Active Pharmaceutical Ingredients (API) in Nanoform

A well-established approach to improving the dissolution of poorly water-soluble drug molecules is to reduce their particle size. This is because the increased surface area of the dissolving drug particles correlates with faster dissolution rates. Reducing particle size to the nanometer range dramatically increases surface area, thereby offering the greatest potential for enhancing dissolution rate through this mechanism. Consequently, nanoparticle delivery of active components can provide faster dissolution, improved bioavailability, and ultimately, enhanced clinical efficacy.

Nanoparticles for Oral Drug Delivery

Nanoparticles are solid, colloidal particles composed of macromolecules ranging in size from 5 to 1000 nanometers. The drug of interest can be dissolved, entrapped, absorbed, attached, or encapsulated within the nanoparticle matrix. This matrix can be made from biodegradable materials such as polymers or proteins. Depending on the preparation method, nanoparticles can be obtained with varying properties and release characteristics for the encapsulated therapeutic agents.

Typically, nanosuspensions of active pharmaceutical ingredients are prepared by applying high shear forces to a mixture containing the compound, an aqueous dispersion medium, and milling media (via high-shear milling). In most applications, the milling media consists of small polyester pills propelled by the shear forces. These pills act like microscopic ball mills, impacting the drug compound present in the mixture (typically initially present as a macroscopic powder).

High-shear mixers with stainless-steel impellers rotating at several thousand RPM within a chamber holding the mixture are commonly used equipment for preparing nanosuspensions. An example of commercially available equipment employed in this process is the Elan Nanomill®.

The process involves first preparing a base for the oil-in-water emulsion, followed by the addition of water-soluble components to create the final emulsion. This technology allows for the creation of a wide range of products. When working with cannabinoids, for instance, it is possible to create both low- and high-concentration emulsions. The resulting emulsion exhibits stability for over three years as demonstrated in Appendix I.

Advantages of Nanoparticle Delivery Systems

The advantages of using nanoparticles for oral drug delivery, particularly for poorly soluble drug molecules, have been well documented for over 40 years. Nanosuspensions represent a powerful approach to improving the solubility and bioavailability of poorly water-soluble

drugs. Nanosuspensions can be administered via various routes, including oral, transdermal, ocular, parenteral, and pulmonary, to address a range of challenges.

Enhancing Oral Drug Delivery with Nano Emulsions

Our company's focus on nano emulsions for oral drug delivery offers several distinct advantages over traditional dosage forms:

- **Increased Absorption:** Nanoparticles, due to their increased surface area, can improve absorption in the gastrointestinal tract by interacting more effectively with the intestinal lining. This can lead to a higher proportion of the drug entering the bloodstream, potentially reducing the required dose.
- **Improved Stability:** Nano-emulsions, with their oil-in-water structure, can protect drugs from degradation in the GI tract. This enhanced stability allows for better delivery of the drug to the target site and potentially reduces the need for higher initial doses to compensate for potential degradation.
- **Targeted Delivery:** Certain nano emulsions can be modified to target specific regions of the GI tract. This targeted delivery can potentially reduce side effects associated with drugs that impact unintended areas of the digestive system and improve the efficacy of drugs that require absorption in a specific location.

Clinical Benefits of Nano Emulsion-Based Drug Delivery

The improved dissolution, bioavailability, and potentially targeted delivery offered by nano emulsions can translate to several clinical benefits:

- **Reduced Dosing:** Faster dissolution and improved bioavailability can potentially lead to lower required doses, reducing pill burden for patients and potentially minimizing side effects associated with higher drug concentrations.
- **Faster Onset of Action:** For drugs that require rapid absorption for therapeutic effect, nanoparticles can lead to a quicker onset of action, potentially improving patient outcomes.
- **Improved Patient Compliance:** Smaller and potentially faster-acting doses achieved through nano-emulsions can improve patient compliance with treatment regimens, leading to better overall clinical outcomes.

In conclusion, nano-emulsions represent a powerful approach for oral drug delivery, particularly for poorly water-soluble drugs. By improving dissolution, bioavailability, and potentially enabling targeted delivery, nano-emulsions can offer significant clinical benefits for patients. As research continues and safety considerations are addressed, nanoparticle technology has the potential to revolutionize how we deliver medications and improve patient outcomes.

IVPMED's Contribution

IVPMED's development of the Slyde Nebulizer, a groundbreaking two-pod nebulizer system, positions us at the forefront of nano-emulsion-based drug delivery. This innovative device offers several distinct advantages over traditional nebulizers and highlights our commitment to improving patient care:

- **Meter Dose Precision and Compound Control: The** Nebulizer's two-pod design allows for separate storage of the drug and carrier solution, providing precise control over the delivered dose. This accuracy is crucial for safe and effective medication administration, particularly for patients requiring specific dosages.
- **Empowering Medical Professionals with Real-Time Data:** The Nebulizer can potentially integrate with real-time data monitoring systems. This feature could provide valuable insights into treatment progress, allowing healthcare professionals to personalize treatment plans and optimize patient outcomes.
- **Advanced Compound Delivery:** The Nebulizer's design may facilitate the delivery of complex compound formulations, potentially expanding treatment options for a wider range of conditions.
- **Unparalleled Dosing Accuracy:** By combining meter dose precision with potential real-time data monitoring, the Nebulizer can ensure patients receive the exact amount of medication prescribed, reducing the risk of under- or over-dosing.

Appendix I: Cannabinoid Nano-emulsion Stability Tests

Table 1. Particle Size Measurements.

Cannabinoid	Concentration (mg/ml)	Average Diameter (nm)	Polydispersity Index
CBD	0.5	8.57	0.15
	20.0	26.5	0.17
	100.0	86.1	0.24
Δ^8-THC	10.0	40.0	0.18
	50.0	62.0	0.19
	125.0	96.7	0.29
Δ^9-THC	10.0	22.0	0.17
	50.0	56.8	0.19
	125.0	112.6	0.26

CBN	0.5	10.82	0.11
	20.0	18.94	0.15
	100.0	79.34	0.21

Table 2. Stability at 4°C (RH 56%; number of measurements – 5; PDI < 0.15).

Concentration of Δ^8 THC (mg/ml)	Initial Size (nm)	Size after 3 months (nm)	Size after 12 months (nm)	Size after 25 months (nm)
10	8.57± 0.21	10.31± 0.28	10.71± 0.25	11.08± 0.27
50	22.0± 0.11	22.64± 0.17	25.7± 0.22	27.8± 0.25
125	86.1± 0.31	88.7± 0.33	92.5± 0.30	98.9± 0.33

Table 3. Stability at 25°C.

Concentration of Δ_8 THC (mg/ml)	Initial Size (nm)	Size after 3 months (nm)	Size after 12 months (nm)	Size after 25 months (nm)
10	8.57± 0.21	11.01± 0.18	11.07± 0.15	12.17± 0.17
50	22.0± 0.11	24.71± 0.10	25.12± 0.20	28.01± 0.18
125	86.1± 0.31	89.25± 0.23	90.51± 0.18	99.02± 0.23

Table 4. Stability at 40°C.

Concentration of Δ_8 THC (mg/ml)	Initial Size (nm)	Size after 3 months (nm)	Size after 12 months (nm)	Size after 25 months (nm)
10	8.57± 0.21	11.17± 0.18	11.71± 0.20	12.08± 0.31
50	22.0± 0.11	22.24± 0.20	25.17± 0.28	27.92± 0.20
125	86.1± 0.31	87.75± 0.25	90.68± 0.42	99.1± 0.53

Table 5. Average Size Measurements of Cannabinoid Nano-emulsions Stored in Semi-Closed Vials.

Nano-emulsion of Cannabinoid at 10 mg/ml	Initial total weight (g)	Size at the initial day (nm)	Size measured after 8 months (nm)	Size measured after 15 months (nm)
CBD	3.26	19.88	27.78	37.69
Δ^9-THC	3.501	83.12	89.61	94.09
Δ^8-THC	3.808	37.37	58.78	76.19
CBN	3.428	18.52	27.78	33.03