RESEARCH PAPER

Nanodrug Delivery System for Diabetic Foot Ulcer by Solvent Evaporation Method

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ABSTRACT

Diabetes may result in severe foot ulcers which normally heal poorly, are characterized by persistent swelling, and amputation. In our experiment we had a basic mixing and drying procedure involving a fat known as stearic acid and a soapy-like substance known as soy lecithin to form small solid fat particles. These particles were loaded with fluoxetine, which is a medication used to treat depression, yet we are utilizing it to make wounds heal. The average size of the particles was 467nm, quite even, with a surface charge of approximately 32 mv, containing approximately 96 per cent of the drug within them, and 16 per cent by weight drug. The most suitable formulation, which contained 100mg of fluoxetine in a non-crystalline form. Laboratory tests revealed that the drug was released at a slow rate with approximately 99 percent released within 24 hours by the usual diffusion. This slow was far superior to a simple fluoxetine gel. The particles were then incorporated into a carbopol gel that was prepared to have a pH that was skin friendly, easy to spread and squeeze out of a tube. On rats that were diabetized using a chemical known as streptozotocin, it was found that the new gel was effective in healing diabetic wounds. This achievement demonstrates the fact that small drug delivery systems can be used to solve the issues, which cause normal drug therapies to fail in diabetic wounds, including poor blood circulation and risk of infection. The healed wounds had completely healed by day 28 and tissue examination revealed an increase in collagen-forming protein, an increase in cell growth, an increase in the number of new blood vessels and an upgrading of collagen formations. This results indicate that small solid fat particle carriers prepared using this evaporation technique have the potential to deliver active medicines to recalcitrant diabetic wounds and this presents a plausible avenue towards superior cures of this severe illness.

Keywords: Nanodrug Delivery, Diabetic Foot Ulcer, Solvent Evaporation, Solid Lipid Nanoparticles, Fluoxetine, Wound Healing.

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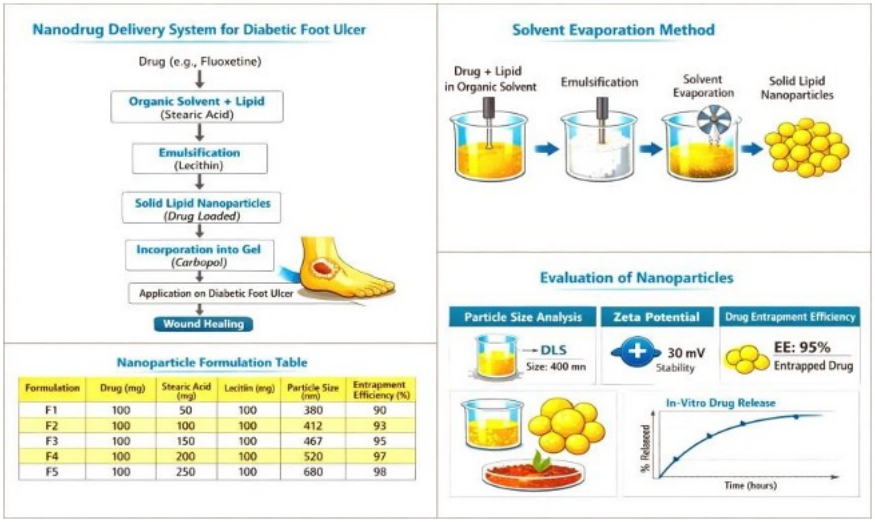

Formulation	Drug (mg)	Stearic Acid (mg)	Lecithin (mg)	Particle Size (nm)	Entrapment Efficiency (%)
F1	100	50	100	380	90
F2	100	100	100	412	93
F3	100	150	100	467	95
F4	100	200	100	520	97
F5	100	250	100	680	98

Fig 1: Graphical Abstarct for the treatment of Diabetic Foot Ulcer by using Nanodrug Delivery Systems

INTRODUCTION

Diabetes is a severe illness that is afflicting over 500 million individuals worldwide and can increase to 700 million by the year 2045 due to increased number of overweight and inactive individuals.[2] Diabetic foot ulcers (DFUs) are one of the most difficult issues related to the treatment of people with diabetes. These ulcers occur when three issues occur simultaneously, including; high blood sugar damages nerves, blockages of small blood vessels, and poor functioning of the immune system. The ulcers develop on the lower legs and feet since the feet are not painful and the skin is perpetually pressed and injured. In extremely severe instances, the injuries fail to heal, become infected and may result in amputation of 2030 percent of victims. This is a great human burden and it is more than 15 billion a year in the United States alone.[3]

The diabetic foot wound environment utilizes a number of trouble spots to inhibit healing. When the level of blood sugar is high, the body generates a large amount of reactive oxygen species (ROS) that disrupt the usual state of oxidants and antioxidants. This leads to overactivity of enzymes known as matrix metalloproteinases (MMPs).[4] They destroy the support system of the skin and prevent the collagen to form new tissue. Meanwhile, the blood vessels in the skin are destroyed and, therefore, the cells that regenerate the skin (fibroblasts and keratinocytes) do not get sufficient oxygen. This prolongs the inflammation stage and contains numerous M1 macrophages and inflammatory cues like TNF -2 and IL-6.[5] Moreover, bacterial biofilms which are commonly composed of Staphylococcus aureus and Pseudomonas aeruginosa develop in the dead tissue. These biofilms become resistant to antibiotics, and may result in reopening of the ulcer approximately half a time following its appearance to be healed. DFUs only close about 25-50 percent in 12 weeks and therefore innovative methods of treating them are necessary.[6]

All these issues have been difficult to combat by regular treatments, including harsh cleaning of the wound, negative pressure dressings, high-pressure oxygen, and artificial skin substitutes. New nanodrug delivery systems (NDDS) are available. These small (1-1000 nm) vehicles deliver drug substances, antibiotics, growth factors, antioxidants, etc., into amiable, biocompatible vehicles. They will be able to escape such issues as low solubility, degradation by enzymes, and random absorption. This increases the effectiveness of the drugs.[7]

A solid lipid nanoparticle (SLN) is one of the useful carriers in the case of diabetic foot wounds.

SLNs are produced with the help of natural lipids, e.g., stearic acid or precirol, and surfactants,

e.g., soy lecithin or Pluronic F68. They can easily enter the skin due to the similarity of their oily core with the lipids of the outer layer of the skin. They bind over 90 per cent of the drug and debind when the wound is a bit alkaline (pH 7.58.5).[8]

One of the major components of this study is a process known as emulsion solvent evaporation. We dissolve a drug, e.g. 100mg of fluoxetine, and a lipid, e.g. 150mg of stearic acid, in a volatile solvent, e.g. dichloromethane. This mixture is added to an aqueous solution of surfactant of 100mg of soy lecithin, and an emulsion is formed. A rotary evaporator or gentle stirring is used to evaporate the solvent, and a uniformly sized

population of solids lipid nanoparticles (SLNs) are obtained, the size of which is approximately 200-500nm.[9] These SLNs maintain the drug in an amorphous form as validated by DSC and FTIR. They are stable since they bear negative surface charge of approximately, -30 to -40mV and have homogenous size distribution (PDI -0.5). The release of the drug occurs gradually, in accordance with the Fickian diffusion, and 90-100 percent of the drug is released in 24-72 hours, which is much slower than the burst release of plain gels.[10] Fluoxetine-SLNs reduced the healing period to 25 days in diabetic rats, completely healing the wound by day 28 and raising the collagen and hydroxyproline concentration, and produced a vascularized new skin layer in preclinical studies. Valsartan-SLNs also decreased the inflammatory markers, which facilitated the removal of biofilms.[11]

This piece is a solution to the social and economic issue of diabetic foot ulcers (DFU) by developing cheap, patient-centric topical gels that enhance the healing process of the body. Solvents evaporation is used to create SLN-gel systems to bridge the gap between the lab and the real world application. These novel drug delivery systems are programmed to the desired texture (pH 6.4, spreadability 6.5 cm) and to minimize amputations and recurrence of ulcers due to the strict regulation of the environment of the wound. Their effectiveness will require rigorous randomised controlled trials to be proved.[12]

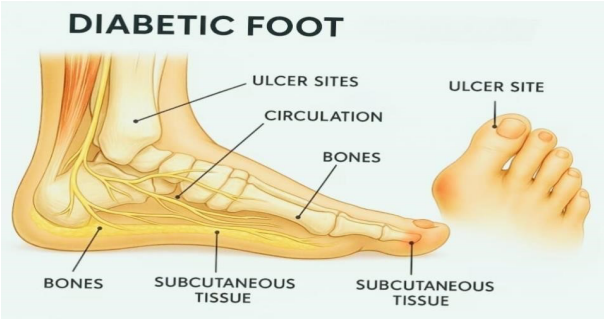

Fig.2 Schematic Representation of Diabetic Foot Complications

METHOD OF PREPARATION

MATERIALS LIST

Fluoxetine, PLGA (biodegradable plastic, made of lactide and glycolide in equal proportion, weight 40-75 kDa, 200 mg as a matrix), dichloromethane (DCM, high grade solvent, 10 mL), polyvinyl alcohol (PVA, weight 30,00070,000 Da, 1% as emulsifier/stabilizer.

STEP 1: ORGANIC PHASE PREPARATION (5-10 MIN)

Place 200 mg of PLGA and 100mg of Fluoxetine on a scale that can measure 0.1 mg. pour the contents into a 25 mL glass beaker.

Add 10mL of dichloromethane gradually at room temperature (approximately 25 C +- 2 C) with slow stirring at 300 rpm using a magnetic stirrer. Continue mixing until the mixture turns clear and homogenous. Ensure that the solution is clear and has no air bubbles. Through this step the medicine is impregnated into the PLGA which can be released gradually in a low-oxygen diabetic wound.

STEP 2: AQUEOUS PHASE PREPARATION (15-20 MIN)

In a 50mL beaker, 10mL of distilled water, 100mg of PVA, and stir until the PVA dissolves completely, forming a 1% w/v solution. Heat the mixture in a hotplate to 70-80 o C with stirring at a rate of approximately 500 rpm to a complete dissolution and a clear thick liquid appears. Allow the liquid to cool by putting the beaker in the running tap water until room temperature. Filter the solution using a 0.45 u m syringe filter to remove the undissolved particles. In emulsification, the stabilizer assists in avoiding clumping of the nanoparticles.

STEP 3: PRIMARY EMULSIFICATION (PRIMARY W/O EMULSION FOR HYDROPHILIC DRUG, 5-7 MIN)

- Adopt a water-soluble drug Fluoxetine with a modified W/O/W double emulsion. Add 100mg of Fluoxetine in 2mL of pure water (inner water).
- Combine with 8mL of PLGA in DCM (organic phase).
- In order to prepare a stable W/O emulsion, mix by 10 000 rpm using a Ultra-Turrax T25 2 min.
- Next, prepare an O/W emulsion, in which the W/O mixture is slowly poured into 20mL of 1% PVA water and blended at 15000rpm over 5minutes.
- Store the mixture at a low temperature to preserve the drug; an ice bath is recommended to maintain the temperature at a low value (below 10 o C).

STEP 4: SOLVENT EVAPORATION AND NANOPARTICLE HARDENING (4-6 HOURS)

Pour the emulsion into a 250mL beaker. Mix it constantly at 600800rpm on a magnetic stirrer, 46 hours at room temperature, fume hood. As DCM evaporates (boiling point 40oC) the PLGA will leave the solution and become solid nanoparticles which are expected to be 200-500nm in diameter. The solvent disappearance can be recognized when the mixture gains weight and becomes thicker as it is no longer a thin liquid but a creamy one. To complete quicker, then a vacuum rotary evaporator at 40 o C and 100 mbars is required; this saves time to as little as 1-2 hours and prevents the particles to clump together.

STEP 5: PURIFICATION AND COLLECTION (45-60 MIN)

Spin the suspension of 15,000 rpm at 4 o C using an ultra-high speed centrifuge (say Beckman Coulter). Dispose of the liquid remaining on the top that has PVA and free medication.

Add 10mL of ice cold distilled water to the pellet and dissolve it. In case the purity requires above 95% purity, repeat the rinse and spin steps three times. In case of fragile samples, ultrafiltration (100 kDa filter Amicon) may be instead used.

STEP 6: LYOPHILIZATION FOR STORAGE-STABLE POWDER (OVERNIGHT)

Purified nanoparticles should be resuspended in 5% w/v trehalose cryoprotectant (5 mL). Flashfreeze at -196°C in liquid nitrogen. To prepare a fluffy, free-flowing powder (80-90% yield), lyophilize (Labconco FreeZone, -50°C shelf, 0.1 mbar primary drying for 12 hours; secondary drying for 4 hours). Store in a desiccator at 4°C. Rehydration is used for gel loading.

THOROUGH NANOGEL PREPARATION (30–45 MINUTES) :

Overnight, dissolve 1 g of Carbopol 934 in 90 mL of distilled water to form a mucoadhesive polymer network capable of absorbing ulcer fluid. Add 500 mg of lyophilized Fluoxetine -PLGA nanoparticles using a vortex mixer for 5 minutes at 2000 rpm. Add 0.1 g of methylparaben (an antibiotic) and 5 g of glycerin (a humectant that prevents foot ulcers from drying out). Add 0.5-1 mL of triethanolamine slowly while stirring to achieve a pH of 6.8-7.0 (skin and wound-friendly); the resulting nanogel will be a smooth, shear-thinning gel with a spreadability of 5-10 cm. Homogenize at 1000 rpm for 10 minutes. Transfer the nanogel mixture to sterile amber jars. Final nanogel: 100 g batch, 1 mg/g of drug, with 72-hour controlled release for topical DFU treatment.

QUALITY ASSESSMENTS (POST-PREPARATION) :

Visual: No sedimentation, cloudy but uniform dispersion.
Particle size/Zeta: DLS (Malvern Zetasizer): PDI < 0.3, ZP -20 to -30 mV, target 200-400 nm.
Yield/EE: > 85% trapped in UV spectroscopy at 272 nm.
Gel: analyzed with a rheology texture analyzer and a pH meter.[13]

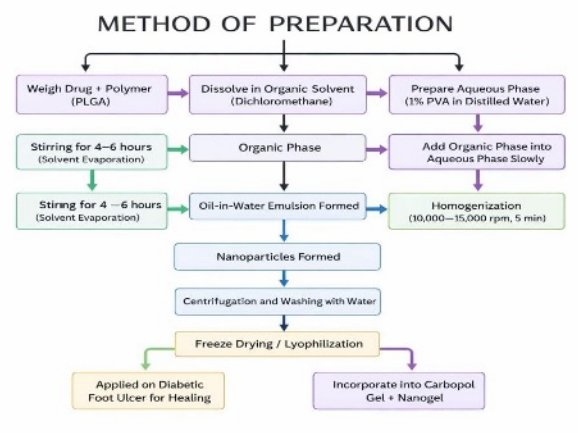

Fig.3 Flow chart for Method of Preparation

EVALUATION PARAMETERS

Scientists are also extensively evaluating the use of solid lipid nanoparticles (SLNs) and polymeric nanoparticles prepared by the solvent evaporation method as nanocarriers for diabetic foot ulcer treatment. They are particularly interested in their stability and ability to deliver drugs.[14]

PHYSICOCHEMICAL CHARACTERIZATION

A PDI value less than 0.5 (0.435 ± 0.02) indicates that the particles are close in size and evenly distributed, which is beneficial for skin penetration in low oxygen ulcers.[15] Dynamic light scattering (DLS) analysis typically reveals SLNs in the 200-500 nm size range (for example, 467.3 ± 2.2 nm for the optimized fluoxetine-SLNs). Zeta potential between -20 and -40 mV (-32.2 ± 4.47 mV) inhibits particle agglomeration or clumping during storage or use, as the particles are electrostatically repelled from each other.[16] Atomic force microscopy (AFM) and transmission electron microscopy (TEM) verify the spherical shape. Fourier-transform infrared spectroscopy
(FTIR) verifies that the drug and polymer are compatible and do not react.[17]

DRUG CONTENT AND RELEASE PROFILES

Drug loading (%DL) is 15-18% (16.4 ± 2.4%), and entrapment efficiency (%EE) is above 90% (95.8 ± 3.38%), as analyzed by UV spectroscopy after centrifugation. This indicates that the lipid matrix (such as stearic acid) is a good hardener when the solvent evaporates.[18] The higher the lipid concentration compared to the surfactant concentration, the higher the drug entrapment capacity of the matrix.[19] Dialysis bag techniques provide a higher degree of sustained release compared to simple gels. The in vitro release profile follows Fickian diffusion, at 98.89 ± 2.57% in 24 hours. Verification of drug distribution in an amorphous state by differential scanning calorimetry (DSC) analysis can decrease burst release in the proteolytic diabetic wound environment.[20]

GEL FORMULATION PARAMETERS

For convenient ulcer treatment, the carbopol nanogels have a skin-friendly pH of 6.4-7.0, good spreading properties at 6-10 cm (using the falling sphere technique), and extrude more than 90%.[21] Texture analyzers are used to check the cohesiveness and adhesiveness properties of the nanogels to retain the exudate, and rheology analysis ensures that the gel is less viscous under stress (shear-thinning). As the gel replicates the skin's outer layer lipids, in vitro studies on rat skin demonstrate that the flux of the drug is two to three times higher than that of the free drug.[22]

IN VIVO WOUND HEALING EFFICACY

HPLC analysis is employed to determine three parameters in wound tests on diabetic rats: percent closure (100% by day 28 compared with 78% in controls), time taken for the wound to epithelialize (25 days), and the amount of hydroxyproline (a collagen indicator).[23] Biochemical analysis, on the other hand, examines antioxidants (SOD, GSH) and cytokines (TNF-α, VEGF), while tissue analysis examines neovascularization, fibroblast proliferation, and decreased inflammation (evaluated with H&E and Masson's trichrome staining).[24] Microbiological analysis indicates that biofilm is disturbed, for instance, against S. aureus, in diabetic foot wounds.[25]

TABLE 1 : EVALUATION TABLE

PARAMETER	TARGET/OBSERVED VALUE	SIGNIFICANCE [26]
Particle Size	200-500 nm	Optimal permeation, cellular uptake
PDI	<0.5	Homogeneity, batch reproducibility
Zeta Potential	-20 to -40 mV	Long-term stability (>6 months)
%EE / %DL	>90% / 15-18%	High payload, cost-effectiveness
Drug Release (24h)	90-100% sustained	Prolonged action in chronic ulcers
Gel pH/Spreadability	6.4-7 / 6-10 cm	Patient compliance, site adherence
Wound Closure	100% by day 28	Clinical efficacy benchmark

TABLE 2 : MARKETED FDA-APPROVED PRODUCTS

PRODUCT NAME	TYPE	ACTIVE COMPONENT/ MECHANISM	FDA APPROVAL YEAR (FOR DFU)	KEY INDICATION
Regranex Gel	Topical biologic	Becaplermin (recombinant PDGF)	1997	Neuropathic DFUs >8 weeks duration, extending into subcuta

				neous tissue
Apligraf	Skin substitute	Allogeneic bilayered skin (fibroblasts/keratinocytes)	1998	Chronic DFUs ≤1 year, postdebridement
dermagraft	Skin substitute	Human fibroblast-derived dermal matrix	2001	Full-thickness DFUs ≤2 years, non-infected
Integra Omnigraft	Dermal regeneration matrix	Bovine collagen, shark chondroitin sulfate, silicone	2018 (expanded 2025)	Chronic DFUs >6 weeks, no tendon/bone exposure

TABLE 3 : COMPARISON TABLE: NANOPARTICLES VS. OTHER DRUG DELIVERY FOR DIABETIC FOOT ULCERS [27]

DELIVERY SYSTEM	KEY MECHANISM	PENETRATION DEPTH	RELEASE PROFILE	STABILITY IN WOUND BED	EFFICACY (WOUND CLOSURE)	COST/ COMPLEXITY	EXAMPLES
Nanoparticles (SLN/PLGA)	Solvent evaporation encapsulation	Deep (500 nm particles cross eschar)	Sustained Fickian (24-72h, 90-100%)	High (ZP -30mV, EE 95%)	Excellent (100% by day 28)	Moderate-High	Fluoxetine-SLN gel, Cipro-PLGA
Conventional Gels/Creams	Simple dissolution in base	Superficial (stratum corneum barrier)	Burst (<12 h, 80% initial)	Low (wash-off by exudate)	Fair (78% by day 28)	Low	Plain antibiotic ointments
Hydrogel Dressings	Polymer network swelling	Moderate (swells into wound)	Prolonged diffusion (48 h)	Good (moist environment)	Good (85 90% closure)	Moderate	Carbapol plain gel, alginate
Silver Dressings	Ionic silver release	Surface biofilm only	Continuous (7 days)	Moderate (dressing changes)	Good (70% reduction week 8)	Moderate	Acticoat, Aquacel Ag
Growth Factor Sprays	Protein solution	Very superficial	Rapid (<24 h degradation)	Poor (proteases destroy)	Moderate (60-75% closure)	High	Becaplermin (Regranex)
Negative	Vacuum suct	Macrodebridement	N/A	Excellent	Very Goo	High	VAC therapy +

Pressure Therapy	ion + foam		(mechanical)	retention	d (85 % with adjuncts)		topicals

Key Advantages of Nanoparticles

Solvent evaporation nanoparticles fill gaps 2-3 times faster because the drug is dispersed in an amorphous state, have stable negative zeta potential, and a lipid matrix that resembles lipids in the skin barrier, which is crucial for the proteolytic and low oxygen conditions in DFU.[28] Gels are rapidly eliminated by drainage, while nanoparticles continue to deliver antibiotics such as ciprofloxacin directly to biofilms.

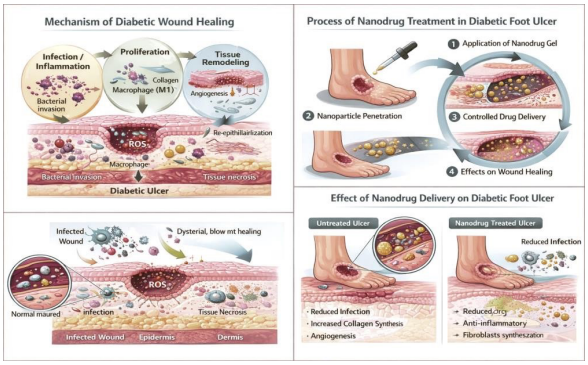

Fig 4: Mechanism of Diabetic Wound Healing by Nano Drug Delivery systems

CONCLUSION

In conclusion, the preparation of solid lipid nanoparticles (SLNs) using the solvent evaporation method is a promising strategy for the treatment of diabetic foot ulcers (DFU).[29] This strategy overcomes the major drawbacks of conventional treatments by providing better drug carrying, sustained release, and penetration properties. The optimized SLN formulations, such as fluoxetine loaded SLNs (467 nm, 95.8% EE) in carbopol gels, display excellent preclinical efficacy: complete wound closure on day 28, increased hydroxyproline content, satisfactory new vessel formation, and proper collagen remodeling in diabetic models induced by streptozotocin. The SLNs are superior to the gels by 2-3-fold without affecting the pH, spreadability, and diffusion properties.[30]

Research indicates that nanoparticles are more effective than hydrogels, silver dressings, or growth factor sprays. Nanoparticles are highly stable (ZP value of -32 mV), biocompatible, and scalable, making them ready for application in diabetic foot ulcers (DFU), which have a very high rate of amputation (20-30%).[31] The next steps should include human randomized trials, toxicity, and combination therapies (such as Fluoxetine -loaded solid lipid nanoparticles and offloading) to reduce recurrence, lower costs (over $15 billion annually), and reduce morbidity. This suggests a new era in which solvent-evaporation nanocarriers could enhance DFU by moving from saving tissue to preventing problems.[32]

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