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Review Article

Advances in *in vivo* Non-invasive Delivery of Gentamicin

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ABSTRACT

Introduction: Parenteral administration of gentamicin is a globally known therapeutic strategy for severe infections, including severe community acquired pneumonia, complex severe acute malnourishment, neonatal and pediatric sepsis. The drug is also prescribed as an ophthalmologic anti-infective. In most cases, the therapeutic course necessitates frequent bolus medication doses, lengthy hospitalization, and ongoing therapeutic monitoring; hence a qualified healthcare provider is required. **Objectives:** Gentamicin is a hydrophilic drug and has a short half-life, making it difficult to achieve appropriate systemic concentrations when taken parenterally. The use of innovative oral medication delivery systems is justified in this context. Furthermore, new delivery strategies can increase the membrane permeability of gentamicin. **Conclusion:** The current analysis provides a detailed summary of gentamicin's research history as well as several developing drug delivery strategies that have been explored. The examples included in the paper give important evidence on innovative delivery systems for gentamicin in the domain of antimicrobial investigations opening a way for upcoming therapeutics that may provide better clinical outcomes.

Keywords: Gentamicin, Non-invasive, Aminoglycoside, Bioavailability, Permeability.

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INTRODUCTION

Gentamicin Sulphate (GS) belongs to the category of antibiotics, namely aminoglycosides, the first antibiotic group to be established as antibacterials, with the initial discovery of streptomycin by Waksman in the year 1963. Studies report a short half-life for GS (2-4 hr). Since GS initially has poor penetration capacity, oral absorption is essentially non-existent.[1,2] Depending on the severity of the illness, the sulphate salt of the medication is injected intramuscularly or (slowly) intravenously once or twice daily. The bactericidal activity of GS is concentration-dependent.[3] When GS reaches the site of action, it enters the cytosol via active transport, hampers ribosomal translation by attaching to the 30S subunit, and ultimately results in cell death. Protein generation is impeded by obstruction of the initiation complex for peptide formation. Misreading of m-RNA results in non-functional proteins, or polysome disintegration into non-functional monosomes.[4,5] Amid the diverse varieties of antibiotics, this category has obtained wide-ranging consideration owing to their wide-scale antibacterial effectiveness and favourable chemical and pharmacokinetic features. The basic and hydrophilic nature of the compounds is due to their configuration, comprised of aminocyclitol rings with single or few amino or sugar groups. They are recognized as polyaminated pseudo saccharides owing to their exclusive stereochemistry of amino and hydroxyl groups in their structure.[6] Initially, the antibiotics were acquired from *Streptomyces griseus* and *Micromonospora purpurea* by fermentation of aerobic microbes residing in soil. Thereafter, different natural and synthetic aminoglycosides arouse, including gentamycin, amikacin and tobramycin, the most frequently employed antibiotics administered via parenteral route. These are extensively utilized in the managements of sepsis and bacterial infection of pulmonary or cardiac concern and urinary tract.[7] It is assumed that aminoglycosides well resist enzymatic inactivation. Conversely, they are associated with nephrotoxicity and ototoxicity issues, which compel pharmacological restrictions. The occurrences of microbial resistance to alternative frequently utilized antibiotics have compelled the aminoglycoside group of antibiotics to continue as a precious and anticipated preference for managing crucial infections, regardless of the adverse effects.[8] It is reported that the difficulty in curing nosocomial infections triggered by gram-negative bacilli is increasing due to the advent of numerous resistance mechanisms, which also restrict the use of a few of the finest drugs in our medical resources. On the worse side, there are a minority of drugs that are functional against multidrug-resistant nosocomial gram-negative organisms.

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Consequently, many clinicians are considering the utilization of aminoglycoside antibiotics once more.[9]

The History of Aminoglycosides -Gentamicin

Streptomycin was the first ever aminoglycoside introduced in clinical practice during the mid-1940s. It was obtained from *S. griseus*. Waksman and his co-workers are known for this discovery in 1943. The drug was unbeaten in treating tuberculosis. Followed by streptomycin, numerous new aminoglycosides were introduced, which include neomycin in 1949 (from *S. fradiae*), gentamicin in 1963 (from *Micromonospora purpurea*), kanamycin in 1957 (from *S. kanamyceticus*), tobramycin in 1967 (from *S. tenebrarius*) and sisomicin in 1970 (from *M. inyoensis*).[10] All aminoglycosides perform good bactericidal efficacy against most gram-negative and few gram-positive bacteria. Since these first-generation aminoglycosides were used extensively, resistance to them developed more often, and some toxicities, notably nephrotoxicity and ototoxicity, grew more pronounced.[11] In 1963, gentamicin was discovered, and after that, it got introduced as parenteral dosage in 1971; it has been broadly utilized in the medicinal domain. The USFDA authorizes gentamicin prescription for routine infection treatment due to *Klebsiella pneumoniae, Escherichia coli, Serratia marcescens, Citrobacter* spp., *Enterobacteriaceae* spp., *Pseudomonas* spp.; *Staphylococcus*; bacterial meningitis; neonatal sepsis; septicemia; ophthalmic, orthopedic, dermal and/or subcutaneous infections; infective endocarditis; peritonitis caused by Pseudomonas and additional organisms (gram-negative); peritonitis caused due to gastrointestinal infections; respiratory; and urinary tract infectious disease.[12] As per WHO 21st EML (World Health Organization Essential Medicines Lists), 2019, gentamicin is categorized under key access group antibiotics. This group comprises antibiotics that are effective against an extensive array of commonly encountered liable pathogens and show lower resistance potential compared to other antibiotics. These antibiotics are mentioned as essential first or second empiric treatment choices for infectious syndromes reviewed by EML expert committee and are enlisted as individual medicines on the Model Lists to improve access and promote appropriate usage. They are crucial antibiotics that should be extensively available, reasonably priced and of reliable quality. GS (2-mL vial injection: 20 mg; 80 mg) is the first preferred drug for – sepsis in infants and complicated severe acute malnourishment and community-acquired pneumonia (severe), whereas the second option drug for gonorrhoea and surgical prophylaxis. Its use is also prescribed in ophthalmological preparations (eye drops 0.3% as a sulfate solution).[13,14]

β-lactams, carbapenems, and fluoroquinolones, a type of wide-spectrum antibiotics with fewer adverse effects, got introduced during the 1970s, and this caused a reduced interest in exploring new aminoglycosides. Isepamycin in 1988 and arbekacin in 1990 are the last known aminoglycosides to be launched in the market, reducing their effectual shares to 2.7% over a decade ago. Soon after, the origination of resistant strains provoked the use of aminoglycosides in managing severe bacterial nosocomial infections.[15] The hydrophilic basic aminoglycosides are cationic and fairly steady at pH 6 to 8. The antibiotics are highly stable metabolically and get distributed in the extracellular space (one-fourth of the lean body mass). Approximately 95% of aminoglycosides are excreted through the kidneys. They have poor membrane permeability due to their polarity.[16] BNF (British National Formulary) and the US (United States) lists streptomycin, gentamicin, neomycin, tobramycin, and amikacin for clinical purpose, and apart from these, aminoglycoside kanamycin as authorized by the USFDA (US Food and Drug Administration).[17]

Obstacles in Delivery of Gentamicin Sulfate

GS is ototoxic and nephrotoxic; hence it must be administered slowly as an infusion drip or intravenous bolus; this is more challenging in poorly equipped medical management setups, particularly in nations which are developing, where access to safe parenteral supplies is inadequate and disease spread through re-use of needles and incorrect sharp disposal is common. Furthermore, gentamicin parenteral administration necessitates safe monitoring and qualified health staff for dosage calculation, which is challenging in an outpatient case. In a specialised demographic, such as paediatrics, discomfort from needle prickling, infections at the injection site, and phobia of needles, i.e. trypanophobia, all lead to decreased patient compliance. Trypanophobia affects about one-fourth of adults, resulting in inadequate medical care.[18,19]

Gentamicin Quantitative Structure Bioavailability Relationship

The parameters that impact the oral bioavailability of a drug molecule encompass the number of hydrogen donors, the presence of heavy atoms, and the occurrence of aminopyridine, benzoquinone and tetrazole groups. 'Rule of five' is a competent tool for rapidly sorting out drug moieties with inferior absorption properties.[20] The rule is termed so, as the marginal value for each of its parameters having values either near to 5 or multiple of 5.[21] This rule claims that if any drug molecule complies with any two of the following parameters given in Table 1, then its intestinal absorption will possibly be unsatisfactory. Adhering to this rule Gentamicin (refer to Figure 1) falls under drugs with poor absorption as, shown in Table 1.

Worldwide Consumption

A commonly used medication is gentamicin.[25] Table 2 lists the oral and parenteral antibiotic entities that make up three-fourths of all antibiotic utilization, the number of countries where they were included on the country-specific DU75 (drug utilization 75%) list, and the median proportional consumption (% of total defined daily doses) in those countries.[26]

Table 1: Parameters for evaluating permeability of Gentamicin (Rule of five).

Parameter	Values as per Rule of five	Values of Gentamicin	References
Molecular Weight	> 500	477.6 (C1)	22
Count of H- Bond Donors	> 5 Nos	8	23
Count of H- Bond Acceptors	>10 Nos	12	
C log P	>5.0	-3.77	24
PSA	>4.15	174.4Å^2	20

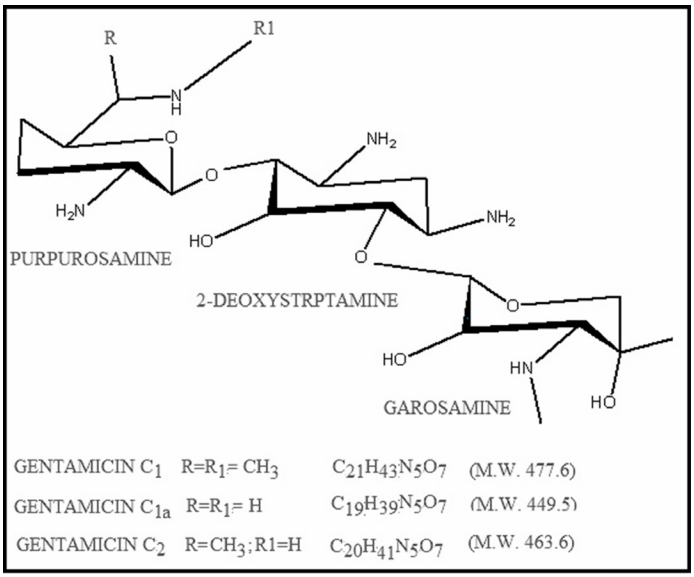

Figure 1: Chemical structure of gentamicin.

Table 2: Survey report on Gentamicin Consumption 26.

Region surveyed by WHO	No. of countries and areas where it appears in the country's DU75	Median proportion (Interquartile range)
African Region	¼	67.8
Regions of America	3/6	10.4(9.4-13.6)
European Region	25/46	7.9 (5.5-14.0)
Eastern Mediterranean Region	1/3	5.4
Western Pacific Region	2/6	12.2(8.4-16.0)

Ozturk *et al.* reported that urinary tract infections, which affect more than 150 million individuals yearly due to community acquisition, are among the most common infections seen in clinical treatment. Future gentamicin consumption is predicted to increase due to the increasing load of these infections.[27]

In 2020, the aminoglycosides market was worth USD 1,673.79 million, and within six years, it is assumed to attain a hike of USD 451.41 million, indicating a 4.11% compound annual growth rate. Gentamicin is typically selected as the first-line medication for many bacterial illnesses in both emerging and developed countries. The drug's use is particularly prevalent in underdeveloped countries, providing a cost-effective treatment option for various infectious disorders. With more doctors using it in combinations, gentamicin demand is rising for various bacterial diseases.[28]

Need For Gentamicin As Non-invasive Formulation

Cefazolin (47%), gentamicin (33%), and ceftriaxone (20%) were the most commonly administered antibiotics in a critical care unit, according to surveillance of parenteral antibiotic use.[29] Orally, the drug moiety is not absorbed significantly. Gentamicin is therefore administered Intramuscularly (IM), Intravenously (IV) and subcutaneously.[30] But it is noteworthy that aforementioned parenteral routes have drawbacks such as a) higher frequency of anaphylactic reactions than with many alternative routes, b) chances of phlebitis or infections at the site of injection, c) painful route for patients as compared to most of the other routes, d) chances of air embolism or vascular clot is there as an outcome of the vascular wall damage, e) once administered removing or lavaging drug is impracticable, except by dialysis, f) difficult in many situations, g) likelihood severe adverse reactions may be the outcome of rapid injection rate h) injection procedure is associated with patient's dislike and psychological discomfort.[31]

According to Murgitroyd *et al.* (2015), the most significant disadvantage of gentamicin administration with substantial clinical consequences is the high incidence of under-dosing. Less than 25% of patients on multidose regimens (for sepsis care) received appropriate antibiotic therapy. The most often noted reason for non-administration in the research was a lack of IV access.[32]

Resistance is determined by the diversity of genotypes in the huge bacterial population and the selective pressures exerted along the antibiotic concentration gradients in the body. It has been proposed that resistance can be circumvented by paying attention to dosage because dosing with an AUIC 0-24/MIC ratio of a minimum of 100 seems to slow the development of bacterial resistance. An antibiotic with strong bactericidal efficacy and tissue and/or serum concentrations more extensive than the MIC or, better, minimal bactericidal concentration throughout the dosage period is equally beneficial in preventing antibiotic resistance development.[33,34]

Table 3: Gentamicin-Oral drug delivery approaches.

Formulation approaches	Model	Observation/ Comments	References.
Poly lactic co-glycolic acid nanoparticles surface modified with chitosan.	Rabbit	Sustained release oral dosage. Potent for oral absorption.	37
Multicomponent-crosslinked carboxymethyl cellulose.	-	Controlled release. Smart pH-sensitive platform for delivery via oral route.	38
Enteric capsule:Labrasol- GM solution and suspension.	Beagle dogs	Labrasol solution provides higher plasma drug levels compared to suspension.	39
Labrasol-SMEDDS, and solidified with Florite RE.	Rats	Florite RE is helpful for oral solid delivery system of drugs with poor absorption properties.	40
Self-nanoemulsifying formulations configured with PEG 4000.	-	High *in vitro* diffusion-reliant permeation obtained.	41
Diethyl ether fraction of Labrasol.	Rat colon	Permeation is better in case of diethyl ether extract compared to Labrasol or its fractions, i.e. hexane, ethyl acetate and aqueous.	42
SMEDDS containing Softisan and Precirol as Lipid Matrix.	-	Likely be useful for oral route for delivery.	43
Phospholipon 90H (P90H)-based PEGylated microscopic lipospheres.		Lipospheres may be useful in oral gentamicin administration.	44
Coadministration with cetomacrogol (polyethylene glycol 1000 monocetyl ether).	Rats	Giving rectally effected in a mean peak gentamicin blood concentration of 8.2 ug/mL, contrasted to 16.5 ug/mL, when the mixture was provided orally.	45
Chitosan nanoparticles employing dextran sulphate as a counterion.		Possibly will offer a potential oral drug delivery formulation.	46
Labrasol Micelle.	Rats	Enhanced membrane permeability.	47
Labrasol microemulsion.	Rat	Augmentation of % BA - 54.2%.	48
PEGylated solidified reverse micellar solutions based solid lipid microparticles.	Rats	A permeation flux of 5.239 μg/cm^2 min plus a permeation coefficient of 1.781. 10^{-6} cm/min within 7 hr was obtained.	49
Saponin extracted from *Acanthophyllum squarrosum* (ATS), *Quillaja saponaria* (QTS) and Tween 20.	Brush border membrane vesicle	Tween 20 was found to put forth best transportation augmenting upshot (3.33 μg/mL drug concentration).	50
Glycosteroid drug transport agent.	Rats	When injected in ileum, in absence of TCOO2: - C_{max} of 0.6μg/mL, after 7 min with decline in levels after 4 hr. With 10mM TCOO2, peak plasma level 7.3 μg/mL within 20 min and maintainted for 90 min with high levels 5.5 μg/mL for 4 hr.	51

Non Penetrative Routes For Gentamicin

Oral

The oldest and most favoured oral route of drug administration and delivery is associated with numerous successful treatments for numerous diseases. Owing to its potential benefits encompassing a competently recognized delivery system, patient acceptance, convenience, affordability, and non-invasiveness, it has been the most chosen and desired drug delivery route in the sphere of pharmaceutical technology.[35] Oral medicines can circumvent the need for penetrative drug delivery via needles.[36] The problems associated with drug bioavailability are one of the primary concerns of formulation research and development. The oral formulation strategies are provided in Table 3.

Gentamicin is inferiorly absorbed from the intestinal tract and is ordinarily obtainable as topical preparations and injectables.[52] Gentamicin oral formulations have already been studied to manage severe diarrhoea in newborns and other gastrointestinal bacterial infections, including infection by *Klebsiella pneumoniae*.[53] Various drug delivery systems are employed to enhance the bioavailability of many low water-soluble and inferiorly permeable drugs.[54-56] Some of the formulation strategies researched for

oral delivery of gentamicin and other aminoglycosides include multicomponent-crosslinked carboxymethyl cellulose hydrogel, self-microemulsifying drug delivery system using labrasol, self-nanoemulsifying formulations structured with PEG (polyethylene glycol) 4000, PEGylated solidified reverse micellar solutions -based solid lipid microparticles, phospholipon 90H (P90H)-based PEGylated lipospheres etc.[57,58]

Nasal

Numerous times nasal route has proven to be a replacement for administering drugs whose systemic availability is limited to intravenous administration. This feature is attributed to the easily accessible huge vascular surface area with porous endothelial membrane, allowing the circumvention of first-pass metabolism.[59,60]

Bile salts, i.e. sodium cholate and sodium taurodeoxycholate were reported to enhance intranasal gentamicin absorption by 41 ± 16% and 34 ± 13% in rabbits.[61] Microparticles employing chitosan hydroglutamate (CH) plus hyaluronic acid (HA) reported bioavailability of 1.1%, 2.1%, 31.4%, 42.9% and 23.3% for pure drug nasal solution, dry powder, microparticulate systems of CH, HA/CH and HA respectively in rabbits, the microparticles also exhibited an enhanced drug permeation in 16HBE14o- cell lines.[62] Use of transporter DS-1 3-o-β-D-galactopyranosyl-(1→2)-β-d-xylopyranosyl-(1→3)-β-D-glucuronopyranosyl-quillaic acid 28-o-β-D-apifuranosyl-(1→3)-β-D- xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-β-D-fucopyranoside has exhibited a 59.7% intranasal absorption in rats.[63]

Pulmonary

In the preceding two decades, drug delivery via the pulmonary route has acquired immense attention. This non-invasive route of drug delivery offers access to both the local area and systemic circulation, with the lungs as the primary part of the respiratory system. Pulmonary drug delivery, i.e., inhalation therapy, offers numerous benefits compared to alternate routes of drug administration, such as it provides a huge vascular surface area present in alveolar sacs making it very suitable for drug absorption.[64]

In rats, chitosan/fucoidan nanoparticles via the intratracheal route (0.27 mg/kg) presented a better AUC (Area Under Curve) and minimum inhibitory concentration ratio compared to (0.5 mg/kg) free drug by IV. It can be utilized in pneumonia treatment.[65]

Studies have demonstrated that compared to the IV route, NanoGENT™ (80% gentamicin sulfate) inhaler can deliver a higher amount of gentamicin to the respiratory tract. NanoGENT™ (utilizing Respirics ACU-30™ dry powder inhaler) delivers 10-15 mg drug with each 25-mg dose.[36]

Transdermal

The transdermal route is defined as one in which the drug is applied to the skin utilizing any device or patch to deliver an adequate amount of the drug through the layers of skin to provide a systemic effect. This route has numerous theoretical benefits, such as bypassing hepatic metabolism of drug and circumventing gastrointestinal irritation.[66]

Dissolving microneedle (500 μm) arrays of gentamicin made up of sodium hyaluronate and polyvinylpyrrolidone were able to permeate a skin simulant to a depth of 378 μm. *In vitro*, Franz Cell study exhibited significant drug delivery over 6 hr. This system was reported to deliver the drug as a replacement for IV/IM route without requiring skilled personnel for dose administration.[67] HPMC (hydroxyl propyl methyl cellulose) matrix-type transdermal patches with gentamicin-loaded PLGA (poly D,L-lactic-co-glycolic acid) nanoparticles are also reported to be effective drug delivery systems as found in case of animal models.[68] Gentamicin microneedle patch has been recognized as a practicable product innovation by the United Nations Commission for Lifesaving Commodities for Women and Children.[69] The costs of manufacturing of novel transdermal hydrogel microneedle patches are not yet known.[36] Patches of PURASORB® polymers amplified permeation flux of 5.161 μg/cm^{2}h and permeation coefficient of 1.032 x 10^{-6} cm/h through rat's skin.[37]

Rectal

From a pharmaceutical or clinical viewpoint, drug administration via the oral route often turns out to be impracticable. In such instances, the rectal route might serve as a rational alternative for local and systemic drug delivery.[70] Gentamicin, due to its low permeability, is reported not to be absorbed when administered rectally in the form of two different liquid phosphate-buffered enema formulations (with and without 1.8 mM lauric acid) and a suppository of cocoa butter base as evaluated in a preclinical study in neonatal minipig model.[71] Though the use of surfactants (non-ionic) has shown positive outcomes. A formulation comprising 12 mg gentamicin, 1 g cetomacrogol and 140 mg of PEG 400 is reported to produce a mean peak gentamicin blood level of 8.2 μg/mL when given rectally in rats.[45] Owing to the fast pharmacological effect, plasma levels and therapeutic efficacy are much higher than oral delivery of the same drug and dose level.[72] Hollow-type suppository using sodium octanoate, sodium hexanoate and glyceryl-1-monooctanoate is found to enhance drug absorption in rabbits.[73] Similar type suppositories of GS and sodium salicylate or sodium caprylate in rabbits exhibited % BA of the drug with salicylic acid 58% and with sodium caprylate 59%. Without these agents, drug absorption was nil.[74] Aqueous microenemas of the drug comprising 20 mg/mL^{-1} phenothiazine in rats improved % BA to 74–146%.[75]

Quite a few investigations on the rectal distribution of GS in animal models have been performed, signifying augmentation in absorption utilizing different adjuvants. In addition, other studies have looked at how fatty acids (sodium octanoate, sodium hexanoate, and glycerol-1-monooctanoate) and phenothiazines can improve the rectal absorption of gentamicin formulations.[73,75] These trials' absorption findings have been positive, pointing to the rectal route as a possible method for gentamicin administration.

Non-invasive Drug Delivery Systems For Other Aminoglycosides

Tobramicin's oral bioavailability is affected by fasting. According to a study, mice subjected to a 15-hr fast had significantly exhibited (25-fold greater) improved oral bioavailability. Since all aminoglycosides are hydrophilic polycations with comparable structural characteristics, it is conceivable that all drug molecules belonging to this group will be absorbed during conditions of physiological fasting.[76]

Considering formulation approaches, aminoglycosides (as shown in Figure 2) other than gentamicin have also been studied for bioavailability enhancement. Reported formulations for non-invasive delivery of aminoglycosides other than gentamicin are tabulated in Table 4.

DISCUSSION

Generally, it has been observed that permeation enhancement via formulation approaches includes nanoparticles, hydrogels or the use of agents such as bile salts, surfactants, lipids etc.

Bile salts and their ionized form are characteristic amphipathic molecules structurally having a steroidal nucleus bearing a hydrophilic part with hydroxyl units (concave a-side) plus a lipophilic part with methyl units (convex b-side), as shown in Figure 3. This specific structure crafts bile salts distinguishable from traditional pharmaceutical surfactants.[80,84]

Dietary fats are primarily emulsified and solubilized by the action of bile salts and acids by developing mixed micelles.[85] Bile salts get compressed in the middle of the phospholipids' polar heads, with their hydrophilic part heading the aqueous phase.[86] The membrane permeation enhancing the ability of bile salts helps lipophilic drug moieties to cross biological membranes, thereby enhancing their bioavailability.[87] Duchateau *et al.* 1986 reported that intranasal coadministration of gentamicin with bile salts in rabbits could augment the bioavailability of the drug significantly. The ability of the trihydroxy bile salts (cholate, taurocholate, and glycocholate) to promote absorption increases with their hydrophobicity. Sodium salts of cholic and taurodeoxycholic acid were recognized to be potent and capable absorption promoters.[61] One of the analogues of cholic acid TCO_2 [methyl 3-β-amino-7α, 12α-di (1′ α-glucosyl)-5β-cholate] was reported to enhance the intestinal bioavailability of the drug.[51]

A wide range of surfactant-based permeation enhancers can alter the integrity of bio-membranes. This absorption enhancer class comprises non-ionic surfactants, acylated amino acids, medium-chain fatty acids, acylcarnitines, bile salts and a spectrum of others (e.g. macrogol-8 glycerides, sucrose laurate, polyoxyethylene-8 lauryl ether, etc.). Clinical investigation for numerous surfactants, such as sodium caprylate, sodium caprate, lauroyl-carnitine chloride, etc., has been performed to study the delivery of macromolecules via the oral route.[88] The absorption enhancing potentiality of non-ionic surfactants is impacted by the hydrophilic-lipophilic balance as well as the dimensions and structure of both the polar group and the non-polar alkyl chain. The lipid bi-layer can easily be penetrated by a surfactant of a medium-length alkyl chain because, in an aqueous solution, it has a greater concentration of monomers and elevated critical micellar concentration compared to a lengthy alkyl chain surfactant. Labrasol is a non-ionic surfactant having a C8 and C10 alkyl chain and an HLB value of 14. It was proven to augment gentamicin intestinal permeation in rats.[55] Compared to labrasol, its diethyl ether fraction exhibits greater enhancement of gentamicin absorption.[78] Cetomacrogol, another non-ionic surfactant, is reported to augment the absorption of gentamicin after oral administration.[45,89]

Fabrication of lipid-based drug delivery systems has proven to be advantageous in increasing the bioavailability of many inferiorly

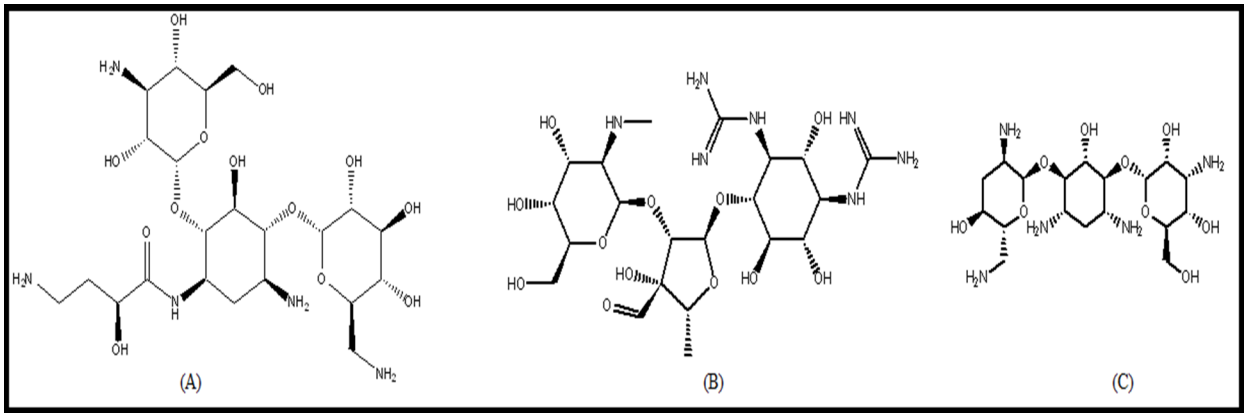

Figure 2: Chemical structure of (A) amikacin, (B) streptomycin and (C) tobramycin.

Table 4: Aminoglycosides (other than gentamicin)- Non-Invasive formulation approaches.

Drug	Approach utilized	Remarks	References
Amikacin	Thiolated Chitosan Nanoparticles for oral drug delivery.	Increases the mucoadhesive properties thereby enhancing rate of drug absorption by promoting permeation of nanoparticles via intracellular space.	77
	Poly D, L-Lactide-co-glycolide Nanoparticles.	Appreciable particle size (260.3 nm) for permeating through small intestine.	78
	Reverse Iontophoresis.	Drug could be extracted across the skin membrane at the negative electrode.	79
Streptomycin	Chitosan nanoparticles (dextran sulphate as a counterion) for oral delivery.	Nanoparticles were comparable to s.c. injection of free drug solution as studied in tubeculosis infected mouse model.	46
	Poly-lactideco-glycolide nanoparticles.	21 times increase in relative BA of drug formulation compared with im free drug injection.	81
Tobramycin	Chitosan nanoparticles using dextran sulphate as a counterion.	In tuberculosis treatment, formulations may provide promising oral drug delivery.	46
	Using CRL-1605 copolymer, an inhibitor of P-glycoprotein for oral delivery.	Significant drug level increase in serum observed in comparison to free drug.	82
	Lipopolysachcharide for oral delivery.	Improvement in drug partition coefficient, indicating enhancement of permeability.	83
	Thiolated chitosan conjugate.	In comparison to buffer only, tobramycin sulphate uptake in presence of 0.5% (w/v) chitosan-NAC was improved 1.3-fold across rat small intestine and 2.7-fold across Caco-2 cell monolayer.	93

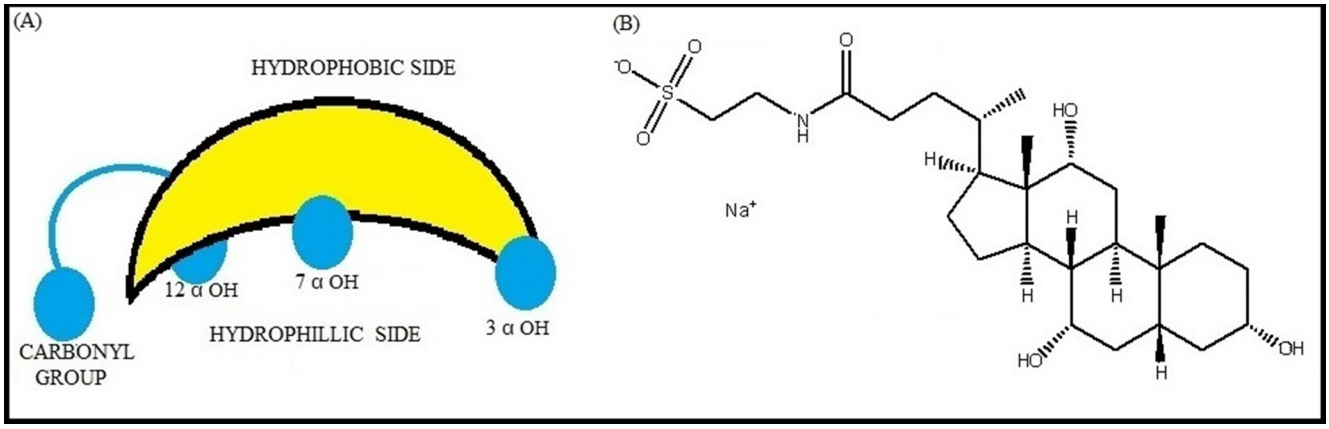

Figure 3: (A) Illustration depicting hydrophilic and hydrophobic side of bile salt molecule and (B) Chemical structure of bile salt (sodium taurocholate).

absorbed compounds by encouraging lymphatic transport. Lipid-based carriers include nano/micro emulsions, SMEDDS, solid lipid nanoparticles, nanostructured lipid carriers, etc.[90,91] Self nano and micro emulsifying drug delivery systems have shown promising abilities in enhancing the permeability of BCS III class drugs. Some such reported formulations include: SMEDDS containing PEG-8 caprylic/capric glycerides, gentamicin coupled SMEDDS having Softisan and Precirol as lipid matrix and self-nanoemulsifying formulations containing PEG 4000, soybean oil, Kolliphor1 EL and Kolliphor1 P188 and Transcutol1 HP.[56,57,59] Nanoparticles are well known to augment cellular uptake of drugs besides enhancing therapeutic intensities at desired locates as well as ameliorating the pharmacodynamic and pharmacokinetic concerns. Nanomaterials offer numerous

features, such as improved biocompatibility, site-specific drug transportation stimulated by environmental, pH, and thermal factors, and the capacity to pass through the blood-brain barrier.[92] Chitosan tailored PLCGA (Poly Lactic Co Glycolic Acid) biodegradable nanoparticles for oral delivery of gentamicin in rabbits has shown significant potentials.[37] Chitosan/fucoidan nanoparticles for gentamicin delivery via pulmonary route is also reported.[65]

Hydrogels are crosslinked Three-Dimensional (3D) polymer networks with high water absorption and retention capacity.[94] Recent advancements include the use of crosslinked, water-swelling biomedical polymers as delivery systems for medicines, peptides, and proteins, as well as, as targeted delivery agents, or as in for making of protein or enzyme conjugates.[95,96] Carboxymethyl cellulose-microcrystalline cellulose hydrogels have the suitable prospects to be utilized as a smart pH-sensitive strategy for oral delivery of gentamicin.[54]

Numerous investigational works have been carried out and are still being conducted to explore orally, nasally, rectally or transdermally applicable dosage forms of poorly absorbed drug moieties, employing permeation augmenters.[97] Several compounds have revealed potent absorption-increasing activity. Hence, regarding permeation augmenters' effectiveness and initial safety data, chitosan, bile salts, cyclodextrins and fatty acids are considered the primary preference for additional studies. For exploring the intestinal route, the drug delivery system must adhere to the epithelium layer of the intestinal wall, thereby paving the way through the paracellular route.[98] Polyacrylates, chitosans, and their derivatives which are multifunctional polymers, function similarly, thereby boosting the permeation of hydrophilic macromolecules through the paracellular pathway; however, their viscous characteristic and slow dissolution rate make the preparation of needed delivery system challenging. An oral dosage form is commonly regarded as unparalleled by maximum consumers' perspective as it eludes the necessity for the use of injections and could be easily self-administered or by guardians for neonates/children, lessening the requirement of a trained health worker for every dose administration.[99]

CONCLUSION

Nevertheless, additional investigations on oral gentamicin formulations are still required, taking into account the palatability of patients for successful intake of the drug. Nasal droppers, inhalers, and microneedle transdermal patches would also be the painless adaptable preference for GS administration. Rectal delivery is an additional needle invasion-free substitute, but owing to its high rate of cultural objection and user non-compliance, implementation of this delivery route may get stalled. While focusing on the fabrication of a novel delivery system for any drug moiety, the utility and acceptability of end users and dose administrators (including those for infants) should be scrutinized and assessed. Reformulation, broad preclinical and clinical studies and cognizance of the mechanism of permeability augmentation are needed for all innovative means investigated to establish the accurate dosing, confirm safety and evaluate the effectiveness, to hold up regulatory assents for assimilation of such formulations concepts in healthcare systems. On the contrary, this would summon an extended timeline.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BA: Bioavailability; **BCS:** Biopharmaceutics classification system; **GS:** Gentamicin sulphate; **SMEDDS:** Self-microemulsifying drug delivery system.

REFERENCES

1. Pucci MJ, Callebaut C, Cathcart A, Bush K. Recent epidemiologicalchanges in infectious diseases. In: Samuel C, David R, Simon E, editors. Comprehensive medicinal chemistry III. Elsevier; 2017;511-52. doi: 10.1016/B978-0-12-409547-2.12405-9.
2. Bethesda MD, American society of health system pharmacists. Drug information; 2016.
3. Leggett JE. Aminoglycosides. In: Bennett JE, Dolin R, Blaser MJ, editors. Principles and practice of infectious diseases. Philadelphia: Content Repository; 2015;310-15.
4. Fitzgerald KT, Newquist KL. Poisonings in the captive reptile. Small Anim Toxicol. 2013;22:229-49. doi: 10.1016/B978-1-4557-0717-1.00020-X.
5. Rybak LP, Ramkumar V. Ototoxicity. Kidney Int. 2007;72(8):931-5. doi: 10.1038/sj.ki.5002434, PMID 17653135.
6. Ramirez MS, Tolmasky ME. Amikacin: uses, resistance, and prospects for inhibition. Molecules. 2017;22(12):2267. doi: 10.3390/molecules22122267, PMID 29257114.
7. Wang J, Zhang H, Yan J, Zhang T. Literature review on the distribution characteristics and antimicrobial resistance of bacterial pathogens in neonatal sepsis. J Matern Fetal Neonatal Med. 2022;35(5):861-70. doi: 10.1080/14767058.2020.1732342, PMID 32102584.
8. Wargo KA, Edwards JD. Aminoglycoside-induced nephrotoxicity. J Pharm Pract. 2014;27(6):573-7. doi: 10.1177/0897190014546836, PMID 25199523.
9. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A. Back to the future: using aminoglycosides again and how to dose them optimally. Back to the Future. Clin Infect Dis. 2007;45(6):753-60. doi: 10.1086/520991, PMID 17712761.
10. Dozzo P, Moser HE. New aminoglycoside antibiotics. Expert Opin Ther Pat. 2010;20(10):1321-41. doi: 10.1517/13543776.2010.506189, PMID 20670208.
11. Sarin R, Behera D, Khanna A, Singh V, Narang P, Deepak TS. Second-line injectable induced ototoxicity in drug resistant tuberculosis: a systematic review of Indian studies. Indian J Tuberc. 2019;66(2):279-87. doi: 10.1016/j.ijtb.2019.04.007, PMID 31151497.
12. Chen C, Chen Y, Wu P, Chen B. Update on new medicinal applications of gentamicin: evidence-based review. J Formos Med Assoc. 2014;113(2):72-82. doi: 10.1016/j.jfma.2013.10.002, PMID 24216440.
13. World Health Organization: (Geneve). World Health Organization Model List of Essential Medicines for Children 7th List. Switzerland: WHO Press; 2019. Available from: http://www.who.int/medicines/publications/essentialmedicines/en/.
14. Organización Mundial de la Salud. World health organization model list of essential medicines. Ment Holist Heal Some Int Perspect. OMS; 2019.
15. Becker B, Cooper MA. Aminoglycoside antibiotics in the 21st century. ACS Chem Biol. 2013;8(1):105-15. doi: 10.1021/cb3005116, PMID 23110460.
16. Ramirez MS, Tolmasky ME. Aminoglycoside modifying enzymes. Drug Resist Updat. 2010;13(6):151-71. doi: 10.1016/j.drup.2010.08.003, PMID 20833577.
17. Maxwell A, Ghate V, Aranjani J, Lewis S. Breaking the barriers for the delivery of amikacin: challenges, strategies, and opportunities. Life Sci. 2021;284:119883. doi: 10.1016/j.lfs.2021.119883, PMID 34390724.
18. Gill HS, Denson DD, Burris BA, Prausnitz MR. Effect of microneedle design on pain in human volunteers. Clin J Pain. 2008;24(7):585-94. doi: 10.1097/AJP.0b013e31816778f9, PMID 18716497.
19. Orenius T, LicPsych P, Säilä H, Mikola K, Ristolainen L. Fear of injections and needle phobia among children and adolescents: an overview of psychological, behavioral, and contextual factors. SAGE Open Nurs. 2018;4:2377960818759442. doi: 10.1177/2377960818759442, PMID 33415191.

20. Clark DE. Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena 1 prediction of intestinal absorption. J Pharm Sci. 1999;88(8):807-14. doi: 10.1021/js9804011, PMID 10430547.
21. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2012;64:4-17. doi: 10.1016/S0169-409X(96)00423-1.
22. Pubchem. PubChem compound summary, CID. Bethesda: National Center for Biotechnology Information. p. 3467, gentamicin; updated 2004 May 16. Available from: ncbi.nlm.nih.gov [internet]; [cited Jul 9 2021]. Available from: http://pubchem.ncbi.nlm.nih.gov/compound/Gentamicin.
23. Florey K. Analytical profiles of drug substances and excipients. 1st ed. New York: Academic press; 1980.
24. Zhao YH, Le J, Abraham MH, Hersey A, Eddershaw PJ, Luscombe CN, *et al*. Evaluation of human intestinal absorption data and subsequent derivation of a Quantitative Structure–Activity Relationship (QSAR) with the Abraham descriptors. J Pharm Sci. 2001;90(6):749-84. doi: 10.1002/jps.1031, PMID 11357178.
25. Kushner B, Allen PD, Crane BT. Frequency and demographics of gentamicin use. Otol Neurotol. 2016;37(2):190-5. doi: 10.1097/MAO.0000000000000937, PMID 26719956.
26. World Health Organization: (Geneve). World Health Organization report on surveillance of antibiotic consumption 2016-2018. Switzerland: WHO Press; 2018.
27. Öztürk R, Murt A. Epidemiology of urological infections: a global burden. World J Urol. 2020;38(11):2669-79. doi: 10.1007/s00345-019-03071-4, PMID 31925549.
28. Mordorintelligence.com [internet]. India: Aminoglycosides market – growth, trends, COVID-19 impact, and forecasts, Inc.; c2000-01; updated 2022 May 31; [cited May 31 2022]. Available from: http://www.mordorintelligence.com/industry-reports/aminoglycosides-market.
29. Yamashita SK, Louie M, Simor AE, Rachlis A. Microbiologic surveillance and parenteralantibioticuse in a critical care unit. Can J Infect Dis. 2000;11(2):107-11. doi: 10.1155/2000/672340, PMID 18159274.
30. Papich MG. Saunders handbook of veterinary drugs-e-book: small and large animal. Netherlands: Elsevier Health Sciences; 2015. doi: 10.1016/b978-0-323-24485-5.00280-1.
31. Chengelis CP. Safety considerations for the administration of agents by the parenteral routes. Inacute toxicology testing. FL: CRC Press; 1988. doi: 10.1201/9781439805213-15.
32. Murgitroyd E, Farquharson S, Poole N. Non-compliance in gentamicin prescribing and administration: a patient safety issue. Cogent Med. 2015;2(1):1007796. doi: 10.1080/2331205X.2015.1007796.
33. Cazzola M, Matera MG, Noschese P. Parenteral antibiotic therapy in the treatment of lower respiratory tract infections. Strategies to minimize the development of antibiotic resistance. Pulm Pharmacol Ther. 2000;13(6):249-56. doi: 10.1006/pupt.2000.0253, PMID 11061979.
34. Schentag JJ. Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUIC to improve efficacy and avoid resistance. J Chemother. 1999;11(6):426-39. doi: 10.1179/joc.1999.11.6.426, PMID 10678784.
35. Asiri A, Mohammad A. Applications of nanocomposite materials in drug delivery. Cambridge: Woodhead Publishing; 2018. doi: 10.1016/B978-0-12-813741-3.00030-3.
36. PATH. Gentamicin for treatment of neonatalsepsis—A landscape of formulation, packaging, and delivery alternatives. Seattle: PATH; 2015.
37. Akhtar B, Muhammad F, Aslam B, Saleemi MK, Sharif A. Pharmacokinetic profile of chitosan modified poly lactic co-glycolic acid biodegradable nanoparticles following oral delivery of gentamicin in rabbits. Int J Biol Macromol. 2020;164:1493-500. doi: 10.1016/j.ijbiomac.2020.07.206, PMID 32735923.
38. Javanbakht S, Nazeri MT, Shaabani A, Ghorbani M. Green one-pot synthesis of multicomponent-crosslinked carboxymethyl cellulose as a safe carrier for the gentamicin oral delivery. Int J Biol Macromol. 2020;164:2873-80. doi: 10.1016/j.ijbiomac.2020.08.168, PMID 32853613.
39. Rama Prasad YV, Eaimtrakarn S, Ishida M, Kusawake Y, Tawa R, Yoshikawa Y *et al*. Evaluation of oral formulations of gentamicin containing Labrasol in beagle dogs. Int J Pharm. 2003;268(1-2):13-21. doi: 10.1016/j.ijpharm.2003.08.008, PMID 14643972.
40. Ito Y, Kusawake T, Ishida M, Tawa R, Shibata N, Takada K. Oral solid gentamicin preparation using emulsifier and adsorbent. J Control Release. 2005;105(1-2):23-31. doi: 10.1016/j.jconrel.2005.03.017, PMID 15908031.
41. Umeyor C, Attama A, Uronnachi E, Kenechukwu F, Nwakile C, Nzekwe I *et al*. Formulation design and *in vitro* physicochemical characterization of surface modified self-nanoemulsifying formulations (SNEFs) of gentamicin. Int J Pharm. 2016;497(1-2):161-98. doi: 10.1016/j.ijpharm.2015.10.033, PMID 26657350.
42. Hu Z, Prasad Yv R, Tawa R, Konishi T, Ishida M, Shibata N *et al*. Diethyl ether fraction of Labrasol having a stronger absorption enhancing effect on gentamicin than Labrasol itself. Int J Pharm. 2002;234(1-2):223-35. doi: 10.1016/S0378-5173(01)00967-X, PMID 11839453.
43. Osonwa UE, Nwabugwu CK, Ugoeze KC. *In vitro* evaluation of gentamicin coupled self-micro-emulsifying drug delivery systems (SMEDDS) containing Softisan and Precirol as lipid matrix. AASCIT J Nanosci. 2015;1(4):50-9.
44. Momoh MA, Esimone CO. Phospholipon 90H (P90H)–based pegylated microscopic lipospheres delivery system for gentamicin: an antibiotic evaluation. Asian Pac J Trop Biomed. 2012;2(11):889-94. doi: 10.1016/S2221-1691(12)60248-2, PMID 23569866.
45. Rubinstein AR, Rubinstein ET, Toitou E, Donbrow M. Increase of the intestinal absorption of gentamicin and amikacin by a nonionic surfactant. Antimicrob Agents Chemother. 1981;19(5):696-9. doi: 10.1128/AAC.19.5.696, PMID 6895294.
46. Lu E, Franzblau S, Onyuksel H, Popescu C. Preparation of aminoglycoside-loaded chitosan nanoparticles using dextran sulphate as a counterion. J Microencapsul. 2009;26(4):346-54. doi: 10.1080/02652040802365182, PMID 18726818.
47. Koga K, Kusawake Y, Ito Y, Sugioka N, Shibata N, Takada K. Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate. Eur J Pharm Biopharm. 2006;64(1):82-91. doi: 10.1016/j.ejpb.2006.03.011, PMID 16750354.
48. Hu Z, Tawa R, Konishi T, Shibata N, Takada K. A novel emulsifier, Labrasol, enhances gastrointestinal absorption of gentamicin. Life Sci. 2001;69(24):2899-910. doi: 10.1016/S0024-3205(01)01375-3.
49. Kenechukwu FC, Momoh MA, Nnamani PO, Attama AA. Solid lipid micro-dispersions (SLMs) based on pegylatedsolidified reverse micellar solutions (SRMS): a novel carrier system for gentamicin. Drug Deliv. 2015;22(6):710-22. doi: 10.3109/10717544.2014.900152, PMID 24724962.
50. Moghimipour E, Tabassi SA, Ramezani M, Handali S, Löbenberg R. Brush border membrane vesicle and Caco-2 cell line: two experimental models for evaluation of absorption enhancing effects of saponins, bile salts, and some synthetic surfactants. J Adv Pharm Technol Res. 2016;7(3):75-9. doi: 10.4103/2231-4040.184588, PMID 27429925.
51. Axelrod HR, Kim JS, Longley CB, Lipka E, Amidon GL, Kakarla R *et al*. Intestinal transport of gentamicin with a novel, glycosteroid drug transport agent. Pharm Res. 1998;15(12):1876-81. doi: 10.1023/a:1011962207882, PMID 9892472.
52. Leggett JE. Aminoglycoside therapy: current and prospective uses. Tex Heart Inst J. 1990;17(4):330-6. PMID 15227525.
53. Tascini C, Sbrana F, Flammini S, Tagliaferri E, Arena F, Leonildi A *et al*. Oral gentamicin gut decontamination for prevention of KPC-producing *Klebsiella pneumoniae* infections: relevance of concomitant systemic antibiotic therapy. Antimicrob Agents Chemother. 2014;58(4):1972-6. doi: 10.1128/AAC.02283-13, PMID 24419337.
54. Dave VS, Gupta D, Yu M, Nguyen P, Varghese Gupta S. Current and evolving approaches for improving the oral permeability of BCS Class III or analogous molecules. Drug Dev Ind Pharm. 2017;43(2):177-89. doi: 10.1080/03639045.2016.1269122, PMID 27998192.
55. Dadwal S, Kumar R, Wadhwa S. Formulation strategies to improve the permeability of BCS class III drugs: special emphasis on 5 fluorouracil. J Emerg Technol Innov Res. 2018;5(12):822-30.
56. Wen H, Jung H, Li X. Drug delivery approaches in addressing clinical pharmacology-related issues: opportunities and challenges. AAPS J. 2015;17(6):1327-40. doi: 10.1208/s12248-015-9814-9, PMID 26276218.
57. Fatima S, Iqbal Z, Panda AK, Samim M, Talegaonkar S, Ahmad FJ. Polymeric nanoparticles as a platform for permeability enhancement of class III drug amikacin. Colloids Surf B Biointerfaces. 2018;169:206-13. doi: 10.1016/j.colsurfb.2018.05.028, PMID 29778036.
58. Bera S, Mondal D. Antibacterial efficacies of nanostructured Aminoglycosides. ACS Omega. 2022;7(6):4724-34. doi: 10.1021/acsomega.1c04399, PMID 35187293.
59. Mato YL. Nasal route for vaccine and drug delivery: features and current opportunities. Int J Pharm. 2019;15(572):118813. doi: 10.1016/j.ijpharm.2019.118813.
60. Türker S, Onur E, Özer Y. Nasal route and drug delivery systems. Pharm World Sci. 2004;26(3):137-42. doi: 10.1023/b:phar.0000026823.82950.ff, PMID 15230360.
61. Duchateau G, Zuidema J, Merkus FWHM. Bile salts and intranasal drug absorption. Int J Pharm. 1986;31(3):193-9. doi: 10.1016/0378-5173(86)90153-5.
62. Lim ST, Forbes B, Berry DJ, Martin GP, Brown MB. *In vivo* evaluation of novel hyaluronan/chitosan microparticulate delivery systems for the nasal delivery of gentamicin in rabbits. Int J Pharm. 2002;231(1):73-82. doi: 10.1016/S0378-5173(01)00873-0.
63. Recchia J, Lurantos MH, Amsden JA, Storey J, Kensil CR. A semisynthetic *Quillaja saponin* as a drug delivery agent for aminoglycoside antibiotics. Pharm Res. 1995;12(12):1917-23. doi: 10.1023/a:1016235705448, PMID 8786966.
64. Javadzadeh Y, Yaqoubi S. Therapeutic nanostructures for pulmonary drug delivery. In: Nanostructures for drug delivery. Netherlands: Elsevier; 2017. doi: 10.1016/B978-0-323-46143-6.00020-8.
65. Huang YC, Li RY, Chen JY, Chen JK. Biphasic release of gentamicin from chitosan/fucoidan nanoparticles for pulmonary delivery. Carbohydr Polym. 2016;138(138):114-22. doi: 10.1016/j.carbpol.2015.11.072, PMID 26794744.
66. Tanner T, Marks RJ. Delivering drugs by the transdermal route: review and comment. Skin Res Technol. 2008;14(3):249-60. doi: 10.1111/j.1600-0846.2008.00316.x, PMID 19159369.
67. González-Vázquez P, Larrañeta E, McCrudden MTC, Jarrahian C, Rein-Weston A, Quintanar-Solares M *et al*. Transdermal delivery of gentamicin using dissolving microneedle arrays for potential treatment of neonatal sepsis. J Control Release. 2017;265:30-40. doi: 10.1016/j.jconrel.2017.07.032, PMID 28754611.
68. Akhtar B, Muhammad F, Aslam B, Saleemi MK, Sharif A. Biodegradable nanoparticle based transdermal patches for gentamicin delivery: formulation, characterization and pharmacokinetics in rabbits. J Drug Deliv Sci Technol. 2020;57:101680. doi: 10.1016/j.jddst.2020.101680.
69. Jonathan H, Stoltenberg R. UN commission on life-saving commodities for women and children; 2012.

70. Hua S. Physiological and pharmaceutical considerations for rectal drug formulations. Front Pharmacol. 2019;10:1196. doi: 10.3389/fphar.2019.01196, PMID 31680970.
71. McAdams DH, Lal M, Lai M, Quintanar-Solares M. Feasibility study for the rectal route of administration for gentamicin evaluated in the neonatal minipig model. J Pharm Sci. 2020;109(2):992-1001. doi: 10.1016/j.xphs.2019.08.003, PMID 31404543.
72. Kumar R. Lipid-based nanoparticles for drug-delivery systems. Nanocarrier Drug Deliv. 2019;1:249-84. doi: 10.1016/B978-0-12-814033-8.00008-4.
73. Matsumoto Y, Watanabe Y, Hori N, Matsumoto M. Duration of absorption-enhancing effect of sodium octanoate, sodium hexanoate or glyceryl-1-monooctanoate on rectal absorption of gentamicin in rabbits. J Pharmacobio Dyn. 1990;13(10):591-6. doi: 10.1248/bpb1978.13.591, PMID 2095398.
74. Matsumoto Y, Watanabe Y, Tojima T, Murakoshi R, Murakami C, Matsumoto M. Rectal absorption enhancement of gentamicin in rabbits from hollow type suppositories by sodium salicylate or sodium caprylate. Drug Des Deliv. 1989;4(3):247-56. PMID 2490276.
75. Fix JA, Leppert PS, Porter PA, Alexander J. The use of phenothiazines to enhance the rectal absorption of water—soluble compounds. J Pharm Pharmacol. 1984;36(4):286-8. doi: 10.1111/j.2042-7158.1984.tb04375.x, PMID 6144788.
76. De Leo L, Di Toro N, Decorti G, Malusà N, Ventura A, Not T. Fasting increases tobramycin oral absorption in mice. Antimicrob Agents Chemother. 2010;54(4):1644-6. doi: 10.1128/AAC.01172-09, PMID 20086144.
77. Atyabi F, Talaie F, Dinarvand R. Thiolated chitosan nanoparticles as an oral delivery system for amikacin: *in vitro* and *ex vivo* evaluations. J Nanosci Nanotechnol. 2009;9(8):4593-603. doi: 10.1166/jnn.2009.1090, PMID 19928123.
78. Fatima S, Panda AK, Talegaonkar S, Iqbal Z, Ahmad FJ. Optimization and designing of amikacin-loaded poly d, l-lactide-co-glycolide nanoparticles for effective and sustained drug delivery. J Pharm Bioallied Sci. 2019;11(1):83-95. doi: 10.4103/jpbs.JPBS_60_18, PMID 30906144.
79. Nicoli S, Santi P. Transdermal delivery of Aminoglycosides: amikacin transport and iontophoretic non-invasive monitoring. J Control Release. 2006;111(1-2):89-94. doi: 10.1016/j.jconrel.2005.11.008, PMID 16413081.
80. Gaowa A, Horibe T, Kohno M, Kawakami K. Bile acid as an effective absorption enhancer for oral delivery of epidermal growth factor receptor–targeted hybrid peptide. J Pharm Sci. 2018;107(5):1322-9. doi: 10.1016/j.xphs.2017.12.012, PMID 29273347.
81. Pandey R, Khuller GK. Nanoparticle-based oral drug delivery system for an injectable antibiotic–streptomycin. Chemotherapy. 2007;53(6):437-41. doi: 10.1159/000110009, PMID 17952004.
82. Banerjee SK, Jagannath C, Hunter RL, Dasgupta A. Bioavailability of tobramycin after oral delivery in FVB mice using CRL-1605 copolymer, an inhibitor of P-glycoprotein. Life Sci. 2000;67(16):2011-6. doi: 10.1016/S0024-3205(00)00786-4, PMID 11072877.
83. Abdelrahim A, Simerska P, Toth I. ILiposaccharides for improved oral delivery of tobramycin. Drug Deliv Lett. 2012;2(2):92-7. doi: 10.2174/2210304x11202020092.
84. Aburahma MH. Bile salts-containing vesicles: promising pharmaceutical carriers for oral delivery of poorly water-soluble drugs and peptide/protein-based therapeutics or vaccines. Drug Deliv. 2016;23(6):1847-67. doi: 10.3109/10717544.2014.976892, PMID 25390191.
85. Holm R, Müllertz A, Mu H. Bile salts and their importance for drug absorption. Int J Pharm. 2013;453(1):44-55. doi: 10.1016/j.ijpharm.2013.04.003, PMID 23598075.
86. Hofmann AF, Hagey LR. Bile acids: chemistry, pathochemistry, biology, pathobiology, and therapeutics. Cell Mol Life Sci. 2008;65(16):2461-83. doi: 10.1007/s00018-008-7568-6, PMID 18488143.
87. Mikov M, Fawcett JP, Kuhajda K, Kevresan S. Pharmacology of bile acids and their derivatives: absorption promoters and therapeutic agents. Eur J Drug Metab Pharmacokinet. 2006;31(3):237-51. doi: 10.1007/BF03190714, PMID 17136862.
88. Maher S, Mrsny RJ, Brayden DJ. Intestinal permeation enhancers for oral peptide delivery. Adv Drug Deliv Rev. 2016;106(B):277-319. doi: 10.1016/j.addr.2016.06.005, PMID 27320643.
89. patent, Vringer D, inventor; Yamanouchi Europe BV, assignee. Topical suspension containing a suspension of solid lipid nanoparticles. US patent 5667 800; 1997.
90. Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov. 2007;6(3):231-48. doi: 10.1038/nrd2197, PMID 17330072.
91. Musiliu A, Tenderwealth J, Kelechi U, Anthony A. Oral gentamicin preparation using solidified lipid particulate delivery system. Int J Pharm Sci. 2017;9(9):22-6.
92. Li J, Cai C, Li J, Li J, Li J, Sun T, *et al*. Chitosan-based nanomaterials for drug delivery. Molecules. 2018;23(10):2661. doi: 10.3390/molecules23102661, PMID 30332830.
93. Hombach J, Hoyer H, Bernkop-Schnürch A. Thiolated chitosans: development and *in vitro* evaluation of an oral tobramycin sulphate delivery system. Eur J Pharm Sci. 2008;33(1):1-8. doi: 10.1016/j.ejps.2007.09.001, PMID 17980561.
94. Wang W, Narain R, Zeng H. Hydrogels in polymer science and nanotechnology. Netherlands: Elsevier; 2020. doi: 10.1016/B978-0-12-816806-6.00010-8.
95. Hamidi M, Azadi A, Rafiei P. Hydrogel nanoparticles in drug delivery. Adv Drug Deliv Rev. 2008;60(15):1638-49. doi: 10.1016/j.addr.2008.08.002, PMID 18840488.
96. Peppas NA. Hydrogels and drug delivery. Curr Opin Colloid Interface Sci. 1997;2(5):531-7. doi: 10.1016/S1359-0294(97)80103-3.
97. Fein KC, Gleeson JP, Newby AN, Whitehead KA. Intestinal permeation enhancers enable oral delivery of macromolecules up to 70 kDa in size. Eur J Pharm Biopharm. 2022;170:70-6. doi: 10.1016/j.ejpb.2021.11.010, PMID 34879228.
98. Dahlgren D, Olander T, Sjöblom M, Hedeland M, Lennernäs H. Effect of paracellular permeation enhancers on intestinal permeability of two peptide drugs, enalaprilat and hexarelin, in rats. Acta Pharm Sin B. 2021;11(6):1667-75. doi: 10.1016/j.apsb.2020.12.019, PMID 34221875.
99. Sahoo D, Bandaru R, Samal SK, Naik R, Kumar P, Kesharwani P, *et al*. Oral drug delivery of nanomedicine. Cambridge: Academic Press; 2021. doi: 10.1016/B978-0-12-820466-5.00009-0.

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