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AN OVERVIEW: METRONIDAZOLE TABLETED MICROSPHERE FOR COLONIC DELIVERY

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ABSTRACT

Microspheres are small spherical particles typically ranging from a few micrometers to a few millimeters in diameter. They are often used as drug carriers due to their high surface area-to-volume ratio, which allows for controlled drug release and targeting. Microspheres can be made from various materials, including polymers, ceramics, and lipids. Tableting is a common pharmaceutical manufacturing process used to compress powders or granules into solid tablets. Tablets are convenient dosage forms that offer accurate dosing, ease of administration, and stability. By incorporating microspheres into tablets, the benefits of both dosage forms can be combined. Tableted microspheres refer to a dosage form that combines the advantages of microspheres with the convenience of tablets.

KEYWORDS: Microsphere, Colon, Tablet, Amoebiasis.

INTRODUCTION

Colonic drug delivery refers to the targeted release of pharmaceutical substances specifically in the colon region of the gastrointestinal tract. This method is employed to improve the therapeutic efficacy and reduce the side effects of certain drugs by delivering them directly to the colon.

There are several reasons why drugs might be targeted to the colon:[1]

- Treatment of Colonic Diseases: Drugs designed to treat conditions such as inflammatory bowel disease (IBD), colitis, or colorectal cancer can benefit from targeted delivery to the colon.

- Local Action: Some drugs act locally in the colon, such as drugs for treating colon cancer or localized infections.
- Systemic Absorption: Certain drugs are absorbed more efficiently in the colon due to its unique physiology, which can help in achieving desired therapeutic levels while minimizing systemic side effects.

Various techniques are employed to achieve colonic drug delivery[2]

1. **pH-Sensitive Coatings:** A lot of formulations include pH-sensitive coatings, which dissolve and release the medication when they reach the more neutral pH of the colon but do not break down in the acidic environment of the stomach and small intestine.
2. **Time-Release** Formulations: These formulations make sure the medication reaches the colon undamaged by releasing the drug after a certain amount of time.
3. **Microbial Degradation**: When a medication is conjugated with polysaccharides, colonic bacteria break them down and release the active ingredient.
4. **Prodrug Approach:** Prodrugs are inert substances that the colon metabolizes to produce the active medication.

Colonic drug delivery systems offer several advantages, including enhanced drug bioavailability, reduced systemic side effects, and improved patient compliance. However, challenges such as variability in colonic transit time and potential interindividual differences in colonic physiology need to be addressed in the design and development of these delivery systems.[3]

TYPES OF COLONIC DRUG DELIVERY

There are various types of colonic drug delivery systems designed to target pharmaceutical substances specifically to the colon. Here are some common types:[4]

1. **pH-Dependent Systems**: These systems take use of the variations in pH throughout the digestive system. The purpose of coatings and formulations is to release the medication by dissolving in the more neutral pH environment of the colon while resisting breakdown in the acidic environment of the stomach and small intestine.
2. **Time-Controlled Release Systems**: These systems are designed to release the drug after a predetermined period, ensuring that it reaches the colon intact. Various mechanisms such as erosion, diffusion, or osmosis control the release of the drug.

3. **Microbially Triggered Systems**: These systems take advantage of the enzymatic activity of colonic bacteria. The drug is conjugated with polymers or other materials that are degraded by colonic bacteria, releasing the active drug at the desired site.
4. **Coating with Enteric Polymers**: Enteric coatings are used to protect the drug from degradation in the stomach and small intestine and ensure its release in the colon. These coatings can be pH-dependent or time-dependent.
5. **Prodrug Approach**: Prodrugs are inactive compounds that are metabolized in the colon to release the active drug. This approach can enhance colonic drug delivery by utilizing enzymatic activity in the colon to convert the prodrug into its active form.[5]
6. **Microbial-Triggered Delivery**: Some systems utilize bacteria-specific enzymes to trigger drug release. These systems rely on the presence of specific bacterial strains in the colon to activate drug release.
7. **Multi-Particulate Systems**: In these systems, drugs are encapsulated in microspheres or nanoparticles, allowing for controlled release and targeting to specific regions of the colon.
8. **Bioresponsive Systems**: These systems respond to changes in physiological parameters such as pH, enzymes, or bacterial activity in the colon to trigger drug release. They can be designed to release the drug in response to specific colonic conditions.

Each of these colonic drug delivery systems has its advantages and limitations, and the choice of system depends on factors such as the physicochemical properties of the drug, desired release kinetics, and patient-specific considerations.

ADVANTAGES OF COLONIC DRUG DELIVERY[6]

Colonic drug delivery offers several advantages over conventional drug delivery methods:

- **Targeted Drug Delivery**: Colonic drug delivery systems allow for the targeted release of drugs specifically in the colon region of the gastrointestinal tract. This targeted delivery can enhance the therapeutic efficacy of drugs intended to treat colonic diseases or conditions localized in the colon.
- **Reduced Systemic Side Effects**: By delivering drugs directly to the colon, colonic drug delivery systems can minimize systemic exposure to the drug, reducing the risk of systemic side effects. This is particularly beneficial for drugs with potential adverse effects on other organs or systems in the body.

- **Improved Bioavailability**: The colon has a unique physiology that can enhance the absorption of certain drugs. Colonic drug delivery systems can take advantage of this physiology to improve drug bioavailability, ensuring that therapeutic levels of the drug are achieved more efficiently.
- **Enhanced Patient Compliance**: Many colonic drug delivery systems offer controlled or sustained release of drugs, reducing the frequency of dosing and improving patient compliance. This is especially important for chronic conditions requiring long-term medication regimens.
- **Protection of Labile Drugs:** Certain medications are susceptible to deterioration in the stomach's acidic environment or in the small intestine's enzymatic activity. Colonic drug delivery systems, which avoid the stomach and small intestine and transfer the medication directly to the colon, can prevent the degradation of these labile medicines.
- **Treatment of Colonic Diseases**: Colonic drug delivery systems are particularly useful for the treatment of colonic diseases such as inflammatory bowel disease (IBD), colitis, or colorectal cancer. By delivering drugs directly to the affected area, these systems can improve therapeutic outcomes and reduce the risk of systemic side effects.
- **Improved Pharmacokinetics**: Colonic drug delivery systems can optimize the pharmacokinetics of drugs by controlling their release kinetics and absorption profiles. This can lead to more predictable drug levels in the body and improved therapeutic outcomes.

Overall, colonic drug delivery offers a promising approach to enhance the efficacy, safety, and patient compliance of various pharmaceutical treatments, particularly those targeted to the colon or associated with colonic diseases.[7]

DISADVANTAGES OF COLONIC DRUG DELIVERY[8]

While colonic drug delivery offers several advantages, it also has some limitations and potential disadvantages:

- **Variable Transit Time**: The transit time of drugs through the gastrointestinal tract, including the colon, can vary significantly among individuals and under different physiological conditions. This variability may affect the consistency and reliability of drug delivery to the colon.
- **Risk of Incomplete Release**: In some cases, colonic drug delivery systems may not achieve complete release of the drug in the colon, leading to suboptimal therapeutic

outcomes. Factors such as formulation characteristics, colonic motility, and gastrointestinal conditions can influence drug release and absorption.

- **Limited Drug Compatibility**: Not all drugs are suitable for colonic drug delivery. Some drugs may have poor solubility or stability in the colonic environment, limiting their effectiveness when delivered to the colon.
- **Potential for Irritation or Toxicity**: Colonic drug delivery systems may cause irritation or toxicity in the colon, particularly if they contain excipients or additives that are not well tolerated by the gastrointestinal mucosa.
- **Complex Formulation Requirements**: Designing colonic drug delivery systems requires careful consideration of formulation factors such as pH sensitivity, coating materials, and release kinetics. Developing and manufacturing these formulations can be complex and costly.
- **Risk of Colonic Microbiota Alteration**: Some colonic drug delivery systems rely on microbial degradation to release the active drug. Alterations in the composition or activity of colonic microbiota, such as those caused by antibiotics or dietary changes, may affect drug release and efficacy.
- **Potential for Colon-Specific Side Effects**: Targeting drugs specifically to the colon may increase the risk of colon-specific side effects such as diarrhoea, constipation, or mucosal irritation.
- **Limited Applications**: Colonic drug delivery may not be suitable for all therapeutic applications or patient populations. Certain conditions or anatomical variations may limit the effectiveness of colonic drug delivery systems.

Overall, while colonic drug delivery offers several advantages, careful consideration of its limitations and potential disadvantages is necessary to ensure safe and effective drug delivery to the colon.[9]

Several strategies can be employed to target orally administered drugs to the colon:[10]

- **pH-Dependent Release Systems**: Utilize pH-sensitive coatings or formulations that resist degradation in the acidic environment of the stomach and small intestine but dissolve in the more neutral pH environment of the colon, releasing the drug specifically in the colon.

- **Time-Controlled Release Systems**: Design formulations that release the drug after a predetermined period, ensuring its arrival in the colon intact. Various mechanisms such as erosion, diffusion, or osmosis can control the release kinetics.
- **Microbially Triggered Release Systems**: Exploit the enzymatic activity of colonic bacteria to trigger drug release. Drugs are conjugated with polymers or materials that are degraded by colonic bacteria, releasing the active drug at the desired site.
- **Coating with Enteric Polymers**: Apply enteric coatings to protect the drug from degradation in the stomach and small intestine and ensure its release in the colon. These coatings can be pH-dependent or time-dependent.
- **Prodrug Approach**: Design prodrugs that are inactive until metabolized in the colon, releasing the active drug. This approach can utilize enzymatic activity in the colon to convert the prodrug into its active form.
- **Multi-Particulate Systems**: Encapsulate drugs in microspheres or nanoparticles to allow for controlled release and targeting to specific regions of the colon. These systems can provide enhanced drug localization and absorption.
- **Bioresponsive Systems**: Develop systems that respond to changes in physiological parameters such as pH, enzymes, or bacterial activity in the colon to trigger drug release. These systems can be designed to release the drug in response to specific colonic conditions.
- **Microbial-Triggered Delivery**: Utilize bacteria-specific enzymes to trigger drug release. These systems rely on the presence of specific bacterial strains in the colon to activate drug release.

Each of these strategies offers unique advantages and challenges, and the choice of approach depends on factors such as the physicochemical properties of the drug, desired release kinetics, and patient-specific considerations. Combination approaches may also be employed to enhance the targeting efficiency of orally administered drugs to the colon.[11]

METHOD OF PREPARATION

- **Preparation of microspheres**: Solvent evaporation was used to create the enteric coated microspheres. Table provided the medication to polymer ratio used in the preparation of the enteric coated microspheres. Using a magnetic stirrer, the polymer was dissolved in 10 millilitres of acetone to create the solution. After then, the medication was scattered throughout the polymer solution. After that, the resultant dispersion was added to a 250

ml vessel together with 30 ml of liquid paraffin, and it was stirred at a minimum speed of 1000 rpm. After two hours of stirring, all of the acetone evaporated. The microspheres that were created after the acetone evaporated were filtered and given four or five hexane washes. The cleaned microspheres were then collected after drying at room temperature.

- **Preparation of tabletted microspheres:** Using Mg stearate 27 as lubricant, cross-povidone as binder, and microcrystalline cellulose as diluents, the optimized MNZ loaded microspheres were compressed to create tablets. A 250 mg tablet was made, and the formulations of batches 1, 2, and 3 (F5, F8, and F14) were optimized to compress a 10 mg tablet of medication. The tablets were coded T1, T2, and T3 for each batch. Table shows the quantity of excipients needed to make a 250 mg tablet and the quantity of microspheres comparable to a 10 mg medication.[69]

Table 1: Formulation Table of Tableted Microspheres.

S.No.	Formulation Code	MNZ Microspheres (mg)	Cross Povidone (mg)	Mg Stearate (mg)	Microcrystalline cellulose (mg)
1.	**T1**	142.5	11.40	2.85	93.25
2.	**T2**	88	7.04	1.76	153.2
3.	**T3**	122.5	9.80	2.45	115.25

Table 2: Materials used in the formulation of Microsphere.

S. No	Chemical Required
1.	Cellulose Acetate Phthalate
2.	HPMC Phthalate
3.	EudragitS100
4.	Light Liquid Paraffin
5.	Polyvinyl Alcohol(cold)
6.	n- Hexane
7.	Hydrochloric Acid
8.	Acetone
9.	Sodium Hydroxide(pellets)
10.	Potassium Dihydrogen Phosphate
11.	Disodium Hydrogen Phosphate

EVALUATION OF MICROSPHERES[70]

- **Percentage yield:** By dividing the weight of the microspheres by the total weight of the additional materials, the percentage yield of microspheres was determined.

$$\text{Percentage yield} = \frac{\text{The amount of microspheres obtained (gm)} \times 100}{\text{The theoretical amount (gm)}}$$

- **Drug content**

Drug content of microspheres was determined by UV spectrophotometer. A weighed amount (equivalent to 25 mg of drug) of drug loaded microspheres was extracted and the absorbance was taken at the specific wavelength to calculate the concentration. The experiment was done in the triplicate.

$$\text{Actual drug content} = \frac{\text{Weight of the drug in microspheres} \times 100}{\text{Weight of the microspheres}}$$

- **Particle size analysis**

The properties of release are mostly determined by particle size analysis. Optical microscopy was used to determine the microspheres' particle size. Using an optical microscope-equipped ocular micrometer and stage micrometer, the project diameter of the microspheres from each formulation was measured. Under a microscope, the slide containing the microspheres was examined in order to perform analysis. By measuring close to 500 particles using an estimated ocular micrometer, the mean particle size was determined.

- **In vitro release studies**

To release the drug from the microspheres, the USP type II (name model) dissolution paddle assembly was used. Enteric coated microspheres weighing 10 mg of medication were distributed in 250 ml of 0.1 N HCl (pH 1.2), which was kept at 37±0.5℃ and swirled at 100 rpm. For two hours, 5 ml of the solution was taken out and added back in every 15 minutes to keep the volume constant. After that, phosphate buffer pH 7.4 was added in place of the dissolving media, and the 5 ml solution was removed until a steady release was seen. Following an appropriate dilution, the sample was subjected to spectrophotometric analysis at a designated wavelength.

EVALUATION OF TABLETS[71]

- **Thickness**

Using calibrated dial callipers, the thickness and diameter of the tablets were measured after a random selection of tablets from each batch. It has a standard deviation of computed and is stated in millimeters.

- **Hardness test**

A tablet's hardness level reveals how well it can tolerate handling-related mechanical shocks. A hardness tester was used to assess the core tablet's hardness. It is stated as kg/cm^2. From

each batch, three tablets were chosen at random and their hardness was measured. Calculations were also being done for the mean and standard deviation.

- **Weight Variation**

Twenty tablets were randomly chosen from each batch, and the average weight was calculated. The tablet was then weighed individually, and the weight difference was reported as a percentage variance after the weight of each tablet was compared to an average weight.

- **Friability test**

The Roche Friabilator (Campbell Electronics, Mumbai, India) was used to test the friability of six tablets for each formulation. This formula can be used to determine friability.

$$F = \frac{Wt_{initial} - Wt_{final} \times 100}{Wt_{initial}}$$

- ***In vitro* disintegration test**

One tablet was used for each of the six tubes in the basket to facilitate the breakdown of the tablets. The assembly was then hung in a beaker filled with 0.1 N HCl (pH 1.2), and the apparatus was left running without the disc for 120 minutes. After the assembly was taken out of the liquid and checked for cracks, the beaker's liquid was replaced with phosphate buffer (pH 7.4). After that, the assembly was once more suspended in the beaker and the temperature was kept at 37±2℃. Every minute, the assembly was lifted and dropped 30 times. The amount of time required for the tablet to completely dissolve and leave no discernible mass inside the device was timed and recorded. Three duplicates of the experiment were conducted.

- ***In vitro* drug release studies**

The USP type II paddle method was used to study the dissolution rate of conventional and microsphere tablets at pH 1.2 for two hours, and then at pH 7.4 in phosphate buffer at 50 rpm until the medication was fully released from the tablet under sink conditions at 37±0.5℃. To maintain a constant volume, aliquots were taken out at certain intervals and replaced with an equivalent volume of dissolving medium. Following an appropriate dilution, the material was examined.

DRUG RELEASE KINETIC DATA ANALYSIS[72]

Several kinetic models have been proposed to describe the release characteristics of a drug from the matrix, these are as following

- **Zero order kinetics**

When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order is linear in such plot, indicating that the release rate is in-dependent of concentration.

$$Qt = Q0 + k0t$$

Where, Q0 is the initial amount of the drug in the dosage form, Qt is amount of drug in the dosage form at time t and k0 is zero order rate constant.

- **First order kinetics**

$$Qt = Q0e - kt \text{ or } lnQt = lnQ0 + kt$$

Where, Qt is the amount of the drug released in time t, Q0 is the initial amount of the drug in the solution and k is first order rate constant.

- **Higuchi Model**

$$Qt = KHt1/2$$

Where, Qt is the amount of the drug released in time t, and KH is Higuchi dissolution constant.

- **Kores Meyer-Peppas Model**

$$Qt = Kptn \text{ or } logQt = logKp + nlogt$$

Where, Qt is the amount of the drug released in time t, Kp is Koresmeyer-peppas release rate constant and n is the diffusion exponent. The release rate constants k and n of each model were calculated by linear regression analysis. Coefficient of determination (r2) was used to evaluate the accuracy of fit.

- **Hixson-Crowell Model**

Hixson and Crowell (1931) recognized that the particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner.

$$W01/3 - Wt1/3 = Kst$$

Where, W0 is the initial amount of drug in pharmaceutical dosage form, Wt is the remaining amount of the drug at time t in dosage form and Ks is an s constant incorporating the surface volume relation. This relation applies to pharmaceutical dosage form such as tablet.

DISCUSSION AND CONCLUSION

It is well known that Amoebiasis is a colon related disease caused by the protozoa E. Histolytica. It is successfully cured by MNZ which kills the protozoa, but problem related with it, its solubility in the gastric region. So, its delayed release is necessary to achieve the complete absorption of drug in colon. In above study delayed release was achieved by coating of drug with pH dependent polymer, which also prevents the bitter taste of drug. Thus, this experimental work can be used in future to improve the patient compliance and absorption of drug in colon to successfully cure of the disease.

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