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DEVELOPMENT OF DISCRIMINATIVE DISSOLUTION MEDIA FOR MARKETED METOPROLOL SUCCINATE EXTENDED RELEASE TABLETS

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ABSTRACT

The present study was undertaken to assess the interchangeability of the various ER metoprolol succinate dosage forms on the basis of their in vitro dissolution characteristics with three commercial SR brands, as it is a cardioselective beta blocker which has been classified as a class I substance according to the BCS [1], meaning that it is highly soluble and highly permeable at a strength of 50 mg . Medias included in dissolution procedure are 0.1 N HCl (pH 1.2), acetate buffer (pH 4.5), distilled water (pH 7.0), and phosphate buffer (pH 6.8) were evaluated, as the drug is readily and completely absorbed throughout the whole intestinal tract [2-4] but is subjected to extensive firstpass metabolism resulting in incomplete bioavailability (about 50%) depending on this intention this indiscriminative study has been taking place for the development of futher technology in formulation of Metaprolol succinate.

Keywords: Metaprolol succinate,discriminative dissolution,extended release tablets.

INTRODUCTION

Drug absorption is resoluted by the release of API at the site from its dosage form,dissolution under specific considerations and the permeability of the drug across the biological membrane. Based on this, in vitro dissolution may be critical in evaluating in vivo performance. The dissolution test is a valuable tool in formulation development. A suitable dissolution method may uncover a formulation problem with the drug product that could

result in a bioavailability problem. The dissolution test should be able to distinguish between acceptable and unacceptable drug formulations as observed by different drug dissolution rates under the same experimental conditions. A suitable dissolution test should be able to reflect changes in the formulation, manufacturing process, and physical and chemical characteristics of the drug, such as particle size, polymorphs, and surface area .The dissolution test is a major requirement for scale-up and post approval changes.The development of an appropriate dissolution test requires the investigator to try different agitation rates, different media (including volume and pH of medium), and different kinds of dissolution apparatus[1]. The current USP-NF (United States Pharmacopeia) lists officially recognized dissolution apparatus. Once a suitable dissolution test is obtained, acceptable dissolution criteria are developed for the drug product and its formulation. Stirring rates must be controlled, and specifications differ between drug products. Low stirring rates (50–75 rpm) are more discriminating of formulation factors affecting dissolution than higher stirring rates. However, higher dissolution rate may be needed for some special formulations in order to obtain reproducible dissolution rates. The temperature of the dissolution medium must be controlled, and variations in temperature must be avoided. Most dissolution tests are performed at 37°C. The final dissolution procedure selected should be robust and able to distinguish small changes in the product formulation.

Metoprololsuccinate is a cardioselective beta blocker that has been classified as a class I substance according to the Biopharmaceutics Classification Scheme BCS ,meaning that it is highly soluble and highly permeable[2].The drug is readily and completely absorbed throughout the whole intestinal tract but is subject to extensive firstpass metabolism resulting in incomplete bioavailability (about 50%). After a single oral dose,peak plasma concentrations occur after about 1-2 hours.The drug is eliminated within 3 to 4 hours,which,depending on therapeutic intention,makes it necessary to administer simple formulations of metoprolol up to 4 times daily. In the current study, three marketed brands of metoprololsuccinate ER (50mg) were subjected to invitro drug release studies over the physiological pH range(1.2-6.8) with different basket stirring speeds to identify the sink and discriminative conditions.

MATERIALS AND METHODS

The marketed brands of Metoprolol succinate of 50mg strength (Helios,Ajantha Pharma Limited,Torrent Pharmaceuticals) were procured from the commercial market.Hydrochloric

acid,Sodium acetate,Glacial acetic acid,Sodium hydroxide,potassium dihydrogen phosphate and distilled water was used throughout the study.USP dissolution apparatus (LABINDIA DS 800) Type II and UV-Visible Spectrophotometer(ELICO SL 244 Double beam) were used.

Saturation Solubility Study

The saturation solubility studies of Metaprolol Succinate were conducted as per BCS guidelines. A single-dose strength (50 mg) of Metaprolol Succinate was added to 250 mL of each medium (0.1 N HCl pH 1.2, acetate buffer pH 4.5, distilled water pH 7.0, and phosphate buffer pH 6.8) placed in 500-mL conical flasks.

***Invitro* DissolutionStudies**

Three different brands of metoprolol succinate ER tablets(Metoprolol XL,MET-XL,Metocord XL labelled as I,II and III) were selected to compare the dissolution profiles.The dissolution tests were carried out on by employing USP Apparatus II at 37±0.5°C. Each dissolution test was performed in triplicate. In each dissolution testing, paddle speeds of 50,75 and 100 rpm were used. Different dissolution media of 0.1N HCl(pH 1.2), acetate buffer(pH 4.5), phosphate buffer(pH 6.8) and distilled water with 900 ml were used[3-5]. Sampling aliquots of 5 ml were withdrawn at regular time interval of 30min and replaced with an equal volume of the fresh medium maintained at the same temperature. After the end of each test time, samples aliquots were filtered through 0.45 µm membrane filter, diluted with respective dissolution medium and analysed spectrophotometrically at 222nm.

Comparison of Dissolution Profiles

A simple model-independent approach using a difference factor (*f*1) and a similarity factor (*f*2) to compare dissolution profiles was used [6,7]. The difference factor (*f*1) calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100 \qquad (1)$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \qquad (2)$$

In equation1,

n is the number of time points, *Rt* is the dissolution value of the reference (pre-change) batch at time *t*, and *Tt* is the dissolution value of the test (post-change) batch at time *t*.

In equation 2,

n is the number of dissolution sampling times, and *Rt* and *Tt* are the individual or mean percent dissolved at each time point for the reference and test dissolution profiles, respectively.

RESULTS AND DISCUSSION

The solubility data of Metaprolol succinate are shown in Table 1. The solubility of Metaprolol succinate was highest in pH 6.8 phosphate buffer (5.941µg/mL). According to the *USP*, the quantity of medium used should not be less than three times that required to form a saturated solution of the drug substance. Phosphate buffer (pH 6.8) was a more suitable medium for dissolution study, as a higher value was obtained compared with other dissolution media.

Table 1. Solubility Studies and Sink Conditions of Metaprolol succinate in Different Fluids

Buffer employed	Solubility (µg/mL)	Sink conditions(C_S/C_d)
0.1 N HCl pH 1.2	0.092	0.0018
Acetate buffer pH 4.5	0.1533	0.0030
Distilled water pH 7.0	2.978	0.0595
Phosphate buffer pH	5.941	0.1188

C_S: Saturation solubility of metoprolol succinate in 900 mL of dissolution medium.

C_d: Dose of metoprolol succinate in ER tablet formulation (50mg)

In vitro drug release studies of commercial brands of Metaprolol succinate Extended Release tablets (i.e., METOPROLOL XL, MET XL 50 ,METOCORD) were performed in four different dissolution media (0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and distilled water) at 100 rpm. The influence of stirring speed on drug release rate was studied in 900 mL of phosphate buffer (pH 6.8) employing three different agitation speeds (50, 75, 100 rpm). Comparisons of the dissolution profiles on the drug release rate, the dissolution media can be ranked as 0.1 N HCl (pH 1.2) > acetate buffer (pH 4.5) > distilled water (pH 7.0) > phosphate buffer (pH 6.8). These experimental results suggest that distilled water is equally suitable to pH 6.8 phosphate buffer for dissolution studies of Metaprolol succinate ER formulations. It may be necessary to conduct further dissolution studies in distilled water to

confirm the absence of dose dumping. The release profiles in various media and different agitation rates were charted in figures 2 to 8.

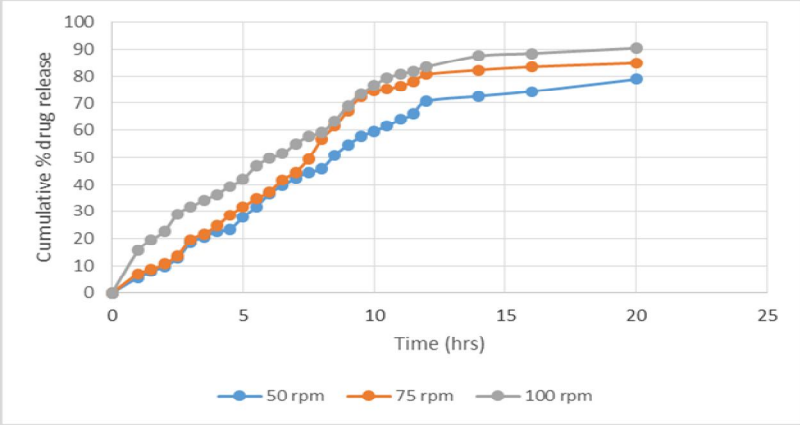

Figure 2:In vitro drug release of Metoprolol XL at different agitation rates in Phosphate buffer pH 6.8

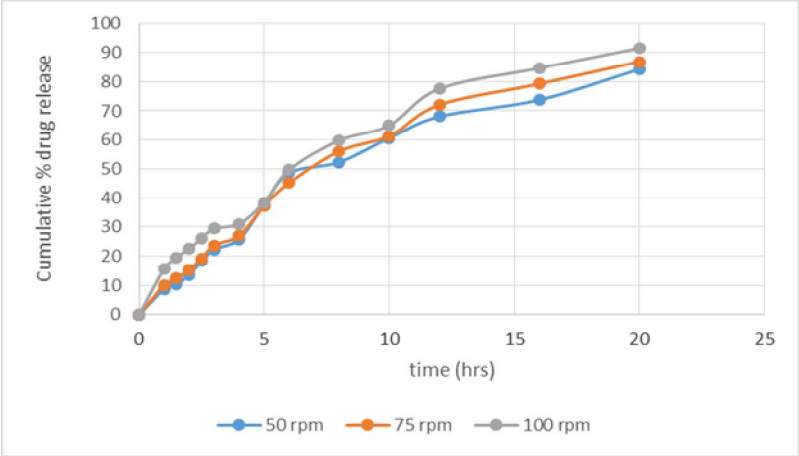

Figure 3:In vitro drug release of Met XL 50 at different agitation rates in Phosphate buffer pH 6.8

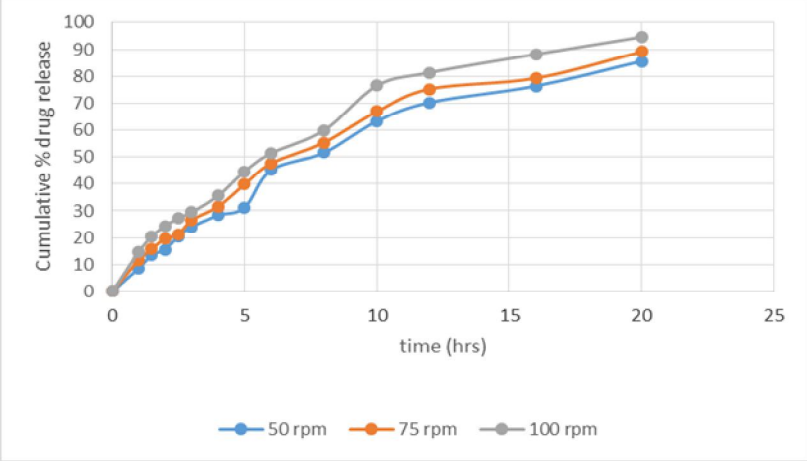

Figure 4 :In vitro drug release of Metocord at different agitation rates in Phosphate buffer pH 6.8

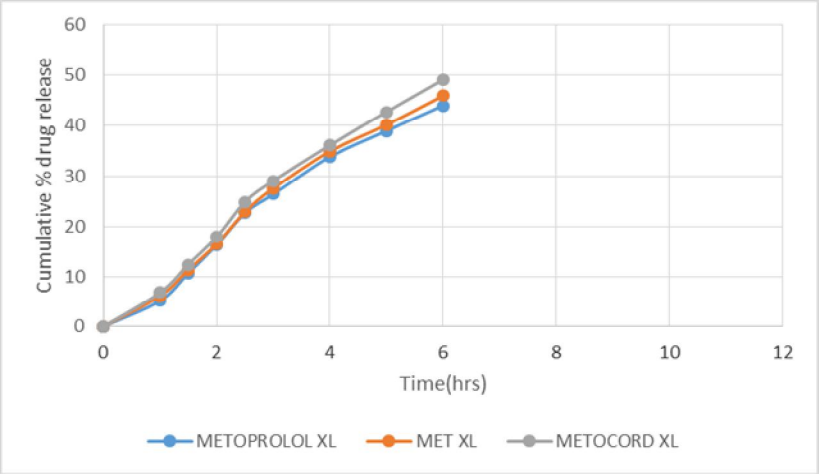

Figure 5 : Comparative in vitro drug release profiles of various marketed brands of Metoprolol succinate tablets in pH 1.2 HCl buffer at 100 rpm

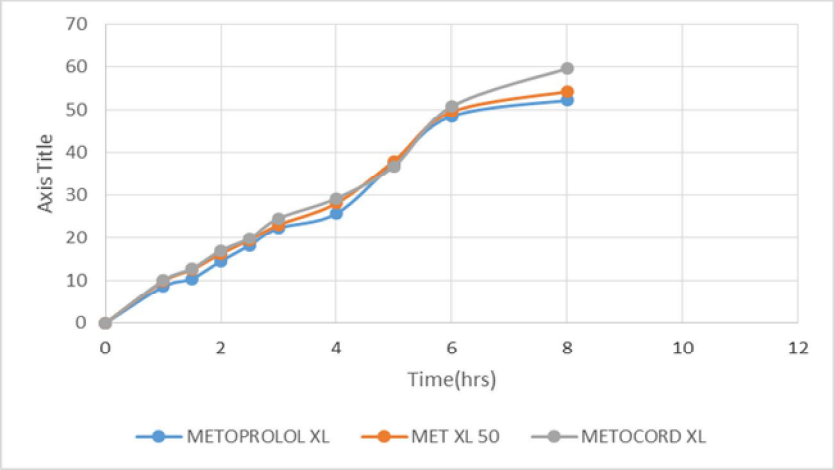

Figure 6 : Comparative in vitro drug release profiles of various marketed brands of Metoprolol succinate tablets in pH 4.5 acetate buffer at 100 rpm

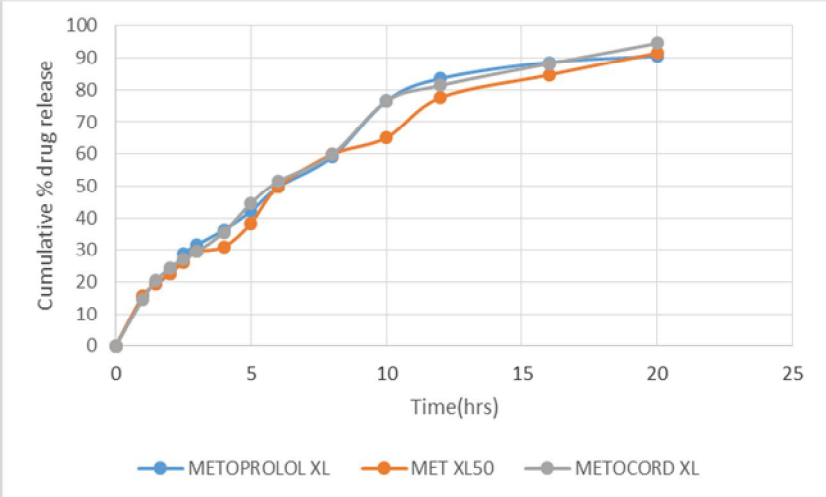

Figure 7 : Comparative in vitro drug release profiles of various marketed brands of Metoprolol succinate tablets in pH 6.8 phosphate buffer at 100 rpm

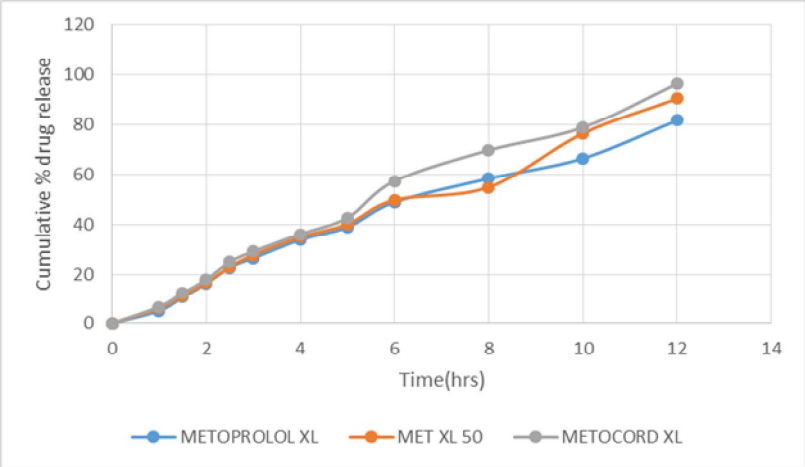

Figure 8 :Comparative in vitro drug release profiles of various marketed brands of Metoprolol succinate tablets in pH 7 distilled water at 100 rpm

The in vitro dissolution parameters of Metoprolol succinate ER marketed tablets at various agitation rates in ph 6.8 phosphate buffer and in different media at 100rpm were tabulated in table 2 and 3 respectively.

Table 2: In Vitro Dissolution Parameters of Metoprolol succinate ER Marketed Tablets at Various Agitation Rates in pH 6.8 Phosphate Buffer.

Agitation speed	Brands	Zero order plot		First order plot			Higuchi plot	Korsmeyer peppas plot		Release rate (mg/hr)	Possible mechanism of drug release
		R	Zero order rate constant K_0 ($mg.h^{-1}$)	R	n	First order rate constant K_1 (h^{-1})	R	R^2	n		
50	METOPROLOL XL	0.911	10.699	0.9625	0.247	0.4563	0.9560	0.996	0.636	2.12	First order non-fickian diffusion
	MET XL	0.925	9.8095	0.976	0.181	0.4226	0.9756	0.998	0.543	2.36	First order non-fickian diffusion
	METOCORD	0.886	8.9977	0.948	0.155	0.3890	0.9366	0.992	0.517	2.40	First order non-fickian diffusion
75	METOPROLOL XL	0.894	8.397	0.940	0.142	0.2642	0.9542	0.992	0.616	2.22	First order non-fickian diffusion
	MET XL	0.921	9.802	0.951	0.213	0.3042	0.9809	0.997	0.711	2.39	First order non-fickian diffusion
	METOCORD	0.951	9.186	0.961	0.078	0.3227	0.9519	0.990	0.536	2.36	First order non-fickian

											diffusion
100	METOPROLOL XL	0.957	7.553	0.974	0.062	0.3787	0.9738	0.981	0.472	2.25	First order non-fickian diffusion
	MET XL	0.9414	8.698	0.9533	0.0488	0.4571	0.9569	0.9683	0.4973	2.41	First order non-fickian diffusion
	METOCORD	0.9646	7.859	0.9849	0.0676	0.3327	0.9411	0.9742	0.5844	2.46	First order non-fickian diffusion

Table 3: *In Vitro* Dissolution Parameters of Metoprolol succinate ER Marketed Tablets in different dissolution media at 100rpm

Dissolution media	Brands	Release rate (mg/hr)	Zero order		Firstorder Higuchi			Korsmeyer peppas plot	
			R	Zero order rate constant K_0 ($mg.h^{-1}$)	R	First order rate constant K_1 (h^{-1})	R	R	n
pH 1.2 HCl buffer	METOPROLOL XL	1.92	0.851	11.29	0.9625	0.4632	0.909	0.9563	0.646
	MET XL	1.96	0.854	9.022	0.9764	0.4726	0.9156	0.987	0.539
	METOCORD	2.10	0.886	8.907	0.9481	0.3275	0.9066	0.9455	0.467
pH 4.5 Acetate buffer	METOPROLOL XL	2.12	0.865	8.497	0.9407	0.2856	0.932	0.959	0.563
	MET XL	2.30	0.923	8.542	0.9512	04215	0.929	0.978	0.645
	METOCORD	2.34	0.904	8.006	0.9619	0.4157	0.941	0.976	0.562
pH6.8 phosphate buffer	METOPROLOL XL	2.25	0.974	8.553	0.9745	0.2687	0.933	0.980	0.459
	MET XL	2.41	0.914	8.742	0.9533	0.4568	0.9216	0.9643	0.530
	METOCORD	2.46	0.966	7.123	0.9849	0.4012	0.9111	0.9742	0.641
pH 7.0 distilled water	METOPROLOL XL	2.3	0.955	7.456	0.8989	0.5230	0.9312	0.9456	0.574
	MET XL	2.4	0.942	8.890	0.9145	0.5691	0.9123	0.9333	0.596
	METOCORD	2.46	0.958	6.895	0.9523	0.8712	0.9455	0.9654	0.654

The mechanism of drug release from the marketed formulations was non- Fickian diffusion[8,9], as the exponential coefficient of Korsmeyer–Peppas equation was between 0.5 and 1.0. To compare the release profiles of the marketed formulations, difference factors (*f*1) and similarity factors (*f*2) were calculated.Two dissolution profiles are considered similar when the *f*1 value is closer to zero (i.e., 0–15) and the *f*2 value is greater than 50. The *f*2 values were greater than 50 at 100 rpm in pH 6.8 phosphate buffer and water. Similarity and Difference factors in pH 6.8 phosphate buffer at various agitation speeds and dissolution media were tabularized in tables 4 and 5 respectively.

Table 4: Similarity and Difference factors in pH 6.8 phosphate buffer at various agitation speeds

	Difference factor (*f*1)			Similarity factor (*f*2)		
Agitation speed	**AB**	**BC**	**CA**	**AB**	**BC**	**CA**
50 rpm	6.57	10.69	9.9	54.5	52.6	60.9
75 rpm	8.6	9.6	8.4	70.2	48.2	52.9
100 rpm	6.6	5.7	7.5	50.8	56.6	67.5

A: METOPROLOL XL ; B :MET XL ; C: METOCORD XL

Table 5: Similarity and Difference factors in various dissolution media

	Difference factor (*f*1)			Similarity factor (*f*2)		
Dissolution media	**AB**	**BC**	**CA**	**AB**	**BC**	**CA**
pH 1.2 HCl buffer	9.5	10.99	11.9	54.5	47.8	40.9
pH 4.5 Acetate buffer	11.4	10.6	12.4	50.2	49.9	52.9
pH6.8 phosphate buffer	6.6	5.7	7.5	50.8	56.6	67.5
pH 7.0 distilled water	7.9	8.5	8.2	60.5	57.2	55.4

A: METOPROLOL XL ; B :MET XL ; C: METOCORD XL

CONCLUSION

The rate of dissolution was dependent on the composition of dissolution medium and the speed of rotation.Distilled water is equally suitable to pH 6.8 phosphate buffer for dissolution studies of Metaprolol succinate ER formulations.

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