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Expert Review

Novel Platforms for Oral Drug Delivery

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Abstract. The aim of this review is to provide the reader general and inspiring prospects on recent and promising fields of innovation in oral drug delivery. Nowadays, inventive drug delivery systems vary from geometrically modified and modular matrices, more close to "classic" pharmaceutical manufacturing processes, to futuristic bio micro-electro-mechanical systems (bioMEMS), based on manufacturing techniques borrowed from electronics and other fields. In these technologies new materials and creative solutions are essential designing intelligent drug delivery systems able to release the required drug at the proper body location with the correct release rate. In particular, oral drug delivery systems of the future are expected to have a significant impact on the treatment of diseases, such as AIDS, cancer, malaria, diabetes requiring complex and multi-drug therapies, as well as on the life of patients, whose age and/or health status make necessary a multiple pharmacological approach.

KEY WORDS: bioMEMS; combination therapy; oral drug delivery; smart polymers; swellable matrix.

THE NEED FOR NOVEL MODIFIED RELEASE SYSTEMS

It is largely recognized that delivery is an integral feature of every new drug as well as an important opportunity for the companies to develop new medicines. In fact, controlled release of drugs is a dynamic activity of pharmaceutical companies, due to the indisputable advancement provided by delivery science to pharmacotherapy. In addition, this activity makes available patented products in a market where the number of new substances is decreasing and the new chemical entities pose more and more administration problems. Nowadays, no drug product enters the market without its own built-in delivery program. This issue is addressed by pharmaceutical technologists with the development of the so called "technology platforms" for drug delivery, i.e., technologies for drug administration based on devices able to contain, meter and deliver the drug at appropriate rate and duration. Oral products represent around 70% of value of the US pharmaceutical market and among the DDSs, oral delivery accounts for 60% of the market. As the number of new biotechnological therapeutics is rapidly increasing with peptides, proteins and other macromolecular drugs becoming available for treating various diseases, one of the most challenging task for pharmaceutical researchers is how to succeed in effectively and safely administer these bio-drugs via the non-invasive, patient-friendly oral route (1). As a matter of fact, low permeability across the gastrointestinal (GI) mucosa and lack of stability in the luminal environment remain the two main causes of the poor oral bioavailability of bio-drugs. For years drug delivery scientists have been proposing approaches to overcome these limitations that would result suitable not only for peptide substances, but also for small molecules with poor biopharmaceutical properties. For instance, nano- and microencapsulation techniques to sustain drug release, non-specific mucoadhesion or the use of penetration enhancers and enzyme inhibitors are some of the explored ideas (2–4). Although these approaches are effective at different extents in improving the oral bioavailability of problematic drugs, some issues remain unsolved especially with respect to optimal and successful oral administration of peptides and proteins.

PK studies play an essential role in oral drug delivery and introduced the concept of medicines tailored to meet the requirements of each individual. Such concept arises from the consideration that individuals are difficult to categorize, as somatic, gender and/or genetic differences generate variability in the outcome of a pharmacological treatment. Thus, personalized medicines are more and more sought for increasing the benefit of a treatment and reducing the risks of unexpected adverse effects.

In order to be really efficient, an oral delivery platform should take into consideration not only of the duration of the therapy, but also its quality. Life expectancy increases year by year also because drug therapy allows for the successful treatment of many diseases. The consequence is an aging population with older patients suffering from multiple diseases and, therefore, taking several medicines at same time. For this particular population, the therapy effectiveness and safety can be hindered by medicine mistaking, dose missing,

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unforeseen drug interactions or inappropriate drug delivery programs. In this respect, the patients would benefit from the use of a "polypill", i.e., a system combining several drugs in one dosage form, in order to simplify and customize the dosage regimen. Therefore, an efficient poly-pharmacy approach can be realized by means of a multiple drug delivery systems constituted by a single dosage unit able to release the active principles to a specific site with programmed rate and duration.

While in the past drug combination in one dosage form was criticized by regulatory agencies which considered it only a ruse for easily registering new products without a real therapeutic benefit and/or innovation, today combination therapy is indeed emerging as a powerful tool for improving the therapy of diseases such as AIDS, malaria, tuberculosis or cancer. For example, malaria is today treated with the concomitant administration of at least two drugs, one of which is artemisinin or its derivative and the second can be clindamycin. With this combination it must be taken into account that the PK of the two drugs is different and also that the therapeutic regimen has to be set properly. A similar approach can be pursued for AIDS therapy as evidenced by the approval in the US of TRUVADA® tablets, a combination of two inhibitors of HIV-1 reverse transcriptase (emtricitabine and tenofovir disoproxil fumarate). One TRUVADA® tablet is bioequivalent to one emtricitabine capsule (200 mg) plus one tenofovir tablet (300 mg) upon single dose administration. Combination therapy in diabetes, as well as in hypertension and hyperlipemia, represents an opportunity which deserves attention. Improvement of the adherence to oral medication regimens as well as economic advantages have been evidenced for combined medicines (5,6).

Innovative drug delivery devices have the potential to make the treatments safer, more effective, convenient or acceptable to patients. Drug delivery systems are complex formulations characterized by at least two elements concurring to determine delivery rate and kinetics. In general, these elements are a polymer and a drug. This point implements the definition of combination products where two components, e.g. drug/device, drug/polymer, drug/drug, are joined. As a matter of fact drug delivery systems are typical combination products, since one component is instrumental to the availability of the other. Combination products increasingly incorporate cutting edge technologies that hold great promises for advancing patient care.

A major issue for an innovative oral drug delivery platform is the realization of an intelligent system or at least the introduction in the DDS a certain level of logic. This would lead to a delivery system not only based on *in vitro–in vivo* correlations, but also expected to be patho-physiologically driven. Such a capability of interaction with the GI tract implies that the drug delivery system should be no longer site indifferent, but it should be able to afford a site-specific drug release. These considerations allow drawing some reference paths for exploring the world of the new platforms for controlled drug release. They include the oral delivery systems manufactured with typical pharmaceutical operations as well as the futuristic micro-electro-mechanical systems (MEMS). All these technologies require the availability of new materials that can contribute to the establishment of the certain level of intelligence of the system. It is beyond scope of this paper to provide an exhaustive review of all the existing systems as this has been done in excellent published reviews and continuous update is available through the proprietary Companies. The aim here is to introduce our vision on modern oral drug delivery and focus on some specific aspects of this topic in order to provide a stimulus for the imagination of the reader interested in the design and development of new oral delivery systems.

ORAL DELIVERY PLATFORMS MANUFACTURED WITH THE TYPICAL PHARMACEUTICAL OPERATIONS

Typically, oral drug delivery devices are manufactured as reservoir or matrix systems. Matrices are the most largely represented DDSs among those manufactured with pharmaceutically accepted and established operations. Despite having been around since four decades, matrices are still the reference starting point for innovations in drug delivery. In our opinion this is due to the fact that they are considered quite reliable in term of delivery, easiness of formulation and manufacture. Furthermore, they are less prone to malfunctioning problems and not completely explored as for capacity of delivery and suitability for flexible delivery rate. Moreover, they can be continuously innovated as new materials for their manufacturing become commercially available.

Matrices are monolithic systems with drug dispersed in a continuum of adjunct (excipient) forming the matrix (7). Usually, pharmaceutical matrices are manufactured by compression or extrusion of powder mixtures. Their essential requisite is the non-immediate disintegration in water since the maintenance of the monolithic structure is crucial for drug release control. Drug release is obtained by elution from the polymeric (in general) continuum that can actively or passively participate to the release. This behavior differentiates the disintegrating tablets from the compressed matrices, the first promptly releasing the drug for immediate dissolution and absorption, the latter slowing down the drug dissolution and, as a consequence, the absorption rate. In the matrix the control element is built up during the system's functioning, as it consists of the external layer partially emptied of the drug. In dependence on the behavior of this external layer, drug release kinetics ranges between square root of time and zero order.

The three classes of matrices, namely inert, erodible or swellable, present different release kinetics. Swellable matrices are the most popular ones for a series of reasons mainly related to the availability of reliable swellable polymers approved for human use that are able to interact with the release environment. The resulting matrix swelling influences the drug release kinetics in dependence on the characteristics of the components and the matrix geometry (8). This is an important element for designing novel delivery systems since the swelling kinetics can be, to some extent, controlled by the formulator (9,10). Swellable matrices are typical moving boundary systems in which the diffusive barrier controlling drug release continuously changes its thickness. This barrier is represented by the gel layer formed on the surface of the matrix solid core, which controls both drug and water transport (11). A similar situation is observed with the other types of matrices whereas a totally different behavior is shown by reservoir systems, in

which the diffusive pathway (membrane thickness) remains constant during the release time. In fact, in inert matrices the diffusional path increases continuously during drug elution. In erodible matrices two different phenomena are observed: the first one is the solvent penetration into the matrix, which is responsible for an increase of the thickness of the diffusional layer; the second one is the matrix dissolution, which causes a decrease of the thickness of this layer. Depending on the relative importance of these two phenomena it is possible that the thickness of the layer remains constant for a certain period of time, thus resulting in a zero-order drug release kinetics. As a general concept, also a swellable matrix can undergo erosion during its release life provided that it is not made of physically or chemically cross-linked polymers, such as it is the case with swellable hydrogels. In this case drug release can either be concomitant or anticipate the matrix dissolution. When the swellable polymer is soluble enough, the polymer dissolution process overlaps swelling. This situation leads to an erosive phenomenon, which, in turn, affects the drug release kinetics. In conclusion, matrices have to be considered versatile systems, in particular when the three different types can be combined in order to adapt and modulate the release rate according to the therapeutic design.

The Geomatrix® technology (9) represents an example of the concept of drug release rate modulation without changing the matrix formulation. The product was developed by coupling a swellable matrix (core of the system) with coating layers applied on selected surfaces of the matrix surface. Depending on its position, the coating alters the swelling behavior, thus affecting the drug release kinetics. Several commercial products with different drugs were manufactured based on this technology. They were characterized by a quasi-constant delivery rate lasting for sufficient time to allow once-a-day administration. The technology was very reliable and more than ten years of marketed products never revealed significant adverse effects related to the dosage form.

More recently, a new drug delivery platform has been developed for tackling the need for flexibility and multifunctionality. The goal is to construct a multi-drug and multikinetics delivery system using the concept of modularity, which allows changing the release kinetics without modifications of the formulation. The new modular approach for preparing controlled release drug delivery systems has been defined «release modules assemblage» technology (12,13).

The module is an individual unit (tablet or matrix) having a specific delivery program. Typically the technology adopts modules that belong to the previously mentioned matrices categories. Thus, the release modules are solid compacts obtained by compression (or other suitable method) of mixtures of powdered excipients and active principle. The resulting tablets have an appropriate shape for the assemblage. In a typical execution of this technology, modules or release units are swellable matrices exhibiting their own typical delivery kinetics. They have cylindrical shape with one base convex (bearing a neat dome-shaped protrusion) and one base concave, accommodating a complementary recession matching with the aforementioned dome protrusion. The dome shape makes straightforward the assembling of two or more modules by stacking, to obtain multi-module systems. The "cupola-like" shape of the convex base inspired the registered name Dome Matrix®.

According to this approach, from two to several release modules can be used for the construction of assemblies that according to the number, composition and orientation of the single modules, can match previously defined release kinetics. The resulting assemblies are administered as such or after introduction into a suitable biocompatible "container" such as a hard gelatin capsule.

Beside the possibility to achieve a pre-established or customized release kinetics, the "release modules assemblage" technology allows for the combination of different active principles, or for the customized dosing and release of a given active principle, in particular when (i) different modules contain different active principles or when (ii) further active principles are included in the hollow space between two assembled modules, or when (iii) modules of equal or different dosage are combined into the same assembly.

Depending on the mode of assemblage different type of assemblies can be obtained. In one basic assembly, the convex base of one module is stuck into the concave base of a second one having the same composition in such a way that a firm pile of modules can be constructed when successive modules are stacked one upon the other. This stacked configuration realized with modules having the same composition could be used for increasing or adapting the dose to be administered by simply adding more modules to the assembled system. When the module is a matrix, two stacked modules contain a double drug dose, but they do not present double release surface relative to the individual release module. In fact, in a two-module pile one convex and one concave base remain hidden. The increase of the number of modules in the assembly results in a change in the volume/area ratio of the delivery system, thus slowing down the fraction of drug released *versus* time, as illustrated in Fig. 1 for piled systems realized by assembling from two to six modules (14).

These modules were originally assembled together by using glue or soldering them with ultrasounds. Later, the modules were firmly assembled without loosing their functional porosity and typical mechanical strength by fitting one

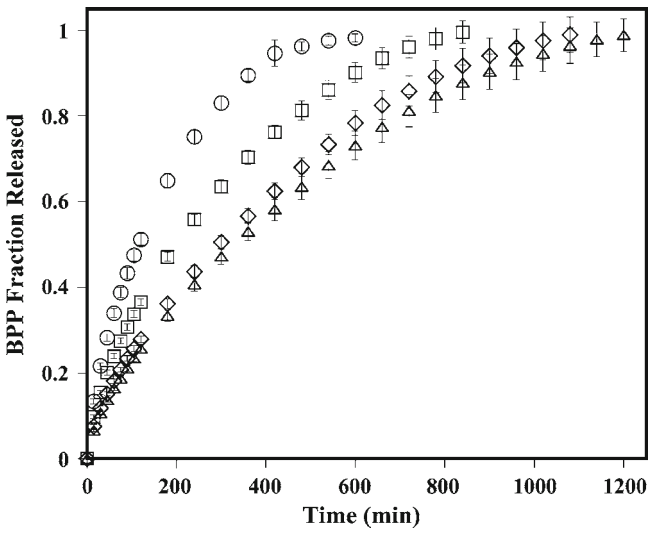

Fig. 1. Buflomedil pyridoxal phosphate fraction released from one module (*empty circles*), two modules (*empty squares*), four modules (*empty diamonds*), six modules (*empty triangles*) assembled in stacked configuration.

module into another one by simply snapping or clicking them. In order to achieve this, they had to be re-designed and manufactured with a geometry allowing their interlocking by clicking. For this reason, modules suitable for the click fitting have projections on the base of one module and a complementary recess or cavity in the base of another module (Fig. 2). In the case of a disc-shaped module, the convex and concave bases of the cylinder (disk) were especially designed for fitting together by friction interlocking. Therefore, the novel release system is the result of the assemblage of individual modules designed in such a way to allow their firm snap fitting. Taking as reference a typical cylinder module with one convex and one concave base, the assembled systems could be obtained by stacking two or more modules with their convex base in contact with the concave base of the adjacent one in such a way to construct a pile. Then, by simply pressing the pile in order to reach the snap or click pressure, the modules firmly fit together (15).

The assemblage of "snap and click" modules can be used not only for time but also for space control delivery. In fact, the combination of two modules, concave base against concave base, results in a system with an inner void space. This assembly, named void configuration, was characterized by an immediate system floatation when it was plunged in water (15). It is possible to assemble two cylindrical modules having one concave and one convex base, with the concave faces facing each other, by fitting them together if they have complementary shape of the rim of the cavities on their surface. In this case the two modules have slightly different shape since one cylinder module has a cavity with a projecting rim complementary to a groove present on a fitting cavity rim of another module (see Fig. 2 right side). Therefore, this assembled configuration creates an inner space in the system that could be either left empty or filled with a substance to be released. In the case of the void space, the system is able to float when sunk in a liquid. The two modules fitted together with their cavities facing each other still have the two opposite convex bases un-engaged and available to be used for assembly with additional modules stacked as a pile.

Modules fitted in void configuration and formulated as swellable matrices, were tested *in vitro* for floatability and in humans for gastro-retention (15). *In vitro* floatation measurements showed that the void assembled system floated from time zero up to more than 5 h, while cylindrical tablets with the same composition and mass never floated. The floating system had gastric residence time in humans significantly longer than a non-floating matrix with the same mass and composition. On average, the floating system and the non-floating matrix remained in the stomach 215 min and 97 min, respectively (15). Fig. 3 shows the position in the human stomach of the void configuration two modules system after 90 minutes.

The assemblage of these modules makes possible to prepare DDS performing different time- and site-controlled delivery in dependence on how the modules have been assembled. In this way, the single dose administered can be easily adjusted, or multi-kinetics can be achieved if the module composition is modified. Beside the two already mentioned configurations (stacked or void) a third "mixed" configuration could be envisaged as well, since one can stack on the convex base of a system assembled in void configuration additional modules, thus obtaining a void-piled configuration allowing the achievement of peculiar drug release programs.

A picture illustrating an application of this concept is presented in Fig. 4 where four separated modules are assembled in one system in order to obtain a device capable to float and to exhibit controlled release kinetics of clindamycin and artesunate for malaria treatment. The idea implies the immediate release of the artesunate dose in the stomach along with a fraction of clindamycin dose, followed by a prolonged release of a second portion of clindamycin dose inside the stomach. Thus, the four modules (see Fig. 4 from left to right) have the following composition:

Module 1. disintegrating module, convex dome base and concave base, 50 mg of artesunate immediate release;
Module 2. swellable matrix, convex base protruded for clicking and concave base, 80 mg of clindamycin prolonged release;
Module 3. swellable matrix, concave base with rim for clicking and convex base protruded for clicking, 80 mg of clindamycin prolonged release;
Module 4. disintegrating module, concave base and convex dome base, 80 mg of clindamycin immediate release.

The four modules, assembled as reproduced in Fig. 4, were clicked to obtain the monolithic system illustrated in the same picture. Upon introduction in the dissolution medium, the system sank and only after disintegration of modules 1 and 4 it started to float onto the medium's surface. The release rate of this assembled system is shown in Fig. 5, where the release curve corresponding to the artesunate and clindamycin immediate delivery modules are reported along with two curves relevant to clindamycin prolonged release

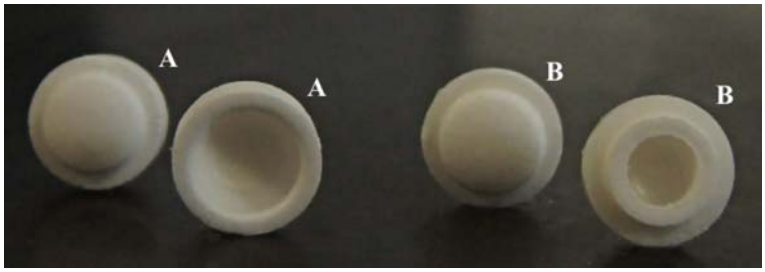

Fig. 2. Two complementary modules for click fitting: (*A*) convex face (*left*) and concave face (*right*); (*B*) convex face (*left*) and concave face (*right*) with rim protrusion.

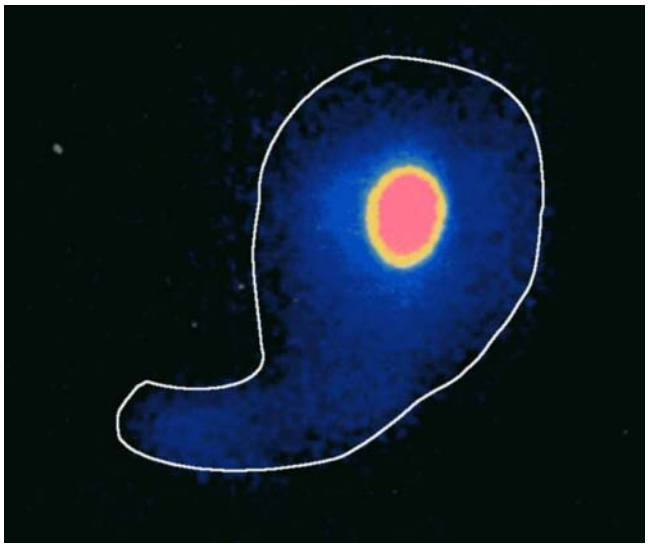

Fig. 3. Gamma camera picture of the stomach area 90 min after the administration to a volunteer of a Dome Matrix® assembly in void configuration and labelled with ^{99}Tc.

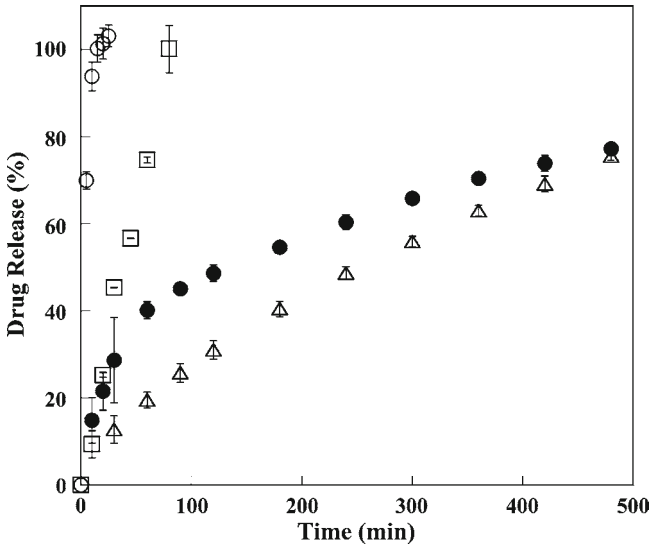

Fig. 5. Drug release profiles from individual and assembled modules: clindamycin 160 mg, void assembly prolonged release (*empty triangles*); clindamycin module immediate release 80 mg (*empty circles*); assembled system with prolonged release plus immediate release modules: clindamycin 240 mg (*filled circles*), artesunate 50 mg (*empty squares*).

void and combined (prolonged plus immediate) assemblies. The release curve of clindamycin is the result of a double release input composed by the contribution of the immediate release module and of the prolonged release modules assembled in void configuration.

THE TABLET OF THE FUTURE: MICROFABRICATED DEVICES AS ORAL DRUG DELIVERY PLATFORMS

In recent years, the developments in the application of micro- and nanosystems for drug administration have opened toward the field of microfabricated devices, such that today it is not unusual to hear about micro-electro-mechanical systems (MEMS) applied to the biomedical field (BioMEMS) as an emerging area of study and research (16–18). The application of MEMS to drug delivery, and to oral drug delivery in particular, could considered as the result of an evolution process that starting from conventional immediate-release (IR) formulations (solutions, tablets, capsules), then passing through the "age" of polymer-based systems for controlled release, eventually has attained the key concept of drug delivery platform. Any dosage form or delivery system (from the simplest tablet to the high-tech "system-on-a-chip") is seen as a combination of two elements, i.e., the drug and the vehicle/system/device required for the drug to be dosed, administered, delivered, targeted, or even absorbed. What changed during this evolution process is the role played by the second element (the formulation/device) in determining the performance and the actual power of the system and, therefore, its complexity. In fact, if an IR tablet is manufactured such that it simply has to rapidly disintegrate and release all drug upon contact with water, regardless to its location (it could be a glass of water or somewhere in the lumen of the GI tract), matrices, reservoirs and osmotic systems allow to program the delivery in a relatively simple, but effective manner to control the time, rate and in some cases the site of drug release. The level of complexity and the number of features of the system further increase when moving to "technology platforms". These are conceived to really behave as "intelligent and autonomous" entities, capable not only to carry the drug and deliver it in a controlled predetermined way, but actually to operate (or not operate) based on their built-in program and a series of technical features that make them sensitive to external signals, endogenous stimuli, therapeutics needs, etc. (19). MEMS represent a powerful tool as delivery platforms for active principles whose efficacy strongly depends on the timing of their delivery and whose pharmacological effects are naturally amplified by the body itself (e.g. hormones, immune-modulators, growth-factors). Owing to their flexibility and programmability, in comparison with polymer-based DDS they increase the level of control over drug release, which can

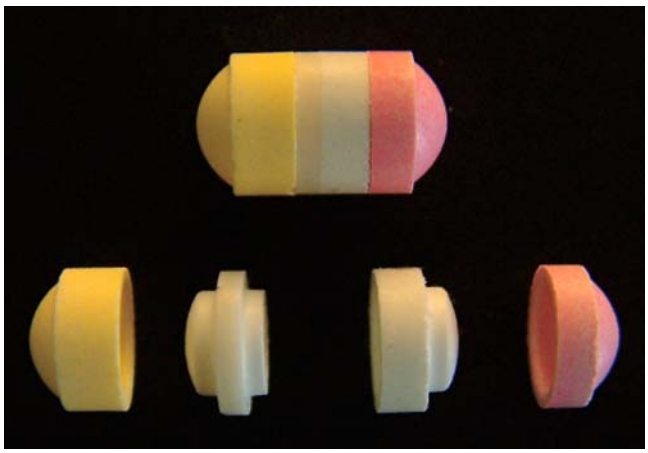

Fig. 4. Assembled system composition for malaria therapy (*from left to right*): one immediate release module of clindamycin 80 mg; two prolonged release modules each containing clindamycin 80 mg for void configuration; one artesunate 50 mg immediate release module. The two immediate release modules are stacked onto the void assembly. After the disintegration of the immediate release modules, the void assembly floats.

be triggered, pulsed and switched on and off. Moreover, their manufacturing based on batch-processing techniques typical of microelectronics industry leads to greater device uniformity and reproducibility (20,21).

In general, MEMS devices are the result of the integration of mechanical elements, sensors, actuators and electronics on a common silicon substrate obtained using microfabrication technology. If microelectronics integrated circuits can be seen as "brain" of a system, MEMS augments this decision-making capability with "eyes" and "arms", to allow the microsystems to sense the environment and react accordingly. Based on this general definition, some additional considerations are required for microsystems designed to release drug doses. In this regard, BioMEMS have to be fabricated from materials that have been demonstrated to be biocompatible and appropriate for drug administration. Originally, the main substrate was silicon, but today alternative materials such as biocompatible polymers (e.g., polymethylmethacrylate, PMMA and polydimethylsiloxane, PDMS) are being investigated, also to improve reliability and flexibility and to decrease manufacturing costs. Furthermore, in order to administer micro-machined devices *in vivo*, they must be smaller than the thickness of most silicon wafers and this requires some modifications in the "top–down" and "bottom–up" fabrication approaches that are commonly applied when manufacturing electronic microsystems. By decreasing their size, these systems become suitable for ingestion (~1 mm), injection into tissues (<200 μm) or even into the circulation (<10 μm) (16).

In MEMS-based drug delivery systems, the "sensing part" enables the system to recognize physiological characteristics or changes around the device (here behaving like polymeric systems sensitive to pH, temperature, analyte concentration, etc.) The actuator is the release component, which operates under a controller that decides the amount of drug and the right time for release. Clearly, a drug reservoir must be incorporated within or on the device, whose very small size currently limits the application of MEMS to the delivery of potent drugs. One option for fabricating the reservoir is to produce silicon microparticles containing an internal reservoir loaded with drug. Alternatively, non-traditional MEMS fabrication techniques and materials can be also exploited to form microwells and reservoirs. For example, microwells as small as ~3 fl/well have been fabricated by micromolding of polydimethylsiloxane on a photoresist-coated silicon wafer (22).

Although a lot of research activities on biomedical applications of MEMS (diagnosis, tissue engineering, molecular recognition) are presently ongoing, relatively few groups of scientists have focused on therapeutic applications such as drug delivery. Moreover, most of the systems proposed so far in this field were intended for implantation, injection or transdermal delivery (23–25).

Nevertheless, an interesting review reported some examples about how a micromachined platform combined with complementary approaches may address some of the shortcomings of current oral delivery systems for peptides and proteins (26). In the reviewed works, the authors presented some prototypes of bioadhesive microdevices with multiple reservoirs to be administered orally for improving the absorption of pharmacologically active biopolymers. The design of such devices started from the identification of the three main attributes that a successful oral delivery system for peptides and proteins should have, i.e., (1) bioadhesion properties for prolonged retention in the GI tract; (2) control of drug release and (3) unidirectional release towards the intestinal epithelium. The combination of these three features to protect the active and enhance its absorption by mucosal cells is not indeed a new concept in oral drug delivery. In fact, gastrointestinal–mucoadhesive patches have been already studied and were made in the form of multilayered systems with techniques and materials similar to those used for making transdermal systems (27). A patch actually possesses a shape suitable for mucoadhesion and, differently from bioadhesive spherical micro-or nanoparticles, the non-adhesive side facing the gut lumen (backing layer) can be impermeable, to avoid drug release and loss into the luminal content.

As the integration of micro-fabrication technology might enable the translation on a smaller scale of some of the functions of a patch system, a MEMS approach was chosen to develop micro-patches based on standard MEMS techniques, including photolithography, etching and thin film deposition and it was proposed in three different substrates [silicon oxide, porous silicon and poly(methylmethacrylate)—PMMA] (28–30). The first reason for this choice was because MEMS technology allows great control over the size and shape of the delivery device, two parameters that can greatly affect the response of the body upon system administration. In fact, micro-fabricated devices may be designed to be flat, thin, and disc-shaped to maximize contact area with the intestinal lining and minimize the side areas exposed to the constant flow of liquids through the intestines. Particle size can be also selected to be small enough to have good contact with the undulations of the intestinal wall and large enough to avoid endocytosis of the entire particle (although nanoparticle endocytosis appears as a method to enhance transport of large molecules across the intestinal barrier, this process can destroy the macromolecule). Clearly, compared to GI-patches the small size of the single micropatch limits the amount of drug that can be loaded, although the problem can be overcome by increasing the number of micropatches administered at one time. Secondly, MEMS techniques can be coupled with surface chemical modification strategies to selectively attach bioadhesive moieties onto the device surface, thus providing mucoadhesion. For this purpose, lectins, a family of proteins able to bind to specific sugar groups expressed by various tissues and cells, including the intestinal mucosa (31), can be exploited. Finally, microfabrication allows creating multiple reservoirs of the desired size to be loaded with many molecules of interest.

Based on these considerations, the delivery system proposed by Ahmed *et al.* consisted in numerous disc-shaped microdevices, modified on just one surface with the bioadhesive agent. These microdevices were intended to be loaded into an enteric capsule for administration and released once the system reached the upper intestine upon capsule dissolution (28,29). The asymmetric coating was crucial for the correct system's orientation: this should be suitable for the drug to be released toward the intestinal lining with limited exposure to enzymatic degradation.

As previously mentioned, the microdevices could be fabricated out of different substrates. In all cases, photoli-

thography (the process by which a photosensitive polymer is exposed to a radiation source through a photomask) was used to pattern the device features, whereas reactive ion etching (RIE) defined the device's geometry. Lectin-derivatization of the microdevices' surface was then performed based on a silicon–avidin–biotin–lectin binding chemistry (26). Finally, the microreservoirs were loaded with pico- to nano-liters of a polymeric solution of the drug by microinjections or capillary action, depending on the type of substrate. As water quickly dried up because of the tiny reservoir volume (silicon oxide and PMMA devices) or under vacuum (porous silicon devices), the drug remained entrapped within the polymer, the latter acting as a timed-release plug in dependence on its own dissolution profile. The use of the polymer increases the system's versatility with respect to time and rate of drug release, as different types of polymers (e.g. pH-sensitive, temperature-sensitive or swellable like hydrogels) may be used in separate reservoirs for different compounds.

From *in vitro* studies performed with Caco-2 cells (30), the lectin-conjugated porous silicon microdevices showed higher binding effectiveness than the naked ones, with differences also due to the lectin's natural origin. Also the transport through paracellular tight junctions of a model peptide (FTIC-labeled insulin) loaded onto the microdevices, tested on the same Caco-2 model, was significantly increased in comparison with a liquid formulation, owing to the high drug concentration obtained at tight junctions. Other authors selected erythropoeitin (EPO) as a drug candidate for this device, given its usual therapeutic dosage, which implies three i.v. injections per week in the treatment of anemia. Based on the volume of each microreservoir and the concentration of the drug solution to be loaded, they calculated that the total weight of microdevices required to fulfill the therapeutic dosage could be easily introduced into an enteric capsule or tablet (29).

Other miniaturized devices for biomedical application exist that are intended for administration into the GI tract, namely a remote controlled capsule (RCC) for human drug absorption studies (Pi X. *et al.*, in Proceedings of the Engineering in Medicine and Biology 27th Annual Conference, Shanghai, China, 2005) and different types of wireless capsules as diagnostic tools (non-invasive endoscopy) (32). Although these devices were not specifically designed to deliver drugs orally for therapeutic purposes, with their integrated robotics, sensing and imaging tools, they prove that the advent of robotics may lead to autonomous medical platforms based on advanced innovative solutions in terms of MEMS technology applied to therapy and diagnosis.

In conclusion, the combination of microfabrication technology, materials science, information science and biology is growing as a powerful tool to design sophisticated drug delivery systems that promise to innovate the pharmaceutical based health care in a foreseeable future. A major role in this developing field will be also played by regulatory agencies, committed to evaluate the quality and safety of complex systems that owing to their complexity belong to the category of combination products. In this sense, the creation in 2002 of the FDA Office for Combination Products (OCP) and the FDA NanoTechnology Interest Group have already contributed to better define the procedures and regulations on the pathway to marketing approval for these innovative products.

THE NEED OF INNOVATIVE MATERIALS FOR INTELLIGENT DELIVERY IN ORAL DRUG DELIVERY PLATFORM

The solution to the biopharmaceutical problems posed by biotech compounds is a challenge that requires significant steps ahead in the capability of making drug delivery systems able to overcome the drawbacks presently posed by the administration via the GI tract and, in some cases, to turn them into advantageous tools for drug absorption. Enabled targeted and triggered delivery in the digestive tract would probably lead beneficial consequences also for improving formulation and delivery of low molecular weight drugs.

Advances in drug delivery can be typically achieved by means of two different approaches:

one can be defined *synthetic* while the other *formulative,* although the border between the two is not so strictly delineated. For instance, new polymeric carriers require to be incorporated in an appropriate formulation, whereas modification of the molecular structure of materials already routinely used by pharmaceutical formulators, may be necessary for affording more efficient and effective drug delivery.

The synthetic approach implies the molecular design of new materials, in most cases polymers, able to change their conformation in aqueous solution as a consequence of an environmental change (33,34). These new polymers may be classified among intelligent or smart materials that, according to the definition of Shahinpoor and Schneider, "are multifunctional due to their unique molecular structure and respond to external stimuli by a characteristic behavior" (35).

In this respect, main emphasis has been given to temperature or pH-sensitive hydrogels. The basic and applied features of this topic were discussed by Peppas and coworkers (36,37). A pH-sensitive polymer network consists of a chemically or physically cross-linked backbone polymer carrying weak acidic or basic functional groups which give the sensitivity to pH (38). Although polymers such as poly (organophosphazene) (39) or thiomers (40) were proposed and studied, the greatest attention was and is being devoted to acrylic and methacrylic polymers. Due to the presence of pendant carboxylic groups these polymers swell or shrink in a controllable manner in response to a pH change. This property implies that the network porosity changes upon interaction with aqueous media at appropriate pH or with biological fluids and represents the key point for the controlled release of drugs and macromolecules loaded into the polymeric network. In fact, the drug release from hydrogels occurs mainly by diffusion (19), thus a desirable delivery in terms of time, rate and space can be obtained by proper design of the three-dimensional structure of the gel. The most important parameters used to characterize the latter are (1) the polymer volume fraction in the swollen state, (2) the average molecular weight of the polymer chains between two adjacent crosslinks and (3) the corresponding mesh size. Starting from the Flory–Rehner theory (41,42) Peppas and Merril (43) and Brannon-Peppas and Peppas (44) provided a

thorough discussion and mathematical models on the hydrogel structure in the absence or presence of ionic moieties, respectively.

In addition, the presence of specific co-polymers or polymer backbones such as *N*-isopropylacrylamide could impart sensitivity to temperature variation in a range that can be selected around the physiological one by appropriate co-monomer mixing during gel preparation (45,46).

Main features of polyacrylic materials as carriers for drug delivery are: (1) protection of the drug from the degradation (both chemical and enzymatic) in acidic medium; (2) drug release control by polymer volume swelling; (3) potential bioadhesion.

Peppas and collaborators (19) have developed a class of graft co-polymers of polymethacrylic acid P(MMA) grafted with polyethylenglycol (PEG), classified as complexation hydrogels, which exhibit pH-dependent swelling behavior owing to the presence of acidic pendant groups as well as to the formation of inter-polymer complexes between the ether groups on the graft chains and the pendant groups in the non ionized (protonated) form. Bell and Peppas (47) demonstrated that the optimal complexation interaction occurs with PEG chain length of 1,000 Da molecular weight.

About one decade ago Lowman and Peppas (48) proposed the use of these graft co-polymer as carriers for protein delivery. They showed that the drug was released or entrapped depending on the pH of the environment surrounding the polymeric network. In the collapsed form at low pH (below the pK_a of the acrylic acid, ≈4.3) the mesh size of the network hindered the release of the drug that conversely was released upon polymer swelling at neutral or slightly basic pH. Later on Lowman *et al.* (49) proved that insulin could be released from such copolymers in a controlled manner when administered orally to both diabetic and healthy rats putting into evidence a strong dose-dependent hypoglycemic effect.

More recently, the same group of scientists (50–54) focused on the optimization of the MAA to EG monomer molar ratio and the particle size for the above mentioned polymers for oral insulin delivery in rats. They reported a bioavailability of about 10%, relative to subcutaneous injection in healthy rats, with particles having a mean diameter <53 μm and a 1:1 MAA-EG molar ratio. It is worthy to note that the above reported results were obtained without the use of absorption promoters or protease inhibitors.

The bioadhesive properties of this material would probably play a prominent role in promoting peptides absorption. De Ascentiis and co-workers (55) first demonstrated bioadhesive properties of P(MAA-g-PEG). More recently Serra *et al.* (56) elucidated the role played by the tethered PEG chains in promoting the interaction with the mucus.

As already stated, biodhesion would be more and more a key feature for improving the efficiency of orally administered drug delivery systems: the localization of the drug on the absorbing mucosa increases the residence time and reduces the release of the drug in the intestinal lumen, thus increasing the rate and extent of drug absorption which would result in an increased bioavailability.

A significant advancement in this direction, has been very recently presented by Wood *et al.* (31). These authors synthesized P(MMA-g-EG) hydrogels where the PEG tethers were functionalized with wheat germ agglutinin, a lectin able to bind to carbohydrates present onto the intestinal mucosa. The new copolymer showed improved bioadhesiveness relative to P(MMA-g-EG) in *in vitro* experiments carried out on Caco-2 monolayers.

This last work demonstrated the great potential offered by an approach looking for specific interaction of the delivery system with physiological functions. However, it also suggests that this potential is still largely unexplored.

These innovative materials can be exploited to better control the release of small molecules as well. Bettini *et al.* (57) studied the swelling behavior and solute (theophylline and methoclopramide HCl) transport in swellable ionic copolymers of 2-hydroxyethyl methacrylate and methacrylic acid in a wide range of co-polymer composition. They showed that the water uptake was mainly governed by the degree of ionization of the polymer, and the diffusion of the non-ionized drug (theophylline) was controlled only by the polymer volume swelling ratio. Interestingly, they also demonstrated that the metoclopramide HCl diffusivity varied with the copolymer composition. This was mainly ascribable to a drug/polymer ionic interaction that provided a further tool for drug release control.

Drug polymer interaction has been proposed as an instrument for drug delivery control with a series of synthetic (58–60) or naturally occurring (61–65), anionic or cationic (66) polyectrolytes. The ionic interaction between lambda carrageenan and basic drugs in oral controlled release matrix tablets was studied by Caramella and collaborators (64). It was observed that different drugs give complexes with quite different characteristics of solubility and drug release kinetics (62,63). The different solubility of the complex resulted in differences in water uptake and gelation properties. A different ability to form a hydrated gel layer around the matrix tablets was visually observed during the drug release experiments. The more soluble complex between carrageenan and metoprolol tartrate showed a thick gel layer, that can explain the diffusive drug release profiles, while the less soluble complex with diltiazem was characterized by a fast water uptake due only to capillarity with no further gelation; this afforded a linear drug release kinetics at both acidic and neutral pH.

Bettini *et al.* (67) highlighted that when the complex solubility is very low, such as in the case of the complex between diltiazem and lambda carrageenan, the complex formation occurs also during dissolution experiments carried out with matrices prepared from a physical blend of the drug and the polymer.

Furthermore, Manzo and collaborators (58) put into evidence that complex dissociation rate is one of the prominent factors in drug release control, and that this can be promoted and modulated by the total ions content in the dissolution medium.

The above cited studies on polyelectrolytes represent examples of a substantially different approach to innovation in oral drug delivery with respect to the synthetic one. In fact they can be considered a substantial part of what we have defined as *formulative* approach.

Though this way to innovation is not, at least in principle, devoted to discovery of breakthrough delivery systems, there is no doubt that it can lead more rapidly to marketed product. As a matter of fact it typically exploit improvement or implementation of drug delivery systems made with known and well characterized materials that are often already approved by the Regulatory Authorities.

The starting point of this approach is obviously constituted by the state of the art in the field. In this respect, the golden standard for the production of oral drug delivery is presently represented by cellulose ethers, in particular hypromellose, formerly known as hydroxypropylmethylcellulose (HPMC) (68), that are extensively used for the production of swellable matrix tablets (69).

Although these polymers afford reliable drug release control, they are quite insensitive to stimuli stemming from changes in the GI tract environment (except for the amount of water), because they do not possess any inherent capability to modify their behavior as a consequence of changes in pH or ionic strength within a physiological range.

In the late 1980s Colombo and co-workers (70,71) presented data concerning the different behavior in terms of drug release kinetics and matrix swelling between non-ionic high molecular weight HPMC, and ionic sodium carboxymethyl cellulose (NaCMC). These authors evidenced that the fast and pronounced swelling of NaCMC matrix afforded a thick gel layer resulting in a lag time in drug release profile as opposed to HPMC matrix which gave rise to a profile characterized by an initial burst followed by a progressive diminution of the release rate.

More recently, similar results have been presented by Conti *et al.* (72) with diltiazem containing matrices prepared with HPMC or NaCMC. Interestingly they showed that matrices prepared with the 1:1 (*w*/*w*) blend of the two polymers resulted in a linear drug release profile at both pH 4.5 and 6.8.

Polymer blending is an attracting topic in the field of oral drug delivery, as it represents quite a simple way for improving the system performance by introducing elements for drug release control that are not the result of the simple sum of the properties of the single components of the mixture. Apart from being used for the preparation of the core of monolithic matrices, polymer blending was also studied in the aim to modify the permeability characteristics of the film in solid dosage forms coated with cellulose esters (73–79). These studies demonstrated that the drug release kinetics can be modulated by altering the coating characteristics, and consequently the drug release mechanism, via the introduction of a "non-coating agent" in the film composition.

In conclusion, far from being exhausted, the research in the field of controlled oral drug delivery is still a vivacious collection of activities. Main challenges rely on the capability of exploiting physiological stimuli and specific chemical functions in GI tract.

Changes in the pH value represent the most studied topic for triggering the release of the drug. However, the list of physiological and pathological factors that can be exploited would be very long. Parameters such as the variation of the ionic strength associated with the meal, the different water content or pressure due to the peristalsis, the presence of specific molecular targets involved in physiological or pathological function, remain largely unexplored.

CONCLUSION

All the examples illustrated here give indications about where to look for ideas toward innovation in the development of oral drug delivery systems. In particular, the solutions offered by MEMS technology are a source of hints to be applied to the pharmaceutical field. In most delivery systems the drug release rate depends on the concentration gradient of the dissolved drug established within the system. Manufacturing a system in which this concentration gradient is not essential for drug release implies that there is a chance to deliver all the substance included in the system. This can be obtained using microfabricated devices, but in some cases also with erodible systems or systems in which the disintegration and release phenomena are balanced. Thus, this concept can be exploited for obtaining DDSs manufactured according to the current GMP protocols that provide delivery kinetics more adapted to the therapy as well as to realize the ideal polypill for multiple drug administration.

We showed that innovation could come from the design of peculiar geometries that allow adaptable (tunable) drug delivery, stemming from volume or surface/volume ratio modifications rather than from formulation changes. The geometry of the delivery system can be exploited also for directing the release toward the wall of the GI tract rather than the lumen, in order to enhance the drug transport through the mucosa. In this respect the bioadhesion capacity of the delivery system would certainly play a crucial role. Site-specific and triggered delivery can be built in solid dosage forms by (1) merging manufacturing technologies, (e.g. compression, coating, extrusion), (2) designing shapes and dimensions or (3) using new intelligent materials bearing the trigger mechanism.

Despite the existence of several polymers useful for the preparation of swellable matrices, HPMC remains the most used one. The quality of this substance is well defined and monographs exist in the most important pharmacopoeias worldwide. The future trends in the field reside on the search of polymers capable to respond to patho-physiological stimuli or biological signals, in order to manufacture oral systems useful for very accurate and reproducible drug delivery in particular section of the GI tract.

In summary, we believe that for a successful therapeutic outcome much attention has to be given to the quality of the therapy, which is strongly dependent not only on the medicine, but also on a proper and complied posology. Therefore, the realization of a therapy of quality means to overcome the hurdle of therapy schemes complicated by too many pills and time schedules meddling with every-day life. Obviously, the best medicine fails if the patient simply forgets his pill! Hence, helping the patient to adhere to his therapy is as important as providing him with the best medicine and this can be done by means of drug delivery systems designed for time and space control as well as for compliance improvement. It may be that Albert Einstein was provocative when saying that "imagination is more important than science", but certainly in drug delivery imagination should be extremely helping.

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