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# "SYNTHESIS AND SOLUBILITY ENHANCEMENT OF PHENYTOIN BY SOLID DISPERSION USING VARIOUS POLYMERS"

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**Abstract**: - The present study was undertaken to synthesized phenytoin using benzil and urea by using microwave synthesizer and solid dispersion of phenytoin was prepared using with different carriers such as PEG -6000, PVPK-30 and D – Mannitol bythe solvent evaporation method for increasing dissolution rate and bioavailability of the drug. Polymers used in solid dispersion techniques are hydrophilic in nature and compatible with drug to enhance drug dissolution rate. These different ratios of solid dispersion were characterized by UV spectroscopy for saturated solubility and dissolution study and it was observed that and dissolution rate was enhanced in the ratio of PEG -6000 (1:3) as compared to other ratios of other carriers.

## Introduction.

The oral drug delivery is the most common and easiest method of delivery because of its convenience and ease of consumption. From a patient's point of viewswallowing a dosage form should be comfortable and easiestmeans of taking the dosage form. As a result, patient compliance and drug treatment is more effective with orally administered dosage form as compared to other routes of administration, for example, parenteral.

Over other types of dosage forms the oral dosage forms have many benefits like accurate dosage, less bulky, greater stability and easy tomanufacturing.In current scenario, the formulation scientists inpharmaindustry faces the challengeto formulate poorly soluble compounds for oral delivery. Nearly 40% of identified potential new drug by R& D are poorly water soluble. Large dose is required to produce desirable effect for the poorlywater soluble drug because they show lower release rate and poor bioavailability so larger dose may leads to toxicity of the drug. So the best option for increasing release rate is improvement of the solubility through formulation approach.

The enhancementsof bioavailability of poorly water-soluble drugs results in poor bioavailability because of low and uncertainty levels of absorption. Drugs which undergo dissolution rate limited, gastrointestinal absorption generally show improved dissolution and bio availability because of reduction in particle size of drug .However, particle size reduction of drugs which often leads to aggregation and agglomeration of particles because of poor wet ability. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have reduced the episodes of these problems and

increase dissolution of poorly soluble drugs. The development of solid dispersions as a practically viable method to increase bioavailability of poorly water-soluble drugs and also overcame the limitations of previous approaches such as salt formation, solubalization by cosolvents, and particle size reduction.

**Solid Dispersion**

Solid dispersion is defined as the dispersion of one or more active pharmaceutical ingredients in an inertcarrier in a solid state.

In 1961, Sekiguchi and Obi were the first to introduce the solid dispersions to increase the dissolution and oral absorption of poorly water-soluble drugs. In this method, the poorly soluble drug and carrier are dissolved in organic solvent and then the mixture is subjected to evaporation to form solid powder. Various water soluble polymers as well as water insoluble polymers are used for the preparation of solid dispersion such as soluplus, polaxamer, HPMCAS, HPMC, PVP K30.

In the BCS i.e. biopharmaceutical classification system drug with the high and low solubility and permeability are classified. Solid dispersion technologies are the most promising technology for improving the oral absorption andbioavailability BCS class II drug.

**ADVANTAGES:**

- To reduced particle size.
- To improve wettability.
- To improve porosity of drug.
- To decrease the crystalline structure of drug into the amorphous form.
- To improve dissolution in water of a poorly water soluble drug.
- To increase drug solubility, dissolution rate, absorption and bio-availability
- Improved stability of the drug.
- To formulate the fast release dosage form.
- To reduce side effect of certain drugs.
- To mask the unpleasant taste and smell of the drug.
- Improvement of drug release from ointments and creams.

**DISADVANTAGES:**

- The instability of drug.
- In solid dispersion temperature and moisture have more adverse effect than on physical mixtures.
- It is difficult to handle because of crudity.

Phenytoin also called as diphenylhydantoin its having a potent anticonvulsant used to treat and prevent generalized grand mal seizures, complex partial seizures and status epilepticus. Phenytoin is acute idiosyncratic drug induce liver disease that can cause severe and fatal.Phenytoin is a hydantoin derivative non sedative with an anticonvulsant activity. Phenytoin act by promoting

sodium efflux from neuron from located in the motar cortex reducing potention prevent cortical seizure foci spreading to stabilizing threshold against hyper excitability.

Phenytoin is one of the most widely used antiepileptic drugs for generalized tonic-clonic simple and complex partial seizures. Occasionally it is used as a slow I.V. drip fortreating status epilepticus. It is also a second choice of drug after carbamazepine fortrigeminalneuralgia. It is used to treat cardiac arrhythmias.

It is poorly water soluble and belongs to BCS class II and ideal candidate for formulation of solid dispersion.

## Materials:

Phenytoin was synthesized in the laboratory using benzil and urea, Polymers such PVPK30, PEG 6000 and Mannitol were provided from the Dipa chemicals, Aurangabad, Maharashtra.

## Methods:

### 1.Synthesis of Phenytoin

Take a Round bottom flask add a required measured quantity of benzil and urea anddissolved in required quantity of ethanol .Then add 30 % NaOH slowly .After that the RBF is fixed in microwave assisted and parameter is set to 425 watt for 2 to 3 min .Then the solution placed in ice bath for cooling the reaction mixture. After cooling the reaction mixture, the conc. HCl is added drop wise until the precipitate Phenytoin is formed .Obtained Phenytoin was filter and wash with distilled water to remove impurities .Obtained Phenytoin was recrystallised with ethanol. The obtained drug is dried properly in hot air oven at 50◦C for 15 -20 mins.

### 2. Identification test for Phenytoin:

Take 10 mg of drug in a dry test tube + 1 ml Ethanol and add 0.05 ml of ammonia solution.Boil for 2 to 3 min and add Cuso4 ( copper sulphate ) in dilute ammonia and shake for sometimes. A pink crystalline precipitate is formed .

### 3.Melting point

First setup Melting point assembly. Then take thiele tube which filled with liquid paraffin.After that take capillary and one end of capillary sealed on burner then fill the drug(Phenytoin) in capillary. Capillary containing drug is tie with thermometer and thermometer is deep in liquid paraffin and hang to the stand .Then apply heat to the side arm of the thiele tube until drug get melted.Observed and record the reading of melting point of Phenytoin on thermometer.**Recorded melting point of Phenytoin is 295 ◦C**

## 4.SOLID DISPERSION OF PHENYTOIN

Solid dispersion of Phenytoin was prepared by using solvent evaporation method. Solid dispersion of Phenytoin with three different polymer that is PEG 6000, PVP-K30,D-mannitol,in ratios of 1:1, 1:2, 1:3, 1:4, 1:5 was prepared.100mg of drug and 100 mg of polymer were taken in china dish and ethanol was use as aevaporating solvent which was added and mix thoroughly .Then mixture was placed on hot plate for evaporation of solvent .Solvent got evaporated completely and dry mass was collected. The powdered solid dispersion was collected in empty vials.

## 5.SATURATED SOLUBILITY

The excess amount of drug wasadded in distilled water this solution was filled in vial. The vials were shaken for 48 hrs. After 48 hrs the solution were filter by whattman filter paper.The filtrates were sonicated by using sonicator upon dilution, the solution were analyzed by UV spectrophotometer and saturated solubility was calculated.

## 6.DISSOLUTION STUDY

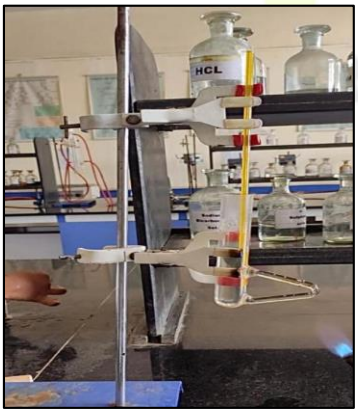
Dissolution and drug release test are in-vitro tests that measure great and extend ofdissolution a release of drug substance from a drug product usually aqueous medium under specified conditions.

The drug dissolution were determined at 37 ◦C at 100 RPM. 100MG of drug and solid dispersion were added to 900ml of distilled water media .After the intervals of 10 min ,20min, 30 min, 40 min, 50 min 5ml of samples were withdrawn and on dilution they were analyzed by UV spectrophotometer.

## RESULTS AND DISSCUSSION

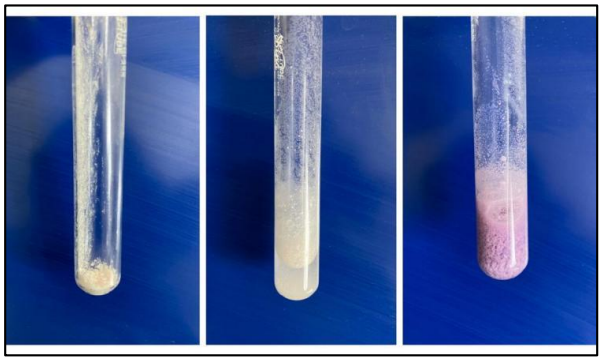
### 1.Physical and chemical characterization of drug:

**Melting point**: The melting range of Phenytoin was found to be 293°C-295°C by capillary method.



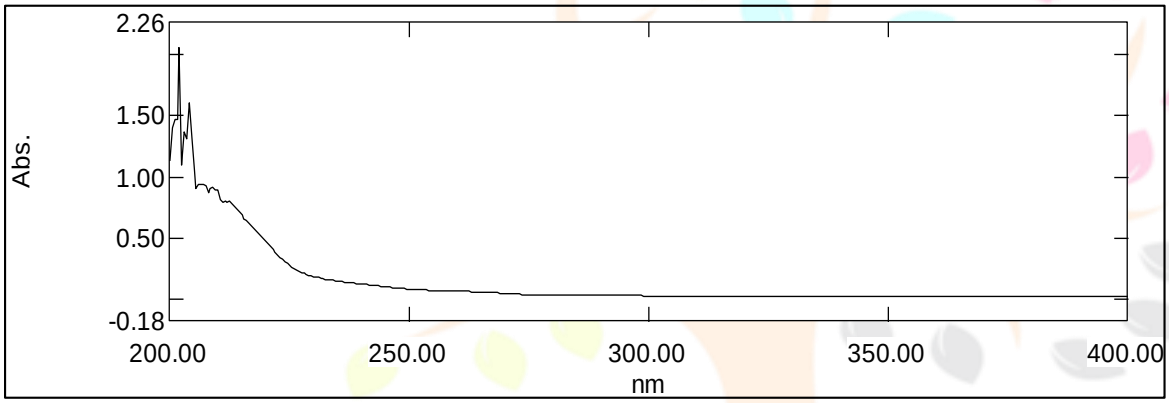

### 2.Identification test:

A pink crystalline precipitate is formed. Hence **phenytoin was confirmed.**



3. UV spectrometric analysis:

The spectra of drug Phenytoin in water was taken by UV spectrometer. The spectrum shows absorption maxima (ƛmax) at 202 nm in fig.




## Methods of analysis:

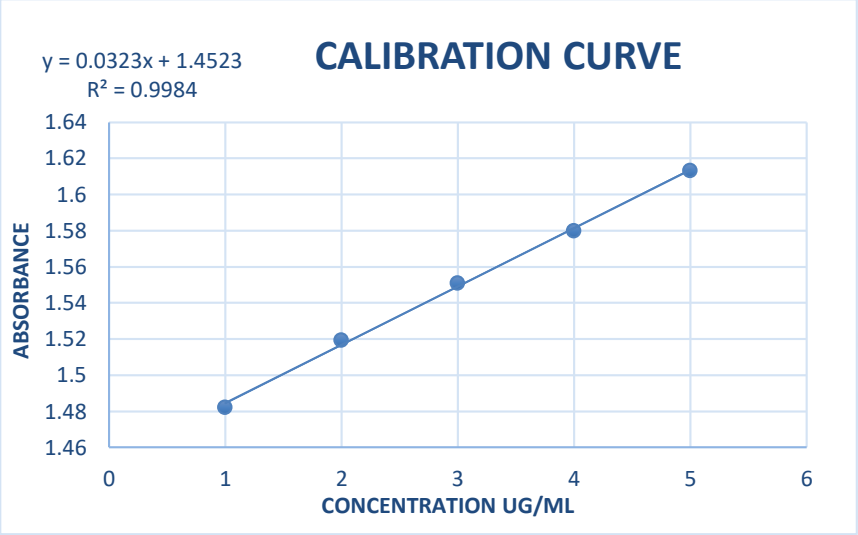
**Development of analytical methods:(UV Spectrophotometric )**

**Preparation of standard stock solution:** 100 mg of drug phenytoin was dissolved in 100 ml of water.Series of dilution were prepared by taking 1 ml from the stock solution and dissolving in 10 ml of water such as 10µg/ml and so on were prepared till 25µg/ml.

## Calibration curve

| Concentation in µg/ml | Absorbance |
|---|---|
| 5 | 1.4822 |
| 10 | 1.51933 |
| 15 | 1.5509 |

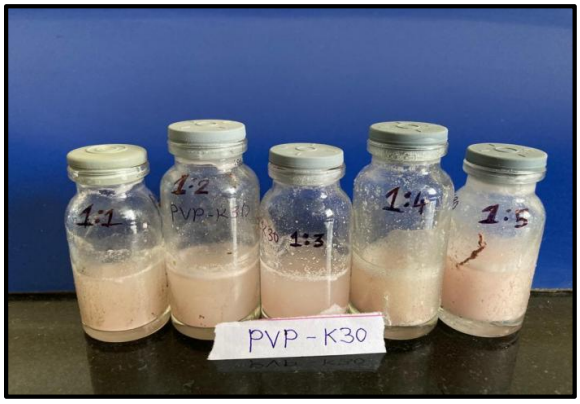
| | |
|---|---|
| 20 | 1.57999 |
| 25 | 1.61333 |




## Saturated solubility

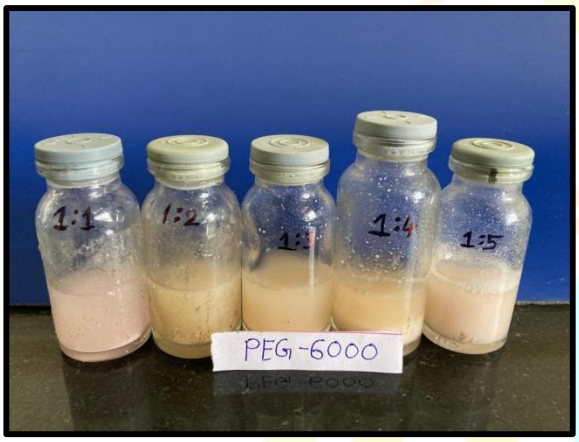
### DRUG: POLYMER (PVP-K30)

| RATIO | SOLUBILITY |
|---|---|
| PHNT | 1.46648248 |
| PHNT+PVPK30(1:1) | 1.466740816 |
| PHNT+PVPK30(1:2) | 1.465772056 |
| PHNT+PVPK30(1:3) | 1.469324176 |
| PHNT+PVPK30(1:4) | 1.46777416 |
| PHNT+PVPK30(1:5) | 1.46712832 |



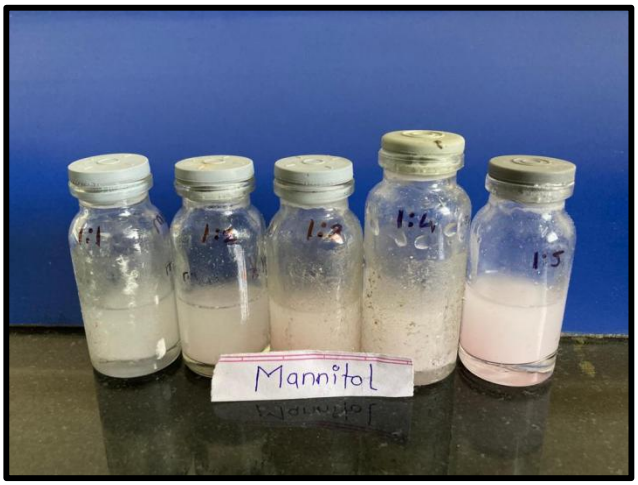

**DRUG: POLYMER (PEG 6000)**

| RATIO | SOLUBILITY |
|---|---|
| PHNT+PEG6000(1:1) | 1.466611648 |
| PHNT+PEG6000(1:2) | 1.46748999 |
| PHNT+PEG6000(1:3) | 1.471384406 |
| PHNT+PEG6000(1:4) | 1.46777416 |
| PHNT+PEG6000(1:5) | 1.46712832 |




**DRUG: POLYMER (MANNITOL)**

| | |
|---|---|
| PHNT+MANNITOL(1:1) | 1.465965808 |
| PHNT+MANNITOL(1:2) | 1.464803296 |
| PHNT+MANNITOL(1:3) | 1.46454496 |
| PHNT+MANNITOL(1:4) | 1.464932464 |
| PHNT+MANNITOL(1:5) | 1.464480376 |




## Dissolution studies:

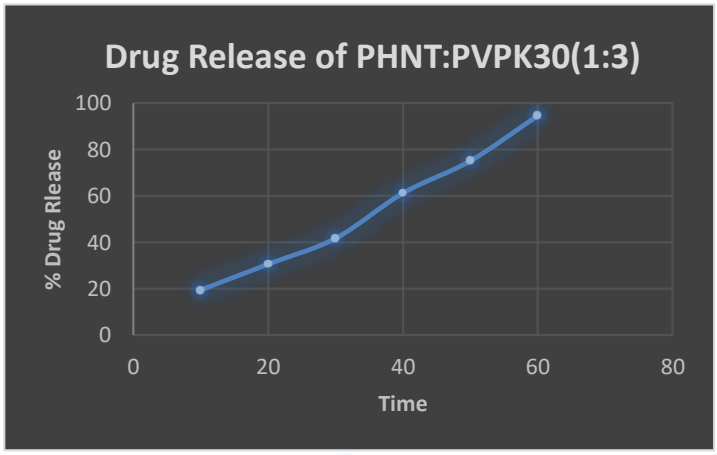
Powdered drug and solid dispersion were subjected to in-vitro drug release.the drug release was found to be increase in PEG 6000 solid dispersion 1:3.


**Drug release of PHNT**

| Time | % drug release |
|---|---|
| 10 | 2.786377709 |
| 20 | 19.50464396 |
| 30 | 33.43653251 |
| 40 | 41.79566563 |
| 50 | 58.51393189 |
| 60 | 86.37770898 |

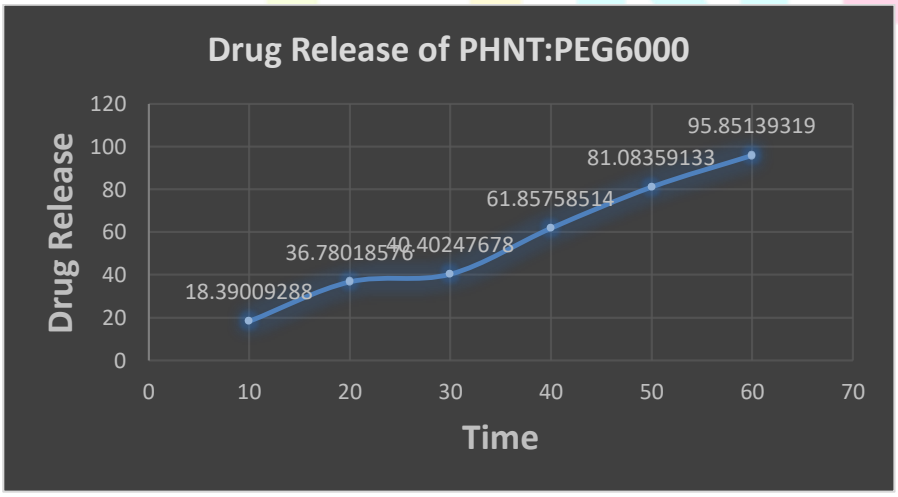
## Drug release of PHNT (PVPK30 1:3)

| Time | % drug release |
|---|---|
| 10 | 19.50464396 |
| 20 | 30.6501548 |
| 30 | 41.79566563 |
| 40 | 61.3003096 |
| 50 | 75.23219814 |
| 60 | 94.73684211 |




## Drug release of PHNT: PEG6000

| Time | % drug release |
|---|---|
| 10 | 18.39009288 |
| 20 | 36.78018576 |
| 30 | 40.40247678 |
| 40 | 61.85758514 |
| 50 | 81.08359133 |
| 60 | 95.85139319 |



## Conclusion -

The present study was undertaken to synthesized and prepare solid dispersion of phenytoin The drug was selected on the basis of poor water solubility. The selected drug was confirmed by using identification test given in Indian pharmacopoeia, melting point and UV spectroscopy analysis The solid dispersion of phenytoin was prepared by solvent evaporation method with three different polymers such as PEG-6000, PVP-K30 and mannitol showed considerable higher drug dissolution in comparison with pure drug. The result showed that solid dispersion of drug and PEG 6000 in the ratio of 1:3 showed improved saturated solubility and in vitro dissolution studies.The present study conclude that solid dispersion technology can be used effectively to enhanced the solubility and drug release of poorly water soluble drug phenytoin.