Formulation and Evaluation of Novel Spray-dried Alginate Microspheres as Pulmonary Delivery Systems of Rifampicin in Rats

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ABSTRACT

Background: Lung administration of anti-biotics in the dry powder form is promising for improved treatment efficiency for pulmonary infections, as it increases drug concentration at sites of infection while minimizing systemic side effects. For poorly soluble molecules like rifampicin, an anti-tubercular drug encapsulated in particulate system in presence of β-cyclodextrin may improve lung delivery. **Materials and Methods:** Present study was aimed to evaluate the pharmacokinetic parameters of rifampicin loaded alginate spray-dried microparticles administered by pulmonary route. Novel spray-dried sodium alginate microspheres were formulated with β-cyclodextrin to form bioadhesive microparticles for sustained release of rifampicin. The particles without β-cyclodextrin and without drug were also prepared. Intratracheal instillation was adopted for lung delivery in comparison with oral delivery of pure drug. **Results:** Around 75% microspheres were in the respirable range, with satisfied aerodynamic characteristics. Aqueous solubility and skin permeation of rifampicin were increased significantly in presence of β-cyclodextrin. The *in vitro* antimycobacterial activity of the formulation showed enhanced activity in presence of β-cyclodextrin. The relative bioavailability of rifampicin alginate microspheres administered by pulmonary route was significantly higher when compared to that of oral route indicating the therapeutic potential of microspheres as a promising alternative to the presently available oral route. **Conclusion:** Along with sustained release of drug from the particulate formulation, the presence of cyclodextrin has the potential to achieve higher therapeutic efficacy by increasing the solubility and permeation of rifampicin.

Key words: Alginate, Aerodymanic Characteristics, β-cyclodextrin, Intratracheal instillation, Pulmonary drug delivery, Spray-dried microspheres.

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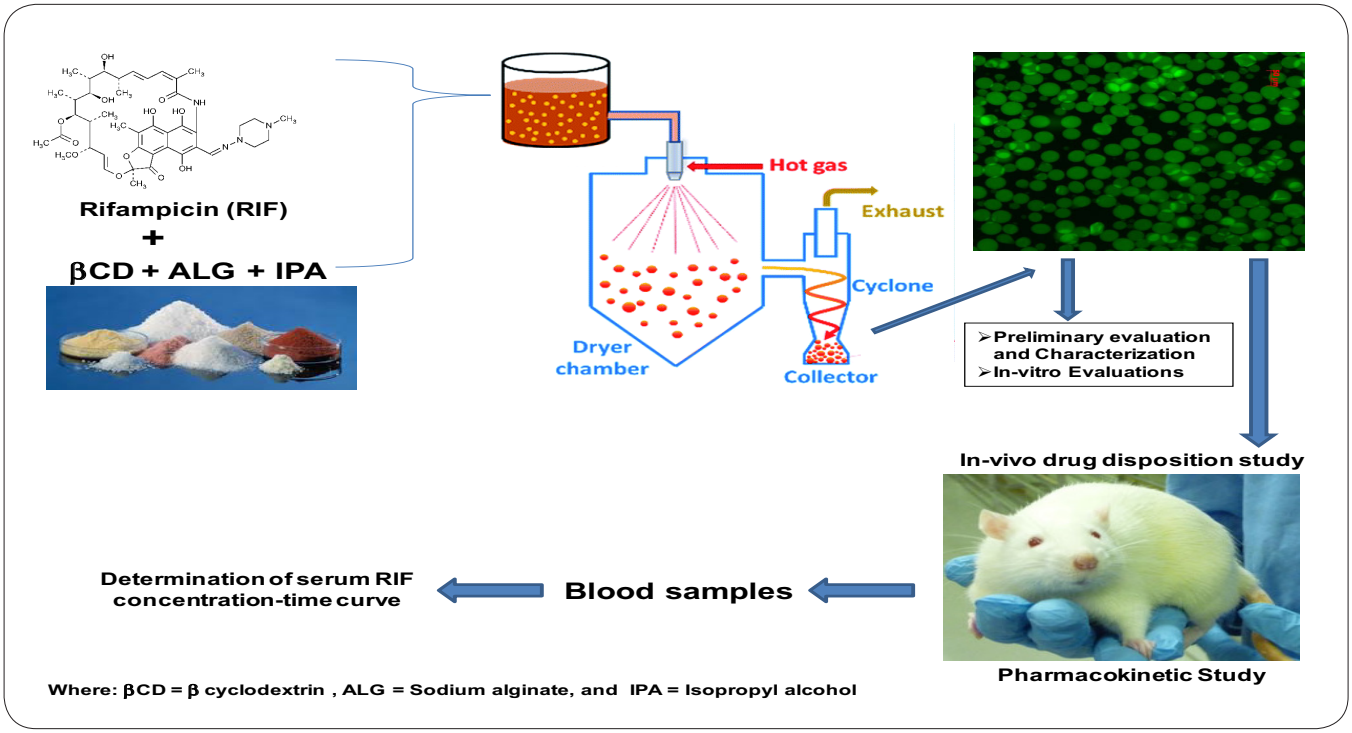
INTRODUCTION

In recent years there is great interest in developing sustained drug delivery systems by using biopolymers to provide many advantages such as reduced side effects, improved drug utilization and decreased dosing frequency when compared with conventional dosage forms.[1] Microparticulate drug delivery system has been widely produced using the spray drying technique and has gained significant importance among the techniques used in the pharmaceutical industries.[2-4] Pulmonary routeis commonly used and has been well accepted as a portal for non-invasive drug delivery for many lung diseases and it is explored for decades as an alternative for systemic as well as local drug delivery. The pharmaceutical scientists are taking advantage of large peripheral surface area (100 m^2) of lung for absorption and thinner (0.1-0.2 μm) alveolar epithelium



Pictorial Abstract

providing shorter distance of air-blood exchange passage.[5,6] Many attempts are being made to improve the patient non-compliance by developing modified lung drug delivery systems of anti-tubercular agents to overcome the daily dosing requirements of the present anti tuberculosis therapy.[7] Targeting anti-tubercular drug delivery to the lung may increase the local therapeutic effect and reduce systemic exposure.[8] Rifampicin (RIF) is a so-called concentration-dependent antibiotic whose antibacterial activity is related to the attainment of highest concentration at the target site.[9] Alginate microparticles bears sustained release properties with additional advantages such as minimum usage of toxic organic solvents and reduced reticuloendothelial system uptake due to stealth nature of alginate. The present study explores the therapeutic benefits of rifampicin encapsulated alginate microparticles when administered by pulmonary route in Wistar rats. Many researchers have reported on particulate delivery of rifampicin via aerosol route by using various synthetic and natural polymers as encapsulating agents. But in the present study first time we attempted to assess the effect of presence of cyclodextrin on solubility, permeation and pharmacokinetics of rifampicin in a sustained release alginate particulate system. Therefore, the aim of present study was to develop and evaluate a natural polymer-based inhalable drug delivery system by using sodium alginate (ALG) as natural polymer in combination with β-cyclodextrin (βCD) as complexing, solubilizing and permeation enhancing agent to prepare rifampicin alginate microspheres (RAM).[10-12]

MATERIALS AND METHODS

Rifampicin IP (Micro Labs Ltd. Hosur, Tamil Nadu, India), sodium alginate and β-cyclodextrin (Alkem Laboratory, Mumbai, India) were obtained as gift samples. All other chemicals, reagents and solvents of analytical grade were purchased locally and used with further purification.

Preparation of microspheres by spray drying

Rifampicin (RIF), β-cyclodextrin (βCD) andsodium alginate (ALG) were weighed in molar ratio of 1:1:1 (SDMSP1); 2:2:1 (SDMSP2) and 1:1:2 (SDMSP3). Solution of isopropyl alcohol (IPA), βCD and ALG were prepared in purified water respectively and resultant solutions were mixed together and was fed to chamber of mini spray drier (Lab ultima-222, Mumbai) from a nozzle with diameter 0.7 mm under the atomization pressure of 1.5 kg/cm^2 with a feed rate of 3ml/min. The inlet temperature was kept at 160^o and outlet temperature at 110 ± 5^o. The aspirator speed was kept at 55%. The procedure is repeated for the preparation of microspheres without βCD and drug free microspheres. The microspheres thus obtained were collected, packed and stored in desiccator until further use.[13]

Preliminary evaluation and Characterization

RAM equivalent to 10 mg of drug was subjected for drug content estimation by dispersing the crushed formulation in 10 ml of methanol and kept aside for 6 h. The content was filtered through nylon disc filter (0.45

μm) and suitably diluted with phosphate buffer of pH 7.4 solution and UV absorbance was measured at 475 nm using UV Visible spectrophotometer (Pharmaspec UV Visible spectrophotometer, Shimadzu 1700, Japan). Drug concentration was determined from the standard graph. The formulation that had the highest drug content was selected for the preliminary characterization and further evaluation.[14,15] Particle size analysis of RAM was carried out by suspending the microspheres in liquid paraffin using particle size analyzer (Malvern Instruments, Malvern U.K) and mean particle size was calculated. The surface morphology of the particles was studied by scanning electron microscopy (SEM) (JEOL, JSM-6360, Japan). Aerodynamic characterization of RAM was carried out on an 8- stage Anderson cascade impactor with a preseparater (Grase by-Andersen, Atlanta, GA, USA) operating at an air flow rate at 60 L/min which stimulate a typical human respiratory flow rate. Mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle fractions (FPF) were calculated according to USP 27 NF 22.

Aqueous solubility study[13]

The aqueous solubility of drug in RAM with βCD in comparison with pure RIF and RAM without βCD was determined at 37° ± 0.5 in pH 7.4 phosphate buffer. Solubility was measured by soaking well dispersed crushed microspheres equivalent to 50 mg drug in 50 mL of solvent. Solute and solvent were placed in the stoppered conical flasks immersed in thermostatic water bath shaker (Remi RS-B12 Mumbai, India) and agitated continuously for 72 h at 37° ± 0.5. After 72 h, solution was filtered through nylon disc filter (0.45 μm) and diluted sufficiently with solvent and absorbance was measured at 475 nm.

In vitro skin permeation study[16]

The permeation study of pure drug and spray dried formulations with and without βCD was carried out across the rat abdominal skin. We carried out this study using rat abdomen skin as a physiological model instead of alveolar tissues/Calu-3 membranes and we already reported in our previous work for the same purpose.[17] The abdominal skin of the rat was excised after anaesthetizing and sacrificing. The surface hair of the skin and adhered epidermal tissues were removed carefully without damaging the skin. Then the skin was mounted on the donor compartment of the Keshary-Chien diffusion cell having a downstream volume of 25 mL. The receptor medium used was 0.05 M phosphate buffer solution of pH 5.2. The 200 μg/mL ascorbic acid added as an antioxidant to prevent oxidative degradation. The diffusion was carried out at 37 ± 1.0° and at 50 rpm for 6 h. The 5 mL samples were removed periodically and estimated the drug content spectro photometrically at 475 nm.

In vitro anti-tubercular activity

The RAM formulations with and without βCD, and pure RIF were evaluated for *in-vitro* anti-tubercular activity. The Mycobacterium tuberculosis $H_{37}RV$ study was performed and interpreted according to the approved procedure of macro dilution anti-microbial susceptibility testing method.[18,19] Test samples were prepared by using dimethyl formamide at concentrations of 100 μgmL^{-1}, 50 μgmL^{-1} and 25 $\mu g\ mL^{-1}$ and were added to the media. Ciprofloxacin (10 $\mu g\ mL^{-1}$) and streptomycin (7.5 $\mu g\ mL^{-1}$) were taken as reference standards. Mycobacterium tuberculosis was inoculated with standard and test samples and incubated at 37° for four weeks. The bottles were inspected for growth of the mycobacterium twice a week for a period of three weeks. Readings were taken at the end of fourth week. The growth of the bacilli results in turbidity which indicates resistance to the samples.

In vitro drug release study

Drug release from spray dried RAM with and without βCD was carried out using modified dissolution method.[20,21] The simulated lung fluid of phosphate buffer pH 5.2 was prepared by adding 200 μg/mL ascorbic acid as an antioxidant to prevent oxidative degradation. The microspheres equivalent to 50 mg of drug was suspended in tubes containing the buffer. The tubes were placed in a shaker bath (Remi RS-B12), operated at 90 cycles/min at 37° running for 72 h. At predetermined intervals of time, 5 ml of the sample was withdrawn and analyzed for drug content at 475 nm using UV-visible spectrophotometer following suitable dilutions. The same amount of fresh media was replaced after each sample withdrawal. The study was performed in triplicate.

In vivo drug disposition study[22-25]

Healthy Wistar rats between 2 and 3 months of age, and weighing 150–200 g were used for the study. The study was approved by the Institutional Animal Ethical Committee of Al-Ameen College of Pharmacy, Bangalore, India (Resolution No. AACP/IAEC/P-34/2006, Dated 26/05/2006). Total of 36 rats were equally divided into six groups. The formulations equivalent to the drug was used at therapeutic dosage of 12 mg/kg body weight.

Group 1 received pure RIF (Instilled intratracheally);

Group 2 received RAM formulation (Instilled intratracheally);

Group 3 received pure RIF (Orally);

Group 4 received RAM formulation (Orally);

Group 5 received RAM formulation without βCD (Instilled intratracheally) and

Group 6 received RAM formulation without βCD (Orally).

The animals were anesthetized with an intraperitoneal injection of urethane and surgery was performed. A small middle incision was made over the trachea of anesthetized animals which are placed in supine position on a 45° slanted support. The trachea was exposed by blunt dissection of the sternohyoideus muscle and a small hole was made in the trachea between the fifth and sixth tracheal rings using a 20-gauge needle. About 10-20 cm length of PE50 tubing was inserted into the hole and advanced to the bifurcation of the trachea. Formulations of 0.5 ml (spray dried alginate microspheres and free pure drug separately suspended in a sterile phosphate buffer pH 5.2) were slowly instilled over a 1 min period using a 1ml Hamilton syringe attached to the PE50 tubing. Following instillation, the tubing was withdrawn and a small drop of cyanoacrylate adhesive was placed over the hole to seal the opening. The skin was closed with 3-0 Dexon sutures. The animals were allowed to recover from anesthesia under a heating lamp and were housed in individual plastic cages with access to food and water for remainder of the study. The pure RIF and encapsulated formulations were also administered intragastrically to oral groups. Blood samples were collected from the tail vein at several time points up to 72 h and plasma was separated. To 2 ml of plasma 0.4 ml of 10% v/v aqueous acetic acid was added to adjust the pH to 4.2. Drug was extracted by shaking with 7 ml of diethyl ether: dichloromethane (2:1v/v). The sample was vortexed for 10 min followed by centrifugation for 10 min at 10,000 rpm and the content was transferred to a tapered test tube and evaporated to dryness under a stream of liquid nitrogen. The resulting residue was reconstituted in 5 µL mobile phase and injected into LCMS system. Thermo, BDS Hypersil Gold C 18 (3 × 50 mm) column was used for the study. The chromatograms were acquired using the computer based software supplied by Agilent technologies. The data was processed by peak area ratio. The concentration of the rifampicin in plasma at different time point was calculated from the following equation using regression analysis of spiked calibration standard with the reciprocal of the square of the drug concentration as weighing factor (1/concentration x concentration).[26]

$$Y = mx + b$$

Where, x=concentration of analyte, m=slope of the concentration curve, Y=peak area of analyte to internal standard and b=y-axis intercept of the calibration curve.

Table 1: Determination of Drug Content of Spray-Dried Microspheres

Formulations	RIF: βCD: ALG	% drug content
PMSP1	1:1:1	62.1 ± 0.4
PMSP2	2:2:1	80.1 ± 0.5
PMSP3	1:1:2	71.2 ± 0.6

Mean ± SD, n=3 PMS 1,2 and 3: spray-dried microspheres, RIF: βCD: ALG: rifampicin: b-cyclodextrin: sodium alginate

Pharmacokinetic Study

Following administration of spray-dried RAM and pure RIF, serum levels were measured to evaluate pharmacokinetics. The serum RIF concentrations at each sampling time point were plotted against time in hours. Maximum serum concentration (C_{max}), time in hours to achieve C_{max} (T_{max}), area under the plasma concentration curve (AUC), serum elimination constant (Kel) and RIF serum half-life ($t_{1/2}$) were determined from RIF serum concentration-time curve. The area under the curve was calculated by the trapezoidal rule and further used to compute relative bioavailability using the following equation:

Relative bioavailability= (ACU_(O-T) of oral encapsulated drug /ACU_(O-T) of oral free drug)×(dose of oral free drug/ dose of oral encapsulated drug)

Statistical analysis of data

Results are expressed as mean ± S.D. Statistical difference was calculated by using one-way analysis of variance (ANOVA) followed by student's unpaired t-test. In cases where the differences in the mean values, p-value< 0.05 was taken.

RESULTS AND DISCUSSION

Alginate microspheres were prepared using an alternative spray drying method and characterized. Microspheres were collected after spray-drying process and 60% yield was obtained.

Drug content of the spray-dried formulations was estimated and the results observed were between 62.12-80.21% (Table 1). All formulations showed very good drug content. Drug contentin the formulations found to be depend on RIF concentration as it decreased as RIF concentration decreased and increased with increase in the concentration of RIF. Due to the high gel porosity of alginate higher drug loading was observed for alginate microspheres in this study. Increase in alginate concentration with constant amount of RIF led to highly viscous solution that reduced drug solubility and therefore the loading capacity. RAM formulation PMSP2 had maximum drug content and was selected for further characterization.

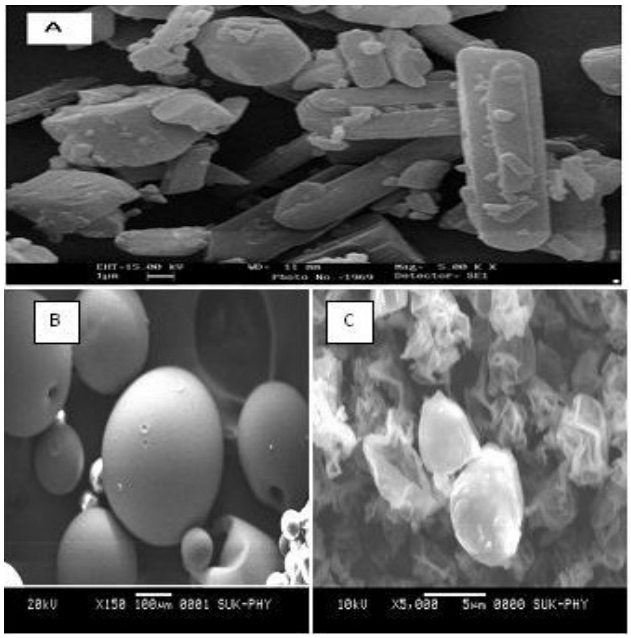


Figure 1: Scanning Electron Microphotographs
Pure Rifampicin (A); Drug-cyclodextrin free alginate microspheres(B); Drug loaded spray- dried alginate microspheres with cyclodextrin (C).

The optimized RAM formulations with and without βCD were subjected for particle size analysis using Malvern instrument. Spray-dried alginate microspheres had an average particle size of 6.634 µm and 6.234 µm respectively. The particle size for both formulations was almost same. The results of size were probably due to the effect of the solution viscosity on the droplet size during the atomization step. In general, the mean size of droplets formed by atomization is proportional to liquid viscosity and surface tension and it indirectly affects the spray-dried powder size. The particle size of spray dried microspheres obtained was dependent on the polymer concentration of the spray solution and the spray flow rate.

SEM study revealed that the pure RIF found to be crystalline in nature with a characteristic shape; whereas the drug-free alginate microspheres were spherical, and free flowing with smooth surface. On the other hand the RAM appeared as small uniform sized particles/ aggregates with wrinkles on the surface (Figure 1). The morphological difference was highlighted for these two different microspheres. Therefore results seem to indicate that the presence of drug and βCD affected the morphological characteristics of microspheres obtained by the spray-drying method. Moreover, SEM micrographs confirmed the porous nature of particle, which is a consequence of the presence of βCD.

Table 2: Aerodynamic Characterization of Spray-Dried Microspheres

Formulation	MMAD (µm)	GSD (µm)	FPF (%)
PMSP2	5.4	1.8	39.5

Mean ± SD, n=3
PMSP2: spray-dried microspheres; MMAD: mass median aerodynamic diameter; GSD: geometric standard deviation; FPF: fine particle fraction.

Aerodynamic characterizations were carried out *in vitro* in order to evaluate the suitability of spray-dried RAM formulation for the pulmonary administration. These studies were performed by dispersing the spray-dried microspheres in solution of phosphate buffer pH 7.4. RAM microsphere aerosols, generated using 8- stage Andersen Cascade Impactor with a preseparater (Grase by-Andersen, Atlanta, GA, USA) operating at an air flow rate of 60 L/min. The samples were collected in a buffer solution in a three stage glass impinge and analyzed. The nebulization efficiency, MMAD, GSD and FPF were calculated according to USP 27 NF 22. The results revealed that nearly 75% of alginate microspheres were in the respirable size range, with a MMAD of 5.424 µm and GSD of 1.821 µm. The FPF of alginate microspheres was 39.5%. The results are shown in Table 2. Nebulization efficiency of the encapsulated depends on the percentage of aerosolized drug that remains encapsulated after nebulization. These studies are of particular importance to have information of the capability of the microspheres to be aerosolized and also to retain the entrapped drug during the process.

The aqueous solubility study was carried out for RAM formulation PMSP2 in comparison to pure drug and RAM formulation without βCD. The pure RIF showed aqueous solubility of 1.958 ± 0.23 µg/ml, whereas, RAM formulation with βCD and without βCD showed 2.657 ± 0.85 µg/ml and 1.983 ± 0.52 µg/ml respectively (Table 3). A 1.5 fold increase in the aqueous solubility was found for the RAM when compared to pure RIF and RAM without βCD. This may be due to decreased crystallinity of RIF by forming inclusion complex with βCD in the formulation.

Permeation study of RAM formulation PMSP2 was carried out across rat skin in comparison with pure drug and formulation without βCD. The percentage of drug permeated per square centimeter of the skin at 6 h was 33.35 ± 0.67, 87.36 ± 0.98 and 35.58 ± 0.39 for pure RIF, RAM formulation with and without βCD respectively. The results are shown in Table 3. The goal of our study was to increase rifampicin concentration in physiological fluid especially in epithelial lining fluid. It was evident from the above results that there was threefold increase in the permeability of drug was achieved in presence of βCD. Again this increase in permeability may be due to the permeation enhancement nature and inclusion complex formation with βCD. Similar results were obtained previously my measuring rifampicin

Table 3: Data Obtained From the Aqueous Solubility and Skin Permeation Study

Formulation codes	Composition	Aqueous Solubility (µg/ml)	% of drug permeated/cm² of the skin at 6 h.
Pure drug	Spray dried pure drug	1.9 ± 0.2	33.3 ± 0.7
PMSP2	RIP:bCD:ALG	2.6 ± 0.8	87.3 ± 0.9
PMSP	RIP:ALG	1.9 ± 0.5	35.5 ± 0.3

Mean ± SD, n=3
PMSP2: spray-dried microspheres; RFP: bCD: ALG: rifampcin: cyclodextrin: alginate.

Table 4: Results of *In-vitro* Anti-Mycobacterial Activity

Samples	Concentration µgmL^{-1}		
	25	50	100
Rifampicin (pure)	R	R	S
Drug loaded alginate micro spheres without bCD	R	R	S
Microspheres with cyclodextrin (PMSP2)	R	S	S
Control: ciprofloxacin (10 µgmL^{-1})	S	-	-
Control : streptomycin (7.5 µgmL^{-1})	S	-	-

S=clear solution indicating no growth, R=cloudy solution indicating growth

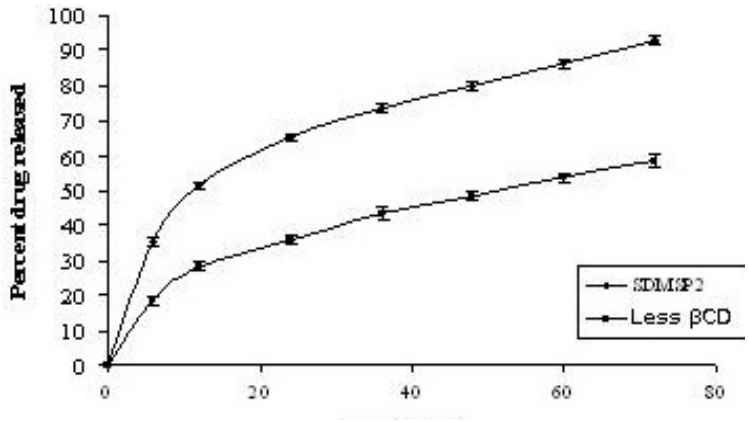


Figure 2: *In vitro* drug release profile in pH 5.2 phosphate buffer
SDMSP2: Sray-dried microspheres with βCD and less βCD

transport across calu-3 cell monolayer in the presence of sulfobutyl ether βCD.[27]

With an aim to evaluate *in vitro* anti-tubercular activity of rifampicin, and its formulations, *in vitro* anti-tubercular activity was performed for rifampicin alone, RAM formulation with and without βCD. The study demonstrated that the RAM had shown no growth of micro-organisms at 50 µg mL^{-1} and 100 µg mL^{-1} concentrations, thus, exhibiting maximum effectiveness when compared to RIF. However, the formulation without βCD had shown similar anti-tubercular activity as that of the RIF. Thus, a reduction in the effective concentration from 100 µgmL^{-1} to 50 µgmL^{-1} was achieved in the RAM formulation PMSP2 which exhibited maximum activity, the data is shown in Table 4. The results of in-vitro anti-tubercular activity of the pure RIF, RAM formulation with and without βCD clearly indicated that there was significant increase in the effectiveness of the drug in presence of βCD in a RAM formulation when compared to pure RIF and RAM formulation without βCD. This may be due to the presence of βCD in the formulation.

In-vitro drug release study was performed for the RAM formulation. Extended *in vitro* release for a period of 72 h was observed from the RAM formulation, PMSP2, In addition, 92.76% of drug was released from PMSP2, in simulated lung fluid of pH 5.2 buffer at the end of 72 h, whereas, 58% of drug was released from the same formulation in the absence of βCD, the release profiles are shown in Figure 2. Hence, the results obtained by release study revealed that the drug release was found to be best from RAM formulation which can be attributed

Table 5: Pharmacokinetics of Drug Loaded Formulations Compared with Oral Free Drug

Group	C_{max} ng/ml	T_{max} h	K_{el}	$T_{1/2}$ h	AUC_{O-t} ng.h/ml	Relative Bioavailability
OFD	85	06	-9.2	0.2	516	6.9
PMSP2	280	48	0.4	1.6	17670	34.2
PMSPb	87	24	2.3	0.9	9869	19.1

Mean ± SD, n=3

OFD: oral free drug, PMSP2: spray dried microspheres with bCD administered by pulmonary route; PMSPb: spray dried microspheres without bCD administered by pulmonary route; C_{max}: maximum plasma concentration, T_{max}: time to reach maximum plasma concentration, K_{el}: elimination half-life, $T_{1/2}$: absorption half-life, AUC_{0-t}: area under the plasma drug concentration over time curve.

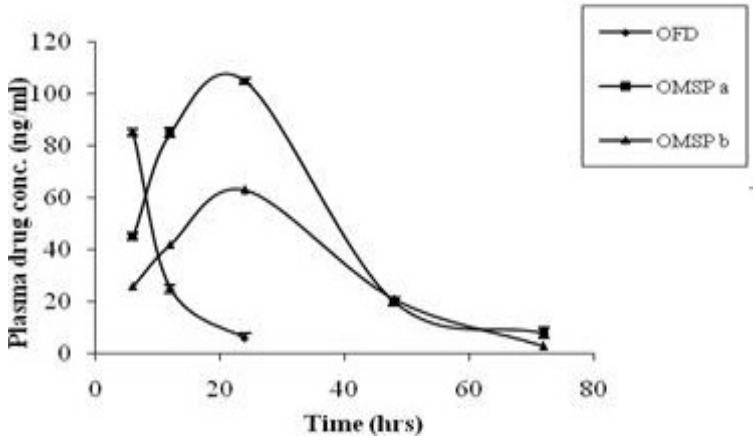


Figure 3: Plasma concentration-time profilesafter oral administration

(OFD): Free rifampicin, (OMSPa): Microspheres with βCD; (OMSPb): Microspheres without βCD

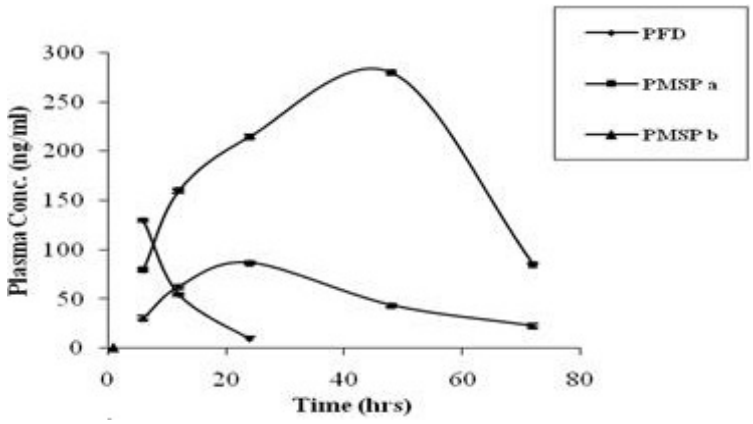


Figure 4: Plasma concentration-time profilesafter pulmonary administration

(PFD): Free rifampicin, (PMSPa): Microspheres with βCD; (PMSPb): Microspheres without βCD.

to the solubilizing action of βCD on rifampicin. As seen from the results microspheres are able to control RIF release rate, and the initial burst effect demonstrated for formulation without βCD is significantly low when compared to that formulation with βCD. Moreover, after this initial burst, both the microspheres released RIF at a lower rate.

A single dose drug disposition study was carried out in rat as animal model. When the RAM formulations were administered through instillation, the RIF was detected in plasma from 4 h onwards and observed up to 72 h when administered by both the routes. In contrast, free drug was cleared from the circulation within 24 h. All the pharmacokinetic parameters, which include maximum serum concentration (C_{max}), time in hours to achieve maximum concentration (T_{max}), and area under the plasma concentration curve (AUC), were found to be higher for RAM upon administration through pulmonary route, resulting in a significant increase in relative bioavailability of drug when compared with free drug. The bio-availability of RIF from RAM was significantly increased, as evident from the plasma profile and pharmacokinetic evaluations compared with free drug. The

pharmacokinetic data is shown in Table 5 and the plasma concentration versus time profiles are shown in Figure 3 and 4. The chemotherapeutic benefits of particulate sustained release drug delivery systems have been developed and reported previously by some researchers.[12,28] The present formulation containing cyclodextrin bear the advantages of all these reported systems in addition enhanced apparent solubility of rifampicin in encapsulated form via the pulmonary route to deliver high drug concentration directly at the site of infection while minimizing systemic biodistribution and toxicity with significantly increased bioavailability. The results supported the role of cyclodextrin present in the alginate microsphere which results in enhancement of RIF solubility and may increase the permeation and concentration of the drug at the site of administration. Alginate encapsulation of RIF may also have formed a biodegradable reservoir, which prolonged the pulmonary residence time of RIF.

CONCLUSION

This study reports for the first time that the effect of cyclodextrin as a solubility and permeation enhancer in the alginate microparticles of rifampicin to improve its bioavailability and in turn therapeutic benefits and patient compliances for effective tuberculosis control. Spray-dried alginate microspheres are a drug delivery system bearing the benefits of sustained release properties of microspheres, with advantages such as absence of organic solvents, no involvement of toxic molecules, and reduced reticuloendothelial system uptake due to the stealth nature of alginate. The developed microspheres demonstrated approximately 6 fold increased bioavailability compared with oral route. The present study explores the therapeutic potential of spray-dried alginate microspheres encapsulating anti-tubercular drug through the pulmonary route in rats. The study also indicates the role of the pulmonary route as a promising alternative to the presently available oral route. The presence of cyclodextrin helped to achieve higher bioavailability and permeation of rifampicin.

CONFLICT OF INTEREST

Authors declared no conflict of interest.

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SUMMARY

- The Spray-dried alginate microspheres of rifampicin demonstrated approximately 6 fold increased bioavailability compared with oral route.
- The present study explores the therapeutic potential of spray-dried alginate microspheres encapsulating anti-tubercular drug through the pulmonary route in rats.
- The study also indicates the role of the pulmonary route as a promising alternative to the presently available oral route.
- The presence of cyclodextrin helped to achieve higher bioavailability and permeation of rifampicin.

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