

## **CHAPTER - II**

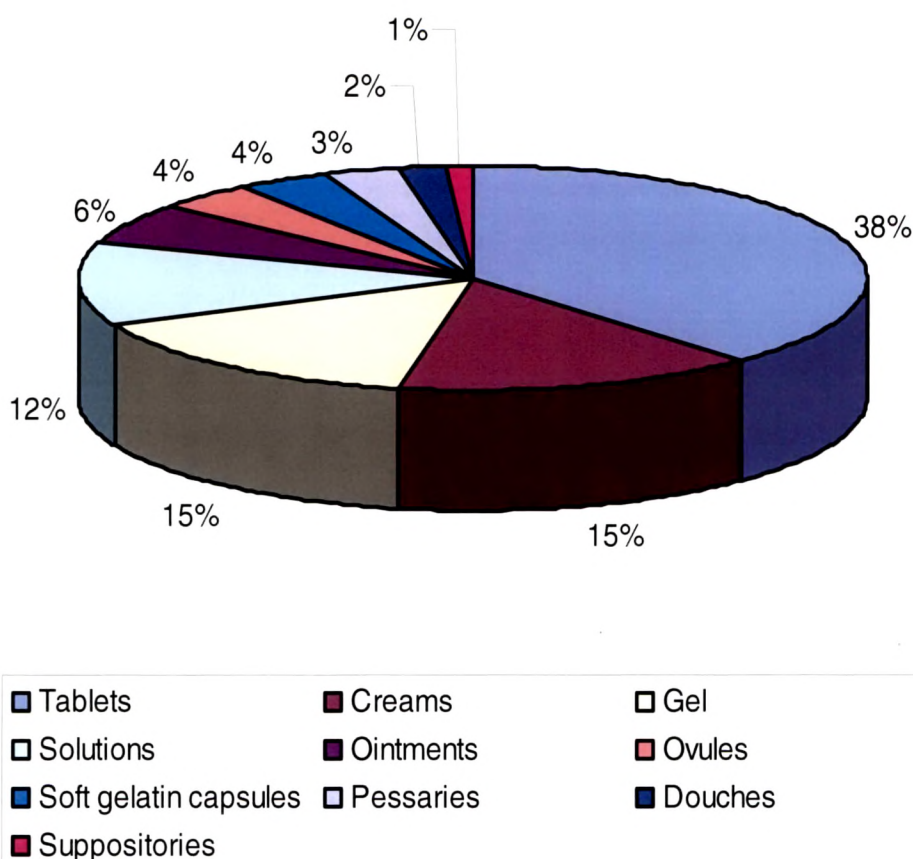
### **SIGNIFICANCE, AIMS AND OBJECTIVE**

## 2.1 Significance

Bacterial vaginosis (BV) and Vulvovaginal candidiasis are the two most common forms of vaginitis in female patients. Vaginitis is one of the most frequent genital infections occurring in women of all age groups (Sobel J.D., 1988). It has been reported that 30-35% of vaginitis episodes are due to *Candida albicans* (*C. albicans*). About 75% of women experience an acute episode of vaginal candidiasis and/or BV once in their lifetime, most commonly during pregnancy or extended use of antibiotics, steroids and oral contraceptives (birth control) with a high estrogen content. In US alone, bacterial vaginitis accounts for an anticipated 10 million office visits per year. It has been reported that BV is present in approximately 15% of private gynecologic patients, 10–30% of pregnant women, and 12–61% of women seen at clinics for sexually transmitted diseases (Mead P.B., 1993). Although BV is curable, if left untreated it can cause complications ranging from pelvic infection to miscarriage to increased susceptibility to sexually transmitted diseases (Schmid G. *et al.*, 2000). Studies in the last decade have established that bacterial vaginosis is a risk factor for the acquisition of HIV.

Now days, bacterial vaginitis is most commonly treated with one of two available antibiotics which may be administered either systemically or vaginally in form of various preparation. Similarly, Vulvovaginal candidiasis is treated with various antifungal agents delivered either vaginally or orally. The perceived convenience of oral medications is often associates with risk of systemic adverse drug reaction and potential to interact with concomitant medication. From such perspective, **topical treatment could represent a rational choice to treat localized vaginal infections and is often recommended by various healthcare practitioners.** However, complete eradication of localized infectious agent is not always possible with the existing therapeutic regimens due to short residency of formulation in vaginal cavity. Some gel based vaginal delivery systems are associated with problems like messiness and leakage of formulations causing inconvenience to users, leading to poor patient compliance. The vast majority of gels, foams, creams, suppositories, and tablets that are presently used as vaginal delivery systems breakdown almost immediately following insertion into the vaginal cavity and have minimal bioadherence to the vaginal walls (Vermani K. *et al.*, 2002). **Therefore, it has been difficult to achieve optimal potential effectiveness of the therapeutic agent with the existing vaginal delivery system.** It has highlighted urgent need of adequate delivery system aimed to hold formulation closed to vaginal mucosa for long time, short-term treatment, achievement of high drug levels at the infectious site, avoidance of first-pass metabolism and safety.

### Vaginal formulation available in indian market



**The best approach to achieve both efficiency and patient compliance is design of bioadhesive vaginal drug delivery systems (BVDDS).** BVDDS can adhere to vaginal mucosa in order to bring drug in contact with target tissues for sufficient period of time and prevent expulsion of formulation. Thus, bioadhesive vaginal drug delivery system is become best alternative to overcome limitations associates with existing vaginal delivery system. It may become a potential delivery system for effective treatment of vaginitis in female patients and can offer substantial benefits for improving women's health.

#### 2.2 Aim of the Present Study

Aim of the present research work was to design and optimization of bioadhesive vaginal drug delivery system which has capability to retain formulation on/at the vaginal mucosa for sufficient period of time and can prevent expulsion of formulation.

### 2.3 Specific Objectives

- Design and optimization of bioadhesive vaginal formulations (film and softgel) by exploring various bioadhesive polymers. Select a formulation based on desirability functions.
- To optimize the formulation with respect to the dependent variables.
- To develop and validate the analytical method for estimation of drugs in their formulations.
- To characterizes the developed vaginal formulation for their physycodynamic properties.
- In vitro and ex vivo characterizations of bioadhesive vaginal formulations.
- Perform the cytotoxicity study for individual drugs and their formulations using MTT (3-[4-5-dimethylthiazol-2-4]-2, 5-diphenyltetrazolium bromide) calorimetric assay method.
- To carry out stability studies of the optimized formulation as per ICH guideline.

### 2.4 Selection of Drug

Itraconazole (ITR) is a new orally active triazole antifungal drug with a broad spectrum of activity. This agent appears to be an attractive alternative for treatment of vaginal candidiasis because of its enhanced activity against *Candida species*, leading to short courses of therapy. Currently, two antibiotics, metronidazole and clindamycin phosphate (CL) are most commonly used for treatment of BV. Both, metronidazole (Eschenbach D.A. *et al.*, 1983) and CL (Livengood C.H. *et al.*1990) have a long history for excellent coverage against the common pathogens (such as *Gardenerella vaginalis*, *Mobiluncus spp.* and *Mycoplasma hominis*) implicated in bacterial vaginosis. Other oral antibiotics such as cephalosporins and ampicillin are also prescribed for the treatment of BV, but are reported to be less effective than metronidazole and CL. But, use of metronidazole associated with multiple side effects including gastrointestinal side effects like reaction associated with alcohol intake and mutagenic and carcinogenic effects. However, a number of studies have shown that intravaginal CL is more effective and better tolerated than metronidazole for BV treatment. Hence, CL and ITR were selected as model drug in present investigation for clinical management of BV and Vulvovaginal candidiasis respectively. But, they are not much effective as delivered through conventional delivery systems due to their short residency in vaginal cavity. Therefore, there is strong need and rationale to develop BVDDS in order to achieve better therapeutic outcome for these therapeutic entities.

## 2.5 Approach

Vaginal drug delivery is selected for clinical management of BV and Vulvovaginal candidiasis because oral medications are often associated with risk of systemic adverse drug reaction and potential to interact with concomitant medication. Vaginal infections are dominated in vaginal cavity. Intravaginal drug delivery system provides close proximity to vaginal cavity which produces therapeutic effect in a very short time period without any systemic side effect.

As product acceptability ultimately determines compliance and use-effectiveness, such information is essential to guide the development of desired vaginal formulation. Usually, commercially available vaginal preparations such as creams, ointments, foams, gels, pessaries, and suppositories require cleansing of the applicator and reuse during course of treatment, which women may find inconvenient. Therefore, polymeric film and soft gel formulations are selected for the vaginal administration due largely to the fact that it was easy to use (applicator not required for their administration), and did not produce a lot of discharge. Advantageously, film and soft gel having smooth surface and enough flexibility which may help to minimize mechanical injury during insertion into vaginal cavity. Also, solid dosage forms are more preferred by women in different regions of the world due to their aesthetic appeal, ease of application and provide unit dosage.

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