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RESEARCH ARTICLE
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DESIGN AND DEVELOPMENT OF LORAZEPAM RECTAL SUPPOSITORIES USING NATURAL POLYMERS.

Swapnil R. Nazarkar[1*], Samrat A. Khedkar[2], Amol A. Ban[3], Rajendra G. Kharade[4], Rachana S. Das[5]

[1*,2,3,4,5]Assistant Professor, Vidya Niketan College of Pharmacy, Lakhewadi
https://orcid.org/0009-0008-4460-4443

***Corresponding Author:-** Swapnil R. Nazarkar
*Assistant Professor Vidya Niketan College of Pharmacy, Lakhewadi

Abstract:
The Objective of present Research work was to develop different suppository bases in order to overcome drawbacks of traditional base and to study release of Phenytoin from developed bases. Cocoa butter was used as a base for one of the formulations while for other formulations combinations of suppository bases were prepared by fusion method. Hydrogenated vegetable oil was combined with cocoa butter, poloxamer 407 and polyethylene glycol 2000. Developed bases were evaluated for physicochemical parameters such as appearance, hardness, weight variation, hydroxyl value, etc and used for the preparation of lorazepam suppository. The suppositories of lorazepam were evaluated for physical parameters, drug content and in vitro drug release studies. The optimized suppository base was characterized by infrared spectroscopy and X-ray diffraction analysis. All the combination of suppository bases showed physical parameters within the prescribed range. Hydroxyl value of developed based showed in the range of 89.76-134.64.From the results, it is evident to prefer poloxamer 407 and polyethylene glycol 2000 with hydrogenated vegetable oil for faster release. The lorazepam suppositories also showed physical parameters within the prescribed limit. Formulation containing poloxamer 407 and hydrogenated vegetable oil showed 99.44% drug release at end of 120min with 61.83% dissolution efficiency and 45.38min mean dissolution time. The infrared spectroscopy indicated compatibility of drug with Excipients and X-ray diffraction and differential scanning calorimetry analysis showed reduction in degree of crystallinity of Phenytoin thus improving dissolution rate of drug. It can be concluded that poloxamer 407 and hydrogenated vegetable oil could be combined to deliver poorly soluble drug like Phenytoin.

INTRODUCTION

The most common routes for administration of drugs or medications are the oral and parenteral route. The oral route isPreferred for systemic delivery of many drugs. However, main drawback of oral route is extensive pre systemic elimination by gastrointestinal degradation and/or hepatic metabolism, low bioavailability, short duration of therapeutic activity and/or formation of toxic inactive metabolite· Many scientists in community and drug industry are engaged in exploring various mucosal routes of delivering such drugs that are poorly absorbed after oral administration. Rectal route was not used extensively and remain unexplored though it has potential as non-invasive route of drug administration. Actually, it is an excellent route of administration due to presence of both systemic and local effect. The rectal route serves as an alternative to oral and

invasive administration. In irritable bowel diseases such as hemorrhoids or where oral administration venous routeis not accessible in that condition rectal delivery of drug is possible. Rectal route offers potential advantages for drug delivery which include: rapid absorption of many low molecular weight drugs, partial avoidance of first pass metabolism, potential for absorption into the lymphatic system, retention of large volumes, possibility of rate controlled drug delivery and absorption enhancement.

Suppositories, one of the oldest forms of medication, have been used for the administration of variety of drugsto produce local and systemic effects. These are prepared by melting suppository base and incorporation of medicaments in molten mass. On rectal administration, suppository base melts at body temperature and medicaments are released. Cocoa butteris the most commonly used suppository base amongst the various suppository bases but it suffers from various drawbacks such as it becomes rancid, undergoes polymerization. Hard fats such as Massa Estarium, Massupol, Suppocire and Witepsol have various disadvantages such as higher melting point. Further, water soluble bases such as polyethylene glycol are hygroscopic in nature and attract water that may lead to local irritation. The most important prerequisite for a successful suppository base is that it should melt at body temperature, avoid the irritation Therefore, attempt is made to prepare combination of suppository bases to overcome the disadvantages of fatty and aqueous suppository bases.

lorazepam is a widely used anti-epileptic drug in the therapy of psychomotor seizures and trigeminal neuralgia. It is BCS class II drug having low solubility due to which it has low absorption and poor oral bioavailability. Use of mucoadhesive polymerscauses adhesion of macromolecules to the rectal mucous membrane due to presence of anionic charge and strong hydrogen bonding groups like hydroxyl, carboxyl or amino group. Phenytoin solid suppository was prepared by using mucoadhesive polymer, chitosan to avoid the first pass effect and avoid leakage of drug from the anus with the help of combination of suppository bases such as cocoa butter and hydrogenated vegetable oil, hydrogenated vegetable oil and poloxamer 407, hydrogenated vegetable oil and PEG 2000, cocoa butter and PEG 2000.
Thus, present investigation aims to develop solid suppository of lorazepam using various concentration of Suppository base combination with the help of natural polymer, chitosan.

MATERIALS AND METHODS:

lorazepam was obtained as a gift sample from Abbott, Mumbai, India. Polyethylene glycol (PEG) 2000, hydrogenated vegetable oil and cocoa butter, was procured from Loba Chemie, Mumbai. Other chemicals and reagents used were of analytical grade.
Preparation of combination of bases:
A different suppositories base was prepared by fusion method. PEG 2000, cocoa butter and poloxamer 407 were combined with hydrogenated vegetable oil in the ratio of 1:19. All the combinations of suppository bases were subjected to the various evaluation parameters such as appearance, hardness, melting point, liquefaction time, meting range, hydroxyl value.

Evaluation of combinations of suppository bases:

Appearance:

For testing the appearance, randomly selected suppositories was cut longitudinally and the surface was examined with naked eye.

Weight variation:

Twenty suppositories were weighed individually and the average weight was determined. The individual weight was compared with the average weight for determination of weight variation.

Hardness:

The hardness of three suppositories from each batch was determined by cutting the middle portion

of suppository. It was measured in its diametric direction using Monsanto hardness tester.

Melting range test:
The formulation was filled to about 1cm height in capillary tubes of 10 cm length and dipped in a beaker containing water. The temperature was raised slowly and the temperature at which the mass liquefies was recorded5.
Inactive metabolite. Many scientists in community and drug industry are engaged in exploring various mucosal routes of delivering such drugs that are poorly absorbed

Liquefaction time:
A simple apparatus fabricated in the laboratory was used. A burette with broken stop cock was taken and cut suitably so that it has a narrow opening on one side and broad opening on another side. The burette was dipped in hot water maintained at 37ºC so that narrow end faces towards hot water. The sample suppository was introduced from the top of the burette through broad end and carefully pushed down its length until it reaches narrow end. A glass rod reaches the narrow end after complete melting of suppository represents the liquefaction time.

Hydroxyl value:
The specified weight (W gm) of suppository was weighed and placed into a 250ml conical flask. 10ml of the APT reagent (acetic anhydride: pyridine: toluene in the ratio of 3:2:10) was added to it and warmed on a water bath until clear solution was obtained. Above solution was kept in an oven (or water bath) at 60□C 30 min and 25ml of distilled water was added to it. The solution was stirred for few seconds to hydrolyse the excess anhydride, and titrated with 1N KOH solution, using phenolphthalein as indicator (A ml). The flask was shaken vigorously near the end point to remove any acid from the upper toluene layer. The blank titration was done as above by omitting the sample (B ml)11.
(B – A) X N X 56.1
Hydroxyl Value= (1)
W Where N, is Normality of the KOH solution

Method of preparation of solid suppository of Phenytoin

Solid suppositories composed of lorazepam were prepared by fusion method using different suppository bases. Polyvinyl pyrrolidone was used as the solubiliser and suitable antioxidant and preservative were added.

Batch	AC(mg)	BC(mg)	CC(mg)	DC(mg)
lorazepam	100	100	100	100
Coca butter	900	450	---------	---------
Hydrogenated vegetable oil	---------	450	450	450
Polaxmer 407	---------	---------	450	---------
PEG2000	---------	---------	---------	450

Evaluation of Phenytoin suppositories:
The formulated suppositories were evaluated for visual characterization, melting range test, breaking strength (hardness), weight variation, liquefaction time and in vitro drug release.

Drug content:
Five suppositories were cut into small pieces. Accurately weighed amount of pieces (100 mg) was transferred into100 ml volumetric flask and 80ml pH 7.4 phosphate buffers was added with continuous shaking for 30 min. Then volume was made upto mark with the buffer. The resulting

solution was filtered, diluted suitably and absorbance of solution was measured at 247nm. The drug content was calculated from the calibration curve (slope 0.050, Intercept 0.022, R2 0.993). Average of three determinations was considered as mean drug content of the suppositories.

In vitro drug release:

In vitro drug release studies of lorazepam suppositories were carried out in USP XXII dissolution test apparatus employing a basket stirrer at 50rpm and using 900ml of phosphate buffer pH 7.4 with tween 80 (2ml) at 37± 0.5ºC. One suppository was used in each test. At predetermined time intervals, 1 ml samples were withdrawn and immediately replaced by 1ml fresh phosphate buffer pH 7.4. The samples were analyzed for drug release by measuring the absorbance at 247 nm using UV- visible spectrophotometer. Cumulative percent of drug released was calculated and plotted against time.

Characterization of optimized suppository of Phenytoin:

Infrared spectrum of Phenytoin was recorded on Attenuatedtotal reflectance-Fouriertransform infrared Spectrophotometer (ATR-FTIR) (IR Affinity, MIRacle10, Shimadzu, Japan). Small quantity of samplewas taken and directly placed on IR platform. Then thespectra were scanned over wavelength region of 3271 to3208 cm^{-1} at resolution of 4 cm^{-1}.

X-Ray powder diffraction (XRD) analysis was performed in order to study the change in the crystallinity of lorazepam within the suppository. XRD of lorazepam, optimized formulation of lorazepam suppository, formulation without lorazepam and poloxamer were recorded using Bruker D2 Phaser Referactrometer using Cu Kα1 radiation with l = 1.5418 Å.

Differential scanning calorimetry (DSC) analysis was conducted to study the interaction in between lorazepamand suppository base. DSC was carried out on the lorazepam and optimized formulation CC, poloxamer 407 and hydrogenated vegetable oil using Model-SDT Q600 V20.9 Build 20 with a computerized data station. Samples were placed in an aluminum pan and heated at a rate of 10°C/min in the temperature range of 35– 350°C. The thermal analysis was performed under nitrogen atmosphere.

RESULTS AND DISCUSSION:

Evaluation of suppository in combination:

Appearance:

All the combinations of suppository bases showed smooth texture and good appearance without fissuring, pitting, fat blooming, and sedimentation except cocoa butter alone. This may be due to presence of fatty acids in the hydrogenated vegetable oil.

Weight variation test:

All the suppositories bases showed average weight within the range of 452 to 485. The weight variation was found to be within the prescribed limit as per IP indicating uniformity in the weights of all combinations of suppository bases.

Hardness

Hardness of suppositories was found to be in the range of 3.3 to 4.5kg/cm2. Suppositories prepared with PEG and hydrogenated vegetable oil was found to be harder than other combinations. If the hardness is more than 4.5 kg/cm2 the suppository will not melt at body temperature easily and it may cause irritation to the rectum whereas if the hardness is less than 3.0 kg/cm2 suppository will melt rapidly before insertion13. Therefore, prepared suppository bases were suitable for the preparation of drug loaded suppositories.

Melting range test:

Melting range of all suppositories was found within the range of 34-42C. Suppository base containing hydrogenated vegetable oil and PEG 2000 showed higher melting range about

34 - 42□C due to higher melting point of PEG 2000 whereas base containing cocoa butter and hydrogenated vegetable oil showed lowest melting range i.e. 34-38□C. This may be due to presence of hydrogenated vegetable oil which has low melting point.

Liquefaction time:
All the batches showed liquefaction time in the range of 5.10 - 7.35 min. It is the time for which the suppositories withstand body temperature of 37^0C which is helpful in convenient handling and release of drug after administration in rectum.

Hydroxyl value:
The hydroxyl value corresponds to the milligrams of potassium hydroxide (KOH) required to neutralize an equivalent amount of acetic acid combined with hydroxyl groups in 1 g of a suppository. Hydroxyl valueof suppositories was found within the range of 89.76 to 134.64.It determines the hydrophilicity of fatty bases exerts effect on rectal absorption[15].

Hydroxyl value of suppository base has influence on the release of drug dissolved in the suppository base. Higher the hydroxyl value faster 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:
Suppository of lorazepam was prepared by fusion method using combination of different bases and chitosan as sustained release polymer. Phenytoin suppositoriesof all the batches showed smooth texture and appearance.
All the suppositories showed average weight within the range of 468 to 493mg (Table 3). The weight variation was found to be within the prescribed limit as per I.P. This indicates the uniformity in weights of suppositories. Hardness of suppositories was found to be in the range of 3.6 to 4.5 kg/cm^2.

Melting time of lorazepam suppositories was found in the range of 31-41□C. PEG and hydrogenated vegetable oil containing suppository showed high melting range 35-41□C due to high melting point of PEG 2000. Cocoa butter and hydrogenated vegetable oil containing suppository showed low melting range (31-36□C). This may be due to fact that the cocoa butter has low melting point than other suppository bases. All the batches showed liquefaction time in the range of 6.23-8.85min. It is the time for which the suppositories with stand body temperature. It is helpful in easy handling and facile release of drug after administration in rectum.

Drug Content:
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 (Table 3).

In vitro drug release:
The release profile of lorazepam from different suppositorybases is shown in figure 1. Drug release was found to be within the range of 90.87 to 99.44 at the end of 120min. The burst release was observed in the range of 8 to 26%at the end of 15min in all the formulations. Higher burst release was observed in the formulation containinghydrogenated vegetable oil and PEG which may be due to high aqueous solubility of PEG[18]. Further, surface associated drug gets easily diffused into the bulk of dissolution medium[10]. Drug release was found to be retarded in the batches containing cocoa butter alone or combination as a base. This is attributed to the fact that cocoa butter being a fat soluble suppository base does not have affinity for dissolution medium[19]. The releaseof drug from the suppositories is in the order of hydrogenated vegetable oil - poloxamer 407> hydrogenated vegetable oil - PEG 2000> hydrogenated vegetable oil -cocoa butter. Maximum drug release was observed in the formulation containing poloxamer 407 and hydrogenated vegetable oil. This is due

to due to presence of hydrophilic as well as lipophilic groups in poloxamer 407. Poloxamer 407 is water soluble and has higher melting points than the other bases. Addition of hydrogenated vegetable oil lowered the melting point of poloxamer 407 so that suppository can be administered easily without irritation. Due to poor water solubility of lorazepam in water dissolutionof drug in lipid soluble bases is slow as compared towater soluble bases.[12]

Release data was fitted into model dependent and independent parameters[20] and are given in table 4. Dissolution efficiency (DE) of suppository formulations was found in the range of 45.88 to 61.83% while mean dissolution time (MDT) was found to be in the range of
45.38 to 59.40min at the end of 120min. Formulation containing poloxamer 407 and hydrogenated vegetable oil base showed higher DE indicating faster release of drug from the formulation. All the formulations followed the Higuchi kinetic model with release exponent in the range of 0.65 – 1.11 indicating non-Fickian diffusion coupled with erosion.

CONCLUSION:

Combination of lipophilic, hydrophic and amphiphilic suppository bases containing hydrogenated vegetable oil with cocoa butter, poloxamer 407 and polyethylene glycol 2000 were prepared in the ratio of 19:1. lorazepam suppositories prepared with those bases release of drug within 120min. The release retardationwas observed in the formulation containing lipophilic base whereas rapid release was observed in the formulation containing hydrophilic bases. The prepared composition of suppository bases can be potentially used for poorly soluble drugs.

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