

# Stability of ITCA 650 for Continuous Subcutaneous Delivery of Exenatide at Body Temperature for 12 Months

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## Introduction

The DUROS® delivery technology provides continuous administration of therapeutic molecules at steady rates. The DUROS device is an osmotically driven pump consisting of a small sterile titanium cylinder (4 mm in diameter and 44 mm in length) that is inserted subcutaneously.

Proteins and peptides can be formulated for use in DUROS devices to provide continuous delivery for chronic therapy. ITCA 650 (DUROS continuous delivery of exenatide) is in phase 2 clinical development for the treatment of type 2 diabetes mellitus.

The aim of this work was to achieve superior formulations with desired stability in DUROS devices and to deliver exenatide at continuous and consistent rates at body temperature for extended periods of time.

## Methods & Materials

Exenatide is a 39-amino acid peptide amide that is synthesized through solid phase peptide synthesis. It has 53% amino acid identity with human GLP-1 and activates the GLP-1 receptor.

The stability of exenatide was evaluated in proprietary suspension formulations at multiple dose levels and in DUROS devices designed to deliver drug for a range of treatment durations. These tests were conducted at temperatures simulating room temperature storage (25°C) and human body temperature (40°C).

Stability of exenatide in DUROS devices was characterized using RP-HPLC, SCX-HPLC, SEC-HPLC, and three bioassay methods.

In vitro delivery of exenatide from the DUROS devices was also performed at 37°C and the quantity of the released drug was measured by RP-HPLC methods as a function of time.

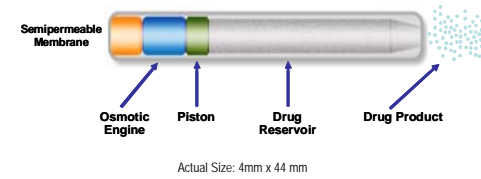
## Exenatide is Stable in DUROS Devices at 25°C and 40°C for at Least 12 Months

	10 mcg per day for 90 days					40 mcg per day for 90 days				
	Timepoint (Months)					Timepoint (Months)				
	0	3	6	9	12	0	3	6	9	12
<b>25°C/60% RH</b>										
Purity by RP-HPLC										
% Exenatide	100.0	100.0	99.8	99.7	99.6	100.0	100.0	99.8	99.8	99.7
% Total Impurity	0	0	0.29	0.28	0.38	0	0	0.17	0.25	0.26
Purity by SCX-HPLC										
% Exenatide	99.4	99.7	99.6	99.2	99.5	99.2	99.7	99.6	99.4	99.6
% Total Impurity	0.60	0.31	0.54	0.85	0.53	0.78	0.34	0.36	0.67	0.45
Purity by SEC-HPLC										
% Monomer	100.0	99.9	99.9	99.7	99.7	99.9	99.9	99.9	99.8	99.8
% Dimer	0.02	0.07	0.15	0.31	0.35	0.11	0.06	0.12	0.24	0.24
<b>40°C/75% RH</b>										
Purity by RP-HPLC										
% Exenatide	100.0	100.0	99.7	NT	99.6	100.0	100.0	99.8	NT	99.6
% Total Impurity	0	0	0.29	NT	0.38	0	0	0.24	NT	0.40
Purity by SCX-HPLC										
% Exenatide	99.4	99.5	98.9	NT	99.1	99.2	99.7	99.4	NT	99.3
% Total Impurity	0.60	0.49	1.10	NT	0.94	0.78	0.33	0.66	NT	0.70
Purity by SEC-HPLC										
% Monomer	100.0	99.9	99.9	NT	99.6	99.9	99.9	99.8	NT	99.7
% Dimer	0.02	0.09	0.15	NT	0.45	0.11	0.07	0.16	NT	0.34

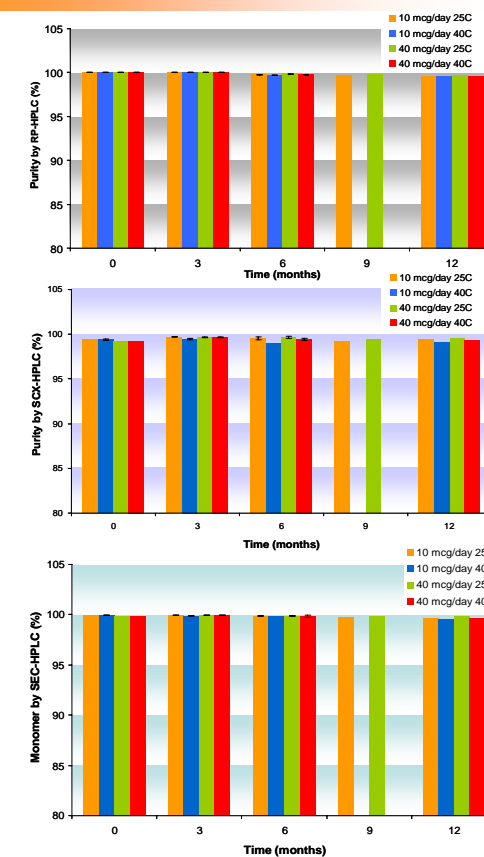
NT: Not tested

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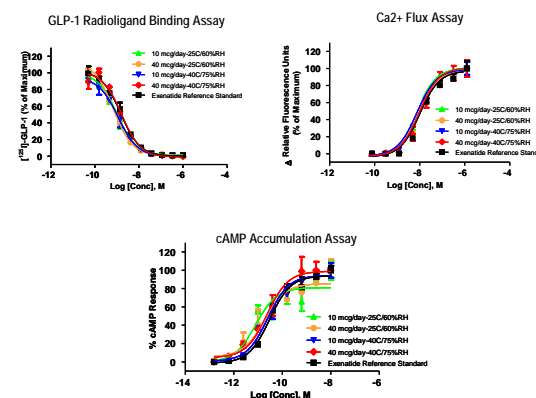
## Diagram of DUROS Device



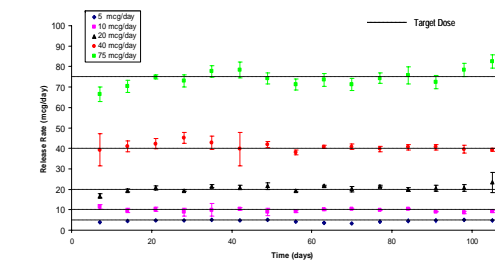
## Representative Stability of Exenatide in DUROS Devices



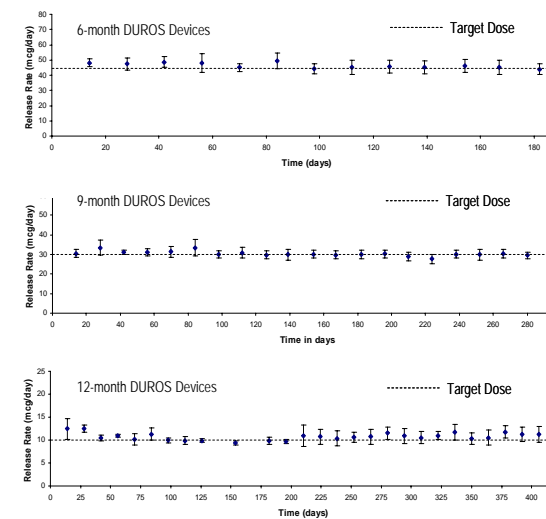
## Exenatide Stability in DUROS Devices - Full Bioactivity Retained



## In Vitro Release Rate of Exenatide from DUROS Devices at 37°C



## ITCA 650 Designed to Deliver Exenatide from 3 to 12+ months



## Results and Discussion

The selected formulations maintained the stability of exenatide in DUROS devices at 25°C and at 40°C for at least 12 months. Results from analysis of the formulation at 12 months for purity were 99.6%, 99.1%, and 99.6% by RP-HPLC, SCX-HPLC, and SEC-HPLC, respectively.

Bioactivity of exenatide remained unchanged throughout the stability studies.

Zero-order drug release profiles for ITCA 650 were observed for multiple dose levels and durations at 37°C. The release rates remained constant for each dose level and duration.

## Conclusions

Exenatide was successfully formulated and exhibited excellent stability in DUROS devices.

DUROS devices delivered exenatide at continuous and consistent rates for durations ranging from 3 to 12 months.

ITCA 650 demonstrated excellent stability for room temperature storage and administration at body temperature for 12 months.

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