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Research Article

Salicylic Acid and Lactic Acid Co-Crystal

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Abstract

A pharmaceutical co-crystal can be designed to improve the solid state properties of an active pharmaceutical ingredient without affecting its intrinsic structure using crystal engineering and to increase the bioavailability of the active pharmaceutical ingredients by merging them in one co-crystal solid product. The objective of this study is to prepare salicylic acid and lactic acid co-crystal using co solvents, such as ethanol (96%), methanol (99%), diethyl ether and acetonitrile either in reflux or grinding techniques. All paradigms are tested using Fourier Transform Infra-Red spectroscopy (FTIR) and the melting point range is tested for part of them and was tested for solubility modifications. The results show that the co-crystal paradigms obtained in reflux techniques in all co-solvents used are satisfied; and more than 80% from the grinding technique samples obtained creates a merged satisfied so-crystals using FTIR spectroscopy. The co-crystals solubility is changed to be sparingly soluble to soluble in water. The co-crystal paradigms melting point was changed to be lower than salicylic acid and higher than lactic acid, the melting point variation change observed is dependent on the target active pharmaceutical concentration and depending on the molar ratio for each co-crystal tested.

Keywords: Crystal Engineering; Co-Crystal; Salicylic Acid; Lactic Acid; API; FTIR

Introduction

A pharmaceutical co-crystal can be designed by crystal engineering with the intention to improve the solid state properties of an active pharmaceutical ingredient without affecting its intrinsic structure. Therefore, crystal engineering was applied to increase the Bioavailability of salicylic acid and lactic acid by merging them in one co-crystal solid product [1]. Poorly water soluble drugs pose significant hurdles for drug bioavailability that in turn affect *in vivo* efficacy and safety in all stages of formulation. Among the biopharmaceutical properties, solubility remains a key issue with drugs often discarded during commercial production due to their low solubility. Improving the solubility of drugs is currently one of the main challenges for the pharmaceutical industry. Many approaches have been adopted for improving the aqueous solubility of drugs including micronation, salt formation, emulsification, solubilization using co-solvents. Over the last decade, there has been growing interests in the design of pharmaceutical co-crystals, which emerges as a potential method for enhancing the bioavailability of drugs with low aqueous solubility [2]. The ability to deliver the drug to the patient in a safe, efficient and cost effective manner depends largely on the physicochemical properties of the active pharmaceutical ingredient (API) in the solid state being studied.

Co-crystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions (primarily hydrogen bonding). The formation of pharmaceutical co-crystals involves incorporation of a given active pharmaceutical ingredient with another pharmaceutically acceptable molecule in the crystal lattice [3,4]. Co-crystals are constructed from intermolecular interactions such as hydrogen bonding contact forces, and hydrogen bonding [5]. A pharmaceutical co-crystal is simply a co-crystal in which at least one of the molecular components is an active pharmaceutical ingredient (API) in conjunction with another type of molecule termed a co-crystal former. More strictly, in order to be useful, the non-API component should be non-toxic with no adverse side effects. Co-crystals have different physical properties such as habit, bulk density, and solubility; compressibility, friability, melting point, hygroscope and dissolution rate.

Formation of a co-crystal often offers scope to transform an amorphous or hard to crystallize active pharmaceutical ingredient into a readily handled, stable crystalline solid. Indeed, it is far more likely to be poor biopharmaceutical characteristics rather than toxicity or lack of efficacy that prevent a candidate active compound progressing in clinical trials [1,6]. The salicylic acid structure is composed of dimeric units through hydrogen bonding as expected with more hydrogen bonding from the hydroxyl group with the carboxylate of the same molecule, as shown in figure 1 [7]. While in lactic acid, the hydrogen bonding between the different molecules is between the hydroxyl groups of one molecule with the carbonyl of the adjacent molecule forming cyclic arrangement composed of six lactic acid molecules as shown in figure 2 [8].

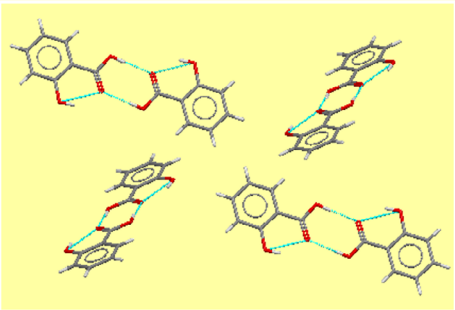


Figure 1: Salicylic acid crystal structures in solution [8].

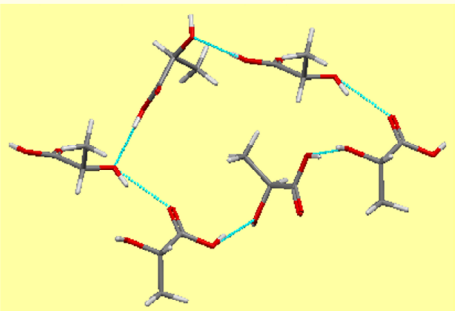


Figure 2: Lactic acid crystal structures in solution [9].

Instrumentation and Methodology

Instruments

Analytical balance (Precisa 125-A), reflux unit apparatus, mortar and pestle, FTIR (AVATAR 320), Fume hood, Melting point apparatus (BUCHI B-545).

Materials

Salicylic acid 100% (Rhodia), Lactic acid 90% (Merck), ethanol 96% (shitzer), methanol (J.T.Baker), diethyl ether (Merck), acetonitrile (J.T.Baker). All components were used as supplied and tested in Beit Jala Pharmaceutical Company for further purification.

Co-crystallization methodology

Salicylic acid and Lactic acid that are proposed as active pharmaceutical ingredients (API's) in this project, they are used as keratolytic compounds. The proposed solvents were Ethanol, Methanol, Diethyl ether and Acetonitrile to be used for the co-crystal formation each one in both co-crystal techniques (solution and Grinding). Currently the most established methods for co-crystal formation are reflux solution and mechanical techniques. In reflux co-crystal synthesis, stoichiometric ratios of active pharmaceutical ingredients (API's) are dissolved in a solvent of choice and super saturation is achieved either through a temperature difference or through evaporation of the solvent.

Reflux Co-crystallization technique

API's target concentration expected to be formulated were mixed with 10 ml of the selected solvent in a round bottom flask and refluxed for 2.5 hours. Collecting the reflux solution in a capped glass ware and loosen the cap screw slightly or making holes in the top part of the cap, allowed to stand for several days (14 - 21 day). Co-crystals were obtained in each solvent, in which the physicochemical properties are notified and tested.

	Salicylic acid and Lactic acid (2:1) molar ratio		
Target Concentration %	**Solvent**	**Salicylic acid (g)**	**Lactic acid (g)**
100%	Ethanol	1.1998	0.4468
100%	Methanol	1.2001	0.4428
100%	Diethyl ether	1.2004	0.4440
100%	Acetonitrile	1.2004	0.4440

Table 1: Salicylic acid and lactic acid target concentrations.

Grinding (mechanical) Co-crystallization technique

There have been great progresses in co-crystal formation via grinding method over the past few years. There are different techniques for co-crystal formation via grinding. Stoichiometric ratios of active pharmaceutical ingredients (API's) are mechanically

agitated (e.g. by grinding in a mill) to induce phase transformations from a physical mixture into co-crystal. Drops of solvent, which are considered as plasticizers, have been shown to impact the crystallization outcome. The grinding method was applied on different molar ratios for each solvent chosen, depending on the accuracy and linearity tests of active pharmaceutical ingredients (API's) in the pharmaceutical validation procedure 50%, 75%, 100%, 125% and 150 % of the target concentration dose. By fixing one active pharmaceutical ingredient (API) concentration and making the variations with the other, as listed in the following table.

	Variable Salicylic acid and constant Lactic acid			Constant Salicylic acid and Variable Lactic acid		
Concentration %	**Tube #**	**Salicylic acid (g)**	**Lactic acid (g)**	**Tube #**	**Salicylic acid (g)**	**Lactic acid (g)**
50	1	0.06	0.0444	1	0.12	0.0222
75	2	0.09	0.0444	2	0.12	0.0333
100	3	0.12	0.0444	3	0.12	0.0444
125	4	0.15	0.0444	4	0.12	0.0555
150	5	0.18	0.0444	5	0.12	0.0666

Table 2: Salicylic acid and Lactic acid variable molar ratios/grinding co-crystallization technique.

This procedure was applied for the four solvents chosen and each solvent for ten different molar ratios.

Results and Discussion

Reflux Co-crystallization technique

The co-crystals obtained from each solvent used in the reflux co-crystal technique were amazing and impressive in their uniformity, physicochemical properties, shape and their order of formation. See the photo pictures bellow for the pure active pharmaceutical ingredient and the co-crystal paradigm obtained in each selected solvent.

The obtained co-crystals were tested individually for their melting point and FTIR spectrum test. The co-crystal formation is readily apparent from the resulting physical properties of the new material. Formation of a co-crystal from Salicylic acid (white powder) and Lactic acid (viscous clear liquid) is immediately apparent from the transparent color of the co-crystal, despite the fact that salicylic acid is white solids and lactic acid is clear liquid. The color arises from the fact that the co-crystal as part of the overall hydrogen bonded crystal packing arrangement, with concomitant reduction of the π- π* energy gap [9].

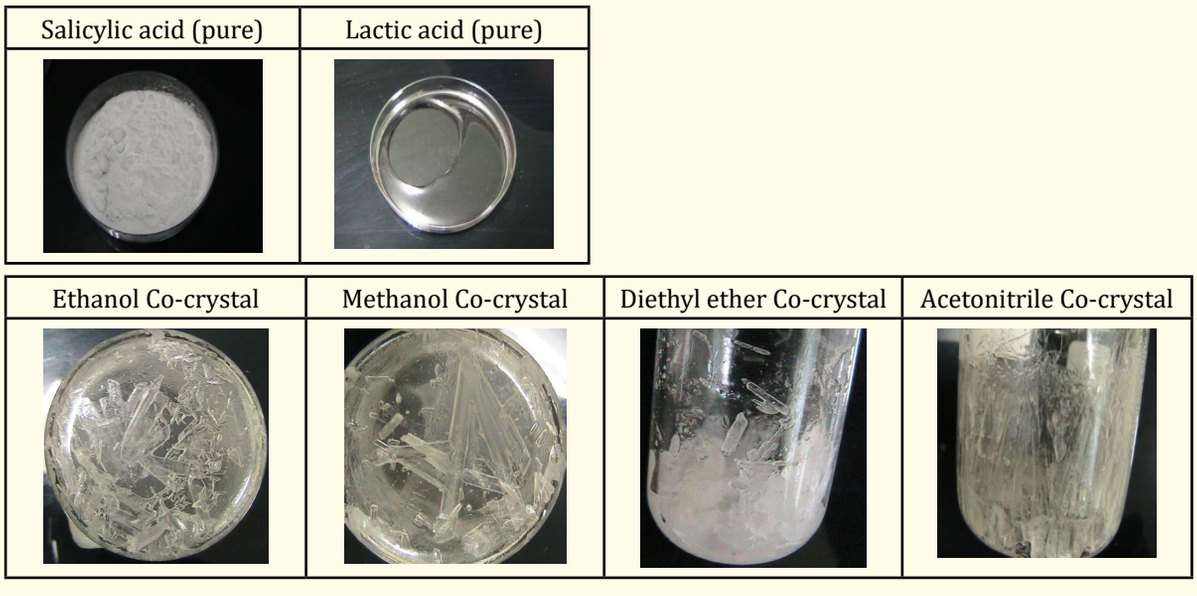


Figure 3: Co-crystals obtained from each co-solvent/Reflux technique.
Note: Diethyl ether Co-crystals seems white in its color due to the co solvent effect of drying, while when they are wet they behave like other solvents in the physical appearance.

The data showed the initial appearance of 1.8:1 ratio for salicylic acid and lactic acid respectively, that the melting point is about 120˚C. In addition to the melting point, FTIR spectroscopy of solid samples (measured for example using KBr salt) can also give a characteristic fingerprint of a particular solid form. Because vibrational spectroscopy depends on bond vibrational modes which are only moderately worried by the molecule's solid state environment, the differences in FTIR spectra between pure active pharmaceutical ingredients forms, or between co-crystal and pure forms, can be relatively major appeared. However, if particular bands are sensitive to solid form (e.g. when there is a significant change in hydrogen bonding mode in different forms) then vibrational spectra represent a useful and facile method of distinguishing different polymorphs and co-crystals. Among many recent patents relating to potential commercial co-crystal products, the possibility of combining two active ingredients in a single co-crystal is an interesting one and has been claimed in the co-crystallization. The combination drug has been suggested to have physical properties and biological activity that are distinct from the individual properties of the two components [10].

The original known and tested FTIR spectrum was as followed for each pure active pharmaceutical ingredient.

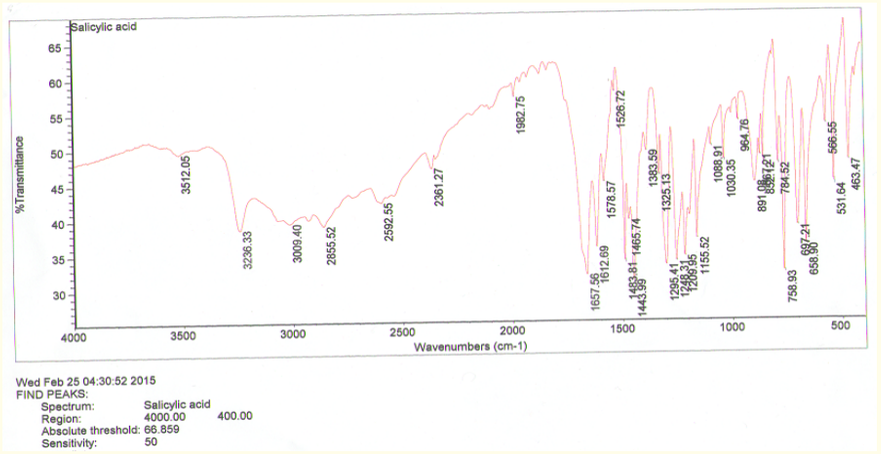
API Major peak	Pure Salicylic acid API FTIR spectrum
 Salicylic acid FTIR major peak	

Figure 4: Pure Salicylic acid FTIR spectrum.

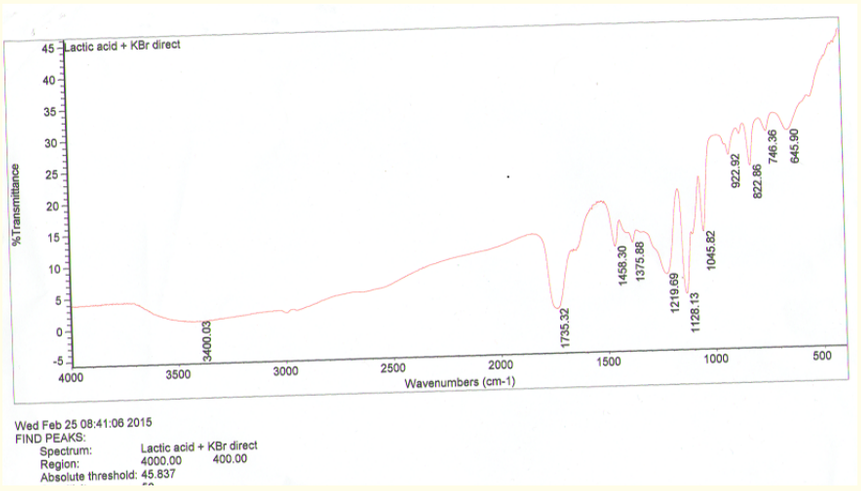
API Major peak	Pure Lactic acid API FTIR spectrum
 Lactic acid FTIR Major peak	

Figure 5: Pure Lactic acid FTIR spectrum.

Grinding (mechanical) Co-crystal technique

The co-crystals obtained from each co-solvent used in the grinding mechanical co-crystal technique were amazing in their uniformity, shape and their order of formation. See the photo pictures bellow for each.

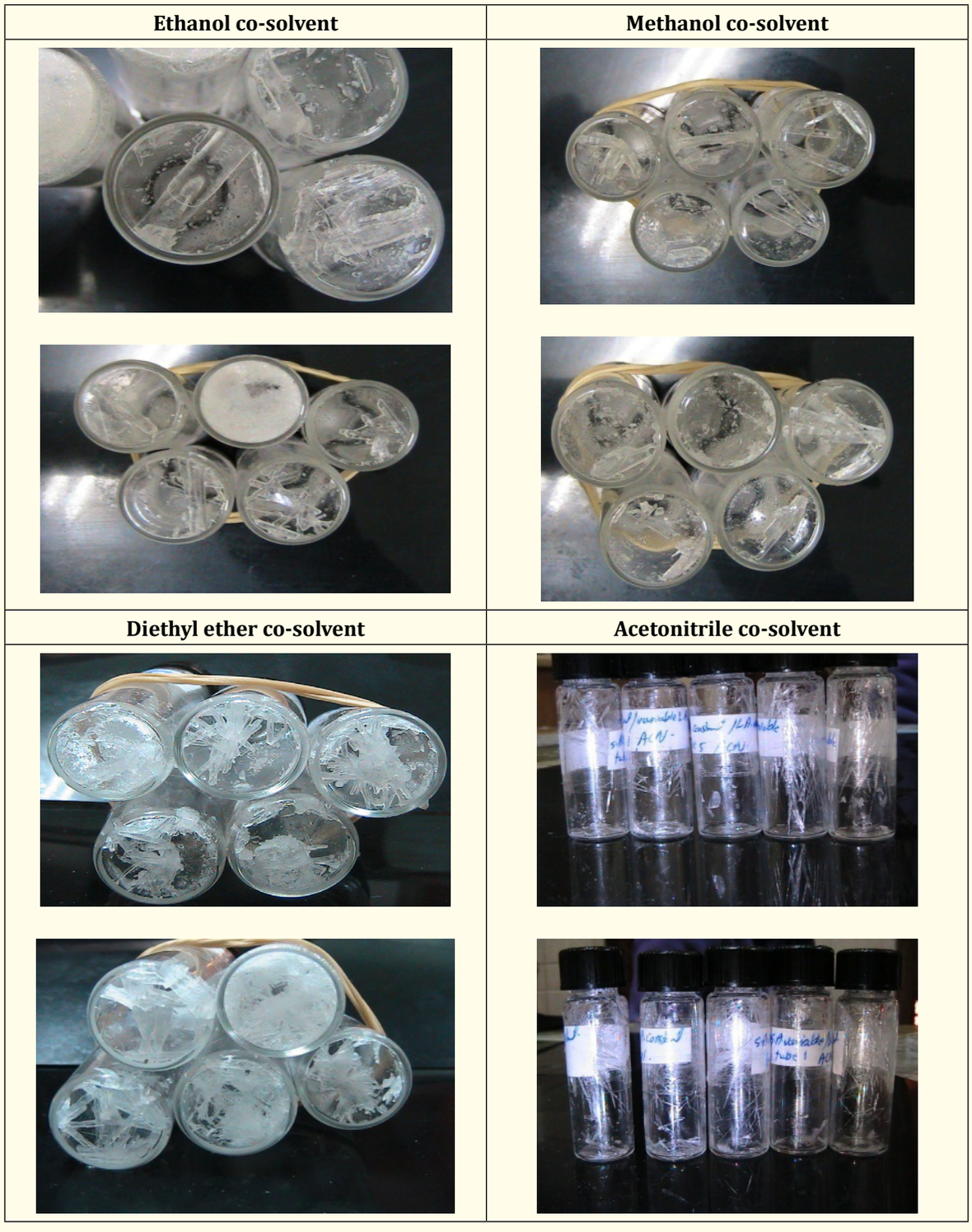


Figure 6: Co-crystal obtained from each co-solvent/grinding technique.

The obtained co-crystals both from Grinding (mechanical) co-crystal technique or reflux solution co-crystal technique were tested individually for FTIR spectroscopy using KBr salt and compared with the pure samples spectrum that was tested before at the beginning, more than 80% of the samples show satisfied co-crystal paradigms.

FTIR spectrum for the obtained co-crystals paradigm according to the grinding technique.

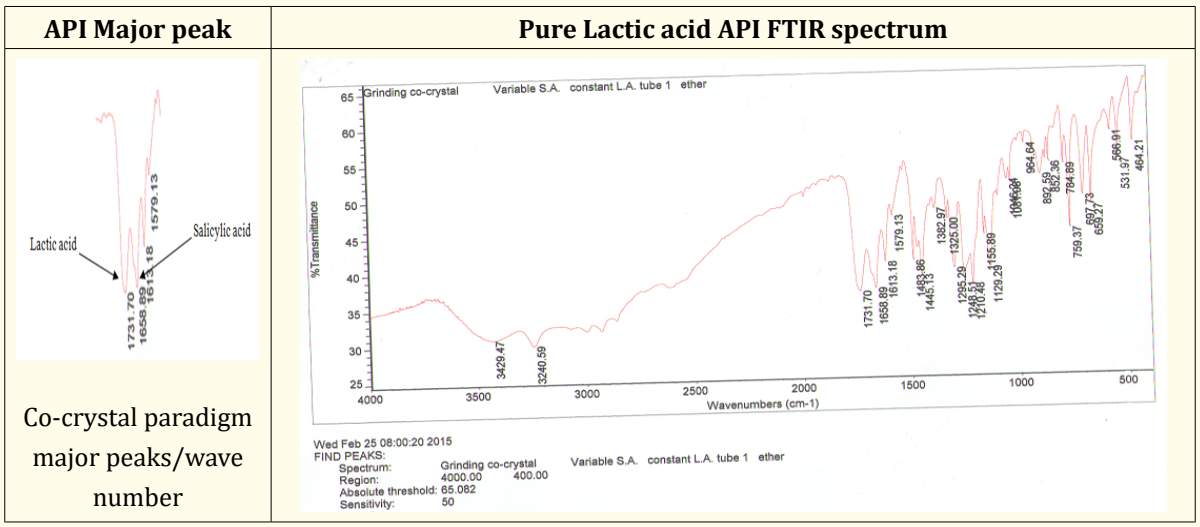


Figure 7: Co-crystal obtained from diethyl ether FTIR spectrum/grinding technique.

Co-crystal solubility in water

It is known that salicylic acid is slightly soluble in water and freely soluble in ethanol (96 per cent), while lactic acid is miscible with water and with ethanol (96 per cent). From previous co-crystal aims mentioned before in the text, it was supposed to change and modify the solubility of the active pharmaceutical ingredients in the new paradigms obtained. The surprise is obtained after testing the co-crystal paradigm, in each solvent prepared previously, in water as a solubility solvent used and the results are: Sample taken from each co-crystal paradigm is about 0.5g, an attempt to dissolve it in 10 ml purified water, using volumetric flask, by sonication for 15 minutes, and the result was not totally soluble. Then the same solution from each paradigm was transferred totally to 25 ml volumetric flask and diluted up to volume with purified water and sonicated for 15 minutes, and the result was also not totally soluble. Then the same solution from each paradigm was transferred totally to 50 ml volumetric flask and diluted up to volume with purified water and sonicated for 15 minutes, and the result was totally soluble. As a conclusion for the solubility test, since salicylic acid is sparingly soluble in water, while lactic acid is miscible in water. Then it was found that each 0.5g co-crystal paradigm is soluble in 50 ml of purified water. Therefore, the solubility is modified in each paradigm co-crystal, which means and assures that new compound is formed.

The co-crystal melting point

Pure salicylic acid pharmaceutical ingredient melting point is about 159°C, while lactic acid pure pharmaceutical ingredient melting point is about 53°C. The expected new co-crystal paradigm melting point is to be lower than 159°C and higher than 53°C, if the paradigm obtained is succeeded as expected and yes, it is, the following data result are for part of the co-crystals tested:

- Co-crystal sample melting Range is 127.6 - 127.7°C
- Co-crystal sample melting Range is 138.3 - 139.4°C
- Co-crystal sample melting Range is 141.5 - 147.8°C
- Co-crystal sample melting Range is 145.2 - 149.1°C

The variation change between the co-crystal melting point ranges is dependent on the target active pharmaceutical concentration and depending on the molar ratio for each co-crystal tested. But even so, there is a clear change in the melting point range which will assure that a new paradigm (composed of merging the

two active pharmaceutical ingredients) is obtained by using any of the solvents suggested ethanol, methanol, diethyl ether or acetonitrile.

Conclusion

The co-crystal paradigm of salicylic acid and lactic acid was obtained clearly in the reflux technique for each co-solvent used, which was tested firstly using FTIR, as well as in the grinding technique at different molar ratios in about 80% of the samples prepared, secondly using melting point range.

Acknowledgment

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