



SEMISOLID DOSAGE FORM OF PHENYTOIN SODIUM

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Article Received on: 14/09/12 Revised on: 01/10/12 Approved for publication: 10/11/12

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ABSTRACT

Phenytoin sodium was formulated in a solid dosage form using different bases; o/w emulsion base, water soluble base, oleaginous base, and vanishing cream base. Bases were prepared in two different concentrations, 5% and 10% w/w. The diffusion of the drug from each of the above bases was investigated. Results indicated that the effect of the type of ointment base on the release rate of phenytoin sodium is significant. The rate and extent of phenytoin sodium release and diffusion through mouse skin was higher from the water soluble base (10% w/w) compared to other ointment bases, the difference was highly significant (P< 0.05).

Keywords: Phenytoin sodium, phenytoin, semisolid dosage form, ointment, topical application.

INTRODUCTION

For decades phenytoin has been used in the treatment of convulsive disorders & became available as 25, 30, 50, and 100mg prompt- and extended release capsules and 50 and 100mg coated tablets.¹ Also available as a clear sterile solution of 250mg /5ml (in a vehicle of 40% propylene glycol and 10% ethanol) for parenteral use² for pediatric purpose it is available as an oral suspension (125mg/5ml).³

Development of fibrous overgrowth of gingival (gingival hyperplasia). This apparent stimulatory effect of phenytoin on connective tissue suggested an exciting possibility for its use in wound healing. In 1958 Shapiro found out that oral phenytoin sodium pretreatment improved pain and accelerates healing of surgically created gingival wound in patients with periodontal disease.⁴ Later on the healing effect of orally administered phenytoin was confirmed by many studies.⁵ However; phenytoin sodium was then applied topically in the healing of burns, diabetic gangrenous ulcers, leprosy ulcers and on wound surfaces.⁶⁻⁹ Also it was effective in treating several skin infections like, impetigo, infected contact dermatitis and infected boils.⁸

These clinical trials together with others organized in many countries confirmed the fact that whether phenytoin is given orally or topically was effective in enhancing wound healing. However, in comparison with the oral administration, topical application of phenytoin in the treatment of epidermolysis bullosa simplex suggested a quicker healing of the ulcers.¹⁰

The pure powder or even the powder from phenytoin capsules were used for the topical application.^{8,9} However, powders are hard to be held on the skin in addition to the difficulty in putting the recommended amount of the powder on the affected area.

The efficiency of phenytoin in the healing process of multiple skin conditions and that the powder form is not the best that could be applied, necessitates the need to prepare phenytoin sodium in a semisolid dosage form to be used for external application in the treatment of skin disorders.

This study was carried out to find a suitable ointment base for the topical application of phenytoin with optimal phenytoin sodium release. In summary the investigation includes;

1. Formulation of the drug using different kinds of ointment bases and drug concentrations (5% w/w and 10% w/w).
2. Studying the diffusion of the drug from these different ointment bases through excised mouse skin.

3. Selection of the best formula regarding the diffusion of the drug and stability studies which include;

- a. Observation of the physical properties which include changes in color, odor, and PH.
- b. Determination of the concentration of the active ingredient over the storage period at different temperature.

METHODS

Preparation of the ointments

The general method employed for the preparation of the ointment bases was fusion method. The drug was then incorporated by triturating using slab and spatula. The quantities of ingredients were taken on weight/ weight basis. Four types of ointment bases were selected for this study for each base; two concentrations 5% w/w and 10% w/w of the drug were used. The procedure for the preparation of each ointment base was as follows:-

Water – soluble base:- The formula was; table 1

The polyethylene glycol 4000 and cetyl alcohol were melted on a water bath at 65°C and the polyethylene glycol 400, which was previously warmed to the same temperature in another beaker, was then added. The mixture was allowed to cool with continuous but gentle stirring until congealing.¹¹

Oil – in – water emulsion base:- The formula was; table 2

The white beeswax and cetyl alcohol were melted on a water bath, and the temperature was raised to about 75°C. The water was also heated to 75°C in another beaker and the sodium lauryl sulfate and propylene glycol were added to it. The aqueous phase was then added to the oily phase with gentle stirring until congealing.¹¹

Vanishing cream:- The formula was; table 3

Melting the stearic acid to 85°C, on a water bath aqueous solution of KOH prepared. this hot alkaline solution is gradually poured into the liquefied fat (stearic acid) while the whole is stirred briskly. The temperature is maintained at 85°C for about 10 minutes after all the hot alkali has been added to stearic acid. The container is removed from the source of heat, stirring continued until the cream thickness sets.¹²

Oleaginous base: - The formula was; table 4

All the above ingredients were mixed and heated gently on a water bath until melting, then the beaker was taken out of the bath and the preparation was stirred gently until congealing.¹³

Preparation of mouse skin

The preparation of mouse skin was carried out according to the following procedure;¹⁴ the full thickness of abdominal surface of the mouse, (Male, 8–12 weeks old, 25–35gm weight) was taken. The skin was shaved lightly with an electrical clipper taking care to prevent any damage to the surface of the skin. After two days of shaving, the mouse was sacrificed by ether inhalation; a rectangular section of abdomen skin was excised from the animal with surgical scissors.

The skin was wiped with cotton tip soaked in ether to remove any adhering fat, and then kept in a phosphate buffer of PH 7.4 for about 1 hour in a water bath at constant temperature of 37°C to remove any UV absorbing materials. The skin was either used immediately or frozen until ready for use.¹⁵

The in vitro diffusion experiment

The containers used as diffusion cells to support the ointments were glass beakers 2.5cm in diameter and 2.2cm in depth, the diffusion cell was completely filled with the ointment and the excess was removed with the edge of a spatula to produce an even, uniform surface of constant dimensions. The weight of ointment required to fill the diffusion cell was approximately 10gm. The excised skin was mounted on the diffusion cell, with the stratum corneum facing the donor compartment i.e. (the ointment) and the dermis facing the receiver compartment (phosphate buffer PH 7.4). The skin was then fixed on the diffusion cell with cotton thread. Then the diffusion cell was inverted and immersed to about half its depth in 500 ml of phosphate buffer PH 7.4 contained in a one liter jar.

The jar was partially immersed in a large water bath equilibrated at 37°C inside the U.S.P dissolution apparatus. The collecting medium (receiver) was agitated using a bladed stainless steel stirrer, the edges of the stirring blade were positioned beside the diffusion cell, and stirring rate was maintained at 100rpm. The diffusion of the drug was followed by monitoring the receiver medium concentration for 5 hours, 5ml samples were pipette by micro filter from the receiver medium after half an hour and replaced each time by 5ml of fresh medium (phosphate buffer PH 7.4). Each experiment was repeated three times. The samples were immediately analyzed for their drug content by UV at 240nm and the absorbance were converted to concentrations following a prepared standard curve. As shown in figure 1.

Stability studies

Stability studies were carried out on the ointment with the best release which was the water soluble base. Phenytoin sodium ointment (10% w/w) was prepared as previously described. The prepared ointment was divided among five groups of air tight amber containers, each group consist of four containers of phenytoin sodium ointment (10% w/w) besides four containers of water soluble base alone as blank were stored. Each group was stored at either of the followings (40°C, 50°C, 60°C, 70°C, and 90°C). The stability studies include the effect of storage time on the followings;

The concentration of the drug

Studying the stability of the drug in the selected ointment base, the concentration of the drug in the ointment base was determined after 1, 15, 30 and 45 days. This was done by dissolving of 100mg of the ointment in 10ml of methanol. The solution was filtered and 1ml of the filtrate was taken and diluted to 10ml with methanol and analyzed spectrophotometrically at 240nm.

A working standard curve figure (1) for the drug was prepared following the same procedure indicated above.

The PH of the ointment

The ointment 2gm were dispersed in 10ml distilled water with stirring then the PH of the mixture was measured using PH meter. The same procedure was repeated to determine the PH of the stored ointments at the indicated time intervals.

Other physical properties of the ointment

Physical properties (color, odor) of the stored ointments were observed over storage period.

Statistical analysis

Analysis of variance (ANOVA) was used for the comparison between figures. AP value of less than 0.05 was considered to be significant.

RESULTS

Effect of different concentrations of phenytoin sodium from different ointment bases: Figures (2, 3, 4, and 5) show the effect of different concentrations of phenytoin sodium 5% w/w, 10% w/w on its diffusion from different ointment bases. A significant difference was obtained comparing the diffusion profiles of the various concentration of phenytoin sodium in each ointment base ($P < 0.05$).

Diffusion of phenytoin sodium from different ointment bases: Figures (6 and 7) illustrate the differences in phenytoin sodium diffusion from various ointment bases containing the concentration 5% w/w, 10% w/w of the drug respectively. Their efficiency for the diffusion process was in the following order for 5% w/w; water soluble base (no.2) > oleaginous base (no.3), O/w emulsion base (no.1) > vanishing cream base (no.4)

This sequence was also true for 10% w/w ointments of phenytoin sodium (figure 7). The differences in the profiles were statistically significant ($P < 0.05$). The water soluble ointment base gave the highest diffusion. So ointment of phenytoin sodium in this base was chosen for further studies.

Effect of storage time and temperature on the stability of the drug in base no.2: No change in the concentration of the drug was observed during the 45 days of storage at all temperatures, indicating that the drug under these conditions was stable.

Effect of storage time and temperature on the physical properties of the selected ointment base no.2: The physical properties of the selected ointment were examined. No changes in the color and odor of the ointments stored at 40°C were noticed, however, a pale yellow color was developed when the ointments were stored at 50°C with the appearance of an odor. These changes were more noticeable at temperature 60°C with the ointment becoming amber in color and the appearance of strong odor, these changes gradually increased with the increase in temperature.

The possible changes in pH over the storage period and at the temperatures indicated were followed; no significant changes in the pH of the ointment were noticed with the pH being around 10.51.

DISCUSSION

The first controlled clinical trial, published in 1958, mentioned the accelerated healing of periodontal patients with surgical wounds treated with oral phenytoin.⁴ This fact stimulated application of phenytoin in wound healing as well as multiple skin disorders such as different types of ulcers, burns, and skin infections such as; impetigo, infected contact

dermatitis and infected boils.⁵⁻¹⁰ In comparison with the orally administered phenytoin in epidermolysis bullosa simplex patients, topical phenytoin showed quicker healing of the ulcers.¹⁰

Some studies have used pure phenytoin or phenytoin sodium powder, powder from phenytoin capsules.^{8,9} However, in a comparative study, four topical phenytoin formulations (gel, cream, phenytoin sodium powder and phenytoin powder) were tried in wound healing using experimental rats revealed that the powder showed best results.¹⁶ A dose of 20 mg/cm²/day of phenytoin powder was recommended to be used topically in wound healing in previous studies.^{8,17}

Topical phenytoin was better than sodium chloride (0.9 %) dressing in the treatment of leprosy trophic ulcers as healing was achieved within a week in the phenytoin group whereas in the control group discharge persisted through the second and third week.¹⁸ However, when used in patients with intractable decubitus ulcers and missile wounds healing ranged from 1 to 3 weeks compared to 6-8 weeks for the group that have been treated with chlorhexidine and hydrogen peroxide.¹⁹

A patent by Lasker introduced said composition "comprising silver ammonium phenytoin complex and a phenytoin in dry, finely divided form". The composition is applied topically directly onto the affected wound or tissue or incorporated in or coated on a dressing (bandage).²⁰

Thus thinking of putting phenytoin sodium in a semisolid dosage form for topical application should be considered. This might have the advantages of being with fewer side effects than systemic administration besides the drug is applied directly to the affected area or tissue. Ointment is the dosage form considered in our labs.

There are a number of ointment bases which might be considered for topical preparations such as; water-soluble base, water miscible base (vanishing cream base), absorption base and oleaginous ointment base which were all considered in this work to select the best formulation that meets the criteria of the ointment. As it is shown in figures 2, 3, 4, and 5 that phenytoin sodium diffusion was found to increase with increasing concentration of the drug in the ointment base.

One important factor that plays a role in percutaneous absorption is the release of the drug from the vehicle, which is dependent on the solubility of the drug in the base.²¹ In this study the rate of diffusion of the drug decreased in the following order; water soluble base > oleaginous base > o/w emulsion base > vanishing cream base.

Highly significant difference ($p < 0.05$) exist in the rate of diffusion of phenytoin sodium from the water soluble base compared to that from other bases. On the other hand, small differences exist in the rates of diffusion of phenytoin sodium from oleaginous base compared with that from o/w emulsion base and that from vanishing cream. A general rule in ointment formulation is that, if the drug is held firmly by the vehicle the rate of release is slow.^{21,22} This may explain the differences in the rates of release of phenytoin sodium from the ointment bases. The high release rate of phenytoin sodium from water soluble ointment base that contains mainly polyethylene glycol may be due to the diffusion of water through the mouse skin and formation of water-polyethylene glycol solution,²¹ which increases the solubility of the drug in the solvent acceptor and then it's rate and extent of release i.e. the soluble base will diffuse through the mouse skin taking the dissolved drug with it. On the other hand, the three ointment bases (oleaginous, o/w emulsion and the vanishing cream) showed very small differences in the

amounts of phenytoin sodium permeated through the mouse skin over 5 hours of diffusion.

Figures 6 and 7 indicate that the diffusion of phenytoin sodium from an ointment base through mouse skin can be altered by modifying the composition of the vehicle. Therefore, when the drug dissolves in the vehicle, the rate of release of the drug decreases and thus the diffusion of the drug will be slow too. Conversely, if the drug has a low affinity for the vehicle, it will be readily released.

Oleaginous base contained primarily yellow soft paraffin with cetyl alcohol and several additional lipoidal constituents. Cetyl alcohol can associate with water and facilitate the release of phenytoin sodium across the mouse skin and this interpreted that the oleaginous base is secondly ranking in the release of the drug. Third base in release is the o/w emulsion from which the release of the drug is due to sodium lauryl sulfate availability in the composition of the base which is known to promote percutaneous absorption by altering drug solubility and affecting the drug concentration in the vehicle as well as altering the skin barrier through surfactant-membrane interaction.²³

The drug was found to be stable in the ointment bases under the conditions forementioned of storage at different temperatures. However, the physical study revealed a change in color and odor at high temperatures, at 50⁰C and over. While there was no change in the pH of the ointment at all conditions.

Table 1

Polyethylene glycol 400	47.5 gm
Polyethylene glycol 4000	47.5 gm
Cetyl alcohol	5.0 gm

Table 2

White beeswas	1 gm
Cetyl alcohol	15 gm
Propylene glycol	10 gm
Sodium lauryl sulfate	2 gm
Water	72 ml

Table 3

Stearic acid	200 gm
KOH	14 gm
Water	800 ml

Table 4

Wool fat	5 gm
Hard paraffin	5 gm
Cetyl alcohol	5 gm
Yellow soft paraffin	85 gm

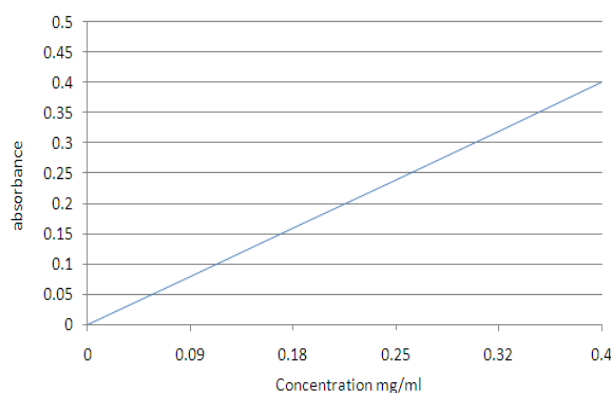


Fig. (1) standard curve of phenytoin sodium in phosphate buffer

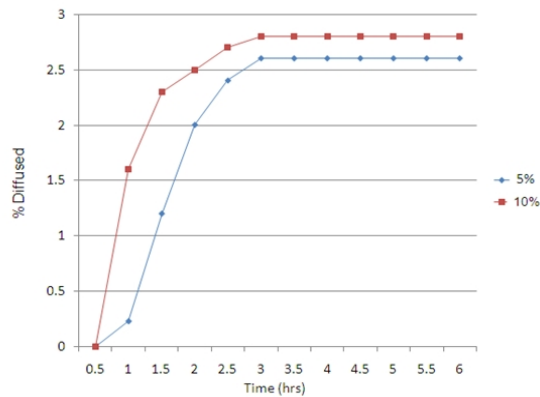


Fig. (2) Diffusion of different concentrations of phenytoin sodium from O/W emulsion base.

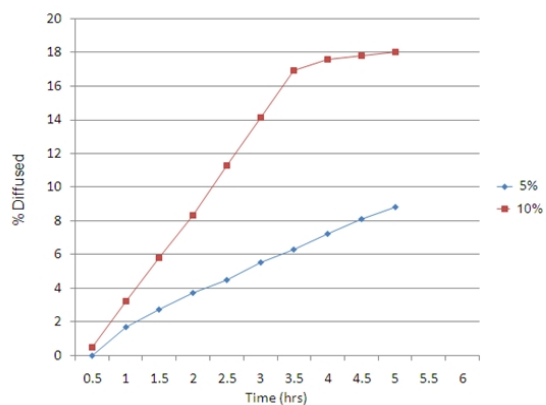


Fig. (3) Diffusion of different concentrations of phenytoin sodium from water soluble base

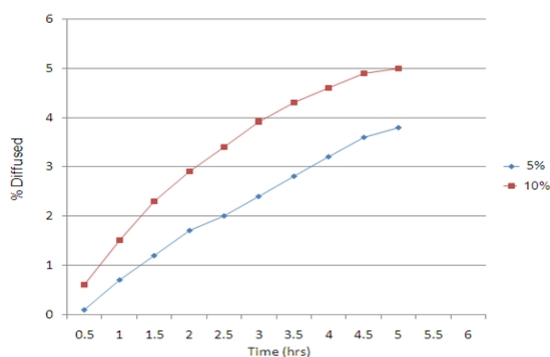


Fig. (4) Diffusion of different concentrations of phenytoin sodium from oleaginous base

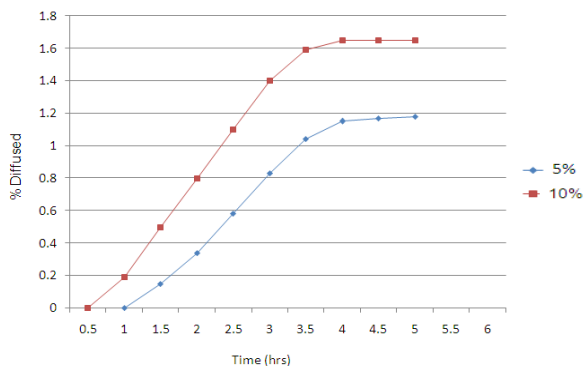


Fig.(5) Diffusion of different concentrations of phenytoin sodium from vanishing cream base

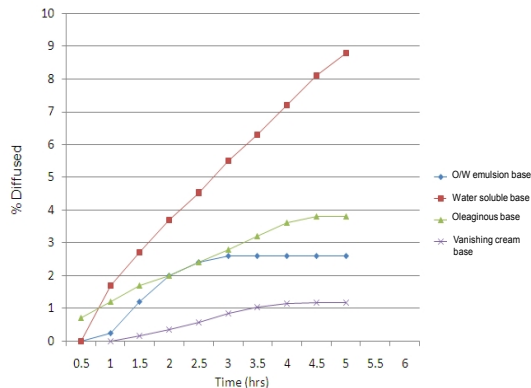


Fig (6) Diffusion of phenytoin sodium (5% w/w) from different ointment bases

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Source of support: Nil, Conflict of interest: None Declared