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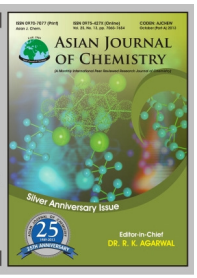

Determination on the Dissolution Rate of Doxepin Hydrochloride Tablets Produced by Different Manufacturers in China with Fiber-Optic Medicine Dissolution/Release Rate Process Test System

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The fiber-optic medicine dissolution/release rate process test system was adopted to investigate the *in vitro* dissolution rate curves of doxepin hydrochloride tablets on sale produced by nine different pharmaceutical factories in China. Furthermore, we compared the difference of the internal quality of these products and analyzed the controllability of quality of the existing dissolution rate method which provided effective method for drugs' quality control and the basis for establishment of dissolution rate method and standard. The paddle method was adopted, with a determination wavelength of 292 nm, temperature 37 ºC, rotating speed of 50 r min^{-1} and the time of detection was 90 min. In different dissolution mediums, the 5 mm fiber-optic probe was adopted to measure the dissolution rate curves of doxepin hydrochloride tablets. Although most of the products of the nine pharmaceutical factories were found to be in accord with the regulation of Chinese Pharmacopoeia 2010. There was great difference in these dissolution curves, indicating that there were great differences in the technological level among the nine pharmaceutical factories. The analytical method used was continuous and convenient and could be used to evaluate the difference of dissolution of solid preparation.

Key Words: Doxepin hydrochloride tablet, Fiber-optic dissolution rate.

INTRODUCTION

The doxepin hydrochloride is a tricyclic antidepressant drug. It is often used to cure the anxiety melancholia and neurotic depression[1,2]. At present, it is the mixture of moderate amount of the *cis*-isomer and *trans*-isomer clinically.

The research on the dissolution rate was focused on determining the dissolution rate of solid preparation. This is one of the most important technological indexes on the effectiveness of solid preparation. The fiber-optic sense technology was adopted in the fiber-optic medicine dissolution/release rate process test system. It could reflect the existing issues in the preparation's technology accurately. So it could be adopted for the research on the preparation's technology and quality standard.

EXPERIMENTAL

All reagents and spectroscopic solvents were provided by Nanchang University. The adopted fiber-optic medicine dissolution/release rate process test system apparatus was FOCSDT-601. The reference standard of doxepin hydrochloride was purchased from National Institutes for Food and drug control. We collected the doxepin hydrochloride tablets on sale produced in different manufacturers in China.

Blank test: We selected three dissolution medium solutions *i.e.*, (a) the hydrochloric acid with pH 1; (b) the pH 4 buffer solution consisting of ethylic acid and natrium aceticum; (c) pH 6.8 buffer solution of phosphate. The blank test was carried out in the FOCSDT-601 with the prepared water and the three dissolution medium solutions. The results showed that the dissolution medium solutions could not disturb the determination.

Selection of detected wavelength: Briefly, 0.0157 mg of doxepin hydrochloride reference standard was weighed accurately into a 100 mL measuring flask and water was added to scale. Then 50 mL of the solution was taken out accurately into a 250 mL measuring flask. It was added into the scale with water. The solution was regarded as the solution of the doxepin hydrochloride tablet dissolved completely. We also prepared the solution in the hydrochloric acid with pH 1.0; the pH 4.0 buffer solution consisting of ethylic acid and natrium aceticum; pH 6.8 buffer solution of phosphate. The four solutions

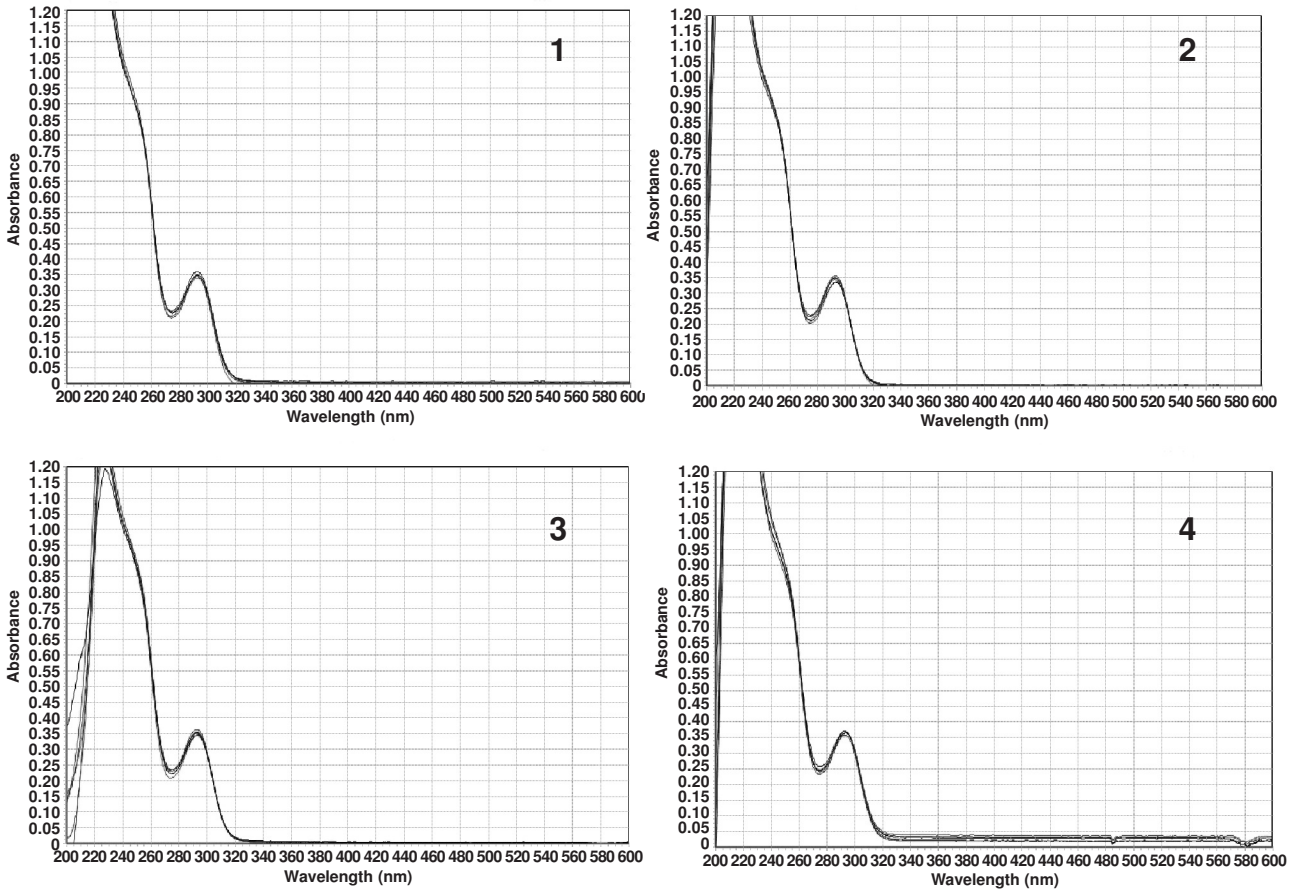

Fig. 1. Dissolution rate of doxepin hydrochloride reference standard in different dissolution mediums (1 was in water; 2 was hydrochloric acid with pH 1; 3 was the pH 4 buffer solution consisting of ethylic acid and natrium aceticum; 4 was pH 6.8 buffer solution of phosphate)

were tested in the FOCSDT-601. The specification of the probe was 5 mm and the volume of solvent was 900 mL. The solution with water was dissolved for 45 min, while the other three solutions were dissolved for 90 min. From the Fig. 1, the maximum wavelength was 292 nm. It was confirmed as the detected wavelength. The reference wavelength was 55 nm.

Selection of apparatus and rotation rate: The stirring basket method was adopted. The rotation rate was 100 rpm. The same batches of doxepin hydrochloride tablets produced by the same pharmaceutical factory were dissolved in the four different dissolution mediums earlier mentioned[3,4]. The results were shown in the Fig. 2.

Linear relation: The moderate amount of doxepin hydrochloride reference standard was taken out. After drying at 105 ºC for 4 h, 30.15 mg of doxepin hydrochloride reference standard was weighed accurately into a 100 mL measuring flask. It was added to the scale with de-aerated water and was regarded as the stock solution. Next, 2, 4, 6, 8, 10 and 12 mL of the stock solution were put into 100 mL measuring flasks. They were added to the scale with de-aerated water to a concentration of 19.4, 38.8, 58.2, 77.6, 97.0 and 116.4 %, respectively. These prepared solutions were analyzed in FOCSDT-601. The results are shown at Table-1 and Fig. 3.

RESULTS AND DISCUSSION

Methodological verification In present experiment of selecting apparatus and rotation rate, we found out that the obtained result of dissolution was much higher than the actual result because accessories were deposited in the groove of probe of fiber in the procession of dissolution. Hence the paddle method was adopted. The rotation rate was adjusted as 50 rpm. The same batches of doxepin hydrochloride tablets produced by the same pharmaceutical factory were dissolved in the four different dissolution mediums earlier mentioned and the results were shown in the Fig. 4. And there was a favorable linear relationship between the concentrations of doxepin hydrochloride and absorbance in the range of 0-120 % of concentrations of doxepin hydrochloride. In addition, when the results with fibre and results with UV method were compared, RSD was 1.2 %. This showed that there was no obvious difference between the results with fibre and results with UV method.

TABLE-1
OBTAINED DATA OF EXPERIMENT ON LINEAR RELATIONSHIP

X	19.4	38.8	58.2	77.6	97.0	116.4
Y	0.064563	0.131883	0.203893	0.282071	0.340434	0.40923

Determination on the doxepin hydrochloride tablets on sale in China: Using the analytical method aforementioned, we analyzed the stripping curve of doxepin hydrochloride tablets on sale produced by nine different pharmaceutical factories in China. We adopted the f2 gene method on evaluating the comparability of stripping curve of doxepin hydrochloride tablets on sale in China.

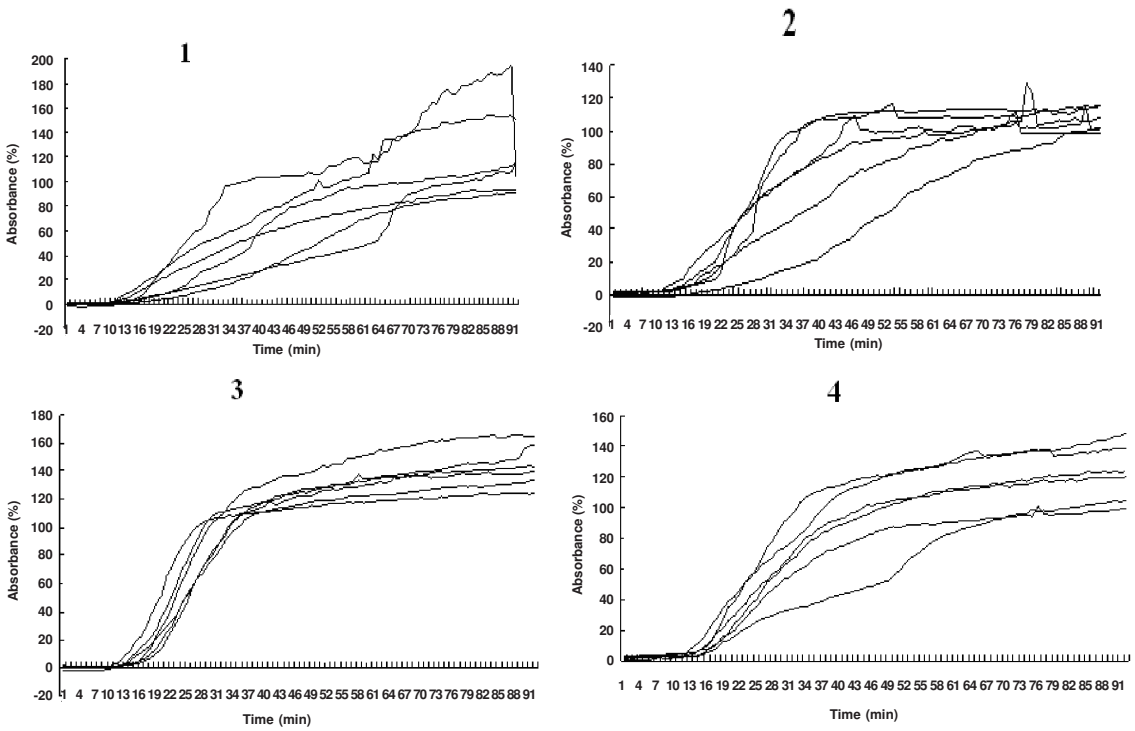

Fig. 2. Stripping curves of same batches of doxepin hydrochloride tablets in different dissolution mediums (1 was in water; 2 was hydrochloric acid with pH 1.0; 3 was the pH 4.0 buffer solution consisting of ethylic acid and natrium aceticum; 4 was pH 6.8 buffer solution of phosphate)

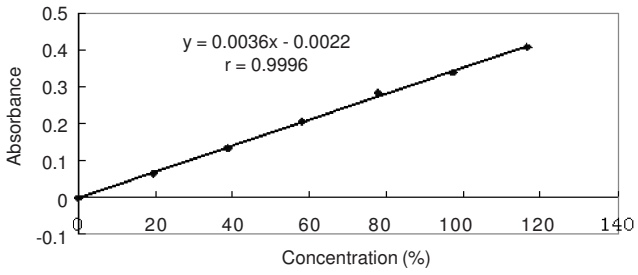

Fig. 3. Linear curve of doxepin hydrochloride

Comparison of stripping curve of the doxepin hydrochloride tablets produced by the same pharmaceutical factory in different dissolution mediums: We determined the stripping curve of the doxepin hydrochloride tablet produced by the same pharmaceutical factory in different dissolution mediums. The tablets were collected from nine pharmaceutical factories. The results are shown at Tables 2-10 and Fig. 5. Besides, we named the nine different pharmaceutical factories as factory 1, 2, 3, 4, 5, 6, 7, 8 and 9.

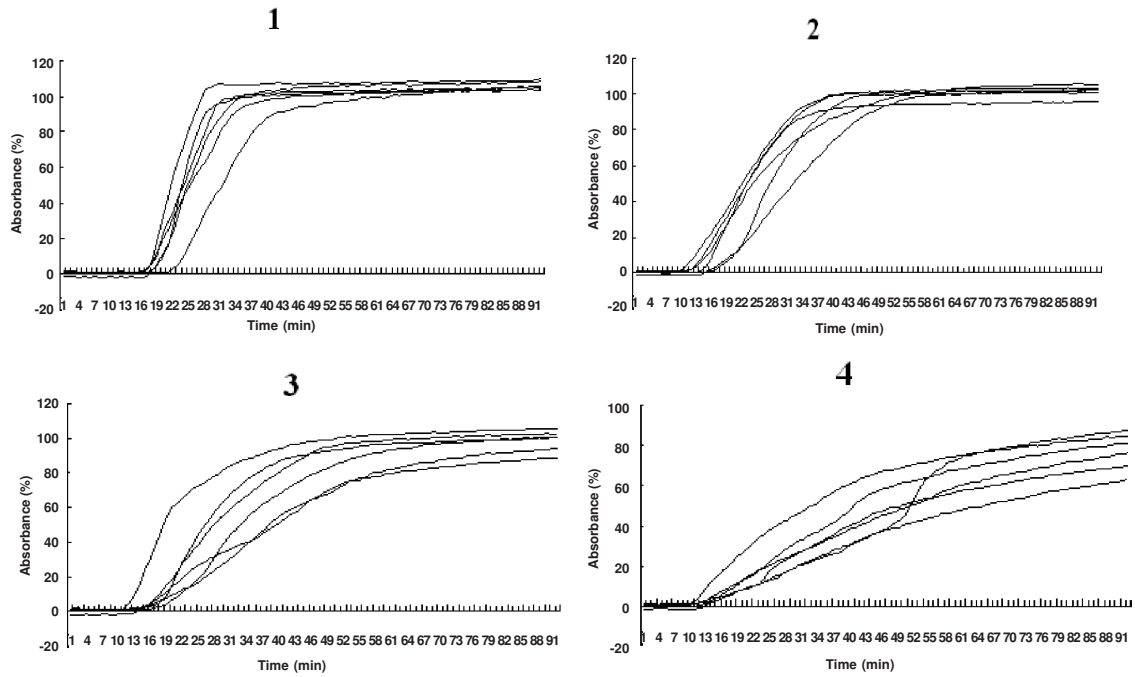

Fig. 4. Results obtained by the paddle method (1 was in water; 2 was hydrochloric acid with pH 1.0; 3 was the pH 4.0 buffer solution consisting of ethylic acid and natrium aceticum; 4 was pH 6.8 buffer solution of phosphate)

TABLE-2
DETERMINATION ON THE DISSOLUTION OF DOXEPIN HYDROCHLORIDE TABLET FROM FACTORY 1

Reference	pH 1	f2	Conclusion	AV	Conclusion
Tested	water	-751.1	Dissimilar	53.6	Dissimilar
Tested	pH 4	-751.1	Dissimilar	60.0	Dissimilar
Tested	pH 6.8	-748.6	Dissimilar	41.7	Dissimilar

TABLE-3
DETERMINATION ON THE DISSOLUTION OF DOXEPIN HYDROCHLORIDE TABLET FROM FACTORY 2

Reference	pH 4	f2	Conclusion	AV	Conclusion
Tested	water	76.7	similar	36.6	Dissimilar
Tested	pH 1	76.7	similar	37.7	Dissimilar
Tested	pH 6.8	47.6	dissimilar	54.4	Dissimilar

TABLE-4
DETERMINATION ON THE DISSOLUTION OF DOXEPIN HYDROCHLORIDE TABLET FROM FACTORY 3

Reference	water	f2	Conclusion	AV	Conclusion
Tested	pH 1	–	–	38.5	Dissimilar
Tested	pH 4	–	–	49.6	Dissimilar
Tested	pH 6.8	–	–	35.8	Dissimilar

TABLE-5
DETERMINATION ON THE DISSOLUTION OF DOXEPIN HYDROCHLORIDE TABLET FROM FACTORY 4

Reference	pH 4	f2	Conclusion	AV	Conclusion
Tested	Water	73.1	Similar	62.7	Dissimilar
Tested	pH 1	61.7	Similar	84.6	Dissimilar
Tested	pH 6.8	58.3	Similar	50.3	Dissimilar

TABLE-6
DETERMINATION ON THE DISSOLUTION OF DOXEPIN HYDROCHLORIDE TABLET FROM FACTORY 5

Reference	pH 1	f2	Conclusion	AV	Conclusion
Tested	Water	–	–	62.9	Dissimilar
Tested	pH 4	76.3	Similar	55.7	Dissimilar
Tested	pH 6.8	–	–	62.8	Dissimilar

TABLE-7
DETERMINATION ON THE DISSOLUTION OF DOXEPIN HYDROCHLORIDE TABLET FROM FACTORY 6

Reference	water	f2	Conclusion	AV	Conclusion
Tested	pH 1	26.6	Dissimilar	69.4	Dissimilar
Tested	pH 4	26.8	Dissimilar	77.5	Dissimilar
Tested	pH 6.8	26.4	Dissimilar	90.0	Dissimilar

TABLE-8
DETERMINATION ON THE DISSOLUTION OF DOXEPIN HYDROCHLORIDE TABLET FROM FACTORY 7

Reference	pH4	f2	Conclusion	AV	Conclusion
Tested	Water	75.7	Similar	58.7	Dissimilar
Tested	pH 1	78.2	Similar	60.4	Dissimilar
Tested	pH 6.8	68.0	Similar	52.0	Dissimilar

TABLE-9
DETERMINATION ON THE DISSOLUTION OF DOXEPIN HYDROCHLORIDE TABLET FROM FACTORY 8

Reference	Water	f2	Conclusion	AV	Conclusion
Tested	pH 1	72.2	Similar	41.6	Dissimilar
Tested	pH 4	87.4	Similar	36.0	Dissimilar
Tested	pH6.8	92.5	Similar	38.1	Dissimilar

TABLE-10
DETERMINATION ON THE DISSOLUTION OF DOXEPIN HYDROCHLORIDE TABLET FROM FACTORY 9

Reference	Water	f2	Conclusion	AV	Conclusion
Tested	pH 1	52.7	Similar	58.4	Dissimilar
Tested	pH 4	51.3	Similar	61.1	Dissimilar
Tested	pH6.8	48.1	Dissimilar	81.6	Dissimilar

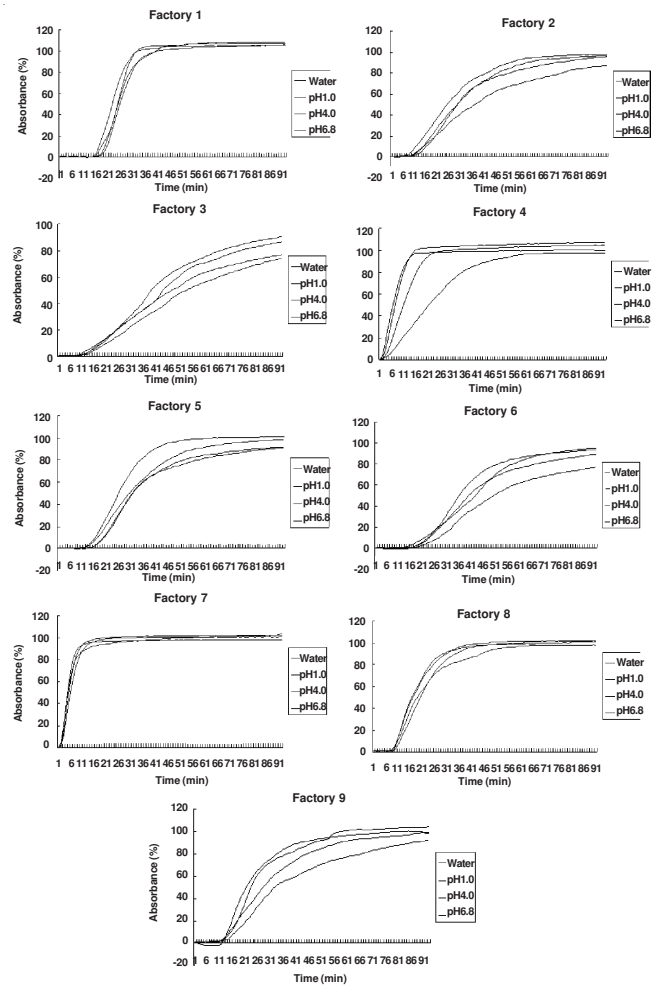

Fig. 5. Stripping curve of the doxepin hydrochloride tablet produced by the different pharmaceutical factories in different dissolution medium

Comparison of stripping curve of the doxepin hydrochloride tablets produced by different pharmaceutical factories in the same dissolution medium: From the results obtained above, we found out that there was little difference between the doxepin hydrochloride tablets produced by factory 4 and tablet produced by factory 7. Besides, their stripping curves were representative. Hence, the hydrochloride tablets produced by factory 4 and factory 7 were selected as reference preparations. The hydrochloride tablets produced by the other factories were regarded as tested preparations. The results were shown in Tables 11-14 and Figs. 6-9.

Conclusion

From the comparison of stripping curves, we found out that stripping curve of doxepin hydrochloride tablets produced by factory 7 was the closest to the standard stripping curve and it could be released in different dissolution mediums

TABLE-11
COMPARISON OF STRIPPING CURVE IN WATER

Reference	Factory 4	f2	Conclusion	AV	Conclusion
Tested	Factory 1	74.3	Similar	111.4	Dissimilar
Tested	Factory 2	58.1	Similar	108.1	Dissimilar
Tested	Factory 3	46.2	Dissimilar	109.3	Dissimilar
Tested	Factory 5	76.2	Similar	63.1	Dissimilar
Tested	Factory 6	–	–	111.3	Dissimilar
Tested	Factory 7	–	–	111.6	Dissimilar
Tested	Factory 8	90.8	Similar	105.4	Dissimilar
Tested	Factory 9	63.4	Similar	108.5	Dissimilar
Reference	Factory 7	f2	Conclusion	AV	Conclusion
Tested	Factory 1	94.7	Similar	60.6	Dissimilar
Tested	Factory 2	51.8	Similar	61.9	Dissimilar
Tested	Factory 3	42.3	Dissimilar	68.0	Dissimilar
Tested	Factory 4	–	–	70.9	Dissimilar
Tested	Factory 5	–	–	71.3	Dissimilar
Tested	Factory 6	72.6	Similar	53.3	Dissimilar
Tested	Factory 8	69.5	Similar	54.7	Dissimilar
Tested	Factory 9	55.0	Similar	59.4	Dissimilar

TABLE-12
COMPARISON OF STRIPPING
CURVE IN pH 1.0 HYDROCHLORIC ACID

Reference	Factory 4	f2	Conclusion	AV	Conclusion
Tested	Factory 1	72.8	Similar	98.7	Dissimilar
Tested	Factory 2	55.8	Similar	95.5	Dissimilar
Tested	Factory 3	–	–	95.5	Dissimilar
Tested	Factory 5	58.1	Similar	84.6	Dissimilar
Tested	Factory 6	75.2	Similar	97.4	Dissimilar
Tested	Factory 7	91.4	Similar	98.1	Dissimilar
Tested	Factory 8	68.5	Similar	90.7	Dissimilar
Tested	Factory 9	59.7	Similar	94.5	Dissimilar
Reference	Factory 7	f2	Conclusion	AV	Conclusion
Tested	Factory 1	49.2	Dissimilar	45.8	Dissimilar
Tested	Factory 2	72.0	Similar	46.7	Dissimilar
Tested	Factory 3	–	–	60.9	Dissimilar
Tested	Factory 4	68.9	Similar	39.3	Dissimilar
Tested	Factory 5	87.0	Similar	57.6	
Tested	Factory 6	59.1	Similar	65.7	Dissimilar
Tested	Factory 8	97.0	Similar	37.2	Dissimilar
Tested	Factory 9	72.8	Similar	42.0	Dissimilar

TABLE-13
COMPARISON OF STRIPPING
CURVE IN pH 4.0 HYDROCHLORIC ACID

Reference	Factory 4	f2	Conclusion	AV	Conclusion
Tested	Factory 1	51.6	Similar	99.0	dissimilar
Tested	Factory 2	57.5	Similar	98.1	dissimilar
Tested	Factory 3	–	–	98.9	dissimilar
Tested	Factory 5	84.9	Similar	38.4	dissimilar
Tested	Factory 6	100.0	Similar	99.0	dissimilar
Tested	Factory 7	–	–	99.1	dissimilar
Tested	Factory 8	74.9	Similar	97.3	dissimilar
Tested	Factory 9	64.8	Similar	97.8	dissimilar
Reference	Factory 7	f2	Conclusion	AV	Conclusion
Tested	Factory 1	56.4	Similar	89.3	dissimilar
Tested	Factory 2	53.9	Similar	88.1	dissimilar
Tested	Factory 3	–	–	88.7	dissimilar
Tested	Factory 4	83.9	Similar	90.9	dissimilar
Tested	Factory 5	–	–	89.3	dissimilar
Tested	Factory 6	84.9	Similar	30.1	dissimilar
Tested	Factory 8	89.8	Similar	79.9	dissimilar
Tested	Factory 9	73.7	Similar	86.8	dissimilar

TABLE-14
COMPARISON OF STRIPPING CURVE IN
pH 6.8 BUFFER SOLUTION OF PHOSPHATE

Reference	Factory 4	f2	Conclusion	AV	Conclusion
Tested	Factory 1	18.6	dissimilar	95.9	dissimilar
Tested	Factory 2	39.8	dissimilar	95.8	dissimilar
Tested	Factory 3	–	–	95.3	dissimilar
Tested	Factory 5	63.6	similar	36.1	dissimilar
Tested	Factory 6	–	–	95.4	dissimilar
Tested	Factory 7	1.2	dissimilar	96.4	dissimilar
Tested	Factory 8	71.3	similar	93.1	dissimilar
Tested	Factory 9	–	–	95.8	dissimilar
Reference	Factory 7	f2	Conclusion	AV	Conclusion
Tested	Factory 1	37.7	dissimilar	98.5	dissimilar
Tested	Factory 2	25.4	dissimilar	94.1	dissimilar
Tested	Factory 3	–	–	96.4	dissimilar
Tested	Factory 4	–	–	98.0	dissimilar
Tested	Factory 5	20.3	dissimilar	99.5	dissimilar
Tested	Factory 6	71.8	similar	57.2	dissimilar
Tested	Factory 8	56.6	similar	81.7	dissimilar
Tested	Factory 9	20.5	dissimilar	96.9	dissimilar

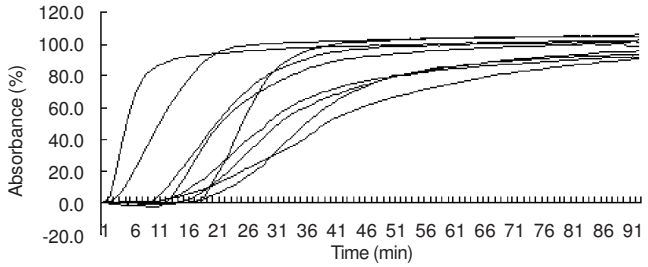

Fig. 6. Comparison of stripping curve in water

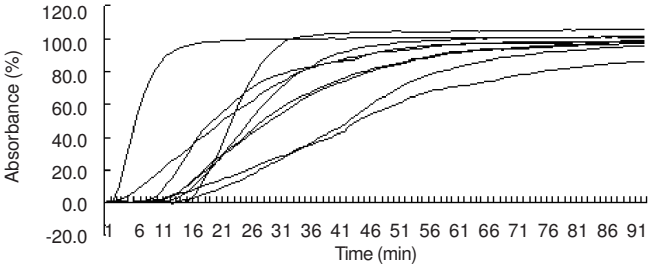

Fig. 7. Comparison of stripping curve in pH 1 hydrochloric acid

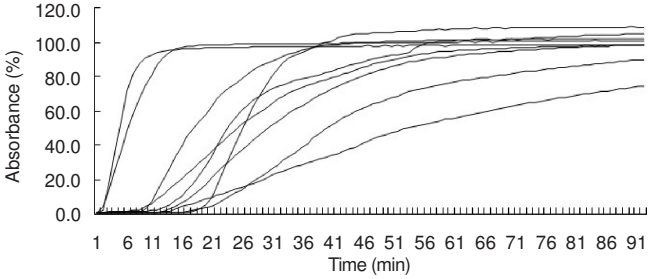

Fig. 8. Comparison of stripping curve in pH 4 hydrochloric acid

equably and well. This indicated that it could be adopted on patients with different body constitution well. The second closest to the standard stripping curve was the stripping curve of doxepin hydrochloride tablets produced by factory 4. The dosage form of the two factories was film coated tablet, while the dosage form of the other factories was sugar coated tablet. So we found out the film coated tablet was much better than

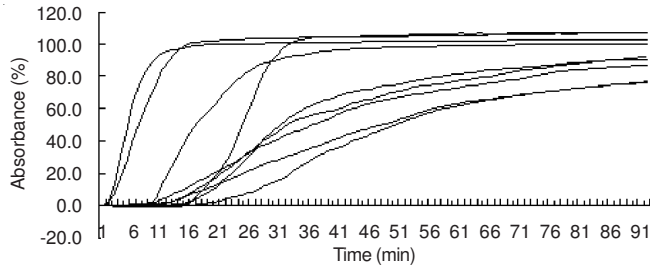

Fig. 9. Comparison of stripping curve in pH 6.8 buffer solution of phosphate

traditional dosage form as sugar coated tablet. Our results therefore established an exoteric and accurate analytical method on evaluating inherent quality of doxepin hydrochloride tablets.

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REFERENCES

1. M.E. Széliga, M.C. Lamas, D.A. Lillo and C. Bregni, *Boll. Chim. Farm.*, **136**, 527 (1997).
2. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms (1997).
3. C. Gido, P. Langguth and E. Mutschler, *Pharm. Res.*, **11**, 800 (1994).
4. C. Gido, P. Langguth, J. Kreuter, G. Winter, H. Woog and E. Mutschler, *Pharmazie*, **48**, 764 (1993).