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Modified-release preparations

With the ever increasing number of modified-release preparations on the market, the debate continues as to whether these products actually fulfil a clinical need or are merely premium priced line-extensions to encourage brand name prescribing.

The recent NHS performance indicators document[1] has once again highlighted modified-release (m/r) preparations as an area where there is often unnecessary prescribing. M/R preparations tend to be relatively expensive and in many cases, the clinical need could be met by a cheaper alternative. This *Bulletin* discusses the various factors that need to be taken into account when deciding if an m/r preparation is appropriate.

What is modified-release?

The term modified-release defines preparations that have been designed in such a way that the **rate or place at which the active ingredients are released has been modified**.[2] This is an all encompassing term that the BNF now uses to cover preparations such as sustained-release, controlled-release and delayed-release. Although theoretically covered by m/r, the BNF has retained the separate term enteric coated.

The sole use of the term modified-release is helpful to simplify the confusing terminology. However, its use conceals the differences between the drug delivery systems, which may be defined as:

SUMMARY

* The use of a modified-release (m/r) preparation cannot be justified unless it offers clear clinical advantages over, often less expensive, conventional-release preparations.
* M/R preparations may be prescribed to:
  - reduce the dosing frequency and improve patient compliance;
  - reduce fluctuations (peaks and troughs) in drug plasma concentrations, in order to reduce concentration-related side-effects or improve effectiveness;
  - control the site of drug delivery in the gastrointestinal tract.
* There is little good quality evidence to suggest that once daily dosing has a clear clinical advantage over twice daily dosing. Missing a once daily dose can result in long periods of subtherapeutic plasma concentrations. Therefore, twice daily dosing may be preferred in patients known to miss doses.
* **Prescribers should always consider whether an m/r preparation is clinically justified**. For those limited situations where this is the case, prescribing by brand ensures the correct preparation is dispensed. Brand name prescribing is particularly important for m/r preparations of **theophylline**, **nifedipine** and **diltiazem**, as there is concern over the clinical implications of switching between inequivalent preparations.
* In general, m/r preparations should be reserved for specific patients where there is a problem with compliance, effectiveness or side-effects which these preparations could help overcome.

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- **Sustained-release** - the drug is released slowly at a rate governed by the delivery system.[3]
- **Controlled-release** - the drug is released at a constant rate and plasma concentrations after administration do not vary with time.[3]
- **Delayed-release** - the drug is released at a time other than immediately after administration[3] i.e. the site of release is controlled.

There are many mechanisms by which drug release from a preparation can be modified (see **table 1**).

Pharmaceutical modification The rate of drug release is reduced by increasing particle size or forming insoluble crystals e.g. *Tegretol Retard* or *Adalat Retard*.
Coated pellets Drug pellets are coated with a slowly dissolving polymer of varying thickness for varied release. The pellets can either be compressed into a tablet or put in a gelatin capsule e.g. *Fenbid*, *Slo-Phyllin* or *Inderal-LA*.
Insoluble matrix The drug is dispersed within an insoluble porous matrix. As fluid enters the matrix, the drug is dissolved and diffuses out slowly e.g. *Slow-K*, *Imdur* or *Betaloc-SA*.
Eroding matrix The drug is dispersed within a soluble matrix. As the matrix is eroded, the drug is slowly released e.g. *MST Continus* or *Phyllocontin Continus*.
Osmotic pump The drug and an osmotic agent are enclosed by a semipermeable membrane. As water is drawn into the tablet, dissolved drug is released in a controlled way through a laser-drilled hole e.g. *Volmax*, *Adalat LA*.
pH sensitive coating The formulation is coated with a polymer of pH dependent solubility for site specific delivery. This can either avoid drug release in the stomach (enteric coating) e.g. *Nu-Seals Aspirin*, or specifically deliver drug to the colon e.g. *Asacol*.

Table 1. Some mechanisms of modified drug release

Why prescribe a modified-release preparation?

M/R preparations may be prescribed to:
- reduce the dosing frequency and **improve patient compliance**;
- **reduce fluctuations** (peaks and troughs) in drug plasma concentrations, in order to reduce concentration-related side-effects or improve effectiveness;
- control the **site of drug delivery** in the gastrointestinal (GI) tract.

Generally, the use of an m/r preparation cannot be justified unless it offers clear clinical advantages over, often less expensive, conventional-release preparations.

Improving patient compliance

By slowing the rate of drug release, m/r preparations allow drugs with short half-lives to be administered less frequently. It is generally well accepted that, for the majority of patients, reducing the dosing frequency to once or twice daily improves compliance.[4]

However, **there is little good quality evidence to suggest that once daily dosing has a clear clinical advantage over twice daily dosing.** Most studies have shown that compliance is either the same, or slightly improved, with a once daily preparation.[5-11] Whilst this improvement has reached statistical significance in some studies,[10-11] its clinical significance is less clear.

The *'once a day is best'* belief is heavily promoted by manufacturers. However, this can have drawbacks. Patients may forget that a dose has already been taken and repeat it later in the day.[11] They may also miss a dose completely. Missing a dose is a particular problem with a once daily preparation as it can result in long periods where drug plasma concentrations are subtherapeutic. Twice daily dosing may, therefore, be preferred, especially if the patient is known to miss doses.[12]

There are many reasons for noncompliance. Polypharmacy is often a factor[11] and the number of drugs should be reviewed and reduced to a minimum before considering m/r preparations. Patients' understanding of their condition and treatment should also be addressed if compliance is a problem.

Reducing fluctuations in drug plasma concentrations

By slowing the rate of drug release, and hence absorption, m/r preparations aim to provide close to constant plasma concentrations over a prolonged period of time.[13]

Levelling out the plasma profile can be advantageous, but only for drugs where there is a close correlation between plasma concentration and either therapeutic effect or toxicity. Reducing high peak plasma concentrations can reduce concentration-related side-effects, particularly for rapidly absorbed drugs such as nifedipine.[14] Minimising the trough may improve effectiveness, for example in maintaining 24-hour blood pressure control with certain antihypertensive agents.[15]

M/R preparations are often used for drugs with a **narrow therapeutic index**, such as theophylline and lithium. This may help to maintain the plasma concentration within the limits of effectiveness and toxicity.[13]

Controlling the site of delivery

M/R preparations can be developed to deliver a drug to a specific site in the GI tract. For example, enteric coated preparations direct delivery to the small intestine, preventing drug release in the stomach. This aims to either protect the stomach from the drug, or protect the drug from the degrading environment of the stomach. Other preparations, such as those containing aminosalicylates for inflammatory bowel disease, are formulated to allow site specific delivery to the colon or small intestine to exert local effects.

Which drugs are suitable as m/r preparations?

Apart from formulations that control the site of drug delivery, most m/r preparations slow the

rate of drug release. To ensure maximum absorption from these preparations, it is essential that the drug is well absorbed throughout the entire GI tract. Drugs which are absorbed only at specific sites, such as iron[16], folic acid and vitamin B_{12}, are not suitable as m/r preparations.[13]

Drugs with a narrow therapeutic index, those which are rapidly absorbed, and those with a short duration of action are often formulated into m/r preparations. Drugs with a long duration of action, such as amitriptyline, do not need to be given frequently and an m/r preparation is unnecessary.

It is also important to consider whether the therapeutic area lends itself to the use of m/r preparations. For example, m/r analgesic preparations with a slow onset of action are of little value when immediate pain relief is required.

For some drugs, an m/r preparation can offer clinical advantages. If **theophylline** is prescribed for nocturnal asthma and early morning wheezing, an m/r preparation given as a single dose at night is advisable.[16] The slow release of theophylline decreases side-effects seen with rapid absorption and ensures therapeutic levels are maintained throughout the night, provided a suitable dose is prescribed.

If **nifedipine** is prescribed for angina or hypertension, an m/r preparation is recommended. Short-acting preparations have been associated with large variations in blood pressure and reflex tachycardia.[16] They have also been controversially linked to an increase in the risk of cardiovascular events (see *MeReC Bulletin* Vol. 9 No. 4). A recent, randomised double-blind trial in 6321 patients with hypertension found *Adalat LA* (a once daily m/r nifedipine preparation) to be as effective as co-amilozide (amiloride/hydrochlorothiazide) in preventing overall cardiovascular or cerebrovascular complications.[17] PRODIGY guidance for prescribing nifedipine in angina and hypertension only offers the drug as an m/r preparation prescribed by brand name.[18]

Conventional-release **carbamazepine** is often prescribed three or four times a day for epilepsy. M/R preparations allow twice daily dosing and may also reduce the incidence of dose-related side-effects.[16,19]

What are the problems with m/r preparations?

The release of a drug from an m/r preparation is dependent on changes in GI transit time. In patients with 'GI hurry' some of the dose may be lost if the preparation passes through the body before drug release is complete. Conversely, if the transit time is delayed, excessive release of the drug or 'dose dumping' can occur. This may cause local GI damage (e.g. with NSAIDs), or acute systemic toxicity.

Breaking, chewing or crushing an m/r preparation can result in the immediate release of possibly toxic amounts of drug. Therefore, patients should be told to swallow most m/r preparations whole. To avoid undue concern, patients should also be informed if there is a possibility of the tablet shell passing through the GI tract unchanged, as with *Slow-K*.

By slowing the rate of drug release and prolonging its action, m/r preparations can cause problems if taken in overdose or if a severe adverse reaction occurs.

Prescribing issues

Prescribers should always consider whether an m/r preparation is clinically justified. This decision should be based on both good quality clinical evidence and the individual requirements of the patient.

For those limited situations where an m/r preparation is appropriate, it is important that the correct preparation, i.e. that intended by the prescriber, is dispensed. As confusion can arise if such prescriptions are written generically, it seems sensible to recommend brand name prescribing for m/r preparations. Of more importance is the problem that different m/r preparations of the same drug have different release characteristics. Therefore, bioequivalence cannot be assumed and all m/r preparations are licensed by brand name.

Switching between m/r preparations of drugs with a narrow therapeutic index may have serious clinical consequences. Therefore, both the Royal Pharmaceutical Society and the BNF recommend brand name prescribing for m/r **theophylline** (or aminophylline) preparations.[16,20] This is also advisable for all formulations of **lithium**.

Brand name prescribing is also recommended for m/r preparations of **nifedipine** and longer-acting **diltiazem**[16,20] where numerous formulations exist. These preparations are available in different strengths and have different licensed dosage regimens (see **table 2**). They are not interchangeable and, due to different release characteristics, even formulations containing the same strength of drug may not be bioequivalent.

If a prescription for an m/r preparation of theophylline, nifedipine or diltiazem is written generically, the pharmacist should contact the prescriber to agree the brand before dispensing.[20]

When local formularies are put in place it would be useful, if an m/r preparation is considered appropriate, to select just one or two brands for inclusion. This ensures familiarity for prescribers and pharmacists, while preventing the need for pharmacies to stock many different brands of one drug. The decision to include a particular brand should be based on licensed indications, supporting clinical evidence, cost and availability. Close collaboration between primary and secondary care is also necessary to ensure treatment continuity for patients.

Conclusion

Many m/r preparations offer no clinical advantage and their use cannot be justified over equally effective, often less expensive, conventional-release preparations in the same class. For some drugs e.g. nifedipine, m/r

Brand name	Available strengths	Licensed dose range	Cost of 28 days therapy
Diltiazem (longer-acting*) once daily m/r preparations			
Adizem XL capsules	120mg, 180mg, 240mg, 300mg	120-300mg once daily	£10.24 - £12.90
Angitil XL capsules	240mg, 300mg	240-300mg once daily	£9.22 - £10.15
Dilzem XL capsules	120mg, 180mg, 240mg	120-360mg once daily	£8.32 - £20.02
Optil XL capsules	240mg, 300mg	240-300mg once daily	£9.22 - £10.15
Slozem capsules	120mg, 180mg, 240mg	120-360mg once daily	£7.00 - £15.20
Tildiem LA capsules	200mg, 300mg	200-500mg once daily	£11.61 - £24.41
Viazem XL capsules	120mg, 180mg, 240mg, 300mg, 360mg	120-360mg once daily	£8.82 - £17.65
Zemtard XL capsules	120mg, 180mg, 240mg, 300mg	120-480mg once daily	£7.65 - £16.30
Diltiazem (longer-acting*) twice daily m/r preparations			
Adizem SR capsules†	90mg, 120mg, 180mg	90-180mg twice daily	£10.56 - £17.60
Angiozem CR tablets	90mg, 120mg	120mg daily-480mg daily in divided doses	£5.53 - £22.12
Angitil SR capsules	90mg, 120mg, 180mg	90-180mg twice daily	£8.45 - £14.08
Bi-Carzem SR capsules	60mg, 90mg, 120mg	60-180mg twice daily	£8.00 - £20.00
Calcicard CR tablets	90mg, 120mg	120mg daily-480mg daily in divided doses	£6.15 - £24.58
Dilcardia SR capsules	60mg, 90mg, 120mg	60-180mg twice daily	£8.30 - £19.79
Dilzem SR capsules	60mg, 90mg, 120mg	60-180mg twice daily	£8.32 - £20.79
Optil SR capsules	90mg, 120mg, 180mg	90-180mg twice daily	£8.45 - £14.08
Tildiem Retard tablets	90mg, 120mg	120mg daily-480mg daily in divided doses	£5.53 - £22.12
Nifedipine once daily m/r preparations			
Adalat LA tablets	20mg, 30mg, 60mg	20-90mg once daily	£8.15 - £25.29
Coracten XL capsules	30mg, 60mg	30-90mg once daily	£6.73 - £16.74
Fortipine LA 40 tablets	40mg	40-80mg daily in one or two divided doses	£7.47 - £14.93
Slofedipine XL tablets	30mg, 60mg	30-90mg once daily	£9.89 - £24.60
Nifedipine twice daily m/r preparations			
Adalat Retard tablets	10mg, 20mg	10-40mg twice daily	£8.50 - £20.40
Adipine MR tablets	10mg, 20mg	10-40mg twice daily	£6.62 - £16.52
Angiopine MR tablets	10mg, 20mg	10-40mg twice daily	£6.24 - £15.40
Cardilate MR tablets	10mg, 20mg	10-40mg twice daily	£6.93 - £20.55
Coracten SR capsules	10mg, 20mg	10-40mg twice daily	£5.83 - £16.18
Coroday MR tablets	20mg	20-40mg twice daily	£9.94 - £19.88
Hypolar Retard 20 tablets	20mg	20-40mg twice daily	£10.12 - £20.24
Nifedipress MR tablets	10mg, 20mg	10-40mg twice daily	£6.62 - £16.52
Nifopress Retard tablets	20mg	20-40mg twice daily	£4.50 - £9.00
Nimodrel MR tablets	10mg, 20mg	10-40mg twice daily	£6.62 - £16.52
Slofedipine tablets	20mg	20-40mg twice daily	£10.32 - £20.64
Tensipine MR tablets	10mg, 20mg	10-40mg twice daily	£7.62 - £19.02

Cost based on 28 days therapy over licensed dose ranges for both hypertension and angina (*Chemist and Druggist*, August 2000).

* Longer-acting formulations differ from the standard formulations of diltiazem 60mg, which are given three times a day. Although the standard formulations are strictly called 'm/r' due to their formulation, they are licensed as generics and there is no requirement for brand name prescribing.

† 120mg also available as tablets.

Table 2. Available diltiazem and nifedipine modified-release preparations

preparations have all but replaced conventional-release preparations. However, the relative merits of any m/r preparation must always be compared with those of other products in the same class. Generally, m/r preparations should be reserved for specific patients where their use would help overcome a particular problem with compliance, effectiveness, or side-effects.

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