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Comparative assessment of opioid reversal marketed and in-house nasal spray formulation by using the Malvern Spraytec

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ABSTRACT

The spray droplet size plays an important role in targeted nasal delivery. The particle size directs the formulation to site of action based on the spray droplet size. The FDA guidance for nasal spray are getting stringent day by day the generic players are struggling to achieve the specification as per guidance. Though the qualitative (Q1) and quantitative (Q2) sameness optimized by generic player but the performance may alter because of recipe used by Innovator Company. The current research focuses on the comparative assessment of spray droplet size of marketed formulation and in-house formulation to understand the performance similarity between them. The Malvern Spraytec instrument used to study the spray droplet size. The method parameters were optimized and the formulations were analysed using same method parameters to avoid the artifacts. The spray droplet size was determined and found to be similar. The employed method used for the analysis can be used for routine analysis.

Introduction

Naloxone nasal spray is life saving medicine used as an opioid reversal in opioid overdosing to rapidly reverse opioid overdose.[1] The formulation consist of 4mg Naloxone HCl along with that the formulation contains EDTA and Benzoalkonium chloride in saline solution.[2] It's mechanism of action includes, binding to the receptors in the brain where opioid binds, effectively it displaces opioid and reverse the effects of opioid. The spray comes in unidose device for single time use which is administered by nasal route placing nasal into one of the nostrils and pressing the plunger to administer the dose.[3] The formulation available as a over counter medicine in US market, and is a crucial tool in addressing the opioid crisis.[4] The unidose spray device is designed in for its ease of use, which allows individuals to administer the medication during an emergency without any expertise.[5]

Naloxone is an opioid antagonist. It act by competing with opioid for these receptor sites, and displaces the opioid from the receptors Naloxone nasal spray acts by rapidly reversing effects of opioid through its action on opioid receptors in the brain.[6] Opioid, like morphine, heroin, or prescription painkillers, shows their effects by binding to specific receptors available in the brain known as opioid receptors (μ- receptors).[7]

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When opioid binds to these receptors get activated, and produce the effects like pain relief, euphoria, and, on overdosing, respiratory depression (slowed or stopped breathing), which can be life-threatening.[8]

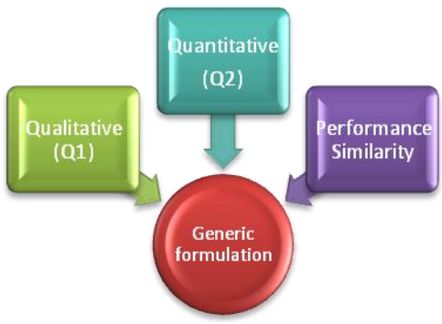

Fig.- 1: FDA Guidance for Generic nasal spray

Once Naloxone binds to the opioid receptors, it blocks the effects of opioid, including their life-threatening impact on breathing. This action can rapidly restore normal breathing and consciousness in someone experiencing an opioid overdose. Naloxone has a relatively short half-life compared to many opioid, which means its effects may wear off faster than the opioid in the system. This is why it's crucial to seek emergency medical help after administering Naloxone, as additional doses or medical intervention might be needed.[9] Naloxone works by competitively binding to opioid receptors and reversing the effects of opioid overdose, particularly the dangerous respiratory depression associated with opioid toxicity.

To show bioequivalence as per FDA guidance, the test (T) product should contain no difference in active and inactive constituents or in other aspects of the expression relative to the reference standard (RS) product that may significantly affect the original or systemic vacuity of the active component. For illustration, the T product can be qualitatively (Q1) and quantitatively (Q2) the same as the RS product to satisfy no difference in inactive constituents. FDA recommends conducting the Droplet size distribution by laser diffraction to show the similarity with the reference standard.[10]

The spray droplet size of Naloxone nasal spray generally ranges between 20 to 100µm.[11] This range ensures that the size of droplets is small enough to be effectively inhaled into the nasal passages and reach the nasal mucosa for absorption.[12]

Droplets size less than 20 µm are keep for lung delivery.[13] Whereas droplets greater than 100 µm may not effectively reach the nasal mucosa alter the absorption of drug also it may cause patient discomfort.[14] The specific formulation and design of the nasal spray device are optimized to achieve this balance and provide effective delivery of Naloxone to reverse opioid overdoses.[15]

Spraytec instrument from Malvern used to analyze the droplet size of the nasal spray. This instrument is often used in research, development, and quality control for pharmaceuticals, and manufacturing.[16] The Spraytec instrument works on the principle of laser diffraction; it measures the particle size distributions of spray droplet. The instrument measures angular intensity of scattered light by a spray droplet which comes in contact with a laser beam. Using an appropriate optical model the size distribution calculated using recorded scattering pattern.[17, 18]

The instrument consists of Helium-Neon laser, Collimating optics, Measurement zone, Fourier lens, Silicon diode detector array, Rapid data acquisition system.[19, 20]

Helium-neon (He-Ne) lasers are commonly used as a source of light in particle size analyzers. Though the He - Ne lasers are cheaper than other types of lasers. But have wide range of application. He-Ne laser emits light at 632.8nm stable wavelength, gives a consistent reference for measurements. Stability in laser intensity is a crucial in particle size analyzer for accurate and repeatable results. The light beam quality produced by He-Ne laser is good. Beam emitted by He-Ne lasers have very low divergence. The light produced by a He-Ne laser is highly coherent.[21]

Fig -2: Instrumentation of Malvern Spraytec

Collimating optics designed to transform the laser beam into a parallel or collimated beam. It consists of lenses and mirrors designed to shape laser beam in parallel path Collimating optics are aligned in such a way that the entire volume of the spray is evenly illuminated. Improves measurement Accuracy and minimize optical distortions which improve the sensitivity and resolution of the measurements.[22]

Measurement zone is an optical setup made between the source of laser beam and the detector it is basically the region within which sample is sprayed which is illuminated by the laser beam to analyze the sample. [23]

Fourier lens analyzes the light scattered by particles in the measurement zone. Fourier lens transform the spatial distribution of light into its frequency components, which is vital for analyzing the scattered light patterns from particles. , the Fourier lens allows the system to capture the angular distribution of scattered light. This angular distribution is directly related to the size and shape of the particles. It performs a spatial Fourier transform, converts scattered light into a frequency domain representation, which is used to determine particle size and distribution. This optical component used to enhance the accuracy, sensitivity, and resolution of the particle size measurement system. Fourier lens helps to improve the resolution of the measurement system by enabling better separation of the scattering patterns of different particle sizes.[24]

Silicon diode detector array is to detect and analyze the scattered light from particles. The determination of particle size distribution performed by measuring the intensity of scattered light at different angles, the array enables accurate determination of particle size distribution. The use of silicon photodiodes helps to provides high sensitivity, broad angular coverage, and reliable performance.[25]

Rapid Data Acquisition system quickly gathers and analyzes data on particle size distribution of spray. This helps to make real-time monitoring of spray characteristics and enable immediate adjustments to get optimal performance and consistency in results.[26]

Method and Materials

The instrument Spraytec Make Malvern works on laser diffraction (Mie Theory and Fraunhofer Approximation with Multiple Scattering correction) having data acquisition rate Rapid 10kHz. Maximum measurement rapid mode 30sec comprise of He-Ne Laser as source of light, 632.8nm with lens 300 mm with parallel beam lens arrangement, Detector with 36 element log-spaced with0.015-17° angular range with automatic rapid align system. Spraytec software integrated with the 21CFR Part 11.[27] The RLD samples were procured from US market. In-house formulation was prepared in the lab using formula obtained by reverse engineering.

Droplet-size analysis of nasal spray was performed by laser diffraction technique using a Malvern Spraytec sizer software. Before starting an experiment, each formulation was taken out from the wrapper and allowed it to stabilize at room temp. Instrument was powered ON prior 30min of experiment. The instrument was initialized and background measurement was performed ensured background laser intensity was below 200, analysis was performed by spraying the formulation in the measurement region. All measurements were made at room temperature (208–238C). The samples were analysed using following method parameters.

Table-1: Method Parameters for the Malvern Spray Tec

Measurement Values and Settings	
Instrument	Spraytec –Open Spray
Rapid measurement	
Trigger	transmission <93%
Trigger delay	0.0 ms
Lens	300mm
Path Length	100.0(mm)
Particulate Refractive Index	1.33+ 0.000i
Scatter start	1
Dispersant Refractive Index	1.00
Scatter end	36
Particle Density	1.00(gm/cc)
Scattering threshold	1
Residual	0.31 (%)
Minimum size	0.10(µm)
Extinction analysis	Off
Maximum size	2500.00 (µm)
Background duration	10sec
Inspect stage after background	enable
Duration per event	150ms
Multiple Scatter	On
Obscuration range	70-90%

Data were reported as volume diameter defined by 10%, 50% and 90% of the cumulative volume undersize (Dv10, Dv50, and Dv90, respectively). Span expressed as (Dv90-Dv10)/Dv50.

Results and Discussion

The Naloxone nasal spray (marketed and in-house) samples were analysed by Malvern Spraytec using the same method parameters to shows the similarity in the results, as per the FDA guidance. The results obtained by the analysis using Malvern Spraytec can be correlated to show the similarity. The results obtained were as within a limit and in accordance with USP chapter 429.

	RLD	In-House
Dv (10)	30.41	30.35
Dv (50)	42.28	42.24
Dv (90)	58.95	58.90
SPAN	0.675	0.675

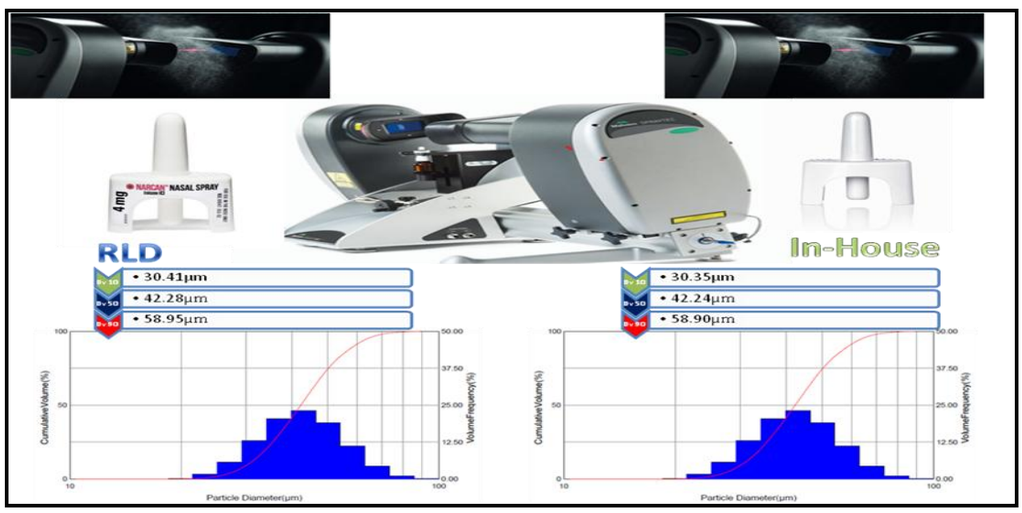

Fig.- 3: Comparative spray droplet size of nasal spray

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