Journal of Drug Targeting

http://informahealthcare.com/drt
ISSN: 1061-186X (print), 1029-2330 (electronic)

J Drug Target, Early Online: 1–19
 DOI: 10.3109/1061186X.2013.805335

informa healthcare

REVIEW

Novel engineered systems for oral, mucosal and transdermal drug delivery

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Abstract

Technological advances in drug discovery have resulted in increasing number of molecules including proteins and peptides as drug candidates. However, how to deliver drugs with satisfactory therapeutic effect, minimal side effects and increased patient compliance is a question posted before researchers, especially for those drugs with poor solubility, large molecular weight or instability. Microfabrication technology, polymer science and bioconjugate chemistry combine to address these problems and generate a number of novel engineered drug delivery systems. Injection routes usually have poor patient compliance due to their invasive nature and potential safety concerns over needle reuse. The alternative non-invasive routes, such as oral, mucosal (pulmonary, nasal, ocular, buccal, rectal, vaginal), and transdermal drug delivery have thus attracted many attentions. Here, we review the applications of the novel engineered systems for oral, mucosal and transdermal drug delivery.

Keywords

Buccal, drug delivery, microfabrication, mucosal, nasal, oral, ocular, pulmonary, rectal, vaginal, transdermal

History

Received 13 November 2012
Revised 24 April 2013
Accepted 11 May 2013
Published online 12 June 2013

Introduction

Advancement in high-throughput screening technology and biotechnology has led to the discovery of an increasing number of drug candidates. Among these drug candidates, many small molecules have the issue of poor water solubility and their oral bioavailabilities are limited [1]. On the other hand, macromolecules, such as peptides and proteins, have also been discovered as potential therapeutic agents. Due to the special physicochemical and pharmacokinetic properties of these molecules, parenteral delivery with frequent injections is commonly used in clinical practice [2]. However, parenteral route is not an ideal route of drug administration. Reuse of the injection needles can cause disease transmission. Trained personnel and strict aseptic techniques are needed while self-administration is usually discouraged. Research has shown that many patients, especially the younger ones have the fear of needles [3]. Consequently, this has necessitated the need for researchers to look for novel drug delivery systems to increase patient compliance and reduce the risk of bio-hazardous waste by needles [4]. Moreover, there is an increasing demand to discover new systems that can deliver poorly water-soluble drugs, target disease sites, minimize systemic toxicities, reduce dosing frequency and enable self-administration [5].

A rapid growth of alternative routes for drug delivery has been observed in the past few decades. It was documented in US Food and Drug Administration (FDA) orange book that many drugs have been approved for pulmonary (65), nasal (31) and transdermal (21) applications [6]. Oral route is the most popular route of drug administration. Other routes such as pulmonary, nasal, ocular, buccal, rectal, vaginal and transdermal are commonly perceived as locally targeting and non-invasive systems capable of minimizing systemic toxicity. With newly developed technologies, they are also considered for systemic drug delivery, especially for the delivery of biological drugs. For example, the administration of insulin has been investigated by utilizing various routes. A small portion has entered the clinical phases and some are already on the market. Buccal insulin (Oral-lyn™) and pulmonary insulin (Exubera®) were launched to the market, although the latter was withdrawn from US market due to lack of consumer demand [7]. The existence of immune cells, i.e. Langerhans and dermal dendritic cells in skin, microfold cells and dendritic cells in the mucosa-associated lymphoid tissue make needle-free immunization potentially possible [8–10]. For example, dissolving microneedles loaded with influenza vaccine showed their effectiveness in stimulating immune response *in vivo* [11].

Drug taken through oral route can be absorbed by oral mucosa if the drug can be retained in the mouth or by gastric and intestinal mucosa if the drug goes into the gastrointestinal tract. In this review, oral delivery refers to gastrointestinal absorption specifically, while buccal delivery refers to drug delivery in the oral cavity. There are certain barriers to

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overcome for drug delivery through these routes. For example, many drugs for oral delivery encounter extensive gut and hepatic metabolisms, which are termed as first-pass effect [12]. Skin is the barrier for transdermal drug delivery while mucosal tissues (intestinal, pulmonary, nasal, ocular, buccal, rectal and vaginal) are more permeable compared to skin [4]. However, poor mucosa absorption exists for drugs with large molecular weights or unsuitable hydrophilic-hydrophobic characteristics [13].

Various technologies have been used to develop drug delivery systems for non-invasive routes. Micro-scale devices have been explored for transdermal and oral drug delivery [14,15]. Microfluidics and engineered tools have facilitated drug delivery through inhalation [16]. Bioadhesive materials have been widely used in transmucosal and transdermal delivery systems [17,18]. To improve mucosal permeability, permeability enhancers such as bile salts and sucrose cocoate are added to mucoadhesive films as well [19,20]. Lithographical approaches have recently been applied to fabricate bioadhesive patches [21].

In the review, we focus on novel drug delivery systems by oral, mucosal and transdermal routes and their engineering approaches. A comparison among them is summarized in Table 1. The applications for injection and implantation are not included here. Previously we have already reviewed nano- and micro-fabricated particulate drug delivery systems, so the same content will not be reviewed in detail here [22].

Chemical engineering and microscale technology

Chemical engineering principles have been utilized to address challenges in drug delivery from various aspects including drug molecule modification, development of new biomaterials and drug delivery systems [23].

Reversible chemical modification of a pharmaceutical substance under physiological conditions, or prodrug concept, is a common approach used to improve pharmacokinetic profile of a drug [24]. For those poorly water-soluble drug molecules, their solubility can be increased by modification with ionisable or polar neutral functional groups, such as phosphates, amino acids or sugar moieties. On the other hand, lipophilic prodrug derivatization can be used to enhance the permeability of hydrophilic substances through lipid membranes. Modification with cell- or tissue- specific transporters can increase the drug targeting and reduce the systemic toxicity. Moreover, prodrugs are less susceptible from rapid metabolism, thus prolonging action time of the drug [24].

Table 1. Different routes of administration and novel engineered drug delivery systems [4,74,75,131,134,190,191].

Route and surface area	Advantages	Disadvantages	Novel engineered systems
Oral (gastric-intestinal) 200 m^2 (small intestine)	Good patient compliance Ease of administration Large absorptive surface area	Strongly acidic environment in stomach Extensive gut and hepatic metabolism	Particulate systems Microfabricated intestinal patches Hydrogels
Pulmonary 70–80 m^2	Rapid onset of drug Large absorptive surface area Good perfusion No first-pass effect	Patient acceptance issues Inconsistent drug deposition Training required for effective administration	Particulate systems Vibrating mesh technology Surface acoustic wave technology
Nasal 160 cm^2	Ease of administration Rapid onset of drug No first-pass effect Possibility to bypass blood-brain barrier	Limited absorption area Dose limited Mucosilliary clearance Enzyme degradation Local irritation	Particulate systems *In situ* gelling systems
Ocular 2 cm^2	Ease of administration No first-pass effect Specific route for posterior eye diseases	Cornea and blood-ocular barrier Clearance by tears Local irritation	Ocular inserts Therapeutic contact lenses Microelectromechanical device Non-invasive iontophoretic device
Buccal 33 cm^2	Ease of administration and termination of treatment No first-pass effect	Small surface area Limited dose Clearance by saliva Taste sensitivity	Buccal adhesive films IntelliDrug Device
Rectal 300 cm^2	Useful in paediatric, geriatric and unconscious patients No gastric irritation Partial avoidance of first-pass effect Ease of termination of treatment	Inconvenient for patients Small surface area Irregular and slower absorption	Sustained-release hollow-type suppositories Drug-laden elastomer
Vaginal 90 cm^2	Rich blood supply No first-pass effect	Cultural sensitivity Gender specificity Local irritation Influence of sexual intercourse	Mucoadhesive systems PEGylated Lipoplex–entrapped alginate scaffold system
Transdermal 2 m^2	Ease of administration and termination of treatment Good patient compliance Large surface area for treatment No first-pass effect Possible sustained delivery	Highly impermeable Local irritation	Microneedles Iontophoresis Electroporation Sonophoresis Thermal ablation

Conjugation to poly(ethylene glycol), or PEGylation not only increases the solubility of drugs and proteins, but also makes drugs more stable in physiological state and prolongs the action time of the drug. Furthermore, reduction or elimination in immunogenicity was also observed in PEGylated protein molecules [25].

One of the advances in drug delivery is the rational design of polymers as carriers for a specific drug molecule. For example, dendrimers are dentritic polymers that have very well-defined nanostructures and high level control over its size, branching density and surface functionality. They are useful nanoscale carriers for drug and gene delivery. Both hydrophilic and phrophobic drug molecules can be formulated with dendrimers [26]. They have been applied in intravenous, oral, pulmonary, nasal, ocular, and transdermal drug delivery systems [26,27]. Efforts have also been made to develop polymers responsive to environment stimuli, such as pH, temperature, ionic strength and biological signals. For example, hydrogels are three dimensional polymeric networks that are able to absorb a large amount of water or biological fluids in their structure due to chemical or physical crosslinking, useful in biomedical applications including drug delivery [28]. Various hydrogel systems have been engineered, such as polysaccharide grafted microgels, interpenetrating network microgels and nanoscale hydrogels. These hydrogels have the ability to sense and respond to the changes in environment and adjust their swelling ratio [29]. Finally, bioadhesives are useful in mucosal and transdermal drug delivery to increase retention time and will be discussed in detail.

Another important feature is the application of polymers to engineer drug delivery systems for sustained release, targeting, breaching transport barriers, and for enhanced intracellular transport [30]. This approach has been applied to many particulate delivery systems. For example, coating the particle surface with certain polymers, such as poly(ethylene glycol) can prolong the circulation of drug carriers *in vivo*. To achieve targeted delivery, the particles can be modified with specific ligands that selectively recogonize certain cell-surface components or receptors. Stimuli-sensitive drug delivery systems can be engineered by incorporation with environment-responsive polymers and particles of magneto-sensitive materials. Modification of drug carriers with cell-penetrating proteins can increase their ability to cross cell membranes. The aforementioned approaches can be combined to fabricate multifunctional drug carriers, for example, with both cell penetration function and stimuli sensitivity [31].

In addition to chemical engineering, nano/micro-scale technologies have been shown to be useful in developing drug delivery systems, by offering structural and functional control of drug carriers [32]. Traditionally, nanoparticles have shown superiority in tackling the problems of drugs with poor water solubility and undesirable pharmacokinetic profiles [33]. Nano- and micro-fabrication technologies can be used to precisely control the homogeneity of micro- and nanoparticles, including their sizes and shapes, to improve their *in vivo* performances [22]. Microfabrication technology has also been utilized to develop devices that provide active and controlled release of drug. For example, microfabrication is an enabling tool for localized delivery of drugs by controlling the reservoir properties of the devices [34].

Bioadhesives for dermal and mucosal membranes

Bioadhesives are useful to prolong the residence time of formulations at the delivery site through close contact and adhesion, which can potentially increase bioavailability at lower concentrations of drug. Controlled release of the active pharmaceutical agent in combination with extended residence time can help to reduce drug administration frequency. Targeted drug delivery to particular tissues is possible by incorporation of target-specific ligands in the bioadhesive. Besides, cost and dose-related side effects may be reduced due to efficiency and localization of the drug delivery [35].

Bioadhesive materials have been utilized in both transmucosal and transdermal delivery systems [17]. However, there are different factors to consider in the fabrication of bioadhesives for mucosa and skin. In general, three main factors determine the characteristics of a substrate for adhesion. The first factor is the chemical composition and structure of the substrate surface that contributes to the thermodynamics of the adhesion; the second factor is the mechanical properties of substrate's contact volume; and the third factor is the surface morphology of the substrate, which controls the effective contact area [36].

Biological surfaces vary greatly in their hydration levels. The main difference between skin and mucous membranes is that the latter is non-keratinized and highly moist due to continuous production of mucus to prevent itself from becoming dry. This makes the mucous membrane behave as a rather hydrophilic substrate for adhesives. In contrast, stratum corneum, the outermost layer of the skin, is hydrophobic in nature to effectively act as a barrier to transepidermal water loss. Although there are considerable morphological and mechanical differences between the skin and mucous membranes, the main factor to be considered for the development of specific adhesives for each type of these substrates is their surface chemical composition, mainly the water content [37].

The initial step in the process of bioadhesion is formation of a series of interactions between surfaced molecular moieties of bioadhesive and the biological substrate. Subsequently, polymeric chains of the bioadhesive interpenetrate into the bio-substrate. It has been shown that by incorporation of specific ligands into the bioadhesives, they can be guided to directly bind to the receptors on the cell surface [38]. This enables targeted delivery of active pharmaceutical agents into the cells since binding to cell surface receptors often results in endocytosis and internalization.

Oral drug delivery systems

Oral drug administration is generally preferred because of its ease of use and good patient compliance. However, many drugs, especially proteins and peptides, have poor oral bioavailability due to their instability, low solubility and/or limited permeability in gastrointestinal tract, therefore not suitable to deliver orally [2,39]. Recent developed systems for oral drug delivery are reviewed below.

Particulate systems

Particulate systems have been employed to improve drug delivery through various routes. Safety and biocompatibility of the materials used to construct the particulate systems need to be considered in the first place. For oral drug delivery, these particulate systems must withstand the harsh conditions of the gastrointestinal tract, such as the acidic environment of the stomach and the abundant enzymes in the intestines. A variety of particulate systems, such as liposomes, microspheres and nanoparticles have been reported to encapsulate the drugs and protect them from the harsh gastrointestinal tract environments [40]. Additionally, the particles can be further optimized for mucoadhesion, cellular uptake and targeting [41]. Mucoadhesive polymers have been employed to prolong the residence time of these particles to increase their oral bioavailabilities. Modification with hydrophilic stabilizing polymers, such as poly(ethylene glycol), can further protect the particles from proteolytic enzymes. Grafting ligands such as antibodies, lectins and peptides at their surfaces can direct the delivery to certain intestinal cells [41,42].

The enzymes and the bile salts in the gastrointestinal tract might destroy the lipid bilayers of liposomes, which will cause the leaking of the loaded drug. It was found that liposomes containing certain lipids, such as gangliosides had a higher stability in bile and pancreatin. Such formulations might survive in gastrointestinal tract [43]. The oral bioavailability of a hydrophilic drug metformin was improved by using liposomes which were coated with chitosan and β-glycerophosphate. Chitosan can increase the mucoadhesiveness of liposomes but it alone is not enough to protect liposomes in gastrointestinal environment because of its high solubility in acidic solutions. Thus, crosslinkage of chitosan with β-glycerophosphate was used to increase the stability of the system in gastrointestinal tract [44].

Mucoadhesive microspheres based on dextran and poly(ethylene glycol) was fabricated to control the release of a hydrophobic drug ketoconazole. Monoacrylated poly(ethylene glycol) was linked to dextran by photopolymerization. The microspheres showed a higher affinity towards aqueous media at pH 8, which indicated its potential as site specific drug delivery system [45]. A vaccine-laden albumin microparticles was modified with a ligand Aleuria aurantia lectin, to target M-cells in the small intestine and demonstrated its potential for oral vaccination [46].

Dendrimers have shown great potential for drug delivery. There are three methods to load drugs into dendrimers. First, since the cores of dendrimers are hydrophobic, it is suitable to form complex with poorly water-soluble drugs. Second, hydrophilic drugs can be coordinated to the highly reactive surface functional groups (like amide, carboxyl and hydroxyl) via ionic interactions. Third, drugs can be covalently linked to the terminals to form dendrimer prodrugs [27]. Polyamidoamine dendrimers were found to have enhancing effect on small intestinal absorption of poorly absorbable drugs with small molecular weights, including 5(6)-Carboxyfluorescein, calcitonin and isothiocyanate-dextrans in rats. However, they failed to increase the absorption of macromolecular drugs including insulin and isothiocyanate-dextrans with an average molecular weight of 9100. It might be because dendrimers loosened the tight junctions of epithelial layer and thus an improvement in the absorption of small molecular weight drugs was achieved [47]. The transepithelial transport and toxicity of polyamidoamine dendrimers as carriers for oral drug delivery has been reviewed by Sadekar and Ghandehari [48].

Delivery of gene silencing nucleic acids via oral route can be enhanced by particulate systems and was reviewed by Akhtar [49]. Extensive reviews on oral particulate systems can be found elsewhere [41,50–52]. Although many technologies have been reported to produce particulate systems, most of them are not easily scalable. Reagents, solvents and materials used in the process have to be considered [53]. Besides, the control over the homogenicity of particle size and shape remains a challenge. Recently, microfabrication techniques were found to be able to precisely control the size and shape of particulate drug delivery systems. These techniques include particle replication in non-wetting templates (PRINT) technology, step and flash imprint lithography, film stretching, flow lithography, flow-focusing microfluidics and bioprinting. Details of these techniques can be found in our early reviews [22].

Microfabricated intestinal patches

Microfabrication techniques, such as three dimensional printing, lithography, etching and thin film deposition, have been explored to fabricate microfabricated intestinal patch systems to enhance oral drug delivery [34,54–56]. Microfabricated intestinal patches combine the advantages of programmed release, increased bio-adhesion, improved tissue selection and penetration. They can be fabricated in flat and thin shape with a mucoadhesive surface to maximize the contact with intestinal linings while limiting the drug release to luminal fluids. Usually, drug is segmented into a reservoir to preserve the stability of bioactive agent and enable high drug concentrations against the intestinal mucosa [14].

In another study, Desai group developed a SU-8 micropatterned device by photolithography. Photopolymerized poly(ethylene glycol) dimethacrylate hydrogels containing therapeutics were introduced to the device. By controlling photo-initiation conditions, such as ultraviolet light exposure time and initiator concentrations, multi-layers of hydrogel with different therapeutic agents were incorporated into the microdevice. The fabrication process is shown in Figure 1 [55]. Biotinylated tomato lectin, together with acrylated-avidin, were also introduced into the hydrogel to increase the bioadhesion of the microdevice. Avidin was first covalently attached to the di-methacrylate hydrogel backbone, and then biotinylated tomato lectin was bound to the avidin. *In vitro* experiments demonstrated that the microdevice with functionalized lectin can attach onto caco-2 cells [57].

The current research of microfabricated intestinal patch is limited to *in vitro* and *ex vivo* models. Nevertheless, this system is potentially useful to improve drug absorption, especially for hydrophilic biomolecules, such as peptides and proteins. Biodegradability of the materials should be considered for the application of such systems *in vivo*. Furthermore, affordable fabrication methods for large scale

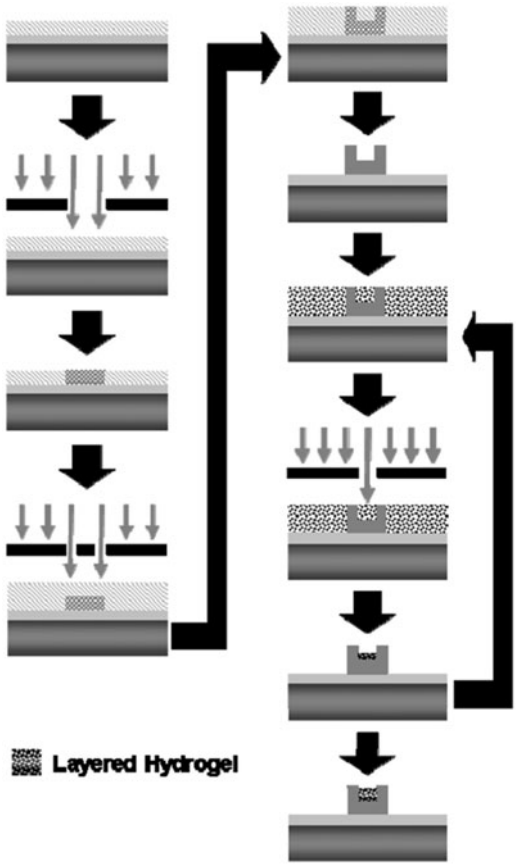

Figure 1. Process flow overview for fabrication of multilayer poly(ethylene glycol) dimethacrylate laden SU-8 microdevice [55].

production need to be developed to turn these proof-of-concept systems into commercial reality [58].

Hydrogels

Hydrogels may swell due to changes in the surrounding environment. They showed great potential as carriers for oral administration of drugs, including fragile proteins and nucleic acids by offering protective mechanisms to these molecules [29]. Hydrogels can be further optimized for mucoadhesion, cellular uptake and controlled release [59]. In particular, *in situ* gelling system is a special hydrogel system. It is homogeneous liquid when administered orally and forms gels at the target site. This property may benefit patients with swallowing difficulty [60].

Poly(methacrylic acid-g-ethylene glycol; P(MMA-g-EG)) hydrogel showed its potential for oral delivery of proteins and peptides, such as insulin, calcitonin and interferon β. The peptides and proteins were incorporated into the hydrogels by equilibrium partitioning. Different incorporation efficiencies were obtained for insulin, interferon β, calcitonin and bovine serum albumin (BSA) [61]. Drugs can be protected from the harsh gastric environment and released in intestinal environment because of the pH-dependent swelling properties of hydrogels [62]. These hydrogels have also been shown to be capable of inhibiting the intestinal enzyme activity by binding to calcium [63,64]. Besides, P(MMA-g-EG) hydrogel nanospheres were able to open the tight junctions between epithelial cells and dramatically reduce the mucosal membrane resistance in Caco-2 monolayers [63,64]. Schoener et al. [65] developed interpenetrating polymer networks composed of P(MMA-g-EG) and poly(*n*-butyl acylate; PBA). The two polymers are not chemically crosslinked but physically entangled. The incorporation of hydrophobic PBA made the hydrogel system suitable for hydrophobic drug delivery. Mucoadhesive properties of the P(MMA-g-EG) hydrogel system were further improved when it was functionalized with wheat germ agglutinin, a lectin which can provide a specific adhesion to mucins in the mucosal layer [28].

A combination strategy of cyclodextrin complexation and hydrogel system was evaluated in oral insulin delivery [66]. Cyclodextrin can be used to enhance drug stability and absorption. Insulin was complexed with methylcyclodextrin (MCD) and then encapsulated in poly(methacrylic acid)-chitosan-poly(ethylene glycol; PCP) hydrogel microparticles. It was found that MCD effectively improved the permeation of insulin through Caco-2 cell monolayers. PCP hydrogel microparticles containing MCD-insulin showed a better biological effect in diabetic animals than the PCP microparticles containing unmodified insulin, but the difference was not significant [66].

Hezaveh et al. reported that the dispersion of genipin and MgO nanoparticles inside carrageenan hydrogels has good control over the drug release under gastrointestinal conditions [67]. Carrageenan is a sulphated polysaccharide extracted from red seaweeds and widely used in the food industry. The model drug methylene blue was first loaded in the MgO nanoparticles. Then, the nanoparticle solution was added to hot carrageenan solution to be embeded inside hydrogels. The nanoparticles serve as nano-sized drug reservoirs inside the hydrogels. A greater control over drug release can be obtained by adding a cross-linking agent genipin into the carrageenan hydrogels, which increased the drug release in intestine medium while decreased drug release in stomach [67].

For *in situ* gelling systems, phase transition can occur due to a change in temperature or cation concentration [60]. It was reported that when two or more polymers were appropriately blended, a new system with desired gelling properties can be obtained [68]. Itoh group investigated *in situ* gelling systems with different combinations of polymers for oral drug delivery. Paracetamol was used as model drug in these systems [60,69–71]. It was found that the mucoadhesive property of chitosan was enhanced with glyceryl monooleate added. Both hydrophilic and hydrophobic molecules, such as lidocaine hydrochloride, ketoprofen and dexamethasone were tested. But the release of all these drugs from the gels was too fast *in vitro*. Incorporation of glutaraldehyde as a crosslinker can retard the drug release. The release of dexamethasone can be further sustained by incorporating in ethylcellulose microspheres [72].

Pulmonary drug delivery systems

Pulmonary drug delivery has been widely explored for the treatment of local respiratory diseases such as asthma and chronic obstructive pulmonary diseases [73]. Pulmonary drug delivery circumvents the first-pass effect, hence reducing doses and side effects. Pulmonary route is also very attractive

for systemic drug delivery because of rapid onset of drug action owing to the large absorptive surface areas, thin epithelial barrier and high blood flow [74]. To be delivered into the lung, drugs can be formulated into aerosols. The deposition of an aerosol in airways is dependent on the physicochemical properties of the drug and the formulation, the aerosol generation device and the respiratory characteristics of the patient [75]. The optimum aerosol size range of 1–5 μm is expected for oral inhalation products. Aerosols larger than 5 μm are more likely to deposit in the upper respiratory tract [16].

A pulmonary drug delivery system includes the development of formulation as well as a suitable aerosol-generation device. The formulation development of pulmonary drug delivery systems will be discussed below. Advances in nebulising techniques, such as vibrating mesh techniques and surface acoustic wave (SAW) technology will be reviewed.

Particulate systems

Micro- and nano-particulate systems, such as liposomes, dendrimers, nanoparticles, nanosuspensions and microspheres have been explored in pulmonary delivery [76–82]. Polyamidoamine dendrimers with positive charge have shown the enhanced bioavailability in pulmonary delivery of low-molecular weight heparin (a negatively charged oligosaccharide) to treat vascular thromboembolism. In this formulation, dendrimer-drug complex was formed [78]. Further studies showed that heparin encapsulated in pegylated dendrimers has a longer circulating half-time and increased pulmonary absorption [76]. In addition to dendrimers, cationic liposomes were used as carriers for heparin and showed enhanced pulmonary absorption. These cationic liposomes were prepared by conventional methods, i.e. lipid dispersion, solvent evaporation and extrusion [77].

Microfabrication technology, such as PRINT has precise control over particle size and shape and showed promising applications in these nanocrocarrier system production [22]. Precise control over particle geometry allows for defined aerodynamic properties, enhancing aerosol performance and differential lung deposition *in vivo*. PRINT technology for dry powder fabrication has been demonstrated to improve aerosol performance applicable to pulmonary drug delivery. The incorporation of various compounds, including small molecules, proteins, nucleic acids, and drug/polymer matrix showed that this particle engineering approach is versatile and gentle. An influenza vaccine produced by PRINT technology has progressed into clinical trial. It showed that this microfabrication technology can be used to produce GMP products [83].

Electrospraying has been explored for the generation of nanoparticles. Charged small droplets with high monodispersity can be generated through electric field control. Since these droplets are charged and self-dispersing, coagulation can be avoided [84]. Chitosan nanoparticles with an average diameter of 124 nm were prepared by electrospray deposition, which showed the potential to be used in pulmonary delivery [85]. Non-viral vectors for gene delivery, monodispersed oligodeoxynucleotide encapsulated lipoplex nanoparticles and plasmid DNA/plolyethylenimine polyplexes with improved delivery efficiency, were generated by one-step coaxial electrospraying [86,87].

Vibrating mesh technology

The recently developed nebulizers using vibrating mesh technology can generate droplets with smaller sizes, which showed high efficiency in delivery of drug into deep lung than conventional nebulizers [73]. Vibrating mesh nebulizers have perorated plate/mesh which vibrates in contact with liquid to generate the aerosol. The oscillation of the mesh was caused by a piezoelectric crystal with a lower frequency compared with ultrasound nebulizers. The devices do not heat up the fluid during atomization, which may be beneficial to liable substances such as proteins. Besides, vibrating mesh nebulizers were demonstrated to be more suitable for delivery of suspensions than ultrasonic nebulizers [73,88].

Products using vibrating mesh technology includes Aerodose, eFlow, MicroAir, AKITA^2 APIXNEB, etc [89]. However, the cost of these devices can be an obstacle for their applications. The vibrating mesh nebulizers have been used to aerosolize liposomes as well as proteins, such like α_1-proteinase and DNase I [90–92]. Elhissi et al. studied vibrating mesh nebulizer to aerosolize liposomes loaded with hydrophilic drugs. The liposomes were made from ethanol-based pro-liposome technology, which disperse concentrated ethanolic solutions of phospholipid within an aqueous phase, which has the advantage of entrapping hydrophilic drugs. Once nebulized by a vibrating mesh nebulizer, a higher nebulization output and smaller droplet size were obtained when NaCl (0.9%) solution was used as the dispersion medium. However, a significant loss of the originally entrapped hydrophilic drug was observed during nebulization [90], although it was reported that vibrating mesh nebulizers have less disruptive effect on liposomes compared with ultrasound and jet nebulizers, because the high mechanical forces of the latter two nebulizers can disrupt the liposome bilayer and cause drug leakage [93,94].

A micro-pump based droplet generator was introduced to prepare mono-dispersed aerosols on demand. This valveless micro-pump was fabricated from polydimethylsiloxane with multiple vibrating membranes and three nozzles/diffusers [95,96]. Numerical stimulation showed that the device has the potential to produce liquid droplets with controlled sizes from nano to micro range by vibrating frequency control. Besides, the droplet size is controlled by the diameter of outlet nozzle [96,97].

Surface acoustic wave technology

Recently, Yeo et al. reported SAW as a novel nebulizing technology for pulmonary delivery as well as an effective tool for nanoparticle generation [16]. SAWs are sound waves possessing amplitude on the nanoscale, propagating on a piezoelectric single crystal substrate. Different from conventional ultrasound, which needs a power input of 10 W and bulk medium to transfer the energy, SAW propagates over a thickness of four wavelengths at a low power requirement (1 W). Thus, SAW atomization provided a potential platform for a novel portable palm-size nebulizer development [98].

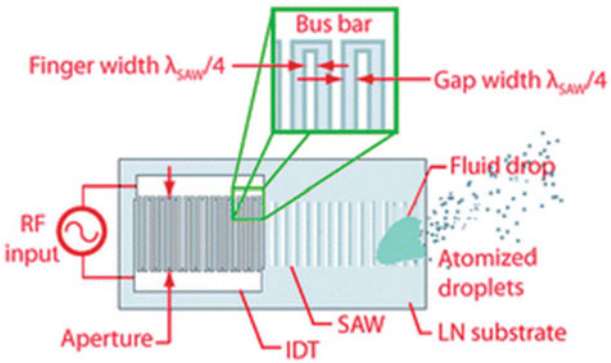

Figure 2. Schematic of the SAW device showing the aluminium–chromium interdigital transducers (IDT) electrodes patterned on the piezoelectric (LiNbO3) substrate. A RF power source supplies the atomizer with a sinusoidal electric signal via the IDT which excites the SAW on the substrate [99].

Figure 2 is an illustration of a SAW device, fabricated by sputtering and photolithography with wet etching techniques. Salbutamol-contained aerosols with a size distribution of $2.84 \pm 0.14\,\mu m$ was generated by using the SAW device and 70–80% of the drug can be delivered to a lung model [99]. Mono-dispersed insulin aerosols around 3 µm and BSA nanoparticles with a size of 50–100 nm can be generated by SAW atomization. It indicated that SAW was a convenient and flexible method for nanoparticle generation. Based on this technology a portable device for pulmonary administration may be developed [100].

Nasal drug delivery systems

Nasal drug administration is naturally an excellent choice for local nasal diseases. Intranasal administration is also attractive for systemic drug delivery, since this easily accessible route is non-invasive, allows fast onset of systemic action without first-pass metabolism and has the possibility to bypass blood-brain barrier. However, for intranasal delivery, drug molecules have to cross the nasal mucosa, which has limited permeability for hydrophilic drugs or drugs with a molecular weight larger than 1000 Da. Besides, mucociliary clearance limits the residence time of drug in nasal cavity. Enzymatic degradation further limited the absorption of proteins and peptides via nasal route [101]. Particle size is one of the critical parameters for nasal sprays and aerosols because particles with different sizes have different deposition behaviour thus affect their *in vivo* uptake. It was reported that particles larger than 10 µm deposit in nasal cavity. Particle size between 2 and 10 µm may go in to the lungs, while particles smaller than 1 µm are exhaled [102]. Different approaches have been used to increase nasal bioavailability of drugs, including prodrug strategy, use of enzyme inhibitors, absorption enhancers, mucoadhesive materials and particulate systems [102].

Particulate systems

Without any enhancement, molecules up to 1000 Da can pass the nasal mucosa. When encapsulated in micro/nano-sized drug carriers, peptides, proteins and vaccines can also be delivered by nasal administration [103]. The particulate systems can protect drugs from enzymatic degradation in nasal cavity and help the drug to cross the nasal mucosa. Liposomes, microspheres and nanoparticles were proved to be beneficial in vaccine delivery by improving immune responses [104–106]. In addition, nanoparticles have the potential in facilitating the transport of drugs from nasal to brain. Zhang et al. demonstrated that a higher concentration of nimodipine in the cerebrospinal fluid can be achieved, when delivered by poly(ethylene glycol)-poly(lactic acid) nanoparticles than by nasal solutions [107]. The detailed application of particulate systems in nasal drug delivery has been reviewed elsewhere [108,109].

In situ gelling systems

To achieve high absorption and sustained release for intranasal administration, *in situ* gelling systems have been studied for nasal drug delivery. *In situ* gels can be administered easily to the nasal cavity in a liquid form, and form gel upon contact with the nasal mucosal surfaces to increase the residence time and diminish mucociliary clearance [110]. Deacetylated gellan gum can form gel at physiological ionic concentrations and was used for intranasal delivery of gastrodin to treat nervous system diseases [111]. Mucoadhesive *in situ* gel was formed for nasal delivery of sumatriptan by utilizing temperature-dependent polymer Pluronic® F127 and mucoadhesive polymer Carbopol® 934P [112]. Another thermo-sensitive polymer, poloxamer, was used to develop nasal *in situ* gels to deliver plasmid DNA constructs [113].

Different from *in situ* gels mentioned above, nasal inserts based on mucoadhesive gelling polymer can be inserted into nasal cavity in a solid form, and form gels through rehydration [114]. This dosage form combines the advantages of solid (better stability and dosing accuracy with acceptable foreign sensation) and prolonged residence of a gel. Freeze-drying technology is normally used for the preparation of these nasal inserts [115]. Such delivery systems have been investigated for peptide, protein and vaccine delivery through nasal route [116,117]. After being applied into nasal cavity, *in situ* gels and nasal inserts both formed gels to retain drugs in the nasal cavity. The formed gels should have enough mucoadhesion to adhere to the nasal cavity for sufficient time to reach predicted therapeutic effect. However, the mucoadhesion should not be too strong to damage the mucosa. The advancement of polymer science facilitated the development of such systems.

Ocular drug delivery systems

Systemic drug delivery to the ocular site is limited due to the presence of a blood-ocular barrier. To achieve a desired therapeutic effect, a large dose is usually used which will cause side effects [118,119]. Traditionally, local drug delivery systems using eye drops or ointments are an alternative to systemic drug delivery. However, this route of application is only able to reach out to the anterior site of the ocular system since the penetration of drug to the posterior site is largely inhibited by the blood-ocular barrier [120]. Moreover, the low corneal and conjunctival absorption (<5%) makes it difficult to produce a therapeutic concentration of the drug [118].

As such, treatments of posterior ocular diseases like retinal disorders remain a challenge. Over the past two decades, various novel drug delivery systems have been developed to overcome the problem posed by the blood-ocular barrier. Among these novel drug delivery systems, a local delivery is preferred due to the prolonged stable drug release and minimization of side effects [121].

Ocular inserts (OIs)

OIs are sterile polymers with drug incorporated inside the polymers or coated on their surfaces. They are to be implanted into the conjunctival sac surgically, hence the term inserts. A large variety of OIs are present due to the difference in drug solubility, drug release mechanism and other factors. Soluble OIs release drug by diffusion as the device slowly dissolves in tears [122]. Unlike soluble OIs, insoluble OIs employ different mechanisms to release drug from the drug reservoir. These mechanisms include diffusion, osmosis and bio-erosion [123]. In general, insoluble OIs consist of drugs and an insoluble solid matrix which acts as a container of the drugs. Two pieces of rate-controlling membranes are present on the top and bottom surfaces of the OIs. Small pores are present in the membrane, which allow tears to enter into the drug reservoir to dissolve the dispersed drug. The solubilised drug is then released to the target site [124].

Two compartments separated by a semi-permeable membrane are found in the OIs that use osmosis. The inner compartment contains a reservoir of drug and is bound by an impermeable rubber membrane. The outer compartment has osmotic agents dispersed and is surrounded by a semi-permeable membrane. Aqueous medium from the tear enters the outer compartment by osmosis, creating a hydrostatic force. Pores are then formed on the rubber membrane due to the force and the drug inside is able to go into the eyes at a controlled rate [124].

OIs that use bio-erosion are made up of biodegradable polymers such as collagen. The drug is incorporated into the solid matrix. As the insert is eroded by the tears in the aqueous environment, the drug is released gradually. Similar to the soluble OIs, biodegradable OIs do not require removal after the drug reservoir is depleted [124].

Generally, OIs serve the purpose of sustained drug delivery into the posterior ocular space. However, it could cause discomfort as they can be felt by the patients, especially the insoluble OIs. It might also obstruct the vision and slip off from the conjunctiva with rubbing on the eye [123].

Therapeutic contact lenses (TCLs)

The use of TCL is growing popular due to the ease of use and improved compliance. However, TCL made solely by hydrogel is not plausible due to the swelling effect when it is placed into the eye which will in turn cause discomfort to the patients as well as a modified drug release profile. Other approaches of making TCL with various polymers also pose some drawbacks [125]. Hence, a TCL with various imprinted materials which have shape and size memory is developed. Venkatesh et al. have worked on imprinted hydrogel with different compositions using free-radical UV photopolymerization at a controlled temperature and non-oxidative environment [125]. Among all, imprinted hydrogel has been proven by Ali et al. to have relatively longer drug release duration of ketotifen up to 5 days. The type of hydrogel employed in making contact lenses is the durable and insoluble hydrogel which has been extensively researched during the past three decades. Its prolonged and stable drug release profile has been established. In addition, the transparency and similar refractive index to the lens, allows it to be imprinted to the lens without affecting the eyesight. Under *in vivo* study, sink condition is assumed and a zero order kinetic drug release is reported [126]. TCL is generally used to achieve a sustained release of drugs to relieve eye allergy for up to 1 day instead of applying eye drops every 2 h [126]. However, long term use of TCL has yet proven to be safe for patients. Its efficacy for ocular disease requiring chronic treatment or suppressant will remain questionable until further modification and proof [127].

Microelectomechanical device (MEMD)

MEMD is a device surgically inserted into the conjunctiva [128]. It consists of three main components: a drug reservoir encapsulated into a silicone rubber in a chip, an electrolysis pump and a parylene cannula (Figure 3A). The pump works to deliver the drug from the reservoir into the intraocular space via a parylene cannula. The pump is able to adjust the rate of drug release as well as to deliver the drug as a bolus or a continuous flow by electrochemical means. The cannula can be adjusted either to the anterior or posterior of the intraocular space to achieve a drug delivery to a specific target site (Figure 3B). Different from other devices which require surgical removal after the drug has run out, MEMD enables refilling of the drug without removing the device. A non-coring syringe needle can be used to refill the drug in to the silicone rubber which is able to withstand multi-puncture and reseal after the removal of the needle [129]. As a result, MEMD is able to provide a sustained stable drug release to the intraocular space without the need to replace the device after the drug reservoir is exhausted, saving the patients from undergoing multiple surgeries to get a long-term use of the device [128].

Non-invasive iontophoretic device

Iontophoresis is a process employing an electric current to deliver drug into the target site. It is also described as injection of drug without a needle and therefore considered as a non-invasive method. Delivery via iontophoresis demonstrates a good penetration into the posterior ocular space, forming a depot which will allow a sustained release of drug (Figure 3C) [130]. However, only *in vivo* trial on rabbits has been carried out to test the drug release profile by the depot so far. Moreover, the relative duration of drug actions is shorter than the drug delivery system described above [127].

Even though ocular route of drug administration is generally considered as non-invasive and the drug release is controlled and prolonged, it would still encounter some patients' non-compliance since most of the drug delivery systems need to be inserted into the eyes which would require surgical procedures. Hence, rather than systemic delivery, localized delivery systems targeting eye disorders are their

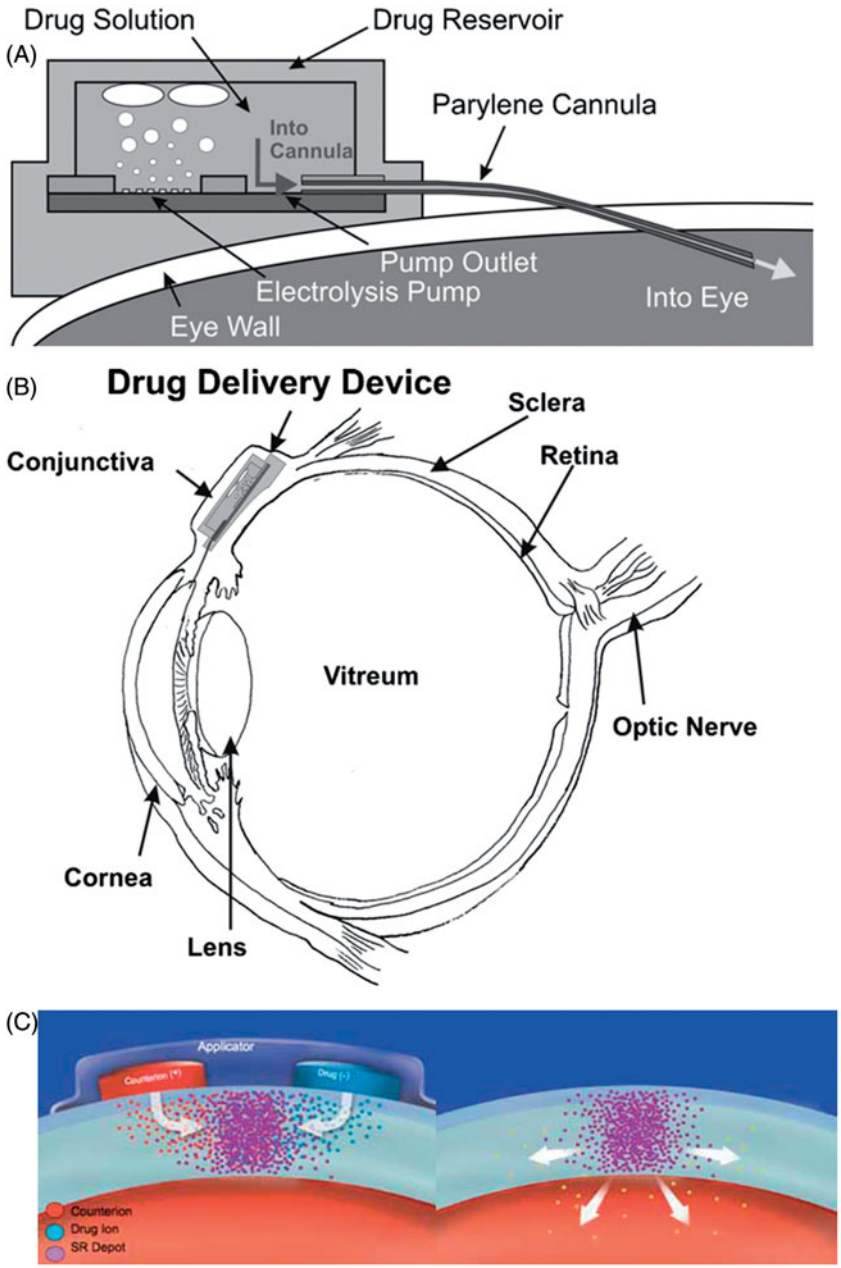

Figure 3. (A) Cross-section of the ocular drug delivery device depicting electrochemical pumping of drug into the eye [128,129]; (B) Conceptual illustration of the implanted ocular drug delivery device [128,129]; (C) Visulex depot-forming methodology [130].

main applications. Moreover, the complexity of the devices makes it potentially difficult to manufacture in large scale and increases overall cost.

Buccal drug delivery systems

With a rich blood supply and relatively good permeability, oral cavity gradually gains its popularity as an alternative route for drug delivery. Sublingual mucosa has been well studied and is a generally acceptable site for drug delivery due to the ease of administration, non-invasiveness, avoidance of first-pass effect and high permeability [131]. However, due to the high saliva flow, the drug is flushed off easily and prolonged drug release is consequently not feasible in the sublingual route [132]. Buccal mucosa is therefore an alternative to the sublingual route because of the possibility for the development of a sustained drug release system. Traditional buccal drug is administered as a gel or a paste. However, the gel or paste is unable to stay at the buccal mucosa for a long time as it is easily removed by tongue movement or washed away by saliva. Moreover, eating food will reduce the amount of drug available to the buccal mucosa. Another concern is the narrow pH range at around 7 which may not be suitable for dissolution of some drugs [132]. In addition, the permeability of buccal mucosa is lower than that of the sublingual mucosa. To increase the contact time of drug with the mucosa and allow a better penetration of the drug, researchers have investigated various permeability enhancers and developed novel drug delivery systems, such as the buccal adhesive film and the IntelliDrug Device (IDD) [132,133].

Buccal adhesive films

Buccal adhesive films are mucoadhesive polymeric films capable of attaching to the buccal mucosa for a desired

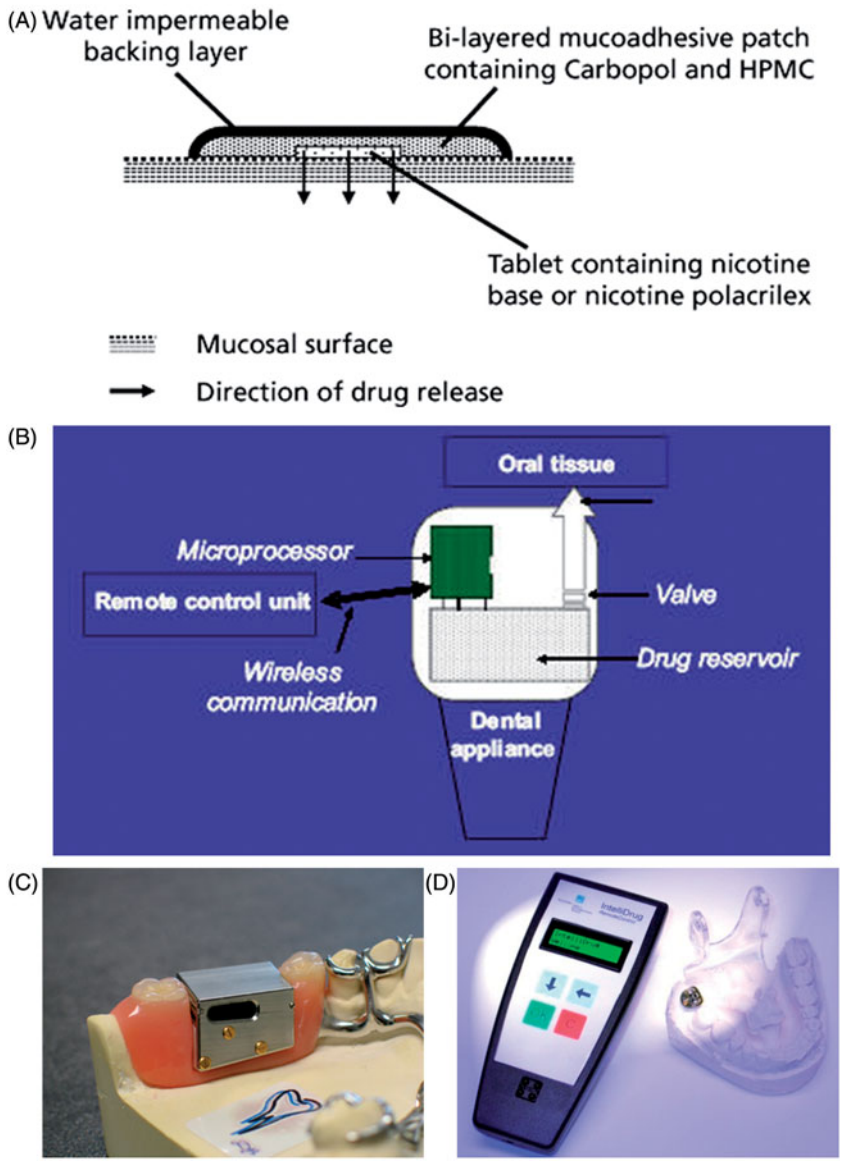

Figure 4. (A) Tri-layered nicotine buccal mucoadhesive patch adhered to the mucosal surface. Diagram was not drawn to scale [135]; (B) Schematic IntelliDrug systems (Adapted from http://www.hsg-imit.de/fileadmin/gfx/pdfs/project_presentation.pdf); (C) The first prototype of IntelliDrug (Adapted from http://www.intellidrug.asm-poland.com.pl/link_solution); (D) The remote control and visualization of IntelliDrug (Adapted from http://www.intellidrug.asm-poland.com.pl/link_solution).

duration without causing irritations [17]. Drug trapped in the matrix is released slowly as the space between the crosslinked networks of the hydrogel is expanded due to swelling, thus a prolonged and stable drug release is achieved. However, it is noted that not all drugs are compatible with a certain type of hydrogel. Thus, a suitable material has to be tested for each drug which might render the production process troublesome. Another concern to be further investigated and possibly solved is the interference of some drugs with the swelling process [134]. In view of the problems in the incompatibility of drug and mucoadhesive film, Rao et al. tested on a novel tri-layered buccal mucoadhesive patch for nicotine delivery (Figure 4A) [135]. This tri-layered patch consists of a bilayered mucoadhesive patch and a water impermeable backing layer with a dry tablet containing nicotine adhered to the centre of the patch. Stability of drug inside the mucoadhesive film is now no longer of a concern, and hence a more rapid onset due to fast drug release was observed.

IntelliDrug device (IDD)

IDD is an innovation developed to treat smoking and drug addiction and chronic diseases [133]. It is a device that resides on the dental arc similar to a tooth and does not interfere with the normal function of the mouth in the patient (Figure 4C). It can either be fixed or detachable. The device consists of a micro-processor, a drug reservoir and a valve for drug release (Figure 4B). The drug reservoir is a compartment containing the drug. A built-in intelligence is achieved by the micro-processor to handle the medication release mechanism. A remote control outside the body works together with the micro-processor via wireless communication to regulate the rate and amount of drug released from the compartment via the valve (Figure 4D). The remote control is also capable to inform the patient on the amount of drug available, thus the time for refill. The drug reservoir is easily accessible so that it allows the drug to be refilled without any surgery. IDD is able to achieve a stable plasma drug concentration with constant drug release profiles. As a result, patients with chronic disease like diabetes can benefit from it due to a stable insulin level. IDD sets out to be a non-invasive way to deliver a drug to the buccal mucosa, to reduce side effects and improve patient compliance.

Buccal route of drug administration is generally accepted by patients. With advancement in adhesive polymer, it is

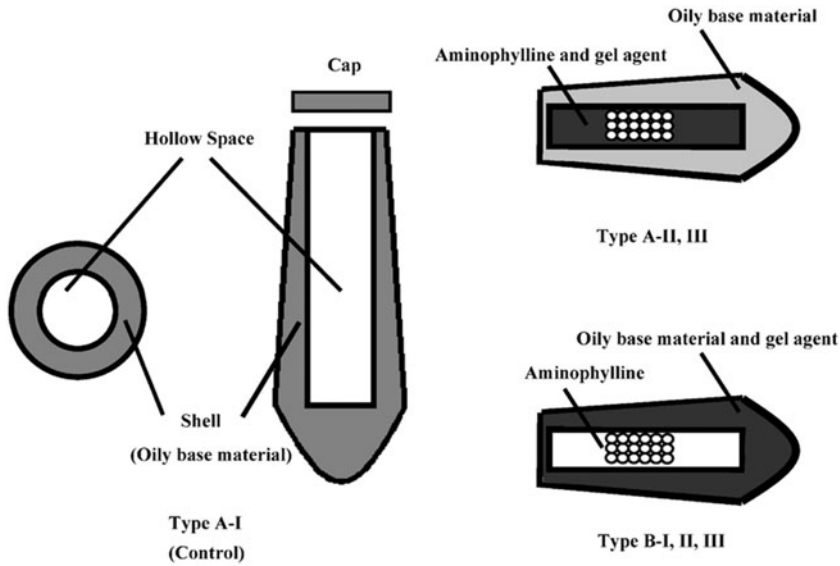

Figure 5. Schematic of hollow-type suppositories [137].

possible for large scale production of buccal adhesives. However, it is noted that individual customization is needed for certain devices. In addition, the feeling of foreign objects in the buccal cavity might pose another problem to the acceptance by patients.

Rectal drug delivery systems

Rectal route has not been the choice for the first-line treatment due to its low permeability and rejection by the patients. However, it is an important route for patients unable to take in pills either due to young or old age, diseases or unconsciousness [136]. Suppository and enema are the two main classes of dosage forms available while only suppository can be used for a relatively sustained effect of action. However, researchers have been investigating into innovations to utilize rectal route of drug delivery effectively. To date, suppository has been modified to allow a long retention time in the anus and release the drug in a controlled manner [137]. In addition, drug-laden elastomers provided insight into exploration of rectal drug delivery systems as well [138].

Sustained-release hollow-type (SR-HT) suppositories

Traditionally, suppositories release the drug by either melting or dissolving. Conventional suppositories have limitations, such as uncontrolled drug release, damage of drug during preparation and leaking of molten bases. To overcome these limitations, SR-HT suppository has been developed by Shiohira et al. It is a suppository with a hollow space acting as a drug reservoir [137]. The study showed that a suppository with a shell made up of an oleaginous base and a gel agent, polyacrylate-sodium polyacrylate co-polymer, attained a slower rate of drug release. The slow and constant drug release profile can help in achieving a stable plasma drug concentration and prolonged drug action time. Theophylline, an anti-asthmatic drug with a low therapeutic index, was investigated in the study. Among the modified suppositories test, one suppository was able to release 80% of the drug in 6 h which is much longer than the other systems (Figure 5). No rectal lesion has been observed in rabbit, indicating a high safety profile of the novel drug delivery system. This type of suppository has its advantage for patients who require a basal level of plasma drug concentration at night and early morning to prevent symptoms such as hypoglycemia, heart attack and bronchial asthma [137,139]. Large scale production of SR-HT suppositories is highly possible by using the well-established manufacturing system. It should be cautioned that this route of drug administration might encounter non-compliance from the patients who deem it as invasive and/or inconvenient.

Drug-laden elastomer

Elastomer is an elastic polymer conventionally termed as rubber. It can be used as a seton in the surgical treatment of anal fistula (an abnormal linkage between the skin surface and the anal canal). A seton can be used to tie the anal fistulous tissue to cut the connection and induce inflammatory response to maintain the sphincter continuity by promoting fibrosis [140]. Besides the cutting and draining action, elastomers can be used to entrap drug and allowing sustained drug release to the surrounding tissue [141]. However, the elasticity of the elastomer may be compromised if excess drug is entrapped in it. A silicone elastomer laden with lidocaine has been fabricated by Li et al. to effectively deliver the analgesic to the anal tissue while the drug-laden elastomer acts for clinical applications [138]. However, improvement in control over drug release from the elastomer would be needed for future development.

Vaginal drug delivery systems

Vaginal route for drug administration has not been extensively investigated though it is a non-invasive way of drug delivery. A combination of factors leads to the unpopularity. First, vaginal drug delivery system is gender specific. In addition, patients might not accept this concept of drug administration even though it is easy to use. Impacts by age, menstrual cycles and possible interference with sexual experience are some other concerns [142]. Traditionally, vaginal route is only used for delivery of drugs with a localized effect such as anti-fungal or contraceptive in the forms of tablets and pessaries. Recent researches show that vaginal route is suitable for

systemic drug delivery due to its rich blood supply network and avoidance of first-pass metabolism [142,143]. However, the permeability of vaginal mucosa is relatively lower than other mucosal surfaces [144]. Novel approaches such as bioadhesive polymers and scaffold systems have been reported to achieve controlled drug release.

Mucoadhesive systems

A low retention time of drug on the surface of vaginal tract has posed a challenge to sustained drug release. Mucoadhesive polymer is a bioadhesive polymer usually employed for a prolonged release of drug on the mucosa [17]. Similar cases have been discussed in the previous routes. In addition to the mucoadhesive film, bioadhesive tablets are also used in vaginal drug delivery system. Digenis et al. formulated Nonoxynol-9 into a solid co-precipitate [145]. It can be incorporated into a multilayer drug delivery system with polyvinylpyrrolidone with or without iodine to act a as a potential spermicide. Kast et al. conjugated thioglycolic into chitosan to improve disintegration and retention on the mucosa surface [146]. Wang and Tang developed a bioadhesive tablet consisting of Carbopol 934P and hydroxypropyl cellulose in the ratio of 1:9 with effervescent as a disintegration agent. This bioadhesive tablet containing ketoconazole was able to act up to 24 h in an *in vivo* study using rats, showing its potential application in the treatment of Candida albicans [147]. Dobaria et al. utilized solvent evaporation technique to produce a mucoadhesive film using hydroxypropyl cellulose and xanthan gum as the polymers [148]. With clindamycin phosphate as an active pharmaceutical ingredient, it showed the potential to be used as a prolonged drug delivery system against bacterial vaginosis [149].

PEGylated lipoplex-entrapped alginate scaffold system

Vaginal administration is potentially useful for siRNA delivery. However, mucus on the vaginal mucosa acts as a barrier to prevent penetration of the nucleic acids and simultaneously remove them. To increase permeability of the mucosa and reduce clearance by the mucus, Wu et al. proposed a model termed PEGylated lipoplex-entrapped alginate scaffold system to overcome the challenges [150]. Natural polysaccharide alginate is able to crosslink to form polymeric scaffold in the presence of bivalent cations like calcium ions. The scaffold is then slowly disintegrated in the presence of monovalent cations like sodium ions, which are found in the body fluid, allowing for a controlled and prolonged release of drug. PEGylation was shown to increase the stability and transport efficiency of lipoplex into the mucosa. Thus, a combination of the muco-inert lipoplex as a gene delivery vector and a biodegradable alginate as the scaffold is able to confer a sustained release of the siRNA into the vaginal mucosa. A freeze-drying method is employed to reduce the swelling of the scaffold in the presence of aqueous environment in the vaginal tract to minimize discomfort to the patients.

Transdermal drug delivery systems

Drug delivery through skin has several advantages, including avoidance of the first-pass metabolism, avoidance of gastrointestinal side effects, possibility of extended therapy, ease of termination when needed, painless and friendly pediatric application [4]. Besides, the existence of immune cells in skin (i.e. langerhans and dermal dendritic cells) makes vaccination via transdermal administration possible [8]. However, the skin, especially the outermost layer, namely stratum corneum, forms a formidable barrier which allows only hydrophobic drugs with a molecule weight less than 500 Da to go through [151]. Great efforts have been made to overcome the skin barrier for transdermal drug delivery. Among these efforts, chemical enhancers have been used to change the lipid structure of stratum corneum to increase the permeability of skin. However, this method only allows the enhancement of small molecules and the amount of drug permeated through skin is limited [8]. Skin irritation is another issue for chemical enhancers [16]. Recently, some microfabricated systems, such as microneedles, iontophoresis, electroporation, ultrasound, and thermal ablation were introduced as active methods to enhance skin permeation. They are currently in various clinical trials and FDA approval process for transdermal delivery of macromolecules and vaccines, including insulin, parathyroid hormone and influenza vaccine [152].

In addition, hair follicles and nails are two important skin appendages. Localized drug delivery systems have been developed for abnormalities related to these skin appendages, such as acne, alopecia, onychomycosis and psoriasis. Hair follicles are also attractive sites for topical vaccinations and regenerative medicine, since there is a high density of immune cells surrounding the hair follicle indundibulum and stem cells residing in the bulge area. Nanoparticles with different sizes showed the ability to target different sites of hair follicles [153]. Physical enhancement, such as iontophoresis and ultrasound, were also reported to facilitate the drug delivery through nail and hair follicles [154–157].

Microneedles

Microneedles are usually referred to be minimally invasive for transdermal drug delivery. By piercing through the stratum corneum, microneedles offer a pain-free method to facilitate the delivery of a large range of drugs through skin, due to the creation of hydrophilic pathway [4]. The pores created in the skin resealed quickly upon removal of microneedles and can exist up to 72 h when occluded with a plastic film or solution [158,159]. Extension of pore existence up to 7 days was also reported [160]. There are currently four ways for delivery of drugs by microneedles. Drug can be delivered by hollow microneedles or applied on the skin as a gel or patch after pretreated by microneedles. In other cases, drug can be delivered by being coated on needles or being incorporated into degradable needles [151]. The enhanced delivery of drug includes hydrophilic drugs, peptides and proteins, to exert either topical effect or systemic effect [161–163]. Microneedles also showed effectiveness in transdermal vaccination with reduced doses of antigens and made self-administration of vaccine possible [164]. Different types of microneedles, hollow or solid can be made of various materials, such as metal, silicon, sugars and polymers [151].

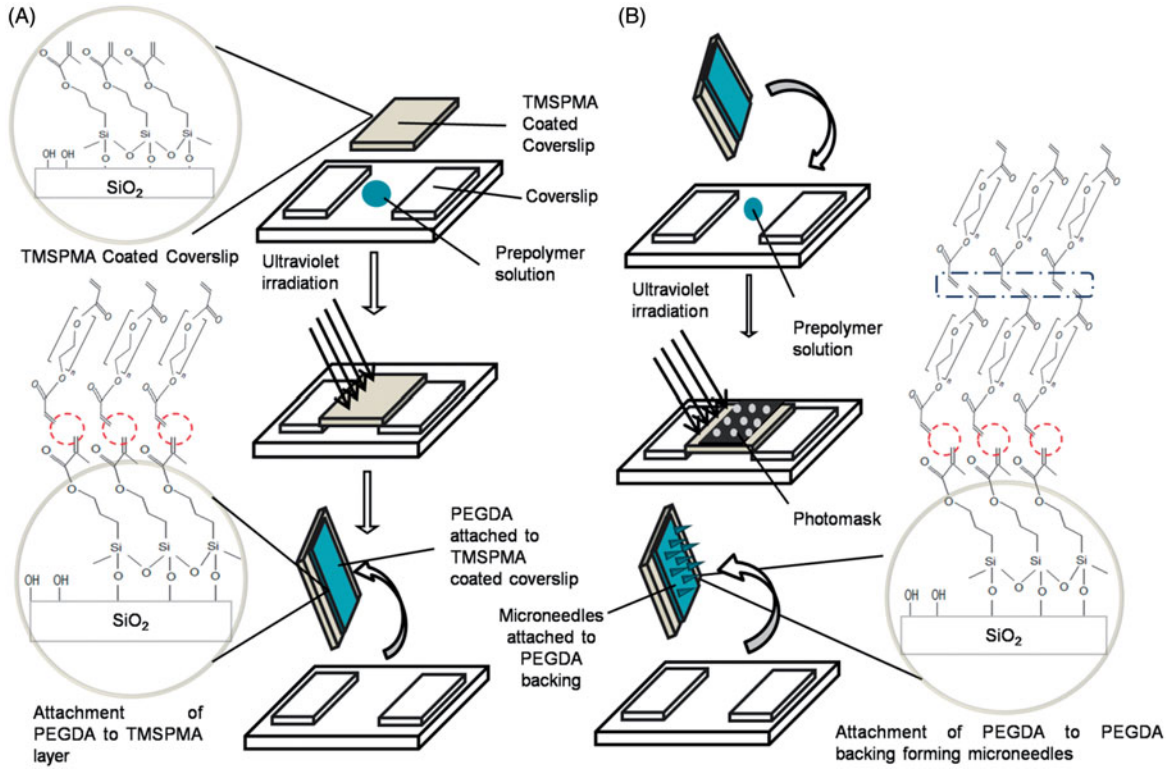

Figure 6. (A) Schematic representation of the fabrication process. Poly(ethylene glycol) diacrylate (PEGDA) is attached to 3-(trimethoxysilyl) propyl methacrylate (TMSPMA) coated coverslip via free radical polymerisation using UV irradiation, forming the backing for microneedles. (B) Using glass slides as support, the PEGDA backing is mounted onto the set-up with PEDGA filled in the enclosed cavity. Subsequently, the set-up is irradiated with UV light. UV light is only able to pass through the clear regions on the photomask, forming microneedles [170].

Microfabrication technologies played a critical role in microneedle fabrication, which include lithography, etching, injection moulding and laser drilling. Gill and Prausnitz fabricated steel microneedle by laser cutting and electro-polishing. A large range of molecules were loaded onto the microneedles by micro-dip coating [165]. A steel hollow microneedle array fabricated from selectively etching a polymer mould was effective for *in vivo* insulin delivery [166]. Rodriguez et al. reported the fabrication of hollow silicon microneedles by electrochemical etching. Microneedles with different pore diameters, pore lengths and wall thicknesses were fabricated [167]. Chabri et al. used silicon microneedles to facilitate the delivery of genes in a lipid based vector. The microneedles were fabricated by using an isotropic etching process [168].

However, metal and silicon microneedles have safety concerns when broken in the skin and silicon is not an FDA-approved material, so microneedles made from biocompatible polymers and sugars are more attractive [169]. Kochhar et al. reported a single step photolithographical method to fabricate poly(ethylene glycol) microneedles by exposing macromer poly(ethylene glycol) diacrylate solution to UV light through a patterned photomask for a few seconds (Figure 6). Drug can be premixed with the macromer solution and encapsulated into both the microneedles and the backing layer, which acted as reservoir for sustained release [15]. BSA was also successfully incorporated into the microneedles without compromising the structures of the protein [170]. In another study, a polymeric hollow microneedle array (Figure 7A) was integrated into a device with a drug reservoir and springs for self-application of drug. The device can be worn on the arm/thigh since an adhesive patch was located around the microneedle array. Animal studies demonstrated that the device can be used to effectively deliver small molecules and proteins [163]. Zhang et al. reported lidocaine-coated microneedles (Figure 7B) with a rapid onset (1 minute) and sustained analgesic action for up to 90 minutes. The drug was loaded on microneedles by dip coating process. This application was believed to be safe since the total lidocaine delivered to the skin was only around 50 μg [161]. Interestingly, the microneedles, which were moulded from medical grade liquid crystalline polymer, bent rather than fractured or broke when applied with extreme force against a rigid surface. This would avoid the risk of broken needles left in the skin [162].

Dissolving microneedles are made of materials that are biocompatible and biodegradable and can dissolve away in skin without any sharps left. It can also eliminate the risks due to improper needle disposal and repeated use [4]. Lee et al. developed a casting method with centrifugation to a micromould to fabricate microneedles from carboxymethyl-cellulose or amylopectin viscous solution. The needles can dissolve within a few minutes. Lysozyme was encapsulated into the microneedles with full enzymatic activity retained [171]. Dissolving polyvinylpyrrolidone microneedles for influenza vaccination were fabricated by photopolymerization of the monomer *N*-vinylpyrrolidone solutions mixed with the lyophilized vaccine in a microneedle mold. Fast dissolution of microneedles was observed when inserted into pig skin (Figure 7C). *In vivo* study demonstrated that this microneedle

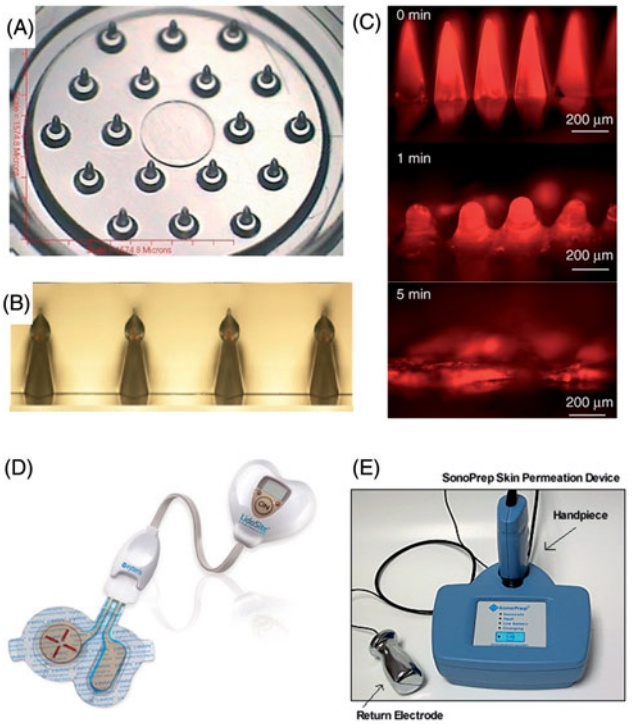

Figure 7. Devices for transdermal drug delivery. (A) Hollow microneedles [163]; (B) Coated microneedles [161]; (C) Polymer microneedle dissolution in pig skin *ex vivo* (Top, before insertion; middle, remaining polymer 1 minute after insertion in skin; bottom, remaining polymer 5 minutes after insertion in skin) [10]; (D) LidoSite, an iontophoresis device (Adapted from http://www.vyteris.com/Our_Products/Lidosite.php); (E) SonoPrep, a sonophoresis device (Adapted from http://blog.andy.org.mx/gadgets/2004/08/).

vaccine patch achieved more efficient lung virus clearance and better immune responses than intramuscular vaccination [10]. Needle-free vaccination can be useful in case of outbreak of a pandemic. It may also prevent the potential risk from hypodermic needles reuse. To get these products commercialized, however, they must be as reliable as conventional products and cost-effective [8].

To achieve painless application, microneedles were usually fabricated in a range of 50 μm to 1000 μm in length. Because of the elasticity of skin and the variations between individuals and skin types, it is difficult to use microneedles to penetrate the skin with good accuracy and reproducibility at desired depths. Therefore, the application of microneedles with an external assistance is necessitated to ensure uniform and reproducible penetration of microneedles into skin. To this end, various innovative microneedle applicators have been designed. A number of companies, such as Clinical Resolution Laboratory, Alza, Corium International, 3 M, NanoBioSciences and BD have disclosed their application designs, which have been reviewed recently [172], where portable and easily-handled microneedle applicators with low cost were advised.

Iontophoresis

For transdermal drug delivery, iontophoresis refers to the use of low level of electric current to delivery ionized drugs through skin [173]. Some iontophoretic transdermal systems have already been approved for clinical use. LidoSite® (Lidocaine hydrochloride and Epinephrine bitartrate) patch is a FDA-approved product to achieve dermal analgesia by iontophoresis on intact skin, while IONSYS™ (fentanyl iontophoretic transdermal system) is to deliver the analgesia fentanyl systemically [174]. LidoSite system consists of a drug-filled patch and a controller. The patch is for one-time use and disposable, while the controller is portable microprocessor-controlled and battery-powered, which can be reused approximately 100 times (Figure 7D). IONSYS is also a battery-supported electronic device. A total of 40 μg of fentanyl is delivered upon activating the dosing button each time. The device can be used for up to 24 h. However, LidoSite and IONSYS are now listed as discontinued products by FDA. The discontinuation of IONSYS in the USA was linked to the recall of products in European market due to the corrosion of a component. Besides, these devices had relatively high cost [152].

Another iontophoretic transdermal patch was demonstrated to facilitate the delivery of sumatriptan for the treatment of migraine in clinical trials. The disposable, single-use transdermal patch was approved by FDA in January 2013 [6]. With initial electric current of 4 mA, sumatriptan was released continuously for 1 h, resulting in fast onset of drug action. Then sustained delivery of drug followed by 2 mA of electric current for 3 h [175]. Iontophoresis was reported not suitable for the transdermal transport of molecules more than 7000 Da [173]. However, with the combination of chemical enhancers, liposomes systems or microneedles, iontophoresis was able to deliver larger molecules, such as insulin and BSA [154,176].

Iontophoresis was also effective in enhancing the drug delivery into hair follicles and nails. Kajimoto et al. found that the liposomal delivery of rhodamine and insulin into the hair follicle was enhanced by iontophoresis, and the optimization of the lipid composition of liposomes and iontophoretic condition were also reported [154]. The enhancement of drug delivery across and into the nail was reported [155,156]. Ionic strength, acidity and current density were important factors to consider in designing such iontophoretic topical systems [155,177].

Electroporation

Different from iontophoresis, high voltage (≥100 V) and short duration (milliseconds) are used in electroporation to produce transient hydrophilic pores in stratum corneum. These pores allow the transport of a large range of molecules through skin, including small molecules, proteins and oligonucleotides [178]. The combinations of electroporation with other enhancement techniques were also studied. Yan K et al. reported that macromolecular drugs can be delivered more effectively when electroporation was used together with microneedle array. The microneedle array containing nine needles was integrated into the device. Each microneedle could act as an electrode for electroporation, thus an electric field was expected to be formed inside the skin barrier [179]. Although the electric field of electroporation is located at the stratum corneum, it may also affect the deeper tissues to cause pain [8]. It was reported that only small region of skin would be affected, but more research should be done on the safety issue of the device.

Sonophoresis

Ultrasound was used to facilitate the drug skin permeation by creating disturbance inside the stratum corneum, termed as sonophoresis. High-frequency sonophoresis ($f > 1$ MHz, therapeutic ultrasound) has been used since 1950s for topical drug delivery. However, low-frequency sonophoresis ($f < 100$ kHz) has been found to be more effective in enhancing the transdermal drug delivery [180]. Low-frequency sonophoresis is reported to be able to facilitate the transdermal delivery of hydrophilic drugs and high molecular weight drugs, including peptides, proteins, vaccine, oligonucleotides, even nanoparticles and liposomes [181]. SonoPrep® is an FDA-approved low-frequency sonophoresis device, which consisted of a battery-powered control unit, an ultrasonic hand piece, a disposable coupling medium and a reference electrode (Figure 7E). It can be used for drug delivery as well as extraction of interstitial fluid for bioassay. Clinical trials showed that it can reduce the onset time of topical anesthetic to 5 minutes [182,183]. When combined with iontophoresis, the onset time was further decreased to 2 minutes [184].

Application of low-frequency ultrasound was demonstrated to enhance the penetration of drugs through bovine hoof membranes, which was used as model nail plate. When the hoof membrane was pre-treated with sonication for 1 minute, the permeation of drug increased significantly [185]. An ultrasound-mediated nail drug delivery device was developed for the topical treatment of onychomycosis. The system is made up of power amplifier, matching network, ultrasound transducer and slip-in mechanical device with drug injection ports. A computer is connected to the device for patients to manage their treatment plan by choosing the energy level, exposure time and the toes to be treated. A preliminary trial showed promising results, but more extensive studies are needed [157].

Thermal ablation

Skin permeation can be enhanced by thermal ablation. With this technique, the stratum corneum was selectively removed with localized heat at a short period of time. A microfabricated device was reported to eject superheated steam at the skin surface in a microsecond with an electrical discharge heating a few microliters of water. The superheated steam was ejected by a microchamber, which was fabricated by laser micromachining and lamination of layers. The microchamber was integrated into a microdevice with two different masks that facilitate the energy transfer from steam jet to the skin. More than 1000-fold increase in permeation was observed for sulforhodamine B and BSA *in vitro* [186]. *In vivo* study demonstrated that human growth hormone and interferon alpha-2B can be delivered by certain thermal ablation treatment [187,188]. Bramson et al. showed the high efficiency of topical vaccine delivery after using thermal energy to create microscopic pores in stratum corneum [189].

Conclusion

With the recent advances in technology, various novel drug delivery systems have been engineered to effectively deliver therapeutics and minimize side effects, to improve patient's quality of life. Microfabricated devices, nanoparticles and mucoadhesives have been applied in oral, mucosal and transdermal drug delivery with success. These routes have even been explored to deliver macromolecules, such as peptides, proteins and vaccines, which are previously considered very difficult to be delivered due to their instability in enzymatic environment and low permeability through mucosa or skin. However, it is noticeable that there are favourable routes of administration for a certain type of drugs or applications. For example, pulmonary and buccal drug delivery systems usually exhibit rapid absorption and are suited to acute and subchronic treatment, while transdermal drug delivery tends to have a sustained release profile and are favourably designed for subchronic and chronic therapy.

Mucosa and skin act as natural mechanical and immunological barrier to protect the human body from external environment. Some delivery systems interfere or disrupt the mucosa or skin physically and/or chemically to increase the permeability of drugs. Therefore, safety should be evaluated before any new drug delivery systems can get into clinical practice. Moreover, quality should be closely monitored especially for complicated drug delivery systems. Some engineered drug delivery systems requiring special expertises for sophisticated designs, which may render a high set-up and maintenance cost, potentially preventing them from successful commercialization. Engineered systems with simple process and low cost may be more receptive by customers and therefore should become the first line of explorations.

Declaration of interest

The study is supported by a Singapore EDB-IPP grant (RL2012-035).

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