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# Interpretation of Sustained Release Effect of BCS Class II Drug by Preparing Complexes

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**Keywords:** Permeation, Dissolution, Ghee, Rosuvastatin, Complexation

**ABSTRACT**

**Objective:** The objectives of our study was to interpret the sustain release effect of preferred drug Rosuvastatin by concocting complex of drug with ghee. **Material and Method:** Paddle apparatus USP type 2 was used for dissolution study and permeation study was performed by the everted intestinal method. The different ratios of complexes were prepared by the solvent evaporation method and evaluated. The complexes were Rosuvastatin calcium with native ghee complex (1:1 to 1:5), Rosuvastatin calcium with oxidized ghee complex (1:1 & 1:5), and complex with adsorbate Rosuvastatin calcium with MCC and oxidized Ghee complex (1:1:1) and Rosuvastatin calcium with aluminum-magnesium silicate and oxidized ghee complex (1:1:1). **Result and discussion:** In dissolution study of Rosuvastatin calcium the percentage drug release was in the range from 35% at 15 minutes and 98% within 90 minutes; while in case of Rosuvastatin calcium with native cow ghee and oxidized cow ghee, the % drug releases decreased to93% to 52% at 90 minutes and 93% to 55% at 90 minutes respectively. The permeation study showed that in the presence of ghee the permeation of Rosuvastatin showed 96% release at 105 minutes and 93% at 75 minutes. **Conclusion:** By comparing the dissolution study of the prepared complex with control drug it was observed that the prepared complexes sustained the drug release.

## INTRODUCTION

The rate of absorption and bioavailability of the poorly water-soluble drug is that the major drawback encountered with the formulation development of recent chemical entities.[1] Solubility and permeability are one among the necessary parameters to realize the desired concentration of drug in circulation for achieving needed medicine response. Due to poor solubility of drugs with water, it is essential to increase the amount of drug given as in the case of oral administration to achieve therapeutic plasma concentration[2].

Rosuvastatin is a 3-hydroxy-3methylglutaryl coenzyme A- reductase inhibitor, developed for the treatment of dyslipidemia which reduces LDL-C and triglycerides (TG) and at raising HDL-C levels thereby. Rosuvastatin calcium is discriminatory and a competitive inhibitor of *HMG-CoA reductase* has poor water dissolving property of drug that addressing drawback of low bioavailability (20%) as their dissolution is rate-limiting issue[3]. so to fulfill the problem of bioavailability, it can be possible to prepare effective sustain release formulation for the drug so that complexation with those substances which can sustain the drug release and should have effectively permeation capability. So here we used cow ghee to sustain the release of drug Rosuvastatin calcium. The literature survey and the previous work performed in the laboratory indicate that the oxidation of ghee which is oxidized in hot air oven decreases the bad cholesterol existing in the ghee and therefore decreases in chances of cardiovascular disease[4]. According to Ayurveda Ghee which is known as 'Gritha', narrate as the best among lipid media due to its quality of inheriting and enhancing the drug potency [7]. It gives many potential benefits to the body, it is used as a massage oil to cure many types of diseases like mantel disorder, hypertension, etc. Ghee has the potentiality to permeate endothelial cells of the blood-brain barrier. According to the literature review, it is a hypothesis that ghee can proliferate the permeability by which can increase in bioavailability of the drugs. So that we attempt to investigate the dissolution study and permeation study of ghee and its complexes with Rosuvastatin calcium. Thus our aim and objective were to interpret the sustain release effect of BCS class II drug Rosuvastatin calcium by preparing the drug ghee complexes which in turn would enhance bioavailability. For fulfilling the aim and objective preparation of complexes and evaluation of physicochemical parameters of ghee and its complexes in which in-vitro drug release study and Ex- vivo permeability study were performed. The complex of the Rosuvastatin calcium was prepared in different ration with native ghee and oxidized ghee by the solvent evaporation method. A dissolution study was

done by using paddle apparatus USP type 2and permeation studies were performed by the everted intestinal method (figure1-3). The permeation study was evaluated by everted intestinal method(figure 4-6).

## MATERIALS AND METHODS

### Material

Rosuvastatin calcium was procured from Mylan laboratory; Hyderabad. Cow ghee was purchased from the local market of Chhattisgarh. Ethanol, Acetone, Sodium chloride, Potassium chloride, Magnesium chloride, calcium chloride, sodium bicarbonate, sodium hydrogen phosphate, sodium dihydrogen phosphate, potassium di-hydrogen orthophosphate were purchased from Sudarshan Chemical, Raipur (C.G).

Freshly slaughtered cockerel intestine bought from the nearest slaughterhouse which was kept in Tyrone's solution at 20°C, till further use. Equipment and assembly for everted intestine were assembled using reservoir (made of glass and plastic container) having a capacity of 250ml with controlling valve for monitoring the flow rate of solution go through the pipe to the assembly, the assembly was prepared in a glass container in which inlet and outlet were made by clamping two pipes in both side of the inverted intestine, one is connected to reservoir as inlet and another pipe are used as an outlet. Electrical assembly is used for oxygen supply to the tissue through the aerator. A Shimadzu-1700 UV visible spectrophotometer with 1 cm matched silica cells was used for spectrophotometric analysis.

### Methods:

**Preparation of Standard Stock Solution**:

An accurately weighed quantity of about 50 mg of Rosuvastatin calcium was taken in a 50 ml volumetric flask dissolved in a sufficient quantity of ethanol then sonicated for 15 min and diluted to 50 ml with the same solvent to get the concentration of 100 µg/ml. This stock solution is used for making dilutions for calibration curve[17].

**Determination of λ Max**:

The standard solution of Rosuvastatin calcium scanned at different concentrations in the range of 200-400 nm and the λ max was determined.

**Preparation of Calibration Curve:** Appropriate aliquots were pipette out from standard stock solution into the series of 10 ml volumetric flask and the volume was made up to the mark with ethanol to get the concentration of 1-10 µg/ml of Rosuvastatin calcium. Solutions of different concentrations were analyzed at their determined wavelength and absorbance were recorded[17].

**Preparation of binary complexes at different ratio:**

Complexes of drug with native and oxidized were prepared. Fusion admixture of Rosuvastatin calcium**:** ghee was prepared by melting the ghee in a beaker over a water bath maintained at 65-70°C temperature. To the molten ghee, an equivalent amount of drug was added and uniformly dispersed by continuous stirring to prepare the binary mixture. The ration 1:1 to 1:5 w/w ratio was selected to maximize the likelihood of observing any interaction the fussed mixture was homogenized and allow to cool slowly to room temperature with stirring. The binary mixture was stored in amber-colored glass bottles. Native ghee was oxidized by heating it in an electric stainless steel oven at 120°C for 50 hours. The complexes in the same ratios were prepared by using oxidized ghee also.

***In-Vitro* Drug Release Study:**

The paddle apparatus USP type 2 was adopted in this study. The release medium consisted of 900 ml of 0.1 N HCl solution. A known quantity from each batch of the drug was placed in the chamber of the release apparatus and agitated at 60 rpm. At predetermined time intervals (15 min.), 5 ml of the release medium was withdrawn, appropriately diluted and absorbance determined at a respective wavelength using a UV spectrophotometer. The volume of the release medium was kept constant by replacing it with 5 ml of fresh 0.1N HCl solution after each withdrawal. The release study was repeated using 0.1 N HCl solution as a release medium and the absorbance was determined at a known wavelength.

***Ex-Vivo* Intestinal Permeation Study:**

Experiments using the everted intestine method: [15]

Six setups of pure drug sample and complexes drug: ghee were prepared and their quantity was taken according to their therapeutic dose respectively. The fresh cock intestine was bought from the slaughterhouse. A 10 cm of intestine was everted and the inlet and outlet

were made by clamping two pipes in both sides of the everted intestine in which one is connected to the reservoir as inlet and another pipe are used as an outlet. This everted intestinal setup was dipped in a beaker containing drug and 6.4 pH phosphate buffer. From the reservoir 7.4 pH phosphate buffer was supplied, about 15 ml volume was filled inside the everted intestine. After each 15 minutes interval, the filled solution inside the intestine was taken out (about 5 ml), the flow rates were controlled by controlling the valve having in reservoir pipe. Again make up the volume with 7.4 pH phosphate buffer up to 15 ml inside the intestine. The procedure was followed for 135 minutes and intermittent samples were collected. After suitable dilutions by UV spectrophotometer, the absorbance was taken at a suitable wavelength. The concentration of drug in each sample was determined by the regression equation.

## RESULTS AND DISCUSSION

### UV Spectroscopy

The absorption maximum of the drug in the Ethanolic solution was found to be 325 nm.

### *In-vitro* release study:

The release study of Control (pure drug) and their Complex with native ghee at different ratios (1:1, 1:2, 1:3, 1:4 and 1:5) were studied and calculated for drug release then graph was plotted between percent Drug Release Vs Time.

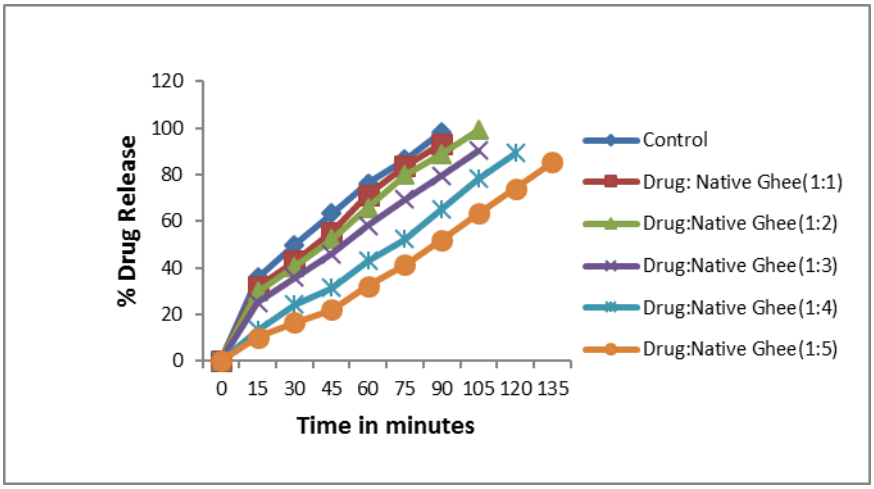


**Figure No. 1: Drug Release of Rosuvastatin calcium Complexes with Native Ghee**

In the series of experiments, it was observed that Rosuvastatin calcium control drug shows 35.89%, 98.23% drug release at 15 minutes and 90 minutes respectively. When preparing a complex with ghee (1:1) it shows decreased % drug release as compared to control drug which was 31.87% at 15 minutes and 93.28% at 90 minutes. Again by increasing the ratio of ghee in complex 1:2 (Drug: Native Ghee) is shows 29.88%,99.98%, and 98.98% drug release at 15,90 and 105 minutes respectively. In drug ghee complex 1:3, it shows 25.14%, 79.56%, and 90.22% in 15, 90, and 105 minutes which were lower than control drug release. In 1:4 ghee complex again it decreases to 13.18%, 65.23%, 89.23% drug release in 15, 90, 120 minutes which means it takes more time to release the drug from the complex. For the 1:5 drug ghee complex, it shows a 10.12% Drug release at 15 minutes, 52.12 at 90 minutes, and 85.21% at 135 minutes (Figure 1).

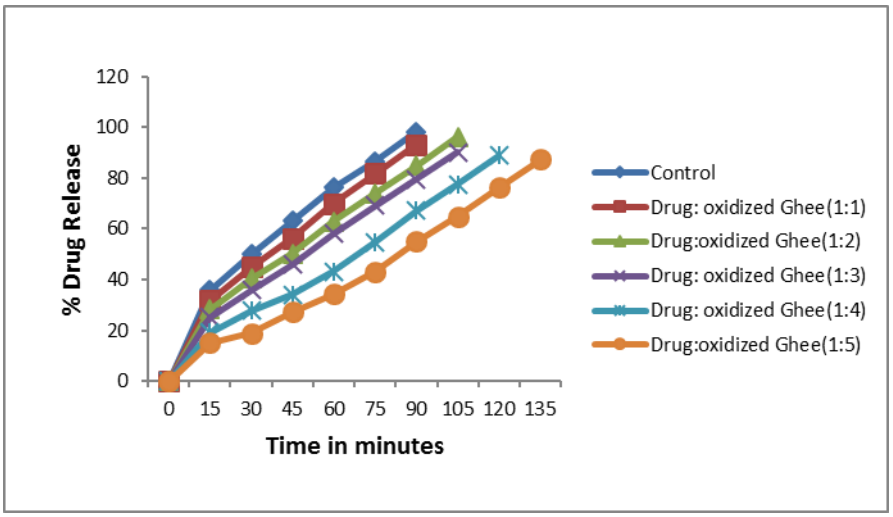


**Figure No. 2: % Drug Release of Rosuvastatin calcium Complexes With Oxidized Ghee**

The complex of Rosuvastatin calcium with oxidized ghee was studied and percent drug releases were calculated. In this experiment drug: oxidized ghee(1:1) shows 31.87% drug release at 15 minutes and 93.28% at 90 minutes and the drug: ghee complex (1:2) shows 28.23% drug release at 15 minutes, 84.98%at 90 minutes, and 96.23% at 105 minutes. Here percent drug release of the drug: oxidized ghee 1:1 and 1:2 was lower than the control drug .and drug: oxidized ghee 1:1 is higher than the 1:2(drug: oxidized ghee) complex. Again when increasing the ration of the drug: ghee complex 1:3 it decreases % Drug release by 25.14%, 79.56 and 90.22% at 15, 90 and 105 minutes. In 1:4 ghee complex shows 19.18% drug release in 15 minutes and 90 minutes it releases 67.15% drug than shows 88.98% at 120 minutes which means it takes more time to release the drug from the complex. For the 1:5

drug ghee complex, it shows 15.12% Drug release at 15 minutes and 55.13% at 90 minutes and then 76.23% at 120 min. than further releases drug 87.29 at 135 minutes (Figure 2).

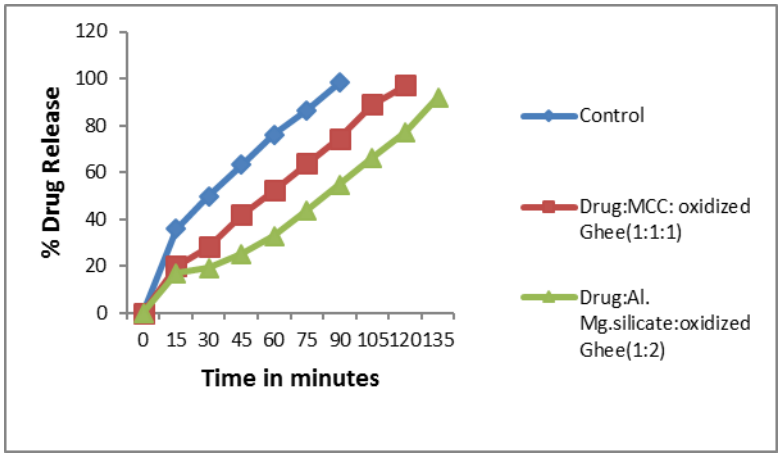


**Figure No. 3: Drug Release of Rosuvastatin calcium Complexes With adsorbate and oxidized Ghee**

The complexion of Rosuvastatin calcium oxidized ghee by adding absorbent was studied and percent drug release was calculated. In this experiment drug: Microcrystalline cellulose: oxidized ghee (1:1:1) shows a higher percent drug release as compare to control drug as 20.13% drug release at 15 minutes, 74.45% at 90 minutes and at 120 minutes it shows 97.23% of drug release. The drug: Aluminium Mg silicate: ghee complex (1:1:1) shows a 16.98% drug release at 15 minutes and 54.87% at 90 minutes and releases 91.88% of the drug in 135 minutes which was lower than control drug. Here when compared that all Rosuvastatin calcium complexes results, it was investigated that the percent drug release of the drug: MCC: oxidized ghee 1:1:1 was lower than control drug but higher than complex of the drug: Al.Mg. silicate: oxidized ghee (1:1:1) (Figure 3).

**Permeation Study:**

The permeation of Rosuvastatin calcium and their complexes at different ratios was studied and calculated for % drug permeation concerning time. The Drug: Ghee complexes 1:1,1:2,1:3,1:4,1:5 were prepared for the permeation study.

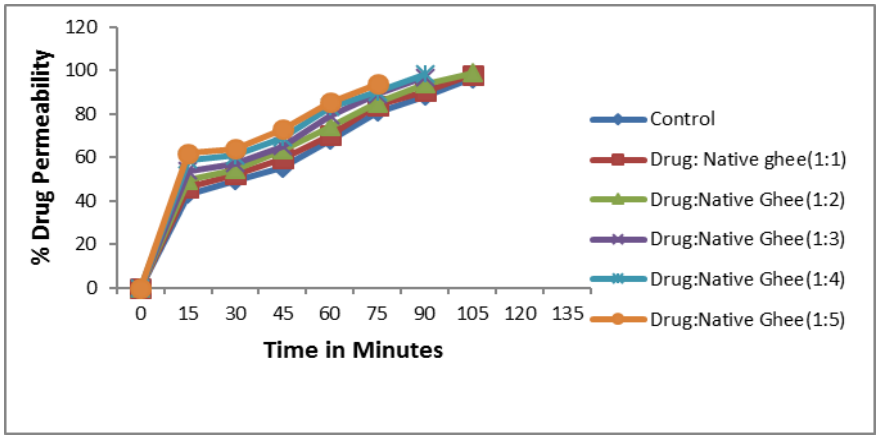


**Figure No. 4: Permeation of Rosuvastatin calcium: native ghee complexes at different ration**

In the series of experiments regarding permeability of Rosuvastatin calcium (it was observed that Rosuvastatin calcium control drug shows permeability as 43.21% in 15 minutes, 90.44 at 90 minutes, It completely releases the drug within in 105minutes as 98.23%. In complex ratio 1:1 it shows 46.23% drug permeation at 15 minutes, 90.44% at 90 minutes and 98.23% permeation at 105 minutes. In 1:2 (drug: ghee complex) it shows 49.58% drug permeation at 15 minutes, 93.88% at 90 minutes, and completely release drug with in120 minutes. In drug: ghee (1:3) % drug permeation at 15 minutes it was 53.89%.96.88 % at 90 minutes. In complex 1:4 (drug: ghee) at 15 minutes the % drug release was 58.94 and increasingly it goes to 98.32 % at 90 minutes of their % drug release. In drug: ghee (1:5) % drug release at 15 minutes it was 61.89%, 93.88% at 90 minutes. From all the permeation study we can conclude that the permeation of drug increases ad increase in the amount of ghee in drug: ghee complex ration. Rosuvastatin calcium complex was also prepared with oxidized ghee. Drug: ghee (1:1) and drug: ghee (1:2) and % drug permeation were observed (Figure 4).

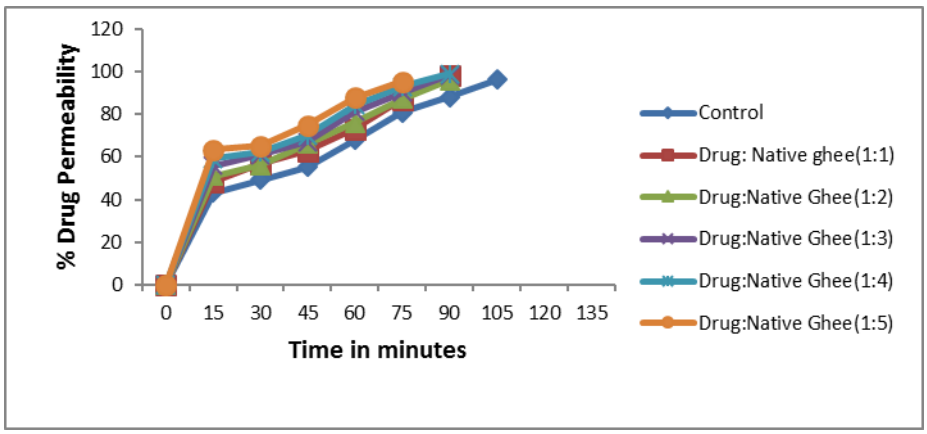


**Figure No. 5: Permeation of Rosuvastatin calcium: oxidized ghee complexes at different ration**

In this experiment the complexes of Rosuvastatin calcium: oxidized ghee was analysed for % drug permeation. In drug: oxidized ghee (1:1) the % drug permeation was 48.33% at 15 minutes, 98.15% at 90 minutes. In drug: ghee (1:2) 51.14% drug permeates at 15 minutes 95.88% at 90 minutes . Here drug: oxidized ghee (1:1) was lower than the control drug. While increasing the ratio 1:3 drug: ghee complexes it increases their release by 55.78% at 15 minutes, 98.23 at 90 minutes. In 1:4 drug: ghee complex it shows 59.14% drug release at 15 minutes, 99.02% at 90 minutes. In 1:5 complex it again increases their release by 63.44% at 15 minutes, 95.33 % at 90 minutes which means it rapidly permeates the drug as the number of ghee increases in the complex ratio(Figure 5).

In the permeation study of complexes, the *adsorbate* was also used in this experiment their % drug permeate was observed.

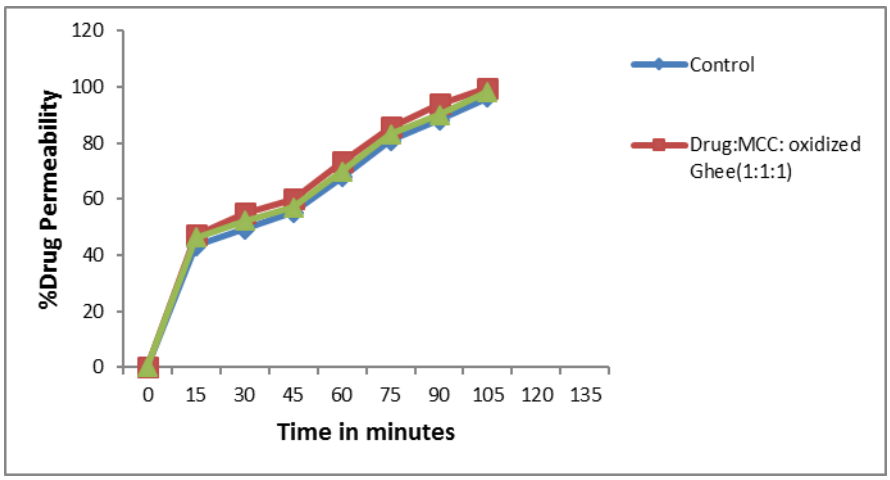


**Figure No. 6: Permeation of Rosuvastatin calcium: oxidized ghee: MCC complexes**

In this experiment the complexes 1:1:1 (Rosuvastatin calcium: Microcrystalline cellulose: oxidized ghee) and 1:1:1 (Rosuvastatin calcium: aluminum magnesium silicate: oxidized ghee) was analyzed for % drug permeation. In drug: Mcc:oxidized ghee(1:1:1) the % drug permeation was 47.25% at 15 minutes,93.88 at 90minutes which increases as 99.56% at 105 minutes. In (drug: Al. Mg. Silicate: oxidized ghee) 1:1:1.46.26% drug permeates at 15 minutes, 90.14 at 90 minutes, and 98.19% at 105 minutes. Here when compared that all Rosuvastatin calcium complexes results, it was investigated that the percent drug permeation of drug: MCC: oxidized ghee 1:1:1 was higher than control drug but lower than drug: native ghee 1:1 complex (Figure 6).

## Differential scanning calorimetry (DSC)

The native ghee exhibited endotherms at 11.28°C and 44.93°C followed by a slanting line up to 300°C. In the case of oxidized ghee, the peaks were sharp as compare to native ghee indicating probably purified material at 13.45°C and 45.04°C. The slanting line of native ghee was here almost straight up to 200°C and thereafter slightly decreases up to 300°C probably indicating a product free of some residual material which was there in native ghee. The melting point of rosuvastatin calcium is 122°C and when complex with native ghee and oxidized ghee these peaks disappeared indicating clear evidence that there is the formation of drug ghee complex in both native and oxidized ghee.

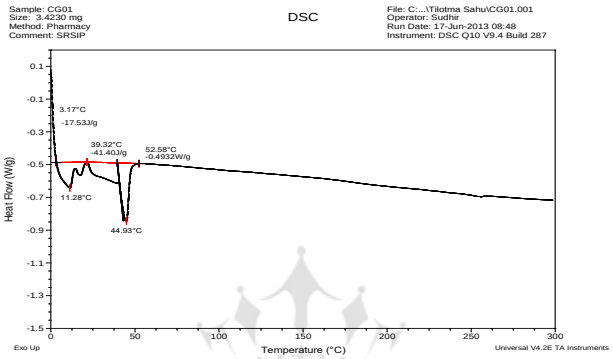


**Fig. 7 – DSC thermogram of native Ghee**

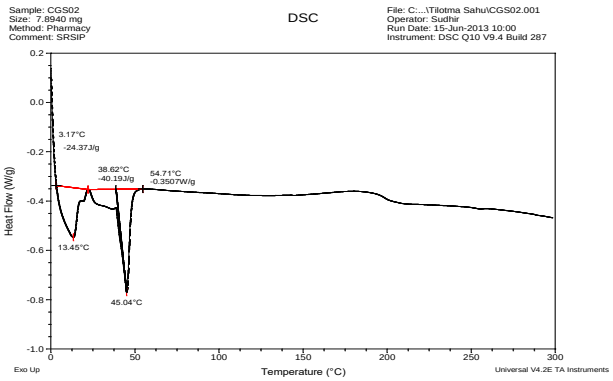


**Figure No. 7a: DSC thermogram of Oxidized Ghee**

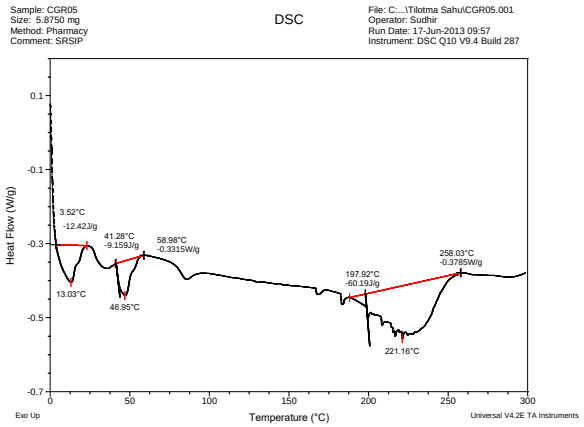


**Figure No. 7b: DSC thermogram of Rosuvastatin Calcium: Native Ghee Complex (1:1)**

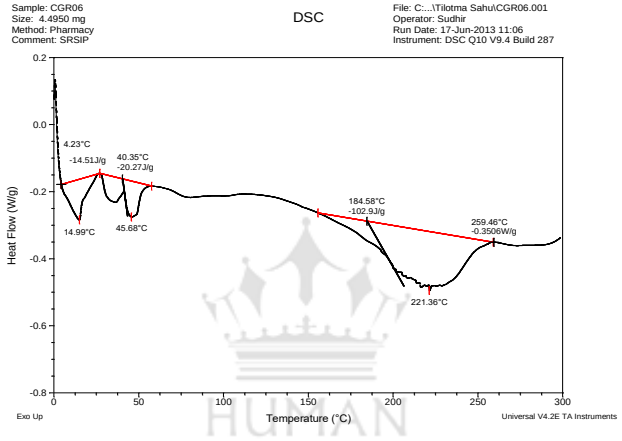


**Figure No. 7c: DSC thermogram of Rosuvastatin Calcium: Oxidized Ghee Complex (1:1)**

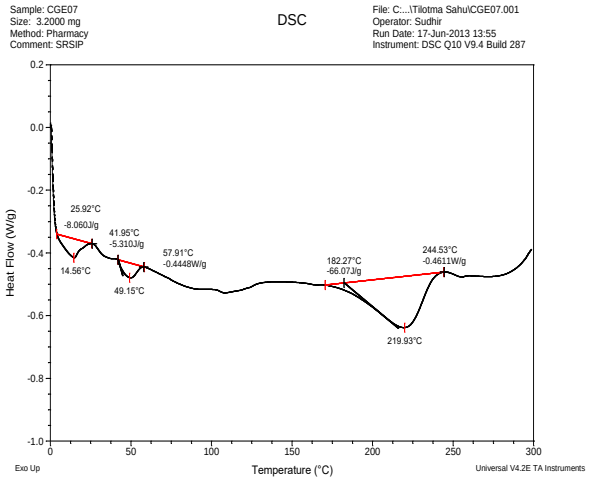


**Figure No. 7d: DSC thermogram of Rosuvastatin Calcium: MCC: Oxidized Ghee Complex (1:1::1)**

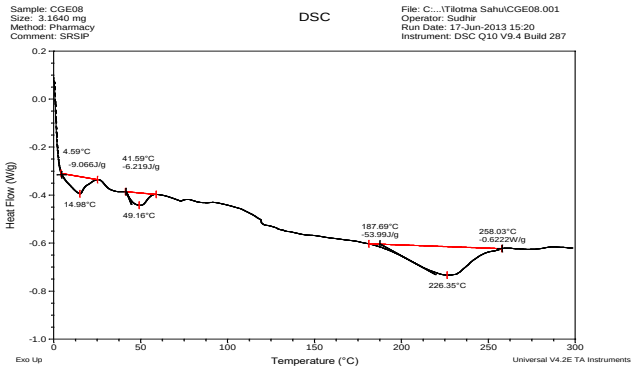


**Figure No. 7e: DSC thermogram of Rosuvastatin Calcium: Aluminum magnesium silicate: Oxidized Ghee Complex (1:1:1)**

## DISCUSSION

Ghee contains a sufficient amount of saturated fats and cholesterol and enhances risk factors for cardiovascular disease.[08] therefore oxidizing ghee by heating it in an electric stainless steel oven at 120°C for 50 hours 17 times the concentration of oxysterol in the preparation. As per Kumar administrating 2-5% oxidized ghee in diet decrease the total cholesterol level by 11-14% as compared to groundnut oil. Oxidized ghee contains enhanced free cholesterol ester fraction in mucosal cells, indicating that esterification process of cholesterol in the intestine is inhibited by ghee lipids (formed in oxidized ghee).[08]Therefore in the present investigation, ghee has been oxidized and used further for research work with the view the oxidized ghee can be used as pharmaceutical aid for the preparation of formulations. In Ayurveda ghee is known to give a soothing effect, hydrates the tissue, and eases the drug permeation across the mucosal membrane as well as establishing the drug permeation for a long period. In the work carried out in an attempt to prepare a stable drug ghee complex which may enhance drug permeability. The release of drugs from Rosuvastatin calcium complex with ghee was shown a lesser release of the drug than control drug. When the amount of ghee was increased, the drug release was lowered, it may because of higher entrapment of the drug material. Complex made with oxidized ghee of rosuvastatin calcium exhibited nearly 82% drug release in 90 minutes in (1:1) drug: ghee complex, while 1:5 complex as obvious exhibited the lower amount of drug release due to entrapment. Finally to take the sticky complexes to the formulation they were made to adsorb on the adsorbates so that the material becomes free-flowing and compressible. The adsorbates choose were the microcrystalline cellulose and aluminum magnesium silicate. The dissolution study of the

drug materials from these adsorbates indicates higher drug release by MCC (microcrystalline cellulose) as compare to aluminum magnesium silicate. Permeation study indicates the just reverse of the dissolution study of rosuvastatin calcium. The number of drugs as compared to control permeated more as the amount of ghee increased. The amount of drug permeation through oxidized ghee is also higher in both cases. More interestingly the amount of drug release through adsorbates may be microcrystalline cellulose and aluminum-magnesium silicate exhibited a similar trend.

## CONCLUSION

The preliminary study of drug ghee complex of rosuvastatin calcium exhibited different physicochemical characteristics thereby interpreting the formation of complexes. Further, the improved permeation supports their formulation steps and hence the drug ghee complexes can be used for the improvement of drug therapeutics.

## REFERENCES

1. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharmaceutics. 2012 Jul 5;2012.
2. Gowardhane AP, Kadam NV, Dutta S. Review on enhancement of solubilization process. Am J Drug Discov Dev. 2014;4(2):134-52.
3. Sarfraz RM, Ahmad M, Mahmood A, Minhas MU, Yaqoob A. Development and evaluation of rosuvastatin calcium based microparticles for solubility enhancement: an in vitro study. Advances in Polymer Technology. 2017 Dec;36(4):433-41.
4. Akbari V, et al;2011; "Optimization of Super Disintegrants And Subliminutesg Agent on Dissolution Rate of Rosuvastatin Orodispersible Tablets By Using A 32 Factorial Design"; PharmacieGlobale (IJCP) , vol.2; issue 1; pp:1-6
5. Zeb A, Uddin I. The coadministration of unoxidized and oxidized desi ghee ameliorates the toxic effects of thermally oxidized ghee in rabbits. Journal of nutrition and metabolism. 2017;7.
6. Nirmala KS, Bhat MS, Sahajananda H. Effect of two types of dietary ghee on serum lipid levels in rats. Journal of evolution of Medical and Dental Sciences. 2016 Jun 20;5(49):3140-5.
7. Ibrahim WM, AlOmrani AH, Yassin AE. Novel sulpiride-loaded solid lipid nanoparticles with enhanced intestinal permeability. International journal of nanomedicine. 2014;9:129.
8. Kumar MV, Sambaiah K, Lokesh BR. Hypocholesterolemic effect of anhydrous milk fat ghee is mediated by increasing the secretion of biliary lipids. The Journal of nutritional biochemistry. 2000 Feb 1;11(2):69-75.
9. Akbari B., Valaki B.et al; Enhancement of Solubility and Dissolution Rate Of Rosuvastatin Calcium By Complexation With B-Cyclodextrin; International Journal of Pharmaceutical & Biological Archives; vol.2(1)2011; pp: 492-501
10. Ballantyneetal; Carstor®( Rosuvastatin Calcium) Tablet; American Heart Journal;2006.
11. Rajkondwar VV, Maini P, Vishwakarma M. Characterization and method development for estimation and validation of Rosuvastatin Calcium by UV–visible spectrophotometry. Int J Theoret Appl Sci. 2009;1:48-53.
12. Kolhe P, Misra E, Kannan RM, Kannan S, Lieh-Lai M. Drug complexation, in vitro release and cellular entry of dendrimers and hyperbranched polymers. International journal of pharmaceutics. 2003 Jun 18;259(1-2):143-60.
13. Deshmukh PK. Dissolution enhancement of rosuvastatin calcium by liquisolid compact technique. Journal of pharmaceutics. 2013 Feb 27;2013.

14. Kumar M, Sharma V, Lal D, Kumar A, Seth R. A comparison of the physicochemical properties of low-cholesterol ghee with standard ghee from cow and buffalo creams. International journal of dairy technology. 2010 May;63(2):252-5.
15. Kale VV, Kasliwal RH, Avari JG. Attempt to design continuous dissolution–absorption system using everted intestine segment for in vitro absorption studies of slow drug release formulations. Diss. Tech. 2007 May 1;5:31-6.
16. Gowardhane AP, Kadam NV, Dutta S. Review on enhancement of solubilization process. Am J Drug Discov Dev. 2014;4(2):134-52.
17. Sevda RR, Ravetkar AS, Shirote PJ. UV Spectrophotometric estimation of rosuvastatin calcium and fenofibrate in bulk drug and dosage form using simultaneous equation method. Int. J. Chem. Tech. Res. 2011 Jun;3:629-35.