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Disease, destination, dose and delivery aspects of ciclosporin: the state of the art

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Since its discovery in 1971, ciclosporin has revolutionized organ transplantation and the treatment of autoimmune disorders. The wide array of applications resulting from its clinical efficacy warrant unique administration strategies and varying doses, times of exposure and extents of distribution, depending on target tissue. The poor biopharmaceutical characteristics of low solubility and permeability makes this uphill task even more challenging for the drug delivery scientist. Efforts underway have explored various body routes employing approaches like emulsions, microspheres, nanoparticles, liposomes, iontophoresis and penetration enhancers. This review attempts a brief holistic view of the 'four Ds' (disease, destination, dose and delivery) surrounding this immunomodulator drug.

Over the past few decades, organ transplantation has seen a steady stream of small technical advances and giant leaps forward, like the introduction of ciclosporin (also known as cyclosporine and cyclosporin) to prevent graft rejection. Ciclosporin was first isolated from crude extract of the fungus *Tolypocladium inflatum gams* by Sandoz in 1971 [1]. In November 1983, the FDA approved ciclosporin for prevention of transplant rejection. Wenger [2] reported the complete chemical synthesis of ciclosporin in 1984.

Ciclosporin is a highly lipophilic neutral cyclic peptide consisting of 11 amino acids, seven of which are N-methylated (Figure 1). Its molecular formula is $C_{62}H_{111}N_{11}O_{12}$ and its molecular weight (MW) is 1202.64 Da. It contains four intra-molecular hydrogen bonds, which impart high rigidity to its cyclic structure [3]. This unusual structural property confers a very low aqueous solubility to this drug. The low water solubility of the drug is a serious problem causing undesirable biopharmaceutical properties, such as erratic bioavailability from oral and topical routes.

To overcome this problem, novel water-soluble prodrugs of ciclosporin have been synthesized. These dipeptide-containing prodrugs exhibit differential tendencies for intramolecular cyclization, depending on the chemical and structural features of the dipeptide ester for subsequent release of the parent ciclosporin [4]. One such novel water soluble prodrug – UNIL088 – generated therapeutic concentrations of ciclosporin in the precorneal area immediately after administration into rabbit eyes [5]. This prodrug exhibited good ocular tolerance and is now under preclinical evaluation.

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Pharmacodynamics of ciclosporin

Mechanism of action

Ciclosporin effectively suppresses T-cell-dependent immune reactions (those underlying transplant rejection and some forms of autoimmunity). Ciclosporin forms a complex with cyclophilin, a cytoplasmic receptor protein present in T lymphocytes, and this complex further binds to calcineurin and inhibits Ca^{2+}-stimulated dephosphorylation of the cytoplasmic component of the nuclear factor of activated T cells (NFAT). As a result, the translocation of the NFAT from the cytoplasm to the nucleus of activated T cells is inhibited. Therefore, gene transcription is not activated, and the T lymphocytes fail to respond to antigen stimulation [6].

Therapeutic uses

Ciclosporin has been widely used for the prophylaxis and treatment of graft rejection in almost all types of organ transplantations. It has significantly enhanced the initial and long-term survival of transplant patients. The drug is also effective in the treatment of various systemic and local immune-mediated disorders, but most of these diseases relapse after discontinuation of the therapy, thus maintenance therapy has to be continued for long periods of time, sometimes lifelong [7]. The therapeutic indications of ciclosporin are summarized in Table 1.

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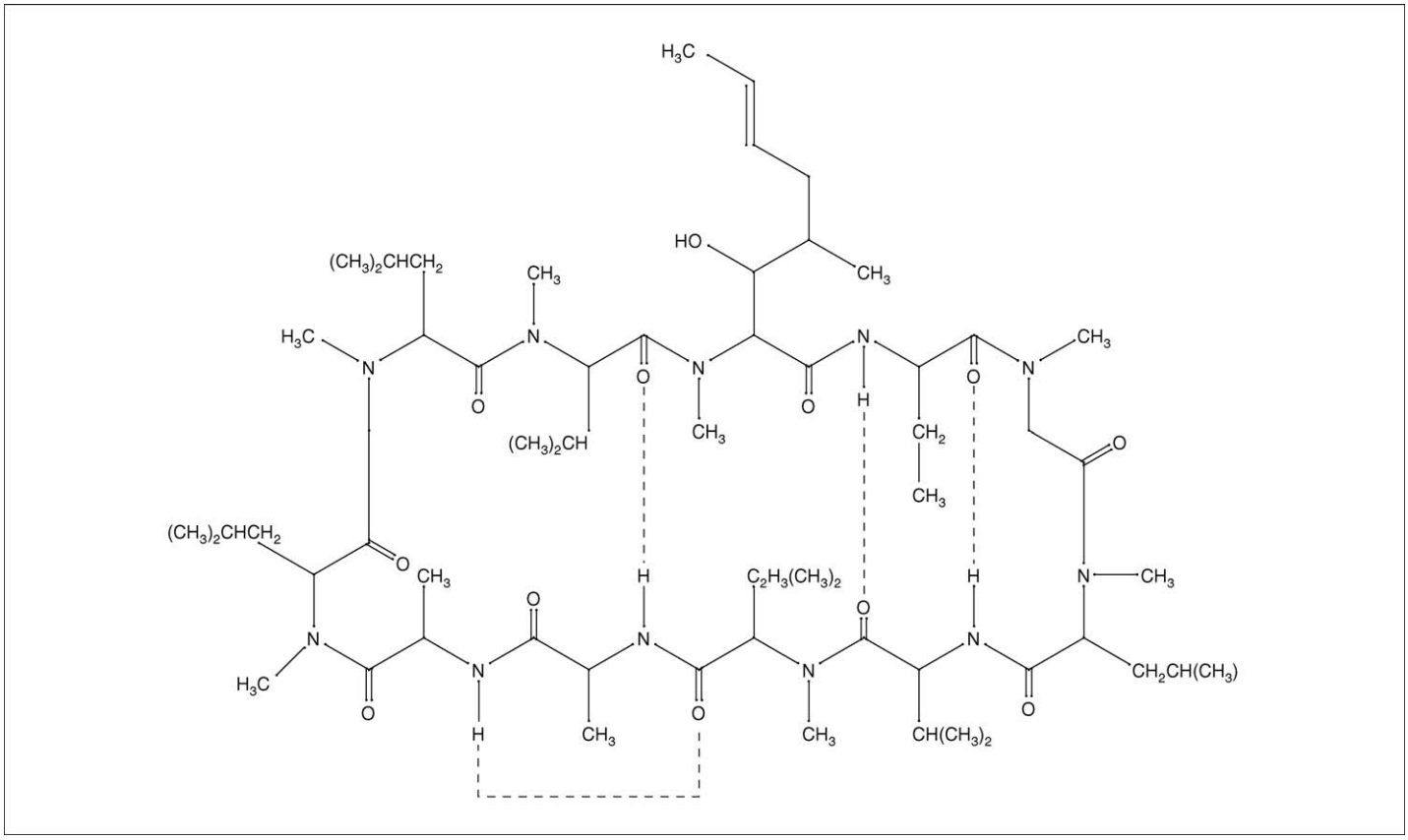

FIGURE 1

Structure of ciclosporin.

Adverse effects

Dose-dependent nephrotoxicity – characterized by an increase in serum creatinine and urea levels – is a major side effect of ciclosporin. Although ciclosporin-induced nephrotoxicity is generally reversible, it can cause irreversible structural changes like interstitial fibrosis in some patients during long term treatment. Therefore, close monitoring of the parameters assessing renal function is required. The mechanisms involved in the ciclosporin-induced nephrotoxicity include increased release of vasoconstrictive factors, such as thromboxane A_2, endothelin and angiotensin II, and decreased release of vasodilating factors, such as prostacyclin and nitric oxide, which lead to intense renal vasoconstriction that often progresses to chronic injury with irreversible structural renal damage [8]. In addition, the increased production of free radicals by ciclosporin also contributes towards the nephrotoxicity as well as other toxic effects like hepatotoxicity and cardiotoxicity [9,10]. The various adverse effects caused by ciclosporin are presented in Table 2.

Dose

Ciclosporin can be administered orally as a liquid-filled capsule or as an oily solution, which is diluted in fruit juice before administration. Concomitant administration of grapefruit or grapefruit juice must be avoided because certain components in grapefruit (bergamottin and 6′,7′-dihydroxybergamottin), inhibit cytochrome P450 3A4 enzyme, leading to increased blood level of ciclosporin, which can results in toxicity [11,12]. The dose of ciclosporin varies depending on the transplanted organ and other immunosuppressive agents administered. For solid organ transplantation, the treatment is started with 10–15 mg/kg/day of ciclosporin. Two weeks after transplantation, the dose is gradually reduced to a maintenance dose of ~2–6 mg/kg/day.

TABLE 1

Therapeutic uses of ciclosporin	
Transplantations	Kidney, liver, heart and lung, bone marrow transplantation and graft-versus-host disease
Systemic immune-related disorders	Rheumatoid arthritis, nephrotic syndrome, myasthenia gravis, aplastic anaemia, autoimmune hepatitis, Crohn's disease and type I (insulin-dependent) diabetes mellitus
Local immune- related disorders	
Ophthalmological disorders	Vernal keratoconjunctivitis, ligneous conjunctivitis, dry eye syndrome, uveitis, Behcet's syndrome and serpgininous choroiditis
Dermatological disorders	Psoriasis vulgaris, atopic dermatitis, pyoderma gangrenosum, alopecia areata, lichen planus and pemphigus erythematosus

TABLE 2

Adverse effects associated with ciclosporin	
Adverse reaction associated with Cremophor® EL vehicle	Anaphylactoid reactions consisted of flushing of the face and upper thorax, acute respiratory distress with dyspnea and wheezing, blood pressure changes and tachycardia
Adverse effects on the different systems	
Urinary system	Nephrotoxicity characterized by fluid retention, raised creatinine and urea concentration and decrease in glomerular filtration rate
Liver and biliary system	Hepatotoxicity
Cardiovascular system	Hypertension, hypermagnesaemia, hyperkalaemia, thrombo-embolic complications, thrombocytosis
Gastrointestinal tract	Non-specific colitis
Central nervous system	Tremor, ataxia, confusion, mental depression, flushing, lethargy, coma, convulsions, leucoencephalopathy, cortical blindness and spasticity or paralysis of limbs
Effect on glucose tolerence	Reduction in insulin production and impaired glucose tolerence
Other adverse effects	Hyperuricaemia, Myopathy, infections, malignancy, gum hyperplasia and hypertrichosis

If the patient is unable to take ciclosporin orally, the therapy can be initiated intravenously (i.v.) with a dose of 3–5 mg/kg/day. In the treatment of autoimmune disorders, lower doses are generally used, and the therapy is generally continued lifelong. The recommended initial dose ciclosporin is 2 mg/kg/day, which can be gradually increased up to 5 mg/kg/day depending on tolerance.

Therapeutic monitoring of ciclosporin

Because ciclosporin is a critical-dose drug with a narrow therapeutic range and variable absorption characteristics, its dosage must be titrated by monitoring of blood levels [13]. Trough ciclosporin level (C_0; blood samples drawn before the next oral dose) has been conventionally used to determine Neoral® dosing. However, trough estimates do not help in predicting accurate dose, so the risk of toxicity or organ rejection cannot be ignored [14].

Estimates of drug exposure using the full area under the time-concentration curve ($AUC_{0–12}$) has been known as a robust predictor of graft loss and incidence of acute rejection. However, the $AUC_{0–12}$ assessment is cumbersome and probably unnecessary because the absorption variability mainly occurs during the first 4 h postdose. Because the maximum immunosuppressive effect of ciclosporin occurs during the first 4 h postdose phase [15,16], monitoring of absorption variability in this period is necessary for making accurate dosing decisions. Accordingly, measuring $AUC_{0–4}$ offers the best combination of accuracy and convenience for assessing absorption variability. However, $AUC_{0–4}$ measurement is impractical in routine clinical practice so ciclosporin concentration 2 h postdose (C_2) monitoring has been adopted as an acceptable single time-point marker for $AUC_{0–4}$ [17]. Large-scale clinical trials using Neoral® C_2 monitoring have demonstrated low acute rejection rates and good tolerability with a low adverse event profile to at least 1 year post-transplant [18].

Biopharmaceutical hurdles

Any drug should have an optimum balance between its hydrophilicity and lipophilicity to permeate and penetrate across various biological lipoproteinaceous barriers so that it gets absorbed and transported to the desired site of action. Ciclosporin is poorly soluble (6.6 μg/ml) in an aqueous medium [19], but is easily soluble in organic solvents. Ciclosporin lacks functional groups that are ionizable in a pharmaceutically useful pH range and therefore manipulation of pH does not enhance its solubility. Furthermore, for the same reason, salt formation, which is a commonly used way of improving solubility, is not feasible. Also, ciclosporin is a highly lipophilic drug [3], having a logP of 2.92. The rigid cyclic structure and high molecular weight of ciclosporin lead to low permeability from all the biological barriers, including gastrointestinal tract, skin and cornea. This unusual structural property together with the low solubility makes it difficult to administer. In having both low solubility [19] and low permeability [20], ciclosporin gets classified as a Class IV drug under the biopharmaceutic classification system [21]. Plagued by poor and erratic bioavailability from oral, transdermal and ocular routes, the delivery of ciclosporin is a challenging task and explains the constant efforts by the pharmaceutical scientists to design effective delivery systems.

Delivery approaches for ciclosporin

Systemic administration of ciclosporin is an effective therapy for the prevention of graft rejection as well as most of the immunoregulatory skin and eye disorders. However, the long term systemic administration of ciclosporin required for the adequate control of local autoimmune diseases (Table 1) often leads to adverse effects. Nevertheless, most of these disorders can be effectively controlled by local administration of the ciclosporin formulations, which reduces the body burden of the drug and minimizes the toxicity associated with the systemic administration. Thus, by integrating the knowledge of the four Ds (as depicted in Figure 2) the therapy of organ transplantation and immune-regulatory diseases can be optimized. The therapeutic need decides the destination, dose and the delivery system. Figure 3 highlights the delivery approaches used for ciclosporin.

Oral delivery systems

Ciclosporin is administered orally, but it undergoes P-glycoprotein (P-gp)-mediated efflux and extensive presystemic metabolism in the gut wall and liver [20,22]. These factors, together with poor solubility and high molecular weight, severely limit its oral absorption. In view of the clinical importance of ciclosporin, much effort has been directed towards designing oral formulations with improved and consistent bioavailability. Different delivery approaches for ciclosporin are depicted in Figure 3.

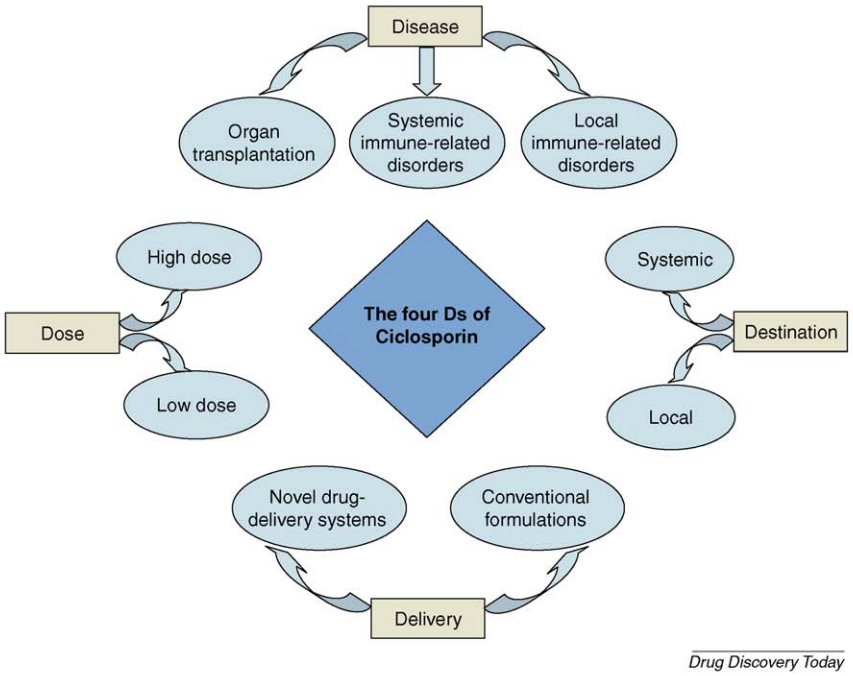

FIGURE 2

Disease, destination, dose and delivery (the four Ds) aspects of ciclosporin. Therapeutic need (disease) is the prime factor that dictates dose, destination and delivery system. High systemic doses of ciclosporin are generally needed for the prevention of organ rejection and in the treatment of the systemic immune-related disorders, whereas relatively lower doses with local administration are desired for the local immune-related disorders.

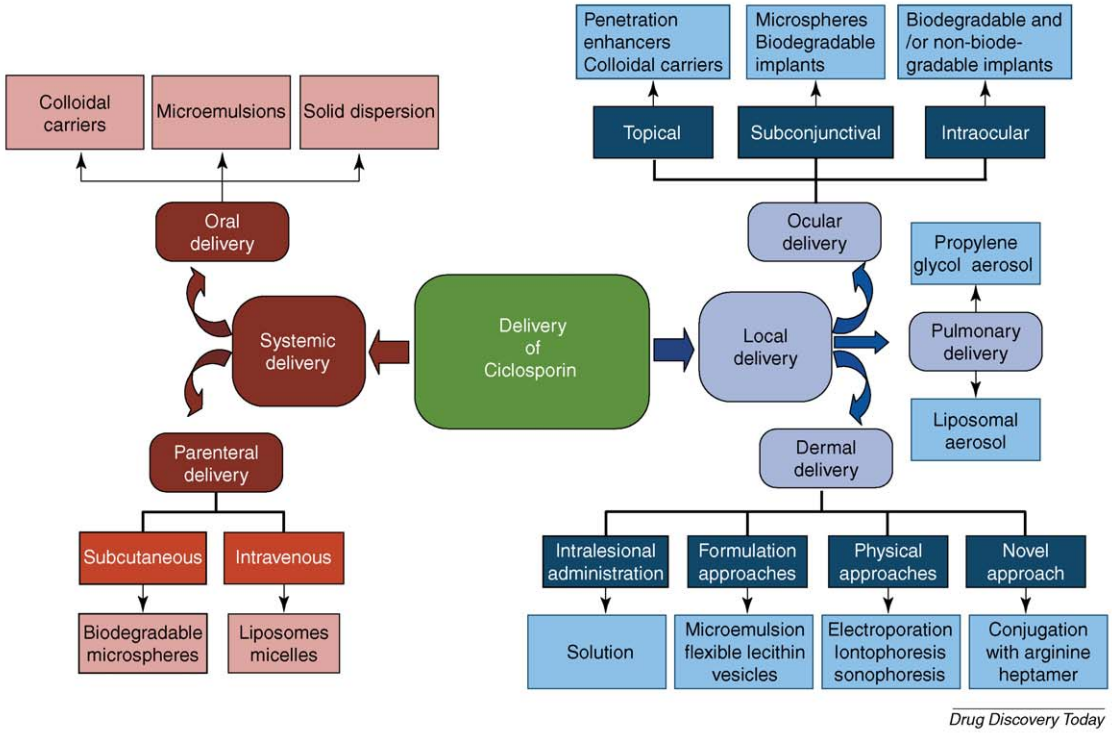

FIGURE 3

Delivery approaches that have been investigated for the delivery of ciclosporin. Different routes, including oral, parenteral, pulmonary, ocular and dermal, have been explored with the use of conventional and novel drug delivery systems in order to achieve the efficient delivery of ciclosporin to the desired site.

Ciclosporin is conventionally available as a soft gelatin capsule or oral solution containing emulsion preconcentrates (Sandimmune®). These formulations show bile-dependent absorption and exhibit significant inter- and intra-patient variability. Thus, a new formulation (Neoral®) was developed which forms a microemulsion with water without action of bile [23]. As a result, the absorption is less influenced by the bile flow, providing improved and more consistent bioavailability.

Microspheres containing solid dispersion of ciclosporin–sodium lauryl sulfate–dextrin improved dissolution rate and bioavailability of ciclosporin in dogs compared with drug powder [24]. Polymeric micelles of polyoxyethylene cetyl ether grafted dextran and hydroxypropylcellulose improved permeability of ciclosporin across Caco-2 cells lines, compared with free ciclosporin, without significant cytotoxicity [25].

Nanoparticulate formulations of ciclosporin have received much attention in recent years. Nanoparticles are preferentially taken up by the M cells of Peyer's Patches, which are part of the lymphoid tissue associated with the gut. The gastrointestinal uptake of nanoparticles is significantly affected by the charge and size of the particles [26,27]. The immunosuppressive activity of ciclosporin is attributed to its selective action on T lymphocytes, which mainly circulate in the lymphatic system. Consequently, targeting the lymphatic system using a nanoparticle approach has been suggested as a possibility to improve the therapeutic efficacy of ciclosporin.

The pH-sensitive nanoparticles of poly(methacrylic acid and methacrylate) copolymer markedly increased the bioavailability of ciclosporin compared with Neoral® in rats [28]. Ciclosporin-loaded poly(isobutyl-2-cyanoacrylate) and polycaprolactone (PCL) nanoparticle formulations exhibited improved immunosuppressive activity *in vitro*. [29]. PCL nanoparticle formulation improved the oral bioavailability of ciclosporin and its uptake by lymphocytes *in vitro* without an increase in adverse effects [30]. Ciclosporin-loaded poly(lactic acid)–poly(ethylene glycol) (PLA–PEG) nanoparticles showed more adequate control of ciclosporin release than conventional PLA nanoparticles [31]. The positively charged nanoparticles of ciclosporin prepared using cationic polymers, such as chitosan HCl or gelatin-A, improved its oral bioavailability compared with Neoral® in beagle dogs. The improved bioavailability could be the result of enhanced electrostatic interaction between positively charged particles and negatively charged mucosal surfaces [27]. Incorporation of ciclosporin into nanoparticulate lipospheres resulted in improved *in vitro* immunosuppressive activity compared with the free drug [32].

Parenteral drug delivery systems

Ciclosporin delivery systems for intravenous administration

One of the major problems associated with i.v. formulation is the toxicity and hemolytic tendency of the Cremophor® EL vehicle that is required to solubilize ciclosporin [33,34]. In addition to toxicities including anaphylactoid reaction, Cremophor® EL also causes leaching of a potential carcinogen – diethylhexylphthalate – from the polyvinylchloride (PVC) tubing of i.v. sets and the PVC containers of i.v. fluids used for infusion of the drug [35,36]. To overcome these difficulties, many research efforts have been made with the main goal of developing formulations that are devoid of Cremophor® EL.

Liposomes are well recognized as carriers for many drugs. The encapsulation of drugs in liposomes often results in distinct changes in their pharmacokinetic and pharmacodynamic properties, leading to improved potency or reduced toxicity of certain drugs. Ciclosporin encapsulated in liposomes showed reduced nephrotoxicity compared with ciclosporin–Cremophor® EL solution in rats [37]. The reduced nephrotoxicity could be the result of lower accumulation of ciclosporin from the liposomal formulation in the kidneys together with the controlled release provided by the liposomal carriers. Liposome-encapsulated ciclosporin has also been shown to reduce urinary kallikrein excretion in rats compared with oily formulation, which is a marker of tubular damage in kidney [38]. Although ciclosporin-loaded liposomes modified with bioadhesive polymer carbopol 941 enhanced the residence time of ciclosporin and achieved twofold higher concentration into the spleen, they did not significantly improve its immunosuppressive efficacy in allogenic rat heart transplantation model compared with standard liposomes [39].

Cholate–lecithin-mixed micelles containing ciclosporin exhibited no significant difference in pharmacokinetic parameters compared with Sandimmune® upon i.v. administration in rabbits, thus presenting a suitable alternative for the Cremophor® EL present in the Sandimmune® [40]. Polymeric micelles of methoxy poly(ethylene oxide)-b-poly(ε-caprolactone) (PEO-b-PCL) showed high thermodynamic stability and provided sustained drug release *in vitro* [41].

Ciclosporin delivery systems for intramuscular and subcutaneous administration

The low and highly variable oral absorption of ciclosporin necessitates the investigation of controlled release systems, which maintain the blood levels of drug within the therapeutic range for a longer time.

Biodegradable microspheres are one possible controlled release delivery system for ciclosporin. Intramuscular injection of ciclosporin loaded PLA microspheres into rats maintained the drug at a high level in the inguinal lymph nodes over one month [42]. In a recent study, ciclosporin loaded microspheres made of poly(lactide-b-ε-caprolactone) PLA–PCL showed a higher initial release of ciclosporin than poly(lactide-co-glycolide) (PLGA). Because the effects of ciclosporin are dose-dependent, the initial burst release might be advantageous in achieving better immunosuppression [43].

Pulmonary delivery systems

Because the normal dose of systemically administered ciclosporin is not able to suppress pulmonary immunoreactivity consistently, ahigher dose of ciclosporin is needed to suppress pulmonary T cells, which might lead to systemic toxic effects. The local application of ciclosporin to the respiratory epithelium using aerosol could achieve higher lung concentrations than through intravenous or oral administration with minimal systemic effects. So, with regards to limiting the systemic effects of ciclosporin and achieving better prevention of acute pulmonary allograft rejection, local immunosuppressive therapy with aerosolized ciclosporin seems to be promising.

The administration of aerosolized ciclosporin prevented pulmonary allograft rejection in a dose-dependent manner in rats [44]. In another study, administration of aerosolized ciclosporin as

propylene glycol dispersion caused dose-dependent reversal of rejection in lung transplant patients [45]. In a recent study, although aerosolized delivery of ciclosporin did not affect the acute rejection, it significantly reduced chronic rejection in lung transplant patients [46]. One such propylene glycol aerosol formulation of ciclosporin, which is currently seeking approval from the FDA, will soon be on the market.

Because a major portion of free ciclosporin is rapidly absorbed into the systemic circulation following aerosolized application to the lungs [47], its incorporation into the colloidal carriers might be advantageous for improving its lung retention. In dogs, aerosolized administration of liposomal ciclosporin resulted in its efficient deposition and retention into the lung, as well as lower levels in blood and the organs [48]. The selective deposition of ciclosporin in the lungs could be helpful in improving immunosuppression and reducing systemic toxicity.

Dermal delivery systems

Site-specific immunosupression has gained much attention in recent years because of its great potential for treating local immunoregulatory skin disorders without causing systemic toxicity [49]. It is always desirable to have a high concentration of ciclosporin in the skin with minimal transdermal permeation, so as to get better immunosupression with lower systemic adverse effects. Site-specific immunosupression can be achieved by topical application of ciclosporin to the skin. However, only moderately lipophilic molecules with a MW of <500 Da can permeate through the stratum corneum [50]. Ciclosporin is a difficult molecule for dermal delivery because it is highly lipophilic and a high MW cyclic compound. Therefore, many efforts have been made to increase the penetration and permeation of ciclosporin into the skin, including the use of formulation approaches, such as penetration enhancers and lecithin vesicular carriers, physical approaches, such as electroporation, iontophoresis and sonophoresis, and novel approachs, such as the use of arginine oligomers as carrier peptides in addition to its direct intralesional administration (Figure 3).

Recently, monoolein, a lipidic penetration enhancer, was found to be effective in improving ciclosporin delivery to the skin. The incorporation of 20–70% monoolein in the propylene glycol solution containing ciclosporin enhanced the delivery of ciclosporin to the skin, with substantially lower transdermal permeation [51]. However, the use of penetration enhancer usually involves pretreatment of the skin, which can cause irreversible change in the nature of the skin.

Vesicular carriers are considered to be important vehicles for the dermal delivery of drugs because they are capable of adsorption and fusion with the stratum corneum, which can promote the accumulation of drugs into the skin. Flexible vesicles (made up of the lecithin and sodium cholate) and conventional vesicles (made up of only lecithin) have been shown to accumulate fairly large amounts of ciclosporin into rat skin [52]. Though both the vesicles were efficient, the flexible vesicles transported more of the ciclosporin to the skin.

Electroporation is a physical approach that involves the application of short high-voltage pulses to the skin to transiently increase its permeability. Ciclosporin was efficiently delivered to the rat skin by electroporation combined with ethanol which was used as penetration enhancer. [53]. Another approach is iontophoresis, which uses an electric field to facilitate the delivery of charged molecules across the skin. Although free ciclosporin cannot be delivered through iontophoresis owing to its nonionic nature, charged carriers like flexible lecithin vesicles were found to be efficient in delivering the ciclosporin to the human skin using iontophoresis [54]. Topical delivery of ciclosporin aided by low-frequency sonophoresis was used successfully for the treatment of patients with alopecia areata [55].

Recently, a novel approach to increasing the transport of ciclosporin into the skin was employed by conjugating ciclosporin to a heptamer of arginine using a pH-sensitive linker to produce R7-ciclosporin conjugate. The topically applied R7-ciclosporin was efficiently transported into cells in mouse and human skin and effectively inhibited cutaneous inflammation [56]. This provides a new promising topical approach for the treatment of inflammatory skin disorders.

Intralesional administration provides an efficient approach for delivering a high concentration of ciclosporin into a diseased site with lower blood levels; it has been shown to significantly improve psoriatic plaques in patients [57]. However, pain at the injection site remains the major drawback of intralesional administration.

Ocular delivery

Ciclosporin has numerous applications in the treatment of severe inflammatory and immune-related ocular disorders. Systemic administration of ciclosporin has been found to be effective in treating many ocular disorders and preventing corneal graft rejection. However, most of these diseases require life-long treatment at relatively high dose to achieve the therapeutic concentration of ciclosporin in the eye, which can lead to the adverse effects. Thus, the local ocular delivery of ciclosporin provides a good alternative to the systemic delivery. At concentrations of 50–300 ng/g of ocular tissue, ciclosporin effectively suppresses the immune response and inflammation in most ocular disorders [58].

Ciclosporin delivery systems for topical administration

The currently available systems for topical administration of ciclosporin use oils, which are poorly tolerated and provide a low ocular bioavailability. This is caused by the high lipophilicity of the oils, which leads to lower partitioning of ciclosporin into the aqueous fluids and cornea. Many formulation approaches, including penetration enhancers, surfactant micelles, anionic and cationic microemulsions, and nanocarriers, have been investigated to increase the ocular bioavailability of ciclosporin.

The efficacy of the penetration enhancer Azone® for improving the delivery of ciclosporin was evaluated in rabbits. Although solution of ciclosporin in Azone® reduced the severity and incidence of graft rejection [59], it was found to be toxic to the corneal epithelium [60]. The use of benzalkonium chloride (0.01%) and Cremophor® EL (10% and 20%) as penetration enhancers resulted in significant enhancement in ciclosporin fluxes across the rabbit cornea. However, although benzalkonium chloride exhibited very good tolerance at this concentration, it induces ocular irritation if used at higher concentration [61].

The micelles of polyoxyl 40 stearate containing ciclosporin provided a 60-fold higher concentration in the cornea when compared with oily solution of ciclosporin after topical application in rabbit eyes [62]. An anionic microemulsion formulation

TABLE 3

Main delivery systems developed for ciclosporin[a,b]

Route	Site of application	Delivery system	Achievements	Status	Brand name (company)
Oral	Oral	Emulsion pre-concentrate for soft gelatin capsule and oral solution	High solubilizing capacity	Approved for clinical use in 1983	Sandimmune® (Novartis)
		Microemulsion pre-concentrate for soft gelatin capsule and oral solution	Improved bioavailability, reduced variability in absorption	Approved for clinical use in 1992	Neoral® (Novartis)
		Microspheres of sodium lauryl sulfate–dextrin	Improved dissolution of ciclosporin and bioavailability		
		Micelles of polyoxyethylene cetyl ether grafted dextran	Enhanced permeability through Caco 2 cell lines		
		pH-sensitive nanoparticles	Enhanced bioavailability		
		poly(isobutyl-2-cyanoacrylate) nanoparticles	improved in vitro immunosuppressive activity		
		PCL nanoparticles	Enhanced lymphocytic uptake, improved bioavailability without increase in toxicity		
		PLA–PEG nanoparticles	Controlled drug release		
		Positively charged nanoparticles	Enhanced bioavailability		
		Nanoparticulate lipospheres	Improved *in vitro* immunosuppressant activity		
Parenteral	Intravenous	Solution of ciclosporin in Cremphor®EL and ethanol	Improved solubilization	Approved for clinical use in 1983	Sandimmune® (Novartis)
		Liposomes	Reduced nephrotoxicity		
		Carbopol 941 modified liposomes	No added advantage over conventional liposomes		
		Cholate–lecithin-mixed micelles	Provided alternate for toxic vehicle Cremphor®EL		
		PEO-b-PCL micelles	Sustained drug release and improved thermodynamic stability		
	Intramuscular	PLA microspheres	Sustained drug release over long time period		
	Subcutaneous	PLA–PCL microspheres	Provided burst release for better immunosupression		
Pulmonary	Lungs	Propylene glycol aerosol	Effective preventing graft rejection in the lung transplant patients	Seeking FDA approval	Pulminiq™ (Chiron)
		Liposomal aerosol	Enhanced retention of drug into the lung.		
Dermal	Topical	Penetration enhancer monoolein	Enhanced dermal delivery with reduced transdermal permeation		
		Lecithin vesicles	Improved ciclosporin deposition into the skin		
		Electroporation combined with ethanol	Improved dermal delivery		
		Iontophoresis with flexible lecithin vesicles	Enhanced transdermal delivery		
		low-frequency sonophoresis	Effective in treating alopecia areata		
		R7-ciclosporin conjugate	Efficient in inhibiting cutaneous inflammation		
	Intralesional	Solution	Effective in treating psoriasis		
Ocular	Topical	Penetration enhancers	Enhanced corneal permeation		
		Micelles of polyoxyl 40 stearate	Higher corneal permeation		
		Anionic microemulsion	Efficient in treating dry eye syndrome	Approved for clinical use in 2002	Restasis® (Allergan Pharmaceuticals)
		Cationic microemulsion	Higher conjunctival and corneal levels with enhanced retention times		
		PCL nanocapsules	High corneal uptake		
		chitosan nanoparticle	Longer retention in cornea, high levels in cornea and conjuctiva		
		Prodrug of ciclosporin UNIL088	Enhanced solubility, good ocular tolerence	Preclinical studies	
	Subconjunctival	PLGA microspheres	High levels in cornea for longer duration		
		Biodegradable implants of PLGA	Improved corneal graft rejection		
	Intraocular	Biodegradable implants of PLGA	improved corneal graft survival		
		Non-biodegradable implants	Controlled release over longer time period	Phase I/II clinical trials	

[a] Grey highlight = based on academic research literature.

[b] Abbreviations: PCL, polycaprolactone; PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); PLA, poly(lactic acid); PLGA, poly(lactide-co-glycolide).

(Restasis®) was developed that could achieve therapeutic ciclosporin concentration in the extraocular tissues upon topical administration to rabbits [63,64]. This formulation significantly improved the signs and symptoms of dry eye disease and exhibited good tolerance in patients in a Phase II clinical trial [65]. Restasis® cleared Phase III clinical trials and received FDA approval in December 2002. Upon topical administration into rabbit eyes, a cationic emulsion of ciclosporin yielded four times higher conjunctival and corneal concentrations compared to the above mentioned anionic emulsion [66]. This cationic emulsion has successfully completed Phase II clinical trials and should soon be submitted to Phase III clinical trials.

Nanoparticles have recently been shown to be promising carriers for the ocular delivery of drugs. PCL nanocapsules achieved five times higher corneal ciclosporin levels compared with oily solution [67]. However, when evaluated in rats, this nanocapsular formulation failed to prolong corneal graft survival as a result of its inability to provide therapeutic levels for an extended period of time [68]. In rabbits, topical administration of novel chitosan nanoparticle formulations achieved and maintained high ciclosporin levels in external ocular tissues for an extended period of time [69]. As mentioned earlier, an electrostatic interaction could be responsible for the long retention period of the nanoparticles.

Subconjunctival administration

Subconjunctival injection of ciclosporin-loaded microspheres of PLGA 50:50 maintained a therapeutic concentration of ciclosporin for 2 weeks in the rabbit cornea [70]. Biodegradable implants of PLGA 85:15 loaded with ciclosporin significantly improved corneal graft survival compared to placebo with good ocular tolerance following subconjunctival implantation [71].

Intraocular delivery

Biodegradable PLGA implants placed in the anterior chamber of rabbit eyes significantly improved corneal graft survival compared with ciclosporin eye drops [72]. Vitrasert®-type non-biodegradable implants loaded with ciclosporin provided prolonged therapeutic concentration in the vitreous following intravitreal implantation. This device effectively suppressed ocular inflammation in a rabbit model of uveitis [73].

Conclusion and future perspectives

Drug delivery technologies have successfully negotiated the difficulties associated with low solubility and permeability of ciclosporin and have enhanced its bioavailability and effectiveness for most routes of administration. Biodegradable polymeric nanoparticles seem to be the most promising candidates for oral delivery and have not only improved its oral bioavailability, but also enhanced the overall therapeutic efficacy by targeting the lymphatic system and providing a sustained release of the drug.

Polymeric micelles and liposomal formulations are effective alternatives to the toxic solubilizing agent Cremophor® EL used in the parenteral formulation. In addition, liposomal formulations have reduced the nephrotoxicity of the drug. A liposomal aerosol of ciclosporin seems to be a very promising formulation strategy for pulmonary delivery because it is capable of efficient lung deposition for long times without higher systemic absorption. Flexible vesicles, penetration enhancer monoolein and R7-ciclosporin can be good formulation approaches for dermal delivery, achieving high concentrations in the skin with minimal transdermal permeation, thereby providing site-specific immunosuppression. For ocular delivery, in addition to prodrugs, colloidal systems like chitosan nanoparticles and positively charged emulsions are the most promising formulation strategies for topical application. However, sustained therapeutic levels in intraocular tissues can only be achieved by biodegradable and nonbiodegradable implants. Thus, despite the need for surgery, biodegradable implants would be the most effective system for treating intraocular disorders.

Thus we have seen that for effective delivery of ciclosporin, one first has to understand the target site, and the concentration of the drug that has to be maintained and for how long. The poor biopharmaceutical properties of ciclosporin require the intervention of novel drug delivery systems, which are at various stages of development. However, at present, only a few formulations of ciclosporin are commercially available and the extensive literature on the delivery of ciclosporin (Table 3) reflects the great medical interest of this challenging drug. In future, with advancement in technology, we shall witness a better management of transplants and therapy of several disorders of the immune system, with concomitant reduction in the adverse effects associated with the drug.

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