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Formulation and Evaluation of Matrix dissolving Tablet of Isoniazid: Controlled Release

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ABSTRACT:
Isoniazidis a cornerstone in the treatment of tuberculosis (TB), yet its conventional administrationis associated with challenges such as frequent dosing and potential hepatotoxicity. Matrix dissolving tablet formulations aim to address these issues by providing controlled drug release, enhancing patient compliance, and minimizing side effects. This review explores various formulation strategies, methodologies employed in developing matrix dissolving tablets of isoniazid, emphasizing the role of both natural and synthetic polymers in modulating drug release profiles. The review paper also covers about formulation of matrix dissolving tablet of Isoniazid and its process of granulation, principle of matrix tablet, types of matrix tablet, advantages, and disadvantages e.t.c.

Keywords: Isoniazid, controlled release, tuberculosis, granulation process, natural and synthetic polymers.

I. INTRODUCTION:

Matrix technologies are widely used for oral controlled drug administration due to their simplicity, ease of production, high level of reproducibility, stability of raw ingredients and dosage form, and ease of scaling up and validation. This is evidenced by the high number of patents filed annually and the commercial success of innovative medication delivery systems using matrix technologies (1). In matrix devices, the medicine is evenly distributed in a hydrophobic or hydrophilic polymer matrix. Thin spots, pinholes, and other imperfections do not affect the release rate of matrix systems, unlike reservoir systems, which can be problematic (2). HPMC, a semisynthetic derivative of cellulose, is commonly used in the development of controlled release (CR) dosage forms due to its swelling and hydrophilic properties (3-5). Tablets are a great carrier material due to their benign nature, ease of handling and compression, ability to hold a high amount of medicine, minimal impact on drug release rates, and easy manufacturing technology (6). Drug release from HPMC matrices is influenced by several formulation factors, including polymer viscosity, particle size, drug/polymer ratio, solubility, particle size, loading, compression force, tablet shape, formulation excipients, coatings, processing techniques, and testing medium (7). Tuberculosis kills more people globally than any other infectious disease (8). Isoniazid is a key "first-line" medication for treating tuberculosis (9). The use of isoniazid for tuberculosis treatment has significant limitations, including severe toxic and unpleasant consequences (10-11). Due to severe toxic effects, patients did not comply with the medication and it was discontinued. Isoniazid undergoes significant pre-systemic metabolism in the small intestine and liver, resulting in plasma concentrations of quick acetylators that are half those of slow acetylators after a 300 mg dose (12). This causes subtherapeutic medication concentrations in the blood, leading to treatment failure and encouraging the growth of isoniazid-resistant Mycobacterium tuberculosis. Isoniazid administered intravenously resulted in similar peak plasma concentrations in both rapid and slow acetylators, with no significant difference. This led to the creation of CR matrix formulations of isoniazid to optimize blood levels in quick acetylators (13). Several studies support the necessity for controlled release formulations of isoniazid (12,14-19). The formulation with 37% free isoniazid and 63% matrix component yielded optimal results. A formulation with 15% free isoniazid and 85% matrix component was devised to attain high plasma concentrations in rapid acetylators while minimizing harmful effects in both fast and slow acetylators (12). However, no literature was discovered on the use of HPMC polymer as a tablet matrix forming material for the development of isoniazid- controlled release formulations. Furthermore, it was critical for the current study to design an oral CR matrix tablet of isoniazid that could offer both immediate release as a free isoniazid portion and controlled release as a matrix component from a single formulation.

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II. MATERIALS AND METHODS:

Isoniazid was purchased from Avra Laboratiories Private Limited, Hyderabad. HPMC (Hydroxylpropylmethylcellulose), gelatin, PEG-6000, Talc, Magnesium stearate, lactose, Povidone K30 etc chemicals are taken from university chemical store.

Methods of Granulation: To prepare matrix dissolving tablet of Isoniazid mainly depends upon two methods:

1. Wet granulation method.
2. Direct Compression.

1- Wet granulation method:

It is the most popular and extensively utilized method. This process consists of several steps, including the weighing of components, mixing, granulation, and screening of damp pass, drying, lubrication, and tablet compression. The main active component, diluent, and disintegrant are combined together before passing through a sieve (sifting). The binding agent solutions are stirred into the initial mixture. The amount of binding agent supplied should be sufficient to prevent the tablet from becoming too wet. If the powder is not properly wetted, the granules become too soft and can be broken down during lubrication, making tablet compression problematic. Tray drying is the most frequent way of drying tablet granules. Tray drying was once the most widely used method of drying tablet granulations, however fluid-bed dryers may replace it as a novel approach. After drying, the granules are permitted to pass through a screen; typically, 60-100 mesh nylon cloth is employed. After dry granulation, lubricant is applied as fine powder to ensure adequate filling of the die cavity.

Fig 1: Wet Granulation Flow Chart.

2- Direct Compression:

Direct compression is the process of compressing powdered material directly into tablets. Direct compression is used when the medicine accounts for a significant amount of the tablet's total weight. Tablets having 25% or less of drug components can be prepared using a suitable diluents that serves as a carrier or vehicle for the drug. Tablets made using the aforesaid procedure are submitted to a compression machine, which can be single or multiple stations.

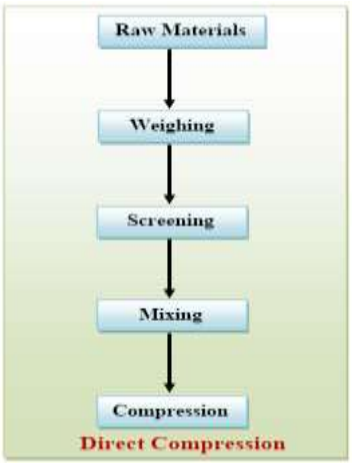

Fig 2: Direct Compression Flow Chart

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S.NO.	INGREDIENTS	USES
1.	Isoniazid Drug	API
2.	HPMC	Matrix-Forming Agent(Controlled Release)
3.	Gelatin	Binder /Stabilizer
4.	Talc	Glidant
5.	Magnesium Stearate	Lubricant
6.	Lactose Monohydrate	Filler /Diluent
7.	Providonek30	Binder
8.	PEG6000	Solubilizer / Wetting Agent

TABLE 1: LIST OF INGREDIENT FOR FORMULATION OF MATRIX DISSOLVING TABLET

Principle of Matrix Tablet:

Matrix tablets are a widely used oral drug delivery system designed to control the release of active pharmaceutical ingredients (APIs) over a prolonged period. The fundamental principle behind matrix tablets is the embedding of the drug in a polymeric matrix structure, which controls the drug's release rate through mechanisms such as diffusion, erosion, or swelling. Upon ingestion, the matrix tablet comes into contact with gastrointestinal fluids, triggering the release of the drug in a controlled manner. The rate and extent of this release depend on the physicochemical properties of both the drug and the matrix-forming polymers.

Matrix systems are generally classified into hydrophilic, lipophilic, or inert matrices depending on the type of polymer used. Hydrophilic matrices, such as those made from hydroxypropyl methylcellulose (HPMC), swell in aqueous media to form a gel-like barrier on the tablet surface. This gel controls the drug's release by slowing its diffusion and erosion from the tablet core (Basak et al., 2008). As the outer gel layer gradually erodes or dissolves, new layers of the matrix are exposed, maintaining a sustained release of the drug over time. In lipophilic or insoluble matrix systems, such as those using ethyl cellulose or waxes, the drug diffuses through a network of pores formed within the hydrophobic matrix as the soluble components dissolve (Vyas & Khar, 2002).

The selection of matrix-forming polymer is critical to achieving desired release kinetics. For instance, polymers with high molecular weight and viscosity tend to slow drug diffusion and extend the release period. Drug release from matrix tablets often follows well-established kinetic models such as zero-order (constant release rate), first-order (concentration-dependent release), or Higuchi model (release proportional to the square root of time), depending on the system design (Costa & Sousa Lobo, 2001).

Matrix tablets offer several advantages, including ease of manufacture, cost-effectiveness, and the ability to minimize dose frequency and enhance patient compliance. Unlike coated or multi- unit systems, matrix tablets can be manufactured using standard tablet compression techniques, which makes them favorable for large-scale production. Furthermore, by controlling the release profile, matrix tablets can reduce plasma drug level fluctuations and improve the therapeutic efficiency of drugs like isoniazid, which require sustained plasma concentrations for effective tuberculosis treatment.

Types of Matrix System:

Due to their ease of use, low cost, and prolonged sustenance of release, matrix systems are one of the most widely employed strategies for the design of controlled release oral drug delivery systems. These systems enclose the drug in a polymeric matrix, from which the drug is slowly liberated through diffusion and matrix erosion processes. Generally, matrix systems can be divided into individual hydrophilic and hydrophobic matrices as well as lipid-based and biodegradable matrices, each having unique properties and mechanisms of drug release. They are as follows:

1. Hydrophilic Matrix:

Hydrophilic matrices belong to the most prepared types due to their versatility with various drug and excipient combinations. Hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), and sodium alginate are classified as water-soluble swellable polymers. These polymers, once hydrated, undergo swelling and gelling phenomena thereby forming a drug-diffusion

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controlling membrane on the tablet surface. A polymer's release rate is dependent on its concentration, viscosity, degree of swelling, and swelling (Maderuelo et al., 2011). In particular, HPMC-based matrices have received greater interest because of the steady gel formation they yield, their non-toxicity, and film-forming properties (Siepmann & Peppas, 2001).

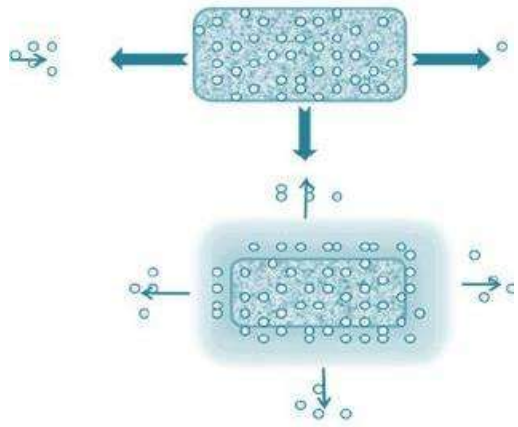

Fig 3. Mechanism of Drug Release from Matrix Tablet.

2. Hydrophobic Matrix:

Hydrophobic matrix systems, on the other hand, utilize water-insoluble polymers or waxes, such as ethyl cellulose, polyvinyl acetate, or carnauba wax, which resist water penetration and thereby sustain drug release primarily through diffusion. These systems are especially useful for water- soluble drugs where burst release from hydrophilic systems may be problematic. Since they do not swell significantly in aqueous environments, the drug release depends on the porosity and tortuosity of the matrix, often requiring pore formers or channeling agents to facilitate release (Zhang et al., 2000).

3. Lipid Matrix System:

Like glyceryl monostearate, stearic acid, and even hydrogenated oils, lipid matrix systems employ lipophilic substances to slow down the release of the active ingredient. In these systems, a lipid matrix where the drug is embedded is formed which retards water penetration and drug diffusion. Increased stability from the lipid matrices is another advantage because they shield sensitive drugs from hydrolysis and oxidation (Maroni et al., 2013).

4. Biodegredable Matrix System:

Biodegradable matrix systems are made of polymers that are capable of bodily degradation over time like polylactic acid (PLA), polyglycolic acid (PGA), or their copolymers (PLGA). These systems are optimal for controlled drug delivery when a prolonged release is needed and the delivery device does not need to be removed. The method of drug release through polymer degradation and diffusion makes these systems especially advantageous for site-specific and implantable delivery systems. Although modification of oral dosage forms is still infrequent due to the inconsistency of the gastrointestinal system's degradation, consideration is increasing because of advances in the chemistry of polymers and drug-polymer systems. (Danhier et al. 2012)

Advantages of Matrix Tablet:

1. Matrix tablets can maintain therapeutic drug levels over an extended period, reducing dosing frequency and enhancing patient compliance.
2. These tablets are easy to manufacture using conventional direct compression or wet granulation methods, making them cost-effective.
3. Matrix systems provide better control over drug release compared to coated dosage forms, reducing the risk of sudden drug release (dose dumping).
4. Reduced frequency of administration due to sustained action leads to better adherence, especially for chronic diseases.
5. By maintaining steady plasma concentrations, matrix tablets lower the risk of peak- related adverse effects.
6. A wide variety of polymers (hydrophilic, hydrophobic, biodegradable) can be used, allowing customization for specific drug release profiles.
7. Matrix systems avoid high plasma peaks and troughs, maintaining consistent drug exposure.
8. Matrix tablets can protect sensitive drugs from degradation due to their compact nature and use of protective polymers.
9. Sustained release allows for drug absorption over a longer period, potentially reducing first-pass metabolism for certain drugs.
10. Matrix tablets can be used for both water-soluble and poorly soluble drugs with suitable polymer selection.

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Disadvantages of Matrix Tablet:

1. Drugs with low aqueous solubility may exhibit incomplete or erratic release from matrix systems.
2. Drug release from matrix tablets can be affected by pH variations and motility throughout the GI tract, leading to unpredictable bioavailability.
3. In case of polymer failure or tablet damage, there may be rapid drug release (dose dumping), which can be harmful, especially for potent drugs.
4. To incorporate sufficient drug and matrix material for prolonged release, the tablet size may be bulky, causing difficulty in swallowing.
5. Once formulated, it is challenging to adjust the dose without re-engineering the matrix system.
6. Matrix tablets are inappropriate for drugs requiring immediate release or those unstable in the GI tract over time.
7. Incompatibility between drug and matrix-forming polymer may affect drug stability or release profile.

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