Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Review On Improving Patient Compliance With Extended Release Matrix Tablets

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Cite this paper as: Vanashri Turke, Dr. Janki Prasad Rai, (2025) Review On Improving Patient Compliance With Extended Release Matrix Tablets. *Journal of Neonatal Surgery*, 14 (32s), 6599-6605.

ABSTRACT

The study explores the necessity, advantages, and techniques of extended-release matrix tablets for continuous drug delivery at predictable rates and reproducible kinetics. It discusses different formulation methods, including wet granulation, direct compression, or solid particle dispersion within a porous matrix made of polymers like HPMC, guar gum, xanthan gum, pectin, and chitosan. The matrix controls drug release rate, with release retardants like HPMC aiding in extended release. Various matrices, such as hydrophilic, hydrophobic, mineral, or biodegradable types, can be used. Some drugs formulated as extended-release matrix tablets include Ambroxol HCl, Clarithromycin, and Indomethacin. These tablets can improve patient compliance by reducing total dose and dosage regimen, which can help treat chronic diseases. The review highlights the types of matrices, mechanisms involved, and evaluation studies.

Keywords: *Matrix tablet, Extended release, Biodegradable Polymer.*

1. INTRODUCTION

Dosage form is a transformation of pure chemical compound into predetermined form by admixing drug compound with different kinds of non drug components collectively known as adjuvants or excipients having specific functions. In other words, dosage forms are the mechanism by which drug molecules are administered to the site of action inside the body to generate their therapeutic effects. The need for dosage forms is for accurate dose, protection from environment (coated tablets and sealed ampoules), protection from gastric juice, masking taste and odor, placement of drugs within body tissues, sustained release medication, controlled release medication, insertion of drugs into body cavities (rectal, vaginal) and use of desired vehicle for insoluble drugs. Depending on the method/route of administration, dosage forms come in several types. These include many kinds of liquid, solid, and semisolid dosage forms such as tablet, capsules, syrups, suppositories, creams, powders, eye drops, ear drops, suppositories etc.

2. TABLETS

Tablets may be defined as, "the solid unit dosage form of medicament(s) with suitable excipients prepared either by molding or by compression". Tablets are usually circular in. shape and may be flat or biconvex. Additives or excipients are mainly incorporated to enhance physical appearance, stability, disintegration, or breakup of tablet after administration. According to Indian Pharmacopoeia, "Pharmaceutical tablets are flat or bi-convex discs manufactured by compressing a drug or a mixture of drugs with or without suitable excipients". The objective of the design and manufacture of the compressed tabletis to deliver orally the correct amount of drug in the proper form, and to have its chemical integrity protected.

Ideal Characteristics of Tablets:

Tablets should be an elegant product, free from defects.

It should have strength to withstand of mechanical shock that may occur during production, packaging, shipping etc.

Tablets must be able to release the medicinal agent in the body in a predictable and reproducible manner.

It must be uniform in weight and drug content.

Tablets should be physically and chemically stable so that no alternation of Active ingredient with time.

Advantages of Tablet Dosage Forms:

1. The tablets are easy to be administered.
2. They are easy to be dispensed.
3. These are more stable dosage form.
4. They maintain the accuracy of dosage.
5. Bitter and nauseous substances can be given easily in tablet form after giving a suitable coating to the tablets to make palatable.
6. They are the lightest and the most compact of all dosage forms.
7. These are an economical dosage form.
8. Easy to handle, convenient to administer and offers greatest dose precision.
9. Have the best combined properties of chemical, mechanical, and microbiological stability of all the oral forms.
10. Ease of swallowing, and less shelf storage space.
11. Suitable for large scale production.
12. Provide protection of medicaments from atmospheric conditions by suitable coating.**1**

Types of Tablets:

Tablets are classified according to their route of administration or function. The following are the four main classification groups as mentioned on Table 5.1.

Table 5.1: Classification of Tablets

Tablets ingested orally	Tablets used in the oral Cavity	Tablets administered by other routes	Tablets used to prepare solutions
• Compressed tablets. • Multiple compressed tablets or press coated tablets • Multilayered tablets: three types i.e. Compression coated tablets, layered tablets and inlay tablets • Sustained action tablets. • Enteric coated tablets • Sugar coated tablets. • Film coated tablets. • Chewable tablets.	• Buccal tablets. • Sublingual tablets. • Lozenge tablets and troches. • Dental cones	• Implantation tablets • Vaginal tablets	• Effervescent tablets • Dispensing tablets. • Hypodermic tablets. • Tablet triturates

We discuss some types of tablets below.

5.1.1 Uncoated Tablets

The uncoated tablet is a single layer or multi-layer of formulation that contains the drugs or medicines and excipients simultaneously without any coating. In general, it is a single compression of granules or multi-layer tablets consisting of

parallel layers prepared by compression of granules of various compositions. These types of pills do not require additional processing after compression. The majority of uncoated tablets are made in such a way that any substances added are not intended expressly to alter the release rate or dissolution rate of their active ingredients. Soluble tablets, dispersible tablets, and effervescent tablets are some types of uncoated tablets.

(i) Compressed Tablets:

These tablets are uncoated and made by compression of granules. Compressed tablets contain water soluble drugs which after swallowing get disintegrated in the stomach and its drug contents are absorbed in the gastrointestinal tract and distribute in the whole body.These tablets are usually intended to provide rapid disintegration and drug release.

(ii) Effervescent Tablets:

These tablets when added in water produce effervescence. So, they dissolve rapidly in water due to the chemical reaction which takes place between alkali, bicarbonate and citric acid or tartaric acid or combination of both. These tablets are to be protected from atmospheric moisture during storage. So, these tablets should be stored in well-closed air tight containers.

(iii) Dispensing Tablets:

The medicaments commonly incorporated in dispensing these tablets include mild silver proteinate, bichloride of mercury merbromin and quaternary ammonium compounds. These tablets contain excipients which gets dissolved quickly to form a clear solution. These tablets are highly toxic if taken orally by mistake. Care must be taken in the packaging and labelling of such tablets in order to prevent their misuse.

(iv) Hypodermic Tablets:

These are compressed tablets which are composed of one or more drugs with readily water soluble ingredients. These tablets are dissolved in sterile water or water for injection and administered by parenteral route. These tablets however are not preferred nowadays, as there are chances that, the solution prepared from hypodermic tablets may be a non-sterile.

(v) Buccal Tablets:

These tablets are to be placed in the buccal pouch or between the gums and lips or cheek where they dissolve or disintegrate slowly and are absorbed directly without passing into the alimentary canal (first by pass effect) leads to increase in the bioavailability of the drug. e.g. tablets of histone.

(vi) Sublingual Tablets:

These tablets are to be placed under the tongue where they dissolve or disintegrate quickly and are absorbed directly without passing into GIT (gastro intestinal tract). e.g. Tablets of glyceryl trinitrate.

(vii) Lozenge Tablets and Troches:

These tablets are designed to exert a local effect in the mouth or throat. These tablets are commonly used to treat sore throat or to control coughing in common cold. They may contain local anesthetics, antiseptic, antibacterial agents, astringents and antitussives. These are prepared by compression at a high pressure or by the molding process and generally contain a sweetening agent, a flavoring agent and a substance which produces a cooling effect along with medicaments.

(viii) Dental Cones:

These are relatively minor compressed tablets meant for placing them in the empty sockets after tooth extraction. They prevent the multiplication of bacteria in the socket following extraction of tooth by using slow-releasing antibacterial compounds or to reducebleeding by the astringent. These tablets contain an excipient like lactose, sodium bicarbonate and sodium chloride etc. These cones generally get dissolved in 20 to 40 minus.

(ix) Chewable Tablets:

These tablets are chewed in the mouth and broken into smaller pieces. In this way, the disintegration time is reduced and the rate of absorption of the medicament is increased e.g. Aluminum hydroxide tablets and phenolphthalein tablets.

(x) Tablet Triturates:

These are small tablets usually cylindrical, molded or compressed, and contain a potent medicament with a diluent. On a small scale, tablet triturates are prepared by using hand-operated tablet triturate moulds but for bulk production, automatic tablet triturate machines are used.

(xi) Implantation Tablets:

These tablets are placed under the skin or inserted subcutaneously by means of minor surgical operation and are slowly absorbed. These may be made by heavy compression but are normally made by fusion. The implants must be sterile and should be packed individually in sterile condition. Implants are mainly used for administration of hormones such as

testosterone and deoxy corticosterone etc.

(xii) Vaginal Tablets:

These tablets are meant to dissolve slowly in the vaginal cavity. The tablets are typically ovoid or pear shaped to facilitate insertion and retention in the vagina. This tablet form is used to release steroids, antibacterial agents, antiseptics or astringents to treat vaginal infections. The tablets are often buffered to promote a pH favorable to the action of a specified antiseptic agent **2**

Various Modified Tablets (Sustained Release, Extended-Release, Fast Dissolving, Multi Layered)

Most conventional (immediate release) oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration. The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. The pattern of drug release from modified-release (MR) dosage forms is deliberately changed from that of a conventional (immediate-release) dosage formulation to achieve a desired therapeutic objective or better patient compliance. types of MR drug products include extended release (ER), delayed release (e.g. Enteric Types coated), and orally disintegrating tablets (ODT).

Several Types of Modified-release oral drug products are:

5.1.3.1 Extended-Release Drug Products (ER)

A dosage form that allows at least a twofold reduction in dosing frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-int acting drug products. Extended-release medications are slowly released into the body over a period of time, usually 12 or 24 hours. There are many advantages of ER formulations like minimize fluctuations in steady drug concentration, improve seizure control, and reduce toxicities associated with peak concentrations compared with IR formulations. The ER formulations also have some limitations in comparison with IR formulations.

The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery. Other terms, such as ER, SR, XL, XR and CD, are also used to indicate an extended-release drug product.

Types of Extended-Release Products:

(a) Diffusion-controlled Products: In these systems, there is a water-insoluble polymer which controls the flow of water. Both diffusional and dissolution processes are involved in the release of these products. In 'reservoir' devices, a core of drug is coated with the polymer and, in 'matrix' systems, drug is dispensed throughout the matrix. Cellulose derivatives are commonly used in the reservoir types, while the matrix material may be plastics, e.g. Methyl acrylate-methyl methacrylate, polyvinyl chloride, hydrophilic polymers such as cellulose derivatives or fatty compounds including carnauba wax. Examples of this type of formulation include Plendil ER, Agon SR, Kapanol and Slow-K.

(b) Dissolution-controlled products: In these products, the rate of dissolution of the drug (and thereby availability for absorption) is controlled by slowly soluble polymers or by micro encapsulation. Once the coating is dissolved, the drug becomes available fordissolution. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled. The pellet dosage forms of diffusion or dissolution-controlled products can be encapsulated or prepared as a tablet. An example of this type of product is Fefol.

(c) Erosion products: The release of drug from these products is controlled by the erosion rate of a carrier matrix. The rate of release is determined by the rate of erosion. An example of this formulation is Sinemet CR.

(d) Osmotic pump systems: The rate of release of drug in these products is determined by the constant inflow of water across a semipermeable membrane into a reservoir which contains an osmotic agent. The drug is either mixed with the agent or is located in a reservoir. The dosage form contains a small hole from which dissolved drug is pumped at a rate determined by the rate of entrance of water due to osmotic pressure. The rate of release is constant and can be controlled within tight limits yielding relatively constant blood concentrations. The advantage of this type of product is that, the constant release is unaltered by the environment of the gastrointestinal tract and relies simply on the passage of water into the dosage form. The rate of release can be modified by altering the osmotic agent and the size of the hole. An example of this type of product is Adalat Oros.

(e) Ion exchange resins: Some drugs can be bound to ion exchange resins and, wheningested, the release of drug is determined by the ionic environment within the gastrointestinal tract. Examples of this type of product are Duro mine containing the basic drug phentermine complexed onto an anionic resin, and MS Contin suspension which uses a polystyrene sulphonate resin.**3**

Drugs that are suitable for extended-release formulations

The extent of fluctuation in drug concentration at steady state is determined by the relative magnitude of the elimination half-

life and the dosing interval. If a drug is given at an interval equal to the elimination half-life, there is a two-fold difference between the maximum and minimum concentrations at steady state.

For drugs with short half-lives and with a clear relationship between concentration and response, it will be necessary to dose at regular, frequent intervals in order to maintain the concentration within the therapeutic range. Higher doses at less frequent intervale will result in higher peak concentrations with the possibility of toxicity. For some drugs with wide margins of safety, this approach may be satisfactory, e.g. amoxycillin has half-life of approximately one hour, but a dosage frequency of 8 hours. This means the very large fluctuations will occur within a dosing interval, but, in view of the low toxicity of this drug, no difficulty with this approach is encountered provided the concentration are above the minimum effective concentration during the dosing interval. On the contrary clinical efficacy may be enhanced by the transiently high bactericidal concentration of the antibiotic e.g. aminoglycosides.

Conversely, drugs with long half-lives can be given at less frequent intervals. There generally no advantage in formulating these drugs as extended-release formulations u less a rapid rate of change of concentration during the absorption phase is responsible f transient adverse effects. The pharmacological effect of some drugs with short half-lives sustained by various mechanisms:

- the drug binds to the tissues e.g. tissue-bound ACE inhibitors. For this drug less frequent dosing is needed even though the drug may have a short half-
- the drugs have irreversible effects e.g. the inhibition of platelet cyclo-oxygen by aspirin.
- the relationship between response and plasma / blood concentrations relatively flat or if the dose administered results in concentrations which are the plateau region of the dose-response relationship e.g. thiazides hypertension.
- the drug is metabolized to pharmacologically active metabolite(s) which are

1. Presence of Food: The presence of food affects the rate of release of drug. Presence of fatty meal increases the absorption of lipophilic drugs.

2. Hepatic first pass effect: Most drugs given orally exhibit poor bioavailability with respect to the given dosage because of the fact that drugs absorbed in the stomach and intestinal regions will go to liver before they reach systemic circulation. This causes extensive metabolism of the drugs decreasing the bioavailability greatly. The oral sustained release dosage forms could not one ward this major defect.

3. Fluctuations in the drug delivery: Because of the effects of environment, food and also the minute defects in the manufacturing some times causes fluctuations in release of drugs take place. Often this may lead to dose dumping causing serious toxic effects.

4. Lack of targeting: As these dosage forms release the drugs to the systemic circulation[4]

DRUG PROPERTIES RELEVANT TO EXTENDED-RELEASE FORMULATION

The design of extended-release delivery system is subjected to several variables of considerable importance. Among these, properties of the drug the route of delivery and the disease treated and length of the therapy have major importance.**5**

A) Physicochemical Properties

a) Aqueous solubility and pKa

A drug's absorptive behavior is influenced by its aqueous solubility and its pKa, which are crucial for controlled release systems. The aqueous solubility of a drug affects its dissolution rate, which establishes its concentration in solution and driving force for diffusion across the membrane. The Noyes-Whitney equation shows that dissolution rate is constant only if the surface area remains constant, but the initial rate is directly proportional to aqueous solubility. Drugs with low aqueous solubility have low dissolution rates and often suffer oral bioavailability problems. The pKa of a compound and the pH of the medium also affect the aqueous solubility of weak acids and bases. Extremes in a drug's aqueous solubility are undesirable for extended-release products, as they may exhibit dissolution-limited absorption and yield an inherently extended blood level. Preparing a slightly soluble form of a drug with high solubility is a possible method for preparing extended-release dosage forms.[6]

b) Partition coefficient

Drugs must diffuse through biological membranes, primarily lipid-like barriers, to be evaluated. The apparent oil/water partition coefficient, defined as K=CO/CW, is a key criterion. Large values of K are oil-soluble and easily partition into membranes. The Haunch correlation suggests that drug activity is influenced by its ability to cross membranes and interact with receptors. Drugs with higher or lower partition coefficients are typically used in extended-release dosage forms.

c) Drug stability

Oral dosage is influenced by drug loss through acid hydrolysis or metabolism in the gastrointestinal tract (GI tract). Solid

drugs degrade slower than suspension or solution drugs. To improve bioavailability, drugs in slowly available extended-release form can be placed. For stomach-stable drugs, controlling units should release contents only in the stomach environment. Drugs with significant stability problems in the GI tract are less suitable for extended-release systems that deliver content uniformly over the GI tract.

D) Protein Binding

Protein binding in plasma or tissue affects drug distribution and hepatic and renal clearance. Some drugs bind with plasma proteins, like albumin, causing drug retention in the vascular space. The drug protein complex can serve as a reservoir for extended drug release, but only for drugs with high binding. Extensive binding to plasma proteins leads to a long half-life, while low binding to plasma proteins may affect controlled drug delivery...

e) Molecular size and diffusivity

Drugs in extended-release systems diffuse through rate-controlling membranes, with diffusivity being influenced by molecular size or weight. In polymers, log D can be empirically related to molecular size, with denser mediums having smaller diffusivity. The molecular size of the diffusing species significantly influences this value.

B) Pharmacokinetic Properties

a) Absorption

The rate, extent, and uniformity of drug absorption are crucial for formulation into extended-release dosage forms. A rate constant for drug release is less than the constant for absorption (Kr<<<Ka). A first-order release rate constant of Kr < 0.17 hr-1 may result in poor bioavailability in patients, making slowly absorbed drugs difficult to formulate into extended-release systems.

b) Distribution

The distribution of a drug in vascular and extravascular spaces is crucial for its elimination kinetics. The apparent volume of distribution and T/P ratio describe its distribution characteristics, relating drug concentration in blood or plasma to total body amount.

c) Metabolism The design of extended-release systems considers drug metabolism, which influences blood levels through enzyme synthesis, intestinal metabolism, and hepatic first-pass effects, affecting chronic dosing.

d) biological half-life

An oral extended-release product aims to maintain therapeutic blood levels over an extended period by ensuring the drug enters circulation at the same rate as it is eliminated. The half-life of a drug is a key factor in determining its suitability for extended-release preparations. Short half-life drugs are ideal for this purpose, but they may require large amounts of drug in each dosage unit. Long half-life drugs are generally not suitable for extended-release preparations.

e) Efficacy and safety

The therapeutic index (TI) is a widely used measure of a drug's margin of safety, calculated as TI = TD50/ED50. A larger TI value indicates a safer drug, while a small TI value makes it poor for extended-release products. A drug is considered relatively safe if its TI value exceeds 10.[7]

3. POTENTIAL ADVANTAGES OF EXTENDED RELEASE DRUG THERAPY

Extended-release products offer three potential benefits:

- Sustained blood levels
- Attenuation of adverse effects
- Improved patient compliance

Sustained blood levels

Dosing size and frequency are determined by drug pharmacodynamics and pharmacokinetic properties. Slower absorption reduces blood concentration fluctuations, allowing higher doses to be given less frequently. Extended-release products can maintain therapeutic concentrations over extended periods.

Attenuation of adverse effects

Conventional dosage forms can cause high peak blood concentrations, leading to adverse effects like hypotension in patients taking rapid-release nifedipine products. Extended-release products avoid these issues, preventing sudden blood pressure reduction and significant hemodynamic changes like reflex Tachycardia. Some conventional release products, like theophylline, also cause transient nausea at sub-toxic concentrations.[8]

Improved Patient Compliance

Short half-lives drugs require frequent dosing to maintain therapeutic blood concentrations. Dosing frequency has an inverse correlation with patient compliance. Extended-release products may improve compliance by reducing daily doses, but this benefits only when conventional formulations require three or more doses daily.

4. RATIONAL FOR EXTENDED-RELEASE DOSAGE FORMS

Extended-release drug delivery systems aim to modify the pharmacokinetics and pharmacodynamics of active drugs by utilizing novel delivery systems or modifying their molecular structure or physiological parameters.

1. Reduction in fluctuation of drug blood levels.
2. Reduce the dosage frequency.
3. Improvement in patient's compliance.
4. More consistent and prolonged therapeutic effect.[9]

5. CONCLUSION

The formulation of extended-release matrix tablets, their benefits and drawbacks, the kinds of polymers utilized, the preparation process, and the assessment criteria have all been the main topics of this review paper. According to the description above, matrix tablets can help with issues related to patient compliance and the effectiveness of the dose form in producing the intended therapeutic response that are present with traditional dosage forms. Along with other advantages, the cost-effectiveness and once-daily dosage are advantages.

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