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# Improving Micromeritic Properties of Ibuprofen: An Agglomeration Approach

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**Abstract**

Ibuprofen is one of the common NSAIDs having poor water solubility, low dissolution, weak flow properties and reduced compressibility. These downsides of ibuprofen crystal upraise crucial challenges during development of a dosage form. The aim of this present work was to modify the physical form of ibuprofen by changing micromeritic properties. Seven different formulations of ibuprofen agglomerates such as F-1, F-2, F-3, F-4, F-5, F-6 and F-7 were prepared to convert the needle shaped ibuprofen crystals into agglomerates so that the desired micromeritic properties can be achieved. In this study, agglomerates of ibuprofen were prepared by Quasi emulsion solvent diffusion (QESD) method in association with two surfactants (sodium lauryl sulphateand Tween 80) at three different concentrations for each. The micromeritic properties of the prepared agglomerates were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose along with the release behavior of agglomerates. From dissolution study, it was observed that the release of drug was directly proportional to the surfactant concentration. Here, it was also revealed that there was no interaction among ibuprofen and other excipients as evident from DSC and FTIR studies.

**Key words**: Ibuprofen, micromeritic property, QESD method, agglomerates, surfactants, drug release.

## Introduction

Ibuprofen was the first member of propionic acid derivatives that was introduced in 1969 as a better alternative to aspirin (Tripathi, 2003). Ibuprofen is the most commonly used and most frequently prescribed NSAID.Gastricdiscomfort, nausea and vomiting are less in ibuprofen as compared to aspirin or indomethacin (Tripathi, 2003). It is a non-selective inhibitor of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Although its anti-inflammatory properties may be weaker than some other NSAIDs, it has prominent analgesic and antipyretic roles. Its effects are due to the inhibitory actions on cyclooxygenases, which are involved in the synthesis of prostaglandins. Prostaglandins have an important role in the production of pain, inflammation and fever (Wahbi *et al*., 2005).

Ibuprofen is available in the market in various dosage forms including tablet or caplets, gels, sprays and liquids. An injectable formulation (Ibuprofen lysine; Neopropen) has been licensed since 2006 (Deerfield, 2006). However; the most common dosage form of ibuprofen is tablet. Hence, the micromeritic properties along with solubility of ibuprofen are the most frequently asked question for designing a dosage form. Ibuprofen falls under class-2 according to the biopharmaceutics classification system [BCS] having poor solubility but high permeability (Potthast *et al*., 2005).

Besides the solubility issue of ibuprofen mentioned above, the flow property and compressibility of ibuprofen are the major challenges to make solid dosage form. Due to the needle like shape of ibuprofen API (Figure 1), it shows very poor flow property and low compressibility in addition to severe problem of sticking to the punches during compression (Rasenack *et al*., 2002). These drawbacks of active ibuprofen may be overcome by different innovative approaches. In this present study, all these drawbacks have been considered to modify active ibuprofen in such a way that subsides all the above mentioned complications. The preparation of ibuprofen agglomerates (Figure 2) is the consequence of these considerations.

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The prepared ibuprofen agglomerates exhibited significantly improved micromeritic properties than untreated drug crystals. Besides, the dissolution test showed that the prepared agglomerates revealed satisfactory dissolution rate.

*Method of preparation of ibuprofen agglomerates:* Preparation of ibuprofen agglomerates were carried out using the quasi emulsion solvent diffusion (QESD) method (Patil *et al*., 2011). Accurately weighted ibuprofen was dissolved in fixed amount of isopropyl alcohol and the temperature of this drug solution was raised to 40°C. Then, proper amount of distilled water (containing different % w/v of SLS or Tween 80) was added drop wise to the drug solution. Before adding this, the temperature was cooled down to 8°C. After that, the mixture was stirred continuously for 30 minutes at 500 rpm using a mechanical stirrer. Then, the separated materials were filtered and washed with two successive portions of cold water (8°C). Finally, filtered materials were kept in an oven at 50°C for about an hour until drying was completed.

*Formulation of ibuprofen agglomerates:* In this study, isopropyl alcohol and distilled water were used as good and poor solvent respectively. In addition, sodium lauryl sulphate (SLS) or Tween 80 was used as a surfactant in this preparation. Different amount of SLS and Tween 80 were added to the distilled water to produce three different concentrations of SLS and tween 80 (0.25% w/v, 0.75% w/v, 1.25%w/v). However, the amount of ibuprofen was fixed for all formulations as shown in table (Table 1)

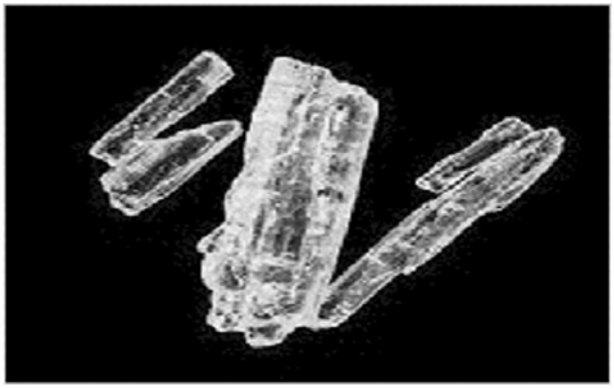


Figure 1. Ibuprofen API.

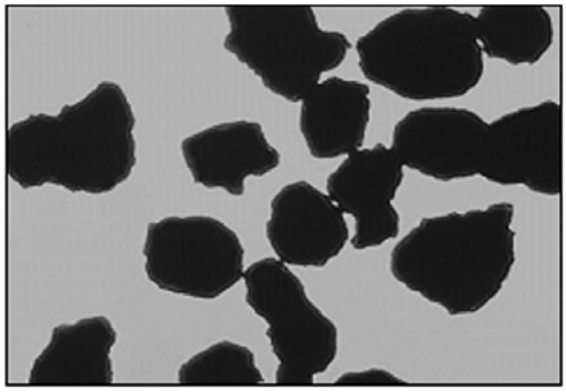


Figure 2. Ibuprofen agglomerates.

**Table 1. Composition of ibuprofen agglomerates preparation.**

| Formulation | Ibuprofen | Sodium lauryl sulphate (SLS) | Tween 80 | Isopropyl alcohol | Distilled water |
|---|---|---|---|---|---|
| F-1 [0.25% w/v of SLS in D. water] | 3000 mg | 150 mg | - | 12 ml | 60 ml |
| F-2 [0.75% w/v of SLS in D. water] | 3000 mg | 450 mg | - | 12 ml | 60 ml |
| F-3 [1.25% w/v of SLS in D. water] | 3000 mg | 750 mg | - | 12 ml | 60 ml |
| F-4 [0.25% w/v of tween 80 in D. water] | 3000 mg | - | 150 mg | 12 ml | 60 ml |
| F-5 [0.75% w/v of tween 80 in D. water] | 3000 mg | - | 450 mg | 12 ml | 60 ml |
| F-6 [1.25% w/v of tween 80 in D. water] | 3000 mg | - | 750 mg | 12 ml | 60 ml |
| F-7(without surfactant) | 3000 mg | 0.0 mg | 0.0 mg | 12 ml | 60 ml |

## Results and Discussion

Evaluated Parameters of prepared ibuprofen agglomerates are as follows:

**Table 2. Evaluated parameters of ibuprofen agglomerates.**

| Parameters | F-1 [0.25% w/v of SLS in D. water] | F-2 [0.75% w/v of SLS in # D. water] | F-3 [1.25% w/v of SLS in D. water] | F-4 [0.25% w/v of tween 80 in D. water] | F-5 [0.75% w/v of tween 80 in D. water] | F-6 [1.25% w/v of tween 80 in D. water] | F-7 (without surfactant) |
|---|---|---|---|---|---|---|---|
| Appearance | White crystals | White crystals | White crystals | White crystals | White crystals | White crystals | White crystals |
| Microscopic view | Near spherical agglomerates | Near spherical agglomerates | Near spherical agglomerates | Irregular agglomerates | Irregular agglomerates | Irregular agglomerates | Irregular mass |
| Yield (%) | 96.7 | 92.03 | 81.12 | 86.38 | 87.88 | 80.16 | 91.33 |
| Friability(%) | <1 | <1 | <1 | <1 | <1 | <1 | <1 |
| Tapped density (gm/ml) | 0.44 | 0.402 | 0.41 | 0.42 | 0.42 | 0.4 | 0.51 |
| Hausner's ratio | 1.19 | 1.13 | 1.06 | 1.18 | 1.20 | 1.2 | 1.46 |
| Carr's index (%) | 15.8 | 11.19 | 5.87 | 14.9 | 16.67 | 15 | 31.37 |
| Angle of repose (θ) | 35.64° | 34.57° | 35.92° | 45.67° | 48.9° | 49.08° | 51.39° |
| Potency (%) | 99.01 | 97.01 | 92 | 74.5 | 83.0 | 86.8 | 99 |

SLS = Sodium lauryl sulphate. # D. water = Distilled water

A typical spherical agglomeration system involved a good solvent, a poor solvent for a drug and a bridging liquid. The selection of these solvent depends on the miscibility of the solvents and solubility of the drug in individual solvents. In this study, the agglomeration of ibuprofen from isopropyl alcohol (good solvent) was performed by the addition of water (poor solvent) containing different concentrations of surfactant. The quasi-emulsion droplets are produced, due to a measurable interfacial tension being established between the good and poor solvents. Here, the surfactants modify the interfacial tension between good and poor solvents.

*Trinocular microscopic observation:* The findings reveal that the addition of sodium lauryl sulphate produces regular shaped agglomerates. In contrast, only an irregular mass of drugs was obtained when the same process was carried out with the addition of Tween 80 or without addition of any surfactant. The surfactants concentration would probably influence in the percentage yield. Trinocular Microscopic view of ibuprofen agglomerates by the six different formulations are shown below (Figure 3).

### Evaluation of Micromeritic properties

*Compressibility/Carr's index:* It is quite evident from the table (Table 4) that the compressibility was increased with the increase of SLS concentration in the formulations F1, F2 and F3. However, this trend was not exactly the same in case of F4, F5 and F6, where tween 80 was used as a surfactant. Here, F2 and F3 showed excellent compressibility. More particularly, the formulation containing no surfactant provided very poor compressibility which indicates the improvement of compressibility in ibuprofen agglomerates.

| Carr's Index | Flow property |
|---|---|
| 5 – 15 | Excellent |
| 12 - 16 | Good |
| 18 – 21 | Fair |
| 23 – 35 | Poor |

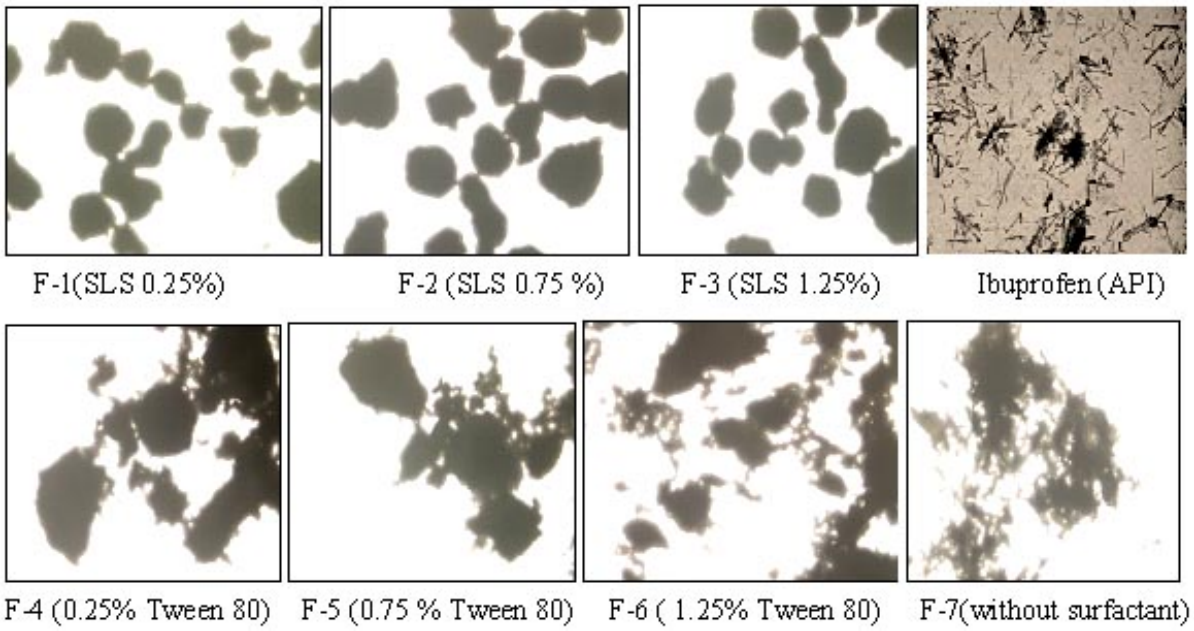



Figure 3. Trinocular microscopic view of ibuprofen agglomerates.

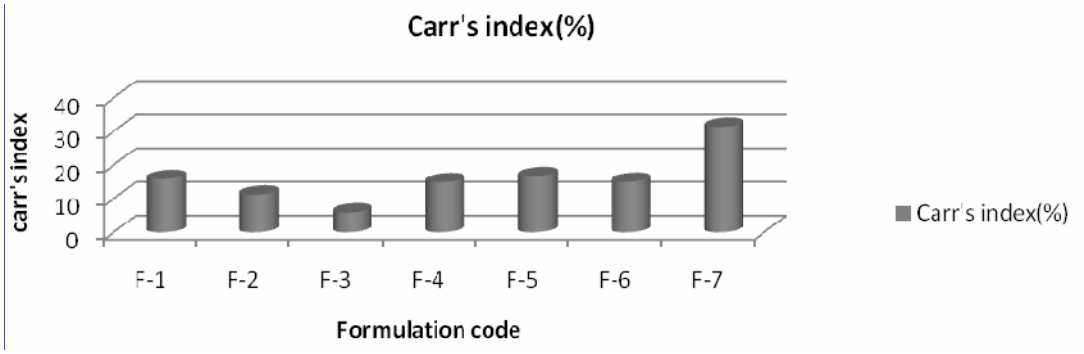



Figure 4. Flow propertywith Car's index of formulated agglomerates.
Here, F-2 & F-3 = Excellent flow property, F-1 & F-4, F-6 = good flow property,
F-5 = Fair flow property, F-7 = Poor flow property

*Hausner's ratio:* In this study, all the formulations except F-7 (agglomerates without surfactant) provided excellent Hausner's ration.

*Angle of repose:* Flow property increase with the decrease of angle of repose. In this study, flow property was found good in three formulations F-1, F-2, and F-3 that were prepared by using sodium lauryl sulphate as surfactant. However, this value was not so impressive when Tween 80 was used. This may be due to the development of smaller, rough and floppy agglomerates that contribute greater interparticle contact area and friction.

Moreover, the comparative low value of angle of repose, Carr's index and Hausner's ratio of ibuprofen agglomerates in (F1, F2 and F3) indicated their good flowability, packability and compressibility.

*Percentage yield:* The yield of prepared agglomerates was greater when sodium lauryl sulphate (SLS) was used as surfactant in comparison to Tween 80 (Table 3). The yields were variable in case of SLS with its different concentrations. On the other hand, there was no significant difference in percentage yield for different concentration of Tween 80.

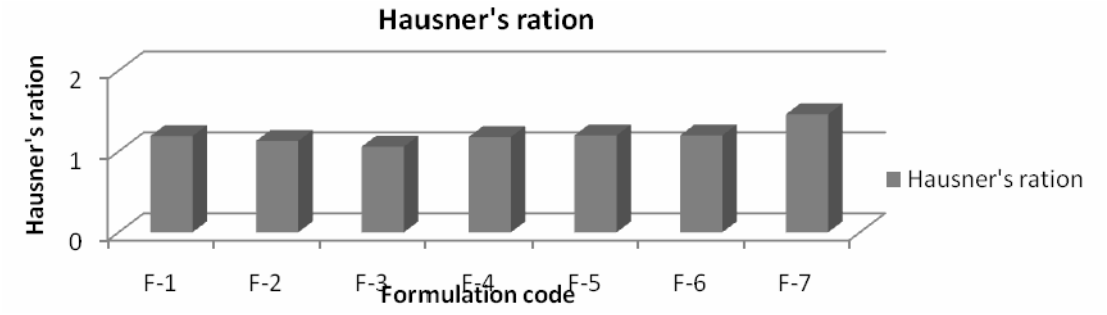



Figure 5. Flow property with Hausner's ration.

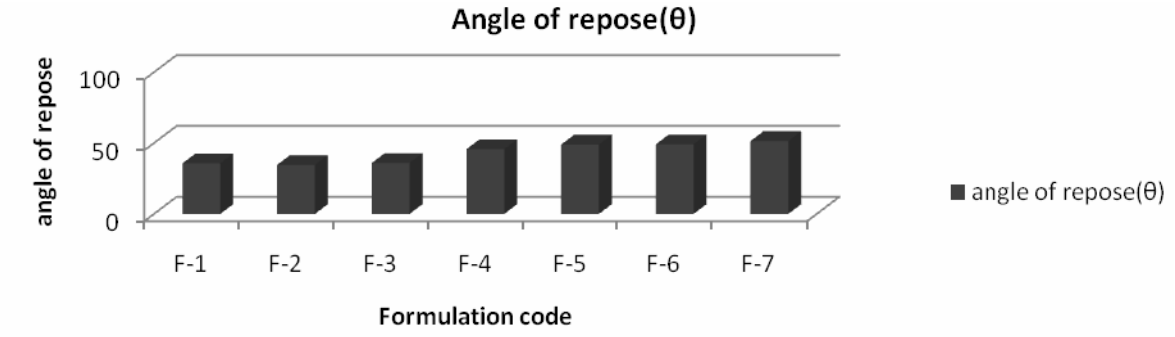



Figure 6. Flow property with angle of repose.

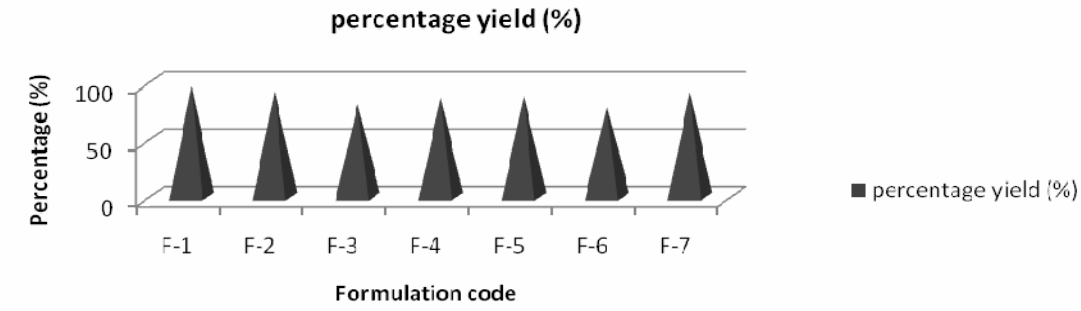



Figure 7. Percentage yield of different formulation.

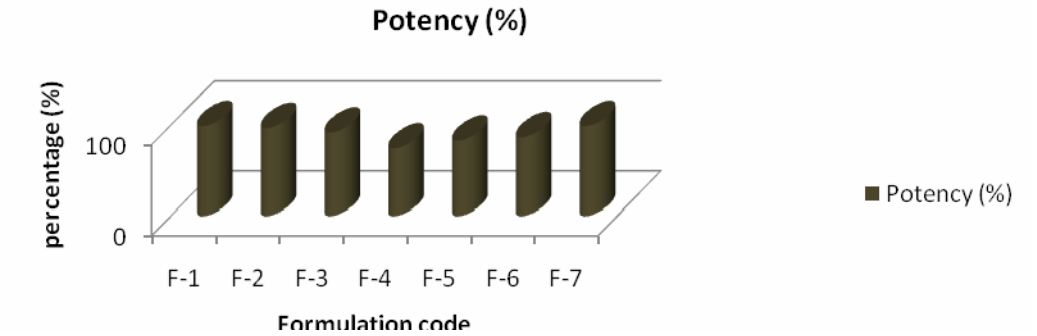



Figure 8. Potency comparison of prepared formulation.

*Potency [drug content]:* Drug content of ibuprofen agglomerates was spectrophotometricallydetermined at 222 nm using 0.1 N HCl media. The calculation was done with the help of standard curve.

*In vitro release study:* The dissolution profiles of ibuprofen agglomerates (figure-11) exhibited improved dissolution behavior. The dissolution rates increased with the increase of surfactant concentrations in the formulations. The reason for this faster dissolution may be linked to better wettability of the spherical agglomerates due to the addition of surfactants in the formulation (Rasenack et al,.2002). More significantly, all the six formulations containing different concentration of surfactants showed better dissolution profile when compared to the untreated ibuprofen API.

*Differential scanning calorimetry (DSC):* DSC analysis was performed in order to evaluate possible solid state interaction between the components to assess the actual drug-excipients compatibility. The thermal curves of pure ibuprofen and sample (API+excipients) were performed which are shown in the following figures 12 and 13. The DSC curve of pure ibuprofen as well as sample exhibited a flat profile initially, followed by a single sharp endothermic peak representing the melting point of pure ibuprofen and ibuprofen in agglomerates. The melting range of the agglomerates was 73.74 to 84.10°C. Since there was no change in the temperature of agglomerates when compared to that of the pure drug (Figure 12), it is quite evident that there was no interaction between the drug and the excipients.

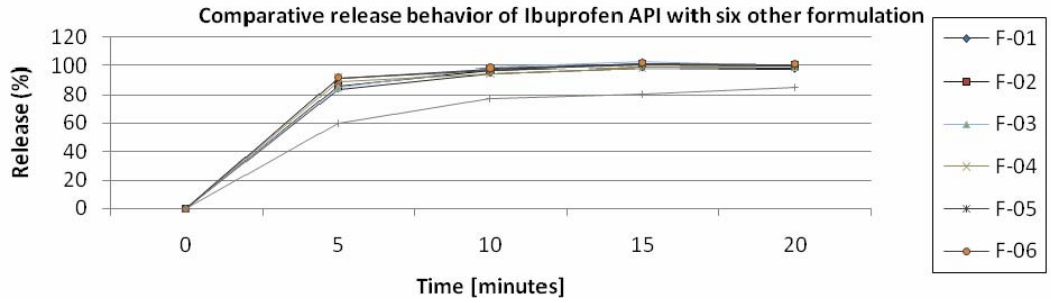



Figure 9. Comparison among dissolution behavior of prepared ibuprofen agglomerates. Here, [F1, F2, F-3 contains 0.25%, 0.75% and 1.25 % SLS respectively in distilled water]. [F4, F5, F6 contains 0.25%, 0.75% and 1.25 % tween 80 respectively in distilled water]

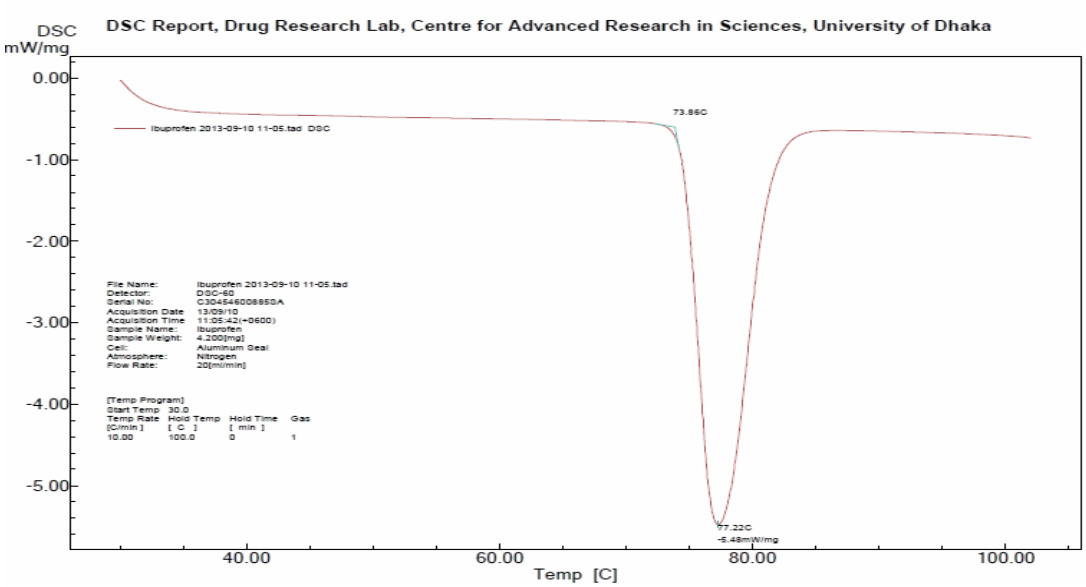



Figure 10. DSC thermogram of ibuprofen API.

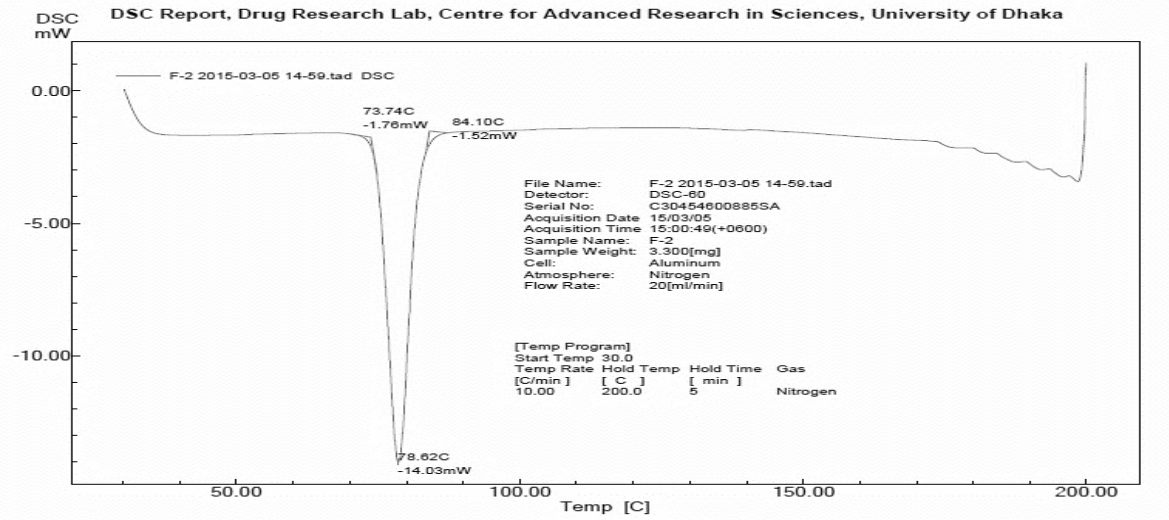



Figure 11. DSC thermogram of prepared ibuprofen agglomerates (F-2).

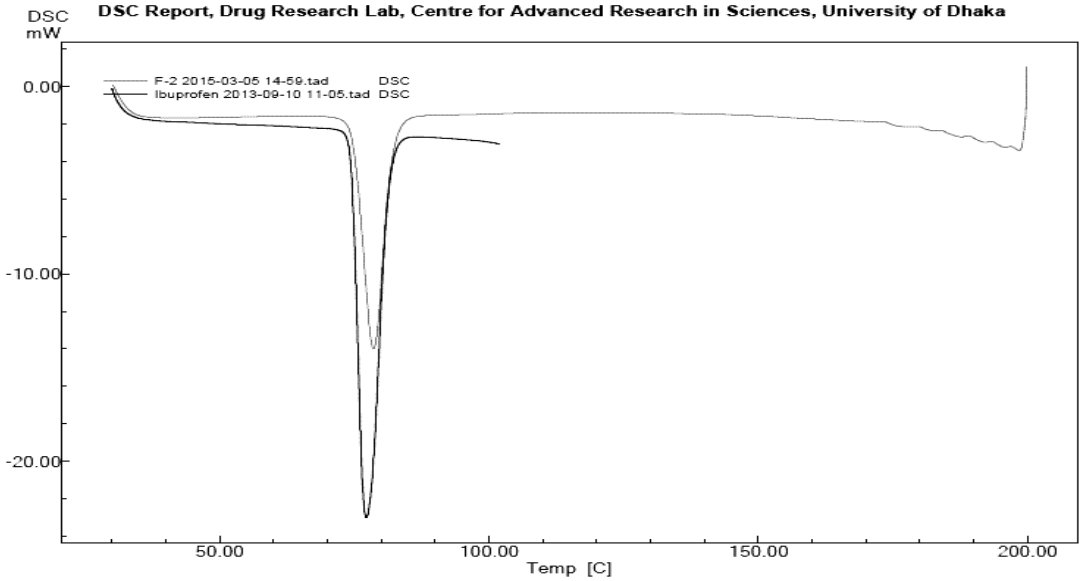
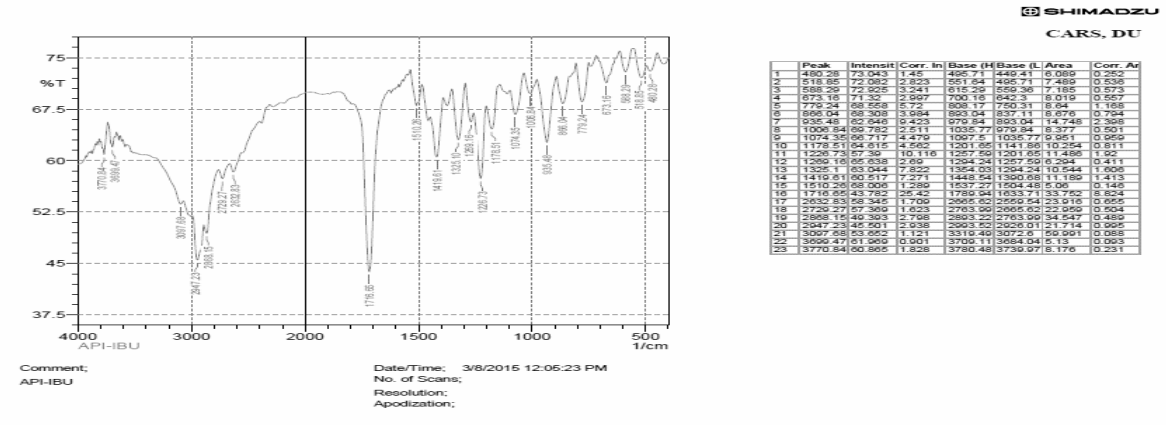
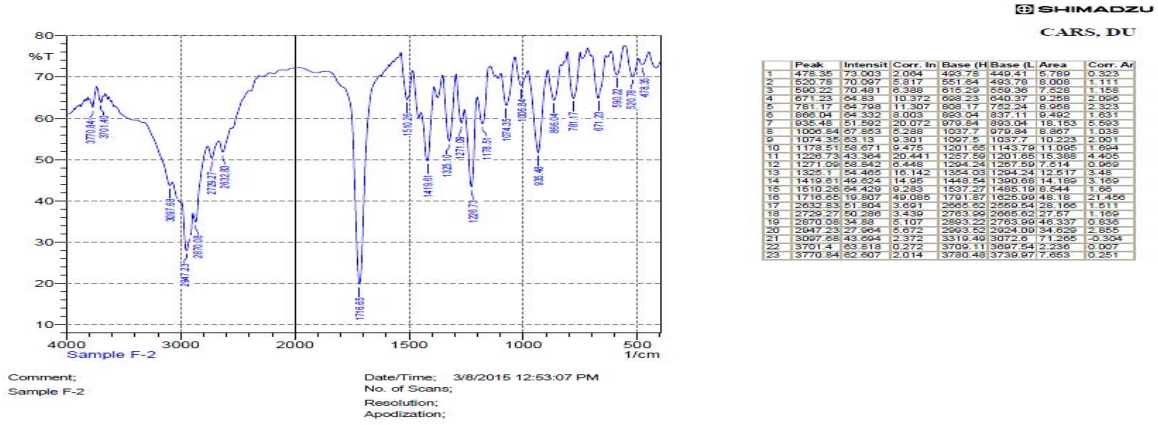



Figure 12. DSC thermogram (ibuprofen API and formulation F-2).



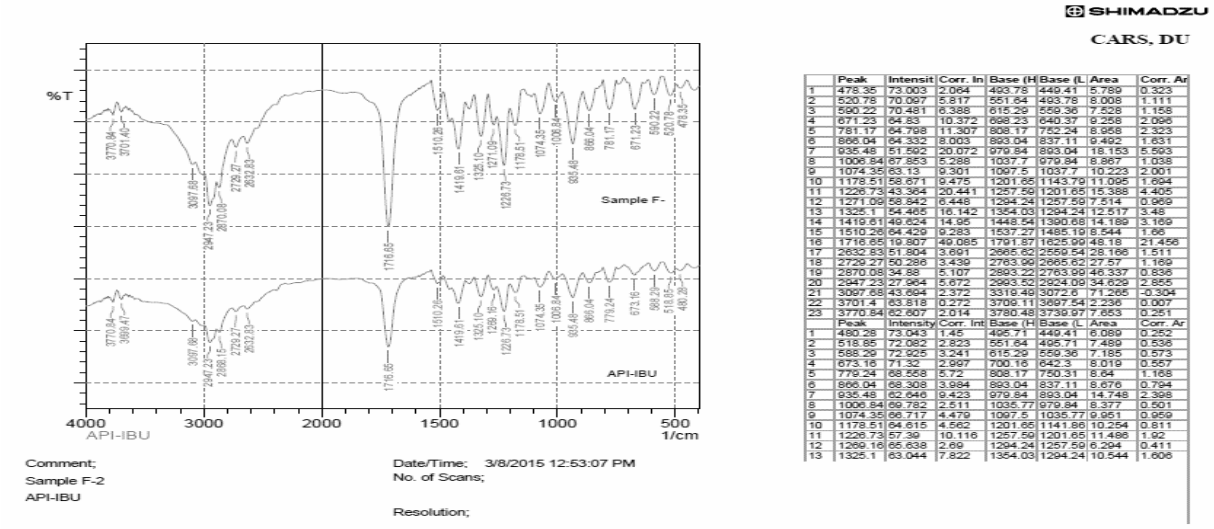

| | Peak | Intensit | Corr. In | Base (H | Base (L | Area | Corr. Ar |
|---|---|---|---|---|---|---|---|
| 1 | 480.28 | 73.043 | 1.45 | 495.71 | 449.41 | 6.089 | 0.262 |
| 2 | 518.85 | 72.082 | 2.823 | 561.64 | 495.71 | 7.469 | 0.536 |
| 3 | 586.29 | 72.925 | 3.241 | 615.29 | 559.36 | 7.185 | 0.573 |
| 4 | 673.16 | 71.32 | 2.907 | 700.16 | 642.3 | 8.019 | 0.557 |
| 5 | 779.24 | 68.558 | 5.72 | 808.17 | 750.31 | 8.64 | 1.168 |
| 6 | 866.04 | 68.308 | 3.984 | 893.04 | 837.11 | 8.676 | 0.794 |
| 7 | 935.48 | 62.648 | 9.423 | 979.84 | 893.04 | 14.748 | 2.398 |
| 8 | 1008.54 | 60.782 | 2.511 | 1035.77 | 979.84 | 8.327 | 0.501 |
| 9 | 1074.35 | 66.717 | 4.479 | 1097.5 | 1035.77 | 9.951 | 0.969 |
| 10 | 1178.51 | 64.615 | 4.562 | 1201.65 | 1141.86 | 10.264 | 0.811 |
| 11 | 1226.73 | 57.36 | 10.116 | 1257.59 | 1201.65 | 11.486 | 1.92 |
| 12 | 1269.16 | 65.638 | 2.69 | 1294.24 | 1257.59 | 6.294 | 0.411 |
| 13 | 1325.1 | 63.044 | 7.822 | 1354.03 | 1294.24 | 10.544 | 1.666 |
| 14 | 1410.51 | 60.517 | 7.271 | 1448.54 | 1390.68 | 11.189 | 1.413 |
| 15 | 1510.28 | 68.008 | 1.289 | 1537.27 | 1504.48 | 5.06 | 0.148 |
| 16 | 1716.55 | 43.782 | 26.42 | 1780.94 | 1633.71 | 33.752 | 8.824 |
| 17 | 2830.53 | 58.345 | 1.709 | 2865.62 | 2839.64 | 23.016 | 0.655 |
| 18 | 2729.77 | 57.369 | 1.623 | 2763.99 | 2865.62 | 22.959 | 0.504 |
| 19 | 2868.15 | 46.303 | 2.798 | 2893.22 | 2763.99 | 34.547 | 0.489 |
| 20 | 2947.23 | 45.501 | 2.938 | 2993.52 | 2926.01 | 21.714 | 0.995 |
| 21 | 3007.58 | 53.652 | 1.121 | 3319.49 | 3072.8 | 59.991 | 0.088 |
| 22 | 3099.47 | 61.969 | 0.901 | 3709.11 | 3684.04 | 5.13 | 0.093 |
| 23 | 3770.84 | 60.865 | 1.828 | 3780.48 | 3736.97 | 8.176 | 0.231 |

Figure 13. FTIR spectra of ibuprofen API.




| | Peak | Intensit | Corr. In | Base (H | Base (L | Area | Corr. Ar |
|---|---|---|---|---|---|---|---|
| 1 | 478.35 | 73.003 | 2.064 | 493.78 | 449.41 | 5.789 | 0.323 |
| 2 | 520.78 | 70.097 | 5.817 | 551.64 | 493.78 | 8.008 | 1.111 |
| 3 | 590.22 | 70.481 | 6.388 | 615.29 | 559.36 | 7.528 | 1.158 |
| 4 | 671.23 | 84.83 | 10.372 | 698.23 | 640.37 | 9.258 | 2.096 |
| 5 | 781.17 | 84.798 | 11.307 | 808.17 | 752.24 | 8.958 | 2.323 |
| 6 | 866.04 | 84.332 | 8.003 | 893.04 | 837.11 | 9.492 | 1.631 |
| 7 | 935.48 | 51.592 | 20.072 | 979.84 | 893.04 | 18.153 | 5.593 |
| 8 | 1006.84 | 87.853 | 5.288 | 1037.7 | 979.84 | 8.867 | 1.038 |
| 9 | 1074.35 | 83.13 | 9.301 | 1097.5 | 1037.7 | 10.223 | 2.001 |
| 10 | 1178.51 | 58.671 | 9.475 | 1201.65 | 1143.79 | 11.095 | 1.694 |
| 11 | 1226.73 | 43.364 | 20.441 | 1257.59 | 1201.65 | 15.388 | 4.405 |
| 12 | 1271.09 | 58.842 | 6.448 | 1294.24 | 1257.59 | 7.614 | 0.969 |
| 13 | 1325.1 | 54.465 | 16.142 | 1354.03 | 1294.24 | 12.517 | 3.48 |
| 14 | 1419.61 | 49.624 | 14.95 | 1448.54 | 1390.68 | 14.189 | 3.169 |
| 15 | 1510.26 | 84.429 | 9.283 | 1537.27 | 1485.19 | 8.544 | 1.66 |
| 16 | 1716.65 | 19.807 | 49.085 | 1791.87 | 1625.99 | 48.18 | 21.456 |
| 17 | 2632.83 | 51.804 | 3.691 | 2665.62 | 2559.54 | 28.166 | 1.511 |
| 18 | 2729.27 | 50.288 | 3.439 | 2763.99 | 2665.62 | 27.57 | 1.169 |
| 19 | 2870.08 | 34.88 | 5.107 | 2893.22 | 2763.99 | 46.337 | 0.836 |
| 20 | 2947.23 | 27.964 | 5.672 | 2993.52 | 2934.09 | 34.629 | 2.855 |
| 21 | 3097.68 | 43.694 | 2.372 | 3319.49 | 3072.6 | 71.265 | -0.304 |
| 22 | 3701.4 | 83.818 | 0.272 | 3709.11 | 3697.54 | 2.236 | 0.007 |
| 23 | 3770.84 | 82.807 | 2.014 | 3780.48 | 3739.97 | 7.653 | 0.251 |

Figure 14. FTIR spectra of ibuprofen agglomerates [F-2].




| | Peak | Intensit | Corr. In | Base (H | Base (L | Area | Corr. Ar |
|---|---|---|---|---|---|---|---|
| 1 | 478.35 | 73.003 | 2.064 | 493.78 | 449.41 | 5.789 | 0.323 |
| 2 | 520.78 | 70.097 | 5.817 | 551.64 | 493.78 | 8.008 | 1.111 |
| 3 | 590.22 | 70.481 | 6.388 | 615.29 | 559.36 | 7.528 | 1.158 |
| 4 | 671.23 | 84.83 | 10.372 | 698.23 | 640.37 | 9.258 | 2.096 |
| 5 | 781.17 | 84.798 | 11.307 | 808.17 | 752.24 | 8.958 | 2.323 |
| 6 | 866.04 | 84.332 | 8.003 | 893.04 | 837.11 | 9.492 | 1.631 |
| 7 | 935.48 | 51.592 | 20.072 | 979.84 | 893.04 | 18.153 | 5.593 |
| 8 | 1006.84 | 87.853 | 5.288 | 1037.7 | 979.84 | 8.867 | 1.038 |
| 9 | 1074.35 | 83.13 | 9.301 | 1097.5 | 1037.7 | 10.223 | 2.001 |
| 10 | 1178.51 | 58.671 | 9.475 | 1201.65 | 1143.79 | 11.095 | 1.694 |
| 11 | 1226.73 | 43.364 | 20.441 | 1257.59 | 1201.65 | 15.388 | 4.405 |
| 12 | 1271.09 | 58.842 | 6.448 | 1294.24 | 1257.59 | 7.614 | 0.969 |
| 13 | 1325.1 | 54.465 | 16.142 | 1354.03 | 1294.24 | 12.517 | 3.48 |
| 14 | 1419.61 | 49.624 | 14.95 | 1448.54 | 1390.68 | 14.189 | 3.169 |
| 15 | 1510.26 | 84.429 | 9.283 | 1537.27 | 1485.19 | 8.544 | 1.66 |
| 16 | 1716.65 | 19.807 | 49.085 | 1791.87 | 1625.99 | 48.18 | 21.456 |
| 17 | 2632.83 | 51.804 | 3.691 | 2665.62 | 2559.54 | 28.166 | 1.511 |
| 18 | 2729.27 | 50.288 | 3.439 | 2763.99 | 2665.62 | 27.57 | 1.169 |
| 19 | 2870.08 | 34.88 | 5.107 | 2893.22 | 2763.99 | 46.337 | 0.836 |
| 20 | 2947.23 | 27.964 | 5.672 | 2993.52 | 2924.09 | 34.629 | 2.855 |
| 21 | 3097.68 | 43.694 | 2.372 | 3319.49 | 3072.6 | 71.265 | -0.304 |
| 22 | 3701.4 | 83.818 | 0.272 | 3709.11 | 3697.54 | 2.236 | 0.007 |
| 23 | 3770.84 | 82.807 | 2.014 | 3780.48 | 3739.97 | 7.653 | 0.251 |

| | Peak | Intensity | Corr. Int | Base (H | Base (L | Area | Corr. Ar |
|---|---|---|---|---|---|---|---|
| 1 | 480.28 | 73.043 | 1.45 | 495.71 | 449.41 | 6.089 | 0.252 |
| 2 | 518.85 | 72.082 | 2.823 | 551.64 | 495.71 | 7.489 | 0.536 |
| 3 | 559.29 | 69.525 | 3.241 | 615.29 | 559.36 | 7.185 | 0.573 |
| 4 | 673.16 | 71.32 | 2.997 | 700.16 | 642.3 | 8.019 | 0.557 |
| 5 | 779.24 | 68.558 | 5.72 | 808.17 | 750.31 | 8.64 | 1.168 |
| 6 | 866.04 | 68.308 | 3.984 | 893.04 | 837.11 | 8.676 | 0.794 |
| 7 | 935.48 | 62.646 | 9.423 | 979.84 | 893.04 | 14.748 | 2.398 |
| 8 | 1006.84 | 69.782 | 2.511 | 1035.77 | 979.84 | 8.377 | 0.501 |
| 9 | 1074.35 | 66.717 | 4.479 | 1097.5 | 1035.77 | 9.951 | 0.959 |
| 10 | 1178.51 | 64.615 | 4.562 | 1201.65 | 1141.86 | 10.254 | 0.811 |
| 11 | 1226.73 | 57.36 | 10.116 | 1257.59 | 1201.65 | 11.486 | 1.92 |
| 12 | 1269.16 | 65.638 | 2.69 | 1294.24 | 1257.59 | 6.294 | 0.411 |
| 13 | 1325.1 | 63.044 | 7.822 | 1354.03 | 1294.24 | 10.544 | 1.606 |

Figure 15. FTIR spectra of prepared ibuprofen agglomerates and ibuprofen API.

*Fourier transform infrared spectroscopy (FTIR) study:* FTIR studies reveals that the ibuprofen agglomerates showed two typical peaks at 2947.23 $cm^{-1}$ due to O-H stretching vibration and at 1716.65 $cm^{-1}$ due to C=O group. There are no significant changes in FTIR spectra of agglomerates when compared to that of the pure drug. The spectra were super imposable which can be easily seen from the figures (Figure 15-16) excepting a few insignificant peaks.

## Conclusions

Ibuprofen is a poorly compressible active pharmaceutical ingredient which also exhibits poor flow property and tendency to stick to the punches during compression. In this study, micromeritic properties of ibuprofen were developed successfully using quasi emulsion solvent diffusion method (QESD). From the present study it can be concluded that:

- The micromeritic properties as well as others evaluation parameters could be better controlled by the surfactant concentration.
- Among all the formulation F-2 was considered as the best because of its better micromeritic properties along with the dissolution profile.

In conclusion, there is further scope to conduct stability study including other solid state properties to confirm the appropriateness of these formulated agglomerates.

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