CHAPTER - 2

LITERATURE REVIEW
Soft contact lenses are widely used because they offer comfort, easy adaptation and a long wearing time. All types of hydrophilic contact lenses require cleaning and disinfection otherwise serious complications like microbial keratitis may develop due to contact lens (CL) wearing. The multipurpose solution therefore should be formulated to be able to kill potentially pathogenic microorganisms. Despite several advantages and immense popularity of hydrophilic lenses, they require far more care than their hard counterpart. This is due to the very basic nature of material of construction which allows penetration of contaminants deep into the lens matrix, sorption of the contaminants leads to many implications like reduced comfort, decreased wearing time, decreased visual acuity, increased infections like conjunctivitis, inflammation of the eye, corneal ulcer, microbial keratitis, scarring of cornea even perforations with permanent loss of vision.

Solution-all in one for hydrophilic contact lenses have been formulated in such a way so that they remove all types of surface and microbial contaminants. Previously there were six different solutions that were used for cleaning, rinsing, soaking, lubricating, deproteinising and disinfecting. The contact lens wearer therefore needed a lot of dedication, inclination, time and money and even omitting a single step could have led to serious consequences and ultimate loss of vision. All these steps were then combined to give rise to a single solution hence contact lens wearer's compliance was increased and so was the popularity of hydrophilic contact lenses. The first multipurpose solution was developed in 1990 in U.S.A. (27). Till now only multinationals have entered and there was no Indian product. Hence it is needed to formulate all in one single step solution for contact lenses and that too an Indian product. An Indian patent at an affordable price. Starr in 1990 gave three principal methods for cleaning and disinfecting contact lenses. The three methods given were (1) heat disinfection (2) chemical disinfection and (3) hydrogen peroxide disinfection. The three methods were able to kill potential pathogenic microorganisms of the eye but heat disinfection was found to be the superior method.
They also gave the concept of multipurpose solution which could cover cleaning, disinfecting, rinsing, soaking, lubricating and deproteinising effect (28).

Donzis et al have reported that oxidative method which was introduced in 1989 was also the surest and most effective method to kill bacteria, fungi, yeast, mould and protozoa. This method was the oxidative method using hydrogen peroxide but it needed neutralization hence it could not be called single step all in one multipurpose solution. Hydrogen peroxide is toxic enough hence to be neutralized before instilling contact lenses. Before the advent of multipurpose solution it remained the best method (29).

McNally et al established the efficacy of one step Hydrogen peroxide system by culturing soft contact lenses before and after exposure to Hydrogen peroxide neutralization disinfections system. The rate of disinfection was 55% for Pseudomonas species and 100% for other bacteria (30).

John et al in 1989 proved that Polyamino propyl biguanide can be used as preservative in multipurpose solution. This particular preservative is antibacterial, antifugal and antiprotozoal covering broad spectrum of microorganisms. It is also non toxic, non irritating to corneal epithelium (31).

John et al have shown that Polyaminopropyl biguanide (0.0005%), Disodium edetate (0.5%) and Poloxamine (0.1%) in multipurpose solution added as disinfectant, chelating agent and surfactant respectively in multipurpose solution were found to be effective in removing trophozoites and cysts of Acanthamoeba adhering to all types of contact lenses Group I, II, III and IV (31). Dawson in the same year used Poly amino propyl biguanide in Baquacin and found it to be antibacterial, antifungal and antiacanthamoeba. It can be used in pool sanitiser as well (32).

Dawson et al also used Polyhexanide as disinfectant in all in one contact lens solution. It was found to have antiacanthamoeba activity and its structure and properties were same as Polyamino propyl biguanide (33).

In 1990, Kilrington used Polyhexanide (PHMB) as a sterilizing substance in contact lens solutions and as the primary active ingredient in Bacquacil (Imperial chemical Industries) a new pool cleaning product (34).
In 1990, Wilson et al. used contact lenses as therapeutic covers and also gave methods of cleaning and disinfecting contact lenses (35). They proved that there were three factors that controlled microbial contamination of contact lenses—

1. The method used and the contact lens solution. It is the cold disinfection care regimen that covers what types of solutions to be used.

2. The age of the contact lens and

3. Contact lens container.

They also proved that cold disinfection using polyhexanide could be an effective method for hydrophilic contact lenses but the surest method was still the heat disinfection (35).

In 1991, Sickler and coworkers observed that Thiomersal, Chlorhexidine and Benzalkonium chloride were toxic to corneal epithelium hence could not be used in multipurpose all in one solution. Sickler and co-workers used methods like cell culture and corneal perfusion in animal and human begins (36).

Porter et al. in 1993 also studied the drugs in contact lens solution and their toxicity. Instead of using animals and human beings they used L-929 fibroblasts underlaying on agar layer. The solid – contact lenses in this case were placed above the cells and by this invitro technique the effect of solution on contact lens and its reactions were established (37).

Gren et al. of U.S.A. in the same year also did the same experiment and same results were obtained but principal weaknesses of the procedure involved were diffusional and solubility limitation imposed by the agar overlay which made difficult to assess the final toxicity, concentration and toxicokinetics of the solution on contact lenses (38).

Seal et al. in 1992 washed the contact lenses and the containers with tap water and another set was rinsed and washed with multipurpose solution. When culturing was done for the presence of free living amoeba it was found that Acanthamoeba species were isolated from the contact lenses and the container used for storing contact lenses if washed and rinsed with tap water but multipurpose solution containing Polyhexanide was found to be antiacanthamoeba (39).
Naseer et al in 1993 showed that by using single step multipurpose solution, the patient compliance can be enhanced and the solution was capable of both lens and the case disinfection. The solution contained Polyaminopropyl biguanide (0.0002%) and Poloxamer as surfactant (0.5%). The pH was 7.45 and viscosity of the solution was 2.0 cps (40). The solution was found to be effective. Their work also indicated that patient or contact lens wearer hygiene is also very important. Hydrophilic lenses need maintenance and proper care regimen.

In 1993 Jung et al developed and evaluated single step multipurpose solution containing preservative, Disodium edetate and non ionic surfactant containing non enzymatic cleaner as deproteiniser. The contact lenses were artificially coated with tear and then after cleaning and rinsing with multipurpose solution – the removal of deposits were studied using Bicinchoninic acid. The efficiency of multipurpose solution to deproteinise lenses were studied. The four commercial solutions containing Polyaminopropyl biguanide, Polyhexamethylene biguanide, Polquad and Hydrogen peroxide neutralization system were studied respectively. Group I and II the non ionic contact lenses gave best results and the solution containing Polhexanide, Poloxamer and Citrate gave good results (41).

Non ionic contact lenses with low water and high water content preferred (Group I and II) were preferred. Such lenses discouraged protein deposition and group II discouraged lipid deposition.

Laibson et al worked on contact lenses and solutions and their effect on corneal ulcer. They showed that multipurpose solution containing 0.001% of Thiomersal was allergic and toxic. This preservative was found to be cytotoxic and hence could not be used in multipurpose solution. Other solutions that contained 0.1% of Sorbic acid, 0.001% of Polquad, 0.005% of Chlorhexidine and 0.0005% of Polyhexanide were found to be effective in multipurpose solution and were not cytotoxic. For formulation of multipurpose solution the above preservatives with non ionic surfactants, buffers and Disodium edetate could be used. They also used 3% hydrogen peroxide but it was found to be ocular toxic although required neutralization. It was not one step disinfection but two steps and problem of recontamination occurred (42).
In 1993, Varga et al developed a solution containing Neomycin, Propamidine, and Polyhexanide. Such a solution was found to be antiparasitic and used as multipurpose solution for hydrophilic contact lenses and could also be used in the treatment of microbial keratitis. However, Varga proved that polyhexanide is the best choice as far as multipurpose solution for soft contact lenses is concerned and did not need neomycin and propamidine for cleaning and rinsing purpose (43).

In 1994, Coulson et al found that multipurpose solution could be easily contaminated than multistage contact lens solution care regimen for hydrophilic lenses. Patient compliance was better because of one bottle system but frequent usage cause easy contamination. They also found that if the contamination level was $10^2 \text{ cfu/ml}$ – the turbidity due to microorganisms was not visible. Turbidity of the level of $10^6 \text{ cfu/ml}$ is visible to the naked eye (44).

Kelly prepared single step multipurpose solution. The single step multipurpose solution used contained preservative, surfactant, buffer, deproteiniser, viscosity imparting agent and chelating agent. All four types of contact lenses were used i.e. Group I, II, III and IV (Netrafilcon, Lidofilcon, Bufilcon and Etafilcon respectively). The adherence to *Acanthamoeba polyphaga* to different types of contact lenses was studied using phase contrast microscopy. More *Acanthamoeba* adhered to Lidofilcon and least to Etafilcon (45).

Beagly et al proved that multipurpose solution could remove *Acanthamoeba* from all types of contact lenses whether it was ionic or non ionic. The concentration of polyhexanide required to remove microorganisms should be in between 0.0001% to 0.0005%. They stated that above 0.0005% concentration of the polyhexanide could be ocular toxic (46).

Apart from *Acanthamoeba* adherence as shown by Kelly, fungi could also adhere and it can enter into the matrix of hydrophilic contact lenses. Fungi adherence was more in neotropical location. It was more in Etafilcon lens as proved in 1995 by Hurtado (47).

In 1995, Cesar et al found that hydrophilic contact lenses were usually contaminated by *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Proteus mirabilis*. They found that disinfectant in multipurpose solution could kill the above three types of bacteria (48).
David et al in 1995 observed that biofilm that develops on hydrophilic lenses encourage *Acanthamoeba*, fungi and bacteria adherence. The best sterilization method was heat disinfection at 70-80°C that helped in the removal of microorganisms and biofilm adherence could be avoided by using multipurpose solution. Hydrogen peroxide also gave good results but disinfection with this compound becomes two steps process (49).

They also used chlorine disinfection method to clean, disinfect hydrophilic lenses. They used sodium hypochlorite (50 mg/L) and found that cysts of *Acanthamoeba* can resist chlorine disinfection. The purpose of multipurpose solution should not only be cleaning, disinfecting and deproteinising but should also be rinsing soaking and lubricating (49).

In 1995, Radford et al proved that *Acanthamoeba* parasites a very rare but potentially devastating corneal infection could can occur even if chlorine disinfection is used. The risk of keratitis was found to be associated with disposable lenses. They proved that 80% of keratitis could be avoided by the use of Polyhexanide in the contact lens solution. It was also found micro-organisms found entangled in biofilm were sessile phenotype and were far more resistant to disinfectants than the planktonic phenotype used in laboratory for *in vitro* test (50).

In 1995, Illingworth et al (51) found that *Acanthamoeba* keratitis a very serious complication associated with contact lens wear is not rare but common in U.K. This could be treated with a combination of Polyhexamethylene biguanide and Propamidine isethionate. They also proved that solution contained Polyhexanide (5 ppm) and Chlorhexidine digluconate (30 ppm) were most effective at rapidly killing bacteria and yeast in 6 hrs. Solution with Polyhexamethylene biguanide (15 ppm) was also effective against bacteria and yeast but very slightly effective against *Aspergillus niger* spores. Thiomersal preserved solution could kill only *Staphylococcus aureus* but soaking overnight with Thiomersal, the solution could kill both *Staphylococcus aureus* and *Aspergillus niger*. The solution containing Chlorhexidine digluconate could also kill *Serratia marcescens* and *Pseudomonas cepacia* but solution containing Benzalkonium could not kill either of the micro organism (51).

Keevan et al (52) also proved that 50 ppm of Polyquad did not kill *Pseudomonas cepacia*. Multipurpose solution containing Benzyl alcohol could not kill *Pseudomonas* hence not
used as preservative for hydrophilic contact lens solution. Then they tried 0.1% of benzyl alcohol, 2% of surfactant and 0.1% of Disodium edetate that could kill vegetative cells of bacteria but did not reduce *Aspergillus niger*.

Stephanie *et al* reviewed the role of disinfectants in contact lens wear and summarized the current available contact lens disinfection systems and provided recommendation of soft contact lens use. They proved that widely recommended preservatives for multipurpose solution for hydrophilic contact lenses were Polyhexanide and Polyquad (53).

Silvany *et al* (54, 55) showed that these two preservatives were the only choices left to be used in single step multipurpose solution because of their antibacterial, antifungal and antiacanthamoebic activities.

In 1995 Stapleton *et al* (56) gave the epidemiology of *Pseudomonas aeuginosa* in keratitis during contact lens wear. They also proved experimentally that only Polyhexanide preserved multipurpose solution could kill *Pseudomonas*.

Turnec *et al* in 1995 showed the antibacterial activity of chemical disinfectants and found comparable to the activity of Hydrogen peroxide neutralization system at their respective active disinfection time against most organisms. Most of the modern preservatives that included Polyhexanide, Polyquad had the activity similar to Hydrogen peroxide moreover when tested under simulated conditions and in same case the activity was even more rapid than peroxide system against the organism tested. The disadvantage of peroxide system is that after neutralization, the peroxide system were no longer able to control an influx of additional organisms, and it was two step system. This study suggested that the incidence and degree of the lens cases contamination can be reduced by the use of preserved solutions for lens storage instructions and by careful patient adherence to cleaning, rinsing and disinfecting (57).

Sousa *et al* in 1996, studied that microbial keratitis caused by *Pseudomonas aeruginosa* is the most common contact lens associated corneal infection. The multipurpose solution used contained Polyhexanide, Polyquarterinum and Polyaminopropyl biguanide. The three solutions were effective against several of ocular pathogens and the addition of synthetic ceropin analog, D3C, the microbiocidal peptides isolated from the haemolymph of the cecropia moth augmented their antimicrobial activity in the presence of contact lens (58).
Key et al, in another development related to microbial activity, found that eyes own defence system is also very important that includes immunoproteins, the mucin of the tear layer and the blinking also helps in washing off. They observed that patients who blink more can eradicate more of *Pseudomonas aeruginosa* with the use of multipurpose solution than those who blink less frequently (59).

Seal *et al* documented the fact that topical Chlorhexidine and Propamidine formulated as multipurpose solution for hydrophilic contact lenses were effective for treating *Acanthamoeba* keratitis provided the drugs were continued for a sufficient period. They did not observe any toxicity or resistance to *Acanthamoeba* isolates (60). They showed the effectiveness of soft contact lenses disinfection system against *Acanthamoeba* on the lens surface. This investigation compared the efficacy of three widely used contact lens disinfection system against an ocular isolate of *Acanthamoeba polyphaga*. These results also showed that rubbing of contact lens surface decrease the number of *Acanthamoeba* and reduce the possibility of other micro-organism (60).

Apart from microbiological activity which is covered as cleaning and disinfecting steps of multipurpose solution, the pH of the multipurpose solution is equally important. If pH of the solution do not match with tears then irritation will occur. The best pH at which no irritation occurred and micro-biological activity also persist is 7.45 as noticed by Tang and his co-workers (61).

Midelfart *et al* have performed systematic examination of the rate and level of contamination of contact lens case in a population of asymptomatic contact lens wearers using commercially prepared chemical disinfection solutions. They found that contact lens container should be rinsed and cleaned by multipurpose solution before soaking the lenses (62).

Gray *et al* also observed that contact lens cases are a recognized potential source of pathogens associated with corneal infection. They also suggested that containers should be thoroughly cleaned and then soft lenses should be stored in multipurpose solution (63).

Campbell *et al* observed that if the contact lenses were not sufficiently cleaned and soaked in multipurpose solution then ocular dryness may also occur. One application of
multipurpose solution requires 10-25 ml to be coated on the lens. They also gave the list of multipurpose solutions available globally (64).

The multipurpose solution was applied on rigid gas permeable lenses and then protein deposition and the removal was studied. The worn lenses were studied using a software and video microscope to measure the light absorbance by contact lenses. The cleaning efficiency as far as protein removal was concerned was studied by Ami Tan and co-workers. They found that with increase in deposition the light absorbance was decreased (65).

Liesegang et al (66) reviewed data on contact lens and the risk associated. Those who use multipurpose solution with strict care regimen did not suffer from redness and those who use disposable lenses did not use multipurpose solution suffered from redness in the eye. This was also proved by Rodriguez et al (67). They carried out deposition and removal studies. They found that Lactoferrin level was decreased in the contact lens wearers suffering from giant papillary conjunctivitis (redness).

Monet and Radford (68), observed that chorine based disinfection did not give good results as proved earlier by McNally (30). Polyhexanide preserved multipurpose solution with Poloxamer as surfactant gave good results. Buffer used was citrate and that also acted as deproteinizer.

Wong et al conducted a hospital based retrospective study to evaluate fungal and bacterial keratitis in contact lens wearers using a case control design to compare risk factors and clinical outcomes (69). They also observed that contact lens wearers usually suffer from bacterial keratitis and with ocular diseases. Fungal keratitis appears more likely to result from ocular trauma. People in India, Singapore, Africa and middle East suffer from fungal keratitis as these are topical warm countries.

Lehtonen et al gave a new preservative for multipurpose solution. It was ethyl 6-O-decanoyl glucoside (EDG) combined with Chlorhexidine acetate to give Ethyl decanoyl glucoside Chlorhexidine (EDGC) (70). Subjects using EDGC had fewer pathological findings than subjects using Polyaminopropyl biguanide (PAPB). EDGC was therefore better than PAPB and can be used in single step multipurpose solution for hydrophilic contact lenses.
Durban et al have found the efficiency of 20 commercially available multipurpose solution for hydrophilic contact lenses. They studied solutions against five bacteria (*E coli*, *P. aeruginosa*, *S. epidermidis*, *S. marcescens* and *B. subtilis*) and one fungus (*Candida albicans*). The solution that contained Polyhexanide, Poloxamine and Disodium edetate gave good results (71).

Presley and co-workers studied multipurpose solution and its effectiveness against *Aspergillus* and found that hydrogen peroxide system gave the best results and next was the polyhexanide preserved solution. The studies were carried out using *Aspergillus fumigatus* (72).

Similar studies were conducted using *Acanthamoeba* by Illingworth et al. A variety of topically applied therapeutic agents were found to be effective in multipurpose solution for hydrophilic contact lenses. These included Propamidine isethionate, Clotrimazole, Polyhexanide and Chlorhexidine. Surfactants used were Poloxamine and Poloxamer. Deproteiniser used were the Buffers Phosphate, Citrate and Hydranate. Disodium edetate when added increased the activity of Polyhexanide. These preservatives were also used in the treatment of microbial keratitis due to contact lens wear (73).

Reinhardt mentioned in the official monograph of Bausch & Lomb that Citrate and Polyammino propyl biguanide is an effective combination in multipurpose solution used for hydrophilic contact lenses (74).

Rosenthal and his co-workers evaluated the antimicrobial activity of chemical hydrogen peroxide and neutralizer in contact lens disinfection. The acute activity storage and recontamination potential of the two disinfection methods were compared by challenging the disinfectants with *Staphylococcus* species, *Pseudomonas, Serratia marcescens, Candida albicans* and *Aspergillus fumigatus*. Chemical disinfectants preserved with Polyhexanide and Polyquad with no additional preservatives were tested. The lens cases from patients using Peroxide neutralizer system tended towards heavier contamination than the ones using Polyhexanide preserved solution and Polyquad preserved solution (75).
Alemany et al worked on nine brands of multipurpose solution. They observed that multipurpose solution with pH range from 6.69 to 7.56 were effective as cleaning, disinfecting, rinsing, soaking, deproteinising and lubricating all in one solution (76).

Niozi and co-workers studied the anti Acanthamoeba activity of multipurpose solution. This study investigated the effect of multipurpose solution on hydrophilic contact lenses using strains of Acanthamoeba in U.K. and South Africa. Polyhexanide and Polyquad were found to be effective (77).

In an in-vivo protein deposit kinetics study on hydrophilic lenses. It was observed that group II lenses were better than group I, III and IV. It was proved that non ionic high water content lenses were better as there were fewer lens deposits on these lenses. Stevenson and his colleagues researched that introduction of multipurpose solution using second generation preservatives has considerably reduced the incidence of Acanthamoeba keratitis in contact lens wearers. The preservatives found to be effective were Polyhexanide, Polyquad and Hydrogen peroxide (78).

Inchijima et al determined oxygen tension on rabbit corneas beneath gas permeable and soft contact lenses after soaking them in multipurpose solution overnight. Oxygen permeability was better in hydrophilic contact lenses than gas permeable lenses. Polarographic determination of oxygen tension provided reliable information about the amount of oxygen available to the cornea under a lens for both open eye and closed eye conditions. Their study showed that the contact lenses hindered oxygen transmission (79).

Willy et al found that contact lenses provide a safe and effective modality for vision correction and 80% complications of contact lens wear were not due to the solution but poor patient compliance. They observed that a sizeable proportion of contact lens wearers do not adequately adhere to recommended contact lens care and many have an inadequate understanding of contact lens care guidelines. Therefore not only the pharmacist job is to take care of the formulation and evaluation of multipurpose solution but the practitioner job is to place more emphasis on patient education at the time of initial contact lens fitting and reinforce such instructions during follow up visits (80).
Christensen *et al.* observed that hydrophilic contact lenses treated with multipurpose solution prevent adsorption of Naphcon A into the eyes. The multipurpose solution contained Polyquad as preservative (81).

Pham *et al.* had developed an effective and reliable test battery that reveals toxicity mechanism of contact lens solutions on cell metabolism and proliferation. Various products like Renu, Complete, Opti free were used. These multipurpose solutions were screened for their toxicity (82).

Leinp and co-workers had conducted a three months randomized comparative cross over test to evaluate the clinical performance of lenses manufactured from Omafilcon A with signs and symptoms of dry eye. The subjects own daily wear soft lenses were used as controls. Their study indicated that the daily wear of nonionic lenses rinsed, soaked, cleaned disinfected, lubricated and deproteinized by multipurpose solution gave better comfort, fewer symptoms, less on eye dehydration and less fluorescein corneal staining than other soft wear contact lenses (83). Iskeleli *et al.* (84) compared the lactate dehydrogenase (LDH) activities in the tears of patients wearing different types of contact lenses and those who do not wear contact lenses at all. There was no statistically significant difference in the LDH activities between soft and semi soft contact lenses. Extended wear soft lenses (hydrophilic lenses) had significantly higher tear LDH activities than control group. Tear LDH activity may be a useful method in evaluating the physiologic response of extended soft contact lens wear.

Ren and coworkers evaluated the effect of hypoxic and hypercapnic stress on bacterial adherence to surface corneal epithelial cells as well as LDH level in the human beings wearing hydrophilic contact lenses using multipurpose solution. Their results showed that longer hypoxic exposure may be required for promotion of increased epithelial cells to *Pseudomonas aeruginosa* binding following hydrophilic lens wear in human (85). Ren further established that hydrophilic lenses which allow greater ultra transmissible oxygen may offer a significant potential advance in safety for extended wear. New ultra hydrophilic lenses did not appear to increase bacterial binding over individual control levels and suppress surface epithelial cell shedding. The hydrophilic lenses which were
worn were treated with multipurpose solution containing Polyhexanide with Citrate as deproteiniser (86).

Pulse et al observed that most clinicians agree that fitting of semi soft lenses (RGP) is also the preferred treatment strategy for some types of patients although many patients have difficulty in adapting to full time daily wear of these lenses. Soft lenses still remain the most popular and convenient lenses to be worn. Successful wear of contact lens was defined by them as a minimum of 14 hours per day without adverse ocular response that would contraindicate either full day daily wear or extended wear (87).

Jupiter et al had found that hydrophilic (soft) contact lens wear is comfortable and successful than hard and semi soft wear. Same quantity of solution as multipurpose containing polyhexanide gave best results with hydrophilic lenses as far as comfort wear was concerned. Semi soft lens wearer developed ptosis without obvious cause during the study wear. They observed that softer material is better than a hard material(88).

Porazinski et al conducted a retrospective study of 47 patients and concluded that those who use multipurpose solution along with enzyme cleaning once a month develop giant papillary conjunctivitis (GPC) than those who do not use enzyme cleaning. Enzyme cleaning cause allergy and hence it should be avoided. Hydrophilic lenses which are frequently replaced were found better than the extended wear lenses as such lenses cause GPC (89).

Sweeney et al had ascertained the incidences of microbial contamination of preserved and non preserved contact lens solutions. The multipurpose solution with Polyhexanide, Disodium edetate and Sorbic and showed the highest percentage of activity and was sterile. Polyhexanide with Disodium edetate was a better formulation than the solution containing only Polyhexanide (90). Lever and Miller evaluated six single bottle of multipurpose lens care solutions and a two component lens care system for disinfection efficacy according to stand alone primary criteria within the recently published US food and drug administration guidelines (91). The solution containing Polyhexanide, Disodium edetate and Poloxamer met the FDA’s acceptance criteria for stand alone disinfectants against all challenge organism which included *Staphylococcus aureus*, *Serratia marcescense*, *Pseudomonas aeruginosa*, *Candida albicans* and *Fusarium solani*. Other
solutions containing Polyquad failed to meet the FDA’s acceptance criteria for *Candida albicans* (91).

Lehtonen *et al* have studied the behaviour of the multipurpose solution containing 0.00025% of chlorhexidine acetate (CHX) and the solution containing CHX and Ethyl-6-O deconyl glucoside (EDG) as 0.05%. The protein content of contact lenses and tryptase activity of tear fluid were measured. They found that combination in multipurpose solution did not really help. Although EDG prevented development of papillary hypertrophy in contact lens wearers (92).

Parra *et al* studied the antibacterial and antifungal effects of soft contact lens disinfection solution. The various types of multipurpose solutions containing Hydrogen peroxide, Polyhexamidine, Polyquad and Polyaminopropyl biguanide (Dymed) were in contact with hydrophilic contact lenses for 14 hrs. All ten preservatives killed *E. coli, S. aureus, P. aeruginosa, S. marcescens*. Polyquad could not kill *Candida albicans* (93).

Kilvington surveyed that incidence of Acanthamoeba keratitis was reduced over two year in Scotland and U.S.A. due to the introduction of multipurpose solution containing Polyhexamethylene biguanide (94).

Landa and coworkers compared the efficacies of the multipurpose solution with and without detergent although preservative was present in all multipurpose solution. The surfactant used were 0.025% w/v of Sodium lauryl sulphate (SLS) and 0.02% w/v of Tauranol. A surface physicochemical analysis of contact lenses were done. The surfactant mixture of SLS and Tauranol could remove 95% of adhered *Pseudomonas aeruginosa* and the one which did not contain the surfactant could not give good results. Hence the multipurpose solution should contain surfactant so that surface activity and removal of bacteria could be enhanced (95).

Sadiq *et al* evaluated the contamination of used disposable soft contact lenses with *Acanthamoeba*. Their studies proved that patients who regularly clean and disinfect their disposable hydrophilic contact lenses using a well formulated multipurpose solution did not suffer from *Acanthamoeba* contamination. The average time of wearing the hydrophilic contact lens was found to be 13.7 hrs. per day. Complete disinfection and
cleaning occurred when the lenses were soaked for 4 to 6 hrs. in the multipurpose solution containing Polyhexanide (96).

Grant et al found that ulcerative keratitis due to contact lenses which is the most serious complication is actually peripheral type called contact lens induced peripheral ulcer (CLPU). The lesions that appear are self-limiting and typically heal within 7 days without treatment. Contact lens induced ulcer is not threatening. Grant found that this could occur maximum in soft contact lens wear (97).

Ilhan and coworkers compared the surface deposits of proteins and lipids on frequent replacement soft contact lenses and conventional daily wear soft contact lenses. Frequent replacement hydrophilic contact lenses regularly treated with multipurpose solution showed fewer deposits than conventional daily wear soft contact lenses. They found that surface deposits can not be prevented totally (98).

John et al had studied the changes in bacterial adhesion resulting from air drying hydrophilic contact lenses. An in-vitro study was conducted on Etafilcon type lenses. These were ionic high water content lenses treated with multipurpose solution. Soft contact lens air drying results in increased bacterial adhesion. Contact lenses and containers therefore should not be dried openly (99).

Seal and co-workers have investigated the risk factors for *Acanthamoeba keratitis* amongst contact lens wearers. Failure to disinfect contact lenses was associated with increased risk of keratitis and hence disinfection (chemical because heat is not practical method) is a must for contact lens wearers (100).

Sharma et al have demonstrated that there are certain factors which leads to *Acanthamoeba keratitis* in contact lens wearers. They determined that the ability of this organism to adhere to corneal epithelial cells (EC) recovered from non lens wearers (NL) and the hydrophilic contact lens wearers. There are many factors that are responsible for amoebic adherence to those who wear contact lenses (101).

Phillips and co-workers observed that lathe cut hydrophilic contact lenses have reduced visual dysfunction compared to spun cast. Lathe cut hydrophilic contact lenses which were rinsed and treated with multipurpose solution offered comfort (102).
Efron et al found that oxygen transmissibility is a key determinant to the physiological response of the cornea to contact lens wear. Group IV lenses were more susceptible to the changes than Group III, II and I. They observed that change in water content altered the oxygen transmission and hence the comfort. Dehydration during contact lens wear can alter the oxygen transmissibility of hydrogel lenses and is quite significant clinically (103).

Rosenthal et al once again established that the care regimen using Polyhexanide for hydrophilic contact lenses is still the surest method of disinfection. Polyhexanide showed the results similar to 3% hydrogen peroxide. Unlike 3% Hydrogen peroxide system, Polyhexanide in the concentration of 0.0002% could retard contamination during storage. This was an express multipurpose disinfection system called MPDS (104).

Buck et al found the amoebicidal activity of a contact lens multipurpose disinfecting solution (MPD). Polyquarternium I, Myristamido dimethylamine was compared to disinfection / neutralization peroxide system against Acanthamoeba castellani and Acanthamoeba polyphaga trophozites and cysts. This MPDS was found to be very effective(105).

Rosenthal et al found that the disinfection activity of multipurpose solution containing Polyquarternium –I and Myristamidopropyl dimethylamine was better than the other solution containing Polyhexanide. The first MPS covered a broader range than the second multi purpose solution and on storage both prevented the re-growth of the organism during extended storage (106).

Corrigan et al determined the levels of Acenobacter species and Gram negative bacteria associated with soft contact lens wear after cleaning and rinsing and then storing in multipurpose solution containing Polyhexanide 0.0001% and Poloxamer 407, 0.1%. It gave good result (107).

Choi et al found that the patients wearing hydrophilic contact lenses with high water content and good oxygen permeability using strict care regimen and using multipurpose solution preserved with 0.0001% Polyhexanide, 0.01% of Disodium edetate and Poloxamer 0.1% did not suffer with bacterial and fungal keratitis. Hence soft contact
lenses thoroughly cleaned and rinsed by multipurpose solution are better than the lenses not treated with multipurpose solution (108).

Kasti et al evaluated the effectiveness of low power microwave irradiation (2,450 MHz., 600W) set at 10% power. Contact lenses were first infected by *S. aureus*, *P. aeruginosa* and *S. epidemidis* and infected vials were placed in non preserved saline and then exposed to 18 minutes to microwave. All contact lenses were disinfected and there was no damage to hydrophilic contact lenses (109).

Rontempo and coworkers carried out deposition studies. They carried out investigations for the mechanism of protein and lipid adherence to hydrophilic contact lenses *in-vivo*. Deposited lipids were removed by Methanol based extraction using HPTLC and protein by extracting with urea using gel electrophoresis. The lenses used were new never worn hydrophilic lenses and deposition was not subject dependent but material dependent. The lenses were treated with multipurpose solution using Polyquad and Hydranate as deproteiniser and it was found to be effective (110).

Pecilli and coworkers also developed a multipurpose solution containing Polyhexanide and proved the solution as antibacterial antifungal and antiprotozoal (111).

Lakkis et al developed and evaluated multipurpose solution for hydrophilic contact lenses and found to be effective against *Pseudomonas aeruginosa*, the most common pathogen of hydrogel contact lenses. It gain access to the eye via contamination of the lens, lens case and lens care solution (112).

Sweeney et al observed the bacterial colonization of soft contact lenses in subjects for successively increasing period, up to 13 nights of wear. Their study showed that increasing the length wear of hydrophilic contact lenses increases the level of microbial colonization of lenses. The contact lenses were washed and rinsed with multipurpose solution only once (113).

Marques (114) observed that multipurpose solution containing 0.001% of Polyhexanide could remove *Aspergillus niger* as it could remove other Gram positive and Gram negative bacteria. Polyhexanide is the broad spectrum second generation preservative used in multipurpose solution.
Martin and coworkers also reported the effectiveness of multipurpose solution with viscosity 1.68 cps, pH 7.46 and preserved with Polyhexanide, Disodium Edetate and Poloxamer. Bacterial keratitis is usually caused by *Pseudomonas aeruginosa* and fungal keratitis by *Aspergillus niger* hence if the multipurpose solution is effective against *Pseudomonas* and *Aspergillus* then it is a perfect multipurpose solution. Acanthamoeba is not prevalent in India but in U.K. and U.S.A. It has been found that Polyhexanide is also active against *Acanthamoeba* as well(115).

Ahaneto and coworkers found that multipurpose solution containing 3 ppm of Polyhexanide and 5 ppm of Polyquad both in separate formulation are effective preservative against *Pseudomonas, Staphylococcus, Serratia, Candida, Aspergillus* and *Acanthamoeba*. Polyhexanide is the surest preservative which could give sterile hydrophilic lenses and prevent recontamination on further soaking the lenses in the solution (116).

Sehgal *et al* observed the adhesibility of *Acanthamoeba castellani* trophozoites and cysts to hydrophilic contact lenses and to human cornea. They observed that older lenses have higher chances of getting colonized with bacteria due to the occurrence of scratches than new lenses where the adherence to bacteria was much lower (117).

Silicone lenses are at greater risk of promoting Acanthamoeba infection if exposed to the organism because of the enhanced attachment characteristic of new material. Hence silicone lenses are not preferred. Even rinsing with multipurpose solution containing Polyhexanide did not effect fully. Although 50% removal was enhanced. Such type of work was also carried out by Beattie *et al* (118).

*In-vitro* uptake and release studies of ocular pharmaceutical agents and drugs were carried out on silicone contact lens, material and p-HEMA (Hydroxy ethyl methacrylate) hydrogel contact lens material by Karlgard *et al* (119). Drugs used in multipurpose solution and the other pharmaceutical agents which were used as additives in the formulation of the all in one solution were studied for their *in-vitro* release behaviour. Drug uptake/release appeared to be a function of lens material toxicity, water and silicon content. Silicone materials released less drugs than p-HEMA. Therefore p-HEMA contact lenses are preferred (119).
Dang et al established the fact that FDA group I lenses show fewer adherence to *Pseudomonas aeruginosa*. Hence non ionic low water content contact lenses treated by multipurpose solution carry lower risk of bacterial contamination than group II- non ionic high water content lenses. Group III and group IV were totally discarded and group I were found to be the best group of contact lenses (120).

Keith et al determined the lysozyme deposits (proteins) on contact lenses. Lysozyme rapidly accumulates on lenses. Out of group, I, II, III and IV types of hydrophilic lenses group IV showed the greater accumulation. The problem could be solved by using Tris buffer as deproteiniser and Citrate buffer for removal of proteins from lenses. These buffers could remove upto 70% of deposits from group III and IV types (121). Citrate buffer is therefore preferred.

Young et al used multipurpose solution on hydrophilic lenses and concluded that a well formulated balanced multipurpose solution containing drug / preservative, buffer, chelating agent, viscosity imparting agent, deproteiniser, lubricant in an ophthalmic vehicle on non ionic hydrogel lenses with greater oxygen permeability (DK) can give good results, increasing patient compliance (122).

Ahuja et al (123) worked on multipurpose solution containing Polyhexanide which prevented the growth of *Aspergillus*. Polyhexanide till date is the proven drug for multipurpose solution used for hydrophilic contact lenses in an ophthalmic base.

The quantitative and qualitative studies other than microbiological studies were carried out in 2004 and 2005. Before 2004, it remained a guarded secret. Non aqueous titrimetry analysis was discussed in 2004 by Hattori et al (124). This method could not detect small concentration i.e. µg/ml. Moreover this method requires solid polyhexanide. The titrant used was 1N Perchloric acid and end point was determined potentiometrically. Polyhexanide in multipurpose solution could not be estimated by this method.

In the year 2005, the analytical method by HPLC was given by Yiping et al (125). This was the only method available for estimation of Polyhexanide hydrochloride. Madhavan et al also worked on PHMB. HCl as the drug used in bacterial and fungal keratitis (126).
In situ studies were conducted by Leng et al (127) using chick chorioallantoic membrane (CAM) as a model tissue for retinal research. CAM has been used in the past also for ocular studies (128).

Stiegemeier, et al evaluated clinically the efficacy of the multipurpose solution containing Polyhexanide. Such system gave contact lenses with less of lysozyme deposition on Group IV contact lenses than on Group II lenses. Multipurpose solution containing Polyquad was less efficient in removal of deposition than Polyhexanide, however both offer the convenience of no rub regimen (129).

Borazjani et al found the disinfection efficiency of contact lens multipurpose solution containing Polyhexanide against Acanthamoeba polyphaga and Acanthamoeba castellanii (ATCC 30868) cysts and trophozoites by biocidal and no rub/rinse regimen testing. They observed that Polyhexanide based system could remove Acanthamoeba. Results were better on conventional hydrogel lenses than silicone hydrogel lenses (130). Polyhexanide proved to be anti acanthamoeba that could kill both cysts and trophozoites.

Stiegemeier, et al evaluated clinically the efficacy of the multipurpose solution containing Polyhexanide. The solution was found to be safe and efficacious when used by symptomatic Group IV contact lens wearers (131).

Nichols investigated the frequency of deposition and impact of various multipurpose solutions on a silicone hydrogel lenses. He concluded that less than 10% of subjects exhibited clinically significant levels of deposition with galafilcon lenses when cleaned with Polyhexanide based multipurpose solution. Rubbing and rinsing steps significantly reduced the depression rate (132).

Epstein evaluated the possible effects of two leading contact lens care products containing Polyquad and Polyhexanide respectively on corneal sensitivity, relative comfort and superficial corneal staining in adapted disposable soft contact lenses wearers. A biguanide product was associated with decreased eye comfort and disturbance to normal corneal sensitivity than Polyquad based on disposable lenses (133).

Rosenthal et al found that the multipurpose solution containing Polyquad showed a low uptake of biocide and maintained fungicidal efficacy against Fusarium solani than the
multipurpose solution containing Polyhexanide. Another multipurpose solution containing Alexidine showed significant uptake of the preservative. The test was done on Group IV contact lenses (134).

Paugh et al proved that use of Polyhexanide based multipurpose solution for contact lens disinfection has been linked to low grade corneal staining. The in vitro data suggested that carboxy methyl cellouse (CMC) neutralized the Polyhexanide and hence CMC should not be used in such multipurpose solutions based on Polyhexanide. Paugh supported the in vitro data with in vivo data (135).

Bharathi et al found that the incidence of Acanthamoeba keratitis amongst the corneal ulcer patients was 1% and it was due to the mud. The Potassium hydroxide preparation is a sensitive diagnostic tool for the detection of Acanthamoeba. Inappropriate therapy results in poor visual outcome. Polyhexanide responded well in such cases. However this was not related to contact lens wear but was a pathological finding (136).