Research Article
CODEN (USA): IJPLCP

ISSN: 0976-7126
Singh *et al.*, 16(6):8-14, 2025

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

Design and Development of a Colloidal Drug Delivery System for IV Formulation of Clopidogrel

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Article info

Received: 18/03/2025

Revised: 27/04/2025

Accepted: 10/05/2025

www.ijplsjournal.com

Abstract

The development of intravenous (IV) formulations for low water-solubility drugs is among the high-priority challenges in pharmaceutical research. Low aqueous solubility defines Clopidogrel, an extensively used antiplatelet medication, limiting its use to acute cardiovascular conditions where the imperative need is instantaneous drug activity. This research is focused on the design and development of a colloidal drug delivery system for the IV formulation of Clopidogrel to enhance its solubility, bioavailability, and therapeutic action. Various formulation strategies such as liposomes, nano-emulsions, and polymeric nanoparticles were researched to enhance drug loading, stability, and sustained release. The engineered formulation was investigated extensively with particle size, zeta potential, drug release, and encapsulation efficiency for assessing stability and performance. Furthermore, preclinical model pharmacokinetic and pharmacodynamic analysis showed improved drug absorption, extended circulation time, and augmented antiplatelet activity compared to oral Clopidogrel formulations in general. The developed nano-based IV exhibited great potential towards the solution of bioavailability issues of Clopidogrel.

Keywords: Collodial, Clopidogrel, IV

Introduction

Poorly soluble drugs pose a major challenge to the formulation scientists in order to increase the bioavailability and develop an intravenous dosage form to get rapid onset of action in cardiovascular emergency. Clopidogrel is poorly soluble drug available as oral formulation, has limitation to use in acute emergency care setting, the challenges associated with the oral therapy were identified. Intravenous formulation of anti-platelet drug such as Clopidogrel in parenteral acceptable solvents are immensely useful for the treatment of emergency ischemic conditions such as acutely developing myocardial infarction, acute coronary syndrome (ACS), or when coronary angioplasty and/or coronary stenting is to be undertaken.

However, Clopidogrel exhibits very poor aqueous solubility posing a major challenge for intravenous formulation development. A number of approaches for preparing intravenous formulations of such poorly water-soluble drugs have been explored including nano-emulsion, cyclodextrin complexation, Liposome, polymeric nanoparticles, lipidic nanosuspension and use of various solvent-cosolvent systems.

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Each of these formulation approaches has its inherent limitations to make their use in intravenous commercial formulations and hence so far injectable Clopidogrel formulation not approved for marketing. The antithrombotic drugs are categorized in three major classes: platelet aggregation inhibitors (PAIs), fibrolytics and anticoagulant. PAIs prevent blood clots by blocking receptor responsible for platelets aggregation and used for long term management of arterial thrombosis.

Colloidal Nature and Mechanism of Action

The colloidal condition is a condition in which minute droplets or particles of the drug are suspended in the carrier system but not dissolved in the medium. The minute particle size raises the surface area, which accelerates drug dissolution, absorption, and blood circulation. Intravenous administration of the colloidal drug carriers protects the active drug from early degradation and controls the release of the drug, generating a sustained drug action.

The mechanism of action of colloidal systems depends on the type of carrier. Some systems work by encapsulating the drug within lipid or polymer-based nanostructures, while others form self-assembling micelles or emulsions that increase drug solubility and transport efficacy. The drug colloidal carriers can be formulated to target tissues that are cells or organs, thus minimizing off-target effects and maximizing drug efficacy.

Types of Colloidal Drug Delivery Systems:

There are various drug delivery colloidal carriers that are employed, each with benefits:

Liposomes

- They are phospholipid vesicles that can entrap hydrophilic and hydrophobic drugs.
- Liposomes stabilize drugs and prolong their blood circulation time.
- They may be targeted using targeting ligands to transfer drugs to targeted tissues.
- **Example:** Doxorubicin-loaded liposomes (Doxil) for cancer therapy.

Micelles

- These are colloidal self-assembled aggregates of amphiphilic molecules having hydrophilic and hydrophobic parts.
- Micelles are very good at increasing hydrophobic drug solubility.
- They hold potential in chemotherapy and drug release controlled by the system.

Nanoparticles

- These are solid drug carriers with nano-size composition from polymers, lipids, or inorganic compounds.
- Nanoparticles provide sustained and controlled release of drugs for enhanced therapeutic effects.
- They are utilized in targeted cancer therapy, gene therapy, and drug delivery systems with targeting property.

Nano-emulsions

- They are thin dispersions of water-in-oil (W/O) or oil-in-water (O/W) systems that enhance the absorption of drugs.
- Nano-emulsions have high stability and avoid precipitation of the drug, and are thus good IV formulation candidates.
- They are used in cardiovascular drugs, antimicrobial drugs, and analgesics.

Clopidogrel

Clopidogrel is one of the most popular antiplatelet medications that inhibits blood clot formation in cardiovascular-risk patients with conditions such as heart attacks, strokes, and peripheral artery diseases. It is mostly prescribed to those who have undergone angioplasty, stent placement, or coronary artery bypass grafting (CABG) in order to prevent clot formation.

Clopidogrel is a drug belonging to the category of drugs called $P2Y_{12}$ inhibitors, which work by preventing platelet aggregation, thus preventing the formation of clots in the blood vessels. It is usually administered with aspirin in the form of dual antiplatelet therapy (DAPT) to give supplementary protection against clot complications.

Mechanism of Action

Clopidogrel is a prodrug, i.e., it is biotransformed in the liver before it gains its active form. The drug gets biotransformed inside the liver by cytochrome P450 enzymes (CYP2C19, CYP3A4, etc.) to form an active metabolite which irreversibly binds to the $P2Y_{12}$ receptor on platelets.

By blocking this receptor, Clopidogrel inhibits platelet aggregation induced by ADP by inhibiting

the formation of blood clots. Because platelets lack a nucleus and are unable to make new $P2Y_{12}$ receptors, the effect of Clopidogrel persists during the life of the platelet (7–10 days) even after stopping the drug.

Uses and Indications

Clopidogrel is employed to prevent blood clots in the following:

Acute Coronary Syndrome (ACS)

- Used to treat unstable angina or myocardial infarction (heart attack).
- Usually taken with aspirin to prevent future heart attacks.
- Ischemic Stroke and Transient Ischemic Attack (TIA)
- Prevents stroke in individuals who have experienced a history of stroke or mini-strokes (TIAs).

Peripheral Artery Disease (PAD)

- Taken to prevent clotting in arteries that supply blood to the legs.
- Post-Stent Placement or Angioplasty
- Used after coronary stent placement to prevent clotting inside the stent (stent thrombosis).
- Given for 3 to 12 months, based on patient risk factors.

Material and Methods

Optimal material and equipment choice depends on success in experiments. Various active pharmaceutical ingredients (APIs), excipients, surfactants, solvents, buffers, and isotonicity adjusters were utilized in the analysis and formulation process in this study. All the products used were sourced from a credible supplier to enable quality and consistency in research. Below is a complete list of materials utilized in this research (Table 3.1).

Table 3.1: Used Materials List

Materials	Category
Clopidogrel bisulfate	Active ingredient
Cholesterol	Lipid
DMPG	Lipid
DMPC	Lipid
Polysorbate 60 (Tween 60)	Surfactant
Kolliphore ELP	Surfactant
Poloxamer 188 (Pluronic F68)	Surfactant
Polysorbate 80 (Tween 80)	Surfactant
Sucrose	Isotonicity adjuster
Sodium citrate	Buffer
Citric acid	Buffer
Sodium hydroxide	pH adjuster
Clopidogrel carboxylic acid	Metabolite
Ethanol	Solvent
Methanol	Solvent
Isopropyl Alcohol	Solvent
Acetonitrile	Solvent
Potassium dihydrogen phosphate	Buffer
Disodium hydrogen phosphate	Buffer

In addition to materials, laboratory equipment of various kinds that is used for weighing, mixing, separation, and analytical analysis was used. Equipment like UV-Vis spectrophotometers, HPLC systems, centrifuges, pH meters, analytical balances, and transmission electron microscopes (TEM) were used with great care with their accuracy and use for research work. Table 3.2 indicates all the equipment along with their model.

Identification Of Drug

Appearance and pH

Prior to formulation development, the acquired sample of Clopidogrel was viewed by eyes to confirm its color and consistency with the reference standards. The pH of the drug solution was also measured using a pH meter to ensure that it complied with stated values.

Fourier Transform Infrared (FT-IR) Spectroscopy

In order to verify the identity of Clopidogrel, Fourier Transform Infrared (FT-IR) Spectroscopy was performed. Potassium bromide (KBr) disc method was employed, where a finely powdered mixture of Clopidogrel and KBr was pressed into a disc and scanned between 4000-400 cm^{-1}. The IR spectrum obtained was matched with a reference spectrum, so that all the characteristic peaks for Clopidogrel functional groups were included.

Table 3.2: Drug and Equipment Used

Instruments	Model
Automated Hematology analyzer	Celltac MEK6420
Analytical weighing balance	BL-220H
Centrifuge	RCF-516
	R-8M
Binocular microscope	LABOMED VISION 2000
FTIR Spectrophotometer	Alpha-1 630
Deep Freezer	PDV
HPLC	2695
FTIR Spectrophotometer	Alpha-1 630
High Pressure Homogenizer	PandaPlus
High Speed Homogenizer	Polytrone PT3100 D
pH Meter	LI615
Magnetic Stirrer	DBK
Transmission Electron Microscope (TEM)	Tecnai 20
Particle size analyzer	Zetasizer ZS
Vortexer	Vortex mixer
Water bath	7505
UV-spectrophotometer	UV-1800

Development of Clopidogrel Nanodispersion (CPN)

Preparation and Composition of Aqueous Media

Clopidogrel nanodispersion was developed by the preparation of aqueous media with surfactants, buffers, and stabilizers, as shown in Table 3.4.

Table 3.4: Aqueous Media Composition for CPN

Ingredients	Concentration (%)
Surfactant	Various
Sodium citrate dihydrate	1.65
Citric acid	0.98
Water	100%
Sodium hydroxide	q.s to pH
Sucrose	4.7

Analytical Methodology

Estimation of Clopidogrel by UV Spectrophotometry

UV spectrophotometry was used for Clopidogrel concentration estimation from various formulations and release studies. Drug absorbance at 220 nm was recorded by a UV-Vis spectrophotometer.

Calibration Curve in Methamphetamine methanol:

Clopidogrel stock solution was kept in methanol and made up to different concentrations by dilution for preparation of solutions. The absorbance values were noted and a calibration curve was drawn to get a linear relationship between concentration and absorbance.

Calibration Curve in Methanolic Phosphate Buffer:

For in vitro release testing, a calibration curve was also developed in methanolic phosphate buffer (pH 7.4). This was used to ensure the dissolution as well as release characteristics of Clopidogrel under physiological conditions.

High-Performance Liquid Chromatography (HPLC) Method

HPLC was utilized for the precise quantitation of Clopidogrel in drug formulations. Chromatographic separation was obtained in an Ultron ES-OVM (Packing L57) column under a mobile phase constituted by a combination of phosphate buffer and acetonitrile.

Results and Discussion

All excipients were used within IIG limit for formulation. Reagents were analytical grade and solvents were HPLC grade.

Identification of Drug

Identification of the drug is essential before initiation of formulation development. Identification of the drug in the present investigations was evaluated based on its appearance, solubility, and by fourier-transform infrared (FT-IR) spectroscopic determination of various functional groups present in the powder drug sample were summarized in Table 4.1.

Table 4.1: Identification tests for CLPD with the inferences

Parameters	Observation	Reported	Inferences
Appearance	White powder	White to off-white powder	Complies
pH of 1% w/v aqueous solution	1.7	Acidic	Complies

Major IR peak (cm^{-1})	1191	1190	C-O stretching
	1751	1751	C=O stretching vibration
	839, 2954	**839,2954**	**C-H bond**

Compliance of observed value with respect to reported specification authenticates the sample to be of Clopidogrel bisulfate. The major observed IR peak was listed in below table. Various functional groups observed in the sample were compared with standard reported FT-IR spectra of Clopidogrel for confirmation.

From the observations of Table 4.1, identification of drug sample was confirmed and concluded that it was Clopidogrel bisulfate and the sample was used for all further formulation development activities.

Conclusion

In present investigations, Clopodogrel loaded colloidal formulations could be successfully prepared and optimized using three formulation approaches including Liposomes, powder for nanodispersion and concentrate for nanodispersion using QbD approach. All the formulations exhibited particle size in nanometer range without any aggregation and stability upon dilution with body fluids proving its suitability for IV administration. Additionally, all of the developed formulations exhibited rapid release during in vitro release studies indicating their potential for providing rapid onset of action upon IV administration, which is the one of the major objectives of the dissertation and is current unmet need in Clopidogrel formulation space. Based on various parameters including cost of excipients, complexity of manufacturing process and storage conditions, CCN formulation was selected for further evaluation. Comparatively simple formulation requiring only low-cost excipients and very simple manufacturing process makes the CCN formulation commercially feasible and viable.

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Cite this article as:
Singh Y.P., Dubey V. and Pandey R. (2025). Design and Development of a Colloidal Drug Delivery System for IV Formulation of Clopidogrel. *Int. J. of Pharm. & Life Sci.*, 16(6):8-14.

Source of Support: Nil
Conflict of Interest: Not declared
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