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PHENYTOIN: PHARMACEUTICAL FORMULATION STRATEGIES AND CLINICAL EFFECTIVENESS-A COMPREHENSIVE REVIEW

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ABSTRACT

This practice school report focuses on the Pharmaceutics domain, with phenytoin selected as the study drug. The objective was to promote collaboration between academia and industry while providing practical insights into the formulation and evaluation of phenytoin sodium injections. The report discusses epilepsy and the therapeutic role of phenytoin, its physicochemical and pre-formulation characteristics, formulation and manufacturing considerations for phenytoin sodium injections, and the evaluation parameters used to assess product quality, safety, and performance. This review integrates theoretical concepts with practical applications, enhancing understanding of the pharmaceutical development process of phenytoin as an antiepileptic drug.

INTRODUCTION

Epilepsy is a neurological disorder that affects millions of people worldwide. It can have a significant impact on an individual's quality of life, affecting their physical and mental well-being, as well as their social interactions. Epilepsy is a chronic non-communicable disease of the brain characterised by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body or the entire body, occasionally accompanied by loss of consciousness.

Certain genetic mutations and family history of epilepsy can increase the risk of developing the condition. Brain injuries, tumours, strokes, and developmental disorders can lead to epilepsy. Infections like meningitis, encephalitis, and neurocysticercosis can trigger epilepsy. Traumatic brain injury, prenatal injury, drug abuse, and certain neurodegenerative disorders

can also be contributing factors. The hallmark symptom of epilepsy is recurrent seizures, which can vary in type, frequency, and intensity.

Epilepsy is mainly treated with antiseizure medications (ASMs), which are the first-line therapy and achieve seizure control in about 60–70% of patients. Monotherapy is preferred, while failure of two suitable drugs defines drug-resistant epilepsy, for which options such as epilepsy surgery, neurostimulation, or ketogenic diet may be considered. Long-term management also requires patient education and adherence to therapy [1].

CLASSIFICATION:

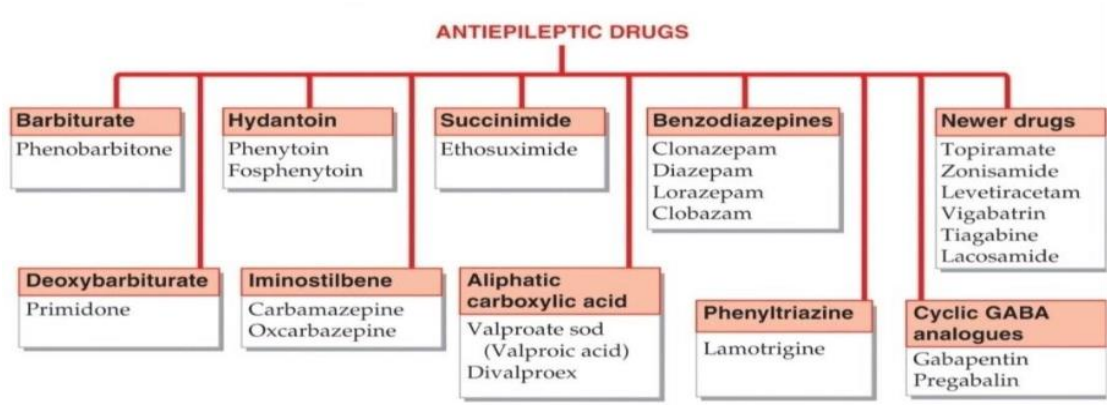

Fig.1: Classification of antiepileptic drugs.[2]

PHENYTOIN

Phenytoin is a well-established antiepileptic drug (AED) primarily used to manage various types of seizures. It belongs to the hydantoin chemical class and has been a cornerstone of epilepsy treatment for decades due to its efficacy and relatively low cost.

It is clinically indicated for the management of generalized tonic-clonic seizures, focal (partial) seizures, and status epilepticus. Additionally, it is used for neurosurgical prophylaxis to prevent seizures [3].

Molecular formula:$C_{15}H_{12}N_2O_2$ Molecular weight:252.273g/mol

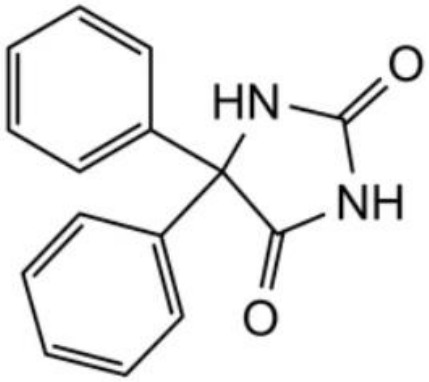

Fig.2: Structure of phenytoin.[4]

Mechanism of action

Phenytoin serves as a first-generation anticonvulsant that primarily works by blocking voltage-gated sodium channels in the neuronal membrane. It selectively binds to these channels during their inactive state, prolonging the refractory period and preventing them from reverting to a resting state. This results in a use-dependent blockade, where the drug specifically inhibits the sustained high-frequency repetitive firing of action potentials—the hallmark of seizure activity—while sparing normal, low-frequency neuronal communication. By obstructing the positive feedback loop required for maximal seizure discharge, phenytoin effectively prevents the spread of focal seizures into adjacent brain tissue [5].

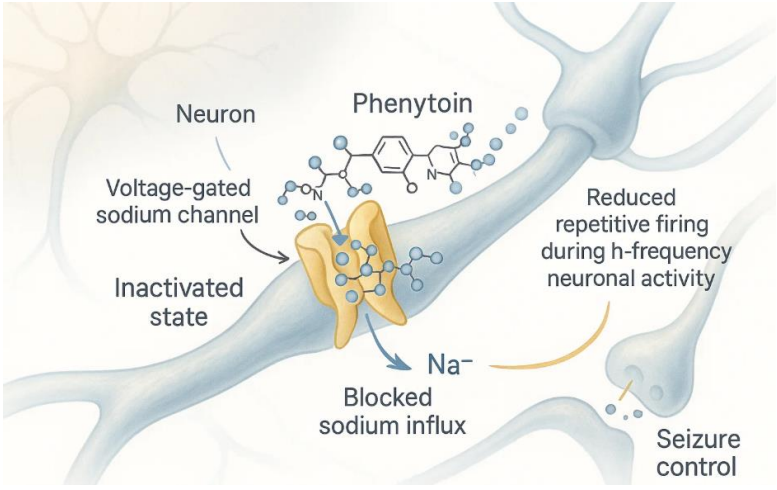

Fig.3: Mechanism of action of phenytoin.

Side effects

- Phenytoin produces several side effects, most of which are dose-related or occur with long-term therapy.

- Early manifestations include: nystagmus, ataxia, diplopia, slurred speech, mental confusion, and drowsiness.
- With prolonged use: gingival hyperplasia, hirsutism, acne, and coarsening of facial features may develop.
- Long-term therapy may also cause peripheral neuropathy and osteomalacia due to interference with vitamin D metabolism.
- Phenytoin can reduce folate levels leading to megaloblastic anaemia and may produce hyperglycaemia.
- When administered during pregnancy, it is associated with fetal hydantoin syndrome [6].

Drug interaction

a) Drug–Drug Interactions of Phenytoin

- Induces hepatic enzymes and reduces the effect of oral contraceptives, warfarin, corticosteroids, and cyclosporine.
- Cimetidine, isoniazid, chloramphenicol, and acute alcohol intake increase phenytoin plasma levels.
- Carbamazepine, phenobarbital, rifampicin, and chronic alcohol use decrease phenytoin levels.
- Valproic acid displaces phenytoin from plasma proteins and increases the free drug fraction.

b) Drug–Food Interactions of Phenytoin

- Enteral tube feeding reduces phenytoin absorption.
- Acute alcohol intake increases phenytoin concentration.
- Chronic alcohol use decreases phenytoin concentration.
- Calcium-rich foods and supplements reduce gastrointestinal absorption.
- Long-term folic acid supplementation lowers phenytoin plasma levels [7].

Contraindications

- Hypersensitivity to phenytoin or hydantoins
- Sinus bradycardia
- Sinoatrial block
- Second- and third-degree atrioventricular block
- Adams–Stokes syndrome

- Concomitant use with delavirdine
- Absence seizures (may worsen condition)
- Severe liver disease
- Pregnancy (relative contraindication).[8]

Marketed formulation of phenytoin

Table 1: Available formulations of phenytoin.[9]

Brand Name	Dosage Form	Strength	Route	Main Use
Dilantin-125	Oral suspension	125 mg/5 mL	Oral	Control tonic-clonic & partial seizures, epilepsy
Dilantin Infatabs	Chewable tablet	50 mg	Oral	Control tonic-clonic & complex partial seizures
Dilantin (extended-release)	Capsule, extended release	30 mg, 100 mg	Oral	Maintenance therapy in epilepsy
Phenytoin sodium injection	Injection solution	50 mg/mL	Intravenous	Treatment and prevention of seizures, especially status epilepticus

PREFORMULATION STUDY

Pre-formulation studies were evolved in 1950 & 1960s. pre-formulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage form that can be mass produced. Pre-formulation investigations are designed to deliver all necessary data especially physicochemical, physico-mechanical and biopharmaceutical properties of drug substances, excipients and packaging materials [10].

IMPORTANCE

- To develop the elegant dosage forms (stable, effective & safe).
- It is important to have an understanding of the physical description of a drug substance before dosage form development.
- It is first step in rational development of a dosage form of a drug substance before dosage form development.
- To choose the correct form of a drug substance.
- To establish compatibility with the common excipients.
- To establish the physicochemical parameters of new drug substance.

- To establish the kinetic rate profile [10].

PREFORMULATION STUDY OF PHENYTOIN

Organoleptic properties:

In pharmaceutical pre-formulation, organoleptic properties are the physical characteristics of a drug substance that can be perceived by the human senses, providing the first indication of its identity and purity. Phenytoin is a white, odorless, crystalline powder with a characteristically bitter taste. These sensory attributes are critical for monitoring stability, as any change in appearance or the development of a yellow color often signals chemical degradation caused by the absorption of atmospheric moisture and carbon dioxide [11].

Physical properties

Determination of Melting point

The melting point of phenytoin was determined using the capillary tube method. A small quantity of the finely powdered drug was filled into a sealed capillary tube and placed in a melting point apparatus. The temperature was increased gradually, and the range at which the drug began to melt and completely liquefied was noted. Phenytoin exhibits a melting point in the range of 295–298 °C, with decomposition indicating high purity and crystalline stability of the drug substance [11].

Determination of solubility

Solubility refers to the maximum amount of a solute that can dissolve in a given quantity of solvent at a specific temperature and pressure to form a homogeneous solution. The solubility of phenytoin was determined by using the shake-flask method, a common approach to evaluating solubility in drug formulation studies. The study involved preparing a saturated solution of phenytoin in various solvents (e.g., water, ethanol, or cosolvent mixtures) and measuring the concentration of phenytoin at equilibrium. The solubility was quantified using high-performance liquid chromatography (HPLC) after the system reached saturation, ensuring that the solute and solvent were in equilibrium. Various formulation techniques, such as the use of solubilizing agents and solid dispersions, were evaluated to improve the dissolution rate and bioavailability of phenytoin [12].

Table 2: Solubility analysis of phenytoin in various solvents [12].

SOLVENT	SOLUBILITY DISCRIPTION
Water	Slightly soluble
Alcohol	Sparingly soluble
Alkaline solution	Freely soluble
Cosolvent mixtures (Eg: propylene Glycol/water)	Increase solubility

Determination of Hygroscopicity

The hygroscopicity of phenytoin was evaluated by exposing the substance to varying humidity conditions. The weight gain was measured over time to assess the water absorption capacity. Phenytoin displayed a moderate hygroscopic nature, with significant moisture uptake observed at relative humidity (RH) levels above 60%. This moisture absorption could influence the physical stability of the drug, particularly in solid dosage forms, leading to changes in crystalline form or dissolution properties [13].

Chemical properties

Partition coefficient

The partition coefficient (P) is defined as the ratio of the concentration of a unionized drug distributed between two immiscible phases, usually n-octanol and water, at equilibrium, and it is commonly expressed as log P. It is a measure of the lipophilicity of a compound and plays an important role in predicting drug absorption, membrane permeability, distribution, and ability to cross biological barriers. Phenytoin (5,5-diphenylhydantoin) is a weakly acidic antiepileptic drug with moderate lipophilicity, having a reported n-octanol/water partition coefficient (log P) of approximately 2.47. This value indicates that phenytoin possesses sufficient lipid solubility to readily cross biological membranes, including the blood–brain barrier, which is essential for its therapeutic action in the central nervous system [14].

Dissociation Constant

The dissociation constant (pKa) of phenytoin is determined experimentally through various methods, with potentiometric titration being one of the most common and reliable techniques. In this method, a known concentration of phenytoin is dissolved in a solution, and a strong acid or base is added while the pH is continuously measured. The pKa is determined from the point of the sharp pH inflection, where the drug undergoes significant ionization. This provides an accurate measurement of the pH at which 50% of phenytoin exists in its ionized

form, which is crucial for understanding its solubility and absorption properties. The dissociation constant of phenytoin has been reported to be approximately 8.3, indicating that it is a weak acid, predominantly unionized at physiological pH (around 7.4), which influences its solubility, absorption, and overall pharmacokinetic profile [15].

Stability studies

Table 3: Stability studies of phenytoin.[16]

CONDITIONS	STABILITY
Room temperature	Phenytoin is stable under normal room temperature in solid dosage forms
High temperature (40°C to 50°C)	Degradation of phenytoin occurs more rapidly with increased temperatures.
Humidity (High moisture)	Phenytoin shows signs of degradation in the presence of excessive moisture.
Light exposure	Phenytoin is relatively stable when protected from light but may degrade with prolonged exposure to direct light.
pH variations	Stability is affected by changes in pH, with degradation occurring more readily under acidic or highly alkaline conditions.

Polymorphism

Phenytoin, a widely used anticonvulsant, has been studied for polymorphism due to its impact on solubility, bioavailability, and stability. Polymorphism refers to the ability of a compound to crystallize in more than one form, which can influence its physical properties, such as solubility and dissolution rate.

Phenytoin exists in at least two polymorphic forms (Form I and Form II), with Form I (bulk) being the more commonly used in pharmaceutical formulations due to its better stability and solubility. Form II (surface-induced phase-SIP), although less common, may exhibit different dissolution characteristics, which could potentially affect the bioavailability of the drug [17].

DRUG EXCIPIENT COMPATIBILITY STUDY

FTIR SPECTROSCOPY

FTIR spectra of pure drug and its mixture with excipients (1:1) were recorded with a FTIR spectrophotometer using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1: 100 and pressed using a hydrostatic press at a pressure of 10 tons for 5 min. The disc was placed in the sample in the sample holder and scanned from 4000 to 500 cm^{-1} at a resolution of $1cm^{-1}$ [18].

The FTIR spectrum of Phenytoin exhibits characteristic absorption bands corresponding to its functional groups. A broad band observed in the region of 3200–3400 cm^{-1} is attributed to N–H stretching vibrations of the imide group, indicating possible hydrogen bonding interactions. Strong absorption bands in the region of 1700–1780 cm^{-1} are assigned to the carbonyl (C=O) stretching of the hydantoin ring, confirming the presence of imide functionality. The aromatic rings of phenytoin are evidenced by C=C stretching vibrations appearing around 1500–1600 cm^{-1}, along with C–H stretching near 3000–3100 cm^{-1}. Additional bands in the range of 1200–1350 cm^{-1} correspond to C–N stretching vibrations, while peaks in the fingerprint region (700–900 cm^{-1}) are associated with out-of-plane bending of aromatic C–H bonds. These spectral features collectively confirm the molecular structure of phenytoin and are consistent with reported vibrational spectroscopic analyses [18].

Table 4: FTIR characterization of phenytoin.

Wavelength (cm-1)	Functional group
3200-3400	N-H stretch (imide)
3000-3100	Aromatic C-H
~1700	C=O (imide) + aromatic C=C
1500-1600	Aromatic C=C
1200-1350	C-N stretch
~1028	Ring/C-N vibration
700-900	Aromatic C-H bending

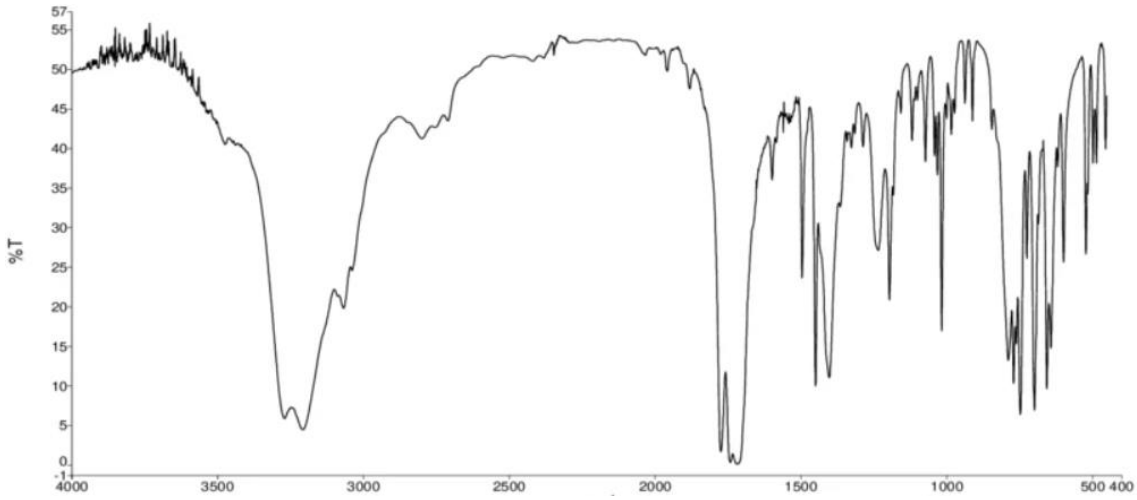

Fig.4: FTIR spectrum of phenytoincm.$^{-1}$

FORMULATION CONSIDERATION

Drug formulation typically involves combining inert materials and excipients with active pharmaceutical ingredients (APIs) to produce viable drug products with desired properties.

The improvements associated with the development of an optimized drug formulation can include enhanced efficacy, longer acting therapeutic effects, reduced side effects, extended API stability and shelf-life, as well as better patient compliance.

INJECTIONS

Injections are fluid preparations intended to be introduced into the body directly into or through the skin, mucous or the serous membranes. Some types of injections are administered in relatively large quantities directly into the venous circulation and are known as infusion fluids. Other solutions, also used in large volumes, are employed for peritoneal dialysis and, while presenting the same problems of sterility and quality control to the producer, must be considered outside the scope of the present review since they are not used for introducing drugs into the body but rather for the removal of toxic waste products in patients with kidney failure [19].

FORMULATION OF PHENYTOIN SODIUM INJECTION

The formulation of phenytoin sodium injection (50 mg/mL) is a specialized process that utilizes a co-solvent system to overcome the drug's poor aqueous solubility and ensure long-term stability[20].

COMPOSITION

Table 5: Formulation of phenytoin sodium injections.

S/N	Ingredient	Quantity (mg/mL)	mg/unit	
			100mg/2ml vial	250mg/5ml vial
1	Phenytoin Sodium	50mg	100 mg	250mg
2	Propylene Glycol	~400mg	~ 800mg	~2000mg
3	Ethanol	~100mg	~200mg	~500mg
4	Sodium Hydroxide	q.s. (to pH ~12)	q.s.	q.s.
5	Water for Injection	q.s. to 1ml	q.s. to 2 ml	q.s. to 5 ml

PREPARATION OF PHENYTOIN SODIUM INJECTION

The preparation involves precise mixing and environmental controls to maintain stability:

1. Preparation of Vehicle: Purge Water for Injection with Nitrogen to remove oxygen, which helps prevent oxidative degradation.

2. Co-solvent Integration: Add and stir the absolute Ethanol and Propylene Glycol into the water.

3. API Dissolution: Add Phenytoin Sodium to the co-solvent mixture and stir until completely dissolved.

4. pH Adjustment: Carefully add 1N Sodium Hydroxide to adjust the pH to 12.0. This high alkalinity is mandatory to keep the phenytoin sodium in its soluble salt form.

5. Final Volume Make-up: Add the remaining Nitrogen-purged Water for Injection to reach the required final volume.

6. Sterile Filtration: Filter the solution through a 0.22 um sterile filter to remove microorganisms and any particulate matter.

7. Aseptic Filling: Fill the solution into clear glass ampoules (typically Type 1 glass), purge the head space with Nitrogen, and seal immediately[21].

EVALUATION OF PHENYTOIN SODIUM INJECTION

EVALUATION

Evaluation is the process of confirming a drugs identity and assessing its quality and purity.

- Identity-Determining the drugs biological sources.
- Quality-The amount of the active ingredients that are present.
- Purity is the degree to which a medicine contains foreign organic components [22].

pH

pH is the measure of concentration of protons (H+) in a solution that is the potential of hydrogen. The pH is determined by the potentiometric method using a pH meter with a glass electrode. In this method, the instrument is first calibrated using standard buffer solutions, after which the electrode is immersed directly in the injection solution. The pH is measured based on the electrical potential difference between the glass and reference electrodes, which corresponds to hydrogen ion concentration and is displayed directly as pH. This is the standard and accurate method used for injectable preparations because it gives precise results without using indicators. For Phenytoin Sodium Injection, the pH is typically maintained in an alkaline range of about 10.0 to 12.0 to ensure the drug remains soluble and stable in solution [23].

Fig.5: Testing of pH using pH meter.

Particulate matter

Particulate matter refers to the presence of unwanted, non-dissolved solid particles in a parenteral formulation. These particles may be visible or sub-visible and can originate from raw materials, manufacturing processes, packaging components, or contamination during handling. Evaluation of particulate matter is an important quality control test because injections must be free from particles that could cause blockage of blood vessels, irritation, inflammation, or embolism. According to pharmacopeial standards, injectable preparations are inspected for visible particles by visual examination and for sub-visible particles using specialized instruments. Ensuring absence of particulate matter helps maintain the safety, sterility, and quality of injections for parenteral administration.

In phenytoin sodium injection, the main type of particulate matter is drug precipitation, especially formation of phenytoin free acid crystals when the solution becomes unstable due to pH changes or improper dilution. It may also contain sub-visible particles that are microscopic crystals and sometimes visible white crystalline precipitates, particularly if the drug is mixed with incompatible IV fluids such as dextrose solutions. Less commonly, particulate matter may arise from manufacturing sources like glass or rubber fragments. Since phenytoin sodium injection is formulated at a high alkaline pH (about 10–12) to maintain solubility, any reduction in pH can lead to crystallization [24].

Sterility

Sterility is defined as the absence of all viable microorganisms, including bacteria, fungi, and spores, in a sterile injectable preparation. It is a critical quality control test for parenteral

products to ensure they are safe for administration directly into the body without causing infection.

Sterility testing of Phenytoin Sodium Injection is performed to confirm the absence of viable microorganisms in the final sterile product. According to pharmacopeial standards (IP/USP), the test is carried out either by the membrane filtration method or the direct inoculation method, followed by incubation in suitable culture media such as fluid thioglycollate medium (for bacteria) and soybean-casein digest medium (for fungi) at specified temperatures. The samples are observed for microbial growth over a defined incubation period. Phenytoin sodium injection must pass this test to ensure it is free from contamination and safe for intravenous administration, as any microbial presence could lead to serious infections [25].

Fig.6: Membrane filtration method.

***In-Vivo* Pyrogen test (Rabbit Test)**

The *In-vivo* pyrogen test detects fever-producing contaminants using healthy rabbits. Prior to injection, the rabbit's body temperatures are recorded over a 90 min pretest period, and only those with stable baseline temperatures are used. Phenytoin sodium injection, warmed to about 37 °C, is administered intravenously (via the marginal ear vein) using pyrogen-free equipment at the prescribed dose (about 10 mL/kg). After administration, rectal temperatures are recorded every 30 minutes for 3 hours, and the maximum rise in temperature for each rabbit is noted. The preparation passes the test if no individual rabbit shows a rise of ≥0.5 °C and the total temperature rise of all rabbits remains within pharmacopoeial limits (typically ≤1.2 °C); otherwise, it fails or requires repeat testing [26].

Fig.7: Pyrogen test.

Stability

Stability is defined as the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating period. The objective of stability study is to determine the shelf life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications. Stability testing also gives information about drug vulnerability to degrade by oxidation, hydrolysis, isomerisation, polymerization, decarboxylation, moisture, heat and light. Stability study is performed for specific time at specific environmental condition according to ICH guidelines [27].

Leakage Test

Leakage test is a quality control test used to verify the integrity of the container–closure system (ampoules, vials, or prefilled syringes) and to ensure the product remains sterile, stable, and free from contamination throughout its shelf life. It detects any microscopic cracks, improper sealing, or defects that may allow entry of microorganisms, moisture, or air, or cause loss of the formulation. The test is commonly performed using methods such as dye ingress test, vacuum/pressure decay test, or bubble emission test, with dye ingress being widely used for ampoules. In this method, the sealed containers are immersed in a colored dye solution (e.g., methylene blue) inside a vacuum chamber; vacuum is applied to remove trapped air and encourage dye entry into any defective units, followed by restoration of atmospheric pressure. The ampoules are then washed externally and visually inspected against a contrasting background for dye penetration. Presence of dye inside indicates leakage (test failure), while absence confirms proper seal integrity. This test is essential

because leakage can compromise sterility, lead to contamination, alter pH, and reduce the safety and efficacy of injectable products [28].

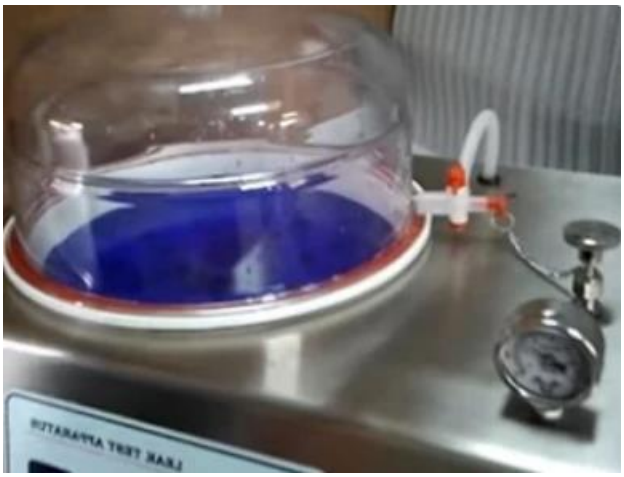

Fig.8: Dye bath test.

Packaging of Phenytoin sodium injection

Types of packing

Primary Packaging: Sterile, single-use glass vials or ampoules sealed with rubber stoppers and aluminum caps. This packaging maintains sterility, prevents contamination, and protects the drug from moisture and air.

Secondary Packaging: Cardboard cartons or boxes that contain the primary containers. These provide additional physical protection and display necessary labeling and product information.

Tertiary Packaging: Bulk shipping cartons or crates used for transport and storage.

Tertiary packaging safeguards multiple units during handling and distribution [29].

LABELLING REQUIREMENTS

The labeling requirements for Phenytoin Sodium Injection include clear identification of the product name, strength (e.g., 50 mg/mL), dosage form, and total volume per container, along with batch number, manufacturing and expiry dates for traceability. The label must also state manufacturer details and regulatory license information. Storage conditions such as “store below 25°C” and “protect from light” are required, along with handling instructions like “do not freeze” and “for intravenous use only.” Safety information including sterility status, “for single use only” (for ampoules), and warnings to inspect for particulate matter or discoloration before administration must also be included to ensure safe use in clinical practice [30].

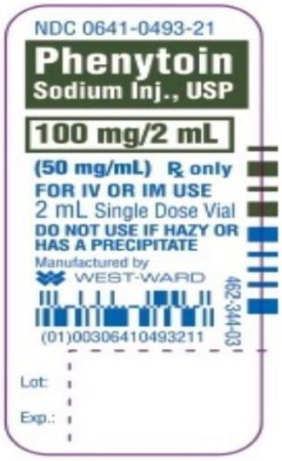

Fig.9: Label of phenytoin sodium injection.

STORAGE AND STABILITY

Phenytoin Sodium Injection require careful handling due to its sensitivity to light and risk of precipitation. It should be stored at controlled room temperature (typically 20–25°C) and protected from light, preferably in its original packaging. The solution must not be refrigerated or frozen, as low temperatures may cause crystallization or precipitation. The injection should be inspected before use, as it may form haze or crystals if improperly stored; in such cases, it should not be administered. Once opened or diluted, it should be used immediately and any unused portion discarded, since it contains no preservative and has limited stability after opening [30].

SPECIAL HANDLING INSRUCTIONS

- Inspect solution carefully for precipitation or crystals before use.
- Maintain strict aseptic technique during preparation and administration.
- Dilute only with 0.9% sodium chloride solution (avoid dextrose-containing fluids).
- Administer immediately after dilution; do not store prepared solution.
- Avoid mixing with other intravenous drugs or solutions in the same line.
- Administer slow IV infusion with monitoring to prevent complications related to precipitation and instability [31].

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