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EVIDENCE FOR COMPLEX FORMATION OF IBUPROFEN WITH GO-GHRITA

R. D. Bawankar [*1], D. M. Sakarkar [1] and A. K. Dorle [2]

Sudhakarrao Naik Institute of Pharmacy [1], Nagpur Road, Pusad – 445204, Maharashtra, India

Department of Pharmaceutical Sciences [2], RTM Nagpur University, Nagpur, Maharashtra, India

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Ibuprofen, Go-Ghrita, Ayurvedic Pharmacopoeia, Physico-chemical, Inclusion complex, FT-IR., *In-vitro* release study, DSC, X-RD, NMR, SEM

Correspondence to Author:
Ram D. Bawankar

Research scholar, Sudhakarrao Naik Institute of Pharmacy, Nagpur Road, Pusad – 445204 (M.S.), India,

E-mail: rambawankar2008@rediffmail.com

ABSTRACT: Present investigation provides evidence for complex formation of Ibuprofen (Ib) with Go-Ghrita (GG). Ibuprofen binary mixture in (1:0.5), (1:1), (1:2), (1:3) w/w proportions were prepared by adding to molten Go-Ghrita kept over a water bath at 65-70^{o}C with continuous stirring. Organoleptic and Physico-chemical properties of GG (procured from Magan Sangrahalaya, Wardha) were as per the specifications given in Ayurvedic Pharmacopoeia (AP) and Indian Pharmacopoeia (IP). All proportions were subjected for FT-IR and *in-vitro* release behaviour (SGF, P^H 1.2 for 2 Hrs and SIF, P^H 6.8 for 7 Hrs) and on basis of it, optimized (1:1) w/w proportions were further analyzed and characterized for Differential Scanning Calorimetry, X-ray diffraction, Nuclear Magnetic Resonance and Scanning Electron Microscopy. Carbonyl stretching of isopropionic acid group to slight higher frequency 1.39 % cm^{-1} (increase) and (–C=O) linked (-OH) band stretching to slight lower frequency 1.09 cm^{-1} (decrease) shown in FT-IR spectra, supported by *in-vitro* release of Ibuprofen 99.16±0.17% of (1:1) w/w in sustenance form than remaining. Exclusion of polymorphic modification in X-RD, Slight lowering of 5^{0}C Tm and enthalpy change of 5.70 % (loss) in DSC, deviation in chemical shift (ranging from -0.041 to +0.030) as well as selective broadening of signals in NMR and entrapment of Ibuprofen crystals in Ib-GG binary mixture shown in SEM photographs, reflecting possible evidence for the formation of inclusion type complex between Ibuprofen and GG.

INTRODUCTION: Go-Ghrita (GG), Sanskrit Indian word is common name for cow ghee. GG, along with other substances, composed of numerous saturated fatty acids like myristic, stearic, lauric, butyric, capric, caprylic and unsaturated fatty acids like linoleic, linolenic, vaccenic and arachidonic acids [1], leads to difficulty in proposing any single chemical structure of it. Among these fatty acids, palmitic acid, a 16:0 saturated fatty acid, constitutes 29.95%, while oleic acid, which is 18: 1 monounsaturated acid with a double bond between 9-10 carbon atoms, is present to the extent of 27.42%[2]. *GG* has been shown to exhibit excellent wound healing property [3] as well as substantial anticonvulsant action [4].

A formulation containing some herbs and GG has been shown to exert remarkable memory enhancing activity [5] and patented in U.S. as an ointment base [6]. Literature repleting with reports on use of GG in designing the sustenance release formulation [7], as well as few of its interaction study with NSAIDs like Acetaminophen [8-10] and Diclofenac sodium [11]

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with use of several sophisticated analytical techniques.

Keeping in mind all such few and rare interactions study of NSAIDs with GG, attempt has been made to examine the nature, type of interaction and complex formation of non reported Ibuprofen NSAID with GG (composing saturated and unsaturated fatty acids). To investigate such phenomenon one or more sophisticated analytical techniques like FT-IR, cumulative % Ibuprofen release from binary mixtures (1:0.5), (1:1), (1:2), (1:3) w/w proportions, DSC, X-rd, NMR and SEM were studied. In addition to this preliminary analysis of GG were carried out prior its used to confirm purity in binary mixture.

Ibuprofen[12] – BCS class II drug, is most frequently used over-the-counter analgesics, due to its proven efficacy and low cost. Chemically, Ibuprofen (Fig. 1) is 2-[4-(2-methylpropyl) phenyl] propanoic acid, which has one chiral center, and thus there are two equal amounts of (R-) and sinister (S+) enantiomers.

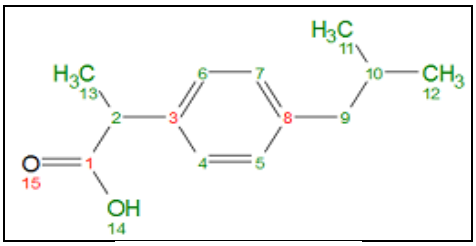


FIG. 1: IBUPROFEN

MATERIALS:

Ibuprofen BP as a gift sample was kindly supplied by Zim Laboratories Ltd., Kalmeshwar, Nagpur. Go-Ghrita was purchased from Magan Sangrahalay, Wardha, India. All other chemicals and reagents used were of analytical grade and were procured.

Experimental Section:

Preliminary analysis of Go-Ghrita:

Organoleptic analysis:

Colour, Odour, Taste and Texture of GG sample was evaluated as described in AP[13].

Physical characterization: Moisture content and Refractive index (reading at 40^{0}C) of GG sample was determined by the method described in AP[13].

Chemical analysis:

Acid and Saponification values:

Acid and Saponification values of GG were determined as per the method described in AP[13].

Iodine and Peroxide values:

Iodine and Peroxide values of GG were determined by pyridine bromide method and titration method as described in AP[13].

Ester value of GG:

Ester value, difference between Saponification value and Acid value was determined as described in AP[13].

Baudouin test for GG:

Sample response for this test is checked to verify purity and adulterant present in it, as described in AP[13].

Free fatty acids (% oleic acid) and Unsaponifiable matter in GG:

Free fatty acids levels of GG sample was determined by the method as described in AP[13] and IP[14].

Preparation of sample:

To the molten GG kept over a water bath at 65-70^{o}C an amount of Ibuprofen was added and uniformly dispersed by continuous stirring to prepare (1:0.5), (1:1), (1:2), (1:3) w/w proportions. The 1:0.5 to 1:3 w/w proportions were selected for observing minimize to maximize the interaction (if any) [15] involved in it. The fused mixtures were homogenized and allowed to cool slowly to room temperature with stirring.

Fourier Transform Infrared Spectroscopy (FTIR):

Fourier Transform Infrared Spectroscopy (FTIR) is a rapid analytical technique that measures vibrations of bonds within functional groups. FTIR spectral studies were carried out using FTIR spectrometer (Perkin Elmer Spectrum 2000, Norwalk, CT). Ibuprofen, GG and their binary mixtures (1:0.5), (1:1), (1:2), (1:3) w/w proportions were smeared onto KBr windows and the spectra were recorded from 500 to 3500/cm.

***In-Vitro* Ibuprofen Release Study:** The % cumulative Ibuprofen release from the binary

mixtures (1:0.5), (1:1), (1:2), (1:3) w/w proportions were studied in 900ml Simulated Gastric fluid (SGF), P^H 1.2 without pepsin for first 2 Hrs and subsequent 7 Hrs in Simulated Intestinal fluid (SIF), P^H 6.8 Phosphate buffer, stirred at 50 rpm, 37ºC ± 0.5ºC by USP - I (Rotating Basket type) method, VIII stations Dissolution Test Apparatus, Electrolab, Mumbai.

Scanning of Ibuprofen was carried out in both SGF and SIF between 200-400 nm and λ_{max} was reported to be at 264 nm. Absorbance of standard calibration curve of Ibuprofen in SGF and SIF were analyzed, after adequate dilutions, at λ_{max} 264 nm on UV Spectrophotometer (UV-1700; Pharmaspec, Shimadzu, Japan) equipped with UV probe software (2.01 version). Data was depicted in Microsoft excel and had correlation coefficient (R^2) 0.997, 0.998 and equation of regression lines Y = 0.018X - 0.002 and Y = 0.020X - 0.001 respectively.

Drug content:

The percent drug content of each binary mixture were determined. Weighed accurately about 50 mg of Ibuprofen binary mixtures (1:0.5), (1:1), (1:2), (1:3) w/w proportions and dissolved in 20 ml of alcohol using the magnetic stirrer for 20 min. To the solution obtained, simulated gastric fluid or simulated intestinal fluid was added and volume was made upto 100 ml. It was then filtered through Whatman filter paper no. 42 and required dilutions were made and absorbance was taken at 264 nm.

Differential Scanning Calorimetry (DSC):

5-10 mg of Ibuprofen sample, GG and their 1:1 w/w binary mixture was weighed into pin holed platinum pans (TG/DTA instruments) and heated under dry nitrogen in 0 - 340^0C scanning range at a rate of 10^0C/min. An empty pan was used as reference. Experiments were carried out in duplicate.

X-Ray Diffraction:

X-ray diffraction of Ibuprofen, GG and their 1:1 w/w binary mixture was carried out on a Rigaku Rotating Anode Diffractometer RUH3R (Tokyo, Japan). Measurement conditions were 40 kV, 30 mA current, at a scanning speed of 2^0/min, step size 0.02 and scanning range from 10–80^0 2Theta.

Nuclear Magnetic Resonance Spectroscopy:

NMR spectra (using Bruker DRX-300 MHz) for Ibuprofen, GG and their 1:1 w/w binary mixture were recorded in the solvent (CD_3OD: $CDCl_3$ 3:1, v/v), using tetramethylsilane (TMS) as an internal standard. Samples (in solution form) were equilibrated in the probe 5 min prior each run.

Scanning Electron Microscopy:

Scanning electron microscopy of Ibuprofen, GG and their 1:1 w/w binary mixture mounted on scanning electron microscope stubs with double-sided carbon tape and observed under 370701-14, S-3700, Scanning Electron Microscope.

Statistical analysis:

The t-test was performed on all collected mean data obtained from physiological evaluation as well as dissolution studies. Significance was accepted at $p \leq 0.05$[16].

RESULT AND DISCUSSION:

Physico-chemical analysis of GG:

Physico-chemical properties of GG given in Table 1 revealed the purity and adulterant free GG. All the tested parameter of GG passes the standards and limit given in Ayurvedic Pharmacopoeia[13] and Indian Pharmacopoeia[14] respectively.

TABLE 1: PHYSICO-CHEMICAL ANALYSIS OF GG

Sr. No	Physico-Chemical parameters of GG	Observations (Mean ± S.D.)	A.P. standards
1.	Moisture content	0.087% ± 0.0290	NMT 0.5%
2.	Refractive index	42 ± 0.0090	40 – 45
3.	Acid value	0.22 ± 0.0190	NMT 0.15 - 0.25%
4.	Saponification value	190.74 ± 0.0210	NMT 225
5.	Ester value	189.79 ±0.0030	NMT 225
6.	Iodine value	25.88 ± 0.0199	NMT 35
7.	Free fatty acids (% oleic acid)	2.73 ± 0.0171	NMT 3%
8.	Unsaponifiable matter (%)	0.4 % w/w ± 0.0025	NMT 1.5% w/w
9.	Baudouin test	No pink color formation	No pink colour
10.	Peroxide value	0.00	Less than 0.5

All the determinations are carried out five times with significance ($p \leq 0.05$)

Fourier Transform Infrared Spectroscopy:

Fig. 2 showing FT-IR spectra of Ibuprofen (A), GG (B) and binary mixture of Ib with GG in different w/w proportions (C – F), reveling retention of characteristics bands as reported in literature [17, 19].

The ability of the GG to form a complex with Ibuprofen depends on the nature of the core-surface groups of GG (composed of saturated and unsaturated fatty acids), electrostatic interactions between the GG and the Ib, and the ability of the Ib to form a conjugate with the GG through chemical bonding. One might expect that the Ib with the carboxylic group may form a complex with surface unsaturated -C=C- fatty acids group (may exists as dimer involving hydrogen bonding) [19] of GG and may physically encapsulate the Ib.

Pure Ibuprofen (**Fig. 2A**) shows a strong carbonyl band absorbance at 1718.39 cm^{-1}, which corresponds to the carboxyl acid group (COOH) where as other smaller peaks in the region 1500–500 cm^{-1} are contributions from the benzene ring[16]. FTIR spectrum of all binary mixture (**Fig. 2 C - F**) 1:0.5, 1:1, 1:2, 1:3 w/w shows disappearance of strong carbonyl band at 1718.39 cm^{-1} of ibuprofen and shifted to slight higher frequency 1742.93 cm^{-1} (i.e. 1.39 % cm^{-1} increase), as well as (–C=O) linked (-OH) band stretching to slight lower frequency 2921.29 cm^{-1} (i.e. 1.09 cm^{-1} decrease) band due to observed band respective at 1742.93 cm^{-1} and 2921.49 cm^{-1} (**Fig. 2B**) of carboxylic and OH group of saturated or unsaturated fatty acid [8, 9] present in GG.

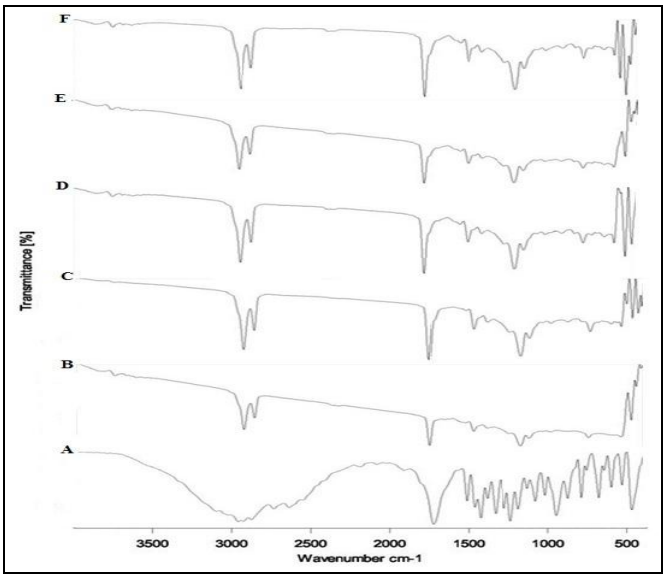


FIG. 2: FT-IR SPECTRA OF A) IBUPROFEN, B) GG, C) BINARY MIXTURE OF IB-GG 1:0.5 w/w, D) 1:1 w/w, E) 1:2 w/w, F) 1:3 w/w PROPORTION.

TABLE 2: FTIR SPECTRUM INTERPRETATION OF IBUPROFEN

Characteristic peaks	Ibuprofen	1:0.5	1:1	1:2	1:3	% Stretching
Carbonyl stretching of isopropionic acid group	1718.39 cm^{-1}	1742.71 cm^{-1}	1742.57 cm^{-1}	1742.55 cm^{-1}	1742.60 cm^{-1}	1.39 cm^{-1} (Increase)
(-OH) stretching linked to (–C=O)	2954.02 cm^{-1}	2921.57 cm^{-1}	2921.29 cm^{-1}	2921.28 cm^{-1}	2921.37 cm^{-1}	1.09 cm^{-1} (Decrease)

Drug content and % Ibuprofen release:

Binary mixtures of various w/w proportions were subjected for Ibuprofen determination and 1:1 w/w found to be highest 98.85± 0.07 in SGF, 98.97± 0.13 in SIF observed slightly less (**Table 3**) in 1:0.5, 1:2, 1:3. The strength and stability of the Ib-GG complex was examined using *in vitro* release study.

Fig. 3 represents more uniform and sustenance zero order release 99.16±0.17 (**Table 4**) of Ibuprofen with R^2 value 0.9931 (Table 5) from 1:1 binary complex in both SGF and SIF, represents the efficacy, integrity and entrapment of Ib in IB-GG binary mixture. The order of % cumulative Ibuprofen release is 1:1 > 1:0.5 > 1:2 > 1:3.

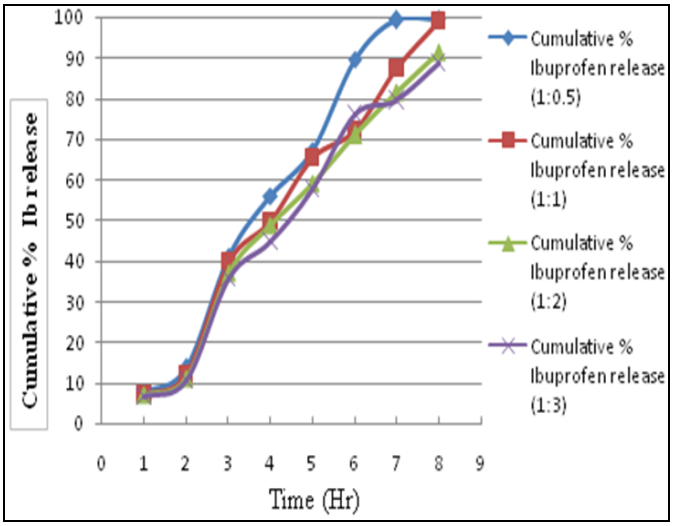


FIG. 3: CUMULATIVE % IBUPROFEN RELEASE FROM (1:0.5), (1:1), (1:2), (1:3) W/W PROPORTIONS.

TABLE 3: PERCENT DRUG CONTENT OF IBUPROFEN FROM BINARY MIXTURES

Sr. No.	Binary mixtures w/w proportion	Drug content* (%) SGF	SIF
1.	1:0.5	95.15± 0.27	96.52± 0.16
2.	1:1	98.85± 0.07	98.97± 0.13
3.	1:2	96.84± 0.23	97.04± 0.31
4.	1:3	97.45± 0.16	96.07± 0.18

(*Represents mean ± S. D.) (n=3)

TABLE 4: CUMULATIVE % IBUPROFEN RELEASE OF VARIOUS BINARY MIXTURES

Sr. No.	Medium	Time (Hr)	Cumulative % Ibuprofen release* 1:0.5	1:1	1:2	1:3
1.	0.1N HCl,	1	7.63±0.81	7.13±1.81	7.06±0.71	6.8±0.72
2.	P^H 1.2	2	13.63±1.72	12.13±0.82	11.23±2.73	10.8±2.28
3.		3	41.23±0.67	39.8±0.71	37.28±2.83	35.97±0.92
4.		4	55.89±1.72	49.82±0.62	48.92±1.04	44.71±1.29
5.	Phosphate	5	67.22±1.87	65.34±0.72	59.05±0.27	57.86±1.23
6.	Buffer, P^H 6.8	6	89.51±1.91	72.16±2.82	70.99±1.83	76.19±1.91
7.		7	99.27±0.71	87.27±0.74	81.67±0.26	79.58±0.99
8.		8	99.25±0.81	99.36±0.17	91.47±1.98	88.74±2.82

(*Represents mean ± S.D.)(n=3)

TABLE 5: RELEASE KINETICS OF VARIOUS BINARY MIXTURES

Release Model	1:0.5 R^2	1:1 R^2	1:2 R^2	1:3 R^2
Zero Order	0.988003386	0.993106749	0.992887086	0.990536068
First Order	0.87895189	0.87436741	0.87703903	0.88385852
Higuchi Release	0.94625087	0.94751185	0.94934934	0.94549569
Corse Mayer Release	-0.217129721	-0.245366501	-0.258414266	-0.256524447
Hixson Crowell Model	0.953695555	0.943430824	0.943941692	0.949910273

Differential Scanning Calorimetry:

The DSC thermograms of Ibuprofen, GG and Ib-GG 1:1 w/w proportions are presented in **Fig. 4**. The following general results can be derived from **Table 6, 7** the melting temperature of binary systems (Fig.4C) are lower than those of single Ibuprofen (Fig.4A). The thermogram of Ibuprofen-GG 1:1 w/w records two sharp endothermic peaks corresponding to their melting point with onset at 76.8^0C and 263.2^0C respectively along with approximately 5.70 % loss in enthalpy ($\Delta H_{observed}$) in comparison to ($\Delta H_{calculated}$) values of system, suggesting the possibility of interaction[20, 21].

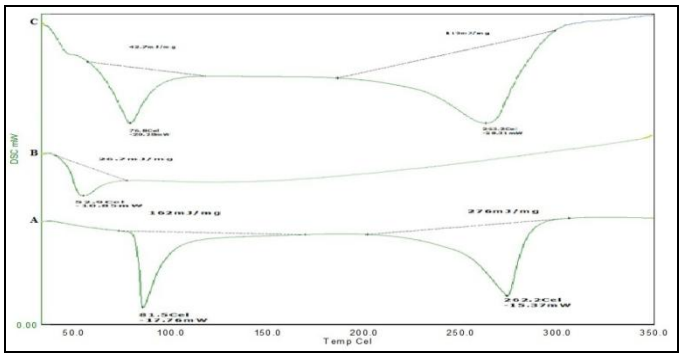


FIG. 4: DSC OF A) IBUPROFEN, B) GG, C) BINARY MIXTURE OF IB-GG 1:1 w/w PROPORTION.

TABLE 6: THERMAL PARAMETERS OF IBUPROFEN, GG AND BINARY MIXTURE 1:1 w/w PROPORTIONS

Sr. No.	Type	T_{peak} (^{0}C)	ΔH (J/g)
1	Ibuprofen	81.5	162
2	GG	52.9	26.7
3	Ib-GG 1:1	76.8	42.7

X-Ray Diffraction:

Almost no change was detected in their diffraction pattern of crystalline nature of Ibuprofen (**Fig. 5**) as well as GG. In the diffraction pattern of the Ib – GG binary mixture, Ibuprofen and GG retained their respective peaks at their positions.

Nuclear Magnetic Resonance Spectroscopy:

NMR spectra of Ibuprofen (Fig. 6A), GG (Fig. 6B) and Ib-GG 1:1 w/w proportion (Fig. 6C) are presented with chemical shift records in Table 8. Ib-GG 1:1 w/w proportion (Fig. 6C) showed more pronounced changes in chemical shift values of different protons (2H, 4-7H, 9H, 10-13H) ranging from -0.041 to +0.030 as well as selective broadening of 9H proton, confirming possible

interactions. Interaction between the two substances relies on the observation of selective line broadening and/or chemical shift displacements of H-NMR spectral signals of a substance bonded with other [11, 22].

TABLE 7: THERMAL PARAMETERS OF IB-GG 1:1 W/W PROPORTIONS

Binary Mixture	1ST Transition		2ND Transition		ΔH_{cal} (J/g)	ΔH_{obs} (J/g)	ΔH % /Result
	T_{peak} (^{0}C)	ΔH (J/g)	T_{peak} (^{0}C)	ΔH (J/g)			
Ib-GG 1:1 w/w	76.8	42.7	263.2	119	170.47	161.70	5.70(loss)

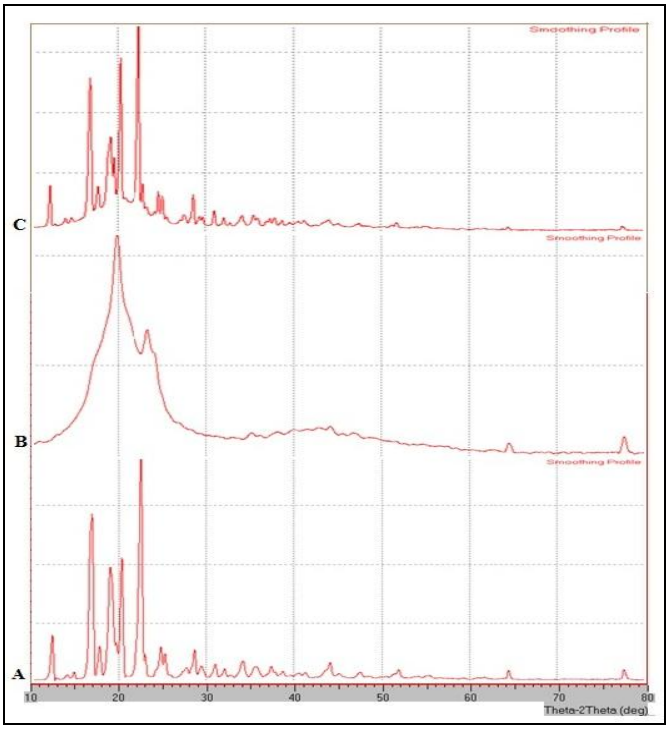


FIG. 5: X- RD OF A) IBUPROFEN, B) GG, C) BINARY MIXTURE OF IB-GG 1:1 W/W PROPORTION.

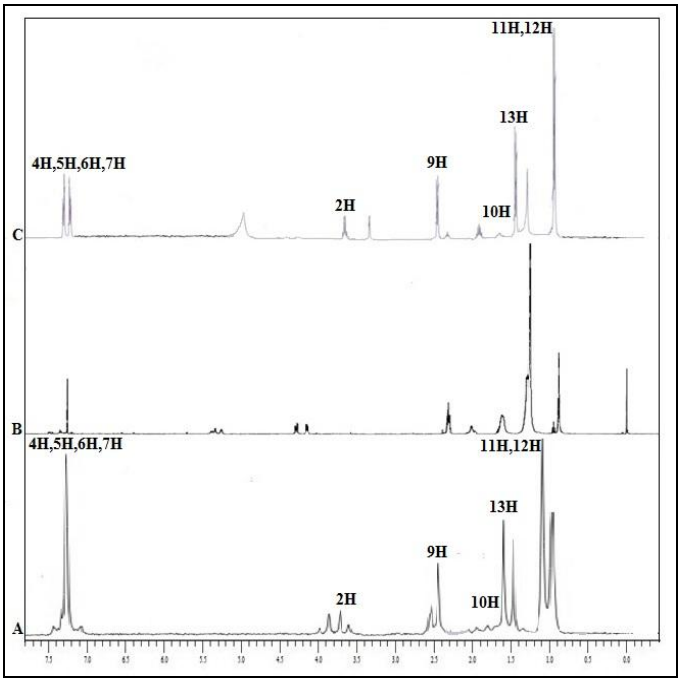


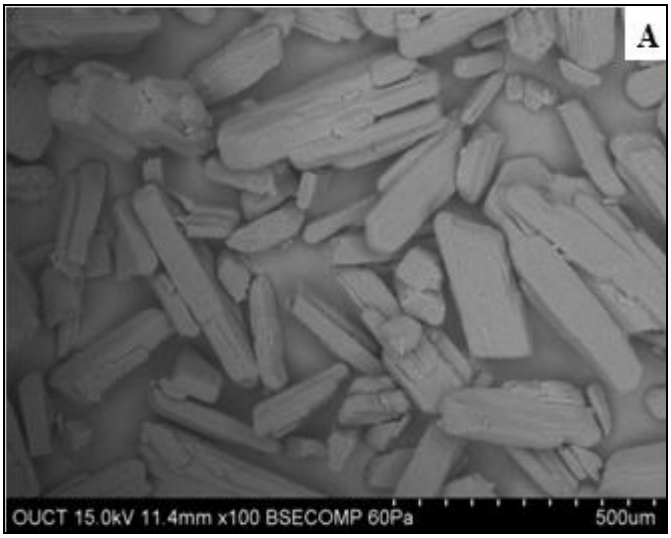
FIG. 6: NMR OF A) IBUPROFEN, B) GG, C) BINARY MIXTURE OF IB-GG 1:1 W/W PROPORTION.

TABLE 8: CHEMICAL SHIFTS (δ) PPM OF PROTONS IN IBUPROFEN AND IB-GG % w/w PROPORTIONS

H/H	Ppm (δ)		$\Delta\delta = (\delta_1) - (\delta_2)$
	Ib (δ_1)	Ib-GG (δ_2)	
2H	3.745	3.704	- 0.041
4,5,6,7H	7.228	7.221	- 0.007
9H	2.470	2.500	+ 0.030
10H	1.941	1.906	- 0.035
11,12H	1.001	1.013	+ 0.012
13H	1.631	1.610	- 0.021

Scanning Electron Microscopy:

Scanning electron micrographs of crystals of Ibuprofen appear stick shaped and particle surface is quite regular as illustrates in Fig. 7 (A) at 100X magnification. In the admixture of Ibuprofen with GG, the open lattice matrix or cage like crystal structures of GG Fig. 7 (B) entrapped the stick shaped Ibuprofen crystals with them (inclusion type complex)[23]; some of them lost their crystal habit while the habit of remaining was modified in the presence of GG, highlighted by arrow in Fig. 7 (C). The degree of entrapped stick shaped Ibuprofen crystals in open lattice matrix or cage like crystal structures of GG may be the determining factor in the diffusion or dissolution of Ibuprofen.



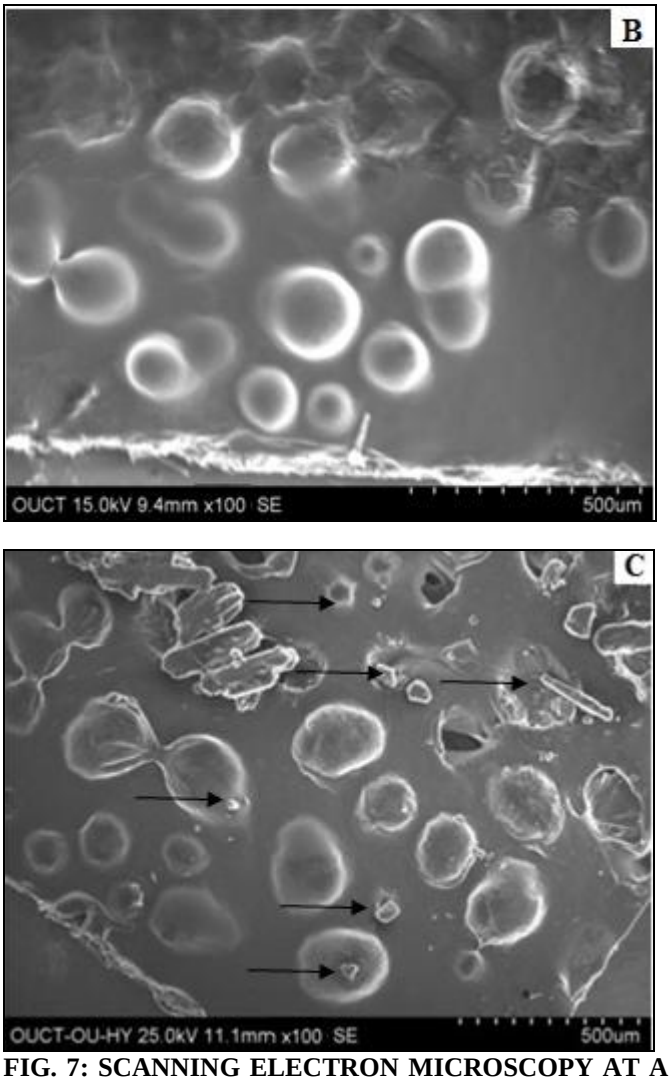


FIG. 7: SCANNING ELECTRON MICROSCOPY AT A MAGNIFICATION OF 100X A) IBUPROFEN, B) GG, C) BINARY MIXTURE OF IBUPROFEN WITH GG (MARKED ARROW SHOWING IBUPROFEN CRYSTALS GET TRAPPED IN CAGE STRUCTURES OF GG)

CONCLUSION: In present investigation, we report the evidence of complex formation of Ibuprofen with Go-Ghrita. The FT-IR spectrum of binary mixtures detected characteristics increase in strong carbonyl band and decrease in (–C=O) linked –OH band. More uniform and sustenance zero order release of 1:1 w/w from *in-vitro* dissolution study (render its selection for optimization), % loss in enthalpy ($\Delta H_{observed}$) in comparison to ($\Delta H_{calculated}$) values of DSC system, suggesting the possibility of interaction. Moreover such complexation phenomenon can be verified by X-RD, NMR and SEM. Retention of respective peaks at their positions in 1:1 w/w binary mixture, revealed crystalline nature of Ibuprofen minimizes the possibility of polymorphic modification in X-RD. Deviation in chemical shift as a slight displacement of proton as well as selective broadening of signals in 1:1 w/w NMR, confirming possible interaction between Ibuprofen and fatty acids present in GG, substantiated by SEM photographs.

SEM further elucidated entrapment of ibuprofen crystal structure in open lattice matrix or cage like crystal structures of GG suggesting inclusion type complex. However, an interesting part is, such sustenance release inclusion complex of Ibuprofen with GG (or other NSAIDs which may form a complex with GG) may be useful in increasing the oral bioavailability or comparing such complex concentration in various biological fluids in experimental animals is under study.

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