

Quantitative and Qualitative Estimation of Three Marketed Tablet Preparations of Ranitidine Hydrochloride, Tiemonium Methylsulfate and Domperidone Commonly used in Bangladesh

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Abstract

This study was aimed to evaluate the pharmaceutical quality of ranitidine hydrochloride, tiemonium methylsulfate and domperidone tablets manufactured in Bangladesh. Ten samples of Ranitidine Hydrochloride, Tiemonium Methylsulfate and Domperidone solid dosage forms available in Bangladesh drug market were assayed spectrophotometrically and their various physical parameters such as weight variation, friability, disintegration, dissolution and hardness were analyzed according to British Pharmacopoeia (BP) and United States Pharmacopoeia (USP). Among them seven ranitidine, seven tiemonium and seven domperidone samples were meet the BP specification (95 – 105% of claimed potency). Study revealed that eight ranitidine, ten tiemonium and seven domperidone formulations of different companies meet the USP specification for in vitro dissolution test in first 30 minutes.

Keywords: Ranitidine hydrochloride; Tiemonium methylsulfate; Domperidone; *In vitro* dissolution; Bangladesh.

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Introduction

H₂-receptor antagonists are also useful in the prevention of stress ulceration and recurrence of gastric and duodenal ulcer. Several H₂ antagonists are currently available in the market as cimetidine, ranitidine, famotidine, nizatidine etc^[1]. Ranitidine hydrochloride (Figure 1), chemically N, N-dimethyl-5-[2-(1-methylamino-2-nitrovinyl)-ethylthiomethyl] furfurylamine hydrochloride (Figure 1) is a H₂-receptor antagonist and is widely used in short term treatment of duodenal ulcer and in the management of hypersecretory conditions^[2]. It is also prescribed in erosive esophagitis, gastric irritation. It is absorbed from upper GIT and has only 50% bioavailability. Colonic metabolism of ranitidine hydrochloride is partly responsible for

poor bioavailability of drug. Hence it was thought that formulation residing at absorption window for prolonged period may be a useful approach to enhance bioavailability of ranitidine hydrochloride^[3]. It is effective by both parenteral and oral routes of administration^[4]. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours^[5]. Ranitidine hydrochloride is also used for the treatment of Helicobacter pylori eradication, gastro esophageal reflux disease and erosive esophagitis^[6,7]. Ranitidine can be found in



many pharmaceutical firms such as tablets, injectable solutions and oral liquids. Peptic ulcer is a common disease worldwide, with an estimated 10% of the population effected. Research has shown that the infection of *Helicobacter pylori* is a key factor in the occurrence and reoccurrence of peptic ulcer^[8,9].

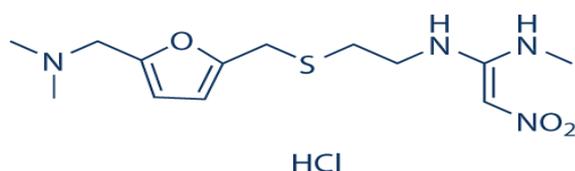


Figure 1: Structure of Ranitidine Hydrochloride.

Tiemonium Methylsulfate (Figure 2) is chemically described as 4-(3-hydroxy-3-phenyl-3-(2-thienyl) propyl)-4-methyl morpholinium methylsulfate (salt). It is a quaternary ammonium antimuscarinic agent with peripheral effect similar to those of atropine and is used in the relief of visceral spasms. It prevents the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle of GI tract^[10].

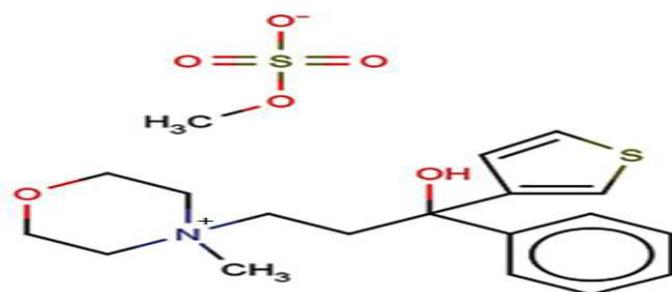


Figure 2: Structure of Tiemonium Methylsulfate.

Domperidone (Figure 3), 5-chloro-1-[1-[3-(2, 3-dihydro-2-oxo-1Hbenzimidazol-1-yl)propyl]-4-piperidinyl]-1,3-dihydro-2 Hbenzimidazol-2-one (Figure 3), is a potent dopamine antagonist used for treatment of nausea and vomiting. Domperidone does not cross the blood-brain barrier and therefore has fewer adverse CNS effects than other dopamine antagonists^[11].

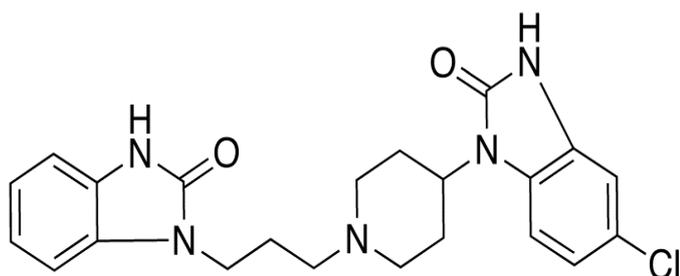


Figure 3: Structure of Domperidone.

Materials

Ten samples of ranitidine hydrochloride, tiemonium methylsulfate and domperidone solid dosage forms were procured from various drug stores. Samples were properly checked for their Manufacturer name, Physical appearance, and Batch

number, Date of manufacturing and Expiry date before purchasing. They were randomly coded, R1 to R10, T1 to T10 and D1 to D10 respectively. Pure ranitidine hydrochloride, tiemonium methylsulfate and domperidone used as reference standards and were collected from Pharmik Laboratories Limited, Chittagong, Bangladesh. Analytical grade hydrochloric acid was used. Distilled water (pH 6.8 ± 0.2 as measured at pH meter (Hanna-HI981.7, USA) was used throughout the work.

Physical Properties of Ranitidine Hydrochloride, Tiemonium Methylsulfate and Domperidone

Weight variation: The weight of tablets represents the net weight of content present per tablet. This test is important because every tablet should have the uniformity of content in order to maintain the dose. In these processes 20 tablets were weighed by a Mettler Toledo B303-S (Switzerland) weighing balance and the average weights were calculated^[12].

Hardness test: Tablet hardness has been defined, as the force required breaking a tablet in a diametric compression test. The resistance of the tablets to chipping, abrasion or breakage depends on its hardness. The hardness test of tablet is a non-pharmacopoeia test. This crushing strength of tablets were determined using a Monsanto hardness tester (Campbell Electronics, India) three times and mean value and standard deviation was calculated^[13].

Friability test: Tablet hardness is not an absolute indication of strength since some formulations, when compressed into very hard tablets tend to “cap” on attrition i.e. losing their crown portions. Therefore, another measure of a tablet’s strength i.e. its friability is tested. Tablets that tend to powder, chip, and fragment when handled, lack elegance and consumer acceptance. The friability test was performed by a Roche friabilator (Campbell Electronics, India). Ten tablets were weighed and placed in a friabilator and was exposed to rolling for 100 revolutions at a rate of 25 rpm. Then tablets were dedusted and reweighed. Percent of loss of weight is measured. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test^[14].

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Disintegration time test: The Disintegration Time (DT) of each sample of all 3 brand was determined by using USP standard Tablet DT machine (Indian equipment corporation, India) in simulated gastric fluid for three times and mean value and standard deviation was calculated^[15].

In vitro dissolution studies: Simulated gastric medium (pH 1.2) was used as dissolution medium. Media (900 ml of simulated gastric juice) was maintained at 37 ± 0.5°C and rotation speed was set at 50 rpm^[16]. Tablet Dissolution tester U.S.P. XXIII (Model-TDT 06, Indian Equipment Corporation, India) was used in our study. After 30 minutes, 5 ml of sample was withdrawn for each sampling. Samples were analyzed spectrophotometrically (UV/VIS Spectrophotometer, UV mini-1240, Shimadzu, Japan) at 314 nm, 214 nm and 286 nm for ranitidine hydrochloride^[17], tiemonium methylsulfate^[18] and domperidone^[19] respectively.

Preparation of simulated gastric medium (pH 1.2): 11.4 ml of Hydrochloric acid (32% w/v) was diluted with sufficient water to produce 1000 ml^[20].

Potency determination of ranitidine hydrochloride: Transfer 0.125 gm of the sample powder was taken in a volumetric flask. Add 100 ml distilled water and sonicate for three minutes. Then dilute 1 ml to 100 ml with water to obtain final concentration of ranitidine hydrochloride. The diluted solution was filtered and measured the absorbance at 314 nm against ranitidine hydrochloride standard solution and calculates the potency^[21].

Potency determination of tiemonium methylsulfate: Initially 0.1 gm tiemonium methylsulfate equivalent powder was taken in a volumetric flask. Then 100 ml distilled water was added. Then 1 ml dilute to 100 ml with water. After filtration then 1 ml of the solution was taken in the absorbance cell and the absorbance

was measured at 214 nm. Repeat the whole procedure with standard tiemonium methylsulfate and calculate the potency^[22].

Potency determination of domperidone: 0.125 gm of Domperidone equivalent powder was taken in a volumetric flask. Then 100 ml distilled water was added. 1 ml dilute to 100 ml with water. After filtration then 1ml of the solution was taken in the absorbance cell and the absorbance was measured at 286 nm. Repeat the whole procedure with standard tiemonium methylsulfate and calculate the potency^[23].

Results and Discussion

Evaluation of Tablets

Weight variation: Weight variations of all thirty samples of 3 brands were determined and found all samples of three brands were satisfied the specification (Table 1)

Table 1: Weight variation of collected samples.

Code	Average weight (gm)	Code	Average weight (gm)	Code	Average weight (gm)
R01	0.3535 ± 0.002	T01	0.3638 ± 0.002	D01	0.154 ± 0.002
R02	0.3012 ± 0.002	T02	0.3521 ± 0.002	D02	0.192 ± 0.002
R03	0.2212 ± 0.003	T03	0.3495 ± 0.003	D03	0.103 ± 0.003
R04	0.2630 ± 0.004	T04	0.3354 ± 0.004	D04	0.132 ± 0.004
R05	0.2460 ± 0.003	T05	0.3070 ± 0.003	D05	0.157 ± 0.003
R06	0.3120 ± 0.002	T06	0.3114 ± 0.002	D06	0.213 ± 0.002
R07	0.3160 ± 0.003	T07	0.3621 ± 0.003	D07	0.105 ± 0.003
R08	0.2770 ± 0.006	T08	0.3102 ± 0.006	D08	0.189 ± 0.006
R09	0.3640 ± 0.005	T09	0.3511 ± 0.005	D09	0.152 ± 0.005
R10	0.3046 ± 0.005	T10	0.3160 ± 0.005	D10	0.147 ± 0.005

Hardness and friability test: These two tests are vital for the tablets to determine the strength. Hardness and friability was determined by all the collected samples and the results are tabulated in the Table 2. It was found in Table 2 that all most all samples were maintained uniform hardness; however one sample of ranitidine hydrochloride (R05) showed much higher hardness than other samples. Others two brands were found good in respect to hardness test. But in friability test a good number of samples were found unsatisfactory (R04, R10, T02, T05, T08, T10, D02, D05, D06 and D09).

Table 2: Hardness and Friability test of collected samples.

Code	Hardness (kg)	Friability (%)	Code	Hardness (kg)	Friability (%)	Code	Hardness (kg)	Friability (%)
R01	3.5 ± 0.5	0.130%	T01	4.5 ± 0.1	0.092%	D01	3.50 ± 0.4	0.064%
R02	3.5 ± 0.2	0.156%	T02	3.5 ± 0.3	2.097%	D02	2.50 ± 0.8	1.066%
R03	5.5 ± 0.2	0.115%	T03	2.5 ± 0.4	0.104%	D03	2.50 ± 0.1	0.118%
R04	3.7 ± 0.3	1.056%	T04	3.0 ± 0.1	0.098%	D04	2.75 ± 0.9	0.090%
R05	8.5 ± 1.5	0.111%	T05	2.5 ± 0.2	1.152%	D05	3.00 ± 0.2	1.071%
R06	4.0 ± 0.2	0.053%	T06	3.0 ± 0.9	0.069%	D06	1.50 ± 0.1	1.051%
R07	4.5 ± 0.1	0.085%	T07	3.0 ± 0.4	0.201%	D07	2.50 ± 0.7	0.028%
R08	5.5 ± 0.2	0.138%	T08	2.5 ± 0.2	3.022%	D08	2.75 ± 0.6	0.044%
R09	4.5 ± 0.5	0.046%	T09	2.5 ± 0.4	0.090%	D09	2.75 ± 0.5	2.093%
R10	5.6 ± 0.2	1.224%	T10	3.0 ± 0.2	1.110%	D10	4.50 ± 0.4	0.089%

Disintegration time and dissolution studies of marketed samples: Disintegration is a vital factor for the release of active ingredient after administration. The active ingredient must be released from the tablet matrix as effectively as possible to allow rapid dissolution. The disintegration time and dissolution studies were thoroughly done with the collected samples and presented in the Table 3. Disintegration times of all the samples were found within the BP range. But dissolution studies showed some unsatisfactory results in two samples of ranitidine (R04 and R06) and three samples of domperidone (D02, D05 and D08), where sample D02 and D05 were far below than the lower limit as per USP specification (more than 80% drug release, in first 30 minutes).

Table 3: Disintegration time (DT) and Dissolution studies of collected samples.

Code	DT (min)	% drug release (after 30 min)	Code	DT (min)	% drug release (after 30 min)	Code	DT (min)	% drug release (after 30 min)
R01	7.0	85	T01	3.5	82	D01	2.0	93
R02	6.0	88	T02	4.5	95	D02	2.0	65
R03	7.0	82	T03	4.0	99	D03	5.0	85
R04	6.0	78	T04	6.0	93	D04	1.0	86
R05	20	83	T05	7.0	88	D05	8.0	67
R06	9.0	72	T06	7.0	87	D06	4.0	82
R07	9.0	81	T07	5.0	98	D07	6.0	96
R08	10	88	T08	5.0	91	D08	5.0	72
R09	6.0	84	T09	6.0	92	D09	4.0	98
R10	8.0	82	T10	4.0	89	D10	3.0	85

Potency determination: To determine the amount of active ingredient present in the sample, potency determination of all samples were done and the results are given in the Table 4.

Table 4: Potency estimation of the collected samples.

Code	Potency (%)	Code	Potency (%)	Code	Potency (%)
R01	98.75	T01	93.21	D01	83.16
R02	99.02	T02	88.21	D02	88.29
R03	101.51	T03	97.54	D03	100.01
R04	86.43	T04	100.91	D04	99.47
R05	88.94	T05	100.24	D05	96.11
R06	99.01	T06	97.44	D06	69.48
R07	100.81	T07	68.71	D07	96.33
R08	101.27	T08	98.91	D08	101.07
R09	89.26	T09	102.08	D09	97.24
R10	97.08	T10	99.85	D10	103.42

Discussion

From the Table 4, it was found that among the tested samples only one ranitidine sample (R07), two timonium samples (T04 and T05) and one domperidone sample (D03) contained the claimed potency. However all together seven ranitidine samples, seven timonium samples and seven domperidone samples were within the BP specification (95 – 105% of claimed potency), which is 70% of tested brands. All the sub-standard samples were below the lower limit. Among these only one sample (T01) was close to the lower limit and other eight brands (R04, R05, R09, T02, T07, D01, D02 and D06) were far below than the lower limit.

Conclusion

At present 95% of the essential of drugs are produced in Bangladesh. The overall quality of the drugs is satisfactory but some spurious and substandard drugs are also available in the market. As these three drugs are widely used in our country, it should check carefully. The present study, although performed on a limited scale yet on the basis of professional judgement the data reported in this study can help Drug Control Authority to get an idea about the quality status of the marketed ranitidine, timonium and domperidone preparations in Bangladesh.

Conflict of Interests

The authors declare that they have no conflict of interest.

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