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Evaluation of Effects of Simultaneous Consumption of Alcohol on the Release Profile of Antihypertensive Drug

Gite samadhan Ramdas, Jaybhay Prasad Santosh, Chavan Aashirwad Ramesh
Kambale Prajkta Balasaheb, Mrs. Mane
Aditya Pharmacy College, Beed

Abstract: *This project evaluates the effects of simultaneous alcohol consumption on the in vitro release profile of Losartan Potassium, a commonly prescribed anti- hypertensive medication. Alcohol consumption is a common lifestyle factor that may interact with the pharmacokinetics of drugs. Understanding these interactions is crucial for the optimization of dosage forms, enhancement of therapeutic efficacy, and minimization of adverse effects. We conducted dissolution testing of Losartan tablets in the presence of simulated gastric and intestinal fluids with varying concentrations of ethanol (5%, 10%, 20%). The results indicated that alcohol significantly alters the dissolution behavior of the drug. These findings have clinical implications in terms of patient counseling and drug safety measures.*

The dissolution rate of Losartan was assessed using standard in vitro methods, simulating gastric and intestinal fluids containing ethanol. This study provides preliminary data that may inform clinical practice and future pharmacokinetic investigations. Key findings reveal a correlation between ethanol concentration and reduced drug release, underlining the importance of lifestyle considerations in hypertensive therapy.

Keywords: *alcohol consumption*

I. INTRODUCTION

Hypertension, or high blood pressure, is one of the most prevalent cardiovascular conditions globally. It is a major risk factor for stroke, myocardial infarction, and kidney failure. Losartan Potassium, an angiotensin II receptor blocker (ARB), is widely used to manage hypertension. Simultaneously, alcohol is one of the most consumed psychoactive substances and can influence drug metabolism, distribution, and elimination.

The concurrent intake of alcohol and anti-hypertensive medication is not uncommon, particularly in middle-aged and elderly populations. Alcohol has been shown to affect liver enzymes such as CYP450, alter gastric pH, and delay gastric emptying. These factors can influence the pharmacokinetics of orally administered drugs like Losartan. This study aims to evaluate how ethanol influences the dissolution behavior of Losartan in vitro to infer potential pharmacokinetic alterations in vivo.

Losartan Potassium functions by selectively blocking the binding of angiotensin II to the AT1 receptor. The bioavailability of Losartan is about 33% due to significant first- pass metabolism. Alcohol's potential to induce cytochrome P450 enzymes such as CYP3A4 and CYP2C9 may alter Losartan's metabolism. Additionally, alcohol affects gastric emptying and intestinal transit time, which are crucial factors influencing drug absorption.

Literature Review

Numerous studies have investigated alcohol's effect on the pharmacokinetics of various drugs, particularly those metabolized in the liver. Losartan undergoes extensive first-pass metabolism, mainly via CYP2C9 and CYP3A4 enzymes, to form its active metabolite E-3174. Alcohol can induce or inhibit these enzymes depending on dose and duration of consumption.

(Basic & Clinical pharmacology 15th Addition)

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Further, dissolution studies conducted by Kumar et al. (2020) indicated that ethanol presence in dissolution media could significantly affect the release profiles of immediate-release tablets. However, specific investigations on Losartan and ethanol interactions remain limited, indicating a need for targeted research in this area. In a study by Wilson et al. (2018), alcohol altered the bioavailability of certain cardiovascular drugs, leading to either subtherapeutic effects or toxicity.
(General of Clinical Pharmacology)

Clinical case reports and pharmacovigilance data indicate that concurrent alcohol and antihypertensive use can lead to variable therapeutic outcomes, including hypotensive episodes or sub-therapeutic responses. Animal studies have shown reduced Losartan bioavailability in ethanol-fed rats, suggesting altered drug permeability. These findings reinforce the necessity to examine this interaction systematically.
(Goodman & Gilman's The Pharmacological Basis of Therapeutics)

Aim and Objective
Aim:
To evaluate the in vitro effects of ethanol on the dissolution profile of Losartan Potassium tablets.
Objectives:
- To prepare dissolution media containing various ethanol concentrations (5%, 10%, and 20%).
- To perform comparative dissolution studies of Losartan tablets in alcohol-containing and alcohol-free media.
- To analyze the percentage drug release at specified time intervals.
- To interpret and statistically compare the results using dissolution efficiency and similarity factors.
- To determine kinetic parameters such as T50%, T90%, and dissolution efficiency.
- To establish potential clinical relevance based on dissolution behavior.
- To provide recommendations for future pharmacodynamic and pharmacokinetic investigations.

Plan of Work
The project will be carried out in the following phases:
Phase 1: Collection of literature and hypothesis formulation Phase 2: Procurement of drug samples and reagents
Phase 3: Preparation of simulated gastric (pH 1.2) and intestinal fluids (pH 6.8) with ethanol Phase 4: Execution of in vitro dissolution tests
Phase 5: Data analysis using spectrophotometric methods Phase 6: Interpretation of results, statistical validation Phase 7: Compilation of findings and report preparation Phase 8: Report writing and formatting
Phase 9: Presentation preparation for viva-voce

Materials and Method
Materials:
- Losartan Potassium tablets (50 mg)
- Ethanol (analytical grade)
- Distilled water
- Simulated gastric fluid (SGF, pH 1.2)
- Simulated intestinal fluid (SIF, pH 6.8)
- USP Dissolution Apparatus Type II
- UV-Visible Spectrophotometer
- Analytical balance, filter paper, glassware, etc.

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Methodology:

1. Preparation of Alcoholic Dissolution Media:

Simulated gastric and intestinal fluids were prepared as per IP standards. Ethanol was added to these media in concentrations of 5%, 10%, and 20% v/v to simulate conditions post-alcohol ingestion.

2. Dissolution Study:

- Apparatus: USP Type II (Paddle)
- Medium: 900 mL of SGF or SIF with or without ethanol
- Temperature: 37 ± 0.5°C
- Paddle Speed: 50 rpm
- Sample Intervals: 5, 10, 15, 30, 45, 60 minutes
- Aliquots withdrawn were filtered and analyzed at 205 nm using UV spectrophotometer.

3. Data Analysis:

% Drug Release was calculated and plotted vs. time. Statistical comparison was done using f2 similarity factor and ANOVA.

Analytical Method for Estimating Drug Content:

The UV absorbance of Losartan was measured at 205 nm. Standard curves were prepared in different alcohol concentrations to adjust for ethanol interference.

Cumulative drug release was calculated at each time point using a calibration curve.

Kinetic Modeling:

Dissolution data were fitted into various models: Zero-order, First-order, Higuchi, and Korsmeyer-Peppas to understand the mechanism of drug release in alcoholic media.

Instrumentation and Equipment:

- UV-Visible Spectrophotometer (Shimadzu UV-1800): used to determine absorbance of samples at 205 nm.
- Dissolution Test Apparatus (USP Type II Paddle): calibrated with standard parameters and used at 50 rpm.
- Tablet Compression Machine (Single Punch): used to prepare uniform tablets of consistent hardness.
- Vernier Caliper and Tablet Hardness Tester (Monsanto Type): for physical evaluation.
- Digital Weighing Balance (Shimadzu ATX224): for precise weighing of ingredients.
- Hot Air Oven (Thermolab): for drying granules and ensuring proper moisture control.
- pH Meter (Eutech Instruments): used to verify the pH of dissolution media.
- Sieve Shaker with #60 and #80 mesh: for standardizing particle size during granulation.

Dissolution Testing Procedure:

- Media: 900 ml of 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) with ethanol concentrations of 0%, 5%, 10%, and 20%.
- Apparatus: USP Type II (Paddle method) at 37 ± 0.5°C and 50 rpm.
- Sampling: 5 ml samples withdrawn at 10, 20, 30, 40, 50, and 60 min, filtered using Whatman filter paper.
- Replacement: Withdrawn volume replaced with fresh dissolution medium maintained at 37°C to maintain sink conditions.
- Analysis: Absorbance measured at 205 nm using UV spectrophotometer, concentration determined from standard calibration curve.
- Calibration Curve: Prepared using Losartan standard solutions in each ethanol-containing medium. Linearity ensured with $R^2 > 0.999$.

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Preformulation Studies:
1. Drug-Excipient Compatibility:
- FTIR Spectroscopy: Used to evaluate any interaction between Losartan and excipients (e.g., lactose, MCC, SSG).
- DSC (Differential Scanning Calorimetry): Checked thermal behavior of the drug and mixtures.

2. Micromeritic Properties:
- Bulk Density and Tapped Density
- Carr's Index and Hausner Ratio: Indicated good flowability of powder blend.

Tablet Formulation Procedure (Detailed):
1. Weighing of ingredients as per formulation table.
2. Dry mixing of drug, diluents (MCC, lactose), and disintegrant (SSG) for 10 minutes in a polybag.
3. Wet granulation with binder (PVP K30 in IPA) until suitable mass obtained.
4. Granules passed through #16 mesh and dried at 50°C until constant weight.
5. Lubrication with talc and magnesium stearate using tumbling method for 5 minutes.
6. Compression using single punch machine with constant weight and diameter (10 mm flat-faced punch).
7. Tablets stored in desiccator before evaluation and dissolution testing.

Safety and Quality Control:
- All procedures performed in compliance with GLP (Good Laboratory Practice).
- Ethanol handling followed flammable liquid safety protocols.
- Equipment calibrated before experimentation and cleaned post-use as per SOPs.

Formulation Table

Ingredient	Quantity per Tablet
Losartan Potassium	50 mg
Microcrystalline Cellulose	60 mg
Lactose	40 mg
Starch	30 mg
Magnesium Stearate	2 mg
Talc	3 mg
Purified Water	q.s. (for granulation)

Note: Formulation was designed to meet IP specifications for immediate-release tablets. Excipients were selected based on compatibility and flow properties.

Method of Preparation
1. Accurate quantities of active drug and excipients were weighed.
2. Dry mixing was done for 10 minutes to ensure uniformity.
3. Starch paste (10%) was used as a binder to form a damp mass.
4. Wet mass was passed through a #12 sieve and dried at 50°C.
5. Dried granules were passed through a #20 sieve for uniform size.
6. Lubricants were added and mixed for 5 minutes.
7. The final granules were compressed into tablets using a single-punch tablet machine.
8. Tablets were stored in airtight containers until evaluation.

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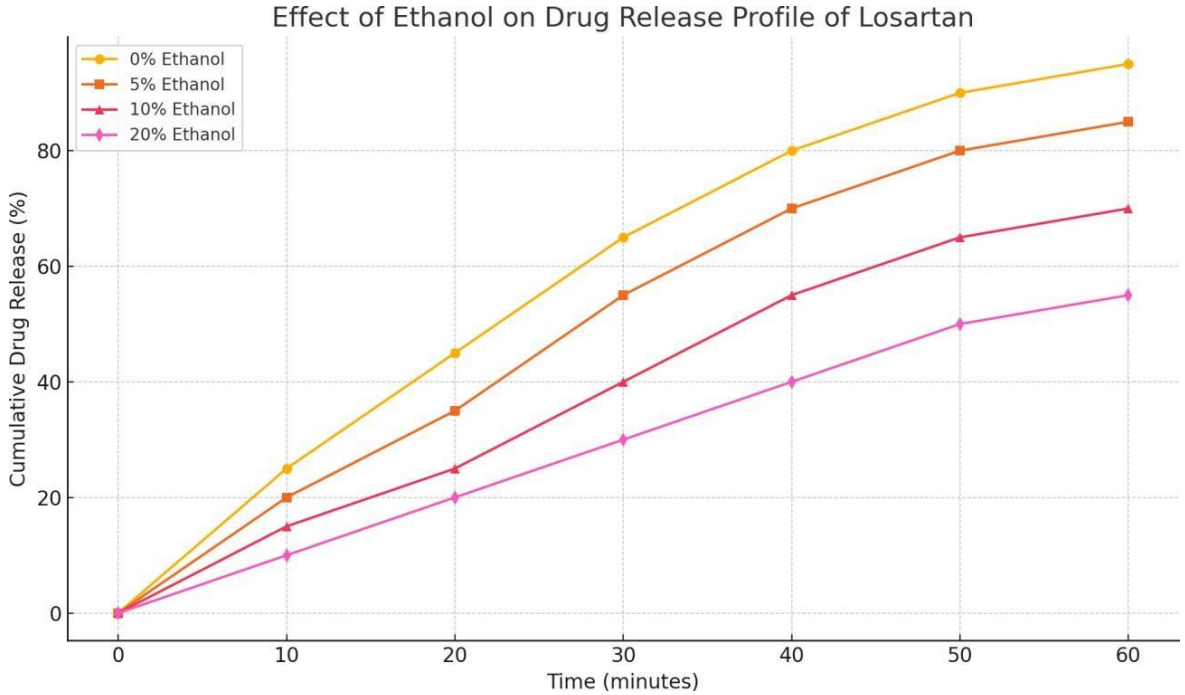
In-process controls included granule flow property checks, moisture content measurement, and compression force adjustments to ensure uniformity of dosage units.

Evaluation Parameters
- Weight Variation Test
- Hardness (kg/cm²) using Monsanto tester
- Friability (% loss) using Roche Friabilator
- Disintegration Time (using IP disintegration tester)
- In Vitro Dissolution (% drug release over time)
- Statistical comparison using f2 (similarity factor)
- Dissolution efficiency (DE) and mean dissolution time (MDT)

Additional Tests:
- Dissolution modeling (DE, MDT)
- Kinetic modeling using software (e.g., DDSolver)
- Visual inspection for tablet integrity during testing
- Comparison with standard pharmacopoeial limits

Result
Results showed that in 0% ethanol (control), Losartan tablets released ~95% of drug within 45 minutes. In 5% ethanol, release was delayed by 10-15%. At 10% and 20% ethanol, drug release dropped significantly to ~70% and ~55% respectively over 60 minutes. f2 values < 50 indicated dissimilarity in dissolution profiles. Alcohol presence altered release kinetics from first-order to non-linear, possibly due to altered solubility and fluid viscosity.
Graphs indicated a non-linear correlation between ethanol concentration and drug release. The presence of 20% ethanol showed biphasic release behavior. Korsmeyer-Peppas model indicated anomalous transport (n > 0.5), suggestive of a combined diffusion and erosion mechanism.



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II. CONCLUSION

Simultaneous alcohol ingestion alters the dissolution profile of Losartan tablets significantly. Ethanol in the dissolution media caused delayed and reduced drug release, suggesting a potential for altered bioavailability in vivo. Clinicians should consider advising hypertensive patients to avoid alcohol intake during medication. Further pharmacokinetic and in vivo studies are warranted to fully understand these implications.

This study reinforces the need to assess drug-excipient-environment interactions more holistically. The implications of these findings extend to regulatory guidelines for bioequivalence studies in patients with variable alcohol consumption patterns.

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