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Development and Characterization of Phenindione Tablet; A Comprehensive Review

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ABSTRACT

This article presents a detailed pharmaceutical and clinical overview of Phenindione, an oral anticoagulant formulated as a tablet dosage form. Though less commonly used today compared to other vitamin K antagonists, Phenindione remains of academic and historical interest due to its distinct pharmacodynamic profile. The study adopts a structured, module-based approach to explore key aspects of Phenindione tablet formulation and evaluation. The first module outlines the rationale for selecting Phenindione as a model anticoagulant, focusing on its mechanism of action, clinical indications, and comparative pharmacological properties. The second module involves preformulation studies, including physicochemical characterization, solubility, and compatibility with common tablet excipients. The third module covers formulation and manufacturing, emphasizing wet granulation techniques, binder selection, and process optimization to ensure uniformity and tablet integrity. The final module includes evaluation and quality control testing of the developed tablet, such as hardness, friability, disintegration, dissolution, and assay, along with a brief discussion of regulatory guidelines and potential clinical implications. This article aims to provide an integrated perspective combining theoretical knowledge with practical experience in the development and evaluation of Phenindione tablets.

Keywords : Phenindione, Compression, Angle of repose, Preformulation

INTRODUCTION:

Anticoagulants are the drugs used to reduce the coagulability of blood. These are agents that inhibit the coagulation cascade. Phenindione is an anticoagulant medicine, which means that it increases the time it takes for your blood to clot. It works by reducing the effects of vitamin K, which is a vitamin your body uses to make blood-clotting factors. Phenindione is prescribed to prevent harmful blood clots from forming if you have a condition that puts you at risk of this happening, such as atrial fibrillation, or if you have had a heart valve replacement. It is also given to prevent any clots that may have already formed in the blood vessels of your legs, lungs or heart from becoming larger and causing problems.[2][1]

MECHANISM OF ACTION

Phenindione inhibits vitamin K reductase, resulting in depletion of the reduced form of vitamin K (vitamin KH2). As vitamin K is a cofactor for the carboxylation of glutamate residues on the terminal regions of vitamin K-dependent proteins, this limits the gamma-carboxylation and subsequent activation of the vitamin K-dependent coagulant proteins. The synthesis of vitamin K dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S is inhibited. Depression of three of the four vitamin K-dependent coagulation factors (factors II, VII, and X) results in decreased prothrombin levels and a decrease in the amount of thrombin generated and bound to fibrin. This reduces the thrombogenicity of clots. [14]

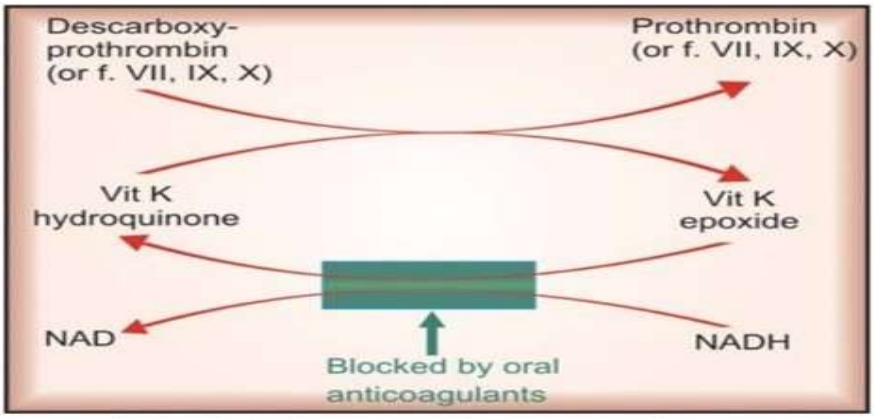

Fig no.1: Mechanism of Phenindione

ADVERSE EFFECT

1. Hypersensitivity Reactions (most serious concern):

- Rash
- Fever
- Eosinophilia
- Hepatitis

2. Hematologic Effects

- Bleeding (like all anticoagulants, especially if not properly monitored. [1]

FORMULTIONS

1. Oral Tablet (Standard and Only Available Form)

- Primary and only commercial dosage form of phenindione.
- Typically, available in:

50 mg tablets (most common)

Occasionally 100 mg tablets (in some regions)

- Administered orally. [12]

Fig no.2: Phenindione tablet

PREFORMULATION STUDIES OF PHENINDIONE

I. Physico-chemical properties

1. Organoleptic properties
2. Solubility
3. Ionization constant
4. Partition coefficient
5. Hygroscopicity
6. Melting point

II. Compatibility studies

III. Flow properties

1. Angle of repose
2. Density
3. Carr's index
4. Hausner's ratio

IV. Solid state characterization

1. Particle size

I.PHYSICO-CHEMICAL PROPERTIES

1. ORGANOLEPTIC CHARACTERS

The color, odor and taste of the new drug 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. Phenindione has creamy white to pale yellow color with unpleasant taste and odourless. [13]

2.SOLUBILITY

Phenindione have low solubility and high permeability, so it falls under BCS classification-II.

SOLVENT	**SOLUBILITY**
Water	Insoluble
Acetone	Soluble
Alkaline solution	Readily soluble
Alcohol	Soluble

Table no.1: Solubility of Phenindione

3.IONIZATION CONSTANT

Ionization constant is defined as the tendency of a compound or ion to dissociate. Many drugs are either weakly acidic or basic compounds and, in solution, depending on the pH value, exist as ionized or un-ionized species. The un- ionized species are more lipid-soluble and hence more readily absorbed. Phenindione is weakly acidic and pKa value is 4.09. [4]

4.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 P of Phenindione is 2.9 which indicate its moderately lipophilic nature.[5]

5.HYGROSCOPICITY

Hygroscopicity is the tendency of a solid substance to absorb moisture from the surrounding atmosphere. Many compounds and salts are sensitive to the presence of water vapor or moisture.

Phenindione is considered as hygroscopic in nature.

6.MELTING POINT

The melting point is the temperature at which a substance changes state from solid to liquid at atmospheric pressure. Melting point of phenindione is 150 °C. [6]

II.COMPACTIBILITY STUDY

FT-IR SPECTROSCOPY

FTIR (Fourier Transform Infrared

Spectroscopy) is used to identify functional groups and confirm the presence and purity of phenindione in tablets. [9]

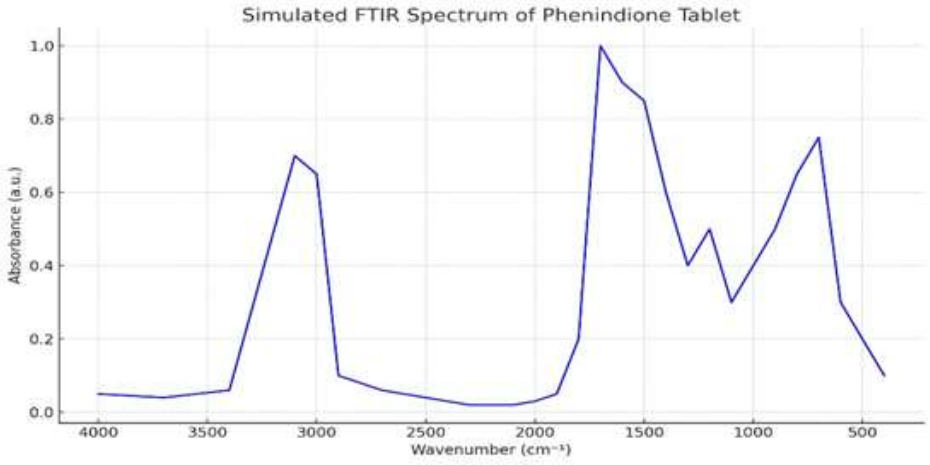

Fig no.3: FTIR spectrum of Phenindione tablet

FUNCTIONAL GROUP	TYPE OF VIBRATION	EXPECTED WAVE NUMBER (cm-1)
Aromatic C-H stretch	Stretching	3100-3000
C=O	Strong stretching	~1700-1725
C=C	Stretching	1600-1450
C-H	Out-of-plane bending	900-700
C-O	For enol or ketone tautomer	1250-1000

Table no.2: FTIR of Phenindione

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. Phenindione has good flow property. [7]

Flowability expected	**Angle of repose**
Excellent / Very Free Flow	25-30
Good / Free Flow	31-35
Fair (discharging aid may not be required)	36-40
Passable	41-45
Poor Flow / Cohesive (active discharging aid required)	46-55
Very Poor Flow / Very Cohesive	56-65
Approximatively no flow	> 66

Table no.3: Flow property of Phenindione

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**.

Bulk density = Weight of powder/ Bulk volume

(b)Tapped density: It is obtained by mechanically tapping the measuring cylinder containing powder.[13]

Tapped density = Weight of the powder/ Tapped volume

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. It is expressed as following ratio:

Carr's index (%) = (taped density-bulk density/ tapped density) x 100

4.HAUSNER'S RATIO

Hausner ratio is expressed as the ratio of tapped density to the bulk density.

Hausner ratio = tapped density/ poured or bulk density

If the value of Hausner ratio is high it indicates that powder is cohesive in nature and possess poor flow property.

High Hausner ratio or Carr's index (%) = more cohesiveness and poor flow [7]

IV. SOLID STATE CHARACTERIZATION

1.PARTICLE SIZE

Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The particle size of phenindione is less than 50µm.[8]

FORMULATION OF PHENINDIONE TABLET

1. Weighing and sieving of ingredients
2. Dry mixing of API and excipients
3. Preparation of binder solution
4. Wet massing
5. Wet granulation
6. Drying of granules
7. Sieving of dried granules
8. Blending with lubricants and glidants

9. Tablet compression

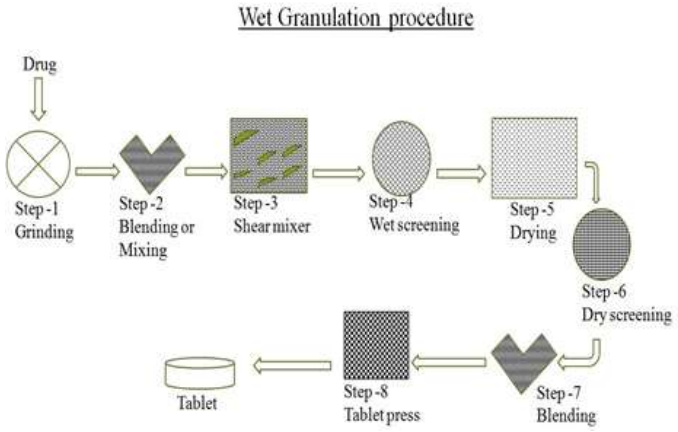

Fig no.4: Formulation of Phenindione tablet

STEP 1: WEIGHING OF INGREDIENTS

INGREDIENTS	**FUNCTION**
Phenindione	Active pharmaceutical ingredient
Lactose monohydrate	Diluent
Maize starch	Filler, binder, disintegrant
Povidone (PVPK30)	Binder
Magnesium stearate	Lubricant
talc	Glidant

Table no.4: Ingredients of Phenindione tablet

STEP 2: DRY MIXING

Mix the sieved phenindione, lactose, and starch in a planetary mixer or ribbon blender for 10 minutes to ensure homogeneity.

STEP 3: BINDER PREPARATION

Prepare a 10% w/v povidone K30 solution using purified water.

Stir until fully dissolved (ensure no lumps remain).

STEP 4: GRANULATION

Slowly add the povidone solution to the dry blend with continuous mixing to form a cohesive wet mass. The endpoint is achieved when the mass can form a ball when compressed in the hand but is not too sticky.

STEP 5: WET SCREENING

Pass the wet mass through a 12-mesh or 16-mesh sieve to form granules.

STEP 6: DRYING

Dry the granules in a tray dryer or fluid bed dryer at 40–50°C until the loss on drying (LOD) is less than 2%.

Typical drying time: 1.5–2 hours depending on equipment and load.

STEP 7: SIZING

Pass dried granules through a 20-mesh sieve to break lumps and achieve uniform granule size

STEP 8: LUBRICATION

Mix granules with talc and magnesium stearate in a blender for 5–10 minutes. Avoid over mixing magnesium stearate, as it can retard dissolution.

STEP 9: COMPRESSION

Compress the final blend using a rotary tablet press fitted with flat-faced punches. Compress the final blend using 8mm convex punch under optimized force to form tablets.[3]

EVALUATION OF PHENINDIONE TABLET

Evaluation of phenindione tablet include following methods:

1. General appearance

A) Organoleptic property

B) Size and shape

2. Hardness
3. Friability
4. Drug content and release
   a) Weight variation test
   b) Content uniformity test
   c) Disintegration test
5. Dissolution test

1.GENERAL APPEARANCE

 Organoleptic Properties:

Strength	**Colour**	**Shape & Texture**	**Marking**	**Coating**
10 mg	Creamy white	Round, flat, beveledged	Scored on one side (break line), engraved **"D10"**	Uncoated

Table no.5: organoleptic properties of Phenindione tablet **Size And Shape:**

Size and shape of a tablet has been determined by its thickness. Size and shape of table plays an important role in its patient compliance as the size of the tablet increases it is not much easier for its administration. Micrometer is the devise which is used to determine the thickness of a tablet.

2. HARDNESS

The ability of a tablet to withstand for mechanical shocks is known as hardness. Pfizer hardness tester is the instrument which is used to determine the hardness of tablet.

Fig no.5: Pfizer hardness tester

3. FRIABILITY

Friability is a measure of how easily a tablet can crumble or break apart under mechanical stress. Roche friabilator is the equipment which is used for the determination of friability. It is expressed in percentage. Percentage of friability is calculated as:

$F= \{(W_{initial})- (W_{final})/ (W_{initial})\} \times 100.$

Fig no.6: Roche friabilator

4. DRUG CONTENT AND RELEASE

A) WEIGHT VARIATION TEST

Weight variation refers to the differences in the individual weights of tablets compared to the average tablet weight in a batch.

SI NO	AVERAGE WEIGHT	Maximum Percentage Difference Allowed
1.	130 Or less	10
2.	130 - 324	7.5
3.	More Than 324	5

Table no.6: Weight variation table

B) CONTENT UNIFORMITY TEST

To ensure that each dosage unit contains the intended amount of active pharmaceutical ingredient (API) within a specified range.

PROCEDURE

- Initially weigh the tablet and then powder it.
- Now the powdered tablet is transferred into a 100 ml volumetric flask and adds 0.1 N HCl up to mark.
- Now filter the solution and discard first few ml of filtrate.
- Take 10 ml of filtrate should be taken into a 50 ml volumetric flask and add 0.1 N HCl up to the mark and analyzed spectrophotometrically at 274 nm and 234.5 nm.

C) DISINTEGRATION TEST

The Disintegration Test is a quality control procedure used to determine the time required for a tablet or capsule to break down into smaller particles or granules under specified condition.

Disintegration is defined as the process of breakdown of tablet into small particles. Disintegration time of a tablet is determined by using disintegration test apparatus as per IP specification apparatus

Fig no.7: Disintegration test

PROCEDURE

- Place each tablet in each 6 tubes of the disintegration apparatus a then add a disc to each tube containing 6.8 pH phosphate buffer.
- The temperature of the buffer should maintain at 37±2°C and run the apparatus raised and lowered for 30 cycles per minute.
- Note down the time taken for the complete disintegration of the tablet without any remitants.

TYPE OF TABLET	DISINTEGRATION TIME
Uncoated tablet	≤ 15 minutes
Flim coated tablet	≤ 30 minutes

Table no. 7: Disintegration time

5.DISSOLUTION TEST

A dissolution test measures how quickly and how much a drug substance dissolves from a tablet dosage form, into a liquid medium under controlled conditions.

PROCEDURE

Apparatus-2:

- It is same as apparatus-1, except the basket is replaced by a paddle.
- The dosage form is allowed to sink to the bottom of the flask before stirring.
- For dissolution test U.S.P. specifies the dissolution test medium and volume, type of apparatus to be used, rpm of the shaft, time limit of the test and assay procedure for.
- The test tolerance is expressed as a % of the labeled amount of drug dissolved in the time limit.
- Dissolution testing and Interpretation can be done in apparatus three stages. [8][10]

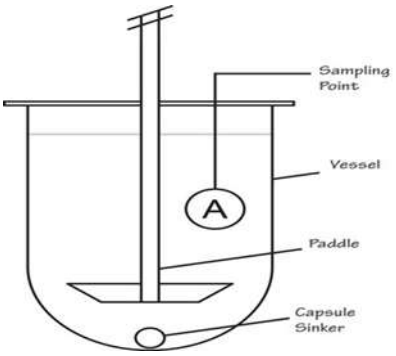

Fig no.8: Dissolution test

LABELLING

The label must contain the following essential information:

A. Outer Pack Label (Carton or Box):

- **Brand Name** and **Generic Name**: Phenindione Tablet
- **Strength**: e.g., Phenindione 50 mg
- **Dosage Form**: Tablet
- **Route of Administration**: Oral
- **Batch Number**

- **Manufacturing Date**
- **Expiry Date**
- **Manufactured by**: Name and address of the manufacturer
- **Storage Conditions**: e.g., Store below 25°C, protect from light and moisture
- **Schedule Warning**: e.g., "Schedule H drug. To be sold by retail on the prescription of a registered medical practitioner only" (India)
- **Warning/Precaution**: e.g., "Use with caution in patients with liver impairment" **B. Blister Strip/Bottle Label:**
- Brand name / Generic name
- Strength
- Batch number
- Mfg. & Exp. date
- Manufacturer's name/logo [11]

PACKAGING

Packing should maintain the drug's **stability, safety, and compliance** with regulations.

PRIMARY PACKAGING	SECONDARY PACKAGING	TERTIARY PACKAGING
Blister Pack (PVC/Alu or Alu/Alu):	Printed Carton:	Shipper Cartons:
– Protects from moisture, contamination, and light	– Contains blister strips or bottles – Includes leaflet with product and dosage info	– For transport and storage – Labeled with:
Tablet Bottle (HDPE with Desiccant):		• Batch details
– Suitable for bulk packaging		• Quantity
– Desiccant maintains dryness and product stability		• Handling instructions (e.g., "Fragile", "Keep Dry")

Table no.8: Packaging of Phenindione tablet.

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