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DESIGN AND DEVELOPMENT OF EXTENDED RELEASE TABLET FORMULATION OF ALOGLIPTIN BENZOATE

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ABSTRACT

In type 2 diabetes mellitus patients, anlogliptin benzoate is a dipeptidyl peptidase-4 (DPP-4) inhibitor that requires frequent dosing due to its short half-life, leading to problems with adherence. To improve therapeutic efficacy and compliance with alogliptin benzoate, this study developed and evaluated an extended-release oral dosage form. Modulating drug release with hydroxypropyl methylcellulose (HPMC) and ethyl cellulose was achieved through direct compression with various hydrophilic and hydrophobic polymers. Analogliptin benzoate is compatible with the selected polymers based on preformulation studies. All of the prepared tablets met pharmacopeial standards for physical properties like hardness, friability, weight variation, and uniformity of drug content. A diffusion-controlled release mechanism was demonstrated by the optimized formulation, following the Higuchi model over 24 hours. The extended-release oral dosage form of alogliptin benzoate developed in this study has the potential to enhance patient compliance by reducing dosing frequency and ensuring consistent therapeutic effects.

KEY WORDS: Alogliptin Benzoate, Oral Dosage Form, Direct Compression, Extended-Release.

INTRODUCTION

Oral routes of delivery have been the most commonly employed due to their ease of administration, patient compliance, least constraints, and cost-effectiveness to manufacturing processes. Patients and physicians alike prefer tablets over other oral formulations on the market. A conventional drug delivery system provides immediate drug release and is referred to as conventional drug delivery system. As a result of such immediate-release products, the drug is absorbed relatively rapidly and the accompanying pharmacodynamics effects are observed relatively quickly [1]. According to the drug pharmacokinetics profile, plasma drug concentrations decline after absorption of drugs from dosage forms. Drug concentrations in plasma eventually fall below their maximum effective concentration (MEC), resulting in loss of therapeutic activity. It is usually necessary to give another dose prior to reaching this point in order to achieve a sustained therapeutic effect [2]. Because oral drug delivery is convenient, safe, non-invasive, and economical, it is still the preferred route of administration, and researchers are seeking ways to incorporate a variety of technologies into oral formulations; even small changes in drug delivery technology can have a significant impact on patient compliance and drug bioavailability [3]. Those drugs that are given orally can benefit from oral extended release drug delivery systems, which have a shorter half-life and high dosing frequency, but are also promising for reducing side effects due to the shorter half-life [3]. The largest share of drug delivery systems will remain drug release medication. At the same time, these extended release products will improve patient compliance. And optimize therapeutic effect and safety [4].

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Oral Solid Dosage Form (OSDF)

An effective drug delivery system (DDS) is a formulation or a device that controls the rate, time, and place at which a drug is released into the body in order to improve its efficacy and safety [5]. This process involves administering the therapeutic product, releasing the active ingredients from the product, and transporting the active ingredients across the biological membrane to the location of action [6]. As an interface between the drug and the patient, the drug delivery system plays an important role. Whether the drug is administered therapeutically through a formulation or through a device is important, as it is the criterion for regulatory oversight by the drug or medicine control agency. A device should be regulated strictly as a device if it is used other than to administer drugs, such as to provide therapeutic effects by physical modality or to prevent complications from the device [7]. A case-by-case decision determines whether a device should be classified as a drug or a device should be classified as a device. The drugs can be delivered in various forms including tablets, capsules, creams, liquids, aerosols, injections, and suppositories.

Oral administration is the predominant route of delivery. In the market, more than 50% of Drug D Delivery Systems (DDS) are designed for oral administration. Patients are more likely to comply with these dosage forms because they are easy to administer. As these systems are developed, however, they are exposed to a wide variety of highly variable conditions during their passage through the gastrointestinal tract, such as food ingestion, type of meal, caloric content volume, viscosity, and physical rate, which affect gastric physiology and, therefore, the dissolution of active drugs from dosage forms [8]. This limitation of conventional DDS can be overcome by using sustainedrelease and controlled-release drug delivery systems, which deliver drugs over an extended period of time and can, reduce undesired fluctuations in drug levels, thus decreasing side effects while improving therapeutic outcomes [9].

There are several new modifications being introduced to sustained release (SR) preparations. "Long acting" or "delayed release" are two terms that describe these preparations in comparison to "rapid" and "conventional" release preparations. In some cases, the term overlaps with "controlled release", which implies a more sophisticated control of release than just a time-based one [10].

MATERIALS AND METHODS

Preformulation Study

Preformulation testing is the first step in rational development of dosage forms of a drug substance. It can be defined ads phase of research and development process of physical and chemical properties of a new drug substance alone and provide a rational for formulation design or support the need for molecular combined with excipients in order to develop stable, safe and effective dosage form. The overall objective of Preformulation studies is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

DESCRIPTION

A small amount of the drug is taken in a petridish and compared with the standard specifications.

Preparation of Calibration Medium

Preparation of Acid Buffer pH 1.2

50 ml of 0.2 M potassium chloride solution is placed in a 200ml volumetric flask. 85 ml of 0.2 M hydrochloric acid is added and made up to the volume with distilled water.

Preparation of 0.2 M potassium chloride

14.911 g of potassium chloride is dissolved in distilled water and the volume is made up to 1000ml.

Preparation of 0.2 M hydrochloric acid

7.292g of hydrochloric acid is distilled to 1000ml with distilled water.

Preparation of Phosphate Buffer pH 7.4

50 ml of 0.2 M potassium di-hydrogen phosphate solution is placed in a 200ml volumetric flask. 22.4 ml of 0.2 M sodium hydroxide is added and made up to the volume with distilled water.

Preparation of 0.2M potassium dihydrogen phosphate

27.218g of potassium dihydrogen phosphate is dissolved in distilled water and the volume is made up to 1000ml.

Preparation of 0.2 M potassium dihydrogen phosphate

8 g of sodium hydroxide is dissolved and made up to 1000ml with distilled water.

Estimation of Absorption Maximum (λ max)

100mg of drug is dissolved in 100ml of acid buffer pH 1.2 and phosphate
buffer pH 7.4 and after suitable dilution and the resultant solution is scanned in the
range of 200-400 nm in UV- spectrophotometer to get absorption maximum

Preparation of Standard Curve

The solutions are analysed by Ultraviolet (UV) spectrophotometer at λ max. Calibration curve is plotted by taking the concentration in X-axis and the absorbance in Y-axis.

DRUG-POLYMER INTERACTION STUDY

Fourier Transform- Infra Red Spectroscopy (FT-IR)

FTIR is a modern and modified form of infrared spectroscopy based on mathematical formula, able to determine the structure of the drug molecule and physical interactions between drugs and polymers [11].

Direct Compression Technique

Extended release tablets of alogliptin benzoate were fabricated by developing the formulae utilizing variable concentrations of two polymers Carbopol 71G-NF, HPMC K100 M. Two hundred fifty milligram tablets containing 100 mg Alogliptin benzoate were manufactured by direct compression technique under standardized condition. For each formulation, the corresponding amount of alogliptin benzoate and Avicel pH 101were accurately weighed and mixed in turbula mixer for 5min and then sieved through a 315-µm screen. The blend of Emcompress and polymers was accurately weighed and mixed with the previous mixture in the turbula mixture for 5 min. Magnesium stearate was added at the end and mixed for further 1 min. The powder mix was then compressed into tablets using multiple punching machine with 8-mm shallow concave punches [12].

Evaluation of Alogliptin Benzoate Extended Release TABLET

Pre compressional evaluation of powder blend [13]

Determination of Flow Properties:

- Angle of Repose
- Bulk density
- Tapped density
- Compressibility index
- Hausner`s ratio

POST – Compression Evaluation of Alogliptin Benzoate Extended Release Tablet [14]

- Thickness
- Hardness
- Weight variation test
- Friability
- *In vitro* dissolution studies

RESULTS AND DISCUSSION

Preformulation

White crystalline and odour less powder.

Standard Curves of Alogliptin Benzoate

The calibration medium (Acid buffer pH 1.2 and Phosphate buffer pH 7.4) was prepared as per I.P 2014.

Estimation of absorption maximum

The λ max of Alogliptin was determined by scanning the diluted concentration of drug solution in buffer solution such as acid buffer pH 1.2 and phosphate buffer pH 7.4. It showed the λ max of Alogliptin benzoate at 277 and 278nm in both buffer solutions. The results were shown in the figure.

Preparation of standard curves

The standard curves of alogliptin benzoate prepared by using acid buffer pH 1.2 and phosphate buffer pH 7.4 were given below.

The linear correlation was obtained for calibration of Alogliptin benzoate in each medium and it obey the Beer`s law within the concentration range of 5-25 µg/ml.

Drug Polymer Interaction Study

Fourier Transform – Infra red Spectroscopy

The FT-IR study was conducted to determine the compatibility between the drug (alogliptin benzoate), polymers (Carbopol 71G-NF, HPMC K100 M), physical mixture and also the best formulation. It was found that there is no appearance or disappearance of peaks obtained from the spectrum results.

Formulation of Sitagliptin Phosphate Extended Release Tablet

Direct Compression Technique

Extended release tablets of Alogliptin Benzoate were fabricated by developing the formulae utilizing variable concentrations of two polymers Carbopol 71G-NF, HPMC K100 M. Two hundred fifty milligram tablets containing 100 mg alogliptin benzoate were manufactured by direct compression technique under standardized condition, according to the formulations. For each formulation, the corresponding amount of alogliptin benzoate and Avicel pH 101were accurately weighed and mixed in turbula mixer for 5min and then sieved through a 315-µm screen. The blend of Emcompress and polymers was accurately weighed and mixed with the previous mixture in the turbula mixture for 5 min. Magnesium stearate was added at the end and mixed for further 1 min. The powder mix was then compressed into tablets using multiple punching machine with 8-mm shallow concave punches.

Precompressional Evaluation of Powder Blend

Angle of repose: (θ)

The angle repose of formulated powder blend in the range of 22°46'-24°26, which indicates good flow properties of powder blend. The results were given in the figure.

Bulk density: (gm/ml)

The bulk density of powder blends was in the range of 0.36-0.48 gm/ml, which indicates, that the powder blends were not bulky. The results were given in the figure.

Tapped density: (gm/ml)

The tapped density of powder blends was in the range of 0.54-0.76gm/ml, which indicates smaller particles to occupy the voids between larger particles. The results were given in the figure.

Compressibility index: (%)

Compressibility index were found to be in between 7.82-11.86% which indicates that the powder blend have excellent flow property for compression. The results were given in the figure.

Hausner`s ratio:

The Hausner`s ratio of powder blend was found to be in the range 0f 1.18-1.22 which indicates good flow properties of powder blend. The results were given in the figure

Post Compressional Evaluation of Alogliptin Benzoate Extended Release Tablets

Tablets of different formulations were subjected to evaluation test such as general appearance, tablet dimension, hardness, friability, weight variation, drug content.

General appearance

The formulated tablets were white in colour, bio-convex and round shape without any scoring on both sides. All the tablets were elegant in appearance.

Tablet dimension

The thickness and diameter of all formulations were found to be in the range 8mm respectively, indicates that the tablets having uniform particle size distribution and no deformity.

Hardness

The hardness of all formulations were found to be in the range of 6.1-7.1 kg/cm2 which indicates good mechanical strength with an ability to withstand physical and chemical stress conditions while handling.

Friability

The friability of all formulations were found to be in the range of 0.43-0.69%, (as per I.P limit less than 1%), which indicates good mechanical resistance of the tablet.

Weight variation

In all formulation, the weight variation of extended release tablets was ranges between 239-233.1mg. All the formulated tablets were passed the weight variation was within the pharmacopoeial limits of ± 5% of the average weight, which proved good uniformity.

Estimation of drug content

The percentage of drug content for F1 to F9 was found to be in the ranges from 54.22% - 96.36% (phosphate buffer pH 7.4) which is within acceptable limits, showed that the drug was uniformly distributed in all formulations. Here the percentage of drug content of all formulations complies with official specifications as per U.S.P (Limit: not less than 40% and not more than 98%). The results were shown in figure 10.

***In-Vitro* Release Kinetics**

In vitro dissolution studies of all the formulations of extended release tablets of Alogliptin were carried out Acidic buffer pH 1.2 and Phosphate buffer pH 7.4. The study was performed for 12 hrs, and cumulative drug release was calculated at different time intervals.

Figure 1: Determination of λ max of alogliptin benzoate using Acid buffer pH 1.2

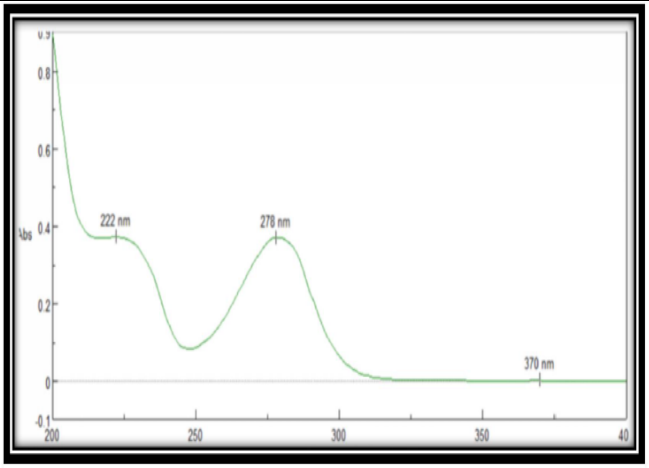


Figure 2: Determination of λ max of alogliptin benzoate using phosphate buffer pH

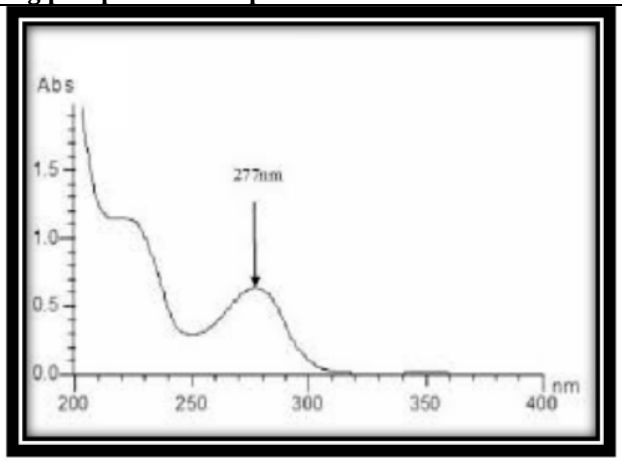


Figure 3: Calibration of alogliptin benzoate in Acid buffer pH 1.2

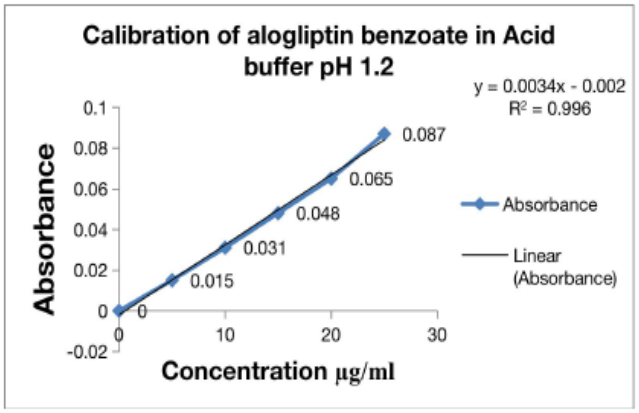


Figure 4: Calibration of Alogliptin benzoate buffer pH 7.4

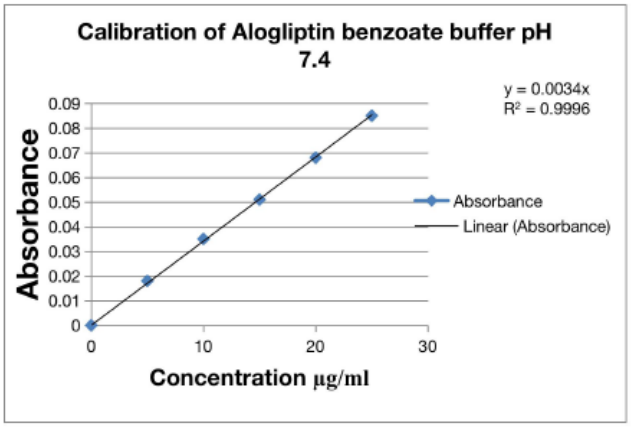


Figure 5: Angle of repose of Formulation (F1-F9)

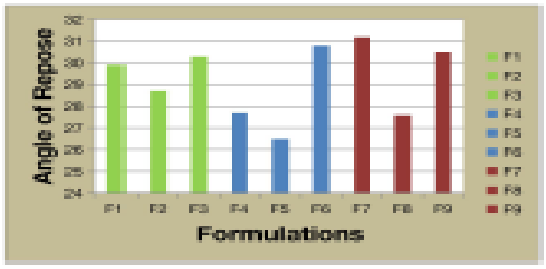


Figure 6: Bulk Density of Formulation (F1-F9)

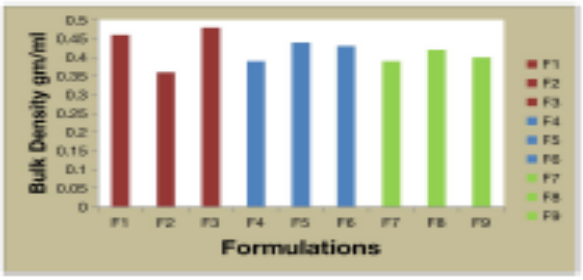


Figure 7: Tapped density of Formulation (F1-F9)

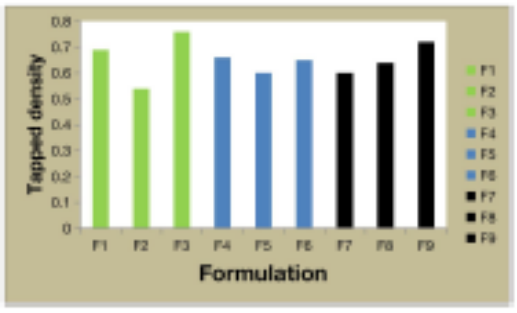


Figure 8: Compressibility index of Formulation (F1-F9)

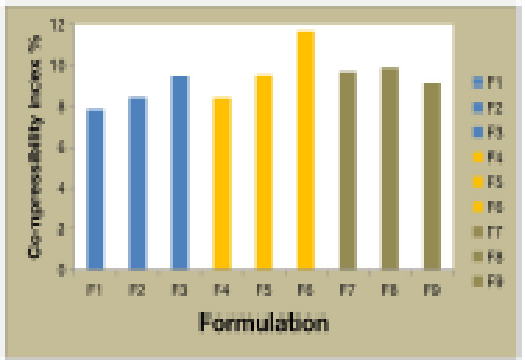


Figure 9: Hausner's ratio of Formulation (F1-F9)

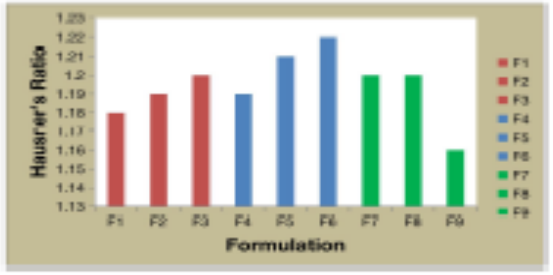


Figure 10: Drug content of Formulation (F1-F9)

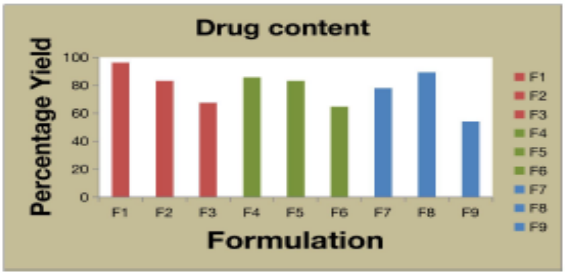


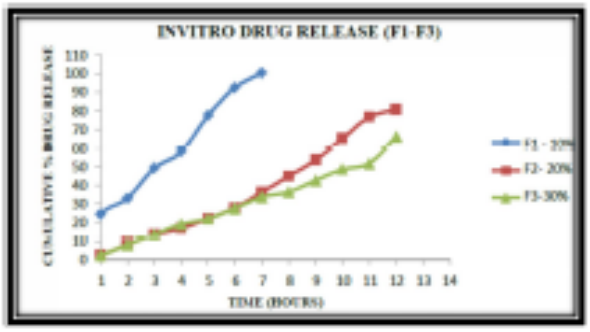
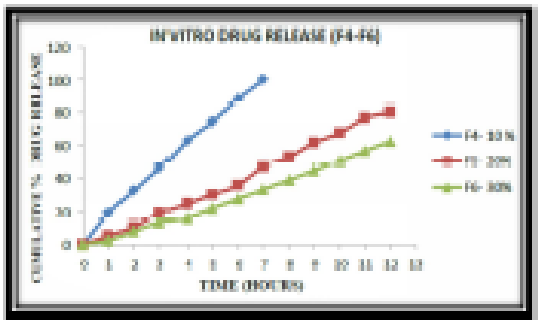
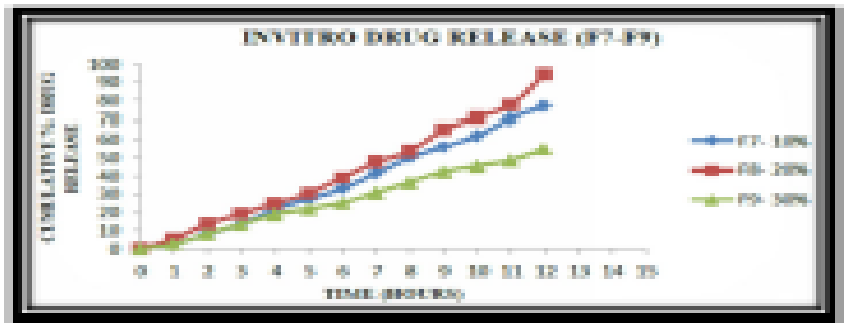
Figure 11: Comparison of In-vitro Release Profile of Extended Release Tablets of Alogliptin benzoate using Carbopol 71G-NF in Different Ratios	**Figure 12: Comparison of In-vitro Release Profile of Extended Release Tablets of Alogliptin benzoate using HPMC K 100 M in Different Ratios**
	

Figure 13: Comparison of In-vitro Release Profile of Extended Release Tablets of Alogliptin benzoate using Carbopol 71G-NF and HPMC K 100 M in Different Ratios



KINETIC ANALYSIS OF *IN VITRO* RELEASE DATA

To analyze the *in vitro* release data, various kinetic, the zero order, the first order, the higuchi and the korsmeyer peppas models were used to describe the release kinetics. The release data (1-12hrs) were analyzed as per Zero order, First order, Hixson crowell, Higuchi`s and peppas equation models to know the pattern of drug release and mechanism of drug release from the extended release tablet.

Korsmeyer Peppas model was found to be the best fitted in all dissolution profile having correlation coefficient (R2) value. The values of n (diffusion exponent) were estimated by linear regression of log cumulative % drug release Vs log time (t) of different formulations. The `n` value could be used to characterize different release mechanism.

According to the Korsmeyer peppas model anomalous (non-Fickian) release was observed in all formulations as indicated from the release exponent which was in the range of 0.70-1.35 for these formulations.

It was found that the optimized formulations F2, F8 Follows first order kinetic model as it has highest R2 value with Korsmeyer peppas mechanism. The "n" exponent value of optimized formulation F2 & F8 was found to be 1.345, 1.090. Hence it shows the optimized formulation followed super case II transport.

CONCLUSION

This study reveals that the drug release rate of Alogliptin benzoate from extended release tablets could be prolonged and controlled depending on the amount of polymers used. The drug release data of most formulations showed a good fit to korsmeyer peppas equations indicating, a combined effect of diffusion and erosion mechanism. In addition when Carbopol 71G-NF was used in combination with HPMC K100M the release of the drug was slower than Carbopol 71G-NF or HPMC K100M alone at the same total polymer concentration.

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