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PHARMACEUTICAL ANALYSIS OF VARIOUS COMMERCIAL BRANDS OF DROTAVERINE: ENSURING PHARMACEUTICAL EQUIVALENCE

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ABSTRACT:

Background: Drotaverine (INN, also known as drotaverin), a benzylisoquinoline derivative, is an active antispasmodic compound. It exhibits stronger efficacy compared to papaverine and is commonly employed in the symptomatic treatment of various conditions. Drotaverine is utilized to alleviate pain associated with irritable bowel syndrome, headaches, menstrual periods, and is also effective in relieving cervical spasms during labor.

Objective of the Study: The aim of this study was to establish pharmaceutical equivalence among three distinct brands of Drotaverine HCL available in Pakistan.

Methodology: Seven key quality control parameters, including weight variation, thickness, hardness, friability, disintegration, and dissolution measured via UV spectrophotometer as per the standards defined by the British and United States Pharmacopeias, were assessed for the three different brands of Drotaverine HCL accessible in Karachi, Pakistan.

Results: The results demonstrate that the selected brands of Drotaverine HCL available in Karachi meet all specifications outlined by the B.P/USP.

Conclusion: Hence, these brands can be considered interchangeable with each other, ensuring consistent quality and efficacy for patients requiring Drotaverine therapy.

Keyword: Drotaverine, BP/USP, quality control, symptomatic treatment.

INTRODUCTION:

Drotaverine (INN, also identified as drotaverin), a bezylisoquinoline derivative, is an antispasmodic active ingredient. Structurally associated but more potent as compared to papaverine (1). Drotaverine is a discriminating inhibitor of phosphodiesterase-4, belongs to the vasodilator, myothropic spasmolytic groups (2). It is used to alleviate pain caused due to irritable bowel syndrome, headache, menstrual periods, and is also used to ease cervical spasm during labor (3). It acts on smooth muscle cells by reducing ionized active calcium presentation because of inhibition of phosphoesterase and adenosine mono phosphate build up within the cells exerting clear and protracted action on smooth muscles of internal organs and vessels, moderately reducing arterial pressure, boost little volume of heart, showing a few anti-arrhythmic action, reducing cerebral vessels tone and enhance their blood-filling(4). Practically it does not produce any action on vegetative nervous system and does not break in to CNS (2). Drotaverine shows entire and quick absorption by gastrointestinal tract. Exhibiting highly variable bioavailability, with 80 to 95% protein binding and hepatic metabolism. Its half-life is 7 to 12 hours (1). The potential side-effects associated with drotaverin are nausea, vomiting, sleep disorders, fainting, dry mouth, constipation, flushing, dermatitis; face, lips, eyelids, tongue, hands and feet swelling; hypotension and fluctuations in pulse rate (5).Animal experiments shows that liver metabolism plays a chief role in the drotaverine elimination (6-8) and metabolites in considerable levels are excreted into bile (7, 9-11).

Drotaverine is contraindicated in patients with severe heart, liver, and kidney disease. This drug should be used with care in patients suffering from a genetic disorder of the skin and blood (5). People suffering from allergic reactions, are pregnant or are breastfeeding are also recommended to evade taking drotaverine (3). Drotaverine may show interactions with a few other drugs like diclofenac, atropine, levodopa and diazepam Drotaverine comes in a form of tablet to be taken orally, with or without food (2). The recommended dosage for adults is usually 40-80 mg, three times a day but it can fluctuate depending on condition (4).For the children between the ages of 1-6 years, the recommended dose is 20 mg, three to four times daily. A child older than 6 years of age, the dosage is normally augmented to 40 mg (4).

The main objective of the study is to compare the physiological performance of all the chosen brands of drotaverine. This will help in evaluating the interchangeability of the brands.

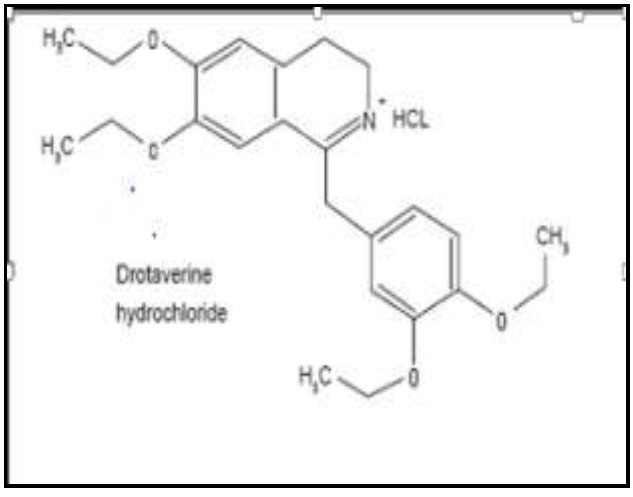

Figure 1: Chemical Structure of Compound(4).

MATERIALS AND METHODS:

Tests were performed to carry out comparative study between three different brands of 40mg of uncoated tablets of drotaverine HCL (Relispa, No spa and Dytra) available in market. Different physicochemical tests were performed between these brands to study comparison between them. These physicochemical tests are as follows:

1. WEIGHT VARIATION TEST:

Weight variation was checked on Electronic Balance PA214C between tablets concerning dose and weight which should comply within BP limits. 20 units of each brand were selected at random. From average tablet weight, percent weight variation was calculated. In order to get ahead of weight variation test, each unit should lie in the limits of the percentage divergence permissible by BP/USP. Standard formula was used to determine upper and lower control limits(12, 13).

2. THICKNESS TEST:

Thickness of each tablet was assessed by determining the level of compaction of 20 units of each brand by using VERNIER CALLIPER. Thickness is an important parameter for consumer's acceptance and to facilitate packaging.

3. HARDNESS TEST:

A sample of 10 tablets from each brand was forced to mechanical stress in order to determine strength of a tablet. A tablet must be rigid enough to stand pressure. Hardness of all the brands was checkered on MH-1 Hardness Tester. The value of each tablet was assessed and mean value was measured and compared with the standard(14).

4. FRIABILITY TEST:

10 tablets from each brand of drotaverine HCL were subjected to a uniform tumbling motion in a FB-1004 friabrilator for specific time frame i.e. 25 revolutions per minute for 4 minutes that is 100 revolutions and the weight loss was measured. The test was performed to check if a tablet got scraped during shipping and also to check capping and lamination of tablet. It is determined by calculating % weight loss by the help of initial and final weight (12-14).

5. DISINTEGRATION TEST:

Disintegration tests were conducted on six tablets from each brand using a disintegration apparatus (USP Type I, DS-0702), employing a basket configuration. Each tablet was individually placed in a tube within the basket rack, submerged in a 900 ml beaker filled with water maintained at 37°C. Disintegration time was meticulously recorded, ensuring no remnants of the tablets remained on the mesh of the basket(12, 15).

6. DISSOLUTION TEST:

For the dissolution test, tablets from each brand were subjected to analysis using a Tablet Dissolution Apparatus (USP Type II, DL-0601) employing a paddle apparatus. In this procedure, each tablet was introduced into a beaker containing 900 ml of dissolution medium, specifically Phosphate buffer with a pH of 6.8. The temperature of the medium was precisely regulated at 37°C ± 5°C throughout the test duration. The dissolution apparatus operated at a speed of 50 rpm for duration of 45 minutes. Post-test, 5 ml aliquots were withdrawn, filtered, and diluted with dissolution medium to a final volume of 25 ml. These diluted samples were then analyzed using a UV-Visible spectrophotometer at a wavelength of 253.8 nm, with Phosphate buffer of pH 6.8 serving as the blank. The absorbance of each withdrawn sample was meticulously recorded, and the concentration of the drug in the samples was calculated according to the established monograph standards (8, 12, 16).

RESULTS:

Table 1: specification of drug with batch number

No.	Name of product	Serial No.	Code No.	Batch No.
1.	RELISPA	BRAND 01	REL 01	WU023
2.	NO SPA	BRAND 02	NOS 02	0383
3.	DYTRA	BRAND 03	DYT 03	130

Table 2: Statistical weight variation table

No.	Serial No.	Batch No.	Average Weight (mg)	S.D	Upper Limit (UCL)	Lower Limit (LCL)
1.	BRAND 01	WU023	141	3.053	152	130
2.	BRAND 02	0383	143	2.363	154	132
3.	BRAND 03	130	246	3.63	264	228

Table 3: weight variation test

No.	Serial No.	Batch No.	Results (g)	BP/USP Limits	Deviation from BP/USP
1.	BRAND 01	WU023	141	7.5%	All passed
2.	BRAND 02	0383	143	7.5%	All passed
3.	BRAND 03	130	246	7.5%	All passed

Table 4: weight variation readings RELISPA (Brand 01)

No.	Weight (Mg)	Mean	Standard Deviation	Upper Class Limit	Lower Class Limit	Comment
1.	143.3	141	3.05	152	130	Passed
2.	139.1					Passed
3.	139.6					Passed
4.	140.6					Passed
5.	147.5					Passed
6.	141.1					Passed
7.	146.3					Passed
8.	142.0					Passed
9.	143.6					Passed
10.	141.7					Passed
11.	139					Passed
12.	137.2					Passed
13.	140					Passed
14.	141.9					Passed
15.	138.5					Passed
16.	136.8					Passed
17.	139.9					Passed
18.	144.4					Passed
19.	137.7					Passed
20.	136.5					Passed

Table 5: weight variation readings NOSPA Brand 02

No.	Weight (Mg)	Mean	Standard Deviation	Upper Class Limit	Lower Class Limit	Comment
1.	143.8	143	2.36	154	132	Passed
2.	147.5					Passed
3.	146.6					Passed

4.	139.4					Passed
5.	139.8					Passed
6.	141.7					Passed
7.	141.1					Passed
8.	143.3					Passed
9.	142.0					Passed
10.	140.9					Passed
11.	140.4					Passed
12.	144.8					Passed
13.	143.1					Passed
14.	142.7					Passed
15.	143.3					Passed
16.	140.2					Passed
17.	142.7					Passed
18.	139.6					Passed
19.	143.0					Passed
20.	146.4					Passed

Table 6: weight variation readings DYTRA Brand 03

No.	Weight (mg)	Mean	Standard Deviation	Upper Class Limit	Lower Class Limit	Comment
1.	245.7	246	3.63	264	228	Passed
2.	243.4					Passed
3.	247.9					Passed
4.	248.5					Passed
5.	245.5					Passed
6.	245.7					Passed
7.	247.5					Passed
8.	249					Passed
9.	248.9					Passed
10.	246.8					Passed
11.	245.5					Passed
12.	246.1					Passed
13.	246.2					Passed
14.	246.8					Passed
15.	243.8					Passed
16.	232.0					Passed
17.	247.2					Passed
18.	246.6					Passed
19.	244.5					Passed
20.	248.9					Passed

Table 7: thickness test

No.	**Serial No.**	**Batch No.**	**Average Thickness**	**S.D**	**Upper Limit (UCL)**	**Lower Limit (LCL)**
1.	BRAND 01	WU023	3.8	0.0	3.8	3.8
2.	BRAND 02	0383	3.2	0.0	3.2	3.2
3.	BRAND 03	130	3.3	0.0	3.3	3.3

Table 8: thickness test RELISPA (Brand 1):

No.	Thickness (mm)	Mean	Standard Deviation	Upper Class Limit (X+3S)	Lower Class Limit (X-3S)	Comment
1.	3.8	3.8	0.0	3.8	3.8	Passed
2.	3.8					Passed
3.	3.8					Passed
4.	3.8					Passed
5.	3.8					Passed
6.	3.8					Passed
7.	3.8					Passed
8.	3.8					Passed
9.	3.8					Passed
10.	3.8					Passed

Table 9: thickness test NO SPA (Brand 02)

No.	Thickness (mm)	Mean	Standard Deviation	Upper Class Limit (X+3S)	Lower Class Limit (X-3S)	Comment
1.	3.2	3.2	0.0	3.2	3.2	Passed
2.						Passed
3.						Passed
4.						Passed
5.						Passed
6.						Passed
7.						Passed
8.						Passed
9.						Passed
10.						Passed

Table 10: thickness test DYTRA (Brand 03)

No.	Thickness (mm)	Mean	Standard Deviation	Upper Class Limit (X+3S)	Lower Class Limit (X-3S)	Comment
1.	3.3	3.3	0.0	3.3	3.3	Passed
2.						Passed
3.						Passed
4.						Passed
5.						Passed
6.						Passed
7.						Passed
8.						Passed
9.						Passed
10.						Passed

Table 11: hardness test

No.	**Serial No.**	**Batch No.**	**Average Hardness**	**S.D**	**Upper Limit (UCL)**	**Lower Limit (LCL)**
1.	BRAND 01	WU023	5.58	0.3994	6.778	4.382
2.	BRAND 02	0383	5.68	0.4341	6.982	0.378
3.	BRAND 03	130	5.68	0.4780	7.114	4.246

Table 12: hardness test RELISPA (Brand 01)

No	Hardness (Kg)	Mean	Standard Deviation	Upper Class Limit (X+3S)	Lower Class Limit (X-3S)	Comment
1.	5.7	5.58	0.3994	6.778	4.382	Passed
2.	5.4					Passed
3.	5.9					Passed
4.	6.3					Passed
5.	5.7					Passed
6.	5					Passed
7.	5.1					Passed
8.	5.9					Passed
9.	5.5					Passed
10.	5.3					Passed

Table 13: hardness test NOSPA (Brand 02):

No.	Hardness (Kg)	Mean	Standard Deviation	Upper Class Limit (X+3S)	Lower Class Limit (X-3S)	Comment
1.	5.9	5.68	0.4341	6.982	4.378	Passed
2.	5.8					Passed
3.	5					Passed
4.	5.43					Passed
5.	5.3					Passed
6.	5.4					Passed
7.	5.6					Passed
8.	6.1					Passed
9.	6.5					Passed
10.	5.8					Passed

Table 14: hardness test DYTRATABLET (Brand 03)

No.	Hardness (Kg)	Mean	Standard Deviation	Upper Class Limit (X+3S)	Lower Class Limit (X-3S)	Comment
1.	5.9	5.68	0.4780	7.114	4.246	Passed
2.	5.8					Passed
3.	6.2					Passed
4.	6.3					Passed
5.	5.2					Passed
6.	6.2					Passed
7.	5					Passed
8.	5.2					Passed
9.	5.3					Passed
10.	5.7					Passed

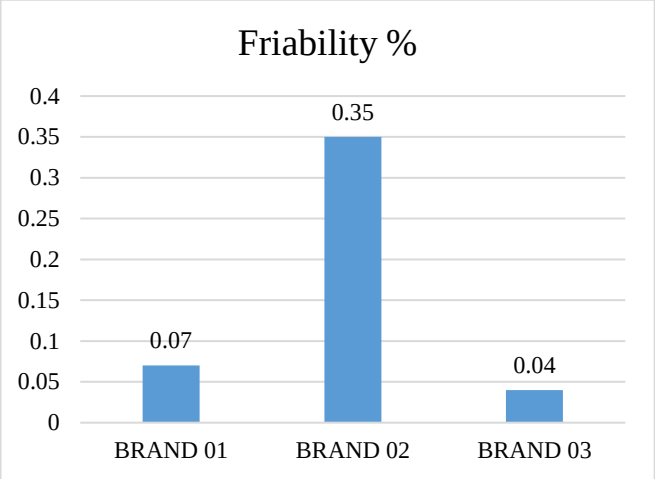

Figure 2: % friability of all brands of Drotaverine

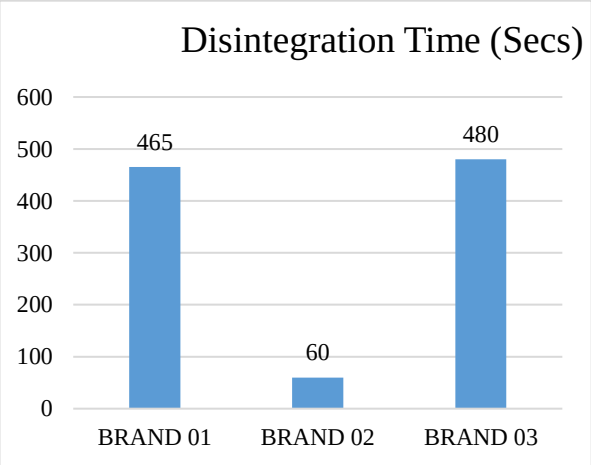

Figure 3: Disintegration Time (Sec) of all brands of Drotaverine

Table 15: Dissolution of all brands of Drotaverine observed in Phosphate buffer of 6.8 pH

No.	Brands	Absorbance at 45 min	Mean Absorbance	Dissolution at 45 min (%)	Mean	Acceptance Criteria	Comments
1.	**Brand 1 (RELISPA)**	0.322	0.331	97.28	99.63	NLT 80%	Within limits
2.		0.327		98.79			
3.		0.33		99.69			
4.		0.363		109.66			
5.		0.311		93.95			
6.		0.326		98.4			
1.	**Brand 2 (NOSPA)**	0.321	0.331	97.88	98.84	NLT 80%	Within limits
2.		0.324		100.3			
3.		0.332		100.9			
4.		0.334		98.7			

No.	Brands	Absorbance at 45 min	Mean Absorbance	Dissolution at 45 min (%)	Mean	Acceptance Criteria	Comments
5.		0.327		91.97			
6.		0.342		103.3			
1.	**Brand 3 (DYTRA)**	0.33	0.331	99.69	99.47	NLT 80%	Within limits
2.		0.326		98.4			
3.		0.322		97.28			
4.		0.332		100.3			
5.		0.342		103.3			
6.		0.324		97.88			

DISCUSSIONS:

20 tablets were weighed randomly drawn from the given sample and mean standard deviation, upper and lower control limits were calculated respectively specified by B.P/USP. According to USP, if the tablet weight is 130mg or less, 10% difference is allowed, if 130mg–324 mg, 7.5% maximum difference is allowed and if it is greater than 324 mg, 5% maximum difference is allowed and not more than two tablets (out of the 20 tablets) should vary from the mean weight by the % difference and no tablet differs from the average weight by twice that percentage. In this study, weight of tablets of our comparing brands lie between 130mg–324mg allowing 7.5% maximum difference and, standard deviation of comparing brands are found to lie within official limits illustrated in the tables given(12, 13).

Mean, standard deviation and upper lower control limits were calculated and given in the tables. It is the only dimensional variable related to the compression process. Tablet thickness is constant batch to batch or within a batch only if the punch tooling is of consistent length if the tablet granulation or powder mix is adequately constant in particle size and size distribution, , and if the tablet press is clean and in excellent operational order. Thickness should be controlled within ± 5% variation of a standard value**.** In this study thickness of tablets of all brands are found to lie between upper and lower control limits and also shown.

Hardness testing is a laboratory technique used by the pharmaceutical industry to test the threshold and structural reliability of a tablets under storage conditions, transportation, and handling before use. It increases consumer's compliance and also important factor that can affect disintegration of a tablet and can alter bioavailability. A crushing strength of 4-8 Kg for uncoated tablets is sufficient. (1Kg=10 Newton). In this case tablets from the given sample are found to lie within the normal range and illustrated in the tables given(12).

Lack of elegance and consumer's acceptance occurs as a result of tendency of tablets to powder, chip, and fragmented when handled leading to dirty processes in such areas of manufacturing as coating and packaging. They can also add to tablet's weight variation or content uniformity problems. In this study 20 tablets selected from each brand were pre-weighed, placed in a friabrilator and subjected tumbling effect for 4 min and 25 rpm. After that these tablets were re-dusted and weighed again and % weight loss was determined. The value of friability (% loss) should be less than or equal to 1%, In this study, % friability is calculated and found to lie within normal range as represented in the given table (8).

For a tablet to absorb and become bioavailable, it must first disintegrate which is its ability to break into its respective fragments and dissolute in the body fluids. Thus disintegration is a time required to breaks it into its fragments (excluding insoluble coatings and capsule shells) and of specific size

which reside on the screen of test apparatus and holds to the lower surface of the discs. According to USP the tablet should disintegrate within 15min (varies for some uncoated tablets). If 1 or 2 tablets do not disintegrate within the specified time, the test must be repeated in 12 more tablets which require that 16 tablets out of selected 18 tablets should disintegrate within official limits. In this case, each brand of drotaverine HCL disintegrates within official limit and presented in the table given.

The time essential for a specified percentage of the active present in a tablet to become available in a solution under a particular set of circumstances is measured by dissolution test. It is planned to present a step toward the evaluation of the physiological accessibility of an active ingredient. In vitro dissolution test is achieved using a diversity of equipment/apparatus. According to USP, each tablet should be entirely dissolved after 45 min at 50 rpm and 37^{o}C. The absorbance of the sample is determined using UV spectrophotometer at wavelength of 253.8 nm and Nospa (multinational) is kept as a reference standard with which other brands are compared. In this study, absorbance is calculated and found to lie within normal range which is NLT 80% of drug dissolve within 45 min and illustrated in the given table(8, 10, 12).

CONCLUSION:

The determination of drotaverine HCL is done through UV spectrophotometer; this technique is employed successfully for analysis because it is fastidious, basic, precise and economic. Our study discovered that all the brands of drotaverine HCL have almost same results which mean there is no significant dissimilarity in the brand's efficacy and therapeutic action. Therefore it can be concluded from above results that all the available brands of drotaverine HCL in local market of Karachi Pakistan are having physicochemical parameters within the specified quality control range so if there is any compliance issue; in terms of cost and other factors, the brands are redeemable.

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Conflict of interest:

The authors have no conflict of in interest

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