CARRIER MEDIATED DRY POWDER INHALER FORMULATION OF RIFAMPICIN: PERFORMANCE EVALUATION

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Abstract

Lung targeting of anti tubercular drug can lead to reduced dose and side effects. In the present study, carrier mediated dry powder formulation of rifampicin was prepared in order to achieve local targeting into the lungs. The formulation was prepared by simply mixing the micronized form of drug with mixture of coarse and fine lactose. Preliminary batches were prepared with different lactose grades such as Inhalac®, Lactohale® and Respitose®.The amount of drug and the amount of fine lactose were optimized using 3^2 factorial design. Andersen cascade impactor was used for carrying out *in vitro* lung deposition studies. *In vitro* toxicity of the formulation was carried out on macrophage J774 cell lines. *In vivo* lung retention studies of the powder were carried out in rats using X- ray imaging technique. Pulmokinetics of the developed DPI was compared to the marketed formulation. On the basis of flow properties, selected coarse and fine lactose were Inhalac® 230 and Inhalac® 400. The mass median aerodynamic diameter ranged between 4.3 - 5.8 µm with FPF of 28.9%. Negligible cytotoxicity with about 75-80% cell viability at 6 and 12 h exposure was observed thus showing no toxicity. The formulation also showed good retention within the lungs when observed for 6 h. A marked increase in the C_{max} was seen in the developed DPI in comparison to the marketed formulation. Thus carrier mediated formulation for rifampicin can serve as a better tool for lung targeting for tuberculosis treatment.

Objectives of work

- To prepare and evaluated dry powder inhaler of rifampicin for lung targeting.
- To carry out *in vitro* toxicity studies using cell lines.
- To carry out the *in vitro* lung deposition studies using Andersen cascade impactor.
- To carry out *in vivo* toxicity studies using histopathology.
- To carry out pulmokinetic studies of DPI and the marketed formulation using rat model.

Method of preparation

Fine lactose + Coarse lactose → Mixed for 10 minutes using vortex mixer

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Vortex mixed for 15 mins. ← Micronized drug+Preblend was kept for 24 hr.

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Evaluation of flow properties and percent assay, content uniformity, emitted dose and fine particle dose.

Optimization of the batches

3^2 full factorial experimental design was used → Amount of drug (X1) and amount of fine lactose (X2) were the independent variables

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Flow properties and fine particle fraction were the response parameters ← Nine batches were prepared

Batch	Independent variables		
	X1 (mg) (Amount of drug)	X2 (mg)	
		Coarse lactose	Fine lactose
A1	50	97.5	2.5
A2	50	95.0	5.0
A3	50	92.5	7.5
B1	100	97.5	2.5
B2	100	95.0	5.0
B3	100	92.5	7.5
C1	150	97.5	2.5
C2	150	95.0	5.0
C3	150	92.5	7.5

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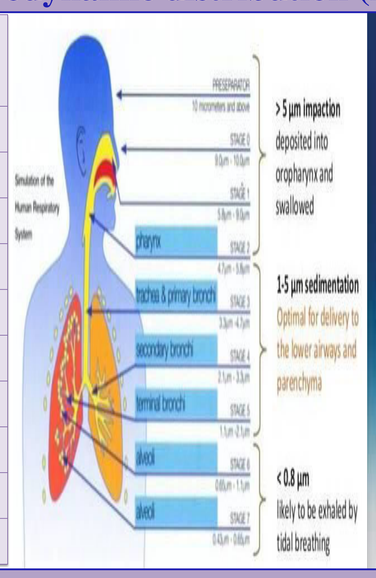
In vitro lung deposition studies by Andersen Cascade Impactor (ACI)

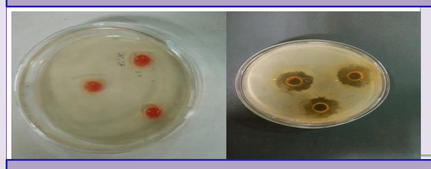
Further, for a drug to act deep into the lungs, sufficient lung deposition is required. Hence the lung deposition studies were carried out. Though in vivo lung deposition studies such as scintigraphy studies can be used to determine how much amount of drug reaches different parts of the lungs, but these are very difficult to carry out as they require a radiolabelled isotope as well as these studies are too expensive. The best alternative to this is to carry out these studies using in vitro methods .

Fine particle fraction and mass median aerodynamic distribution (MMAD)

Batch	FPF (%)	MMAD (µm)	GSD
A1	22.1	5.8	2.1
A2	22.1	4.6	2.1
A3	23.0	5.7	2.1
B1	28.4	5.2	2.1
B2	27.5	4.6	2.0
B3	26.9	4.3	2.0
C1	25.4	4.7	2.1
C2	24.8	4.4	2.0
C3	25.2	4.8	2.0
D1	26.9	4.9	1.9

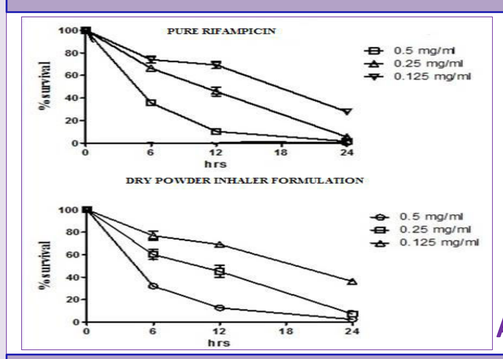


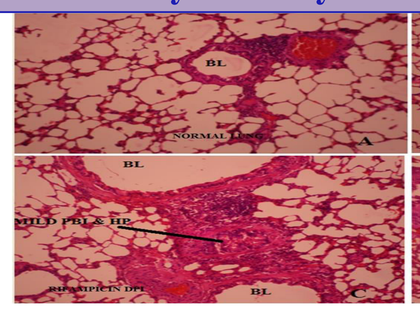
Antimicrobial activity



Dry powder formulation of rifampicin with carrier exhibited similar antimicrobial activity against *B. subtilis* as that of pure rifampicin.

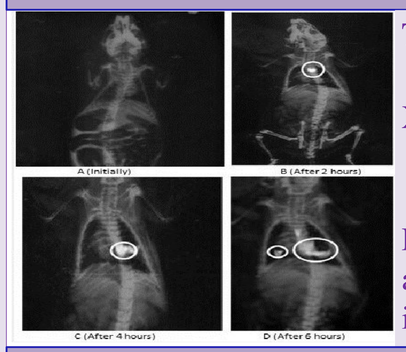
In vitro and In vivo cytotoxicity studies





A. Normal lung B&C. DPI treated lungs D. Marketed formulation

In vivo lung retention studies



The *in vivo* lung retention studies performed by X ray imaging

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X-ray images taken after 2,4 and 6 hr. of administration.

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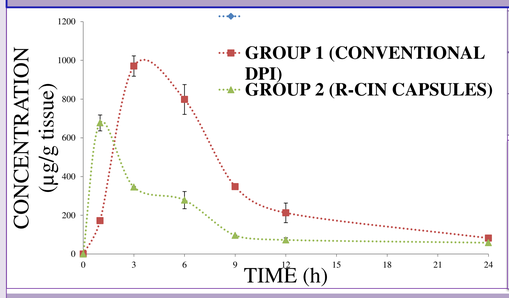
Formulation slowly traveled towards the peripheral part of the lungs after 4 and 6 hr indicating the potential retention of the formulation into the lungs .

Pulmokinetics of the developed DPI fand the oral marketed formulation



Group	Cmax	Tmax	AUC_{0-24}	$t_{1/2}$
I	970.76± 61	3± 0.1	8783.33 ±101	10.26 ± 1.2
II	677.03± 48	1± 0.2	4140.50±85	3.33 ± 0.6

A marked increase in Cmax of dry powder formulation suggests the potential of lung targeting for the treatment of several respiratory diseases.

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2. M. Paranjpe, C.C. Muller-Goymann, Nanoparticle-mediated pulmonary drug delivery: a review, International journal of molecular sciences, 15 (2014) 5852-5873.