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A SURVEY ON QUALITIES OF DRUGS COMMERCIALLY AVAILABLE IN THAILAND

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ABSTRACT

In our programme on quality evaluation of generic drug products, over ten items of those commercially produced by local manufacturers were investigated for their *in vitro* qualities as compared to those of innovator's using pharmacopeial methods. On the basis of pharmacopeial specification, substandard qualities were found in 14 items out of 17. For each generic drug, there is a great variation in qualities among different manufacturers. All tested samples of all products pass the pharmacopeial standard with regard to weight variation and content uniformity. Failure to meet the percent labelled amount limit was observed for spironolactone and ranitidine tablets. An achievement in disintegration test was generally shown, though in the recent pharmacopeia, no requirement on disintegration was specified. Failure to pass the dissolution specification was demonstrated in tablets of paracetamol, cimetidine, ranitidine, ibuprofen, spironolactone, naproxen sodium, danazol, hydroxyzine, terfenadine, ketotifen, metronidazole, alprazolam, cotrimoxazole and ampicillin. For drugs locally manufactured, their qualities on the basis of pharmacopeial requirement, still need improvement, particularly to enhance the dissolution property.

INTRODUCTION

A large number of drug industries in Thailand have now led to increasing amounts of generic drug products with various competitive marketing strategies, among those, the price range and qualities are of major concern for hospitals and medical professionals. An argument on drug product quality still existed, the preference on favoring a more established brand with proven effectiveness over the less well known generic one may be associated with undesirable high cost whereas therapeutic efficacy has been claimed indifference. The continuing recognition that there is currently no data or evidence to ensure all accepted compendial standard as specified in the pharmacopeia encouraged the establishment of Srinagarind Hospital Drug Evaluation Program. In this exclusive program, all generic propietary names;

particularly those produced by non-innovator's manufacturers, either locally manufactured or imported; were evaluated for their *in vitro* essential properties in comparison with an innovator's product. For some selected drug items, comparative bioequivalency will be further carried out to make certain *in vivo* data, especially for those whose correlation between *in vitro* and *in vivo* parameters are not reported. In this present study, seventeen drugs, with 2-6 brand names each, were evaluated for their *in vitro* qualities and the outcomes as compared with the pharmacopeial requirements, were reported.

MATERIALS AND METHODS

In this study, 17 generic drug products were randomly sampled from the hospital pharmacy and general drug stores. All brand names, a number of each propietary name available, the price range and a number of brands tested were listed in Table 1.

Table 1. Lists of the number of brand names, price range and the number of brands tested for each generic drug.[1]

Generic name	No. of brands available	Price range (Baht)	No. of brands tested
Paracetamol 500 mg Tablet	21	0.13 – 0.58	5
Cimetidine 200 mg Tablet	21	2.00 – 9.00	5
Ranitidine 300 mg Tablet	4	8.50 – 17.50	4
Allopurinol 300 mg Tablet	6	8.50 – 13.21	4
Ibuprofen 400 mg Tablet	10	1.53*	4
Spironolactone 25 mg Tablet	4	2.50 – 2.70	3
Naproxen Sod 275 mg Tablet	3	2.00 – 3.00	2
Nitrazepam 5 mg Tablet	5	0.45 – 0.50	4
Danazol 200 mg Capsule	3	29.00 – 32.40	4
Hydroxyzine 10 mg Tablet	9	0.60*	3
Terfenadine 60 mg Tablet	6	5.60*	3
Ketotifen 1 mg Tablet	10	2.00 – 4.98	3
Metronidazole 200 mg Tablet	10	0.45 – 20	4
Alprazolam 0.25 mg Tablet	2	*	2
Ampicillin 500 mg Capsule	23	2.20 – 4.00	5
Glafenine 200 mg Tablet	5	1.50 – 2.11	3
Cotrimoxazole Tablet	40	0.55 – 2.50	5

* *no data available*

Each commercial brand of each item was designated as A, B, C, D and so on. An innovator's product, designated as A, of each generic item was simultaneously investigated for comparative purpose by the same procedures. The information of an innovator's product with regard to its trade name, manufacturer and distributor was listed in Table 2. A reference standard or a working standard of each drug was kindly supplied by appropriate manufacturers or distributors and was used as a reference for all tested samples of each drug. The *in vitro* parameters of quality to be evaluated were weight variation, content uniformity, the percent labelled amount of an active ingredient, disintegration time and the extent of dissolution. The methods for weight variation and content uniformity were carried out by general procedures of the USP XXII.[2] To determine the disintegration time, the USP XXI disintegration methods for uncoated tablets were the one of choice.[3] For most cases, the USP XXII indicates procedures for % labelled amount of active ingredients and the dissolution in each monograph for the following: Cimetidine,[4] Ranitidine,[5] Allopurinol,[6] Spironolactone,[7] Danazol,[8] Hydroxyzine,[9] Ibuprofen,[10] Naproxen sodium,[11] Alprazolam,[12] Ampicillin,[13] Cotrimoxazole[14] and Paracetamol[15]. The remaining generic drugs were assayed for their active ingredients by the high-performance liquid chromatography in our laboratory and their dissolution methods were modified from those of the USP.

Table 2 Detailed information of an innovator's product

Generic name	Trade name of an innovator's product	Manufacturer/Distributor
Paracetamol	Calpol	Glaxo-Vidhyasom/Wellcome
Cimetidine	Tagamet	Smith Kline & French/Diethelm
Ranitidine	Zantac	Glaxo-Vidhyasom/Glaxo
Allopurinol	Zyloric	Glaxo-Vidhyasom/Glaxo
Ibuprofen	Brufen	Boots Manufacturing/Boots
Spironolactone	Aldactone	Olic (Thailand)/Searle
Naproxen sodium	Synflex	F.E.Zuellig/Syntex
Nitrazepam	Mogadon	Roche/Diethelm
Danazol	Ladogal	Sterling Pharm./Winthrop
Hydroxyzine	Atarax	Warner Lambert/UCB
Terfenadine	Teldane	Olic (Thailand)/Merrel Dow
Ketotifen	Zaditen	Hoechst Pharma/Sandoz
Metronidazole	Flagyl	May & Baker England/Baker England/Rhone Poulene
Alprazolam	Xanax	Upjohn
Ampicillin	Amcillin	Dumex/East Asiatic
Glafenine	Glifanan	Hoechst Pharma/les lab. Roussel
Cotrimoxazole	Bactrim	Olic (Thailand)/Roche

RESULTS AND DISCUSSION

Table 3 summarized the acceptable limit and criteria for the percent labelled amount of an active ingredient and the extent of dissolution specified in each monograph.

Table 3 An acceptable limit for the percent labelled amount (%LA) and the extent of dissolution.

	%LA (Lower-Upper limit)	Dissolution %dissolved (time)
Paracetamol	95.0 – 105.0	80% (30 min)
Cimetidine	90.0 – 110.0	75% (15 min)
Ranitidine	90.0 – 110.0	80% (45 min)
Allopurinol	93.0 – 107.0	75% (45 min)
Spironolactone	95.0 – 105.0	75% (60 min)
Danazol	90.0 – 110.0	65% (30 min)
Hydroxyzine	90.0 – 110.0	75% (45 min)
Ibuprofen	90.0 – 110.0	70% (30 min)
Naproxen sod	90.0 – 110.0	70% (45 min)
Alprazolam	90.0 – 110.0	80% (30 min)
Ampicillin	90.0 – 120.0	75% (45 min)
Cotrimoxazole	93.0 – 107.0	70% (60 min)

Weight variation and the content uniformity of all tested samples, though their data were not shown, passed the general requirement of the USP. The results of *in vitro* qualities of tested drugs, %LA, disintegration time, dissolution and conclusion were listed in Table 4.

Table 4 ***IN VITRO*** **QUALITIES OF TESTED PRODUCTS**

Generic name	Brand	%LA pass/fail	Disintegration pass/fail	Dissolution pass/fail	Conclusion pass/fail
Paracetamol	A	P	NR	P	P
	B	P	NR	P	P
	C	P	NR	P	P
	D	P	NR	F	F
	E	P	NR	F	F
Cimetidine	A	P	NR	P	P
	B	P	NR	F	F
	C	P	NR	P	P
	D	P	NR	F	F
	E	P	NR	P	P
Ranitidine	A	P	NR	P	P
	B	P	NR	F	F
	C	P	NR	F	F
	D	P	NR	P	P
Allopurinol	A	P	NR	P	P
	B	P	NR	P	P
	C	P	NR	P	P
	D	P	NR	P	P
Ibuprofen	A	P	NR	P	P
	B	P	NR	F	F
	C	P	NR	F	F
	D	P	NR	P	P
Spironolactone	A	P	NR	P	P
	B	P	NR	F	F
	C	P	NR	F	F

Table 4 (cont.)

Generic name	Brand	%LA pass/fail	Disintegration pass/fail	Dissolution pass/fail	Conclusion pass/fail
Naproxen sod	A	P	NR	P	P
	B	P	NR	F	F
Nitrazepam	A	P	NR	P	P
	B	P	NR	P	P
	C	P	NR	P	P
	D	P	NR	P	P
Danazol	A	P	NR	P	P
	B	P	NR	P	P
	C	P	NR	F	F
Hydroxyzine	A	P	NR	P	P
	B	P	NR	P	P
	C	P	NR	F	F
Terfenadine	A	P*	NR	P**	P
	B	P*	NR	P**	P
	C	P*	NR	F	F
Ketotifen	A	P*	NR	P**	P
	B	P*	NR	F	F
	C	P*	NR	P**	P
Metronidazole	A	P	NR	P**	P
	B	P	NR	F	F
	C	P	NR	P**	P
	D	P	NR	F	F
Alprażolam	A	P*	NR	P	P
	B	P*	NR	F	F
Ampicillin	A	P	NR	P	P
	B	P	NR	P	P
	C	P	NR	P	P
	D	P	NR	F	F
	E	P	NR	P	P

Table 4 (cont.)

Generic name	Brand	%LA pass/fail	Disintegration pass/fail	Dissolution pass/fail	Conclusion pass/fail
Glafenine	A	P*	NR	P**	P
	B	P*	NR	P**	P
	C	P*	NR	P**	P
Cotrimoxazole	A	P	NR	P	P
	B	P	NR	P	P
	C	F	NR	F	F
	D	F	NR	F	F
	E	F	NR	F	F

NR : Not required

P : Pass as compared to any specified monograph

P : Pass as compared to general recommended requirement : 90-110 %LA for ≤ 20 mg per tab or capsule; or 95-105 %LA for > 20 mg per tab or capsule*

*P** : Pass as compared to general recommended requirement (70% in 30 minutes)*

F : Fail

The criteria, "Pass" or "Fail" are based on comparison with the minimum requirement or limit of each specified monograph. Any failure parameter, at least one or more, led to the conclusion as "Fail" for each particular sample. In this study, the assay results, as indicated by the percent labelled amount (%LA), in most cases were shown to meet the acceptable limit, except for tablets of spironolactone and ranitidine whose active ingredient percentage was rejected in one commercial brand of each drug. In the recent compendial requirement of the USP XXII, the disintegration time limit is not specified for all tested items. However, statistically significant difference in disintegration time among different manufacturers were noted in some cases. Interestingly, the most crucial property in this study was the extent of dissolution where the failure to meet the requirement was found in tablets of paracetamol, cimetidine, ranitidine, ibuprofen, spironolactone, naproxen sodium, hydroxyzine, terfenadine, ketotifen, metronidazole, alprazolam, cotrimoxazole and capsules of danazol and ampicillin. In was demonstrated, however, that this property met the required specification for tablets of paracetamol, allopurinol, nitrazepam and glafenine.

Table 5 Rejected properties of tested drugs

	Failure	
	% Sample Tested (of all products)	%Drug Items
Weight variation	0	0
Content uniformity	0	0
%LA	6.45 (4/62)	11.76 (2/17)
Dissolution	33.87 (21/62)	82.35 (14/17)

Table 6 Conclusion for *in vitro* evaluation

	Pharmacopeial Specification	
	Accepted	Rejected
All tested samples	41/62 (66.13%)	21/62 (33.87%)
The number of tested items	3/17 (17.65%)	14/17 (82.35%)

As shown in Table 5, the failure rates, as of %drug items, were 2 out of 17 items (11.76%) and 14 out of 17 items (82.35%) for the %LA and the extent of dissolution at a specific time, respectively. In our program, there was a great variation in those tested parameters among different manufacturers for an identical generic drug. For those items, not all tested brands failed to satisfy the minimum criteria, particularly in this present study all innovator's brand names of all tested drugs met the required standard. However, the unsatisfied %LA, as of %tested samples of all products, was shown to be 4 out of 62 samples (6.45%) and the unaccepted dissolution outcome was 21 out of 62 samples (33.87%). All tested brands which passed the compendial standard with respect to dissolution included tablets of allopurinol, nitrazepam and glafenine. Moreover, statistically significant difference in the extent of dissolution was remarkably observed between some commercial brands and the innovator's for some drug products. The conclusion arised from the result of at least one parameter led to "Pass" or "Fail" as shown in Table 4 for each particular drug. Table 6 summarized the number and the percentage of tested items whose acceptance were 66.13 and 17.65, respectively, whereas the failure to meet the pharmacopeial specification was 33.87% and 82.35% respectively.

CONCLUSION

In our evaluation program of some commercially available drug products in the country, there are a certain number of drugs which failed to meet the pharmacopeial specification. All innovator's brand names of all tested drugs were, however, demonstrated to satisfy all minimum requirements. Among those unaccepted products, a parameter which mainly gives rise to the substandard quality is a dissolution property. It is recommended, based on the pharmacopeial specification, that for noninnovator's products, particularly for those locally manufactured, their critical qualities still need improvement, especially to enhance the dissolution property.

REFERENCE

1. TIMS. The Index of Medical Specialties. 1990; 19(1): 17, 21, 22, 24, 59, 62, 85-88, 109-115, 120-124, 148-9, 169-172, 190-197, 240-242.
2. The United States Pharmacopeia and the National Formulary XXII, Mack Printing Co, Easton, PA. 1990;1617.
3. The United States Pharmacopeia and the National Formulary XXI, Mack Publishing Co, Easton, PA. 1985: 1242.
4. The United States Pharmacopeia and the National Formulary XXII Mack Printing Co, Easton, PA. 1990;310.
5. Ibid., 1210
6. Ibid., 371
7. Ibid., 1273
8. Ibid. 380
9. Ibid., 675
10. Ibid,. 683
11. Ibid., 919
12. Ibid., 39
13. Ibid., 88
14. Ibid., 1294
15. Ibid., 14