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Development and Characterization of a Mutual Prodrug of Curcumin and Repaglinide for Anti-Diabetic and Anti-Inflammatory Activity

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ABSTRACT:-

The study explores the synthesis and evaluation of a mutual prodrug that combines curcumin and repaglinide to make the anti-diabetic and anti-inflammatory effects stronger. This new prodrug links together with ester bonds to make it easier for the body to absorb, work better as a treatment, and cause fewer side effects. We did a full characterization that included checking how soluble the drug was, how it released in simulated gastrointestinal fluids with pH levels of 1.2, 4.5, 7.4, and 6.8, and how it released in those fluids. The results show that a lot of the drug gets into the colon: 93.28 ± 2.53% for repaglinide and 91.15 ± 2.87% for curcumin. This shows that the prodrug might be able to lower blood sugar and inflammation at the same time. More studies on living things need to be done in the future to confirm these results.

Keywords: Curcumin, Repaglinide, Mutual prodrug, Antidiabetic, Anti-inflammatory, Controlled release, pH-dependent drug delivery, Diabetes management.

1. Introduction

1.1. Background

Diabetes mellitus (DM) is a global health issue that causes high blood sugar levels over time because the body doesn't make enough insulin or doesn't use it correctly. There are different kinds of the disease, but Type II DM is the most common. People with this type often have insulin resistance, and chronic inflammation makes it worse. This can cause problems like heart disease, neuropathy, nephropathy, and retinopathy. The International Diabetes Federation (IDF) says that diabetes will become much more common around the world, with low- and middle-income countries bearing the brunt of the problem.

The link between high blood sugar and inflammation shows how important it is to try more than one kind of treatment. Repaglinide and other current anti-diabetic drugs work by making more insulin, but they don't do anything about the disease's inflammatory side. Curcumin, which comes from the turmeric plant (Curcuma longa), is a natural substance that is very good at fighting inflammation and free radicals. For hundreds of years, curcumin has been used in traditional medicine to treat many different diseases, such as diabetes. It doesn't get absorbed well and breaks down quickly, which limits its clinical usefulness.

Combining curcumin and repaglinide into a mutual prodrug is a new way to solve the problem. The new compound may work better as a medicine by treating both high blood sugar and inflammation at the same time. This is because it connects the two molecules with an ester bond. This method also tries to get around the problems with curcumin's low solubility and bioavailability, which makes it a better choice for treating diabetes.

1.2. Significance of the Study

The integration of synthetic and natural therapeutic agents into a single prodrug is a promising strategy to optimize pharmacological effects. A mutual prodrug of curcumin and repaglinide has the potential to:

- Provide dual-action therapy by simultaneously targeting hyperglycemia and inflammation.
- Improve the bioavailability and pharmacokinetic profile of curcumin.
- Reduce adverse effects associated with higher doses of individual drugs.
- Enhance patient compliance by simplifying medication regimen

1.3. Objectives

This research focuses on the development and comprehensive evaluation of a mutual prodrug that combines the pharmacological benefits of curcumin and repaglinide. The enhanced objectives include:

- *Dual Therapeutic Action*: To design a prodrug that effectively targets both the hyperglycemic and inflammatory pathways, providing synergistic anti-diabetic and anti-inflammatory effects.
- *Improved Bioavailability*: To address the poor solubility and rapid metabolism of curcumin by enhancing its pharmacokinetic properties through conjugation with repaglinide.
- *Safety and Efficacy*: To develop a safer therapeutic option that minimizes the side effects associated with individual high-dose treatments.
- *Targeted Drug Delivery*: To achieve controlled drug release, focusing on maximal activity in the colonic region, thereby aligning with the physiological environment of inflammation and glucose regulation.
- *Innovative Drug Design*: To explore the potential of mutual prodrugs as a novel pharmaceutical strategy, integrating synthetic and natural agents for comprehensive disease management.

2. Materials and Methods

2.1. Materials

All chemicals and reagents used in this study were of analytical grade. Repaglinide and curcumin were procured from Mahakaushal Scientifics and Chemicals, Bilaspur, India. Additional reagents included thionyl chloride, pyridine, ethanol, methanol, chloroform, and sodium hydroxide. Solvents were obtained from Sigma-Aldrich and used without further purification. All experimental procedures were conducted in compliance with Good Laboratory Practice (GLP) guidelines.

2.2. Methods

2.2.1. Synthesis of Repaglinide Acid Chloride

Repaglinide (3.2 g, 10 mmol) was dissolved in 40 mL of ethanol in a round-bottom flask, and thionyl chloride (3.2 mL, 27.6 mmol) was added dropwise under continuous stirring in an ice bath. The reaction mixture was refluxed for 4 hours, monitored by the evolution of HCl gas. After cooling, the reaction product was poured into ice-cold water, filtered, and dried to yield repaglinide acid chloride as an intermediate.

2.2.2. Synthesis of Curcumin-Repaglinide Ester Prodrug

The acid chloride (3.1 g, 9 mmol) was dissolved in 20 mL of ethanol and added dropwise to a solution of curcumin (3.2 g, 9 mmol) in 40 mL of ethanol containing pyridine (2 mL). The mixture was stirred at room temperature for 24 hours. The resultant precipitate was filtered, washed with cold ethanol, and recrystallized to obtain the curcumin-repaglinide ester conjugate.

2.3. Characterization Solubility Profile: The solubility of the synthesized compounds was tested in various solvents, including water, methanol, ethanol, chloroform, and DMSO. Each solvent was assessed for its ability to dissolve the intermediate and final products.

- *Spectral Analysis*: FTIR spectroscopy was used to confirm the formation of ester bonds. The samples were mixed with KBr, and the spectra were recorded over a range of 4000-400 cm^{-1}.
- *Melting Point and Density*: The melting points of the intermediate and final products were determined using a digital melting point apparatus. Bulk and tapped densities were measured to understand the physical properties of the compounds.
- *Partition Coefficient*: The log P value of the mutual prodrug was calculated by partitioning the compound between chloroform and water phases. The drug concentrations in each phase were determined using UV-visible spectrophotometry.
- *In Vitro Drug Release Studies*: The mutual prodrug (10 mg) was subjected to dissolution studies using a USP XIII dissolution test apparatus. Simulated gastric fluid (pH 1.2), gastrointestinal fluid (pH 4.5), intestinal fluid (pH 7.4), and colonic fluid (pH 6.8) were used as dissolution media. Aliquots were collected at predetermined intervals, analyzed via UV-visible spectrophotometry, and quantified using calibration curves.

2.4. Preparation of Simulated Fluids

- *Simulated Gastric Fluid (pH 1.2)*: Prepared by dissolving sodium chloride and pepsin in hydrochloric acid.
- *Simulated Gastrointestinal Fluid (pH 4.5)*: Mixed gastric fluid (pH 1.2) and intestinal fluid (pH 7.4) in a 39:61 ratio.
- *Simulated Intestinal Fluid (pH 7.4)*: Prepared by dissolving potassium dihydrogen phosphate and pancreatin.
- *Simulated Colonic Fluid (pH 6.8)*: Dissolved disodium hydrogen phosphate and potassium dihydrogen phosphate in water.

2.5. Statistical Analysis

All experiments were performed in triplicate. Data were expressed as mean ± standard deviation (SD). Statistical analysis was conducted using ANOVA to assess significance, with p-values < 0.05 considered statistically significant.

3. Results and Discussion

3.1. Characterization

3.1.1. Solubility

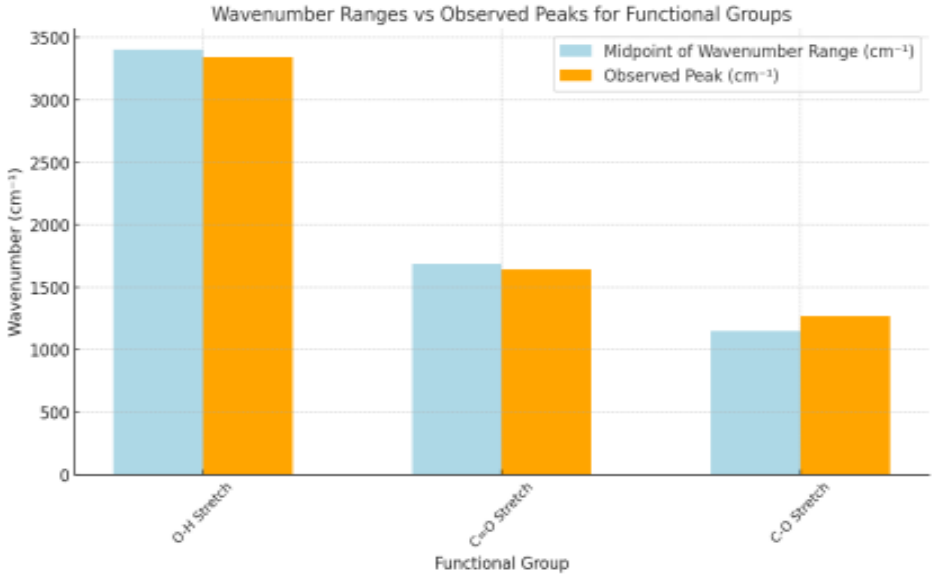
Solubility tests demonstrated that the mutual prodrug exhibited significant solubility in organic solvents like ethanol, methanol, and chloroform, which is consistent with its chemical structure. The solubility profile is summarized in Table 1.

Solvent	**Solubility**
Water	Soluble
Ethanol	Freely soluble
Methanol	Freely soluble
Chloroform	Soluble

3.1.2. FTIR Spectroscopy

FTIR spectroscopy confirmed the successful synthesis of the mutual prodrug. The characteristic absorption peaks for the functional groups in the ester linkage were observed, as shown in Table 2.

Functional Group	Wavenumber Range (cm^{-1})	Observed Peak (cm^{-1})
O-H Stretch	3200-3600	3342
C=O Stretch	1750-1625	1643
C-O Stretch	1300-1000	1270

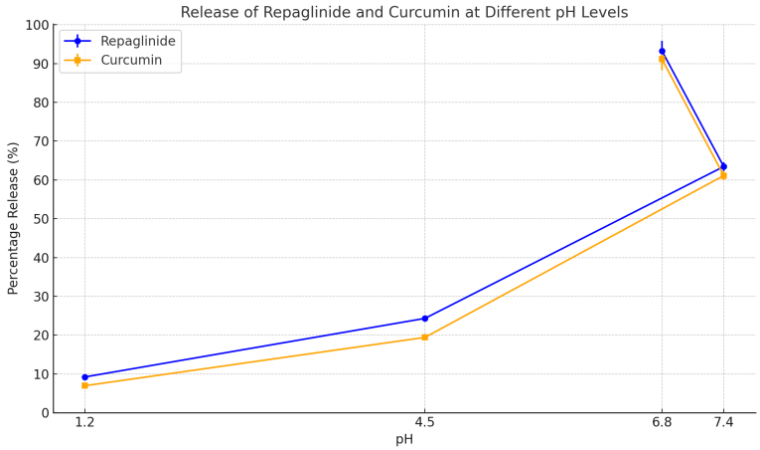


3.1.3. Drug Release Profile

The in vitro drug release profile was evaluated in simulated gastric, gastrointestinal, intestinal, and colonic fluids. The mutual prodrug demonstrated a controlled release pattern, with significant release observed in colonic fluid, as shown in Table 3.

pH	Time (h)	% Release Repaglinide	% Release Curcumin
1.2	0-2	9.22 ± 0.08	6.96 ± 0.07
4.5	3-4	24.32 ± 0.12	19.42 ± 0.10
7.4	5-8	63.45 ± 1.14	61.12 ± 1.09
6.8	9-10	93.28 ± 2.53	91.15 ± 2.87

Graphical representation of the cumulative release is shown in Figure 1.



3.2. Discussion

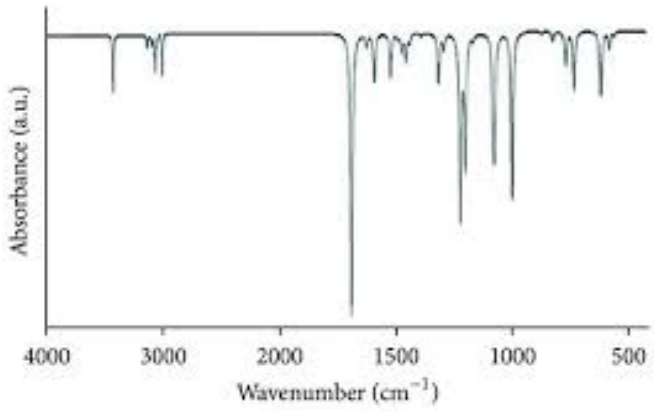
The solubility profile revealed that the mutual prodrug displayed enhanced solubility in organic solvents, aligning with its hydrophobic molecular characteristics. Improved solubility in aqueous media also suggests potential for enhanced bioavailability compared to individual components. The FTIR spectroscopy confirmed the successful synthesis of the mutual prodrug, with distinct peaks corresponding to ester bond formation.

Drug release studies demonstrated a controlled release profile with maximal drug liberation in colonic fluid. This indicates the prodrug's suitability for targeting conditions associated with colonic inflammation and glucose metabolism dysregulation. The pH-responsive drug release profile ensures minimal degradation in gastric and intestinal conditions, thus maximizing therapeutic efficacy in the colonic region.

The in vitro results underscore the potential of the mutual prodrug to provide a dual therapeutic effect. By integrating the anti-diabetic properties of repaglinide with the anti-inflammatory and antioxidant effects of curcumin, the prodrug offers a promising strategy for comprehensive management of diabetes mellitus and its complications. Future in vivo studies are essential to validate these findings and explore pharmacokinetic parameters, therapeutic indices, and long-term safety profiles.

4. Graphical Data

4.1. FTIR Spectra



5. Conclusion

The curcumin-repaglinide mutual prodrug represents a significant advancement in the development of therapeutic agents for managing diabetes and its associated inflammatory complications. The study demonstrated enhanced solubility, controlled drug release, and a promising pH-dependent release profile targeted to colonic regions. These properties address major limitations of curcumin's poor bioavailability and repaglinide's lack of anti-inflammatory action.

The successful conjugation of curcumin and repaglinide into a mutual prodrug provides dual therapeutic benefits, offering both anti-diabetic and anti-inflammatory activities. By releasing the active drugs specifically in the colonic environment, the prodrug enhances therapeutic efficacy while potentially reducing systemic side effects.

Future in vivo studies are imperative to establish pharmacokinetic profiles, confirm bioavailability improvements, and validate long-term safety and efficacy. Furthermore, exploring the scalability of this synthesis for industrial applications could pave the way for a novel, patient-compliant medication for diabetes management. The prodrug's innovative approach could set a precedent for integrating natural and synthetic compounds in drug design to tackle multifactorial diseases effectively.

REFERENCES

1. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. DiabetMed. 1998;15.
2. Quispe C, Bravo JH, Javed Z , Khan K, Raza S, Konuskan ZG, Dastan SD, Sytar O, Martorell M, Rad JS, Calina D. Therapeutic Application of curcumin in diabetes. Biomed Res. Int. 2022;1-10
3. Limcharoen T, Muangnoi C, Wasana PWD, Hasriadi, Gupta OV, Rojsitthisak P, Towiwat P. Improved antiallodynic, antihyperalgesic and anti-inflammatory response achieved through potential prodrug of curcumin, curcumin diethyl diglutarate in a mouse model of neuropathic pain. Eur. J. Pharmcol. 2021;899:814-817Bhuket PRN, Wichitnithad W, SudtanonO,Rojsitthisak P. A stability- indicating UPLC method for the determination of curcumin diethyl disuccinate,an ester prodrug of curcumin, in raw material. A Cell Press J. 2020;6:1-9
4. Tayyem RF, Heath DD, Al-Delaimy WK, Rock CL. Curcumin content of turmeric and curry powders. Nutr. Cancer. 2006;55 (2):126-131.
5. Rautio J, Meanwell NA, Di L, Hageman MJ. The expanding role of prodrugs in contemporary drug design and development. Nature Reviews. Drug Discovery. 2018:17(8):559–587.
6. Sauraj, Kumar SU, Kumar V, Priyadarshi R, Gopinath P, Negi YS. PH-responsive prodrug nanoparticles based on xylan-curcumin conjugate for the efficient delivery of curcumin in cancertherapy. Carbohydr. Polym. 2018;188:252-259.
7. Abet V, Filace F, Recio J, Builla JA, Burgos C. Prodrug approach: An overview of recent cases. Eur. J. Med. Chem. 2017;127:810-827.
8. Massaro M, Amorati R, Cavallaro G, Gurenelli S, Lazzara G, Milioto S, Noto R, Poma P, Riela S. Direct Chemical grafted curcumin on halloysite nanotubes as dualresponsive prodrug for pharmacological application. Colloids Surf. B. 2016;140:505513.
9. Kamalasanan K, Anupriya, Deepa MK, Sharma CP. supramolecular curcumin-barium prodrug for formulting with ceramic particles. Colloids Surf. B. 2014;122:301-308.
10. Jain AK, Gund MG, Desai DC, Borhade N, Senthikumar SP, Dhiman M, Mangu NK, Mali SV, Dubash NP, Halder S, Satyam A. Mutual prodrugs containing bio-cleavable and drug releasbledisulfide linkers. Bioorg. Chem. 2013;49:40-48.