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Assessment of quality of paracetamol and ranitidine drugs by spectroscopic studies

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Abstract: Four tablet samples containing 500 mg of paracetamol and five tablet samples containing 150 mg of ranitidine were collected from local pharmacies of Dhaka city to evaluate the quality by physical, Fourier transform infrared (FT-IR), Ultraviolet-visible (UV-Visible) and ^{1}H & ^{13}C nuclear magnetic resonance (NMR) spectroscopic studies. Weight variations of paracetamol and ranitidine tablets were 0.11-3.09% and 0.97-1.02%, respectively, which are in the allowed variation of 5%. The pH, average moisture and average ash content of paracetamol tablets were 6.45-6.95, 0.62±0.03-2.28±0.93% and 0.01±0.01-1.12±0.02%, respectively and ranitidine tablets were 5.46-5.55, 10.07±2.47-17.58±5.32% and 1.14±0.25-3.95±0.28%, respectively. The prominent IR absorption bands of standard paracetamol were 3350, 3150, 2924, 1656, 1563, 1441, 1013 and 715 cm^{-1} for the presence of N-H, O-H, C-H, C=O, C=C (two absorbance bands), C-O and =C-H functional groups, respectively and standard ranitidine were 3257, 1620, 1381, 1191, 951, 759 and 697 cm^{-1} for the presence of secondary N-H-furan overlap, C=C-NO, N-O, C-N, C-S, aromatic (C-H) and sp^3 (C-H) groups, respectively. The λ_{max} of standard paracetamol and ranitidine were 294 and 332 nm in the UV spectrum, respectively. ^{1}H and ^{13}C NMR spectral data of the standard paracetamol, ranitidine and samples were identical.

Keywords: Paracetamol, Ranitidine, Physicochemical properties, FT-IR, UV-visible, ^{1}H NMR, ^{13}C NMR.

INTRODUCTION

A drug is a naturally occurring or pharmaceutically synthesized substance that is used primarily to bring about a change in the existing process or state such as physiological, psychological or biochemical (Shan, 2018). In another word, a drug is a chemical substance of known structure which administers to a living organism and produces a biological effect (Rang et al., 2011). Paracetamol is one of the common drugs which is used as over the counter (OTC) medicine for the relief of pain and fever (Bertolini et al., 2006, Giri et al., 2012). It is available in different brands in the Bangladeshi pharmaceutical market in different dosage forms such as tablets, capsules, drops, elixirs, suspensions and suppositories (Bruno et al., 2019, Alsaifi & Alyahawi, 2018). It is generally administered in tablet formulation. Structurally paracetamol consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the para (1, 4) pattern (Bales et al., 1985). The IUPAC name of paracetamol is N-(4-hydroxyphenyl)acetamide (Amit, 2010). It is an analgesic and antipyretic drug. Generally, it is certified for reducing fever in people of all classes. It is commonly used for the relief of headaches,

other minor to major aches and pains associated with many parts of the body (Sahale et al., 2011). It is generally safe for humans in recommended dosages. If healthy adults take regular doses up to 4,000 mg a day then it shows little evidence of toxicity (Machado et al., 2015). Overdose of paracetamol causes hepatic necrosis or renal failure when concentrations in serum exceed 150 μg/ml after 4h ingestion (Saeed, 2017). Ranitidine is another common type of household drug. It is classified as an H2-receptor antagonist. H2-receptor antagonists are a significant class of highly effective drugs that are used for various acid-peptic diseases (Pahwa et al., 2016). Acid secretion is stimulated by gastrin which is inhibited by H2-receptor antagonists (Barry et al., 1992). Ranitidine is a histamine H2-receptor antagonist that is structurally different from both histamine and cimetidine. The chemical structure of ranitidine contains a furan ring. The IUPAC name of ranitidine is N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N^1-methyl-2-nitro-1,1-ethylenediamine hydrochloride (Pahwa et al., 2016). This drug is used in the short-term treatment of active duodenal ulcers and gastric hyper-secretory conditions. The action of ranitidine is selective since high concentrations of this drug do not affect β-adrenoreceptor, histamine H1 and muscarinic receptor mediated responses (Oliva et al., 2008). Additionally, ranitidine may be a specific and long-acting antagonist. It is effective for both parenteral and oral routes of administration (Grant et al., 1989). The effective dose of ranitidine is 150 mg, which requires administration four times a day for the treatment of erosive esophagitis (Islam et al., 2017). It also has side effects such as chest tightness, difficulty in breathing which are found in rare cases (Weissman et al., 2018). According to the modern definition, the quality of the drug requires the presence of active ingredients as it claimed on the label of the drug specifications. Quality of drug depends on some criteria such as drug must contain the same quantity of active ingredient from one dosage unit to the next, be free from extraneous substances, maintain its potency, therapeutic availability and appearance until used and upon administration release active ingredient for full biological availability (Banker, 2002). Official standards of good quality medicines are strength, quality, purity, packaging and labelling. Poor quality medicines do not meet these official standards (Liya et al., 2014). The purpose of this work is to evaluate the quality of paracetamol and ranitidine tablets by physical and spectroscopic techniques *i.e.*, FT-IR, UV-visible, ^{1}H & ^{13}C NMR.

MATERIAL AND METHODS

Sample collection: Four tablet samples of paracetamol and five tablet samples of ranitidine from different prominent pharmaceutical companies were purchased from local pharmacies in Dhaka city. Tablet shapes were round and caplet. The batch number and expiry dates of the sample were properly checked and recorded. The samples were coded properly such as for paracetamol is PA and for ranitidine is RA in Table 1.

Chemicals and reagents: Two types of organic solvents were used in the laboratory during the research work such as methanol (Merck KGaA, Darmstadt, Germany) and dimethyl sulfoxide (RCI Labscan Limited, USA).

Weight variation, moisture and ash content: The tablets of each manufacturer were weighed individually and average weights of tablets were determined (Shoeb et al., 2021). The percentage of weight variation was also calculated by the following equation.

$$\text{Weight variance (\%)} = \frac{Individual\ weight - Average\ weight}{Average\ weigh} x\ 100$$

The solubility of a few mg of powdered samples were tested in 1 ml distilled water (Cold and Hot), methanol (Cold and Hot) and DMSO (Cold). The pH of collected samples were observed in 100 mL distilled water at 30 ^{0}C. The collected samples were individually powdered using mortar and pestle. These powdered samples were taken on the empty crucible and weight

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taken by analytical balance. The process was repeated once again for each tablet. These crucibles were heated in the oven for three hours at 105 ^{0}C for the determination of moisture content. After three hours of heating the crucibles were taken out from the oven, cooled down through a desiccator and weighed

the crucibles by analytical balance. The crucibles were heated again in the oven for four hours at 700 ^{0}C for the determination of ash content. Weight of individual crucible was taken after cooling through a desiccator. The following equations were used for the determination of moisture and ash content in the tablet samples.

$$\text{Moisture content (\%)} = \frac{Weight\ of\ Sample\ before\ heating - Weigh\ \ of\ Sample\ after\ heating}{Wei\quad of\ Sample\ before\ heating} \times 100$$

$$\text{Ash content (\%)} = \frac{Weigh\ \ of\ sample\ after\ ashing}{Weight\ of\ sample\ before\ heat} \times 100$$

Table 1.Weight variation with relative standard deviations (RSD) of tablets

Sample code	PA-1	PA-2	PA-3	PA-4	RA-1	RA-2	RA-3	RA-4	RA-5
Weight (mg) of 5 tablets from each company	570.40	550.20	592.10	611.70	298.50	249.50	305.50	261.30	248.10
	551.60	554.40	570.30	615.50	294.40	252.20	308.10	255.20	246.80
	568.80	551.50	583.70	602.50	281.90	255.80	301.70	256.00	249.70
	558.10	553.70	602.60	615.60	295.10	254.90	306.20	254.20	250.10
	552.30	550.80	593.70	609.80	289.50	257.30	300.80	259.30	245.60
Average weight (mg) ± SD	560.20 ±8.93	552.10 ±1.84	588.50 ±12.18	611.00 ±5.38	291.90 ±6.44	253.90 ±3.09	304.50 ±3.10	257.20 ±2.99	248.10 ±1.90
Weight variation (%) of 5 tablets from each company	1.82	0.34	0.61	0.11	1.02	0.98	1.00	1.02	1.01
	1.54	0.41	3.09	0.74	1.01	0.99	1.01	0.99	0.98
	1.54	0.11	0.82	1.39	0.97	1.00	0.99	0.99	1.02
	0.37	0.29	2.40	0.75	1.01	1.00	1.00	0.98	1.02
	1.41	0.24	0.88	0.20	0.99	1.01	0.98	1.01	0.97
RSD (%)	1.60	0.33	2.07	0.88	2.21	1.22	1.02	1.16	0.89

Spectroscopic profiling: The FT-IR spectra of standard paracetamol, ranitidine and collected samples were recorded on a Shimadzu Fourier Transformation Infrared Spectrophotometer (IRPrestige-21, Shimadzu) over a range of 400-4000 cm^{-1}. Here, KBr was used as the background. The diffuse reflectance method was implemented. In this method, a few mg of sample were taken with an equivalent amount of KBr and ground in a mortar with a pestle to pressurize into a pellet. The KBr pellet was taken in a reflectance cell and spectrum was recorded. The double beam UV-Visible Spectrophotometer (UV-1800, Shimadzu) was used to record the UV spectrum of paracetamol, ranitidine and samples using DMSO as a solvent. About 1 mg of powdered sample and 1 ml of DMSO were taken in a vial. It was properly mixed using Ultrasonicator (Powersonic 610, Hwashin Technology Company). At first, DMSO was taken in a cube of UV spectrophotometer to set the background. Then, the mixture of the vial was taken in another cube. A beam of light was passed through a transparent cell containing a solution of an absorbing substance and recorded the spectrum. The ^{1}H and ^{13}C NMR spectra of standard paracetamol, ranitidine and samples were recorded using the NMR (Bruker 400 MHz) instrument. The method was to dissolve about 1 ppm of powdered sample into DMSO and then filtering to get the NMR spectra. All chemical shift values were reported in ppm to the nearest 0.1 ppm level.

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RESULTS AND DISCUSSION

Weight variation tests of paracetamol and ranitidine samples manufactured by different pharmaceuticals were performed and the results are shown in Table 1. The British Pharmacopoeia (2011) rule is that more than two of the individual tablets' weight should not deviate from the average mass by more than the allowed percentage deviation and none should deviate by double the allowed percentage deviation. Average weight and their corresponding percentage deviation allowed are indicated in the Table 2.

Table 2. Allowed relative standard deviation (Sengupta, 1988)

Average weight (mg)	Percentage deviation allowed
Less than 80	10
Greater than 80 and less than 250	7.5
Greater than 250	5

As seen from Table 1, the range of the relative standard deviation of the manufactured paracetamol tablets were 0.33%-2.07% and ranitidine tablets were 0.89-2.21%. The average weight of paracetamol tablets were 552.10±1.84-611.00±5.38 mg and ranitidine tablets were 248.10±1.90-304.50±3.10 mg. The amount found in this study is well below the allowed deviation which is 5%. So, the tablets showed very little weight variability.

Table 3. pH, moisture and ash content in paracetamol and ranitidine tablets

Sample code	pH	Average Moisture (%)± SD	Average Ash (%) ± SD
PA-1	6.55	0.95 ± 0.06	0.11 ± 0.07
PA-2	6.67	0.62 ± 0.03	0.01 ± 0.01
PA-3	6.45	2.11 ± 0.05	0.01 ± 0.01
PA-4	6.95	2.28 ± 0.93	1.12 ± 0.02
RA-1	5.46	12.68 ± 0.13	2.72 ± 0.28
RA-2	5.47	13.85 ± 1.00	3.58 ± 0.23
RA-3	5.46	10.07 ± 2.47	1.14 ± 0.25
RA-4	5.47	17.58 ± 5.32	2.78 ± 1.11
RA-5	5.55	12.38 ± 1.07	3.95 ± 0.28

Standard paracetamol and ranitidine were soluble in 1 ml distilled water (cold and hot), methanol (cold and hot), DMSO (cold). But all the paracetamol and ranitidine samples were only soluble in 1 ml DMSO (cold). Ranitidine samples were also sparingly soluble in methanol (cold and hot). pH of standard paracetamol at aqueous solution is 6.50 and ranitidine is 6.72 to 7.50 (Nisar et al., 2011, Loyd, 2017). The pH, average moisture and ash content of paracetamol samples were 6.45-6.95, 0.62 ± 0.03-2.28 ± 0.93 and 0.01 ± 0.01-1.12 ± 0.02, respectively and ranitidine were 5.46-5.55, 10.07 ± 2.47-17.58 ± 5.32 and 1.14 ± 0.25-3.95 ± 0.28, respectively (Table 3) . Both the samples might be slightly acidic but ranitidine is more acidic than paracetamol in comparative views. The prominent IR absorption bands of standard paracetamol and ranitidine are tabulated in Table 4.

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Table 4. Assignment of FT-IR absorption bands of standard paracetamol and ranitidine.

Paracetamol				
Absorption (cm^{-1})	Intensity	Vibration	Functional groups	Literature values (cm^{-1})
3350	Strong, sharp	Stretching	N-H (amide)	3300
3150	Strong, broad	Stretching	O-H (phenol)	3400-3300
2924	Strong	Stretching	C-H (alkane)	3000
1656	Strong, sharp	Stretching	C=O (amide)	1715
1563, 1441	Strong	Stretching	C=C (aromatic)	1600, 1475
1013	Medium	Stretching	C-O	1100-1000
715	Medium	Bending	=C-H (aromatic)	900-690
Ranitidine				
3257	Weak (Broad)	Stretching	Secondary N-H and furan group overlap	3500-3300
1620	Strong	Stretching	C=C-NO	1600-1550
1381	Medium	Stretching	N-O	1400-1000
1191	Strong	Stretching	C-N	1350-1000
951	Strong	Stretching	C-S	1000-900
759	Strong	Bending	Aromatic (C-H)	900-690
697	Strong	Bending	sp^3 (C-H)	700-650

The FT-IR spectrum of the standard paracetamol and ranitidine were taken as a reference to assess the FT-IR spectra of the paracetamol and ranitidine samples. The FT-IR spectra were recorded on a Shimadzu FT-IR spectrophotometer over the range of 400-4000 cm^{-1}. All of the FT-IR spectra of paracetamol and ranitidine samples were analyzed and the bands are the ones that were found in the FT-IR spectrum of standard paracetamol and ranitidine. The first band of standard paracetamol was related to the strong and sharp stretching of N-H (amide) group, located in the region of 3350 cm^{-1} whereas the strong and broad band located at 3150 cm^{-1} can be assigned to the stretching of the O-H (phenol) group present in the benzene ring. Other important bands present in the spectrum were observed at 2924, 1656, 1563, 1441, 1013, 715 cm^{-1}, respectively (Table 4) which were appeared due to the absorption associated to the stretching of C-H (alkane), C=O (amide), C=C (aromatic), C-O and out of plane bending of =C-H (aromatic) groups, respectively (Pavia et al., 2018). On the other hand, the first band of standard ranitidine was related to the weak and broad stretching of secondary N-H of the amide-furan group overlap, located in the region of 3257 cm^{-1} whereas the strong band located at 1620 cm^{-1}, which can be assigned to the stretching of C=C-NO group. Other important bands present in the spectrum were observed at 1381, 1191, 951, 759, 697 cm^{-1}, respectively (Table 4), which were appeared due to the absorption associated to the stretching of N-O, C-N, C-S, aromatic (C-H), sp^3 (C-H) groups, respectively (Pavia et al., 2018). The excipients did not create interference in these regions. So, all the samples could be qualitatively analyzed. These are the characteristic bands which can be used for qualitative purposes since these do not overlap with the bands of the other functional groups. The λ_{max} of standard paracetamol in water was 243 nm but in DMSO it becomes 300 nm (Adadey and Sarfo, 2016). DMSO is polar aprotic solvent which forms a strong bond to the excited state. As a result, ground and excited state band gap decreased and wavelength increased which is known as bathochromic shift (red shift). The λ_{max} of paracetamol sample in DMSO (50 mg/L) was found at 294 nm. Similarly, the λ_{max} of standard ranitidine in water was 313 nm but in DMSO it became 332 nm. The λ_{max} of ranitidine samples in DMSO (12.5 mg/L) were observed at 332 nm.

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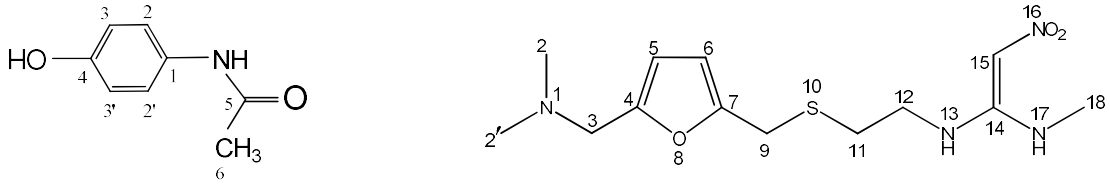
The ^{1}H and ^{13}C NMR spectral data were used to compare the samples with the standard paracetamol and ranitidine (Fig. 1).



(a) (b)

Fig. 1. Structure of (a) paracetamol and (b) ranitidine

The ^{1}H NMR spectral data of standard paracetamol showed the chemical shift of proton attached to the N of singlet at 9.63 ppm, hydroxyl proton of singlet at 9.13 ppm, two protons (*ortho*) of doublet at 7.33 ppm and two protons (*meta*) of doublet at 6.67 ppm and three protons of singlet at 3.40 ppm for methyl group. The ^{13}C NMR spectrum of the standard paracetamol revealed the presence of eight carbons with one carbonyl, six carbons of benzene ring and one methyl carbon. The signal at δ_C 129.80 ppm was attributed to the quaternary carbon of the benzene ring and other two signals of aromatic hydrogen carbons were observed at 120.10 and 113.80 ppm, respectively for ortho carbons at 2, 2′ and meta carbons at 3, 3′. Again, signals at δ_C 151.90, 167.10 and 22.50 ppm were assigned to the carbons at 4, 5 and 6 containing hydroxyl, carbonyl and methyl groups, respectively.

^{1}H NMR spectral data of standard paracetamol (DMSO) δ (ppm): δ_H 9.63 (-N-H, s), 9.13 (-O-H, s), 7.33 (2H, d, *J* = 8.40 Hz, H-2, 2′), 6.67 (2H, d, *J* = 8.40 Hz, H-3, 3′), 3.40 (3H, s, H-6).
^{1}H NMR spectral data of sample PA-1 (DMSO) δ_H (ppm): 9.63 (-N-H, s), 9.12 (-O-H, s), 7.33 (2H, d, *J*= 8.4 Hz, H-2,2′), 6.15 (2H, d, *J*= 8.4 Hz, H-3,3′), 3.34 (3H, s, H-6).
^{13}C NMR spectral data of standard paracetamol (DMSO) δ_C (ppm): 167.10 (C-5), 151.90 (C-4), 129.80 (quaternary carbon), 120.10 (C-2, 2′), 113.80 (C-3,3′), 22.50 (C-6).
^{13}C NMR spectral data of sample PA-1 (DMSO) δ_C (ppm): 167.10 (C-5), 152.10 (C-4), 129.70 (quaternary carbon), 120.70 (C-2, 2′), 114.00 (C-3,3′), 22.50 (C-6).

^{1}H NMR data of ranitidine showed chemical shifts at δ_H 6.65, 6.32, 4.16, 3.89, 3.68, 3.36, 2.86, 2.61 and 2.36 ppm for the presence of furan ring ^{1}H at H-5 and H-6,^{1}H at H-15, methylene ^{1}H at H-9, H-12, H-3 and H-11, methyl ^{1}H at H-18, H-2/2′, respectively. Similarly, the ^{13}C NMR spectrum of the standard ranitidine revealed the presence of thirteen carbons with four carbons in furan group, three methyl carbon, four methylene carbon, two olefinic carbons; one carbon attached with nitro group and another one with amine group. The signals at δ_C 112.90 and 108.00 ppm were attributed to the carbon of the furan ring while at δ_C 51.30, 68.00, 41.10, 28.10, 25.90, 23.70 ppm were assigned to the carbon of 3, 12, 2/2′, 18, 11 and 9 containing methyl, methylene, double bond carbon and methylene carbon, respectively.

^{1}H NMR spectral data of standard ranitidine (DMSO) δ (ppm): 6.65 (1H, d, H-5), 6.32 (1H, d, H-6), 4.16 (1H, s, H-15), 3.89 (2H, s, H-9), 3.68 (2H, t, H-12,), 3.36 (2H, s, H-3), 2.86 (2H, t H-11), 2.61 (3H, s, H-18), 2.36 (6H, s, H-2,2′).
^{1}H NMR spectral data of sample RA-1 (DMSO) δ (ppm): 6.66 (1H, d, H-5), 6.31 (1H, d, H-6), 4.15 (1H, s, H-15), 3.90 (2H, s, H-9), 3.69 (2H, t, H-12), 3.37 (2H, s, H-3), 2.87 (2H, t, H-11), 2.60 (3H, s, H-18), 2.35 (6H, s, H-2,2′).

^{13}C NMR spectral data of standard ranitidine (δ_C 39.52, DMSO) δ (ppm): 112.90 (C-5), 108.00 (C-6), 51.30 (C-3), 68 (C-12), 41.10 (C-2,2′), 28.10(C-18), 25.90 (C-11), 23.70 (C-9).

^{13}C NMR spectral data of sample RA-1 (δ_C39.52, DMSO) δ (ppm): 112.80 (C-5), 108.00 (C-6), 51.20 (C-3), 64 (C-12), 41.00 (C-2,2′), 28.20 (C-18) ,25.80 (C-11), 23.70 (C-9).

The ^{1}H and ^{13}C NMR spectrum and spectral data of collected samples were compared with those of spectrum and spectral data of standard paracetamol and ranitidine which were found identical. These spectrums give clear concepts about the structure of the active ingredient of paracetamol and ranitidine. This observation leads to the conclusion that the qualitative determination of pharmaceutical tablets can be carried out possible by ^{1}H and ^{13}C NMR experiments.

CONCLUSION

The present study evaluated the quality of four paracetamol and five ranitidine tablets available in the local market in Bangladesh by physical and spectroscopic *i.e.*, FT-IR, UV-visible, ^{1}H & ^{13}CNMR studies. The range of weight variation of paracetamol and ranitidine tablets were well below the allowed limit of 5%. The FT-IR spectrum displayed several characteristic bands of paracetamol and ranitidine in both standards and samples. The λ_{max} of paracetamol and ranitidine of both standards and samples were also matched in the UV-visible spectrum. The ^{1}H and ^{13}C NMR spectral data of standard paracetamol and ranitidine were compared with samples and found identical. Thus, it may be concluded that the manufacturers are maintaining the quality of those drugs which is a positive indication for the public health in Bangladesh.

DECLARATION OF CONFLICT OF INTEREST

No conflict of interest.

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