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FORMULATION AND INVITRO EVALUATION OF TRANDOLAPRIL SOLID LIPID COMPACT NANOPARTICLE

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ABSTRACT

In this study, Trandolapril was formulated into tablets using Solid Lipid Nanoparticles (SLNs) with varying concentrations of Compritol 888 ATO (5%, 10%, and 15%). SLNs were prepared by melting the lipid, dissolving Trandolapril in ethanol, and adding surfactant (Polysorbate 80) and co-surfactant (PEG 400), followed by high-speed homogenization. The SLNs were then converted into tablets with excipients like microcrystalline cellulose, Neusilin®, and Aerosil. Characterization using FTIR and DSC confirmed no interaction between the drug and excipients. Entrapment efficiency was found to be 81.36%. Flow properties of granules were also evaluated. Dissolution studies using USP Type I apparatus in pH 6.8 buffer showed improved drug release for SLN-based tablets compared to a marketed sample (Aurobindo Pharma, USA), especially at lower Compritol concentrations.

KEYWORDS: Trandolapril, Solid Lipid Nanoparticles.

1. INTRODUCTION

Hypertension is a chronic disorder and a major risk factor for cardiovascular diseases, stroke, and kidney failure. Oral administration is the most common route for antihypertensive drugs, but poor water solubility and low bioavailability limit the

effectiveness of many, including Trandolapril. Trandolapril, an ACE inhibitor and prodrug, is hydrolyzed to its active form, trandolaprilat. It belongs to BCS Class II with poor water solubility and oral bioavailability (4–9%), and a half-life of ~6 hours. To overcome these limitations, nanocarrier-based systems such as lipid-based nanoparticles have emerged. Among them, **Solid Lipid Nanoparticles (SLNs)** offer advantages like improved solubility, protection from degradation, lymphatic absorption (bypassing first-pass metabolism), controlled drug release, and enhanced bioavailability. SLNs are biocompatible, stable, and suitable for both lipophilic and hydrophilic drugs. In this study, Trandolapril is incorporated into SLNs using full factorial design to optimize formulation. Due to its lipophilic nature, incorporation into SLNs enhances aqueous solubility and therapeutic efficacy, as confirmed by in vitro dissolution studies. Additionally, **Nanostructured Lipid Carriers (NLCs)**—second-generation lipid carriers—address SLNs' limitations like low drug loading and drug expulsion by using a blend of solid and liquid lipids, allowing for greater drug accommodation and stability. Thus, SLNs and NLCs provide promising strategies for improving the oral delivery of poorly soluble drugs like Trandolapril.

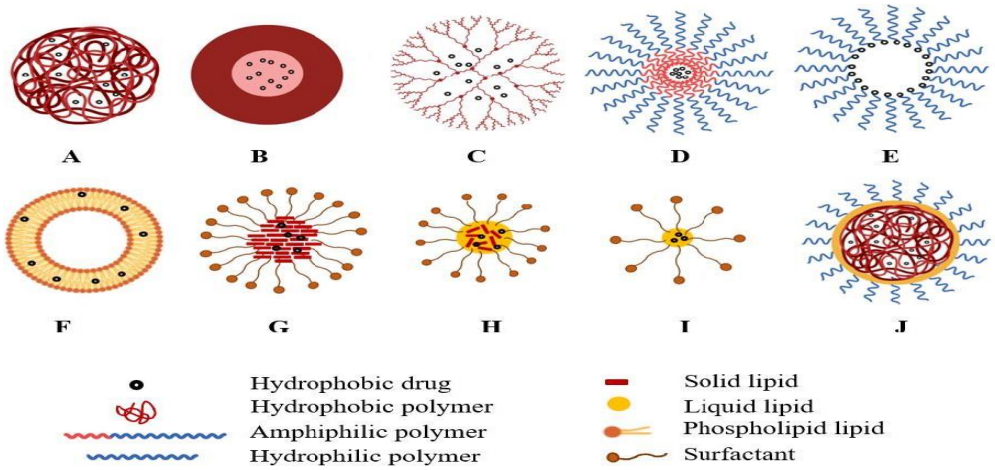


Figure 1: Overview of different types of drug loaded nanocarriers: A) polymeric nanospheres, B) polymeric nanocapsules, C) dendrimers, D) polymeric micelles, E) polymeric drug conjugates, F) liposomes. G) solid lipid nanoparticles (SLNs), H) nanostructured lipid carriers (NLCs), I) nanoemulsions (NEs) and J) lipid polymer hybrid nanoparticles (LPHNs).

2. Polymeric Nanocarriers

2.1 Polymeric Nanoparticles (PNPs)

Polymeric nanoparticles (PNPs) are colloidal drug delivery systems ranging from 1 to 1000 nm, composed of natural (e.g., chitosan, sodium alginate, gelatin) or synthetic polymers such

as polylactides (PLA), polylactide-co-glycolides (PLGA), polyglycolides (PGA), polyanhydrides, polyorthoesters (POE), polycyanoacrylates, polycaprolactone (PCL), polymalic acid (PMLA), and polymethacrylic acid (PMAA). PNPs are favored for their ease of formulation, biodegradability, biocompatibility, high stability, and controlled drug release. They effectively deliver drugs to targeted sites, with proven applications in cancer, fungal infections, vaccines, and HIV therapy. Structurally, PNPs are categorized into nanocapsules, where the drug is enclosed within a polymer shell, and nanospheres, where the drug is uniformly dispersed. Notable studies have shown enhanced uptake of antiretrovirals like saquinavir and zidovudine using PNPs. However, limitations include potential accumulation in organs like the liver and spleen, biocompatibility concerns with non-biodegradable polymers, nanotoxicity, and regulatory restrictions, as only a few polymers are approved for clinical drug delivery.

2.2 Dendrimers

Dendrimers are highly branched, nanoscale synthetic molecules first developed in the 1980s by Donald Tomalia. The name originates from the Greek word "dendron" (tree), reflecting their tree-like structure, which offers numerous surface functional groups for modification and internal cavities for drug encapsulation. Dendrimers are known for their monodispersity, multivalency, and high physical stability. They can be engineered to encapsulate hydrophobic drugs by featuring hydrophilic surfaces and hydrophobic cores. Common dendrimer polymers include polyamidoamines (PAMAM), polypeptides, polypropyleneimines (PPI), polyglycerols, and polyesters. In HIV therapy, PPI dendrimers conjugated with mannose significantly improved efavirenz uptake by monocytes/macrophages—12 times more than the free drug—while minimizing cytotoxicity. However, clinical use is limited by toxicity, biocompatibility issues, complex synthesis, and high production costs.

2.3 Polymeric Micelles

Polymeric micelles are nanosized (10–200 nm) supramolecular structures formed by the self-assembly of amphiphilic polymers above their critical micellar concentration (CMC). They consist of a hydrophobic core that encapsulates poorly soluble drugs and a hydrophilic shell, typically made of PEG, which enhances stability, prolongs circulation, and reduces immune system clearance. PEGylation prevents aggregation and minimizes uptake by the reticuloendothelial system (RES), improving bioavailability. Polymeric micelles have been explored in drug delivery for cancer, HIV/AIDS, and ocular diseases. For example,

poloxamine micelles increased the solubility of efavirenz by 8,400 times and improved its bioavailability in pediatric formulations. However, challenges include premature disintegration in the bloodstream and low drug-loading capacity.

2.4 Polymeric Drug Conjugates

Polymeric drug conjugates are prodrugs in which drugs are chemically linked to hydrophilic polymers like polyethylene glycol (PEG) or poly(HPMA) to improve water solubility, bioavailability, and systemic circulation time. This strategy also protects drugs from degradation and enhances targeting while reducing immune responses. For example, conjugation of zidovudine with PHEA improved its stability, extended half-life, and allowed controlled release. However, challenges include regulatory hurdles due to altered pharmacokinetics, complex synthesis, heterogeneous structures, low drug loading, and concerns with polymer toxicity and biodegradability. These limitations complicate clinical translation, though some non-oral formulations have been approved.

3. Lipid Nanocarriers

Lipid nanocarriers have emerged as a promising drug delivery route to overcome the problems of other drug delivery systems e.g. polymeric nanocarriers. They are of special interest as carriers for hydrophobic drugs, with poor water solubility. They have the advantages of being low in toxicity as they are usually made of physiological lipids, highly compatible and offer improved bioavailability for encapsulated drugs. They also provide protection for the loaded drugs from the harsh conditions of the GIT, can be designed to produce controlled release formulations, they are usually less expensive than other drug delivery systems and easy to scale-up.

3.1 Lipid-based Nanocarriers Types

Lipid-based nanocarriers vary by structure and lipid type. **Liposomes** have aqueous cores surrounded by phospholipid bilayers, while **SLNs** contain solid lipid cores, **nanoemulsions (NEs)** have liquid lipid cores, and **nanostructured lipid carriers (NLCs)** combine both solid and liquid lipids. **Lipid-polymer hybrid nanoparticles (LPHNs)** consist of a polymeric core coated with phospholipids. Despite being lipid-based, these carriers differ in size, shape, and composition. Surfactants play a crucial role in stabilizing nanoparticles by reducing interfacial tension and preventing agglomeration. Proper surfactant type and concentration are essential; for instance, increasing polyvinyl alcohol (PVA) concentration may cause particle aggregation due to hydrogen bonding, while Tween 80 can reduce particle size by interacting

effectively with the lipid core. Thus, surfactant choice significantly influences nanoparticle properties like size, stability, and entrapment efficiency.

3.1.1. Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs), introduced in the 1990s, are colloidal carriers (50–1000 nm) composed of a solid lipid core stabilized by surfactants. Unlike emulsions and liposomes, SLNs use lipids that remain solid at room and body temperature, protecting drugs from degradation and enhancing the bioavailability of poorly soluble drugs like rizatriptan and darunavir. SLNs are biocompatible, biodegradable, and can be prepared without organic solvents using scalable methods like high-pressure homogenization. Their solid core reduces drug leakage compared to nanoemulsions and allows controlled or immediate drug release, depending on formulation. Common lipids used include glyceryl monostearate, stearic acid, and especially Compritol 888 ATO®, known for its high drug entrapment capacity due to its complex structure and long-chain fatty acid content. SLNs can be incorporated into tablets or capsules after drying. However, challenges like lipid crystallization can affect stability and cause drug expulsion during storage. This can be addressed by optimizing drug loading, which helps limit polymorphic transitions and improves long-term stability.

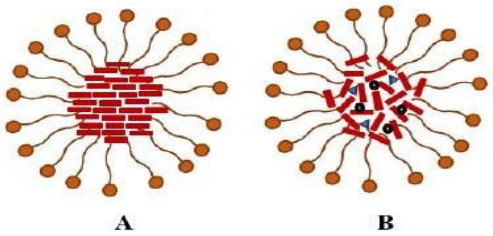


Figure 2: Diagram showing the structure of (A) Blank SLNs showing a core of perfect crystal structure. (B) Drug loaded SLNs showing cores with amorphous structure, where the drugs disrupted the crystal structure of the solid lipids.

Table 1: List of different solid lipids, surfactants, active ingredients, and methods of preparations of SLNs reported in the literature.

Solid Lipid	Surfactant	Active ingredient	Method of Preparation	Targeted disease	Reference
Glyceryl monostearate, Compritol 888 ATO® and Precirol ATO 5	Tween and Cremophor	Terbinafine	Microemulsi on technique	Fungal infection	1
Compritol 888 ATO®	Taurocholate sodium salt and Epikuron 200	Riluzole	Microemulsi on technique	Lateral sclerosis	1
Glyceryl monostearate,	Soya lecithin	Methotrexa te	Solvent diffusion	Lymphoma	2

Compritol 888 ATO®, stearic acid and tristearin					
Glyceryl monostearate, Compritol 888 ATO® and Precirol ATO 5	Span 80, Soya lecithin, poloxamer and Tween 80	Darunavir	High- pressure homogenisati on	HIV/AIDS	2
Palmitic acid and stearic acid	Poloxamer 407 and pluronic® F-127	Fenofibrate and nabumetone	Ultrasonicati on	Hypercholest er-olemia and rheumatoid arthritis	2
Tristearin	Phospholipon 80	Rizatriptan	Solvent injection	Migraine	2

3.1.2 Nanoemulsions (NEs)

Emulsions are mixtures of two immiscible liquids—typically oil and water—where one forms droplets (dispersed phase) within the other (continuous phase). They can be simple (O/W or W/O) or multiple (O/W/O, W/O/W). **Nanoemulsions (NEs)** are advanced emulsions with droplet sizes between 20–200 nm, offering greater surface area, enhanced stability, and better drug absorption. Due to their small size, NEs resist sedimentation and are non-toxic, making them suitable for oral and mucosal delivery. They are especially effective for delivering poorly water-soluble drugs like vitamin D, darunavir, and eugenol, improving solubility, bioavailability, and offering sustained release. Common preparation methods include high-pressure homogenization and spontaneous emulsification.

Table 2: List of different liquid lipids, surfactants, active ingredients, and methods of preparations of NEs reported in the literature.

Liquid Lipid	Surfactant/ Cosurfactant	Active ingredient	Method of Preparation	Targeted disease	Reference
Soybean oil	Egg lecithin and Tween 80	**Darunavir**	High pressure Homogenisation	HIV	3
Sunflower oil	Lecithin, pea proteins, sugar ester and a combination of Tween 20 and glycerol monooleate	**Carvacrol, limonene and cinnamaldehy de**	High pressure Homogenisation	Bacterial infection	4
MCT	Tween 20, 40, 60, 80 and 85/ sodium dodecyl sulphate	**Vitamin D**	Spontaneous emulsification	Vitamin D deficiency	4
MCT	Tween 20, 40, 60, 80, and 85	**Vitamin E acetate**	Spontaneous emulsification	Antioxidant for cardiac diseases	4
Soybean oil	Soybean lecithin, Tween 80 and poloxamer 407/ propylene glycol	**Camphor, menthol and methyl salicylate**	High pressure Homogenisation	Topical therapy of arthritis	4
MCT	Starch	**Eugenol**	High pressure Homogenisation / micro fluidization	Cancer and inflammatory diseases	4

Vegetable oils, rich in medium or long-chain triglycerides, are commonly used in pharmaceuticals due to their biodegradability, renewability, and safety. Oils like sunflower, castor, coconut, and soybean oil are often used in nanoemulsion (NE) formulations, with soybean oil and MCTs being the most preferred. However, their instability and sensitivity to pH and temperature, along with the need for high emulsifier concentrations and energy-intensive preparation methods, pose challenges. In HIV therapy, NEs have shown promise in enhancing the oral bioavailability of poorly soluble drugs. For instance, saquinavir-loaded NEs improved brain targeting and absorption, while atazanavir NEs increased oral bioavailability by 2.57 times compared to its aqueous form. Flaxseed oil-based NEs also significantly raised plasma and brain drug concentrations, demonstrating the potential of NEs in effective HIV drug delivery.

3.1.3 Nanostructured Lipid Carriers (NLCs)

These are second-generation lipid-based nanocarriers developed to overcome the limitations of Solid Lipid Nanoparticles (SLNs) and Nanoemulsions (NEs). They are formed by mixing liquid lipids with solid lipids, which disrupts the perfect crystal structure, improving stability. A study using Differential Scanning Calorimetry (DSC) showed that NLCs have reduced crystallinity and are more amorphous than SLNs. This structure allows for higher drug loading, especially for hydrophobic drugs, and provides better control over drug release, as the drug is encapsulated in oil compartments within the solid lipid matrix.

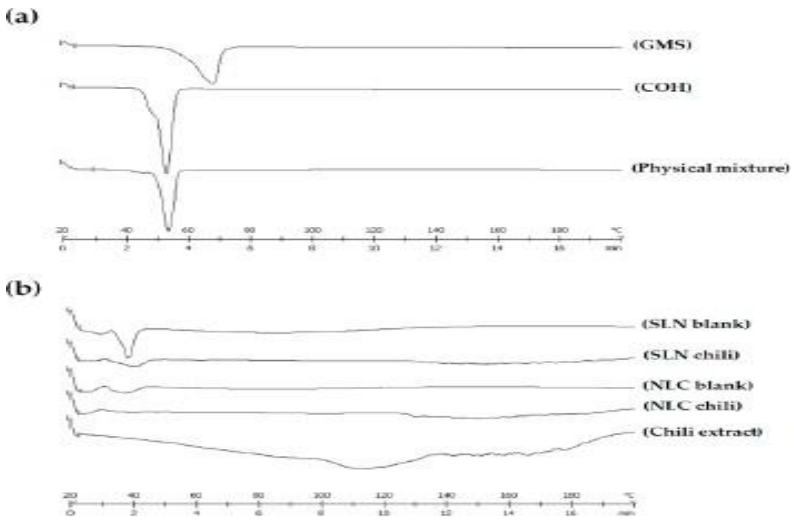


Figure 3: DSC thermograms of (a) the pure solid lipid and physical mixture, and (b) freeze- dried formulations. Abbreviations: SLN, solid lipid nanoparticles; NLC, nanostructured lipid carriers; GMS, glyceryl monostearate; COH, cetyl alcohol. This figure has been adopted from journal article by Anantaworasakul et al.

NLCs have been well reported in the literature in the treatment of many diseases like different types of cancer, high blood pressure, HIV/AIDS, see Table 3. For the synthesis methods, high pressure homogenisation and microemulsification are commonly used. Precirol ATO 5 and Compritol 888 ATO® are among commonly used solid lipids in the synthesis of NLCs, while oleic acid, MCT Campul are among the most used oils, see Table 3.

Table 3: List of different solid and liquid lipids, surfactants, active ingredients, and methods of preparations of NLCs reported in the literature.

Solid Lipid	Liquid lipid	Surfactant	Active ingredient	Method of Preparation	Targeted disease	Reference
Preciro l ATO 5	MCT and Captex 500	Pluronic® F-127 and sodium taurocholate	Bicalutamide	***Hot high-pressure homogenisation***	Prostate cancer	3
Stearic acid	Oleic acid	Poloxamer 188	Resveratrol	***Solvent injection***	Breast cancer	3
Cetyl palmitate	Isopropyl myristate, caprylic acid and oleic acid	Tween 80	Mefenamic acid	***Microemulsion template strategy***	Non- steroidal anti- inflammatory (NSAIDs)	4
Preciro l ATO 5	Capmul MCM EP	Solutol®HS- 15, Poloxamer-407 and Poloxamer-188	Olmesartan medoxomil	***Hot high-pressure homogenisation***	High blood pressure	4
Compri tol 888 ATO®	Oleic acid	Tween 80	Lopinavir	***Hot-meltmicroemulsification***	HIV	5

Like other lipid nanocarriers, NLCs have been reported in the literature for the targeting of HIV. Pokharkar*et al.* studied NLCs for the intranasal drug delivery of efavirenz (EFV) as a route for brain targeting. EFV-NLCs with a mean particle size of 162 nm and 95.7% entrapment efficiency was successfully synthesised. This optimised formulation showed a 95% drug release over 24 hours duration with 4.5% increase in the drug targeting potential to the CNS.150 Another study involved the oral absorption of RTV by loading into NLCs (RTV-NLCs), the NLCs were synthesised using emulsification probe sonication method using myristic acid, capmul MCM EP as lipids and poloxamer 188 as a surfactant. The produced NLCs showed high permeability during membrane studies.

3.2.4 Lipid Polymer Hybrid Nanoparticles (LPHNs)

These are core-shell particles made of a biodegradable polymer core and a lipid monolayer, often coated with lipid-PEG. The **polymer core** holds hydrophobic drugs, while the **lipid layer** (typically phospholipids) provides electrostatic stabilization and improves drug entrapment and oral bioavailability. Adding **lipid-PEG** improves particle stability in

electrolyte-rich environments like phosphate-buffered saline (PBS), preventing aggregation by steric stabilization. PEG also increases blood circulation time by avoiding rapid clearance by the RES system—important for injectable drugs. LPHNs combine the advantages of both lipid and polymer systems: **enhanced cellular uptake, high stability, controlled drug release**, and **structural integrity**. They are promising for targeting hard-to-reach areas, such as HIV reservoirs in the lymphatic system. Common materials include **PLGA** and **soybean lecithin**. (see Table 4)

Table 4: List of different polymers, phospholipids, surfactants, active ingredients, and methods of preparations of LPHNs reported in the literature.

Polymer	Lipid	Bulk stabiliser	Active ingredient	Method of Preparation	Targeted disease	Reference
PLGA	DSPE-PEG2000-NH2	Lutrol® F 127	Docetaxel	Self-assembled nano precipitation	Breast cancer	106
PLGA	Phosphatidyl-choline	d-α-tocopheryl polyethylene glycol 1000 succinate	Levofloxacin, ciprofloxacin, and ofloxacin	Modified emulsification solvent- evaporation	Lung biofilm infection therapy	107
PCL	Soybean lecithin	Polyvinyl alcohol	Itraconazole	Emulsification solvent evaporation method	Fungal infection	108
PLGA	Soybean lecithin	DSPE-PEG	Anti-carcinoembryo nic antigen (CEA) half antibody	Self-assembled nanoprecipitatio n	Pancreatic cancer	109
Chitosan	Glyceryl monooleate	Pluronic F127	Enoxaparin	Modified self-assembled nanoprecipitatio n	Deep vein thrombosis, and pulmonary embolism	110
PLGA	Soya phosphatidylch oline	DSPE-PEG	Gemcitabine hydrochloride	Modified double emulsion solvent evaporation	Various cancer types	111
PLGA	Cationic lipid dioleyltrimethy lammonium propane	Polyvinyl alcohol	Budesonide	Double emulsion solvent evaporation	Chronic obstructive pulmonary disease	112

The core-shell structure of LPHNs can be confirmed using TEM analysis with uranyl acetate staining, which highlights the lecithin shell as dark rings around the polymer core. The size of LPHNs is influenced by several factors, particularly the lipid-to-polymer weight ratio. According to Zhang et al., the optimal ratio is 10–20% w/w; exceeding this leads to the formation of larger liposomes due to excess lipid, while lower ratios result in insufficient coating and particle aggregation. Another factor affecting size is the viscosity of the polymer,

which relates to its molecular weight. High molecular weight polymers create more compact nuclei, resulting in smaller nanoparticles.

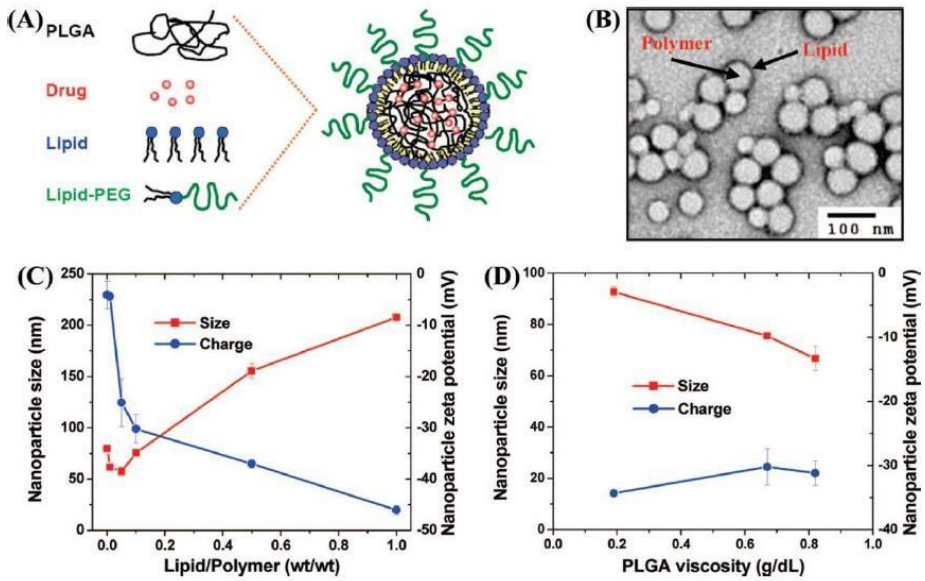


Figure 4: Development of LPHNs (A) Schematic illustration shows the formulation of LPHNs. The LPHNs comprise a hydrophobic PLGA core, a hydrophilic PEG shell, and a lipid (lecithin) monolayer at the interface of the hydrophobic core and the hydrophilic shell.

(B) TEM image demonstrated the structure of the LPHNs proposed in (A). Uranyl acetate was used to stain lipids to enhance their electron contrast. (C) Effect of lipid/polymer weight ratio on LPHNs size and surface zeta potential. (D) Effect of PLGA polymer molecular weight indicated as inherent viscosity on LPHNs size and surface zeta potential. The figure was adopted from a study by Zhang et al.

4. Methods of Preparation of Lipid-Based Nanoparticles

Most lipid-based nanocarriers are prepared using traditional nanoparticle techniques such as high-pressure homogenization, emulsification/solvent evaporation, microemulsion, double emulsion, and solvent injection methods. However, **Lipid–Polymer Hybrid Nanoparticles (LPHNs)** are unique in that they follow two main preparation routes: the **two-step** and **one-step** methods. In the **two-step method**, polymeric nanoparticles and lipid vesicles are prepared separately and then combined. This can occur through **electrostatic adsorption** of lipids onto the polymer core (conventional) or by **spray drying** a mixture of polymer particles and lipid solution (non-conventional). In contrast, the **one-step method** allows simultaneous formation of the polymer core and lipid shell in a single process.

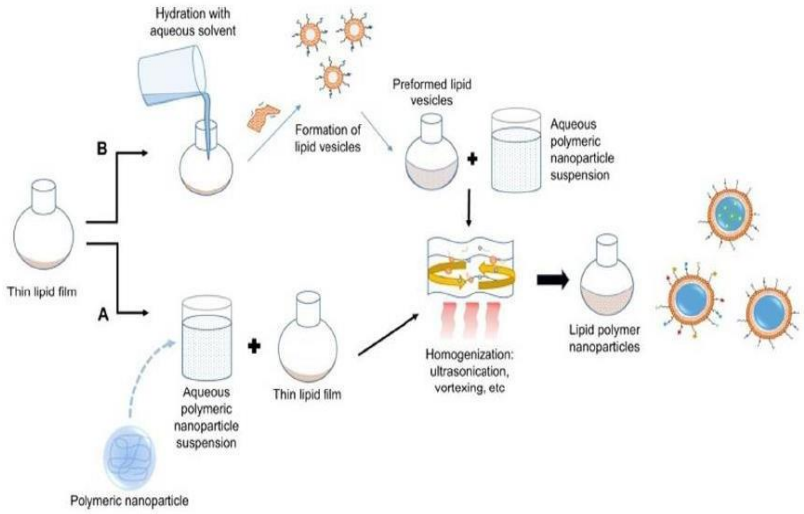


Figure 5 Different approaches to prepare LPHNs through the two-step method. In the method (A) an aqueous suspension of polymeric nanoparticles is added to the pre-formed thin lipidic film. On the other hand, in the method (B), pre-formed lipid vesicles are added to the polymeric nanoparticles. Figure was adopted from a review article by Soares et al, (117)

4.1 High Pressure Homogenisation Method

In both hot and cold homogenization, the drug is first dissolved or dispersed in melted lipid. In the **hot method**, this mixture is added to a hot surfactant solution to form a coarse pre-emulsion, which is then processed using high-pressure homogenization at elevated temperatures. The resulting nanoemulsion is cooled to solidify. In the **cold method**, the lipid–drug mixture is first solidified using liquid nitrogen, ground into a fine powder (50– 100 μm), and then dispersed in a surfactant solution and homogenized at room temperature. While this method is more scalable, both approaches require high energy input. The hot method may cause **drug degradation** and **drug loss to the aqueous phase**, whereas the cold method often results in **larger particles** with **broad size distribution**.

4.2 Solvent Injection/Nanoprecipitation Method

The **solvent injection method**, introduced by Schubert et al. in 2003, involves dissolving lipids and hydrophobic drugs in a water-miscible organic solvent (e.g., ethanol, methanol, acetone). This organic phase is injected into a surfactant-containing aqueous solution under stirring. As the solvent diffuses into the aqueous phase, it causes **supersaturation**, leading to **lipid/drug precipitation** and **nanoparticle formation**. The process includes five key steps: injection, supersaturation, nucleation, particle growth, and stabilization. Proper surfactant levels are essential to prevent **coagulation**, as they stabilize the newly formed nanoparticles.

Without surfactant, particles tend to aggregate. In systems like SLNs and NLCs, local supersaturation within shrinking droplets triggers **nucleation**, followed by particle growth as solutes deposit onto the nuclei until equilibrium is restored.

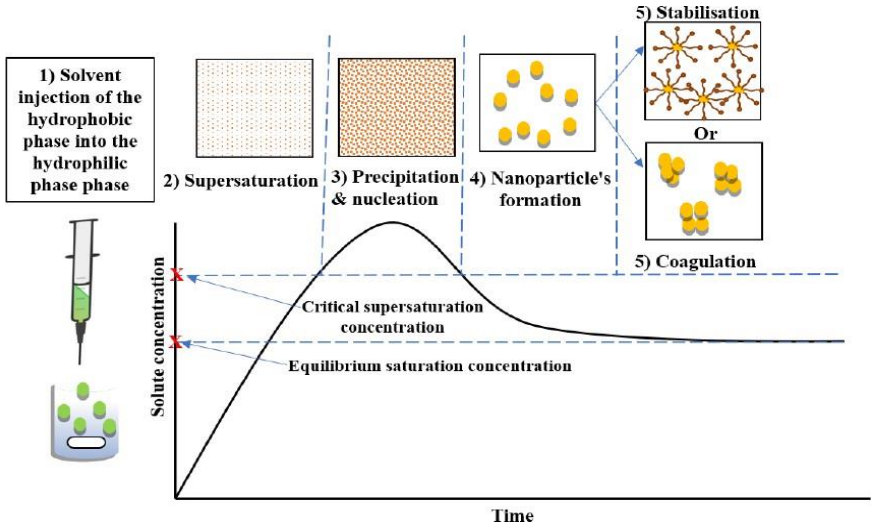


Figure 6: Schematic representation of the different steps of nanoprecipitation by solvent injection. These steps are: 1) injection of the hydrophobic phase into the aqueous phase, 2) supersaturation as the concentration of the lipid increase above the saturation concentration, 3) precipitation and nucleation as the concentration of the lipid increases beyond the critical supersaturation concentration, 4) growth and nanoparticles formation as the concentration of the lipid in the bulk solution decreases below the critical supersaturation concentration and 5) stabilisation in the presence of a surfactant with appropriate concentration, or coagulation in case of the absence of the surfactant.

The **solvent injection method** is a simple, fast, and low-cost technique used for preparing various lipid-based nanoformulations. In this method, lipids and drugs are dissolved in a water-miscible organic solvent (e.g., acetone, ethanol) and injected into a stirred aqueous surfactant solution, leading to nanoparticle formation. Dong et al. used this method to synthesize SLNs loaded with fenofibrate, achieving particle sizes below 200 nm. Hu et al. showed that incorporating oleic acid into NLCs enhanced drug loading and reduced particle size compared to SLNs, due to reduced crystallinity. For nano emulsions (NEs), solvent injection causes spontaneous emulsification as oil supersaturates in the aqueous phase, forming fine droplets. One study prepared carbamazepine-loaded NEs with a 150 nm size and 95% drug encapsulation using castor oil, acetone–ethanol, and polysorbate 80. The mechanism for forming **LPHNs** differs slightly—polymer and drug dissolved in an organic solvent are injected into a heated aqueous phase containing phospholipids and surfactants.

Phospholipids then coat the polymer nanoparticles without forming vesicles, aided by the elevated temperature. Compared to other methods, solvent injection offers several advantages: it's rapid, requires no complex equipment or high pressure, and is suitable for both lipid and polymeric nanocarrier systems.

4.2.1 Challenges of the Solvent Injection Technique

Although **solvent injection** is generally viewed as a simpler and milder alternative to high-energy methods like high-pressure homogenization, some reported procedures involve multiple steps that make the process more complex. For instance, additional steps such as **pre-emulsion formation**, **acid addition**, or **post-injection homogenization** are sometimes required. Jain et al. described a solvent diffusion method for NLCs involving several steps—mixing lipids in acetone, injecting into a heated aqueous phase, long stirring, pH adjustment with hydrochloric acid, and repeated centrifugation. Such multi-step protocols introduce more variables, making the process time-consuming and harder to reproduce. Similarly, **NEs** made by solvent injection often require both **lipophilic and hydrophilic emulsifiers**, and sometimes **glycerol** to adjust isotonicity. Therefore, simplifying the solvent injection process—by reducing steps and limiting surfactant use— would be a significant advantage for scalable and consistent nanoparticle production.

5. Spray Drying

Spray drying is a widely used drying technique in the food and pharmaceutical industries, where a liquid feed is atomized through a nozzle under pressure to form fine droplets, and the solvent is quickly evaporated using hot gas. Compared to **freeze drying**, spray drying is **faster, simpler, more cost-effective**, and suitable for **large-scale production**. However, in **lab-scale applications**, it often results in **low product yield** due to losses on the chamber walls. Additionally, spray drying tends to produce particles with a **larger average size** and **broader size distribution** than freeze-drying, as nano-size formation depends heavily on atomization forces.

6. Freeze-Drying

Freeze-drying (lyophilisation), introduced in the 1940s, is widely used to stabilize pharmaceutical products, including lipid-based nanocarriers. It improves the stability of nanoparticle dispersions by preventing hydrolysis, Ostwald ripening, and settling, and enables their incorporation into tablets or capsules. Unlike spray drying, freeze-drying can produce **smaller particles**, allows **drying in the final container**, and minimizes

contamination and product loss, making it more suitable for **lab-scale** and **sterile product** preparation. The process is based on **sublimation**, where water transitions directly from ice to vapor under **vacuum and low temperature**, bypassing the liquid phase. This occurs below the triple point of water (0.001 °C and 0.006 atm), resulting in a dry, stable product.

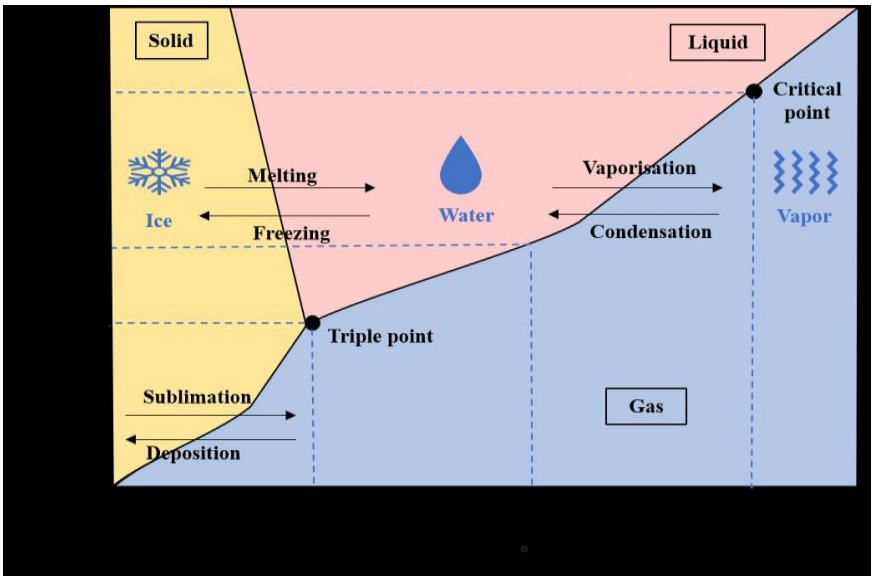


Figure 7: Typical phase diagram of water under pressure. Water present in three different states: 1) solid in the form of ice crystals, 2) liquid in the form of water droplets and 3) gas in the form of water vapor. For successful freeze drying, sublimation of water from the solid state directly to the gaseous state without converting to the liquid state is essential. The sublimation takes place at pressure and temperature below the triple point (i.e., 0.001 °C and 0.006 atmospheres).

The freeze-drying process includes **freezing**, **primary drying (sublimation)**, and **secondary drying (desorption)**. **Freezing** is the most critical step, where ice crystals form and separate from a concentrated phase containing nanoparticles, drug, and additives. **Fast freezing** (e.g., with liquid nitrogen) produces smaller ice crystals, helping maintain **nanoparticle size and structure**. In **primary drying**, heat causes ice to sublimate, leaving a porous matrix. **Secondary drying** removes bound water. Since nanoparticles are delicate, **cryoprotectants** like sugars and polymers (e.g., sucrose, trehalose, mannitol) are used to prevent aggregation by forming protective layers, creating glassy matrices, and isolating particles. Maintaining temperatures **below the glass** aggregation.

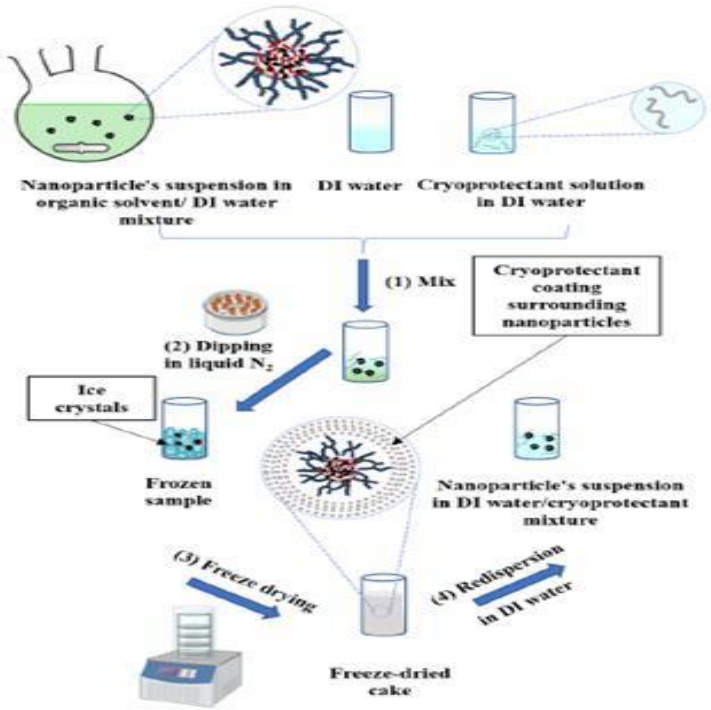


Figure 8: Schematic illustration of the freeze-drying steps of nanoparticles suspension using cryoprotectants. These steps are: 1) mixing of the nanoparticle's suspension, DI water and cryoprotectant solution in a single vial, 2) freezing of the samples by dipping in liquid nitrogen, 3) placing the frozen samples in the freeze dryer for few days until the complete removal of the water and/or organic solvent and 4) redispersion of the freeze-dried powdered material in DI water prior to administration using manual shaking or a vortex.

7. Literature Review

Solid Lipid Nanoparticles (SLNs) are submicron-sized carriers (50–1000 nm) made from physiological lipids that remain solid at room temperature, enabling controlled drug release by reducing drug mobility. Drug release from SLNs is influenced by particle size and the interaction between the drug and lipid matrix. Generally, SLNs show a burst release, which can be minimized by increasing particle size or using different lipids. For instance, prednisolone-loaded SLNs provided prolonged release compared to tetracaine and etomidate due to lipid matrix differences. Chen et al. showed pH-sensitive SLNs released doxorubicin faster at pH 4.7 due to weakened electrostatic interactions. Lipase activity on SLNs can be controlled using PEGylation to improve stability. Drugs with high lipophilicity (Log P > 5), low water solubility, and good oil solubility are ideal for SLNs, as they promote lymphatic transport and bypass first-pass metabolism, improving bioavailability.

8. AIM AND OBJECTIVE

Trandolapril solid lipid nanoparticles (SLNs) are formulated by encapsulating the drug within a lipid matrix, which can be adapted into tablet dosage forms for controlled drug release. This study focuses on developing Trandolapril SLNs using appropriate lipids and surfactants and comparing their dissolution profile with a conventional immediate-release tablet to evaluate improvements in drug release and bioavailability for hypertension management.

9. Plan of Work

9.1 Design of Experiments

9.2 Many studies have shown that the **liquisolid compact (LSC) technique** is effective in enhancing the dissolution rate of poorly water-soluble drugs. Introduced by Spiras in 2002, this method involves converting liquid drugs into free-flowing, compressible powders using carrier and coating materials. Lipophilic drugs can be formulated into LSCs without structural modification. **Solubility studies** were conducted in various pH media (0.1N HCl, pH 4.5, pH 6.8, and pH 7.4 buffers) and solvents (Polysorbate 80, Labrafil, PEG-400). Drug-solvent mixtures were shaken for 10 hours at 25°C, filtered, and analyzed via UV-Vis spectrophotometry to determine drug solubility. For formulation trials, **Compritol 888 ATO** was selected as the lipid carrier, and excipients were chosen based on literature support. A **three-trial factorial design** was planned by varying Compritol concentrations at 5% (Trial I), 10% (Trial II), and 15% (Trial III), keeping other excipient levels constant. (Table 5).

Table 5: Qualitative and Quantitative Formula.

Ingredients	Quantity	Use
Trandalopril	2 mg	API
Tween 80	2 mg	Surfactant
PEG 400	8 mg	Co-Surfactant
Compritol 888 ATO	23 mg	Surface active agent
MCC pH 102	29.62 mg	Diluent
Croscarmellose Sodium	6.9 mg	Disintegrant
Neusilin	150 mg	Stabiliser, Dissolution Enhanser
Colloidal Silicon Dioxide	0.58 mg	Glident
Povidone K30	6.9 mg	Binder
Ferric Oxide Yellow (L)	1 mg	Colorant

Table 5a: Design of Experiments with Factorial variations in using Compritol 888 ATO (The tablet weight is retained at 250 mg by adjusting the MCC quantity).

Trial No.	Trandolapril +surfactant+PEG400 Quantity (mg)	Compritol 888 (mg)	Factorial Level	MCC (Avicel pH 102) (mg)	CCS (mg)	Neusilin (mg)	Aerosil (mg)	PVP K30 (mg)	Ferric Oxide Yellow(mg)	Tablet weight (mg)
T1	12	11.5	-1	41.12	6.9	150	0.58	6.9	1	230
T2	12	23	0	29.62	6.9	150	0.58	6.9	1	230
T3	12	34.5	+1	18.12	6.9	150	0.58	6.9	1	230

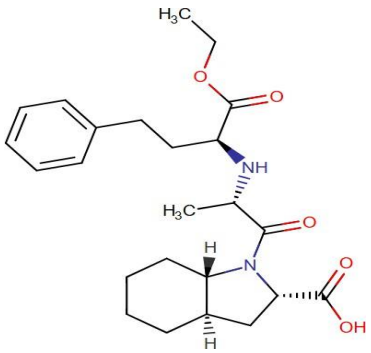
10. MATERIALS AND METHOD

10.1 Materials

Trandolapril (active pharmaceutical ingredient)Trandolapril sample is obtained as a gift from Hetero Drugs Ltd., Hyderabad, India. Avicel pH 102, Colloidal Silicon dioxide, PEG- 400, Neusilin, croscarmellose sodium, Povidone (PVP K30) received as a gift sample from Sai Mirra Innopharm Pvt. Ltd., Chennai, India. The following are the materials used for their functionality in the formulation design.

- Compritol® 888 ATO-is a glyceryl behenate, which is a solid lipid with excellent emulsifying properties. (It has been widely used in the formulation of SLNs due to its biocompatibility, stability, and ability to encapsulate hydrophobic drugs).
- Surfactant (e.g., Polysorbate 80, Tween 80)
- Co-surfactant (e.g., PEG400)
- Organic solvent (e.g., ethanol)
- Purified water

10.2 Trandolapril- (Active Pharmaceutical Ingredient)



(2*S*,3*aR*,7*aS*)-1-[(2*S*)-2-[[(2)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-2,3,3*a*,4,5,6,7,7*a*-octahydroindole-2-carboxylic acid.

Figure 9: Trandolapril Structure.

Trandolapril is a prodrug ACE inhibitor used to treat **hypertension**, **congestive heart failure**, and to improve survival after **myocardial infarction**. It belongs to the **dipeptide** class and is a **non-sulfhydryl** compound. In the **liver**, it is converted to its active form, **trandolaprilat**, which inhibits **angiotensin-converting enzyme (ACE)**—blocking the conversion of **angiotensin I to angiotensin II**, a key regulator of blood pressure in the **renin-angiotensin-aldosterone system (RAAS)**. Trandolapril also helps slow **kidney disease progression** in hypertensive diabetic patients with **microalbuminuria** or **nephropathy**.

10.2.1 Mechanism of Action

Trandolapril acts on **two isoforms of ACE**: the **somatic form**, a 1277-amino-acid glycoprotein with **N- and C-domains**, and the **testicular form**, which is smaller and involved in **sperm maturation**. The **C-domain** regulates **blood pressure**, while the **N-domain** supports **hematopoietic stem cell differentiation**. **Trandolaprilat**, the active metabolite, inhibits both domains—preferentially the C-domain—by blocking the conversion of **angiotensin I to II**, thereby reducing blood pressure and increasing **plasma renin activity** due to disrupted negative feedback. **Absorption** is about **40–60%**, but due to first-pass metabolism, **bioavailability** is low (4–14%). After **oral administration**, ~33% is excreted in urine (mainly as trandolaprilat) and ~66% in feces. **Half-lives** are ~6 hours for trandolapril and ~10 hours for trandolaprilat, with an **effective elimination half-life** of 16– 24 hours due to binding with tissue ACE. **Toxicity** from overdose typically leads to **severe hypotension**, with common side effects including **cough, headache, and dizziness**. In animal studies, the **oral LD50** ranged from **3990–4875 mg/kg in mice**, **5000 mg/kg in rats**, and **1000 mg/kg in dogs**, with low or no observed mortality.

10.2.2 FTIR Characterisation of Trandolapril API

IR Spectroscopy detects frequencies of infrared light that are absorbed by a molecule. Molecules tend to absorb these specific frequencies of light since they correspond to the frequency of the vibration of bonds in the molecule. Most of the bands that indicate what functional group is present are found in the region from 4000 cm-1 to 1300 cm-1. Their bands can be identified and used to determine the functional group of an unknown compound. Solid samples are prepared by crushing the sample with a mulling agent which has an oily texture. A thin layer of this mull is applied on a KBr salt plate to be measured.

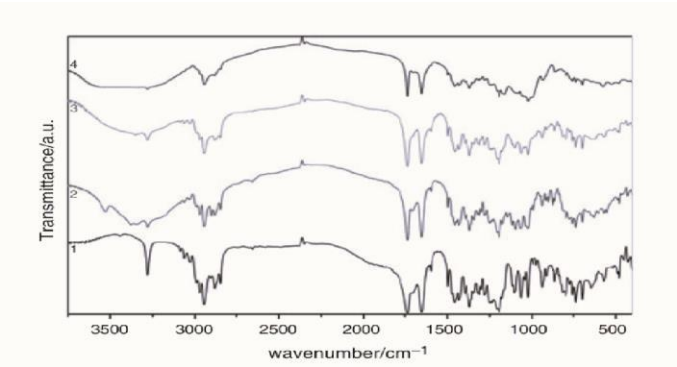


Figure 10: FTIR spectrum of Trandolapril with inactive ingredients used in formulation.

Trandolapril with SLN conjugate is subjected to FTIR as such (1) and in combination with MCC (2), Nusilin (3), Croscarmellose sodium (4).

Trandolapril SLN Conjugate is subjected to 1:1 mixture of the major ingredients used in tablet formulation to check the compatibility of the inactives with the active drug. The thermograph shows no variation in the main thermograms characteristic for trandolapril between 1000 to 2000 wave number. The typical waves of Trandolapril is not obscured by the presence of excipient as evidenced in the IR spectras.

10.2.3 Differential Scanning Calorimetric Study

In DSC study, energy is given to a sample cell and a reference cell. Temperatures of both cells are raised simultaneously over time. The difference in the input energy required to match the temperature of the sample for an endothermic or exothermic reaction is identified. Normally the sample API (Trandolapril) with excipient individually are compared for any thermal interactions by keeping in aluminium pan and temperature is raised gradually (with a ramp of 20˚ C)

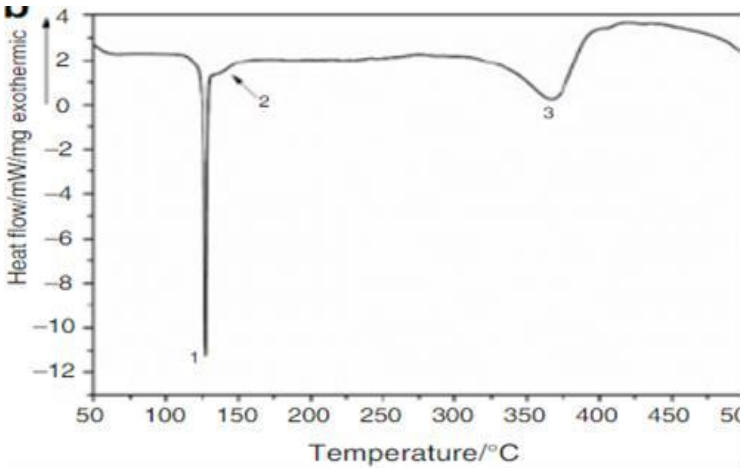


Figure 11: DSC Thermogram of Trandolapril.

In Figure 11, the DSC curve of trandolapril is obtained. It was found that trandolapril is stable until the onset of its melting when a cyclization phenomenon occurs, resulting in a small mass reduction. The main degradation step, occurs between 215 and 400 °C.

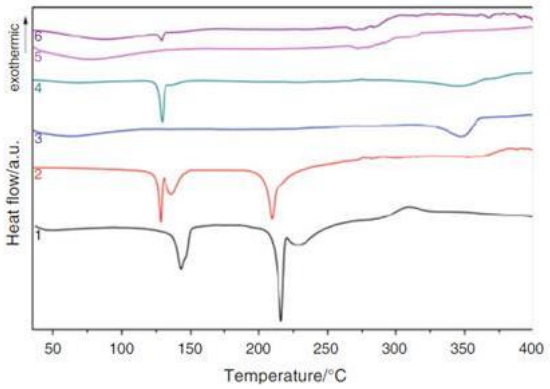


Figure 12: The DSC thermogram of Trandolapril (1),Tradolapril with MCC (2), PVP k30 (3), Nucilin (4),Croscarmellose sodium (5), PEG 400 (6).

11. Evaluation of Trandolapril-loaded solid lipid nanoparticles

11.1 Entrapment Efficiency

Entrapment efficiency is an important parameter for characterizing solid lipid nanoparticles. In order to attain optimal encapsulation efficiency, several factors were varied, including the type and concentration of the lipid and surfactant material used. The entrapment efficiency of SLN dispersion was determined by the centrifugation method. SLN dispersion (containing an equivalent to 5 mg of drug) was centrifuged at 15000 rpm for one hour in a refrigerated centrifuge to collect the supernatant liquid. The collected liquid was filtered to measure the free drug concentration after suitable dilution with a fresh phosphate buffer pH 8.4. The absorbance was measured at 220 nm in a UV spectrophotometer to calculate the entrapment efficiency using the following formula:

Entrapment efficiency = Wt. of drug incorporated/Wt. of drug initially taken × 100

The entrapment efficiency of the SLN dispersions was found to be 81.36%.

11.2 Bulk Density and Tapped Density

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the inter-particulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in grams per mL (g/mL). The tapped density is an increased bulk density attained after mechanically tapping a container

containing the powder sample. The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample. After observing the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped, and volume or mass readings are taken until little further volume or mass change is observed. The mechanical tapping is achieved by raising the cylinder or vessel and allowing it to drop, under its own mass, a specified distance by either of 3 methods as described below. Devices that rotate the cylinder orvessel during tapping may be preferred to minimize any possible separation of the mass during tapping down.

Hausner ratio is a number that is correlated to the flowability of a powder or granular material.

The Hausner ratio is calculated by the formula

$$H = \frac{\rho_T}{\rho_B}$$

Where PBis bulk density of the powder, and □T is the tapped bulk density of the powder.

The **Hausner ratio** is used to evaluate the **flowability of powders**, with values above **1.25–1.4** indicating **poor flow**. It is related to the **Carr index**, another flowability measure, through a mathematical formula. The **angle of repose**—another indicator of flow—is measured using the **fixed cone method**, where powder is poured through a funnel to form a cone, gradually raising the funnel to reduce particle impact. The **angle** is calculated by taking the **inverse tangent** of the ratio of the cone's height to **half its base width**. This angle helps in designing granules with suitable flow properties. **Smooth granules** have low friction and a **low angle of repose**, while **rough or sticky granules** have higher friction and a **higher angle**, indicating poorer flow.

Table 6: The bulk and tapped densities of the granules used for compression of tablets are done (Single determination) using tap density apparatus USP.

Trial	Bulk Density	Tap Density	Hausner's Ratio	Carr's Index	Angle of Repose
T1	0.431	0.491	1.14	12.4	31
T2	0.428	0.477	1.11	10.25	26.3
T3	0.429	0.49	1.14	12.45	31.11

11.3 Dissolution Study

Dissolution testing measures the extent and rate of solution formation from a dosage form, such as tablet, capsule, ointment, etc. The dissolution of a drug is important for its bioavailability and therapeutic effectiveness. The three trials and the market sample are subjected to release studies using USP Type I dissolution apparatus at 75 rpm with a constant temperature at 37°C ± 0.5°C. Dissolution medium used was pH 6.8 phosphate buffer (900 mL). The samples were withdrawn (5 mL) at different time interval namely 10 minutes, 30 minutes and 45 minutes. After filtration through 0.22 µ filter, the concentration of Trandolapril was determined UV spectrophotometrically at 220 nm.The comparative dissolution profile was done with a market sample Trandolapril 2 mg Tablets (Generic) manufactured by Aurobindo Pharma(USA).

Table 8: Comparative Dissolution Profile of Trials of Trandolapril Tablets with Market Sample.

Sample Details	Time (minutes) Average of six determinations rounded off to whole value		
	10	30	45
Trial I	65	87	98
Trial II	68	88	97
Trial III	72	91	99
Market sample	62	83	93

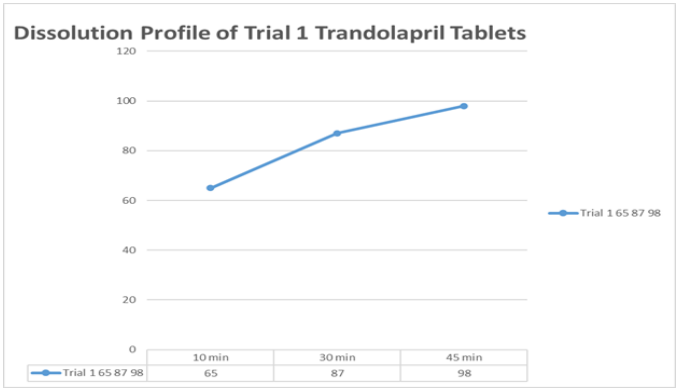
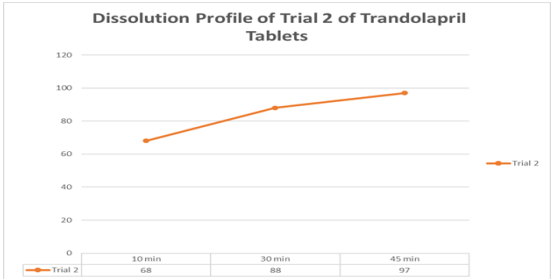


Figure: 13



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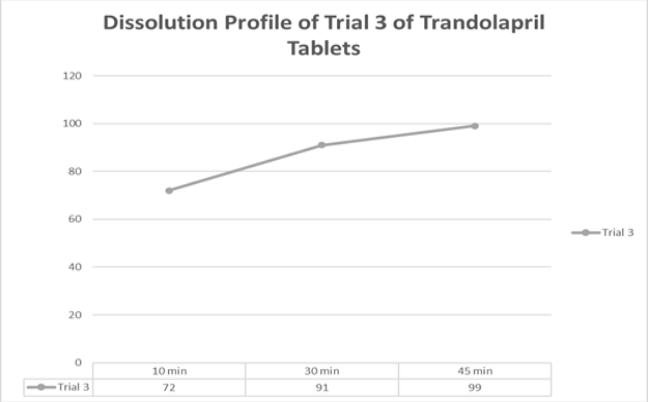

Figure: 15.

12. Estimation of Trandalopril Tablets

12.1 ASSAY

12.1.1 Chromatographic conditions: The analysis of the drug was carried using a Waters HPLC system equipped with a reverse phase C18 column quaternary pump, and a UV absorbance detector and running on Waters Empower software (FR2). a 20 µl injection loop is used for sample and standard injection.

12.1.2 Chemicals and Solvents: Solvents like HPLC grade water and acetonitrile (Rankem) used. Potassium dihydrogen phosphate and orthophosphoric acid were obtained from Rankem.

12.1.3 Preparation of phosphate buffer: Seven grams of Potassium di hydrogen Phsphate was weighed, dissolved and diluted to 1000 mL with HPLC water. 2 mL of Triethylamine was added and pH adjusted to 3.0 with orthophosporic acid.

12.1.4 Preparation of mobile phase and diluents 300 mL of the phosphate buffer was mixed with 700 mL of acetonitrile. The solution was degassed in an ultrasonic water bath for 5 minutes and filtered through 0.45µ filter under vacuum.

12.1.5 Chromatographic conditions

Mobile phase consist Conditions of Acetonitrile Phosphate buffer in the ratio of 70:30 at a flow rate of 08 mL/min and pH of buffer was adjusted to 3.0 UV detection was performed at 225nm. The mobile phase was degassed by an ultrasonic water bath for 5 min. Filter through 0.45µ filter under vacuum filtration. The column was equilibrated for at least 30 min with the mobile phase flowing through the system.

13. Preparation of the Trandalopril Standard & Sample Solution

13.1. Standard Solution Preparation

Weigh and transfer 10mg of Trandalopril Working standard into a 10 mL volumetric flask add about 7 mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.4 mL of the above stock solution into a 10mL volumetric flask and dilute up to the mark with diluent. Mix well and filter through 0.45µm filter.

13.2. Sample Solution Preparation

For assay, five Trandolapril tablets were weighed to determine the **average tablet weight**. A sample equivalent to **10 mg of Trandolapril** was accurately weighed and transferred into a **10 mL volumetric flask**, dissolved in **7 mL of diluent**, sonicated, and diluted to volume. After filtration through a **0.45 µm filter**, **0.4 mL** of this stock was further diluted to **10 mL** and filtered again. Similarly, for the **three trial batches**, powdered samples equivalent to 10 mg of Trandolapril were dissolved in a **40:60 v/v mixture of phosphate buffer and acetonitrile**, sonicated for 15 minutes, diluted, shaken for another 15 minutes, and filtered. Six replicate injections of the standard solution were made to ensure **system suitability**, with **tailing/fronting ≤ 2%** and **RSD ≤ 2%**. The average **peak area** from chromatograms was used to calculate drug content. Assay results for **Trial I, II, and III** were **99.76%, 99.65%, and 99.17%**, respectively. The **main peak retention time** was approximately **2.69 minutes**.

Figure: 16 Standard Peak of Trandolapril

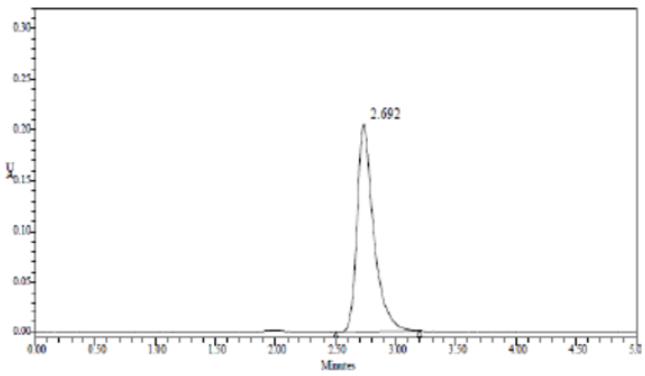

Figure 17: Sample Peak of Trandolapril for trial I. No difference in RT and peak shape was observed for the other Trials.

14. Stability Studies

Stability studies are performed for the formulated Trials for accelerated condition as per ICH guideline 40°C ± 2°C / 75 ± 5 %RH (relative humidity) at interval of 1 month to 3 months

period. The samples are withdrawn at 30, 60, 90 days and analyzed for drug content, *in vitro* release studies were performed. The results were meeting the predetermined specification.

15. RESULTS AND DISCUSSION

From the FTIR data, the thermograph shows no variation in the main thermograms characteristic for trandolapril between 1000 to 2000 wave number. The typical waves of Trandolapril is not obscured by the presence of excipient as evidenced in the IR spectras.

The DSC thermograms indicates (Figure 12) the drug excipient compatibility nature. The thermograph is distorted and the main peak is not visible when using the polymers like PVP K30, PEG 400, etc. which is a normal phenomenon observed during the interaction studies. The drug nature as such is not affected when the polymer interaction happens. This is supported by the thermograms obtained by the interaction of the active with the inactive ingredients during the FTIR studies mentioned earlier in this work. The f2 similarity factor calculated for the Market Sample values against the three trials.

The **f2 value**, also known as the similarity factor, is used to compare the dissolution profiles of two formulations, typically a test (generic) and a reference product. It is calculated using the following formula:

$$f_2 = 50 \times \log\left(\left\{1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right\}^{-0.5} \times 100\right)$$

Where:

- $\mathbf{f_2}$: Similarity factor (ranges from 50 to 100; higher values indicate more similarity)
- **n**: Number of time points
- **R□**: Percent drug dissolved from the reference product at time **t**
- **T□**: Percent drug dissolved from the test product at time **t**

Conditions for Calculation

1. **Time Points**: At least 3-4 sampling points are recommended (excluding the 0-time point).
2. **Dissolution Percentages**: The % drug dissolved should not exceed 85% for the data used.
3. **Standard Deviation**: The coefficient of variation (CV) should be low (less than 20% at early points and less than 10% at other points).
4. **Result Interpretation**: An **f2 value between 50 and 100** suggests that the dissolution profiles are similar.

Computing the f2 for each trial (T1, T2, T3) against the updated Market Sample.

The calculated f2f similarity factors for the trials compared to the updated Market Sample are:

- Trial I vs Market Sample: f2=68.82
- Trial II vs Market Sample: f2=64.35
- Trial III vs Market Sample: f2=54.24

Since all f2 values are above 50, the dissolution profiles of all trials (T1, T2, and T3) are similar to the Market Sample. The f2 was higher for Trial Formulations containing lesser Compritol. This enhancement could be attributed to the improved dispersibility and surface area provided by Compritol 888 whenin low concentration, facilitating the release of trandolapril. The tablet physical evaluation parameters like thickness, hardness and the inprocess parameters showed a consistency across the trials which indicated a feasibility for the manufacture of the process.

16. SUMMARY AND CONCLUSION

The study aimed to develop and evaluate compressed tablets containing **Trandolapril solid lipid nanoparticles (SLNs)** and compare their **dissolution profile** with a marketed product. Three formulations were prepared using varying concentrations of **Compritol 888** (5%, 10%, 15%) to assess its effect on drug release. Granule properties such as **bulk density**, **tap density**, **Hausner ratio**, and **Carr's index** were measured, confirming good **flowability** and **compressibility** suitable for tablet production. Formulations with **lower Compritol 888 content** showed **enhanced dissolution rates**. **DSC and FTIR studies** confirmed the compatibility of active and inactive ingredients, while **HPLC assay** results across all batches remained consistent with the expected values. In conclusion, Trandolapril SLNs in tablet form—especially with lower lipid content—demonstrated **improved dissolution**, good manufacturing properties, and potential for **scaling up**, making it a promising approach to enhance Trandolapril's **therapeutic efficacy**. Further research is recommended to optimize formulation and evaluate long-term **stability** and **pharmacokinetics**.

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