochemical properties considered important for the bulk drug substance as well for the expected dosage forms will dictate how many tiers would be necessary to select a salt form. There may also be rare situations where all salts progressed from a lower tier to a higher one are unacceptable for development. For example, the solubility of all salts at tier 2 may be unacceptable or chemical stability of all the salts at tier 3 may be poor. If this happens, additional salt forms or free acids/bases should be considered prior to reevaluating any salt that was dropped at an earlier tier. Also, the criteria of progression from a lower tier to the next higher one may depend on the physicochemical properties of the available salts. If, for example, all salts are found to be highly hygroscopic, it might be necessary to progress some of them to a higher tier, keeping in mind that, if selected, they might require special manufacturing and storage conditions.



3. Experimental

3.1. Materials

The following salts of BMS-180431 were used during salt selection: sodium, potassium, calcium, zinc, magnesium, arginine, and lysine. A few other salts were also prepared; however, they were found to be noncrystalline and, therefore, not considered for salt selection.

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