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Formulation Development And Evaluation Of Suitable Gastroretentive Unit Dosage Form Containing Remogliflozin

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Abstract:

This study aimed to develop a once-daily gastro-retentive floating matrix tablet for Remogliflozin using polymers as a rate-controlling polymer and as a swelling agent. The formulations were created and assessed afterwards checked for stability, drug content, and in vitro release profile. The results indicated that higher viscosity grades of polymers achieved desirable outcomes at lower concentrations compared to lower viscosity grades. The FT-IR spectrum, it was revealed that there was no drug-excipient incompatibility. The in vitro release data and drug release mechanism for the optimized formulation adhered to the zero order non-fickian diffusion controlled release mechanism. It showed controlled drug release up to 12 h and stable at 40 °C/75 % relative humidity for a period of 3 months may possibly be a better delivery system for drug like drug. Consequently, it can be concluded that using higher viscosity grades polymers offers a more effective release-retarding capacity, making them promising polymers for gastro-retentive floating drug delivery systems.

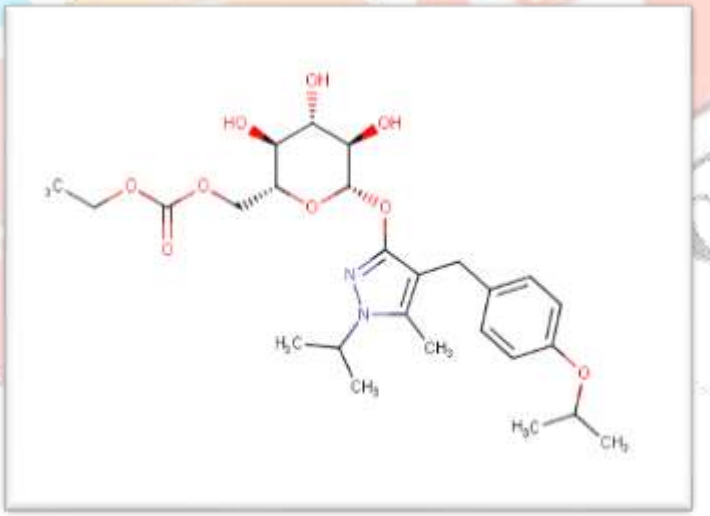
Keywords: Gastro, Retentive, Formulation, Remogliflozin

INTRODUCTION

The primary characteristic of gastro retentive systems is their ability to remain in the stomach for an extended period. The short gastric residence time of conventional oral dosage forms often leads to incomplete drug absorption, erratic plasma drug levels, and the need for frequent dosing.[1,2]. The goal is to enhance the therapeutic efficacy and bioavailability of the drug by optimizing its release pattern[3,4]. Certain types of drugs can benefit from using gastro retentive devices.[5,6,7] oBy maintaining the drug in the stomach, gastro retentive systems enhance drug absorption, especially for drugs that undergo absorption primarily in the stomach or upper part of the small intestine..[8,9,10,11]

Remogliflozin Etabonate is an orally available prodrug of remogliflozin, a benzylpyrazole glucoside-based inhibitor of renal sodium-glucose co-transporter subtype 2 (SGLT2) with antihyperglycemic activity. Upon administration and absorption, the inactive prodrug is converted to its active form remogliflozin and acts selectively on the sodium-glucose co-transporter subtype 2 (SGLT2). The AUC0 ∞ of RE is 31.1 h·ng/mL. the overall bioavailability of remogliflozin from RE is low because of extensive metabolism. The elimination of remogliflozin metabolites takes place by renal excretion (92%).

Figure No.1.: Remogliflozin



Materials and Methods [16-35]

Materials

HPMC (K4M, K15M, K100 LV), Carbopol 71G, Sodium alginate, Xanthan gum, Karaya gum, Microcrystalline cellulose, Anhydrous citric acid, Magnesium stearate and Talc were purchased from SD Fine Chemicals, Mumbai. All other chemicals and reagents used were of analytical grade.

Methods

The melting point of Remogliflozin etabonate was found to be in the range of 152 -156ºC. Their melting points were confirmed with the reported melting point (Madhura et al., 2010). Remogliflozin Etabonate. Soluble in acetone, methanol and DMSO and practically insoluble in water. (https://www.ipc.gov.in/images/Remogliflozin_Etabonate_1.pdf)

The IR spectrum was obtained in the solid state with potassium bromide. The IR spectrum of Remogliflozin etabonate is presented in Fig. bellow. Observed peaks are shown in Table 22 and 23; these peaks are similar to reported peaks of Remogliflozin etabonate official spectrum. (SK Manirul Haque et. Al., Sustainable Chemistry and Pharmacy, Volume 35, October 2023, 101193)

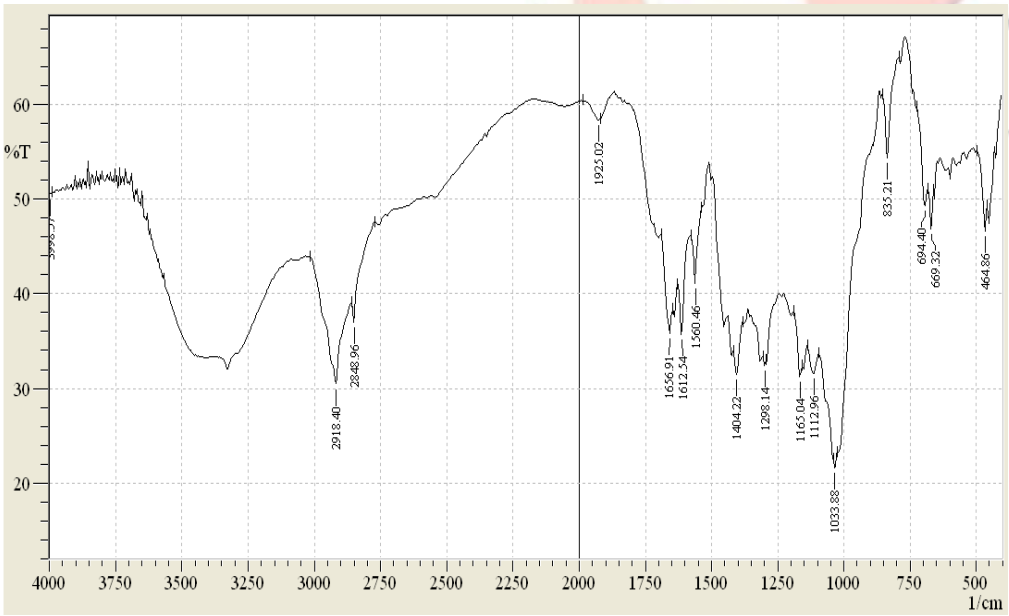


Fig. No. 2 FTIR spectrum of Remogliflozin

UV Spectrophotometric Determination of λ max for Pregabalin in simulated gastric fluid:

Calibration curve of Remogliflozin etabonate in glycine buffer pH 3.0 and pH 1.2 was studied; plots of area verses concentration was found to be linear between the range of 10 to 60 µg/ml. The r2 value of the calibration curve was found to be 0.9769. Results of standard calibration curve of Remogliflozin etabonate in glycine buffer (pH 3) are shown bellow in Fig. No.3.

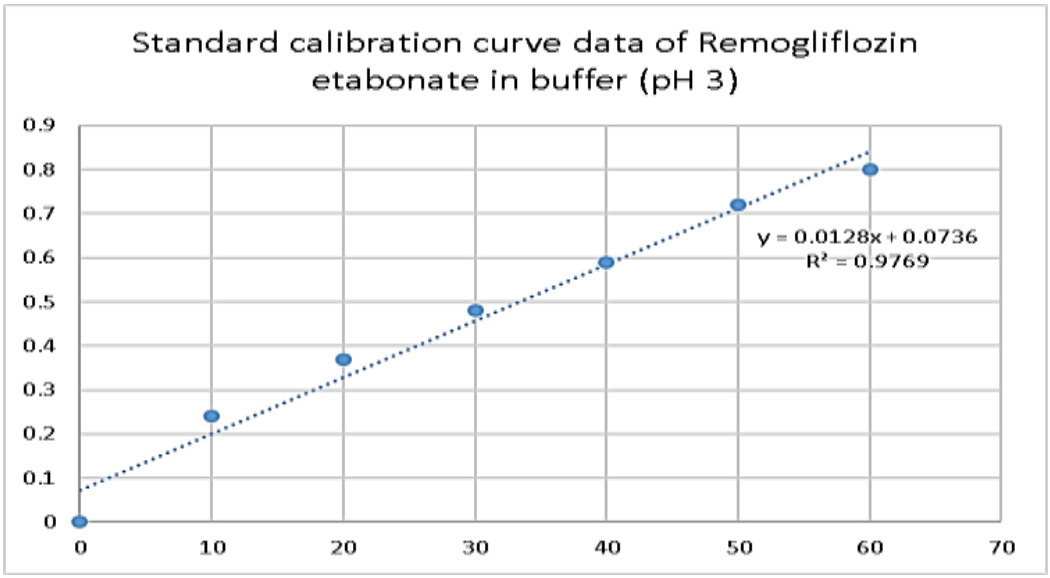


Fig. No. 3. Standard calibration curve data of Remogliflozin etabonate in buffer (pH 3)

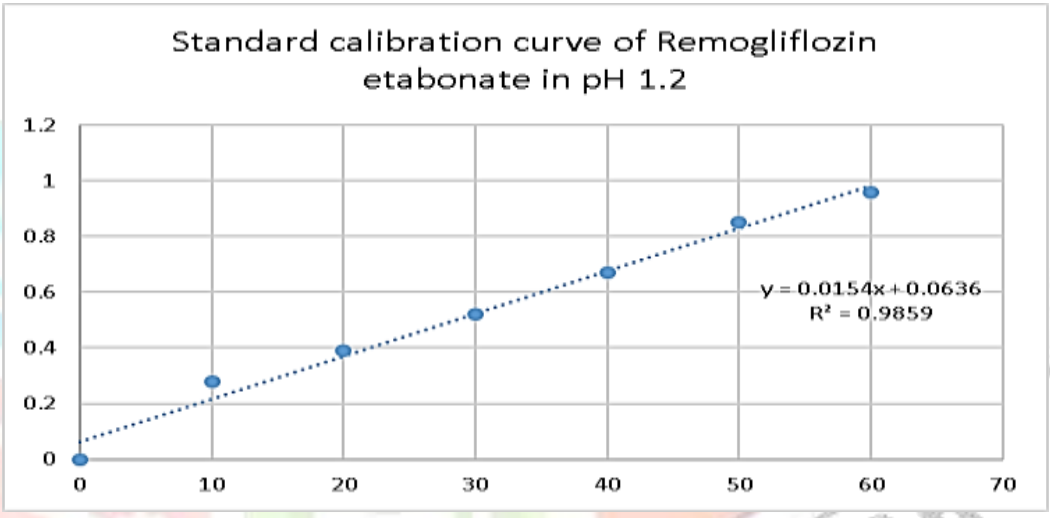
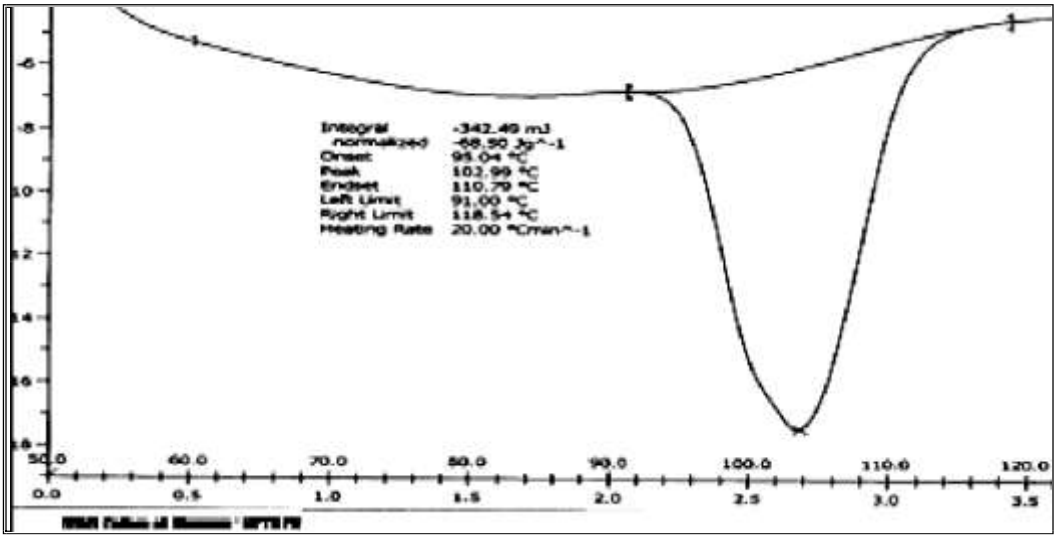


Fig. No. 4. Standard calibration curve of Remogliflozin etabonate in pH 1.2

Drug excipients compatibility study

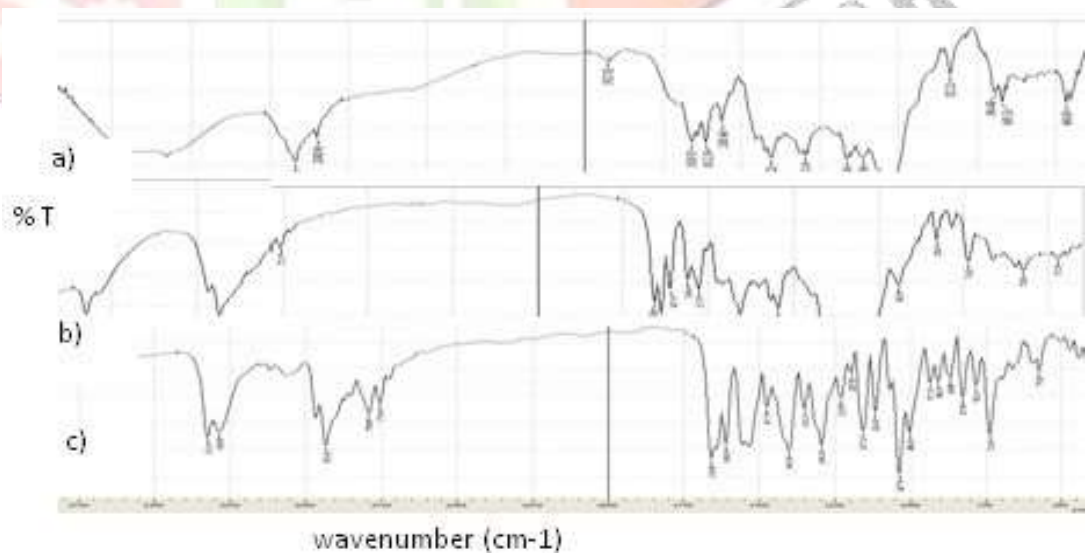
DSC study of Remogliflozin etabonate physical mixture

The drug, drug-excipients physical mixture studies reveal that there were no significant change in position of peak in thermogram of drug, drug-excipients was recorded. The DSC thermogram of Remogliflozin etabonate exhibited a single sharp endothermic peak at 98.79 ^{0}C related to its melting transition temperature shown in Fig. drug excipients physical mixture shows melting endothermic peak of drug at 100.92 ^{0}C shown in Fig. From drug excipients compatibility study, it was concluded that the given drug was compatible with all the excipients and it was confirmed by DSC study.



ii. FTIR spectroscopy study of Remogliflozin etabonate

The drug excipients studies reveal that there were no physical changes in drug and excipients mixtures. The drug excipients studies reveal that there was no physical change in drug and excipients mixtures. The major IR peaks observed Remogliflozin etabonate were O-H (Alcohol) 1265, N–H bend (Amine) 1591, C=C Stretch (Alkenes) 1642, C=O Stretch (Ketones) 1746, Hydrogen bonded asymmetric (primary Amide) 3343, (N=O)2 (Nitro compound) 1506, C-H Bending (Alkanes) 1464,1422, C – H Bending (Aldehyde) 1383. Spectral observation indicated that the principal IR peaks observed spectra of drug were close to those in spectra of excipients indicated that there was no interaction between drug and excipients shown in Fig. 4.



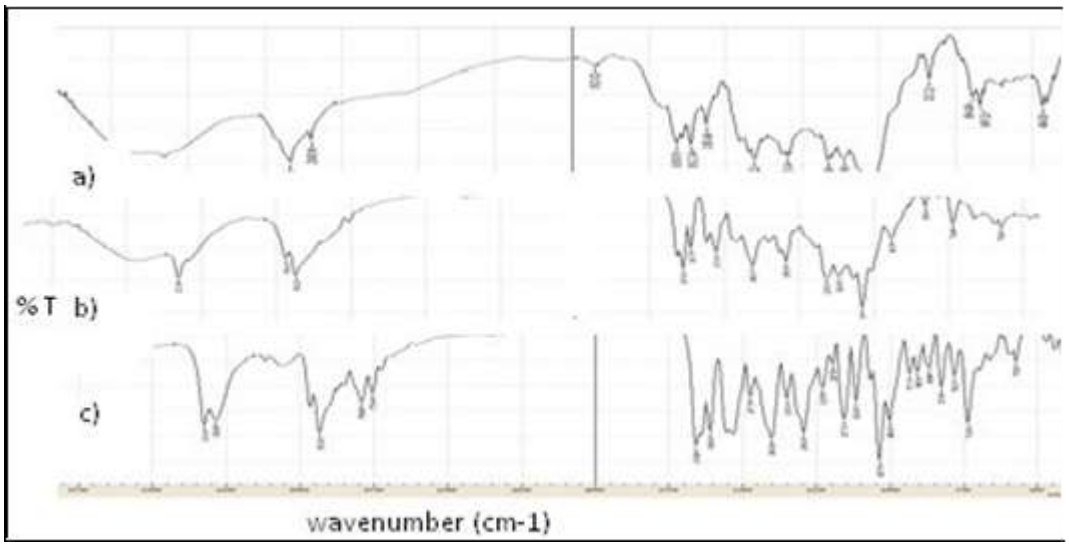


Fig. No. 4 FTIR spectrum of Remogliflozin etabonate with excipients

Pregabalin gastro retentive drug delivery system

Evaluation of precompression parameters of powder blend

The powder blend of various formulations shows good flow property. Results of various formulations revealed that the powder blend can be directly compressed into tablets

Evaluation of Post Compression Parameters for Remogliflozin Tablets

Physicochemical parameters of the formulations X1 to X9 were within the acceptance limit. All the batches passed the Pharmacopoeial limits. The drug content was found to be within a narrow range as specified in pharmacopoeia (90-110 %) in all the formulations. Almost all the batches showed uniform thickness and drug content. All batches passed weight variation test and found to be within range (± 5 %) and friability was less than 1.0 %, it indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage, transportation and until they are consumed.

Preparation of Gastro retentive tablets of drug

Remogliflozin tablets were prepared by the direct compression method. Eachtablet contained about 250 mg of the drug. All the ingredients were sifted through sieve no. 40 and magnesium stearate was passed through sieve no 60. The required quantities of the materials were mixed thoroughly for 15 minutes in polybag and lubricated with magnesium stearate for 3 minutes. Compositions of all the formulation were given X1 to X9.

Swelling study

Swelling is also a very important factor to ensure drug dissolution of the formulation. The hydration ability of the formulation influences; (i) tablet buoyancy (ii) adhesion ability of swellable polymers and (iii) drug release kinetics. drug composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. The ability of hydrogel to absorb water is due to the presence of hydrophilic groups. As reported by (Bertram

and Bodmeier, 2006), the ability of hydrogel to absorb water is due to the presence of hydrophilic groups. The hydration of these functional groups results in water entry into the polymer network leading to expansion and consequently an ordering of the polymer chains. The hydration of these functional groups results in water entry into the polymer network leading to expansion and consequently an ordering of the polymer chains. It assumed that swelling behavior of these hydrophilic tablets starts with water diffusion into the glassy HPMC material where the water plasticizes the polymer and reduces its glass transition temperature (Tg). When Tg has decreased to ambient temperature, a transformation from a glassy state to a rubbery state occurs. As the water continues to enter the tablet, a highly concentrated polymer solution is formed, denoted as a gel layer. The solvent continues to penetrate the tablet, the gel layer, and the dimensions of the swollen tablet increase, a process normally referred to as the swelling process.

a. Swelling study (for floating gastro retentive formulation)

The floating tablets of drug composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug released from the matrix tablet. The floating tablets containing HPMC K4M with HPMC K100 LV (X9) showed constant increased in swelling because HPMC showed higher swelling and can maintain their matrix integrity for more than 7-8 h, this erosion of polymer dominates over water sorption after 7 h hence the reduction in tablet weight occurs after 8 h because of constant erosion of matrix. The floating tablets containing Xanthan gum with HPMC K100 LV (X7) showed less swelling index at the beginning but was found thick gel formation at the end of 8 h also maintains their matrix integrity up to 6 -7 h but released rate was slightly less due to formation of thick gel matrix than HPMC K4M with HPMC K100 LV. The swelling index of formulation X7 was 120±10 % at 10 h and 150±10 % at 10 h respectively.

In vitro drug released study

The drug release of various formulations was studied in vitro using USP type II apparatus set at 100 rpm. A buffer medium with pH 3.0 (900 ml) at 37.5 ± 0.5 °C was used. A 10 ml sample was withdrawn at 1, 2, 4, 6, 8, 10 h time intervals over a period of 12 h and replaced with the same dissolution media (Kiortsis S et al., 2005, Atyabi F et al., 1996). The withdrawn samples were analyzed.

In order to evaluate different hydrophilic matrixing polymers used to prepare Floating Gastroretentive tablets four different polymers like HPMC K4M, Xanthan gum, Carbopol 71G and Sodium alginate in combination with low viscosity polymer HPMC K100 LV were selected for floating tablets of Remogliflozin etabonate and their individual drug released profile was evaluated. The gastroretentive tablets with formulations X1 to X9, containing combinations of Xanthan gum and HPMC K100 LV in different ratios exhibited cumulative percent drug release values of 99.00 ± 0.22, 90.00 ± 2.89, 99.20 ± 3.87, 99.20 ± 3.87, 91.00 ± 3.20, 99.80 ± 0.52, 96.00 ± In the presence of Xanthan gum, HPMC K100 LV produces a firm gel that entraps the gas for a longer time and delays the release of the drug. HPMC K4M which has a high rate of hydration, disintegrated in the presence of sodium lauryl sulphate, and thus *in vitro* drug released was more rapid compared with Xanthan gum with HPMC K100 LV (X7). This sustained release of the drug from formulation X7 could be attributed to the formation of a thick gel structure that delayed drug release (88.37 % at the end of 12 h). However, the formulation H9, containing HPMC K4M with HPMC K100 LV, was found to have a profile close to the theoretical profile (which was determined using the equations for an immediate release dose and maintenance dose).

Kinetic modeling of drug release for Floating Gastroretentive tablets

The data obtained from the *in vitro* drug released studies of formulation X1-X9, were fitted to zero-order, first-order, Higuchi Korsmeyer Peppas equations, and the data were analyzed. The r^2 value of the optimized formulation X9 was found 0.999. The n values of the optimized formulation (X9) was found to be 0.510, which fall in the range $0.35<n<0.50$ and k value was 17.61 with good floating properties. The value of the diffusion exponent indicates that the drug release follows non-Fickian release mechanism.

Stability studies

On the basis of the *in vitro* drug dissolution studies, it may be concluded that formulation X9 is most stable. It showed controlled drug release up to 12 h and stable at 40 °C/75 % relative humidity for a period of 3 months may possibly be a better delivery system for drug like drug. There were no significant changes in the physicochemical parameters and drug contents.

Conclusion

In conclusion, the tablets (X9) had a short buoyancy lag time, a total floating time of more than 10 h and sustained release up to 12 h. Best performing formulation X9 was stable at 40 °C / 75 % relative humidity for 3 months. This novel gastro retentive dosage form could be fascinating for enhancement of bioavailability and the stomach specific delivery of Remogliflozin etabonate. From the above study it could be concluded that floating gastro retentive drug delivery system is most stable system. The system with Xanthan gum with HPMC K100LV cannot deliver the drug over a prolonged period because of its slower swelling and thick gel formation of the polymers, resulting in a lack of hydrogel formation. These polymers were thus found to be unsuitable for Remogliflozin etabonate tablets. HBS may be a better delivery system for drugs like Remogliflozin etabonate. The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the methodology procedure in successful development of Remogliflozin etabonate tablets.

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