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Study of Binary Mixture of Paracetamol and Go - Ghrita

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ABSTRACT

Present investigation deals with study of binary mixture of Paracetamol with Go-ghrita (GG) by examining the nature as well as type of interaction if any and whether it forms a binary mixture or not. Formation of such complex if any in the form of binary mixture of Paracetamol with Go-ghrita needs to investigate by FT-IR and cumulative % Paracetamol release from binary mixtures 1:0.5, 1:1, 1:2 and 1:3 w/w proportions. In addition to this preliminary analysis of GG were carried out prior its used to confirm purity in binary mixture.Paracetamol and GG binary mixtures1:0.5, 1:1, 1:2 and 1:3w/w proportions(selected as to find out the minimum to maximum interaction with it) were prepared by adding to molten Go-Ghrita kept over a water bath at 65-70°C with continuous stirring. Organoleptic and Physico-chemical properties of GG (procured from Magan Sangrahalaya, Wardha) were as per the specifications are given in Ayurvedic Pharmacopoeia (AP) and Indian Pharmacopoeia (IP). All binary mixtures were subjected to *in-vitro* release behavior (SGF, pH 1.2 for 2 Hrs and SIF, pH 6.8 for 7 Hrs), showed nonsustained release of Paracetamol from *in-vitro* dissolution study, releasing Paracetamol in 4 hrs, leading to failure our aim as a drug candidate for complex formation. Moreover, FT-IR study of 1:0.5, 1:1 % w/w binary mixture were devoid of Paracetamol characteristics N-H stretching, O-H stretching, C-H stretching, C-NH stretching and =C-H bending peaks and significant changes in carbonyl-stretching band, seems to be because of disruption of already existing hydrogen-bonding network in Paracetamol and formation of new hydrogen bonds between amino group of Paracetamol, confirming the probability of some sort of interaction between Paracetamol and cow ghee, limiting its selection for further analysis by sophisticated instruments.

1. 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 repelling 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]with use of several sophisticated analytical techniques.

Present investigation deals with study of binary mixture of Paracetamol with Go-ghrita by examining the nature as well as type of interaction if any and whether it form a binary mixture or not. Formation of such complex if any in the form of binary mixture of Paracetamol with Go-ghrita needs to investigate by FT-IR and cumulative % Paracetamol release from binary mixtures 1:0.5, 1:1, 1:2 and 1:3w/w proportions. In addition to this preliminary analysis of GG were carried out prior its use, to confirm purity in binary mixture.

Paracetamol[12](Fig. 1) –BCS class III drug, is a pain reliever and a fever reducer. Paracetamol is used to treat many conditions such as headache, muscle aches, arthritis, backache, toothaches, colds, and fevers.

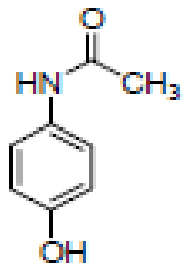

Fig. 1: Structure of Paracetamol

2. MATERIALS

Paracetamol IP 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.

3. EXPERIMENTAL SECTION

3.1 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°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].

3.2 Preparation of Paracetamol binary mixture prepared with GG

To the molten GG kept over a water bath at 65-70°C an amount of Paracetamol was added and uniformly dispersed by continuous stirring to prepare 1:0.5, 1:1, 1:2 and 1:3w/w proportions. The 1:0.5 to1:3 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.

3.3 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). Paracetamol, GG and their binary mixtures1:0.5 and 1:1w/w proportions were smeared onto KBr windows and the spectra were recorded from 500 to 3500/cm.

3.4 In-vitro Paracetamol Release Study

The % cumulative Paracetamol release from the binary mixtures 1:0.5 and 1:1w/w proportions were studied in 900ml Simulated Gastric fluid (SGF), pH 1.2 without pepsin for first 2 Hrs and subsequent 7 Hrs in Simulated Intestinal fluid (SIF), pH 6.8 Phosphate buffer, stirred at 50 rpm, 37ºC ± 0.5ºCby USP - I (Rotating Basket type)method, VIII stationsDissolution Test Apparatus, Electrolab, Mumbai. Scanning of Paracetamol was carried out in both SGF and SIF between 200-400 nm and λ_{max} was reported to be at 245 nm and 238.5 nm respectively. Absorbance of standard calibration curve of Paracetamol in SGF and SIF were analyzed, after adequate dilutions, at λ_{max}245 nm and 238.5 nm respectively 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)0.998, 0.997 and equation of regression lines Y = 0.010X + 0.003 and Y = 0.017X - 0.004 respectively.

3.5 Drug content

The percent drug content of each binary mixture was determined. 50 mg of Paracetamol binary mixtures of 1:0.5, 1:1, 1:2 and 1:3 w/w proportions was weighed accurately 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 up to 100 ml. It was then filtered through Whatman filter paper no. 42 and required dilutions were made and absorbance was taken at respective λ_{max} on UV spectrophotometer.

3.6 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].

4. RESULT AND DISCUSSION

4.1 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.	Physicochemical 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 ($p \leq 0.05$)

4.2 *Fourier Transform Infrared Spectroscopy*

FT-IR spectra of Paracetamol (Fig.2A) and cow ghee (Fig.2B) and data summarization table 2 showed its characteristics bands as reported in literature[17-21.]

The FT-IR spectrum of binary mixture of Paracetamol with cow ghee in 1:0.5 w/w (Fig.2C) and 1:1 w/w (Fig.2D), reveled shifting of characteristic C=O stretching, N-H bending, C=C stretching and =C-H bending to slightly lower frequency peaks at 1648.71 cm^{-1}, 1557.04 cm^{-1}, 1507.31 cm^{-1} and 801.32 cm^{-1} from Paracetamol frequency band peak 1654.42 cm^{-1}, 1562.73 cm^{-1}, 1507.48 cm^{-1} and 802.11 cm^{-1} respectively whereas, Paracetamol characteristics N-H stretching, O-H stretching, C-H stretching, =C-H bending and C-NH stretching peaks at 3324.32 cm^{-1}, 3162.74 cm^{-1}, 2880.43 cm^{-1}, 1878.00 cm^{-1} and 1173.16 cm^{-1} were disappeared in 1:0.5, 1:1 w/w binary mixture of Paracetamol with cow ghee.

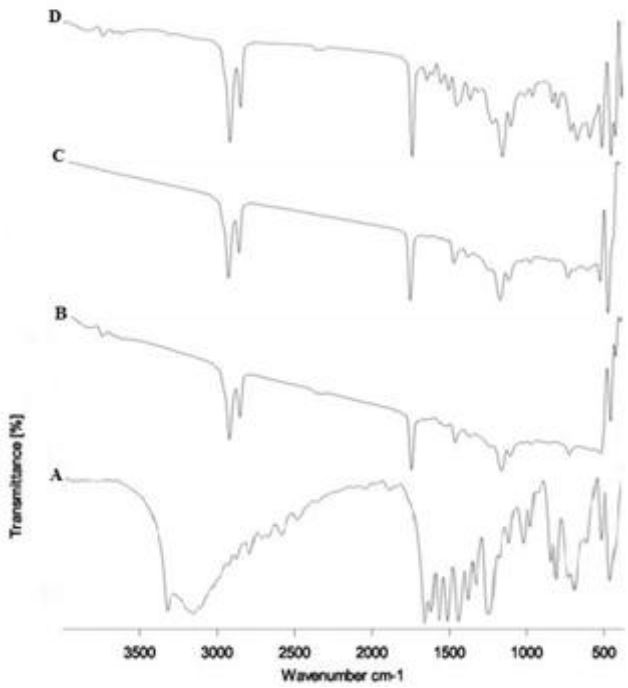

Fig. 2: FT-IR Spectra of A) Paracetamol, B) GG, C) Binary mixture of Par -GG 1:0.5 w/w and D) 1:1 w/w proportion.

Table 2: FTIR spectrum interpretation of Paracetamol

Characteristic peaks (cm^{-1})	Par (cm^{-1})	1:0.5 (cm^{-1})	1:1 (cm^{-1})	% Stretching (cm^{-1})
N-H stretching	3324.32	------	------	------
O-H stretching	3162.74	------	------	------
C-H stretching	2880.43	------	------	------
=C-H bending	1878.00	------	------	------
C=O stretching	1654.42	------	1648.71	0.34 decrease
N-H bending	1562.73	------	1557.04	0.36 decrease
C=C stretching	1507.48	------	1507.31	0.01 decrease
C-NH stretching	1173.16	------	------	------
=C-H bending	802.11	------	801.32	0.09 decrease

4.3 Drug content and % Paracetamol release

Paracetamol content in each binary mixture was determined and were lies in the range of 99.18 ± 0.34 to 99.77 ± 0.05% in simulated gastric fluid and 99.09 ± 0.29 to 99.61 ± 0.09% in simulated intestinal fluid. However, table 3 shows that prepared 1:1 w/w binary complex have maximum Paracetamol content in both the fluid.

Fig.3 and table 4 showed nonuniform sustained release from prepared (1:0.5, 1:1, 1:2 and 1:3 % w/w) complexes, releases more than 90% Paracetamol in first 3 Hrs, failing the aim to sustained release through complex formation. Moreover, table 6.4 shows the dissolution conditions used for cumulative % Paracetamol release study.Table 6.10, reflecting nonsustained release behaviour of Paracetamol, leading to difficulty in interpreting release model as R^2 value from 1:0.5, 1:1, 1:2 and 1:3 doesn't close to one.

Table 3: Percent Paracetamol content from binary mixtures

Sr. No.	Binary mixtures w/w proportion	Drug content* (%)	
		SGF	SIF
1.	1:0.5	99.45 ± 0.12	99.54 ± 0.16
2.	1:1	99.23 ± 0.31	99.09 ± 0.29
3.	1:2	99.77 ± 0.05	99.43 ± 0.33
4.	1:3	99.18 ± 0.34	99.61 ± 0.09

(* Represents mean ± S. D.) (n=3)

Table 4: Cumulative % Paracetamol release of various binary mixtures

Sr. No.	Medium	Time (Hr)	Cumulative % Paracetamol release*			
			1:0.5	1:1	1:2	1:3
1.	0.1N HCl, P^H 1.2	1	49.20±0.75	43.4±0.53	44.84±0.98	43.72±0.37
2.		2	49.23±0.89	51.03±0.62	48.56±0.78	49.46±0.24
3.	Phosphate Buffer, P^H 6.8	3	94.99±1.01	94.89± 1.28	94.15± 1.31	94.52± 1.32
4.		4	99.59±1.07	99.99± 0.01	99.80± 0.20	99.41± 0.37
5.		5	99.59±0.26	99.99± 0.02	99.80± 0.11	99.41± 0.31
6.		6	99.59±0.13	99.99± 0.01	99.80± 0.16	99.41± 0.29
7.		7	99.59±0.41	99.99± 0.03	99.80± 0.15	99.41± 0.56
8.		8	99.59±0.31	99.99± 0.02	99.80± 0.19	99.41± 0.44

(*Represents mean ± S.D.) **(n=3)**

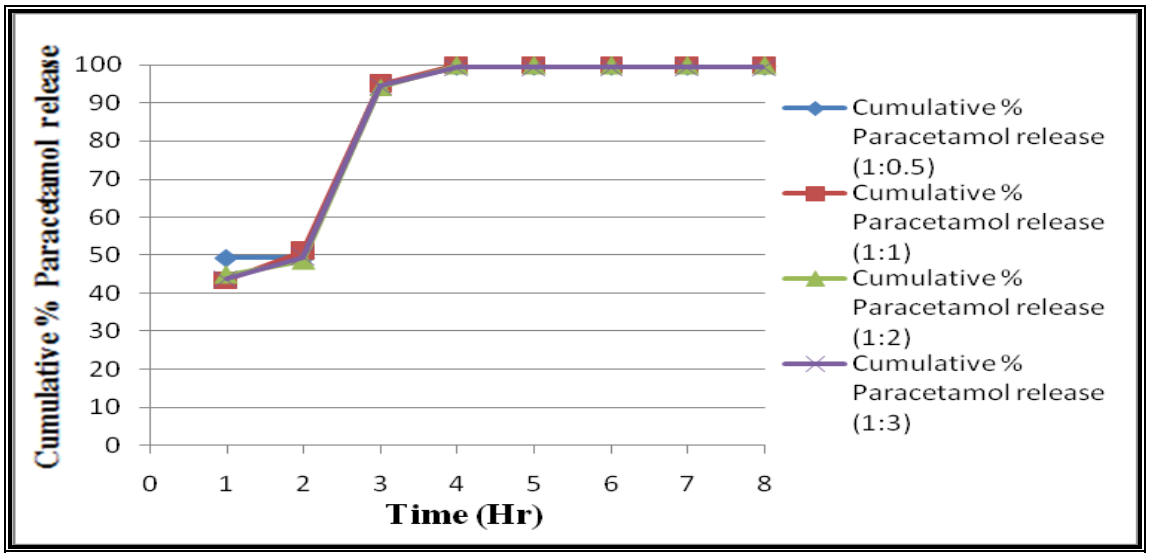

Fig. 3: Cumulative % Paracetamol release from 1:0.5 - 1:3 w/w proportions.

Table 5: Release kinetics of various binary mixtures

Release Models	1:0.5	1:1	1:2	1:3
	R^2	R^2	R^2	R^2
Zero Order	0.8592	0.8667	0.8671	0.8662
First Order	0.6796	0.6859	0.6876	0.6870
Higuchi Release	0.9442	0.9475	0.9468	0.9464
Corse Mayer Release	-0.4834	-0.4585	-0.4627	-0.4606
Hixson Crowell Model	0.7732	0.7758	0.7797	0.7774

5 CONCLUSION

Present study has demonstrated that, prepared binary mixtures of Paracetamol with cow ghee in 1:0.5, 1:1, 1:2 and 1:3 % w/w proportions, showing non sustained release of Paracetamol from *in-vitro* dissolution study, releasing Paracetamol in 4 hrs, leading to failure our aim as a drug candidate for complex formation. Moreover FT-IR study of 1:0.5, 1:1 % w/w binary mixture were devoid of Paracetamol characteristics N-H stretching, O-H stretching, C-H stretching, C-NH stretching and =C-H bending peaks and significant changes in carbonyl-stretching band, seems to be because of disruption of already existing hydrogen-bonding network in Paracetamol and formation of new hydrogen bonds between amino group of Paracetamol, confirming the probability of some sort of interaction between Paracetamol and cow ghee, limiting its selection for further analysis by sophisticated instruments.

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