

A Bioequivalent 120mg Pseudoephedrine HCl Extended-Release Monolithic Tablet

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SUMMARY:

The purpose of these studies were to determine the bioequivalence of a SCOLR Pharma extended-release pseudoephedrine tablet to the reference listed drug *Sudafed® 12-Hour*. This product, using SCOLR's patented CDT® technology is bioequivalent and able to deliver drug similar to the reference drug in a more compact design.

INTRODUCTION:

Pseudoephedrine hydrochloride is a BCS Class I drug and possesses an elimination half-life of 9-16 hours and 55-75% of the administered dose excreted as unchanged drug. Pseudoephedrine HCl is currently available in two ER tablet formulations: 120mg/12-hour wax matrix and 240mg/24-hour osmotic pump. An osmotic pump system allows release to occur throughout the 24-hour once-a-day delivery period, but the delivery system is cost-intensive to manufacture and requires blister packing due to the instability of the osmotic membrane.

The SCOLR 120mg ER formula is bioequivalent to the wax-matrix reference listed product and its smaller size offers significant manufacturing advantages.

EXPERIMENTAL METHODS:

Tablet Formulation Design, Development and In Vitro Evaluation: The tablet comprises an HPMC-based hydrophilic matrix and selected controlled-release modifying agents. The drug load of the tablets was approximately 50% and the tablets were manufactured on a Manesty high-speed rotary press.

Dissolution testing described here was with a USP Type II dissolution apparatus with a paddle speed of 50rpm in 900mL dH₂O media.

Typically, six tablets of each product were tested, and samples of the dissolution media were removed via an automated sampling system (VanKel VK7000, peristaltic pump & Varian Cary 50 spectrophotometer).

In Vivo Study Design: Two pharmacokinetic studies under fasted and fed conditions were carried out. Each study was a single dose two-way crossover, pharmacokinetic study of controlled-release pseudoephedrine 120mg tablets and the current 120mg RLD in normal healthy non-smoking subjects.

Fasted study: A total of 26 subjects, (14 men and 12 women) were included in this study. The study consisted of two periods in which equal numbers of patients were randomly assigned to each treatment. Venous blood samples were collected over a 36 hr. period of time post drug administration.

Fed study: A total of 62 subjects, (33 men and 29 women) were included in this study. 61 subjects completed the study. The study was conducted as above, with the exception that each subject consumed an FDA High Fat breakfast within 30 min. of dosing.

Fasted Study Pharmacokinetics: Table 1 contains the key pharmacokinetic values obtained in the fasted study. The 90% confidence intervals for the geometric mean Test-to-Reference area and peak concentration ratios were within the bioequivalence interval 0.80-1.25. Other parameters were also comparable.

Fed Study Pharmacokinetics: Table 2 confirms that for the Fasted study, the SCOLR formulation also demonstrates bioequivalence to the reference listed drug. Some differences in AUC are noted particularly in the 3-9hr interval. C_{max} is also slightly inferior. In addition, the SCOLR formulation was well tolerated by all subjects in both fed and fasted studies.

Table 1. Summary of Statistical Comparisons for SCOLR 120 mg Pseudoephedrine ER Tablets and 120mg Sudafed® 12hr Tablets, Fasted Study.

Parameter	Least-Squares Means ¹		Ratio ²	CV% ³	90% Confidence Interval ⁴	
	Test	Reference			Lower	Upper
AUC 0-t (ng-hr/mL)	3776	3665	1.030	-	0.974	1.087
AUCinf (ng-hr/mL)	3898	3766	1.035	-	0.980	1.090
C _{max} (ng/mL)	300	280	1.073*	-	1.034	1.113
T _{max} (hour)	5.19	5.21	0.996	-	-	-
Ke (1/hour)	0.1300	0.1296	1.004	-	-	-
T _{1/2} (hour)	5.49	5.46	1.005	-	-	-
Ln-Transformed:						
AUC 0-t (ng-hr/mL)	3678	3551	1.036	12.2	0.977	1.097
AUCinf (ng-hr/mL)	3801	3659	1.039	12.0	0.982	1.100
C _{max} (ng/mL)	295	275	1.073*	7.68	1.035	1.113

- Least-squares geometric means for ln-transformed data.
 - Ratio calculated as Test least-squares mean divided by the Ref. least-squares.
 - Estimated in-trial subject coefficient of variation, CV%=100*SQRT(e^{MSE} - 1), where MSE is the mean square error term from the ANOVA.
 - Confidence interval on the ratio.
- * Comparison was detected as statistically significant by ANOVA (α=0.05)

Graph 1. Least-Squares Mean pseudoephedrine Plasma Concentrations (N=23).

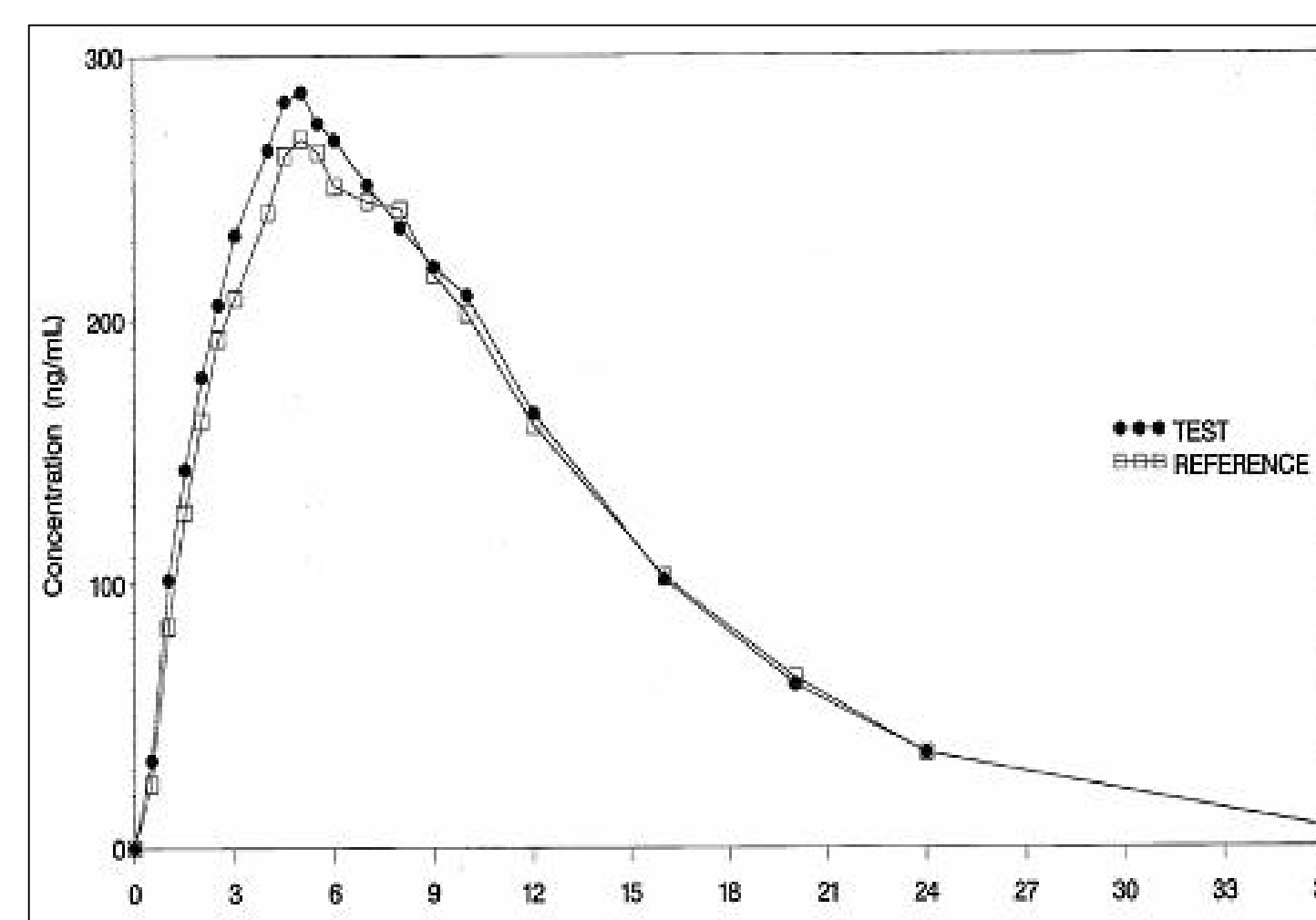
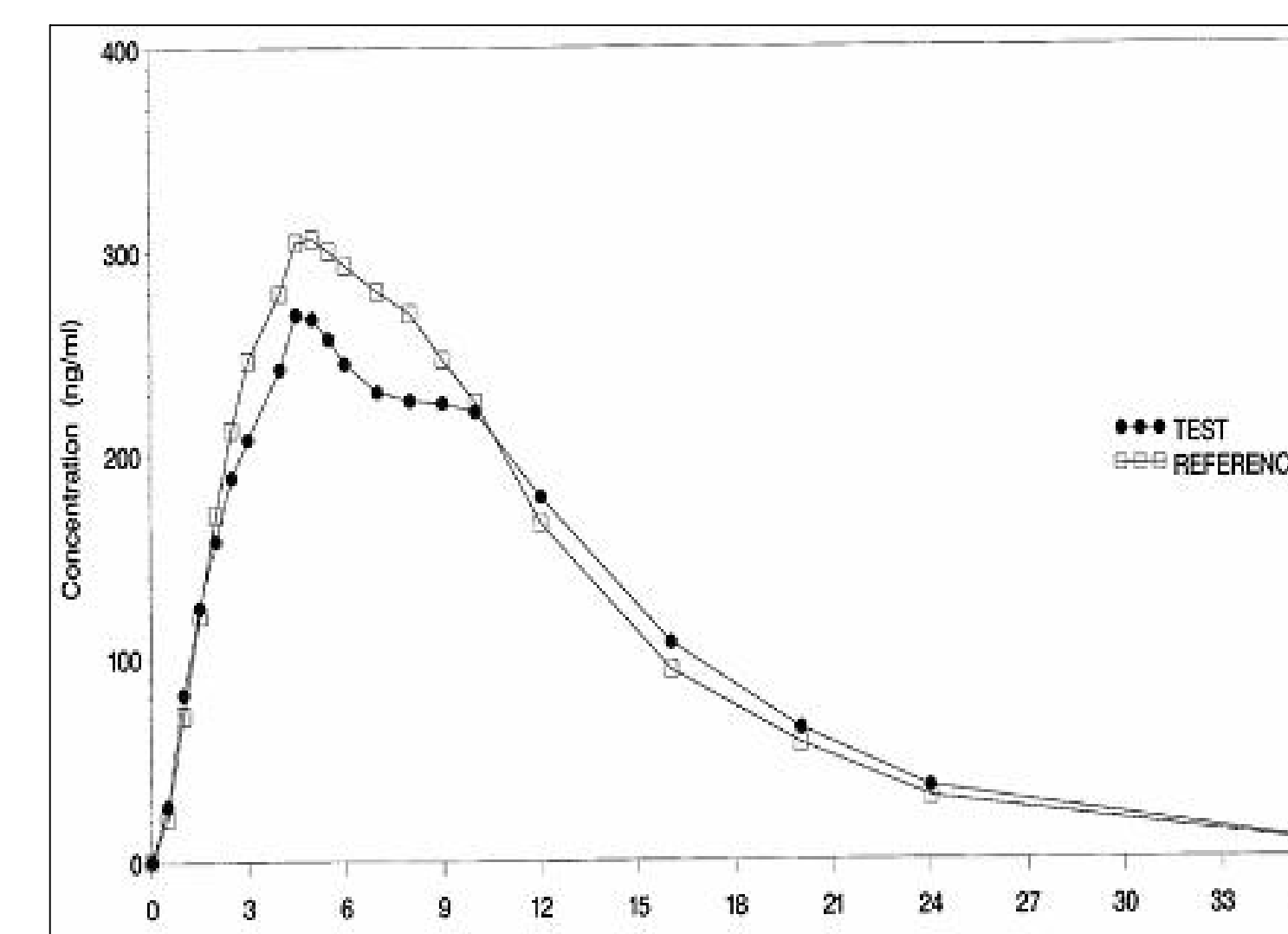


Table 2. Summary of Statistical Comparisons for SCOLR 120 mg Pseudoephedrine ER Tablets and 120mg Sudafed® 12hr Tablets, Fed Study.

Parameter	Least-Squares Means ¹		Ratio ²	CV% ³	90% Confidence Interval ⁴	
	Test	Reference			Lower	Upper
AUC 0-t (ng-hr/mL)	3744	3859	0.970	-	0.940	1.000
AUCinf (ng-hr/mL)	3844	3953	0.973	-	0.943	1.002
C _{max} (ng/mL)	297	327	0.908*	-	0.870	0.946
T _{max} (hour)	6.14	5.26	1.167*	-	-	-
Ke (1/hour)	0.1348	0.1364	0.988	-	-	-
T _{1/2} (hour)	5.26	5.23	1.006	-	-	-
Ln-Transformed:						
AUC 0-t (ng-hr/mL)	3660	3749	0.976	9.48	0.948	1.005
AUCinf (ng-hr/mL)	3759	3842	0.978	9.22	0.951	1.007
C _{max} (ng/mL)	288	320	0.902*	12.4	0.869	0.938

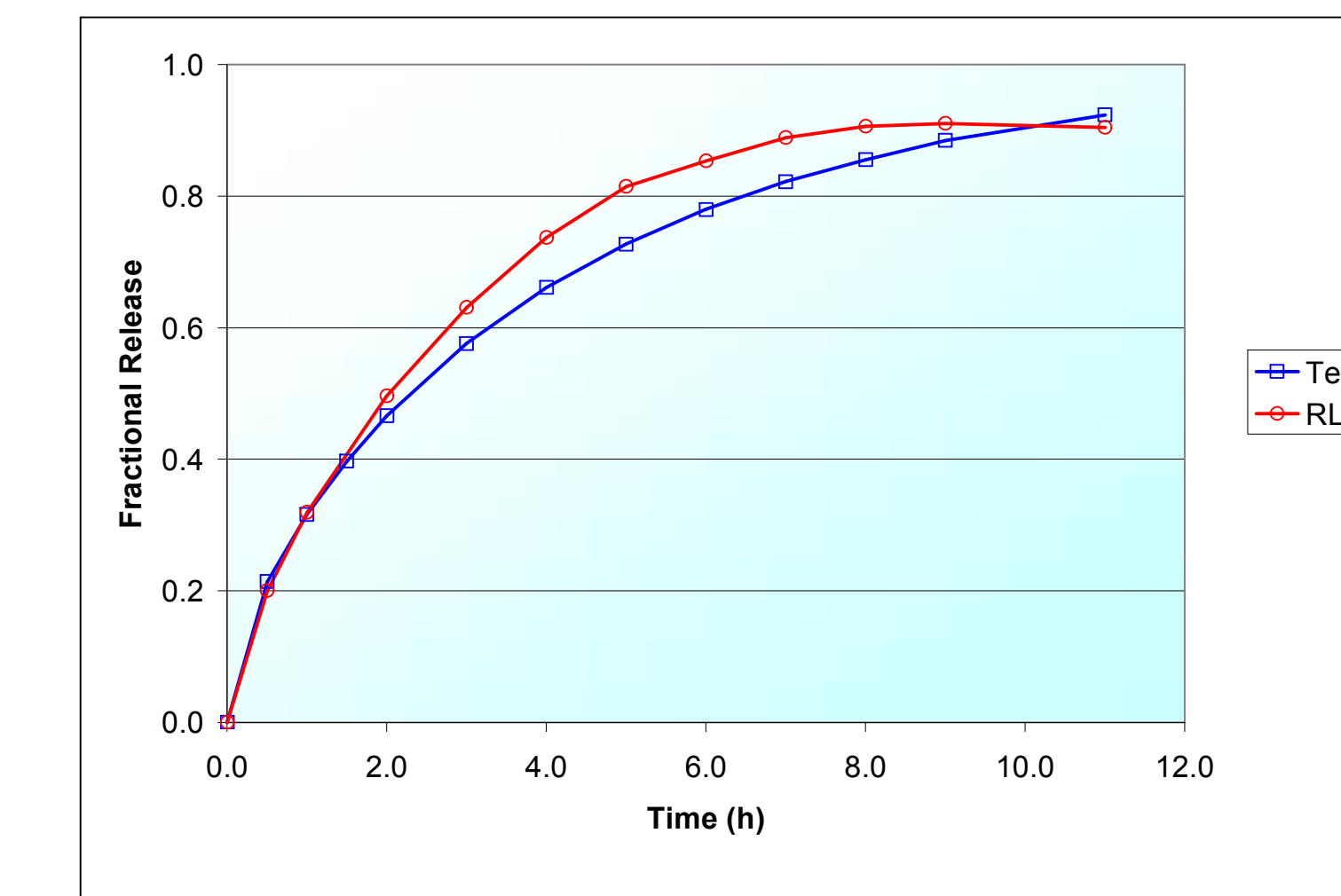
- Least-squares geometric means for ln-transformed data.
 - Ratio calculated as Test least-squares mean divided by the Ref. least-squares.
 - Estimated in-trial subject coefficient of variation, CV%=100*SQRT(e^{MSE} - 1), where MSE is the mean square error term from the ANOVA.
 - Confidence interval on the ratio.
- * Comparison was detected as statistically significant by ANOVA (α=0.05)

Graph 2. Least-Squares Mean pseudoephedrine Plasma Concentrations (N=59).



In Vitro Dissolution Comparison: Graph 1 shows the comparison in dissolution performance for the SCOLR hydrophilic polymer-based formulation and the wax-matrix reference listed drug with USP type II apparatus under standard conditions. Each is capable of a modified first order release profile.

Graph 3. In Vitro Dissolution of SCOLR 120mg Formula vs. RLD.



CONCLUSION:

We have demonstrated bioequivalence for the SCOLR Pharma 120 mg extended-release pseudoephedrine formulation to the reference listed drug. This tablet is a monolithic, direct compression formulation that is very efficient to manufacture, is of desirable size, and inexpensive to manufacture.

REFERENCES:

Pillay, *et. al.* Monolithic tablet for controlled drug release. U.S. Patent 6090411. (2001)

