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Original Article

Formulation and Evaluation of Sustained Release Metronidazole Tablet

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ABSTRACT

Metronidazole, an antibiotic commonly used to treat infections caused by anaerobic bacteria and certain protozoa, has a broad spectrum of activity. However, its frequent dosing regimen due to its short half-life often leads to poor patient compliance and fluctuations in plasma drug concentrations. The development of sustained-release formulations of metronidazole aims to improve its therapeutic effectiveness, enhance patient adherence, and minimize side effects.This study focuses on the formulation and evaluation of sustained-release (SR) tablets of metronidazole. The SR formulation was designed to release the drug gradually over an extended period, providing a controlled plasma concentration and reducing the frequency of dosing. The formulation was developed using various excipients, including hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), which are known to control the release rate of the active pharmaceutical ingredient (API).The prepared tablets were characterized for their physicochemical properties, including drug content uniformity, hardness, friability, and in vitro release behavior. The in vitro release studies demonstrated that the SR tablets exhibited a consistent release profile, maintaining therapeutic plasma concentrations over a prolonged period compared to conventional immediate-release formulations. Furthermore, stability studies confirmed that the tablets remained stable under accelerated conditions for the intended shelf life.The pharmacokinetic studies in human volunteers revealed that the sustained-release formulation resulted in a more stable plasma concentration of metronidazole, reducing peaks and troughs, thereby enhancing its therapeutic efficacy and minimizing side effects. The results suggest that sustained-release metronidazole tablets can significantly improve patient compliance and the clinical management of infections, offering a promising alternative to conventional metronidazole dosage forms.

Keywords: Metronidazole, sustained release, tablet formulation, patient compliance, pharmacokinetics, hydrophilic polymers, controlled release

INTRODUCTION

protozoa, and other microorganisms, making it a key therapeutic option in the treatment of infections such as bacterial vaginosis, trichomoniasis, amebiasis, and intra-abdominal infections. Typically administered in immediate-release formulations, metronidazole requires frequent dosing due to its relatively short half-life of approximately 8 hours. This frequent administration can lead to issues of poor patient adherence, resulting in suboptimal therapeutic outcomes and increased risk of drug resistance[1]. To overcome these challenges, the development of sustained-release (SR) formulations has emerged as a promising strategy. Sustained-release systems are designed to release the active pharmaceutical ingredient (API) gradually over an extended period, ensuring more consistent plasma drug concentrations, reducing the frequency of dosing, and ultimately improving patient compliance. By minimizing the fluctuations in drug levels, sustained-release formulations can also enhance the efficacy and safety of the drug, reducing the occurrence of side effects commonly associated with peak plasma concentrations[2]. Sustained-release tablets of metronidazole are particularly beneficial because they offer controlled release over a longer duration, reducing the dosing frequency from multiple times a

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day to once or twice daily. This can be especially advantageous in managing infections that require prolonged treatment regimens, such as those involving protozoal infections or chronic bacterial conditions. Additionally, controlled-release formulations may reduce the gastrointestinal side effects often encountered with immediate-release forms of metronidazole, such as nausea, headache, and abdominal discomfort[3]. The goal of developing sustained-release metronidazole tablets is to maintain therapeutic plasma concentrations over an extended period, thereby improving clinical outcomes, enhancing patient compliance, and optimizing the pharmacokinetics of the drug. This formulation is typically achieved using excipients like hydrophilic polymers, which control the rate of drug release through hydration and gel formation. This paper aims to discuss the formulation and evaluation of metronidazole sustained-release tablets, focusing on the design of the formulation, its in vitro and in vivo performance, and the potential clinical benefits in terms of efficacy, safety, and patient adherence[4].

OBJECTIVES

The primary objectives of developing sustained-release (SR) tablets of metronidazole are as follows:

1. a more controlled release, potentially leading to a better overall safety profile To Develop a Controlled Release Formulation Formulate sustained-release metronidazole tablets that ensure the gradual and controlled release of the active ingredient over an extended period, reducing the need for frequent dosing and improving the therapeutic efficacy of the drug.
2. To Improve Patient Compliance, enhance patient adherence to the prescribed treatment regimen by reducing the frequency of administration, thus making treatment more convenient and consistent for the patient[5].
3. To Minimize Plasma Drug Fluctuations, achieve a more stable plasma drug concentration profile, reducing the peaks and troughs associated with immediate-release formulations and minimizing the risk of side effects due to high plasma concentrations.
4. To Optimize the Formulation with Suitable Excipients
   Identify and incorporate appropriate excipients (e.g., hydrophilic polymers like hydroxypropyl methylcellulose, or HPMC) to achieve the desired release rate of metronidazole, ensuring that the drug is released in a controlled manner over a prolonged period[6].
5. To Assess the In Vitro Release Profile Evaluate the in vitro drug release profile to ensure that the sustained-release formulation meets the required specifications for prolonged and controlled drug release, simulating conditions found in the human gastrointestinal tract.
6. To Conduct Pharmacokinetic Studies, perform pharmacokinetic studies to compare the sustained-release tablet's performance to that of conventional immediate-release tablets, assessing parameters such as the time to peak concentration, the area under the curve (AUC), and the duration of therapeutic plasma levels[7].
7. To Evaluate the Stability of the Formulation, perform stability studies to determine the shelf life and the stability of the sustained-release metronidazole tablets under accelerated conditions, ensuring the formulation maintains its effectiveness over time.
8. To Improve the Safety Profile of Metronidazole, Minimize the gastrointestinal side effects (e.g., nausea, headache, and abdominal discomfort) associated with conventional metronidazole formulations by providing[8].

MATERIAL AND ITS ROLE:

1. Metronidazole:

Role in Formulation:

Active Pharmaceutical Ingredient (API): Metronidazole is the core active ingredient in the formulation. The goal is to deliver a controlled, sustained release of the drug over time. Therapeutic Action: Metronidazole is an antibiotic used primarily to treat infections caused by anaerobic bacteria and protozoa. In sustained-release formulations, the release of the drug is controlled to maintain effective blood concentrations over an extended period, reducing the frequency of dosing. Properties: It is poorly soluble in water, which means the formulation must be designed to slow down its release, improving its bioavailability and ensuring consistent therapeutic effects[9].

2. Calcium Chloride ($CaCl_2$):

Role in Formulation:

Granulation Aid: Calcium chloride is often included in formulations to aid in the wet granulation process. It helps improve granule formation and acts as a stabilizer, promoting better cohesion between the powder particles during granulation.

Enhancing Flow Properties: It can improve the flowability of the granules, which is crucial for uniform tablet compression.

Tablet Integrity: Calcium chloride can also be used to maintain the structural integrity of the tablets, especially in formulations requiring controlled release.

Properties: Calcium chloride is a hygroscopic salt, which can help facilitate binding during the granulation process and ensure uniformity in tablet weight and size[10].

3. Magnesium Stearate:

Role in Formulation:

Lubricant: Magnesium stearate is used as a lubricant in the final stage of tablet formation. It reduces friction during tablet compression, preventing the tablet from sticking to the punches and die of the tablet press.

Flow Enhancer: It also improves the flowability of the powder blend, ensuring that it moves smoothly into the tablet press.

Tablet Finish: Magnesium stearate helps achieve a smooth surface and consistent quality in the finished tablets.

Properties: Magnesium stearate is a hydrophobic fatty acid, which is highly effective in reducing friction and preventing caking during powder handling. However, it must be used in small amounts (usually around 0.5–1%) because excessive amounts can interfere with drug release in sustained-release formulations[11].

4. Agar:

Role in Formulation:

Gelling Agent: Agar is a natural polysaccharide derived from red algae and is used in some sustained-release formulations as a gelling agent. It forms a gel-like structure in the presence of water, which helps control the release of the active drug from the tablet matrix.

Matrix System: In sustained-release tablets, agar contributes to forming a hydrophilic matrix that swells when exposed to gastrointestinal fluids, allowing for gradual drug release.

Properties: Agar has excellent gelling properties, and its ability to form a gel allows for controlled hydration and swelling, which is ideal for extended-release formulations. It can help maintain a steady drug release rate, preventing a rapid burst of drug release[12].

5. Microcrystalline Cellulose (MCC):

Role in Formulation:

Binder and Filler: MCC serves as both a binder and a filler in tablet formulations. It holds the powder ingredients together, ensuring that the tablet remains intact during compression. It also adds bulk to the formulation.

Controlled Release: As a matrix material, MCC helps control the release of the drug over time. It can swell in the presence of water, forming a gel that slows the release of the drug.

Enhancing Tablet Mechanical Properties: MCC helps improve the compressibility and tablet hardness, ensuring that the tablets are robust enough to withstand handling without breaking.

Properties: MCC is highly porous, which aids in the absorption of water and promotes gradual drug release. It is also biocompatible and inert, making it a reliable excipient for controlled-release formulations[13].

6. PVP K30 (Polyvinylpyrrolidone K30):

Role in Formulation:

Binder: PVP K30 is used as a binder in the granulation process, ensuring that the powdered ingredients stick together during tablet formation. It improves the cohesiveness of the granules, making them easier to compress into tablets.

Solubilizer: PVP K30 can also act as a solubilizing agent, especially in formulations containing poorly soluble drugs like metronidazole. It can improve the dissolution rate and help achieve consistent drug absorption.

Granulation Aid: In wet granulation, PVP K30 forms a viscous solution that helps bind particles together, improving granule formation and uniformity.

Properties: PVP K30 is water-soluble, non-toxic, and has excellent adhesive properties, making it ideal for use in pharmaceutical formulations. It forms a clear solution when dissolved in water and helps enhance tablet hardness and dissolution characteristics[14].

7. Talc:

Role in Formulation:

Lubricant and Glidant: Talc is primarily used as a lubricant and glidant in tablet formulations. It reduces friction during tablet compression and ensures that the powder mixture flows smoothly into the tablet press.

Preventing Sticking: Talc helps prevent the tablet from sticking to the punches and die of the tablet press during manufacturing.

Improving Tablet Appearance: Talc contributes to the smoothness and finish of the tablet surface, improving the overall aesthetic and functional quality of the tablet.

Properties: Talc is a fine, soft mineral (magnesium silicate) that is highly adsorbent and lubricating, making it effective in improving the flow of powders and the smoothness of tablet surfaces[15].

Formulation Table:

Ingredient	Function	Per Tablet (mg)
Metronidazole	Active ingredient	150
Agar	Matrix former	18
MCC (Microcrystalline Cellulose)	Diluent	12
PVP K30	Binder	5
Calcium Chloride	Cross-linking agent	5
Talc	Glidant	5
Magnesium Stearate	Lubricant	5
Total Weight		200 mg

Step by Step Procedure

1. Pre-formulation Studies

Objective: To determine the compatibility and characteristics of metronidazole and excipients.

Physicochemical Characterization of Metronidazole:

Solubility: Check the solubility of metronidazole in different solvents to understand its bioavailability.

Particle Size: Measure the particle size and distribution. Metronidazole's dissolution rate depends on its particle size.

Stability: Evaluate the stability of metronidazole in the intended formulation under various conditions of temperature and humidity.

Selection of Excipients:

Choose excipients based on the drug release mechanism, such as Hydroxypropyl Methylcellulose (HPMC) or Polyvinylpyrrolidone (PVP) for sustained-release properties.

2. Granulation Process

Objective: To convert the powder blend into granules that are easier to compress.

A. Wet Granulation:

Step 1: Weighing of Ingredients

Accurately weigh metronidazole and all excipients (MCC, PVP K30, calcium chloride, agar, etc.) according to the formulation.

Step 2: Blending of Powders

Blend metronidazole with excipients such as Microcrystalline Cellulose (MCC), Agar, and Calcium Chloride in a suitable mixing equipment (e.g., a rapid mixer granulator) to achieve a homogeneous mixture.

Step 3: Preparation of Granulation Liquid

Dissolve PVP K30 in water or alcohol to create a binder solution.

Step 3: Granulation

Add the binder solution slowly to the blended powder mixture while continuously mixing. The mixture should form a cohesive, moist mass.

Step 4: Drying

Dry the granulated mass using a fluidized bed dryer or tray dryer to reduce the moisture content to an optimal level (around 2–4%).

Step 5: Screening of Granules

After drying, pass the granules through a sieve (usually 20–40 mesh) to ensure uniform granule size for uniform compression

Formulation of the Sustained-Release Matrix

Objective: To design a matrix system that allows controlled drug release.

Step 1: Blending of Granules

Mix the prepared granules with excipients like Talc (as a glidant) and Magnesium Stearate (as a lubricant) to improve the flow and compression characteristics of the granules.

Step 2: Incorporation of Controlled-Release Polymers

If using a hydrophilic matrix, mix Hydroxypropyl Methylcellulose (HPMC) or Agar to form a controlled-release system.

These polymers will swell upon contact with water, creating a gel matrix that controls the rate of metronidazole release.

Step 3: Final Blending

Ensure that all ingredients are thoroughly mixed, ensuring uniformity in the tablet formulation.

5. Tablet Compression

Objective: To compress the granules into tablets of uniform size and weight.

Step 1: Compression Set up the tablet press machine. The die size and punch shape should be selected to meet the desired tablet size and shape.

Step 2: Compression of Granules

Compress the final granules into tablets using a rotary tablet press. Apply controlled compression force to achieve tablets with the desired hardness, weight, and appearance.

Step 3: Tablet Testing

Test for tablet hardness and friability to ensure that the tablets are durable enough to withstand handling during packaging.

6. Tablet Coating (Optional)

Objective: To provide additional control over drug release or to mask taste.

Step 1: Film Coating (if required)

Apply a thin coating of film (e.g., ethyl cellulose or HPMC for further release control or aesthetic purposes).

The coating can also serve to mask the taste of the metronidazole, which is often bitter.

Step 2: Enteric Coating (if required)

If needed, apply an enteric coating to protect the drug from stomach acid, ensuring that it is released only in the intestines.

7. Evaluation of Tablets

Objective: To evaluate the quality, safety, and effectiveness of the sustained-release tablets.

Step 1: Tablet Weight Variation

Ensure uniformity in tablet weight by checking several tablets for consistency.

Step 2: Tablet Hardness and Friability

Measure the hardness of the tablets (e.g., using a hardness tester). Tablets should be sufficiently hard but not too brittle.

Friability testing ensures that the tablets can withstand handling and transport without breaking or crumbling.

Step 3: Disintegration Test

Test the disintegration time using a disintegration apparatus. The tablets should disintegrate slowly, consistent with the sustained-release design.

Step 4: Dissolution Testing

Conduct in vitro dissolution tests to evaluate how the drug is released over time.

Use a suitable dissolution medium (e.g., phosphate-buffered saline or 0.1N HCl) and study the release profile over several hours. The release should be slow and steady, showing sustained release.

8. Stability Testing

Objective: To ensure the stability and shelf life of the sustained-release tablets.

Step 1: Accelerated Stability Testing

Store tablets under accelerated conditions (e.g., high temperature and humidity) to assess stability over time. This helps predict the shelf life of the tablets.

Step 2: Long-Term Stability

Store tablets at recommended conditions (usually room temperature and controlled humidity) and periodically test them for physical appearance, dissolution profile, and potency.

9. Packaging

Objective: To package the tablets for storage and transport.

Step 1: Blister Packaging

Package the tablets in blister packs or bottles, depending on the market requirements and stability considerations.

Ensure that packaging protects the tablets from moisture and light.

Step 2: Labeling

Label the product with necessary information, including dosage, expiration date, storage conditions, and batch number[16].

Pre-Compression Parameters:

Bulk Density:

An accurately weighed sample was carefully introduced into a 10ml graduated cylinder with the aid of funnel. Typically, the initial volume was noted. Carefully levelthe product without copacting, if necessary, and read the unsettled apparent volume V0, to the nearest graduated unit. Calculate the bulk density in g/cm3 by the formula.

Bulk Density = Weight of Sample/Volume of Sample

Tap Density:

The tapped density was obtained by dividing the mass of a powder by the tapped volume in cm. The sample is carefully introduced into a 10ml graduated cylinder. The cylinder was dropped at 2 second intervals onto a hardwood surface 100 times from a height of 1 inch. The tapped density of each formulation was then obtained by dividing the weight of sample in grams by the final tapped volume in cm3 of the sample contained in the cylinder. It was calculated by using equation given below

Tap Density = Weight of Sample/Tapped Volume

Carr's Index:

The Carr's index was evaluated for the flow ability of the powder by comparing the pour density and tapped density of dispersion

Carr's Index= Tap Density-Bulk density/Tap density×100

Hausner's Ratio:

Hausner's ratio (H), another index of flow ability (O'Donnell, P. et.al 1997)

Hausner's Ratio = Tap density/Bulk density

Angle of Repose:

A weighed quantity of granules was passed through a funnel fixed on a stand at a specific height. A static heap of powder with only gravity acting upon it was tending to form a conical mound. The height of the heap (h) and radius (r) of lower part of cone were measured.

Tan θ = height of pile/radius of pile[17].

Post-Compression Study:

Weight Variation Test:

For the weight variation test, 20 tablets from each batch were selected at random and their average weight was determined using an electronic balance. Then, the average weight was calculated and compared with the individual weight of each tablet.

Hardness Test:

A Monsanto hardness tester (Cad Mach) was used to determine the hardness of the tablets. Ten tablets were selected at random from each batch for the study. Each tablet was placed between the plungers and the handle was pressed, and the force of the fracture was recorded. Their crown to crown thickness was also determined using a vernier caliper.

Friability Test:

The friability was determined by placing 10 tablets in a Roche friability tester for 4 min at 25rpm. The tablets were dropped at a height of 6 inches in each revolution. Tablets were de-dusted using a soft muslin cloth and reweighed.

The friability was given by the formula: Friability = (1-Wo/W) × 100

Where, Wo is the weight of the tablets before the test and W is the weight of the tablet after the test[18].

RESULT AND DISCUSSION:

The study aimed to formulate a 200 mg sustained-release (SR) matrix tablet of Metronidazole using agar as a natural polymer and calcium chloride as a cross-linker, ensuring sustained drug release over 8–12 hours.

Pre-Compression Evaluation:

Parameter	Observation	Standard	Remarks
Angle of Repose	26.7°	< 30° = Good	Good flow property
Bulk Density	0.51 g/cm³	—	—
Tapped Density	0.59 g/cm³	—	—
Carr's Index	13.5%	5–15% = Good	Acceptable
Hausner's Ratio	1.16	< 1.25 = Good	Good flowability

Post-Compression Evaluation:

Parameter	Result	Standard Limit	Conclusion
Tablet Weight	200.4 ± 1.3 mg	±5%	Within acceptable range
Hardness	6.3 ± 0.4 kg/cm²	4–8 kg/cm²	Satisfactory mechanical strength
Friability	0.45%	< 1%	Pass

In Vitro Drug Release (Phosphate buffer pH 6.8):

Time (hr)	% Drug Release
1	18.2%
2	27.9%
4	45.5%
6	62.3%
8	76.9%
10	88.7%
12	95.4%

CONCLUSION:

The present study successfully developed a sustained-release formulation of Metronidazole (200 mg) using agar and calcium chloride as matrix-forming agents. The formulated tablets exhibited satisfactory pre-compression and post-compression parameters, including acceptable hardness, friability, weight variation, and uniform drug content, aligning with pharmacopeial standards (USP, 2020)

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