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# PROCESS OPTIMIZATION AND REACTION OPTIMIZATION OF ANTIEPILEPTIC DRUG PHENYTOIN

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## ABSTRACT

A simple, clean, fast, efficient and economical, microwave-assisted method for the synthesis of Phenytoin has been developed. The antiepileptic drug Phenytoin is synthesized by reaction between Benzil and Urea. The activation of Benzil and Urea is a type of pinacole-pinacolone rearrangement reaction. Comparison of microwave assisted synthesis with the conventional methods of synthesis demonstrates advantages related to shorter reaction time and in some cases better reaction yields. Moreover, microwave activation is a very convenient method for the synthesis of phenytoin resulting in good yield and purity.

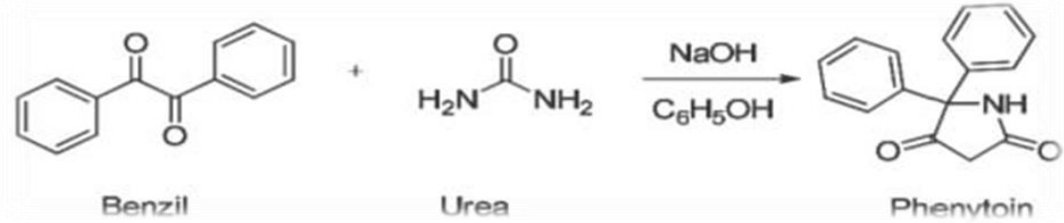
**KEYWORDS:** Process Optimization, Reaction Optimization, Antiepileptic Drug, Phenytoin.

## INTRODUCTION

Traditionally, organic synthesis is carried out by conductive heating with an external heat source. This is a comparatively slow and inefficient method for transferring energy into the system, since it depends on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture. Microwave-enhanced chemistry is based on the efficient heating of materials by "microwave dielectric heating" effects. This phenomenon is dependent on the ability of a specific material to absorb microwave energy and convert it into heat. Synthesis of phenytoin requires ethanol as solvent and two hours of reflux in the conventional methods. The synthesis of phenytoin by the reaction of urea with Benzil in presence of aqueous sodium hydroxide in absence of solvent (ethanol) under microwave irradiation is described. The products are obtained in quantitative yields and excellent purities.

Phenytoin is used to control certain type of seizures, and to treat and prevent seizures that may begin during or after surgery to the brain or nervous system. Phenytoin is in a class of medications called anticonvulsants. It works by decreasing abnormal electrical activity in the brain.Phenytoin is classified as a hydantoin derivative and despite its narrow therapeutic index it is one of the most commonly used anticonvulsants.

**Preparation of Phenytoin from Benzil and Urea**




**Experimental Work: Proposed Method**

- Place 5.3 g (0.025mol) of benzil, 3.0 g (0.05 mol) of urea, 15 ml of aqueous sodium hydroxide solution (30%) and 75 ml of ethanol in a round bottomed flask of 100 ml capacity.
- Set up reflux condenser to the flask and boil using a Microwave for 6 min at specific power (method A) at $90^0$-$100^0$ C and for 7 min at power (method B) at $100^0$-$120^0$ C.
- Cool it at room temperature.

- And, pour the reaction mixture into 125 ml of water and mix carefully.
- Allow the reaction mixture to stand for 15 min.
- And then filter the product under suction to remove an insoluble by-product.
- Render the filtrate strongly acidic with concentrated hydrochloric acid.
- And then cool in ice-water.
- And immediately filter off the precipitated product under suction.
- Recrystallize at least once from Hydrochloric Acid to obtain about 2.8 g (44%) of pure 5, 5-diphenylhydantoin, Melting Point 297-298 °C

In microwave assisted synthesis two methods were used. In method-A intensity (power) of the wave were kept specific time for irradiation was varied the yield. In Method-B intensity of the wave was varied and time for the irradiation was increased.

In all two methods time required for the reaction was reduced and also the reaction can be carried if the solvent changed to acetic acid and sodium nitrate. The yield was also increased as compared to the conventional method.

**Calculation of Phenytoin by Proposed Method (Reaction Optimization):-**

Molecular Weight of Benzil = 210.23 gm/mol

Molecular Weight Phenytoin = 252.26 gm/mol

Weight Taken Of Benzil = 5.3 gm

Practical Yield (at $90^0$ - $100^0$ C) = 4.17 gm

Practical Yield (at $100^0$ - $120^0$ C) = 4.20 gm

$$\text{Theoretical Yield} = \frac{\text{Mol.weight of precursor}}{\text{Mol.weight of product}} \text{ x}$$

Quantity of precursor taken

$$= \frac{210.23}{256.26} \text{ X } 5.3$$

$$= 4.34 \text{ gm}$$

$$\text{Percentage yield} = \frac{\text{Percentage yield}}{\text{Theoretical yield}} \text{ X } 100\ \%$$

- **at $90^0$ - $100^0$ C**

$$\% \text{ yield} = \frac{4.17}{4.34} \text{ X } 100\ \% = 96.10\ \%$$

- **at $100^0$ - $120^0$ C**

$$\% \text{ yield} = \frac{4.20}{4.34} \text{ X } 100\ \% = 96.94\ \%$$

## RESULT AND DISCUSSION

The Biltz synthesis is a common way to synthesize phenytoin starting from benzil and urea. The microwave heating effectively reduced the reaction time from (2-20) hours to a few minutes (1-10 minutes). Synthesized phenytoin compounds were characterized by their physical, chemical and spectral data.

**Comparison of the time taken by Proposed Microwave Reaction Optimization and time taken by conventional optimization.**

| Sr. No. | Method | Solvent Used | Temperature | Time | % yield |
|---|---|---|---|---|---|
| I | Conventional Method | Sodium Hydroxide& Ethanol | $100^0$C | 2 hrs | 89.30% |
| II | Green Chemistry Approach | Sodium Nitrate & Acetic Acid | $80^0$C | 1.5hrs | 95.95% |
| III(A) | Proposed Method (Process Optimization & Reaction Optimization) | Sodium Hydroxide& Ethanol | $90^0$C -$100^0$C | 6 min | 96.10% |
| (B) | | | $100^0$C-$120^0$C | 7 min | 96.94% |

## SUMMARY AND CONCLUSION

We synthesized Phenytoin by optimizing the process and reaction at specific temperature for specific time. In Proposed method (Process optimization & reaction optimization) synthesis of Phenytoin was increased when temperature and time was increased. If it is compared to conventional method and green chemistry approach the time consumed was very less and the % yield of compound was high. From the above result, it would be concluded that it is very convenient method due to enhanced reaction rates, higher yields, improved purity, ease of work up after the reaction and eco-friendly reaction conditions compared to the conventional methods. In process optimization , microwave irradiated synthesis of phenytoin was carried out to get higher yield with less reaction time period as compared to conventional method.

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