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Research Article

FORMULATION AND OPTIMIZATION OF SUSTAINED RELEASE TABLETS OF LINAGLIPTIN USING HYDROPHILIC POLYMERS

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ABSTRACT

The sustained release tablets containing Linagliptin (SR) were successfully formulated using the direct compression method. Evaluation of the powdered blends across all trials revealed compliance with official standards for flow properties, including angle of repose and compressibility index. The tablets exhibited consistent physiochemical characteristics such as thickness, hardness, weight variation, and friability. The optimized formulation L8 demonstrated a sustained drug release profile, releasing 8.7% of Linagliptin in the first hour, with sustained release continuing up to 24 hours. Stability studies over three months confirmed no significant changes in the physical and chemical properties of formulation L8, remaining within acceptable limits. Drug release kinetic analysis indicated adherence to zero order kinetics (R^2=0.966), highlighting controlled and consistent drug release. These results suggest that formulation L8, prepared by direct compression, is a promising and effective sustained release tablet for the treatment of HIV infection.

Keywords: Linagliptin, Sustained release tablets, Direct compression, Formulation L8, Zero-order kinetics.

INTRODUCTION

Oral drug delivery systems remain the most widely used route of administration due to their convenience, cost-effectiveness, and high patient compliance. Conventional oral dosage forms such as tablets and capsules generally release the drug immediately after administration, resulting in rapid drug absorption and fluctuation in plasma drug concentrations. Such fluctuations may lead to sub-therapeutic or toxic levels of the drug. To overcome these limitations, modified-release drug delivery systems have been developed to control the release rate and duration of drug action (Robinson and Lee, 1987; Aulton, 2007). Modified-release formulations are designed to alter the rate or site of drug release in order to achieve prolonged therapeutic activity, improved bioavailability, and enhanced patient compliance. Among these systems, sustained-release (SR) dosage forms are particularly important because they maintain therapeutic drug concentrations for an extended period while reducing dosing frequency (Collett and Moreton, 2002). Sustained-release drug delivery systems provide uniform plasma drug levels, minimize side effects, and enhance patient adherence to therapy (Chien, 1992).

Matrix tablets are among the most widely used sustained-release systems due to their simplicity of manufacturing and ability to control drug release through diffusion, erosion, or swelling mechanisms. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and natural polymers like guar gum are frequently employed as matrix-forming agents to regulate drug release (Siepmann and Peppas, 2012). Hydrophobic polymers such as ethyl cellulose can also be used to retard drug diffusion and prolong the release profile (Colombo et al., 2000). Linagliptin is an oral dipeptidyl peptidase-4 (DPP-4) inhibitor used in the management of type-2 diabetes mellitus. It enhances insulin secretion and decreases glucagon release by inhibiting the degradation of incretin hormones such as glucagon-like peptide-1 (GLP-1) (Gallwitz, 2013). Linagliptin exhibits prolonged biological activity and high protein binding, making it a potential candidate for sustained-release formulations aimed at improving therapeutic outcomes and maintaining stable plasma drug levels. Therefore, the present study aimed to formulate and optimize sustained-release matrix tablets of Linagliptin using hydrophilic and hydrophobic polymers by direct compression technique and to evaluate their

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physicochemical properties, in-vitro drug release profile, and release kinetics.

MATERIALS AND METHODS

Materials

Linagliptin was obtained from Chandra Labs, Hyderabad. Hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and microcrystalline cellulose were procured from Avantor Chemicals. Guar gum, starch, talc, and magnesium stearate were obtained from Mylan Chemicals. Lactose monohydrate was used as a diluent in the formulation.

Instruments

The instruments used in the study included a UV-Visible spectrophotometer (Nicolet E100), dissolution apparatus (Labindia DISSO 2000), single-punch tablet compression machine (Cadmach), electronic balance, Roche friabilator, Monsanto hardness tester, pH meter, and hot air oven.

Pre-formulation Studies

Drug Identification and Characterization

Preformulation studies were conducted to determine the physicochemical properties of Linagliptin including appearance, solubility, and melting point.

Solubility Study

Solubility of Linagliptin was evaluated in various solvents including water, 0.1 N HCl, methanol, and ethanol.

Melting Point Determination

Melting point was determined using the capillary method to confirm purity and identity of the drug.

Standard Calibration Curve

A standard calibration curve was prepared by dissolving Linagliptin in 0.1 N HCl and phosphate buffer (pH 6.8). Serial dilutions ranging from 10–30 µg/ml were prepared and absorbance was measured at 294 nm using a UV-Visible spectrophotometer. The calibration curve was plotted between concentration and absorbance.

Drug–Excipient Compatibility Study

Compatibility between Linagliptin and selected excipients was investigated using Fourier Transform Infrared Spectroscopy (FTIR) employing the potassium bromide pellet method.

Formulation of Sustained-Release Tablets

Sustained-release tablets were prepared by the direct compression method. Linagliptin and excipients were passed through sieve #40. Drug and polymers were blended uniformly. Magnesium stearate and talc were added as lubricants and glidants. The final powder blend was compressed using a single-punch tablet compression machine with a 9-mm round punch. Nine formulations (L1–L9) were prepared using varying concentrations of polymers such as HPMC K100, guar gum, and ethyl cellulose.

Evaluation of Powder Blend

Bulk Density

Bulk density was determined by measuring the volume occupied by a known weight of powder.

Tapped Density

Tapped density was determined by tapping the graduated cylinder until constant volume was obtained.

Carr's Compressibility Index

Carr's index was calculated using bulk density and tapped density values to assess flow properties.

Hausner's Ratio

Hausner's ratio was calculated to evaluate powder flow characteristics.

Angle of Repose

Angle of repose was determined by the fixed funnel method to assess flowability of powder blends.

Evaluation of Tablets

Hardness

Tablet hardness was measured using a Monsanto hardness tester.

Friability

Friability was determined using a Roche friabilator at 25 rpm for 100 revolutions.

Weight Variation

Twenty tablets from each batch were weighed individually and compared with pharmacopeial limits.

Thickness

Tablet thickness was measured using a vernier caliper.

Drug Content

Drug content was determined by dissolving powdered tablets in phosphate buffer (pH 6.8) and measuring absorbance using UV spectroscopy.

In-vitro Dissolution Study

Drug release studies were performed using USP dissolution apparatus II (paddle method) at 50 rpm in 900 ml dissolution medium. The medium consisted of 0.1 N HCl

for the first 2 hours followed by phosphate buffer pH 6.8 up to 24 hours at 37 ± 0.5°C. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically.

Drug Release Kinetics

Release data were fitted into different kinetic models including: Zero-order kinetics, First-order kinetics, Higuchi model, Korsmeyer–Peppas model to determine the mechanism of drug release.

Stability Studies

The optimized formulation was subjected to accelerated stability testing at 40 ± 2°C and 75 ± 5% RH for three months according to ICH guidelines.

RESULTS AND DISCUSSIOIN

Table 1. Calibration curve data for Linagliptin in 0.1N HCL.

Concentration (µg/ml)	Absorbance
0	0
10	0.167
15	0.261
20	0.339
25	0.428
30	0.528

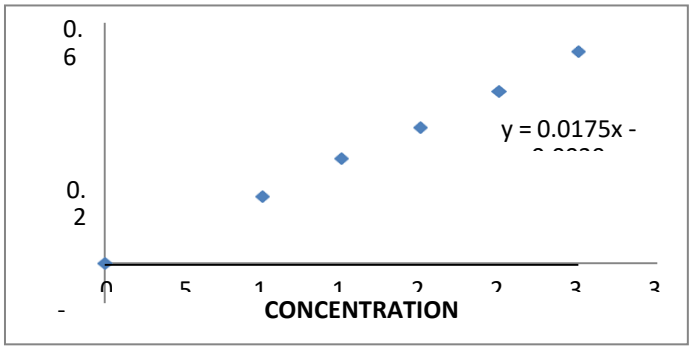

Figure 1. Standard graph Of Linagliptin in 0.1N HCL.

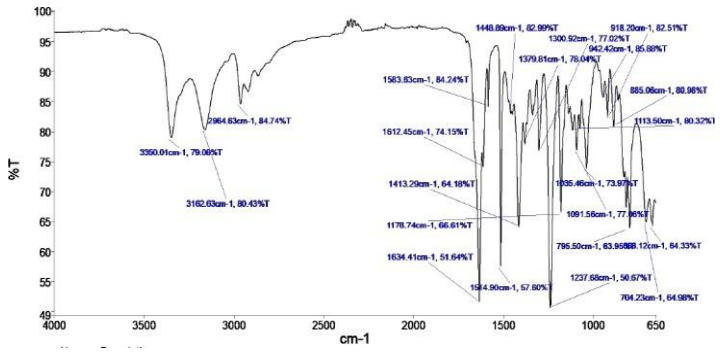

Figure 2. FTIR spectra of Linagliptin Optimized formulation.

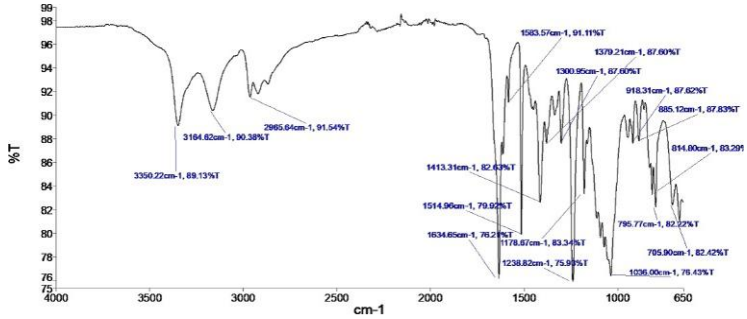

Figure 3. FTIR spectra of Linagliptin Optimized formulation.

INVITRO DISSOLUTION STUDIES FOR SR TABLETS SSOLUTION STUDY (SR TABLETS):

Acidic Stage:

Medium : 0.1N HCL
Type of apparatus : USP - II (paddle type)
RPM 50
Volume : 900ml
Temperature : 37ºC± 0.5
Time : 2hrs

Buffer Stage:

Medium : 6.8pH phosphate
bufferType of apparatus : USP - II (paddle
type)
RPM 50
Volume : 900ml
Time : 24hrs

In vitro dissolution for SR tablets were done initially in 0.1N HCL for 2hrs and next in 6.8phosphate buffer for 24hrs.

Table 2. Cumulative percentage drug release from sustained release tablets.

Time (Hrs)	L1	L2	L3	L4	L5	L6	L7	L8	L9
					Dissolution medium 0.1N HCL				
0.5	7.4	4.2	4.5	8.1	5.1	4.5	5.8	4.8	4.5
1	12.6	8.4	9.2	12.3	7.4	8.6	8.6	8.7	8.6
2	20.6	16.2	18.6	16.8	8.7	11.1	12.3	15.7	11.1
					6.8pH phosphate buffer				
3	29.1	22.4	24.8	21.6	28	35.4	17.8	19.8	17.5
4	33.8	28.2	33.4	28.7	37.6	49.6	22.8	23.8	26.6
5	40.8	32.9	41.8	35.3	43.8	58.7	26.6	29.8	31.1
6	45.6	37.2	50.3	42.8	51.4	65.2	31.8	35.2	38.4
7	54.3	41.7	58.6	50.2	63.4	71.8	39.3	42.8	49.6
8	63.4	48.3	64.5	55.8	74.2	76.5	44.9	49.2	58.7
10	71.8	55.8	73.8	63.8	85.6	83.4	51.8	58.9	65.2
12	80.6	66.6	81.7	74.5	94.7	90.8	62.3	68.7	71.8
16	100.4	86.4	100.8	100.3	100.1	96.7	76.6	84.5	76.5
20	-	100.1	-	-	-	98.2	83.6	92.5	83.4
24	-	-	-	-	-	-	89.3	100.2	90.8

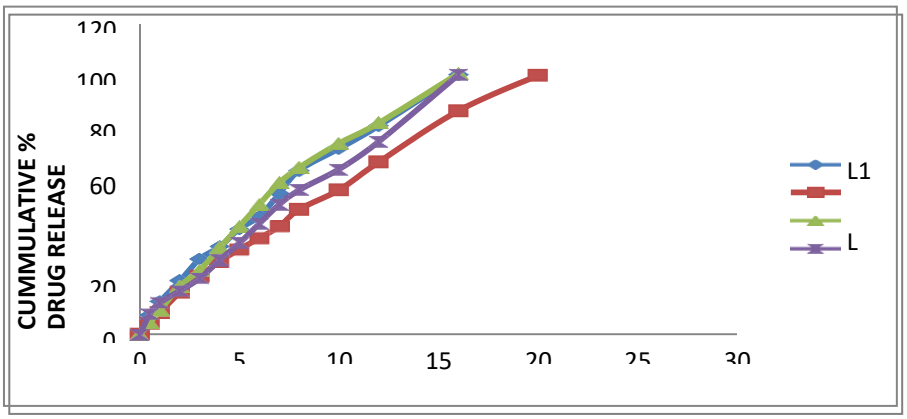

Figure 4. Dissolution graph for sustained release formulations for L1-L4.

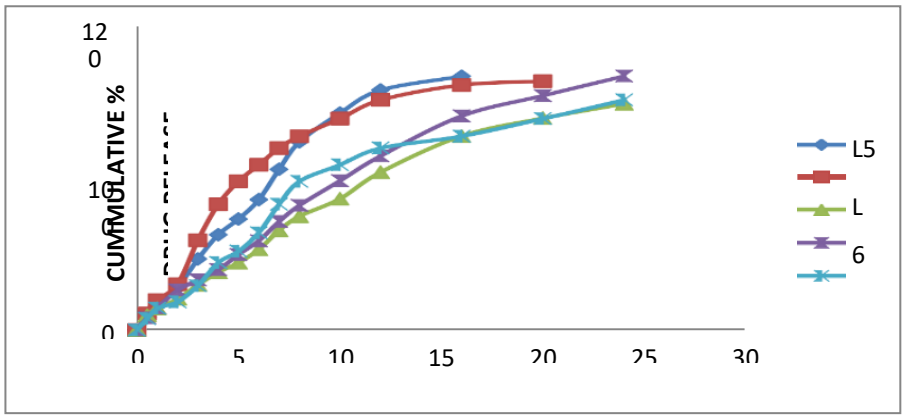

Figure 5. Dissolution graph for sustained release formulations for L5-L9.

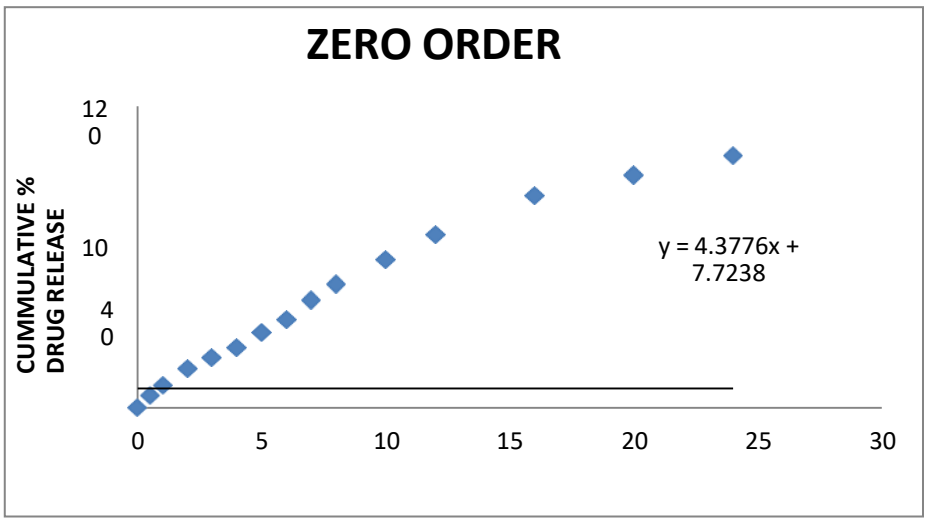

Figure 6. Zero order release graph for L8 sustained release formulation.

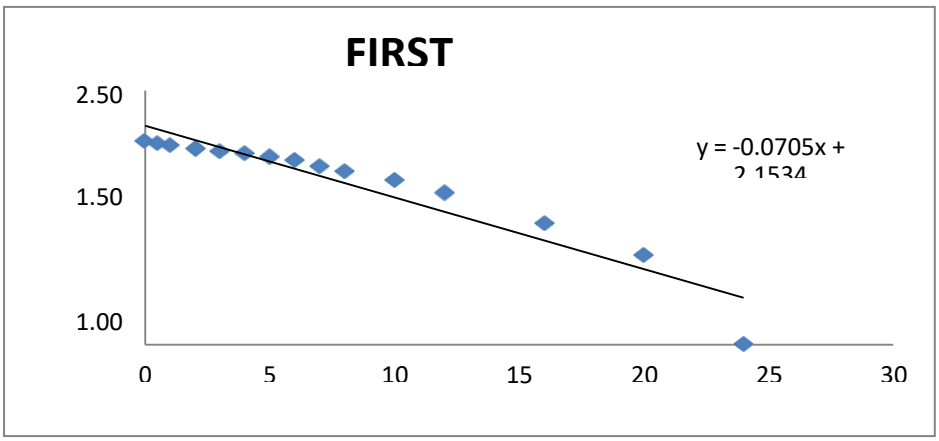

Figure 7. First order release graph for L8 sustained release formulation.

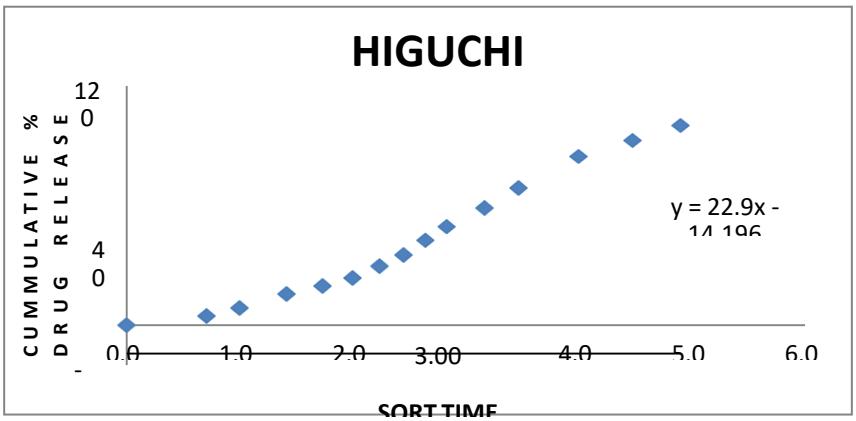

Figure 8. Higuchi model graph for L8 sustained release formulation.

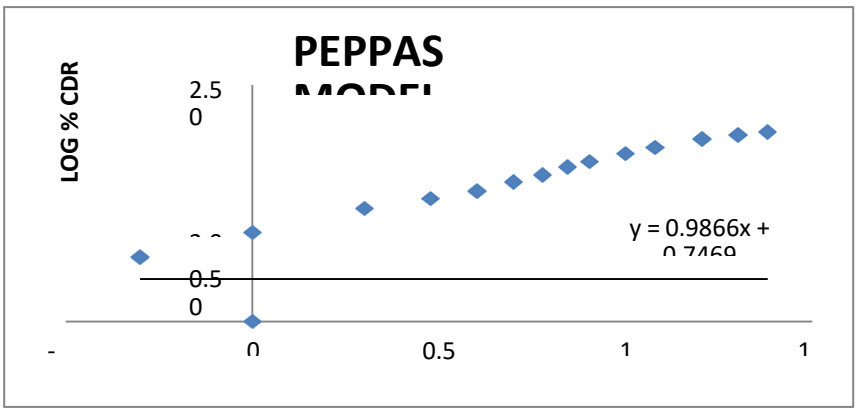

Figure 9. Peppas model for L8 sustained release formulation.

Table 3. Release kinetics for F6 formulation for sustained release tablets.

	ZERO % CDR VsT	FIRST Log % Remain VsT	HIGUCHI %CDR Vs √T	PEPPAS Log C VsLog T
Slope	4.377954307	-0.07006789	22.901741	0.986122716
Intercept	7.723702764	2.153275267	-14.198042	0.746785353
R 2	0.966174674	0.898800624	0.9654198	0.831088599

Preformulation studies confirmed that Linagliptin appeared as a white to yellowish powder and was slightly soluble in water but soluble in acidic medium such as 0.1 N HCl. The melting point was found to be 190–196°C, indicating purity of the drug. The calibration curve of Linagliptin exhibited a linear relationship between concentration and absorbance within the range of 10–30 µg/ml, indicating adherence to Beer-Lambert's law. FTIR studies confirmed the compatibility of Linagliptin with the selected excipients, as no significant shifts or disappearance of characteristic peaks were observed. Evaluation of the powder blends demonstrated good flow properties as indicated by acceptable values of bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose. Post-compression evaluation of tablets showed that all formulations complied with pharmacopeial limits for hardness, friability, thickness, weight variation, and drug content. Among all formulations, formulation L8 containing ethyl cellulose exhibited an optimized sustained-release profile. It showed approximately 8.7% drug release in the first hour and sustained release up to 24 hours, indicating effective matrix control of drug release. Release kinetics analysis demonstrated that the optimized formulation followed zero-order kinetics ($R^2 \approx 0.966$), suggesting a controlled and constant release pattern. Stability studies indicated that the formulation remained stable under accelerated conditions with no significant changes in physical properties or drug content.

CONCLUSION

The present study successfully developed sustained-release matrix tablets of Linagliptin using hydrophilic and hydrophobic polymers through the direct compression technique. Preformulation studies confirmed the suitability of Linagliptin for sustained-release formulation. The

powder blends exhibited good flow properties and were suitable for tablet compression. All prepared formulations complied with pharmacopeial quality control parameters including hardness, friability, weight variation, and drug content. Among the prepared formulations, L8 demonstrated an optimal sustained-release profile with controlled drug release for up to 24 hours. Drug release kinetics indicated that the optimized formulation followed zero-order kinetics, ensuring consistent drug delivery. Stability studies further confirmed the formulation's stability under accelerated conditions. Therefore, the developed sustained-release matrix tablets of Linagliptin may serve as a promising oral drug delivery system for the effective management of type-2 diabetes mellitus by providing prolonged therapeutic action and improved patient compliance.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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