Proceeding of ICNM - 2009

1st International Conference on Nanostructured Materials and Nanocomposites (6 – 8 April 2009, Kottayam, India)

Published by : Applied Science Innovations Private Limited, India.
http://www.applied-science-innovations.com

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NANO-DRUG PARTICLE INHALATION TECHNOLOGY: NOVEL FORMULATIONS AND THEIR CLINICAL IMPLICATIONS

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Drug administration by inhalation is a preferred route for treating localized respiratory conditions, and indeed for systemic drug absorption. Theoretically, instant local action and higher pharmacological action in the lung at a significantly reduced dose leading to reduction in adverse effects, and fast systemic absorption circumventing the need for painful intravenous injections, are the benefits of inhalation therapy. However, in clinical practice, the method has largely failed because of poor lung targeting by the conventional technology using micronized particles.

Using nanotechnology, the problem has been largely circumvented because the drug delivery to the lung increases manifolds. We have developed several nano-based inhalation formulations, including Dry Powder Inhalation and nebulizable respiratory solutions, for various clinical applications, and shown their distinct clinical advantage over the conventional technology. An example is nano-salbutamol, that has been shown extremely useful in treating acute mountain sickness through user studies in Ladakh, and continuing studies suggests a beneficial role in bronchial asthma, COPD, pulmonary hypertension and interstitial lung diseases. Other novel products include nano-particles of fluticazone, alphaketoglutarate, atropine and a few chelating agents. We are performing clinical trials with these in different clinical settings. Nano-fluticazone may have a role in non-cardiogenic pulmonary edema and inflammatory pneumonitis of toxic origins.

Nano-alphaketoglutarae Dry Powder Inhalation has been specifically made for hydrogen cyanide inhalation toxicity seen so commonly in fire-fighters and that can be lethal in larger concentrations. Nano-atropine DPI shall find its use as a life-saving medicine in field treatment of nerve gas poisoning, as the bioavailability is significantly better than intramuscular injection.

By performing radiolabeling of the drug particles and using gamma scintigraphy on humans, we have been able to demonstrate 10-16 times better drug delivery to the lung, prior to conduction of extensive clinical trials. Scintigraphy in humans helps in calculating exact dose of the drug internalized and deposited in lungs. This data helps in deciding the dose and frequency of administration of the formulation in human beings.

The communication describes common development features of all the formulations, with nano-salbutamol sulphate inhalation as the case in point. It relates to the provision of dry powder inhalers by forming nanosized particles of inhalable drugs with salbutamol sulphate as the case point, in order to augment the drug penetrability and particularly enhance the deposition in the lungs. Salbutamol sulphate (SBM), an antiasthmatic was developed into a nanosized formulation by different techniques like solvation, high pressure homogenization and spray drying which were then compared on the basis of particle shape, particle size and particle size distribution.

In case of solvation method the nanosuspension was prepared by dispersing SBM into a nonsolvent with excipients. The particles obtained were in the range of 2-10 μm.

The second attempt was made by passing the suspension of SBM through high-pressure homogenizer at 10,000-15,000 psi. A treatment of six cycles of homogenization gave a nanosuspension with a size range 50-100 nm. The only drawback seemed to be low product yield and high processing time (3-4 hr).

The third technique, spray drying, was further explored. SBM was stirred on magnetic stirrer at 1200 rpm and finally dried by using spray dryer at an inlet and outlet

temperature of 75 °C and 56 °C respectively. The feed rate for spray dryer was kept to be 91 ml/hr. Particle size distribution was in the range of 50-100 nm. Keeping in view the positive outcomes in terms of higher yield and lower processing time, the spray drying technique was taken to give the optimized formulation.

Nanosized particles, thus obtained were evaluated for particle size, surface topology and particles size distribution, by Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), and Quasi-Elastic Light Scattering (QELS) technique respectively. The nanosized particles were subjected to investigate changes on the physical stability of the powder using Fourier Transform Infrared Spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD) analysis.

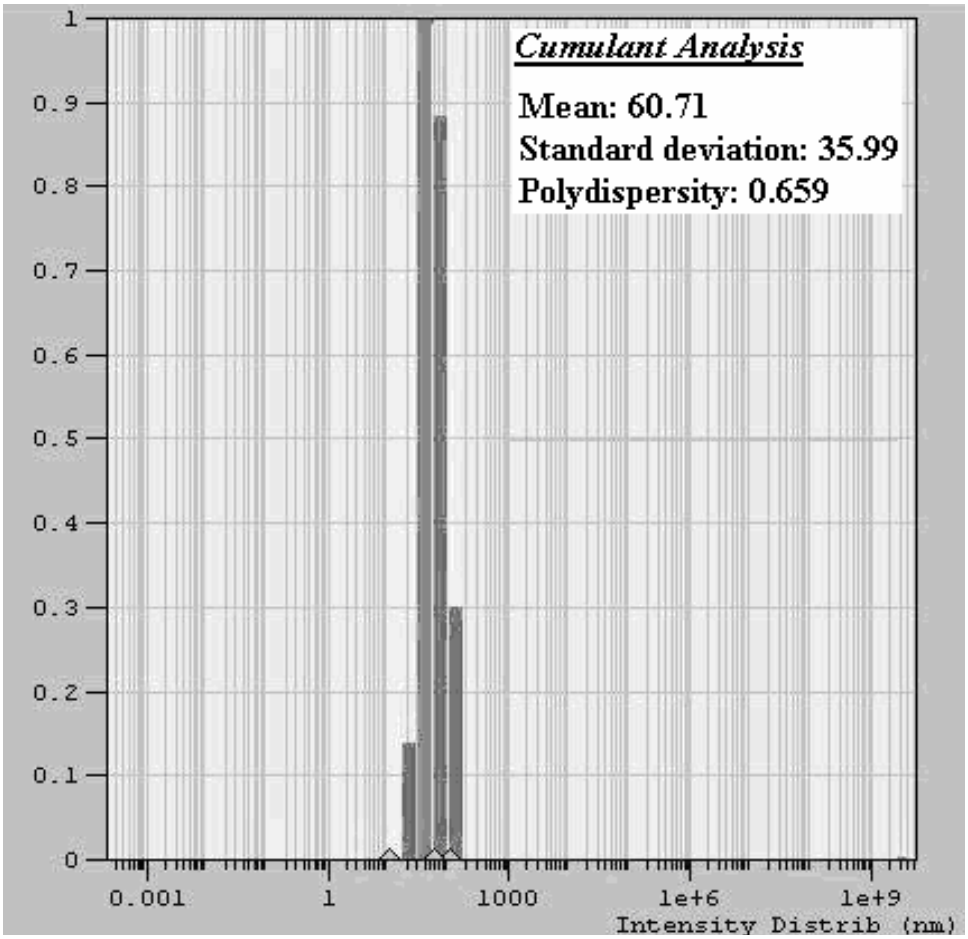

Fig. 1. Particle size distribution of Nano-SBS prepared by liquid anti-solvent precipitation followed by spray drying technique. (Mean particle size (SD) : 60 ± 35)

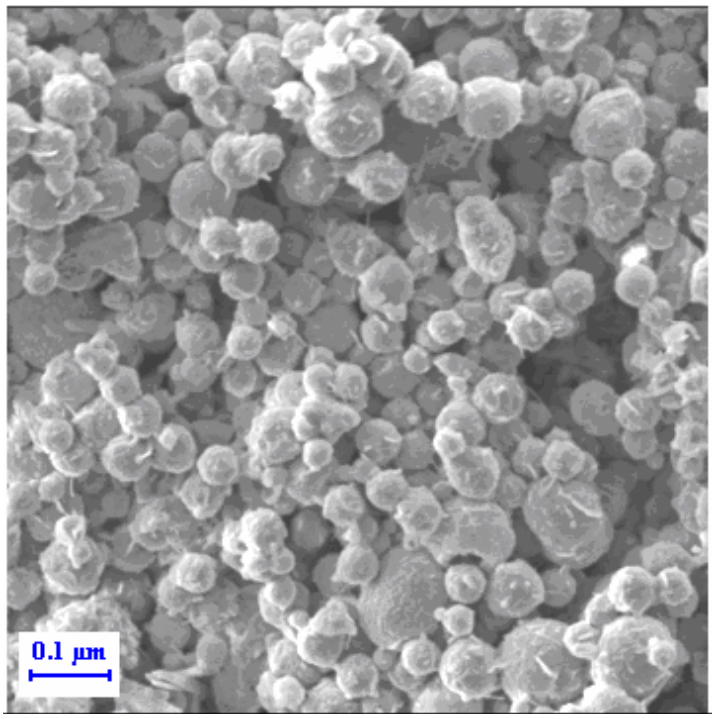

Fig. 2. SEM photomicrographs of a Nano-SBS powder.

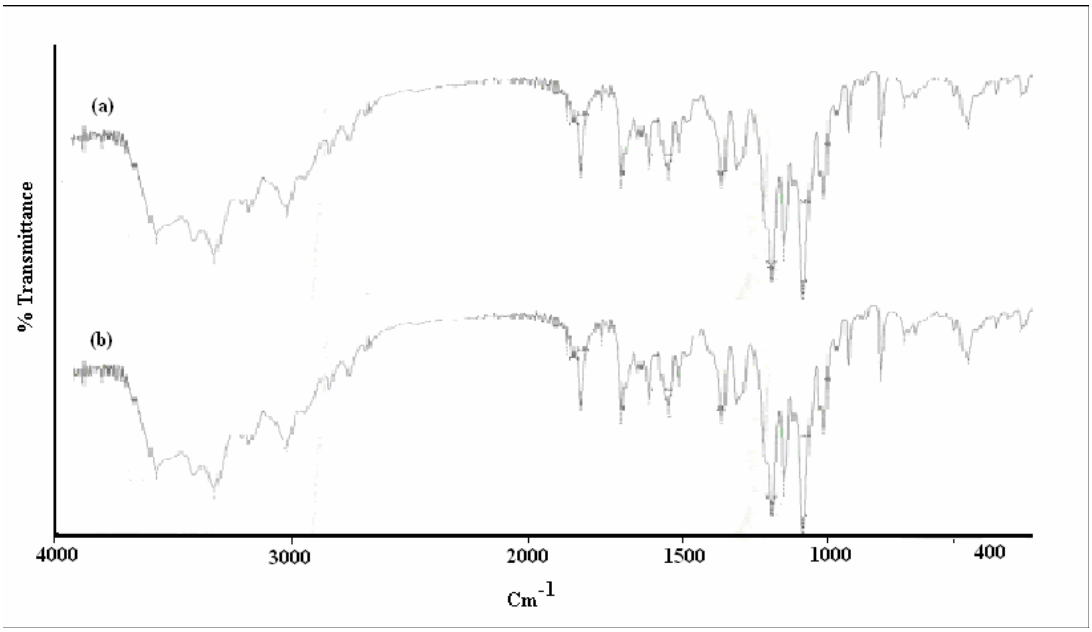

Fig. 3. FT-IR spectras of micronized SBS and nano-SBS**.**

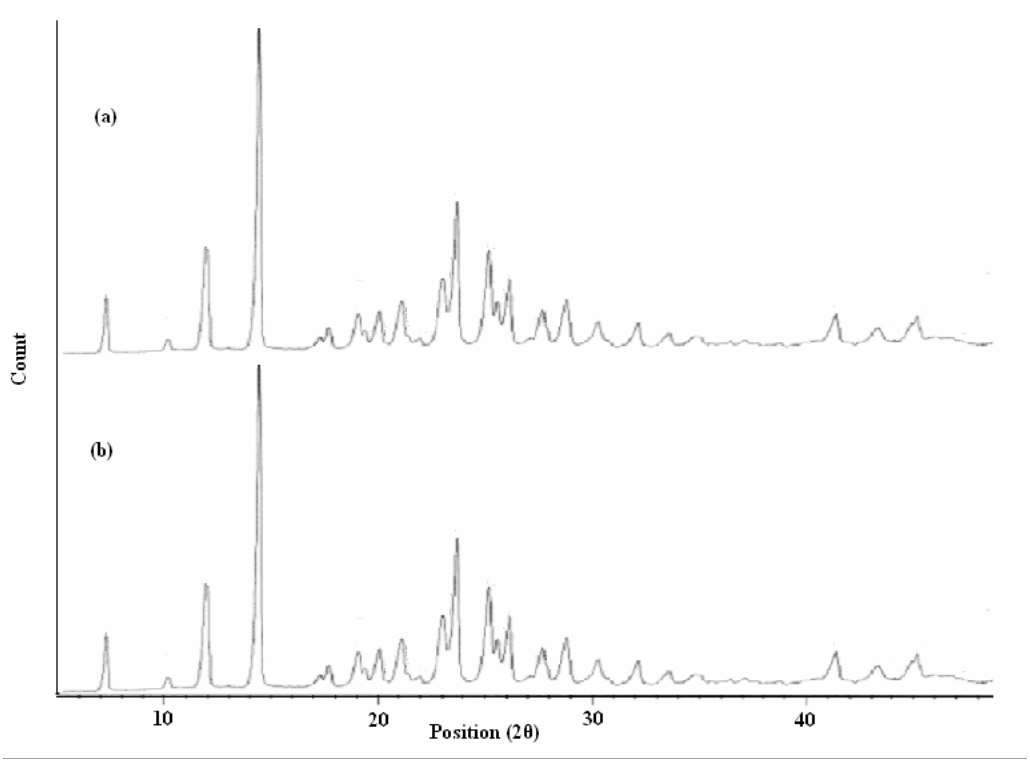

Fig. 4. Comparative XRD pattern of micronized SBS and nano-SBS**.**

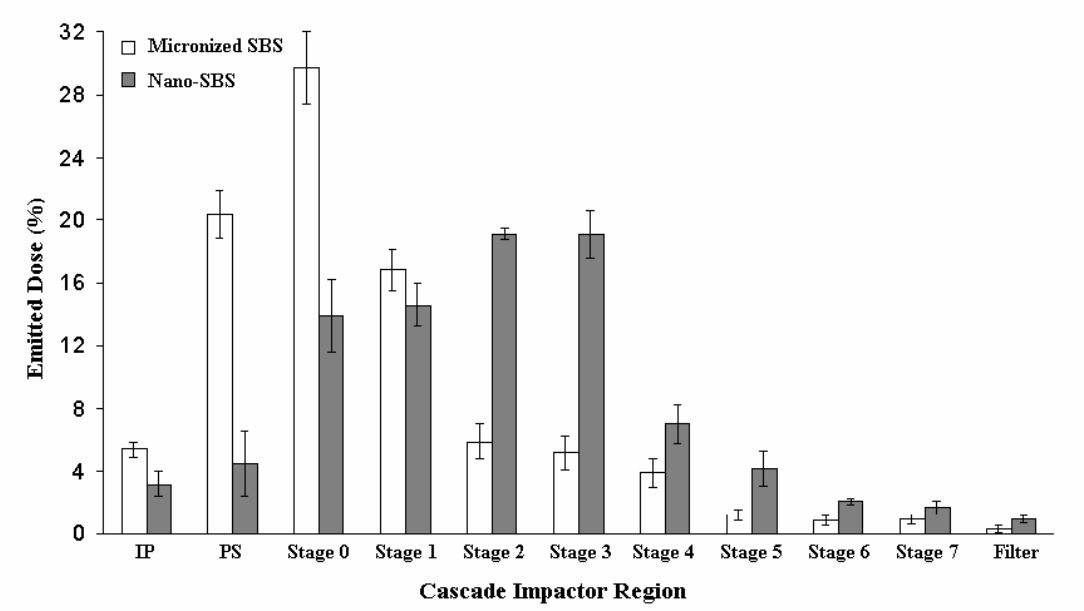

Fig. 5. ACI deposition profiles for micronized SBS and nano-SBS formulations showing mean (SD) percent emitted dose deposited on each stage of the ACI using Rotahaler® at 60 L min−1 (n=6) .

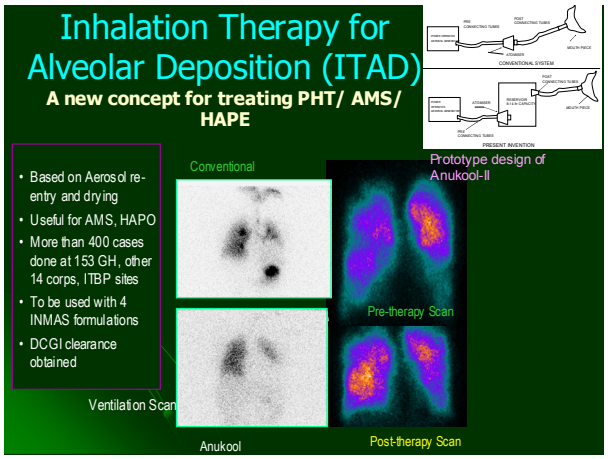

Fig 6: Human scintigraphy with nano-drug inhalation therapy offering proof-of-concept.

Table 1: Andersen Cascade Impactor (ACI) results for the DPI formulations measured using an airflow rate of 60 L min-1 (n=6)

	Nano-SBS	Micronized SBS
Emitted dose (%)	91.3 ± 3.20	90.8 ± 2.90
Respiratory fraction a (%)	69.7 ± 5.20b	32.1 ± 3.10
Total recovery	96.3 ± 1.18	97.2 ± 2.38
MMAD (μm)	1.61 ± 0.01	3.08 ± 0.04
GSD (μm)	1.82 ± 0.02	4.24 ± 0.08

a Respiratory fraction calculated as ratio of total drug deposited in the lower stages of the ACI (stage 2 to 8) to total theoretical dose
b$P < 0.001$ vs. micronized SBS.

Clinical trial with Nano-salbutamol in Acute Mountain Sickness (carried out at ITBP sector Hq, Leh)

Benign acute mountain sickness is very frequent at high altitude. Presently acetazolamide based therapy is prescribed which is not very effective. We recently observed that adding ethanol to salbutamol sulphate respiratory fluid and using a large spacer produces submicron sized drug aerosols with enhanced lung deposition. This may results in reduced pulmonary artery pressure and increased blood oxygen. *Objectives:* to introduce 0.25% salbutamol sulphate Inhalation Therapy for Alveolar Deposition (ITAD) formulation for treating benign AMS, and to conduct phase-2 clinical trial with the formulation as a stand-alone therapy in comparison with acetazolamide based conventional treatment. *Methods*: After developing and characterizing the new salbutamol-sulphate formulation that has the property to produce submicron-sized or nano-sized inhalable particles upon nebulization, the test formulation was given as a

stand-alone therapy to four times a day for 2-4 days to 44 subjects with benign mountain sickness. Control group of 32 AMS subjects was given acetazolamide-based oral treatment for the same duration. Efficacy of the two treatments was compared using Lake Louise score, pulse-oxymetry, hospital stay,1-min walk test, and response rate at 36 and 48 h. Response rate was defined as complete disappearance of symptoms. *Results*: In 48 h, Lake Louise score reduced very significantly in test group compared to conventional treatment (0.9 after 48 h from 5.1 compared to 1.9 from 3.8 using acetazalamide)($p < 0.001$) . Complete response with the test formulation was significantly faster than control treatment at 36 & 48 h ($p < 0.001$) resulting in shorter hospital stay ($p < 0.01$). Blood oxygen improved significantly with test formulation though the effect on heart rate and exercise capacity was marginal. Significantly, diastolic pressure also reduced within 2 days. The study suggests that stand-alone treatment with nebulized submicron-sized salbutamol sulphate is significantly superior to acetazolamide-based oral treatment for managing benign acute mountain sickness in medical units at high altitude.

Table-1: Comparison of quantitative parameters of Grp A(test formulation) and Grp B(conventional treatment)

Parameter	**Grp A(pre-treatment)**	**(48h)**	**Grp B(pretreatment)**	**(48 h)**
LL Score	5.01	0.9*[1]	3.81	1.87*[2]
Response Rate(LL < 1)(36 h)		79.5%		10 %**[1]
Response Rate (48 h)		96%		18%**[2]
Mean Hospital stay		2 days		3 days**[3]
SPaO2	88.3%	93.64%*[3]	91.46%	90.12%*[4]
HR/min	85.15	79.5%*[5]	83.65	80.59*[6]
Systolic BP	127	125.7	124.18	128
Diastolic BP	98.68	84.95*[7]	83.06	84.31
Walk test Oxygen dip		- 1.75%		- 1.87%**[4]
Walk test HR increase		+ 4.75		+ 7.35%**[5]

Intragroup comparison		Intergroup comparison	
*[1]	P < .01	**[1]	P < .001
*[2]	P < .05	**[2]	P < .001
*[3]	P < .01	**[3]	P < .01
*[4]	P > .05(insignificant)	**[4]	P > .05
*[5]	P < .05	**[5]	P < .05
*[6]	P > .05(insignificant)		
*[7]	P < .01		