

From bench to bedside: designing oral drug formulations*

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The development of drugs over the last twenty years has yielded candidates which are more potent, but are more difficult to formulate into oral medicines. In addition, there is enthusiasm for employing extended release or colon targeted dosage forms for which the utility of in vitro tests is extremely limited.

Modern dose form design has turned to the adoption of clinical techniques, especially gamma scintigraphy, in which a non-absorbed additive such as a technetium-99m labelled radiopharmaceutical is added to the formulation. This allows the position of the formulation to be related to the plasma concentration-time profile so that each administration provides the maximum amount of information. Other techniques including magnetic resonance imaging and magnetic moment imaging are also useful. Variability in drug absorption in patients is a mix of physiological factors such as posture, the time of feeding relative to the dose and bowel habit together with factors imposed by formulation constraints: the need for water for disintegration and dissolution and the amount of agitation. Imaging techniques are extremely useful in disassembling these additive factors. Bench to bedside prediction is the ultimate goal but the influence of daily activity has to be borne in mind in formulation design.

Throughout the last fifty years, there has been a flowering in the design of drug delivery platforms. These efforts have included attempts to target specific regions of the gut in order to optimise drug exposure. Simple elements include delayed, extended and colon targeted systems, flash-dispersion systems, pelleted formulations and time-release devices. Sustained release systems became fashionable in the search for improvements in therapy, focusing on increased patient compliance with reduction of the potential risk of problems associated with fluctuating high and low tissue drug concentrations. Simple enteric coating allowed the pharmaceutical scientist to increase exposure within the small intestine. Further improvements achieved more than just avoiding acid degradation with the objective of treating the poorly accessible proximal colon. This held out the possibility of optimised treatment of diseases that show chronobiological patterns including neoplastic, respiratory, and gastrointestinal diseases (1) and improved treatment of conditions such as ulcerative colitis, which were difficult to treat effectively due to early loss of drug in the proximal gut.

Better analytical techniques generated data that assisted comparison between formulations of the same drug but did not always assist in optimisation of a medicine. Although pharmacological activity generally correlated well to the concentration of drug in plasma, variability in the absorption phase often did not allow formulation effects to be clearly discriminated. Central to the development of new dosage forms therefore was the increased use of imaging techniques to begin to relate the location of the formulation to the blood concentration-time profile; and using that data in the beginning of a physiologically based approach to pharmacokinetics (2–4). Later, the problems for formulators changed as larger, more hydrophobic entities caused problems of solubility and the small doses revealed the importance of gut efflux transporters, whose importance had been masked by the low potency of early drugs. Now we see a new generation of problems. Cheap drugs for all have to be balanced to the demand for individualised medicines: no longer 'one size fits all' but perhaps tailored oral dosage forms, especially for children and the elderly people.

The gut: survive, thrive, avoid

The gut is designed for the efficient absorption of food, although an unrefined diet is a mixture of nutrients, roughage and occasionally harmful nutrients or xenobiotic substances. The body must therefore balance the needs of adjusting the digestive process to maximise the efficiency of nutrient assimilation whilst minimising systemic exposure to poisons. As humans were originally hunter-gatherers, the unintentional ingestion of foreign compounds would have been a common occurrence since seeds from some genus of berries contain potent alkaloids: part of the armoury in the war between plants and animals. An initial physiological response to poisons is to notice the smell, the bitter or offensive taste and to spit out the offending material; however, Etkin reports that the Kenyah Leppo' Ke tribe of Borneo identify plant extracts that have strong chemosensory attributes to be effective medicines. Bitter-tasting extracts are selected for treatment of medical conditions associated with fever whereas astringent plants are used for the treatment of gastrointestinal disorders. The terpenoid content, particularly those that are highly volatile with a citrus-like smell and taste are prized (5).

The tablet or capsule is an extremely convenient method of transporting and delivering medicine. The dosage forms are aesthetically pleasing; the bad taste of medicine masked, and the product safe and efficacious. It is not until we start to undo the work of the formulator that we reveal new issues: children reject medicines with aftertaste and elderly patients may not be able to swallow their medication. The crushed tablets that they are given in nursing homes may be rendered ineffective, or simply forgotten. Revolutions in these fields will be slow to occur but they will happen provided that the healthcare environment nurtures commercial viability. So, there is scope for innovation.

Variability

In a perfect world, pharmacokinetic parameters are stable, materials have uniform solubility along the gut and factors such as regional permeability and transit are not important. For this reason, a direct relationship between the amount absorbed, calculated by deconvolution of the plasma

concentration-time profile, and the amount in solution (predicted from *in vitro* measurements) should be observable - a perfect *in vivo-in vitro* correlation (IVIVC). It is often remarked that every patient dosing is an experiment with an unknown outcome. This clinical aphorism is often relayed to students but is most pertinent when conducting clinical trials of new drugs of formulations in the clinic. Under rigorous conditions of dosing and close supervision, we expect to be able to reduce variability to such low levels that subtle effects of formulation are obvious. In practice, physiological factors often produce marked inter and intra-subject variation. Why should this be so?

To be effective, a drug must reach the desired site of action in sufficient quantities to activate the target receptors. This is influenced by three main groups of influences broadly classified into physico-chemical, pharmacological and physiological parameters. The factors are not independent and strong interactions occur; for example, low solubility or low absorptive flux would limit drug and/or metabolite absorption, if gastrointestinal transit were rapid but would be less evident when gut movements are slowed. In addition, the conditions in the gut vary, particularly with regard to pH, tightness of inter-cellular junctions and surface area. In pragmatic terms this gives rise to extreme variability between subjects, sometimes associated with an observable 'window of absorption', usually revealed by imaging or intubation studies.

Using imaging to identify transit issues in the gastrointestinal tract

The Anger gamma camera became a standard instrument in medical physics and radiopharmaceutical investigation in the late 1960s and was adopted by our group to measure whole gut transit (6). The key advantage of the technique was that simultaneous administration of technetium-99m and indium-111 allowed both the dosage form and the meal to be monitored and greatly helped in the interpretation of quote "windows of absorption" and meal effects. In addition, the number of applications of technetium-labelled chemistry increased, together with a wider range of imaging isotopes, and led to the adoption of gamma scintigraphy as a key method for

optimising formulations and understanding the relationship between behaviour of the dosage form in the gut or another organs, and the plasma concentration time profile.

In human volunteers, there is some concern about utilisation of radioisotopes and so alternative technologies are urgently sought. Weitschies and colleagues have investigated the labelling of dosage forms with magnetic material and then to use a magnetic sensor system to track the movement and dispersion of the formulation inside the gastrointestinal (GI) tract (7, 8). Two techniques are commonly used: a small amount of ferric oxide incorporated

into the formulation which is subsequently magnetised or, second, the formulation is labelled using a sealed small magnet with a very high magnetic moment. The first technique allows the operator to measure dispersion of the core of tablets and capsules whereas the second is useful for measuring transit of an object in the gut. Using a small portable detector coupled to a laptop, the performance of enteric coatings can be followed by constructing the core from ferric oxide and a binder and may be administered without worries about toxicity or radiation exposure (Figure 1).

Highly sensitive magnetic moment imaging is expensive and there is much interest in developing a smaller laptop control device. Small portable systems have begun to appear on the market, although sensitivity is limited and siting is important to avoid ferromagnetic disturbance. In collaboration with Prof. Weitschies (9), we have compared gamma scintigraphy and magnetic moment imaging in the same environment and found good agreement between the two techniques (Figure 2). We have also used magnetic resonance imaging; a technology that has shown great improvements over the last 15 years. A review of the 3 technologies was published recently (3).

The complexity provided by the dynamic interactions between control systems in the gut and the formulation provides a fascinating arena of study. Food, posture, disease and time of dosing all cause changes in the length of time that the dosage form will spend in different regions of the gastrointestinal tract. The pattern of transit also impacts on exposure, which may not be desired; for example, a tablet containing paracetamol will be converted to inactive metabolites in extensive metabolisers if oesophageal adhesion occurs (10). The ability of tablets to transit the oesophagus is related to several properties of the formulation including size, surface area, shape and coating. Channer and Virjee showed in 1985 that the clearance of plain, sugar-coated, enteric-coated and film-coated tablets in 34 patients was strongly influenced by coating and by posture (11). The authors reported 100% clearance of film-coated tablets in 13s; whereas full clearance of the plain uncoated formulation was observed in only 60% of subjects at this time. The tendency of a tablet to stick increases with surface area,

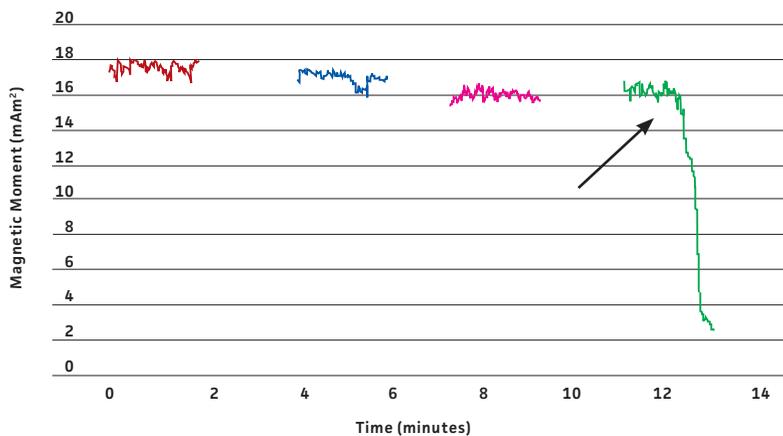


Figure 1. Loss of core integrity in an enteric-coated tablet at 12 minutes, measured by decrease in magnetic moment.

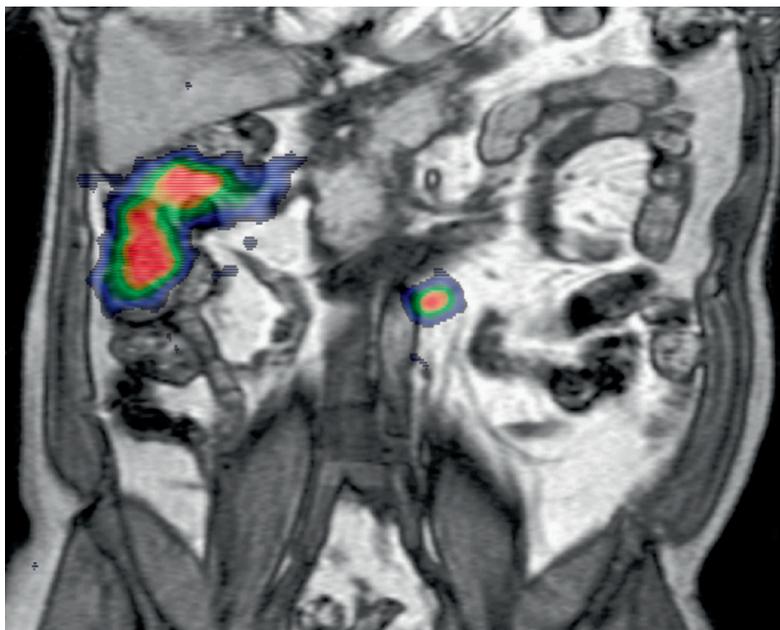


Figure 2. Combined magnetic resonance (MRI) and gamma camera image of a delayed release device with released contents at the top of the ascending colon in a volunteer.

and coated tablets tend to be less sticky than uncoated tablets (12, 13). Nordt and colleagues compared iron poisoning with chewable versus solid ferrous sulphate tablets and reported inflammation of the upper GI tract and histological evidence of significant erosion of the surface epithelium associated with the solid ferrous sulphate preparation (14). The group concluded that similar issues would never be noted with the chewable formulation, nicely illustrating that better formulations were highly desirable.

The time to swallow a tablet is usually assessed scintigraphically as between 4-7s (15). Tablets that take longer than 15s to clear from the oesophagus are usually classified as adherent (16). As we age, there is a noticeable slowing of behaviour with a decrease in reaction time, slowing of cognitive processes and a decline in somatosensory, visual and auditory sensitivity, coupled with muscle weakness and tendon stiffness. Although the process of swallowing is almost an automatic physiological manoeuvre in the young, adaptive cerebral changes in the co-ordination of the swallowing reflex are seen in the elderly, suggesting that the brain cortical region has to increase the time to allow for pharyngeal triggering (17). Essentially this time is needed to correct for dysfunction in the handover from the oral to the cricopharyngeal phases.

The stomach: an important role in drug absorption

Although acid secretion is one of the most important aspects of gastric function that is studied in patients, there are other aspects of gastrointestinal physiology which become important in formulation development, particularly gastric emptying. Drugs are not directly absorbed from the stomach to the systemic circulation to any significant extent, and therefore the length of time in which a formulation remains in the upper GI tract may contribute either to a lag phase or for drugs that are well absorbed in the upper GI tract, increased systemic exposure. For those drugs, which are soluble and well absorbed (biopharmaceutics classification system class 1 drugs), the rate of gastric emptying will be a predominant variable in absorption. For some diseases such as diabetes mellitus, abnormal gastric motility

occurs in approximately 60% of the patients and disorders of vagal function can be discriminated. In particular, phase 3 contractions of the inter-digestive migrating motor complex may be absent (18) and the pressure gradients operating across the stomach and duodenum are diminished (19). This results in an abnormal processing of solids, although liquid emptying may be normal. Normal oesophageal and gastric function may be restored in non-insulin dependent patients with diabetes mellitus by treatment with erythromycin estolate 250 mg, three times a day (t.d.s.) for 2 weeks (20).

The filling stomach is non-uniform, with channels of liquid travelling around consolidating food masses and as food is digested, small particles empty with the liquid phase. It has been generally accepted that preparations that dissolve or form particles of less than 2 mm in diameter pass through the stomach in a similar fashion to liquids and are less likely to be influenced by gastroparesis (18). Particles can empty as boluses, mix in with the food, or partially stratify according to when during the meal the formulations are consumed (21).

Effervescent formulations

Oral bisphosphonates used in the treatment of osteoporosis are recognised as potential oesophageal irritants (22) and there have been documented cases of adverse gastrointestinal events reported during bisphosphonate therapy including dyspepsia, dysphagia and oesophageal ulcers. Case reports suggest that these adverse events are usually due to failure to comply with dosage instructions (23). When beagle dogs are exposed to alendronate solutions at pH 2, oesophageal irritancy was noted with solutions with a pH lower than 2. At pH 3.5 exposure was completely benign (24). A recent study conducted by our group explored the concept that if the bisphosphonate was present in the stomach under a less acid environment, there would be an upper GI tract injury sparing potential even if the gastric contents were refluxed (25). The study simultaneously evaluated gastric emptying and gastric pH in young volunteers after administration of Fosamax tablets and a novel effervescent formulation with a high buffering capacity. The data showed marked increases in gastric pH during emptying up to 90% of the gastric contents.

This faster emptying is probably most important where an onset of action should be as fast as possible, for example, in the amelioration of post-operative dental pain. Møller and colleagues compared the effectiveness of 2 paracetamol preparations (26). Median pain relief occurred at 20 min for the effervescent formulation versus 45 min for the conventional formulation. Effervescent formulations at the top of the stomach generate sufficient flow to move round consolidated food - the influence of the Magenstrasse, described by German radiologists many years ago. Our data shows that faster emptying can be achieved in both the fed and fasted states by addition of suitable formulation excipients (27, 28). Interest in gastric distribution patterns was revived by the finite modelling analysis of Brasseur's group at Penn State (29) that showed how particles were either turbulently mixed outside the Magenstrasse, or passed through quickly from the fundus to the antrum.

Larger matrices can stay in the stomach for extended periods of time, slowly dissolving and bathing the duodenum with released drug. If food is taken at regular intervals, then according to the size of initial calorie intake in the morning, the lag time from an enteric-coated tablet will be extended (30). There has been interest, and some argument concerning the behaviour of floating and swelling dosage forms which show gastroretentive behaviour. It is known that large meals will exert a delay in the emptying of dosage forms and therefore confusion concerning either a calorific effect or formulation effect exists in the literature. Work in the dog has suggested that both small controlled-release and large gastric retentive tablets produced equivalent effects and in the fasted state, Gastroretentive devices were unsuccessful. Diet, or rather sufficient calories, is the key factor in determining gastric residence time in the dog (31). Another factor to be considered is the stratification mentioned earlier. Gastroretentive devices may be designed to be mucoadhesive, but buoyancy might contribute to prolonged residence, since in the fundus the rates of shear are low. Thus floatation and stratification are sometimes not clearly discriminated as separate mechanisms (32).

Controlling the rate of gastric emptying

If gastric emptying is an important confounding factor in *in vivo-in vitro* relationships (sometimes referred to as IVIVR), it follows that if we could make gastric emptying more reliable, we should be able to study dissolution events rather than vagaries of stomach physiology. In our laboratories, we have been examining meals that will provide low intra- and inter-subject variability. This was for the purposes of establishing a model for gastro-paresis. Previous reports had suggested that dosing with glyceryl trinitrate might cause headaches and nausea in naive subjects, mimicking a state which we could attempt to reverse. Unfortunately, it was found that the emptying of the test liquid meal was extremely uniform even after calories had been consumed 3 hours before. The intra-subject and inter-subject variation was extremely low. From this we conclude that for true stabilisation of GI transit, the contents of the meal have to be uniform and the calorific value sufficient to trigger a fed response in gastric emptying.

Drugs with low flux

The higher molecular weights of current active pharmaceutical ingredients (API) in discovery yields huge challenges for the formulator. In order to improve clinical performance, enabling excipients have to be employed in complex formulation strategies including nanoparticulate, lipid and amorphous drug forms. The highly potent, and selective API may have poor solubility and inherently low rates of absorption, which makes decisions about commercial development sometimes marginal. In addition, there may be a requirement to develop extended-release formulations, which permit longer absorption phases for challenging molecules. The issues then revolve around the time available for absorption or dissolution of the molecule within the window of normal gut transit. Our knowledge of regional gut transit time comes from a combination of research from clinical colleagues and pharmaceutical sciences. The small intestine is the main organ for digestion and equally the point of entry of most orally administered drugs. The exposure is largely dependent on the rate of gastric emptying and filling

of the large bowel, since mass movements from caecum to mid-bowel allow the colon to refill from the terminal ileum.

Formulations contain material such as lactose or mannitol as agents to increase the handlability of the tablets, and are added to produce desired characteristics of the formulation. The effervescent ranitidine oral formulation, which contains sodium acid pyrophosphate, was investigated by Koch and colleagues (33). Small intestinal transit time was found to be decreased significantly by the presence of the excipient and this resulted in a decreased extent of ranitidine absorption. Since most elderly patients take relatively large numbers of tablets, the combined effect of excipients should be borne in mind when considering treatment failure.

Occasionally, groups of volunteers with fast transit are encountered (Figure 3). Within a volunteer panel, it was found that there was a subgroup that displayed a pharmacokinetic profile following a single oral dose of gefitinib that was different to the rest of the group. The individual elimination profiles tended to show monophasic elimination patterns rather than biphasic patterns observed in the majority of the subjects and they also absorbed lower amounts of the drug. There were no clinical indexes or histories which divided this cohort from the main volunteer bank except that mass movements of colonic contents from the caecum to the mid-transverse colon were very evident (34). This suggests that in the study of poorly absorbed drugs, or investigations of controlled-release formulations designed for colon targeting or extended release, it would be useful to ask each volunteer to keep a bowel diary.

Colonic drug delivery

Compared to the small intestine, the colon is much shorter and has significantly less surface area. In addition, the motility is limited to occasional propulsive movements with little stirring which causes a problem for systems where water has to ingress. This was a particular problem for a novel formulation designed to target the colon that worked by a controlled rate of opening. During development, various markers to detect release were investigated and quinine dihydrochloride suggested as the probe as

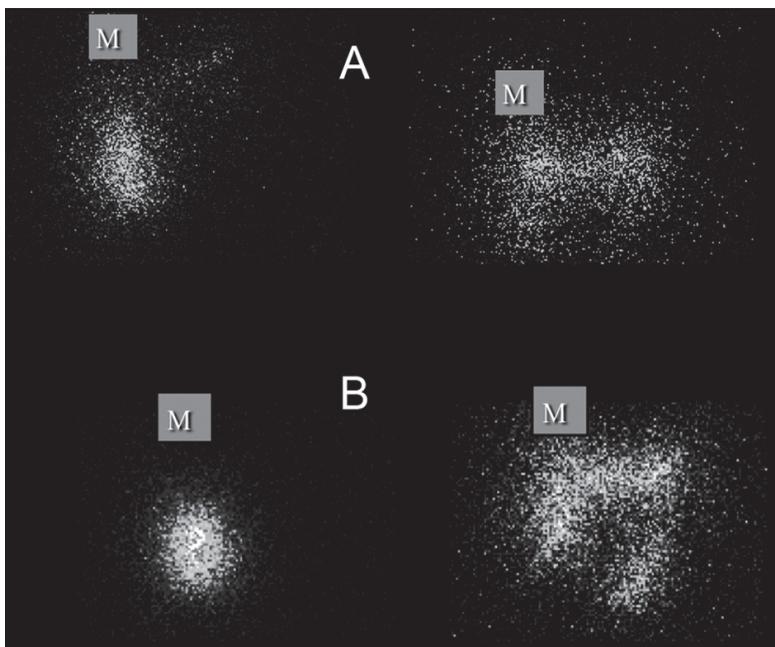


Figure 3. Comparison of rapid colon transit in a normal individual (A) and a subject with fast transit (B). Note the rapid transit of the marker from the caecum, through to the descending colon. "M" covers the marker in the image. Images are taken 30 minutes apart.

it is easy to analyse and does not markedly affect motility. This was loaded into the test article and given to volunteers (35). Although the release mechanism could be precisely controlled, release in the middle of the colon failed to produce adequate blood levels of the quinine probe (36). The transverse colon periodically fills with gas following fermentation of soluble fibre but is generally collapsed in the morning. Studies by the Weitschies and the Reppas group agree that about 30 mL of water is available in the caecum at the head of a meal for drug absorption. In the descending colon, the consolidation of faeces inhibits dissolution and absorption of drug through the gut wall shuts down. For our system, there simply was not enough water to enter the device and cause dissolution, particularly in the transverse colon. It appears therefore that only the caecum and the ascending colon are reliable areas for drug absorption and this provides a very narrow target with a residence time of between 3 and 5 hours. Once-a-day dosing in the morning to target exposure of the tissue for longer than eight to ten hours is probably unrealistic.

In patients with normal bowel function, the transit of pellets through the colon is very much slower than seen with large

non-disintegrating units. For this reason dispersed dosage forms are best suited for delivery of drugs to the large bowel (37, 38); however, in conditions where the colon contents are markedly fluid, the sieving function of the ascending colon is lost with all material transferred to the left side (39). This is one of the causes for poor treatment of left-sided colitis during the acute phase of inflammation associated with diarrhoea (40).

Concluding remarks

Optimising drug formulations cannot be achieved without an awareness of causes of variability in formulation distribution, affected by physiological variables in a way that cannot be mimicked on the bench. Each type of formulation can interact according to posture, the intake of food, the timing of the medication and no doubt the medical history of the patient. In these studies, the use of imaging techniques has been invaluable, providing information that can be input into physiologically based simulations, aiding in translational studies and extrapolation to different patient subsets where they occur.

sium-99m) lisatakse uuritavasse ravimpreparaati. Selline metodoloogiline käsitlus võimaldab positsioneerida seedetraktis ravimpreparaadi asukoha igal ajahetkel ja määrata seal ravimpreparaadi kui terviku seisundit. Samuti on sellisel viisil võimalik selgitada uuritava toimeaine farmakokineetiliste parameetrite (eelkõige toimeaine eri ajahetkedel mõõdetud vereplasmakontsentratsioonide) ning manustatud ravimivormi seedetraktis edasilikumis- ja/või lahustumiskiiruse seoseid. Selliste seoste sedastamine võimaldab koguda igast üksikust manustatud ravimpreparaadist maksimaalse info, mis omakorda vähendab edaspidi vajalike kliiniliste katsete mahtu. Kliinilistest uurimismeetoditest kasutatakse suu kaudu manustatavate tahkete ravimivormide seisundi hindamiseks seedetraktis sageli ka magnetresonants- ja magnetmomentkuvamise tehnikat.

On teada, et uuritavas patsiendirühmas ei sõltu toimeainete imendumise varieeruvus mitte ühest konkreetsest ja selgesti kindlaks tehtavast asjaolust, vaid see on pigem mitmesuguste toimeaine saatust mõjustavate tegurite summa. Enamasti on sellised tegurid oma olemuselt füsioloogilised, näiteks patsiendi kehaasend konkreetse ravimpreparaadi manustamisel, tema sooletegevuse iseärasused, toitumiskäitumine ning eriti vedeliku tarbimine enne ja pärast suukaudse ravimivormi sissevõtmist jms. Kõik need tegurid mõjustavad tahke ravimivormi desintegratsiooni ja toimeaine lahustumist soolesisus ning neil on seeläbi suur tähtsus toimeaine lõpliku ravitoime kujunemisel. Nimetatud füsioloogiliste tegurite uurimisel on eelistatud meetoditeks saanud erinevad kuvamistehnikad, sest nende rakendamine võimaldab lahutada füsioloogilisi liittegeureid algkomponentideks ning seeläbi uurida seedetraktis iga üksiku teguri tähtsust üldises suu kaudu manustatud tahke ravimivormi saatuses.

Ravimivormide ja konkreetsete ravimpreparaatide arendamisel on osutunud ajalooliselt edukaks ning tänapäevalgi laialdaselt kasutatavaks võtteks prekliiniliste ja alusuuringute kliinilisse raviolukorda ekstrapoleerimine. Siiski ei ole ainult selline käsitlusviis nüüdisaegsete ravimivormide loomiseks piisav. Uudsete ravimpreparaatide arendamisel tuleb arvestada ka patsiendi tavapärase füsioloogilise aktiivsuse või teatud iseäralike tegevuste mõjusid.

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Võtmesõnad:
suukaudsed ravimpreparaadid, kuvamismeetodid, füsioloogiline varieeruvus, toimeaine modifitseeritud vabanemine, farmakokineetika

KOKKUVÕTE

Suukaudsete ravimivormide tee teadusest praktikasse

Clive G. Wilson¹

Ravimite uurimistöös on viimase paarikümne aastaga sünteesitud hulgaliselt uusi toimeainete kandidaatmolekule, mille toime on varasematest oluliselt tõhusam, kuid millest on siiski keeruline toota suu kaudu manustatavaid ravimivorme. Niisuguste uute ravimpreparaatide arendamise teeb iseäranis keeruliseks asjaolu, et lisaks suukaudsetele ravimivormidele, mille toimeaine vabaneb tavapäraselt, soovitakse järjest rohkem turule tuua toimeaine modifitseeritud vabanemisega (eelkõige toimeainet prolungeeritult vabastavaid ja käärsoole-spetsiifilisi) suukaudseid ravimipreparaate.

Uudsete suukaudsete ravimivormide arendamise väljakutsete lahendamiseks kasutatakse tänapäeva ravimitööstuses üha rohkem kliinilisi analüüsimeetodeid, mille puhul märgistatud toimeaine (nt tehneet-

Erineva tehnoloogilise lahendusega uued ravimpreparaadid käituvad inimorganismis erinevalt ja see sõltub olulisel määral patsiendi füsioloogilistest iseärasustest. Seega on kuvamismeetodite asjakohane rakendamine eespool nimetatud protsesside mõistmiseks oluliseks metodoloogiliseks võimaluseks siirdemeditsiini sõlmküsimate lahendamisel ning erinevate patsientide ja patsiendirühmade heaolu tagamisel.

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