Research Article

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International Journal of Drug Development and Research
1791-809X

2022
Vol. 14 No. 7: 966

Transdermal Drug Delivery Systems Enhancement in Skin Permeation Using Electroporation and Gold Nanoparticle

Shanaya K*

Department of Biology, Emory University School of Medicine, Greece

Corresponding author: Shanaya K

shanaya@K23.co.in

Department of Biology, Emory University School of Medicine, Greece

Citation: Shanaya K (2022) Transdermal Drug Delivery Systems Enh*ancement* in Skin Permeation Using Electroporation and Gold Nanoparticle. Int J Drug Dev Res J, Vol.14 No. 7: 966.

Abstract

To compare the performance differences between transdermal products, in vitro drug release tests are often utilised and mandated by numerous authorities. The outcome, however, is insufficient to make a reliable prediction of the drug release in vivo. The traditional USP apparatus 2 and 5 methods and a new approach for assessing drug release from patches have both been investigated in this study. On a synthetic skin simulator, durogesic patches—used here as a model patch—were applied, and three moisture levels (29, 57, and 198 L cm^2) were assessed. The artificial skin simulators were taken out at 1, 2, 3, 4, 6, and 24 hours and removed using a hydrochloric acid solution with a pH of 1.0. Isocratic reverse phase high-pressure liquid chromatography was used to determine the drug concentrations in the extractions. The outcomes demonstrated that the drug release rate increased as the moisture level on the synthetic skin simulator rose. The new approach's medication release outcomes had a better association with the release rate stated on the product label than the traditional USP method did. In the early stages of development, this innovative technique may be able to distinguish between the drug releases rates of various transdermal drug delivery system formulations.

Poor skin permeability makes it difficult to deliver drugs via transdermal (TRD) delivery at the necessary therapeutic rate. Using the complementary effects of skin electroporation and gold nanoparticle (GNP), a unique TRD enhancement technique was developed in the current work. The model medicine chosen was diclofenac sodium (DS). The polyvinyl alcohol/poly (dimethyl siloxane)-g-polyacrylate skin adhesive matrix was used to create an electro-sensitive patch. To improve skin permeability and electrical conductivity, respectively, GNP/carbon nanotube nanocomposite (GNP-CNT) was introduced into the matrix using GNP and CNT. By adjusting the GNP-CNT concentration, it is possible to fine-tune the device's characteristics by changing the device's thermomechanical properties, water vapour permeability (WVP), drug encapsulation efficiency (DEE), and drug release profile.

Keywords: Thermomechanical; Transdermal; Deliver Drug

Received: 29-Jun-2022, Manuscript No. IJDDR-22-12932; **Editor assigned:** 4-Jul-2022, Preqc No. PQ-12932; **Reviewed:** 18-Jul-2022, QC No.Q-12932 **Revised:** 21-Jul-2022, Manuscript No. IJDDR-22-12932 (R); **Published:** 28-Jul-2022, DOI: 10.36648/1791-809X-16.07-966

Introduction

To produce therapeutic benefits or to offer local effects of medications, transdermal patches transport medication across the skin to the circulatory system. One of the fastest-growing drug administration routes, it offers a number of benefits over more conventional delivery systems, including controlled release rate, more stable plasma concentration, noninvasive administration, less frequent dosing, and straightforward use without specialised medical assistance [1]. However, one issue with transdermal delivery systems is stratum corneum penetration, which restricts the size and characteristics of drug molecules that can pass

through. In light of this, for many transdermal delivery systems, the skin additionally acts as a rate-limiting step in addition to the delivery device. Generally speaking, the transport across the stratum corneum, stratum corneum partitioning, and skin hydration all affect the flux across the skin [2].

An essential tool for characterizing transdermal drug delivery systems is the in vitro drug release test (TDDSs). This kind of test is frequently utilised for numerous purposes during drug development since it is less expensive and simpler to conduct than in vivo research, particularly for screening procedures and stability assessment of new formulations [3]. The authorities' preferred in vitro release testing method for transdermal delivery systems is USP apparatus 5 (paddle over disc), USP apparatus 6 (spinning cylinder), and USP apparatus 7 (reciprocating holder), but USP apparatus 2 has also been employed in some in vitro investigations of transdermal patches [4]. The outcomes of these USP approaches for some TDDS, however, were shown to be difficult to connect with in vivo performances, particularly for patches where skin resistance is dependent on as the dominant factor for the regulated release. Since permeation tests provide a more comparable release profile to in vivo outcomes when developing transdermal formulations, USP procedures are consequently more beneficial in TDDS quality control processes. Some well-known examples include flow-through diffusion cells, Franz diffusion cells, and horizontal-type permeation systems [5].

In these techniques, a skin or artificial membrane is positioned in between the patch and the buffer to simulate the effects of resistance and penetration. According to a number of studies, the accuracy of the approach may be impacted by skin hydration, variations in skin type, or synthetic membranes. Therefore, a simple testing method that could simulate skin's resistance and penetration effect and test under low moisture conditions could be useful in the creation of novel TDDS formulations [6].

The model test patch in this investigation was durogesic. It is a transdermal patch for the treatment of moderate to severe chronic pain that contains fentanyl controlled-release. The dose is available in four different strengths, with a stated release rate of 2.38 g cm2 h1 for 72 hours [7]. The contact area of the patch has a direct relationship with the dose strength. Fentanyl delivered transdermally causes a depot to form in the top layers of skin, according to earlier studies. The drug depot buildup slows down the drug's transport to the systemic circulation. This suggests that the key rate-limiting step for the fentanyl patches is the diffusion and penetration over skin [8].

Hepatitis B causes over 5 lakh fatalities annually due to increased rates of infectious diseases acquired via contact with contaminated needles. Additional parenteral injection outcomes in phlebitis, discomfort, and hypothermia. However, different medications taken orally have significantly less bioavailability due to the first pass hepatic degradation. In this case, non-invasive and patient-friendly TRD medication administration is investigated. Therapeutic cargo is moved over the skin for systemic dispersion during TRD medication delivery. The transport of hydrophilic compounds via the skin is still difficult, despite the fact that the TRD route has a number of advantages, including the avoidance of first pass hepatic metabolism, simple cessation of the therapy, painless administration, and self-administration. This issue is brought on by the stratum corneum's mechanical stiffness and dense packing, which act as a barrier.

To improve the transit of hydrophilic molecules via the skin, many techniques have been developed during the past few decades. The SC barrier function has a great deal of potential to be broken, according to earlier research on TRD devices such micro needles. Nevertheless, they generated microscopic holes that remained open for at least a day, leading to bacterial infection. When nanoparticle systems were introduced, they demonstrated an amazing capacity to enhance skin transportation. Over 500 study publications have been written about the liposomes' attractiveness among these classes and their behaviour that enhances penetration. However, according to some publications, when used without conjugating with penetration enhancers, they only show a modest augmentation impact. Dendrimers and micelles are examples of smaller polymeric structures that have the ability to penetrate skin only through a shunt channel, severely lowering the device's quality. Using chemical penetration enhancers, such as pyrrolidones, terpenes, azones etc., to reduce the skin barrier features has received the most research attention. However, accounts explaining the localised skin irritation brought on by their use are available in the literature [9]. According to earlier studies, these methods do not circumvent the SC barrier as effectively as conventional TRD patches, and hydrophilic drug delivery across the epidermis takes a long time to reach steady state.

In the current effort, the skin barrier is easily broken down for the easy transport of diclofenac sodium (DS), a prototypical hydrophilic medication, by combining skin electroporation and gold nanoparticle (GNP), both of which have been found to increase skin permeability. An innovative method for temporarily disrupting and permeating lipid bilayers in response to brief, high voltage pulses is skin electroporation. In order to provide a local driving force for drug diffusion, it creates aqueous pavement across the lipid bilayers. The permeability of hydrophilic molecules on skin is dramatically increased by high voltage electric pulse exposure, according to published research. A strong electric pulse or high power is required for electroporation, even if it offers the ability to provide programmed TRD flow of pharmacological molecules. The requirement for high power makes downsizing difficult and necessitates routine battery replacement. It is generally known that polymeric hydrogels' insufficient electrical conductivity prevents them from generating the necessary electrical stimulations to maximise SC disruption. A promising strategy to overcome the aforementioned drawbacks has been explored: decorating polymeric networks with carbon nanotubes (CNTs) with advantageous electrical characteristics.

Carbon nanotubes (CNTs) have a cylinder-shaped nanostructure. It has been investigated as potential materials for sensing, catalysis, and numerous biomedical applications because of its outstanding thermomechanical and electrical capabilities. The development of next-generation medication delivery systems may offer a variety of opportunities thanks to CNTs, one of these. Although unpurified and defective CNTs are cytotoxic, their cyto-compatibility is still a contentious issue [10]. According to published research, oxidised and functionalized CNTs are non-

toxic and therefore appropriate for medicinal uses. In contrast to other nanomaterials, oxidised CNTs have an empty interior that can be used for drug encapsulation due to the presence of active functional groups that allow hydrogen bonding interactions with diverse drug molecules.

Recent research, however, has shown that GNPs have the innate ability to alter the TRD delivery paradigm because they physically alter the SC bilayer, which promotes the easy diffusion of therapeutic payloads into deeper skin layers. On SC, brief and reversible openings are produced by GNP's interaction with lipid bilayers. Pissuwan looked into TRD administration of ovalbumin combined gold nanorod in an oil-based formulation and found that GNP greatly increased ovalbumin's skin permeability. The SC is penetrated by thiol-coated GNP, which later diffuses to deeper skin layers, according to earlier work. In this case, DS was delivered via the ability of GNP to cause lipid modification.

The TRD device's membrane serves as its primary structural component, clenching drug molecules at the very end and allowing them to spread slowly toward the skin's surface. Furthermore, the device's ability to promote skin adherence is connected to its therapeutic effectiveness. Numerous studies have already highlighted the extraordinary skin adhesion behaviour of silicones, polyisobutylenes, and acrylates. Using Poly (dimethyl siloxane)-g-Polyacrylate (PDMS-PA), which is believed to have better adhesiveness than their tidy counterparts, our group has described a novel method for creating TRD devices. Due to its exceptional hydrophobicity and biocompatibility, which prevents skin occlusion, polyvinyl alcohol (PVA) was chosen as the matrix.

This article describes the creation of a brand-new skin adhesive TRD device that is PVA/PDMS-PA based and reinforced with GNP-CNT hybrid nanofiller. We are aware of no prior reports describing the improvement of skin penetration employing the synergistic action of electroporation and GNP. The membrane can also simultaneously enhance the skin's adherence and permeability characteristics. The goal of this study was to create a simple, picky test procedure that could mimic skin's moisture content and drug diffusion. The method was intended to help in the early development stage of TDDS formulation screening by offering a good indicator of the in vivo performances and release rates.

Materials and Methods

Materials

The Durogesic patches, a commercial matrix-type transdermal patch available from Janssen-Cilag in Belgium in two strengths of 12 and 75 g/hr, served as the study's model patch. Fentanyl base was a gift from the Swedish company Orexo AB (MacFarlan and Smith, Edinburgh). The Freudenberg Group manufactures dish sponge cloth (Wettex) (Norrkoping, Sweden). The fabric is 2 mm thick and is constructed of 65% cellulose and 35% cotton. It functioned as a drug reservoir for this study and a synthetic skin simulator (SSS) to simulate drug resistance and penetration. Gas pycnometer measurements revealed that it had a real density and porosity of 2.0543 g cm_3 and 93.7%, respectively. Monopotassium phosphate (KH_2PO_4), 37% fuming hydrochloric acid (NaOH), and sodium hydroxide (NaOH) were all acquired from Sigma-Aldrich in reagent grade.

PDMS-PA, PVA (98-99% hydrolyzed), sodium citrate dihydrate, and gold (111) chloride trihydrate (HAuCl43H2O) were provided by Sigma-Aldrich (USA). We bought CNT and DS from Tokyo Chemical Industry (Japan). Merck Specialities Pvt. Ltd. provided all solvents (Mumbai).

Drug Release Test of Durogesic Patch on SSS

The SSS of the associated patch size (5.25 cm2 for a 12 g/hr patch or 31.5 cm2 for a 75 g/hr patch) was made with three different moisture levels (29, 57, and 198 L cm2) and phosphate buffer at pH 6.8 and placed on a clean, flat surface. Using the SSS at room temperature and humidity, the Durogesic patch was applied. To prevent patch displacement, the patch and SSS were mounted on a parafilm sheet and had the top of the parafilm covered with a flat metal plate. The environment of the experiment. The patch was transferred to a fresh piece of wet SSS after 1, 2, 3, 4, 6, and 24 hours, and the old SSS was collected and soaked in HCl solution (pH1.0).

Synthesis of GNP-CNT

Based on previous literature, GNP-CNT was created. 1.0 weight percent of HAuCl4 solution received 50.0 milligramme of CNT following acid treatment. To properly disperse the CNT, the mixture was sonicated for 15.0 minutes. After that, the suspension was heated to boiling while being further diluted and rapidly agitated. By adding the necessary amount of sodium citrate, the final GNP of the desired size was achieved. Until the colour of the suspension did not change, the reaction was maintained.

Characterization and analysis

A transmission electron microscope (FEI, TEC-NAIS Twin microscopy) operating at 100 KV was used to study the GNP-CNT particles. With a Siemens D5000 X-ray diffractometer (Germany) outfitted with Ni filtered Cu K radiation and an X-ray tube operating at 40 kV and 30 mA, X-ray diffraction (XRD) spectra of CNT and GNP-CNT were acquired over the 2 ranges from 10° to 80°. Using a micro-Raman spectrometer called the Lab Ram UV HR, Jobin-Yvon, Raman spectra of CNT and GNP-CNT were collected. A high resolution FE-scanning electron microscope, the Nova Nano SEM NPEP 252, was used to analyse the surface morphology and microstructures of membranes incorporating GNP-CNTs. At room temperature, a tensile tester was used to measure the tensile strength (TS) and elongation at break (Eb) of membranes.

By keeping the device at room temperature for 30 and 60 days, the impact of storage duration on tensile qualities was also investigated. With a heating rate of 10 °C/min and a temperature range of 30-800 °C, thermogravimetric analysis (TGA) was carried out using a TG analyser (TA Q50) in a nitrogen-filled environment. A thickness gauge was used to measure the thickness of the films that contained GNP-CNTs.

In vitro skin permeation test

The University of Kerala's animal ethical council approved the skin permeation tests before they were conducted. The prolonged inhalation of chloroform outcomes in the culling of 45-week-old male Wister rats. The processed excised rat skin was prepared in the same manner as described in our earlier study prior to the

permeation test. The experiment was carried out in a modified Franz diffusion cell with a receiver compartment with a capacity of 10.0 mL filled with phosphate buffer saline and an exposed area of 3.2 cm_2. The donor chamber was attached to the receptor compartment of the diffusion apparatus after the test membrane had been installed. The dermis side of the circular skin sample was carefully positioned down to the donor chamber of the diffusion cell.

Following that, at the donor chamber, the TRD membrane was delicately cast into the middle of the skin specimen. Continuous stirring was given by the entire apparatus, which was thermostated at 37.0 1.0 °C. By taking the aliquots out of the receiver chamber at specified intervals and immediately replacing them with new buffer, the amount of DS that had permeated was calculated. A spectrophotometric method of DS quantification was used. To investigate how applied voltage affected the DS release profile, the membrane with the maximum permeability was used. Two electrodes that were in contact with the TRD device and the skin of the rat received several electric voltages (5.0 and 10.0 V). Three separate DS permeation tests were performed.

Cell viability assay

HaCaT cells were used in the MTT assay to evaluate the produced membranes' ability to support living cells. In a nutshell, HaCaT cells were plated into 96-well plates and kept at 37.0 °C with 5.0% CO2. The cells were treated with various concentrations of the optimised membrane after 24 hours. The media was then taken out, 50.0 L of MTT (2.0 mg/mL) was added, and it was incubated for 6 hours in the dark. After dissolving the crystal with 10.0 L of DMSO, the plate was quickly read. The cell viability was assessed as previously described. The tests were carried out three times.

Environmental fitness assay

By examining how much bacterial growth there was on the prepared films, Giri's assessment on environmental fitness was verified. The E. coli stain, which was cultivated in a nutrient broth, was the target of the test. In a nutshell, equal amounts of PV0, PV0.5, PV1.0, PV1.5, and PV2.0 were added to regular LB agar, mixed uniformly, and autoclaved for 10.0 min at 15.0 Psi pressure and 120.0 °C. The suspensions were then transferred to petri dishes, hardened, and stained with E. coli. The stained dishes were kept at 37.0 °C for a total of 72.0 hours to promote bacterial growth. Following this, the plates were examined for any obvious signs of growth, and those that prevented microbial development were deemed appropriate for TRD use.

Results

Effect of the Amount of Moisture on the SSS on Release Rate

As collected moisture between the patch and skin is typically unavoidable and affects the rate of drug transport through the skin, drug release rates from the model patches were assessed on the SSS with various moisture levels. As the humidity level rose over the course of 24 hours, the data showed, the medication release rate also increased. Under low and moderate moisture levels, release rates for both strengths of the patches were comparable, but under high moisture conditions, they significantly increased. Release patterns recorded under low and moderate moisture conditions on SSS were more in line with the patch's claimed clinical release. The association between the release profile of the bigger patch and the claimed clinical release was higher. The two primary processes in the process of making the TRD device are (1) preparing the GNP-CNT and (2) depositing the CNT on a PVA-based matrix, followed by the encapsulation with DS. As a common technique for the production of GNP-CNT, citrate reduction has been used. According to earlier studies, formulations created without advance mixing resulted in significantly less GNPs that were deposited on the side wall of CNTs. When HAuCl4 and CNT are thoroughly homogenised, HAuCl4 molecules adhere to the side wall of CNT in a well-organized manner. TEM picture, XRD profile, and Raman spectroscopy all supported the viability of the GNP-CNT synthesis. Information-supporting TEM images of unmodified CNT and GNP-CNT are shown.

In vitro skin permeability test

The permeability of DS's skin was examined in the first investigation to see if GNP altered it. After the TRD device was deployed, DS was discovered in the diffusion cell's receptor chamber. The amount of DS in the chamber gradually rose, and the patch without GNP (PV0) supplied about 58.0% of it in 22.0 hours. Approximately 68.0 and 73.0% of the loaded DS had been delivered across the skin by the end of this time for PV0.5 and PV1.0, respectively. According to these outcomes, the TRD DS permeability significantly increased as GNP concentration was increased. How much permeability was increased by GNP up to a 1.5% nanofiller level was related to its propensity to modify lipids. As soon as GNP interacted with SC, the brief and reversible openings it produced immediately destroyed SC's considerable barrier characteristic. The lipids in SC arranged themselves in a head-to-head and tail-to-tail pattern, with the head-to-head segment potentially creating nanoscale holes. There are roughly 5.0 107 natural intercellular holes per square centimetre of SC, according to earlier articles. Extracellular apertures' sizes vary, nonetheless, from one individual to another. The productive perturbation of the lipid packing caused by GNP, the size of the holes increased, increasing permeability. GNP may effectively disrupt the lipid bilayers because of its huge surface area and nanometric particle size, which allows it to be fully in contact with the lipid packing.

Cell viability assay

Cell viability of the optimised PV1.5 patch was assessed in order to assess the device's biological safety after the successful manufacturing and characterization of the TRD device. On HaCaT cell lines, MTT assays were used to evaluate the vitality of the cells. Cell viability was determined to be 90.7, 88.0, 87.1, 86.4, and 82.3% for each of the five PV1.5 doses used: 1.50, 3.00, 6.25, 12.50, and 25.00 mg/mL. The assay's showed that none of the dosages of PV1.5 were harmful to HaCaT cells. Oddly, exposure to even larger doses of PV1.5 did not in a noticeably noticeable decline in cell viability. According to published research, substances with a cell viability of more than 80% are considered non-toxic.

Environmental fitness assay

Microorganism buildup on the TRD film surface causes the production of biofilm, which ultimately prevents the device from working. Bacterial colonisation and the development of biofilms are the outcomes of microbial survival upon surface adherence. Only if the device has antibacterial qualities may cell proliferation be restricted. The potential of the various nanometric particles that make up GNP to inhibit microbial colonisation has recently received extensive research. One of the major challenges is enhancing GNP's anti-microbial potential while maintaining their biocompatibility. According to Seo and colleagues, conjugating different-sized nanometric materials can stop microbial growth with barely detectable cytotoxicity. Excellent anti-microbial properties are displayed by CNT, which inhibits the growth of microorganisms by three mechanistic hypotheses: cell wall disruption, cell wall puncturing, and oxidative stress. In addition to CNT, GNP also provided remarkable defence against the formation and invasion of bacterial biofilms within the TRD device. Previous studies have shown that GNP can bind to bacteria in large amounts, leading to cell wall rupture, ROS accumulation, and ultimately cell death. Numerous microorganisms' secreted phospholipases and aspartyl proteinases were remarkably effective in destroying the hosts' materials. By employing electrostatic interactions to inactivate these enzymes, GNP shields the TRD device from bacterial harm.

Discussion

The SSS method was created as an easy-to-use screening tool for transdermal formulations during the early stages of research. However, during the experiment, inaccuracies in the measurement of the drug release profiles may have resulted from insufficient drug extraction from the SSS and drug release from the edges of the patch. At lower pH levels, fentanyl dissolves significantly more easily, and following extraction, drug diffusion was thought to be in equilibrium. Extraction should be deemed to be finished and substantially all of the medicine should have been released from the SSS. After the initial extraction, we discovered that a minor amount of fentanyl was further released from the SSS.

Conclusions

It has been designed and tested to measure the transdermal drug delivery system's release rate using a straightforward, inexpensive, and selective method. The cornerstone of this technique is a moistened synthetic skin simulator (SSS), which offers release resistance as well as a moisture and reservoir function for the medication discharged from the model patch. On SSS, it was discovered that the drug release rate rose as the humidity level did. Comparing this method to the traditional in vitro release USP method, it became clear that this approach provided a more reliable means to assess the drug release profile. In the early stages of the study and development of transdermal drug delivery systems, it can be very useful when screening various formulations. The combination of GNP and electroporation was used for the first time in this study to increase skin penetration. By adding GNP-CNT reinforcement, an electrically sensitive TRD film was created from a PVA/PDMS-PA matrix. The thermomechanical characteristics, DEE, and DS permeation profile were significantly improved by the addition of GNP-CNT. 1.5% GNP-CNT with 10.0 V applied bias produced the greatest penetration enhancement effect. The disruption of lipid packings, the development of new aqueous pathways, and the heat effect are the primary causes of the improvement in DS delivery that is brought about by the introduction of an electric field. When GNP and electroporation were used together, a much larger percentage of DS was given than with GNP alone.

Acknowledgment

The author would like to acknowledge his Department of Biology, Emory University School of Medicine, Greece for their support during this work.

Conflicts of Interest

The author has no known conflicts of interested associated with this paper.

References

1 Bhatnagar S, Kwan JJ, Shah AR, Coussios CC, Carlisle RC (2016) Exploitation of sub-micron cavitation nuclei to enhance ultrasound-mediated transdermal transport and penetration of vaccines. J Control Release 238: 22-30.

2 Lahiji S F, Dangol M, Jung H (2015) A patchless dissolving microneedle delivery system enabling rapid and efficient transdermal drug delivery. Sci Rep 5: 7914-7956.

3 Rambharose S, Kalhapure RS, Akamanchi KG, Govender T (2015) Novel dendritic derivatives of unsaturated fatty acids as promising transdermal permeation enhancers for tenofovir. J Mater Chem B 3: 6662-6675.

4 Schoellhammer CM, Srinivasan S, Barman R, Mo SH, Polat BE, et al. (2015) Applicability and safety of dual-frequency ultrasonic treatment for the transdermal delivery of drugs. J Control Release 202: 93-100.

5 Tang H, Kobayashi H, Niidome Y, Mori T, Katayama Y, et al. (2013) CW/pulsed NIR irradiation of gold nanorods: effect on transdermal protein delivery mediated by photothermal ablation. J Control Release 171: 178-183.

6 Cevc G, Vierl U (2010) Nanotechnology and the transdermal route: a state of the art review and critical appraisal. J Control Release 141: 277-299.

7 Pegoraro C, MacNeil S, Battaglia S (2012) Transdermal drug delivery: from micro to nano. Nano part 4: 1881-1894.

8 Bachhav YG, Mondon K, Kalia Y N, Gurny R, Möller M (2011) Novel micelle formulations to increase cutaneous bioavailability of azole antifungals. J Con R 153: 126-132.

9 Karande P, Jain A, Mitragotri S (2004) Discovery of transdermal penetration enhancers by high-throughput screening. Nat Biotech 22: 192-197.

10 Williams A C, Barry B W (2004) Penetration enhancers. Adv Drug Deliv Rev 56: 603-618.