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DEVELOPMENT OF GASTRORETENTIVE BILAYER FLOATING TABLETS FOR ENHANCED ANTIDIABETIC DRUG DELIVERY

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Abstract

The present research work was an attempt to design a formulation of Bilayer floating tablets with Teneligliptin as sustained release layer and evogliptin as immediate release layer for the treatment of type II diabetes mellitus. The extended release was prepared by wet granulation method using HPMC K 100M as sustained release polymer and sodium bicarbonate as gas generating agent to reduce floating lag time. Immediate release layer was prepared by direct compression using sodium starch glycolate as super disintegrant. Gastro retentive floating drug delivery systems have been designed to increase its residence time in the stomach. The granules were evaluated for bulk density, tapped density, Compressibility index, and hausner's ratio. The granules showed satisfactory flow properties. The tablets were subjected to weight variation test, hardness test, friability test, drug content test and swelling index. All the tablets were passed the tests. With the incorporation of a gas generating agent the floating lag time was 27 sec, and the duration of floating was >8hrs. The drug release from the prepared tablets was sufficiently sustained (more than 8hrs). The release kinetics of the Bilayer floating tablet was evaluated using regression coefficient analysis. The formulated tablets show a Zero order drug release and the mechanism is correlated well with Korsmeyer peppas mode with super case II transport mechanism. Stability studies did not show any changes in physical appearance, physicochemical properties, and drug release.

Keywords: Bilayer tablets, Gastro retentive floating drug delivery systems, Bilayer floating tablet

1. INTRODUCTION

Diabetes may be characterized by hyperglycaemia. These may help in insulin secretion defects and both insulin action. Due to development of insulin resistance the inadequate insulin secretion and tissues dimension may lead to abnormalities of fats, carbohydrate and metabolism of protein. These may lead to change or may increases the concentration of blood glucose level. These may damage many systems of the body like blood vessels, nerves. According to the survey it was concluded that 0.5 to 3% of person was surfer from these diseases. Now a days its reaches to more than 7 %. Around 200 to 300 million people are affected and it should be double or triple in next few years.[1,2]

It is a heterogenous disorder. These may arise from interactions of genetic and environment and a lifestyle factor. Insufficient insulin production and a genetic factor is causing the type 2 diabetes. It may be resistance to the insulin target tissues. Erectile dysfunction, blindness, poor healing wound, failure of kidney and heart diseases may form during long term diabetes. Type 2 diabetes is more common than type 1. Statical data of India shows that around 57 to 60 million of patients is been affected in year 2025. This will make the India in world largest diabetic population.[3,4]

Type 1 diabetes mellitus

This is also known as insulin dependent diabetes mellitus (IDDM). It contains 5 to 10% of population. In this type of insulin defficency immune system of the body may did not see the insulin producing cells in the pancreases as a foreign particle and destroys them. For example, islets of Langerhans, blood glucose. These may produce normal glucose level and may reduce the sugar level. This is known as islet of Langerhans. Blood glucose level is use for normalized the sugar level and destruction of β- cells. This may include the antibiotic cell of islet, insulin to autoantibodies, GAD to antibodies, tyrosine phosphate and IA-2 β.[5,6]

Type 2 diabetes mellitus

This may know as non-insulin dependent diabetes mellitus. This diabetes may affect 90 to 98% of the population. This may be linked to modern style factor. This was common in adults. This may be decreased the disease condition. This may decline the insulin action. It has heterogeneous disorder by progressive decline and inability of pancreatic beta cells of insulin resistance or dysfunction of beta cells. This disease may be associated with obesity, age older and has a history of diabetes.

Gestational diabetes

this diabetes may be arising in 1 to 2% of pregnant women. This may be arising due to the cause of malfunction of receptor of insulin and placenta hormone. This may be occurring in trimester stage of pregnancy and it will affect both mother and children. Gestational diabetes may be added the intrauterine risk factor which is may increases the genetic risk of obesity and diabetes. This may arise the permanent evolution in later life.[7,8]

2. MATERIAL AND METHODS

2.1 Pre-formulation Study

The drug identification and verification was carried out through UV spectroscopy and DSC thermography. Calibration curves of Teneligliptin and Evogliptin were obtained in pH 1.2 hydrochloric acid buffer using UV-Visible spectrophotometer. Each drug was exactly weighed and dissolved in pH 1.2 HCl buffer to make stock solutions of about 15 mg of each drug into volumetric flasks. Aliquots from 0.07 to 1.5 mL were withdrawn and appropriately diluted to be evaluated across the wavelength range 200-400 nm for determination of λmax and calibration profile of the pharmaceuticals. A critical preformulation parameter of solubility investigations was conducted. Solubility of the drug was determined by continuous shaking for 24 hours at 37°C. The solutions were then filtered through Millipore filter and finally analyzed by spectrophotometry.

A few pharmaceuticals were mixed with polymers for DSC analyses to investigate thermal characteristics and compatibility. The drug–polymer combinations were encapsulated in ampoules and kept at 37.0 ± 0.5°C for 28 days before analysis. FTIR analyses were done using FTIR spectrophotometer using KBr pellet method in the range of 400-4000 cm-1. The pelletization was carried out under hydraulic pressure for spectral analysis.

Drug-excipient interactions studies carried out using DSC and FTIR techniques. Teneligliptin, Evogliptin and the formulations of both with excipients were stored for 1 month under the stability conditions of 40°C/80%RH. The samples were subjected to ocular examination and were subsequently analyzed using HPLC, DSC and FTIR methods. Thermal testing was performed by putting the samples into aluminum crucibles and scanning them between 50-400°C to obtain the thermograms and assess compatibility.

Formulation and Evaluation of Bilayer Floating Tablets

Immediate-release tablets of Teneligliptin were prepared using direct compression technique using sodium starch glycolate as a superdisintegrant. The medicine and excipients were mixed together, sieved through No.40 mesh and pressed in a Rimek Minipress-1 tablet press. The physical properties of the formulated tablets were evaluated, which included weight variation, hardness, friability, thickness, drug content, disintegration time, dissolution profile, wetting time, swelling index and water absorption capacity. The dissolution tests are performed with USP dissolution apparatus type II in 0.1 N HCl at 37 ± 0.5°C at the rate of 60 rpm.

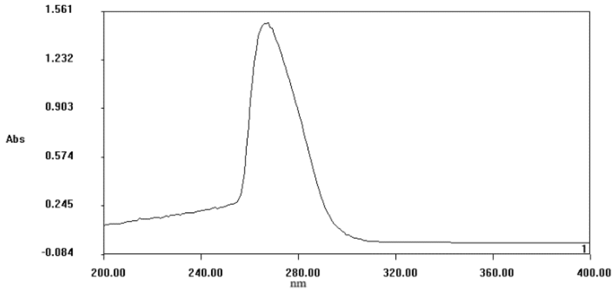
Evogliptin sustained release tablet was produced by wet granulation method using isopropyl alcohol as granulation media and HPMC as granulation excipients. The granules were then dried at 50°C and compressed into tablets. Zero Order Kinetic Model, first Order Kinetic Model, Higuchi Model and Korsmeyer–Peppas model were used to evaluate the kinetics of drug release.

Finally, bilayer floating bioadhesive tablets containing Teneligliptin and Evogliptin were developed with direct compression method with proper concentration of both the drugs to achieve immediate and sustained release profile for effective diabetes management.

3. RESULTS

3.1 Pre formulation Study

3.1.1 UV spectroscopy



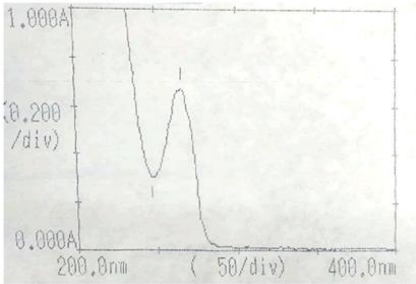
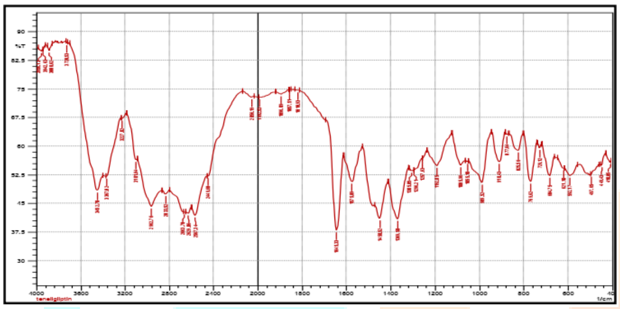


Figure 1. Teneligliptin Figure 2. Evogliptin

3.1.2 IR spectrum



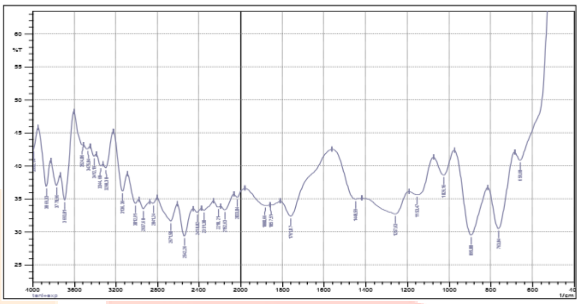
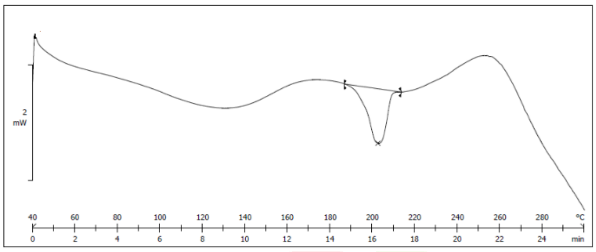


Figure 3: Teneligliptin Figure 4. Evogliptin

3.1.3 DSC study



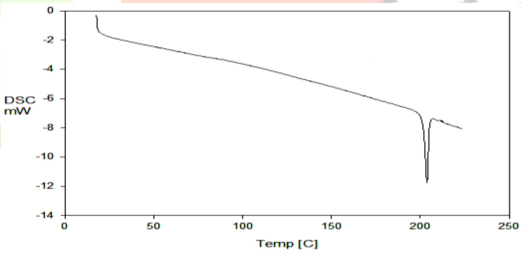
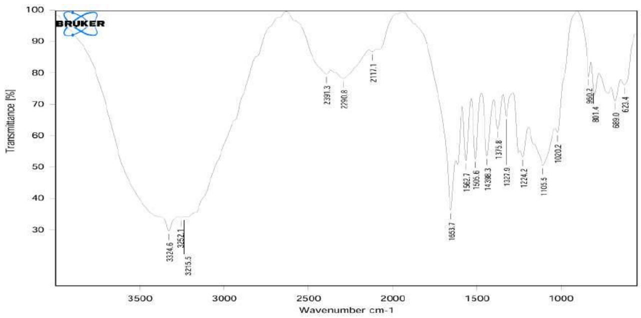


Figure 5. Pure Teneligliptin Figure 6. evogliptin

3.1.4 DRUG-EXCIPIENT INTERACTIONS



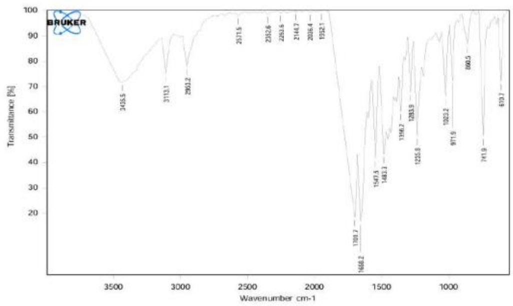
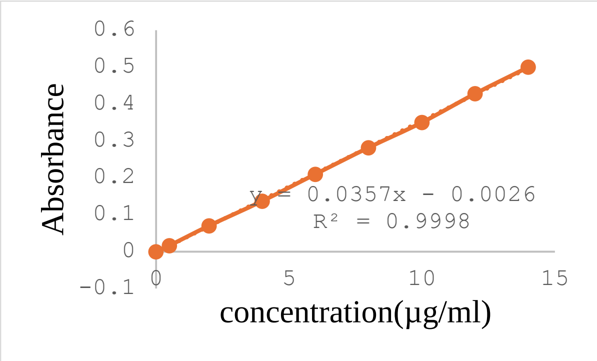


Figure 7. FTIR of Teneligliptin mixture Figure 8. FTIR of Evogliptin and Na CMC mixture

3.1.5 Calibration Curve of Teneligliptin and evogliptin



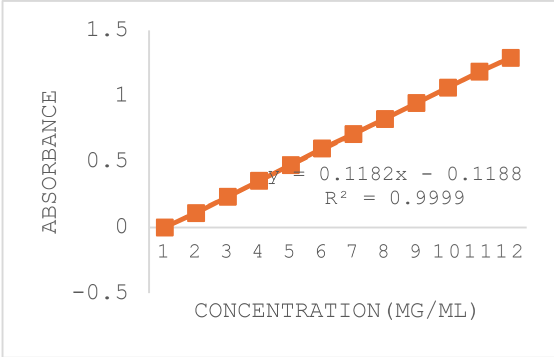
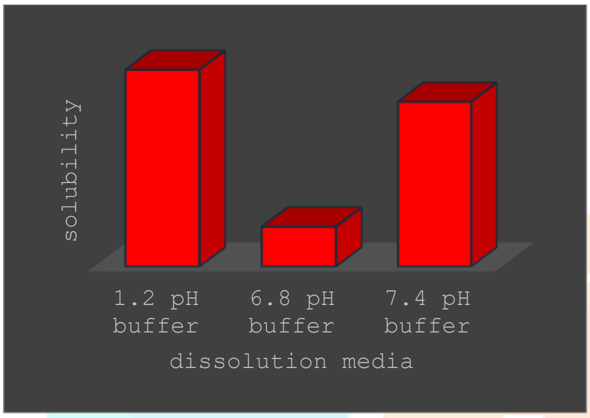


Figure 9. Standard Calibration Curve of Teneligliptin Figure 10. Evogliptin (pH 1.2 HCl buffer)

3.1.6Solubility Study of Teneligliptin and evogliptin



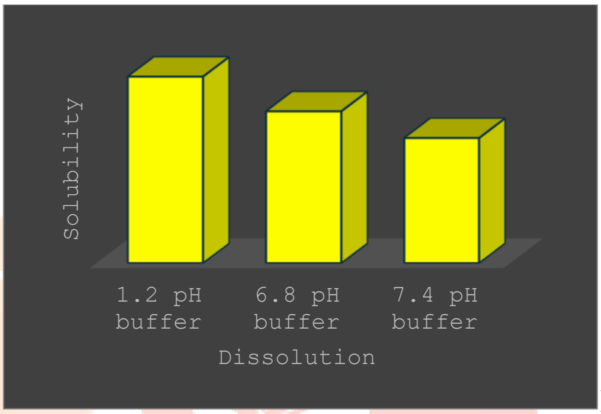


Figure 11. Teneligliptin solubility data Figure 12. Evogliptin solubility study

3.2 Dissolution study of immediate release layer tablet

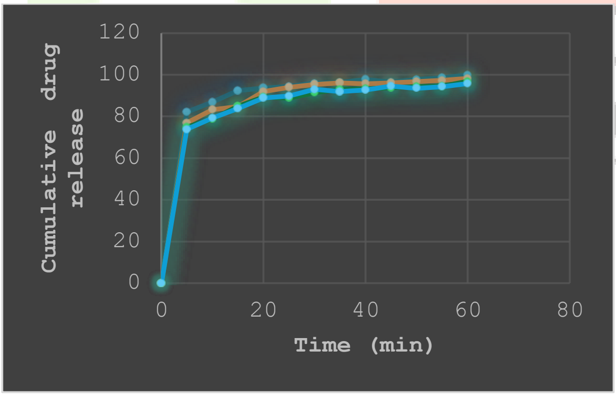
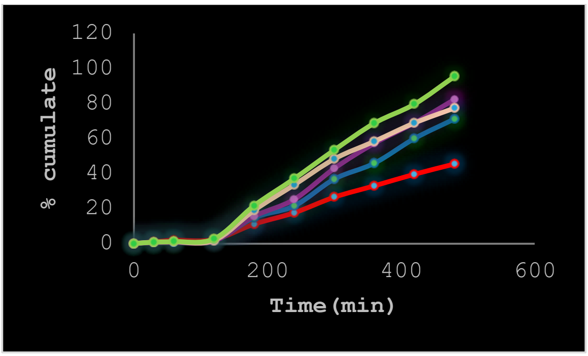


Figure 13. Immediate release layer tablet

3.3 floating bio adhesive sustained release layer tablets



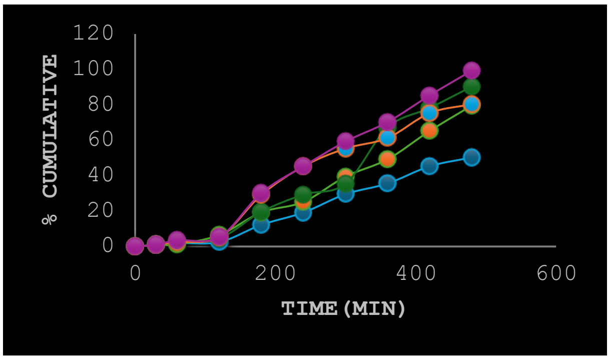
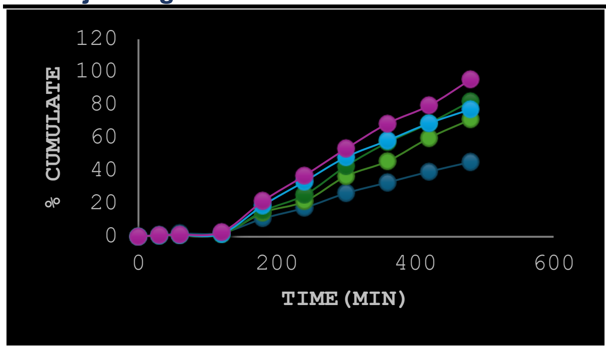


Figure 14. Sustained release layer tablets HPMC K4M (F1-F5) Figure 15. Sustained release layer tablet HPMC K4M (F6-F10)



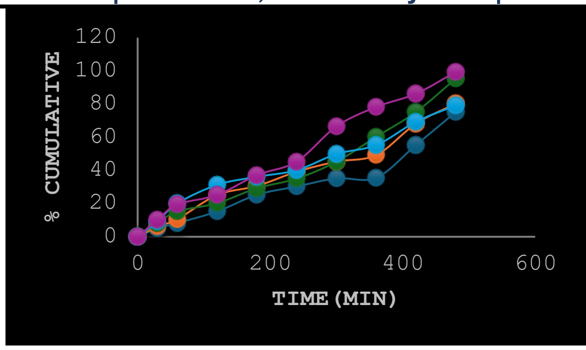
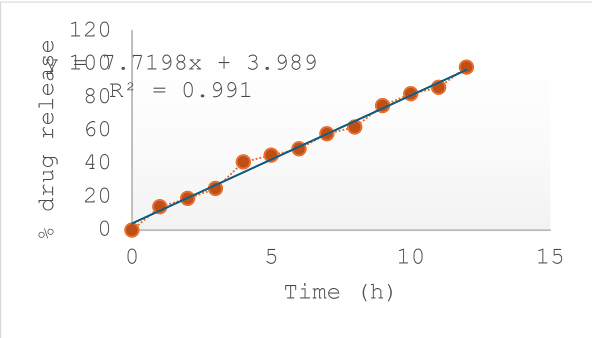


Figure 16. Sustained release layer tablets (Na CMC) (F1-F5) Figure 17. Sustained release layer tablet (Na CMC) (F6-F10)

3.4 Drug release kinetics



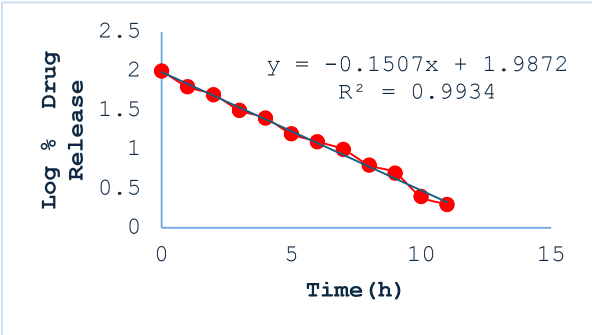
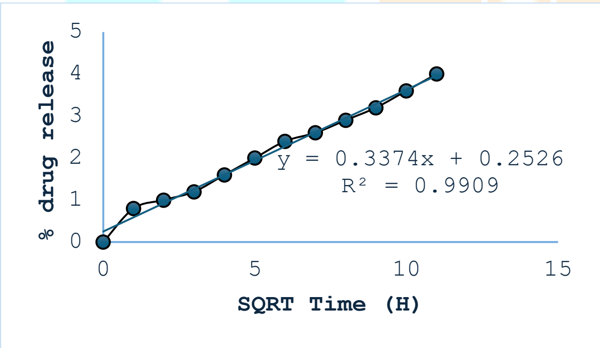


Figure 18. zero order kinetics studies Figure 19. first order kinetic studies



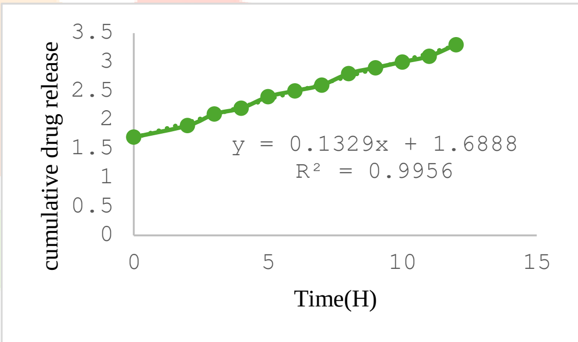


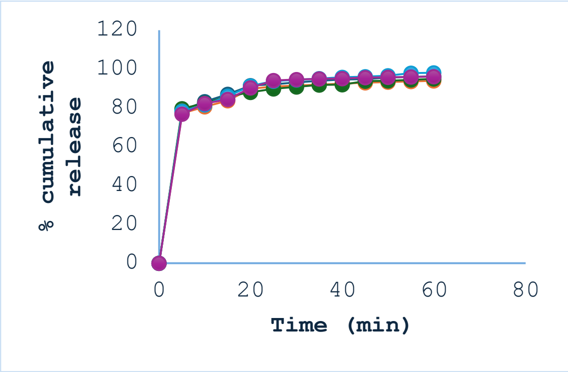
Figure 20. Higuchi release kinetic studies Figure 21. Peppas release kinetic studies

3.5 Bilayer Floating Tablets

3.5.1 Determination of buoyancy lag time (BLT)

Figure 22. Floating behaviour of Bilayer tablet at various interval of time

3.6 Dissolution study of optimized bilayer floating bio adhesive tablets



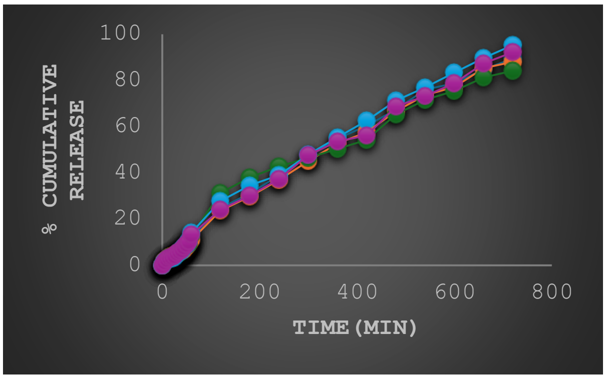


Figure 23. Bilayer floating bio adhesive tablets (Immediate release layer) Figure 24. Bilayer floating bio adhesive tablets (sustained release layer)

4. SUMMARY AND CONCLUSION

The study focused on the development of gastroretentive bilayer floating tablet containing Teneligliptin and Evogliptin to improve the diabetes control. An approach involving GRDDS methodology was used to achieve prolonged retention and high bioavailability of the medication in the stomach.A GRDDS methodology was employed to achieve a prolonged retention and high bioavailability of the medication in the stomach. UV spectrophotometric investigation showed maximum absorption wavelength of 267 nm and 266 nm with a very high linear correlation of $r^2 = 0.999$. The compatibility of the medications with the excipients was confirmed by DSC and FTIR analyses. The PEO, HPMC and HEC polymers were compressed into tablets and evaluated for the physicochemical properties, buoyancy and drug release profile. The new formulation showed a sustained release for 23 hours and stability for six months in ICH stability conditions.

5. REFERENCE

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