Open access Journal International Journal of Emerging Trends in Science and Technology

DOI: http://dx.doi.org/10.18535/ijetst/v10i11.01

A Review of gentamicin sulphate oral preparation containing natural oil (pumpkin seed oil) for systemic indication

Authors

Somtochukwu R Ewuzie[a]*, Calistus D Nwakile[a], Emmanuel M Uronnachi[b], Chukwuebuka E Umeyor[c], Ogechukwu C Dozie-Nwakile[d]

[a]Department of Pharmaceutics and Pharmaceutical Technology, Nnamdi Azikiwe University Awka, Anambra State, Nigeria.

[b]Department of Pharmaceutics and Pharmaceutical Technology, Nnamdi Azikiwe University Awka, Anambra State, Nigeria.

[c]Department of Pharmaceutics and Pharmaceutical Technology, Nnamdi Azikiwe University Awka, Anambra State, Nigeria.

[d]Drug Delivery and Nanomedicines Research Group, University of Nigeria, Nsukka.

*Corresponding Author

Somtochukwu R Ewuzie

Abstract

Delivery of gentamicin sulphate through the oral route has always been difficult because the drug is not permeable in the intestinal mucosa. There is hardly any oral preparation of this valuable drug effective for many gram-negative and gram-positive organisms. This work reviewed research works to aid achieve this systemic circulation of orally-administered gentamicin sulphate prepared with a natural oil. Natural oils have not only proven a great deal of source of bioactive phytochemicals but also can be a proven vehicle for oral preparations as they can confer some desirable antimicrobial synergism with conventional therapies. Various bioavailability studies of gentamicin sulphate were reviewed which revealed a great importance of a specialized formulation need that either enhances entrapment of the drug in a mix, sustained release formulation, or as solid-lipid microparticles e.t.c. These are all pharmaceutically possible and can be achieved using a natural oil as a vehicle plus permeation enhancers for such oral drug preparation.

Keywords *include systemic bioavailability, natural oil, oral administration, gentamicin sulphate.*

Introduction

Gentamicin sulphate drug is a highly water-soluble drug but has low intestinal permeability and thus classified as Class III based on the Biopharmaceutics Classification System (BCS). As such, many of its commercially available pharmaceutical dosage forms are either intravascular or as transdermal patches or cream.

This review article is a prelude-research that birthed a successfully-done investigation of a specially formulated oral gentamicin preparation co-formulated with pumpkin seed oil for systemic indication. The pumpkin seed oil, derived from

pumpkin seeds (*Cucurbita maxima*) was extracted using Soxhlet extractor and petroleum ether, as the solvent. The choice of pumpkin seed oil was majorly because of its readily availability as a natural oil that proved in the same research of *in vitro* antimicrobial activity against resistant strain of our organism of interest. The formulation of gentamicin sulphate with this oil appeared very beneficial and economical especially with growing concerns of antimicrobial resistance (AMR). Some of the research questions presented and well answered were as thus: Can the formulation be systemically bioavailable when taken orally? and can the pumpkin seed oil and the permeation enhancer used elicit synergistic activity on the test organism?

The Review

Systemic Infections of Microorganisms

Microorganisms may not normally be detrimental to the body but the presence of pathogenic ones pose a serious threat. They have virulence features that enable invasion, colonization, and disease induction in body regions other than the gastrointestinal system. A microorganism like *E. coli* can result to extraintestinal pathogenic *Escherichia coli* (ExPEC) infections. Septicemia, meningitis, pneumonia, osteomyelitis, septic arthritis, pyelonephritis, urinary tract infections, sepsis, pneumonia, surgical site infections, and infections in other extraintestinal regions are among the human disorders brought on by ExPEC. ExPEC-induced diseases represent a large burden in terms of medical costs and productivity losses. In addition to human illnesses, ExPEC strains also cause extraintestinal infections in domestic animals and pets. A commonality of virulence factors has been demonstrated between human and animal ExPEC, suggesting that the organisms are zoonotic pathogens. ExPEC strains have been isolated from food products, in particular from raw meats and poultry, indicating that these organisms potentially represent a new class of foodborne pathogens. (Smith, Fratamico, and Gunther, 2007). There is firm evidence linking their invasive potential to the expression of the polysaccharide capsule at the cell surface; this relationship is particularly strong with gram-negative bacteria causing sepsis and meningitis in the newborn infant and in adolescents. The rates of mortality and morbidity associated with these infections remain high despite recent advances in intensive care management and the introduction of newer, more potent antibiotics. (Mushtaq, Redpath, Luzio and Taylor, 2004). In order to lessen the severity of the illness and stop the establishment of new drug resistance which jeopardizes a good therapeutic outcome, newer therapeutic techniques against the main pathogens in meningitis, sepsis, and other life-threatening systemic infections are urgently required.

Gentamicin Sulphate

Gentamicin is a bactericidal antibiotic that works by binding the 30-s subunit of the bacterial ribosome, thus preventing protein synthesis. It is systemically inactive when administered orally, much like all other aminoglycosides. This is due to the fact that it is not significantly absorbed from the small intestine. To treat infections, it is given parenterally via the intravenous and intramuscular routes or topically. It appears to be completely eliminated unchanged in the urine. Due to Gentamicin's highly soluble and highly polar nature, it does not cross cell membranes efficiently, which has been seen as an important drawback for the therapy of intracellular infections such as brucellosis, due to low antibiotic levels achieved inside infected cells. More than 90 % of aerobic Gram-negative isolates remain susceptible to gentamicin. (Sanghavi, 2019). Gentamicin is one of the most commonly prescribed antibiotics because it has been shown to be the most effective in treating a variety of bacterial infections, including bone infections, endocarditis, and life-threatening sepsis, especially in newborns and people with weakened immune systems. As a result, it is listed as one of

the essential medications by the World Health Organization. Le, Ojano-Dirain, Nelson, Prieskorn, and Miller (2014) in their publication reiterated that 'no current drug or therapy has been approved to prevent gentamicin induced hearing impairment'. About 25 – 30 % of the administered dose of gentamicin is bound by serum protein; it is released as the drug is excreted. As said earlier, Gentamicin is excreted principally unchanged in the urine by glomerular filtration. Aminoglycosides have good activity against many multi-drugs resistant gram-negative bacilli and are therefore important for treating serious infections due to these organisms in adults and children including neonates. Use of these drugs can result in ototoxicity and nephrotoxicity. Ototoxicity is irreversible as there is no present drug or treatment for it and it has been seen to result in cochlear damage, vestibular damage or both. This has been seen as one of the adverse effects of Gentamicin.

The most popular method of administering gentamicin is intramuscular (IM) injection. Intravenous administration (IV) may be used for specific indications when the IM route is ineffective. For both delivery methods, the dosage is the same. During treatment, it is preferable to monitor the peak and trough serum levels. The demand for an oral alternative to parenteral distribution has prompted a revived interest in a number of excipients, such as intestinal permeation enhancers that increase the bioavailability of oral medications. The formulation of gentamicin (GM) for oral administration has complicated oral GM therapy. The distribution of the drug via the oral route has largely curbed this development due to pre-systemic breakdown and low penetration across the gut wall. The creation of innovative dosage forms to support the absorption of weakly permeable medicines across the intestinal epithelium is the main problem in oral medication administration. Although therapeutic success has not yet been attained, research on oral absorption/permeation enhancers that improve intestinal permeability was initially started 50 years ago. Lack of sufficient repeatability interest and perceived safety issues have both hampered developments. Some selected permeation enhancement techniques that are advantageous for increasing permeability of poorly permeable drugs like gentamicin (GM) has been reviewed. (Al-snafi, 2014).

In order to obtain sufficient gentamicin absorption in the gut, novel delivery systems must be developed which should be able to overcome the barriers present in the oral route. The barriers that are to be centered on include: the acidic environment in the stomach, basal cell membrane, capillary wall, tight junction the digestive and proteolytic enzymes in the small intestine, the low permeability of the intestinal epithelium to large hydrophilic gentamicin and finally the first pass metabolism of the drug in the liver. (Al-snafi, 2014). Locally deactivating the proteolytic enzymes of the GI tract can be accomplished by using protease inhibitors like aprotonin, chymostatin, EDTA, and leupeptin. To use these protease inhibitors safely, however, they must be joined to high molecular weight hydrophilic matrices in order to prevent their absorption and potential cell damage. Additionally, permeation enhancers have been employed to reversibly open the intestinal epithelium's tight junctions and enable the paracellular pathway's passive absorption of peptides and proteins. It has been observed that two (2) main types of compounds, calcium chelators and surfactants, can promote the absorption of macromolecules and hydrophilic substances by increasing the permeability of tight junctions. Surfactants result in the irreversible exfoliation of the intestinal epithelium, whereas chelating agents can trigger actin filament breakdown via extracellular Ca+2 depletion. Both of these compounds interact with the phospholipid bilayer of the intestine and cause cell toxicity; therefore, they cannot be employed as permeation enhancers for hydrophilic macromolecules like

peptides or proteins. Trimethyl chitosan (TMC), a kind of chitosan, and other mucoadhesive polymers can cling to the intestinal membrane and interact with the actin filaments of the tight junction to reversibly open them and let hydrophilic peptides pass through the membrane. These mucoadhesive polymers have been shown to be non-toxic, and since they interact specifically with actin filaments and don't interfere with the enterocytes' phospholipid bilayers, they are frequently used to induce the paracellular transport of hydrophilic macromolecules through open water-filled channels. As innovative carriers for the delivery of lipophilic and hydrophilic drugs as well as vaccines, microparticulate and nanoparticulate drug delivery systems have garnered enormous interest. There is a solid consensus that appropriately sized nanoparticles can pass through mucosal membranes undamaged and transfer their pharmacological load to the systemic circulation. Nanoparticles should be able to prevent hydrophilic medications from degrading in intestinal fluids and enhance their penetration and permeation through the intestinal mucosal epithelium in the case of hydrophilic drugs. Due to their particle size and surface charge, suitable nanoparticles have mucoadhesive characteristics. Only a small portion of nanoparticles can transport hydrophilic drug molecules across enterocytes and deliver their drug load at the serosal location, which is typically insufficient for a therapeutic impact, according to some frequently conducted research. It was also demonstrated that a sizable portion of the nanoparticles could enter the intestinal epithelial cells. The exception is when antigen-containing micro and nanoparticles are transported across so-called M-cells with a specific particle absorption mechanism that can trigger a strong enough immune response. (Al-snafi, 2014).

Pumpkin Seed Oil (PSO) as a good adjuvant

Pumpkin is botanically named *Cucurbita spp.* and its seed is known locally in South-eastern Nigeria as *'mkpuru ugu'.* The Pumpkin seed oil could be available commercially in the market and can be obtained by domestic cold press process or solvent extraction process. Rezig *et al.* (2018) presented a study mainly aimed at evaluating the chemical composition and the bioactive compounds of pumpkin seed oil of the 'Béjaoui' Tunisian species using both cold pressing and solvent extraction methods. They revealed that the seed oils contained substantial amounts of unsaturated fatty acids, particularly oleic and linoleic acids, with values ranging respectively from 28.19 % for cold pressed pumpkin seed oil to 30.56 % for pumpkin seed oil extracted by pentane and from 43.86 % for pumpkin seed oil extracted by pentane to 46.67 % for cold pressed pumpkin seed oil of the total amount of fatty acids. They showed that the investigations of different seed oils revealed that extraction techniques had significant effects on the antioxidant activity and the γ-tocopherol. Ugur and Hassan (2011) explained their result for the extraction of pumpkin seed oil using supercritical carbon dioxide determined at the operating pressure of 20–30 MPa. The oil compositions were determined by gas chromatography analysis and the results showed that the compositions of pumpkin seed oil which were obtained by means of organic solvent extraction and supercritical fluid extraction were similar. Nwabanne (2012) states that fluted pumpkin seeds are high yielding oil seeds and can serve as a commercially rich source of vegetable oil. After his research, he noted that parameters such as temperature, time and volume of solvent plus particle size affect the oil yield.

PSO provides many health benefits including antioxidant, cardiovascular health boost, treatment of benign prostatic hyperplasia (BPH), and reduction of hair loss. (Morakul, Veerawat, and Varaporn, 2019). Pumpkin seeds are also often used in traditional medicine in the management of erectile dysfunction (Ademiluyi, Oyeniran, Jimoh, Oboh and Boligon, 2019). However, there is insufficient information about the possible

biochemical rationale behind the practice. Postmenopausal women have also experienced higher prevalence of hypertension than age-match men and evidence from animal studies have demonstrated the antihypertensive effects of pumpkin seed oil (PSO) on these subjects. PSO is also often incorporated into cream emulsions to provide multifunctional effects on the skin (Ong, Chu, Tan, and Nyam, 2020).

Shaban and Sahu (2017) also noted some facts of interest for further research, saying that:

"Pumpkin seeds improve sexual stimulation and intromission and ejaculatory latency. On the other hand, pumpkin plant extract caused a significant reduction in sperm count with primary and secondary abnormalities by producing further zinc and protein. Therefore, pumpkin seed oil but not the plant extract has been used in preclinical studies to explore its role in both the prevention and treatment of infertility in male animal models".

Literature has also revealed that PSO has suspected activities on gastrointestinal organisms like *E. coli* and *S. aureus*. (El-Aziz and El-kalek, 2011). Dotto (2020) even claimed that pumpkin seed oil could be more effective for gram positive bacteria. These same organisms have been explained as having great potentials of causing systemic infections in humans and animals.

Conventional Researches on Systemically-absorbed Gentamicin Sulphate Drug

A study on gentamicin bioavailability in the lungs by Al-Amoud, Clark, Assi and Chrystyn (2005) following inhalation from two jet nebulizers has suggested the use of urine pharmacokinetic methods to estimate the amount of relative drug deposition in the lungs after inhalation. The investigations after aminoglycoside inhalation, have mainly examined amikacin and tobramycin of which are in same group as Gentamicin sulphate. The publication of the work described limited oral bioavailability using total urine drug excretion. It explained a relationship between serum tobramycin concentrations after nebulized dosage, which results in a tmax of 2 h, and lung deposition as determined by gamma scintigraphy. The latter could not have been ascertained from total urine drug excretion. However, urinary excretion profiles have always been identified through regular sampling in research on relative lung deposition. With the goal of determining whether tmax is prolonged, the study looked into the urinary pharmacokinetics of gentamicin after nebulization. In order to see if the aerodynamic properties of the emitted dosage could affect lung deposition, the properties were also measured. Following oral administration of an 80 mg dose, nebulization using a Pari LC + (PARI) or MicroNeb III (MN) device, or intravenous administration of a 40 mg dose, serial urine samples were taken from 10 volunteers. The nebulized dosages' *in vitro* aerodynamic properties were also identified. All subjects signed informed consent forms and the University of Bradford Ethics Committee approved the experiment. Using a Pari LC + (PARI) chamber connected to a PariBoy compressor (Pari GmbH, Germany) or a MicroNeb III (MN) chamber connected to a Medix AC-2000 Hi-Flo compressor, the study allowed healthy volunteers receive an oral dosage of 80 mg of gentamicin dissolved in 10 ml of water (Medix Ltd, UK). Additionally, they got a 40 mg bolus IV injection of cidomycin from Hoechst Marion Russell in the UK. Each of these dosages was given seven days apart in a random order. The nebulized doses contained 0.9% sodium chloride and were prepared up to 4 ml (Steri-Neb, Ivax, UK). A nose clip inhibited nasal inhaling during nebulization, and an exhalation filter was fastened to the mouthpiece exhaust to capture used gentamicin. The subjects were instructed to breathe normally during nebulization through their mouths until sputtering started. To find out how much gentamicin was left after nebulization, the chamber and mouthpiece were washed with distilled water. The amount of any substance detected on the exhalation filter was calculated

after it was desorbed into distilled water. Subjects had their bladders empty prior to each study dose (ORAL, PARI, MN, and IV), and they also submitted urine samples 0.5, 1, 2, 4, 6, 9, 12, and 36 hours after each dose. Each time urine was collected, it was combined, and aliquots were put into plastic vials and kept at 4 °C. Urine samples were taken at the start of dosing for the nebulized doses. Before being analyzed by high performance liquid chromographs, all samples were kept at 20 °C. The intraday variability for nominal values of 0.5-10 mg l1 ranged from 5.4 to 3.5%, and the limit of detection was 0.25 mg. According to the CEN (Committee European de Normalization) technique, the *in vitro* aerodynamic particle size characteristics of gentamicin released from each nebulizer system (n = 10) were assessed, with the exception that the medication itself was examined as opposed to a tracer ion. The pharmacokinetic study had ten healthy volunteers, four of whom were female. They were 32.0 (7.6) years old on average, and they weighed 69.7 (13.5) kg on average. After ORAL administration, no gentamicin was found in any of the urine samples. Following IV treatment, the mean (SD) gentamicin half-life was 4.3 (1.7) hours, and 38.4 (0.9) mg were eliminated in the urine. The median (range) tmax values for their urine excretion profiles after administration by PARI and MN were 3.0 (1.5-5.0) and 3.0 (0.57-5.0), respectively. 24 hours after nebulization, no gentamicin was actually excreted.

In another study by Abu-Basha, Idkaidek, and Al-Shunnaq, (2007); 50 female broiler chickens were examined for the pharmacokinetics and bioavailability of gentamicin sulphate (5 mg/kg body weight) following a single intravenous (IV), intramuscular (IM), subcutaneous (SC), and oral administration. Blood samples were taken prior to treatment at 5, 15, and 30 minutes, and 1, 2, 4, 6, 8, 12, 24 and 48 hours thereafter. *Bacillus subtillis* ATCC 6633 was used as the test organism in a microbiological assay to evaluate the amounts of gentamicin. The quantitation threshold was 0.2 g/ml. Statistical moment theory-based non-compartmental methods were used to analyze the plasma concentration-time curves. The elimination half-life (t 1/2), mean residence time (MRT), volume of distribution at steady state (Vss), volume of distribution by area (Vd,area), and total body clearance (ClB) were respectively 2.93 ±0.15 h, 2.08 ±0.12 h, 0.77 ±0.05 L/kg, 1.68 ±0.39 L/kg, and 5.06 ±0.21 ml/min per kg following intravenous administration. The mean peak plasma concentrations (C max) after IM and SC dosing were 11.37 ±0.73 and 16.65 ±1.36 g/ml, respectively, and were reached at post-injection durations (t max) of 0.55 ±0.05 and 0.75 ±0.08 h. After IM and SC administration, the t 1/2 was 2.87 ±0.44 and 3.48 ±0.37 hours, respectively. After intramuscular treatment, the Vd, area and ClB were 1.49 ±0.21 L/kg and 6.18 ±0.31 ml/min per kg, respectively, while after subcutaneous administration, they were 1.43 ±0.19 L/kg and 4.7 ±0.33 ml/min per kg, respectively. When given intramuscularly, gentamicin has a lower absolute bioavailability (F) (79%) than when given subcutaneously (100%). Between i.m. and s.c administration, significant changes in the kinetics data were found. Gentamicin had a 6.46% *in vitro* protein binding in the chicken plasma.

In another study by Rama *et al.* (2003), Labrasol was discovered to enhance rat intestinal gentamicin (GM) uptake. In the investigation, labrasol-containing GM formulations were put into hydroxypropylmethyl cellulose (HPMC) capsules and wrapped in Eudragit L100 (Eud L) and Eudragit S100 (Eud S) films before being tested on beagle dogs. The outcomes of the *in vitro* drug release assays were unable to distinguish between the three distinct GM formulations and between the two different types of enteric capsules. With Eud L and Eud S capsules, oral administration of GM solution at a dose of 50.0 mg of GM and 0.60 ml of labrasol per dog produced Cmax values of 2.38 ± 0.50 microg/ml and 2.30 ± 0.42 microg/ml,

respectively. With Eud L and Eud S capsules, respectively, the AUC values were also higher at 4.35 ± 1.31 microg h/ml and 5.34 ± 0.95 microg h/ml. As GM is prepared as a suspension in labrasol, Cmax values are reduced by two to four times and AUC values are increased by more than 2.5 times when compared to when GM is prepared as a solution. The data mentioned above show that solution formulation outperformed suspension formulation. The GM solution formulation was applied on an absorbent synthetic sponge, which was then enclosed in Eud L and Eud S capsules. Although lower than solution formulations, the Cmax and AUC values obtained with the sponge formulation were higher than those of suspension formulations. Between Eud L and Eud S capsules used to encapsulate GM formulations, there was no appreciable variation in the amount of GM absorption.

In another study by Alkrad and Alruby (2018) utilizing nonionic surfactants, five nonionic microemulsions (MEs) for oral and transdermal administration were created. The diameters of the droplets and the rheological characteristics of the MEs were characterized. Additionally, using Fourier Transform Infrared Spectroscopy, GS encapsulation in the MEs was investigated (FTIR) and using a Franz diffusion cell, the transdermal release was assessed via the skin of a rat. Additionally, the rat study comparing the oral bioavailability of one of these formulations to an aqueous solution of GS used one of these formulations. The MEs met the requirements for colloidal characteristics and additionally, the alignment of the surrounding surfactants and the encapsulation of GS in the MEs were successfully demonstrated using FTIR. 1.892 mg/cm2*h was the best transdermal flux of MEs. In compared to the oral solution, the same ME demonstrated a relative bioavailability of 239.7%.

Nanoscaled Metal-Organic Frameworks (nanoMOFs) have recently been proposed as innovative drug delivery systems due to their high porosity and adaptable composition and structure, which have been shown to have significant capabilities and the possibility for regulated release of various active ingredients. Gentamicin (GM), a broad-spectrum aminoglycoside antibiotic used to treat bacterial septicemia, was reported a great deal of therapeutic potential, but its encapsulation inside brand-new nanocarriers is required due to the bioavailability and toxicity drawbacks that come with high doses and repeated administration. In the study by Unamuno, Salles, and Blanco-Prieto (2018); a straightforward impregnation method was used to encapsulate GM in two different porous biocompatible Fe and Zr-carboxylates nanoMOFs. The resulting GM-containing solid was fully characterized using a wide range of techniques, including X-ray powder diffraction, Fourier transform infrared spectroscopy, thermogravimetric analysis, N2 sorption, scanning electron microscopy, dynamic light scattering, fluorescence spectroscopy, and molecular simulations. The biocompatible mesoporous iron (III) trimesate nanoparticles (NPs) MIL-100(Fe) were used to achieve high reproducible encapsulation rates of up to 600 g of GM per mg of formulation (MIL: Materials from Institut Lavoisier). Studies on *in vitro* GM administration were also conducted utilizing a variety of simulated physiological oral and intravenous settings. Complete antibiotic release occurred within 8 hours when using protein-free media, but release rates were slower when proteins were present. Additionally, two different cell lines were used to test the *in vitro* toxicity of GM-containing MIL-100(Fe) NPs: adherent fibroblastoid cells (NIH/3T3) and a leukemia-related monocyte (THP-1). With IC50 values up to 1 mg mL-1, these nanoMOFs demonstrated a mild cytotoxic profile that allowed for acceptable cell growth after 24 hours. Finally, tests of antibacterial activity were performed on *S. aureus, S. epidermidis, and P. aeruginosa*, three Gram-positive bacteria and one Gram-negative bacterium, respectively. Since the released GM's antibiotic activity was conserved, GM-loaded

MIL-100(Fe) NPs displayed the same activity as free GM.

In the research conducted by Kenechukwu, Momoh, Nnamani and Attama (2014), the aim of their study was the formulation and assessment of new PEGylated Solidified Reverse Micellar Solutions (SRMS)-based Solid Lipid Microparticles (SLMs) for enhanced gentamicin sulphate oral bioavailability which they successfully achieved. In their work, differential scanning calorimetry was used to create and describe a lipid matrix (SRMS) that contained 15 % w/w Phospholipon® 90G (P90G) in 35 % w/w dika wax (Irvingia gabonensis) (DSC). Gentamicin (1.0, 2.0, or 3.0 % w/w), PEG 4000, and the SRMS were used to create SLMs, and their physicochemical and pharmacokinetic properties were assessed. Franz's cell and phosphate-buffered saline (PBS, pH 7.4) as the acceptor medium were used for the *in vitro* permeation of gentamicin from the SLMs through the artificial membrane (0.22 m pore size), and clinical isolates of *Pseudomonas aeruginosa* and *Staphylococcus aureus* were used for the bio-evaluation. Gentamicin-loaded SLMs with sizes ranging from 34.49 2.56 to 53.52 3.09 m were stable and unevenly shaped. The SLMs displayed time-dependent and capacity-limited bioactivity as well as sustained drug penetration. Overall, SLMs containing 2 % weight percent SRMS, 3 % weight percent gentamicin, and PEG 4000 entrapped the most drug, produced the highest IZD against the test organisms, and had the highest permeation flux (5.239 g/cm (2). min) and permeation coefficient (1.781 10(-6) cm/min) within 420 min, while pure gentamicin produced the least. Additionally, preliminary *in vivo* pharmacokinetic investigations revealed that the improved formulation's AUC-24 was 1507 g/h/ml, compared to 678 g/h/ml for the oral drug solution. This revealed that the improved formulation increased the systemic bioavailability of gentamicin by 2.2 times. It is anticipated from their research that PEGylated SRMS-based SLMs made with hetero-lipid from Irvingia gabonensis will provide a dependable gentamicin delivery mechanism.

To determine if gentamicin sulphate may be used as sustained release formulations, it and gentamicin oleate (GO) were encapsulated in liposomes made of phosphatidylcholine (HPC) and cholesterol (CHOL) (molar ratios 7:7:2 and 5:5:l, respectively) (Cabanes, Reig, Garcia-Anton, and Arboix, 2008). The pharmacokinetic investigation included five groups of five animals (rabbits), and the following treatments were determined: 3 mg/kg of GS intravenously, 3 mg/kg of GS intramuscularly, 3 mg/kg of liposome-containing gentamicin sulphate (LGS) intramuscularly, 3 mg/kg of gentamicin oleate (LGO) intramuscularly. The peak plasma concentration (Cmax) of gentamicin after intramuscular administration of LGS was eight times lower than that after intramuscular administration of GS, and the area under the concentration-time curve (AUC) was four times lower for the liposomal version. In comparison to values computed for free GS, the apparent elimination half-life measured following administration of LGS indicated a three-fold increase. The apparent half-life of encapsulated GO showed a three-fold increase compared to I.M GO after the same dose of LGO was administered, and the Cmax obtained indicated a 2–5-fold decrease in respect to peak concentrations of free GO. When the animals were given large liposomes containing gentamycin intramuscularly, the drug was released slowly from the injection site, prolonging the plasma concentrations of the drug throughout the body.

Another data highlighted the sustained or controlled release of gentamicin as possibilities for curbing *Pseudomonas* infections. Abdelghany *et al.* (2012) created a gentamicin formulation of such properties utilizing poly(lactide-co-glycolide) (PLGA) nanoparticles. They showed that increasing the pH of the formulation, lowering the hydrophilicity of the drug, and

enhancing entrapment, obtaining levels of up to 22.4 g/mg PLGA, can improve the entrapment of the hydrophilic drug into a hydrophobic PLGA polymer. These particles showed a regulated release of gentamicin for up to 16 days during conventional incubation conditions. These particles were examined *in vitro* against *P. aeruginosa* PA01 biofilm and planktonic cultures as well as in a 96-hour peritoneal murine infection model. According to decreased plasma and peritoneal lavage colony-forming units and corresponding drops in the surrogate inflammatory markers - interleukin-6 and myeloperoxidase compared to free medication administration by 96 hours, the particles considerably increased antibacterial properties in this animal.

Conclusion

The works by Rama et al., 2003; Kenechukwu et al., 2014; Unamuno et al., 2018 and Alkrad & Alruby (2018) all revealed the possibilities of delivering a systemically-absorbed oral gentamicin preparation after a complex formulation but containing permeation enhancers to aid its oral bioavailability. Gentamicin sulphate encapsulation from specialized oral formulations (into microemulsions or nanoemulsions as may be required) remain very desirable to achieve target delivery of the drug into the systemic circulation. A simple cost-effective formulation with a natural oil (with inherent antimicrobial activity) like pumpkin seed oil should be the bane of every further research on this topic to help curb the effects of antimicrobial resistance and thus benefit from the broad-spectrum antimicrobial activities of this drug.

Conflict of Interest:

The authors declare no conflict of interest.

Authors' Declaration: The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgments

This review work/article including the further research/lab work from this study was fully supported by the Department of Pharmaceutics and Pharm. Technology of Nnamdi Azikiwe University, Awka; Anambra State of Nigeria, under the guidance and technical support of the head of department (H.O.D) whom is also a co-author – Dr. Nwakile Calistus D.

References

1. Abdelghany, S., Quinn, D., Ingram, R., Gilmore, B., Donnelly, R., Taggart, C. and Scott, C. (2012). Gentamicin-loaded nanoparticles show improved antimicrobial effects towards Pseudomonas aeruginosa infection. *Int J Nanomedicine*; *7*:4053-63. doi: 10.2147/IJN.S34341.
2. Abu-Basha, Idkaidek, and Al-Shunnaq (2007). Comparative Pharmacokinetics of Gentamicin after Intravenous, Intramuscular, Subcutaneous and Oral Administration in Broiler Chickens. *Vet Res Commun 31*, 765–773. Retrieved from https://doi.org/10.1007/s11259-006-3565-0
3. Ademiluyi, A., Oyeniran, O., Jimoh, T., Oboh, G., and Boligon, A. (2019). Fluted pumpkin (Telfairia occidentalis) seed modulates some markers of erectile function in isolated rat's corpus cavernosum: Influence of polyphenol and amino acid constituents. *J Food Biochem, 43(11):* e13037. doi: 10.1111/jfbc.13037.
4. Al-Amoud, Clark, Assi and Chrystyn (2005). Determination of the bioavailability of gentamicin to the lungs following inhalation from two jet nebulizers. *Br J Clin Pharmacol, 59(5):*542-5. doi: 10.1111/j.1365-2125.2005.02360. x. PMID: 15842552; PMCID: PMC1884834.
5. Alkrad, J., and Alruby, A. (2018). Nonionic microemulsions for oral and

transdermal delivery of gentamicin. *Pharmazie, 73(1):*9-15. doi: 10.1691/ph.2018.7098. PMID: 29441944.

6. Al-snafi, A. (2014). *International Journal for Pharmaceutical Research Scholars (IJPRS).* (October), 671–677.
7. Cabanes A., Reig F., Garcia-Anton J.M, and Arboix M. (1998). Evaluation of free and liposome-encapsulated gentamycin for intramuscular sustained release in rabbits, Research in Veterinary Science 64(3), pp. 213-217.
8. Dotto, J. and Chacha, J. (2020). The potential of pumpkin seeds as a functional food ingredient: A review. *Scientific African, 10,* e00575, ISSN 2468-2276, Retrieved from https://doi.org/10.1016/j.sciaf.2020.e00575.
9. EI-Aziz, A. and EI-Kalek, H. (2011). Antimicrobial proteins and oil seeds from pumpkin (Cucurbita moschata*). Nature and Science, 9(3).* Retrieved from http://www.sciencepub.net/nature
10. Kenechukwu, F., Momoh, M., Nnamani, P. and Attama, A. (2014). Solid lipid micro-dispersions (SLMs) based on PEGylated solidified reverse micellar solutions (SRMS): a novel carrier system for gentamicin. *Drug Deliv., 22(6):*710-22. doi: 10.3109/10717544.2014.900152. PMID: 24724962.
11. Le, P., Ojano-Dirain, R., Nelson, D., Prieskorn, and Miller (2014). Assessment of nutrient supplement to reduce gentamicin-induced ototoxicity. *J Assoc Res Otolaryngol;15(3):*375-93. doi:10.1007/s10162-014-0448-x. PMID: 24590390; PMCID: PMC4010593.
12. Morakul, B., Veerawat, T., and Varaporn, B. (2019). *Niosomal delivery of pumpkin seed oil: development, characterisation, and physical stability, 36(2):*120-129. https://doi.org/10.1080/02652048.2019.1607597. PMID: 30982383.
13. Mushtaq, N., Redpath, M., Luzio, P. and Taylor, P. (2004). Prevention and cure of systemic Escherichia coli K1 infection by modification of the bacterial phenotype. *Antimicrob Agents Chemother, 48(5):*1503-8. doi: 10.1128/AAC.48.5.1503-1508.2004. PMID: 15105097; PMCID: PMC400570.
14. Nwabanne (2012). Kinetics and Thermodynamics Study of Oil Extraction from Fluted Pumpkin Seed. *International journal of multidisciplinary sciences and engineering, 3 (6).*
15. Ong, T., Chu, C., Tan, C., and Nyam, L. (2020). Preparation and Evaluation Pumpkin Seed Oil-based Vitamin E Cream Formulations for Topical Application. *J Oleo Sci., 69(4)*:297-306. Retrieved from https://doi.org/10.5650/jos.ess19250.PMID: 32249259
16. Rama, P., Eaimtrakarn, S., Ishida, M., Kusawake, Y., Tawa, R., Yoshikawa, Y., Shibata, N., and Takada, K. (2003). Evaluation of oral formulations of gentamicin containing labrasol in beagle dogs. *Int J Pharm; 268(1-2):*13-21. doi: 10.1016/j.ijpharm.2003.08.008. PMID: 14643972.
17. Rezig, L., Chouaibi, M., Ojeda-Amador, R., Gomez-Alonso, S., Salvador, M., Fregapane, G., and Hamdi, S. (2018). *Cucurbita maxima* Pumpkin Seed Oil: from the Chemical Properties to the Different Extracting Techniques. *Notulae Botanicae Horti Agrobotanici Cluj-Napoca 46,* 663-669. doi: http://dx.doi.org/10.15835/nbha46211129
18. Sanghavi (2019). Drug Guideline: Gentamicin. *ICU Medical Director,* 1–4. Retrieved from https://www.aci.health.nsw.gov.au/data/assets/pdf_file/0009/306369/liverpoolGentamicin.pdf
19. Shaban, A. and Sahu, R. (2017). Pumpkin Seed Oil: An Alternative Medicine. *Int J Pharmacogn Phytochem Res., 9(2):*11. doi:10.25258/phyto. v9i2.8066. PMID: 34924730; PMCID: PMC8681145.

20. Smith, J., Fratamico, P., and Gunther, N. (2007). Extraintestinal pathogenic Escherichia coli. *Foodborne Pathog Dis. Summer;4(2):*134-63. doi: 10.1089/fpd.2007.0087. PMID: 17600482.
21. Uğur and Hasan. (2011). A green separation process for recovery of healthy oil from pumpkin seed. *Journal of Supercritical Fluids - J SUPERCRIT FLUID*. 58. 239-248. 10.1016/j.supflu.2011.06.002.
22. Unamuno, I., Salles, H., and Blanco-Prieto (2018). Biocompatible porous metal-organic framework nanoparticles based on Fe or Zr for gentamicin vectorization. *Eur J Pharm Biopharm, 132*:11-18. doi: 10.1016/j.ejpb.2018.08.013. PMID: 30179739.