The potential value of nanomedicine and novel oral dosage forms in the treatment of HIV

James J Hobson¹, Andrew Owen² & Steve P Rannard^{*,1}

¹Department of Chemistry, University of Liverpool, Crown Street, Liverpool, L69 7ZD, UK

²Department of Molecular & Clinical Pharmacology, University of Liverpool, Pembroke Place, Liverpool, L69 3GF, UK

*Author for correspondence: S.P.Rannard@liverpool.ac.uk

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Despite the tremendous progress made in the fight against HIV/AIDS, it is still a global healthcare issue. The most recent estimates place the number of infected patients worldwide in excess of 36 million (upper limit >40 million) [1], but the success of antiretroviral therapies (ARV) can be observed as the significant decline in both mortality and morbidity of HIV+ patients [2]. This success has, however, led to the need for increasing access to ARVs, the majority of which are required in low- and middle-income countries. The lack of resources and an access to continuing clinical care mean that simple and patient-preferred dosage formulations are essential. Oral dosage forms are both easy to distribute and prescribe in resource limited settings, as well as consistently being the preferred administration route for patients receiving life-long medications.

The challenge for oral dosed nanomedicines

The oral administration route presents significant challenges for administration of ARVs, due to the inherent poor water solubility of many key regimen components, which in turn leads to high prescribed daily doses in order to achieve a therapeutic concentration *in vivo*. Although oral dosing is the preferred patient route, it does come with an associated pill burden and fatigue, which can negatively impact patient adherence. In diseases such as HIV, strict adherence with the ARV regimen is absolutely essential in order to prevent the emergence of resistant viral strains and subsequent treatment failure. Thus, there is a considerable scope for the improvement of current oral regimens and the reformulation of existing ARVs using nanotechnology and nanomedical approaches. An in-depth review of oral nanoformulations of ARVs has previously been reported [3]; the purpose of this editorial is to provide an overview of very recent developments in oral dosing for sustained release, tuned release and pediatric patients.

Oral dosing comes in many formats, including, but not limited to solid tablets, liquid capsules, soft gels, liquids and emulsions [4]. The format used for a given therapeutic will differ based upon the compatibility of the active within the formulation, and also after the consideration of the clinical setting. In pediatric patients for example, oral dosing is most practical in liquid form, but the challenge of solubilization of poorly water soluble ARVs renders this approach particularly troublesome. Children are a special patient population and cannot simply be thought of as ‘small adults’; as such there is also a particular need for easy dose tailoring. Indeed both pediatric and geriatric populations pose similar challenges in the development of effective drug formulations due to issues with swallowing tablets and the need for nonstandard dose sizes [5].

For solid dosage forms, strategies have been previously reported in which pills are split or ground into powders in order to try and alter the dosage of a standard sized tablet [6]. This can lead to problems with ensuring that accurate drug quantities are administered, as well as affecting the stability and efficacy of the active pharmaceutical ingredient (API) by breaking up the formulation. As many solid dosage forms have poor solubility in water, simply

dispersing a ground tablet into an aqueous liquid and attempting to alter the dosage by variation in administered volume is just not reproducible or effective.

Recent relevant advances for oral dosing

Very recent reports have focused on the development of a branched-polymer stabilised nanoemulsion that could be used to deliver poorly water-soluble drugs in aqueous systems. This was shown to be effective for two HIV drugs that are widely used (efavirenz and lopinavir), and delivered ‘on demand’ concentrations of active drug by simply diluting the stock emulsion with water [7]. The nanoemulsion also showed improved intestinal permeation in *in vitro* models, with no negative effects observed on antiviral activity when the drugs were encapsulated in the nanoemulsion. The nanoemulsion also appeared to protect against exposure to metabolic enzymes that would potentially cause inactivation, and to drug efflux transporters, such as p-glycoprotein [8]. Further work is now needed to validate this system in an *in vivo* setting, but this opens possibilities for easily achievable personal dosing of HIV therapeutics with improved bioavailability, which may be especially applicable to pediatric populations due to the liquid format.

For pediatric patients that can tolerate swallowing a tablet, other strategies to novel nanoformulations for pediatric patients include emulsion templated freeze drying and emulsion spray drying. Within recent reports, solid drug nanoparticles with high loadings of lopinavir and efavirenz, relative to inactive excipients, were described that could be delivered in a scalable tablet form [9,10]. Standard pediatric formulations of lopinavir are not widely available, and due to its poorly soluble nature, standard practice is to deliver the drug in combination with ritonavir in a large volume of alcohol (relative to drug), which is clearly not ideal for pediatric patients and neonates. The nanoformulation approach used in this work provided similar *in vivo* pharmacokinetic profiles for lopinavir, without the need for organic solvents. In combination, the work demonstrated the potential advances within the nanomedicine field that are contributing to improved therapies.

A therapeutic area gaining increasing traction targets ‘personalized medicine’ [11], referring to any treatment that has been specifically designed for an individual or small patient group, based upon genetic or other patient-specific factors. Being able to tailor therapeutic regimens should lead to more effective (both in a sense of efficacy and cost) and well-tolerated outcomes. In a proof of concept study, Sun and Soh demonstrated a novel method of producing orally dosed tablets with customizable release profiles [12]. Their unique approach utilized commercially available 3D printing technology to print a mold and cavity, into which dye (in place of a therapeutic drug) within a biodegradable polymer was cast. Surrounded by both a degradable polymer without dye and an impermeable polymer container, the release of the dye was tuned by simply altering the shape of the mold. They were able to demonstrate a multitude of release profiles including pulsing, increasing, decreasing and stepped release, but virtually any profile could be achieved in principle. The combination of two dyes being released from the same tablet, but with independent release profiles, was also shown. This would be of great use in the treatment of HIV, where it is necessary to combine multiple ARVs into a single regimen, often with large variations in metabolism rates. Sustained release profiles from tablets that have been produced via 3D printing techniques have also been demonstrated by Khaled *et al.* [13]. If these techniques are coupled with advances in the resolution achieved by commercial 3D printing, then it may be possible to produce very defined personalized tablets easily and cheaply. Combination with solid drug nanoparticles or drug-loaded nanocarriers may create effective future therapies.

Long-acting drug release

For HIV therapy, sustained release profiles over many days, weeks or months is of significant value. Much work is being undertaken to produce long-acting injectable formulations of ARVs [14], in which a depot of drug is injected directly into the muscle of patients. This depot then releases the drug at a steady rate, delivering therapeutic concentrations for up to 8 weeks after injection [15]. Long-acting dosage forms are the key to tackling the issue of patient adherence; however, injectable formulations are not tolerated by all patients and can include painful side effects at the site of injection. There is also the difficulty in providing access to long-acting injectables in resource limited settings, where the provision of trained healthcare workers to administer the injections is often absent. Work by Kirtane *et al.* has sought to improve adherence by developing a sustained release tablet formulation for three ARVs (dolutegravir, cabotegravir and rilpivirine) that was able to achieve therapeutic concentrations in plasma with once weekly dosing [16]. Their method consisted of forming a tablet with six drug-loaded flexible arms centered around a core of elastomer. The entire structure is packed into a capsule which dissolves in the stomach, allowing the tablet to fold out into a star shape. Each of the arms can be formulated with a different polymer, allowing for

differing or staggered release of numerous drug compounds, enabling sustained plasma concentrations. Addition of nano-engineered drug particles to this innovative delivery mechanism may greatly enhance the potential of the approach. This once weekly format is also particularly suitable for pre-exposure prophylactic treatment, in which at-risk HIV negative populations are given ARVs to prevent infection if exposed to the HIV virus. The authors conducted population-based mathematical modelling which predicted a once weekly oral pre-exposure prophylactic format providing up to 20% increased efficacy when compared with a daily oral format.

Conclusion

In summary, advances in the nanoformulation of existing therapeutics combined with novel delivery platforms, look set to continue to positively enhance currently available therapies. There is likely to be a shift towards more personalized medications, and thus improved efficacy of available regimens. This will not only assist in the fight against HIV/AIDS but could also extend to multiple disease states in which optimized drug regimen are lacking. Optimization of drug delivery should lead to reduction in the amount of drug required to produce a therapeutic benefit, thus increasing the number of patients who are able to access vital medicines. With the growing burden of chronic diseases, including HIV, on national healthcare provision globally, the scene is set for nanomedicine to extend its contribution outside of its traditional acute disease focus.

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