

The trouble with making combination drugs

Drug compound interactions in a tablet are still difficult to predict

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Combining treatments into one tablet is becoming a more popular strategy than ever, and with good reason. Reducing the number of treatments that a patient needs to take increases compliance for long-term drug therapies, and simplifying disease management has proved to be crucial for treating conditions such as HIV in developing countries and cardiovascular disease in the Western world (see BOX 1). In lucrative developed-world markets, combination drugs have the added benefit of helping to cushion the impact of generic competition and to extend the life-cycle of top-selling drugs (BOX 2).

Two announcements in the past few weeks, though, have highlighted both the promise and pitfalls in creating combination treatments. The World Heart Federation has announced an initiative together with the Spanish National Centre for Cardiovascular Research to develop a polypill containing an angiotensin-converting enzyme (ACE) inhibitor, statin and aspirin for the secondary prevention of cardiovascular disease as early as 2009. Within days, Merck announced that it was delaying the approval submission of its 3-in-1 combination pill MK-524B for cholesterol because of an 'unspecified formulation problem'.

Although no one in the field disagrees with Merck's statement that the formulation issues with MK-524B are not a significant setback for the drug, they say that this serves as a vivid reminder that formulating and manufacturing combination drugs is not as straightforward as is widely thought. With more ambitious



Formulating combination drugs is much more difficult than widely thought.

combination drugs being proposed at a growing rate, researchers say they need to find ways of improving the science behind formulating combination drugs.

"Trial and error has worked pretty well for easy molecules, so there hasn't really been a great financial incentive to try to improve this situation," says Kenneth Morris, Professor of Industrial and Physical Pharmacy at Purdue University. "But as interest grows in developing more,

and more complex, combination drugs, we will need to develop the science that will allow the process to occur in a timely enough manner."

The difficulties in formulating and manufacturing combination drug products are often invisible to the wider community, and so the problems behind developing these drugs can be trivialized. Part of the problem is that an air of mystery still surrounds the field — perhaps unsurprisingly, as industry scientists are reluctant to discuss any company or product-sensitive information regarding the development of these treatments.

For chemists and engineers in the field, however, the issues behind formulating and manufacturing combination drugs are all too familiar. "Making a tablet out of one drug is an underrated problem in itself, so making a tablet out of multiple active pharmaceutical ingredients is a much tougher proposition," says Allan Myerson,

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Just because two or more treatments work in combination in a patient does not mean that they are amenable to packing into a single tablet. If the solid form of one drug is less soluble than another, this can affect how each drug gets released into the bloodstream. If one dose is much lower than another there can be problems in making sure that the low-dose drug is distributed uniformly in the tablet. Compounds can react with each other, either chemically or physically, or one compound might be chemically more stable than another, or more sensitive to moisture than another, all of which can affect the shelf-life of the drug.

At the moment formulating these combinations relies to a large degree on trial and error. To create a stable and effective combination drug, formulators typically try simple approaches first, such as altering formulations, and then move onto increasingly complex solutions like isolating the compounds in different layers. Naturally, the more complex the solution, the more time and effort that has to be spent finding it. “All the problems are, in a sense, solvable,” says Myerson. “It is just a matter of time and money.”

The development of Atripla, a 3-in-1 treatment for HIV that was approved by the FDA in July this year, illustrates some of the difficulties faced when developing combination drugs. Combining Gilead's

Box 1 | HIV and CVD combination drugs

Several fixed-dose combination drugs have been approved for HIV and cardiovascular disease, filling a real healthcare need for simpler and less costly treatment regimens.

HIV*

- Combivir (GlaxoSmithKline): zidovudine and lamivudine
- Truvada (Gilead): emtricitabine and tenofovir
- Epzicom (GlaxoSmithKline): abacavir and lamivudine
- Atripla (Gilead/Bristol Myers Squibb): emtricitabine/tenofovir and efavirenz
- Trizivir (GlaxoSmithKline): zidovudine/lamivudine and abacavir

Cardiovascular disease

- BiDil (NitroMed): isosorbide dinitrate and hydralazine hydrochloride
- Vytorin (Merck/Schering Plough): ezetimibe and simvastatin
- Caduet (Pfizer): amlodipine and atorvastatin

*Lamivudine/zidovudine and nevirapine has been tentatively approved by the FDA

Box 2 | Sustaining the success of statins through combination drugs

As well as increasing patient compliance, fixed-dose combinations can help prolong the life-cycle for lucrative drugs in Western markets. So it's no surprise that companies are looking to combine the blockbuster statins with other drugs.

- Zocor (simvastatin) plus niacin (MK-0524A) — Merck
- Crestor (rosuvastatin) plus fibrates (ABT-335) — AstraZeneca/Abbott
- Lipitor (atorvastatin) plus cholesteryl ester transfer protein (torcetrapib) — Pfizer
- Statin plus ACE inhibitor plus aspirin (specific treatment and company details unknown)

Truvada, itself a combination of tenofovir and emtricitabine, with Bristol-Myers Squibb's Sustiva (efavirenz) produced a mixture that melted easily — the first formulation in effect turned to glue. It took a year and four more formulations to produce a combination drug that could release the same level of the three drugs in a patient's blood as the three drugs taken separately. After much deliberation, the solution was to separate Truvada and Sustiva in layers within the tablet to allow each drug to dissolve at its own rate.

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The difficulty that researchers face is that they still have a poor understanding of how powdered drug compounds can interact within a tablet. A great deal is known about the behaviour within materials like metal powders. But much less is known about the interactions that go on between small organic molecular crystals, whose structures are much more flexible and held together with much weaker forces. Add to that the interactions of binders and excipients used in tablets, such as cellulose and starch, which can enhance and mask properties of an active pharmaceutical ingredient, and it's easy to see why formulators say that a greater theoretical understanding of the physical interactions that can take place between the solid forms of drug compounds is sorely needed.

There has been good progress in this area of material science over the years. For instance, engineers are now beginning to understand how compacting drugs into tablets can deform the particles of the active compound. But understanding the interactions that can go on in a drug is a long way from being a predictive science. What is really needed, says Morris, is a set of ‘mixing

rules’: guidelines that could help researchers predict what mixtures of components in what proportion will result in the drug product properties that are needed, or best avoided.

Some big companies have become very strong in the area of particle–particle interaction and prediction. But by and large companies have been reluctant to invest significant resources into this field, says Morris, as many view this part of the process “as a cost centre, not a profit centre”. Stephen Byrn, Head of the Department of Industrial and Physical Pharmacy, at Purdue, agrees. “These are long-term issues; this isn't something that companies are going to fund and get something that they are going to be able to use in a year,” says Byrn.

Byrn says the best solution is for governments to step in and fund academic research that actively includes industrial members. In Europe, there are already centres that specialize in drug formulation, such as the Basel-based Institute of Pharmaceutical Technology, led by Hans Leuenberger, and the Institute of Pharmaceutical Innovation headed by Peter York in the University of Bradford in the UK.

In the US, funding for industrial pharmacy programmes has decreased markedly over the past decade and a half, to the extent that a whole generation of potential expertise has effectively been lost. But a consortium of 11 universities led by several Purdue scientists called the National Institute of Pharmaceutical Technology and Education (NIPTE) hopes to change this. NIPTE is trying to stimulate the development of centres of excellence that combine the expertise of pharmaceutical sciences and engineers.

“These centres of excellence would help train scientists who could then go out and develop new strategies,” says Byrn. “The goal is to create some form of predictive rules so that we can look at particles, make some kind of measurements and then predict whether we could mix them without having something like degradation going on.” A bill to help set up these centres of excellence is now in Congress, and the consortium hopes to receive funding in 2008.