Per oral extended release products - An overview


ABSTRACT

The use of extended-release products offers some potential advantages in patient convenience, compliance and therapeutic outcomes. However, the range of drugs for which clinically significant advantages have been shown is limited. Prescribers and pharmacists should be aware of these products and have knowledge of their clinical use in selected patient groups. In some instances, the formulation is probably serving a marketing objective rather than a clinical objective.

Key words: Extended-release, Formulation, Marketed product, Clinical significant.

INTRODUCTION

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for years. Early modified-release products were often intramuscular injections of suspensions of insoluble drug complexes, e.g. procaine penicillin, protamine zinc suspensions, insulin zinc suspensions or injections of the drug in oil, e.g. fluphenazine decanoate (Gowda, K V et al., 2006). Advances in technology have resulted in novel oral modified-release dosage forms. Many terms are used to describe modified-release products including extended-release, prolonged-release, controlled-release, controlled-delivery, slow release and sustained-release. These preparations, by definition, have a reduced rate of release of active substance. In general, these terms are interchangeable. Delayed-release products are modified-release, but by definition is not extended-release (Martindale, 2002). They involve the release of discrete amount(s) of drug some time after drug administration, e.g. enteric-coated products, and exhibit a lag time during which little or no absorption occurs (Kawashima Y et al., 1981). While a number of such modified-release products are available as both prescription and over-the-counter drugs, only a limited number have been developed to extend patents or to create a marketing advantage over conventional-release products, rather than because of clinical advantage.

Advantages

Extended-release products offer three potential benefits:

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

Sustained Blood Levels

The size and frequency of dosing is determined by the pharmacodynamic and pharmacokinetic properties of the drug. The slower the rate of absorption, the less the blood concentrations fluctuate within a dosing interval. This enables higher doses to be given less frequently. For drugs with relatively short half-lives, the use of extended release products may maintain therapeutic concentrations over prolonged periods.

Attenuation of adverse effects

With conventional dosage forms, high peak blood concentrations may be reached soon after
administration, with possible adverse effects related to the transiently high concentration. An example is hypotension in patients taking rapid-release nifedipine products. The use of an extended-release product avoids the high initial blood concentrations which cause the sudden reduction in blood pressure and other significant hemodynamic changes such as reflex tachycardia. (Opie LH et al., 1995). Another examples are the transient nausea at sub-toxic concentration of some conventional-release products such as theophylline. (Table-1)

**Improved Patient Compliance**

Drugs with short half-lives often need to be given at frequent intervals to maintain blood concentrations within the therapeutic range. There is an inverse correlation between the frequency of dosing and patient compliance. A reduction in the number of daily doses offered by extended-release products has the potential to improve compliance. However, this advantage probably only occurs when conventional formulations need to be given three or more times a day.

<table>
<thead>
<tr>
<th>Drug product &amp; form</th>
<th>Manufacturer</th>
<th>Marketed Name</th>
<th>Drug Name</th>
<th>Characteristics</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed release Tablets</td>
<td>Knoll</td>
<td>E-Mycin</td>
<td>Erythromycin tablet</td>
<td>Tablets enteric coated with cellulose acetate phthalate, carnauba wax, and cellulose polymer.</td>
<td>antibiotic</td>
</tr>
<tr>
<td>Delayed release Tablets</td>
<td>Procter&amp;Gamble</td>
<td>Asacol</td>
<td>Mesalamine tablet</td>
<td>Tablets coated with Eudragit S (methyl acrylic acid copolymer B), a resin that bypasses the stomach and dissolves in the ileum and beyond.</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Delayed release capsules</td>
<td>Astra-Merck</td>
<td>Prilosec</td>
<td>Omeprazole capsules</td>
<td>Enteric coated granules of omeprazole placed in capsules</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td>Extended-Release coated particles and Beads</td>
<td>Astra-Merck</td>
<td>Toprol-XL</td>
<td>Metoprolol succinate tablets</td>
<td>Drug pellets coated with cellulose polymers compressed into tablets</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Extended-Release coated particles</td>
<td>Astra-Merck</td>
<td>IndocinSR</td>
<td>Indomethacin capsule</td>
<td>Coated pellets for SR formulation includes polyvinyl acetate-crotonic acid copolymer and hydroxyl propyl methyl cellulose</td>
<td>Analgesic-Anti-inflammatory</td>
</tr>
<tr>
<td>Extended-Release coated particles</td>
<td>Smithline Beecham</td>
<td>compazine</td>
<td>prochlorperazine capsule</td>
<td>Coated pellets in capsule formulated to release initial dose promptly with addition drug for prolonged release</td>
<td>Anti nausea, Anti vomiting</td>
</tr>
<tr>
<td>Extended-Release Inert Matrix</td>
<td>Abbott</td>
<td>Desoxyn</td>
<td>Methamphetamine HCI tablet</td>
<td>Drug impregnated in an inert, porous, Plastic matrix, drug leaches out as it passes slowly through the GI tract.</td>
<td>Attention deficient disorder</td>
</tr>
<tr>
<td>Extended-Release Inert Matrix</td>
<td>Parke-Davis</td>
<td>Procanbid</td>
<td>procainamide</td>
<td>Extended-release tablets with core tablets of a no erodible wax matrix coated with cellulose polymers</td>
<td>Ant arrhythmic</td>
</tr>
<tr>
<td>Extended-Release Hydrophilic/Erod ing Matrix</td>
<td>Robins</td>
<td>quinidex</td>
<td>Quinidine sulfate</td>
<td>Extended-release provided by hydrophilic matrix that swells and slowly erodes</td>
<td>Ant arrhythmic</td>
</tr>
<tr>
<td>Extended-Release Hydrophilic/Eroding Matrix</td>
<td>Roxane</td>
<td>Oramorph SR</td>
<td>Morphine sulfate</td>
<td>Sustained-release hydrophilic matrix system, based on polymer hydroxypropyl methylcellulose</td>
<td>Analgesic for severe pain</td>
</tr>
<tr>
<td>Extended-Release microencapsulated K-Dur Microburst release system</td>
<td>Key</td>
<td>K-Dur</td>
<td>Potassium chloride</td>
<td>Immediately dispersing drug microcapsulated with ethyl cellulose and hydroxypropyl cellulose.</td>
<td>Potassium depletion</td>
</tr>
<tr>
<td>Extended-Release osmotic</td>
<td>Pfizer</td>
<td>Glucotrol XL</td>
<td>Glipizide tablet</td>
<td>Controlled-release GITS osmotic system. Ingredients include polyethylene oxide, Hydroxypropylcellulose, cellulose acetate and cellulose acetate</td>
<td>Analgesic for severe pain</td>
</tr>
</tbody>
</table>
### Disadvantages

- High cost
- Unpredictable and often poor *invitro, invivo* correlations
- Dose dumping
- Reduced potential for dosage adjustment
- Increased potential for first pass clearance and poor systemic availability
- Effective drug release period is influenced and limited by G.I. residence time for oral controlled release formulations

For many controlled-release products, the release rate can be altered by various factors including food and the transit through the gut. There may be some differences in the release rate one dose to another, but these have been minimized by modern formulations. Extended-release products contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage forms has potential problems. While some extended-release products can be divided to provide half-doses, others should only be taken whole Modified release products should never be crushed or chewed as the slow release characteristics may be lost and toxicity may result (Schall R, et al., 1997). This is particularly important in patients unable to swallow whole tablets, a problem commonly affecting the elderly. The large size of extended-release products may cause difficulties in ingestion or transit through the gut. These problems may result in some drugs, e.g. slow-K, causing local tissue damage in patients who have a pathological or drug-induced reduction in gut motility.

### Rational for extended-release dosage forms:

Increase in time interval required between doses. This provides a reduction in the total number of doses required per day. Reduction in fluctuation of drug blood levels about the mean. A controlled release dosage form decrease the drug concentration’s fluctuation by

1. **Reducing the blood levels** ($C_{max}$) thus potentially reducing dose related adverse effects and
2. **Increasing the minimum plasma concentration** ($C_{min}$) thereby increasing efficacy if a threshold concentration is required. The plasma concentration stays within therapeutic range that is “therapeutic occupancy time”.

### Potential bioavailability problem of extended release products

The potential problems inherent in oral extended-release dosage forms generally related to,

1. Interaction between the rate, extent and location that the dosage form release the drug
2. The regional differences in G.I tract physiology (Aggarwal, et al., 2001)

Some potential problems requiring evaluation are as follows:

- GI transit times and regional absorption
- Decreased systemic availability due to incomplete absorption
- Decreased bioavailability due to increased first pass metabolism
- Dose dumping
- Effect of food
- Effect of diurnal variation
- Increased variability

### Characteristic that makes a drug unsuitable for extended-release formulation:

- Short elimination half-life, <2 hr

<table>
<thead>
<tr>
<th>Extended-Release Osmotic</th>
<th>Searle</th>
<th>Covera-HS</th>
<th>Verapamil HCl</th>
<th>A COER osmotic system</th>
<th>Antihypertensive, Antianginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended Release</td>
<td>Biovail</td>
<td>Tramadol HCL</td>
<td>Tablets-release tablet with ethyl cellulose polymer</td>
<td>Analgesic</td>
<td></td>
</tr>
<tr>
<td>Extended Release Film Coat</td>
<td>Mylan</td>
<td>Ansaid</td>
<td>Flurbiprofen tablet</td>
<td>Tablets film coated, Enteric coated with, carnauba wax, and micro crystal loose polymer.</td>
<td>Analgesic Anti inflammatory</td>
</tr>
<tr>
<td>Extended Release Film Coat</td>
<td>Merck</td>
<td>Relafen</td>
<td>Nalbumeone tablet</td>
<td>Tablet film coated with microcrystalline cellulose polymer.</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Extended Release(sodas)</td>
<td>GlaxoSmithKline</td>
<td>Innopran XL</td>
<td>Propranolol HCL</td>
<td>Microencapsulation (beads)(Sodas) speroid oral drug absorption system.</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Extended Release Hydrophilic/Erosion Matrix</td>
<td>Merck</td>
<td>Dolobid</td>
<td>Diflunisal tablet</td>
<td>Tablet hydrophilic matrix system, based on polymer hydroxypropyl methylcellulose</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Extended Release Coated Particle Beads</td>
<td>Noven</td>
<td>Ritalin LA</td>
<td>Methylphenidate hydrochloride capsule</td>
<td>Extended-Release Microencapsulation(beads)</td>
<td>CNS stimulant</td>
</tr>
<tr>
<td>Extended Release Film Coat</td>
<td>AstraZeneca</td>
<td>Seroquel XR</td>
<td>Quetiapine fumarate</td>
<td>Tablets film coated with microcrystalline cellulose polymer</td>
<td>Psychotropic agent</td>
</tr>
</tbody>
</table>
- Long elimination half-life, >8 hr
- Narrow therapeutic index
- Large doses
- Poor absorption
- Active absorption
- Low or slow solubility
- Time course of circulating drug different to that of pharmacological effect
- Extensive first-pass clearance

**Characteristic that makes a drugs are suitable for extended-release formulation:**

The extent of fluctuation in the 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 concentration 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 intervals will result in higher peak concentration with the possibility of toxicity. For some drugs with wide margins of safety, this approach may be satisfactory, e.g. amoxicillin has a half-life of approximately one hour, but a dosage frequency of 8 hours. This means that very large fluctuations will occur within a dosing interval, but, in view of the concentrations 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 (Gohel, M.C. et al., 1995) e.g. amino glycosides.

**RELEASE RATE AND DOSE CONSIDERATION:**

The dosage forms can be considered to release their active drugs into an absorption pool immediately (Robinson JR, 1966). Conventional dosage forms include solutions, capsules, tablets, emulsions, etc.

![Diagram](image)

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

- The drug binds to the tissues e.g. tissue-bound ACE inhibitors. For these drugs, less frequent dosing is needed even though the drug may have a short half-life (Goodman and Gilman’s 1996).
- The drugs have irreversible effects e.g. the inhibition of platelet cyclo-oxygenase by aspirin.
- The relationship between response and plasma/blood concentration is relatively flat or if the dose given results in concentration which are in the plateau region of the dose-response relationship e.g. thiazides in hypertension.
- To pharmacologically The drug is metabolized active metabolite(s) which are more slowly cleared then the parent drug e.g. Quinapril, trandolapril, venlafaxine.

For immediate release dosage forms $K_r \gg \gg K_a$ or alternatively absorption of drug across a biological membrane is the rate-limiting step in delivery of the drug to its target area.

For non-immediate release dosage forms, $K_r \ll K_a$, that is, release of drug from the dosage form is the rate limiting step. This cause the above kinetics scheme to reduce to.

Thus, the effort to develop a delivery system that release drug slowly must be directed primarily at altering the release rate by affecting the value of $K_r$. The ideal goal in designing a controlled-release system is to deliver drug to the desired site at a rate...
according to needs of the body, i.e. a self-regulated system based on feedback control but this is a difficult assignment. The pivotal question is at what rate should drug be delivered to maintain a constant blood drug level? This constant rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at constants rates just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. That is, release from the dosage form should follow zero-order kinetics, as shown by

\[ K_D = \frac{\text{Rate In}}{\text{Rate out}} = K_1 C_d V_d \]

\[ K_1 = \text{Zero order rate constant for drug release (amount/time)} \]
\[ K_{\infty} = \text{First order rate constant for overall drug elimination time} \]
\[ C_d = \text{Desired drug level in the body (amount/volume)} \]
\[ V_d = \text{Volume space in which the drug is distributed.} \]

To achieve a therapeutic level promptly and sustain the level for a given period of time, the dosage from generally consist of two parts: an initial primary dose, \( D_0 \), which release drug immediately and a maintenance or sustaining dose, \( D_{\infty} \).

The total dose, \( W \), thus required for the system is

\[ W = D_0 + D_{\infty} \]

To maintain drug blood levels with the therapeutic range over the entire time course of therapy, most controlled-release drug delivery systems are, like conventional dosage forms, administered as multiple rather than single doses. For an ideal controlled-release system that releases drug by zero-order kinetics, the multiple dosing regimens are analogous to that used for a constant intravenous infusion. For those controlled-release systems having release kinetics other than zero-order, the multiple dosing regimens are more complex (Williams PG., et al, 1989).

Types of extended release products

**Diffusion-controlled products**

In these systems, there is a water-insoluble polymer which controls the flow of water and the subsequent egress of dissolved drug from the dosage form. Both diffusion and dissolution processes are involved. In reservoir devices, a core of drug is coated with the polymer and, in matrix systems; the drug is dispersed throughout the matrix. Cellulose derivatives are commonly used in the reservoir types, while the matrix material may be plastics, e.g. methylacrylate-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, slow-K, and kapanol.

**Dissolution-controlled products**

In these products, the rate dissolution of the drug (and thereby availability for absorption) is controlled by slowly soluble polymer or by microencapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate drug release can be controlled (Marcel Deker 1987). Some preparations contain a fraction of the total dose as an immediate-release component to provide a pulse dose soon after administration. The pellets dosage forms of diffusion-or dissolution controlled products can be encapsulated or prepared as a tablet. These products should not be chewed as the coating may be damaged. One of advantages of encapsulated pelleted products is that the onset of absorption is less sensitive to stomach empting. The entrance of the pellets into the small intestine (where the majority of drug absorption occurs) is usually more uniform than with non-disintegrating extended-release tablet formulations. An example of this type of product is Fefol.

**Erosion products**

The release of drug from these products is controlled by the erosion rate of a carrier matrix. The rate of drug from these products is controlled by the erosion (Rippie, E.G et al1969). An example of this formulation is sine met CR, with this product; some patients may experience a later onset of effect after the morning dose, compared to conventional levodopa tablets, because of the delayed release of the drug.

**Osmotic pump systems**

The rate release of drug in these products is determined by the constant inflow of water across a semi permeable membrane into a reservoir which contains an osmotic agent. The rate release is constant and can be controlled within tight limits yielding relatively constant blood concentration (Selly, J.P.et al 1999). 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.

**Ion exchange resins**

Some drugs can be bound to ion exchange resins and, when ingested, the release of drug is determined by the ionic environment within the gastrointestinal tract(Rampise NS.et al 2010) Examples of this type of product are duromine containing the basic drug phentermine complexed onto an anionic resin, and MS contin suspension which uses a polystyrene sulphonate resin.

**Switching To Extended-Release Products**

Where a prescriber wishes to transfer a patient from an immediate-release to an extended-release product, generally to equivalent total daily dose should be the same (Lin, S.Y.et al1989). In some cases, an effective response of the extended release product. In view of the complexity of extended release product and
the potential for greater variability, both inter-and intra-subject, patients should be monitored to ensure that the anticipated benefit of switching to such products is actually obtained.

Resolution management guidelines

People with developmental and intellectual disabilities (Tran TT et al., 2009) In future the new patient management resource for the disabilities covers the general practice care of people with disabilities as well as broader social, developmental and environmental issues. Now current research rapid growing for assessment, communication and management of people with development and intellectual disabilities for specific syndromes such as autism, Down’s syndrome, psychiatric disorders, epilepsy, sexuality, women’s health issues. The new edition of therapeutic guidelines: cardiovascular focuses on the primary management of cardiovascular disease. In revising this text, the writing group has paid attention to multiple risk factor management and the current evidence-based approach to rheumatoid arthritis and osteoarthritis.

CONCLUSION

Wide range of drugs is formulated now in a variety of different per oral extended-release dosage forms. However, only those which result in a significant reduction in dose frequency and/or a reduction in toxicity resulting from high concentration in the blood or gastrointestinal tract are likely to improve therapeutic outcomes. To be a successful extended-release product, the drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time, and may be absorbed at a rate and will replace the amount of drug being metabolized and excreted. The per oral extended release formulations must have the following properties. They exhibit neither very slow nor very fast rates of absorption and excretion. They are uniformly absorbed from the gastrointestinal tract. They are administered in relatively small doses. They possess a good margin of study. And they are used in the treatment of chronic rather than acute conditions. Clinical considerations in the use of Oral-release Dosage forms: Patients should be advised of the dose and dosing frequency of extended-release products. Patients stabilized on a extended-release products should not be changed to an immediate-release products without consideration of any existing blood level concentration of the drug. Also, once stabilized, patients should not be changed to another extended-release product unless there is assurance of equivalent bioavailability.

The life cycle of a drug includes introduction of the new molecule entity, initial product introduction, and later, possibly a new patient or patients obtained by the introduction of controlled release formulation of the existing immediate-release products. This and the addition of new therapeutic indications for these products provide an attractive financial option for pharmaceutical companies.

REFERENCES

Ranpise NS, Kulkarni NS, Mair PD, Ranade AN. Improvement of water solubility and in vitro dissolution rate of aceclofenac by complexation with beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin. Pharm Dev Technol. 2010; 64-70.