



Effect of pH on the Dissolution of Erythromycin Stearate Tablets Available in Local Market

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Accepted on: 03-08-2013; Finalized on: 30-09-2013.

ABSTRACT

Dissolution, being an important process for transfer of solid substance into solution, is affected by pH changes that effects ionization of drug, consequently *in-vivo* behavior of the drug is altered. We investigated the effect of a slight change in pH on the dissolution behavior of erythromycin stearate tablets and its dissolution kinetics. Dissolution profiles of erythromycin tablets were later compared with some of the brands available in the local market. Six tablets of innovator product were individually tested at pH 6.8, 7.0 and 7.2 phosphate buffers using USP 28 / NF 23 (2005) guidelines. The cumulative mean dissolution behavior of innovator erythromycin stearate tablets at different pH showed that the drug release at pH 6.8 and 7.0 is almost the same at all sampling times except at 120 minutes where pH 7.0 appears to be superior as compared to pH 6.8. In case of pH 7.2, more drug was release from 15-60 minutes sampling time as compare to pHs 6.8 and 7.0 but from 90 minutes onwards up to 120 minutes, a slower drug release was obtained. Statistical analysis revealed a significant difference ($\alpha=0.05$) among the dissolution profiles of erythromycin stearate innovator product in phosphate buffers (15-120 minutes) ($p<0.05$) but a non-significant difference were found at 60 and 75 minutes ($p>0.05$). It appears that higher pH might facilitate initial quicker dissolution and consequently quicker absorption and bioavailability of innovator erythromycin stearate tablets and vice versa. Dissolution data when subjected to various kinetic models, showed that the erythromycin stearate followed the Weibull model at pH 6.8 and 7.0 that indicates a linear relationship exists at these pH values between the logarithm of the dissolved amount of drug versus logarithm of time plot while the Higuchi model appears to be suitable at pH 7.2 that indicates drug release is a diffusion process at pH 7.2. Using a model independent approach, none of the selected brands showed similarity with the innovator. Close monitoring of commercial brands from time to time is thus mandatory to maintain quality of available brands.

Keywords: Dissolution, erythromycin stearate, kinetics, model independent.

INTRODUCTION

Although various dosage forms are available in the market, tablets share more than 80% of the market¹. Tablets are a solid dosage form intended for oral administration of drugs. It offers numerous advantages to the manufacturer, physician, pharmacist and patient. One problem associated with a compressed tablet is that after ingestion, it must be disintegrated i.e; converted into smaller particles, and these particles should be dissolved into solution (dissolution) to be absorbed by gastrointestinal mucosa (Fig. 1).

Physicochemically, "Dissolution is the process by which a solid substance enters the solvent phase to yield a solution"³. Dissolution plays a central role in all phases of drug development (Fig. 1). In some cases, *in-vitro* dissolution testing may be used in lieu of *in-vivo* bioequivalence studies⁴.

Dissolution is a complex process and various factors affect the dissolution of drugs. These factors include: agitation, temperature, dissolution medium, pH of dissolution medium, surface tension and viscosity of the dissolution medium⁵. Since the drug is generally absorbed in a unionized form⁶, pH of the dissolution media is controlled carefully during the development of a dissolution method. The pH of the medium effects ionization of the

drug which in turn affects the *in-vivo* behavior of the drug.

"Erythromycin Stearate is the stearic acid salt of Erythromycin, with an excess of stearic acid; the percentages of erythromycin A, erythromycin B, and erythromycin C is not less than 55.0 percent, calculated on the anhydrous basis"⁷. In an acidic medium as in the stomach, erythromycin dissolution occurs rapidly, whereas in neutral or alkaline pH the drug salt is relatively stable. Consequently, erythromycin tablets are enteric coated or contained a less water-soluble erythromycin salt to protect against rapid acid dissolution in the stomach. The dissolution rate of erythromycin powder varied from 100% dissolved in 1 hour to less than 40%, depending of the pH of the medium. The slow dissolving active pharmaceutical ingredient also results in slow-dissolving drug products. Therefore, powdered raw drug material dissolution is a very useful *in-vitro* method for predicting the bioavailability problems of the erythromycin product in the body⁸. Erythromycin is used in the treatment of severe campylobacter enteritis, chancroid, diphtheria, legionnaires' disease and other *Legionell* infections, neonatal conjunctivitis, pertussis, respiratory-tract infections, trench fever, combined with neomycin, for the prophylaxis of surgical infection in patients undergoing bowel surgery etc⁹.



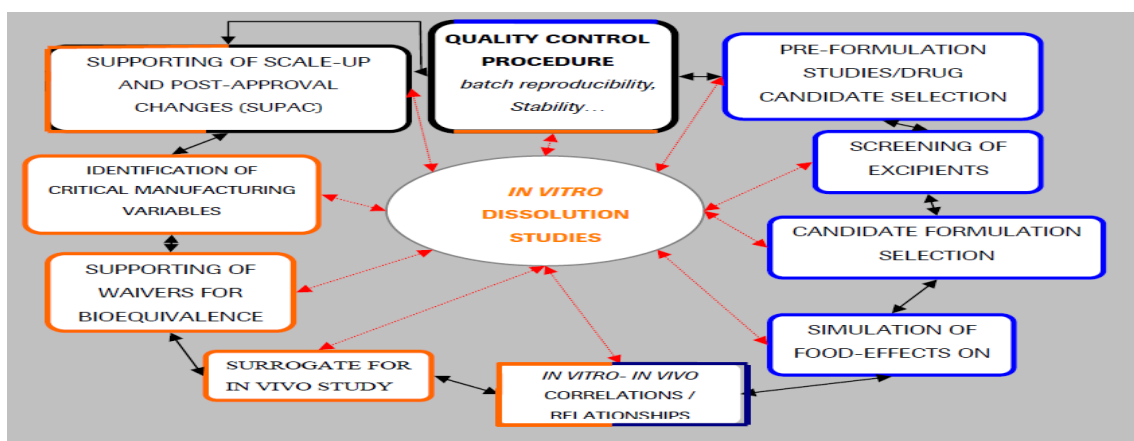


Figure 1: The central role of dissolution testing (early phases of development shaped in blue, late phases in orange, market in black; dotted red arrows show the interplay of dissolution and black arrows show the interaction between the different development phases)².

According to Biopharmaceutics Classification System (BCS), it belongs to class 4 drugs that is low solubility and low permeability and is not eligible for a biowaiver¹⁰. To the best of our knowledge, no work is available in the open literature which studied a slight change in pH on the dissolution behavior of erythromycin stearate tablets. Therefore, the present work was designed with the following objectives:

- To study the effect of a slight change in pH on the dissolution of innovator erythromycin stearate tablets.
- To study dissolution kinetics of innovator erythromycin stearate tablets at different pH values.
- To compare the dissolution profile of a erythromycin tablet (innovator) with two randomly selected brands available in the local market.

MATERIALS AND METHODS

Apparatus

Dissolution apparatus (ERWEKA, GMBH, Germany), spectrophotometer (UV-150-02, Shimadzu, Japan), water bath (Gallenkamp, Thermostirrer 95, England), pH meter (Jenway, UK), balance (Metler Toledo, Switzerland), glass ware (All Pyrex, England).

Reagents and standards

Erythromycin stearate reference standard was kindly gifted by Abbott Laboratories, Ltd., Karachi, Pakistan. Other chemicals such as potassium dihydrogen phosphate, sodium hydroxide, sulfuric acid and methanol were purchased from Merck, Germany and was used as such.

Erythromycin Tablets

Erythromycin stearate 250 mg tablets (innovator) manufactured by Abbott laboratories, Pakistan Ltd., and two commercially available brands A and B in the same strength were randomly purchased from the local market of Karachi.

Dissolution Medium

Medium 1: 0.05 M phosphate buffer, pH 6.8; volume 900 mL

Medium 2: 0.05 M phosphate buffer, pH 7.0; volume 900 mL

Medium 3: 0.05 M phosphate buffer, pH 7.2; volume 900 mL

Preparation of dissolution Mediums

Phosphate buffers 0.05 M (pH: 6.8, 7.0 and 7.2) were prepared according to USP 28 / NF 23 (2005) guidelines⁷.

Procedure

Dissolution test of erythromycin stearate innovator product was carried out using apparatus 2 (paddle type) with 100 rpm as recommended by the USP 28 / NF 23 2005 using 0.05 M phosphate buffers at pH 6.8, 7.0 and 7.2 respectively. Six tablets were individually tested at above mentioned pH maintained at 37 ± 0.5 °C. 10 mL samples were drawn at 15, 30, 45, 60, 75, 90, 105 and 120 minutes and replaced immediately with the same medium to maintain a constant volume of dissolution medium. Samples drawn were immediately filtered, extracted and analyzed on a UV spectrometer at 236 nm wavelength. Dissolution studies of the two selected commercial brands were carried out only in phosphate buffer pH 6.8 as recommended by USP 28 and the same sampling times and procedure for extraction was followed as described for the innovator product (Reference). Briefly: 5 mL portions of working standard solution were transferred to two 25mL volumetric flasks, one served as a blank. Similarly 5mL portions of the test solution were transferred to two 25 mL volumetric flasks, one of which served as a blank for that test solution. To each of the flask designated as a blank, 2 mL of 0.5 N sulfuric acid was added and to the remaining flasks 2 mL of water was added. After standing for 5 minutes with intermittent swirling, 15mL of 0.25 N sodium hydroxide was added to all flasks, diluted with dissolution medium to volume (25 mL) and mixed. The flasks were then heated in a water bath at 60 ± 0.5 °C for 5 minutes and allowed to cool to room temperature. The absorbance of each solution was determined by using UV spectrometer

at 236 nm. The amount of erythromycin $C_{37}H_{67}NO_{13}$ dissolved was determined from the test solution in comparison with the solution obtained from the working standard solution.

RESULTS AND DISCUSSION

A slight change in pH, dissolution kinetics and comparative dissolution profiles using a model independent approach were studied in the present work. The selected model drug was erythromycin stearate which has a pH-dependent stability profile⁸.

Six tablets of innovator were individually tested at pH 6.8, 7.0 and 7.2 in phosphate buffer, sampled at various time intervals and analyzed by UV spectrometer at 236 nm. Final calculation was performed to determine drug release at different time intervals followed by one way ANOVA (Microsoft Excel, 2007) at 0.05 level of significance and dissolution kinetics of erythromycin stearate at various pHs. Dissolution of selected brands of erythromycin stearate was carried out in pH 6.8 phosphate buffer and the results were compared with the innovator at the same pH value. Fig 2-4 shows the dissolution behavior of innovator erythromycin stearate tablets in phosphate buffer at pH 6.8, 7.0 and 7.2 respectively while Fig 5 presents comparative dissolution (Mean \pm SEM) profile of innovator erythromycin stearate tablets at different pH values studied.

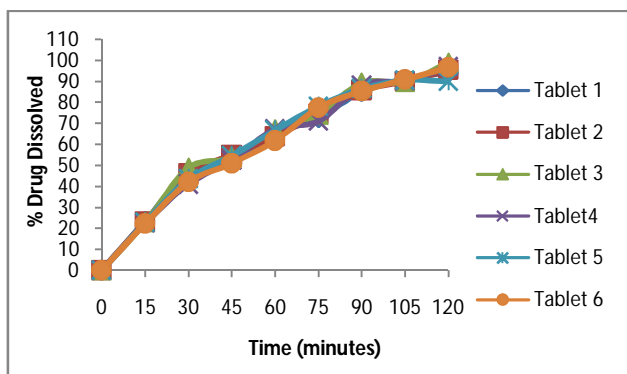


Figure 2: Dissolution profile of innovator erythromycin stearate 250 mg tablets in phosphate buffer (pH=6.8), n=6 tablets

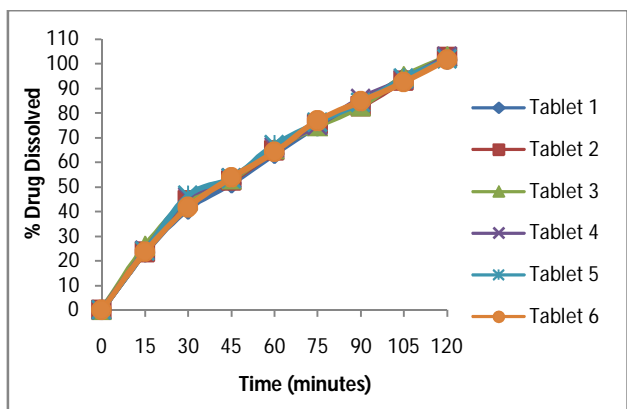


Figure 3: Dissolution profile of innovator erythromycin stearate 250 mg tablets in phosphate buffer (pH=7.0), n=6 tablets

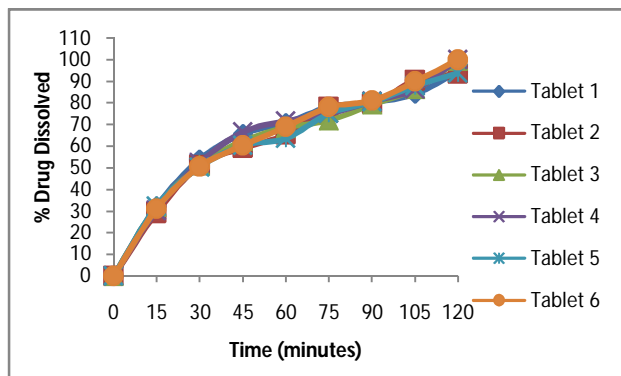


Figure 4: Dissolution profile of innovator erythromycin stearate 250 mg tablets in phosphate buffer (pH=7.2), n=6 tablets

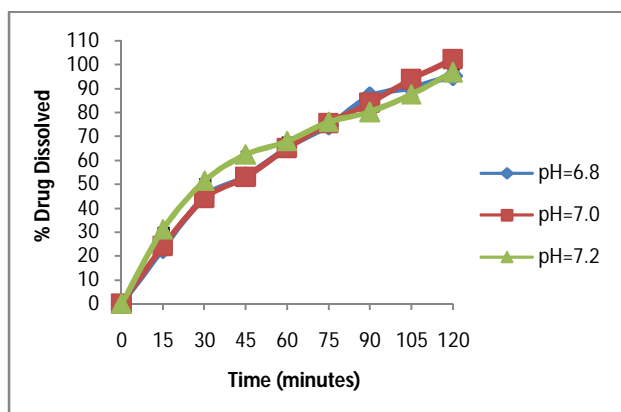


Figure 5: A comparison of cumulative percent dissolution profile of innovator erythromycin stearate 250 mg tablets in phosphate buffer (pH=6.8, 7.0 and 7.2) (n=6 tablets; Mean \pm SEM)

At pH 6.8, the amount of drug release at 15 and 105 minutes were approximately same (Mean \pm SEM : 22.92 \pm 0.15 and 90.48 \pm 0.21 respectively) while in samples drawn at 30, 45, 60, 75 and 90 minutes, a slight change in drug release were obtained among the innovator tested tablets. However at 120 minutes drug release likewise 15 and 105 minutes is almost same (Mean \pm SEM : 95.35 \pm 1.24) except tablet number five which showed at 90 minutes already complete dissolution.

At pH 7.0, more or less a similar release pattern was found as that of pH 6.8, but in this case more than 100% of the drug was released at 120 minutes sampling time resulting superimposability of all the curves at all sampling times except at 30 minutes (Mean \pm SEM : 44.09 \pm 0.91) which showed a slight change in drug release among the innovator tested tablets.

At pH 7.2, a greater variation in drug release among the innovator tested tablets were observed. Only at 15 and 90 minutes (Mean \pm SEM: 31.12 \pm 0.51 and 80.22 \pm 0.29 respectively) and to some extent 30 minutes (Mean \pm SEM : 51.53 \pm 0.55), the curves are superimposable while for the rest of the time intervals (45, 60, 75, 105 and 120 minutes), variability in drug release was evident (Fig. 4).

The cumulative mean dissolution behavior of innovator erythromycin stearate tablets at different pHs showed

that the drug release at pH 6.8 and 7.0 is almost same at all sampling time except at 120 minutes where pH 7.0 appears to be superior as compare to pH 6.8 (Fig. 5). At pH 7.0 the maximum is reached somewhat later than at pH 6.8. In case of pH 7.2, greater drug release were found at 15, 30, 45 and 60 minutes time intervals as compared to pHs 6.8 and 7.0 but from 90 minutes onwards up to 120 minutes, a slower drug release was obtained (Fig 5). However, at 60 and 75 minutes sampling interval, erythromycin stearate tablets tested at different pH values showed a similar drug release pattern (Fig. 5). One way ANOVA at 0.05 level of significance detected a significant difference among the dissolution profiles of erythromycin stearate innovator products in phosphate buffer (pH: 6.8, 7.0 and 7.2) at 15, 30, 45, 90, 105 and 120 minutes time intervals ($p < 0.05$) but a non-significant difference were detected at 60 and 75 minutes time intervals ($p > 0.05$).

In the present study, it appears that erythromycin dissolution increases with an increase in pH till 75 minutes. After 75 minutes onwards, a decrease in its dissolution of the remaining erythromycin was observed. It means that higher pH might facilitate quick dissolution and consequently quicker absorption of this drug and vice versa.

The combined effects of pH and surfactant on the dissolution of piroxicam was studied by Jinno *et al*¹¹. The intrinsic dissolution rate of piroxicam was measured in the pH range from 4.0 to 7.8 with 0%, 0.5%, and 2.0% sodium lauryl sulfate. The model was found to be useful in predicting the dissolution of an ionizable water insoluble drug as a function of pH, surfactant and for *in vitro-in vivo* correlations.

The effect of pH on *in vitro* dissolution of sulphonylurea preparations and mechanism of antacid-sulphonylurea interactions were studied by Lehto *et al*¹². One tablet of each sulphonylurea preparation was placed in a dissolution chamber containing dissolution medium at pH 2, pH 6 or pH 9. Samples were drawn at specified time intervals. The amount of glibenclamide dissolved from the non-micronized formulation within 2 h was 1.2, 4.5 and 76% at pH 2, pH 6 and pH 9, respectively and from micronized formulation was 21, 29 and 100%. In case of glipizide, the amount dissolved within 2 h at pH 2, pH 6 and pH 9 was 3.9, 24 and 92%, respectively. It was concluded that the high pH of the gastric contents may be responsible for this interactions. In 1983 Carlson *et al*¹³ examined the effect of pH on the disintegration and dissolution of ketoconazole tablets. 900 ml each of the five different buffer solutions (pH 2 to 6) was added in a basket dissolution device stirred at 500 rpm at 37°C for 60 minutes. One 200-mg ketoconazole tablet was added to dissolution medium. Samples were drawn at specified time intervals and analyzed spectrometrically. Higher dissolution rates of ketoconazole were found at pH 2 and 3, (> than 85% complete after five minutes) and slower dissolution was found at higher pH.

The dissolution data in various pH media is useful in predicting the bioavailability of the drug product. Likewise the work of Lehto *et al*¹² on sulphonylurea preparations, we in the present study also found greater dissolution rate of erythromycin stearate tablets at high pH value (pH 7.2) but this appeared only at initial time points as compare to pH 6.8 and 7 and later a slower release of the drug was obtained. Conversely to our study, Carlson *et al*¹³ in case of ketoconazole tablets found lower dissolution rate at high pH. This might be due to the physicochemical characteristics of active ingredient and the dissolution medium employed in these studies. However, in the present work, the amount of drug released at 120 minutes using different pH media meets USP 28 / NF 23 (2005)⁷ dissolution specifications for erythromycin stearate tablets, that is not less than 75% (Q) of the labeled amount of erythromycin stearate must be dissolved in 120 minutes.

Dissolution data of erythromycin was then applied to first order, zero order, Hixon-Crowell, Higuchi, Weibull and logistic¹⁴. It is evident from Table 1 that Weibull gave highest determination coefficient at pH 6.8 and 7.0. This indicates a complex release mechanism with an S-shaped curve at pH 6.8 and 7.0 respectively. But Higuchi appears to be suitable for describing dissolution kinetics of erythromycin at pH 7.2 which indicates that release process is diffusion controlled at higher pH.

Table 1: Kinetic parameters calculated for innovator erythromycin stearate tablets at different pH values

		pH		
		6.8	7.0	7.2
First order	RMSE	3.8213	5.8367	3.9974
	K ₁	0.019	0.020	0.021
	r ²	0.9770	0.9513	0.9637
Zero order	RMSE	11.4089	10.0180	16.0410
	K ₀	0.922	0.945	0.929
	r ²	0.7958	0.8564	0.4150
Hixon-Crowell	RMSE	2.4867	3.8410	6.3041
	KHC	0.005	0.005	0.006
	r ²	0.9902	0.9789	0.9097
Higuchi	RMSE	4.9138	5.4723	2.6230
	kH	8.589	8.763	8.754
	r ²	0.9619	0.9572	0.9844
Weibull	RMSE	2.8830	3.9255	3.7231
	β	1.772	2.973	1.117
	r ²	0.9906	0.9843	0.9773
Logistic	RMSE	5.5084	7.7131	4.7856
	β	3.911	4.086	3.147
	r ²	0.9590	0.9271	0.9554

RMSE: Root mean squared error (it determines the width of confidence intervals for predictions); K: rate constant, r²: coefficient of determination, β; Shape parameter

Finally when dissolution data of innovator product was compared with two commercial brands (A and B) using model independent methods as described by Moore and Flanner¹⁵, none of the selected brands showed similarity with the innovator (Table 2). This might be due to changes in sources of active drug, excipients utilized and

the manufacturing process. However, failure of *in vitro* dissolution does not mean that the drug will also behave similarly in the *in vivo* environment. This dissimilarity in dissolution profiles also indicates that monitoring of commercial brands from time to time is mandatory to maintain quality attributes of the available brands.

Table 2: Difference (f1) and similarity (f2) factors for reference versus test products

Model independent approach	Acceptance Criteria (Range)	Commercial Brand A	Commercial Brand B	Decision
f1	0-15	20.80	38.85	Rejected
f2	50-100	38.62	27.82	Rejected

CONCLUSION

From the present study, it is evident that a slight change in pH might affect dissolution kinetics and hence *in-vivo* performance of the drug. Further, it is also necessary to compare innovator with the commercial brands to monitor their quality.

Acknowledgements: The Principal author is very grateful to Abbott Laboratories, Pakistan Ltd for providing erythromycin stearate reference standard and providing assistance throughout the present research project and for Mr. Salman Mehmood, University of Karachi for providing excellent assistance in the completion of this manuscript.

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Source of Support: Nil, Conflict of Interest: None.

