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Controlled Release Formulations of Metronidazole: A Comprehensive Review

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KEYWORDS

Metronidazole, Controlled release, Mucoadhesive formulation, Patient compliance.

ABSTRACT:

Background: Metronidazole antibiotic which are used in treatment of anaerobic bacteria and protozoa It has a short half-life drug out from body very quickly, as a results patients are required to take multiple doses throughout a day to maintain its therapeutic effect. For long term use may lead to missed doses So this can make treatment inconvenient. To improve long term patient compliance and drug delivery-controlled release (CR) formulations of metronidazole introduced, these systems release metronidazole slowly over an extended period several types of delivery systems like biodegradable carriers, mucoadhesive, micro particles increase retention time of drug at the site of infection. For example, natural polymer like alginate and chitosan have also been make more biocompatible and safer for long term used. With new techniques are launched hot melt extrusion and spray drying it can create more reliable and with maintain drug stability and reproducible formulations and precise control for fast drug is released.

Conclusions: Controlled release of metronidazole have several advantages from traditional medicinal forms its better treatment in both systemic and localized infections especially for in specific site of treating chronic infections. These innovations give better therapeutic compliance and patient easier to administration.

1. Introduction

Metronidazole synthetic nitro imidazole class of antibiotic widely used due to broad spectrum activity against anaerobic activity and protozoa. its play a vital role in treatment of vaginosis and trichomoniasis amebiasis, clostridium difficile associated diarrhea, other gastrointestinal and periodontal infections [1-3]. One of major conventional drawback is short half-life approximately 6 to 8 hours, due to its frequent necessities of dosing required to maintain effective plasma concentrations [4-5]. This frequent dosing can lead to poor patient adherence and increased chances of adverse effects, in long term therapies, the bitter taste of metronidazole in oral formulations affecting administration particularly among paediatric and geriatric populations [6]. To overcome these drawbacks researcher have explored controlled release (CR) deliver systems, which offer deliver of metronidazole at a constant rate over an extended period.CR formulations are designed to maintain therapeutic drug levels in the plasma or at the site of infection, reduce dosing frequency, and overall treatment enhance outcomes [7-8]. Controlled release formulations are useful in where metronidazole is required for sustained local action such as vaginal mucosa, colon, periodontal pockets [9].

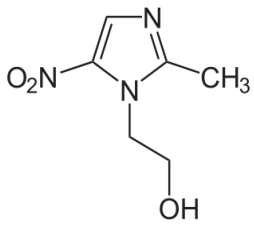

Figure 1: Structure of Metronidazole 2- (2methyl-5-nitro-1H-imidazol-1-yl) ethanol

Different types of CR systems are developed for metronidazole like matrix tablets, bio-adhesive gels, microspheres, nanoparticles and vaginal and rectal formulations [10-12]. chitosan and alginate based mucoadhesive gels used for vaginal infections improved local efficacy and increase longer residence time and Similarly colon-targeted systems that utilize pH-sensitive polymers or enzyme-triggered release mechanisms and to deliver metronidazole directly to the large intestine, minimize systemic absorption and

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maximizing local action [13]. In formulation techniques, such as hot-melt extrusion, spray drying, and solvent evaporation, still enabled the creation of reliable and reproducible CR systems. In recent years, innovative technologies like 3D printing have opened new doors for producing customized drug delivery platforms that deals with patient-specific needs and pharmacokinetic requirements [14]. These drug deliveries not only enhance therapeutic performance but also support the move toward personalized medicine.

In overall summary of how traditional medicine of metronidazole to controlled release of metronidazole are significant shift. By addressing issues related to dosing frequency, drug targeting, and patient compliance, these novel drug delivery systems have highly impact in clinical management of infectious diseases.

Reasons for Metronidazole's Controlled Release:

Short Biological Half-Life

Its biological half-life of roughly 6–8 hours, metronidazole must be taken several times a day in order to maintain therapeutic plasma concentrations. Then treatment results may result from this frequent dosing schedule and decreased patient compliance [15].

Bitter Taste (Oral Masking Required)

One major problem with metronidazole is its unpleasant, bitter taste, which is particularly old and paediatric patients. By reducing the amount of time, a drug is exposed to the taste buds, controlled-release matrix systems can increase its acceptability and palatability [16].

Dosing Must Be Done Frequently

Poor adherence may result from the frequent prescribing of metronidazole two to three times a day due to its short half-life and time-dependent killing mechanism. By preserving extended plasma drug levels, controlled release less need for repeated doses [17].

Fluctuation in Plasma Drug Levels

Drug plasma levels variable with conventional formulations, which can cause toxicity or sub-therapeutic concentrations. A steady-state plasma concentration is provided by controlled-release systems, which have less adverse effects and increase effectiveness of drugs [18].

Types of Controlled Release Formulations

Controlled release (CR) formulations are designed to deliver drugs over an extended period, ensuring stable therapeutic levels and reduced dosing frequency. Common types include:

Matrix Systems: Diffusion and erosion are the methods by which drugs are released from hydrophilic (like HPMC) or hydrophobic (like ethyl cellulose) polymers [19].

Reservoir systems: which are zero-order release kinetics but needs intricate fabrication, have a rate-controlling membrane encircling the drug core [20].

Osmotic Systems: These systems use osmotic pressure to regulate the release of drugs through semi-permeable membranes; the release is not affected by food or pH [21].

Mucoadhesive systems are perfect for localized therapy because they prolong residence time at mucosal sites (oral, vaginal, and rectal) [22].

Topical Controlled Release

In dermal or vaginal infections, topical controlled-release formulations of metronidazole have hydrogels and emulgels, allow for localized delivery with less systemic exposure [23]. Bacterial vaginosis can be effectively treated with bio adhesive gels because they have long-lasting antimicrobial activity and retention [24]. Targeted delivery to mucosal sites is vaginal and rectal systems, such as suppositories and mucoadhesive gels, which enhance treatment results for local infections [25]. Because metronidazole's high polarity and low lipophilicity restrict skin penetration. So that transdermal drug delivery systems have received less attention [26].

Formulation Techniques for Controlled Release of Metronidazole

Wet and Dry Granulation

In order to create compressible powders for tablet manufacturing, granulation is necessary. In wet granulation, a binder solution (such as PVP or HPMC) is mixed with metronidazole then dried and compressed into tablets. This technique improves content homogeneity and flow ability particularly in hydrophilic polymer-based sustained-release matrix tablets [27].

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For medications that are sensitive to moisture, in dry granulation using roller compaction or slugging is recommended. Using dry granulation with polymers such as Carbopol and HPMC K15M, Elkomy et al. created floating sustained-release metronidazole tablets, which resulted in controlled release over a 12-hour period and prolonged gastric retention [28].

Evaporation of Solvents in Microspheres and Microcapsules

In this method microspheres or microcapsules frequently used. A volatile organic solvent is used to dissolve or disperse the drug and polymer (such as PLA, ethyl cellulose, or Eudragit) before they are emulsified in an aqueous phase. Solid microspheres are created in case of when solvent evaporates. Using ethyl cellulose and the solvent evaporation technique Ghosh and Majithiya created metronidazole microspheres that demonstrated high entrapment efficiency and sustained release profiles over a 10-hour period [29].

Ionotropic Gelation (Beads and Nanoparticles)

Ionotropic gelation is a mild and aqueous-based method used to prepare beads or nanoparticles, especially with alginate, pectin, or chitosan. In this technique, metronidazole is dispersed in a polymeric solution (e.g. sodium alginate) then dropped into a crosslinking solution (e.g., calcium chloride) and forming gel beads. Krishnaiah et al. developed alginate-based beads for colon-targeted delivery of metronidazole using this method, achieving release in the colonic region with minimal gastric release [30].

Extrusion by Hot Melt (HME)

To create a homogenous matrix, Hot melt involves in melting the polymer and drug together at high temperatures and pressures. It provides high number of materials passing and does away with the need for solvents. To regulate drug release, hydrophobic polymers such as ethyl cellulose or Eudragit RS are frequently employed.

Patel et al. showed that HME could create sustained-release systems with enhanced drug stability and decreased burst release without being affected underutilized for metronidazole [31].

Spray Drying

By spraying into a hot air stream, spray drying turns a drug-polymer solution into a dry powder. This process works well for creating nanoparticles, microspheres, and amorphous dispersions.

For vaginal administration, Bonferoni et al. prepared chitosan-based metronidazole microparticles using spray drying, which provided improved muco-adhesion and controlled release [32].

3D Printing (Personalized Dosing)

A state-of-the-art method that offers exact control over geometry, porosity, and drug distribution is 3D printing. Tablets with complex designs are created for personalized medicine using semi-solid extrusion and fused deposition modeling (FDM).

Moulari et al. used 3D printing to create gastro retentive tablets loaded with metronidazole. A major breakthrough in patient-specific CR therapy was made possible by the system's ability to provide customized release profiles [33].

Evaluation of Controlled Release Formulations

In-Vitro Release Studies (Using USP Apparatus I/II)

To describe CR behaviour and in vivo performance, in-vitro drug release testing is crucial. It is common practice to use USP Dissolution Apparatus I (basket) or II (paddle). Using USP Apparatus II in phosphate buffer (pH 6.8), Dowling and McCarthy [34] metronidazole release from HPMC-based matrix tablets and showed viscosity-dependent release profiles. In a similar vein, Elkomy et al. [35] investigated floating metronidazole tablets using USP II with 0.1 N HCl and reported a sustained release over a 12-hour period.

The mechanism of release is analyzed using mathematical models like Higuchi, Korsmeyer–Peppas, and zero/first-order kinetics [36].

Drug Content Uniformity

Uniform drug content verifies dose accuracy per unit, which is crucial in controlled release systems where even small changes can have a big impact on release kinetics. Usually, HPLC or UV-visible spectroscopy are used to evaluate it [37].

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metronidazole-loaded microspheres for consistent drug content, obtaining 96.4–101.2% drug loading with <5% RSD, representing exceptional content homogeneity**.**

Mucoadhesive Strength

In formulations of vaginal, buccal, or gastrointestinal mucosa mucoadhesive strength has vital role. It describes a formulation's capacity to stick to mucosal surfaces, extending residence time and enhancing localized drug action. Usually from a texture analyzer, mucin interaction assay, or modified balance method are used to measure mucoadhesion. Adhesion is significantly influenced by a polymer's capacity to hydrate and establish hydrogen bonds with mucin (e.g., chitosan, Carbopol, HPMC).

Swelling and Erosion Studies

These tests calculate the behaviour of polymeric CR systems in relation to dissolution media. While erosion aids in release through matrix breakdown, swelling affects the diffusion barrier.

The swelling index of metronidazole floating tablets made with guar gum and HPMC was measured by Kumaran et al. [38]. In 0.1 N HCl, the tablets swelled considerably, creating a gel layer that gradually regulated drug release. Erosion studies were conducted by Elkomy et al. [39], which proven that erosion played a role in the prolonged drug release in HPMC-Carbopol matrices.

Pharmacokinetic Studies (In Vivo)

In vivo pharmacokinetic (PK) studies are performed in animal models or humans to determine the controlled-release formulations affect:

- Cmax (maximum plasma concentration)
- Tmax (time to reach Cmax)
- AUC (area under the plasma concentration-time curve)
- t½ (elimination half-life)

Such studies help establish bioavailability and ensure therapeutic consistency compared to immediate-release formulations [40]. compared CR and IR formulations of metronidazole in healthy volunteers. The CR tablet showed delayed Tmax and extended plasma levels over 12 hours, confirming sustained release.

Stability Testing (as per ICH Guidelines)

To make sure the medication retains its potency, safety, and quality over time in a variety of environmental settings, stability studies are carried out. ICH guidelines (Q1A-R2) state that formulations need to go through:

- Six months of accelerated testing at 40 ± 2 °C and 75 ± 5% RH
- Long-term testing: 12–24 months at 25 ± 2 °C and 60 ± 5% RH
- Light, heat, humidity, and pH stressors are all included in stress testing.

Drug content, physical appearance, pH, viscosity, dissolution, and microbial contamination are among the parameters evaluated. Ghosh and Majithiya [41] performed 3-month accelerated testing on metronidazole microspheres. No significant change in drug content or release profile was observed, its confirming good stability.

Recent Developments in Controlled-Release Metronidazole

The mains aim development of controlled release formulations of metronidazole is increasing bioavailability and the site-specific delivery, patient compliance and the common use of chitosan and alginate matrices in nanoparticle-based systems has shown great promise for mucoadhesion and sustained release, improving targeting for gastrointestinal and periodontal infections [42]. Its local therapeutics(vaginal)applications have seen the successful development of smart hydrogels such as thermos responsive chitosan–poloxamer systems, which provide the advantages of controlled release and improved mucosal retention [43]. With a prolonged gastric residence time of more than 12 hours and exceptional in vitro floating behavior, floating drug delivery systems (FDDS) that combine bio adhesive polymers and gas-generating agents are appropriate for treating H. pylori infections [44].

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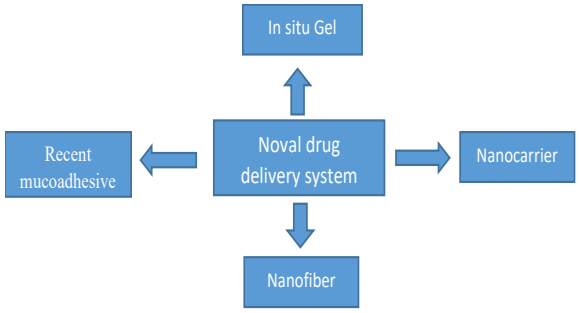

Figure 2: Fig. of Development of control Release Metronidazole

In addition, 3D printing technologies such as fused deposition modeling (FDM) allow for the precise fabrication of gastro retentive tablets designed to patient-specific needs, enabling programmable release over extended periods [45]. In addition, dual-drug delivery systems co-loading metronidazole with agents like doxycycline or enzymes (e.g., DNase) are emerging as powerful tools for synergistic therapy in mucosal and periodontal infections by enhancing bio film penetration and antimicrobial synergy [46].

Bio responsive and hybrid systems that react to physiological stimulus like pH, redox potential, enzymatic activity in oral and topical delivery systems. The precise release of metronidazole at the site of infection or inflammation is the goal of these Controlled release (CR). In thiolated polymers have been investigated because of their improved mucoadhesive and enzyme-sensitive properties, which enable localized drug activation in vaginal or colonic settings [47]. The pH-sensitive polymers such as Eudragit S100 have also used to release metronidazole selectively in the colon, which is particularly useful in the treatment of inflammatory bowel diseases and colonic infections [48] and metronidazole incorporation into electrospun nanofiber mats, composite wound dressings for dermal infections represents another significant development. These systems used for diabetic ulcers and chronic wounds because they provide local action and antimicrobial action with less systemic absorption. Because of their controlled moisture balance and biocompatibility, metronidazole-loaded chitosan mats have shown improved wound healing in addition to effective bacterial inhibition [49]. Moreover, metronidazole-loaded silica aerogels and scaffolds have been investigated for their slow degradation rates and ability to control drug diffusion over extended periods [50]. Emerging in situ forming systems, such as injectable gels and liquid crystals, offer promising parenteral delivery strategies. These systems can be administered via syringe and solidify upon contact with body solutions, forming a depot that slowly releases metronidazole over several days [51] Such systems being evaluated for abscesses and anaerobic infections where prolonged local therapy is required.

In oncology, innovative moving of metronidazole as a hypoxia-targeting agent has led to its encapsulation in lipid–polymer hybrid nanoparticles. These Nano systems exploit the hypoxic microenvironment in solid tumors for selective cytotoxicity, thereby reducing off-target effects [52] recently reported enhanced antitumor activity and reduced systemic toxicity using this approach, positioning metronidazole as a dual-functioning antimicrobial and radio sensitizer.

The 3D printing in controlled-release systems continues to grow, particularly in personalized medicine. Patients with variable gastric pH or metabolic rates can benefit from tablets with custom geometry and drug layering, offering designed of the release profiles. [53] its exhibits such gastro retentive 3D-printed scaffolds for metronidazole, with changed porosity and release kinetics based on individual patient needs.

Besides from current trends in regulatory trends and green manufacturing approaches are influencing formulation design. Biodegradable polymers, solvent-free methods (e.g., hot melt extrusion), and scalable technologies such as microfluidics are increasingly adopted to meet safety, environmental, and cost criteria [54].

Together, these developments highlight a paradigm shift away from traditional dosage forms and toward more complex, patient-centred metronidazole delivery systems.

Challenges and Future Directions in Controlled-Release Metronidazole

Metronidazole controlled-release (CR) technologies are still a number of issues with formulation science and regulatory pathways, clinical management The bitter taste of metronidazole is one of the main issues, which presents difficulties when it comes to oral and paediatric dosage forms. To improve palatability and compliance,

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the bitter profile needs the use of efficient taste-masking techniques. Although they have demonstrated some success, methods such as lipid-based microspheres, complexation with Cyclodextrins, and coating with ethyl cellulose frequently make manufacturing or impact release kinetics more difficult [55].

furthermore, it's still technically difficult to combine controlled release and taste masking in the same system. Optimizing local versus systemic delivery presents another difficulty. Local delivery systems (such as gels, hydrogels, and mucoadhesive inserts) provide targeted action and reduced systemic toxicity for vaginal or gastrointestinal infections. Oral CR tablets must provide sufficient bioavailability while preventing burst release for systemic infections, such risk for metronidazole for anaerobic bloodstream pathogens [56]. It's still a goal to design systems that can deliver metronidazole throughout at site locally and systemically openly based on clinical need. Another method major bottleneck is the scaling up of multiparticulate systems, like microspheres, beads, or pellets. While multiparticulates enhance steady drug dispersion and lower the risk of dose-dumping, their production frequently involves details procedures like fluid bed coating, extrusion-spheronization, and spray drying. It can take a lot of resources to ensure mechanical toughness and batch-to-batch reproducibility at the industrial scale [57].

Additionally, regulatory concerns continue to affect the adoption of CR systems that deal novel excipients or nanomaterials. Regulatory agencies require wide toxicity, stability, and biodegradability data before approving such materials, especially in pediatric or mucosal applications. For demand, while polymers like PLGA or chitosan are widely studied, their grade, source, and modification need comprehensive safety validation, which may delay clinical translation [58].

In Future direction the combination of CR technology with targeted delivery, such as colon-specific systems for inflammatory bowel disease (IBD) or colorectal infections. Polymers like Eudragit S100, which dissolve at pH >7, or biodegradable polysaccharides metabolized by colonic bacteria (e.g., pectin, guar gum), allow colon-targeted metronidazole delivery. However, achieving dual control over site-specific and time-controlled release technically complex and remains under development [59].

The development of 3D printing, stimuli-responsive systems, and personalized medicine may address many of these limitations. Technologies that allow customized release kinetics, patient-specific dosage, and better combination with electronic health monitoring are expected to dominate future CR systems. However, these developments must overcome scalability, cost-effectiveness, and regulatory standardization challenges before wide clinical adoption**.**

Conclusion

Metronidazole formulations with controlled release (CR) proposal an innovative method for exploiting antimicrobial treatment, especially for localized repetitive, and chronic infections. While its efficacy the traditional metronidazole therapy often demands due to their frequent dosing because of its short half-life (~8 hours), which can result in poor patient adherence and fluctuating plasma concentrations. likely steady-state plasma levels, prolonged drug release, decreased dosing frequency, and maybe fewer side effects, CR systems overcome these drawbacks.

Frequent CR systems, such as mucoadhesive tablets, hydrogels, beads, nanoparticles and 3D-printed scaffolds, have been developed as a result of recent advancements. Controlled drug delivery systems increase the bioavailability and reduce systemic toxicity and prolonging the drug's residence time at the infection site.

Its formulations have also been improved by developments in polymer science. For inflammatory bowel disorders (IBD) and anaerobic infections, pH-sensitive polymers like enzyme-degradable carriers like chitosan and pectin permit site-specific release in the colon or vaginal mucosa. and the nanoparticle-based systems that used biodegradable polymers provide targeted delivery, better penetration into biofilms.

New opportunities for creating patient-specific, customizable dosage forms with release profiles have been made possible by the use of modern manufacturing processes like hot-melt extrusion, solvent evaporation, spray drying, and mainly 3D printing. These developments are in line with the objectives of point-of-care delivery and personalized medicine.

In conclusion, CR formulations of metronidazole not only optimize drug pharmacokinetics but also improve

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therapeutic efficacy, reduce adverse effects, and enhance patient compliance. As regulatory acceptance of novel drug delivery systems and excipients improves, and as clinical data on safety and efficacy accumulates, such formulations are composed to become standard therapeutic options in managing anaerobic and chronic infections.

Consent for Publication

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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