LOGAN INSTRUMENTS CORP.

Application Note

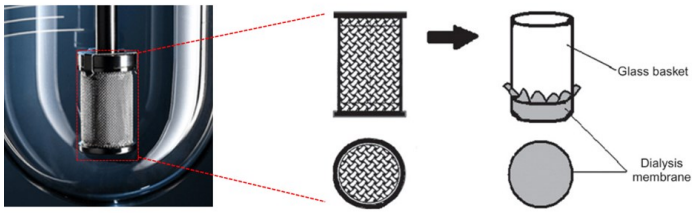
Apparatus for Dissolution Testing of Nanoparticles

Introduction

Development of nanocrystalline drugs for medicines is of interest because of their improved solubility, permeability and bioavailability compared with conventional dosage forms. Evaluating in vitro release is an important step in the development and quality control of these preparations. Various attempts have been made to create effective uniform testing protocols for nano-crystalline drugs. A particular challenge is the wide range of dosage forms for which nanocrystalline drugs are appropriate. Testing apparatus must mimic environments beyond traditional oral sold dose administration.

Various methods have been tried to measure release profiles of nano-crystalline drugs, including USP Apparatus I (basket), II (paddle) and IV (flow through cell). Difficulties with these methods include: immediate dissolution, filter clogging, adsorption onto filter and glass beads and difficulty maintaining a constant flow rate, have led to wide variability in results.

The preferred method utilizes closed dialysis membrane "bags" to contain the nano-crystals while the larger volume of release media is agitated around the membrane. Technical problems still exist with these approaches, in particular blinding of the membrane and leakage from the bag. To date there has not been a specific, commercially available device to enable this method that can be incorporated into a standard dissolution apparatus and workflow.

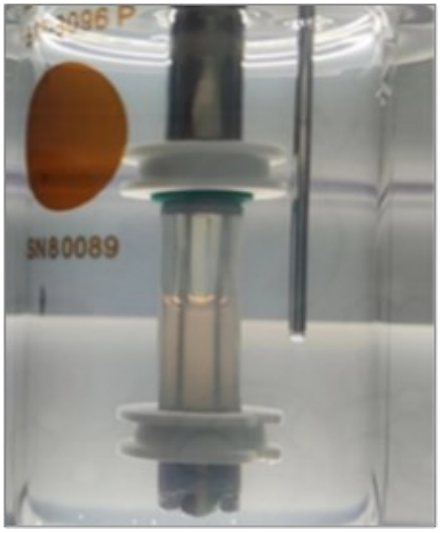


"Closed bag" nanoparticle dissolution apparatus

Logan's Solution

Logan Instruments Corporation has developed a purpose designed device to allow the dialysis membrane method to be used within a reciprocating flow through cell apparatus. The novel device consists of a frame that supports a dialysis membrane. The user selects the most appropriate membrane depending on the formulation. The membrane is secured to the frame using O-rings.

The nano-crystals are introduced into the interior cylinder void created by the membrane. The complete assembly is then fitted inside the flow cell and flooded with release medium. The apparatus uses a pump to constantly flow the release medium at a suitable temperature into the lower end of the flow-through cell. The release medium is filtered through the upper end of the flow-through cell. The concentration of the drug in the release medium is sampled and measured at suitable time points.



The dialysis membrane prevents the nanoparticles from entering the dissolution medium.

The mechanical reciprocating motion of the apparatus releases the nanoparticles int the medium though the membrane. The concentration of the drug in the release medium is sampled and measured at suitable time points.

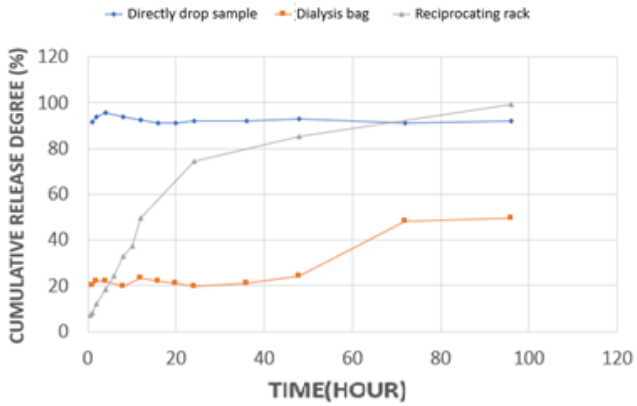
Results

Direct Drop - When the sample is dropped directly into the release media the sample diffuses rapidly throughout the system, resulting in rapid release and making it difficult to record differential behavior of formulations.

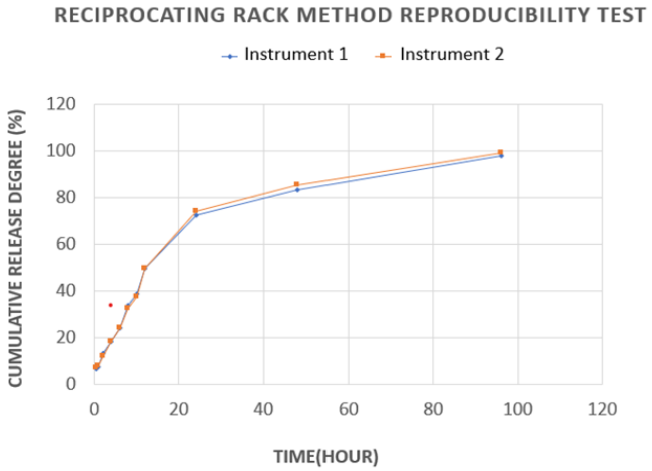
Dialysis Bag - When the sample is contained in a dialysis bag the sample is stationary and prone to precipitation.

Reciprocating Rack – The sample is contained preventing too rapid dissolution, but because of the reciprocating agitation the preparation is mobile within the frame preventing clogging of the membrane and limiting precipitation.

Following the observation of precipitation within the dialysis bag, a further refinement of the design was created. A conical bottom frame was tested and experiments run to compare the flat-bottomed and conical-bottomed nano-frames to observe the release of paclitaxel nanocrystal preparations using LOGAN's SYSTEM ADR III-7 reciprocating frame method.



Graph shows significant differences between dissolution methods



Graph shows good reproducibility between different instruments

0.6 mg/ml PXT nanocrystal

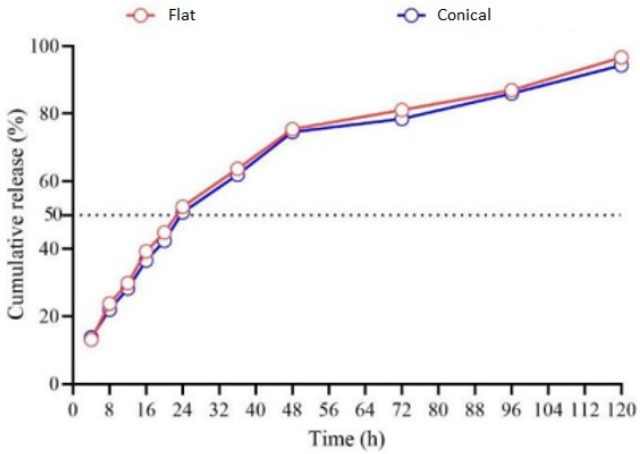


Figure 1a Cumulative release profile of 0.6 mg/ml paclitaxel nanocrystals in dialysis bags using flat or conical bottom frames.

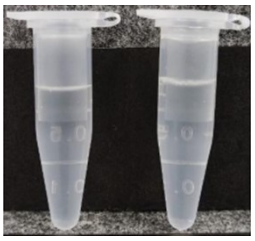


Figure 1b 120 h appearance of 0.6 mg/ml paclitaxel nanocrystal formulation in dialysis bag at end of release. Left flat-bottom frame, right conical bottom frame.

- No significant difference between release rates of PXT-NC using flat or coned frames.
- No precipitation

0.8 mg/ml PXT nanocrystal

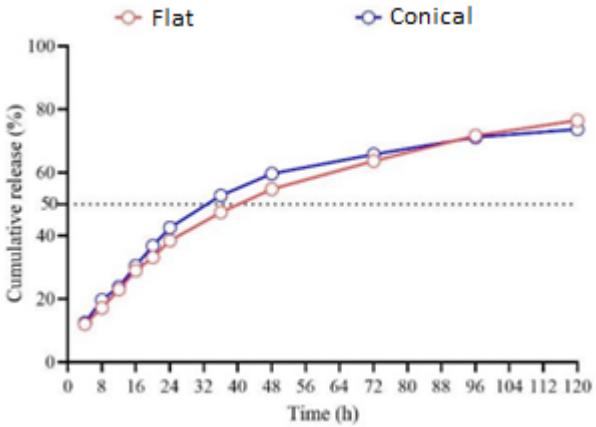


Figure 2a Cumulative release profile of 0.8 mg/ml paclitaxel nanocrystals in dialysis bags using flat or conical bottom frames.

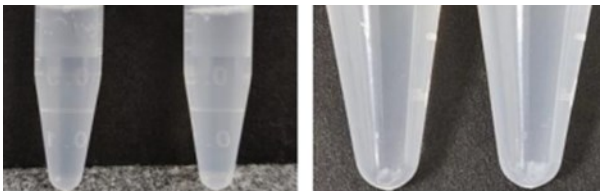


Figure 2b Appearance of 0.8 mg/mL paclitaxel nanocrystal formulation in dialysis bag at the end of release at 120 h (left) and after low -speed centrifugation (right)

- Cone bottom gives slightly faster release than flat bottom during early stages. Cone bottom helps disperse NCs.
- Overall lower total release than 0.6mg/ml
- Turbidity and precipitation

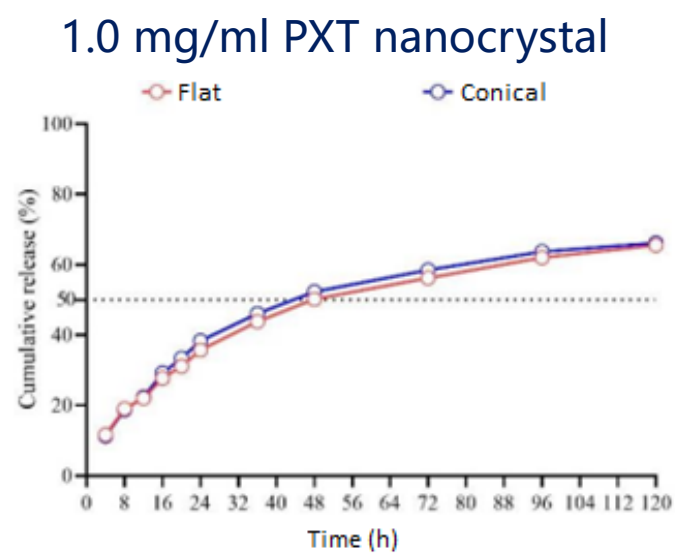


Figure 3a Cumulative release profile of 1.0 mg/ml paclitaxel nanocrystals in dialysis bags using flat or conical bottom frames.

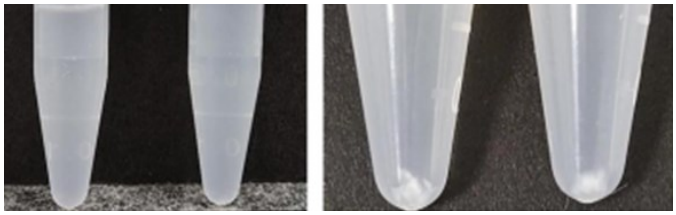


Figure 3b Appearance of 1.0 mg/ml PXT nanocrystal formulation in dialysis bag at end of release at 120 h (left) and after low-speed centrifugation (right)

- Cone bottom gives slightly faster release than flat bottom during early stages. Come bottom helps disperse the NCs
- Overall lower total release than 0.6 mg/ml and 0.8 mg/ml
- Turbidity and precipitation

Results

When using flat-bottomed or conical-bottomed nano frames for comparison of release tests in the Logan SYSTEM ADR III-7 reciprocating frame with paclitaxel nanocrystal formulation loaded into dialysis bag, it was found that:

(1) When no turbidity was observed, there was no significant difference in the release results. The release results of the flat-bottom or conical-bottom nano frames were not significantly different, and paclitaxel was completely released from the nanocrystalline formulation.

(2) When turbidity was present, there was a significant difference in the release results between flat-bottom and conical-bottom nano-frames, with the conical-bottom nano-frames improving the release effect, but paclitaxel was not completely released from the nanocrystalline preparations.

(3) The cumulative release rate of flat-bottom or conical-bottom nano-frames decreased further as turbidity increased.

When turbidity was generated during the release process, the conical-bottom nano-frames could improve the particle dispersion to a certain extent but could not resolve particle coalescence.

Conclusion

The new nano-drug dissolution system (compound frame method) is now used to promote drug release by reciprocating the frame to make the medium flow across the membrane surface, generating shear force. Using the Logan ADR III-7 apparatus the sample can be moved to fresh release medium by changing the row, which can eliminate the affect of drug accumulation in the medium. Also the sample can be moved to different medium if the study requires progression through alternative media such as change in pH

The reciprocating frame method is reproducible, functional and standardized, and can be used for the in vitro release of nano-injection formulations.

For more information please contact
Logan Instruments Corp. at
info@loganinstruments.com or through our
website www.LoganInstruments.com

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