Project Proposal - Dr Adrian Morse

An Investigation into the Use of Liquid Crystals for Controlled Release Drug Delivery Systems

The general aim of this project is to investigate the use of liquid crystals as controllable diffusion agents in implantable drug delivery systems. Controlled release can increase the efficiency of drugs, thus speeding patient recovery and reducing both side-effects and healthcare costs. The majority of controlled release devices produced thus far have release rates that are either constant or decay with time. For certain drugs, however, efficacy may be improved if the release is pulsed. The unique behaviour of liquid crystals gives a mechanism by which such pulsing can be achieved.

To date there have been only a few worldwide studies of controlled release drug delivery systems based on liquid crystals, although these studies have shown great potential. There have, however, been many studies of liquid crystals in optical displays and in surfactant chemistry (soaps and detergents). This project will concentrate on the material aspects of liquid crystals as mediators in controlled release drug systems, although the project will necessarily involve collaboration with researchers in the fields of pharmacy, chemistry and biology.

Controlled Drug Release - An Overview

The development of new and more potent drugs in recent years has encouraged the pharmaceutical industry to focus its attention on the design of new drug delivery systems. There are a number of reasons why interest in controlled release drugs has grown [1]. Firstly there has been an emergence of genetically engineered pharmaceuticals, such as peptides and proteins, that often cannot be delivered orally and require delivery to the body in a precisely controlled manner without invoking immune response or biological inactivation. Secondly, controlled release drug delivery can maintain blood plasma levels in a therapeutically desirable range and adjust drug delivery patterns to meet the varying demands of endogenous rhythms. Thirdly, there are the possibilities of re-patenting old drugs by applying the techniques of controlled release drug delivery systems.

Conventional methods of drug delivery, whereby single doses are administered at regular time intervals, cannot maintain a constant specified drug concentration in blood plasma. A plot of drug concentration in blood plasma as a function of time is characterised by an initial period of increasing concentration followed by a period where the drug concentration decreases. The rise/fall rates depend on factors such as the method of drug delivery and the presence of food, posture, gastric emptying times and diurnal rhythms. As a result, the time of onset, intensity and duration of drug action are unpredictable. Similarly, the time taken for the drug to be eliminated from the body by metabolism or excretion can vary widely. When a second dose is administered, the blood plasma drug concentration levels begin to rise again, producing a 'saw-tooth' drug concentration profile (figure 1). It is clear that problems may arise for those drugs with a small therapeutic range. The aim of controlled release drug delivery systems is to avoid these variations in blood plasma drug concentration and hence eliminate any periods in which the drug concentration is too low to be effective or so high that the patient is subjected to any unnecessary side-effects.

Rationale for Implantable Drug Delivery Systems

The main advantage that implantable systems have over conventional oral delivery systems is that the gastrointestinal tract (GIT) is avoided. This means that the variables associated with the GIT, such as gastric emptying time, pH variation and enzymatic and bacterial action, are avoided [1]. This is important for drugs that have poor oral absorption and for those, such as the new protein and peptide drugs, which

are metabolised in the GIT. Other advantages of implantable systems include the possibility of administering drugs with short half lives, the possibility of better drug targeting through implantation near the site of action, and the elimination of regular administration. There are also psychological advantages to the patient, who experiences less pain, less anxiety and less disruption of daily routine.

There are of course also disadvantages, such as the need for surgical implantation, biocompatibility of the implanted materials, sterilisation procedures, and cost of manufacture. The many advantages of implantable drug delivery systems must be weighed against these disadvantages.

Drug Release Mechanisms in Implantable Systems

Implantable rate-controlled drug delivery systems can be classified in three groups:

i) pre-programmed ii) feedback regulated iii) externally modulated

The pre-programmed systems are by far the most common. They are usually controlled by diffusion processes. In *reservoir* systems, the drug is in a central reservoir and diffuses through a surrounding membrane [2]. In *matrix* systems, the drug is spread throughout a polymer matrix [3]. The diffusion rates of both systems can be made to give zero order release kinetics by manipulation of the device geometry.

Feedback regulated systems are perhaps the ultimate aim of controlled drug delivery. The system has the ability to monitor the surrounding chemical environment, process the information, and modify drug release accordingly [3]. Such systems are in the experimental stage.

Externally modulated devices, in which drug release is activated by external stimuli, are still, like feedback regulated devices, in the experimental stage. Such devices are the main focus of this proposal. The aim of these systems is to control the rate of drug delivery by the regulation of an external force, usually operated by the patient, so that drug levels can be increased on demand. The main mechanisms under investigation include temperature changes, electric and magnetic field effects, ultrasound, and ultra-violet irradiation [4].

To date, there have been only a few studies in the area of externally modulated devices. Magnetically modulated devices have been demonstrated based on a dispersion of drugs and magnetic beads within a polymer matrix [5]. Electrically controlled devices have also been demonstrated [6,7]. These are based on the swelling effect of electric fields on a hydrogel, or on the action of the electro-osmotic effect on membranes. There have also been studies on ultrasound controlled devices, which are based on the erosion of a polymer matrix due to acoustic cavitation [8], and on temperature controlled devices, which rely on drastic volume changes in certain polymers as function of temperature [9]. Liquid crystals will now be introduced before their use in externally modulated implantable drug delivery systems is discussed.

Liquid Crystals

Liquid crystals [10] are materials that do not pass directly from the solid phase to the liquid phase, but show one or more intermediate phases. These ‘liquid crystal’ phases are true thermodynamic phases and possess a state of order in-between those of crystalline solids and conventional liquids. The phases can form as a function of concentration in a solvent and/or as a function of temperature. The origin of such phases is the presence of anisotropic forces around certain organic molecules, which leads them to self-assemble. The molecular anisotropy causes anisotropy to appear in many of the physical parameters of the bulk system, unlike conventional liquids, which are isotropic. For example, anisotropy in the optical behaviour can make the materials birefringent, and anisotropy in the dielectric properties can make the molecules respond to electric fields by rotating. In liquid crystal display devices, the birefringence is quickly altered by rotating the molecules with an electric field - with the addition of polarisers the viewer sees a corresponding change in the amount of light passing through the device.

The type of liquid crystal phases that form depend primarily on the size and shape of the constituent molecules. In fact, a single material can show many liquid crystal phases, ranging from highly ordered crystal-like phases to the *nematic* phase, in which the only long-range order is in the orientation of the molecules. A typical heated system might melt from a crystal into a highly ordered liquid crystal and then undergo another enthalpy change on entering a nematic phase. On further heating, the system would become a conventional isotropic liquid. Such *thermotropic* liquid crystal phases form solely as a function of temperature. The molecules of thermotropic liquid crystals may be low molar mass or polymeric.

Liquid crystals that form as a function of concentration (as well as temperature) are called *lyotropics*. These phases form due to the self-assembly of amphiphilic molecules, which contain both hydrophobic and hydrophilic entities. Their appearance is widespread in the detergent (surfactant) industry where products exploit their ability to reduce surface tension and remove oily deposits.

Each different lyotropic or thermotropic phase has its own self-diffusion and viscosity coefficients, and these coefficients will depend on the direction of measurement through the bulk system.

Liquid Crystals in Controlled Release Drug Delivery Systems

Liquid crystals are ideal candidates for use in externally regulated controlled release drug delivery systems for two principal reasons. Firstly they show tremendous responses to applied stimuli such as temperature, electric and magnetic fields and ultraviolet radiation. Such properties as diffusion coefficients, viscosity, rheology, and elasticity can be carefully controlled *in situ* [11]. Secondly they are abundant in biology [12]; cell membranes, DNA and bile are just a few examples of liquid crystal systems in the body. This abundance means that the problems of finding biocompatible materials to use in implants are minimised.

The majority of work undertaken in this area has concentrated on the use of lyotropic liquid crystals in *sustained* release systems, which release drugs over many hours [13], as opposed to a responsive release to external stimuli. In fact, lyotropic liquid crystals are also being investigated with a view to their use in controlling the release of drugs from creams applied to the body [14]. As far as liquid crystals in externally regulated systems are concerned, there have been few studies. A Japanese group led by Nozawa [15] has been looking into the possibilities of using liquid crystals to develop temperature-responsive drug delivery systems based on the change of diffusion coefficient with phase change. Bhasker *et al* [16] have been examining the effects of electric fields on liquid crystalline membranes – in which a molecular reorientation with respect to the membrane wall adjusts the diffusion rate of drugs through this wall. Other electric-field studies on liquid crystals for controlled drug release have been carried out by Chen [17] at the University of Toronto, and by Himmelstein [18] at the Nebraska Medical Centre, U.S.A. Basic studies on the use of ultraviolet radiation to control liquid crystal based drug delivery are being carried out at the University of Manchester [19]. Ultraviolet radiation can cause a *cis*-to-*trans* molecular reconfiguration in photochromic liquid crystals, and a subsequent change in diffusion coefficients in such systems.

Proposal Specifics

The main aim of the proposed project is a general study of the use of thermotropic and lyotropic liquid crystals for controlled release drug delivery systems. The study would involve experiments to quantify the response of biocompatible liquid crystals to temperature, electric and magnetic fields and ultraviolet radiation and *in vitro* experiments to determine the diffusion rates of supplied drugs through membranes and polymer matrices based on these liquid crystals. The emphasis would be on the physics of drug delivery. Liquid crystal materials would be bought in or synthesised in collaboration with other organisations. Drugs would be bought in or obtained in collaboration with pharmaceutical companies. High molecular weight drugs may be obtained in cooperation with the envisaged macromolecules group. *In Vivo* experiments would be carried out in arrangement with hospitals and pharmaceutical companies.
Diffusion studies would primarily be performed in the laboratory using a spectrophotometer, but could be supplemented with studies using nuclear magnetic resonance and neutron radiation facilities [20]. Viscosity

measurements would be performed in the laboratory using a cone and plate viscometer. Sample preparation and liquid crystal phase identification would be performed in the laboratory using a differential scanning calorimeter and a polarising optical microscope.

Group Interaction

The research group interactions within the new university can be shown schematically below:
[IMAGE]

Contacts outside the university could include the following:

- Departments specialising in liquid crystal synthesis, such as those in Zaragoza University, CSIC-Zaragoza, Southampton University* (UK), Manchester University* (UK), and Hull University* (UK).

- Departments specialising in liquid crystal materials research such as those in la Universidad del Pais Vasco, and la Universidad Politecnica de Madrid, Manchester University* (UK) and the Materials Science Centre (polymers group) at UMIST* (UK).

- Chemical companies in Spain and abroad which might produce liquid crystals such as Merck, Raychem, Chisso, Nissan Chemical, Hoechst and Unilever.

- Interested drugs companies in Spain and abroad such as CPI (Alicante), Viviar (Region Valenciana), Gamir (Region Valenciana), Quimica Farmaceutica Bayer (Barcelona), Instituto Berna de España (Madrid), Esteve Química (Madrid), 3M Healthcare* (UK) and ICI (UK).

- Hospitals within and possibly outside Spain.

- The mentioned groups currently engaged in liquid crystal research for controlled drug delivery [13-19].

Those organisations with which I already have contacts are denoted by an asterisk *. I also have contacts within most of the liquid crystal research groups in Britain and am familiar with many groups from around the world. In addition, I am familiar with the large scale facilities for x-ray and neutron diffraction in the U.K. and France.

References:

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6. D'Emanuele, A. *et al*., Release of drugs by means of an electrophoretically modulated delivery system, Proceed. Inter. Symp. Cont. Rel. Bioact. Mater. 16, 1989, pp 45-46.
7. Kost, J and Langer, R, Responsive polymer systems for controlled delivery of therapeutics, Trends in Biotech. 10, 1992, pp127-131.
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11. Engstrom, S *et al*, Liquid crystal phases as delivery systems for drugs I, Proceed. Intern. Symp. Cont. Rel. Bioact. Mat. 15 1988, pp 105-106.
12. Bodde, HE, *et al*, Liquid crystal creams for controlled skin moisturisation, Proceed. Intern. Symp. Cont. Rel. Bioact. Mat. 15 1988 pp 280-281.
13. Nozawa, I, *et al*, Preparation of thermo-responsive membranes I, J. Biomed. Mat. Res. 25, 1991, pp 577-588.

14. Bhaskar, BK *et al*, Effect of an applied electric field on liquid crystalline membranes: control of permeability. J. Mem. Sci. 24, 1985, pp 83-96.
15. Professor Yu Chen, Department of Chemical Engineering and Applied Chemistry, Toronto University, Canada.
16. Professor Ken Himmelstein, Department of Pharmacy, University of Nebraska Medical Centre, Omaha, USA.
17. Dr Tony D'Emanuele, Department of Pharmacy, Manchester University, UK.
18. For example: Institut Laue Langevin, Grenoble, France and Rutherford-Appleton Research Centre, Abingdon, UK.

(Nominal) Four Year Plan

1st year	0-6 months	Build laboratory, assemble equipment, establish contacts within and outside university (ongoing), review literature (ongoing).
	7-12 months	Commence basic experiments in controlled drug release (mimic other research groups in first instance), apply for grants from local, national and international sources (ongoing).
2nd year	0-6 months	Take on first PhD. students, publicise group within and outside university (ongoing), strive for involvement in European Union projects, continue basic experiments to mimic other research groups, attendance at relevant conferences (ongoing).
	7-12 months	Begin original investigation.
3rd year		Take on more PhD. students. Produce first published paper. Continue original investigation.
4th year		Continue original investigation. Produce more published papers, consider the future direction of the laboratory and growth prospects (possible entry into associated areas e.g. studies of the effects of electric and magnetic fields on cells).

Equipment Necessary for Project

I) Minimum Requirements

Laboratory (with sink unit and blackout curtains) + one office + phone + networked computer

Fixed assets: approximate price in pesetas (x 1000)

polarising microscope	2000
ultraviolet radiation accessory for microscope	600
camera and microphotograph kit	60
precision heating stage and controller	1000
photodiode and amplifier	40
digital function generator	260
cathode ray storage oscilloscope	380
high voltage wideband amplifier	30
digital multimeter	200
cone and plate viscometer	1000
diffusion flowcells	2 x 60
high-strength permanent magnets	10
1 Tesla electro-magnet	200
differential scanning calorimeter	1700
spectrophotometer + dedicated p.c.	1600
office based personal computer	300
laser printer	100
software (word processing, graphs, data	300

analysis)	
specialist books	60 + ?
sample preparation area:	
fridge	30
specialist sample handling equipment	30
microbalance	500
hot plate with magnetic stirrer	45
ultrasound cleaning bath	200
drying cabinet for glassware	110
general glassware	40
TOTAL	10915 +

"Disposable" assets:

sample cell construction materials	40 p.a
liquid crystal supply (if bought in)	400 p.a
drug supply	?
polymer matrix material	?
electrode material	40 p.a
TOTAL	480 + p.a

II) Very Useful, but Non-Essential, Items

Colour inkjet printer for presentations etc.	100
mini-library area	?
laminar flow cabinet for sample preparation	220

III) Shared Resources Expected

photocopier, fax machine, internet server provider, stationary supplies, library access, general mechanical workshop facilities (lathe, drill etc.), overhead projector, scanner, toxic fume extraction cupboard and possibly a small electronics component store.

My suitability for running the project:

My curriculum vitae will point to the fact that I have always worked in multidisciplinary teams in both academic and industrial environments, a feature essential to the proposed project. I have much experience in thermotropic and lyotropic liquid crystals and am familiar with many of the experimental arrangements to measure the material characteristics of these systems. My time as a lecturer, and more recently as a postdoctoral researcher, has given me valuable experience in the supervision of projects and people.
I would also bring with me a detailed knowledge of alternative experimental procedures practised in the UK. I already have contacts in many relevant institutions and would be keen to promote new ones. I am open-minded, adaptable and am always keen to learn and implement promising new ideas.