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Infectious diseases

Formulation design: new drugs from old

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Advances in molecular biology, and of physiological and disease processes, often identify opportunities for improving the performance of a medication. Performance enhancement might concern providing more options for administration, less frequent administration or simply providing medication that is more acceptable to the user. Possibilities also exist, depending on the kinetics and dynamics of drug action, and its dose–response relationships for improving efficacy or reducing side effects.

Introduction

When a compound progresses to a medicinal product the complexities of disease and drug action, and the diversity of patient response can mean that nuances of drug behaviour might not be manifest in pre-commercial clinical trials. As the medication becomes more widely used, however, new insights might emerge on modes of action, side effects and patient response. At the same time, advances in molecular biology, receptor pharmacology, as well as better understanding of the clinical condition can create possibilities for new indications and better treatment of the existing indication by dosage form re-design. Concurrently, technologies might emerge to enable more efficient, effective or convenient ways of delivering drug.

Consequently, there is potential to “re-invent” established drugs by re-formulation so that they are safer, more effective

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The properties of any drug are a composite of the innate activity and properties of the compound as modulated by the formulation in which it is to be presented. To optimise their clinical effectiveness, the design of these formulations is becoming an increasingly important part of the development of new agents. However, the application of formulation technologies has also enabled the resurrection of older molecules and produced some surprising shifts in usage. Here, Crowley and Martini summarise how the understanding of physicochemical and pharmacological properties combined with formulation technologies has been applied to improve absorption (intestinal, buccal and transdermal) and prolong therapeutic effects in addition to allowing access to other routes of delivery (i.e. intrabronchial and so on). There are now multiple examples where the application of these principles has provided significant clinical benefit, in terms of effectiveness, safety or convenience, and has clearly provided a novel path forward for many older antibacterial agents.

or convenient. This article reviews such possibilities for creating “new drugs from old”.

Strategies for performance enhancement

Possibilities for enhancing the effect of a medication depend on the clinical condition being treated, the mode of action of the drug, including side effects, the dose–response relationship, its biopharmaceutical and physicochemical properties, and how it is administered. Table 1 summarises various possibilities and constraints.

Enhancing oral absorption

Many medicinal agents are highly lipophilic and poorly soluble because they are designed to optimise specificity and potency. Yet, a material must be in solution to be

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Table 1. Possibilities for improving performance of a medication

Strategy	Pro	Con	Latest developments	Who is working on the strategy? ^a	References
Improve absorption	Lower dose; more consistent plasma levels	No single "generic" approach	Many technologies are available that purport to evince this effect	Many organisations and groups offer diverse technologies	[1–9,12,13]
Deliver drug in a novel way	Enhance convenience and compliance and avoid first-pass metabolism	Dose usually must be low and physicochemical properties of drug must be suitable	There is currently much interest in intranasal and buccal delivery is for drugs destroyed by gastric acid or enzymatic digestion	Novadel	[10,11,17]
Prolong effect	Reduce dose frequency	Timecourse of action must reflect pharmacokinetics	Crowded field with respect to technologies and strategies	SkyePharma, Alza, Elan, Egalet, Perrigo (but field is crowded)	[18–20,24]
Enhance patient convenience	Can enhance compliance and hence efficacy	Usually only applicable to medicines for children	Strategy will be disease, patient and drug-specific	Egalet, Elan	[19,20]

^a Egalet, <http://www.egalet.com>; Elan, <http://www.elan.com>; Alza, <http://www.alza.com>; Novadel, <http://www.novadel.com>; Perrigo, http://www.perrigo.com/index_flash.shtml; SkyePharma, <http://www.skyepharma.com>.

transported to the systemic circulation. However, it must also be sufficiently lipophilic to partition from the aqueous intestinal contents to the enterocytes lining the small intestine. It might be difficult to incorporate such competing features in a chemical structure. Consequently, absorption might be sub-optimal, variable, dose dependent or combinations of these, leading to plasma level variations and unreliable therapeutic response or greater incidence of side effects. Local effects are also possible, consequent to poor absorption. Gastrointestinal side effects during treatment with broad-spectrum antibiotics have been ascribed to unabsorbed antibiotic killing symbiotic bacteria and subsequent overgrowth of resistant flora.

Absorption can be influenced by the physico-chemical properties of the drug, the amount administered and by patient physiology (including disease effects). Optimising absorption could involve using a different solid state form of the drug, altering the properties of the existing form,

formulation with materials that enhance absorption, exploiting the physiology of the gastrointestinal (GI) tract or capitalising on pre-hepatic metabolic and transport systems (Box 1).

Solubility or rate of dissolution can be improved by using a salt, or other solid-state form with higher solubility than the original form. A more soluble drug does not necessarily perform better *in vivo* because solubility in the GI tract might reflect local pH, presence of common ions or other solubility-determining conditions, regardless of the properties of input drug [1,2]. Nevertheless, there are cases whereby bioavailability was enhanced by judicious salt selection [3].

Rate of dissolution can be improved by reducing particle size to increase the interface with the dissolving medium. The bioavailability of the antifungal, griseofulvin, was so enhanced when micronised that the effective dose was reduced by 50% [4]. Nano-sized particles are now being considered to boost absorption of poorly soluble drugs. Plasma levels of the anti-inflammatory drug naproxen were higher and absorption was faster when administered orally to rats as nanoparticles, compared with conventional drug particles [5].

Techniques such as crystal engineering and molecular encapsulation have also been employed to enhance solubility. Co-crystal formation involves the crystalline alignment, during synthesis, of drug with materials having complementary crystallographic configurations. The dicarboxylic acids, succinic and tartaric acids, which are non-toxic seem particularly suitable for co-crystallisation with nitrogen heterocycles (*viz.* many drugs). Solubilities of co-crystal forms of the antifungal, itraconazole, were superior to that of the conventional crystalline form [6].

Cyclodextrins are cyclic glucose polymers with hydrophilic outer surfaces and hydrophobic cavities that can dimension-

Box 1. Formulation approaches for enhancing oral absorption

Enhance solubility and/or dissolution rate of the active ingredient

- Use a more soluble salt form of the drug
- Use other more soluble form, for example, amorphous form or more soluble polymorph

Alter rate of passage through the GI tract

- Slow transit rate by prolonging gastric retention or reducing intestinal transit rate

Surmount *in vivo* metabolic barriers

- Formulate for absorption via the lymphatic route
- Avoid P-glycoprotein (PGP) recycling
- Avoid Cytochrome P450 (CYP450) metabolism

ally accommodate compounds with molecular masses of 400–500. If the attraction between the pendant groups within the cavity and guest drug molecule is strong, a stable molar complex is formed with the good solubility of the host cyclodextrin. Dissociation “releases” the contained molecule in molecular dispersion that might facilitate absorption.

The GI tract and absorption

Absorption can be affected by gastric pH, GI motility and presence of food or other materials. Formulation to alter GI transit-time can, therefore, lead to more complete or more consistent absorption. Oleic acid, bile salts and lecithin reportedly slow gastric emptying and small intestinal transit rate, possibly allowing longer residence time for dissolution and absorption. However, results to date have been variable [7,8]. Citric acid and other organic acids have also been shown to slow gastric emptying [9]. However, the levels required might be too large, and therefore, impractical for most dosage forms.

Lymphatic absorption

The small intestine is drained by the hepatic portal vein, making the liver the first “port of call” following absorption from the small intestine. Levels of drug reaching general circulation can be greatly reduced by hepatic or pre-hepatic metabolism. Absorption via the lymphatic system offers the potential for avoiding such first-pass destruction [10]. Co-formulation with triglycerides enhanced lymphatic absorption of the antimalarial, halofantrine [11]. However, the low lymph-to-blood flow ratio restricts lymphatic absorption to highly lipophilic drugs ($\log P > 5$) that have good solubility in triglycerides (>50 mg/ml). Not many drugs have these features, so this route of absorption has limited potential.

Permeability enhancement

Hydrophilic molecules tend to remain in the intestinal lumen, not partitioning to the more lipophilic enterocyte wall. Co-formulation with so-called permeation enhancers can increase passage across the intestinal epithelium [12]. However, the maximum absorbable dose of a drug is a product of its solubility and permeability [13]. Although there is potential for significantly enhancing solubility, by using the approaches discussed earlier the scope for enhancing permeability is much less. Furthermore, permeability enhancers can damage intestinal epithelium during chronic dosage. They can also boost absorption of co-administered drugs, and thus affect safety. Nevertheless, they are being considered as formulation adjuvants for hydrophilic peptides that are potential therapeutic agents.

Surmounting metabolic barriers

P-glycoprotein (PGP) in the enterocytes ejects (or “recycles”) many lipophilic drugs [14]. Certain lipids have been reported

as being PGP inhibitors but there are no reports of use in commercial products.

Cytochrome P450 3A4 (CYP450) is responsible for pre-hepatic metabolism of many drugs. Grapefruit juice is reported to be a powerful inhibitor of this enzyme and enhances the bioavailability of cyclosporin, triazolam and nifedipine, all of which are metabolised by CYP450. The components in grapefruit juice that evince this effect are reputedly flavinoids [15,16]. Co-formulation of such materials with CYP450-susceptible drugs could result in higher and more consistent systemic levels. However, absorption of any co-administered medication that is also susceptible to pre-hepatic metabolism would be affected.

Novel modes of delivery

An ideal delivery system provides the right amount of drug to the right part of the body, at the right time and for the requisite period. Formulation strategies to attain such objectives include:

- delivering the same drug by a different route;
- prolonging the therapeutic effect;
- providing unique dosage regimens or plasma profiles;
- improving patient compliance.

Delivering the drug by a different route

Patient convenience and compliance can suffer if the drug has to be administered by injection or other inconvenient mode of delivery. Much effort has been expended for instance (albeit unsuccessfully to date) to develop a non-injectable form of insulin. There are many physical, enzymatic barriers to delivery by non-invasive routes in cases where oral dosage is not feasible: drug-related factors such as dose, and dose response can also be constraining. Despite such *caveats* there are outstanding examples of creative delivery, to optimise effect and reduce side effects. These include:

- delivery to the lungs by inhalation;
- transdermal delivery;
- delivery across nasal or buccal mucosa.

The antibiotic tobramycin is delivered to the endobronchial region in the treatment of cystic fibrosis as a solution by inhalation. Beta agonists and corticosteroids (alone or in combination) are also delivered by inhalation to treat asthma, providing rapid onset of bronchodilation in the case of beta agonists and reducing the dose of steroid, thereby avoiding side effects from the larger doses that would have to be given by the oral route.

Such delivery requires that dose of drug be low; otherwise the pleural cavity gets “flooded” with particles or liquid, leading to coughing and possible expulsion of inhaled drug. Dose response must also be relatively “flat” because most of

the delivered drug does not reach the pleural cavity but impacts various parts of the trachea and bronchial tree, leading to inconsistent levels at the site of action. An additional requirement, particularly with medication for children is that the drug does not have an objectionable taste as some particles impact taste buds at the back of the oral cavity when inhaled.

The delivery (inhalation) device is a crucial component in such delivery systems and needs to be patient-friendly, robust and capable of reliably delivering an accurate dose.

Traditionally, antibacterials and antiseptics have been formulated as ointments, creams or lotions, for application to wounded, infected or otherwise traumatised skin surfaces to evince a “local” effect. A more esoteric mode of dosage is to deliver therapeutic agents across intact skin. Once again, the physicochemical properties, potency and pharmacodynamics of the drug need to be appropriate, with high potency (low dose) as a pre-requisite. This rules out virtually all current conventional anti-infectives owing to their high dose but, conceptually this mode of delivery could be feasible for any future low-dose antibacterials or antivirals.

With respect to other therapeutic areas, the motion-sickness drug, scopolamine is low dose, and has appropriate skin permeation characteristics to enable formulation as a transdermal patch. Peaks and troughs and their associated side effects are obviated by the slow delivery via the transdermal route (Fig. 1): a classic case of a “new drug from old”.

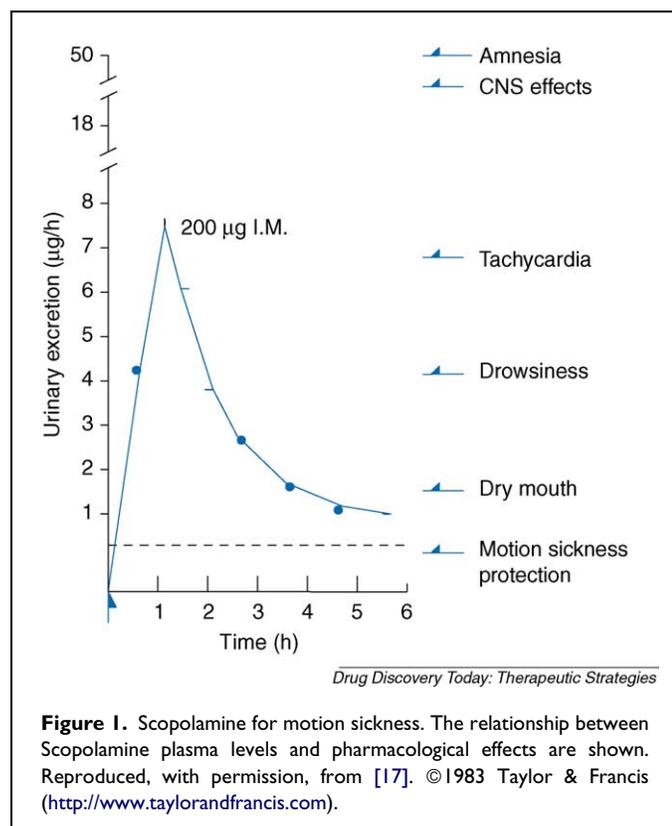


Figure 1. Scopolamine for motion sickness. The relationship between Scopolamine plasma levels and pharmacological effects are shown. Reproduced, with permission, from [17]. ©1983 Taylor & Francis (<http://www.taylorandfrancis.com>).

Transdermal delivery has merit where the disease is chronic, the patient might be forgetful or lack awareness (e.g. in Alzheimer’s disease) and where convenience and compliance are important. Medication can be delivered over longer periods than from an oral dosage form because delivery is not limited to the time taken for an oral dosage form to transit the region of good absorption in the GI tract (usually no more than about 6 h). Weekly application could be feasible. However, transdermal delivery is only possible with low dose drugs that are not irritant to or metabolised by the skin and have permeation characteristics that afford passage through the stratum corneum [17]. Attempts have been made to broaden its applicability by co-formulating drug with penetration enhancers to disrupt the stratum corneum or by using forms of energy such as iontophoresis or phonophoresis to “power” transdermal flux (micro-size power devices being incorporated in the patch). However, success has been limited and side effects such as irritancy by the enhancers or devices have constrained applicability.

Delivery across nasal or buccal mucosa affords opportunities for delivering peptides or other labile drugs that are highly potent (low dose) and do not have steep dose-response relationships. These routes usually provide rapid onset of action, making them attractive for conditions such as angina, asthma, and migraine. An additional advantage can concern clinical states that militate against oral dosage, for example, motion sickness or migraine. Knowledge to define target pharmacokinetic profiles for such delivery might not always be available when developing a compound for first commercial product. Hence, such delivery systems are invariably “second generation”.

Prolonging the therapeutic effect

If there is a good association between timecourse of drug in the biosystem, and pharmacological activity there is a rationale for prolonging systemic levels beyond the time dictated by the pharmacokinetics of the drug. This is theoretically achievable by slowing the rate of absorption, which in turn might be achieved by slowing release of drug from the dosage form. As the relationships between kinetics and the dynamics of drug action cannot be easily determined during a fast-moving development programme, such modified release presentations tend to be “second generation” products.

Antibacterials are probably an exception to the general rule that preclinical studies do not usually provide useful information on the time course of drug action. It is somewhat surprising therefore, bearing in mind the usually good association between animal efficacy studies and performance in humans that traditional antibacterial medications have invariably been “immediate release” units, that is, there have been few attempts to modify the pharmacokinetics or other delivery characteristics to evince a better therapeutic effect or reduce dosing frequency. This might reflect the non-chronic

Table 2. Antibiotic products providing prolonged plasma levels

Product	Dosing regimen	Advantage
Augmentin XR (amoxicillin–clavulanate)	Twice daily	Efficacy against resistant respiratory organisms
Biaxin XL (clarithromycin)	Once daily	Improved compliance and tolerability
Cipro XR/XL (ciprofloxacin)	Once daily	Higher plasma concentrations and lower inter-subject variability

nature of much antibacterial therapy. A twice or thrice daily dosage regimen is not such a burden over a 5–10-day treatment period compared to, for example treating hypertension, where once-daily preparations abound. The situation might be changing however. Sustained release presentations of amoxicillin–clavulanate, ciprofloxacin and clarithromycin have recently been made available (Table 2) [18–20]. In the case of the former product, the intent is to provide pharmacokinetic cover for efficacy against resistant upper respiratory tract pathogens. The finding that “time above MIC” is an important determinant of antibacterial activity and that, for amoxicillin this time must be in the region of 30% of the dosage interval (for activity against resistant *Streptococcus pneumoniae*) [21,22] provided a pharmacokinetic target for the design of Augmentin XR [23] (Fig. 2). The sustained release of clarithromycin and ciprofloxacin products provides more convenient dosage and might be better tolerated than the conventional products.

Providing unique dosage regimens or plasma profiles

A recent and novel concept for antibacterial therapy concerns “pulsing” the antibacterial agent, it being claimed that sub-inhibitory levels dosed as three or four pulses provides a more effective bactericidal effect, with reduction of the total dose administered [<http://www.advancispharm.com/innovations/technology>].

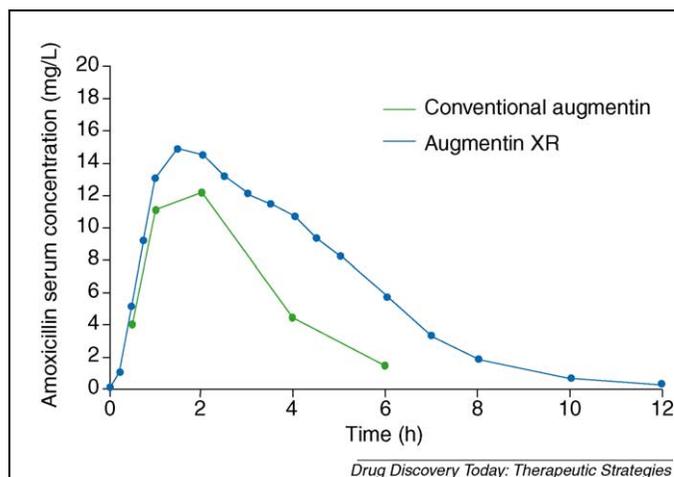


Figure 2. Plasma levels obtained with a pharmacokinetically enhanced, extended-release formulation of Augmentin (Augmentin XR) compared with conventional (immediate release) product. Reproduced, with permission, from [23].

The novel approaches to “re-inventing” antibacterial agents that are exemplified here are laudable, in the light of antibacterial resistance development and the continuing failure to find new agents with genuinely novel modes of action.

Choice of technology to modify release from the dosage form and prolong or otherwise influence activity is determined by factors such as pH-solubility profile of the drug, consistency of absorption throughout the GI tract and the pharmacokinetics, dynamics and dose–response relationships. Not every drug can be reformulated to modify its effects and a clear pharmacokinetic or plasma level target is required if a programme is to succeed. Properties required to make a drug amenable to formulation for prolonged action are summarised in Table 3 [24] but the over-riding requirement is that relationships between plasma levels, duration of action, and side effects are well established so that target plasma-time profiles can be defined.

Enhancing patient convenience

Patient convenience can be enhanced by many of the approaches listed here. For instance, less frequent dosage or non-invasive delivery can be expected to improve compliance. Reformulation of liquid oral products to improve taste can also be important for antibiotic products because children are a major patient group for such medication. This can be achieved by coating bitter tasting drug, use of a less soluble form (taste being a function of amount in solution) or altering pH to a value where palatability is better (or solubility less). Each case has to be judged on its merits and needs to bear in mind the physico-chemical properties of the drug in question.

Table 3. Ideal properties of drugs for formulation for prolonged release

Parameter	Ideal properties
Functional groups	Basic
Maximum dose (mg)	500
Solubility (mg/ml)	0.1–1.0 over range pH 1–8
Permeability (cm/s)	$>1.5 \times 10^{-5}$
Molecular weight (Da)	1–600
Partition coefficient (log P)	2–4
Elimination half life (h)	2–8
Therapeutic index	Wide
Stability in biological systems	Resists chemical, enzymatic and bacterial degradation

Conclusions and perspectives

The elucidation of the mechanisms of action of mature drugs, and of better insights on physiological and pathological processes, allied to the emergence of genomics, diagnostics and dosage form technologies provide many opportunities to develop new medications from mature drugs. Many such developments concern new clinical indications where conventional dosage forms are appropriate but there are also cases where creative dosage form design can give a drug a new lease of life.

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