Chapter 9
Pharmaceutical Applications of Natural Polymers

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List of Abbreviations

API	Active pharmaceutical ingredients
BTCA	Butanetetracarboxylic dianhydride
CMC	Carboxymethyl cellulose
CNS	Central nervous system
DB	DamarBatu
DMAP	4-dimethylaminopyridine
HGH	Human growth hormone
HPMC	Hydroxypropylmethyl cellulose
Lo	Lecithin organogel
NaCMC	Sodium carboxy methyl cellulose
N-IPAAm	*N*-isopropylacrylamide (NIPAAm)
pAA	Polyacrylic acid
PEG	Polyethylene glycol
PELA, PLA	Polylactic acid
PLGA	Poly(DL-lactic-*co*-glycolic acid)
PLLA	Poly(L-lactic acid)

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PSA	Pressure sensitive adhesives
PVA	Polyvinyl alcohol
SPG	Shirasu porous glass
TDD	Transdermal drug delivery

9.1 Introduction

Natural polymers have a very broad range of applications in both the polymer and pharmaceutical industries. The pharmaceutical industry is a very broad field where there is a continued need to consider various applications. It is logical, therefore, to state that understanding the roles of natural polymers in the pharmaceutical industry helps in turn the polymer industry to determine the broader applications of these polymers and incorporate the desired requirements to meet the end applications (e.g. provide various functionalities). Drug delivery methods form a key part of the pharmaceutical applications of polymers. In the next section of this chapter, we discuss portals of drug administration into the human body which gives an overview of the possibilities of applications of natural polymers. The chapter then discusses some specific applications in detail. Transdermal drug delivery, nasal drug delivery, vaginal, ocular, oral drug delivery methods using natural polymers are discussed with some example case studies. As hydrogels play important roles in drug delivery, a separate section is dedicated in discussing the applications of natural polymer-based hydrogels in drug delivery.

9.2 Portals of Drug Administration in the Human Body

The controlled delivery of drug molecules requires either a device or a vehicle for administration into specific localised tissues or systemic distribution via plasma fluid in blood. The human body has several portal entries for drug administration as outlined in Fig. 9.1. These portals are intramuscular (Suh et al. 2014), percutaneous (Ge et al. 2014), intrathecal (Freeman et al. 2013), subcutaneous (Kinnunen and Mrsny 2014), gastrointestinal (Varum et al. 2013), ocular (Mignani et al. 2013), intravenous (Mignani et al. 2013), nasal (Tian et al. 2014), pulmonary (Beck-Broichsitter et al. 2012), sublingual (Patel et al. 2014), baccal (Patel et al. 2014), rectal (Lautenschläger et al. 2014) and vaginal (Valenta 2005). Intravenous, intramuscular, percutaneous, intrathecal, subcutaneous and transdermal are collective terminologies associated with parenteral administration. Pulmonary drug administration through the lungs is the least common portal delivery because of a limited number of excipients, especially natural polymeric excipients with reduced polydispersity of size and ideal particle densities concerning the drug particle formulation (Sanders 1990; Pilcer and Amighi 2010).

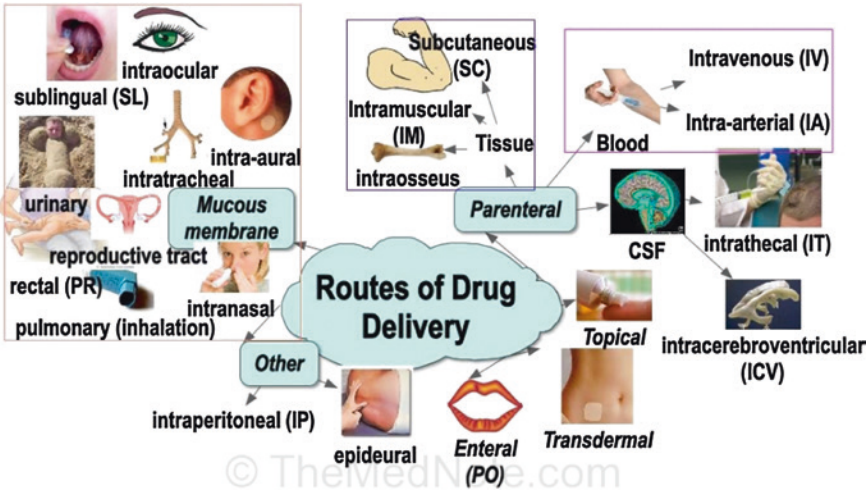

Fig. 9.1 An outline of main portals for drug administration (Adopted from www.themednote.com with permission)

9.3 Transdermal Drug Delivery Devices

Polymers are used extensively in transdermal drug delivery systems. They control the rate of drug release from the device, act as primary packaging parts, coatings, penetration enhancers and provide ease in drug device handling and structural support to the device in the form of a backing layer. Their unique properties make them ubiquitous component of transdermal patches. As petrochemical-based resources for the production of synthetic polymers become more expensive and in short supply, the production of transdermal drug delivery device components from more readily available natural polymers becomes eminent. This section of the review looks at the application of natural polymers in transdermal drug delivery. The different parts of the transdermal drug delivery system are discussed such that the use of natural polymers in each individual part, namely, the matrix, adhesive layer, rate controlling membrane, backing layer, release liner and penetration enhancer are then discussed. Further areas to be explored are also suggested.

Polymers are used more extensively in transdermal drug delivery (TDD) than any other material as they possess unique properties which are significant to the drug delivery process (Kim 1996). They are effective in aiding the control of drug release from carrier formulations (Cleary 1993). Polymers commonly used in TDD include cellulose derivatives, polyvinylalcohol, chitosan, polyacrylates, polyesters such as PLGA, PELA, and PLA and silicones. Natural polymers are a preferable option in TDD as they are readily available, inexpensive, potentially biodegradable and biocompatible and can undergo various chemical and surface modifications to fit the requirement of the TDD system. A TDD system comprises

of a combination of one or more polymers and an embedded drug to be delivered into or through the skin in a controlled and sustained manner (Tojo 2005).

Polymers used for TDD systems are required to be chemically inert and pure according to high analytical product yields. It should also possess adequate physical properties which correspond with the intended application. The material must not age easily and be suitable for processing. Furthermore, biodegradability and safety are paramount properties in the design of a TDD patch system due to the long-term exposure of the skin in contact with the patch (Pietrzak et al. 1997).

This section focuses on the application of natural polymers in transdermal drug delivery. The next subsections discuss the different types of transdermal drug delivery systems explaining each one is separate subsection. Section 9.3.2 discusses the use of polymers in transdermal drug delivery with specific focus on natural polymers. Within the section the different parts of a transdermal drug delivery system are discussed. The properties and function of each is first described and some recent studies of developing natural polymers in the specific area are then outlined.

9.3.1 Types of Transdermal Drug Delivery Systems

TDD systems are classified into three types, namely, reservoir, matrix and microreservior system (Kandavilli et al. 2002; Chein 1987). Each of these is described below.

9.3.1.1 Reservoir System

The reservoir system comprises of a reservoir of drug in the form of a suspension, solution or liquid gel embedded between an impervious backing layer and a rate controlling membrane. Suspensions and solutions are two distinct types of liquid mixtures. The definition of a suspension and a solution is well understood. The definition of a liquid gel can sometimes be difficult to formally express. A gel is a semi-solid, colloidal solution consisting of one or more crosslinked polymers dispersed in a liquid medium. A liquid gel is softer, less resilient and easily spreadable colloid gel. The reservoir could also be the drug dispersed within a solid polymer matrix. An adhesive polymer is often placed between the rate controlling membrane and the skin.

9.3.1.2 Matrix System

The matrix system comprises of drug molecules dispersed within a polymer matrix. The matrix system is of two types, the drug in adhesive system and the matrix-dispersed system. In the drug in adhesive system, the drug is dispersed in a polymer

adhesive. The drug loaded adhesive polymer is then spread by solvent casting or in the case of hot-melt adhesives, where, it is melted onto an impervious backing layer. Additional layers of adhesive polymer are then applied on top of the reservoir. *In the matrix-dispersed system,* the drug is dispersed homogeneously in a polymer matrix which is either lipophilic or hydrophilic. The polymer is then placed on a backing layer and above this matrix, an adhesive layer surrounds the matrix perimeter.

9.3.1.3 Microreservoir System

This system combines the reservoir and matrix-dispersed systems. The drug is first suspended in aqueous solution in a water soluble polymer. This is then dispersed homogeneously in a lipophilic polymer, which results in the formation of microscopic spheres of drug reservoirs dispersed within a polymer matrix.

9.3.2 Natural Polymers in Transdermal Drug Delivery

Polymers have been used in transdermal drug delivery as far back as the 1980s. Most transdermal patches contain a matrix of cross-linkage of linear polymer chains from which the drug is to be absorbed into the skin (Tojo 2005). Polymers used in transdermal drug delivery include cellulose derivatives, polyvinyl alcohol, polyvinylparrolidone, polyacrylates, silicones and chitosan. Both natural and synthetic polymers have been used either as matrices, gelling agents, emulsifiers, penetration enhancers or as adhesives in transdermal delivery systems. For example Sun (1986) reported the successful delivery of testosterone into lab rats using a transdermal delivery system with a silicone elastomer as synthetic polymer matrix. Another group explored the use of pectin hydrogels for the transdermal delivery of insulin. Pectin hydrogels loaded with insulin were administered to diabetic rats with type 2 diabetes mellitus. The results obtained showed that the transdermal patch delivered insulin across the skin in a dose dependent manner with pharmacological effect (Tufts and Musabayane 2010). More recent studies explored the use of natural polymers such as rubber latex as backing layer adhesive in nicotine patches (Suksaeree et al. 2011). There is, therefore, scope for research into the use of natural polymers in transdermal drug delivery.

Although synthetic polymers seem to be more commonly employed in the development of TDD systems, natural polymers from plant and animal sources are emerging as a preferred alternative as they pose the advantage of being biocompatible, biodegradable, degrading into non-toxic monomers and are more readily available (Sharma et al. 2011; Chang et al. 2010). Synthetic polymers derived from petroleum sources and synthetically modified polypeptides are known to have limited pharmaceutical implementations due to toxicity and slow biodegradation rates (Shi et al. 2014; Deming 2007; Kim et al. 2014). The following section discusses the use of natural polymers in the different parts of a transdermal patch system.

9.3.2.1 Controlled Release Systems

Natural polymers in combination with other natural and/or synthetic polymers have been used in hydrogels for pharmaceutical application. A recent study looked at the development of controlled release system based on thermosensitive chitosan-gelatin–glycerol phosphate hydrogels for ocular delivery of latanoprost, a drug used in the treatment of glaucoma (Cheng et al. 2014). The formulation can be delivered via subconjunctival injection reducing the need for repeated dose administration and possible side effect from conventional treatments of the condition (Gaudana et al. 2010; Cheng et al. 2014)

9.3.2.2 Matrix

Polymers are attractive for use as matrices in transdermal patches due to certain useful properties which they possess. In addition to being biodegradable and biocompatible, they contain various functional groups that can be modified as required and combined with other materials and tailored for specific applications.

When exposed to biological fluids, biodegradable polymers will degrade releasing the drug that is dissolved or dispersed within them (Gilding and Reed 1979). There are on-going research studies into the application of natural polymers in TDD as polymer matrices. In this area biocompatibility and biosafety are a paramount requirement (Pietrzak et al. 1997). Release of APIs (active pharmaceutical ingredients) from a polymer matrix occurs via various mechanisms including polymer erosion, diffusion, swelling followed by diffusion and degradation. The mechanism initiated depends on the type of system (Sharma et al. 2011).

The use of various natural polymers as matrices has been explored by different research groups. These include natural polymers of chitosan, a polycationic (pH 6.5 or less in solvent) natural polysaccharide which is obtained from one of the most abundant polysaccharides in nature, chitin (Pillai et al. 2009). Chitin is a natural polymer which forms the shells of crustaceans, some insects, fungi, yeasts and plants. Chitosan is deacetylated chitin with a degree of deacetylation ranging from 60 to 95 % (Zheng et al. 2001; Knaul et al. 1999).

The rate of drug delivery from a chitosan matrix can be controlled by varying the manner in which the chains are crosslinked (Säkkinen et al. 2004). The most common crosslinkers used for fabrication of chitosan gels are glutaraldehyde, formaldehyde, glyoxal, dialdehyde starch, epoxy compound, diethyl squarate, pyromellitic dianhydride, genipin, quinone and diisocyanate (Berger et al. 2004; Mohamed and Fahmy 2012). Preparations of chitosan in the form of beads, microspheres and gels have been shown to deliver drugs such as local anaesthetic drugs, lidocaine hydrochloride and anti-inflammatory drugs, prednisolone (Sawayanagi et al. 1982; Nishioka et al. 1990; Hou et al. 1985). Chitosan has also been used as a matrix for transdermal delivery of large protein molecules such as insulin. It

is robustly physicochemically stable and possesses mucoadhesive property which makes a good candidate for TDD (Dodane and Vilivalam 1998; Krauland et al. 2004; Pan et al. 2002; Ma and Lim 2003; Mao et al. 2005).

Pectin is also another natural polymer used in TDD matrices. Pectin is a water soluble polysaccharide composed of different monomers, mainly D-galacturonic acid, sourced from the cell walls of plants which grow on land. Pectin is commercially extracted from fruits and its appearance ranges from a white to light brown powder. Recent studies on application of pectin in TDD have looked at modifying pectin to act as matrix for TDD (Graeme et al. 1999). In a study by Musabayane et al. (2003), pectin was used as a matrix for delivery of chloroquine through the skin; The results showed that pectin was effective as a matrix for TDD delivery of chloroquine resulting in more effective and convenient treatment of malaria (Musabayane et al. 2003). Soybean lecithin has also been used as gel matrices to deliver scopolamine and dcoxatenol transdermally (Willimann et al. 1992). Lecithin is a component of cells that is isolated from soya beans or eggs. It is processed into Lecithin organogel (LO) to act as a matrix for topical delivery of many bioactive agents into and through the skin. When purified and combined with water it shows excellent gelating properties in non-polar solvents. LO provides a temperature independent resistant to microbial growth as well as being a viscoelastic, optically transparent and non-birefringent micellar system. LO is a dynamic drug delivery vehicle as it dissolves both lipophilic and hydrophilic drugs. It effectively partitions into the skin thereby acting as an organic medium to enhance permeation of otherwise poorly permeable drugs into the skin (Raut et al. 2012).

A combination of more than one polymer can also be used in a TDD matrix and this also applies to natural polymers. For example Siddaramaiah (2009) developed a matrix comprising of xanthan gum and sodium alginate. In vitro evaluation of the TDD system showed good compatibility and controlled release of the model drug Domperidone following in vitro release in a glass diffusion cell.

Other natural polymers that are being explored for use as matrices in TDD include collagen, gelatin, agarose from seaweed, natural rubber, polyethylene obtained from bioethanol, and polylactide (PLA), a polyester of lactic acid which is produced from starch or cane sugar fermentation by bacteria (Sharma et al. 2011).

9.3.2.3 Rate Controlling Membrane

Rate controlling membranes are used when the TDD patch is a reservoir type such that the rate at which the drug leaves the device is regulated by the membrane which is either a porous or non-porous membrane. Various natural polymers are being explored for use as rate controlling membranes. These polymers usually have attributes such as good film forming properties and variable film thickness. Mundada and Avari (2009) developed an optimised formulation of DamarBatu (DB), a natural gum from the hardwood tree of the Shorea species such as *S. virescens* Parijs, *S. robusta* and *S. guiso*. The optimised formulation was shown

to successfully deliver Eudragit RL00, the model drug. Following in vitro drug release, skin permeation studies and other analysis concluded that Eudragit RL100 is a suitable film for TDD (Mundada and Avari 2009). In other studies DB has also been evaluated as a rate controlling membrane for TDD of a model drug diltiazem hydrochloride (Mundada and Avari 2009).

Gum copal, a biological polymer gum has also been tested as a film for TDD (Mundada and Avari 2009). The effect of different plasticisers was tested on the effectiveness of gum copal as a rate controlling membrane. The effectiveness of the film produced was estimated from tensile strength of the film, uniformity of the thickness, moisture absorption, water vapour transmission, elongation, foldability and drug permeability. PEG400 was found to be the plasticizer which gave the best permeability amongst those tested. However, a more sustained delivery was achieved in vitro with a formulation containing 30 % w/w DPB (dibutylphalate).

Another natural polymer with good film forming properties is zein. It is a protein obtained as a by-product from the processing of corn. Zein shows potential as a low cost and effective alternative to synthetic films for TDD (Elisangela et al. 2007).

9.3.2.4 Adhesives

Adhesives are required in TDD systems to ensure the device remains in contact with the skin. For TDD the selected adhesive must meet certain criteria such as skin compatibility, biodegradability and good adhesion over long period due to the long-term contact with the skin and drug formulation (Kandavilli et al. 2002).

Pressure sensitive adhesives (PSA) are materials which adhere or stick to the surface following application of normal finger pressure and remains attached exerting a strong holding force. When removed from the attached surfaces, PSAs should ideally leave no residues (Pocius 1991). Adhesion refers to a liquid-like flow which causes wetting of the skin surface as pressure is applied with the adhesive remaining in place after the removal of the applied pressure. The adhesion is achieved as a result of the elastic energy that has been stored during the breaking of bonds caused by applied pressure. The effectiveness of the PSA is, therefore,an attributable to the relation between viscous flow and stored elastic energy (Franz et al. 1991). Synthetic polymers seem to have dominated the adhesives used in TDD. Commonly, used ones include acrylic, polyisobutylene and silicones (Dimas et al. 2000; Barnhart and Carrig 1998; Tan and Pfister 1999).

Use of adhesives on skin is an idea that has been around for many decades, one of the earliest applications being in bandages for wound healing by Johnson and Johnson company in 1899 (Subbu and Robert 1998). When deciding on what kind of polymer to incorporate as an adhesive, an understanding of the properties of the skin is essential. The surface energy of the skin, which acts as the adherent in the case of TDD, must be greater than or equal to the surface energy of the adhesive (Subbu and Robert 1998). Furthermore the skin properties vary with the factors

such as age, gender, race and environmental conditions. Therefore, the effect of properties such as moisture content of skin and the viscometric property of the adhesive should be established (Subbu and Robert 1998).

Adhesives in transdermal patches may exist as a single adhesive layer or a drug in adhesive type, the latter is preferred as the simplest to apply however, it is rather complicated to produce. For drug-in-adhesive type patches, issues which must be addressed include the tendency of the drug or adhesive to crystalize. This will have an effect on the drug delivery rate as it permeates through the adhesive layer (Variankaval et al. 1999).

Pressure sensitive adhesives generally comprise an elastomeric polymer, a resin for tack, a filler, antioxidants, stabilisers and crosslinking agents. Although synthetic polymers seem to be more commonly used as adhesive in TDD systems, the development of adhesives from natural polymers is becoming a rather attractive area of interest (Doherty et al. 2011). Various sources in nature have been explored for obtain adhesives.

Carbohydrates are readily available polymers of plants. Cellulose, starch and gums are the most common forms that are used in production of adhesives (Baumann and Conner 1994). There are studies which have been focused on the production of adhesives obtained from cellulose recovered from domestic and agricultural waste. These include soy protein, raft lignin and coffee bean shells (Weimer et al. 2003; Chung and Washburn 2012; Khan and Ashraf 2005). Adhesives formed from carbohydrates include carboxymethyl cellulose (CMC), hydroxyethyl cellulose, ethyl cellulose, methyl cellulose, cellulose acetate and cellulose nitrate. Those formed from starch such as tapioca, sago and potatoes can be more readily converted to adhesives following modification through heating, alkali, acidic or oxidative treatment (Baumann and Conner 1994). The adhesives often require further additives during processing. Recent studies focused on extracting natural polymeric adhesives include that by Hoong et al. (2011) which studies acacia mangium bark extracts as a source of natural polymer adhesives. The dicotyledonous tree bark which is commonly grown in Malaysia as a source of raw material for veneer, pulp and paper showed a promising prospect as an alternative to adhesives produced from petrochemicals.

In other works adhesive production from waste materials such as de-inked waste paper has been studied (Mishra and Sinha 2010). In a particular study de-inked waste paper from magazines were washed using detergent under stirring. This was then followed by further processing under heat at 150 °C and treatment with acid and ethylene glycol. The glycosides which resulted from the breaking down of the cellulose were then transesterified using rice-bran castor and soy oils to convert it to polyols. Polyurethenes are then produced from the polyols. The adhesives produced using the methods described when tested showed strong adhesive properties than the commercial adhesives and also showed significant water resistance. Marine organisms (Waite 1990) and bacteria have also been shown to be the sources of natural adhesives. The main limitation with these sources is the expensive production process.

9.3.2.5 Penetration Enhancers

Polymers are also used as penetration enhancers to aid the permeation of drugs across skin. Polyethylene glycol solution is an example of such penetration enhancers of prodrugs across skin models (Hikima and Tojo 1993). However use of polymers as additives in formulations also carries some limitations such as inhibiting the bioconversion of the drug (Tojo 2005). Transdermal films incorporating 0.5 % tenoxicam have been developed from varying ratios of glycerol, PEG 200 and PEG 400. Using Fourier transform infrared spectroscopy, it was found that increasing the concentration of PEG enhanced the penetration of tenoxicam into the skin (Nesseem et al. 2011). Polymers are also employed as other formulation additives in the form of viscosity enhancers and as emulsifiers. Chitosan, a natural polymer has been used as a penetration enhancer, which acts by opening up the tight junctions which exists between epithelial cells (Cano-Cebrián et al. 2005; Mao et al. 2005; Gao et al. 2008; Avadi et al. 2005; Kotzé et al. 1997).

Recently, research studies aimed at fabricating micron-sized penetration enhancers which partially disrupt the stratum corneum layer creating a more permeable pathway for drugs to enter into the skin via natural polymers is emerging. For example a study by You et al. (2011) where dissolving polymer microneedles were fabricated from silk Fibroins obtained from bombyx mori silk worm. The resulting structures were rapidly dissolving microneedles with adjustable mechanical parameters and were biocompatible with skin. Maltose has also been used to fabricate dissolving polymer microneedle using traditional casting methods as well as using the extrusion drawing method (Lee et al. 2011). More recent studies have looked at the application of hydrolyzed collagen extracted from fish scales for production of microneedles as mechanical penetration enhancers (Olatunji et al. 2014).

9.3.2.6 Backing Layer

The backing layer comes in contact with the drug matrix or reservoir therefore the chemical inertness of the material used for the backing layer is required. The backing layer must also be compatible with the excipient formulation. Back-diffusion of the drugs, penetration enhancer or excipient must not occur even over a long period of contact. While maintaining chemical inertness it must also be ensured that the backing layer is flexible enough to allow movement, transmission of moisture vapour and air in order to prevent skin irritation during long-term contact with skin. Adequate transmission of moisture vapour and air also prevents the weakening of the adhesive hold on the skin surfaces (Kandavilli et al. 2002; Rolf and Urmann 2000a). In more modern designs of TDD patches, the backing layer could be solidified with the reservoir to form a single structure such that it serves as a storage space for the reservoir (Rolf and Urmann 2000b; Kandavilli et al. 2011). More recent studies have explored the use of natural polymers as backing layer of nicotine transdermal patches from natural rubber latex (Suksaeree et al. 2011).

9.3.2.7 Release Liner

The adhesive side of the transdermal patch is usually covered with a liner which protects the adhesive and the rest of the patch during storage. Although mostly for packaging purpose, the liner is in direct contact with the adhesive layer throughout the storage period. The material used as a release liner should be chemically inert (Wokovich et al. 2006) and resistant to the permeation of the drug, penetration enhancer and moisture. The liner should also not cross link with the adhesive such that it becomes difficult to remove (Pfister and Hsieh 1990). Example of a release liner used in commercial TDD is the ScotchPak^{TM} 1022 and Scotchpak^{TM} 9742 liner which are produced from fluoropolymers by 3M Drug Delivery Systems (available in 3M product catalogue Product ID 70000065659).

Although currently the use of synthetic polymers seem to dominate that of natural polymers in TDD, there is increasing research interest in incorporating natural polymers in new ways in TDD systems (Valenta and Auner 2004). This is attributable to the desire to produce pharmaceutical products with more desirable environmental impacts, reduce dependency on fast diminishing petrochemical resources and developing more sophisticated TDD systems with better effectiveness and biosafety (Klingenberg 2013). However, there is yet to be a transdermal drug delivery system which is developed fully from natural polymers. The dependency on synthetic polymers therefore still persists. Future research efforts directed towards developing novel natural polymers from new biological sources. Consequently as new polymers emerge, extensive studies will be required to identify the physical and chemical properties of the new biomaterials. Furthermore developing newer processing methods and new combinations of polymers could be optimised leading to improved effectiveness in transdermal drug delivery.

Natural polymers have proven valuable in transdermal drug delivery systems. They have a wide range of applicability and pose several advantages over synthetic polymers in this application. Nature offers an abundant supply of polymers with numerous properties. Understanding these sources and properties allow us to further modify these polymers to suit specific requirements. The area of transdermal drug delivery still faces certain limitations such as skin irritation and limited range of drugs which can be delivered through this means. Exploring new polymers from natural sources could provide new solutions and offer clinical and commercial development in the area of transdermal drug delivery.

9.4 Topical Drug Delivery

Delivery of drugs into the body topically can be employed to treat conditions which exist on or close to the surface of the skin. This could vary from aches and bruises to severe burns and mild and chronic conditions such as eczema and psoriasis. This form of delivery refers to when a drug formulation is applied directly to the external skin surface or surface of the mucous membrane of the vaginal, anal,

oral, ocular or nasal area for local activity (Joraholmen et al. 2014; Mekkawy et al. 2013; Gratieri et al. 2011; Singla et al. 2012). Topical delivery through the other entry routes (i.e. oral, vaginal, ocular, etc.) is not to be confused with the other forms of delivery which are discussed in other sections of this chapter.

9.4.1 Advantages and Disadvantages

Topical delivery is relatively convenient and has relatively better patience compliance than, e.g. oral or intravenous injection which could impose adverse impacts such as nausea, low bioavailability due to metabolism of drug in the gastrointestinal tract, needle phobia and general preferences. The specificity of topical delivery is also advantageous as it can be directly applied to the affected area to act locally, similarly the medication can be easily terminated by simply cleaning off the medication. Topical delivery particularly becomes a favourable option where other routes of entry into the body are deemed unnecessary or unsuitable depending on the individual or nature of drug. In cases where for instance oral delivery of the drug could induce adverse effect which could even is more severe than the actual condition being treated. For instance many of the adverse effect associated with antifungal drug fluconazole are gastrointestinal related and could be avoided by applying a topical formulation for effective delivery of the drug (Mekkawy et al. 2013).

Main challenges in the area of topical drug delivery alongside skin irritation and allergic reaction include skin penetration into target region especially for drugs with large particle size. In particular, situations such as in fungal infection where the penetration into the stratum corneum is further inhibited as an attack mechanism of the pathogen to prevent shedding of the stratum corneum, penetration enhancement of the topical agent becomes of relative importance in the effectiveness of the drug formulation (Del Palacio et al. 2000; Mekkawy et al. 2013).

9.4.2 Composition of a Topical Formulation

The main components of a topical formulation includes a vehicle which could be in the aqueous form, mainly water or alcohol, or it could be an oil such as mineral oils, paraffin, castor oil, fish liver oils, cotton seed oil, etc. A vehicle should maintain effective deposition and even distribution of the drug on the skin; it should allow delivery and release to the target site and maintain a pharmacologically effective therapeutic concentration of the drug in the target site. In addition to these properties a suitable vehicle should be well formulated to meet patient's cosmetic acceptability and be well suited for the anatomic site.

Emulsifiers are important to maintain stability and the distribution of the water and oil emulsion throughout the shelf and usage lifespan of the formulation.

Typical synthetic emulsifiers include polyethylene glycol 40 stearate, sorbitan monooleate (commercial name: Span 80), polyoxyethylene sorbitan monooleate (commercial name Tween 80), stearic acid and sodium stearate. Natural polymers used as emulsifiers include starch, gum acacia, alginates, xanthan gum, irvingia gabonensis mucilage, and tragacanth gum (Ogaji et al. 2011). Gelling agents are also important in increasing the bulk of the drug and thicken the topical formulation according to stable viscoelasticity. Examples include sodium alginate, cellulose in modified forms as sodium carboxymethyl cellulose (NaCMC), hydroxypropylmethyl cellulose (HPMC) and hydroxypropyl cellulose (HPC) (Mekkawy et al. 2013).

9.4.3 Types of Topical Formulations

Topical drug delivery systems could be in the form of gels, emulgels, emulsions, liposomes, liquids, powders and aerosols. Gels and emulgels are relatively new forms of topical delivery formulations. Gels are formed when a large amount of aqueous or hydro-alcoholic solutions are entrapped within a network of colloidal solid particles or macromolecules, while emulgels are a combination of a gel and emulsion. Emulgels are targeted at addressing the limitation of gels to delivery of hydrophilic compounds by enabling the delivery of hydrophobic compounds better than using gels or emulsions. To create emulgels for hydrophobic drugs, oil-in-water (o/w) emulsions are needed to entrap the hydrophobic drugs followed by addition of a gelling agent to the emulsions, while for hydrophilic drugs; a water-in-oil (w/o) emulsion is used. The desirable features of an emulgel include more effective cutaneous penetration, greaseless, spreadability, extended shelf life compared to gels or emulsions, biofriendly, non-staining, water soluble, moisturising and a generally transparent and pleasing appearance.

9.4.4 Natural Polymers in Topical Delivery Systems

Natural polymers are used in topical drug delivery as gelling agents, emulsifiers, stabilizers, thickeners, etc. Cellulose, alginates, chitosan, albumin, starches and xanthan gum are examples of natural polymers which have been applied in the production of topical formulations (Timgren et al. 2013; Gratieri et al. 2011; Laxmi et al. 2013). The derivatives of cellulose such as HPMC or CMC are particularly common candidates in topical formulations and they pose a good alternative to the commonly used carbopol, a synthetic polymer (Singla et al. 2012).

Gels are of interest for topical delivery of pharmaceutical agents as they are easy to apply, spread and remove, thus encouraging patience compliance. Excipients used in topical delivery of psoralen using natural polymers; pectin, xanthan gum, egg albumin, bovine albumin, sodium alginate and guar gum are compared in

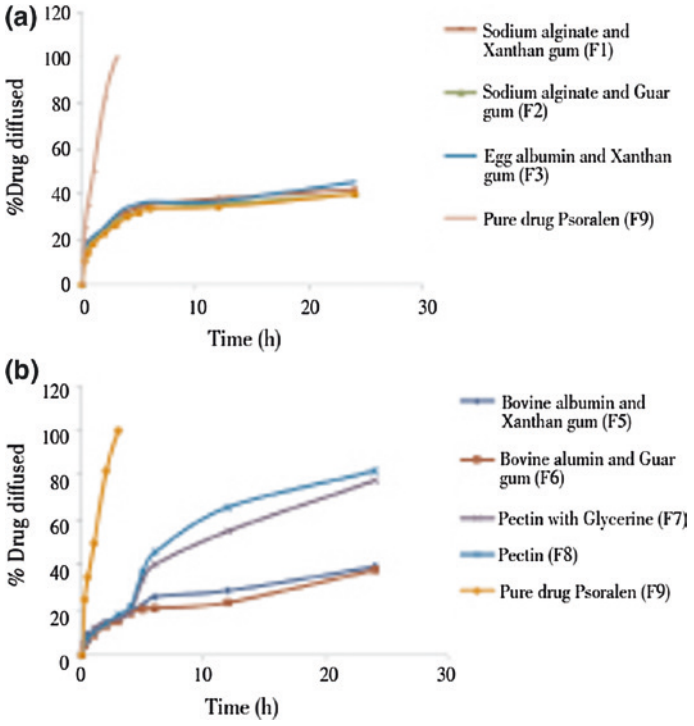

Fig. 9.2 Comparing diffusion profiles of topical drug, psoralen using various natural polymer-based excipients (**a**) and (**b**). Sourced from Laxmi et al. (2013) under creative commons attributed licence

Fig. 9.2. Table 9.1 shows the reagent component concentrations of the respective polymer, humectant, drug, solvent, antioxidant and preservatives in a developmental formulation of Psoralen, labelled F1–F8 (Laxmi et al. 2013). Psoralen is a drug used in the treatment of skin conditions such as psoriasis, vitiligo, mycosis fungoides and eczema, but also possesses antitumor, antibacterial and antifungal properties. It belongs to a class of furanocoumarins compounds found in the *psoralea corylifolia* L. plant (Ahmed and Baig 2014).

The psoralen gel formulations were prepared by first mixing the polymer in water and stirring continuously at 37 °C. This was followed by addition of gelling agent and continued mixing until a homogenous dispersion was attained. The required drug dissolved in methanol was then added followed by addition of antioxidant, preservatives and humectants. The mixture was then stirred until a homogenous mixture was obtained.

All polymers used showed good compatibility with the drug. This is important as an interaction between the excipient and the drug formulation will likely affect the drug activity and could also pose some adverse health effects. This is not to say that all natural polymer excipient do not interact with the drug compound or

Table 9.1 Various formulations of Psoralen using natural polymer excipients adopted from Laxmi et al. (2013) under creative commons Licence

Materials	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Psolaren (g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium alginate (g)	0.75	0.75	–	–	–	–	–	–
Egg albumin (g)	–	–	0.75	0.75	–	–	–	–
Bovine albumin (g)	–	–	–	–	0.75	0.75	–	–
Pectin (g)	–	–	–	–	–	–	4	5
Xanthan gum (g)	0.50	–	0.75	–	0.75	–	–	–
Guar gum (g)	–	0.50	–	0.75	–	1.75	–	–
Menthol (g)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
σ-Tocopherol (g)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Barbaloin (g)	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Glycerin (mL)	–	–	–	–	–	–	5	–
Eugenol (mL)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Methanol (mL)	10	10	10	10	10	10	10	10
Distilled water to make (mL)	50	50	50	50	50	50	50	50

psoralen in particular. The tendency of interaction between excipient and drug compound depends in the specific drug and specific polymer. While a polymer might show the desired biomechanical properties, release kinetics, bioactivity, etc. the applicability may be limited if there is interaction between the polymer being used as excipient and the active drug compound. For instance, nanofibrillar cellulose gels show good potential for drug delivery (Laurén et al. 2014); however, nanofibrillar cellulose possesses various carboxyl and hydroxyl groups which may interact with drug compounds in different ways. This, therefore, must be investigated for every new formulation.

Interaction between excipient and drug compound is commonly evaluated using FTIR. Compatibility is indicated when the characteristic peaks of the pure drug are retained in the FTIR spectra of the drug formulation with the excipients present. Figure 9.3 shows the FTIR spectra of pure psoralen next to that of formulation of psoralen in albumin and xanthan gum as polymer excipients.

Of the polymers investigated, the formulation containing xanthan gum and egg albumin showed the best drug incorporation, release kinetics and in vitro antipsoriatic activity (Laxmi et al. 2013).

Topical delivery system should possess sufficient pseudoplasticity and controllable release kinetics. Sodium alginate and derivatives of cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose and hydroxypropyl cellulose when applied as excipients for topical delivery of fluconazole showed desirable pseudoplastic behaviour. This pseudoplastic behaviour is a shear thinning property that allows the topical formulation to be effectively spread with ease on the affected area while remaining in the required region for localised and sustained

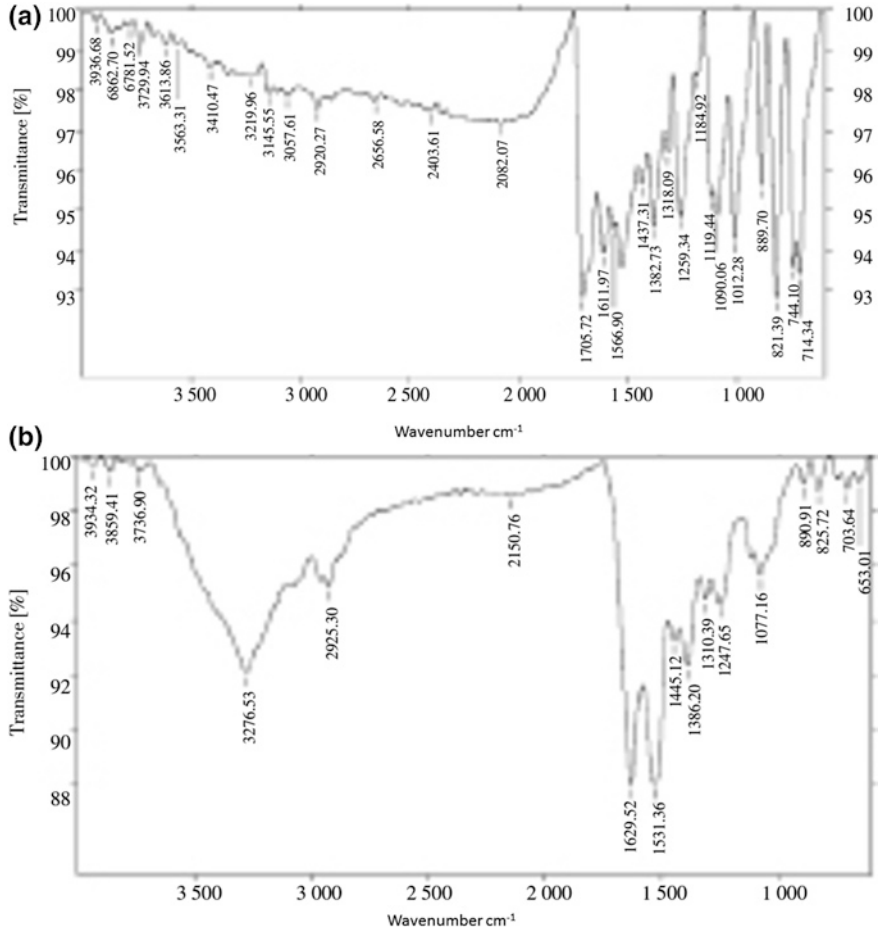

Fig. 9.3 FTIR spectra of psolaren (**a**) and psolaren in a formulation of egg albumin and Xanthan gum (**b**). Sourced from Laxmi et al. (2013) under creative commons attributed licence

delivery. The release kinetics and viscosity also vary with the concentration of the polymer such that the release rate and viscosity can be varied as required by varying the concentration of the polymer as desired. Although a synthetic gelling agent, carbopol showed the best drug release profile and anti-fungi activity; the other polymers also had sufficient antifungal activity and drug release rate (Fig. 9.4).

Over the 3 h observed, the release rate of the fluconazole increased as the concentration of the polymer id reduced (Mekkawy et al. 2013). This can be attributed to increased porosity as polymer concentration reduces, allowing easier permeation of the drug compound through the polymer matrix of the gel.

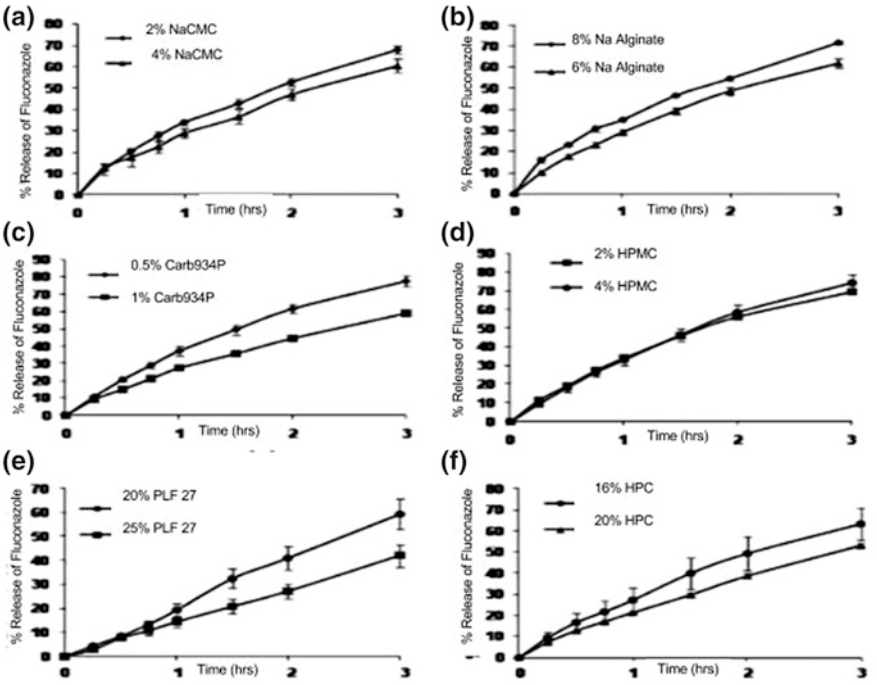

Fig. 9.4 Effect of various polymer excipients on the release profile of fluconazole from prepared gel

The ability to control and predict release kinetics of drug formulation is important in the effective drug delivery. Here, we see gels from natural polymers showing controllable parameters comparable to that of synthetic polymers.

In the treatment of fungal keratitis, delivery and bioavailability of the antifungal agent can be enhanced by using chitosan-based formulations either in gel or solution. Topical formulations of fluconazole using chitosan solution and a gel system of chitosan with a thermoresponsive polymer poloxamer as vehicles showed improved bioavailability of fluconazole in the eye compared to aqueous solutions. The aqueous solutions used as eye drops have limited effectiveness due to the eye's inherent defence mechanism which prevents penetration of foreign substances (Fig. 9.5). The chitosan-based formulation in solution and gel when tested on rabbit models in vivo and across porcine cornea ex vivo at a time of nearly 2 h retained the drug in the desired area allowing more of the drug to penetrate leading to increased bioavailability (Fig. 9.5) (Gratieri et al. 2011).

The mucoadhesive property of chitosan also makes it applicable for application in topical gels for localised and effective delivery topically. In the case of pregnant women where care must be taken to avoid systemic absorption of certain drugs such that the drug being administered to treat the mother does not get to the child as the drug, although beneficial to the mother might pose harm to the child. It is therefore desired that the drug be localised to the affected tissue as

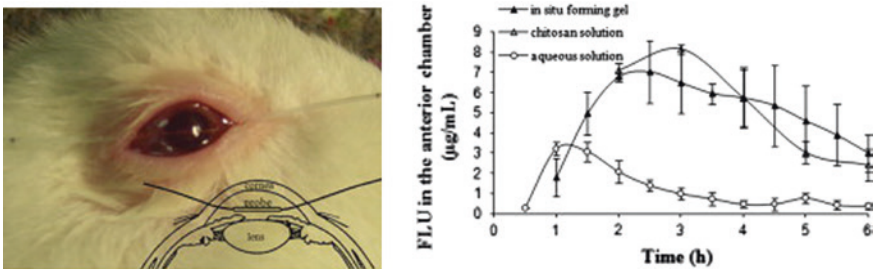

Fig. 9.5 Enhanced topical ocular delivery of fluconazole using chitosan-based solution and gel (Gratieri et al. 2011). Reproduced with permission from Elselvier (Licence number 3631870446393)

best as possible. An example is the delivery of clotrimazole using chitosan-coated liposomes for the treatment of vaginal infection which occurs during pregnancy (Joraholmen et al. 2014). Vaginal infection although might heal without treatment in non-pregnant women, in pregnancy must be treated to prevent complications at child birth or affect development of the child. Drug treatment provides adverse effects involving current drug regimens because of very high therapeutic levels in the bloodstream despite favourable long durations of action. For example, trichomoniasis is a vaginal infection when treated with metronidazole before 37 weeks pregnancy substantially increases the adverse effects of preterm labour and low birth rate babies (Hainer and Gibson 2011). The drug metronidazole is commonly prescribed to pregnant women in oral dosage form (500 mg or 250 mg) (Hainer and Gibson 2011). Further research in decreasing the adverse effects, maintaining an ideal therapeutic level and long sustainable duration of action for metronidazole is much sought after. Chitosan-coated liposomes containing 0.1, 0.3 and 0.6 % w/v concentration of chitosan and a drug concentration of 22 g/mg lipid of Clotrimazole, show good localised delivery of the drug (Joraholmen et al. 2014). The retention of the drug in the vaginal tissue was also significantly increased by use of chitosan, (Fig. 9.6). Interestingly, it was also shown that the

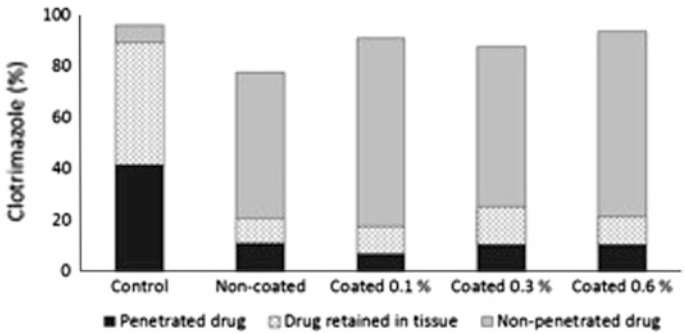

Fig. 9.6 Comparing retention of the drug clomirazole at vaginal site using varying concentration of chitosan. Reproduced with permission from Elselvier Licence number 3631861429984

clotrimazole-containing liposome system with lower concentration of chitosan showed better mucoadhesive property than the higher concentration of chitosan. The topical formulation effectively adheres to the tissue preventing penetration into the systemic flow such that the drug does not cross the placenta to the child but remains in the tissue where it is needed to act.

9.5 Oral Drug Delivery Systems

Drug delivery through the oral route is one of the most common forms of drug delivery into the body (Elsayed et al. 2009; Muheem et al. 2014). Oral drug delivery refers to the intake of medicaments into the body through the mouth by swallowing, chewing or drinking. These 87 dosage forms could be in form of solid or liquids as tablets, capsules, powders, liquids. Oral dosage forms could be targeted at any tissue in the body and for a variety of purposes from general pain relief to regulation of insulin in diabetes patients.

9.5.1 Advantages and Disadvantages of the Oral Route

In certain cases, the oral route becomes more than just an alternative to other routes of drug delivery. For example, insulin delivery, where oral route provides an administration which is closer to the natural physiology of the body by delivering the drug into the liver which is the target tissue. The drug passes into the liver via the pancreatic β cells through the hepatic portal vein. This is unlike in the case of other delivery routes such as parenteral or nasal which aim to deliver the drug directly into the systemic circulation. While this route is favourable in avoiding the first pass metabolism, it is not in line with insulin's natural physiological pathway (Rekha and Sharma 2013; Muheem et al. 2014).

Protein drugs such as insulin pose a particular challenge in oral delivery as they are more likely to follow the paracellular route rather than the lipophilic membrane route which most other drugs follow. This makes them more susceptible to enzymatic degradation.

The main limitations in oral delivery route are the first pass metabolism and biodegradation in the gastrointestinal tract which adversely impacts on the bioavailability of the drug in vivo. Scientific focus in the area of oral drug delivery looks at developing oral formulations which can successfully pass through the gastrointestinal tract while still remaining potent, resist enzymatic degradation at the mucous membrane, can be effectively transported through the complex structure of the mucous membrane, get absorbed into the targeted tissue and have the desired pharmacological activity after passing through the mucous layer (Muheem et al. 2014).

9.5.2 Current Challenges and Natural Polymer-Based Innovations in Oral Drug Delivery

Mucoadhesive polymers are applied with the aim of developing a delivery system which enables the drug to attach to the mucous membrane for enhanced permeation and sustained delivery. However, limitation of this procedure lies in the constant renewal of the mucous layer which inhibits mucoadhesive drug delivery systems (Muheem et al. 2014; Ponchel and Irache 1998).

Although rate of drug absorption using any kind of route (e.g. oral, nasal, topical) depends on factors such as age, diet and state of health of the patient (Morishita and Peppas 2006), the drug properties also has a significant effect on the rate of absorption and effectiveness. The drug properties which affect oral delivery include molecular weight, particularly drugs with molecular mass greater than 500–700 Da like protein drugs such as insulin. Lower molecular weight drugs are generally easier to absorb.

While their oral delivery would be of much significance pharmaceutically, delivery of proteins and peptides-based drugs orally have particularly proven challenging. This is mainly due to their generally large molecular weight and the tendency to be digested in the body without serving their purpose. There are about two known oral protein and peptide drugs in clinical development and these are Interferon-alpha and human growth hormone (HGH) while more are being studied for potential pharmaceutical application. Of much interest is the oral delivery of insulin.

Research approaches in enhancing the oral delivery of proteins include reducing the particle size and using biodegradable nanoparticles (Bakhru et al. 2013).

9.6 Parenteral Drug Delivery Systems

Parenteral delivery concerns the delivery of drugs invasively through the skin, eye, vein, artery and spinal cavity. Substantial efforts in formulating a documented plan in the development of hypodermic needles was first initiated by Lafargue in 1836 (Howard-Jones 1947). Lafargue immersed the lancet in morphine and diluted the morphine by a once repeated immersion into water before self-injection (Howard-Jones 1947). The hypodermic needle is a cylindrical tube with an elliptical shaped bevel end forming a sharp tip for the purpose of cutting into skin (Hamilton 1961). Hypodermic needles are conventionally fabricated from medical grade stainless steel. The luer lock is the plastic connector between the hypodermic needle and syringe body. Polyethylene and polypropylene are medical grade thermoplastics moulded into the luer lock (Gilson and Windischman 1983). The syringe body is composed of medical grade plastic. Medical grade thermoplastics can be moulded into complex geometries in a process known as injection moulding. Medical grade plastics are regulated by USP with the aim of analysing if a grade of plastic reacts

with mammalian cells cultures. There is no published material about syringes constructed from natural polymer materials. This is because most natural polymers may not be easily mouldable by injection moulding and end product assurance towards medical grade is less likely due to the risk of by-product toxicity if a reagent in a natural polymer blend is unstable despite high desirable yields. Hypodermic needles and syringes are usually disposable and single use only. Complex blended natural polymers such as sorn starch blended with clay, mineral montmorillonite and modified natural rubber latex were injection moulded thus resulting in good tensile strength and elastic modulus properties (Mondragón et al. 2009). The constraints for complex blended polymers are greater costs than conventional process, longer duration in process manufacturing and end product can be unaesthetically pleasing. In the past, syringes were constructed from borosilicate glass and autoclavable for reuse thus producing less of an ecological impact.

9.6.1 Advantages and Disadvantages of Parenteral Drug Delivery

Parenteral drug delivery is still a common and widely accepted route to drug administration. The main advantages are bypassing gastrointestinal tract metabolism, rapid drug delivery with target-based response and is an alternative route for patients with difficulty ingesting their medication or are completely sedated (Breymann et al. 2010; Jain 2008). The disadvantages are depth-related localised pain, likelihood of peripheral nerve injury and accidental piercing of a blood vessel at hypodermis level (Jain 2008).

9.6.2 Properties of Parenteral Drug Molecules

Injection-based parenteral drug molecules are usually high molecular weight, more ring-based structural configuration, high counts for proton acceptors and lowest Log_{10} o/w (Vieth et al. 2004). Fluid-based drug formulations are ideal for flow-based transfer along hollow hypodermic needles. Surface tension forces are the usual forces that allow fluid to travel along capillary tube. The volumetric flow rate of a fluid inside a microcapillary is defined by the Hagen–Poiseuille (Eq. 9.1) (Holzman 1998; Allahham et al. 2004).

$$Q = \Delta P\left(\frac{\pi r^4}{8\,\mu L}\right) \tag{9.1}$$

where Q is the volumetric flow rate inside the hypodermic needle, ΔP is the pressure difference from Eq. 9.2, F is the injection force, f is the frictional force from the tube and syringe walls, A is the interior cross-sectional area of the tube

and r is the internal tube radius, μ is the fluid viscosity and L is the hypodermic needle length.

$$Q = \Delta P\left(\frac{\pi r^4}{8\,\mu L}\right) \tag{9.2}$$

The characteristic of fluid flow is expressed by the Reynolds number, *Re* (Eq. 9.3) (Ashraf et al. 2010)

$$Re = \frac{\rho \mathrm{d} V}{\mu} \tag{9.3}$$

where ρ is fluid density, d is the internal tube diameter, V is the fluid volume. A Reynolds number of 2100 or less indicates laminar flow and turbulent flow is above this value (Ashraf et al. 2010).

9.6.3 Current Proprietary Parenteral Devices

Parenteral devices are commonly injectables and examples of current devices available on the market are mentioned. Injectable devices for the delivery of soft implants subcutaneously are patented and commercially available from Rexam (www.rexam.com). Also pre-filled drug syringes is registered Safe 'n' Sound, patented and commercially available from Rexam (www.rexam.com). A self-injector trademarked SelfDose for the safe delivery of drugs is in the format of an adaptor for fitting syringe formats is commercially available from West Pharma (www.westpharma.com). Another self-injector device has a window indicator regarding usage and is trademarked Project, patented and commercially available from Aptar (www.aptar.com).

9.6.4 Future Challenges of Parenteral Devices

In this chapter, we have discussed microneedles as minimal invasive parenteral devices because the needles are fabricated to penetrate a known depth in skin layers than a hypodermic needle. Natural polymers have the potential to support the sustained release of drugs in the skin and can prove advantageous for the biodegradable class of microneedles. However, the challenge arises to strengthen the microneedles with the result of all microneedles piercing the skin at a reproducible depth. Synthetic biodegradable polymer such as poly(DL-lactic-*co*-glycolic acid) PLGA and poly(L-lactic acid) (PLLA) possess high mechanical strength (Ishaug et al. 1994; Leung et al. 2008). The possibility of enhancing the natural polymeric formulation with blended synthetic, polymeric fibres in providing improved mechanical strength properties is one direct solution.

9.7 Nasal Drug Delivery Systems

Nasal delivery is one of the oldest drug delivery systems originating from Ancient Indian Ayurveda called Nasya Karma. The mucosal epithelium inside the nasal cavity is an area for non-invasive drug delivery. This epithelial layer located in the inferior turbinate of the nasal cavity is highly vascularised with a significant absorption area (150 cm^2) and projections of microvilli in epithelial cells (Grassin-Delyle et al. 2012; Lan Kang et al. 2009). The nasal cavity is covered with mucous membrane comprising of goblet cells, columnar cells and basal cells (Fig. 9.7). Most cells of the nasal cavity have cilia apart from columnar cells in the anterior cavity (Fig. 9.7). A collective group of microvilli are known as cilia. Cilia move rhythmically in waves with a function to clear mucus from the nasal cavity into the nasopharynx followed by the oesophagus before finally moving towards the gastrointestinal tract. The microvilli contribute to the large surface area thus highly desirable for effective drug absorption into the nasal mucosa. The nasal mucosa is neutral pH and permeable to numerous drug molecules. Mucosa is usually comprised of lipids, inorganic salts, mucin glycoproteins and water. The main functions of mucus are lubrication of surfaces and protection. The function of protection are goblet cells and mucus glands of nasal epithelium that prevent the absorption of foreign chemicals and decrease residence time for any applied drugs that are in surface contact with the epithelial lining. The purpose for nasal drug delivery is to target the drug systemically such as peptides or proteins in the bloodstream locally (Illum 2012) such as a nasal allergy, nasal congestion, sinus, and to target the central nervous system (CNS) such as bypassing the blood-brain

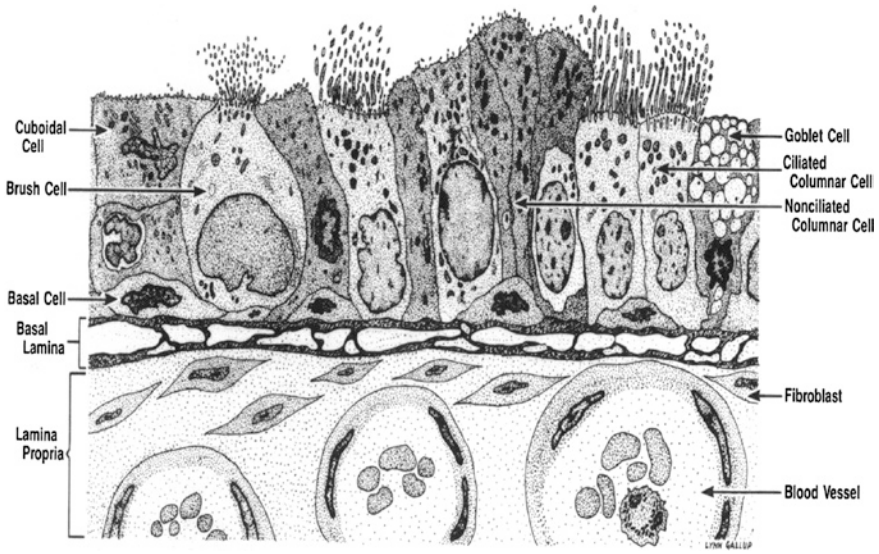

Fig. 9.7 Histology of the nasal cavity morphology (Uraih and Maronpot 1990)

barrier (Illum 2012). The purpose of targeting the CNS is to develop drugs for rapid treatment of migraine, headaches, advanced neurodegenerative illnesses such as Alzheimer's and Parkinson's disease.

9.7.1 Advantages and Disadvantages of Nasal Drug Delivery

The advantages of nasal drug delivery are avoidance of potential gastrointestinal and hepatic first pass metabolism (Grinberg and Gedanken 2010; Lan Kang et al. 2009), low molecular weight drugs have a good bioavailability via the nasal route, straight forward self-administration and protein-based drugs are able to absorb through the nasal mucosa as an alternative to parenteral drug delivery (Grassin-Delyle et al. 2012). The disadvantages of nasal drug delivery are possibility of irreversible cilia damage on the nasal mucosa caused by the drug formulation (Grassin-Delyle et al. 2012), high molecular weight molecules and polar molecules may not permeate or result in low permeation thorough nasal membranes (molecular weight threshold: 1 kDa) (Illum 2012; Grassin-Delyle et al. 2012), clearance of mucosa frequently by cilia has the potential to decrease or prevent full drug absorption (Patil and Sawant 2009), nasal mucosa could denature and change the structure of some drugs through enzymes and possible incompatibility observed between drug and nasal mucosa interaction (Grassin-Delyle et al. 2012).

9.7.2 Natural Polymers in Nasal Drug Delivery

Mucoadhesive microspheres, liposomes, solutions, gels and Mucoadhesive hydrogels are vehicles commonly adopted in the nasal delivery of drugs. Starch, Chitosan, alginate, dextran, hyaluronic acid and gelatin are natural polymers adopted for nasal drug delivery. Mucoadhesion is defined as the contact between the drug formulation and the mucin surface. The concept of mucoadhesion is to allow sustained drug delivery in nasal membranes by prolonging the contact time between the drug formulation and nasal mucosa layers in the cavity (Duan and Mao 2010). Mucoadhesion promotes drug absorption and lowers the chances of complete mucociliary clearance (Patil and Sawant 2009).

Starch is a biodegradable polysaccharide which can be readily processed into microspheres (Grinberg and Gedanken 2010). Starch microspheres commercially available under the name Spherex are used in nasal drug delivery (Pereswetoff-Morath 1998; Grinberg and Gedanken 2010). Drugs such as Insulin (Duan and Mao 2010), morphine (Illum et al. 2002), inactivated influenza (Coucke et al. 2009) and Salbutamol (Xu et al. 2014) are examples of starch loaded intranasal drugs at developmental stage.

Chitosan is a natural polysaccharide with mucoadhesive properties thus it has very good binding properties to nasal epithelial cells and the covering mucus layer

(Illum 2003). The cationic nature of chitosan readily permits the electrostatic attraction with the negatively charged mucosal surface (Martinac et al. 2005). There has been a wealth of research published on chitosan for intranasal delivery according to variable salt forms, degrees of acetylation, variation in derivatives, variation in molecular weights and variation in physical form such as gel, microspheres (Casettari and Illum 2014). Drugs such as Loratadine (Martinac et al. 2005), Zolmitriptan (Alhalaweh et al. 2009) and Insulin (Chung et al. 2010) are examples of loaded chitosan-based intranasal drugs at developmental stage. However, there is yet to be a marketed nasal drug product containing chitosan as the drug absorption enhancer. A morphine intranasal formulation containing chitosan (Rylomine) has already published phase 2 clinical trials and has already pursued phase 3 clinical trails (Javelin Pharmaceuticals; Casettari and Illum 2014; the Pharma Letter).

Alginate is a divalent cation-induced rapid gelation, natural polysaccharide with greater mucoadhesion strength as compared with chitosan, PLA and carboxymethyl cellulose (Patil and Sawant 2009). Usually alginate gel is blended with one or more mucoadhesive polymers in order to improve the strength and drug loading efficiency of the vehicle (Pal and Nayak 2012). Drugs and macromolecules such as bovine serum albumin in representing a water soluble antigen (Lemoine et al. 1998) Carvedilol (Patil and Sawant 2009) and Terbutaline Sulphate (Moebus et al. 2009) are examples of alginate loaded intranasal drugs at developmental stage. There appears to be no significant proprietary drugs containing alginate as the vehicle for intranasal drug delivery.

9.8 Hydrogel-Based Drug Delivery Systems

The need in optimised semi-solid, biocompatible, polymeric formulations in drug loading and routes of entry in the human body is still a growing area in pharmaceutics. Gel-and ointment-based drug formulations are normally oily and thick in appearance (Mueller et al. 2012). A common purpose of such semi-solid, polymeric gel/ointment formulations are to enhance the viscoelasticity (Teeranachaideekul et al. 2008; Silva et al. 2007) and improve target-based pharmacokinetics such as enhanced permeability of luteinizing-hormone, releasing hormone (LH–RH) from polycarbophil hydrogels inside the vagina compared with solution (Valenta 2005). In terms of viscoelasticity, an example in enhancing pseudoplastic properties for oral Ibuprofen is Carbopol-based hydrogels (Silva et al. 2007). Limitations for semi-solid formulations such as topical applications concerning transdermal drug routes of delivery are one common area (Dubey et al. 2007). Hydrogels can be considered as a semi-solid matrix for the purpose of controlled drug release (Jacobs 2014; York 1996). Hydrogels can change structural configuration during certain temperature or pH-induced environments in bodily systems (Cai et al. 2013; Nguyen and Lee 2010). Usually, hydrogels are known to release trapped drug molecules by swelling in watery plasma solvent (Li et al.

2014b). Distinct variability from conventional swelling mechanism of active molecule release are thermoresponsive hydrolysis of block copolymers hydrogels and full dissociation of polycationic poly(allylamine) hydrochloride and polyanionic polystyrene sulfonate complex microgel during increase pH (Buwalda et al. 2014; Rondon et al. 2014). A growing demand for hydrogel-based drug delivery since 1980 onwards shows increasing treads (Fig. 9.8).

This section focuses on hydrogels obtained from natural polymers. It outlines the structure and function of natural polymeric hydrogels in the area of Pharmaceutics-based drug delivery. The distinct sub-classification of a less common form of hydrogels, known as microgels, explains this difference. Also, another area of this review focuses on the physico-chemical properties of hydrogels as a drug delivery system with ideal pharmacokinetic targeting areas.

A hydrogel is a solid or semi-solid hydrophilic matrix comprising of polymeric macromolecules crosslinked by varying combinations of hydrogen bonding, Van der Waals, ionic electrostatic-based and covalent-based intermolecular interactions (Laftah et al. 2011; Huang et al. 2007). Hydrogels possess matrix swelling or shrinkage properties in physico-chemical solvent media such as pH, temperature and ionic strength of electrolytes in solution (Chang et al. 2010; Li et al. 2014b). Usually, solvent ion concentrations at medium ionic strengths allow for ion exchange between polyelectrolyte gel and solvent ions resulting in osmotic pressure increases inside hydrogel and thus causing swelling (Richter et al. 2008). Polymeric hydrogels such as *N*-isopropylacrylamide (*N*IPAAm) are influenced by higher ionic strength of electrolytes and temperature in solution and they can swell above their critical solution thresholds (Díez-Peña et al. 2002; Sharpe et al. 2014). *N*IPAAm has swelling properties as the nitrogen groups' hydrogen bond with water at *N*IPAAm lower critical solution temperature of 34 °C (Lee and Fu

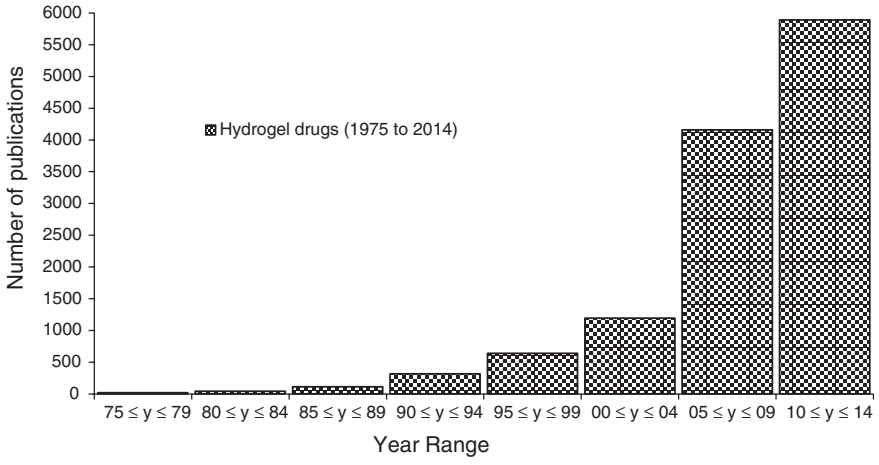

Fig. 9.8 The number of hydrogel drug publications according to year range (Web of Science)

2003). Also the deprotonation of carboxylic acid groups in hydrogels such as polyacrylic acid (polyAA) and interpenetrating network of chitosan combined poly(sodiumacrylate-*co*-hydroxyethyl methacrylate) (SCPSC) in high pH results in ionic repulsion and induces swelling (Fig. 9.9) (Yang et al. 2011; Mandal and Ray 2014).

The equilibrium swelling ratio of SCPSC was significantly 1.6 folds greater in pH 7 buffer medium when compared with pH 3.9 (Mandal and Ray 2014). The polymeric macromolecules in hydrogels can be cationic, anionic or entirely neutral with regard to interacting with another macromolecule or drug molecules (Van Vlierberghe et al. 2011; Singh and Lee 2014). The crosslinking of hydrogels combines highly desirable characteristics such as mechanical strength, pseudoplasticity, drug and macromolecular intermolecular interactions and plasma swelling (Zhao et al. 2014; Kurland et al. 2014). The porosity of the crosslinked hydrogel

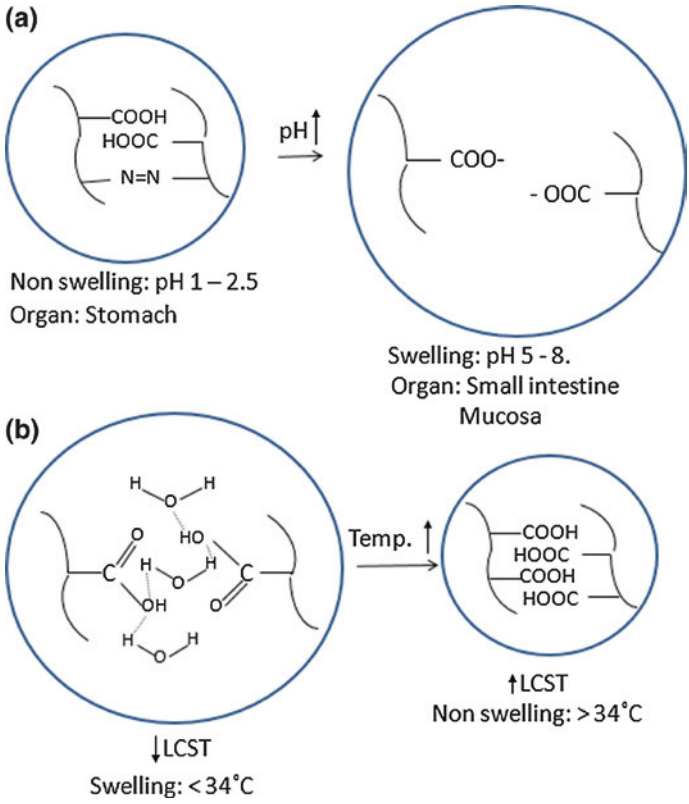

Fig. 9.9 A schematic representation of swelling according to **a** pH with a hydrogels such as crosslinked azo polyacrylic acid (pAA) (Adopted from Yang et al. 2011). **b** Temperature with hydrogels such as PNIPAM with PNIPAM/IA (Adopted from Yang et al. 2011) with permission from Royal Society of Chemistry Licence number 3631871241621

matrix determines aqueous solvent adsorption and rate of drug release (Hoare and Kohane 2008). However, the insolubility of hydrogels to water is attributed to the networking arrangement of crosslinks between polymer chains thus maintaining physical structure (Gupta et al. 2002). Nevertheless control in the polymeric swelling release rates of drugs with possible subsequent degradation of hydrogels is very much a sought after challenge in matching the duration of drug release across a therapeutic range and target specificity in the body. There are constraints and possible major limitations in stabilising porous combination of polymers in defined mass ratios in attaining desirable controlled release of drug molecules. However, the complex chemical structures of hydrogels can pose challenging in synthesis coupled with mass reproducibility and end product purification (Martín del Valle et al. 2009). Although synthetic polymers seem to have largely dominated over natural polymers in the past decade due to their relatively long service life, high water absorption capacity and gel strength and the possibility of tailored degradation and functionality, natural polymers are highly sort after for their biocompatibility, availability and low cost. (Ahmed 2015). Hydrogels from natural source usually require inclusion of synthetic components as, for example crosslinkers or the hydrogel could be a blend of both natural and synthetic polymers for improved functionality, degradation or biocompatibility (Kamoun et al. 2015). In the following sections we look at some common natural polymers and their recent applications as hydrogels.

9.8.1 Hydrogels in Transdermal Patches

The architecture of a transdermal patch comprises a drug reservoir or a polymer-drug matrix trapped between two polymeric layers as a laminated layer-by-layer arrangement (Sarkar et al. 2014). A study of the effect of mucilage derived from indigenous taro corns combined with hydroxypropylmethylcellullose (HPMC) was a patch vehicle in the slow IV drug release of an antihypertensive drug, Diltiazem (Sarkar et al. 2014). Patches have been developed for targeting the drug molecules through full skin thickness passive diffusion in the systemic circulation so that receptors or pathogens in the body are affected by the drug (Suksaeree et al. 2014; Arkvanshi et al. 2014). A cellulose polymer derived from bacteria, plasticised with glycerol using solvent evaporation techniques as a potential patch demonstrated a reduced lidocaine permeation flux in skin epidermis when compared with a hydroxypropylmethylcellulose gel (Trovatti et al. 2012). The observation of a low permeation flux is an example of implementing further optimisation-based studies by using chemical penetration enhancers effecting SC barrier properties at possible higher concentrations. Proprietary patches available as pharmaceuticals are Nicorette® (Nicorette.co.uk) in nicotine delivery to wean addiction, Ortho Evra® (Orthoevra.com) in norelgestromin/ethinyl estradiol delivery to decrease blood levels of gonadotrophins and inhibiting ovulation and chances of pregnancy and

Exelon®Patch (Novartis.com) in rivastigmine delivery to inhibit cholinesterase by reversible inhibition in delaying the progression of Alzheimers disease. Those proprietary patches mentioned are examples outlining three completely different therapeutic before current growing trends emerged since the 1980s (Wiedersberg and Guy 2014). The major benefits of patch-based delivery are reduction in adverse effects such as gastrointestinal disturbances caused by high dose oral rivastigmine as compared with a rivastigmine patch (Reñéa et al. 2014), reduction in peak plasma concentrations and interventions of prior dose adjustments periodically from oral and fast intraveneous delivery (Reñéa et al. 2014; Arkvanshi et al. 2014). The sensitivity of patient's skin to transdermal patches is a major concern because of the likelihood of allergic reactions if the patched skin area is left covered for a long duration (Reñéa et al. 2014).

9.8.2 Nanoparticles for Controlled Delivery

The controlled release of active drug molecules sustained at therapeutic thresholds in specific targets of the body according to the length of treatment is a major focus in pharmaceutics research (Soppimatha et al. 2001; Ashley et al. 2014). A significant gap for nanoparticle mediated drugs to enter the pharmaceutical drugs market exists because of the sophisticated pathological targeting mechanisms and therefore traditional pharmacology cannot distinctly characterise nanoparticle drugs (Brambilla et al. 2014). Themoresponsive Poly(NIPAAm-*co*-AAm) hydrogels were shown to have a *z*-diameter of 156.0 nm after encapsulating gold-silica nanoparticles and forming nanoshells by collapsing to absorb the gold-silica at 40–45 °C at 780 nm (Strong et al. 2014). A chemotherapeutic agent, doxorubicin was loaded into the Poly(*N*-isopropylacrylamide-*co*-Acrylamide) Poly(NIPAAm-*co*-AAm) nanoshells by 1.12 folds greater than without nanoshells arrangement (Strong et al. 2014). The crosslinkers in NIPAAm-*co*-AAm hydrogels can reversibly collapse into a dehydrated globular conformation above their lower critical solution temperature, normally above physiological body temperatures, to release the drug (Sershen et al. 2000; Fundueanu et al. 2013). Poly(NIPAAm-*co*-AAm) is a synthetic polymer. Nevertheless Poly(NIPAAm) has been commonly crosslinked with natural chitosan because of pH sensitive properties of the amino groups (Li et al. 2009). The cytotoxicity of Poly(NiPAAm-*co*-chitosan) containing 5 mg/ml NIPAAm nanoparticles encapsulated with paclitaxel resulted in 60 % viability of human lung cancer cells thus proving favourable toxicity (Li et al. 2009). Complementing the 60 % cell viability, the cumulative release of Paclitaxel was increased by 1.86 fold in extracellular tumour conditions of pH 6.8 compared with pH 7.4 at the same physiological temperatures (Li et al. 2009). Nanoparticle drugs are usually between 10 and 200 nm in size with generally high efficacies (Noble et al. 2014). Liposomes are mainly natural phospholipids nanoparticles as highly advantageous drug delivery vehicles because of the potential to deliver

hydrophobic drugs and biocompatible properties (Noble et al. 2014). Liposomal synthesised PEG nanoparticles loaded anti-cancer carfilzomib allowed the inhibition in tumour growth and subsequently proved to be up to fourfolds more cytotoxic to tumours compared with unloaded carfilzomib (Ashley et al. 2014). Liposomes synthesised with PEG prevents any aggregation of nanoparticles and adsorption of plasma-based serum proteins that promote immediate clearance (Noble et al. 2014). The advantage of drug nanoparticles in drug therapy is the reduction in systemic toxicity and greater drug loading in nanospheres (Ashley et al. 2014). A huge vacuole still remains for research into drug hydrogel nanoparticles containing higher concentrations of ideal naturally sourced polymers.

9.8.3 Hydrogels for Wound Dressing

Wound dressing is an immediate first aid response in superficial and chronic skin wounding injuries. The general treatment of skin wounds is to minimise scarring, microbial infection, pain, protection from further trauma and absorption of excess exudates from open lacerations (Mayet et al. 2014). Conventional gauzes and pads based on cotton and synthetic rayon polyester bandages need regular changing and tend to be more expensive than modern dressings (Boateng et al. 2008). Also conventional bandages are known to keep the wound bed dry and slow down the natural skin healing process due to restricted new cell migration and healthy tissue removal when bandage requires changing (Boateng et al. 2008; Rolstad et al. 2012). Hydrogels are an ideal dressing material for absorbing excess exudates, allowing enough moisture of the wound bed and filling irregular-shaped wound cavities (Lee et al. 2014; Tran et al. 2011). A synthesised gelatine-hydroxyphenylpropionic acid hydrogel was studied because of well-known biocompatible and tissue adhesive properties (Lee et al. 2014). A gelatine-hydroxyphenylpropionic acid hydrogel loaded with human dermal fibroblast resulted in a 1.9 fold wound closure in mice compared with phosphate buffer solution control after four days (Lee et al. 2014). The focus on hydrogels for wound dressing may seem irrelevant in the area of traditional pharmaceutics as defined in the section Portals of drug administration in the human body. The importance of a new area of study relating to emergency trauma shows the need for the application hydrogels compounds.

9.8.4 Polymeric Crosslinking in Hydrogels

An important characteristic of a hydrogel is the polymeric strand crosslinking. Crosslinking of hydrogels with morphologically cross-hatched or entangled macromolecular architecture allows a 3D structure and avoids immediate dissolution of separate macromolecular strands in hydrophilic solvent (Hennick and van Nostrum 2012).

Physical crosslinking of polypeptides are attributed to ionic bonding, hydrogen bonding and hydrophobic interactions in aid of bipolymeric crosslinking (Nonoyama et al. 2012; Hu et al. 2010). Physically crosslinked hydrogels are inhomogeneous due to more than one type of intermolecular-based interaction (Hoffman 2002).

Chemically crosslinked hydrogels involve covalent linkages in bridging two different polymeric strands and the use of crosslinking agents that can react with specific functional groups in polymeric macromolecules (Hennick and van Nostrum 2012). Chemically crosslinked hydrogels permit bigger volume increases during sol-gel transition than physically crosslinked hydrogels (Jonker et al. 2012). The use of chemical crosslinking agents to bind-specific functional groups for crosslinking polymers is shown in Table 9.2. The process and target application of hydrogel and microgel polymers is outlined in Table 9.3.

9.8.5 Natural Polymers in Hydrogels

Polysaccharides such as hyaluronic acid, chondroitin sulphate, chitosan, carboxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, bacterial cellulose and sodium alginate are common examples of carbohydrate derived polymers in hydrogels (Van Vlierberghe et al. 2011). Examples of proteins used in hydrogels include gelatine, collagen, elastin, ovalbumin, β-lactoglobulin and silk fibroin from both plant and animal sources (Jonker et al. 2012). Polymer strands from natural, synthetic and partially synthetic sources are acquired as drug delivery vehicles (Gupta et al. 2002). Polypeptides have straight chained or helical assemblies in their gross macromolecular arrangement such as β-pleated sheets and α-helix respectively (Woolfson 2010). Amino acids in polypeptides, containing Ala, Glu, Lys and Gln occur more in α-helices compared with Thr and Val in β-pleated sheets, in-conjunction to Gly and Pro usually located in the turn area of molecule (Woolfson 2010). Two hydrophobic regions in the macromolecular structure of anti-parallel conformation assemble to form the β-pleated sheet (Fig. 9.10) (Nonoyama et al. 2012; Woolfson 2010). Polypeptide structure hydrogels overall are the most suitable in mimicking natural extracellular crosslinking matrix (Yao et al. 2014).

Hyaluronic acid (HA)-based hydrogel particles have been investigated for drug delivery using trimethoprim (TMP) and naproxen as model drugs. Hyaluronic acid was modified with an aqueous solution of sodium bis (2-ethythexyl) sulfosuccinate (AOT)-Isoctane microemulsion system. This formed hyaluronic acid particle which were further modified by oxidizing to aldehyde (HA-O) using treatment with $NaIO_4$ followed by reacting with cysteamine thus forming thiol ligands onto the surface of the HA particles. The final HA-based hydrogel particles were formed by radical polymerization of the HA particles with anionic and cationic monomers 2-acrylamido-2-acrylamido-2-methyl-propanosulfonic acid and 3-acrylamidopropyl-trimethyl-ammonium chloride, respectively. The HA-based hydrogel particles derived demonstrated good pH dependent size variation and

Table 9.2 Chemical agents for the chemical crosslinking of functional groups in hydrogels

Crosslinker	Functional gps	Reaction or functional gp interactions	Chemical reaction conditions
Glutaraldehyde (Berger et al. 2004; Costa-Júnior et al.2009)	Di-aldehydes (Berger et al. 2004)	Imine group formed by Schiff base formation (Berger et al. 2004; Costa-Júnior et al. 2009). Acetal group formation from hydroxyl groups (Costa-Júnior et al. 2009)	No heat required and slow addition is usual (Costa-Júnior et al. 2009)
Poly(ethylene glycol)–propion dialdehyde (PEG–diald) (Luo et al. 2000)	Amine (Luo et al. 2000)	Azide addition (Luo et al. 2000)	Unimolecular addition of PEG-diald and polymer in ambient temperature conditions (Luo et al. 2000)
Methylene bis-acrylamide (Berger et al. 2004)	Acrylamide, ethylene (Berger et al. 2004; Bhattacharyya and Ray 2014)	Variable (Berger et al. 2004)	
Genipin (Song et al. 2009; Muzzarelli 2009)	Amino acid groups and secondary amino group in acidic and neutral pH (Muzzarelli 2009)	Amino acid groups (Song et al. 2009). Condensation reactions in acidic or neutral conditions and aldol condensation in basic conditions (Muzzarelli 2009)	Set pH conditions (Muzzarelli 2009)

Table 9.3 Recent examples of hydrogels developed in drug delivery

Polymer	Composition	Process[a]	Target/delivery[a]	Reference(s)
Casein	100 %	Temperature-based gelation	BSA molecule into buffered solution	Song et al. (2009)
Poly(*N*-isopropylacrylamide-*co*-Acrylamide) poly(NIPAAm-*co*-AAm)	NIPAAm and AAm, 83.3:16.7 (% mol ratio)	Poly(NIPAAm-co-AAm) synthesis: free radical copolymerisation with AIBN initiator. Microsphere process: W/O emulsification and copolymer solubilised by acidic DI water and crosslinking using glutaraldehyde	Propranolol and lidocaine	Fundueanu et al. (2009)
Alginate (Monomer unit: 1,4-linked b-D-mannuronic acid and a-L-guluronic acid)	Methacrylated alginate (5.7–45.3 %)	Photocrosslinking of methacrylated alginate at 365 nm and 0.05 % w/v Irgacure D-2959 photo initiator	Bovine chondrocytes for cytocompatibility for cell culture	Jeon et al. (2009)
Sodium carboxymethylcellulose (NaCMC): cellulose	NaCMC: cell (5:5–9:1 by wt). A hydrogel film	Solubilisation of cell and NaCMC and crosslinking with epichlorohydrin (ECH)	In vitro release of Bovine Serum Albumin (BSA)	Chang et al. (2010)
Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PF127) and Poly(methyl vinyl ether-*co*-maleic anhydride) (GZ)	GZm/PF127 molar ratio from 1 to 20 (GZm is the monomer, methyl vinyl ether-co-maleic anhydride)	Esterification between carboxyl groups of maleic anhydride and hydroxyl groups of PF127. Subsequent solvent evaporation of tetrahydrofuran followed by precipitate copolymer filtration and collection	BSA, glucoprotein rKPM-11 and dextran in PBS (pH 7.4)	Moreno et al. (2014)

[a]The process are the main experimental conditions, reagents or crosslinking reagents in preparing hydrogels. The target/delivery is the active molecule or drug studied for encapsulation or controlled release from hydrogel

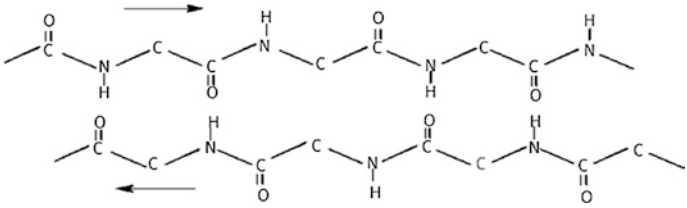

Fig. 9.10 An anti-parallel orientation for a β-pleated sheet (Adopted from Woolfson 2010)

swelling properties. This is important for applications such as controlling and tuning the rate of drug delivery in different parts of the body. This takes advantage of the remarkable ability of HA to demonstrate variety of swelling kinetics in different pH environment (Burke and Barrett 2005; Ekici et al. 2014). Other natural polymers which tend to form hydrogels with pH dependent swelling kinetics include alginate. Arginine grafted alginate hydrogels are also potential carriers for protein drugs enabling oral delivery. This can be used to orally deliver proteins while limiting the effect of metabolism in the gastrointestinal tract prior to reaching the target area (Eldin et al. 2014).

Nanocellulose has had increasing application in the pharmaceutical area in recent times. Current interests in exploring the industrial application of nanocellulose extend to their use as hydrogels for drug delivery. Nanofibrillar cellulose derived from wood pulp was developed into injectable hydrogel for localised and controlled release of large and small compounds in vivo. Although further studies are required to establish the nature and possibility of interaction between the hydrogel material and the active drug, studies carried out so far show that nanofibrillar cellulose has good potential as an injectable hydrogel drug delivery system. This application exploits the shear thinning property of nanofibrillar cellulose hydrogel which makes it possible to inject with ease using a syringe while still maintaining its viscosity (Bhattacharya 2012). This allows for localised and targeted delivery to easily assessable regions using injections. Nanofibrillar cellulose hydrogel also has the advantage of ease of preparation without need for an external source of gel activation unlike most other hydrogels being explored for the same application. The external activators could be chemicals or irradiation methods which could invoke toxicity or complication of the delivery process. Nanofibrillar cellulose-based hydrogels, however possess intrinsic pseudoplasticity which makes them suitable an injectable hydrogels (Laurén et al. 2014).

Chitosan and its various derivatives have also been expired as hydrogels for drug delivery. Due to the robust chemical property, chitosan can be crosslinked using a crosslinker such as genipin and glutaraldehyde with a variety of other natural polymers to obtain desired functionality. For example, chitosan is crosslinked with gelatin for improved rigidity and with starch for improved flexibility and cohesion (Giri et al. 2012).

Cellulose is a highly abundant natural polymer in plants, bacteria, algae and fungi phylum. The unbranched chains consist of 1,4 glycosidic linkage of monomer units, D-glucopyranose (DGP) and presence of three hydroxyl groups per

DGP monomer (Kamel et al. 2008; Carter Fox et al. 2011). Cellulose polymers consist of amorphous and crystalline arrangements in which the hydrolysis properties of cellulose are found to be more unfavourable in higher crystalline arrangements (Walker and Wilson 1991).

Sodium Carboxymethylcellulose (NaCMC) is a cellulose derived water soluble polymer (Sannino et al. 2009). NaCMC is grossly anionic because of the negative electron density with respect to the carboxymethyl substitution region. Hence, polyanionic NaCMC has the potential to electrostatically interact with gelatine below its isoelectric point (Devi and Kumar 2009). NaCMC and gelatine are biocompatible as NaCMC is biologically excreted and gelatine is degraded by natural enzymes (Rathna and Chatterji 2003). NaCMC is able to hydrogen bond with water molecules hence hydrogel NaCMC crosslinked gelatine possesses swelling properties which is reported by Tataru et al. (2011). Individual polymers of NaCMC and gelatine have the tendency to swell in ambient temperature water. As far as we know there is no published literature comparing swelling rates of individual NaCMC and gelatine with post bipolymeric NaCMC: gelatine microgel. Ionic interactions are dominant intermolecular forces in crosslinking polyanionic NaCMC with polycationic polymers such as polyvinylamine (PVAm) (Chang and Zhang 2011). The degree of substitution (DS) defines this structure when hydroxyl groups in the glucopyranose monomer are replaced with carboxymethyl groups in which the number of substituted hydroxyls accounts to the degree of substitution (Rokhade et al. 2006). The higher the DS and quite significantly the lower the MW of NaCMC allows for increased in ionic conductivity (Lee and Oh 2013). The discharge capacity of NaCMC (0.9 DS and 250 kDa) up to 0.5 current density (C-rate) was 165 mAh g^{-1} compared with NaCMC (0.9 DS and 700 kDa) at 155 mAh g^{-1} (Lee and Oh 2013). Potentiometric titration with hydrochloric acid as a carboxylate proton donor coupled with Infrared spectroscopy in knowing the relative amount of carboxyl groups is implemented in calculating DS (Pushpamalar et al. 2006).

Gelatin is another natural polymer which finds wide application as hydrogels for drug delivery. Hydrogel made from gelatin and polyvinyl alcohol (PVA) has been developed for application in delivery of anti-cancer drug Cisplatin. The anti-cancer drug encapsulated within the macrocycle cucurbit(7)uril was incorporated in hydrogel formulations containing between 0 and 4 % PVA. The hydrogel formed demonstrated a controllable swelling and degradation rate which was PVA concentration dependent. As the concentration of PVA in the hydrogel formulation increases, the release rate of encapsulated drug decreases such that the release rate of the drug can be controlled by varying the concentration of the PVA in the hydrogel formulation. Hydrogel containing gelatin only inhibited cancer cell growth by 80 % while hydrogel containing 2 % PVA inhibited cell growth by 4 %. At 4 % cell growth inhibition was 20 %. When compared to intraperitoneal injection of free cisplatin at high dose of 150 μg, subcutaneous implantation of the gelatin PVA hydrogels at just 30 μg of cisplatin achieved the same effectiveness such that the use of the gelatin/PVA hydrogel improved the effectiveness of the anti-cancer drug (Oun et al. 2014).

A globular whey protein of high abundance from cow's milk is β-lactoglobulin which has the potential in binding hydrophobic molecules via hydrogen bonding and van der Waals interactions (Livney 2010; Lee and Hong 2009). Chitosan forms a complex coacervates with β-lactoglobulin at pH 6.5 (Lee and Hong 2009). Pectin which is an anionic polysaccharide coacervates with β-lactoglobulin and has an apparent mean particle diameter below 1000 nm and zeta potential reaching −40 mV above pH 6 for formulations containing pectin 0.5 % w/w (Jones et al. 2009). Here, very low zeta potential values outline particle repulsion and minimal particle aggregation (Jones et al. 2009). As far as we know there is currently studies performed in the encapsulation and release of drugs using β-lactoglobulin as a co-polymer in a hydrogel.

9.8.6 The Preparation Techniques of Hydrogels

There are numerous valid engineering techniques in the preparation of natural hydrogels. Natural polymers such as gelatin, κ-carrageenan, agarose and gellan gum in hot solutions undergo random coil to helix transitions with the support of ionic salts such as Na^+ which lowers the repulsive forces between same electrostatic charges, allowing ionic interaction and the polymeric crosslinking to occur (Fig. 9.10) (Coutinho et al. 2010; Gulrez et al. 2011). The polymer κ-carrageenan can further form a superhelical network when a number of helices aggregate in the presence of ions and a gel is formed (Viebke et al. 1994).

Polymers possessing charged functional groups such as chitosan, carboxymethylcellulose, gellan, gelatin, alginates and pectin can be crosslinked with multivalent ions of opposite charges, which is known as ionotropic gelation (Patil et al. 2012). Polyanionic molecules such as alginic acid and l-carrageenan can be reversibly crosslinked by cations such as Ca^{2+}, Zn^{2+} and Fe^{3+} (Bracher et al. 2010; Agulhon et al. 2012). An ionotropic crosslinking interaction between a divalent cation and polyanionic groups between two chains of sodium alginate is by chelate complex with glucuronic acid groups (Fig. 9.11) (Ahirrao et al. 2014).

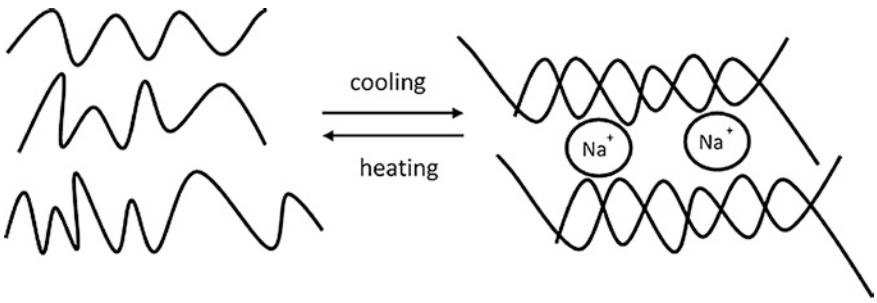

Fig. 9.11 Illustration of random coil to helical transition of anionic, natural polymers, e.g. gellan gum during the cooling of a hot polymeric solution

A recent study by Boppana et al. (2010) combined polyanionic sodium carboxymethylcellulose with polycationic albumin via Al^{3+} ions to induce electrostatic interactions by ionotropic gelation prior to chemical crosslinking using glutaraldehyde. The entrapment efficiency of a drug, simvastatin, was between 74 and 82 % in a bipolymeric sodium carboxymethylcellulose and albumin hydrogel network (Boppana et al. 2010). Slightly different to ionotropic gelation, a process known as complex coacervation involves the electrostatic attraction of oppositely charged polyelectrolytes such as precipitate or gel in solution because of change of factors such as pH, ionic strength and polymeric mass ratios (Jin and Kim 2008; Hoffman 2002). An alginate/β-lactoglobulin lipid droplets contained in hydrogel matrices were complex coacervated with alginate ($–NH_3^+$) and cationic chitosan (–COO–) at acidic pH ranges of 3.5–6.5 in the formation of beads for gastrointestinal active molecule delivery (Li and McClements 2011). An example of a complex coacervate bipolymer is sodium carboxymethylcellulose and gelatin in the formation of a complex coacervate.

Chemical crosslinking of two non-ionic polymers can be enzyme catalysed in the addition of a crosslinking agent forming covalent bonds on specific functional groups in forming a hydrogel (Hoare and Kohane 2008; Hennick and van Nostrum 2012). An example is a crosslinker, 1, 2, 3, 4-butanetetracarboxylic dianhydride (BTCA) forming ester linkages with the hydroxyl groups on β-mannose or α-galactose monomers present in guar gum with enzyme, 4-dimethylaminopyridine (DMAP) (Fig. 9.12) (Kono et al. 2014).

Monomers of low molecular weight can undergo radical polymerisation using photoinitiators forming photopolymerised hydrogels such as dextran and glycidyl acrylate (Hennick and van Nostrum 2012; Nguyen and West 2002). The

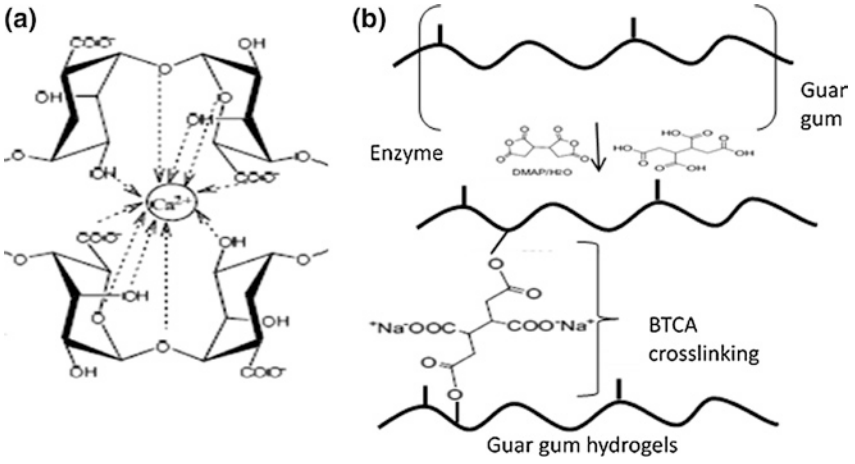

Fig. 9.12 Schematic outlines in the preparation of hydrogels. **a** An ionotropic interaction formed by chelation between Ca^{2+} and alginic acid (Adopted from Ahirrao et al. 2014). **b** Chemical crosslinking of guar gum with BTCA crosslinking agent and enzyme. Reused under creative commons attribution licence

advantages of photopolymerisation are rapid curing rates during processing, lower production of heat and spatial and temporal control of process polymerisation reactions (Nguyen and West 2002; Burdick and Prestwich 2011). Hyaluronic acid is radically polymerised with methacrylic anhydride under basic conditions in producing methacrylated hyaluronic acid (Burdick and Prestwich 2011).

The manufacturing considerations in bulk production of hydrogels of bead morphology use microengineering processes in attempting to optimise control and batch wise consistency requirements. Micromoulding is an engineering process recently employed in the production of hydrogel microneedles composed of NIPAAm particles suspended in 50/50 polylactic-*co*-glycolic acid (PLGA) (Kim et al. 2012). The micromould implemented in the fabrication of NIPAAm hydrogel microneedles were poly-di-methyl siloxane and molten PLGA was added to pre-filled NIPAAm particles in the mould followed by curing at 150 °C and −100 kPa pressure in a vacuum oven (Kim et al. 2012). Microfluidics is a specialist area concerned with the fluid dynamics and engineering of micron scale confinement of flowing fluids (Domachuk et al. 2010). A phospholipid polymer, poly(2-methacryloyloxyethyl phosphorylcholine (MPC)-*co*-*n*-butyl methacrylate (BMA)-*co*-4-vinylphenyl boronic acid (PMBV) and poly (vinyl alcohol) (PVA) were crosslinked with the aid of a microfluidic device (Fig. 9.13) (Aikawa et al. 2012). The PMBV and PVA were separately injected and droplets were pinched off after gelation induced by contact, the flow rate ratio between paraffin oil and polymer was high in order to decrease the diameter of hydrogel droplets (Aikawa et al. 2012).

The main disadvantage of microfluidics is the possibility of channel clogging due to gelation of gel beads when external gelation by ionotropic crosslinking is adopted (Mark et al. 2009). Photolithography implements a source of radiation, usually UV, directed onto the fluid material containing a photoinitiator in propagating crosslinking reactions according to polymerisation kinetics via transparent areas of the photomask that outline the pattern (Fig. 9.14) (Helgeson et al. 2011).

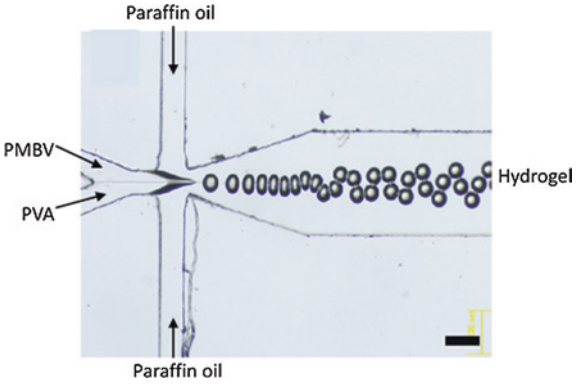

Fig. 9.13 Microfluidic device in the generation of hydrogel microparticles of PMBV/PVA (Adopted from Aikawa et al. 2012) reused with permission from American Chemical Society Licence number 3631861429984

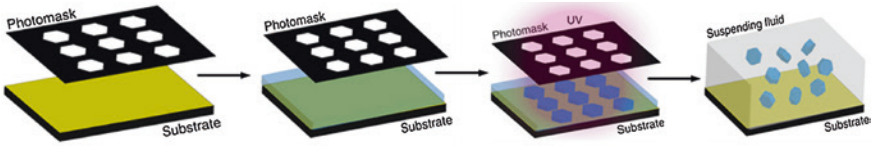

Fig. 9.14 Outline of photolithography for a polymeric hydrogel (reproduced from Helgeson et al. (2011) with permission from Elsevier, licence number 3631910827880

Hydrogels made photoresponsive can evoke changes in degree of swelling, shape, viscosity or elasticity properties (Tomatsu et al. 2011). They are functionalised as photoresponsive when a polymer is modified with supramolecular interacting groups, formation of photoresponsive low molecular weight gelators into a supramolecular hydrogel and addition of photoresponsive groups in hydrogel modification (Tomatsu et al. 2011). A recent study by Xiao et al. (2011) fabricated methacrylated gelatine and silk fibroin interpenetrating polymer network hydrogels using 2-hydroxy-1-[4-(hydroxyethoxy)-phenyl]-2-methyl-l-propanone (Irgacure 2959) as the photoinitiator under UV radiation. The mass ratios of crystallised silk fibroin crosslinked with methacrylated gelatine defined the mechanical stiffness and the rate of degradation (Xiao et al. 2011). Photolithography and micromoulding require a lot of capital investment relating to the precision fabrication of photomasks, photocrosslinking reagents and moulds (Mark et al. 2009).

Membrane emulsification involves injection of the dispersed phase through a microporous membrane into the continuous phase of an immiscible liquid under pressure. The purpose of membrane emulsification is to obtain monodisperse particles from controlled membrane pore size and pore size distributions for average emulsion diameters (Akamatsu et al. 2010). Chitosan-coated calcium alginate particles with a diameter of 4.4 μm were produced from a w/o emulsion using Shirasu porous glass (SPG) membranes (Akamatsu et al. 2010).

9.8.7 Microgels

Microgels are hydrogel microparticles that are colloidally stable in aqueous solutions (Gao et al. 2014; Vinogradov 2006). Temperature-responsive microgels undergo a rapid change in hydrodynamic particle diameters in temperature-based hydrating or dehydrating polymers in aqueous solution at the lower critical solution temperature (Yang et al. 2013). Techniques for the preparation of hydrogels can be copied or adopted for microgels as long as there is no non-particulate morphology such as film or deviation towards a pure polymeric formulation. There are three important factors in using microgels in drug delivery. The first factor concerns the stability of microgels as a stable dispersion in physiological conditions mimicking blood plasma because the microgel drug has to circulate systemically

before significant controlled release of the drug (Oh et al. 2008; Pich and Adler 2007). The second factor is the degradation kinetics in allowing sustainable release leading to clearance after complete degradation of the microgel (Oh et al. 2008). The third factor is controlling the microgel particle diameter to less than 200 nm in diameter to pass blood vessels or enter cells membranes (Oh et al. 2008).

9.8.8 Microgels from Natural Polymers in Drug Delivery

Current research in formulating and pharmacokinetic-based testing of microgel drugs is still being pursued. Most recently, plasmid DNA macromolecules were loaded in microgels by an inversion microemulsion polymerisation technique with ethylene glycol diglycidyl ether (EGDE) crosslinking reagent for cancer research therapy (Costa et al. 2014). A novel pH sensitive microgel was prepared using a salt bridge interaction between polyanionic carboxymethylcellulose (CMC) and tertiary amide of cationic (2-hydroxyethyl) trimethylammonium chloride benzoate (TMACB) linked with β-Cyclodextrin (β-CD) at pH 8.0 (Yang and Kim 2010). β-CD was crosslinked with CMC using TMACB and a model drug, calcein was loaded successfully (Yang and Kim 2010).

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