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Review Article

A Review on Formulation and Evaluation of Mirabegron Extended-Release Tablets

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ABSTRACT

A type of modified-release dosage form known as an extended-release (ER) tablet is designed to release the active pharmaceutical ingredient (API) gradually over a long period of time. The human body metabolizes and excretes drugs at different rates. Fast drug absorption may result in peak plasma concentrations that could be harmful, whereas fast clearance in conventional formulations causes subtherapeutic levels that necessitate frequent dose. Extended-release formulations get around these issues and ensure a long-lasting therapeutic effect by modifying the kinetics of medicine release. This study includes Extended-Release Tablets' Drug Release Mechanism, benefits of extended-release tablet, limitations, Extended-release tablet development and manufacturing.

INTRODUCTION

Extended-Release Tablets

A type of modified-release dosage form known as an extended-release (ER) tablet is designed to release the active pharmaceutical ingredient (API) gradually over a long period of time[1]. As opposed to immediate-release tablets, which release the medication quickly, extended-release pills ensure maintained drug levels in the circulation, reducing dosing frequency and improving patient adherence[2].

Need of Extended-Release Tablets

The main goal of extended-release systems is to keep drug plasma concentrations within the optimal therapeutic window in order to boost efficacy and lower volatility. This approach is particularly beneficial for chronic conditions like diabetes, hypertension, pain management, and

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neurological disorders where consistent drug levels are necessary for effective disease control[3].

Extended-Release Tablets' Drug Release Mechanism

Numerous processes govern the controlled release of pharmaceuticals in extended-release tablets**.**

1. **Controlled by Diffusion**- The drug is enclosed in a semi-permeable membrane in reservoir systems, and release occurs as a result of diffusion across the barrier. When a drug is dispersed within a polymer matrix in matrix systems, diffusion occurs through the matrix material.
2. **Systems with Dissolution Control**- The medication is either enclosed in a slowly dissolving carrier or covered with a coating that dissolves gradually to control the release rate.
3. **Systems under osmotic control**- Uses an osmotic pressure gradient to regulate the release of medications. The medication is administered at a controlled rate via a laser-drilled hole in a semi-permeable membrane that surrounds a core containing the medication and osmotic agents.
4. **Resins that exchange ions**- The drug attached to ion-exchange resins is released when the pH of the gastrointestinal system varies.
5. **Systems of Erosion and Swelling-** When the tablet's polymers come into contact with stomach contents, they expand and create a gel barrier that limits pharmaceutical distribution. The matrix slowly breaks down in erosion-based devices, permitting continuous drug delivery.

Benefits of Extended-Release Tablets

Reduced Dosing Frequency: Patients enjoy greater convenience when they need fewer doses per day.

Consistent Medication Levels: Minimizes fluctuations in plasma medication concentration, which lessens side effects.

Improved Patient Compliance: Reduces the possibility of skipping doses, which is beneficial for the treatment of long-term conditions.

Decreased Chance of Adverse Reactions: reduces the possibility of harm by avoiding sudden increases in drug concentration[4].

Extended-Release Tablet Limitation

Absorption Variability: Various factors, such as meal consumption, gastrointestinal motility, and stomach pH, can affect how well a medicine is absorbed.

Dumping Risk: If the release mechanism fails, a large amount of medication may be released suddenly, which could be dangerous.

Complex Manufacturing Process: Requires quality control and state-of-the-art formulation technology

Not Appropriate for All Drugs: Extended-release formulations may not be the best choice for medications with extremely short or lengthy half-lives, low solubility, or limited therapeutic windows.

Matrix Tablets

Since matrix tablets offer the most economical choice for sustained and controlled release solid dosage forms, they represent a promising approach for creating extended-release pharmacological therapies. These tablets are referred to as "oral solid dosage forms where the drug or active ingredient is uniformly distributed within either hydrophilic or hydrophobic matrices that act as agents to slow down the release rate."

As a result, blood levels of the active pharmaceutical ingredient can be kept within a specific range, staying above the minimum effective level but below the hazardous level. It is clear that this kind of sustained-release tablet has the potential to be a reliable sustained-release dose form with a precise release profile[5]. Depending on the kind of polymer and release rate retardant used, two kinds of matrix tablets can be identified[6].

Hydrophilic tablets with a matrix

Hydrophilic matrix systems are currently among the most interesting drug delivery techniques. They are most commonly used to control the release rate of pharmaceuticals due to their affordability, broad regulatory acceptability, and adaptability in reaching a desired drug release profile. These systems are referred to as swellable-controlled release systems. The basic processes needed to create the matrices, like mixing and compressing the materials, are the same as those needed to generate ordinary tablets. Coating and granulation prior to mixing are complementary procedures commonly used in matrix tablet manufacture. Usually, additional excipients are added as lubricants, diluents, and anti-adhesives. In order to make hydrophilic matrices, two main types of polymers are used. A. Cellulose derivatives include methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, and hydroxypropyl methylcellulose (HPMC). B. Natural, Semi-synthetic or non-cellulose Polymers such as Agar-agar, alginates, molasses, and galactose polysaccharides, chitosan, and modified[7].

Hydrophobic matrix tablets

This method provides delayed release from an oral dose form by compressing the medication into a tablet after mixing it with an inert or hydrophobic polymer. A network of channels between compressed polymer particles has allowed the dissolving drug to disperse, causing a continuous release.

Although insoluble polymers are used, this is the only method that allows for controlled drug release without the use of polymers. In these formulations, the step that regulates the rate is liquid penetration into the matrix. One possible method of drug release in these types of tablets is diffusion. Some types of matrix tablets become inert in the presence of water and gastrointestinal fluid. The insoluble component of the formulations aids in maintaining the physical dimension of the hydrophobic matrix during drug release. To regulate drug release, soluble ingredients like lactose may need to be included in the formulation. Thus, the diffusion of the active component from the system is the release mechanism, and the related release characteristic may be described using the Higuchi equation, which is also referred to as the square root of time release kinetics[8].

Aspects of physicochemistry that affect matrix tablet release

1. **Dose Size:** For medications taken orally, there is a maximum limit on the bulk size of the dose. A single dose of 0.5 to 1.0 g is frequently considered the upper limit for conventional dosage forms, such as sustained-release formulations. Compounds that require larger dosages can occasionally be produced as liquids or administered in divided amounts. Another important factor to take into account is the margin of safety associated with administering a large dose of a drug with a narrow therapeutic range[9].
2. **Ionization, pKa, and water solubility**: The majority of drugs are weak bases or acids. Since the non-ionized form of a medication tends to penetrate lipid membranes more successfully, it is crucial to comprehend the relationship between a compound's pKa and

the milieu in which it is absorbed. Presenting the medication in its non-ionized form facilitates drug absorption. Delivery techniques that rely on diffusion or dissolution will also be impacted by the drug's solubility in wet environments. Since the stomach is acidic and the small intestine is more neutral, these dosage forms must function in varying pH environments; as a result, the release dynamics need to be understood.

3. **Partition Coefficient**: In order for a drug to affect other bodily areas, it must cross several biological membranes once it reaches the gastrointestinal (GI) tract. Since these membranes are typically believed to be lipophilic in nature, the partition coefficient of lipophilic drugs is crucial in determining how well they can flow through these barriers. Lipophilic compounds with a high partition coefficient typically have limited water solubility and endure for extended periods of time in lipophilic tissues. Conversely, compounds with a very low partition coefficient have a low amount of bioavailability because they have a hard time getting through membranes. Furthermore, partitioning may also have an impact on diffusion through polymer membranes.
4. **Stability**: Drugs taken orally may undergo acid-base and enzymatic breakdown. Since solid medications have a slower rate of degradation, this is the suggested method of delivery for challenging individuals. For dosage forms that are unstable in the stomach, systems that extend release over the whole GI tract transit or delay release until the dosage form reaches the small intestine are especially advantageous. Compounds that become unstable in the small intestine may have a lower bioavailability when delivered from a sustained-release formulation. This happens because the medicine is more readily available in the small intestine and is therefore more prone to break down[10].

Biological elements influencing Matrix tablet release

1. **The gastrointestinal tract's pH** - The pH varies along the gastrointestinal (GI) tract: stomach acid (pH 1-3) Small Intestine: neutral to slightly alkaline, pH 6–7.5 Colon: mildly acidic to neutral pH 6–7 Impact: The rate at which medications are released can be altered by pH-sensitive polymers (such enteric coatings or pH-dependent hydrogels) depending on the environment**.**
2. **Gastrointestinal System Transit Time** - How long the matrix tablet is exposed to different parts of the GI tract depends on the transit time. Two to four hours for the stomach, depending on whether you're fed or fasted. Between three and six hours for the small intestine. More than 20 hours in the colon
3. **Enzyme Activity**- Examples of digestive enzymes in the GI system that may degrade particular drug molecules or polymer matrix are proteases, lipases, and amylases. Impact: In polymers that are susceptible to enzymatic degradation, like natural gums or biodegradable polymers, drug release may be accelerated or uncontrolled.
4. **Motility of Digestion-** GI motility patterns that impact the mechanical stress on the matrix tablet include peristalsis and segmental contractions. Impact: Tablets with lower mechanical integrity may degrade too quickly in circumstances with high motility.
5. **The Presence of Food -** Changes in GI pH and transit time cause bile to be released, which dissolves lipophilic drugs. Physically interacting with the dosage form. Effect: Different fed and fasted states may result in

different release patterns, especially for drugs that rely on diffusion or erosion mechanisms.

6. **Absorbing Capacity -** The drug's release and absorption are impacted by the permeability of the GI epithelium. Impact: Drugs with low permeability or a narrow window for absorption (such those taken in the upper stomach) may have limited bioavailability.
7. **The Mucus Barrier -** Drug diffusion through the GI system may be hindered by a mucus layer covering it. Impact: Mucoadhesive polymers may interact with this layer to prolong the tablet's residence time, which could affect the release of medication.
8. **Disease States -** Diarrhea, Crohn's disease, and irritable bowel syndrome are GI disorders that impact pH, motility, and enzymatic activity. Effect: Under such conditions, unpredictable drug release and absorption characteristics may arise[9].

DRUG PROFILE OF MIRABEGRON[11]-

IUPAC NAME- 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-[2-[[(2*R*)-2-hydroxy-2 phenylethyl] amino] ethyl] phenyl] acetamide
Molecular Formula: $C_{21}H_{24}N_4O_2S$
Molecular weight: 396.51 g/mol
Melting Point: 144°C
CAS No.: 223673-61-8
Nature: White to off-white crystals or powder
Colour: White to Pale Yellow
Elimination half- life: 26-31 hours
Protein binding: 71%
Volume of Distribution: 1670 L
Clearance: 13 L/h
Lambda max: 251nm
Bioavailability: 35% at a dose of 50 mg
Solubility: DMSO- 79 mg/mL; Ethanol- 8 mg/mL; Water- Insoluble
Odour: Odourless
Taste: Bitter
Category: β 3 Agonist

The drug's pharmacology

1. Mechanism of action- A selective agonist of the β3-adrenergic receptor, mirabegron is mostly located in the bladder's detrusor muscle. When β3-receptors are activated, the detrusor muscle relaxes throughout the micturition cycle's storage phase, expanding bladder capacity without compromising voiding.
2. Pharmacodynamics- By encouraging bladder relaxation, mirabegron improves bladder compliance and lessens symptoms of an overactive bladder, including urgency and frequency.

3. Pharmacokinetics-

- **Absorption:** Mirabegron has a 29%–35% bioavailability and is quickly absorbed when taken orally.
- **Distribution:** Widely dispersed; approximately 71% of plasma proteins bind to it.
- **Metabolic processes:** It is mostly metabolized by CYP3A4 and CYP2D6, as well as by non-CYP-mediated pathways.
- **Excretion:** Mainly eliminated as metabolites in the form of urine (55%) and feces (34%). About fifty hours is the elimination half-life. 3.5 hours after oral treatment is the Time to Peak (Tmax).
- **Typical adverse effects** Hypertension, Nasopharyngitis, UTI, or urinary tract infection. Headache, Angioedema is uncommon but dangerous. One is tachycardia. A rise in blood pressure.

Drug Interactions

- **CYP2D6 Inhibitors:** Mirabegron has the ability to inhibit CYP2D6, which may raise the plasma concentrations of medications that are processed by this enzyme, such as desipramine and metoprolol. Urinary retention may worsen if anticholinergics are taken alongside antimuscarinic medications.

- **CYP3A4 or CYP2D6**-affecting medications may change how Mirabegron is metabolized.

Mirabegron's pharmacological effect- Urination requires the coordination of complex physiological processes as well as multiple anatomical systems, including the brain, spinal cord, and urinary tract. Incontinence symptoms can be caused by conditions that affect different tissues and processes. The micturition reflex and bladder control are controlled by innervation of the sympathetic and parasympathetic nervous systems. Acetylcholine, dopamine, and serotonin are the neurotransmitters that regulate voiding; serotonin decreases bladder contractility, while dopamine encourages urine storage and faster voiding[12]. Acetylcholine facilitates voiding by causing the muscarinic M2 and M3 receptors in the bladder detrusor muscle to contract. Acetylcholine facilitates voiding by causing the muscarinic M2 and M3 receptors in the bladder detrusor muscle to contract. By inhibiting the neurons that control the detrusor muscle spasms, anticholinergic drugs relax the bladder's smooth muscle and encourage fuller bladder filling. β-adrenergic receptors, which include β1, β2, and β3 subtypes, mediate smooth muscle relaxation in the bladder, urethra, and prostate. Sympathetic stimulation of these receptors may promote relaxation and enhance bladder compliance during the micturition cycle's filling phase. Mirabegron has little to no effect on other smooth muscle groups and operates as an agonist only at the β3-receptor[13].

CONCLUSION

The goals of this study are to effectively meet the creation and assessment of Mirabegron extended-release (ER) tablets using different grades of polymers. This can result in Extended-Release tablet formulation to improve therapeutic outcomes, offer prolonged drug release, and increase patient compliance, especially for the treatment of chronic illnesses like overactive bladder syndrome

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