International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 2120-2128 www.ijprajournal.com ISSN: 2456-4494

An Overview of Lipid-Polymer Half-Breed Chitosan Based Isoniazid Loaded Nanoparticle in the Treatment of Tuberculosis

*Gouranga Sundar Roy[1], Manichandra Das[2], Jyotirmoy Bondyopadhyay[3], Raktimava DasSarkar[1], ParthaPratim Das[4], Raja Majumder[1].

[1]*Department of Pharmacognosy, Bengal School of Technology (A College of Pharmacy), Delhi-Road, Sugandha, Hooghly, West-Bengal, India, 712102.*

[2]*Department of Pharmaceutics, B. C. Roy Institute, Hooghly, West-Bengal, India, 712135.*

[3]*Department of Pharmacology, B. C. Roy Institute, Hooghly, West-Bengal, India, 712135.*

[4]*Department of Pharmaceutical Technology, School of Medical Science, Adamas University, Barasat-Barrackpore Road, Barbaria, P.O Jagannathpur, District-24 Parganas (North), Kolkata, West Bengal, India, 700126.*

Submitted: 17-12-2022 Accepted: 31-12-2022

ABSTRACT

The oral route is a commonly used method of drug administration. Therefore; numerous scientists are at present attempting to foster proficient oral medication conveyance frameworks. Utilizing lipid transporter frameworks such as SLNs (strong lipid nanoparticles), liposomes, and nano-structured lipid transporters (NLC) has limitations, like drug spillage and scatterings with high-water content. Subsequently, LPNs (lipid polymer crossover nanoparticles) were investigated by scientists to give an improved impact utilizing the properties of the two polymers and lipids. Isoniazid stacked polymer lipid half-breed nanoparticles might be ready by twofold emulsification and a dissolvable vanishing strategy. Further, The PLNs could be upgraded based on different boundaries like molecule size, PDI and capture effectiveness. For in-vivo examinations, a remedial portion of isoniazid can be directed by oral course to Wistar rodents for the assessment of medications in the lungs and plasma.

INTRODUCTION

Lipid-polymer half-breed nanoparticles (LPHNPs) are a new kind of nanoparticle drug delivery system that combines the advantages of lipids and polymers.LPHNPs are strong, submicron-sized particles that are made up of in combination called lipid andpolymer. In the half-breed framework, many bioactive atoms may be entangled, adsorbed, or covalently connected, including medications, qualities, proteins, and focusing ligands. LPHNPs are cutting-edge centre shell nanostructures, reasonably got from both liposome and polymeric nanoparticles (NPs), where a polymer centre remaining parts are wrapped by a lipid layer. Even though they have collected critical interest, they stay not yet broadly taken advantage of or omnipresent. As of late, a major change has happened in the planning of LPHNPs, described by progress from a two-move toward a one-step system, including coordinated self-get together of polymers and lipids.

Characteristic of LPHNPs

- The polymer core is responsible for stability during storage, controlled release, as well ashigh structural integritycapabilities.
- The lipid and lipid-PEG layers are responsible for the high bioavailability and biocompatibility.
- Additionally, this inner lipid layer serves as a molecular gate to reduce content leakage when LPHNPs are being produced.
- Additionally, by restricting inward water diffusion, the inner lipid layer lowers the rate of polymer breakdown of the LPHNPs product, allowing for sustained release kinetics of this content.
- A wide selection of polymer-lipid combinations, all of which are biocompatible.

POLYMER

Due to its adaptable biocompatibility, biodegradability, and regular beginning, chitosan has been utilized as a NP material.To treat lung disorders, it may be possible to use drug-loaded nanoparticles to deliver medications to the lungs. The effective TB treatment may be made possible by delivering therapeutic drugs to the site of action for lung disorders.The primary antituberculosis drug used to treat TB is an organic compound called isoniazid.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 2120-2128 www.ijprajournal.com ISSN: 2456-4494

Biodegradable nanoparticulate frameworks certainly stand out as potential medication conveyance vehicles. A perfect hydrophilic carrier system is formed by the polysaccharide chitosan (CS), which is considered to be a good medicinal material due to its biocompatibility and biodegradability.[1] Furthermore, chitosan is tissue-compatible and non-toxic in several investigations.A new suggestion has been made to use nanoparticles, which can be formed using a broad range of NPs andpolymers, as pulmonary delivery methods for proteins and peptides.[2]Chitosan is a particularly alluring polysaccharide in this respect because of its considered minimal biodegradability, harmfulness, and mucoadhesive properties.[3]CS has been exhibited to prompt low or missing poisonousness in cell lines illustrative of the pneumonic course.[4,5]Our group has demonstrated the readiness of CS or TPPNPs (chitosan or tripolyphosphate) by a very gentle and quick ionotropic gelation technique between CS and its counter particle TPP that showsa strong limit for protein relationship (as strong as 90%), and an enhancement of peptide retention through a few epithelia, including the intestinal, nasal, and ocular.[6]Additionally, to enhance the aerosolization patterns of protein-loaded chitosan nanoparticles, microspheres have recently been reported to be produced.[7] Such nanoparticle-loaded microspheres, which were formed by spray-drying NPs in mannitolsolution, showed that they were biocompatible with respiratory epithelial cell layers and had sufficient aerodynamic characteristics for lung delivery.[8] The stability of liposomes has been reported to be unaffected by spray drying, and research on the spray-drying of solid lipid NPs showed that now the presence of carbohydrates such as trehalose, mannitol, as well as lactose raised the stability of the spray-dried product by preventing the coalescence of the lipids.[9,10]Chitosan nanoparticles are formed using an ionotropic gelation process that relies on the relations of the positively-charged amino CS along with negatively-chargedPenta-sodium tripolyphosphate (TPP)groups. This method has been utilised to get CS nanoparticles prepared for protein and peptide delivery.[11]

TUBERCULOSIS

The most prevalent cause of mortality in young people globally is TB, a highlyand common infectious chronic granulomatous bacterial infection.[12]The common and fatal respiratory infection known as tuberculosis (TB) is often brought on by the mycobacterium entering the respiratory system as aerosol droplets[13]. Alveolar macrophages do not directly phagocytose germs; instead, they process bacterial antigens and transmit them to lymphocytes.After that, by localised lymphatic dissemination to territorial lymph hubs in the lungs and the destruction of host cells, the number of bacteria substantially increases (3 to about two months after contamination). Later, bacilli dispersal from the tainted lungs too far off exceptionally inundated organs (for example CNS, elastic bone, liver, kidneys and genitalia) happens (90 days after contamination). At this point, severe TB meningitis or disseminated TB may occasionallycause death. Pleurisy develops 3 to 7 months after the disease due to the arrival of microorganisms to the pleura.Finally, there may be extrapulmonary symptoms, such as lesions in the joints and bones.[14]Weakness, night sweats, fever, weight loss, and dry cough are TB symptoms.Globally, the WHO ("World Health Organization") predicted that 9.4 million new TB occurrences will occur in 2008.South-East Asia and Africa, respectively, had the majority of cases (55%) and 30%. China, India, South Africa, Indonesia, and Nigeria are the 5 nations with the highest numbers of cases.Approximately 15% of these TB cases were HIV+in 2008; 13% patients were in South-East Asian and 13% in African areas ["Global Tuberculosis Control 2011 (http://www.who.int/tb/publications/global report/2011/gtbr11_full.pdf")].

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 2120-2128 www.ijprajournal.com ISSN: 2456-4494

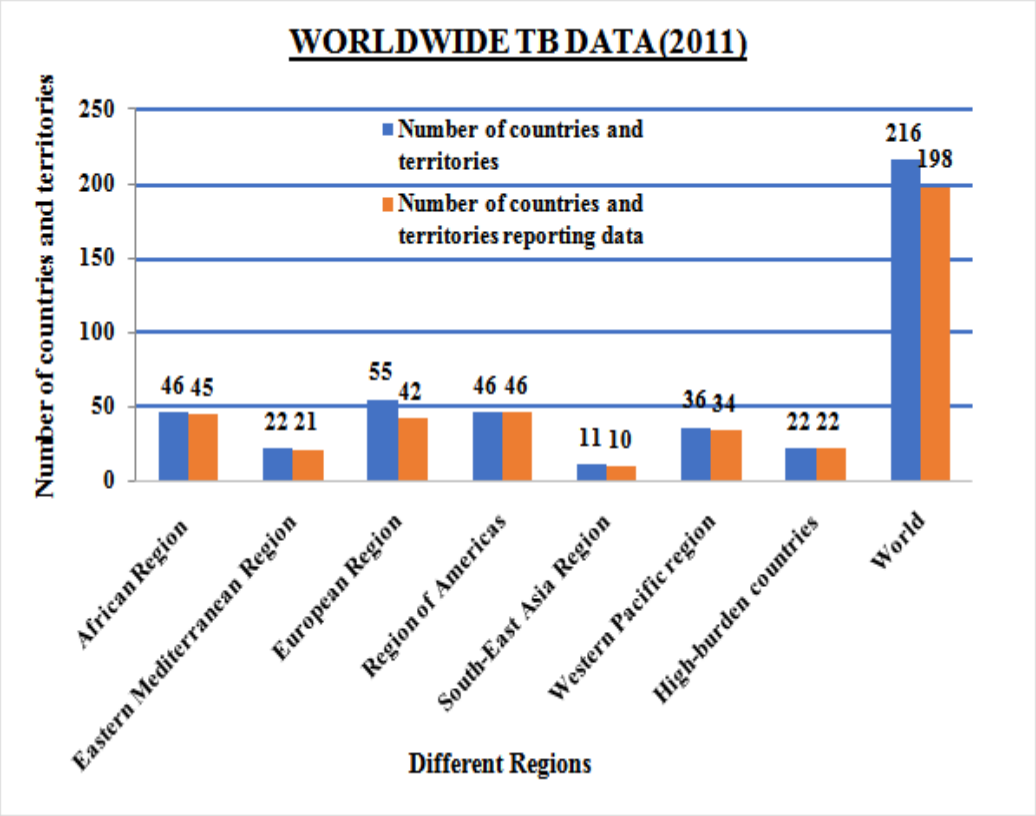

Figure No.1: Data reporting for the worldwide TB data collection program in 2011

Table No.1: List of API'sas therapy choicein the treatment of Tuberculosis

FIRST LINE DRUGS	DRUG (API)	BRAND NAME
	• Isoniazid	• Rimactazid DT
	• Rifampicin	• Rifadin
	• Pyrazinamide	• Zinamide
	• Ethambutol	• Myambutol
SECOND LINE DRUGS	**DRUG (API)**	**BRAND NAME**
	• Clofazimine	• Lamprene
	• Ethionamide	• Trecator
	• Clarithromycin	• Biaxin
	• p-amino salicylic acid	• Paser
	• Cycloserine	• Closina
	• Amikacin	• Amiklin

ISONIAZID

Isoniazidalso known as iso-nicotinyl hydrazine (INH) is an organic compound that is the first-line medication in the prevention and treatment of tuberculosis. Isoniazid is a prodrug and must be activated by a bacterial catalase-peroxidase enzyme that in M. tuberculosis is called KatG.(Suarez, Ranguelova et al. 2009) KatG couples the isonicotinic acyl with NADH to form an iso-nicotinic acyl-NADH complex. This complex binds tightly to the enoyl-acyl carrier protein reductase known as InhA, thereby blocking the natural enoyl-Acp M substrate and the action of fatty acid synthase. This is the process, which inhibits the synthesis of mycolic acid, required for the mycobacterial cell wall. A range of radicals is produced by KatG activation of isoniazid, including nitric oxide,[15]which has also been shown to be important in the action of another anti-mycobacterial prodrug PA-824.[16]Treatment of tuberculosis can be done by conventional therapy as well as inhalational therapy.Conventional

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 2120-2128 www.ijprajournal.com ISSN: 2456-4494

therapy has some disadvantages these are the following.

DISADVANTAGES OF CONVENTIONAL THERAPY

• High dose frequency is required.
• The drug not only discharges to the specific site but also to the whole system.
• It may produce systemic side effects.

To overcome the above disadvantages of conventional therapy nowadays inhalational therapy is usually preferred

MICROPARTICLES

Microparticles are circular particles somewhere in the range of 0.1µm and 100µm in diameter. They may be divided into two categories; microcapsules and microspheres. In contrast to microcapsules, which contain a core of one substance encased in a shell of another, microspheres are homogeneous mixes of polymers and active substances.

Advantages of microparticles:

Microparticles are suitable for a range of medication delivery applications and offer various advantages.

• They provide improved repeatability in the medicine release process due to their small molecular size.
• They provide superior control over the drug's release rate.
• Microparticles enable various types of release, including modified, instantaneous, pulsed, delayed, protracted, andsustained.
• They enable the development of dosage forms for administration to the lungs through the application of coatings.
• They have the potential to further increase bioavailability due to their smaller molecular size.

Disadvantages of microparticles:

Apart from the above advantages microparticles have some disadvantages

• A microparticle having an aerodynamic diameter of more than 5µm is not suitable for inhalational therapy; this is a major drawback of microparticles in inhalational therapy.
• Microparticles produce high permeability and degradation of the drug during the polymerization which causes toxicity.

NANOPARTICLES

To overcome the disadvantages of microparticles, the nanoparticle has been developed by the researcher. A small object known as a nanoparticle function as a single entity for its properties and transport.Sizes of nanoparticles range from 1 to 500nm. Due to the vast array of possible applications in biomedical domains, nanoparticle research is now a topic of significant scientific interest.

Advantages of nanoparticles

• The biological prospects for medication administration to the lungs are made possible by relatively narrow size distribution and small size.
• It is possible to develop a controlled release of active medicine over an extended time.
• Drug incorporation protection against chemical deterioration.
• NPs that can be both lyophilized and spray-dried.

Disadvantages of nanoparticles

These are very small particles, having an aerodynamic diameter below 1µm. It is not suitable for inhalation therapy. The appropriate particle size for inhalational therapy is 2-4 µm.

The multidisciplinary area of logic known as nanotechnology is likely to see risky developments. Parts of this discipline have seen the completion of the development of nano-scale drug delivery devices.Traditionalrecombinant proteins, drugs, immunizations, and most recent nucleotides, may all be delivered using nanoparticles.[19]

A rapidly growing discipline, nanotechnology is a result of the development of innovation and science.Numerous new avenues have opened up as a consequence of the current innovations becoming gradually more accessible, which were impossible to attempt to imagine in the past.

NPs have been concentrated widely as particulate transporters in a few drug and clinical fields. Nanoparticles can be utilized to give focused on the (cell/tissue) conveyance of medications, to enhance oral bioavailability of solubilized drugs for intravascular distribution, to support drug impact in the target tissue, to support the dependability of helpful specialists against enzymatic corruption, and more.

These are the potential advantages of NPs.

- It may prevent medicines from degradation.
- It may enhance the substance's physical properties.
- Decrease in the number of dosages needed.
- Improve the experience of receiving care while lowering expenses

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 2120-2128 www.ijprajournal.com ISSN: 2456-4494

- Permit insoluble drug delivery.
- While in circulation, they should not lose their therapeutic effectiveness or activity.
- Work on improving the specialists' oral bioavailability who aren't truly used orally.In the present review, we looked at how well isoniazid nanoparticles may affect the drug's oral bioavailability.

Chitosan nanoparticles

Chitin, a distinctive biopolymer obtained from the shells of scavenger shells like crabs, lobsters, and shrimp, is transformed into chitosan, a modified normal starch polymer, by the process of fractional N-deacetylation. After cellulose, chitin is the polysaccharide that occurs most often in nature. It is a polysaccharide that is biocompatible, non-toxic, and organically preserved. Due to their improved stability, low toxicity, easy and gentle manufacturing, and potential to provide a flexible route of administration, chitosan nanoparticles have attracted increased interest as drug delivery carriers.Their sub-micron size makes them suitable for non-invasive mucosal administration methods such the mucosa of the oral, nasal, and ocular mucosa.Chitosan has several excellent properties for polymeric nanoparticle carriers, including being biocompatible, non-toxic, biodegradable, and relatively inexpensive.Moreover, it has emphatically charged and displays retention improving impact. These characteristics make chitosan a very desirable substance for a medicine transporter. Over the most recent twenty years, chitosan nanoparticles have been widely evolved and investigated for drug application.

Problem with drug

Isoniazid therapy has been used to account for severe and sometimes fatal hepatitis, which may still occur even after multiple extended periods of therapy.As one gets older and drinks more, their risk of getting hepatitis increases. Patients who have been administered isoniazid need to undergo thorough examinations and regular follow-up conversations.Before starting isoniazid medication and sometimes throughout treatment, hepatic enzymes, particularly AST and ALT (formerly SGOT and SGPT respectively) should be evaluated in patients aged 35 and older. An expanded gamble of deadly hepatitis related to isoniazid has been accounted for in ladies, especially Hispanic and dark ladies. During the week after delivery, the risk might also increase. In these populations, more meticulous monitoring should be taken into consideration, maybe with more regular laboratory testing (http://www.drugs.com/cons/isoniazid-oral-intramuscular.html).

UPTAKE OF LPNs FROM THE ORAL ROUTE

Uptake of LPNs viathe oral route may bypass the first pass the process of absorption, which starts in the mouth and goes through the small intestine, stomach, and colon is crucial. Drugs additionally go through ingestion through GIT film by at least one vehicle component as same as miniature/macromolecules[17].Ingestion of nanoparticulate frameworks happens by at least one instrument.Any NP system's absorption is dependent on the many mechanistic absorption theories and their underlying qualities, which ultimately influence absorption. NPs are colloidal medicine carriers that may be used to deliver medications orally. Adequate particle absorption into lymphatics has typically been shown for non-designed NPs of 50–1000 nm and microspheres 10μm [18]. However, microparticles were maintained in the intestines of mice andrats for extended periods and only absorbed 2-3% through Payer's patches. Additionally, NPs were taken up by the digestive tract as particle form and transported to different organs of the body's lymphatic systems.There are two potential processes for NP uptake:

(1) Payer's patches in the intestine undergo intracellular absorption through the M cells.

(2) Paracellular/intercellular uptake.

Additionally, lipid-based systems with self-emulsifying excipients produce chylomicrons through lipase for delivery into the lymphatic system to boost absorption (similar to the long-chain fatty acids absorption through promoted chylomicrons creation). Assimilation of lipids begins in mouth through lipase chemicals. When it enters the digestive system, they are immediately exposed to lipase, which is found in pancreatic juice and bile acid released from the liver's nerve bladder. This process reduces the lipid vesicle to small beads, or more modest fatty oils (TGs), which are then completely converted into MGs (monoglycerides), free unsaturated fats, andglycerol. In addition, the MGs interact with the bile salt generated by micelles that penetrate the epithelial barrier before undergoing a second conversion to TGs with the aid of the endoplasmic reticulum and becoming chylomicrons. Because such chylomicrons are not very small, they may enter the circulation and go straight to the liver. In this method, blood flow from the thoracic channel to the jugular vein follows the main transit to the

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 2120-2128 www.ijprajournal.com ISSN: 2456-4494

lymphatic stream.Lipids may thus avoid liver metabolism. The whole plan is shown in.Therapeutic molecules may be effectively transferred from the intestinal lymphatics through thoracic lymph duct to the systemic circulation using the rough M cell uptake.The molecular sieving of large-sized NPs occurs directly into the lymphatics rather than being delivered to the blood capillaries because the intercellular connections between the endothelial cells of lymphatic capillaries are more open than those of blood capillaries at the capillary level.It was discovered that the M-cell absorption of NPs was size-dependent, irrespective of the animal model (i.e., the uptake increases as the size decreases).Nanoparticulate systems may effectively enhance MRT (mean residence time) and BA to improve treatment effectiveness. The retention of ineffective solvent drugs and the targeting of drug transporters to the lymphatics are both facilitated by lymphatic delivery. The drug's plasma concentration is also increased and the hepatic first-pass effect is avoided with the lymphatic diffusion of NPs. The transcellular process, in combination with enterocytes' stimulation of chylomicron production, significantly improved the absorption process. The configuration of chylomicrons allows for the breakdown and osmosis of lipophilic atoms into nonpolar centres, which improves the retention of lipophilic drugs.SLNs differ from polymeric NPs in terms of absorption through lipase-mediated chylomicron production since SLNs have a lipid core in addition to M cell uptake.

Advantages of Polymer hybrid nanoparticle over other oral routes

The development of nanotechnology has rekindled interest as a major medication delivery pathwayin the lungs for systemicas well aslocaltreatment. The large surface area and the insignificant barriers of lungs that prevent access to their outermost regions make them an ideal entry point for various beneficial treatments. NPs give new plan choices to both scattered fluid bead dose structures like metered portion nebulizers and inhalers, as well as dry powder details. In comparison to traditional dosage forms, nanoparticle definitions provide several advantages, including improved drug disintegration characteristics and the possibility for intracellular drug delivery.Unadulterated drug NPs, polyelectrolyte structures, polymeric NPs, and drug-stacked liposomes in particular provide some helpful outcomes to deliver drugs to and through the lungs. Additionally, methods for delivering nanoparticles with qualities appropriate to improve access to the peripheral lung are being investigated.

ORAL ADMINISTRATION OF NP-BASED TB DRUGS

The possibility of oral administration is provided by nanoparticle stability. Numerous studies have looked at how nanoparticles behave in the gastrointestinal tract[20-22]. The following is generally how nanoparticles are absorbed:

i. By transcytosis through M-cells,
ii. Via transit through the epithelial cells of the gastrointestinal mucosa and intracellular uptake,
iii. Via ingestion through Peyer's patches.

Pandey and colleagues demonstrated that the nanoparticles significantly improved the viability of the over-the-counter TB medications after oral administration and supported their arrival [23]. Three bleeding edge drugs, RMP (rifampin), INH (isoniazid), and PZA (pyrazinamide) were co-encapsulated in PLG (polylactide-co-glycolide)NPs. In the flow, the medications may be found for 4 days (RMP) and 9 days (PZAand INH) after giving this strategy to mice just orally; for 9 to 11 days, favourable concentrations in the tissues were sustained. It's noteworthy to observe that 12 to 24h after organisation; free (unbound) medications were removed from plasma.M. tuberculosisinfected mice therapy with the medications delivered by nanoparticles (five oral doses every ten days) eliminated the germs from the organs. Only after routinely organising 46 doses of free drugs did they have the ability to establish bacterial latitude. In guinea pigs, comparable viability of the medicines attached to nanoparticles was also seen[24]. Consolidation in microparticles was less effective at the same time because both the medication stacking limit and the plasma half-life of the bound drugs were decreased. [25, 26]PolymericNPs behaviour in the gastrointestinal tract is affected by their bio adhesive qualities; the link between NPs and the mucosa improves the retention of the associated drug, hence enhancing its bioavailability.Because the lectin-united transporters are bio-recognised by glycosylated structures in the digestive system, lectins have therefore been shown to further promote muco-adherence to the drug.[27]Covalent bonding of raw grain agglutinin was appropriately used to improve the effectiveness of PLG-based designs for anti-TB medications.[28]RIF, INH, and PZA were combined with raw grain agglutinin-covered PLG nanoparticles in mice, and this greatly increased the serum half-life: RIF blood levels were detectable

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 2120-2128 www.ijprajournal.com ISSN: 2456-4494

for 6 to 7 days, and PZAand INH for 13 to 14 days (vs 4-6 days and 8-9 days for non-modified NPs).Every 3 drugs were present in the spleen, liver, and lungs for 15 days.After three oral portions managed each 14 d, the lectin-changed plans allowed for bacterial independence in these organs (in comparison to 45 daily dosages of free medicine). According to the authors, the extended absorption time window and localised heightening of the gradientconcentration between the serosaland luminalmembranesides are made possible by lectins' promotion of sustained adhesion of the drug-containing wheat germ agglutinin-grafted NPs to the intestinal surface.

POTENTIAL FOR THE INHALATION FORM APPLICATION

The likely benefits of direct conveyance of the TB medication to the lungs incorporate the chance of diminished foundational poisonousness and accomplishing higher medication focus at the fundamental disease site. Additionally, medications that are inhaled are not subject to first-pass metabolism, unlike those that are administered orally. The mass middle streamlined measurement of nanocarriers might be a barrier to using them for pulmonary administration, a fundamental boundary for the molecule statement in the lungs, which is in many cases excessively little. But different reports were demonstrated the potential of using nanoparticles for pulmonary medication delivery.[29]Research on the pharmacokinetics and bactericidal effects of anti-TB medicines delivered through the respiratory tract in guinea pigs.[30]A suitable facemask associated with the blower nebulizer system was used to deliver the part.Co-encapsulated PLG nanoparticles containing RMP, PZA, and INH were administered to guinea pigs by nebulizer. As a consequence, the lungs and plasma both had sustained amounts of the restorative medication for up to 11 days. This effect was identical to what was seen with oral administration of similar drugs' nanoparticulate details.Even though 46 daily dosages of an oral controlled medication were supposed to have the same restorative effect, no tubercle bacilli could be discovered in the lung of guinea pigs exposed to M. tuberculosis after just five treatmentdosages. Infected guinea pigs responded more better to the combination of nebulized PZA, RMP, and INH in raw grain agglutinin-functionalized PLG nanoparticles; three doses given twice weekly for 45 days were enough to have a sanitising impact in the spleenand lungs.[28]The medications also had a cleaning effect when paired with strong lipid nanoparticles.[31]No tubercle bacilli were discovered in the lungs/spleen of infected guinea pigs after seven doses of treatment with drug-stacked strong lipid nanoparticles.Strong lipid nanoparticles must demonstrate substantial advantages, like the arrangement (physiologic mixtures) and the chance of enormous scope creation leaned toward by the possibility to stay away from natural solvents in the assembling system.[21]

Observation

For the treatment of tuberculosis, isoniazid-based polymer-lipid-hybrid nanoparticles may be a viable and affordable alternative. Their primary advantages, which include improved disease management and more practical and affordable directly monitored therapy, are higher drug bioavailability and lower dosage frequency. The viability of numerous drug delivery methods, such as oral and inhalation routes, is another significant benefit of nanoparticles. Furthermore, the nanoparticles' remarkable stability predicts a lengthy shelf life. The regulated, targeted medication administration provided by chitosan nanoparticles has various potential advantages. Chitosan nanoparticles demonstrated a superb potential for isoniazid attachment.

The conclusion is that further research on this unique approach is a potential first step for our mankind.

REFERENCES

[1]. J Kreuter. Infection 1991;19: S224–S228.
[2]. MJ Alonso. Nanoparticulate drug carrier technology, in S. Cohen, H. Bernstein (Eds.), Microparticulate systems for the Delivery of Proteins and Vaccines, Marcel Dekker, New York, 1996, pp. 203–242.
[3]. Q Zhang, Z Shen, T Nagai. Int J Pharm 2001;218:75–80.
[4]. Grenha B Seijo, C Remun˜an-Lopez. Eur J Pharm Sci 2005; 25:427–437.
[5]. S Hirano, H Seino, Y Akiyama, I Nonaka. Polym Mater Sci Eng 1988;59: 897–901.
[6]. M Dornish, A Hagen, E Hansson, C Peucheur, F Vedier, O Skaugrud. Safety of ProtasanTM: ultrapure chitosan salts for biomedical and pharmaceutical use, in A. Domard, G.A.F. Roberts, K.M. Varum (Eds.), Advances in Chitin Science, Jacques Andre Publisher, Lyon, 1997, pp. 664–670.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 2120-2128 www.ijprajournal.com ISSN: 2456-4494

[7]. Paull R, Wolfe J, Hebert P, Sinkula M, Investing in nanotechnology, Nature Bio-technology, 2003, 21, 1134-1147.
[8]. BI Florea, M Thanou, HE Junginger, G Borchard. J Control Release 2005;110:353–361.
[9]. R Fernandez-Urrusuno, P Calvo, C Remun˜an-Lopez, JL Vila-Jato, MJ Alonso. Pharm Res 1999; 16:1576–158.
[10]. Behrens AI, Vila-Pena MJ Alonso, T Kissel. Pharm Res 2002; 19: 1185–1193. [15] P Goldbach, H Brochart, A Stamm. Drug Dev Ind Pharm 1993; 19:2611–2622.
[11]. P Goldbach, H Brochart, A Stamm. Drug Dev Ind Pharm 1993; 19:2611–2622.
[12]. Dube, D., G. P. Agrawal, et al. (2012). "Tuberculosis: from molecular pathogenesis to effective drug carrier design." Drug Discov Today **17**(13-14): 760-773.
[13]. Kaufmann, S., McMichael, A. Annulling a dangerous liaison: vaccination strategies against AIDS and tuberculosis. Nat Med **11** (Suppl 4), S33–S44 (2005).
[14]. Smith, I. (2003). "Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence." Clin Microbiol Rev **16**(3): 463-496.
[15]. Timmins, G. S., S. Master, et al. (2004). "Nitric oxide generated from isoniazid activation by KatG: source of nitric oxide and activity against Mycobacterium tuberculosis." Antimicrob Agents Chemother**48**(8): 3006-3009.
[16]. Ahmad, Z., C. A. Peloquin, et al. (2011). "PA-824 exhibits time-dependent activity in a murine model of tuberculosis." Antimicrob Agents Chemother**55**(1): 239-245.
[17]. Florence AT .1997. The oral absorption of micro-and nanoparticulates: neither exceptional nor unusual. Pharm Res.14: 259 – 266.
[18]. Bargoni A, Cavalli R, Caputo O, Fundar ò A, Gasco MR, Zara GP. 1998. Solid lipid nanoparticles in lymph and plasma after duodenal administration to rats. Pharm Res. 15: 745 – 750.
[19]. Langer R., Biomaterials in drug delivery and tissue engineering: one laboratory's experience, Acc Chem Res, 2000, 33, 94-101.
[20]. Florence AT. Issues in oral nanoparticle drug carrier uptake and targeting. J Drug Target 2004;12:65–70.
[21]. Bummer PM. Physical chemical considerations of lipid-based oral drug delivery: solid lipid nanoparticles. Crit Rev Ther Drug Carrier Syst2004;21:1–20.
[22]. Florence AT, Hussain N. Transcytosis of nanoparticle and dendrimer delivery systems: evolving vistas. Adv Drug Deliv Rev 2001;50:S69–S89.
[23]. Pandey R, Zahoor A, Sharma S, Khuller GK. Nanoparticle-encapsulated antitubercular drugs as a potential oral drug delivery system against murine tuberculosis. Tuberculosis (Edinb) 2003;83:373–378.
[24]. Sharma A, Pandey R, Sharma S, Khuller GK. Chemotherapeutic efficacy of poly (DL-lactide-co-glycolide) nanoparticle encapsulated antitubercular drugs at sub-therapeutic dose against experimental tuberculosis. Int J Antimicrob Agents 2004;24:599–604.
[25]. Ain Q, Sharma S, Garg SK, Khuller GK. Role of poly [DL-lactideco-glycolide] in the development of a sustained oral delivery system for antitubercular drug(s). Int J Pharm 2002;239:37–46.
[26]. Dutt M, Khuller GK. Chemotherapy of Mycobacterium tuberculosis infections in mice with a combination of isoniazid and rifampicin entrapped in poly (DL-lactide-co-glycolide) microparticles. J AntimicrobChemother2001;47:829–835.
[27]. Gabor F, Bogner E, Weissenboeck A, Wirth M. The lectin-cell interaction and its implications to intestinal lectin-mediated drug delivery. Adv Drug Deliv Rev 2004;56:459–480.
[28]. Sharma A, Sharma S, Khuller GK. Lectin-functionalized poly (lactideco-glycolide) nanoparticles as oral/aerosolized antitubercular drug carriers for the treatment of tuberculosis. J AntimicrobChemother 2004;54: 761–766.
[29]. Pandey R, Khuller GK. Antitubercular inhaled therapy: opportunities, progress and challenges. J AntimicrobChemother2005;55:430–435.
[30]. Pandey R, Sharma A, Zahoor A, Sharma S, Khuller GK, Prasad B. Poly (DL-lactide-co-glycolide) nanoparticle-based inhalable sustained drug delivery system

for experimental tuberculosis. J AntimicrobChemother2003;52:981–986.

[31]. Pandey R, Khuller GK. Solid lipid particle-based inhalable sustained drug delivery system against experimental tuberculosis. Tuberculosis (Edinb) 2005;85:227–234.

[32]. J. Sung, D. Padilla, L. Garcia-Contreras, J. VerBerkmoes, D. Durbin, C. Peloquin, K. Elbert, A. Hickey, D. Edwards, Formulation and pharmacokinetics of self-assembled rifampicin nanoparticle systems for pulmonary delivery, Pharmaceutical Research 26 (2009) 1847–1855.

[33]. Suarez, J., K. Ranguelova, et al. (2009). "An oxyferrousheme/protein-based radical intermediate is catalytically competent in the catalase reaction of Mycobacterium tuberculosis catalase-peroxidase (KatG)." J Biol Chem **284**(11): 7017-7029.