5.0.OTHER PERSPECTIVE OF RESEARCH WORK

5.0. OTHER PERSPECTIVE OF RESEARCH WORK

1] FORMULATION, CHARACTERIZATION AND *IN-VITRO* DRUG RELEASE OF AZT MICROENCAPSULATED BIOADHESIVE VAGINAL TABLET

Bioadhesive vaginal tablet (BVT) offers unique carrier system, customized for adhering to vaginal mucosa. BVT drug delivery is a promising area to achieve controlled drug release over long time and enhanced bioavailability. The microcapsules (MP) were generally used for enhancing bioavailability, controlled release and targeted drug delivery. The aim of the study was to develop a newer prolong releasing AZT microencapsulated bioadhesive vaginal tablet (MBVT) to treat HIV infections with increased patient convenience. The objective of the present study was to prepare, characterize and evaluate *in vitro* drug release profile of MBVT for treatment of AIDS using AZT as a model drug.

The MPs were prepared by the solvent evaporation method and characterized. The encapsulation efficiency was within 67.12±0.39 to 99.1±1.49%. Fourier Transform Infra Red (FTIR) spectroscopy revealed no chemical interaction between drug and polymer. Scanning Electron Microscopy (SEM) demonstrated the MPs, discrete and nearly spherical. Thus, very good, free flowing AZT MPs was developed. The drug release from the MPs was observed up to 10 hrs. The MP1 was found to release the drug of about 64.84% only, even after 10hrs, thus concluded to have sustained drug release profile for longer period of time when compared to other MPs. From the drug release profile of all the microcapsules, MP7 was found to release the drug fastest of about 97.73%, up to 10hrs, thus chosen to prove whether MPs were retarding release or not when compressed into tablet. MP7 microparticle (containing drug: polymer ratio 1:7) was selected and

evaluated further in order to achieve one objective of this study. To achieve second objective, prepared microcapsules (MP7) were compressed into tablet by direct compression and characterized. *In vitro* drug release study of MBVT2 (n=0.529) showed to release drug about 13.52% and MBVT4 (n=0.298) showed to release drug 19.35% only up to 10^{th} hrs following case I Fickian ($n \leq 0.5$) transport mechanism with good bioadhesion and swelling property.

2] FORMULATION, *IN VITRO AND IN VIVO* PHARMACOKINETICS OF ANTI-HIV VAGINAL BIOADHESIVE GEL

Inexpensive and female-controlled pre-exposure prophylaxis strategies to prevent mucosal transmission of the virus, is urgently needed with the rising prevalence of human immunodeficiency virus (HIV-1and HIV2) infections in women. AZT loaded bioadhesive vaginal gel may become one of the very useful strategies, as it can be used not only for controlled release but also for enhancing bioavailability. Drug delivery through vaginal gel is a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability over longer periods of time. The aim of the study was to develop a newer prolong releasing AZT (AZT) bioadhesive vaginal gel to treat HIV infections with increased patient convenience. AZT loaded bioadhesive vaginal gel was prepared successfully by using cold mechanical method. F3 formulation containing carbopol:HPMC (1:3) was selected and evaluated in order to achieve objectives of this study. *In vitro* drug release study of F3 showed in 24h drug released following case I Fickian ($n \leq 0.5$) transport mechanism and *in vivo* drug release was found much better (T_{max}), (C_{max}) and bioavailability (F) comparison with oral pour drug solution. It was also showed good extrudability, spreadability and bioadhesive strength. A generalized protocol, for the further research, in this area will surely expected to yield significant outcome with improved drug delivery system.

3] PROLONG RELEASE BIOADHESIVE VAGINAL FILM OF ANTI-HIV DRUG (AZT): FORMULATION AND *IN VITRO* EVALUATION

The present study concerned with the development and characterization of bioadhesive vaginal film (VF). AZT containing VF were prepared by solvent casting method using different ratios of Acrycoat S 100 (AC) or Ethyl cellulose (EC) to Hydroxy propyl methyl cellulose (HPMC) and di butyl phthalate(DBP) as a plasticizer. The optimized films were found to be transparent, flexible and soft and evaluated for mechanical properties by modified instrument, drug content, folding endurance, *in vitro* drug release with release kinetic and % moisture content bioadhesive strength by modified pan balance method. The films were found higher drug content and flexible. The VF10 (containing AC: HPMC 4:1) was selected. *In vitro* drug was found of AZT over 11 hr obeying zero order followed by Higuchi kinetics and Case II non-Fickian (anomalous) diffusion control, indicating the rate of drug release is due to the combined effect of drug diffusion and polymer relaxation with a sufficient bio adhesion quality with good mechanical properties. The results were compared statistically and found with satisfactory correlation. Thus in conclusion preparation protocol of VFs studied may be adopted for a successful development of newer drug delivery system for treatment and prevention for AIDS.

4] MICROENCAPSULATED BIOADHESIVE VAGINAL GEL FOR PROLONG RELEASE OF METRONIDAZOLE: FORMULATION DEVELOPMENT AND CHARACTERIZATION

The present study concerned with the development and characterization of Microencapsulated Bioadhesive Vaginal Gel (MBVG). Metronidazole encapsulated microcapsules were prepared by thermal change method using ethyl cellulose as rate controlling polymer in different ratios. The microcapsules were found to be discrete, spherical with free flowing properties and evaluated for particle size analysis, shape (scanning electron microscopy), flow properties, wall thickness, drug encapsulation efficiency, and *in vitro* release performance. The selected microcapsule formulation (MC3, containing drug: polymer ratio 1:4) was incorporated in gels with a variety of bioadhesive polymers. The MBVGs were evaluated for pH, spreadability, extrudability, viscosity, vaginal irritation test, *in vitro* drug release, drug release kinetics, bioadhesion test, accelerated stability of selected gel formulation. *In vitro* drug release rate for selected MBVG (F5 gel, containing 1 % w/w of drug loaded microcapsules and 0.6 % w/w of carbopol 974) was found to sustain metronidazole over 36 h obeying zero order kinetic with a good bioadhesion quality. The results were compared statistically and found with satisfactory correlation. Thus in conclusion preparation protocol of MBVG studied may be adopted for a successful development of newer drug delivery system of other drugs for administration to vagina.

5] *IN VIVO - IN VITRO* CORRELATION (IVIVC) OF MICROENCAPSULATED ANTIRETRO VIRAL BIOADHESIVE VAGINAL TABLETS

The aim of the current study was to evaluate the *In vitro* dissolution tests for enabling the prediction of *in vivo* performance after selection of vaginal modified-release (VMR) dosage form. The selection of ideal formulation, the whole work was divided in two phases. In first phase, AZT loaded microcapsules (MP) was prepared by using solvent evaporation method. The encapsulation efficiency was observed to be in the range of 36.42 ± 7.53 to 87.33 ± 12.80 %. The FTIR study showed no chemical interaction between drug and polymer. SEM study depicted that drug loaded ethyl cellulose MP was in micro size. MP was shown 91.81±2.8 to 99.14±0.49 % drug release up to 24 followed by Fickian case I release transport mechanism. To obtain second objective, prepared MPs (MP4) were incorporated into Tablets with various bioadhesive polymers. From *In vitro* drug release profile data, it was evidenced that the formulation F3 showing only 94.03±1.60 % drug release up to 32 hrs in constant manner in comparison to other formulations followed by non Fickian case release transport mechanism. *In vivo*, the percentage absorption of F3 standard was investigated by administering the product to each group containing three female Newzealand white rabbit. Formulation were comparing with existing marketed products there by a predicting mathematical model relationship between an *in-vitro* property of a dosage form and an *in-vivo response. Then* the *in vitro* results were compared with the *in vivo* data by means of Level A *in vitro–in vivo* correlation (IVIVC). The *in vitro* dissolution tests were able to predict almost correctly that the absorption of AZT. The results demonstrate good correlations between *in vitro* drug release and *in vivo* drug absorption.

6] DESIGN, FORMULATION, EVALUATION AND *IN VITRO-IN VIVO* CORRELATION OF ANTI-HIV BIOADHESIVE VAGINAL FILM

The study was aimed towards the formulation development and correlates the pharmacokinetic parameter by evaluating the *in-vitro* and *in-vivo* data of AZT loaded bioadhesive vaginal film. Vaginal films are preferable in terms of flexibility, comfort and self insertion. The AZT loaded films (ZLF) were prepared by solvent casting method. The polymers like HPMC and sodium alginate, and plasticizers along with drug were blended in a suitable solvent in different ratios. The films were found to be translucent, soft, flexible and easily removable from the glass mould. From FT-IR study, it was found that there was no chemical interaction between drug and polymer. Vaginal films were evaluated for pH, folding endurance, swelling index, moisture content, drug content, mechanical property, bioadhesive strength and *in-vitro* drug release. The prepared film were smooth, elegant in appearance, uniform in thickness, and showed no visible cracks and showing good folding endurance. Among the various formulations (ZLF1 to ZLF4), ZLF2 showed excellent physicochemical characters and enhance the drug release 89.72% up to 32 hrs. To describe the kinetic of drug release from film, ZLF-2 formulation followed Higuchi square root kinetic (R^2= 0.995) and have non–fickian release rate characteristic of drug. Release pattern of formulation ZLF-2 exhibited a sustained release, in controlled manner over extended period of time. To determine the surface morphology of the film formulation (ZLF-2), scanning electron microscopy (SEM) of the drug loaded film was performed. Scanning electron photographs of ZLF-2 shows that drug particles are distributed on the surface of the formulation also showed that the particles are porous in nature. The maximum drug permeation from the formulation ZLF-2 through goat vaginal membrane in acetate buffer pH 4.7 after 32 hrs it was found to be of 90.52%.

Thus ZLF-2 film was selected for further study for *in-vivo* experiment by using New Zealand white female rabbit species. ZLF-2 was selected for *in vitro-in vivo* correlation *(IVIVC)* study and using the plasma concentration data of various pharmacokinetic parameters was calculated. According to the theory, first degree of correlation was established by comparing the *in-vitro* and *in-vivo* parameters of the same formulation. The cumulative % drug dissolved and cumulative fraction drug absorbed were compared. The time required for 50% release, and 90 % release and plasma concentration of AZT from film both *in vitro* and *in vivo* condition was compared and found to be sustained in action shown. From the *in vitro-in vivo* correlation (*IVIVC*) study concluded that optimized formulation showed good degree of correlation (degree A correlation).The preferred formulations i.e. ZLF-2 was examined in *in-vivo* rabbit model using high performance liquid chromatography (HPLC). The plasma drug concentration was estimated with the standard curve equation and compared with the standard Zidovir tablet data. The plasma drug concentrations of test and standard Zdovir tablet were calculated and a comparative study of plasma concentrations of formulation and standard samples were performed. In comparison to the Zidovir oral solution (using ZIDOVIR conventional tablet) with vaginal test formulation it was found that vaginal formulation give more prolonged release of drug in plasma throughout the period of 32^{th} hrs.