WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Development and Characterization of Warfarin Suspension; A Comprehensive Review

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ABSTRACT

This article presents a comprehensive pharmaceutical and clinical overview of Warfarin, a widely prescribed oral anticoagulant, formulated as a suspension for patients requiring individualized dosing or those with difficulty swallowing tablets. Utilizing a structured, module-based approach, the article examines various aspects of Warfarin suspension across four integrated domains. The first module discusses the rationale for selecting Warfarin as a representative oral anticoagulant, considering its well-established efficacy in the prevention and treatment of thromboembolic conditions. The second module focuses on preformulation studies, including physicochemical properties, solubility, pH stability, and excipient compatibility—critical parameters for ensuring the stability and bioavailability of the suspension. The third module addresses the formulation and compounding of Warfarin suspension, emphasizing techniques for achieving accurate dosing, and physical stability. The final module involves evaluation and quality control testing of the prepared suspension, along with an overview of regulatory considerations and potential challenges in extemporaneous preparation and commercial formulation. This article aims to integrate theoretical understanding with practical experience, providing a multidisciplinary perspective on the development, evaluation, and therapeutic application of Warfarin suspensions.

Keywords : Anticoagulant, Suspension, preformulation, stability

INTRODUCTION:

Anticoagulants are medicines that help prevent blood clots. They're given to people at a high risk of getting clots, to reduce their chances of developing serious conditions such as strokes and heart attacks.[2] Warfarin is an anticoagulant used to prevent and treat venous thrombosis and thromboembolic events, as well as conditions such as myocardial infarction and atrial fibrillation. Warfarin inhibits the synthesis of vitamin K-dependent clotting factors, reducing clotting ability Inappropriate dosing significantly increases the risk of thromboembolism, bleeding, and hospitalization.

MECHANISM OF ACTION[1]

Warfarin competitively inhibits the vitamin K epoxide reductase complex subunit 1 (VKORC1), an enzyme essential for activating available vitamin K. Through this mechanism, warfarin can deplete functional vitamin K reserves, thereby reducing the synthesis of active clotting factors. The hepatic synthesis of coagulation factors II, VII, IX, and X, as well as coagulation regulator proteins C and S, requires vitamin K. Vitamin K is an essential cofactor for synthesizing these vitamin K-dependent clotting factors.[18]

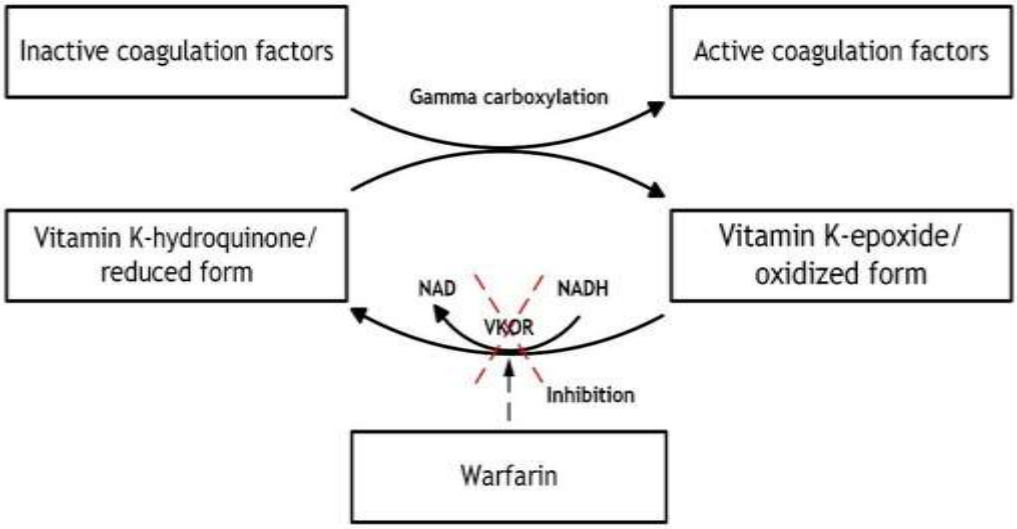

Fig:1, Mechanism of action of warfarin

PHARMACOKINETICS[1]

Absorption: Warfarin is rapidly and completely absorbed. The onset of action is typically 24 to 72 hours, and the duration of action is 2 to 5 days. Peak plasma concentrations are achieved in approximately 4 hours. A peak therapeutic effect is generally seen 5 to 7 days after initiation. However, the patient's international normalized ratio (INR) may increase within 36 to 72 hours after initiating treatment.

Distribution: Warfarin has a relatively small distribution volume (0.14 L/kg) and undergoes 99% protein binding.

Metabolism: Hepatic metabolism, primarily through the CYP2C9 enzyme. Other minor enzymatic pathways for metabolism include CYP2C8, 2C18, 2C19, 1A2, and 3A4. Research has shown that genetic variations in CYP2C9 affect an individual's warfarin clearance. The half-life of warfarin is generally 20 to 60 hours; this is highly variable among individuals.

Elimination: Warfarin is primarily eliminated as metabolites by glomerular filtration in the kidney (92%)

ADVERSE EFFECT

- Hemorrhage
- Abdominal pain
- Bloating
- Flatulence
- Altered sense of taste
- Purple toe syndrome

USES

- Prophylaxis and treatment of venous thrombosis and arising pulmonary embolism
- Prophylaxis and treatment of thromboembolic complications from atrial fibrillation or cardiac valve replacement
- Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events after myocardial infarction
- Secondary prevention of recurrent stroke and transient ischemic attacks [17]

FORMULATIONS

1. Oral Tablet (Most Common)

Primary and standard form of warfarin sodium. Used for long-term anticoagulation

2. Powder for Oral Suspension (Rare/Compounded Form)

Sometimes prepared in compounding pharmacies, especially for: pediatric patients' geriatric patients with swallowing difficulty patients requiring very small doses.[19]

PREFORMULATION STUDIES

I. ORGANOLEPTIC EVALUATION

The color, odor and taste of the new drug must be recorded using descriptive terminology. It is important to establish a standard terminology to describe these properties in order to avoid confusion among scientists using different terms to describe the same property.[3] Warfarin is white to off white with odorless and bitter taste.

II.PHYSICO-CHEMICAL CHARACTERIZATION

A) SOLUBILITY[5]

Solvent	Solubility
Water	Insoluble
Acetone	Readily soluble
Dioxane	Readily soluble
Alcohol	Moderately soluble

Table:1, Solubility of warfarin

B) DISSOCIATION CONSTANT (pKa):

The dissociation constant is a value that describes the extent to which a compound ionizes or dissociates into its ions when dissolved in water. The relative concentrations of un-ionized and ionized forms of a weakly acidic or basic drug in a solution at a given pH can be readily calculated using the Henderson-Hasselbalch equations:

For bases:

$$pH = pKa + \frac{unionized}{ionized}$$

For acids:

$$pH = pKa + log\frac{ionized}{unionized}$$

Warfarin observed macroscopic pKa, was 5.03-5.06[6]

C) PARTITION COEFFICIENT

The lipophilicity of an organic compound is usually described in terms of a partition coefficient; log P, which can be defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases.

$$log\ log\ p = log\frac{(concentration\ of drug\ in\ organic\ phase\ )}{(concentration\ of\ drug\ in\ aqueos\ phase)}$$

Drugs having values of P much greater than 1 are classified as lipophilic, whereas those with partition coefficients much less than 1 are indicative of a hydrophilic drug. Partition coefficient of warfarin was 3.1.[11]

D) MELTING POINT

The melting point is the temperature at which a solid becomes a liquid. Melting point of warfarin is 151-161°C [11]

E) POLYMORPHISM[5]

Many drug substances can exist in more than one crystalline form with different space lattice arrangements. This property is known as polymorphism. The different crystal forms are called polymorphs. When polymorphism occurs, the molecules arrange themselves in two or more different ways in the crystal; either they may be packed differently in the crystal lattice or there may be differences in the orientation or conformation of the molecules at the lattice sites.[7] warfarin is mainly existed in two polymorphs they are clathrate and anhydrous.

F) PARTICLE SIZE AND SHAPE DISTRIBUTION

Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. Particle size of warfarin was 20 µm.[12]

G) HYGROSCOPICITY

Hygroscopicity is defined as the ability of a compound to absorbs moisture from surrounding environment. Warfarin is non-hygroscopic in nature.[16]

II.COMPATABILITY STUDIES

1.DRUG EXCIPIENT COMPATIBILITY STUDIES

The drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already be in existence for known drugs.[6]

A simple and effective method for detecting changes in pharmaceutical-excipient combinations is Fourier-Transform Infrared Spectroscopy (FTIR). [15]

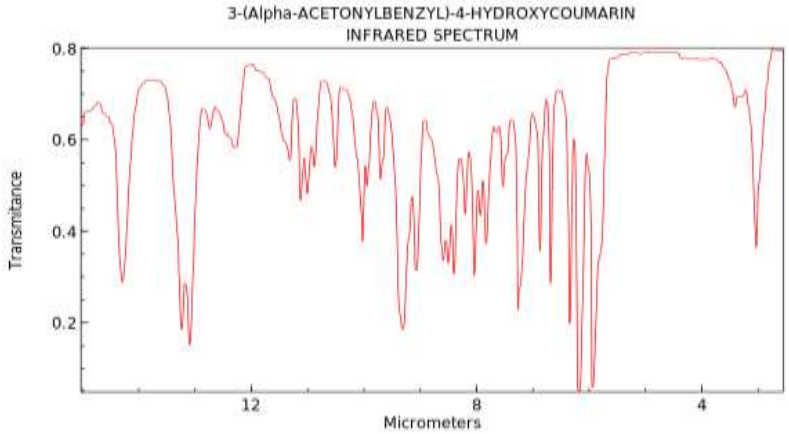

Fig no;2 FTIR spectrum of warfarin

Functional group	Stretching
O-H	~3200-3600
C=O	~1680-1720
C=C	~1500-1600
C-H	~3000-3100
C-O	~1000-1300

Table no;2 FTIR of warfarin

III. WETTING AND DISPERSIBILITY

- Wetting refers to how easily the suspension medium (usually water) spreads over the surface of drug particles**.**
- Proper wetting and dispersibility are essential for dose uniformity, stability, and patient acceptability.[6]
- Warfarin is hydrophobic nature; therefore, warfarin powder may require the addition of wetting agents to enhance its wettability.
- The commercial warfarin oral suspension includes xanthan gum as suspending agent to enhance redispersibility
- Polysorbate 80 serves as a wetting agent in the formulation, aiding in the uniform dispersion of warfarin particles[10]

III.FLOW PROPERTIES

1.ANGLE OF REPOSE

The maximum angle which is formed between the surface of pile of powder and horizontal surface is called the angle of repose.[20]

2.DENSITIES

The ratio of mass to volume is known as density

Types of density:

(a) **Bulk density:** It is obtained by measuring the volume of known mass of powder that passed through the screen. It is expressed as **g/cm^3**[20]

(b)Tapped density: It is obtained by mechanically tapping the measuring cylinder containing powder.

3. CARR'S INDEX

To measure Carr's compressibility, index a volume of powder is filled into a graduated glass cylinder and repeatedly tapped for a known duration. After tapping the final volume of powder is measured.

4.HAUSNER'S RATIO

Hausner's ratio is expressed as the ratio of tapped density to the bulk density. Hausners ratio or carr's index indicate more cohesiveness and poor flow property [13]. Warfarin sodium is known to have fine particle size and low bulk density, high tapped density, and high angle of repose then it is likely to exhibit poor flowability, which would be reflected in high Carr's Index and Hausner Ratio values.[20]

FORMULATION OF WARFARIN SUSPENSION

Suspensions are those course dispersions in which internal phase i.e., coarse powder is dispersed into the external phase i.e., liquid vehicle. Internal phase that consists of solid particles that are uniformly suspended in sufficient amount of vehicle by the addition of individual or combined form of suspending agents. Vehicles in external phase are commonly aqueous in nature in oral preparation, on the other side organic and oily liquids are used for non-oral preparations. Nowadays, many suspensions are marketed in the form of powder which are suspended into specified amount of vehicle just before use because of stability considerations.[9]

Warfarin suspension was prepared by simple suspension compounding method.[14]

INGREDIENTS	FUNCTION
Warfarin sodium	Active anticoagulant
Propylene glycol	Co-solvent/stabilizer
Liquid maltitol (75%)	Co-solvent, sweetening agent
Purified water	Dissolution medium
Benzoic acid	Preservative
Xanthan gum	Suspending agent
Aluminium magnesium silicate	Suspending agent
Polysorbate	Wetting agent
Citric acid	Buffer agent
Masking flavor	Taste masking

Table no;3 ingredients of warfarin suspension

Dissolve the Preservative & Solubilizers:

- In a beaker, add approximately 60 mL of purified water.
- Add benzoic acid, propylene glycol, and polysorbate 80. Stir until fully dissolved.

Prepare the Suspension Base:

- Slowly sprinkle xanthan gum and aluminium magnesium silicate into the above solution with continuous stirring.
- Allow to hydrate for 15–30 minutes to avoid lumping.
- Mix using a magnetic stirrer or high-shear mixer for uniformity.

Adjust pH (if needed):

- Use citric acid and disodium phosphate to adjust the pH to around 6.8–7.2 for optimal warfarin stability.

Dissolve Warfarin Sodium:

- In a separate beaker, dissolve the accurately weighed warfarin sodium in a small amount of water.

- Ensure complete dissolution.

Incorporate API into Suspension:

- Add the warfarin solution into the hydrated base slowly with stirring.

Add Sweetener & Flavour:

- Add liquid maltitol (acts as sweetener and viscosity enhancer).
- Add masking flavour as required for palatability (e.g., cherry, tutti frutti).

Make up the Volume:

- Add purified water q.s. to 100 mL.
- Mix thoroughly until a smooth, uniform suspension is obtained.

Packaging:

- Dispense into amber plastic bottles with child-resistant caps.
- Store at controlled room temperature (15–25°C) unless otherwise specified.[13]

EVALUATION OF WARFARIN SUSPENSION

1.VISUAL INSPECTION

INSPECTION	APPEARANCE	INDICATES
Color and odor	Uniform color, characteristic odor	Stability and identity.
Clarity	Slightly cloudy to opaque, no phase separation.	Homogeneity and uniform dispersion.
Sedimentation	Loosely settled, should redisperse easily.	Good flocculation.
Caking	No hard cake at the bottom.	Indicates a properly flocculated suspension.
Redispersibility	Easy redispersion with mild shaking.	Physical stability
Particle	No large, gritty or aggregated particles visible.	Redispersibility
Foam or bubbles	Minimal foaming should dissipate quickly.	Excess foaming may indicate formulation issues.
Foreign particle	No visible contaminants or microbial growth.	Clean compounding and proper storage

Table no;4 visual inspection of warfarin suspension

2.SEDIMENTATION METHOD

(i) Sedimentation Volume

The volume of sedimentation is measured with the help of a measuring cylinder.

Then sedimentation volume is calculated as per the equation given;

$$\mathbf{F = V_u / V_0}$$

Where,
F = sedimentation volume

V_u = the ultimate height of sediment

$V_{0 =}$ the initial height of the total suspension[21]

3. ELECTRO KINETIC METHOD

In the electrokinetic method, the zeta potential is measured with the help of the microelectrophoresis apparatus and zeta plus. Because of this, the stability of the dispersed system is obtained.

With the help of zeta plus the zeta potential of the prepared suspension is measured

Zeta potential of warfarin particles is typically in the range of -20 to -40 mV in aqueous suspension at pH 6-8.[21]

4.RHEOLOGIC METHOD[9]

Maintaining optimal viscosity is crucial for the stability and pourability of suspensions. Increased viscosity slows particle settling, enhancing stability by preventing sedimentation and caking. However, excessive viscosity can hinder pourability, making dosing inconvenient for patients. Thus, a balance is needed to ensure both stability and ease of use. Warfarin suspensions typically have a viscosity between 200 and 600 centipoise (cP). It is determined using Brookfield viscometer

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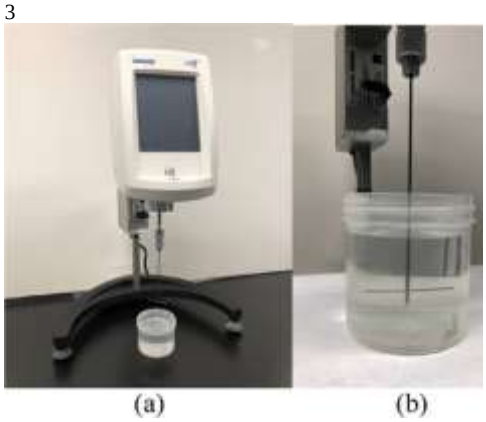

Fig no;3, Brookfield viscometer

5.MICROMERITIC METHOD

Photo microscopy method

To estimate and determine the changes in particle size distribution and crystal form the microscope may be used. By attaching the Polaroid camera to the piece of the monomolecular microscope the fast processing of photomicrographs is increased. With the help of photomicrographs, you can determine the stability as well as changes in the physical property of the suspension. USP grade warfarin sodium is often supplied as micronized powder, with particles in the 1-5µm range

Fig no,4; microscope

PACKAGING AND LABELLING

- **Primary packaging**: Amber colored plastic or glass bottle.
- **Secondary packaging**: A labeled cardboard box containing the primary container (usually an amber glass or plastic bottle)
- **Closure**: child resistance, tamper evident
- **Label info**: strength dose, shake warning, BUD, storage warnings.
- **Accessory's**: oral syringe or cup for accurate dosing.
- **Storage**: Do not store above 25 °C
- **Expiry date**: closed:24 months, after first opening:28 days

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