RESEARCH ARTICLE

Preparation and Evaluation of PLGA-based Nanoparticles

Ram K Choudhary[1], Kandukuri A Kumar[2], Srividya Kommineni[3], Minal Narkhede[4], Jyothirmayee Devineni[5*]

[1]*Government Pharmacy Institute, Patna, Bihar, India.*
[2]*Srinivasarao College of Pharmacy (Affiliated to Andhra University), P. M. Palem, Visakhapatnam, Andhra Pradesh, India.*
[3]*Department of Technical Services, Upsher-Smith Laboratories, Maple Grove, Minnesota, USA.*
[4]*Department of Pharmaceutics, SMBT College of Pharmacy, Dhamangaon Nashik, India.*
[5]*Department of Pharmaceutics and Biotechnology KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, India.*

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ABSTRACT

The current study aimed to increase the stability and therapeutic efficacy of the antitubercular medication rifampicin by reducing or preventing its breakdown in the stomach pH state. Ascorbic acid was used as an antioxidant in the preparation of rifampicin-loaded Poly(lactic-co-glycolic acid) (PLGA) nanoparticles for the investigation. A multistep emulsion process was used to create dig-laden nanoparticles, and different techniques were then used to assess the final product. Ten different kinds of formulations were created for this study. According to the study's findings, ascorbic acid can increase rifampicin's stability and bioavailability by reducing its breakdown in acidic pH conditions. The results also show that changing the ascorbic acid concentration makes a statistically important difference in the way the medicine breaks down.

Keywords: Nanoparticles, Novel drug delivery systems, PLGA, Rifampicin, Ascorbic acid.

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INTRODUCTION

The disease tuberculosis (TB) is a prevalent and extremely transmissible chronic granulomatous bacterial infection caused by *Mycobacterium tuberculosis*.[1] About one-third of the world's population, or 2 billion people, are affected by tuberculosis, and an extra 3 million people die each year from it.[2] India is the site of 20% of all newly diagnosed cases of tuberculosis globally each year.[3]

Tubercle bacilli infections are predominantly transmitted through respiratory routes. Healing is a frequent consequence of infection-induced lung lesions, except in rare cases where calcification may occur in the pulmonary or tracheobronchial lymph nodes.[4] Reactivation after this latent phase, which is penetrated by over 90% of initially infected individuals, carries a lifetime risk.[5] Through lymphohematogenous bacilli dissemination, the first infection could turn into pulmonary TB, pulmonary, meningeal, or other extrapulmonary involvement, or in approximately 5–10% of hosts who appear normal and up to 50% of people with advanced HIV illness have spread the disease (miliary TB).[6,7]

In contrast to extrapulmonary tuberculosis, pulmonary tuberculosis is more prevalent. Antennae and skeletal joints, pericardium, pleura, lymph nodes, eyes, epidermis, and gastrointestinal tract are some of the organs and tissues that can be impacted by extrapulmonary tuberculosis.[8,9]

Weight loss, fatigue, fever, and nighttime perspiration are among the initial symptoms. During the later phases, there is an increased visibility of localized symptoms such as wheezing, chest pain, hemoptysis, and hoarseness.[10,11]

First-line and second-line pharmaceuticals constitute the principal classifications of anti-TB medications.[12] Giving antitubercular drugs (ATDs) every day or several times a week increases the chance that a patient will not follow through with their treatment. This could lead to treatment not working and the development of drug resistance.[13] ATD formulations have the potential to enhance patient adherence through the reduction of medication dosing frequency.[14] The World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) said that a four-drug fixed-dose combination (FDC) should be used to deal with these issues.[15] First-line medications for the treatment of tuberculosis have been shown to be highly efficacious against *M. tuberculosis*. Rifampicin is widely acknowledged as the least stable among the four medications, and contemporary studies suggest that its degradation rate is highest in the presence of isoniazid.[16,17]

**Author for Correspondence: drdjyothirmayee9@gmail.com*

Rifampicin is a semi-synthetic macrocyclic antibiotic that comes from *Streptomyces mediterranei.* It is very good at getting rid of tubercle bacilli that are mostly dormant. Rifampicin functions by impeding RNA transcription, thereby impeding the synthesis of mycobacterial DNA-dependent RNA polymerase.[18] Moreover, it is established that cytochrome P450 activity is present. When RIF comes into contact with acidic stomach acid, it can break down into even less available forms, such as 1-amino-4-methyl piperazine.[19] At 7.4 to 8.2, the compound oxidizes to an insoluble or deacetylated quinone derivative. The principal byproducts of rifampicin degradation are rifampicin N-oxide, rifampicin quinine, 25-desacetyl rifampicin, and rifampicin N-oxide.[20]

Antioxidants with a low molecular weight, such as vitamins C and E, prevent oxidative injury to human cells through a variety of mechanisms. It has been shown that supplementation with vitamin C can alter a variety of human immune system indicators, and active macrophages and neutrophils contain high concentrations of vitamin C. Vitamin supplementation may therefore be advantageous.[21,22]

Although rifampicin undergoes degradation in acidic environments, it remains effectively assimilated within the pH range of 1-2. As an antioxidant, vitamin C can be added to rifampicin-PLGA nanoparticles to stop them from breaking down and make rifampicin more stable.[23] In order for a drug molecule to get from where it is administered to where it needs to be at a dose high enough to have therapeutic effects and stay there long enough, it needs to be delivered. Even though there are many liquid drug delivery methods on the market right now, nanoparticles are one of the best ways to reach this goal.[24] Nanoparticles are the best way to deliver drugs because they have many useful qualities. Because they can directly pass through intestinal permeability barriers through transcellular and paracellular routes, the encapsulated medication is transported more efficiently into the circulation. Given the intracellular nature of tuberculosis in this particular case, it is expected that the nanoparticles will gain access to the compromised cell.[25]

The biodegradable nano system poly-d, l-lactide-co-glycolide (PLGA) is one of the best used in drug delivery studies because it can be broken down by water in the body, creating biodegradable metabolite monomers like lactic acid and glycolic acid. This polymer is associated with minimal systemic toxicity due to the body's ample capacity to metabolize these two monomers.[26]

Because of this, the study's goal was to make and test PLGA nanoparticles that had rifampicin added to them. Furthermore, an *in-vitro* inquiry was undertaken to determine whether the antioxidant ascorbic acid impacted rifampicin's stability in the gastrointestinal milieu.[27]

To address the issue of medication resistance and improve patient adherence, the literature review emphasizes the importance of employing a fixed dosage regimen consisting of ethambutol, rifampicin, isoniazid, and pyrazinamide when treating tuberculosis. Rifampicin appears to be the most effective treatment option for tuberculosis; however, its poor oral bioavailability from the FDC formulation is due to gastric degradation. Although rifampicin degrades in an acidic environment and its concentration rises when isoniazid is present, it is absorbed efficiently within the pH range of 1 to 2. As a result, the bioavailability of rifampicin is altered. The development of any technique capable of stabilizing rifampicin against degradation in the intestines will yield therapeutic benefits.[28,29]

Nanoparticles make it easier for the medicine they hold to get into the bloodstream because they can directly cross intestinal permeability barriers via transcellular and paracellular routes. Since tuberculosis is an illness that happens inside cells, the pathogens will likely get into the affected cell in this case. The literature study shows that PLGA is one of the best biodegradable nanosystems for the development of nanomedicine because it breaks down in the body into the biodegradable metabolite monomers lactic acid and glycolic acid. Because of these things, the current study used ascorbic acid as an antioxidant to make the rifampicin-PLGA nanoparticles more stable.[30]

MATERIALS AND METHODS

Preparation of PLGA based Nanoparticles

PLGA nanoparticles loaded with rifampicin and ascorbic acid were created using the emulsification/solvent evaporation method, which entailed creating a stable emulsion and continuously swirling an organic solvent until it evaporated. Ten different formulation types were prepared in order to conduct the investigation. Ascorbic acid was administered in three separate ratios, as noted in Table 1, and the drug: polymer ratio was always taken as 1:1.[31-33]

Procedure

PLGA nanoparticles loaded with drugs were made using a multi-step emulsion process. Ten mL of dichloromethane, which contained the polymer, were filled with 50 mg of rifampicin and the right amount of ascorbic acid. The drug-to-polymer ratio was set at 1:1. To make a w/o main emulsion, pure water was mixed with medicine and polymer in DCM. After that, sonication was used to break it up for 15 minutes. The first emulsion was mixed with 8 mL of a 1% w/v poly vinyl

Table 1: Design formulation with drug and ingredient s

S. No	*Formulation number*	*Ingredients with drug*
1	F1	Rifampicin
2	F2	Rifampicin + PLGA (1:1)
3	F3	Rifampicin + PLGA+ Ascorbic acid (1:1:0.5)
4	F4	Rifampicin + PLGA + Ascorbic acid (1:1:1)
5	F5	Rifampicin + PLGA + Ascorbic acid (1:1:1.5)
6	F6	Rifampicin + PLGA + Ascorbic acid (1:1:2)
7	F7	Rifampicin + PLGA + Ascorbic acid (1:1:2.5)
8	F8	Rifampicin + PLGA + Ascorbic acid (1:1:3)
9	F9	Rifampicin + PLGA + Ascorbic acid (1:1:3.5)
10	F10	Rifampicin + PLGA + Ascorbic acid (1:1:4)

Alcohol solution in water and stirred with a magnetic mixer to make the second w/o/w multiple emulsion. After that, it was constantly moved all night to get rid of the DCM totally. We spun the nanoparticles at 9000 to 10,000 rpm for 15 minutes. Then we cleaned them three times with distilled water and dried them in a vacuum.[34,35]

Evaluation of PLGA based nanoparticles

The produced nanoparticles were then characterized. Among the criteria that are established are particle size, size distribution, shape, surface morphology, polydispersity Index, and zeta potential. The shape and surface morphology of the nanoparticles were determined using scanning electron microscopy (SEM). The average particle size and polydispersity index (PDI) of the nanoparticles were ascertained by means of laser light scattering. Using a zeta sizer, the nanoparticles' zeta potential was ascertained.[36, 37]

Morphological study of PLGA based nanoparticles

A scanning electron microscope was used to look at the shape of PLGA nanoparticles that were filled with rifampicin and ascorbic acid. To make samples, particle suspensions were diluted in distilled water and then stuck to pieces with double-sided tape. After the particles were dried in the air, a thin layer of platinum film was put on them. These were then looked at with a scanning electron microscope.[38]

PLGA based nanoparticles particle size characterization

A laser particle size detector was used to find out the nanoparticles' particle size, size distribution, and polydispersity index after the right steps were taken to dilute them.[39]

Zeta potential study of PLGA based nanoparticles

Using a zeta sizer and U-shaped tube at 25°C, the electrophoretic mobility of the nanoparticles revealed their surface charge.[40]

In-vitro drug release study of PLGA based nanoparticles

The vessel of the USP dissolution device type 2 was filled with a 0.1N HCL solution. The paddle was set to rotate at 100 rpm, and the temperature was kept at 37 ± 0.2ºC. 0.1N HCL was used to correctly weigh, dissolve, and thin out RIF-loaded PLGA nanoparticles with ascorbic acid in different amounts. The solution that was made was moved right away to the dissolving bath. At 15, 30, and 60 minutes, specimens were taken out. A portion of 0.5, 1, 2, 3, 4, and 5 mL was taken out right away with 100 mL of pH 1.2 medium and a cyclomixer. The USP dissolution device type 2 vessel had a 0.1N HCL solution added to it. The temperature was kept at 37 ± 0.2°C with a paddle that turned at 100 rpm.[39,40] RIF-loaded PLGA nanoparticles with different amounts of ascorbic acid were weighed out and mixed with 0.1N HCL until the volume reached 100 mL. The liquid that was made was quickly added to the bath for dissolving. After 15, 30, and 60 minutes, the samples were taken out. With a cyclomixer, 100 mL of pH 1.2 medium was mixed with 0.5, 1, 2, 3, 4, and 5 mL of an amount right away. Spectrophotometry was used to measure the samples at 475 nm, and the %degradation was calculated. Spectrophotometry was used to look at the samples at 475 nm, and the %degradation was found.[40]

RESULTS AND DISCUSSIONS

Characterization of the PLGA based Nanoparticles

Scanning electron microscopy

A representation of the rifampicin-ascorbic acid-filled PLGA nanoparticles that were made can be seen in Figure 1. The surface of the nanoparticles was smooth and round, and most of them were spread out in one direction.

SEM was used to look at the nanoparticles' form and surface. The SEM pictures showed that the nanoparticles were round and had a smooth surface. Most of them were spread out in a single direction. The width of the main population is given by a laser particle size analyzer, and the range of sizes that are spread out is given by a PDI. The size range is around 50 µ. The PDI shows how the bits in a polymer sample are spread out. There are particles together if the PDI number is greater than 0.5. This time, the nanoparticles had polydispersity numbers that ranged from 0.309 to 0.354. Nanoparticles' sizes can be changed by things like the amount of surfactant, the drug/polymer ratio, and the speed of the spinning. Since these things didn't change during the study, it's not possible to say how they changed the nanoparticles' average size. Table 2 showed the polydispersity index and the average particle size of all the samples.

The diameter of the mass population is given by the laser particle size analyzer. It was between 363 and 391 nm, or 19 to 24 nm. Polydispersity index is a way to figure out how the bits in a polymer sample are spread out. The range is between 0.00 and 0.50 in this case. Particles are sticking together if

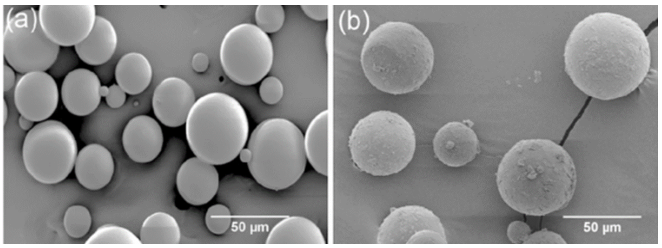

Figure 1: SEM picture of the PLGA nanoparticles loaded with rifampicin and ascorbic acid

Table 2: The particle size and polydispersity measure that all the samples had on average

S. No	*Formulation number*	*Mean diameter (nm) ± SD*	*PDI*
1	F1	376 ± 19	0.314
2	F2	377 ± 21	0.318
3	F3	375 ± 17	0.309
4	F4	381 ± 22	0.314
5	F5	373 ± 23	0.318
6	F6	385 ± 22	0.321
7	F7	363 ± 23	0.352
8	F8	389 ± 24	0.324
9	F9	366 ± 19	0.356
10	F10	391 ± 23	0.354

Table 3: Rifampicin + Ascorbic acid (F6)

Time (min)	*Absorbance (Abs)*			*Concentration (Conc.)*			*Percentage drug release (%)*			*Mean % drug release ± SD*
	T1	*T2*	*T3*	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*	
0	0	0	0	0	0	0	0	0	0	0
15	0.366	0.361	0.359	38.00	37.00	37.00	33.00	33.00	33.00	33.00 ± 0.010%
30	0.389	0.391	0.388	44.00	43.00	43.00	39.00	39.00	39.00	39.00 ± 0.010%
60	0.444	0.442	0.443	46.00	46.00	46.00	41.00	41.00	40.00	41.00 ± 0.011%
p-value										**0.0040

the polydispersity number is higher than 0.50. This number is between 0.309 and 0.354.

Zeta potential study of PLGA based nanoparticles

The word "zeta potential" refers to how stable a sample is. It's possible for molecules and particles that are very small to be steady, which means they won't stick together. The nanoparticles that were made had a zeta potential of -46.9, which means that they could not stick together. Also, they were interested in how the antioxidant ascorbic acid affects keeping rifampicin stable in a pH 1.2 setting that is like the stomach. After the nanoparticles were made, they were tested in a number of different ways. "Zeta potential" tells you how stable a sample is. It's possible for molecules and particles that are very small to be steady, which means they won't stick together. At low zeta potential, attraction is stronger than rejection. Particles with a high zeta potential are electrically stable because of this. Due to electric resistance, charged particles (those with a high zeta potential) are less likely to stick together. Aggregation is easier when the zeta potential is lower. The nanoparticles that were made had a zeta potential of -46.9, which means they could not stick together.

In-vitro stability study of PLGA based nanoparticles

A study was done on the stability of rifampicin PLGA nanoparticles and rifampicin mixed with ascorbic acid (F6) in a pH 1.2 buffer (Table 3).

It took an hour to do the *in-vitro* breakdown study. The five formulas were used to do it. The first form is made up of only rifampicin. Second is PLGA nanoparticles with rifampicin on their own. The amount of ascorbic acid went up in the next three forms, but the amount of rifampicin to PLGA stayed the same. To study dissolution, drinks with a pH of 1.2 were used. These were meant to be like the stomach's acidic environment. At certain times, samples were taken out and looked at with a UV spectrophotometer. It was found out how much of the drug was released from the nanoparticles after 15, 30, and 60 minutes, and how much of the drug was broken down. The *in-vitro* drug dissolving study showed that the formulations F1 through F10 released a certain amount of drug after 60 minutes. The results are shown in Table 3. It is clear from the data that ascorbic acid slowed down the breakdown of rifampicin. As the amounts of ascorbic acid rose, the breakdown slowed down even more. Statisticians studied the percentage drug degradation profile and discovered that as the content of ascorbic acid increased, the percentage degradation changed in

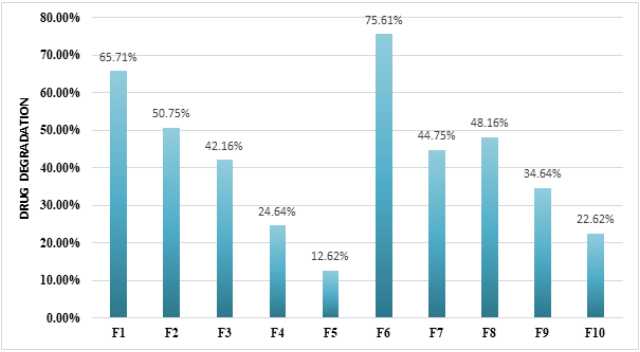

Figure 2: *In-vitro* %drug degradation study

a way that was statistically significant (*p < 0.0150). Ascorbic acid, an antioxidant, might stop rifampicin from breaking down too quickly in the stomach and stopping its harmful side effects.

Comparative %drug degradation profile

Rifampicin is the first drug used to treat TB. People take it by mouth in a set amount with isoniazid, pyrazinamide, and ethambutol to keep them from becoming resistant to drugs, which could happen if they only took those drugs. Rifampicin, on the other hand, is less bioavailable because it breaks down in the gut. Rifampicin breaks down in stomach acid, and the rate at which it breaks down depends on the pH (Figure 2). Some research suggests that the reason why rifampicin isn't absorbed well from combination goods could be because it breaks down faster in stomach conditions, and INH speeds up this process.

If the pH is too low, rifampicin breaks down, but if the pH is too high, it functions well. In acidic conditions, rifampicin breaks down into 3-FRSV, and in alkaline conditions, it reacts with air to make rifampicin quinine, which is a powerful quinone derivative. It has a lot of antimicrobial effect *in-vitro* but none *in-vivo*. Since the stomach is acidic, the formation of 3-FRSV can be a major factor affecting the bioavailability of rifampicin which should not be ignored. Any way to stop or slow down the breakdown of rifampicin in the gut would be helpful for therapy. This is true whether rifampicin is used alone or with another anti-tuberculosis drug. This would help control tuberculosis more effectively and make rifampicin more bioavailable.

A previous study found that adding ascorbic acid to the reaction medium stopped the reactive side reaction that would have broken down rifampicin. In a different study, it was found that adding ascorbic acid to plasma can protect rifampicin from

breaking down. This can stop the breakdown completely, which keeps the drug stable for 12 hours.

CONCLUSION

The study's results show that ascorbic acid can keep rifampicin from breaking down too quickly in stomach acid, which makes it more stable and effective as a medicine. The study also discovered that the percentage drug breakdown profile changed in a way that was statistically significant when the concentration of ascorbic acid was higher. More studies in living things are needed to find out how well PLGA nanoparticles loaded with rifampicin and ascorbic acid work as a medicine.

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