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Scale-Up Effects on Dissolution and Bioavailability of Propranolol Hydrochloride and Metoprolol Tartrate Tablet Formulations

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ABSTRACT This study evaluated the effects of batch size on the in vitro dissolution and the in vivo bioavailability of immediate release formulations of propranolol hydrochloride and metoprolol tartrate. The formulations were manufactured as small and large batches (6 kg and 60 kg for propranolol; 14 kg and 66 kg for metoprolol), and dissolution was performed using USP Apparatus I at 100 rpm and pH 1.2. Two panels of 14 subjects each were randomly assigned to receive the small and large batches of either propranolol or metoprolol in an open, randomized single-dose study. Blood samples were collected over a 24-hour (propranolol) or 18-hour (metoprolol) period and analyzed by validated methods. As determined by the f_2 metric (similarity factor), the dissolution of the small and large batches of propranolol and metoprolol was similar. The mean C_{max} and AUC_{inf} for the small batch of propranolol were 79.0 µ g/L and 536 µ g/L/hr, and for the large batch they were 83.5 µ g/L and 575 µ g/L/hr. C_{max} and AUC_{inf} for the small batch of metoprolol were found to be 95.5 µ g/L and 507 µ g/L/hr and for the large batch, 95.1 µ g/L and 495 µ g/L/hr. The 90% confidence intervals for the small and large batches were within the 80% to 120% range for lnC_{max}, and $lnAUC_{inf}$ for both the propranolol and metoprolol formulations. These results suggest that the scale-up process does not significantly affect the bioavailability of highly soluble, highly permeable drugs and in vitro dissolution tests may be useful in predicting in vivo behavior.

KEYWORDS: Metoprolol, Propranolol, Scale-up, Bioavailability, Dissolution

INTRODUCTION

Formulation and processing changes may directly influence the dissolution and bioavailability of a pharmaceutical formulation during development, manufacture, and product optimization. The process of scale-up may also alter dissolution and bioavailability. The joint workshop between the Food and Drug Administration (FDA) and the American Association of Pharmaceutical Scientists (AAPS) provided the scientific foundation for scale-up and postapproval changes required for immediate release products [1]. This joint workshop, subsequent research, and focused deliberations evolved into guidelines titled scale-up and postapproval changes for immediate release (SUPAC-IR) products [2]. SUPAC-IR proposed ranges for various classes of drug and excipient levels that could be considered major or minor formulation changes. These guidelines provide recommendations for postapproval changes in (1) the components or composition, (2) the site of manufacture, (3) the scale-up of manufacture, and (4) the manufacturing (process and equipment) of an immediate release oral formulation [2]. SUPAC-IR provides for levels of change in scale of manufacture, site of manufacture, manufacturing process, and equipment and composition.

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To systematically evaluate compositional, manufacturing, and scale changes on dissolution and bioavailability, 6 drugs representing various biopharmaceutical classes [3] were studied under a collaborative agreement between the University of Maryland and the FDA [4]. The selection of drugs representing a specific biopharmaceutical class provides the best opportunity to generalize the findings of the research. The overall mission of this research was to establish a scientific foundation for new regulatory policies on scale-up and postapproval changes for oral solid dosage forms.

The drugs evaluated in this report were propranolol hydrochloride and metoprolol tartrate. Both are Biopharmaceutical Class I agents that are freely soluble in water. Their permeability appears to be high because both are rapidly and almost completely absorbed following oral administration [3]. Previous work examined the influence of formulation and processing parameters classified as critical manufacturing variables on the bioavailability of 3 propranolol and metoprolol formulations manufactured to release in slow, moderate, or fast patterns [5,6]. Specifically, it was found that Level 2 changes outlined in the SUPAC-IR documentation did not significantly influence the in vitro dissolution or in vivo bioavailability of the propranolol or metoprolol formulations. This work has been extended to examine the influence on the in vitro dissolution and in vivo bioavailability of increasing the batch size from 6 kg to 60 kg for propranolol and 14 kg to 66 kg for metoprolol.

MATERIALS AND METHODS

The materials used in this study were propranolol hydrochloride (SIMS, Firenze, Italy), metoprolol tartrate (Assia Chemical Industries, Ltd, supplied by Cetes Chemical, Harrison, NY), microcrystalline cellulose (Avicel PH 102; FMC Corp, Philadelphia, PA), lactose monohydrate (Fast-flo 316; Foremost Wisconsin Dairies, Baraboo, WI), dibasic calcium phosphate dihydrate (Emcompress® ; E Mendell Co, Patterson, NY), povidone (Plasdone, K29/32; ISP, Wayne, NJ), sodium starch glycolate (Explotab® ; E Mendell Co), magnesium stearate (Code 2255; Mallinckrodt Specialty Chemicals Co, St Louis, MO), and colloidal silicon dioxide (Cab-O-Sil M5; Cabot Corp, Tuscola, IL). All materials used in this study complied with current USP/NF compendial specifications. Metoprolol tartrate and propranolol hydrochloride standards were obtained from Sigma Chemical Company (St Louis, MO). Dextromethorphan and dextrophan were obtained from Research Biochemicals International (Natick, MA). Mobile phase components were of high-performance liquid chromatography (HPLC) grade and other chemicals were at least ACS certified.

Formulations

Two 80-mg formulations of propranolol hydrochloride were evaluated in this study: the innovator product, Inderal® , and a previously described slow-releasing immediate release formulation [5]. Three batch sizes of the propranolol formulation were examined: 6 kg (20 000 units), 12 kg (40 000 units), and 60 kg (200 000 units).

A 100-mg slow-releasing formulation of metoprolol tartrate was evaluated in this study at batch sizes of 14 kg (42 000 units) and 66 kg (200 000 units) [6]. The composition and scale-up variables for both metoprolol and propranolol formulations are presented in **Tables 1** and **2**, respectively.

Table 1. Propranolol Hydrochloride and Metoprolol Tartrate Tablet Formulations

Ingredients	% tablet weight
Propranolol	
Propranolol hydrochloride, USP	26.7
Microcrystalline cellulose, NF	20.0
Lactose monohydrate, NF	52.8
Magnesium stearate, NF	2.0
Manufacturing Parameters	
Tablet weight	300 mg
Compression force	1200 kg
Lubricant blend time	2 min
Metoprolol	
Ingredients	**% tablet weight**
Intergranular	
Metoprolol tartrate, USP	30.3
Lactose monohydrate, NF	q.s. 100
Microcrystalline cellulose, NF	20.0
Sodium starch glycolate, NF	3.0
Povidone K29/32, USP	5.0
Extragranular	
Sodium starch glycolate, NF	1.5-4.5
Microcrystalline cellulose, NF	20.0
Magnesium stearate, NF	1.5
Colloidal silicon dioxide, NF	3.0 or 5.0
Manufacturing Parameter	
Tablet weight	300 mg
Compression force	600 kg

Table 2. Scale-Up Variables for Formulations Used in the Propranolol and Metoprolol Clinical Bioavailability Study

Scale-Up Variables for Propranolol			
V-Blender (cu ft)	Batch size (kg)	Units	Site of Manufacture
0.5	6	20 000	UMD
1.0	12	40 000	UMD
5.0	60	200 000	UMD
Scale-Up Variables for Metoprolol			
Unit Size (Equipment)	Batch Size (kg)	Units	Purpose
PMA 10	2.0 (1X)	6 000	CVA Study
PMA 65	14.0 (7X)	42 000	IVIVC Study
PMA 150	33.0 (17X)	100 000	Scale-up
PMA 300	66.0 (33X)	200 000	Scale-up

Dissolution Testing

Dissolution tests were conducted on coated tablets according to the USP XXII monograph for propranolol hydrochloride tablets and metoprolol tartrate [7]. The dissolution conditions were USP Apparatus I, 100 rpm, 1000 mL, 0.1N HCl, at 37oC for propranolol and USP Apparatus I and 100 rpm with 900 mL of simulated gastric fluid TS (test solution) for metoprolol. Dissolution samples were collected at 5, 10, 15, 20, 25, and 30 minutes and analyzed spectrophotometrically at wavelengths of 289 nm for propranolol and 275 nm for metoprolol.

To study the effect of pH on drug release, dissolution testing as specified in SUPAC-IR (Case C dissolution)[2] was performed on all formulations (propranolol and metoprolol) at pH 1.2, 4.7, and 7.0 using the aforementioned dissolution conditions. The dissolution profiles were compared using the similarity factor f_2. Clinical batches were packaged in 60 mL HDPE (high density polyethylene) bottles containing a CRC (child resitant closure) cap and stored at controlled room temperature (20° C 25oC) for 6 months. Stability samples were collected at 0, 1, 3, and 6 months, and dissolution tests were performed to study the effect of long-term storage on these formulations.

Bioavailability Studies

An open, randomized, fasting, single-dose, 3-propranolol treatment, crossover study was performed with 14 healthy, nonsmoking, male and female subjects. The treatments were as follows: (1) small batch, (2) large batch, and (3) Inderal® 80-mg tablet. After an overnight fast, subjects were administered 1 tablet, and blood samples were collected over a 24-hour period. Plasma samples were stored at -80^{o}C before analysis with a validated HPLC method.

An open, randomized, fasting, single-dose, 2-metoprolol treatment crossover study was performed with 14 healthy, nonsmoking subjects. After an overnight fast, subjects were administered 1 tablet (small or large batch), and blood samples were collected over an 18-hour period. Samples were separated and the plasma samples were analyzed for metoprolol concentrations.

The protocols for propranolol and metoprolol were approved by the Institutional Review Board at the clinical site (Harris Laboratories, Lincoln, NE), the University of Maryland Institutional Review Board, and the Research Involving Human Subjects Committee at the FDA. All subjects gave written informed consent.

Analytical Methods.

Propranolol was analyzed by a validated HPLC method using fluorescence detection and solid-phase extraction. The analytical column used was a Zorbax C-8 reverse-phase column (Mac-Mod Analytical, Inc., Chadds Ford, PA), and the mobile phase consisted of 0.25% phosphoric acid and acetonitrile (74:26, vol/vol). The validated range of quantifiable concentrations for the analyte was between 3 and 200 ng/mL. The intraday and interday coefficients of variation were no more than 12% for all standard and control samples.

A gas chromatography method for quantitation of metoprolol in human plasma was developed and validated by Harris Laboratories. The method involved extraction of the drug and internal standard from the sample,

derivitization with trifluoroacetic anhydride, and separation on a 30 m DB5 capillary column using an electron capture detector. The linearity range for the metoprolol assay was 4 to 375 ng/mL, with a limit of quantitation of 4 ng/mL. The intraday and interday coefficients of variation for 6, 100, and 280 ng/mL ranged from 1.8% to 8.2%.

Pharmacokinetic Data Analysis

The propranolol and metoprolol concentration versus time data were evaluated using the Phast program (Phoenix Scientific Software, Montreal, Canada). The highest plasma drug concentration measured for a subject was the C_{max}. The time at which C_{max} occurred was defined as T_{max}. The AUC_{inf} (area under the curve) was also determined. The elimination rate constant was determined by linear regression of the linear portion of the log(concentration) versus time profile.

Bioequivalence and Statistical Analysis.

A parametric general linear model was applied to each of the above-defined pharmacokinetic variables using SAS GLM (general linear method) procedure. In addition, the logarithmic transformations of C_{max} and AUC_{inf} were also evaluated by use of the same model. The analysis of variance model included the following factors: sequence (SEQ), subject within sequence (SUBJECT [seq]), period (PHASE), and formulation (TREATMENT). The 2 one-sided hypotheses were tested at the 5% level for the parameters by constructing 90% confidence intervals (CIs) for the ratio of the test and reference means. The 90% CIs were obtained from the anti-log of the lower and upper bounds of the 90% CIs for the differences in the means of the log-transformed data. Bioequivalence was concluded if the 90% CIs of the ratio of the product means fell within the range of 80% to 120% of the ratio of the test and reference means for the untransformed parameters or within the range of 80% to 125% for the log-transformed parameters.

RESULTS AND DISCUSSION

In vitro dissolution studies. Profiles of the cumulative propranolol fraction dissolved from the 6 kg (small batch), 12 kg, and 60 kg (large batch) propranolol tablets are illustrated in **Figure 1A**.

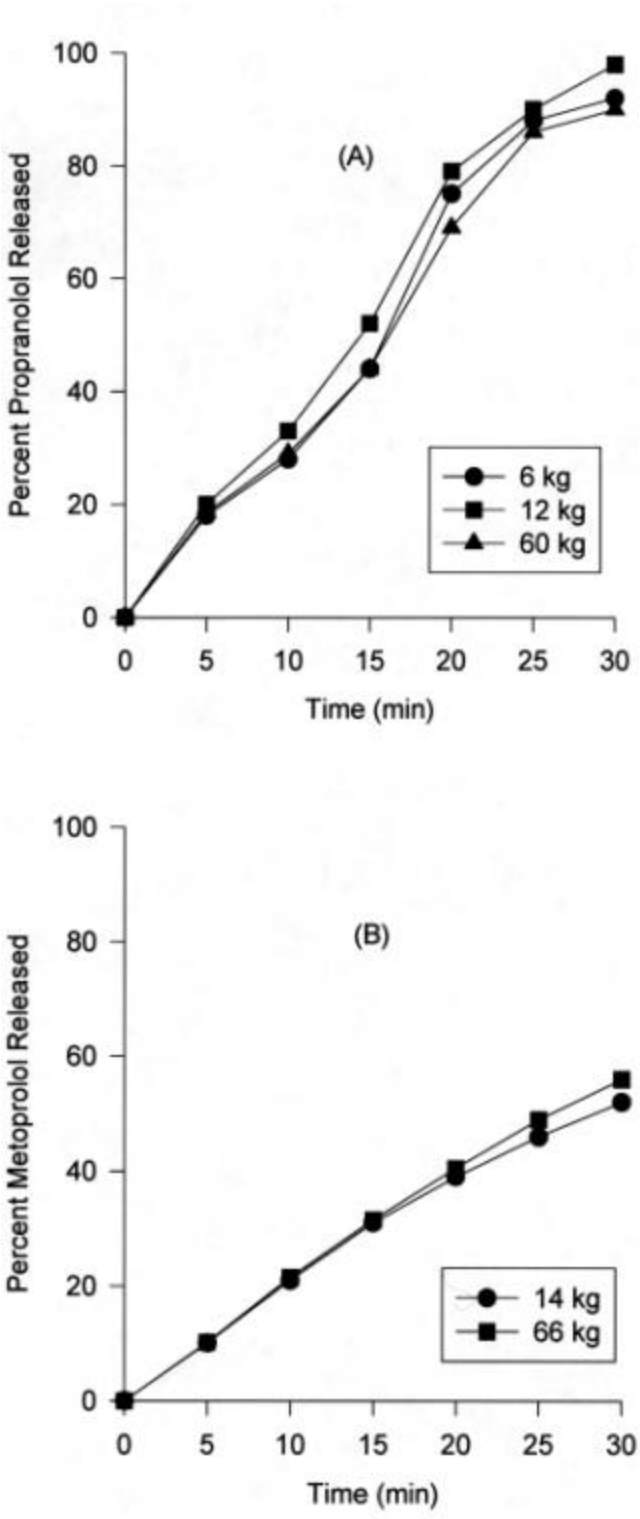
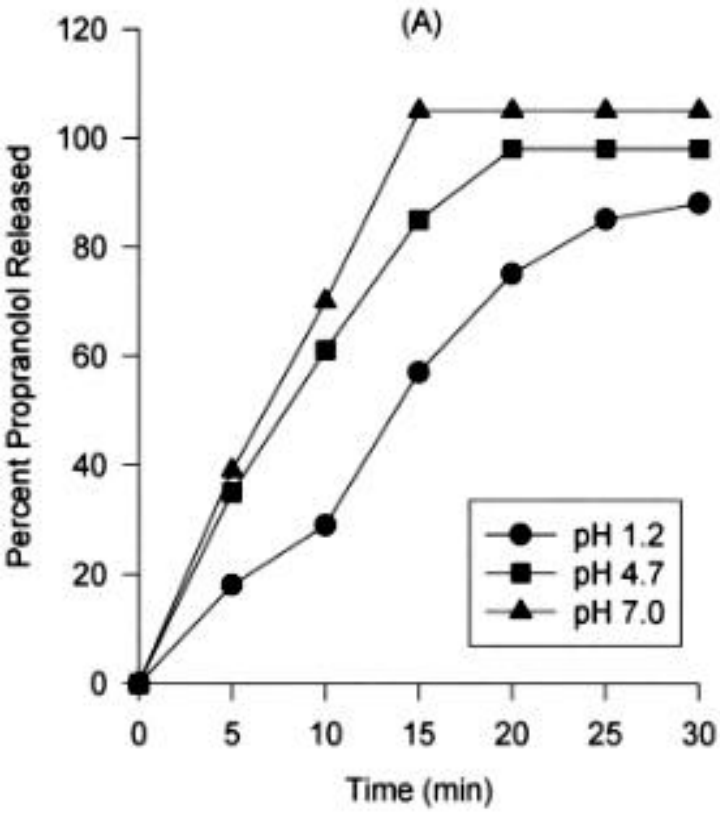


Figure 1. The effect of scale-up on the mean dissolution versus time profiles for (A) the 6 (●), 12 (■), and 60(▲) kg batch sizes of propranolol tablets and (B) the 14 (●) and 66 (■) kg batch sizes of metoprolol tablets using USP Apparatus I, pH 1.2, 100 rpm.



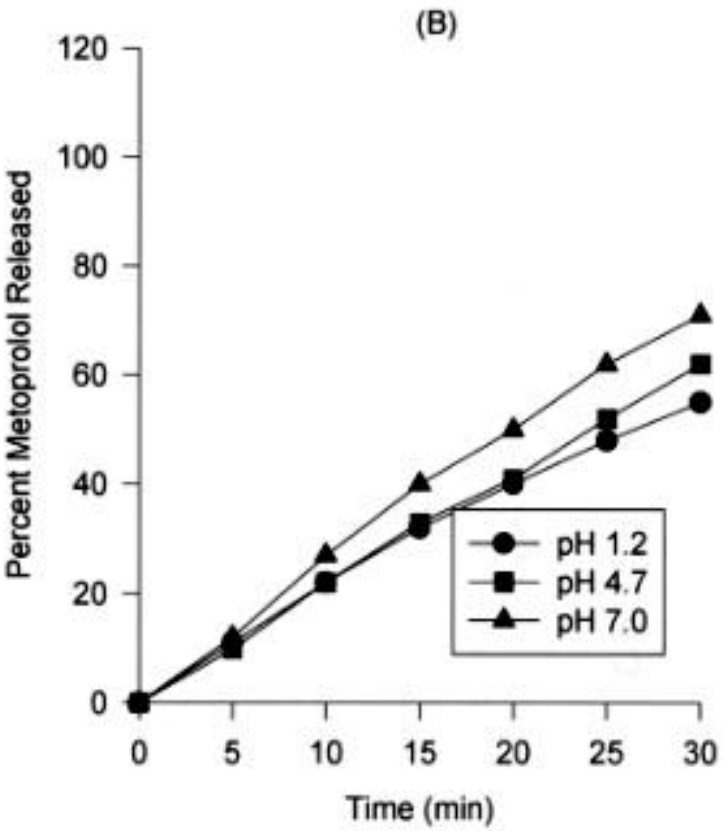


Figure 2. The effect of pH on the mean dissolution versus time profiles for (A) 60 kg batch of propranolol tablets at pH 1.2 (●), pH 4.7 (■), and pH 7.0 (▲) and (B) 66 kg batch of metoprolol tablets at pH 1.2 (●), pH 4.7 (■), and pH 7.0 (▲).

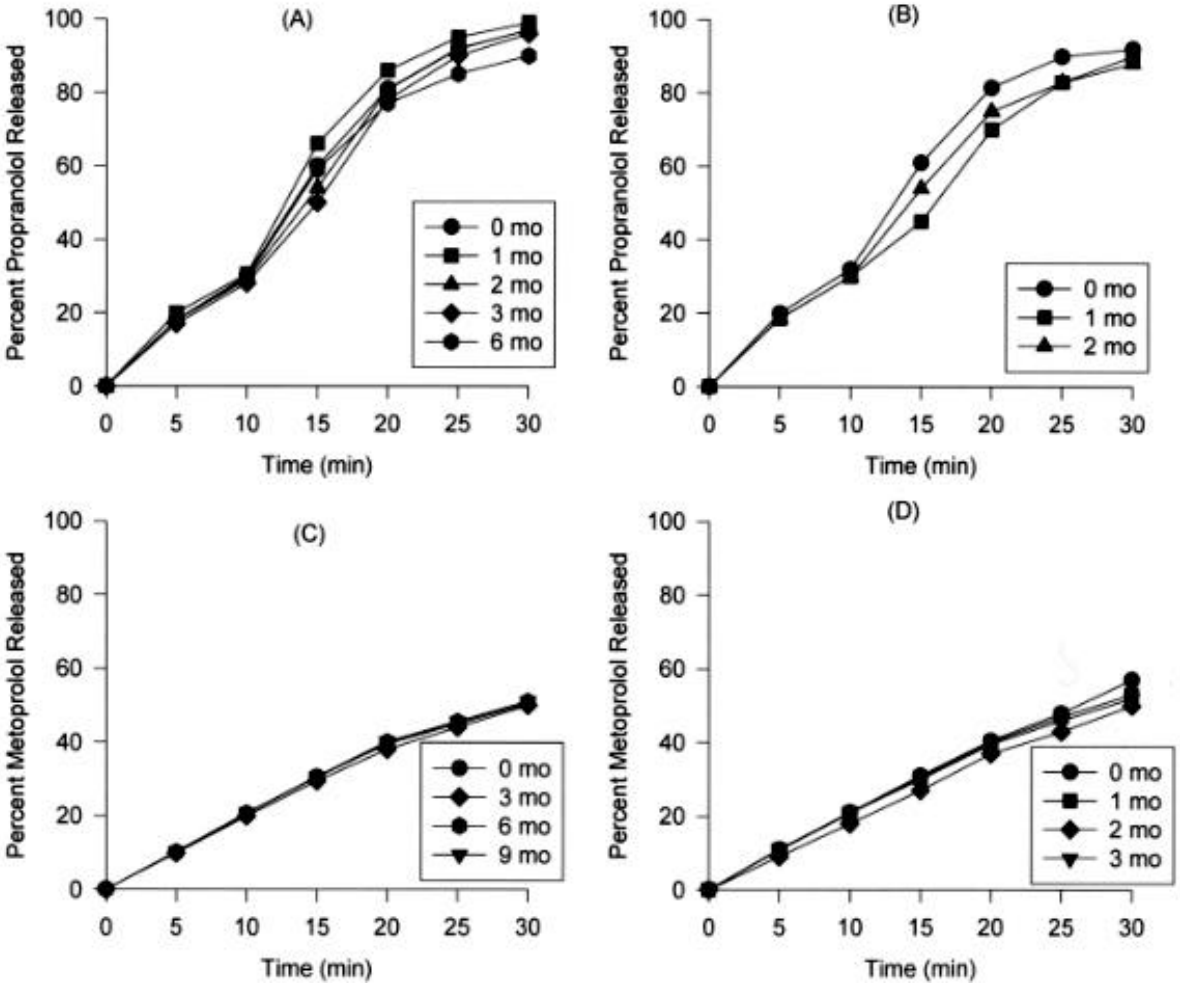
The corresponding f_2 metric values for the 6 kg, 12 kg, and 60 kg batches of the slow-releasing propranolol were all greater than 50, suggesting that the dissolution from the various batch sizes was similar. **Figure 1B** presents the dissolution of metoprolol from the 14 kg and 66 kg batches (f_2 > 50). Scale-up does not alter the dissolution of propranolol or metoprolol based on the batch sizes evaluated.

Figure 2A presents the effect of pH (1.2, 4.7, and 7.0) on the dissolution of the propranolol 60-kg batch. The dissolution of propranolol at pH 1.2 was not similar to drug release at pH 4.7 (f_2 < 50) or pH 7.0 (f_2 < 50). However the dissolution was similar when drug release at pH 4.7 and 7.0 were compared (f_2 > 50). The Case C dissolution of the metoprolol 66-kg batch is presented in **Figure 2B**. The pH of the dissolution media does not have a significant effect on the release time of metoprolol.

The dissolution profiles of both the small (**Figure 3A**) and large batches (**Figure 3B**) of propranolol were unaffected by storage at controlled room temperature (20° C-25°C) over a 0- to 6- and 0- to 2-month period, respectively. The stability of the metoprolol tablets was also unaffected by the storage conditions as measured by the dissolution profiles for the small (**Figure 3C**) and large (**Figure 3D**) batches.

The dissolution profiles of the clinical batches (6 kg and 60 kg) of propranolol and the innovator product are presented in **Figure 4A**.

Figure 3. (next page - top) Mean dissolution profiles examining the stability of (A) 6 kg batch size of propranolol tablets at 0, 1, 2, 3, and 6 months; (B) 60 kg batch size of propranolol tablets at 0, 1, and 2 months; (C) 14 kg batch size of metoprolol tablets at 0, 3, 6, and 9 months; and (D) 66 kg batch size of metoprolol tablets at 0, 1, 2, and 3 months.


(A)
Percent Propranolol Released
Time (min)
0 mo
1 mo
2 mo
3 mo
6 mo
(B)
Percent Propranolol Released
Time (min)
0 mo
1 mo
2 mo
(C)
Percent Metoprolol Released
Time (min)
0 mo
3 mo
6 mo
9 mo
(D)
Percent Metoprolol Released
Time (min)
0 mo
1 mo
2 mo
3 mo

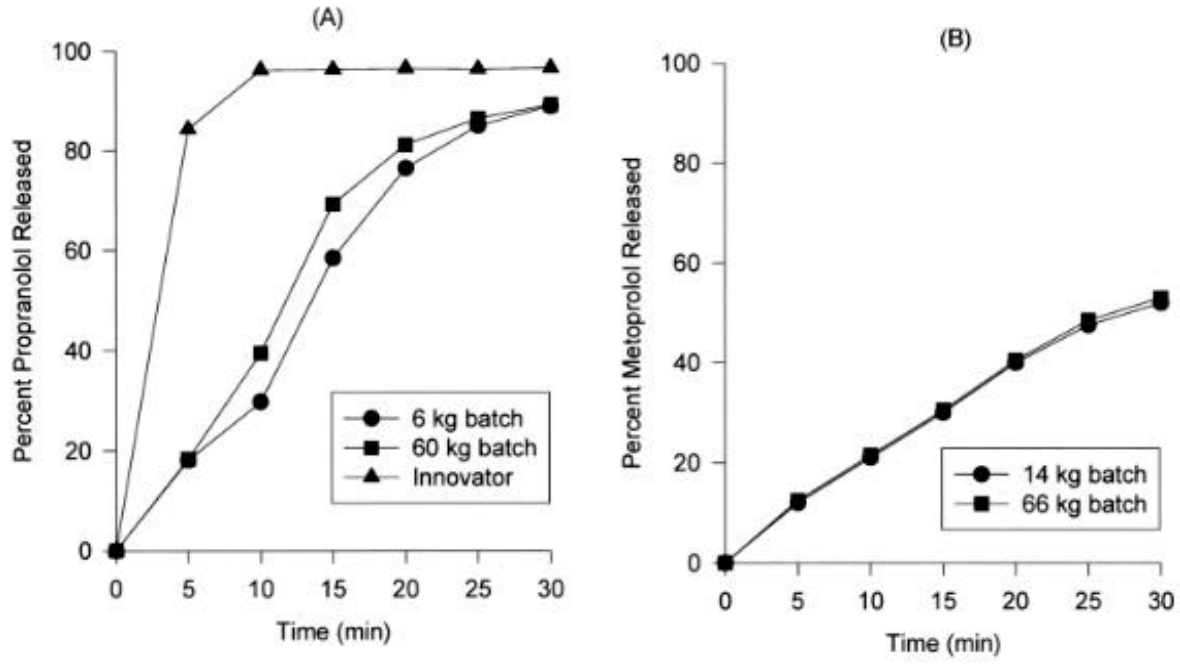

(A)
Percent Propranolol Released
Time (min)
6 kg batch
60 kg batch
Innovator
(B)
Percent Metoprolol Released
Time (min)
14 kg batch
66 kg batch

Figure 4. (previous page – bottom) The effect of scale-up on the mean dissolution versus time profiles for (A) the 6 (●) kg and 60 (■) kg batches and the innovator (▲) tablets of propranolol, and (B) the 14 (●) kg and 66 (■) kg batch sizes of metoprolol tablets.

The dissolution of the innovator product exceeded both the small- and large-batch propranolol formulation profiles after 5 minutes. The dissolution profiles of the clinical batches (14 kg and 66 kg) for metoprolol are presented in **Figure 4B.**

Propranolol in vivo studies

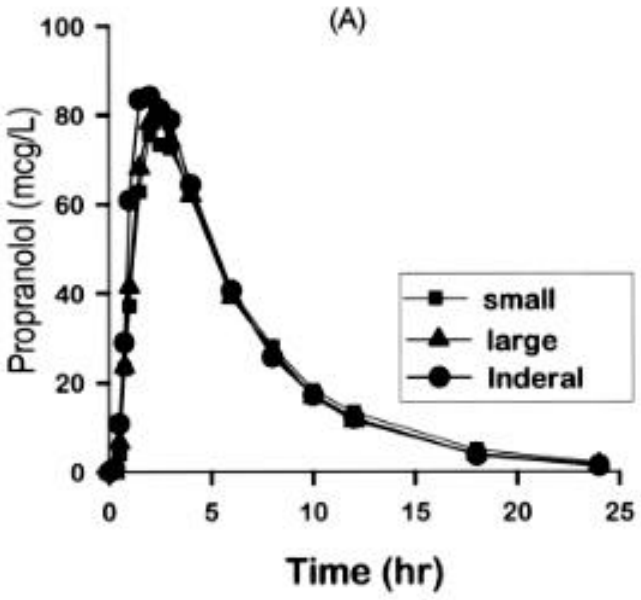
Fourteen subjects completed the study and 2 subjects withdrew voluntarily. The mean (+ SD) age, height, and weight of the 14 subjects who completed the study were 35 + 7.8 years, 68.2 + 3.2 inches, and 166 + 24 pounds, respectively. No serious or unexpected adverse experiences occurred. **Figure 5A** shows the mean propranolol concentration versus time profile after the administration of the small batch, large batch, and Inderal formulations. **Table 3** summarizes the mean (+ SD) propranolol pharmacokinetic parameters.

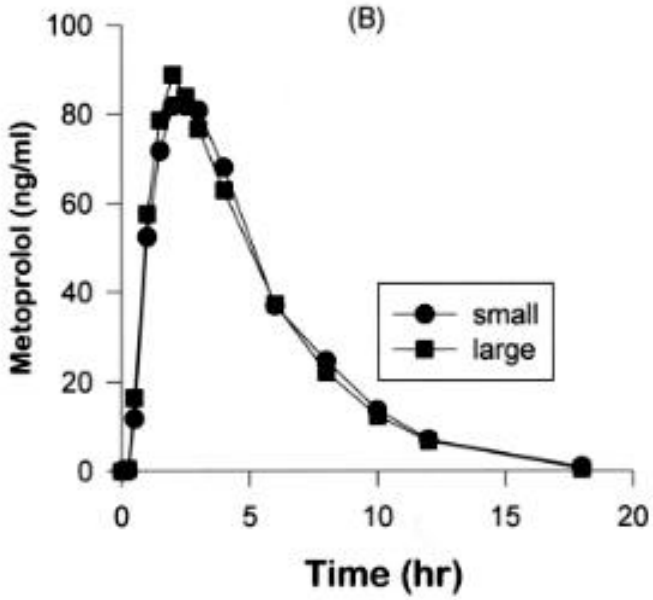
Figure 5. The effect of scale-up on the mean plasma drug concentration versus time profiles for (A) 6 (●) kg and 60 (■) kg batches and the innovator (▲) tablets of propranolol, and (B) the 14 (●) kg and 66 (■) kg batches of metoprolol tablets after single-dose administration to healthy volunteers.

Table 3. Mean (SD) Pharmacokinetic Parameters for Propranolol after the Administration of the Small (6 kg), Large (60 kg), and Inderal Treatments and Mean (SD) Pharmacokinetic Parameters for Metoprolol after the Administration of the Small (14 kg) and Large (66 kg) Batches .

Formulation	C_{max}(mg/L)	T_{max}(hr)	AUC_{inf} (mg/L/hr)
Propranolol			
6 kg batch	79.0 (32.0)	2.3 (0.5)	536 (254)
60 kg batch	83.5 (31.3)	2.3 (0.4)	546 (232)
Inderal®	89.8 (24.9)	2.1 (0.6)	575 (199)
Metoprolol			
14 kg batch	95.5[a] (39.7)	2.2 (0.6)	507 (248)
66 kg batch	95.1 (42.7)	2.0 (0.7)	495 (255)

C_{max} indicates the highest plasma drug concentration measured for a subject, AUC_{inf} = area under the curve.





In general, the influence of scale-up on the bioavailability parameters was minimal. The mean C_{max} for the small batch was lower than the mean C_{max} of the large batch (79.0 vs 83.5 µ g/L). The extent of absorption was slightly higher for the large-batch formulation (AUC_{inf} = 546 µ g/L/hr) as compared with the smaller batch (AUC_{inf} = 536 µ g/L/hr). T_{max} was identical for both the small and large batch sizes (2.3 hr). The rate of absorption was faster for Inderal (C_{max} = 89.8 µ g/L and T_{max} 2.1 hr) than for the small and large batches. The faster absorption noted for Inderal was also observed in the dissolution data. None of the observed differences in C_{max}, T_{max}, or AUC_{inf} were found to be statistically significant among the tested formulations.

The results from the two one-sided *t* tests and the 90% CIs for C_{max} and AUC_{inf} are shown in **Table 4.**

Table 4. Ratio of Least-Squares Means and Confidence Intervals (CIs) for Propranolol and Metoprolol Pharmacokinetic Parameters

Formulation	Ratio lnC_{max}	90% CI lnC_{max}	Ratio $lnAUC_{inf}$	90% CI $lnAUC_{inf}$
Propranolol				
6 kg/60kg	95.2	83.9 - 108.2	103.7	92.4 - 103.8
6kg/Inderal®	84.8	74.7 - 96.3	93.7	82.6 - 106.3
60 kg/Inderal®	89.1	78.4 - 101.2	90.4	79.7 - 102.6
Metoprolol				
14 kg/66kg	99.9	91.3 - 109.2	97.9	92.4 - 103.8

The 90% CIs for the small and large scale batches were within 80% to 120% for $lnAUC_{inf}$ (92.4-103.8) and lnC_{max} (83.9-108.2), but there was insufficient power to determine bioequivalency. The 90% CIs for lnC_{max} for both the small (74.7-96.3) and large (78.4-101.2) batches compared with Inderal were outside of the 80% to 120% range, whereas $lnAUC_{inf}$ CIs were within the range at 82.6 to106.3 (small batch) and 79.7 to 102.6 (large batch). These results strongly suggest that the process of scale-up does not alter the in vivo absorption rate or the extent of absorption of this formulation of the highly soluble, highly permeable propranolol hydrochloride.

Metoprolol Study:

Fourteen subjects completed the study and 2 subjects withdrew voluntarily. The mean (+ SD) age, height, and weight of the 14 subjects who completed the study were 28 + 4.7 years, 69.5 + 3.8 inches, and 168.3 + 30.9 pounds, respectively. No serious or unexpected adverse experiences occurred. **Figure 5B** presents the mean metoprolol concentration versus time profile after the administration of the small batch and large batch. **Table 3** summarizes the mean (+ SD) metoprolol pharmacokinetic parameters. No significant differences were found for C_{max} (95.5 µ g/L vs 95.1 µ g/L), T_{max} (2.2 hr vs 2.0 hr), or AUC_{inf} (507 µ g/L/hr vs 495 µ g/L/hr) between the small and large batches, respectively. Further, the results from the two one-sided *t* tests and the 90% CIs for C_{max} and AUC_{inf} (**Table 4**) suggest that the batches are bioequivalent.

CONCLUSIONS

This research examined the influence of scale-up on the in vitro dissolution and in vivo bioavailability of 2 highly soluble and permeable drugs, propranolol and metoprolol. Previous work found that broad differences with in vitro dissolution that resulted from SUPAC-IR Level 2 changes had no effect on the dissolution or bioavailability of metoprolol or propranolol formulations [5,6]. In this study it was important to examine if previously identified critical manufacturing variables [5,6] would be enhanced in a larger scale batch size and thus alter dissolution and bioavailability. Indeed, lower dissolution results were seen for the scale-up batches of both the metoprolol and propranolol formulations. Within the range of manufacturing scales represented (ie, 6 kg-60 kg for propranolol and 14 kg-66 kg for metoprolol), there was

no significant impact of a 10 X scale-up using similar equipment. Further, in vivo bioavailability was not altered with scale-up. In conclusion, the results suggest that the scale-up of highly permeable and highly soluble drugs does not significantly affect either in vitro dissolution or in vivo performance. It is likely that greater scale-up factors will not result in dissolution differences greater than those found bioequivalent in this body of work.

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