CHAPTER 1

Introduction

1.1 Surgical Site Infections and its Management

Surgical site can be defined as any cut or operation by using manual or instrumental practice by well-trained or expert surgeon for better health or comfort of patient. Wound can be defined as injury to the body part caused by cut, rupture, damage or break of skin or surface of the body. Surgical site is a good example of wound (Fig. 1.1) (Leaper, 2010).

![Fig. 1.1 Images of Surgical Site (a) Surgical Operation & (b) Knee Operation Cut Site](image)

1.1.1 Surgical Site (Wound) Infection

Surgical site infection is a term associated with the damage of such operated site. Wound infection can be defined as the presence of replicating nuisance microorganisms within a wound that cause host injury temporarily or permanently. There are major chances of infections to surgical site (Mangram et al., 1999).

These infections may be due to any external part or device or contact of infected material. Along with, there are so many factors which are responsible for surgical site infections. Some common reasons are; cause of implant or any external material used in operation like; scaffold, suture etc. In some cases, immune suppressive drugs can increase the risk of infection. Laxity of aseptic technique is also one of the major factors responsible for SSI (Hawn et al., 2011). Deviation to established surgical principles, un-warranted reliance upon antibiotic therapy for prophylaxis. There is a major possibility of SSI when microbial contamination occurs. Microbial contamination can
be classified as exogenous (External contacts from breaks) and endogenous (Internally from skin or surface muscle) (Scott and Bloomfield, 1990).

According to universal law of nature any animal body cannot accept external materials, bodies, microbes, devices or climatic change easily (Fig. 1.2). It starts to reproduce self-defensive system with the help of immune power. But unfortunately when there is a power of external factors is more; in that case, there will be less resistance and thus results in a growth of harmful bacteria. Bacteria can be defined as simple cell structures which are further categorized according to their cell wall and shape.

Bacteria can be mainly classified as cocci having spherical shaped cells, bacilli having rod like structure and spirochetes are like spirals and can be arranged singly (Lowy, 2013). After gram staining gram positive bacteria show purple and gram negative bacteria show red staining. There are mainly two types as gram positive and gram negative bacteria as shown below (Fig. 1.3 and 1.4).
1.1.2 Impacts of Surgical Site Infection

Wounds or surgical infections cause, increase discomfort, anxiety and sometimes leads to death. It is estimated that surgical wounds and therefore caused infections results in an increased length of hospital stay. Hence the prevention, care and management of wound infections have a major impact on both patient health and cost of treatment. Surgical site infections may result to create critical situation for patent (Kirkland et al., 1990).

The cost of surgery includes longer time stay in hospitals, nursing care, cost of medicine and dressings, readmission for treatment and sometimes repetition of surgery. Unfortunately this is directly associated with health and health economics of patient. This is fatal if not treated and cured properly. Thus there will be a loss of health as well as wealth. That is the reason surgical site infections are important to monitor and needs to take appropriate care. For wound care there are number of strategies available (Whitehouse et al., 2002; Lissovoy et al., 2009).
1.2 Available Strategies for Wound Care

Antibiotic treatment is preferable and mostly used to treat infections in wound care. There are various dosage forms available to treat the wound infection in surgical side. These dosage forms are having their own benefits and limitations (Rhoads et al., 2008; Omeara et al., 1999). Following are existing dosage forms which are used for antibiotic drug delivery.

1.2.1 Oral Route of Administration

It is a traditional route of medication and having wide range of drugs category administered by this route. It is having major benefit that easy to take and carry. But having some limitations like, not useful for the unconscious patient. Also in antibiotic drug delivery related to wound care, cause of low bioavailability through this route most of drugs are not feasible by this route.

Amino glycoside category drugs are not generally preferred. Since they are not absorbed from the gut. For gut decontamination oral administration can also be applied. In oral route of administration cause of ‘first pass effect’ most of the drugs degrades (Verma et al., 2010).

1.2.2 Pulmonary Route of Administration

Pulmonary route of administration is popular mostly for asthma care. Research is going on delivery of other category drugs through this route. In wound care category up to day, no such product is reported and approved by FDA. Aminoglycoside category drug delivery through pulmonary route is reported with limited data (Fiegel et al., 2008). No such commercial product is available for aminoglycoside drug delivery.

1.2.3 Topical and Transdermal Drug Delivery System

Various marketed formulations available for delivery of aminoglycoside drugs through dermal route. These are specially prescribed for local or skin infections. Burn care products are mostly delivered by this route. It is most popular for products also. It is having a limitation that aminoglycosides are comparatively slowly absorbed by this route. Also it is not advised to apply directly on wound. Shiozuka et al. (2010) reported transdermal drug delivery for aminoglycosides and Gentamicin sulphate (GE) as a model drug. Skin infections can be treated by using transdermal patches. One of the
major drawbacks of transdermal patches is that it cannot be applied to wounds directly. Also there is no such reported and FDA approved product available.

1.2.4 Liposomal Drug Delivery

Kimballs biology pages “Cell membranes” defined liposomes as spherical vesicle having at least one lipid bilayer and can be used for administration of nutrient and pharmaceutical drugs (Schiffelers et al., 2001). Gubernator et al. (2006) reported antibiotic drug delivery by using liposomal drug carrier system. Liposome is universal drug carrier system and having various advantages than traditional routes of administration. Main objective behind this research was improving bioavailability of antibiotics and peptides. There is also focus on reducing toxicity and improvement in pharmacokinetics. But cost of such drug delivery system is notable. Common man can rarely afford such medicines.

1.2.5 Neosome Drug Delivery System

Neosome is a non-ionic surfactant based vesicle and generally formed by non-ionic surfactant and cholesterol. (Abdelbary and El-gendy, 2008). Structurally these are similar with liposome. (Briones et al., 2008) reviewed and mentioned that Neosomal drug delivery system is applicable for delivery of antibiotics. Along with other characteristics it is also non affordable to common man. Also needs to develop a formulation with well justified scientific data. Such any commercial approved drug product is not available in the market.

1.2.6 Ethosome Drug Delivery

Godin and Touitou (2005) have discovered the thosomes and examined lipid vesicular systems embodying ethanol at high concentration. Thus this process is named as Ethosomes. These are dermal type of drug carriers which helps drug to enter in systemic circulation by penetrating it through skin (Pandey et al., 2015). It is having its own limitations like this is applicable mainly for high lipophilic drugs. Also clinical data associated with antibiotic drug delivery is not sufficiently available. Antibiotic drug delivery may increase cost as low yield problem (Godin et al., 2003).
1.2.7 Ophthalmic Solutions for Drug Delivery

Ophthalmic solutions can be defined as the pyrogen-free solution and also used for ocular administration. It is one of the popular routes of antibiotic administration in ear and eyes care (Rusczak and Friess, 2003). But it is not having any application regarding wound care. There are number of products developed by this formulation and available in market.

1.2.8 Parenteral Form of Drug Administration

This is one of the famous routes of drug administration. According to safe medication practices dosage form which are given to avoid first pass effect and fast relief comes under this category. These include sterile liquid formulations used to cure many diseases (Eposito et al., 2007). Cause of fast elimination process of Gentamicin sulphate for reaching to C\textsubscript{max} higher concentration of Gentamicin sulphate is required. After maintaining the C\textsubscript{max} only there will be a medical effect.

Thus high dose of Gentamicin sulphate may produce number of side effects. Thus in case of amino glycosides drug administration ototoxicity and nephrotoxicity are seen principally with this form of administration. It is already reported in case of Gentamicin sulphate.

In intravenous route of administration drug product is directly injected in blood stream. And in intramuscular route of administration drug product is directly injected in muscle. Parenteral type of dosage form is generally administered by these routes. Antibiotics are widely delivered by this route of drug delivery. Antibiotics are used to treat urinary tract infections, wound infections, central nervous system (CNS) infections, generalized septicemia infections, infection of skin and soft tissue, infection caused by burning, progressive and deep-seated infection of eyes, infections caused due to surgery like knee replacement etc., can be treated by using antibiotic and delivery through this dosage form (Stone, 1984). As explained previously there are many side effects associated with administration antibiotic through this route of administration.
1.2.9 Implants or Medical Devices as Drug Delivery Vehicles

Implant can be defined as a substance which is manmade device or substance and can be used as alternate to organ, or to staunch the wounds viz. sutures, or scaffolds or insert, stepples etc. Implant which can be used for animal treatment is a good example of medical devise. Thus medical device can be defined as any medical or pharmaceutical device which can be used to treat disease or body disfunction or illness. It can be instrument, contrivance, apparatus, implant, machine etc. Food and drug administration approved medical devices are generally recognized in official NF or USP (National Formulary or United States Pharmacopeia) or any other reference pharmacopeia and its supplements. Medical devices are generally intended for its use in the better life of human being or animal by means of diagnosis, cure, treatment etc.

One of the important criteria to use medical device is its suitability or compatibility towards human being or animal body. It should not create any sub material which may degrade in body and form toxins. But these are best drug carriers which can allow to reach appropriate quantity of drug at site of action. Also it is beneficial for patient by optimum use of drug. Number of drugs are now a days delivered through implant or medical device and which has proven its importance. Controlled delivery of drug is important and difficult to achieve in this case. Therefore patent has to monitor throughout the treatment.

1.2.10 Antibiotic Prophylaxis

Bernard et al. (1999) represented the antibiotic prophylaxis in surgery. According to that antibiotic prophylaxis can be defined as a treatment of antibiotic drug for preventing microbial infection during surgery. Hirota et al. (2003) reported guidelines associated with antibiotic and antibacterial prophylaxis related to surgical site infections. According to Khuri et al. (2007) surgical site infection is a term used to encompass the surgical wound and infections involving the body segments like cavity, bones, joints, meninges and other tissues involved in the operation in the procedure that requires application, use or insertion of implants or prosthetic devices.

Silver et al. (1996) briefly explained antibiotic prophylaxis is performed prior to surgery to control infections. For efficacy, continuous dosing of antibiotics is mandatory. Most popularly aminoglycosides are used for antibiotic prophylaxis. Aminoglycosides are antibacterial category of drugs having old history. These are
applicable for gram positive and gram negative bacteria. The aminoglycoside category drug which acts against gram positive as well as gram negative is called broad spectrum antibiotic. Gentamicin is one of the best example of it. Gentamicin is well known and FDA approved broad spectrum antibiotic. There are a variety of dosage forms are available for Gentamicin. Aminoglycoside act by inhibiting protein synthesis in microbes. It results in growth inhibition and thus control. Aminoglycoside mislead the protein synthesis process by attaching an amino modified glycoside sugar. Nomenclature of aminoglycoside is based on origin bacteria. For example, the aminoglycosides with the suffix mycin are derived from Streptomyces genus and micins are derived from micro monospora.

This nomenclature is not specific for aminoglycosides. But there is no difference in activity of aminoglycoside though this mycin and misin name is different.

1.3 Localized Delivery of Antibiotic Using Biodegradable Polymer

Antibiotics are having adverse effect on body when taken long time to avoid or recover the infection. According to Page et al. (1993) antibiotic medication during prophylaxis creates toxic adverse effects. There are so many evidences reported about this fact. Not all but majority patients face this toxicity problem. He reported case study on aminoglycosides for antibiotic prophylaxis and its adverse or toxic effects. Amidon et al. (1995) reported when drug is having low bioavailability; for better effect high concentration of such drug is to be given to the patient. This excess quantity of drugs accumulates in blood or body fluids and creates toxic effects.

To deliver optimum drug at the site of action is another important need. Optimum drug is a quantity of drug required to heal or cure the illness. Optimum drug can reduce the toxicity levels and improve the health practice. Thus local delivery of drug is preferable. Such types of delivery systems are mostly value added in case of toxic drugs which can create various systemic side effects (such as the oncology drugs and antibiotics).

Another objective is to improve drug delivery system which is beneficial to the patients by providing appropriate effective action. Convenience and safety with reduced side effects and improved bioavailability of the drugs is another important objective. Also decrease in drug dose administration, up and down of drug concentration in blood and brain barrier.
One of the important purposes is to avoid hepatic first pass effect. Aminoglycoside category drugs are mostly administered through parenteral, ophthalmic or topical route of administration. Thus this concept is applicable only in case of when drug will have administered orally or by track where it passes through gastric intestinal fluids.

1.4 Clinical Applicability

Surgical site infection is an infection mainly associated with any infection it may superficial or deep in body and creates dysfunction in that specific area or part by means of damage of body tissue, bad smell, pain etc. It is fatal in case where the deep incision is there and the immune power of patent is less (Horseman et al., 2011). Surgical site infections (SSIs) basically start with surrounding and implant or device or suture like external part when incorporated in body (Cheadle, 2006). Body resists outside materials and thus infection occurred. To control this infection, high dosing of antibiotics is required pre and post-surgery (Horan et al., 2008). Now days, implants are prepared by using biodegradable polymers (Middleton and Tipton, 2000). Antibiotic drug loaded implant will be helpful for preventing SSIs.

1.5 Rational Behind Selection of Aminoglycoside Drug

Aminoglycosides are category of drug having at least two amino sugars and aminocyclitol linked by glycoside bonds. Aminoglycoside category drugs are having inherent toxicity when used without any monitoring and control. As we discussed, in most of the cases amino glycosides are widely used as antibiotic in prophylaxis for controlling infections during and after the surgery. For attaining medical effectiveness during wound care, higher concentrations of such drugs are needed. However, there are reported problems associated with use of higher concentration of amino glycosides in critical operations or surgery or implantations or any other such type of treatments. Amino glycosides are also having side effects to cause nephrotoxicity (kidney damage) and ototoxicity (ear damage) (Avent et al., 2011).

Activity of Gentamicin is well known and studied from longer time. As discussed in aminoglycosides category general action; it inhibits protein synthesis in microbes and thus inhibit its growth. Elaborately, binding of Gentamicin impairs the translational proofreading which leads to misreading of the RNA message and
premature termination, or both, and so to inaccuracy of the translated protein product. Thus it inhibits the protein synthesis and resultant growth of microbe (Fig. 1.5).

Finally, a further cell-membrane effect also occurs with aminoglycosides; functional integrity of the bacterial cell membrane can be lost, later in time courses of aminoglycoside exposure and transport.

![Fig. 1.5 Schematic Diagram for Aminoglycoside as Inhibitor of Protein Synthesis](image)

Thus for pharmaceutical development purpose aminoglycoside category of drug class is selected. This research may improve applicability of such drugs for wound care. Gentamicin sulphate is a model drug selected as it is a broad spectrum antibiotic and widely used for its antibacterial activity. There are number of side effects reported about it and to overcome this challenge delivery of Gentamicin sulphate through biodegradable implant planned.

1.6 Aminoglycoside Category Drug as a Model Drug

1.6.1 Physicochemical Properties of Gentamicin Sulphate (Table 1.1)

Gentamicin Sulphate is (2R, 3R, 4R, 5R)-2-[(1S,2S,3R,4S,6R)-4,6-diamino-3-[(2R,3R,6S)-3-amino-6-[(1R)-1-(methylamino) ethyl] oxan-2-y1] oxy-2-hydroxy-cyclo- hexyl] oxy-5-methyl-4-(methyl amino) oxane-3,5-diol; sulfuric acid (Fig. 1.6)

![Fig. 1.6 Chemical Structure of Gentamicin Sulphate](image)
Table 1.1 Physicochemical Properties of Gentamicin Sulphate (Pub Chem CID 3467)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>C21H45N5O11S</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>575.675 g/mol</td>
</tr>
<tr>
<td>Water solubility</td>
<td>100 mg/mL</td>
</tr>
<tr>
<td>Log P</td>
<td>-3.1</td>
</tr>
<tr>
<td>Melting point</td>
<td>218°C to 237°C</td>
</tr>
</tbody>
</table>

1.6.2 Mechanism of Action of Gentamicin Sulphate

Against Gram-Negative Bacteria: Taber et al. (1987) and Jao and Jackson (1964) reported that in gram-negative bacteria, positively charged Gentamicin is electrostatically attracted to the negative surface charge of the outer membrane that contains abundant amounts of lipopolysaccharide. According to Bell et al. (1991) positively charged Gentamicin displace divalent captions from binding sites that cross-link and stabilize lipopolysaccharide chains that are critical for stabilization of the outer membrane causing permeabilization of the outer membrane, which promotes the uptake of antibiotic and other large molecules. This process is similar to the mechanism of action of polymyxins, and can be antagonized by elevated concentrations of Mg²⁺ that stabilize the outer membrane. Against Gram-Positive Bacteria: According to Pankey and Sabath (2004) in gram-positive bacteria, negatively charged teichoic & lipoteichoic acids that extend through the peptidoglycan cell wall are initial sites of ionic attraction for positively charged Gentamicin sulphate. Briefly; Gentamicin prevent protein synthesis in microbe. In first step by binding irreversibly to the 30S ribosomal subunit protein and 16S rRNA of bacteria. Which prevents the formation of initiation complex with messenger RNA. This is initial step of protein synthesis. Here, four nucleotides of 16S rRNA and single amino acid S12 of protein are bound by Gentamicin. This is a main factor responsible for decoding confusion. This leads to anticodon of tRNA by interacting with wobble base. Thus misreading of mRNA inhibits the protein synthesis by inserting incorrect amino acids in to the polypeptide leading to toxic peptides. Thus it results in to the breakup of polysomes into nonfunctional monosomes.
1.6.3 Toxicodynamics of Gentamicin sulphate

Nephrotoxicity is one of the major side-effect of Gentamicin sulphate and which occurs due to accumulation of Gentamicin sulphate in nephrons of kidneys. According to Morin et al. (1980) when Gentamicin sulphate administered it accumulates in to the renal cortex. Pharmacokinetics of Gentamicin Sulphate is summarized in Table 1.2. It is fatal when the concentration of Gentamicin sulphate reached and concentrating ability of kidney becomes weak. Further he reported that, nephrotoxicity appears to be mostly associated with duration for which serum concentration exceeds 2 µg/ml. The exact mechanism of this toxicity is not reported. This toxicity observes approximately 5 to 25% of patents. It may recover after dialysis if treated properly and within time.

Another one of the major toxicity associated with administration of aminoglycoside is ototoxicity. This is associated with temporary or permanent loss of hearing ability. Selimoglu (2007) reported that when concentration of Gentamicin sulphate is serum exceed more than 10 µg/ml it results into the ototoxicity and vestibular toxicity. It is also reported that when Gentamicin sulphate accumulates in endolymph and perilymph there is a progressive destruction of ventricular and cochlear cells. If this happens repeatedly

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS Class</td>
<td>III (Low permeability – high solubility)</td>
</tr>
<tr>
<td>IV/IM Bioavailability</td>
<td>Approx. 95%, When given by IV or IM route. The average peak plasma concentration (Cmax) is 4 µg/mL when given about 1mg/kg. T max reached after dosing about 30 to 90 minutes.</td>
</tr>
<tr>
<td>Metabolism &amp; Excretion</td>
<td>No metabolism... Peritoneal dialysis and hemodialysis are useful techniques used for extraction of Gentamicin sulphate from body. Clearance rates are 5 to 10 mL per minutes but it is drastically varies.</td>
</tr>
<tr>
<td>Half life</td>
<td>Half-life of Gentamicin sulphate varies according to age and weight and reported about five to five and half hours. (Cutler et al (1972))</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>About 0% to 10%</td>
</tr>
<tr>
<td>Volume of distribution by route of administration</td>
<td>About 25% of lean body weight. Also equal to extracellular fluid volume. Low in secretions and most tissues. High in renal cortical tissue, endolymph and perilymph of the inner ear.</td>
</tr>
</tbody>
</table>
Gentamicin sulphate may produce progressive destruction of these cells and leads to permanent or temporary loss of hearing ability. Some examples are discussed in table 1.3 related to targeted delivery of antibiotics to avoid discussed side-effects. Neuromuscular toxicity is reported which is associated with administration of Gentamicin sulphate. Albiero et al. (1978) and Avent et al. (2011) studied and reported that administration of Gentamicin sulphate in some cases shown the paralysis to the patient because it was observed that higher concentration of Gentamicin sulphate in serum resulted in neuromuscular blockage. But it happens very rarely. This side effect also not having complete information about the exact process.

### 1.7 Local Delivery of GE Through Biodegradable Implant

Polymers with controlled biomedical degradation characteristics can be used as an important part of tissue engineering and drug delivery therapies. Many types of natural and synthetic biodegradable polymers have been investigated for medical and pharmaceutical applications. While use of natural polymers, such as cellulose and starches, is still common in biomedical research, synthetic biodegradable polymers are increasingly used in pharmaceutical and tissue-engineering products.

Synthetic polymers can be prepared with chemical structures tailored to optimize physical properties of the biomedical materials and with well-defined purities and compositions superior to those attainable when using natural polymers. There are now several established chemical classes of synthetic biodegradable polymers that offer
good biocompatibility and can be selected to tune rates of biodegradation and mechanical strength.

Poly (glycolic acid) (PGA), Poly (lactic acid) (PLA), Poly-Caprolactone (PCL) and their copolymers have been researched for a wider range of applications than any other type of biodegradable polymers. PLA/PGA is biodegradable polyesters that degrade in the body by simple hydrolysis of the ester backbone to non-harmful and non-toxic compounds. The degradation products are either excreted by the kidneys or eliminated as carbon dioxide and water through well-known biochemical pathways.

Current applications of the polymers include surgical sutures and resorbable implants, with significant interest to further expand the use of these materials to drug encapsulation and delivery applications. Since PLA/PGA polymers are considered safe, non-toxic and biocompatible by regulatory agencies in virtually all developed countries, additional applications of these materials can be brought to market sooner and are more cost effective than those utilizing novel polymers with unproven biocompatibility.

1.8 Merits of Inventing Dosage Form of Gentamicin sulphate

Gentamicin sulphate is a broad spectrum antibiotic of Aminoglycoside category of drugs. Administration of Aminoglycosides as antimicrobial agent is well accepted and practiced in medical field. As discussed early, there are many adverse effects associated administration of Aminoglycosides. We have selected Gentamicin sulphate as a model drug which is having major adverse effects like ototoxicity and nephrotoxicity. Cause of high elimination of this drug, for medical activity higher concentration is required to maintain in blood. Thus higher dosing is required. Parenteral and topical are accepted routes of administration. Here we planned to design, evaluate and study the local delivery device for Gentamicin sulphate.

When we plan to design new dosage form; there are so many things we have to keep in mind. It avoids first pass effect. It deals with the transfer of drug to the site of action without systemic circulation. Thus optimum use of drug is needed. After the completion of surgery as material degrades simultaneously; controlled release of drug is there. It avoids rounds of taking medication. Cause of optimum dose there are less chances of nephrotoxicity and ototoxicity. Therefore, in order to overcome the
aforementioned limitations there is a scope to prepare a device which should be biodegradable with controlled delivery of active at targeted site.

There are some models prepared and studied for their characteristics.

<table>
<thead>
<tr>
<th>Form</th>
<th>Route</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cream</td>
<td>Topical</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Liquid</td>
<td>Ophthalmic</td>
<td>3mg/mL</td>
</tr>
<tr>
<td>Ointment</td>
<td>Ophthalmic</td>
<td>0.1 - 0.3%</td>
</tr>
<tr>
<td>Ointment</td>
<td>Topical</td>
<td>0.1 – 0.3%</td>
</tr>
<tr>
<td>Solution</td>
<td>Auricular (otic)</td>
<td>** 0.1%</td>
</tr>
<tr>
<td>Solution</td>
<td>Intravenous</td>
<td>*0 to 40mg/50mL30min</td>
</tr>
<tr>
<td>Solution</td>
<td>Ophthalmic</td>
<td>0.1%</td>
</tr>
<tr>
<td>Solution / drops</td>
<td>Auricular (otic)</td>
<td>** 0.1%</td>
</tr>
<tr>
<td>Solution / drops</td>
<td>Ophthalmic</td>
<td>3 mg/mL</td>
</tr>
</tbody>
</table>

*Depend on site of action/age/period of administration  
** Not confirmed

1.9 Era of Biodegradable Polymers for Drug Delivery

There are several biodegradable polymers available and used for controlled drug delivery as their well-known and to overcome the drawback of reoperation of non-biodegradable implants, PLGA polymer based biodegradable implants have been developed (Jain, 2000). There is a wide use of polymer for medical devices such as surgical sutures and staples. PLGA was approved by US FDA for parenteral administration and the ease to be shaped into an implant by several techniques, using copolymers of PLGA and PLA as a carrier for biodegradable implants have more benefit than other polymers (Jeong et al., 1997; Soppimath et al., 2009).

Moreover, these can be degraded into the acidic by-products and can be eliminated by the normal pathway from the body, thus avoiding a removal process after the end of drug duration (Jain, 2000). However, PLGA and PLA degrade into the acidic by-products, which can induce the undesired foreign body reactions (Li et al., 2010).
When degradation of PLGA and PCL occurred, first they convert into their monomers like glycolic acid, lactic acid and caprolactone. These degradants can be easily metabolized by animal and human metabolic system (Torres et al., 2007) and eliminate by natural physiological pathway. Schematic diagram for degradation, metabolism is presented in Fig. 1.7 (Garvin et al., 2005). After conversion of PLGA into its monomers; lactic acid and glycolic acid, as shown in figure lactic acid gets changed into pyruvic acid and gets metabolized by tri-carboxylic acid metabolism cycle.

Water and carbon dioxide are excretion products of this metabolism process. Similarly, monomer of glycolic acid (extracted in urine) first converts into glycine. This glycine then transfers to serine to change in pyruvic acid. Then by similar mechanism glycolic acid monomer also metabolize through tri-carboxylic acid cycle and pyruvic acid gets extracted in waste and urine. After getting in urine and water these are eliminated. Thus a simple degradation procedure is reported for biodegradation of PLGA polymers.

Poly-caprolactone is also reported as a biodegradable polymer and used as a drug carrier in several dosage forms. Well known application of PCL in the manufacture of biodegradable implants (Zhang et al., 2003). Poloxamer and Magnesium stearate are not biodegradable but approved for application used in very less quantity (less than 0.5%). Degradation of biodegradable polymers is mainly depending on pH of the surrounding fluid, temperature of the system, composition of fluids, viscosity of fluids etc. The degradation rate may vary according to change in these conditions. In comparison to metal implants, biodegradable implants are more expensive due to the cost of the polymer carriers but now a day’s research is going on to synthesise biodegradable polymers by green methods with less cost.
Zoladex® is a PLGA and PLA based drug carrier system in the form of prefilled syringe developed and marketed by Astra Zeneca Canada. It is prepared by using hot melt extrusion process. Zoladex® is a brand name of biodegradable implant where PLGA is used for its biodegradable property and has been designed to treat the prostate cancer. Goserelin acetate is main active ingredient of this system and it is a Deca-peptide analogue of hormone known as lutinizing (LHRH) which is releasing hormone during the activity. It uses PLGA or PLA as a carrier for the drug delivery system. It
has been reported that Zoladex® (A product of AstraZeneca Pharma) system release the drug up to 1 to 3 months continuously.

PLGA, PLA, PCL and their different combinations have been proved compatibility in animal and human body. There are good numbers of study data available about toxicity, degradation mechanisms and applications of these biodegradable polymers in drug industry (Jain, 2000). There is a wide scope to prepare modified, advanced target oriented drug delivery systems by using these biodegradable polymers. Number of types of drugs with different properties can be incorporated in to these biodegradable polymers (Park et al., 2011). Advanced research has been proving that anticancer, antibiotics, steroids, retroviral etc., category drugs can be delivered by using implants prepared by using biodegradable polymers.

We have identified this scope of wide range of applications of biodegradable polymers and delivery of antibiotics to targets for value added benefits. Wound care and management is one of the most important and vast area of health care system. There are well practiced methods available for wound care and management. But those methods are not efficient to take care of wound and patient. Thus to prevent or cure wound infections large dosing of antibiotics is required. There are so many adverse effects reported which are associated to use of those antibiotics. We have identified this opportunity and decided to prepare a wound care product for better life of human and animal.

Wound care products can be preparing by using PLGA and co polymers of it. Aminoglycosides are widely used for its antimicrobial and antibacterial activity. Thus in this study we developed a device having aminoglycoside drug loaded and release it with respect to time as controlled manner. There is a wide scope to design such delivery system for better effect with low toxicity and patient comfort.

Antibiotics are having adverse effect on body when taken long time to avoid or recover the infection (Bagnall et al., 2009). Not all but majority patients face this toxicity problem. Clark (1977) reported when drug is having low bioavailability; for better effect high concentration of such drug is to be given to the patient. This excess quantity of drugs accumulates in blood or body fluids and creates toxic effects. In case of aminoglycosides it creates major side effects like ototoxicity and nephrotoxicity.

To deliver optimum drug at the site of action, the drug can be delivered at the site where action is needed and hence systemic exposure of the drug can be reduced by delivering it locally. This becomes especially important for toxic drugs which are
related to various systemic side effects (such as the chemotherapeutic drugs and antibiotics). Cause of optimum dose there are less chances of nephrotoxicity and ototoxicity. Therefore, in order to overcome the aforementioned limitations there is a scope to prepare a device which should be biodegradable with controlled delivery of active at targeted site.

There are some models are prepared and studied for their characteristics. A list of some marketed products by various inventors is shown in Table 1.5

<table>
<thead>
<tr>
<th>S/No</th>
<th>Product Name</th>
<th>Drug</th>
<th>Delivery technology</th>
<th>Inventor</th>
<th>Carrier polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gliadel</td>
<td>Carmustine</td>
<td>Implant</td>
<td>MGI Pharma</td>
<td>Polifeprosan 20</td>
</tr>
<tr>
<td>2</td>
<td>Atridox</td>
<td>Doxycycline</td>
<td>Implant</td>
<td>Tolmar</td>
<td>PLA</td>
</tr>
<tr>
<td>3</td>
<td>Profact Depot</td>
<td>Buserelin</td>
<td>Implant</td>
<td>Sanofi-Aventis</td>
<td>PLGA</td>
</tr>
<tr>
<td>4</td>
<td>Lupron Depot</td>
<td>Leuprolide</td>
<td>Implant</td>
<td>Abbott</td>
<td>PLGA</td>
</tr>
<tr>
<td>5</td>
<td>Zoladex</td>
<td>Goserelin</td>
<td>Implant</td>
<td>AstraZeneca</td>
<td>PLGA</td>
</tr>
<tr>
<td>6</td>
<td>Vivitrol</td>
<td>Naltrexone</td>
<td>Microparticles</td>
<td>Cephalon</td>
<td>PLGA</td>
</tr>
<tr>
<td>7</td>
<td>Implanon</td>
<td>Etonogesterol</td>
<td>Implant</td>
<td>Organon</td>
<td>PLGA</td>
</tr>
</tbody>
</table>

1.10 Research Envisaged

The best controlled mechanism would be delivery of drug exclusively to the targeted cells or cellular components. That means the development of delivery mechanisms that would equal or surpass the selectivity of naturally occurring effectors (e.g., peptide hormones). As in the case of hormone action, drug targeting would probably involve a recognition event between the drug carrier mechanism and specific receptors at the cell surface.

The most obvious candidates for the targetable drug carriers are cell-type specific immune-globulin. The concept of targeted drug delivery is different than localized drug delivery. The latter simply implies localization of the therapeutic agent at an organ or tissue site, while the former implies subtler delivery to specific cell types.
1.11 Demerits of Traditional Route of Drug Administration

- Less efficacy
- Low bioavailability
- Non localized drug delivery
- Higher dose required
- High toxicity
- Not comfort in critical case
- High cost of treatment
- Dose time management

1.12 Merits of Modified Route of Drug Administration

- Increased efficacy
- Optimum bioavailability
- Localised drug delivery
- Optimum dose required
- Low toxicity
- Comfort in critical case
- Cost effective treatment
- No dose time management

The rationale for developing antibiotic drug delivery system for wound care segment is based on following considerations;

1.12.1 Novel Drug Delivery System

It is mandatory to give high dose of Gentamicin sulphate to maintain $C_{max}$ of the drug in body for its pharmacological effect. So there are major side effects of overdose or long time administration of it. With reference to this challenge we planned to design a novel drug delivery system which will be loaded aminoglycoside category drug. We selected Gentamicin Sulphate a broad spectrum antibiotic drug as a model drug.

1.12.2 Localized Delivery of Drug

The product can be implanted directly at the site where drug action is needed and hence systemic exposure of the drug can be reduced. This becomes especially
important for toxic drugs which are related to various systemic side effects (such as the chemotherapeutic drugs).

1.12.3 To Improve Delivery System

Which is not only beneficial to the patients as they are less cumbersome and easy to abide by but also reduce the complications associated with the induction of the drug in the body.

1.12.4 To Provide Convenience, Safety with Reduced Side Effects

Bioavailability and effectiveness of the drugs. Also decrease peaks and valleys of drug blood & brain levels, decrease dose and frequency of administration for the patients and clinicians using them.

1.12.5 To Avoid Hepatic First Pass Effect

Drugs that are taken up into the body through the gastrointestinal mucosa will be transported to the liver via the portal vein before going into general circulation. As the liver is the main metabolic organ of the body, if the drug is susceptible to metabolic degradation in the liver, this may considerably reduce the activity of the drug. This phenomenon is known as the hepatic first pass effect. In case of aminoglycoside first pass effect is not applicable till administration through oral route.

1.12.6 To Provide the Incentive for New Patents for Older Drugs

New uses for older drugs, a decreased cost and time for FDA approval and an ability to maintain or increase their market share.

1.13 Scope

Antibiotics are category of medicines which works against biotic system of body. In that along with nuisance; useful bacteria can be killed. That’s reason use of antibiotic is full of risks and drawbacks. Aminoglycosides are one of such category antibiotics. There is a wide range of route of administration for aminoglycosides but having some limitations and side effects, thus there is a scope for design novel drug delivery system (NDDS) for aminoglycoside. As per literature several methods are reported for the preparation of bio-degradable products, but there is a scope for drug
loaded device preparation. There is a gap for localized delivery of aminoglycoside category drug (broad spectrum antibiotic) as a wound care at the site of action.

Optimum use of drug can provide convenience, safety & better efficacy. To provide superior quality medicine with effective treatment and cost reduction. Use of biodegradable polymer for drug delivery is value added topic now a days and thus there is a scope for new formulation strategy.

There is a scope to develop and validate several analytical tools & methods for better product quality and performance check. As per literature several methods are reported for the preparation of bio-degradable products, but there is a scope for drug loaded device preparation. Drug release and stability of drug product is challenging area of research. Thus there is a wide scope to study drug release and related efficacy tests.

1.14 Specific Aim

Design of new dosage form for antibiotic drug delivery using biodegradable polymer composition.

1.15 Objective

- To design a biodegradable drug delivery system for antibiotic drug delivery system.
- To select synergistic composition of excipients free from any interaction with active ingredient.
- To perform drug and excipients interaction study by using various techniques and establish compatibility data between them.
- To develop or verify and validate simple and cost effective analytical methods for optimizing monitoring the process and quality of products.
- To take trials for optimizing the formulation.
- To perform in vitro release study for monitoring drug release.
- To perform characterisation study of exposed dosage form for polymer behaviour during drug delivery.
The proposed Ph.D. thesis consists of following six chapters

1. Introduction
2. Analytical methods
3. Composition and pre-formulation studies
4. Formulation strategy selection and process optimization
5. In-vitro drug release, implant characterization and microbiological study
6. Summary and conclusion

1.16 Work Plan

Work was divided in to six parts which are interlinked with each other (Fig. 1.8). First part is introduction, scope of work, objectives, and brief introduction of dosage form design, pre-formulation studies were explained. In wound care to prevent or control antibiotics are used. Aminoglycosides are widely used for this treatment. As discussed earlier there are so many systems available to deliver aminoglycoside drugs. But we have identified, designed and studied a unique composition of active and inactive ingredients. In work plan, all concepts are verified about the design of this unique aminoglycoside drug delivery system.

Gentamicin Sulphate was selected as a model drug as discussed earlier it is a broad spectrum antibiotic from aminoglycoside category. All rest excipients were selected according to their activity. Like Poloxamer 188 as anti-inflammatory agent, Magnesium stearate as lubricant, Poly-Caprolactone as a plasticizer and PLGA as binding polymer. IIG limits were studied and according to that in allowable limit only excipients were selected. As discussed, this is a unique composition and needs to study the compatibility between drug and excipients.
As it is not reported this synergistic composition previously than this, as a part of formulation development it is mandatory to study the compatibility between drug-excipient, excipient-excipient and drug with all excipients. It is important because at initial stage of formulation only study of the interaction between drug and excipient(s)
is required as it may lead to form any impurity or toxin. Also it is important to verify the drug property, its efficacy etc.

There are good numbers of research articles available by using which compatibility study can be perform. In most of the accepted studies spectroscopic, thermal and chromatographic techniques are in lead. Thus initially, drug and excipient compatibility study is necessary to perform by using thermal technique like DSC and spectroscopic technique like XRD, IR and UV.

In part two of the work plan analytical methods are explained. These analytical methods were used for monitoring and qualifying the formulation process and study the device performance. Analytical methods play important and crucial role for the proper development of implant. In this part with reference to literature list of analytical methods prepared. By using this data according to requirement analytical methods were developed, validated and methods from reference were verified for their applicability.

It is mandatory that for correct interpretation of formulation process, all analytical methods to be developed and validated. Reference methods to be verified before analysis. Here in this part methods based on chromatography, spectroscopy, thermal, microbial methods were identified, developed, validated and verified accordingly.

In part three of work plan, selection and optimization of formulation strategy, process optimization, implant casting etc., to be performed. Formulation strategy was optimized on the requirement of polymer blend preparation.

In process monitoring of this blend was performed. The impact of excipient on viscosity of blend was studied. Uniformity in viscosity of biodegradable implant blend represent the uniformity in mixing process and uniform distribution of implant composites. There are number of methods available for casting of implant. But for ease and availability of equipment’s, a drug loaded polymer film was casted and studied for its evaluation. By using viscosity, microscopy etc., formulation process was optimized. Formulation process optimization, preparation of device, its quality and performance check is studied in part four and five.

In-vitro and in-vivo drug release study of implant was performed for understanding the drug release. For polymer degradation study GPC and SEM was used. Mechanical property of implant was studied by studying mechanical property change in implant. In part six, drug release from implant, degradation behaviour, morphological changes were studied. Drug release from biodegradable implant is by
diffusion, degradation or both simultaneously (Jain 2000). Degradation and diffusion is very common phenomenon of drug release. Drug release can be controlled in polymer degradation if degradation rate is faster than diffusion rate (Park et al., 1993). Drug release from implant is depend upon size, shape, site of application, polymer composition etc. Hopfenberg demonstrated a model for surface degradation and drug release (Equation 1.1)

\[
\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{c_0 a_0}\right)^n \tag{1.1}
\]

Where \(M_t\) is amount of drug release at time \(t\), \(M_\infty\) is total drug release from the implant, \(k_0\) is rate constant of erosion and \(C_0\) is concentration of drug in matrix, \(a_0\) is size of implant.

There are another well-known two models are considered during optimization of drug release as Higuchi and Korsmeyer-Peppas model. Our drug is uniformly dispersed in polymer matrix and thus Higuchi model (Equation 1.2) (Higuchi 1961) can be applied to study drug release mechanism.

\[
Q = \sqrt{D(2W - Cs)Cs t} \tag{1.2}
\]

Where \(Q\) is the amount of drug release in time \(t\), \(D\) is the diffusion coefficient of drug in dispersed matrix, \(C\) is total concentration of drug in matrix, \(W\) represents total amount of drug is per unit volume in system, \(Cs\) demonstrates the solubility of drug. Time is represented by \(t\).

Formulation was optimized for the drug release according to above models.