PREFACE

This dissertation is being submitted in consonance with the rules and regulations for the degree of Doctor of Philosophy in Pharmacy of University of North Bengal, West Bengal and the entire work embedded in this dissertation was undertaken by the present author in the Department of Pharmaceutics Laboratories of Himalayan Pharmacy Institute, Majhitar, Rangpo, East Sikkim 737136.

This work was primarily aimed at studies on formulation development and evaluations of anti-HIV bioadhesive microencapsulated vaginal gel delivery systems.

This project plan was aimed at formulation of extended release Zidovudine (AZT) loaded anti-HIV bioadhesive microencapsulated vaginal gel (AZMBVG) using ethyl cellulose as the release decelerating polymer to provide continuous protection by increasing the viscosity of the cervical mucus against heterosexually transmitted HIV infection as microcapsules in general effectively control the release of drugs and produce efficacious therapeutics due to increase in effective surface area to micron size.

This work was also set sights on evaluation and in-vivo pharmacokinetics and thereby the efficacy of newer drug delivery systems developed.

The object focus of this work is concerned with

1. ***One objective*** *of this study was formulation development of sustained release vaginal microcapsules for anti-HIV drugs using ethyl cellulose as coating polymer material.*

Zidovudine (AZT), with a short elimination half-life of about 1 hr, high dose of 250 mg in every 4 hr while 300 mg twice a day, in some cases, low systemic bioavailability(64%) due to rapid hepatic fast-pass metabolism, was chosen as a model drug of choice. The antiretroviral drug, AZT, a nucleoside reverse transcriptase inhibitor, is taken up by the host cells where it is

converted into its triphosphate form. Subsequently, by competitive inhibition, it inhibits the reverse transcriptase, therefore, viral replication stops. Also it is incorporated into the viral DNA chain which is growing (during replication) and terminates the lengthening of the viral DNA chain, thereby stopping viral replication.

2. Preparation, characterization and optimization of the formulation parameter for the drug loaded microcapsules (AZMCs).

3. Selection of suitable drug loaded microcapsule preparation for further evaluations.

4. Generalized analytical development as is required for microencapsulated drug delivery systems.

Pursuing the first objective, the work stages included

I) Studies for development of microencapsulation processes for preparation of AZMCs with different drug: ethyl cellulose ratios.

II) Studies for Selection of optimized drug: polymer ratio

III) Studies of evaluation parameters like drug content, encapsulation efficiency, scanning electron microscopy (SEM), Fourier transforms infrared spectroscopic analysis (FTIR) and micromeritic analysis.

IV) Drug release kinetics, modeling studies and stability study with selected microencapsulated drug delivery systems.

*In **second objective**, optimized AZMC were encompassed in bioadhesive gel to form AZMBVGs.*

*Pursuing the **second** objective, the work stages included*

I) Studies on development of AZMBVGs with selected AZMC4

II) *Evaluations of selected AZMBVGs like percent yield, drug content, spreadability, extrudability, bio adhesive strength, swelling index study and viscosity.*

III) *Drug release kinetic and modeling studies with selected AZMBVG drug delivery systems.*

IV) *Further studies like In-vitro drug permeation study using goat vaginal membrane, vaginal irritation study, in vivo drug release studies in High Performance Chromatography(HPLC) systems, pharmacokinetic study and stability study of AZMBVG.*

Further study of without microencapsulated gel (BVG1) with different drug: bioadhesive polymer ratio was prepared. For development of alternative delivery systems optimized batches of AZT microcapsule (ZMC4 : bioadhesive polymer 1:1) were incorporated in tablet (MBVT) by direct compression method using various grades of bioadhesive polymer, such as Hydroxyl Propyl Methyl Cellulose (HPMC), Carbopol 934, Carbopol 940 and Guar Gum with other formulation excipients and Vaginal Film (VF) of AZT was prepared by solvent casting method containing different ratios of Acrycoat S-100 (AC) or Ethyl Cellulose (EC) and HPMC in di-butyl phthalate or glycerol or sorbitol or PEG 400 as a plasticizer were prepared.

*Pursuing **third** objective, the work stages included*

1. *Selected optimized BVGs, MBVT and VF evaluation for further study.*
2. *Further studies in other parameter, like percent yield, drug content, spreadability, Extrudability, bioadhesive strength, swelling index study and viscosity.*

3. *Drug release kinetic and modeling studies with selected BVGs, MBVT and VF drug delivery systems.*

Among them AZMBVG4 and BVG1 chosen for further study as only to be investigated under title, aim and scope of this research.

The dissertation is broadly divided in four sections

The introduction part deals with a review of developments in the field of microencapsulated bio adhesive vaginal gel as controlled drug delivery systems are concerned. Different preparative techniques practiced were reviewed in view of their impact on trends and developments in microencapsulation technology. In pursuing such studies, drug microencapsulation technology and bioadhesive delivery, bioadhesive mechanisms, different bioadhesive polymers and HIV life cyle were reviewed from different relevant object angles. Various drug microencapsulation methods, preparation methods of gel, advances on vaginal gel delivery systems, pharmacokinetic studies, vaginal irritation and stability studies in field were reviewed and discussed.

The Experimental work part deals with plan of the research work and methods with results and discussion preparative techniques used in drug microencapsulation and microencapsulated bio adhesive vaginal gel process development using AZT as representative drug. Process parameterization studies for selection of drug loading for microencapsulation and microencapsulated bio adhesive vaginal gel preparation, characterization and in vitro- in vivo drug release kinetics were studied including pharmacokinetic parameters, vaginal irritation, stability studies and statistical analysis.

Conclusion encompasses major observation data interpretation for the entire work undertaken; its implications understood pharmacokinetic study, vaginal irritation and statistical consideration to achieve the objectives as perceived.

Other perspective of research work encompasses major observation data for the other formulations like vaginal tablet, vaginal gel and vaginal films with different evaluation parameter and optimization of formulation, relevant in due progress of the vaginal gel. As we come across different interesting facts related to other formulations, we find it note worthy to report.

Achievement encompasses major contribution by author during his entire research work. The author has presented his work in different scientific forums at national and international level with three best papers awarded and financial assistance under international travel support scheme by Government of India, Ministry of Science & Technology and Department of Science & Technology (DST) file no: SR/ITS/03635/2009-2010. The author has also received one more international travel supported by Indian Council of Medical Research (ICMR), Department of Health Research (Ministry of Health &Family Welfare) file no: 3/2/TG-4/MPD-2010.

List of publication encompasses the author has published his work in different national and international journal and six research papers with national journals and two research papers in international had already published out of this work.

The entire work and the introductory part have taken help of various literatures and past contribution of different researchers including contribution of our research group members and these were enlisted systematically in the References sections.

The introductory review part has taken additional support from several volumes of Advance drug delivery reviews' Elsevier Science, L.B.Peppas, M.Vert, Polylactic and glycolic acid as drug delivery carriers In: D.L.Wise, Peppas, D.J. Tarantolo, A.M. Klibanov, N.A.Peppas, editors. Hand Book of Pharmaceutical Controlled Release Technology, Marcel Dekker INC, New York, Encyclopedia of controlled Drug Delivery,in:Mathiowitz (Eds), Microencapsulation.

AwilyInterscience, NewYork, A.A.Hincle, H.S.Kas,in:Microencapsulation technology: interfecial polymerization method. In D.L.Wise, L.B.Peppas, D.J.Tarantolo, A.M.Klibanov, N.A.Peppas, editors. Hand book of pharmaceutical controlled release technology, Marcel Dekker, New York, 2005, L.B.Peppas, M.Vert,Polylactic and glycolic acid as drug delivery carriers In: D.L.Wise, Peppas, D.J. Tarantolo, A.M. Klibanov, N.A.Peppas, editors. Hand book of pharmaceutical controlled release technology,Marcel Dekker, New York,2005. S.P. Vyas, R.K. Khar, in:Microcapsules, Targeted and Controlled Drug Delivery – Novel Carrier Systems, CBS Publisher and Distributors, New Delhi, 2002. N.S. Parmar, Shivprakash, in: Biopharmaceuticals and pharmacokinetics considerations in the development of controlled release drug products, Controlled and Novel Drug Delivery, CBS Publisher and Distributors, New Delhi, 2007and different internet based search engines like Pubmed.gov, medline.com, google.com etc.

Occasional help was sought for, from various University department including (1) Department of Physics and Chemistry, University of Burdwan,(2) Division of Pharm.Tech. Chemical Technology,University of Calcutta,(3) All India Institute Of Medical Sciences, New Delhi ,(4) Department of Pathology, Sikkim Manipal University of Health Sciences, Tadong, Sikkim at various stages of the work.