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Innovation of Natural Product as Suppository Base†

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The ideal properties of ghee paved the way for the development of natural product suppository using ghee as a suppository base. It has ability to decrease the low density lipoproteins cholesterol level in plasma, the capability of smoothening the skin and its lipophilic character facilitates better absorption. Suppositories administered *via* vaginal or rectal route melts at the body temperature for the targeted delivery. Sulphanilamide, an antimicrobial drug is used as the model drug. The objective of the present work is to study the role of ghee as a base in addition with bees wax at varying composition like 1:1, 2:1 and 1:2. The prepared suppositories are evaluated for their physical parameters. The influence of polymer like hydroxy propyl methyl cellulose (5, 10 and 15 %) on drug release is also studied. The results proved that increase in ghee ratio enhances the drug release whereas increased ratio of bees wax showed a decline in release.

Keywords: Sulphanilamide, Bees wax, Cow ghee, Hydroxy propyl methyl cellulose.

INTRODUCTION

Indian system of traditional medicine has its unique position in the history of medicine. Similarly ghee's role as a medicament holds the same age, apart from its nutritional values it possesses best medicinal properties like enhancing the physical and mental strength and also in removing the impurities from our body. Ghee increases intelligence, memory power and the other uses include rejuvenation of skin, boosts body energy, detoxifies and nourishes body, increases clarity of voice, increases semen secretion, effective against eye disorders and wound healing activity, decreases the LDL cholesterol in plasma, increases gastric acid secretion for digestion and improves appetite[1-4]. Suppositories are the solid dosage forms which can be inserted into the cavity of vagina or rectum or urethra for local or systemic effect, where it melts at body temperature and disperse or dissolve in cavity fluids to release the drug. Generally there are three types of suppositories namely vaginal, rectal and urethral suppositories. Semisolid bases act as a vehicle to carry drug which includes the fatty bases, water soluble bases, emulsion bases, hydrocarbon bases, that are selected based on the physicochemical properties of the drug and the desired therapeutic drug release effect. The specifications for an ideal base includes non-toxicity to tissues, non-irritation to mucous membranes, compatibility with variety of drugs, melting point range near to body temperature, solubility and miscibility in cavity fluids and stability on cold storage[5]. Ghee meets all these conditions as it has softening ability, well suited with all drug types even from olden days, easily melts and in case of proper storage it can be used for longer period even many years by reason of its anti-ageing property . In ancient time Chinese and Indian system of medicine advised patients to take some oral medicines along with ghee which is believed to enhance the activity[6].

Sulphanilamide is used as the model drug which has antimicrobial activity and is used to treat vaginal candidiasis, absorbed easily through vaginal mucosa and aids for local action. Sulphanilamide molecular weight is 172.2 and the water solubility is about 7.5 g/mL at 25 ºC with the melting point range 164-166 ºC[7].

Suppositories are preferred for patients having difficulty in swallowing or in unconscious state and also for individuals who suffer from nausea, vomiting and gastrointestinal ulcers. The route of administration of suppositories possess specific advantage that it would not be affected by first-pass metabolism, conditions of the stomach (acidic pH) and degradable gastrointestinal enzymes. The objective of the present work is to study the role of ghee as a suppository base in combination with beeswax. The effect of addition of hydroxy propyl methyl cellulose (HPMC) on sustained release of drug from the suppository bases is also studied[8,9].

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EXPERIMENTAL

Sulphanilamide and hydroxy propyl methyl cellulose (3000 cP, 50 cP) were purchased from SD Fine Chem Ltd, Mumbai, India. Branded Cow Ghee that was available in market was procured. Bees wax of I.P. grade was purchased from Otto Pvt Ltd. All other chemicals used in the study were of analytical grade.

Preparation of cow ghee based suppositories: Suppositories were prepared by fusion or melt molding method, where the drug is dispersed in molten suppository bases. Beeswax and ghee of different ratios (1:1, 1:2, 2:1) were weighed and the wax was melted in water bath, followed by the addition of ghee, then the required dose of drug was incorporated to the molten mixture[10]. The appropriate amount of base required for the preparation of different ratio suppositories was calculated individually from the displacement value obtained from medicated and the nonmedicated suppositories.

$$P = (N \times S) - \frac{D}{F}$$

where, P: amount of base required, N: number of prepared suppositories, S: size of mold used, D: amount of drug that is required, F - displacement value[11].

Displacement value of the medicament[12] was determined using the following procedure. At first nonmedicated suppositories were prepared with base without drug and the average weight of six suppositories was taken as 'a' mg. Six medicated suppositories were prepared by adding 40 % of drug with base and its average weight was noted as 'b' mg. The amount of base 'c' mg and medicament quantity 'd' mg was calculated so that the weight of the base displaced by the 'd' mg of medicament could be known which was given as '(a-c)' mg. Finally displacement value of the medicament was determined using equation:

$$\text{Displacement value of the medicament} = \frac{d}{(a-c)}$$

The formula for the preparation was designed to obtain the total weight of suppository as 1 g, each containing 250 mg of sulphanilamide as labeled dose.

Preparation of sustained release suppositories: The suppository formulations containing the polymer along with the drug were also prepared by the fusion method, wherein the kneaded mixture of polymer and drug was added to the melted bases to get uniform dispersion. The weighed amount of drug along with the hydroxy propyl methyl cellulose was well triturated in mortar and pestle by adding of approximately 1 mL of ethanol into it. This kneaded mixture was dispersed in base and the homogeneous molten mixture was then poured into the suppository mold and kept aside at room temperature for twelve hours followed by refrigeration for another twelve hours, to solidify the dosage form and finally wrapped in aluminium foil.

Evaluation of suppositories

Weight uniformity and dimensions: The prepared suppositories were weighed and the average weight was calculated. The uniformity of weight was checked for the deviation limits of ± 5 % from its average value. The physical appearance of the suppositories was noted and the dimensions (height and diameter) were measured using Vernier caliper (Mitutoyo, Japan).

Hardness test: Monsanto hardness tester (Dolphin^{TM}) was used to determine the crushing strength of suppositories. This helps in identifying the mechanical strength of suppositories during packaging, shipping and handling.

Melting time test: Suppositories were kept in water bath and maintained at 37 ºC. The time taken for the melting of the suppositories was noted and that should not exceed 1 h.

***in vitro* dissolution studies:** The USP/NF XXIV type-1 rotating basket method (DS 8000, Labindia, Mumbai, India) was used for the drug release studies, wherein the suppositories were placed inside the basket rotating at 50 rpm and immersed in phosphate buffer medium of 500 mL (pH 7.4) and maintained at 37 ºC. Aliquot samples of 10 mL were withdrawn at periodic time intervals of every 1 h and the vessels were replaced with same amount of fresh medium each time, to maintain the sink condition. The samples were analyzed using UV-visible spectrophotometer (Evolution 201, Thermoscientific) at the maximum absorbance wavelength of 258 nm. The concentration of drug present in each samples were estimated using the standard calibration graph and the percentage drug released at each time points was calculated from the data[13-15].

Drug release kinetics: The mechanism of drug release from the suppositories was studied by fitting the obtained dissolution data to various mathematical kinetic models such as zero-order, first order, Higuchi, Korsmeyer-Peppas and Hixon models[16], wherein the R^2 value obtained from the respective plots were noted. Also from the slope value obtained from the Korsmeyer-Peppas kinetics model, the mode of drug release from the dosage form was checked.

Fourier transform infrared spectroscopic studies (FTIR): The suppositories were subjected to infra red spectroscopy analysis by ATR method, since the solid dosage could not be pelletized using KBr mechanism due to its sticky nature because of presence of bees wax, ghee and high viscosity grade HPMC. The spectrum was recorded in the wave number range of 4000-400 cm^{-1} and was compared with the standard spectra of the pure drug, bees wax and HPMC to identify the possibility of drug-excipient chemical interactions[17].

Thermal analysis: The change in thermal property of sulphanilamide in the suppository as compared to the pure drug was studied using Thermo Gravimetric-Differential Scanning Calorimetry (TA instrument, Q100, USA). Around 2-5 mg of the samples were placed in an aluminium pan and heated at the rate of 10 ºC/min upto 500 ºC. The result was represented as, thermogram showing endothermic or exothermic changes and weight loss, with respect to heat flow and temperature[17].

RESULTS AND DISCUSSION

Significance of ghee as suppository base: The role of ghee as a suppository base was studied at different combination ratio with bees wax. As ghee exhibit in solid state in cold condition and slightly molten state at room temperature, the combined effect of ghee along with bees wax was studied to obtain a solidified mass at room temperature which can melt

at body temperature to release the drug *in vivo*. The lipophilic character of ghee can provide enhanced permeation effect for crossing the biological membranes in a better way[18].

Formulation suitability of base and polymers: The fusion method of preparation of suppository mass was most efficient which resulted in uniform dispersion of the drug and polymer and also the different combinations of ghee and beeswax in the ratios of 1:1, 2:1 and 1:2 resulted in uniform weight distribution of each suppository containing 250 mg dose of Sulphanilamide drug. Similarly the sustained release suppositories[19] were formulated using kneaded mixture of drug and HPMC at 5, 10 and 15 % (two viscosity grades 50 cP and 3000 cP).

Standards of quality control parameters: The prepared suppositories were evaluated for various physical parameters as per quality control standards and found to have satisfactory results as shown in Table-1. The uniformity of weight was achieved within the pharmacopoeial limits in all the composition of the formulations. The height and diameter of the formulations was in the range of 12-13.13 mm and 7.5-8 mm, respectively. The mechanical strength measured as hardness of suppositories was in the range of 2.5-3 Kg/cm^2 [20]. The suppositories took a minimum melting time of 15 min up to a maximum of 45 min.

Effect of ghee and bees wax combination on drug release: The *in vitro* dissolution studies done using rotating basket method for 6 h which showed sustained release of sulphanilamide from the HPMC suppositories along with the bees wax and ghee as bases (Fig. 1). The drug release was higher in case of 2:1 ratio of ghee and beeswax suppository, due to the melting of ghee at room temperature and its miscibility with the media, which proved that the increase in concentration of ghee in the suppository can increase the drug release. The formulation with 1:2 ratio provide slow release of drug because of the rigidity, insolubility and immiscibility of beeswax, even then its capacity to retard drug release and maintain structure integrity of the formulation over a period of time can be advantageous. The formulation containing 1:1 ratio of the bases provided sustained release of the drug and also showed better stability during handling.

Role of polymer concentration on drug release: The release of sulphanilamide drug from the suppository base at 1:1 ratio in presence of HPMC of two grades 50 cP (Fig. 2) and 3000 cP (Fig. 3) was found be sustained with respect to the concentration of the polymer kneaded with drug. There was a gradual decrease in drug release with increasing concentration of HPMC as 5, 10 and 15 %. The viscosity grades of the HPMC also influenced the sustained release effect whereby, the 3000 cP grade provided high retardation effect than the 50 cP grade and proved as a better choice for the preparation of sustained release suppositories[21-23].

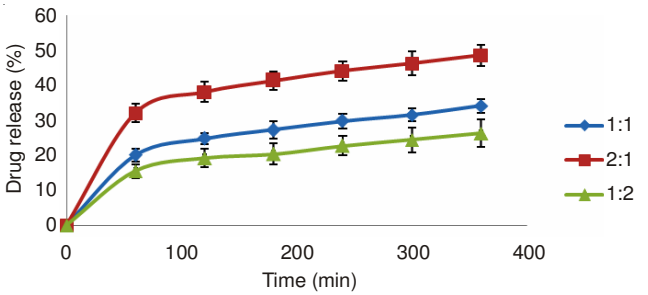

Fig. 1. Drug release profile of suppositories prepared using different combinations of ghee and beeswax

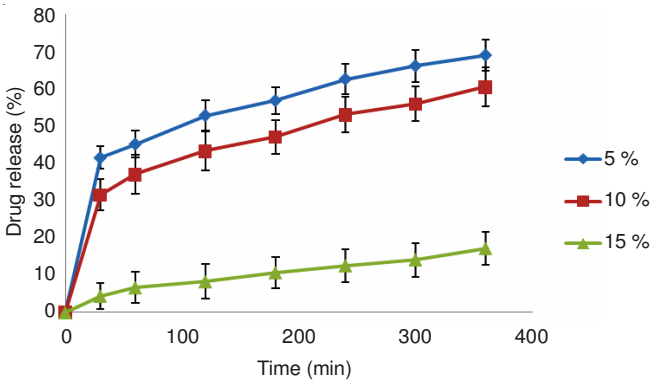

Fig. 2. Drug release profile of HPMC 50 cP incorporated suppositories using 1:1 ratio of ghee and beeswax

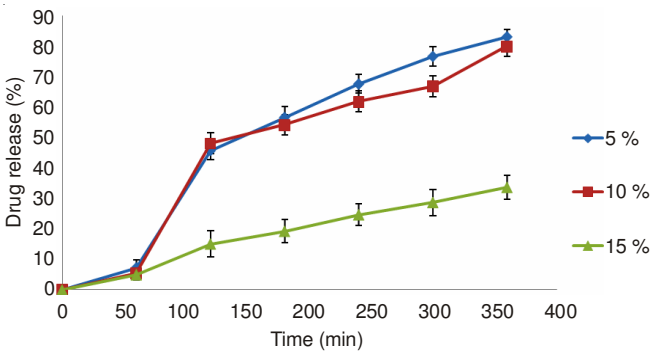

Fig. 3. Drug release profile of HPMC 3000 cP incorporated suppositories using 1:1 ratio of ghee and beeswax

TABLE-1
QUALITY CONTROL TESTS OF SULPHANILAMIDE SUPPOSITORIES

Ratio (%)	Weight variation (g)	Height (mm)	Diameter (mm)	Hardness (kg/cm^2)
1:1	0.502 ± 0.0016	12.99 ± 0.042	7.93 ± 0.041	3 ± 0.07
2:1	0.536 ± 0.0071	12 ± 0.070	7.63 ± 0.26	2.5 ± 0.09
1:2	0.531 ± 0.0054	13.13 ± 0.082	8 ± 0.0	3 ± 0.088
HPMC 50 cp 5 %	0.507 ± 0.0037	12.67 ± 0.204	7.93 ± 0.041	3 ± 0.098
HPMC 5 cp 10 %	0.527 ± 0.005	12.63 ± 0.512	7.53 ± 0.25	2.5 ± 0.098
HPMC 5 cp 15 %	0.519 ± 0.014	12.77 ± 0.414	7.96 ± 0.041	2.5 ± 0.1
HPMC 3000 cp 5 %	0.482 ± 0.013	12.7 ± 0.49	7.67 ± 0.29	2.5 ± 0.099
HPMC 3000 cp 10 %	0.514 ± 0.0011	13.13 ± 0.041	7.87 ± 0.041	3 ± 0.02
HPMC 3000 cp 15 %	0.517 ± 0.0041	13.07 ± 0.11	7.87 ± 0.041	2.5 ± 0.067

TABLE-2
RELEASE KINETICS OF SULPHANILAMIDE SUPPOSITORIES

Ratio (%)	R^2					*n*-Value
	Zero order	First order	Higuchi	Korsmeyer-peppas	Hixon-Crowell	
1:1	0.4908	0.6323	0.9352	0.9993	0.5887	0.288
2:1	0.3410	0.6019	0.8824	0.9999	0.5252	0.226
1:2	0.4971	0.6009	0.9354	0.9979	0.5681	0.290
HPMC 50 cp 5 %	0.0535	0.5369	0.7933	0.9973	0.4043	0.218
HPMC 5 cp 10 %	0.2505	0.5763	0.8702	0.9969	0.4827	0.265
HPMC 5 cp 15 %	0.8543	0.8772	0.9860	0.9894	0.8699	0.555
HPMC 3000 cp 5 %	0.9201	0.9430	0.8963	0.9467	0.9620	0.770
HPMC 3000 cp 10 %	0.8844	0.9329	0.8795	0.9194	0.9329	0.737
HPMC 3000 cp 15 %	0.9792	0.9908	0.9161	0.9895	0.9884	0.847

Mechanism of drug release from the suppositories: The suppositories prepared with bees wax and ghee at 1:1, 1:2 and 2:1 ratio were found to follow Korsmeyer- Peppas kinetics wherein the log of percentage drug release was more linear when plotted against log value of time (Table-2). Also the corresponding *n*-value < 0.45 in Table-2 indicated Fickian diffusion mechanism of drug release from the cylindrical matrix. When the release retarding polymer like HPMC was incorporated in the suppository matrix, the mechanism of drug release was found to be modified. With HPMC 50 cP grade, the mechanism of drug release followed Korsmeyer-Peppas model whereas HPMC 3000 cP grade followed I-order kinetics, especially at high concentration of polymer. So, a concentration dependent drug release profile was observed, where the *n*-value in the range of 0.555-0.847 indicated anomalous non-Fickian diffusion mechanism. The mode of drug release can be attributed to the swelling of the polymer and diffusion of drug from the matrix[24].

Drug polymer interactions: The standard IR spectra of sulphanilamide was found to show bands at 3479, 3377 and 3269 cm^{-1} corresponding to the asymmetrical and symmetrical N-H stretching vibration of the functional groups R-SO_2-NH_2 and N-H_2. The sharp peaks at 1830 and 1697 cm^{-1} to indicate the C=C aromatic bending and stretching, respectively, followed by the C-C stretch at 1314 cm^{-1} and S=O stretch at 1160 cm^{-1} and finally C-H bending at 971 cm^{-1} and 902 cm^{-1} corresponding to the substituted benzene ring[25,26].

The presence of sulphanilamide drug in the suppository was confirmed by its characteristic peaks at 3472, 3359.70 and 3254.31 cm^{-1} for its functional groups and C-C stretch at 1304.96 cm^{-1} and S=O stretch at 1155.81 cm^{-1}, where all the peaks showed a slight shift in its region, due to weakening of the bonds with respect to weak interactions between the drug and the polymers used. Also the sharp peaks seen at 2921.58 and 1745.46 cm^{-1} were identified as the characteristic peaks of bees wax due to C-H stretching and C=O stretching, respectively[27]. The spectra also revealed a sharp peak at 3619.33 cm^{-1} due to O-H stretching and another sharp peak at 899.83 cm^{-1} due to C-O stretching of the HPMC polymer.[28] The presence of the individual characteristic peaks of the drug and the polymers in the suppository proved that there is no chemical interaction between them (Fig. 4).

Thermal analysis: The DSC curve of the pure drug showed a sharp endothermic peat at 166.26 ºC which indicated the melting point or the fusion temperature. A small peak observed at 129.58 ºC corresponds to the intermediate value of phase

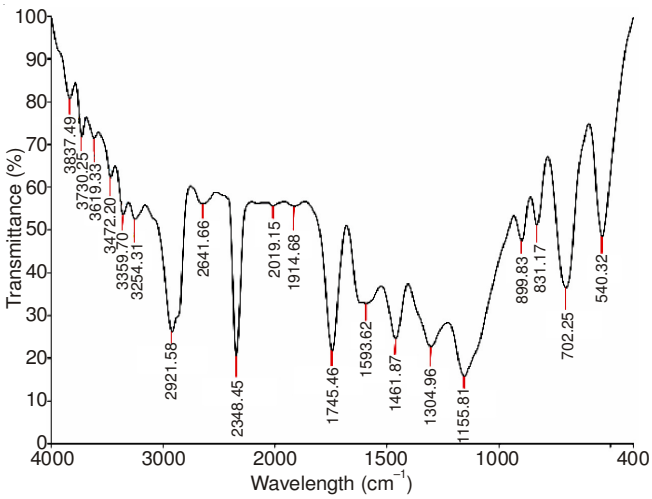

Fig. 4. FTIR spectrum of suppository with HPMC polymer incorporated in 1:1 ratio of ghee and beeswax

transition temperature of the polymorphic β and γ forms of sulphanilamide. The peaks observed at 286.95-335.48 ºC indicated the decomposition point where the sudden weight loss was observed at the corresponding temperature in TG curve[29,30].

In the suppository formulation, the sharp endothermic peak at 53.53 ºC indicated intermediate value of melting point of HPMC and bees wax (47.9 and 63 ºC, respectively) and the small peak at 142.89 ºC showed the Tg temperature of HPMC[31]. The melting point of the drug at 166.80 ºC was not modified in the formulation, which proved that there was no change in the solid state nature of the drug in addition to the polymers during the preparation. Also, an exothermic peak at 267.28 ºC was observed for HPMC followed by the decomposition peaks of the drug and polymer from 304.76-412.17 ° C, with corresponding weight loss shown in the TG curve of the sample (Fig. 5).

Conclusion

Ghee's remarkable permeation and significant absorption already noticed by the traditional medicine suggests it as a vehicle for per-oral and other routes. In this study it was proved as a good choice of suppository base however combinations are worthful than the individual role conversely the HPMC content improves the bioavailability and also provided a sustained release effect of the formulation. Further studies in ghee can help to use it as a better natural ingredient for many other pharmaceutical preparations in future.

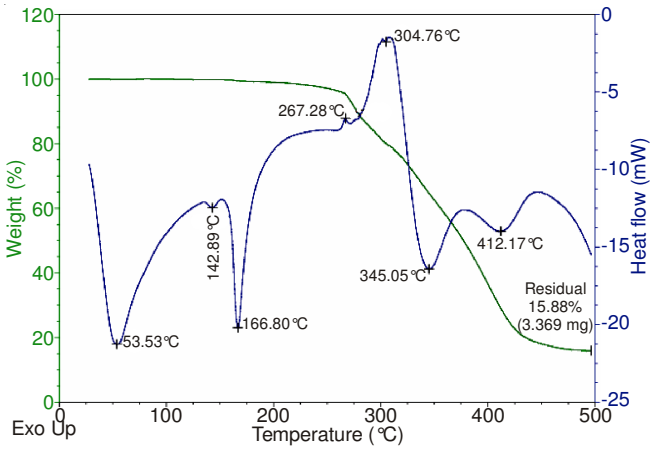

Fig. 5. DSC thermogram of suppository with HPMC polymer incorporated in 1:1 ratio of ghee and beeswax

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