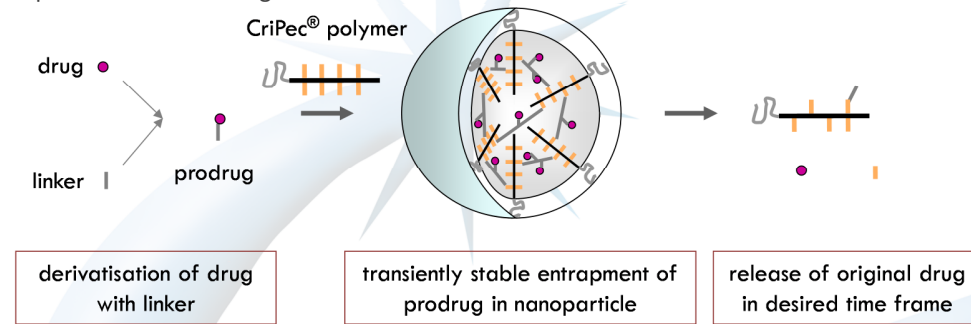


### Introduction

Cristal Delivery is a nanomedicine company that creates clear value for patients in areas of unmet medical needs. Our patented nanoparticulate drug carrier platform increases efficacy, safety and convenience of pharmaceutical products through tuneable and controlled drug release inside the body. Cristal Delivery is developing a proprietary product portfolio based on innovative combinations of its technology with development-stage as well as marketed drugs. Moreover, it offers pharmaceutical companies facing the “patent cliff” customised solutions to improve the therapeutic performance of their drug products.

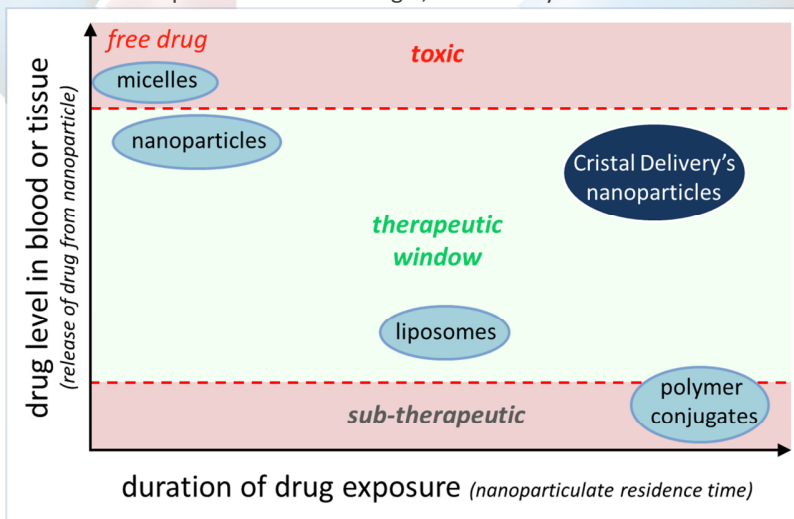
### The platform technology: CriPec®

Cristal Delivery has created a unique platform technology that transforms bioactive compounds into transiently stable nanoparticles, so-called CriPec®. This results in a superior control of pharmacokinetic parameters and tailored target drug levels. The basic concept is depicted in the following scheme:



### Unique features of CriPec® nanoparticles

Upon administration, the ideal nanoparticulate drug carrier is characterised by titration of residence time (determining duration of drug exposure) and of drug release (determining height of drug levels) into the therapeutic window. As seen in figure below, CriPec® nanoparticles have a high score on both features. Consequently, Cristal Delivery’s nanoparticles have a unique position in the nanomedicine field as they combine the best features of known nanoparticles into one single, tuneable system.

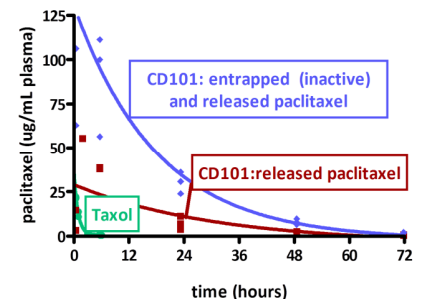


### Development stage

Prototype molecules (e.g. paclitaxel and dexamethasone) have been transformed into CriPec® nanoparticulate products. The experimental data packages provide substantial preclinical proof of concept of CriPec® with regard to improved pharmacokinetics, safety, efficacy and ease of manufacturing. These data underscore the broad potential and safety of CriPec®-based products in a variety of therapeutic areas.

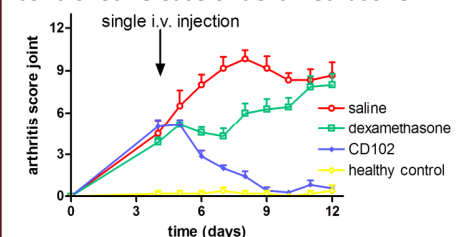
### Example 1: paclitaxel

Nanoparticulate paclitaxel (CD101) assured the absence of high peak levels while sustained paclitaxel release from the long-circulating, non-toxic CriPec® nanoparticles resulted in prolonged therapeutic levels up to at least 60 hours. Taxol (the current commercial formulation) blood levels fell rapidly below the therapeutic levels of approximately 1 µg/mL. The blood profile of CD101 versus Taxol after intravenous administration of equal dosages to healthy mice is depicted below.



### Example 2: dexamethasone

Mice with collagen antibody induced arthritis in the knee joint were treated by a single intravenous administration. Only our nanoparticulate dexamethasone (CD102) resulted in a pronounced suppression of the joint swelling, illustrating the enhanced localisation and controlled release of dexamethasone.



### Manufacturing

The manufacturing and storage of CriPec® nanoparticles is characterised by simplicity, reproducibility and efficient drug entrapment, offering significant advantages over other nanoparticulate formulations (e.g. liposomes). The main features are depicted in the tables below.

Characteristic	Beneficial properties
Process	Offline from fill & finish
# of synthesis steps	2
Drug to polymer ratio	> 15% (w/w)
Entrapment efficiency	> 75%
Reproducibility	Monodisperse particles, predictable drug entrapment

### End product

Characteristic	Beneficial properties
Impurities	No toxic solubilisers or organic solvents
Sterilisation	Filtration through 0,22 µm
Stability in solution	Stable upon several freeze-thaw cycles
Storage	Long-term storage as frozen or lyophilised product

### Potential therapeutic compounds

The type of compounds that benefit optimally from CriPec® are described below. Drug release rate depends on the type of prodrug used, which in turn is custom-based.

Characteristic	Properties
Log P	Hydrophilic and hydrophobic
Molecular weight	Low molecular weight compounds and shorter peptides
Route of administration	Parenteral (s.c., i.p., i.v. and others)

### In vivo performance

CriPec® nanoparticles show a long-lasting blood circulation, comparable to liposomes but with reliable and tuneable drug release. Other *in vivo* properties are depicted below.

Characteristic	Beneficial properties
Injection	Easy to administer, flexible as bolus or infusion
Blood profile	Long circulation
Tissue targeting	Increased accumulation at inflamed tissue Improved disposition (passive or active targeting)
Drug release	No burst release so no (unwanted) peak levels Tuneable release rate
Drug exposure	Sustained levels (days to weeks) Lower dosing frequency
Safety	Nanoparticulate drug is inactive No local toxicity at site of injection MTD at least above 1700 mg polymer/kg No unexpected toxicity nor accumulation

In summary, CriPec® nanoparticles display the benefits of prolonged blood circulation, including sustained presence at the site of action, and with a true control of release of entrapped drug molecules. This profile outperforms other technologies and products currently available.

### Potential applications of CriPec®

- To reduce peak levels upon administration
- To avoid burst release
- To improve solubility without compromising safety
- To improve disposition, and to target to specific cells
- To reduce injection frequency and to increase patient compliance
- To prepare long-circulating nanoparticles without the manufacturing complexities of existing technologies
- To create sophisticated solutions where conventional technologies have failed

### Patents

The CriPec® technology and corresponding products are protected by two granted patent families while two other patent families are pending.

### Partnerships

We are actively pursuing strategic partnerships with pharmaceutical companies to conduct custom-made feasibility and development studies.

### Contact

For more information about CriPec® and/or Cristal Delivery, please contact:

Cristianne Rijcken, PharmD PhD,  
Chief Executive Officer  
Cristal Delivery B.V.  
Padualaan 8  
3584 CH Utrecht  
The Netherlands  
+31 30 430 0222  
cristianne.rijcken@cristaldelivery.com  
www.cristaldelivery.com