

# Designing and Developing Suppository Formulations for Anti-Epileptic Drug Delivery

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**Abstract:** *The purpose of present research work is to expand various suppository bases in order to control disadvantage of traditional base and to analyses the release of Phenytoin from this bases. Cocoa butter, White bees wax, Hydrogenated vegetable oil used as base and prepared by fusion method. Improved base is estimated for physicochemical parameters like appearance, hardness, weight variation, hydroxyl vale and this bases used in the preparation of Phenytoin suppositories. Suppositories of Phenytoin were estimated for physical parameter drug content, In vitro drug release reports. Selected suppositories bases were specify by X-ray diffraction, Infra Red spectroscopy studies. Physicochemical parameters of suppositories base show within limit. Hydroxyl value of bases observed in limits 89.76-134.64. From the result it is analyzed white bees wax , cocoa butter and Hydrogenated vegetable oil show fast release. Physicochemical parameters of Phenytoin suppositories show within limit. Product contains white bees wax , Hydrogenated vegetable oil shows 99.44% drug release at 120 min. within 71.83% dissolution efficiency. Infra Red spectroscopy shows affinity of drug with adjuvant and X-ray diffraction also differential scanning calorimetry show reduction in degree of crystallinity of Phenytoin. Also it can be analyzed white bees wax, hydrogenated vegetable oil combination useful for poorly water soluble drug like Phenytoin. Using fusion method this formulation was designed with combination of bases like Hydrogenated vegetable oil, cocoa butter, white bees wax . Thus finally it can be concluded that white bees wax, Hydrogenated vegetable oil combination is more suitable for poorly water soluble drug like phenytoin.*

**Keywords:** Phenytoin, Suppository base, Rectal delivery, Lipid-Based –Vehicles

## I. INTRODUCTION

About 95% drugs are administered by oral and parenteral route. Oral route is used because of easy administration of formulation. But there is disadvantages in oral route that are gastrointestinal degradation, less bioavailability, less therapeutic activity. So many research industries are involved to develop in mucosal route for administration of drug that are various disadvantages after oral administration.(1-3) It is also observed there is rare study on rectal route. Many scientists proves that it is much better route of administration because of systemic and local effect. It is alternative route for oral and parenteral. When oral and parental route is not accessible so we can preferred rectal administration of drug. This route gives rapid absorption, avoid first pass metabolism. Suppositories are one of the best medications used to inject within different drugs to produce local and systemic effect. For that requirement fatty or oily type bases after melting the bases add API and transfer it into molten mass. So at body temperature it melts and releases the API.(4) Most common suppositories base is used cocoa butter but it is observed that it consist no. of disadvantage like rancid. Some other base like Massa Estarium, Masupol, Witepsol having higher Melting point. Poly ethylene glycol having more hygroscopic so it can irritation on rectal route. The basic aim while designing any formulation it should melt at body temperature. The main objective to design the new combination of the base is to prevent this disadvantages.(5-9) phenytoin is mostly used as anti epileptic drug in the treatment of psychomotor seizures. Due to low solubility and poor bioavailability it is classified in BCS class-II type drugs. Mucoadhesive adjuvant responsible for adhesion of molecules to rectal mucosal membrane.(10-12) So we can use Mucoadhesive adjuvant like chitosan during designing suppositories with combination of various bases like cocoa butter, Hydrogenated vegetable oil, white bees wax, . so



current research objectives is to design semi-solid suppositories of Phenytoin using combination of suppositories bases which is naturally occurring polymer like chitosan. (13)

## II. METHODS AND MATERIAL

Drug sample is collected from Abbott pharmaceutical Pvt.Ltd, Mumbai, India. White bees wax, hydrogenated vegetable oil and cocoa butter is purchased from Loba Chemie, Mumbai.

### Preparation of combination of bases:

Using fusion method different suppositories base is prepared like hydrogenated vegetable oil is combine with , cocoa butter and white bees wax. All the bases analyzed by using the test like appearance, hardness, melting point, liquefaction time, meting range, hydroxyl value.

## III. EVALUATION OF COMBINATIONS OF SUPPOSITORY BASES:

### Appearance:

Take five suppositories and cut it by lengthwise to examine its area by naked eye.

### Weight variation:

For weight variation test we will take 20 suppositories. Weigh separately and also calculate average weight and separate weight compare with average weight.

### Hardness:

From each batch of five suppositories are used for hardness analyzed by cutting the middle portion of suppository and its diameter is measured using Monsanto hardness tester.

### Melting range test:

For determination of Melting range test take a capillary transfer weighted amount of suppositories up to 4cm. and dip this capillary into beaker containing water slowly increase the temperature after some time it liquefies measure that temperature.

### Liquefaction time:

For the determination of liquefaction time take burette with broken stop cock. From the one side opening dip in hot water whose temperature is maintained at 37°C. The sample suppository formulation is fill in to burette through broad end and transfer towards another end of burette at liquefaction time a glass rod reaches the narrow end after complete melting.(14)

### Hydroxyl value:

Accurately weighted quantity of suppository is transfer into 500ml conical flask. Add 20ml acetic anhydride: pyridine: toluene in the ratio of 3:2:10. The above solution is placed in an Hot air oven at 50 C 20 min and 30ml of distilled water was added to it. The mixture is stirred for 5 min to hydrolyse the excess anhydride, and titrated with 1N KOH solution, and phenolphthalein as indicator the determination of end point. The flask is triturate vigorously near the end point to remove any acid from the upper toluene layer.

## IV. METHOD OF PREPARATION OF SOLID SUPPOSITORY OF PHENYTOIN

Table no. 01- Solid suppositories composed of Phenytoin were prepared by Fusion method using different suppository bases.

Batch	A (mg)	B (mg)	C (mg)	D (mg)
Phenytoin	100	100	100	100
Coca butter	900	450	-----	-----
Hydrogenated vegetable oil	-----	450	450	450
White bees wax	-----	-----	450	-----



### **V. EVALUATION OF PHENYTOIN SUPPOSITORIES:**

The prepared suppositories was evaluated by visual characterization, melting range test, breaking strength (hardness), weight variation, liquefaction time and in vitro drug release.(15)

#### **Drug content:**

The five assumptions are broken down into smaller parts. An accurately weighed aliquot (100 mg) was taken A 100 ml volumetric flask and 80 ml of pH 7.4 Phosphate buffer were added with continuous shaking for 30 min. The audio is then buffered. The resulting solution was filtered, diluted appropriately, and the absorbance of the solution was measured at 205 nm. The drug content was calculated from the calibration curve (slope 0.050, Intercept 0.022, R<sup>2</sup> 0.993). The average of the three determinations was calculated as the average drug content of the estimate.(16)

#### **In vitro drug release:**

In vitro drug release studies of Phenytoin were conducted in a USP XXII dissolution test containing basket stirrer 50rpm and 900ml phosphate buffer having Ph 7.4 with tween 80 at 37 degrees Celsius each basket contain one suppositories formulations. At specific time interval 2ml sample collected and replace 2 ml phosphate buffer Ph 7.4. Using UV-Spectroscopy sample should be analyzed at absorbance 205n. and percent drug release was calculated.(17)

#### **Characterization of optimized suppository of Phenytoin:**

The infrared spectrum of Phenytoin was recorded on an Attenuated Total Reflectance-Fourier Infrared recorder Spectrophotometer (ATR-FTIR) (Near IR, MIRacle10, Shimadzu, Japan). A small number of samples were taken and placed on the direct IR platform. The spectra were then investigated in the wavelength region of 3271 to 3208 cm<sup>-1</sup> at a resolution of 4 cm<sup>-1</sup>. X-ray powder diffraction (XRD) analysis was performed to investigate the Change in crystalline of Phenytoin in the assay. XRD of Phenytoin, Formulation Optimum Phenytoin prediction, Formulation without Phenytoin and white bees wax recorded with Bruker D2 Phaser Refractometer using Cu K $\alpha$ 1 radiation at  $\lambda = 1.5418 \text{ \AA}$ . Basic DSC of Phenytoin and optimized CC, white bees wax and hydrogenated vegetable oil was done using Model-SDT Q600 V20.9 Build 20 with a computerized data station. The sample was placed in 1an aluminum pan and heated at a rate of 10 ° C / min in the temperature range of 35-350 ° C. Thermal analysis was carried out in a nitrogen atmosphere.(18-20)

### **VI. RESULTS AND DISCUSSION**

#### **Evaluation of suppository in combination:**

##### **Appearance:**

Prepared suppository bases observed good appearance and texture and it does not show any fissuring, pitting, fat blooming, and sedimentation. Only cocoa butter occurs this problems due to contain of fatty acids in the hydrogenated vegetable oil.

##### **Weight variation test:**

Prepared suppository bases observed average weight in limit of 452 to 485. And this test is within limit with reference to I.P. of all formulations.

##### **Hardness**

Prepared suppository bases observed in the range of 3.3 to 4.5kg/cm<sup>2</sup>. Formulation prepared from white bees wax and hydrogenated vegetable oil was found to be harder. If the hardness is more suppositories will not melt at body temperature and if the hardness of suppository is less they will melt rapidly before insertion. So combination of Hydrogenated vegetable oil is suitable for the preparation of suppositories.

##### **Melting range test:**

Prepared suppository bases melting range found within the range of 34-42 C base containing Hydrogenated vegetable oil and white bees wax observed higher melting range about 34 – 42 C wand the base containing cocoa butter and hydrogenated vegetable observed lowest melting range i.e. 34-38 C. and this is due to presence of hydrogenated vegetable oil which has low melting point.

##### **Liquefaction time:**

All the prepared suppositories observed liquefaction time within limit of 5.10 – 7.35 min. and this test is useful in easy handling and release of drug after administration in rectum.



**Hydroxyl value:**

The hydroxyl value gives to the milligrams of potassium hydroxide (KOH) required neutralizing an equivalent amount of acetic acid combined with hydroxyl groups in 1 g of a suppository. Hydroxyl Value of suppositories was found within the range of 89.76 to 134.64. It gives the hydrophilicity of fatty bases exerts effect on rectal absorption. Hydroxyl value of suppository base has affects on the release of drug dissolved in the suppository base. Higher the hydroxyl value more will be the release of the drug. The lower value indicates hydrophobic character of the base and retardation of drug release.

**VI. PREPARATION OF PHENYTOIN SUPPOSITORY**

All the suppositories observed within the limit average weight of 467 to 494mg. The weight variation was observed within limit as per I.P. from this concluded that there is uniformity in weights of suppositories. Hardness of suppositories was observed in the range of 3.6 to 4.5 kg/cm<sup>2</sup>. Melting time of Phenytoin was found to be 31-41 C. due to high melting point of PEG 2000. PEG and Hydrogenated vegetable oil containing suppository observed more melting range 35-41 C. and suppository found low melting range (31-36 C). Due to Cocoa butter and hydrogenated vegetable oil this is because of the cocoa butter has low melting point than other suppository bases for the preparation of Suppository using fusion method it contain Different Suppository bases and the drug containing suppositories of all the batches observed smooth texture and appearance.

**DRUG CONTENT:**

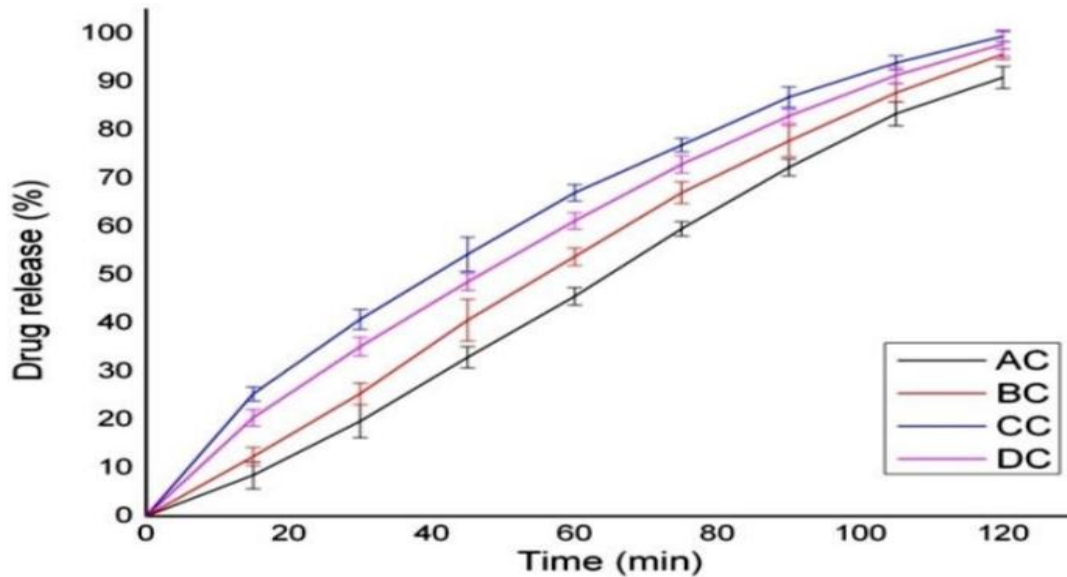
**Table no. 02. Drug content of all batches was found in the range of 95.17 to 97.85%. This ensures that there is a minimum loss of drug during manufacturing of suppositories.**

Batch	Batch weight variation (mg)	Hardness (kg/cm <sup>2</sup> )	Melting range (° c)	Liquefaction time (min)	Drug content (%)
A	467±3.12	377.85±0.27	464±3.12	377.85±0.27	466±3.12
	4.5±0.1632	95.17±2.36	95.17±2.36	95.17±2.36	4.5±0.1632
B	494±2.66	365.23±0.18	497±2.66	365.23±0.18	495±2.66
	3.8±0.1931	97.85±3.14	3.8±0.1931	97.85±3.14	3.8±0.1931
C	475±3.45	409.15±0.11	481±3.45	410.15±0.11	475±3.45
	3.6±0.2635	96.96±2.29	3.6±0.2635	96.96±2.29	3.6±0.2635
D	489±5.85	415.58±0.74	486±5.85	420.58±0.74	490±5.85
	4.2±0.3135	96.87±3.36	4.2±0.3135	96.87±3.36	4.2±0.3135

**IN VITRO DRUG RELEASE:**

The drug release of Phenytoin from different suppository bases. Was found within the limit 90.87 to 99.44 at the end of 120min. The breaking of suppositories release was observed in the range of 8 to 26% at the end of 15min in all the formulations. Higher breaking of suppositories release was found to be in the formulation containing hydrogenated vegetable oil and white bees wax which may be due to high aqueous solubility of PEG. Surface associated drug gets easily diffused into the bulk of dissolution medium. Drug release was observed in retarded in the batches containing cocoa butter alone or combination as a base. This is characteristics of the cocoa butter being a fat soluble suppository base does not have affinity for dissolution medium. The drug release from the suppositories is in the order of Hydrogenated vegetable oil – white bees wax > Hydrogenated vegetable oil -cocoa butter. Highest drug release was found to be in the formulation containing white bees wax and hydrogenated vegetable oil. Because of presence of hydrophilic as well as lipophilic groups in white bees wax .melting points and water solubility is high in the white bees wax. combination of hydrogenated vegetable oil lowered the melting point of white bees wax so that suppository can be administered easily without irritation into the body system. Poor water solubility of Phenytoin in water dissolution of drug in lipid soluble bases is slow as compared to water soluble bases.



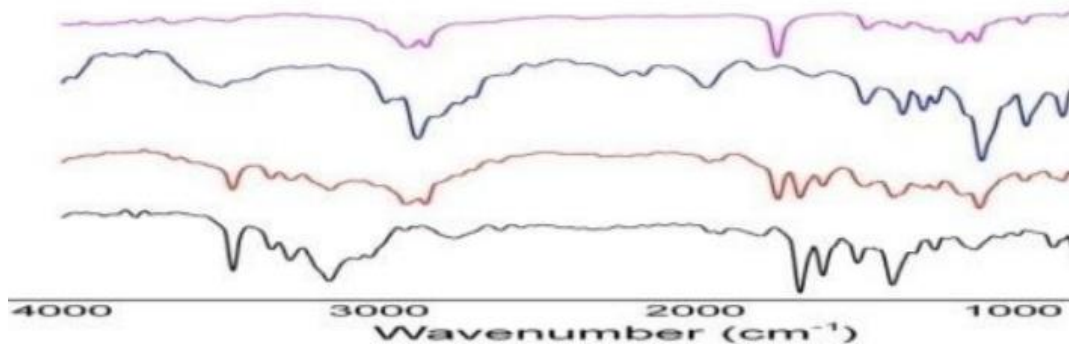


**Figure 1. In vitro release of Phenytoin from different bases**

Release report fitted into model dependent and independent parameters and gives Dissolution efficiency of suppository within the limit 45.88 to 61.83% and mean dissolution time (MDT) was found to be in the range of 45.38 to 59.40min at the end of 120min. White bees wax and hydrogenated vegetable oil base observed more DE indicating faster release of drug from the formulation. All the prepared suppositories followed the Higuchi kinetic model with release exponent in the range of 0.65 –1.11 indicating non-Fickian diffusion coupled with erosion.

#### Characterization of optimized suppository of Phenytoin

Submissiveness in the study of drug and excipients was performed by infrared spectroscopy. The ATR-FTIR spectra of Phenytoine observed peaks 3271 and 3208  $\text{cm}^{-1}$  for the NH group and at 3068  $\text{cm}^{-1}$  for the aromatic C-H X-ray powder diffraction analysis was performed to check It has been shown that polymorphic changes of the drug. The spectra of physical mixture of drug, white bees wax, and hydrogenated vegetable oil Observed characteristic distinct peaks of drug and Excipients with same intensity. So finally it is observed that there is no any between the drug and Excipients



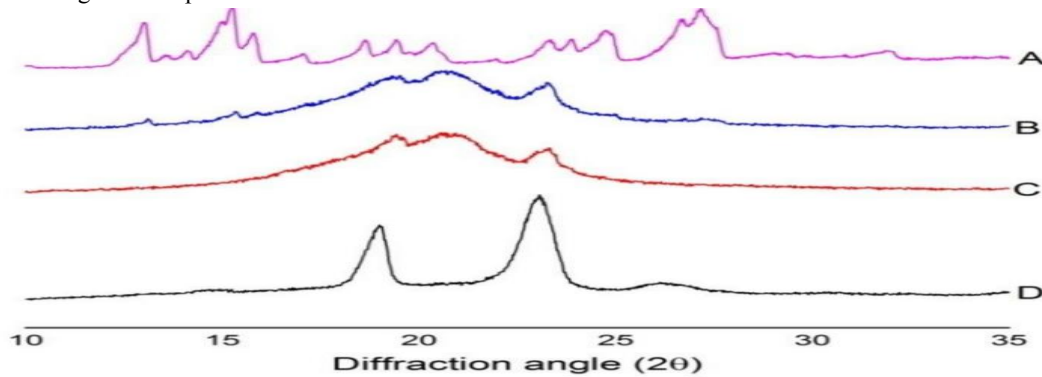
**Figure 2. Overlay ATR-FTIR spectra of Phenytoin (A), physical mixture (B), white bees wax (C) and Hydrogenated vegetable oil (D)**

X-ray diffraction is given in figure 3. XRD of the formulation gives drug in crystalline form. XRD data observed at  $2\theta$  angle 9.00, 12.20, 18.00, 15.76 and 25.50. Reflections of Phenytoine (specific peaks) was not observed in the case of suppository formulation (batch CC) show the conversion of drug from crystalline to amorphous. Solubilization of



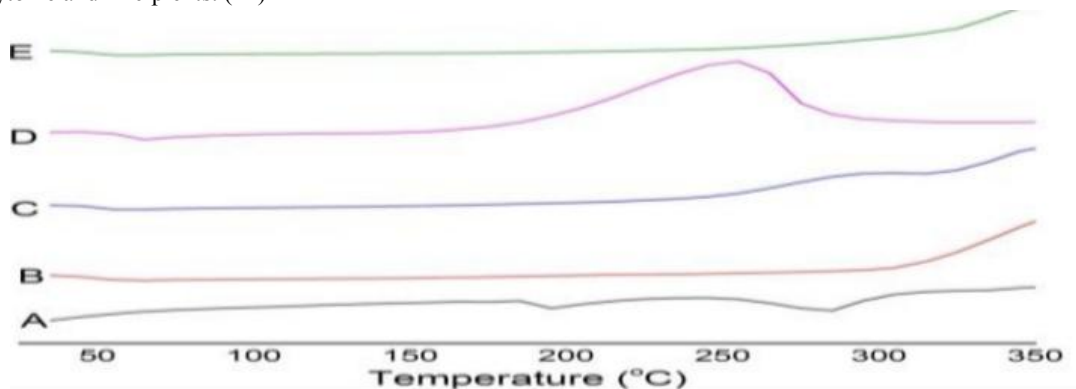


Phenytoine may provide to the consequent development in the apparent solubility and so the dissolution rate of Phenytoine, (aromatic C=C). The XRD pattern of physical mixture of drug, white bees wax, and hydrogenated vegetable oil showed characteristic distinct peaks of drug and Excipients. so there is no any evidence interaction between the drug and Excipients.



**Figure 3. Overlay XRD of Phenytoine (A), Batch CC With drug (B), Batch CC without drug (C), white bees wax (D)**

The DSC of the drug (A) in Figure 4 show. Endothermic peak of drug detected at 295°C and correlate to the melting temperature Phenytoine such sharp endothermic peak that Phenytoine used was in pure crystalline state. The DSC of the Phenytoine with suppository base formulation did not show any peaks which show lack of interaction between Phenytoine and Excipients. (21)



**Figure 4. Overlay DSC of Phenytoine (A), Batch CC With drug (B), Batch CC without drug (C), white bees wax (D), Hydrogenated vegetable oil (E)**

## VII. CONCLUSION

A 19:1 combination of lipophilic, hydrophilic and Amphiphilic surfactants containing hydrogenated vegetable oil and cocoa butter, white bees wax was prepared. Drug contain suppositories show drug release in 120 min. Delayed release was observed in formulations containing lipophilic bases, while rapid release was observed in formulations containing hydrophilic bases. Compositions prepared from bases that are considered to be potentially useful for insoluble drugs.

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