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Phenytoin Drug using with Suppository Base for in Rectal Delivery System

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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, poloxamer 407, PEG2000 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 Polaxmer 407 and PEG2000 and hydrogenated vegetable oil show fast release. Physicochemical parameters of Phenytoin suppositories show within limit. Product contains poloxamer 407, 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 poloxamer 407, 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, poloxamer 407and PEG2000. Thus finally it can be concluded that poloxamer 407, Hydrogenated vegetable oil combination is more suitable for poorly water soluble drug like Phenotine.

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, poloxamer 407, PEG2000. So current research objectives is to deign 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 Pharmacetical Pvt.Ltd, Mumbai, India. glycol (PEG) 2000, 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 PEG 2000, cocoa butter and poloxamer 407. All the bases analyzed by using the test like appearance, hardness, melting point, liquefaction time, meting range, hydroxyl value.

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 37ºC. 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 50C 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.

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	AC (mg)	BC (mg)	CC (mg)	DC (mg)
Phenytoin	100	100	100	100
Coca butter	900	450	----	----
Hydrogenated vegetable oil	----	450	450	450
Polaxmer 407	----	----	450	----

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, R2 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 stireer 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-1 at a resolution of 4 cm-1. 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 Poloxamer recorded with Bruker D2 Phaser Refractometer using Cu Kα1 radiation at l = 1.5418 Å. Basic DSC of Phenytoin and optimized CC, poloxamer 407 and hydrogenated vegetable oil was

done using Model-SDT Q600 V20.9 Build 20 with a computerized data station. The sample was placed in an 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]

III. 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/cm2. Formulation prepared from PEG 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℃ base containing hydrogenated vegetable oil and PEG 2000 observed higher melting range about 34 - 42℃ and the base containing cocoa butter and hydrogenated vegetable observed lowest melting range i.e. 34-38℃. 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.

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$^{2.}$ Melting time of Phenytoin was found to be 31-41℃. due to high melting point of PEG 2000. PEG and hydrogenated vegetable oil containing suppository observed more melting range 35-41℃.and suppository found low melting range (31-36℃). 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 Weight variation (mg)	Batch Weight variation (mg)	Hardness (kg/cm2)	Melting range (□C)	liquefaction time (min)	Drug content (%)
AC	467±3.12 4.5±0.16 32	37 7.85±0.27 95.17±2.36	464±3.12 4.5±0.16 32	37 7.85±0.27 95.17±2.36	466±3.12 4.5±0.16 32
BC	BC 494±2.66 3.8±0.19 31	36 5.23±0.18 97.85±3.14	BC 497±2.66 3.8±0.19 31	36 5.23±0.18 97.85±3.14	BC 495±2.66 3.8±0.19 31
CC	CC 475±3.45 3.6±0.26 35	40 9.15±0.11 96.96±2.29	CC 481±3.45 3.6±0.26 35	410.15±0.11 96.96±2.29	CC 475±3.45 3.6±0.26 35
DC	DC 489±5.85 4.2±0.31 35	41 5.58±0.74 96.87±3.36	DC 486±5.85 4.2±0.31 35	420.58±0.74 96.87±3.36	DC 490±5.85 4.2±0.31 35

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 PEG 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 - poloxamer 407> hydrogenated vegetable oil - PEG 2000> hydrogenated vegetable oil -cocoa butter. Highest drug release was found to be in the formulation containing poloxamer 407 and hydrogenated vegetable oil. Because of presence of hydrophilic as well as lipophilic groups in poloxamer 407.melting points and water solubility is high in the Poloxamer 407.combination of hydrogenated vegetable oil lowered the melting point of poloxamer 407 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.

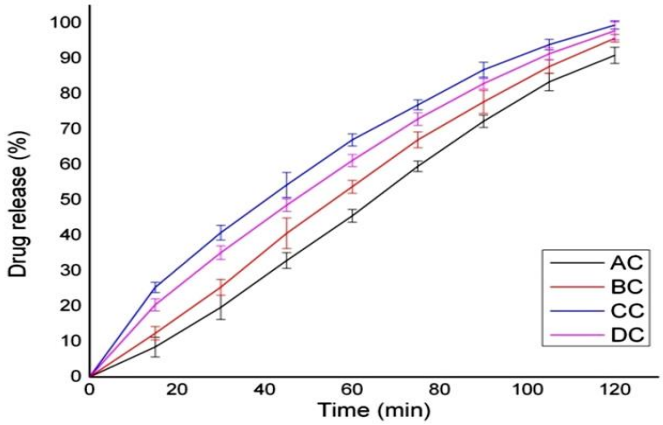

Figure 1. *In vitro* release of Phenytoin from different bases.

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. poloxamer 407 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 Phenotine

Submissiveness in the study of drug and excipients was performed by infrared spectroscopy. The ATR-FTIR spectra of Phenotine observed peaks 3271 and 3208 cm –1 for the NH group and at 3068 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, poloxamer, 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

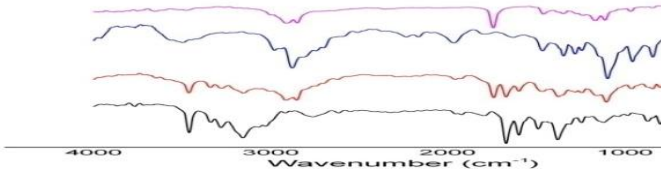

Figure 2. Overlay ATR-FTIR spectra of Phenytoin (A), physical mixture (B), poloxamer 407 (C) and hydrogenated vegetable oil (D)

X-ray diffraction is given in figure 3.XRD of the formulation gives drug in crystalline form. XRD data observed at 2θ angle 9.00, 12.20, 18.00, 15.76 and 25.50. Reflections of Phenotine (specific peaks) was not observed in the case of suppository formulation (batch CC) show the conversion of drug from crystalline to amorphous. Solubilization of Phenotine may provide to the consequent development in the apparent solubility and so the dissolution rate of Phenotine, (aromatic C=C). The XRD pattern of physical mixture of drug, poloxamer, and hydrogenated vegetable oil showed characteristic distinct peaks of drug and Excipients. So there is no any evidence interaction between the drug and Excipients.

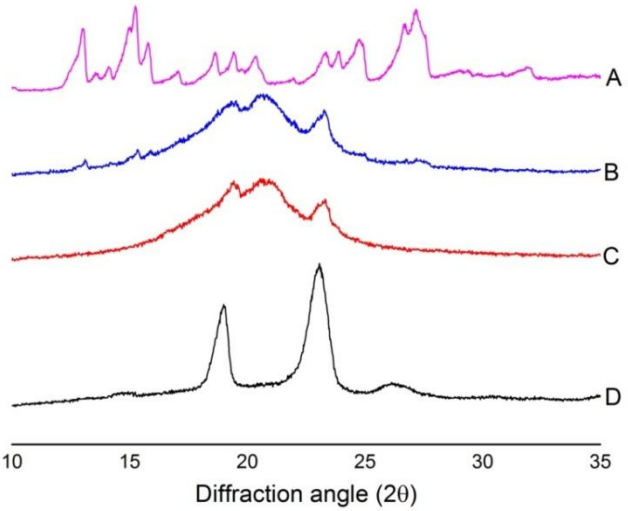

Figure 3. Overlay XRD of Phenytoin (A), Batch CC with drug (B), Batch CC without drug (C), poloxamer 407 (D)

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

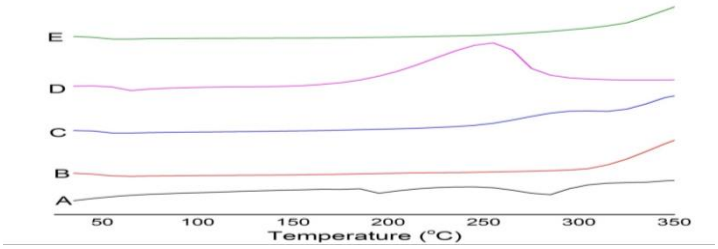

Figure 4. Overlay DSC of Phenytoin (A), Batch CC with drug (B), Batch CC without drug (C), poloxamer 407 (D), Hydrogenated vegetable oil (E)

IV. CONCLUSION

A 19:1 combination of lipophilic, hydrophilic and amphiphilic surfactants containing hydrogenated vegetable oil and cocoa butter, poloxamer 407 and polyethylene glycol 2000 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.

V. REFERENCES

[1]. Fumoleau P, Giovannini M, Rolland F, Votan B, Paillarse JM. Ondansetron suppository: An effective treatment for the prevention of emetic disorders induced by cisplatin-based chemotheraphy. Oral Oncol. 1997;33(5):354–8.

[2]. Salunkhe NH, Jadhav NR, Mali KK, Dias RJ, Ghorpade VS, Yadav a. V. Mucoadhesive microsphere based suppository containing granisetron hydrochloride for management of emesis in chemotherapy. J Pharm Investig. 2014;44(4):253–63.

[3]. Jadhav UG, Dias RJ, Mali KK, Havaldar VD. Development of in situ-gelling and mucoadhesive liquid suppository of ondansetron. Int J ChemTech Res. 2009;1(4):953–61.

[4]. Prasanna LJ, Rao RN. Rectal drug delivery: A promising route for enhancing drug absorption. Asian J Res Pharm Sci. 2012;2(4):143–9.

[5]. Swamy P V, Farhana L, Shirsand SB, Ali Y, Patil A. Design and Evaluation of Rectal Suppositories of Carvedilol. Int J Pharm Sci Nanotechnol. 2009;2(3):654–60.

[6]. Havaldar VD, Yadav A V., Dias RJ, Mali KK, Ghorpade VS, Salunkhe NH. Rectal suppository as an effective alternative for oral administration. Res J Pharm Technol. 2015;8(6):759.

[7]. Koliqi R, Polidori C, Islami H. Prevalence of Side Effects Treatment with Carbamazepine and Other Antiepileptics in Patients with Epilepsy. Mater Sociomed. 2015;27(3):167–71.

[8]. Dias RJ, Mali KK, Ghorpade VS, Havaldar VD, Mohite VR. Formulation and Evaluation of Carbamazepine Liquisolid Compacts Using Novel Carriers. Indian J Pharm Educ Res. 2017;51(S2): S69–78.

[9]. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int J Pharm. 1992;78(1-3):43–8.

[10]. Jawahar N, Jayaprakash S, Maria GS, Nagarajan M, Moorthi D, Jubie S, et al. Design and evaluation of Sustained release suppositories if nimesulide. Indian J Pharm Sci. 2005;67(5):558–61.

[11]. Fleming J. Rapid method for the of hydroxyl values. J Soc Cosmet Chem. 1966; 630(17):625–30.

[12]. Shinoda M, Akita M, Hasegawa M, Nadai M, Hasegawa T, Nabeshima T, et al. Pharmaceutical evaluation of carbamazepine suppositories in rats. Biosci Biotechnol Biochem. 1995;18(9):1289–91.

[13]. Patel JK, Patel RP, Amin AF, Patel MM. Formulation and evaluation of mucoadhesive glipizide microspheres. AAPS PharmSciTech. 2005;6(1): E49–55.

[14]. Swamy PV, Ali MY, Anand Kumar Y, Prasad K, Srinivaslu N. Design and evaluation of rectal drug delivery systems of non- steroidal anti-inflammatory drug. Int. Curr Pharm J. 2012;1(7):165–70.

[15]. Schmllt M. Influence of the Hydrophilicity of Suppository Bases on Rectal Absorption of Carprofen, a Lipophilic Nonsteroidal Anti-inflammatory Drug. J Pharm Sci. 1990;79(4):359–63.

[16]. Wakita K, Kuwabara H, Furusho N, Tatebe C, Sato K, Akiyama

[17]. H. A Comparative Study of the Hydroxyl and Saponification Values of Polysorbate 60 in International Food Additive Specifications. Am J Anal Chem. 2014;05(03):199–204.

[18]. Hermann TW. Recent research on bioavailability of drugs from suppositories. Int J Pharm. 1995;123(1):1–11.
[19]. Baria AH, Patel RP, Suthar AM, Parmar RB. Formulation Development and Evaluation of Sustained Release Aceclofenac Suppository. Int J Pharm Sci Drug Res. 2009;1(2):71–3.
[20]. Saleem M, Taher M, Sanaullah S, Najmuddin M, Ali J, Humaira S, et al. Formulation and evaluation of tramadol hydrochloride rectal suppositories. Indian J Pharm Sci. 2008;70(5):640.
[21]. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Vol. 13, European Journal of Pharmaceutical Sciences. 2001. p. 123–33.

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