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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.

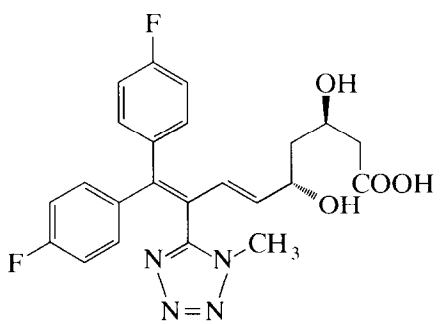
Based on the review of literature (Berge et al., 1977; Hirsch et el., 1978; Gould, 1986; Serajuddin et al., 1986) and our experience in product development, we identified low hygroscopicity, integrity of crystal form at different storage conditions, aqueous solubility, and chemical stability as primary 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.

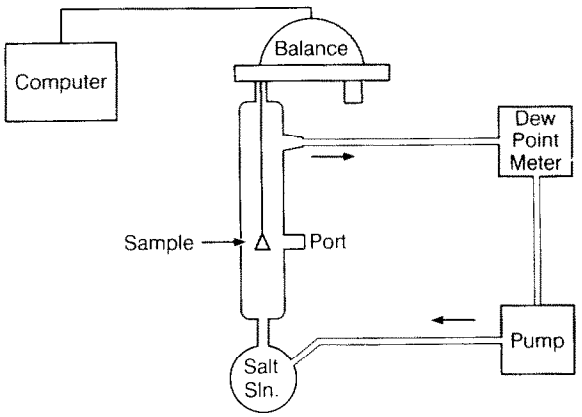


Fig. 1. Schematic diagram of the moisture sorption-desorption apparatus.

3.2. Moisture sorption studies

The rate and extent of moisture sorption at different humidity conditions were determined by using a Cahn Digital Recording Balance fitted with a system to maintain and monitor specific relative humidity conditions. The system consists of a tubular glass chamber surrounding the pan of the balance, a flask for the humidity-controlling salt solution, a peristaltic pump to circulate the saturated air, and an in-line chilled mirror dew point meter for the determination of relative humidity within the system. Saturated aqueous solutions of $MgCl_2$, $Mg(NO_3)_2$ and NaCl were used at room temperature to maintain 33, 52 and 75% R.H. conditions, respectively. Anhydrous $CaSO_4$ (Drierite®, Hammond, OH) provided the 6% relative humidity condition. Once assembled, a closed system is formed wherein the desired relative humidity condition can be readily attained. The sample can be placed on the pan of the balance through the access port with practically no perturbation of the humidity inside the chamber. Once a sample ($\sim$ 10 mg) reaches equilibrium at a particular relative humidity, the environment surrounding the sample may be changed to a different humidity condition by changing the flask containing the salt solution. The atmosphere within the glass chamber attains the new humidity condition within 5 min of such a change, and the sample then reaches equilibrium with this new atmospheric condition. Highly reproducible moisture sorption data were obtained by this method. In a separate study, when multiple samples (15 mg each) from the same batch of a drug substance were equilibrated at different humidity conditions, the final weights at each humidity condition were within ± 0.02 mg. This indicated that for a 2% moisture uptake, the precision of the experiment would be $\pm 6.6\%$, while for a 10% moisture uptake it would be within $\pm 1.5\%$. Also, when the equilibrium moisture contents of a sample measured at different humidity conditions are compared, the influence of any artifacts such as the adsorption of moisture to the sample pan is also minimal; for example, in a moisture uptake run without any sample on the pan, the weight gain between 6 and 75% R.H was < 0.01 mg. A schematic diagram of the moisture sorption/desorption apparatus is given in Fig. 1.

3.3. Determination of moisture content

The moisture contents of samples exposed to different relative humidity conditions were determined primarily by thermal gravimetric analysis (TGA) using a DuPont 2000 Thermal Analyst system. However, since the weight loss in the TGA represents both water and any other volatile material, initial moisture contents of all samples as well as moisture contents of specific samples after equilibration at different humidity conditions were confirmed by coulometric titration using a Brinkman 684 Karl-Fischer Coulometer. The TGA was performed by weighing accurately about 10 mg of sample on an open sample pan and then heating the sample at a rate of 10°C per min. During the experiment, dry nitrogen was purged over the sample at a rate of 40 cm^3 per min. For coulometric analysis, sample sizes were selected to yield 1–3 mg of water. The accuracy of the system was ensured by titrating 2 mg of water (10 μl of a 20% w/v solution of water in methanol) where the results varied between 97.5 and 102% of theoretical.

3.4. Differential scanning calorimetric (DSC) analysis

The energetics of the moisture-solid interaction in samples, e.g., hydrate formation, was determined by DSC analysis. A sample sealed in an aluminum pan with a pin hole was heated at a rate of 5 or 10°C per min from room temperature to about 200°C using a DuPont 2000 Thermal Analyst system.

3.5. Powder X-ray diffraction (XRD) analysis

Powder X-ray diffraction patterns of the samples were collected using a Phillips APD 3720 powder diffraction system with a vertical goniometer in the $\theta/2\theta$ geometry. The X-ray generator (model XRG 3100) was operated at 45 kV with a copper radiation source. A scintillation detector was used to scan the range between 2 and 32° 2θ. A sample was packed in a 1.5 cm × 1.0 cm sample holder with a thickness of 2 mm and its initial powder pattern was determined. The sample holder was then stored overnight in a desiccator with a particular relative humidity, and the powder X-ray diffraction analysis was then repeated. The top surface of the powder bed was fully exposed to the atmosphere, and, since the thickness of the powder bed was small, there was no barrier to the diffusion of moisture into the bed. By this procedure, it is also possible to determine the change in crystal structure when a sample equilibrated at one relative humidity is reequilibrated at a different humidity condition. Since the samples were not disturbed after the initial packing, the parameters such as size and orientation of particles remained unchanged.

3.6. Determination of solubility

The solubilities of various salts under simulated gastric and intestinal pH conditions were determined by equilibrating excess of solid material with 0.01 M HCl and water at room temperature using a Burrell® wrist action shaker. The solids were equilibrated with water for 24 h; however, since the preliminary studies showed that the compound is relatively unstable in acidic media due to the formation of its lactone form (~ 5% degradation at pH 2 in 6 h at room temperature) shaking with 0.01 M HCl was performed for 2 h only. The pH values of the solutions were recorded prior to their filtration through 0.45 μm pore size Millipore filters. The solutions were assayed for drug concentrations using high-pressure liquid chromatography (HPLC).

3.7. Determination of solid-state stability

Accurately weighed samples of salts (~ 10 mg each) were stored at 40 and 50°C in closed 4 cm^3 glass vials and at 40°C/75% R.H. in open glass vials. For photostability studies, samples stored in closed clear glass vials were exposed to 900 footcandle fluorescent light; the vials stored under a similar condition with aluminum foil wrappers around them served as controls. The stability samples were assayed at different intervals by HPLC.

3.8. Screening of drug-excipient compatibility

Drug-excipient compatibility screening studies were performed on arginine and lysine salts of BMS-180431 using a procedure reported earlier (Serajuddin et al., 1991). Ternary or quaternary mixtures of the drug and excipients (drug:excipient, 1:7) were weighed into 4 cm^3 glass vials, approx. 20% water was added to the contents of vials (70 μl water to 320 mg powder in a vial), the vials were sealed tightly, and stored at 50°C. Samples stored at room temperature without added water served as controls. Each drug-excipient mixture consisted of 40 mg of drug, 250 mg of a diluent (tricalcium phosphate, mannitol or microcrystalline cellulose), and 30 mg of a third component which was a disintegrant, binder or lubricant. Duplicate samples of each mixture were withdrawn, examined visually for any physical change, and analyzed chemically using HPLC.

3.9. HPLC analysis

The samples were dissolved in a 40:60 v/v mixture of acetonitrile and water, and analyzed by HPLC using a 4.6 mm × 250 mm reversed

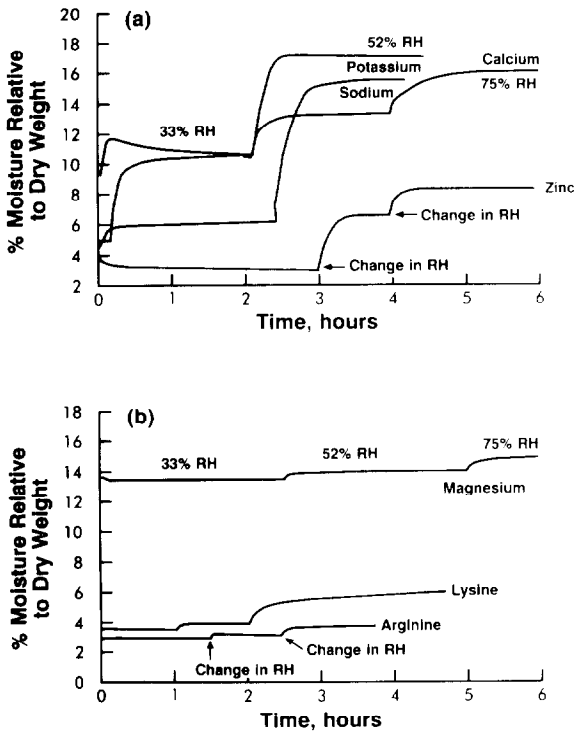


Fig. 2. Moisture sorption by (a) potassium, sodium, calcium and zinc salts, and (b) magnesium, lysine and arginine salts of BMS-180431 at 33, 52 and 75% R.H. The initial moisture contents were determined separately by TGA. The % R.H. was changed to the next higher value after the sample reached equilibrium moisture content at the lower % R.H. The typical changes in % R.H. are indicated by arrows.

phase column (YMC-C18 column, S-5; YMC, Inc., Morris Plains, NJ), a Waters autoinjector and an Applied Biosystems Spectroflow 783 detector. The mobile phase consisted of a 40:15:45 v/v mixture of acetonitrile, methanol and a phosphoric acid solution (0.1% H_3P0_4 in water), and had a final pH of 2.5. The flow rate of the mobile phase was 1 ml/min and the run time after each injection was 20 min. The sample volume was 20 μl, and the detection was by ultraviolet light absorbance at a wavelength of 296 nm.

4. Results and discussion

4.1. Moisture sorption (tier 1)

Moisture sorption curves for various salts when exposed to 33% R.H., followed by 52 and 75% R.H., as determined by recording weight gain or loss using a Cahn balance, are shown in Fig. 2. The initial moisture content varied from salt to salt. Also, when multiple lots of the same salt were received, the initial moisture content varied depending on the extent of drying of the samples (not shown in figure). As shown in Fig. 2, the moisture sorption rates were very rapid; the samples reached equilibrium in < 10 min when exposed to 33, 52 or 75% R.H. Initial moisture contents as well as equilibrium moisture contents of various salts under these three different humidity conditions are tabulated in Table 1.

Table 1
Moisture contents of various BMS-180431 salts initially and after equilibration at different humidity conditions

Salt	% moisture relative to dry weight			
	Initial	33% R.H.	52% R.H.	75% R.H.
Sodium	4.4	4.4	16.0	ND
Potassium	9.5	10.6	17.1	ND
Calcium	5.0	10.4	13.4	16.1
Zinc	4.1	2.9	6.5	8.3
Magnesium	13.8	13.5	14.0	14.9
Arginine	2.8	3.0	3.2	3.8
Lysine	3.2	3.6	4.0	6.0

ND, not determined.

The energetics of the interaction of water with these salts were examined by DSC. The loss of moisture from the metal salts (sodium, potassium,

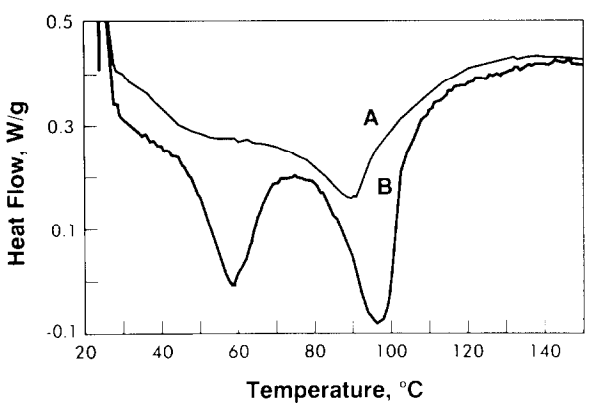


Fig. 3. DSC scans of BMS-180431 calcium salt indicating its dehydration behavior. Scan A shows the sample as received for testing and scan B is for the sample equilibrated at 75% R.H.

calcium, zinc and magnesium) occurred in two stages, which is exemplified by the DSC scan of the calcium salt as shown in Fig. 3A and B where two dehydration endotherms at 59 and 97°C were observed. The endotherm at 59°C disappeared when the calcium salt was equilibrated at 6% R.H., indicating a lower energy of salt-water association than the endotherm at 97°C which represents more tightly bound, possibly cation-associated, water. The presence of a dehydration endotherm for a metal salt at a relatively low temperature (for example, 30–70°C temperature range for the calcium salt in Fig. 3B) also suggests the possibility that the loss of moisture may occur when heat is applied or developed during processing, e.g., drying of bulk drug substance, compression of powders or granules in the tablet press, etc. In contrast, the DSC scans of the amino acid salts as received (Fig. 4) did not indicate the presence of any hydrate. The DSC scans remained essentially unchanged after the exposure of samples to humidity conditions between 33 and 75% R.H., indicating that there was also no hydrate formation during this humidity challenge test.

Additionally, Table 1 shows that arginine and lysine salts have very low fluctuations in moisture content (0.4% or lower) within the range of 33–52% R.H, which is prevalent under most manufacturing conditions. Although the magnesium salt had high initial moisture content, it was relatively nonhygroscopic between 33 and 75% R.H. For other salts, the fluctuation in moisture content between 33 and 52% R.H. was > 3%. Based on these considerations, arginine, lysine and magnesium salts were selected for the next stage (tier 2) of evaluation.

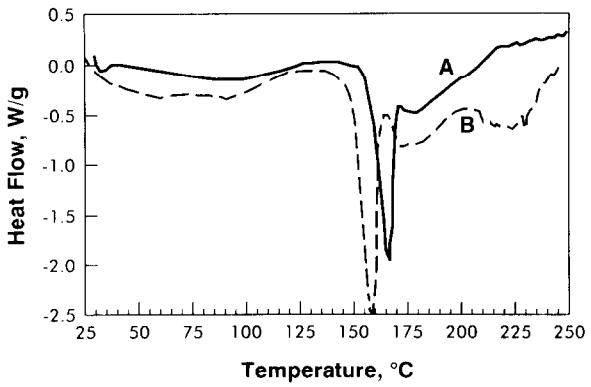


Fig. 4. DSC scans of arginine (A) and lysine (B) salts of BMS-180431 as received for testing.

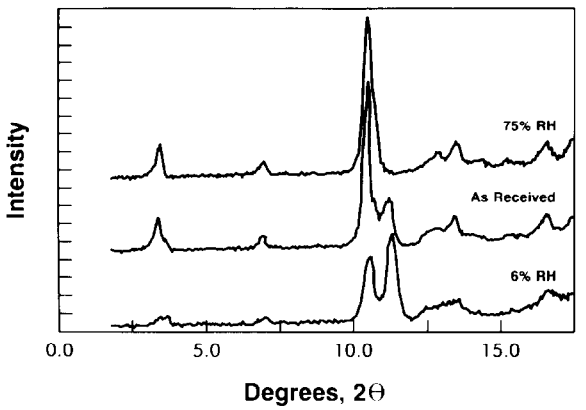


Fig. 5. Powder X-ray diffraction patterns of BMS-180431 magnesium salt as received for testing and after equilibration at 6 and 75% R.H.

4.2. Crystal structure and solubility (tier 2)

Arginine, lysine, and magnesium salts selected because of their low hygroscopicity were further evaluated for any change in crystal structure under expected extremes of humidity conditions during storage or accelerated stability testing. This is important because changes in crystal form in the bulk material may affect the physical (and/or chemical) stability and performance of solid dosage forms and must be controlled. For example, Yamaoka et al. (1982) observed cracking of tablets when the drug substances present changed from an anhydrate to a hydrate under high-humidity conditions.

The powder X-ray diffraction patterns of arginine and lysine salts remained unchanged within the humidity range of 6–75% R.H. However, the magnesium salt showed changes in its powder XRD patterns which could be attributed to a change in the crystal form (Fig. 5). The sample stored at 6% R.H. loses intensity in the higher angle peaks as well as the major reflections at 11° 2θ, and gains intensity in the peak at 11.5° 2θ.

The 75% R.H. pattern completely loses the 11.5° 2θ reflection while maintaining the 11° 2θ peak.

As mentioned earlier, solubilities of the salts of BMS-180431 were also studied at this stage. While the two amino acid salts were freely soluble in water (> 200 mg/ml as free acid content), the magnesium salt was only slightly soluble (3.7 mg/ml as free acid content). The pH values of the saturated solutions of these salts in water were between 6.8 and 7.6. All three salts, however, exhibited comparable solubilities under acidic pH conditions due to the conversion of BMS-180431 to the free acid ($pK_a = 4.4$); the solubilities at pH 2.5–2.9 varied between 0.61 and 0.67 mg/ml. These results indicate that these salts would have adequate solubilities for their complete dissolution of the expected dose of 25 mg under gastrointestinal pH conditions if formulated as solid dosage forms. However, the limited solubility of the magnesium salt in water could present difficulties in the preparation of drug solutions for oral and parenteral use. Due to the change in crystal form and the limited solubility of magnesium salt, it was dropped from further consideration.

4.3. Solid-state stability and drug-excipient compatibility (tier 3)

The solid-state stability evaluation of arginine and lysine salts for 4 weeks at a temperature as high as 50°C and at 40°C/75% R.H. did not show any significant degradation. Both salts, however, showed some susceptibility to light; the potencies of the arginine salt after exposure to 900 footcandle light for 1 and 2 weeks were 94.7 and 87.9%, respectively, while those of the lysine salt stored under the same condition were 97.4 and 95.0%, respectively. This difference in the light stability of arginine and lysine salts may not be of any practical significance because both salts would require protection from light.

A short-term compatibility screen with some excipients commonly used in solid dosage forms, namely, tricalcium phosphate, mannitol, microcrystalline cellulose, croscarmelose sodium, cross-linked polyvinylpyrrolidone, and magnesium stearate, was conducted to further evaluate the arginine and lysine salts. Lactose was not selected as one of the excipients due to expected incompatibility of amino acid counter ions with lactose. The stabilities of the salts in the presence of various excipients were comparable; the loss in potency after exposure to 50°C for 1 week in the presence of 20% water was < 2%. Both salts alone and their drug-excipient mixtures developed slightly yellow color when exposed to 50°C with 20% added water, while placebo formulations exposed to similar conditions remained colorless. This indicated that color-masking of solid dosage forms might be required if either of the salts was selected, and there would be no advantage in the selection of one salt over the other.

4.4. Decision on salt selection

Based on low hygroscopicity, stable crystal structure, and chemical stability including compatibility with excipients, either the arginine or the lysine salt of BMS-180431 could be the candidate for further development. For the final selection of one of these two salts, comments from various departments involved in the drug development process were sought. Upon consideration of their comments with respect to ease of synthesis, ease of analysis, marketing preference, etc., the arginine salt was selected for further development.

5. Summary

A systematic three-tier approach was applied to the selection of the optimum salt form of BMS-180431 in an expeditious manner. At tier 1, seven salts of BMS-180431 (sodium, calcium, zinc, magnesium, potassium, lysine and arginine) were screened for their hygroscopicity and the nature of moisture present. Four salts (sodium, potassium, calcium and zinc) were eliminated at this stage due to their excessive hygroscopicity over the expected ambient humidity range of pharmaceutical manufacturing plants. The remaining three salts were elevated to tier 2 for the evaluation of any change in their crystal structures under extremes of relative humidity conditions

and the determination of aqueous solubility. No change in crystal structures of arginine and lysine salts was observed when they were exposed to 6 and 75% relative humidity conditions. The two salts were also freely soluble in water. On the contrary, the magnesium salt exhibited humidity-dependent change in crystal structure and it was only slightly soluble in water. The magnesium salt was, therefore, dropped from further consideration, and the amino acid salts were elevated to the next tier. At tier 3, the solid-state thermal and light stabilities and the drug-excipient compatibilities of arginine and lysine salts were shown to be equivalent. It was concluded that arginine and lysine salts of BMS-180431 have comparable physicochemical properties and that both salts are superior to the others with respect to their suitability for pharmaceutical dosage form design. After careful evaluation of other factors such as ease of synthesis, ease of analysis, marketing preference, etc., the arginine salt was recommended for development.

The hygroscopicity studies at tier 1 were completed in 2–3 days and the tier 2-studies took one week. The most time-consuming part of the process was the stability testing at tier 3, which required four weeks of time; this could be completed in less time if the development schedule was tighter. Thus, the entire salt selection process may take approx. 4–6 weeks. Since the preparation of salt form is the last step in a chemical synthesis process, it has been our general experience that such a salt selection study can be completed while the chemists are still involved in scaling up the chemical synthesis process, thus avoiding any delay in the developmental program.

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