

Poster Session 3 – Drug Delivery

201
Controlled release of ketorolac from biodegradable microspheres: in-vitro and in-vivo evaluation

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Ketorolac is a potent non-narcotic analgesic compound with cyclooxygenase inhibitory activity that has been developed for oral and parenteral use for the treatment of moderate to severe postoperative pain. The absorption of ketorolac appears to be both rapid and complete. However, a relatively short half-life (4–6 h) necessitates frequent administration. The purpose of this study is to assess the in-vitro characteristics and in-vivo pharmacokinetics of ketorolac-loaded microspheres.
An oil-in-water solvent evaporation method was used to incorporate ketorolac into poly (D,L-lactide-co-glycolide) (PLGA)-based microspheres (Shiga et al 1996). Hydrophilic polymer, 0.1–0.5% (w/w) hydroxypropyl methylcellulose (HPMC), was added to modify the drug released from PLGA-based microspheres. The morphology of the microspheres was evaluated using scanning electron microscopy (SEM). Drug content and in-vitro dissolution samples were analysed by an HPLC method. SEM examination of microspheres revealed that the surfaces were rougher in PLGA-HPMC preparations as compared with PLGA-based microspheres. Encapsulation efficiency of the process ranged from 60 to 70% for 30% w/w drug-loaded microshperes. The in-vitro dissolution of ketorolac from PLGA-HPMC microspheres indicated that 90% of incorporated drug was released in 168 h, while only 75% of drug was released from PLGA-based microspheres. The more HPMC added into PLGA, the slower the initial released of drug from microspheres.
For in-vivo evaluation in male New Zealand white rabbits, PLGA–0.1% HPMC microspheres were selected and compared with ketorolac injection solution as control. Each formulation was injected intramuscularly at dose of 3 mg kg^{-1} into rabbits, and ketorolac plasma concentrations were monitored for up to 72 h by HPLC. The pharmacokinetic profile of ketorolac solution showed a very fast absorption from the injection site with a Cmax of 11158 ng mL^{-1} at 0.33 h and fast elimination of ketorolac with a t/ of 1.6 h. The pharmacokinetic profile of ketorolac-loaded microspheres showed controlled-release characteristics after intramuscular injection, with a Cmax of 1270 ng mL^{-1} at 2.7 h, and gradually decreased in drug concentration up to 24 h. The relative bioavailability of ketorolac-loaded microspheres to injection solution was 86%. Comparison of the pharmacokinetic profile and the in-vitro drug release profile reflected a faster release of drug from the microspheres in-vivo than from in-vitro.

Shiga, K., Muramatsu, N., Kondo, T. (1996) *J. Pharm. Pharmacol.* **48**: 891–895

202
Preparation and characterisation of an anti-adherent biomaterial coating

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The hindrance of bacterial attachment to a biomaterial surface provides an optimal means of preventing colonization and subsequent implant-associated infections. Hydrogel polymers are regarded as some of the most biocompatible medical device materials to date although they are still susceptible to bacterial adhesion and encrustation. A novel polymeric coating has been designed which has been found to dramatically reduce these phenomena with respect to one of the most commonly used biomaterial coatings, poly(2-hydroxyethyl methacrylate) (pHEMA).
Poloxamers, amphiphilic non-ionic polymers, are A-B-A block copolymers with a central hydrophobic segment of poly(propylene oxide) and two lateral hydrophilic segments of poly(ethylene oxide) (Ivanova et al 2001). Poloxamer 188, with 80% weight of poly(ethylene oxide) groups (Passerini et al 2002), has been chemically modified by the esterification of a terminal hydroxyl group using methacryloyl chloride to give a polymerisable derivative. Subsequent copolymerisation with HEMA provided a novel copolymer with a comb-like structure.
Polymers were prepared with 1%, 5% and 10% modified poloxamer:HEMA (w/w) and the polymerisation reaction was initiated using 0.5% 2, 2'azoisobutyronitrile (AIBN) (w/w). A HEMA control polymer was also prepared along with a pHEMA polymer containing 5% poloxamer (w/w).
The adherence of a hydrophilic *Escherichia coli* isolate to the polymers was investigated in-vitro along with the levels of encrustation of calcium and magnesium salts after suspension in artificial urine over a one week period. The samples were tested in triplicate and the results of the studies are shown Table 1.

Table 1 Adherence of *E. coli* to polymers and encrustation with calcium and magnesium salts

Polymer	Adherence (%)	Encrustation (μg cm^{-2})	
		Magnesium	Calcium
HEMA control	0.0836 ± 0.0031	0.024 ± 0.0002	0.069 ± 0.003
HEMA poloxamer control	0.0205 ± 0.0142	0.021 ± 0.003	0.051 ± 0.004
1%	0.0155 ± 0.0058	0.017 ± 0.003	0.036 ± 0.004
5%	0.0083 ± 0.0050	0.009 ± 0.001	0.014 ± 0.002
10%	0.0072 ± 0.0116	0.002 ± 0.0001	0.009 ± 0.004

Studies have shown that the incorporation of poloxamer 188 into the HEMA hydrogel reduces the percentage adherence of *Escherichia coli* by a factor of 4 and also lowers the encrustation of magnesium and calcium salts to the surface. Copolymerisation of modified poloxamer with HEMA however provides a more resilient surface against adherence and mineral deposition with the 10% copolymer proving to be the most anti-adherent material.

Ivanova, R., et al (2001) *Colloids and Surfaces A: Physicochem. Eng. Aspects* **183–185**: 41–45
Passerini, P., et al (2002) *Eur. J. Pharm. Sci.* **15**: 71–78

203
Ex-vivo perfusion bioassay technique for monitoring the bioactivity of inhalable protein-coated microcrystals (PCMCs)

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Insulin is a hormone responsible for glycaemic control and therefore is essential in the treatment of diabetes. The pulmonary route is an alternative to conventional means of administering insulin therapy. We have developed insulin protein-coated microparticles (PCMCs) suitable for pulmonary drug delivery, but a major problem is monitoring insulin bioactivity (Ross et al 2001). Perhaps not so widely known is that insulin is a vasodilator of vascular smooth muscle. Measuring the vasodilatory effect of insulin, we investigated the bioactivity of an insulin PCMC formulation (1 year old).
The bioactivity of the insulin PCMC, a potential candidate for pulmonary drug delivery, was determined on a Danish Myo Tech P110 pressure myograph system along with a commercial insulin preparation. Twelve-week-old mesenteric resistance arteries from Male Wistar rats were isolated and immersed in a physiological salt solution (PSS) and attached to 2 opposing hollow glass micro-cannula (outer diameter 80 μm). The PSS was gradually warmed to 37°C while the pressure remained at less than 5 mmHg for 1 h. A perfusion interface program was then activated which gradually pressurised the arteries up to 40 mmHg over a period of 15min followed by equilibration for a further 15 min after gassing with 95% O_2/5% CO_2 to achieve a pH of 7.4 at 37°C. After normalisation by two

washes of 123 mM KCl and exposure to 1–10 mM noradrenaline (norepinephrine), the arteries were exposed to intraluminal application of each insulin preparation to produce a full cumulative concentration–response curve (yet to be determined). This was achieved by gradual infusion directly into the lumen via a fetal microcannulae inserted to the tip of the glass mounting cannula, controlled by computer at a constant pressure.

Table 1 shows the attenuation of the contractile response of noradrenaline (norepinephrine) for both the commercial insulin and the insulin PCMCs. It can be seen that the attenuation increases as the concentration of insulin in both preparations increases. The vasodilatory effect of the 2 preparations is similar. The error associated with this pilot study is quite large. However, a more robust experimental protocol has been introduced that significantly reduces this variation (data not shown). In conclusion, the results clearly show that insulin loading onto the microcrystal support is fully active and does not seem to undergo any denaturation.

Table 1 Insulin-mediated relaxation to noradrenaline (norepinephrine) preconstriction

Log M	Commercial insulin	Insulin-loaded PCMCs
−11	100 (0)	100 (0)
−10	84 (7)	84 (14)
−9	65 (23)	68 (22)

100 = 100% constriction. Data are the means of 3 (s.d.), the values do not show a significant difference ($P > 0.05$)

Ross, A. C., et al (2001) *BPC Science Proceedings*: 70

204
Insulin absorption from nasal formulations in sheep

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Previous studies have demonstrated that a lyophilised bioadhesive nasal dosage form can achieve sustained absorption of nicotine in sheep (McInnes et al 2000). The potential application of the lyophilised nasal insert for enhancement of nasal insulin absorption was investigated. Nasal insulin delivery would have the advantage of avoiding the conventional painful injection route.

Nasal formulations were studied in four sheep, as a pilot to a main study. Sheep 1–3 were dosed intra-nasally with 110 IU human insulin in nasal insert (2% K4MP before lyophilisation), powder and spray formulations respectively. Sheep 4 received a subcutaneous (s.c.) dose of 11 IU. Intranasal doses were delivered to the turbinate site of the nasal cavity. Blood samples were collected at –5, 2, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min, centrifuged and the plasma stored at –20C. Blood glucose levels were determined at the time of sampling. Plasma insulin content was determined using an I^{125} radioimmunoassay. Plasma (0.1 mL) was added to antibody-coated tubes, vortexed with 0.9 mL I^{125} buffer and incubated for 18 h. The tubes were then aspirated and washed twice with distilled water. Radioactivity was counted using a gamma counter. Results are shown in Table 1.

Table1 Plasma insulin data

Dosage form	C_{max} (μIU mL^{-1})	T_{max} (min)	AUC[a] (μIU h mL^{-1})	Relative AUC[b]
Lyophilised insert	114.5	120	230.0	73.2
Powder	44.74	20	22.66	7.22
Spray	248.8	20	60.61	19.30
S.C.	187.7	30	314.0	100

[a]Area under the curve. [b]Relative to subcutaneous dose (100%)

The lyophilised nasal insert displayed a high C_{max} and prolonged plasma insulin profile similar to the subcutaneous dose, with a delayed T_{max}. AUC values determined show that the nasal insert formulation achieved significantly greater insulin absorption than the powder and spray formulations. The nasal powder formulation displayed a lower C_{max} followed by a rapid return to baseline levels. These findings for the intra-nasal formulations are consistent with previous observations in sheep with intra-nasal nicotine (McInnes et al 2000). Damage to the sheep's nasal mucosa may explain an anomalous high C_{max} observed for the spray, as the peak was not mirrored by a significant reduction in blood glucose levels.

Plasma insulin data was otherwise confirmed by blood glucose levels. The nasal insert formulation achieved a sustained reduction in blood glucose levels, to 46% of baseline levels. This profile was similar to the subcutaneous dose (48% of baseline), with a slight delay in onset. Powder and spray formulations reduced glucose levels to 75% and 85% of the baseline, respectively. The pilot study suggests the nasal insert formulation is capable of achieving a sustained absorption profile of insulin similar to that of the subcutaneous route.

McInnes, F., Thapa, P., Stevens, H. N. E., et al (2000) *AAPS Pharm. Sci*: **2**: s2121

205
Final year MPharm drug delivery research projects — do they help in the professional development of pre-registration pharmacy graduates?

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Students at the Welsh School of Pharmacy are currently required to undertake an individual research project in their final year, the contribution of which towards the degree is greater than that in the former three year BPharm programme. This increased contribution of the project has been reported as a success by staff in that it has allowed more time for students to reflect on the project. Also, further time has been allocated to research methods and design, searching and evaluating the literature and the analysis and presentation of data (Anon 2001). It was decided to obtain the views of students who undertook research projects in Drug Delivery in the academic session 2000–2001 on the skills learnt during their individual research projects.

In February 2002, questionnaires were sent to pre-registration pharmacy graduates from Cardiff who undertook a final year Drug Delivery project in 2000–2001. Content analysis was used to categorise the responses. A response rate of 71% was achieved; 24% were males. A total of 30% of respondents were employed in hospital and 70% in community pharmacy. Students were asked the question "What skills did you learn or improve during your drug delivery research project that helped with your development as a pre-registration student?" Those responses indicated by more than one graduate are presented in Table 1.

Table 1 Categories of responses received from pre-registration graduates (%)

Able to work independently	(13)
Time management skills	(38)
Scientific writing skills	(13)
Presentation of scientific data	(8)

Other responses received from single respondents were: aseptic techniques, critical literature evaluation, copying with conflict, innovation, self-motivation, problem-solving, IT skills, team work, coping with pressure, information searching. Three students stated 'None' and all three were females undertaking community pharmacy pre-registration year training.

Although three students stated their projects resulted in no skills having been learnt, many graduates were able to identify a number of skills that were learnt or improved during their Drug Delivery project which, in their view, helped in their

professional development. A study investigating students' views on small group research projects concluded that students appreciated the significance of their projects to their future careers in pharmacy (Converse at al 1999). Our findings appear to support this conclusion and indicate that the majority of respondents from our sample acknowledge the importance of specified transferable skills learnt and developed while at university and are able to see a relevance to their pharmacy careers. Clearly, further work is required to establish whether or not the findings are generalisable between cohorts of students from the same school of pharmacy, graduates from different schools and also those undertaking research projects in different areas of pharmaceutical, clinical and social sciences.

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Converse, C. A., et al (1999) *J. Pharm. Pharmacol.* **51** (Suppl.): 198

206
Biochemical and functional evidence of P-gp expression in the lung alveolar epithelial barrier

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P-glycoprotein (P-gp) is a member of the ATP-binding cassette superfamily of transport proteins that serve to transport a variety of molecules ranging from ions to proteins across cell membranes (Gottesman & Pastan 1993). In man, two P-gp genes have been cloned — MDR1 and MDR3. The former is constituitively expressed in the enterocytes of the small intestine, proximal tubules of the kidney and the luminal membranes of endothelial cells forming the blood–brain barrier. Based upon the tissue distribution of this efflux pump within important pharmacological barriers, its role in the protection of the organism from harmful compounds (Schinkel et al 1997), and the fact that the alveolar region of the lung is in constant contact with inhaled xenobiotics, leads to the hypothesis that P-gp is expressed in the alveolar blood-gas barrier, no previous published studies have addressed this.

In this study, expression and microanatomic localisation of P-gp in primary isolates of alveolar type II cells and in-vivo lung tissue were addressed using a combination of flow cytometry and immunocytochemistry. For analysis of P-gp protein expression rat and human primary alveolar epithelial cultures were probed with the monoclonal antibodies C219, and MRK-16, respectively. In addition the functional expression of P-gp in primary rat ATII cells and select control human cell lines was examined using a specific P-gp substrate rhodamine-123, following a previously described method (Lee et al 1994). The polarised nature of drug efflux was assessed by the characterisation of bi-directional radio-labelled vinblastine transport across alveolar cell monolayers cultured on semi-permeable supports. Studies were undertaken in the presence or absence verapamil.

Immunocytochemistry undertaken using whole rat and human lung tissue revealed the presence of P-gp within the alveolar epithelium. P-gp expression in isolated primary rat alveolar cells was validated using the rt-PCR methodologies utilising gene-specific primers. Flow cytometric distributions of immunofluorescence of rat primary alveolar epithelial culture (192 h post seeding) showed 1.4 fold greater fluorescence for the monoclonal anti P-gp antibody compared to the isotypic control lending further verification to the existence of P-gp in the alveolar epithelium. Permeability coefficients for vinblastine transport across alveolar cell monolayers were calculated as 1.77 and 5.71×10^{-6} cm s^{-1} in the apical to basolateral (A→B) and basolateral to apical directions (B→A) respectively. In the presence of a P-gp inhibitor (40 μM verapamil) vinbastine permeability in the B→A direction was reduced to 2.73×10^{-6} cm s^{-1} whereas permeability in the A→B direction was unaffected.

Our results identify the functional expression of P-gp alveolar epithelial cells. Furthermore the polarised transport of vinblastine across monolayers of rat primary alveolar cells indicates the active excretion of potentially toxic waste products of normal metabolism and xenobiotics (drugs and inhaled environmental pollutants) from the alveolar epithelial cell back into the alveolar airspace away from the systemic circulation. An understanding of the barrier properties of the alveolar epithelium with respect to the function of drug efflux pumps such as P-gp has important implications for systemic drug delivery via the pulmonary route and may ultimately expand the number of therapeutics delivered through the lungs.

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Lee, C. S., et al (1994) *Mol. Pharmacol.* **46**: 627–638
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207
Recombinant caveolin-1 expression systems in the study of caveolae-mediated macromolecule endocytosis

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Caveolae are morphologically evident as omega-shaped invaginations of the plasma membrane. They may also exist in a variety of other forms including flattened domains. At least in some cell types, caveolae appear to undertake the endocytic and transcytotic movement of macromolecules, and indeed microbes and microbial toxins. A principal component constituting the membranes of caveolae in non-muscle cell types is caveolin-1, a key protein influencing the structural properties of caveolae. However, the universality between cell types of caveolae detachment from the plasma membrane to mediate endocytosis is still controversial. Beyond this, questions arise as to the rate and cargo-carrying capacity of caveolae, and the constitutive versus ligand-stimulated nature of caveolae internalisation. In the pharmaceutical sciences two key barriers where caveolae could be considered as worthwhile targets to be exploited for the enhanced delivery of macromolecule therapeutics are the lung alveolar type I epithelium (the limiting barrier for inhaled macromolecule absorption), and the brain microvascular endothelium, the anatomic basis to the blood–brain barrier. To address some of these questions within the pharmaceutical sciences we have begun to exploit recombinant systems in combination with more traditional biochemical pharmacology approaches.

Primary rat lung alveolar epithelial type II cells (ATII) were isolated and cultured over an 8 day period within which they undergo transition to an alveolar epithelial type I cell (ATI) phenotype. Like their in-vivo counterparts, the in-vitro ATII cell displays low to neglible caveolin-1 and no morphologically determined caveolae, while the in-vitro ATI cell displays high expression and morphological evidence of caveolae formation. Using both fluorescent (FITC-label quantitated for each cell by FACS) and radioactive (^{125}I-label) BSA probes the ATI cells showed a 7-fold greater BSA cell association compared with the ATII cell. This association was inhibited upto 85% by reduced temperature (4°C), the selective caveolae inhibitor, filipin, and also by inhibition of the SNARE complex. Filipin had no effect upon BSA association in the caveolae-negative ATII cells or upon the ATI cell association of the clathrin probe, transferrin. Plasmid systems were constructed containing inserts coding full length human caveolin-1 protein (an ecdysone-inducible mammalian expression system - pIND/pVgRXR system, and a CMV driven pTarget mammalian expression vector). Transfection of a constitutive caveolin-negative cell line, HEP3B, led to the expression of caveolin-1, formation of caveolae, and a significant increase in the cell association of FITC-BSA (up to three-fold higher than respective control treatments). This increased FITC-BSA was abolished by filipin treatment and low temperature. While these increased cell associations are indicative of increased internalisation they could also still reflect the trapping of macromolecule with tubulo-vesicular caveolae organelles that remain contiguous with the extracellular environment. To address these latter issues in our target barrier cells live-cell imaging is being explored using N- and C-terminally linked GFP chimeric

caveolin-1 protein constructs (pcDNA3.1/NT-GFP-TOPO and pcDNA3.1/CT-GFP-TOPO).

In conclusion, in-vitro ATI cultures functionally express caveolae and are able to mediate the increased cell association of BSA. Defining the exact nature of caveolae membrane kinetics and dynamics requires the use of recombinant expression systems and live cell imaging techniques.

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208
Evaluation of an immortalised brain capillary endothelial cell line, b.End3, to serve as a model for drug uptake studies at the blood–brain barrier (BBB)

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In-silico and experimentally determined physico-chemical parameters are useful high-throughput profiling tools to assess the permeability of a given barrier to xenobiotics (Kerns 2001). However, for a number of reasons (e.g. cellular architecture, metabolism and transporter functions) biological models still have a key role in molecule selection. Biological models are essential for mechanistic studies addressing the potential of carrier-mediated pathways in barrier permeability. The criteria to judge the appropriateness cell culture models of the BBB have been discussed recently by Gumbleton & Audus (2001). For transendothelial BBB permeability experiments the primary or low passage bovine or porcine brain microvascular cell systems seem to offer the only current viable models (Gumbleton & Audus 2001), although their use requires a high level of technical and time resource. The only brain microvascular continuous cell line available commercially is the immortalised mouse cell line b.End (clones 3 or 5). Here, in comparison to 1st passage porcine brain model, we have assessed the restrictive nature of b.End3 cell monolayers to the transendothelial penetration of a paracellular probe, sucrose, and a transcellular probe, propranolol. Further, we have evaluated the potential usefulness of b.End3 cells in experiments that adopt an alternative study design involving solute uptake as the endpoint. For the latter, we have characterised the functional expression of key BBB transporters in the bEnd3 cells, including the glucose transporter - GLUT1, the large neutral aminoacid transporter - LAT1/4F2hc, and P-glycoprotein (P-gp).

Transendothelial studies were undertaken with confluent b.End3 monolayers grown on Transwell inserts. Transendothelial electrical resistance (TEER) of the native monolayers approximated 30–50 Ω cm^2 , with modulating conditions such as astrocyte (C6 cells) conditioned media (ACM), astrocyte co-culture, or the use of cAMP modulators failing to result in TEER exceeding 130 Ω cm^2. In contrast the 1st passage porcine BBB cell model (PBCEC) achieved TEER between 600 and 900 Ω cm^2. None of the b.End3 monolayer conditions resulted in acceptable discrimination between propranolol and sucrose probes, e.g. b.End3 + ACM + cAMP modulation resulted in permeabilities ($\times$ 10^{-6} cm s^{-1})for propranolol and sucrose of 23.4 $\pm$ 5.9 and 16.4 $\pm$ 5.2, respectively. The equivalent values for the PBCEC model were 18.4 $\pm$ 0.7 and 3.25 $\pm$ 1.0. In agreement with in-vivo estimates and data from other cell lines the Michaelis–Menten parameters, K_m and V_{max}, for D-glucose transport via GLUT1 were 16.4 mM and 7.55 nmol/mg protein/10min, respectively. Similarly, for l-phenylalanine transport via LAT1/4F2hc the K_m and V_{max} were 16.7 μM and 439.9 $\pm$ 19.6 pmol/mg protein/10min. Intriguingly LAT1 function was modulated by ACM with decreases in the affinity to a K_m of 48.3 $\pm$ 19.6 μM. The b.End3 cells also expressed functional P-gp as evidenced by flow cytometry assays using the classic P-gp substrate rhodamine-123 and the inhibitor verapamil.

In conclusion, monolayers of b.End3 do not represent a model for transendothelial BBB transport investigations. The cells, however, functionally express transporters of interest in studies of BBB solute or drug uptake, that will allow mechanistic issues of BBB carrier-mediated transport to be addressed.

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209
Vesicular delivery of acetazolamide in glaucoma

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Acetazolamide is used orally for the reduction of IOP (intraocular pressure) in patients suffering from glaucoma. It is used in the pre-operative management of closed angle glaucoma or as an adjunct therapy in the treatment of open angle glaucoma. To obtain the desired lowering in IOP, large oral doses of acetazolamide are used, and this usually results in a wide array of side effects due to the wide distribution of the enzyme in all body organs, the most common of which are diuresis and systemic acidosis (Everitt & Avron 1990). In some cases severe dyscrasias may also occur. Scientists throughout the world have attempted to formulate topical formulation of acetazolamide by adapting a number of approaches to enhance its ocular bioavailability. These include use of higher concentration of the drug (Flach et al 1984), multiple dosing, salt or modified form of the drug, or different drug delivery systems including impregnated contact lenses (Friedman et al 1985), gels (Manners et al 1993), cyclodextrins (Loftsson et al 1994), liposomes (El-Gazayerly & Hikal 1997) and increased viscosity of the vehicle (Kaur et al 2000).

The potential advantage of liposomes as drug carrier appears well established. Encapsulation of the drug in the vesicular structures can protect the drug from enzymatic degradation, prolong their residence time, control release rate and improve transcorneal penetration (Lee et al 1985). Niosomes (non-ionic surfactant vesicles), while similar in physical properties, have higher stability, a lower cost and a greater ease of preparation (Saettone et al 1996).

Niosomes of acetazolamide were prepared using different methods including film hydration, solvent evaporation and reverse phase evaporation method. These methods were compared based on entrapment efficiency, drug leakage and aggregation behaviour, so as to obtain efficacious vesicular dosage forms of acetazolamide. To increase the corneal residence time of the drug, charge inducers were also added. Niosomes thus prepared were incorporated into an ocular formulation in the form of eye drops using appropriate formulation additives like vehicle, preservatives, etc. In-vitro/ex-vivo release studies were carried out using both dialysis membrane and pig cornea. At the same time the formulation was characterized for its physicochemical properties (viscosity, osmotic pressure and pH) and stability studies.

The topical ocular formulation of acetazolamide was possible using vesicular drug delivery system. Using this approach, the bioavailability of the drug can be enhanced and at the same time the side effects related to oral delivery can be reduced significantly.

Thus it was concluded that vesicular systems can emerge as potential formulation for topical ocular drug delivery.

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