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Characterization of Ibuprofen Solid Dispersion Part-II: FT-IR and DFT studies

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The Fourier transform infrared spectra of ibuprofen (2-[4-(2-methylpropyl)phenyl]propanoic acid), skimmed milk powder and solid dispersion of ibuprofen was recorded in the solid phase. The equilibrium geometry, harmonic vibrational frequencies and infrared intensities of ibuprofen were calculated by density functional B3LYP method with the 6-311G(d,p) basis set. The scaled theoretical wavenumbers showed very good agreement with the experimental values. A detailed interpretations of the infrared spectra of ibuprofen is reported. Comparison of FT-IR spectra of plain drug, skimmed milk powder and solid dispersion of ibuprofen indicates that a chemical interaction takes place between skimmed milk and ibuprofen while forming the inclusion complex for solid dispersion.

Key Words: FT-IR spectra, DFT, Ibuprofen, Vibrational analysis, Solid dispersion, Inclusion complex.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) possess aqueous solubility problem. Preparation of solid dispersions of these drugs with water-soluble carriers have been suggested to increase water solubility and dissolution rate and hence, to improve bioavailability[1-5].

Skimmed milk is a water-soluble carrier[6,7]. Due to its amino acid and surface active agent content, it improves aqueous solubility of the drug substance dissolved in it[7]. Considering this property, Topaloglu *et al.*[8,9] used skimmed milk as a carrier to form solid dispersions of poorly water-soluble drug substances. Several NSAIDs (*e.g.* indomethacin, sulindac, tenoxicam) have been formulated in the form of solid dispersion with skimmed milk[9-12]. Lyophilization technique was employed. As a consequence, the aqueous solubility of these drug substances has been improved. Additionally, their gastric side effects were considerably reduced[12].

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Ibuprofen is a non-steroidal anti-inflammatory drug with poor aqueous solubility[13,14]. Its oral absorption dissolution rate is limited. The poor solubility and gastric side effect of the drug has long been a problem in pharmaceutical industry. Solubility problem of the drug results in difficulties during the formulation process for oral dosage forms (*e.g.* tablets). Its bioavailability is also low due to poor solubility characteristics.

In this study, we suggested formulating solid dispersions of ibuprofen employing the method of Topaloglu *et al.*[8] with the assumption that this method could result in increased dissolution rate and hence improved bioavailability as well as maintaining its therapeutic response.

Formation of a solid dispersion of drugs leads to reduction in particle size to almost molecular level and the drugs were transformed from crystalline to amorphous state[15]. The amorphous form of the drug particles possesses better dissolution profile than the crystalline form[16]. Thus, the state of the drug particles in the solid dispersion should be characterized by means of X-ray spectroscopy, thermal analysis techniques such as DSC, DTA/TG and also FT-IR analysis. In the first part of this study, DTA/TG analysis was carried out[17]. In the second part, FT-IR analysis was conducted. Literature survey reveals that to the best of our knowledge no density functional theory frequency calculations of 2-[4-(2-methylpropyl)-phenyl]propanoic acid (ibuprofen) have been reported so far. Therefore, we have undertaken the detailed theoretical and experimental investigation of the vibrational spectra of the ibuprofen. We compared and characterized FT-IR spectra of plain drug, skimmed milk powder and solid dispersion. These data was confirmed by scanning electron microscope studies.

EXPERIMENTAL

Ibuprofen is a gift from Eczacibasi Pharmaceuticals Manufacturing Co., Turkey. Skimmed milk used in this study had fat less than 1 % and purchased from Miss Milk Products Co., Turkey. All other reagents and chemical substances were of analytical grade.

Preparation of skimmed milk powder

Skimmed milk (SM) was lyophilized until the humidity ratio was lowered to 3 %. On the basis of our preliminary studies, the duration of lyophilization process was chosen as 72 h to reduce humidity. In the end of lyophilization process, 25 mL of SM yielded approx. 2.625 g skimmed milk powder (SMP). This lyophilized skimmed milk powder was then sieved through 250 μm mesh and kept in a scintillation vial in a desiccator for further experiments.

Preparation of the solid dispersions of ibuprofen

Solid dispersions of ibuprofen were prepared employing the method of Topaloglu *et al.*[8]. 500 mg Ib was suspended in 50 mL of SM. Next, the obtained suspension was mixed upon continuous stirring in a water bath with constant temperature at 50°C for 0.5 h. It was freezed and lyophilized (Christ Freeze Dryers, Freeze Dryer Alpha 1-2LD, Germany) for 2 d. The yield of the solid dispersion of Ib was sieved through 250 μm mesh.

Instrumentation

The room temperature attenuated total reflection Fourier transform infrared (FT-IR ATR) spectra of the 2-[4-(2-methylpropyl)phenyl]propanoic acid, skimmed milk powder and solid dispersion were registered using Varian FTS1000 FT-IR spectrometer with Diamond/ZnSe prism (4000-525 cm^{-1}; number of scans: 250; resolution: 1 cm^{-1}) (Fig. 1).

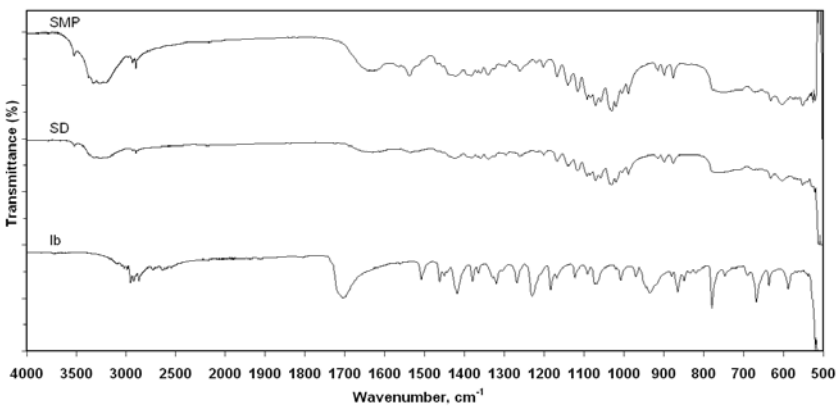


Fig. 1. FT-IR spectrum of 2-[4-(2-methylpropyl)phenyl]propanoic acid (Ib), skimmed milk powder (SMP) and solid dispersion (SD) recorded at room temperature

Scanning electron micrographs of Ibuprofen and solid dispersion of ibuprofen were taken. Each sample was mounted on stubs using conductive double-sided carbon tape and sputter-coated with gold/palladium in sputter coater (Polaron SC7620, UK) for 90 s at 9 mA. The samples were examined and digital images captured using a JEOL JSM-5500 (Tokyo, Japan) scanning electron microscope (SEM) at an accelerating voltage of 5 kV.

Computational details

The entire calculations were performed at B3LYP levels on a double Xeon/3.2 GHz processor with 4 GB Ram computer using Gaussian 03W[18]

program package, invoking gradient geometry optimization[19]. Initial geometry generated from standard geometrical parameters was minimized without any constraint in the potential energy surface at Hartree-Fock level, adopting the standard 6-311G(d,p) basis set. This geometry was then re-optimized again at B3LYP level, using basis set 6-311G(d,p). The optimized structural parameters were used in the vibrational frequency calculations at the DFT levels to characterize all stationary points as minima. Then vibrationally averaged nuclear positions of 2-[4-(2-methylpropyl)-phenyl]propanoic acid were used for harmonic vibrational frequency calculations resulting in IR frequencies together with intensities. We have utilized the gradient corrected density functional theory (DFT)[20] with the three-parameter hybrid functional (B3)[21] for the exchange part and the Lee-Yang-Parr (LYP) correlation function[22], accepted as a cost-effective approach, for the computation of molecular structure, vibrational frequencies and energies of optimized structures. The assignment of the calculated wavenumbers is aided by the animation option of GaussView 3.0 graphical interface for gaussian programs, which gives a visual presentation of the shape of the vibrational modes[23]. Furthermore, theoretical vibrational spectra of the 2-[4-(2-methylpropyl)phenyl]propanoic acid were interpreted by means of PEDs using VEDA 4 program[24].

RESULTS AND DISCUSSION

Solid dispersion of ibuprofen was prepared with skimmed milk using lyophilization technique. Next, FT-IR analysis of plain drug (Ib), lyophilized skimmed milk (skimmed milk powder) and solid dispersion was carried out. FT-IR spectra were computationally analyzed for further studies. FT-IR data were compared to SEM results.

Molecular geometry

The optimized structure parameters of ibuprofen calculated by DFT-B3LYP level with the 6-311G(d, p) basis set are given in Table-1 in accordance with the atom numbering scheme in Fig. 2. To the best of our knowledge, experimental data on the structure of ibuprofen are not available in the literature. Hence, we could not compare the calculation results given in Table-1 with the experimental data. The optimized structure can only be compared with other similar systems for which the crystal structures have been solved[25,26]. For example, the optimized bond lengths of C-C in phenyl ring fall in the range from 1.392-1.399 Å for B3LYP/6-311G(d, p) method, which are in good agreement with those of experimentally reported values for C-C bond length of phenyl ring of similar molecule[25,26].

TABLE-1
COMPUTED GEOMETRY PARAMETERS OF IBUPROFEN FOR DFT-B3LYP/6-311G (d,p) LEVEL OF CALCULATIONS

Length (Å)					
R(1,2)	1.399	R(6,19)	1.086	R(10,27)	1.094
R(1,6)	1.399	R(7,8)	1.549	R(10,28)	1.096
R(1,7)	1.513	R(7,20)	1.096	R(11,12)	1.522
R(2,3)	1.392	R(7,21)	1.096	R(11,13)	1.537
R(2,16)	1.085	R(8,9)	1.534	R(11,29)	1.092
R(3,4)	1.398	R(8,10)	1.534	R(12,14)	1.353
R(3,17)	1.084	R(8,22)	1.098	R(12,15)	1.206
R(4,5)	1.397	R(9,23)	1.092	R(13,30)	1.092
R(4,11)	1.527	R(9,24)	1.094	R(13,31)	1.093
R(5,6)	1.392	R(9,25)	1.096	R(13,32)	1.091
R(5,18)	1.085	R(10,26)	1.094	R(14,33)	0.969
Angle (°)					
A(2,1,6)	117.7	A(1,7,20)	109.5	A(8,10,28)	110.9
A(2,1,7)	121.6	A(1,7,21)	109.0	A(26,10,27)	107.8
A(6,1,7)	120.7	A(8,7,20)	108.7	A(26,10,28)	107.6
A(1,2,3)	121.4	A(8,7,21)	108.3	A(27,10,28)	107.7
A(1,2,16)	119.3	A(20,7,21)	106.4	A(4,11,12)	109.4
A(3,2,16)	119.3	A(7,8,9)	112.1	A(4,11,13)	112.4
A(2,3,4)	120.6	A(7,8,10)	110.3	A(4,11,29)	107.6
A(2,3,17)	119.7	A(7,8,22)	107.4	A(12,11,13)	110.5
A(4,3,17)	119.7	A(9,8,10)	111.0	A(12,11,29)	107.0
A(3,4,5)	118.3	A(9,8,22)	107.9	A(13,11,29)	109.7
A(3,4,11)	121.3	A(10,8,22)	108.0	A(11,12,14)	111.9
A(5,4,11)	120.4	A(8,9,23)	111.7	A(11,12,15)	125.6
A(4,5,6)	120.9	A(8,9,24)	110.8	A(14,12,15)	122.5
A(4,5,18)	119.5	A(8,9,25)	110.8	A(11,13,30)	109.9
A(6,5,18)	119.6	A(23,9,24)	107.9	A(11,13,31)	110.9
A(1,6,5)	121.2	A(23,9,25)	107.8	A(11,13,32)	110.7
A(1,6,19)	119.5	A(24,9,25)	107.6	A(30,13,31)	108.6
A(5,6,19)	119.3	A(8,10,26)	111.1	A(30,13,32)	108.7
A(1,7,8)	114.8	A(8,10,27)	111.5	A(31,13,32)	107.9

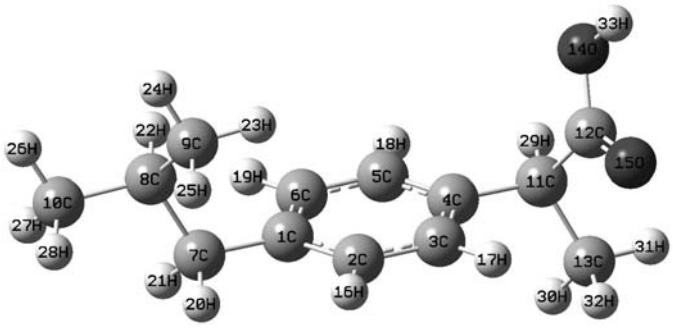


Fig. 2. Atom numbering scheme of 2-[4-(2-methylpropyl)phenyl]propanoic acid

Vibrational frequencies

We have calculated the theoretical vibrational spectra of the ibuprofen using DFT method with 6-311G(d) basis set. The vibrational frequencies have been collected in Table-2. We have compared our calculation of present compound with their experimental results. Comparison of the frequencies calculated at B3LYP with experimental values (Table-2) reveals the over-estimation of the calculated vibrational modes due to neglect of anharmonicity in real system. Therefore, we have used the scaling factor value of 0.9614 for B3LYP/6-311G (d,p)[27]. Experimental fundamentals are in better agreement with the scaled fundamentals which are found to have a good correlation for DFT/B3LYP (r = 0.9999) method. In order to investigate the performance and vibrational frequencies for the present compound, the mean deviation, mean absolute deviation and standard deviation between the calculated harmonic and observed fundamental vibrational frequencies were also calculated. The mean deviation, mean absolute deviation and standard deviation are 1.93, 8.60 and 12.0, respectively. Also the average absolute error of the calculated frequencies was found less than 0.8 %. Gauss-view and Veda 4 program was used to assign the calculated vibrational frequencies[23,24]. The assignments made at higher levels of theory with reasonable deviations from the experimental values, seem to be correct.

TABLE-2
VIBRATIONAL WAVE NUMBERS OBTAINED FOR IBUPROFEN AT DFT/6-311G(d,p)[a,b]

Exp.	Frequencies		IR intensity		Red mass	Force constant	Vibrational assignment, PED (%)
	Un-scaled	Scaled	Rel.	Abs.			
3630	3750	3605	58	23	1.1	8.82	OH Str (100)
3047	3181	3059	4	2	1.1	6.52	CH Str (99)
3047	3168	3046	19	8	1.1	6.47	CH Str (98)
3047	3158	3036	14	6	1.1	6.39	CH Str (99)
3020	3150	3029	13	5	1.1	6.35	CH Str (99)
3020	3125	3005	15	6	1.1	6.34	CH Str (95)
2983	3104	2984	31	12	1.1	6.25	CH Str (93)
2983	3098	2979	37	15	1.1	6.22	CH Str (96)
2955	3085	2966	50	20	1.1	6.17	CH Str (90)
2955	3080	2961	62	25	1.1	6.15	CH Str (93)
2955	3073	2954	9	4	1.1	6.12	CH Str (97)
2955	3070	2952	7	3	1.1	6.02	CH Str (96)
2924	3050	2932	18	7	1.1	6.05	CH Str (95)
2924	3039	2922	29	12	1.0	5.64	CH Str (100)
2903	3021	2904	49	20	1.0	5.61	CH Str (73)

Exp.	Frequencies		IR intensity		Red mass	Force constant	Vibrational assignment, PED (%)
	Un-scaled	Scaled	Rel.	Abs.			
2903	3014	2898	44	18	1.0	5.57	CH Str (78)
2903	3012	2896	11	4	1.1	5.62	CH Str (90)
2870	3001	2885	4	1	1.1	5.74	CH Str (88)
1707	1816	1746	250	100	9.5	18.47	CO Str (85)
1579	1653	1590	1	0	5.8	9.38	CC Str (49)
1562	1612	1550	0	0	6.0	9.18	CC Str (46)+ CCC Bend (12)
1508	1543	1484	26	10	2.4	3.42	HCC Bend (64)
1462	1512	1454	12	5	1.0	1.41	HCH Bend (75)
1450	1506	1448	5	2	1.1	1.41	HCH Bend (60)
1443	1501	1443	10	4	1.1	1.40	HCH Bend (71) + HCCC Tors (15)
1443	1498	1441	3	1	1.1	1.41	HCH Bend (61)
1435	1493	1435	5	2	1.0	1.38	HCH Bend (74) + HCCC Tors (13)
1435	1491	1434	1	1	1.0	1.37	HCH Bend (74)
1419	1485	1428	1	0	1.1	1.40	HCH Bend (56)
1379	1454	1398	10	4	2.4	3.03	CC Str (24) + HCC Bend (10)
1365	1423	1368	7	3	1.2	1.47	HCH Bend (94)
1340	1413	1358	15	6	1.2	1.45	HCH Bend (89)
1340	1403	1349	8	3	1.3	1.47	HCH Bend (87)
1330	1398	1344	42	17	2.0	2.27	CO Str (12) +HCC Bend (35)
1321	1372	1319	3	1	1.3	1.45	HCC Bend (47)
1321	1370	1317	0	0	1.4	1.59	HCC Bend (19) + CCCH Out (32)
1307	1359	1307	1	0	1.5	1.67	HCC Bend (27) + HCCO Tors (30)
1285	1344	1292	1	1	2.1	2.20	CC Str (15) + HCC Bend (11)
1269	1316	1266	2	1	1.3	1.35	HCCC Tors (38) + CCCH Tors(26)
1260	1310	1260	1	0	1.5	1.53	HOC Bend (32) + HCC Bend (13)
1230	1282	1233	6	2	1.8	1.74	HOC Bend (12) + HCC Bend (16)
1203	1245	1197	2	1	1.6	1.46	HCC Bend(10) + HCCC Tors (67)
1184	1228	1180	3	1	2.3	2.05	CC Str (30)
1169	1216	1169	10	4	1.9	1.64	CC Str (46) + HCC Bend (27)
1169	1207	1160	10	4	1.5	1.27	CC Str (25) + HCC Bend (28)
1155	1188	1142	11	5	1.8	1.48	CC Str (11) + HCCC Tors (28)
1122	1164	1119	205	82	2.3	1.86	CO Str (31) + HOC Bend (15)
1097	1146	1102	21	9	1.5	1.13	CC Str (12) + HCC Bend (26)
1091	1133	1090	5	2	2.2	1.64	CC Str (35)
1072	1104	1062	24	10	1.8	1.29	CC Str (10) + HCC Bend (16)
1068	1095	1053	14	6	1.6	1.12	HCCC Tors (26)
1056	1081	1040	42	17	2.1	1.43	CC Str (17) + HCCC Tors (11)
1008	1039	998	5	2	2.8	1.80	CCC Bend (84)
970	1010	971	3	1	2.0	1.19	CC Str (27) + HCCC Tors (14)
945	986	948	0	0	1.4	0.79	HCCC Tors (75)
935	970	932	0	0	1.4	0.78	HCCC Tors (60) + CCCC Tors (16)
920	967	929	0	0	1.5	0.80	CC Str (31) + HCCC Tors (29)

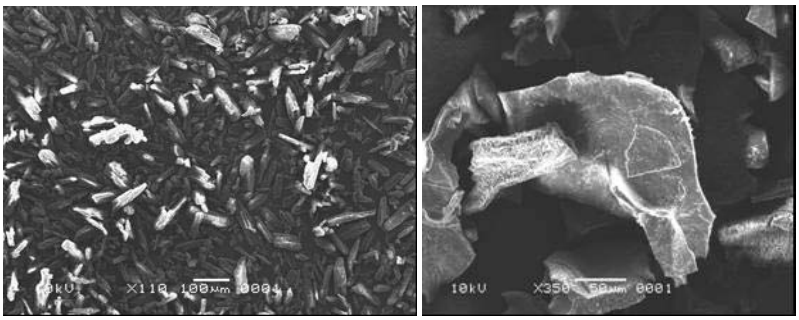
Exp.	Frequencies		IR intensity		Red mass	Force constant	Vibrational assignment, PED (%)
	Un-scaled	Scaled	Rel.	Abs.			
914	951	914	1	0	1.9	1.04	CC Str (46)
879	932	896	2	1	1.2	0.63	HCCC Tors (41)
866	892	858	2	1	1.5	0.71	HCCC Tors (27)
848	870	836	19	8	1.8	0.78	HCCC Tors (44)
835	855	822	3	1	2.1	0.89	HCCC Tors (27)
819	853	820	4	1	1.7	0.73	CC Str (12) + HCCC Tors (41)
810	834	802	0	0	2.8	1.17	CC Str (23)
779	820	788	13	5	4.0	1.60	OCOC Out (36)
771	803	772	7	3	2.2	0.84	CC Str (29) + HCCC Tors (11)
747	751	722	9	4	3.9	1.30	CCCC Tors (50)
691	721	693	38	15	2.8	0.86	CC Str (14) + CCC Bend (11)
667	666	640	20	8	3.9	1.03	OCO Bend (25) + CCC Bend (11)
636	648	623	36	15	2.7	0.67	CCC Bend (13) + HOCC Tors (30)
619	629	605	53	21	2.0	0.48	OCO Bend (20) + HOCC Tors (37)
582	565	544	34	14	3.0	0.56	CCC Bend (16) + CCCC Out (10)
532	555	533	6	3	2.6	0.48	HOCC Tors (13) + CCCC Out (24)
-	446	428	6	3	3.5	0.41	OCC Bend (16) + CCCC Out (19)
-	423	406	1	0	2.4	0.25	CCC Bend (27) + CCCC Out (17)
-	419	403	0	0	2.9	0.30	HCCC Tors (33) + CCCC Tors (58)
-	407	391	0	0	2.6	0.26	CCC Bend (38)
-	382	367	1	0	2.9	0.25	CCC Bend (50)
-	345	331	1	0	3.4	0.24	CCC Bend (23) + CCCC Out (11)
-	316	304	0	0	3.5	0.21	OCC Bend (13) + CCC Bend (30)
-	297	286	1	0	2.7	0.14	CCC Bend (11) + CCCC Tors (13)
-	252	243	1	0	1.8	0.07	CCC Bend (21)
-	245	235	0	0	1.5	0.05	CCC Bend (12) + HCCC Tors (24)
-	227	219	0	0	1.1	0.03	HCCC Tors (69)
-	219	211	0	0	1.1	0.03	HCCC Tors (79)
-	196	189	0	0	2.9	0.07	CCC Bend (36)
-	157	151	0	0	3.8	0.06	CCC Bend (28) + CCCC Out (16)
-	111	106	0	0	4.8	0.03	CCC Bend (17) + CCCC Out (44)
-	69	66	0	0	3.0	0.01	CCCC Tors (46)
-	53	51	0	0	3.9	0.01	CCCC Tors (69)
-	49	47	1	0	4.1	0.01	OCCC Tors (32) + CCCC Tors (40)
-	39	38	1	1	5.8	0.01	OCCC Tors (49)
-	29	27	0	0	3.6	0.00	CCCC Tors (86)

[a]Harmonic frequency (cm^{-1}), IR intensities (km mol^{-1}), reduced mass (amu) and force constants mdyne/Å).

[b]Str: stretching; Bend: Bending, Tors: Torsion, Out: Out-of-plane bending.

In aromatic compounds, ν(C–H) stretching frequencies appear in the range of 3100-3000 cm^{-1}. The vibrations at 3047 and 3020 cm^{-1} are assigned to aromatic ν(C–H) stretch[28-31]. Five more ν(C–H) stretching frequencies at 2983, 2955, 2924, 2903 and 2870 cm^{-1} were observed in the spectrum. First three bands are asymmetric ν(C–H) stretching band and the other bands symmetric ν(C–H) stretching band for $-CH_2-$ and $-CH_3$ groups. These assignments are also supported by the literature[28-31]. The IR band appearing at 3630 and 1707 cm^{-1} is assigned to ν(O–H) and ν(C=O) stretching mode of vibrations[29-31].

The shape of the bands changed dramatically for the inclusion compound, as compared to those for ibuprofen and skimmed milk powder. These results indicated that the vibrating and bending of an ibuprofen molecule was restricted due to the formation of an inclusion complex and ibuprofen was held by the inner structure of the skimmed milk, which is composed of surface active agents and amino acids. Furthermore, the absorption intensity in inclusion complex was significantly different from ibuprofen and skimmed milk powder. The FT-IR peaks of the inclusion complex are 30-50 % weaker than the free ibuprofen molecule and skimmed milk powder indicating the inclusion of the ibuprofen molecule into the skimmed milk.



(a) (b)

Fig. 3. Scanning electron micrographs of ibuprofen (a) and solid dispersion (b)

All these results were confirmed by solubility, SEM and DSC studies of Sahin *et al.*[32]. SEM pictures of ibuprofen and solid dispersion (Fig. 3)[32] indicate that in solid dispersion, ibuprofen particles in solid dispersion are in almost amorphous form, which allows one to conclude that reduction of particle size was mostly achieved by formation of an inclusion complex with skimmed milk. Although ibuprofen is held by skimmed milk to form an inclusion complex, it can maintain its therapeutic efficacy as demonstrated by *in vivo* studies carried out by Sahin *et al.*[32]. Analgesic and anti-inflammatory activities of plain drug and solid dispersion were tested using hot plate and hind paw oedema tests, respectively. Solid dispersion

composed of an inclusion complex of ibuprofen showed benefiting analgesic and antiinflammatory effect in comparison to the plain drug. This indicates that formation of an inclusion complex with the water-soluble carrier, skimmed milk, doesn't influence the therapeutic effect of ibuprofen as it doesn't interfere with the chemical structure of the compound.

Conclusions

The room temperature attenuated total reflection Fourier transform infrared spectra of the ibuprofen, skimmed milk powder and solid dispersion were registered. Optimized molecular structures and vibrational characteristics of ibuprofen have been obtained from DFT calculations. Scaling factors results are in agreement with experimental ones. Thus, all observed IR bands of ibuprofen are assigned with the comparison of the theoretical results. Comparison of FT-IR spectrum indicates that a chemical interaction takes place between skimmed milk and ibuprofen while forming the inclusion complex for solid dispersion. All these data are in good agreement with the findings of Sahin *et al.*[32] in SEM, DSC and *in vivo* studies.

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