Solid-state flurbiprofen and methyl–*β*–cyclodextrin inclusion complexes prepared using a single-step, organic solvent-free supercritical fluid process.

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ABBREVIATIONS

DE, dissolution efficiency; DP, percent drug dissolved; DSC, differential scanning calorimetry; Me–*β*–CD, methyl–*β*–cyclodextrin; SC-CO_2, supercritical carbon dioxide; SEM, rpm, revolutions per minute; Scanning electron microscopy; XRPD: X-ray powder diffraction.

ABSTRACT

The aim of this study was to enhance the apparent solubility and dissolution properties of flurbiprofen through inclusion complexation with cyclodextrins. Especially, the efficacy of supercritical fluid technology as a preparative technique for the preparation of flurbiprofen-methyl–*β*–cyclodextrin inclusion complexes was evaluated. The complexes were prepared by supercritical carbon dioxide processing and were evaluated by solubility, differential scanning calorimetry, X-ray powder diffraction, scanning electron microscopy, practical yield, drug content estimation and *in vitro* dissolution studies. Computational molecular docking studies were conducted to study the possibility of molecular arrangement of inclusion complexes between flurbiprofen and methyl–*β*–cyclodextrin. The studies support the formation of stable molecular inclusion complexes between the drug and cyclodextrin in a 1:1 stoichiometry. *In vitro* dissolution studies showed that the dissolution properties of flurbiprofen were significantly enhanced by the binary mixtures prepared by supercritical carbon dioxide processing. The amount of flurbiprofen dissolved into solution alone was very low with 1.11 ± 0.09% dissolving at the end of 60 min, while the binary mixtures processed by supercritical carbon dioxide at 45 °C and 200 bar released 99.39 ± 2.34% of the drug at the end of 30 min. All the binary mixtures processed by supercritical carbon dioxide at 45 °C exhibited a drug release of more than 80% within the first 10 min irrespective of the pressure employed. The study demonstrated the single step, organic solvent-free supercritical carbon dioxide process as a promising approach for the preparation of inclusion complexes between flurbiprofen and methyl–*β*–cyclodextrin in solid-state.

Keywords: Dissolution rate; Flurbiprofen; Inclusion complexes; Methyl–*β*–cyclodextrin; Solubility; Supercritical fluid technology.

1. Introduction

The water solubility of a drug is a key indicator for the solubility of drug molecules in the intestinal fluids and its contribution to bioavailability. The success of a pharmaceutical formulation relies on how effectively it makes the drug molecules available at the site of absorption. However, poor water solubility and the resulting poor oral bioavailability of most drugs available on the market has long been a problem to pharmaceutical scientists, as the dissolution is quite often the rate-limiting process in the absorption of a drug (Charman and Stella, 1991; Takagi *et al.*, 2006). The ability to increase the water solubility of a drug is thus very important to enhancing its therapeutic efficacy. Several strategies to improve the water solubility and dissolution rate of poorly soluble drugs have been reported (Gupta *et al.*, 1997; Ambade *et al.*, 2008; Tokumura *et al.*, 2009; Rudrangi *et al.*, 2011; Oh *et al.*, 2011; Bontha *et al.*, 2012; Rudrangi *et al.*, 2015a; Kaialy and Al Shafiee, 2015), among which is the inclusion complexation with cyclodextrins (Jain and Adeyeye, 2001; Bandi *et al.*, 2004; Cirri *et al.*, 2005; Vega *et al.*, 2013; Rudrangi *et al.*, 2015a; Rudrangi *et al.*, 2015b).

Cyclodextrins are a family of non-reducing cyclic oligosaccharides composed of (α–1,4)–linked α–D–glucopyranose units. They possess a hydrophobic cavity and a hydrophilic exterior (Kfoury *et al.*, 2015). The hydrophobic cavity can accommodate a poorly water-soluble drug, whilst the hydrophilic exterior facilitates high water solubility (Rudrangi *et al.*, 2015a).

Flurbiprofen [2-(2-fluoro-4-biphenylyl)propionic acid] is a potent chiral non-steroidal anti-inflammatory drug approved by the Food and Drug Administration for the treatment of rheumatoid arthritis and osteoarthritis (Davies, 1995). It also has profound analgesic effects and is indicated in the treatment of gingivitis and alveolar bone resorption in periodontitis (Heasman, P.A. *et al.*, 1990). However, it has poor water solubility (5-13 µg mL^{-1}) and

dissolution rate (Anderson and Conradi, 1985), which limits both its therapeutic application and efficacy. Hence, there is a need to enhance the water solubility and dissolution rate of flurbiprofen.

Several formulation strategies have been reported to improve the solubility and dissolution rate of flurbiprofen, such as dry elixir (Kim and Yoon, 1995), solid dispersion (Habib *et al*., 1998; Oh *et al*., 2011), salt formation (Gupta *et al*., 1997), microemulsion (Park *et al*., 1997; Ambade *et al*., 2008), inclusion complex with cyclodextrins (Tokumura *et al*., 2009; Li *et al*., 2010) and cycloamyloses (Baek *et al*., 2011).

Flurbiprofen has an affinity for different cyclodextrins forming inclusion complexes. The favourable effect of natural *β*–cyclodextrin (Muraoka *et al*., 2004; Cirri *et al*., 2005; Tokumura *et al*., 2009; Li *et al*., 2010; Baek *et al*., 2011) and its derivatives, such as hydroxypropyl–*β*–cyclodextrin (Govindarajan and Nagarsenker, 2005; Vega *et al*., 2013), hydroxyethyl–*β*–cyclodextrin and methyl–*β*–cyclodextrin (Cirri *et al*., 2005) on its pharmaceutical properties has been previously reported. For example, Cirri *et al*. (2005) reported that flurbiprofen and methyl–*β*–cyclodextrin (Me–*β*–CD) complexes prepared in the 1:1 molar ratio using kneading and co-evaporation techniques exhibit higher solubility and dissolution profiles than flurbiprofen alone or in a state of a physical mixture. In spite of their success, the complexes prepared by the co-evaporation and kneading methods required an organic solvent. Organic solvents are potentially hazardous and their presence in the final product (complexes) is highly undesirable and often requires energy-intensive drying steps involving a great deal of time to remove the residual solvent (Al-Marzouqi *et al*., 2007; Al-Marzouqi *et al*., 2009). Hence, there is a need to avoid the use of organic solvents in the preparation of drug-cyclodextrin complexes.

Pharmaceutical scientists relentlessly try to avoid the usage of toxic organic solvents and exchange those to more environmentally friendly alternatives with similar properties. One of those effective alternatives is the use of supercritical fluids. A supercritical fluid is a substance that exists above its critical point, where the phase boundaries diminish. Carbon dioxide is the most commonly employed supercritical fluid because of its low critical parameters. Supercritical carbon dioxide (SC-CO_2) has provided an excellent green alternative to harmful organic solvents and the use of SC-CO_2 processing technique in the preparation of drug-cyclodextrin complexes has been reported (York, 1999; Kompella and Koushik, 2001; Sunkara and Kompella, 2002; Türk *et al*., 2007; Lee *et al*., 2008; Rudrangi *et al*., 2015a; Rudrangi *et al*., 2015b).

The application of supercritical carbon dioxide processing in the preparation of flurbiprofen-Me–*β*–CD complexes has not yet been investigated. Therefore, the aim of this study was to evaluate supercritical fluid technology as a preparative technique for the preparation of flurbiprofen-Me–*β*–CD inclusion complexes in solid-state. Inclusion complexes were prepared by physical mixing and SC-CO_2 processing at various working (temperature and pressure) conditions. The prepared complexes were then characterized by solubility studies, differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), scanning electron microscopy (SEM), practical yield, drug content evaluation and dissolution studies.

2. Materials and methods

2.1. Materials

Flurbiprofen (≥ 98.5%, molecular weight: 244.26 g/mol) and Me–*β*–CD (average molecular weight: 1310 g/mol, extent of labeling: 1.6-2.0 mol CH_3 per unit anhydroglucose) were purchased from Sigma-Aldrich (Gillingham, Dorset, UK). Ethanol was obtained from Fisher

Scientific (Loughborough, UK). Carbon dioxide (99.9%) was obtained from BOC Ltd (Guildford, Surrey, UK). All reagents were used as received.

2.2. Preparation of binary mixtures of flurbiprofen with Me–*β*–CD

All binary mixtures were prepared in a 1:1 molar ratio of flurbiprofen to Me–*β*–CD. The processed samples were stored in desiccators until further use.

2.2.1. Physical mixing

Required quantities of flurbiprofen and Me–*β*–CD were accurately weighed and tumble-mixed at 100 rpm for 15 min using a Turbula® T2F mixer (Willy A. Bachofen AG – Maschinenfabrik, Muttenz, Switzerland).

2.2.2. Supercritical carbon dioxide process

The SC-CO_2 process was carried out in the static mode to achieve the inclusion of flurbiprofen in the Me–*β*–CD. The complexes were prepared using an extraction apparatus supplied by Thar Process Inc., USA as described in detail elsewhere (Rudrangi *et al.*, 2015b)..

The physical mixtures of flurbiprofen and Me–*β*–CD were placed in a sample cell. Carbon dioxide was pumped from a cylinder *via* a cooling unit into the sample cell. The physical mixtures were processed at six different working conditions [35 °C/100 bar, 35 °C/150 bar, 35 °C/200 bar, 45 °C/100 bar, 45 °C/150 bar and 45 °C/200 bar] in order to study the influence of temperature and pressure on the inclusion complex formation.

2.3. Analysis of the prepared binary mixtures

Having prepared these model complexes by supercritical carbon dioxide processing, the next aim is to compare the physical properties with those of complexes prepared using physical mixing.

2.3.1. Solubility studies

Saturation solubility of flurbiprofen was measured in triplicate by adding excess amounts of the drug to 10 mL of deionised water in sealed glass containers. The solutions were agitated for 72 hours at 25 °C. The solutions were then filtered (0.45 μm filter pore size) and assayed for drug concentration by ultra-violet spectroscopy (Cary 100 UV-vis, Agilent Technologies, USA) after dilution.

Phase solubility diagram was obtained according to the method reported by Higuchi and Connors (1965). Samples were prepared by adding excess flurbiprofen (in an amount above its solubility), to a 10 mL deionised water containing successively increasing concentrations (0, 2.5, 5, 10, 12.5, 15, 20 and 25 × 10^{-3} M) of Me–*β*–CD, in sealed glass containers. The solutions were agitated (200 rpm) at 25 °C for 72 hours. Following equilibrium, the solutions were then filtered and assayed for drug concentration by UV spectroscopy as described above. Phase-solubility diagram was represented as the concentration of total dissolved flurbiprofen against the concentration of Me–*β*–CD. The binding constant ($K_{1:1}$) for flurbiprofen-Me–*β*–CD complexes was calculated from the slope of the curve.

2.3.2. Differential scanning calorimetry (DSC) analysis

DSC analysis of flurbiprofen, Me–*β*–CD and the flurbiprofen-Me-*β*-CD complex systems was carried out using a FP-90 central processor (Mettler-Toledo, LLC, UK). The instrument was calibrated using indium as the reference material. For each sample, about 5 mg of each sample was accurately weighed, hermetically sealed in an aluminium pan, and then heated

from 50 to 150 °C at a heating rate of 10 °C min^{-1}. The control study was carried out to investigate the effect of SC-CO_2 processing on flurbiprofen alone.

2.3.3. X-ray powder diffraction (XRPD) analysis

X-ray powder diffractograms of flurbiprofen, Me–*β*–CD and the flurbiprofen-Me–*β*–CD complex systems were obtained on a D8 Advance X-ray Diffractometer (Bruker, Germany) in theta–theta Bragg–Brentano geometry using reflection mode. Data were collected between 2-40º 2*θ*, with a step size of 0.006º and a time of 0.5 s per step using Cu Kα radiation. A control study was carried out to investigate the effect of SC-CO_2 processing on flurbiprofen alone.

The degree of crystallinity (% crystallinity) of the flurbiprofen-Me–*β*–CD complex systems was determined using the amorphous subtraction method as reported previously (Rudrangi *et al.*, 2015a).

2.3.4. Scanning electron microscopy (SEM) analysis

The surface morphology of flurbiprofen, Me–*β*–CD and the flurbiprofen-Me–*β*–CD complex systems was examined by means of Hitachi SU-8030 scanning electron microscope (Tokyo, Japan). The powder samples were securely fixed on an aluminium stub using double-sided adhesive tape and then were made electrically conductive by coating in vacuum with a thin layer of chromium (~300 Å) at 30 W for 30 seconds. The photomicrographs were taken at an excitation voltage of 1.0 kV and a magnification of ×350.

2.3.5. Practical yield

The efficiency of a processing method used for the preparation of inclusion complexes can be measured by determining the practical yield of the binary systems. The percentage practical yield of the binary systems was determined using the following equation:

$$\text{Practical yield (\%)} = \left[\frac{\text{Practical weight of the binary mixture}}{\text{Theoretical weight (Drug + Cyclodextrin)}}\right] \times 100$$

2.3.6. Evaluation of the flurbiprofen content

Flurbiprofen-Me–*β*–CD binary system, equivalent to 10 mg of the drug, was accurately weighed and dispersed in ethanol (10 mL), in which both the drug and cyclodextrin are soluble. The mixture was agitated (100 rpm) at 25 ± 0.5 °C for 30 min and the resultant solution was filtered (0.45 µm filter pore size) and assayed for the concentration of total flurbiprofen by UV spectroscopy after dilution. Determination of the flurbiprofen content in the complexes allows the verification that there is no loss of flurbiprofen during the (complex) preparation process.

2.3.7. *In vitro* dissolution studies

In vitro dissolution studies of flurbiprofen from all drug-carrier binary systems, and for flurbiprofen alone, were conducted in triplicate using USP Type II paddle method (Hanson G2 Vision® Classic 6, Chatsworth, CA) with deionised water as the dissolution medium. The samples, corresponding to 1000 mg of flurbiprofen were dispersed into 900 mL of the dissolution media maintained at 25 ± 0.5 °C and stirred at 100 rpm. Aliquots (5 mL) were withdrawn and filtered (0.45 µm filter pore size) at the specified time intervals (2, 5, 10, 20, 30 and 60 min) and the drug concentration was determined by UV spectroscopy at a λ_{max} of 246 nm. The same volume of fresh medium was added to the vessel and the correction for the cumulative dilution was calculated. The parameters used to characterize the dissolution curves were the percentage of flurbiprofen dissolved at 30 min, and the dissolution efficiency at 30 and 60 min. The dissolution efficiency was calculated according to Khan (1975). DE_{30min} was calculated from the area under the dissolution curve at 30 min and expressed as a

percentage of the area of the rectangle described by 100% dissolution in the same time of the total amount added.

2.3.8. Molecular docking studies

Molecular docking studies were conducted to study the possibility of molecular arrangement of inclusion complexes between flurbiprofen and Me–*β*–CD. Molecular docking studies of flurbiprofen into Me–*β*–CD were conducted using Glide (grid-based ligand docking) application implemented in the Maestro 9.3 software package (Schrodinger, LLC, New York, USA, 2012) as reported earlier (Rudrangi et al., 2015b). Docked flurbiprofen and Me–*β*–CD complexes were visualised and molecular surface complex pictures were generated using Maestro.

3. Results and discussions

3.1. Solubility studies

Aqueous solubility of flurbiprofen at 25 °C was 12.29 ± 1.05 µg mL^{-1} and 30.68 ± 0.5 µg mL^{-1} after 1 h and 24 h, respectively. No further improvement was observed in drug solubility after 24 h.

Cirri *et al.* (2005), Li *et al*. (2010) and Baek *et al*. (2011) reported a drug solubility of 40 µg mL^{-1}, 10.45 ± 3.22 µg mL^{-1} and 5.12 ± 1.22 µg mL^{-1} in water at 25 °C after 24 h, 120 h and 168 h, respectively. Herzfeldt and Kummel (1983) reported a drug solubility of 8 µg mL^{-1} and 31.2 µg mL^{-1} in pH 1.2 and 7.5 buffered solutions at 25 °C after 24 h, respectively. Varma and Pandi (2005) reported a drug solubility of 48.2 µg mL^{-1} in water at 27 °C after 72 h.

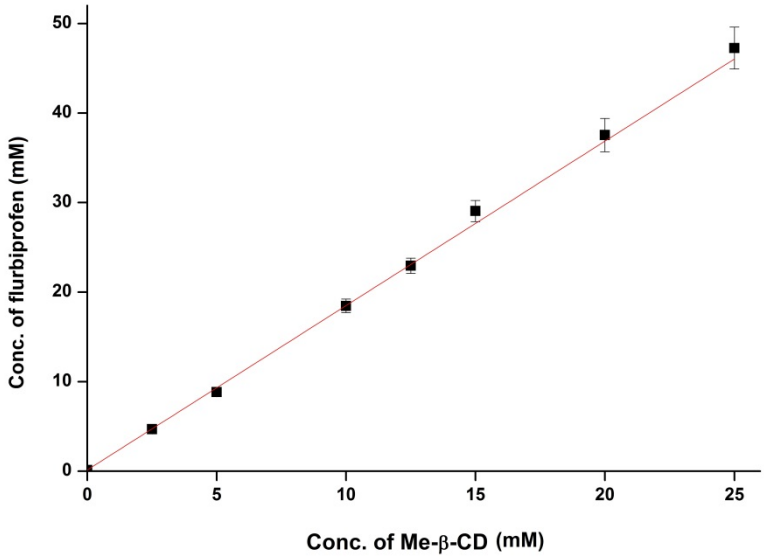


Fig. 1. Phase solubility studies of flurbiprofen with increasing concentrations of Me–*β*–CD at 25 °C and in deionised water.

The solubility of flurbiprofen increased in a linear fashion with the concentration of Me–*β*–CD (Fig. 1), forming A_L-subtype complexes (presumably 1:1 stoichiometry). The binding constant of the complexes ($K_{1:1}$ = 16856 ± 1244 M^{-1}) was calculated from the slope of the curve. Similar phase solubility profile was reported for flurbiprofen-Me–*β*–CD complexes in water by Cirri *et al*. (2005). The authors reported the stability constant values of $K_{1:1}$ = 11570 M^{-1} and 9660 M^{-1} in unbuffered water (pH ≈ 4.5) at 25 °C and 37 °C, respectively, and the values of $K_{1:1}$ = 1480 M^{-1} and 1085 M^{-1} in phosphate buffer (pH 5.5) at 25 °C and 37 °C, respectively.

Rudrangi and co-workers carried out the phase solubility studies of indomethacin and olanzapine formulated with Me–*β*–CD in phosphate buffer medium (pH 7.4) and de-ionised water (pH 7.1) at 37 °C, respectively. Rudrangi *et al.* (2015a) reported an A_N-subtype phase solubility diagram with a stability constant of $K_{1:1}$ = 167 M^{-1} for the indomethacin-Me–*β*–CD

complexes while Rudrangi *et al.* (2015b) reported an A_L-subtype phase solubility diagram with a stability constant of $K_{1:1}$ = 304 M^{-1} for the olanzapine-Me–*β*–CD complexes.

3.2. Solid-state analyses

The DSC traces of the unprocessed flurbiprofen and SC-CO_2 processed flurbiprofen (Fig. 2a) showed sharp melting endotherms at 118.26 °C and 118.27 °C, respectively, confirming that SC-CO_2 process has not altered the crystallinity of the drug, as further substantiated by XRPD analysis (Fig. 2b). Similar results were reported by Rudrangi *et al.* (2015a and b) for indomethacin and olanzapine when processed with SC-CO_2.

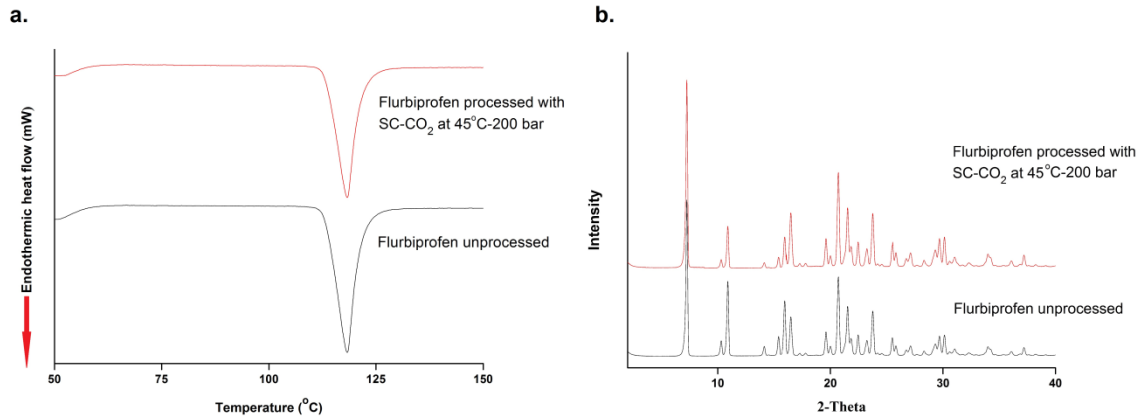


Fig. 2. Control study: DSC traces (**a**) and X-ray powder diffractograms (**b**) of unprocessed flurbiprofen and flurbiprofen processed with SC-CO_2 at 45 °C/200 bar.

The DSC traces and X-ray powder diffractograms of flurbiprofen, Me–*β*–CD and flurbiprofen-Me–*β*–CD (1:1 molar) binary systems prepared by physical mixing and SC-CO_2 processing are presented in Figs. 3a and 3b, respectively.

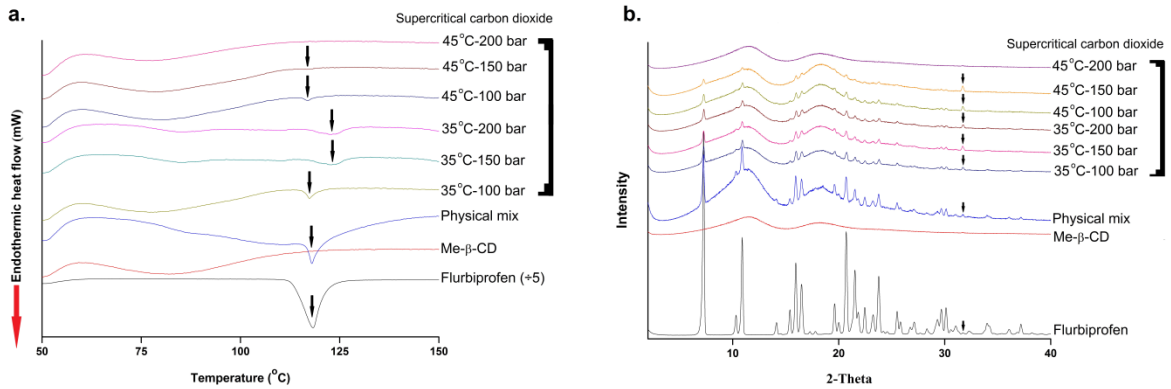


Fig. 3. DSC traces (**a**) and X-ray powder diffractograms (**b**) of flurbiprofen, Me–*β*–CD and flurbiprofen-Me–*β*–CD (1:1 molar) binary systems prepared by physical mixing and SC-CO_2 processing (the flurbiprofen thermogram has been reduced by a factor of 5).

The DSC trace of Me–*β*–CD was characterized by a broad endothermic event between 60 °C and 120°C ascribed to its dehydration (Banchero *et al.* (2013); Rudrangi *et al.* (2015a)). The XRPD pattern of Me–*β*–CD displayed two broad features at 11° and 18° indicating its predominately-amorphous nature.

The DSC traces of the binary mixtures prepared by physical mixing or SC-CO_2 processing (at 35 °C/100 bar, 35 °C/150 bar, 35 °C/200 bar, 45 °C/100 bar and 45 °C/150 bar) showed endothermic peaks of reduced intensity in comparison to the unprocessed pure flurbiprofen. This was confirmed by XRPD analysis, which showed the physical mixture of flurbiprofen and Me–*β*–CD to have similar diffraction pattern to that of the respective individual components but with a reduction in the intensity of drug peaks. The reduced intensity of the DSC endothermic peaks and the reduced XRPD intensities for the drug suggest an incomplete inclusion of flurbiprofen in the cavity of Me–*β*–CD. The DSC trace of the binary mixtures prepared by SC-CO_2 processing at 35 °C/150 bar and 35 °C/200 bar showed broad endothermic peaks of drug shifted to higher temperatures, potentially attributable to the partial inclusion of the drug into cyclodextrin (Marques *et al.* (1990)).

A complete disappearance of the flurbiprofen melt peak was observed in the inclusion complexes prepared by SC-CO_2 processing at 45 °C/200 bar, indicating interactions between flurbiprofen and Me–*β*–CD and the formation of inclusion complex with partially crystalline nature , as suggested by Charoenchaitrakool *et al.* (2002) and Rudrangi *et al.* (2015a and 2015b). This was supported by XRPD analysis, which showed the complexes prepared by SC-CO_2 processing at 35 °C/100 bar, 35 °C/150 bar, 35 °C/200 bar, 45 °C/100 bar and 45 °C/150 bar to have a considerable diminution of the diffraction peaks. A close analysis of the diffraction patterns of these samples and their comparison with that of the pure flurbiprofen showed an increase in the intensity of the drug peak at 2θ equal to 31.73°. This change may be attributed to a partial recrystallization of the drug during SC-CO_2 processing or the formation of the inclusion complex between flurbiprofen and Me–*β*–CD as suggested by He and Li (2009) in the case of borneol and Me–*β*–CD complexes.

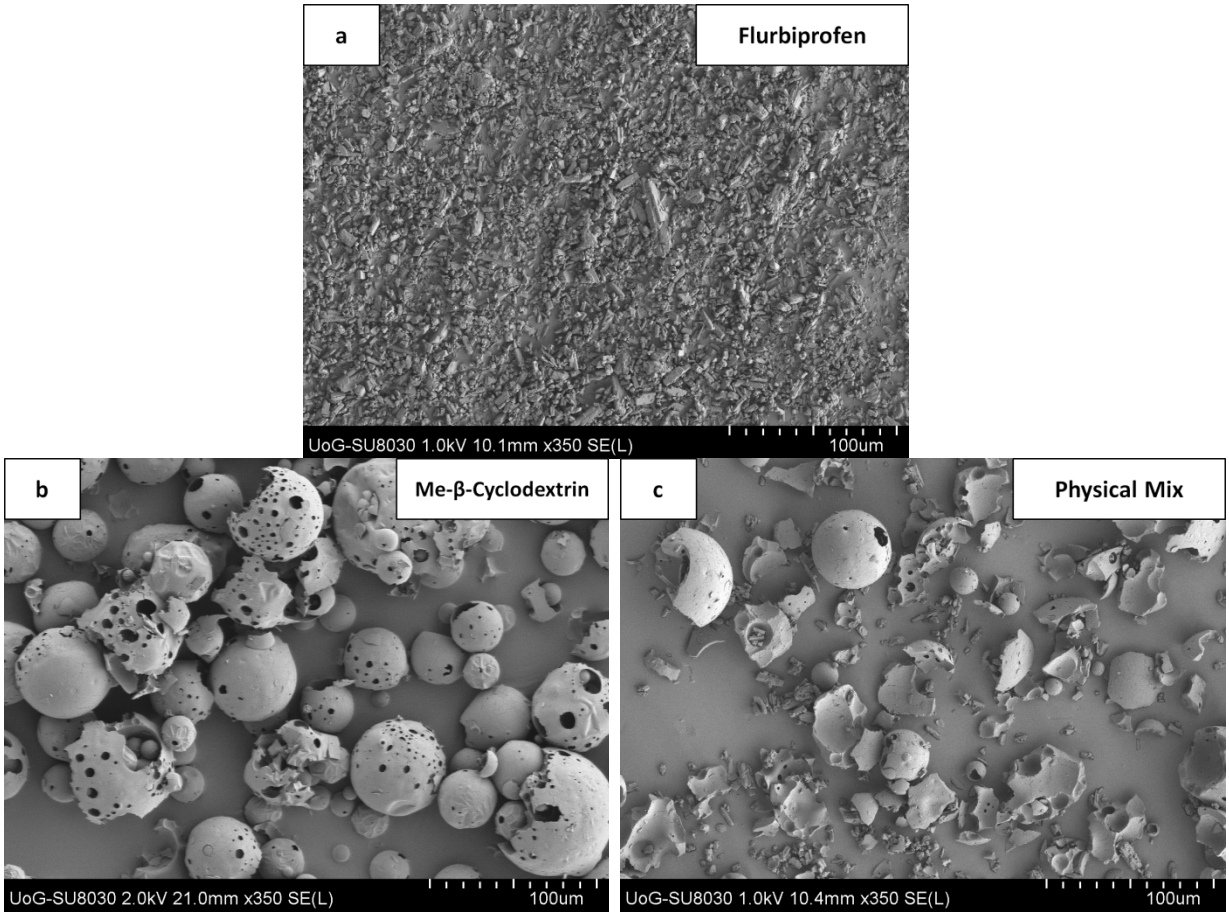
A complete disappearance of the drug peaks but the retention of two broad features similar to that of the pure Me–*β*–CD was observed in the diffraction pattern of the complexes prepared by SC-CO_2 processing at 45 °C/200 bar suggesting a complete complexation between flurbiprofen and Me–*β*–CD.

The decrease in the degree of crystallinity of the drug was observed in the following order: SC-CO_2 45°C/200 bar (0% crystalline) > SC-CO_2 45°C/150 bar (1.40% crystalline) > SC-CO_2 45°C/100 bar (3.09% crystalline) > SC-CO_2 35°C/200 bar (3.49% crystalline) > SC-CO_2 35°C/150 bar (3.64% crystalline) > SC-CO_2 35°C/100 bar (4.69% crystalline) > Physical mixing (8.99% crystalline).

3.4. Scanning electron microscopy analysis

From SEM analysis, unprocessed pure flurbiprofen (Fig. 4a) appeared as columnar crystals (8-40 µm) with a smooth surface. Pure Me–*β*–CD appeared as perforated hollow spheres in

the size range of 10-90 µm (Fig. 4b). The physical mixture product showed a mixture of small columnar crystals (10-15 µm) and broken hollow spheres (50-75 µm) (Fig. 4c). Comparable morphologies of the complexes prepared by physical mixing and SC-CO_2 processing at 35 °C/100 bar, 45 °C/100 bar and 45 °C/150 bar (Figs. 4d, 4g and 4h, respectively) with raw the materials suggests that some flurbiprofen-Me–*β*–CD interaction had taken place in the solid-state. In the complexes prepared by SC-CO_2 processing at 35 °C/150 bar, 35 °C/200 bar and 45 °C/200 bar (Figs. 4e, 4f and 4i, respectively) the original morphology of the raw materials disappeared, and the products appeared as aggregates with an irregular morphology.



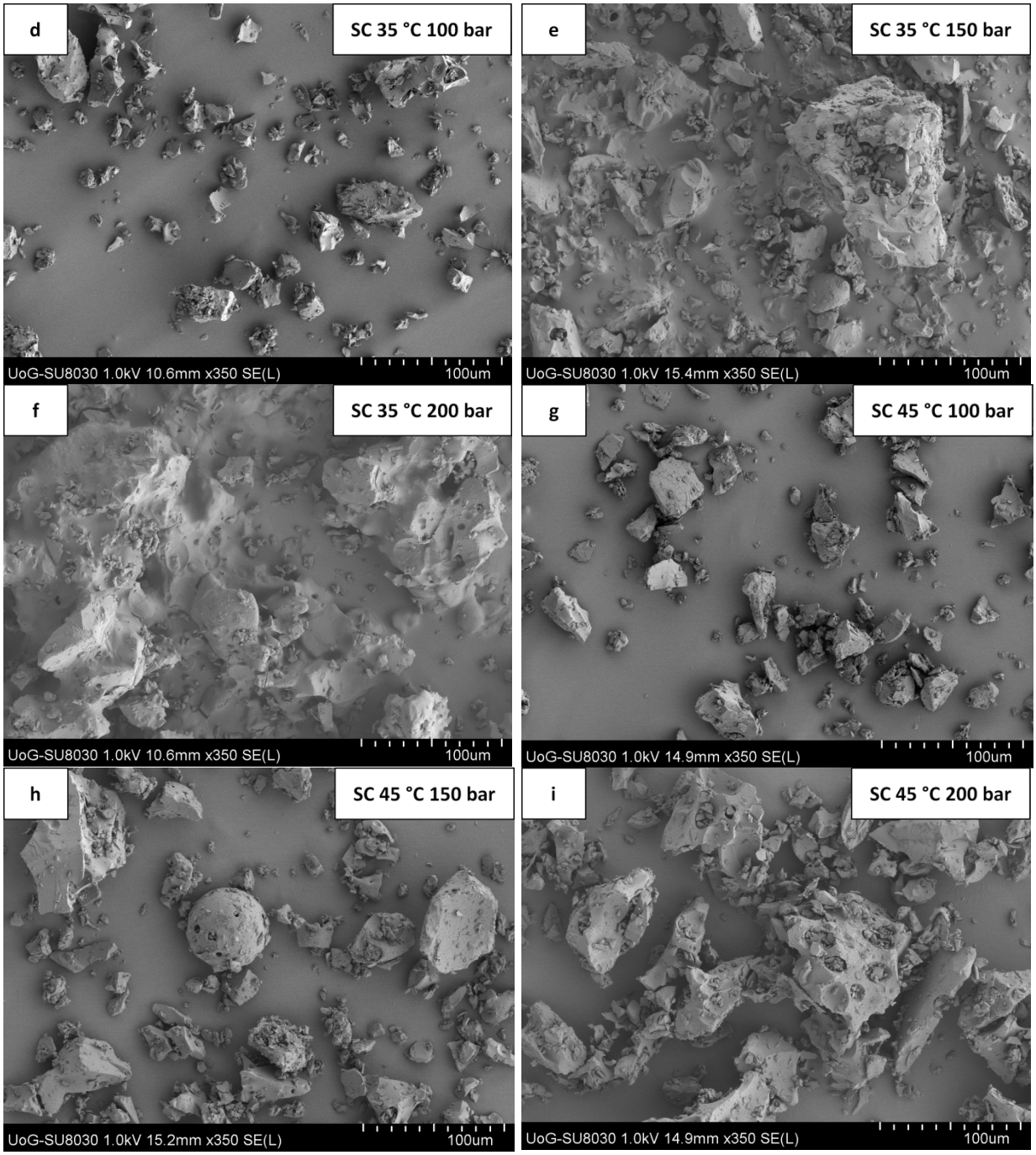


Fig. 4. SEM photomicrographs of flurbiprofen (**a**), Me–*β*–CD (**b**) and flurbiprofen-Me–*β*–CD binary systems prepared by physical mixing (**c**), SC-CO_2 processing at 35 °C/100 bar (**d**), 35 °C/150 bar (**e**), 35 °C/200 bar (**f**), 45 °C/100 bar (g), 45 °C/150 bar (**h**) and 45 °C/200 bar (**i**).

3.5. Practical yield

The percentage practical yield of all the binary mixtures is tabulated in Table 1. It was observed that all the binary mixtures prepared by SC-CO_2 processing resulted in the loss of

mass of the complexes to some extent. The practical yields of the binary mixtures prepared by SC-CO_2 processing were above 96% (w/w).

Table 1. Percentage practical yield of flurbiprofen-Me–*β*–CD binary systems.

Method	**Practical yield (%)**
Physical mixing	99.5 ± 0.2
Supercritical carbon dioxide processing	
35 °C/100 bar	98.4 ± 0.7
35 °C/150 bar	97.8 ± 0.2
35 °C/200 bar	98.4 ± 0.6
45 °C/100 bar	97.6 ± 0.2
45 °C/150 bar	96.3 ± 0.1
45 °C/200 bar	97.9 ± 0.8

3.6. Evaluation of the flurbiprofen content

The percentage drug content the binary mixtures ranged from 94.59 ± 0.31% to 97.88 ± 0.18%, which is within the acceptable range (85-115%) provided in the United States Pharmacopoeia 29 (USP 29, 2006).

Table 2. Drug content in flurbiprofen-Me–*β*–CD binary systems (mean ± SD, n=3).

Method	**Drug content (%)**
Physical mixing	94.59 ± 0.31

Supercritical carbon dioxide processing	
35 °C/100 bar	97.88 ± 0.18
35 °C/150 bar	96.62 ± 0.21
35 °C/200 bar	95.51 ± 0.37
45 °C/100 bar	95.63 ± 0.42
45 °C/150 bar	98.34 ± 0.16
45 °C/200 bar	96.58 ± 0.63

3.7. Dissolution studies

All the binary systems exhibited better dissolution profiles than the drug alone (Fig. 5). This enhancement can be attributed to the surfactant-like properties of cyclodextrin and the formation of inclusion complexes between flurbiprofen and Me–*β*–CD in the solid-state (Lin, and Kao, 1989; Guyot *et al*., 1995). The highest improvement of the drug dissolution properties was obtained from the binary mixture prepared by SC-CO_2 processing at 45 °C/200 bar, followed by the mixtures processed at 45 °C/150 bar and 45 °C/100 bar.

The increase in the dissolution properties of flurbiprofen was observed in the following order: SC-CO_2 45 °C/200 bar > SC-CO_2 45 °C/150 bar > SC-CO_2 45 °C/100 bar > SC-CO_2 35 °C/200 bar > SC-CO_2 35 °C/150 bar > SC-CO_2 35 °C/100 bar > physical mixture.

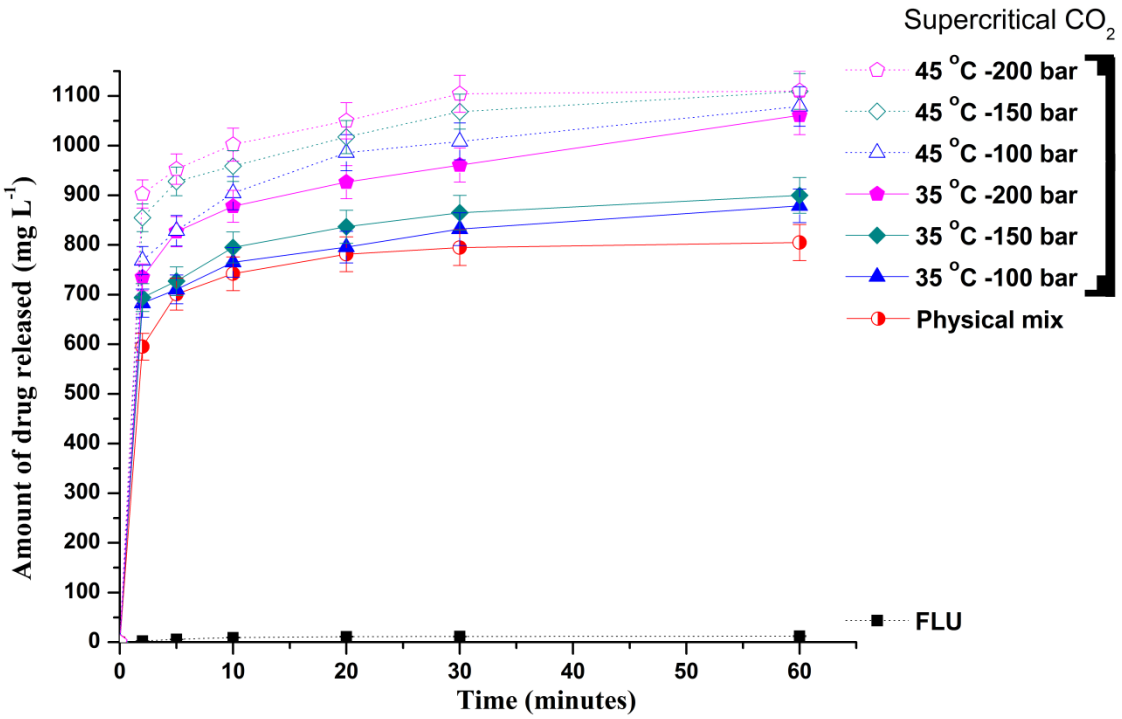


Fig. 5. Dissolution rate profiles of flurbiprofen and flurbiprofen-Me–*β*–CD binary systems prepared by physical mixing and SC-CO_2 processing.

The percent flurbiprofen dissolved at 30 min (DP_{30min}) and the dissolution efficiency at 30 min ($DE_{30\ min}$) is presented in Table 3. The amount of flurbiprofen released from drug alone was very low with 1.11 ± 0.09% dissolving at the end of 60 min, whereas the binary mixture obtained by physical mixing exhibited a significant increase in the dissolution with 72.47 ± 3.23% of flurbiprofen dissolved at the end of 30 min.

It is also evident from the results (Fig. 7 and Table 3) that the degree of the improvement in the dissolution rate is dependent on not only the method of preparation but also the processing conditions used for the preparation of complexes. All the SC-CO_2 processed systems exhibited higher apparent drug dissolution than the physical mixture systems; however, considerable differences were observed in the degree of enhancement. The binary mixtures prepared by SC-CO_2 processing at 35 °C/100 bar exhibited a faster drug release

compared to the mixtures processed at 45 °C/200 bar after 30 min (74.9 ± 3.0% *versus* 99.4 ± 2.3%). All the binary mixtures prepared by SC-CO_2 processing at 45 °C exhibited a drug release of more than 80% within the first 10 min, irrespective of the pressure employed. Both the temperature and pressure showed a positive influence on the formation of the inclusion complexes in the solid-state.

The instantaneous dissolution properties offered by all the binary mixtures are attributable to the improvement in drug wettability due to the high aqueous solubility (greater than 2000 mg mL^{-1} as reported by Banchero *et al*., 2013) and the superior complexing properties of Me–*β*–CD (Cirri *et al*., 2005).

Table 3. Percent flurbiprofen dissolved (DP) at 30 min and dissolution efficiency (DE) at 30 min from flurbiprofen and flurbiprofen-Me–*β*–CD binary systems prepared by physical mixing and SC-CO_2 processing.

Product	**DP_{30} (%)**	**DE_{30min} (%)**
Flurbiprofen	1.1 ± 0.1	0.8 ± 0.2
Physical mixing	72.5 ± 3.2	64.8 ± 2.7
Supercritical carbon dioxide processing		
35 °C/100 bar	74.9 ± 3.0	65.2 ± 2.8
35 °C/150 bar	77.8 ± 3.2	68.2 ± 2.8
35 °C/200 bar	86.5 ± 3.1	76.5 ± 2.8
45 °C/100 bar	90. 8 ± 3.3	80.8 ± 3.0
45 °C/150 bar	96.2 ± 3.2	85.5 ± 2.8
45 °C/200 bar	99.4 ± 2.3	88.38 ± 2.8

3.8. Docking studies

The single best pose of flurbiprofen docked in the cavity of Me–*β*–CD is presented in Fig. 6.

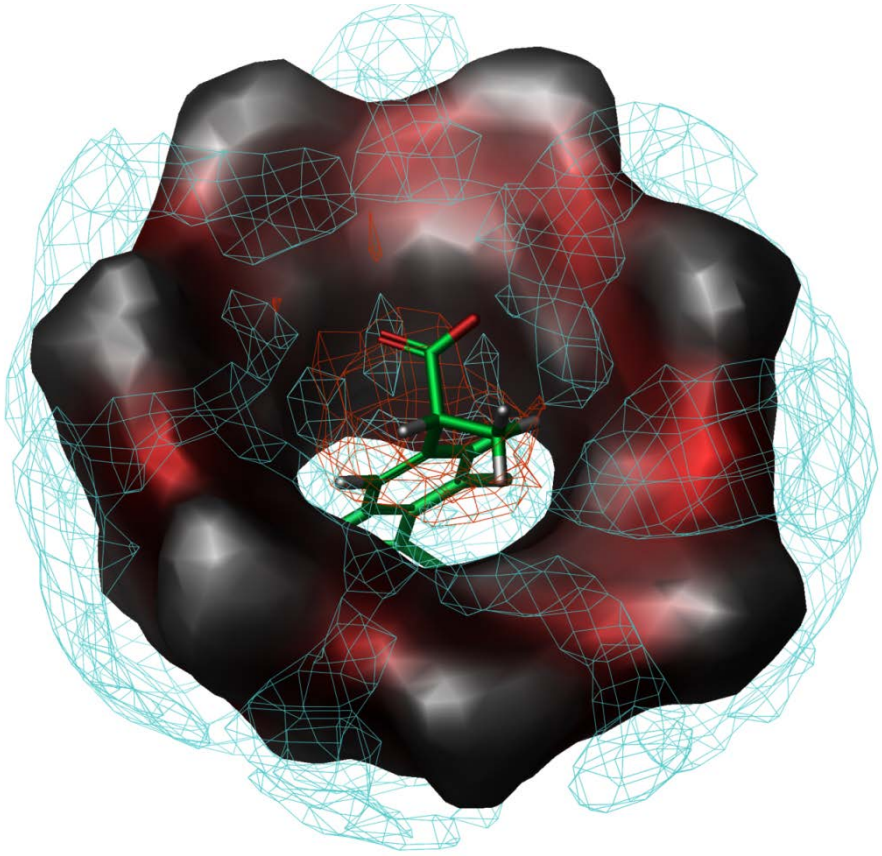


Fig. 6. Representation of the complex between Me–*β*–CD (orange) and flurbiprofen (green) obtained by molecular docking (1:1 stoichiometry).

Flurbiprofen is coloured in green and the figure has a molecular surface (grey with a reddish tint in the depths), mesh surface of the hydrophilic area (cyan mesh) and the hydrophobic area (orange mesh at the mid depth of Me–*β*–CD). The figure shows the binding of flurbiprofen in the cavity of Me–*β*–CD through phenyl group presumably due to its hydrophobicity. Secondary hydrogen bonding exists between the oxygen atom of Me–*β*–CD and the hydrogen atom of flurbiprofen. The binding affinity (GLIDE energy), van der Waals energy and docking score for the inclusion of flurbiprofen in Me–*β*–CD are -20.660 kcal mol^{-1}, -20.303 kcal mol^{-1} and -4.259 kcal mol^{-1}, respectively.

Computational molecular docking studies of indomethacin and olanzapine with Me–*β*–CD were carried out by Rudrangi and co-workers using the Glide application. The binding affinity (GLIDE energy), van der Waals energy and docking score for inclusion of indomethacin in Me–*β*–CD were 27.880 kcal mol^{-1}, -28.941 kcal mol^{-1} and -4.882 kcal mol^{-1}, respectively (Rudrangi *et al.*, 2015a), while the binding affinity, Van der Waals energy and docking score for inclusion of olanzapine in Me–*β*–CD were -24.13 kcal mol^{-1}, -21.57 kcal mol^{-1} and -3.09 kcal mol^{-1}, respectively (Rudrangi *et al.*, 2015b).

Conclusions

A novel solid inclusion method for the complexation flurbiprofen into methyl–*β*–cyclodextrin using supercritical carbon dioxide carrier was shown. The possibility of flurbiprofen-methyl–*β*–cyclodextrin interactions of different efficiencies in the solid-state was demonstrated. Products obtained by the supercritical carbon dioxide processing exhibited the highest apparent drug dissolution followed by the physical mixture and the drug alone. All the products processed by SC-CO_2 at 45 °C offered more than 80% drug release within the first 10 min irrespective of the pressure employed. Both the temperature and pressure showed a positive influence on the formation of the inclusion complexes in the solid-state, with temperature playing even a higher role. The method proposed involves no toxic solvent residues, thus the products obtained provide minimal side effects in humans, compared to those obtained by other techniques that require the use of organic solvents. The preliminary data suggests that the complexation of flurbiprofen with methyl–*β*–cyclodextrin will lead to better therapeutic efficacy.

Acknowledgements

The authors would like to thank Ian Slipper (University of Greenwich, UK) for his technical assistance with X-Ray powder diffraction and scanning electron microscopy studies. Madhu

Battu (BITS-Pilani, Hyderabad campus, India) is thanked for his support in molecular docking studies.

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