## Chapter 2

<table>
<thead>
<tr>
<th>Chapter No.</th>
<th>Title</th>
<th>Page no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Review of literature</td>
<td>62-77</td>
</tr>
<tr>
<td>2.1</td>
<td>Review of literature on mucoadhesive vaginal tablet</td>
<td>62</td>
</tr>
<tr>
<td>2.2</td>
<td>Review of literature on microemulsion based vaginal gel</td>
<td>67</td>
</tr>
<tr>
<td>2.3</td>
<td>Review of literature on vaginal <em>in situ</em> gel</td>
<td>69</td>
</tr>
<tr>
<td>2.4</td>
<td>References</td>
<td>75</td>
</tr>
</tbody>
</table>
2.1. Review of literature on mucoadhesive vaginal tablet

Ghosh T et al. (2011)\(^1\) prepared zidovudine loaded microencapsulated bioadhesive tablets for sustained drug delivery through vagina. The microcapsules of Zidovudine were prepared by solvent evaporation method in different ratios (1:2-1:7), then evaluated to select the best microencapsulated formulation. The microcapsule formulation selected was then incorporated in tablet by direct compression method using various grades of bioadhesive polymers such as carbopol-934, carbopol-940, sodium carboxy ethyl cellulose and sodium alginate. The prepared tablets (F1 to F12) were subjected to various evaluations. Zidovudine release from the tablet formulations was slow and sustained over longer period of time. Among all formulations batch containing carbopol-934 (1:1) was found to be the best optimized microencapsulate vaginal bioadhesive tablet formulation with regards to practical drug content, swelling index, bioadhesive strength study as well as sustained drug release property.

Bernkop-Schnurch A et al. (2009)\(^2\) designed and evaluated a novel vaginal delivery system for nystatin based on mucoadhesive polymers. L- cysteine and cysteamine, respectively, were covalently attached to poly (acrylic acid), and the two different thiolated polymers were evaluated \textit{in vitro} regarding their swelling behavior, mucoadhesive properties and release behavior. Tablets comprising these thiolated polymers and nystatin demonstrated a high stability in vaginal fluid simulant pH 4.2 and an increase in weight by swelling whereas control tablets comprising unmodified poly (acrylic acid) disintegrated and dissolved. The mucoadhesion time of tablets on freshly excised bovine vaginal mucosa on a rotating cylinder and the total work of adhesion of gels and tablets increased significantly due to the formation of disulfide bonds between the thiolated polymer and cysteine rich subdomaines of the mucus layer. The drug nystatin was released more slowly out of thiomer tablets and gels than out of PAA control tablets and gels. Therefore these thiolated polymers are promising delivery systems for nystatin providing a prolonged residence time and a sustained drug release \textit{in vitro} under physiological relevant conditions.

Cevher E et al. (2008)\(^3\) prepared vaginal bioadhesive tablets of natamycin which was complexed with gamma-cyclodextrin (NT-gamma CyD) to increase the solubility and stability of NT in aqueous solutions and reduce the side effects of the drug without
decreasing antimycotic activity. Favorable interactions between the NT and gamma CyD and formation of the 1:1 inclusion complex were observed. The sustained drug release of NT was achieved to over 8 hr periods by altering the polymer component of formulations which was responsible for differences in water absorption and erosion behavior of the tablets. Bioadhesion studies have clearly indicated that enhancement of mucoadhesion was achieved by inclusion of carbopol 934P and by tailoring the ratio of carbopol 934P in the formulation, a high mucoadhesion to vaginal mucosa can be achieved. Hence, the formation of complex between NT and gamma CyD and effective combination with polymers attain a bioadhesive and sustained release formulation of NT suitable for vaginal delivery and the effective treatment of candida infections.

Wang L et al. (2008) had developed bioadhesive tablet formulations of ketoconazole for vaginal delivery. Carbomer (carbopol 974P, carbopol 934P), hydroxypropylmethyl cellulose (HPMC) and hydroxypropyl cellulose (HPC) were used as candidate bioadhesive polymers. Effervescent was incorporated into the formulations as a disintegration agent. The swelling behavior and bioadhesive strength of the drug-free tablets were investigated. The swellings, tackiness and in vitro release were studied on the tablets. A good sustained effect and a moderate bioadhesion were obtained with the tablets. The formulation containing 100 mg of effervescent, with the carbopol 934P: HPC ratio of 1:9 seemed to be the optimum one for the tablet. In vivo drug residence tests were carried out by administering the preferred formulation to female rats. The results showed that the drug remaining followed a one-order model. Even after 24 hr of administration in vagina of rats, 17% of the original employed drug was retained on the vaginal tissue.

Garg S et al. (2007) developed rapidly disintegrating, bioadhesive and sustained release vaginal tablets of an iodophore, polyvinylpyrrolidone (povidone iodine), their evaluation and comparison with the marketed formulations. The formulation development included drug-excipients compatibility studies, optimization of performance parameters like disintegration time, bioadhesion and drug release profile and comparison of physical properties and performance parameters with the marketed formulation. The developed formulation provided a sustained release of polymer complexed iodine (up to 8 hr), rapid disintegration (< 1 min), desired bioadhesive properties and retention for a prolonged time.
Baloglu E et al. (2006) developed a bioadhesive vaginal tablet formulation of ornidazole by using different polymer mixtures, to evaluate the bioadhesive tablet properties, and to investigate the irritation potential of the formulations to the rat vaginal tissue. Vaginal tablets of ornidazole were directly compressed with bioadhesive and swellable polymer mixtures as release-controlled agents. Carbopol 934 (Cp), pectin (Pc), hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (Na CMC), and guar gum (GG) were used in different ratios. Bioadhesive properties, swelling capacity, release studies, and histological studies of the formulations were carried out. The bioadhesive strength between bovine vagina and surface of the tablets was determined by tensile experiments, and it was found to be dependent on Cp content. The release mechanism was described and found to be non-Fickian for all formulations. Dissolution data were evaluated statistically. No histological damage was found except one formulation containing high amount of guar gum.

Sharma G et al. (2006) designed a bioadhesive dosage form of clotrimazole using a combination of bioadhesive polymers carbopol 934P, sodium carboxymethyl cellulose and sodium alginate in different ratios. The bioadhesive strength was evaluated by measuring the force required to detach the tablets from porcine vaginal mucosal membrane. Carbopol 934P showed maximum bioadhesion and required maximum force for detachment; the force required for detachment was directly proportional to its content. The swelling index was a function of the concentration of the hydrophilic polymer and the formulations containing carbopol 934P and sodium carboxymethyl cellulose were found to swell to a greater extent than those containing carbopol and sodium alginate. In vitro release studies showed that the batch consisting of 2:1 ratio of carbopol 934P/sodium alginate released clotrimazole over 24 hr. The similarity factor showed that the dissolution profiles of fresh and aged tablets were similar; suggesting good stability of vaginal tablets prepared using a combination of carbopol 934P and sodium alginate.

Garg S et al. (2004) developed rapidly disintegrating bioadhesive vaginal tablet of PSS and evaluate its efficacy and safety as topical microbicide. A tablet formulation containing 300 mg PSS and pharmaceutically acceptable excipients were developed and optimized. Inhibition of hyaluronidase, cervical mucus penetration, sperm motility, HIV, HSV, and Lactobacillus by tablets was studied and compared with
PSS. Tablets were also studied for bioadhesion and retention in isolated sheep vaginal model. PSS tablets disintegrated rapidly (in less than 60 sec) in small volume of fluids (10 mL) and formed smooth, homogenous, viscous and bioadhesive dispersion, which is likely to be retained in vaginal cavity for prolonged intervals. At accelerated conditions (40°C /75% RH), tablets were found to be stable for a period of six months. Further, the absence of sperm immobilization, cytotoxicity and no inhibition of normal vaginal microflora (Lactobacillus) demonstrated the potential of PSS tablets as safe and effective vaginal microbicide for prevention of STDs and conception.

Karasulu HY et al. (2004) developed more effective treatment for vaginal candidiasis, ketoconazole (KTZ) was formulated in bioadhesive tablet formulations. The bioadhesive vaginal tablets delivery of KTZ was prepared by direct compression of sodium carboxymethyl cellulose or polyvinylpyrrolidone or hydroxypropylmethyl cellulose (HPMC-E50). Dissolution studies of bioadhesive tablets and commercial ovules were carried out with a new basket method (horizontal rotating basket). These bioadhesive tablets containing 400 mg of KTZ showed a zero-order drug release kinetic. It was found that, in vitro antifungal activity of KTZ was dependent on its concentration and contact time with yeast cells. These results indicated that a new bioadhesive vaginal tablet formulations might be further developed for safe convenient and effective treatment of vaginal candidiasis.

El-Kamel AH et al. (2002) prepared Metronidazole vaginal tablets by direct compression using four single bioadhesive polymers namely: sodium carboxymethylcellulose (NaCMC), methylcellulose (MC), hydroxypropyl- methylcellulose (HPMC) and carbopol 934, and HPMC/NaCMC mixture in different ratios. The drug-polymer ratio was 1:4. The drug dissolution rate at pH 4.8 from single polymer tablets followed the sequence: MC > Carbopol > NaCMC > HPMC, while in water it was: MC > NaCMC > Carbopol > HPMC. Drug dissolution rate from tablets containing NaCMC: HPMC (2:1) was an intermediate between that from either NaCMC or HPMC tablets. Swelling studies indicated an increase in swelling indices with time at 37 °C for both blank and medicated tablets. Measurement of mucoadhesion gave the same rank order for both medicated and blank tablets namely: NaCMC > Carbopol > HPMC > MC. Adhesion behavior of tablets prepared from NaCMC: HPMC (2:1) was intermediate between that of NaCMC and HPMC tablets.
Generally, the presence of drug increased the adhesiveness of the formulation while that of the mucolytic agent decreased it.

**El-Kamel AH et al. (2002)** developed mucoadhesive vaginal tablets of Metronidazole by directly compressing the natural cationic polymer chitosan loosely cross-linked with glutaraldehyde, together with sodium alginate with or without microcrystalline cellulose (MCC). Sodium carboxymethylcellulose (CMC) was added to some of the formulations. The drug content in tablets was 20%. Drug dissolution rate studies from tablets were carried out in buffer pH 4.8 and distilled water. Swelling indices and adhesion forces were also measured for all formulations. The formula containing 6% chitosan, 24% sodium alginate, 30% sodium CMC, and 20% MCC showed adequate release properties in both media and gave lower values of swelling index compared with the other examined formulations. Moreover, its release properties (% dissolution efficiency, DE) in buffer pH 4.8, as well as release mechanism (n values), were negligibly affected by aging. Thus, this formula may be considered a good candidate for vaginal mucoadhesive dosage forms.

**Kast CE et al. (2002)** prepared and evaluated a new bioadhesive vaginal drug delivery system for clotrimazole. Chitosan, a cationic biopolymer derived by deacetylation of chitin, was modified by the introduction of thioglycolic acid (TGA). The modification was achieved by utilizing a carbodiimide to link the carboxylic acid moieties of TGA covalently to the primary amino groups of chitosan. The amount of added carbodiimide was thereby varied, resulting in chitosan-TGA conjugates A and B with 160 microM (= micromole) and 280 microM thiol groups per gram polymer, respectively. In order to characterize the new polymers the water uptake, the disintegration behavior, the bioadhesive properties utilizing the rotating cylinder method, as well as the release of clotrimazole from tablets based on these derivatives were studied. Results of this study demonstrate that these new chitosan-TGA conjugates are very promising vehicles for the vaginal application of clotrimazole in treatment of mycotic infections.
2.2. Review of literature on microemulsion based vaginal gel

Nair R et al. (2010)\(^{13}\) developed and evaluated microemulsion based gel for the vaginal delivery of ciclopiroxolamine (CPO). The solubility of CPO in oils and surfactants was checked to identify components of the microemulsion. The ternary diagrams were plotted to identify the area of microemulsion existence. Various gelling agents were evaluated for their potential to gel the CPO microemulsion without affecting its structure. The prepared formulations of ciclopiroxolamine microemulsion based gel (CPO-MBG) was evaluated by checking its spreadability, rheological studies, gel strength, bioadhesion study, mucoadhesive strength, *In-vitro* diffusion studies and *In-vivo* studies. The efficacy of the CPOMBG gel was evaluated in *vivo* in using rabbits. The CPO-MBG showed good *in vitro* bioadhesion and antifungal activity. The CP-MBG has potential be successfully used for the topical treatment of vaginal candidiasis.

Bachhav YG et al. (2009)\(^{14}\) developed and evaluated microemulsion based gel for the vaginal delivery of fluconazole (FLZ). The solubility of FLZ in oils and surfactants was evaluated to identify components of the microemulsion. The ternary diagram was plotted to identify the area of microemulsion existence. Various gelling agents were evaluated for their potential to gel the FLZ microemulsion without affecting its structure. The bioadhesive potential and antifungal activity of the FLZ microemulsion based gel (FLZ-MBG) was determined in comparison to the marketed clotrimazole gel (Candid-V® gel) by *in vitro* methods. The vaginal irritation potential of the FLZ-MBG was evaluated in rabbits. The clinical efficacy of the FLZ-MBG and Candid-V® gel was evaluated in females suffering from vaginal candidiasis. The FLZ-MBG showed significantly higher (P<0.05) *in vitro* bioadhesion and antifungal activity as compared to that of Candid-V® gel. The small-scale clinical studies indicated that the FLZ-MBG shows faster onset of action than Candid-V® gel although no difference was observed in the clinical efficacy.

Bachhav YG et al. (2009)\(^{15}\) developed and evaluated microemulsion-based gel for the vaginal delivery of clotrimazole (CMZ). The solubility of CMZ in oils and surfactants was evaluated to identify components of the microemulsion. The ternary diagram was plotted to identify the area of microemulsion existence. Various gelling agents were evaluated for their potential to gel the CMZ microemulsion without affecting its structure. The bioadhesive potential and antifungal activity of the CMZ
microemulsion-based gel (CMZ-MBG) was determined in comparison to the marketed clotrimazole gel (Candid-V® gel) by in vitro methods. The chemical stability of CMZ in CMZ-MBG was determined as per the International Conference on Harmonization guidelines. The CMZ microemulsion exhibited globule size of 48.4 nm and polydispersity index of 0.75. Carbopol® ETD 2020 could successfully gel the CMZ microemulsion without disturbing the structure. The CMZ-MBG showed significantly higher (P<0.05) in vitro bioadhesion and antifungal activity as compared to that of Candid-V®gel. The stability studies indicated that CMZ undergoes acidic pH-catalyzed degradation at all the storage conditions at the end of 3 months.
2.3. Review of literature on vaginal *in situ* gel

Fetih G *et al.* (2012)\(^6\) developed pluronic-based *in situ* gelling formulations of metronidazole (MTZ) for treatment of bacterial vaginosis, aimed at prolonging the residence time, controlling drug release, enhancing efficacy, decreasing recurrence, and increasing patient compliance. The *in situ* gel formulations were prepared using different concentrations of pluronic F-127 (PF-127) alone and in combination with pluronic F-68 (PF-68). The prepared formulations were evaluated for their gelation temperature (*T*\(_{gel}\)), *in vitro* drug release, rheological properties, mucoadhesion properties and tolerability by vaginal mucosa in tissue levels. The *T*\(_{gel}\) decreased with increasing PF-127 concentration. The *T*\(_{gel}\) was modulated by addition of PF-68 to be within the acceptable range of 25-37 °C. With increasing pluronic concentration, the *in vitro* drug release decreased, viscosity and mucoadhesive force increased. Histopathological examination of rabbit vaginas from the control and treated groups revealed normal histology of the vagina and cervix. Based on the *in vitro* evaluation of prepared formulations, the *in situ* gelling liquid formulated with PF-127/PF-68 (20/10 %, \(m/m\)) was selected for further clinical evaluation.

Raja Kumar KJ *et al.* (2012)\(^7\) had developed mucoadhesive local drug delivery system for antifungal drug ciclopirox olamine particularly for vaginal thrush. The viscosity of *in situ* system was found to be in the range (250 to 400 cps) for the sol, whereas for the gels it was up to (47640 cps). The maximum gel strength and mucoadhesion was found to be up to (120 sec) and (4211 dynes/cm\(^2\)) respectively. The ‘r’ values for Hixoncrowell ranged from 0.867 to 0.961 and that of Higuchi kinetics ranged from 0.841 to 0.971. It was understood that J code formulation were following predominantly first order release. Different techniques, FTIR spectroscopy and differential scanning calorimetry (DSC) were used to estimate the crystallinity degree and incompatibility. Additionally the *in vitro* anti fungal effect was appreciable in the formulations.

Patel GM *et al.* (2011)\(^8\) developed novel mucoadhesive, thermoresponsive vaginal gel for microbicide with gelation temperature 24-35 °C. Poloxamer 407 (P407) or: and poloxamer 188 (P188) were used to confer the temperature-sensitive gelation property. The mixtures of P407 (15%) and P188 (15–20%) existed as a liquid at room temperature, but gelled at 30-36 °C. To modulate the gel strength and the bioadhesive force of ciclopiroxolamine gel, mucoadhesive polymer such as polyox WSR N-60K
was used. Among bioadhesive polymers, polyox polymer enhanced gel strength most efficiently. These polymers reinforced the bioadhesive forces 4-7 fold compared to P407/P188 (15:15) alone and 3-6 fold compared to P407/P188 (15:20) alone. Differential scanning calorimetry (DSC) was employed to investigate the effect of poloxamer gel on the conformational changes of rat vaginal membrane. The in-situ gelling liquid with polyox polymer inserted into the vagina of women without difficulty and leakage and retained in the vagina at least 6-8 hr. These results suggest that in situ-gelling and mucoadhesive vaginal microbicide gel for women can be further developed as a more convenient and effective vaginal dosage form for treating sexually transmitted disease.

**Park JS et al. (2010)**\(^{19}\) was formulated the antifungal agent amphotericin B (AmB) in a vaginal gel using Pluronic®-based multiblock copolymers (MBCP-2) to achieve better therapeutic efficacy and patient compliance in the treatment for Candida vaginitis,. To increase its aqueous solubility, the drug was incorporated as its inclusion complex with hydroxypropyl-γ-cyclodextrin (HP γ CD). The formation of the AmB inclusion complex was characterized using different techniques including XRD, FT-IR spectrophotometry, DSC, and SEM. The sol–gel transition diagrams were determined by the inversion method at temperature intervals of 2 °C. Moreover, a histopathology study was performed to determine whether vaginal tissue damage was caused by repeated doses. The inclusion complex between AmB and HP γ CD was completely formed, and the aqueous solubility of AmB was improved by the formation of the inclusion complex. The sol–gel transition diagrams showed that the aqueous solutions of MBCP-2 gelled at body temperature, and the gelation temperature of the polymer solutions was dependent on polymer concentration. In vitro drug release results indicated that MBCP-2 exhibited a sustained release of AmB in pH 7.4 and pH 9.0 buffers, whereas at pH 5.0, it presented a constant release that was completed within 3 days. There was no visible sign of inflammation or necrosis in vaginal tissues after repetitive intravaginal application. In conclusion, the thermosensitive vaginal gel might be useful in the delivery of an antifungal agent for local treatment.

**Gupta H et al. (2009)**\(^{20}\) developed and optimized a chitosan (bioadhesive and permeation enhancer) and gellan gum (ion activated gelling polymer) based in situ gel system of clindamycin for vaginal application. Vaginal preparations, although
generally perceived as safer most, still they are associated with a number of problems, including multiple days of dosing, dripping, leakage and messiness, causing discomfort to users and expulsion due to the self-cleansing action of the vaginal tract. These limitations lead to poor patient compliance and failure of the desired therapeutic effects. For effective vaginal delivery of antimicrobial agents, the drug delivery system should reside at the site of infection for a prolonged period of time.

The developed formulation was characterized for various in-vitro parameters e.g. clarity, refractive index, pH, isotonicity, sterility, viscosity, drug release profile, statistical release kinetics, bioadhesive force, retention time, microbial efficacy, irritation test and stability studies. To simulate vaginal conditions, a synthetic membrane (cellophane hydrated with modified simulated vaginal fluid) and sheep vaginal mucosa were used as model membranes. The developed formulation was found to be non irritant, bioadhesive with good retention properties. Developed formulation shows matrix model release kinetic by PCP dissolution software. The developed formulation is thus a viable alternative to conventional vaginal dosage forms.

Haris NM et al. (2009)\(^{21}\) formulated and evaluated in situ vaginal gel of secnidazole, based on ion activated system. The system utilizes polymer that exhibit sol-to-gel phase transition due to change in physicochemical parameters. Ion trigger system using gellan gum (0.1-0.75 % w/v) along with sodium carboxymethylcellulose was used to prolong release of secnidazole (1.0% w/v). Formulations were evaluated for gelling capacity, viscosity, gel strength, mucoadhesive force, spread ability, microbiological studies and in vitro release studies. The transformation of sols occurs in presence of monovalent/divalent cation in dissolution medium. Effect of calcium carbonate and other process parameters were optimized and found to be satisfactory. The viscosity found to be in a range of 0.005 to 0.085 for sols, whereas for gels 16 Pa.S. Formulation showed pseudoplastic flow with thixotropy. The gel strength (using texture analyzer) and mucoadhesion was found to be up to 6.5 gm and 4.0 gm respectively. The optimized formulation was able to release the drug for 360 min.

Lu WY et al. (2009)\(^{22}\) have checked the effects of carrageenan on sustained-release properties of poloxamer 407-based vaginal in situ gel. After formulation of composite gel systems composed of carrageenan and poloxamer 407, in vitro release profiles and in vivo local drug residence after vaginal administration in mice was investigated.
using acyclovir as the model drug. Rheological experiment was conducted to investigate effects of carrageenan on temperature-dependent viscoelasticity of poloxamer 407-based gels. It appeared that carrageenan and poloxamer 407 could form composite gel systems with good thermosensitivity similar to gels containing only poloxamer 407. In the in vitro release experiment, carrageenan significantly decreased the release rate of acyclovir, retarded the dissolution of poloxamer 407 and slowed the gel erosion (weight loss) in a concentration-dependent manner. In vivo local drug residence experiment indicated that carrageenan significantly prolonged local residence of acyclovir and further showed a synergistic bioadhesive effect with acrylic acid polymers (Carbopol®). In conclusion, carrageenan was able to improve the sustained-release properties of poloxamer 407-based in situ gel, indicating that the combination of carrageenan and poloxamer 407 may find use in the development of vaginal in situ gel drug delivery systems with prolonged local residence and thus better clinical outcome.

Rotonda ML et al. (2008) has been studied the influence of hyaluronic acid (HA) on the gelation properties of poloxamers blends with the aim of engineering thermosensitive and mucoadhesive polymeric platforms for drug delivery. The gelation temperature (Tgel), viscoelastic properties and mucoadhesive force of the systems were investigated and optimized by means of rheological analyses. Poloxamers micellar diameter was evaluated by Photon Correlation Spectroscopy (PCS). Moreover in order to explore the feasibility of these platforms for drug delivery, the optimized systems were loaded with acyclovir and its release properties studied in vitro. By formulating poloxamers/HA platforms, at specific concentrations, it was possible to obtain a thermoreversible gel with a Tgel close to body temperature. The addition of HA did not hamper the self assembling process of poloxamers just delaying the gelation temperature of few Celsius degrees. Furthermore, HA presence led to a strong increase of the poloxamer rheological properties thus indicating possible HA interactions with micelles through secondary bonds, such as hydrogen ones, which reinforce the gel structure. These interactions could also explain PCS results which show, in systems containing HA, aggregates with hydrodynamic diameters much higher than those of poloxamer micelles. Mucoadhesion experiments showed a rheological synergism between poloxamers/HA gels and mucin dispersion which led to a change of the flow behavior from a quite Newtonian to a pseudo-
plastic one of their mixture. *In vitro* release experiments indicated that the optimized platform was able to prolong and control acyclovir release for more than 6 hr.

**Bilensoy E et al. (2006)** has been formulated in a vaginal gel of Clotrimazole (1%) using the thermosensitive polymer Pluronic F127 (20%) together with mucoadhesive polymers such as Carbopol 934 and hydroxypropylmethylcellulose (0.2% for both). To increase its aqueous solubility, clotrimazole was incorporated as its inclusion complex with 1:1 molar ratio with β-cyclodextrin. The inclusion complex was thoroughly characterized using various techniques, including 1H NMR spectroscopy, FT IR spectrophotometry, differential scanning calorimetry, scanning electron microscopy, phase solubility studies, and determination of stability constant (k1:1). The gelation temperature and rheological behavior of different formulations at varying temperatures were measured. *In vitro* release profiles of the gels were determined in pH 5.5 citrate buffer. It was observed that complexation with cyclodextrin slowed down the release of clotrimazole considerably. Carbopol 934, on the other hand, was found to interact with β-cyclodextrin, inducing precipitation. As far as rheological properties are concerned, thermosensitive in situ gelling was obtained with formulations containing drug: cyclodextrin complex rather than with free drug. Thus, the optimum formulation for a controlled-release thermosensitive and mucoadhesive vaginal gel was determined to be clotrimazole: β-cyclodextrin 1% with 0.2% hydroxypropylmethylcellulose in Pluronic F127 gel (20%) providing continuous and prolonged release of active material above MIC values.

**Bilensoy E et al. (2006)** had formulated anticancer agent 5-fluorouracil in a vaginal gel using the thermosensitive polymer Pluronic® F127 together with alternative mucoadhesive polymers e.g., hyaluronic acid, Carbopol 934 and hydroxypropylmethylcellulose to achieve a better therapeutic efficacy and patient compliance in the treatment for HPV-induced cervical cancers. To increase its aqueous solubility and to achieve the complete release of 5-FU from the gel, the drug was incorporated as its inclusion complex with either β-cyclodextrin or hydroxypropyl- β cyclodextrin. These were characterized in vitro by determining the gelation temperature and the rheological behavior of different formulations along with the in vitro release profiles of these formulations in pH 5.5 citrate buffer. Complete release of 5-FU from gels were obtained with both complexes of β -CD and HP- β -CD and cytotoxicity studies against HeLa human cervical carcinoma cells.
demonstrated that 1% 5-FU:CD complexes were equally effective as 1% free 5-FU indicating better therapeutic efficacy with lower dose.

**Kim CK et al. (2002)** developed more effective treatment for vaginal candidiasis, clotrimazole (CT) was formulated in mucoadhesive thermosensitive gels (MTG). Several MTG formulations composed of poloxamers (P) 407, 188, and polycarbophil (PC) were prepared. P188 and PC increased the mucoadhesiveness but reduced the syringeability of liquid forms of the gels. Based on the balance between the mucoadhesiveness and syringeability, MTG composed of P407/P188/PC (15/15/0.2 or 15/20/0.2) were further studied. Of the two MTG, the formulation with 15% of P188 gelled at higher temperature and revealed lower elastic modulus. In vitro, sustained release of CT from MTG was observed. In vivo antifungal activity of CT, tested against *Candida albicans* vaginitis in female rats, was significantly prolonged after vaginal delivery using MTG. At 10 days post-dose, the c.f.u. of *C. albicans* was more than 10⁴-fold decreased in MTG-treated groups. Moreover, the vaginal delivery of CT in MTG enhanced the viability of epithelial cells without affecting the morphology of vaginal mucosa. These results indicate that CT-containing vaginal MTG might be further developed for safe, convenient, and effective treatment of vaginal candidiasis with reduced dosing interval.

**Kim CK et al. (2002)** studied various rheological properties of clotrimazol e gels and evaluated for predicting their performance in vagina. Two kinds of thermosensitive and mucoadhesive formulations were composed of poloxamer 407 (P407, 15%), polycarbophil (0.2%), and different amounts of P188 (15 vs. 20%). Both formulations were Newtonian at 20 °C but non-Newtonian at 37 °C. Although both liquid formulations gelled below the vaginal temperature, they differed in gelation time and viscoelastic properties in the presence of vaginal fluid simulant. At body temperature, the formulation with 20% of P188 gelled within 35 s but it took two times longer for the other one gelled. Upon dilution with simulated vaginal fluid, the formulation with 20% of P188 retained the rheology of a gel, but the other one lost the viscoelastic properties typical for a gel. Moreover, after dilution with simulated vaginal fluid, the elastic modulus was orders of magnitude higher in the formulations with 20% of P188 relative to the other one. These results indicate that the rheological evaluation at the physiologic conditions needs to be preceded to develop more effective in situ-gelling vaginal formulations.
2.4. References


