

“DEVELOPMENT, OPTIMIZATION AND CHARACTERIZATION OF RALOXIFENE HYDROCHLORIDE BEARING ORGANOGELS FOR TOPICAL DELIVERY”

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IN

PHARMACEUTICS

By

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May, 2017

DEDICATED TO MY
ALMIGHTY LORD

BIBI SATYA DEVI JI
&
RANGAR BADSHAH JI
(Banga/Toronto)

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The expertise in this study belongs to those acknowledged above. All errors are mine.

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ABSTRACT

Organogels has become one of the most multipurpose and effective vehicles to transdermal delivery of drugs to skin. Organogels are generally solid or solid gel-like material, which contains both solid and liquid components, within three-dimensional network, formed with help of gelators. Raloxifene hydrochloride is an estrogen receptor modulator used in management or to prevent osteoporosis in postmenopausal women were formulated in the organogels for the sustain and transdermal delivery of drug through skin. Different oils along gelators was tested for formation of organogels and among all palm oil was selected for further formulation with variation in concentration. Formulation and characterization of the palm oil and soya lecithin based organogels was studied, evaluated. Different concentrations ratio of the palm oil and soya lecithin were used along with co-surfactant for the optimization composition of the organogels. In the microscopic studies we found that spherical droplets and fibre like structures were found depending upon the concentration of the surfactant and co-surfactant. The mechanism of formation of the organogel is also based upon the concentration of the surfactant and co surfactant which was confirmed from the spherical droplets and fiber like structures observed in the SEM analysis. By FTIR it was confirmed there is no interaction between the drug and excipients. Organoleptic properties were evaluated for different formulation (F1-F8). Invitro diffusion studies were carried by using franz diffusion cell. From the result it was concluded that all have release above 80% of drug release for 8hrs. Results reveal that formulation F3 were released to highest and sustained manner release and they were formed by fibre like structures mechanism. From above all results we can conclude that raloxifene hydrochloride can be administered as the organogel with the expectation of the better availability.

Key words: organogels, raloxifene hydrochloride, surfactant, co surfactant, structure, mechanism

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LIST OF ABBREVIATIONS AND SYMBOLS

S. No.	Symbol/	Meaning
1.	%	Percentage
2.	° C	Degree Celsius
3.	FTIR	Fourier transform infrared
4.	Hal	Hydrogen chloride
5.	IP	Indian Pharmacopoeia
6.	USP	United State Pharmacopoeia
7.	max	Maximum wavelength
8.	Mg	Milligram
9.	µg	Microgram
10.	Nm	Nanometer
11.	Po/w	Partition coefficient
12.	Rpm	Rotation per minute
13.	UV	Ultra-violetspectroscopy
14.	PB	Phosphate buffer
15.	Rlx	Raloxifenehydrochloride

INTRODUCTION

CHAPTER 1

Introduction

1.1 Autoimmune Disease

Autoimmune disease in itself is a very broad term, which includes the several diseases, which are generally caused by the improper functioning and working of the human's immune system. Here antibodies are produced by the person's own immune system which starts to destruct the individual's own cells and tissues. There may be the several reasons, which lead to the occurrence of autoimmune diseases. Body's immune system identifies some part of the body as the pathogen and therefore starts attacking it. Autoimmune disease can be limited to the tissue or to the whole organ. (Page *et al.* 2011) As we know the there is generally the misguidance attack on the body, which causes the destruction of the bossy cells and tissues. Around 80 different types of the autoimmune diseases are studies as they may attack the any tissue or any organ of the body. Autoimmune diseases affect the different parts of the body, which can be clearly understood, from the following figure.

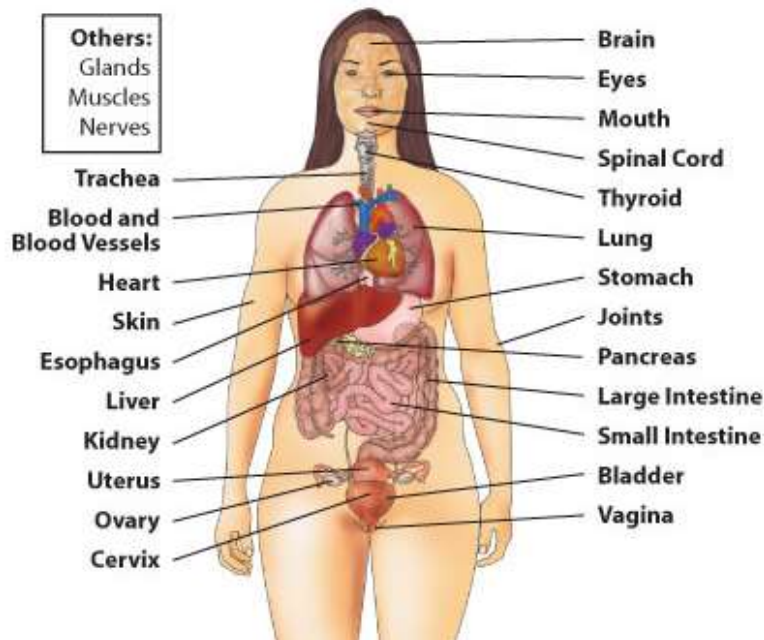


Figure 1.1 Body parts that can be affected by the autoimmune diseases

Actually autoimmune disorder is a very complicated process in itself. There are several

mechanisms lying behind the autoimmune disorders some of which are cellular and other is molecular. (Ray *et al.* 2012)

There are the numbers of examples that are presented for the auto immune disorders, some of them are described as under.

Table 1.1 Examples of selected human autoimmune diseases.

Diseases	Major autoimmune mechanism	Self antigen
Rheumatoid arthritis	Auto-antibodies, immune complexes	Connective tissues, IgG
Ankylosingsponkylitis	Immune complexes	Vertebrae
Multiple sclerosis	TH ₁ cells and T _c cells, auto-antibodies	Brain or white matter
Systemic lupus erythematosus	Auto-antibodies, immune complexes	DNA, nuclear protein, RBC and platelet members
Scleroderma	Auto-antibodies	Nuclei, heart, lungs, GIT, kidney
Sjogren’s syndrome	Auto-antibodies	Salivary gland, liver, kidney, thyroid.

1.1.1 Autoimmune diseases overall ratio in the world

If we look upon the epidemiology it is found there is the gradual increase in the autoimmune disorders throughout the western countries of the world. The increase in percentage was generally observed in the GIT, neurological, endocrinological and rheumatic autoimmune disorders. If we talk about the rheumatoid arthritis it is the disease from which the people are suffering the most. There is the more than 7% percentage increase in the disease if compared to the last statics. On the other hand gastrointestinal and endocrinological has also increased the more than the 6% whereas the neurological autoimmune disease has shown the increase more than the 3%. Therefore we can say that autoimmune diseases are increasing in the world to the large extent every year. Thus the necessary steps should be taken for the prevention of all these

diseases. (Lerner *et al.* 2015) The graph and table mentions below represent the increase in the percentage of the different autoimmune diseases.

Table 1.2 The net %/year increases of diseases categories.

Autoimmune disorders	Increase in percent worldwide
Neurological	3.7
Gastrointestinal	6.2
Endocrinological	6.3
Rheumatic	7.14

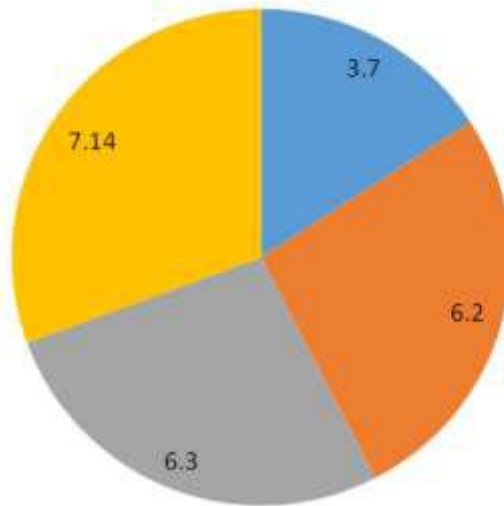


Figure 1.2 the net %/year increases of diseases' categories.

1.2 Rheumatoid Arthritis

Rheumatoid arthritis is generally an autoimmune disorder in which there is inflammation in the various parts of the body, which may be due to the improper functioning of the immune system of the body. The patient suffering from the rheumatoid arthritis generally suffers from the deformity swelling pain and the destruction of the various joints. (Emery *et al.* 2003) The actual cause of the rheumatoid arthritis is still unknown and if we talk about the prognosis, it is also guarded by the various factors. Although mostly joints are affected by the rheumatoid arthritis but this can affect the body systemically also. (McInnes *et al.* 2011) Various body joints are affected by the rheumatoid arthritis like: small joints of the hands and feet, wrists, elbow,

shoulders, knees, ankles etc. If we talk about the risk factors there are so many, for instance genetic, gender, hormone, age, environment, smoking etc. (Emery *et al.* 2003). Also the etiology of rheumatoid arthritis is multifactorial and the cause may be endocrinal, genetic, immunological or infectious. There is not any particular test or laboratory for the diagnosing of the rheumatoid arthritis but there are several rheumatic factors like IgM, antibodies are diagnosed in more than the half of the rheumatic patients but it is not necessary that it is always found due to the rheumatic arthritis. (Grover *et al.* 2011). The figure below mentions the brief about the rheumatic arthritis.

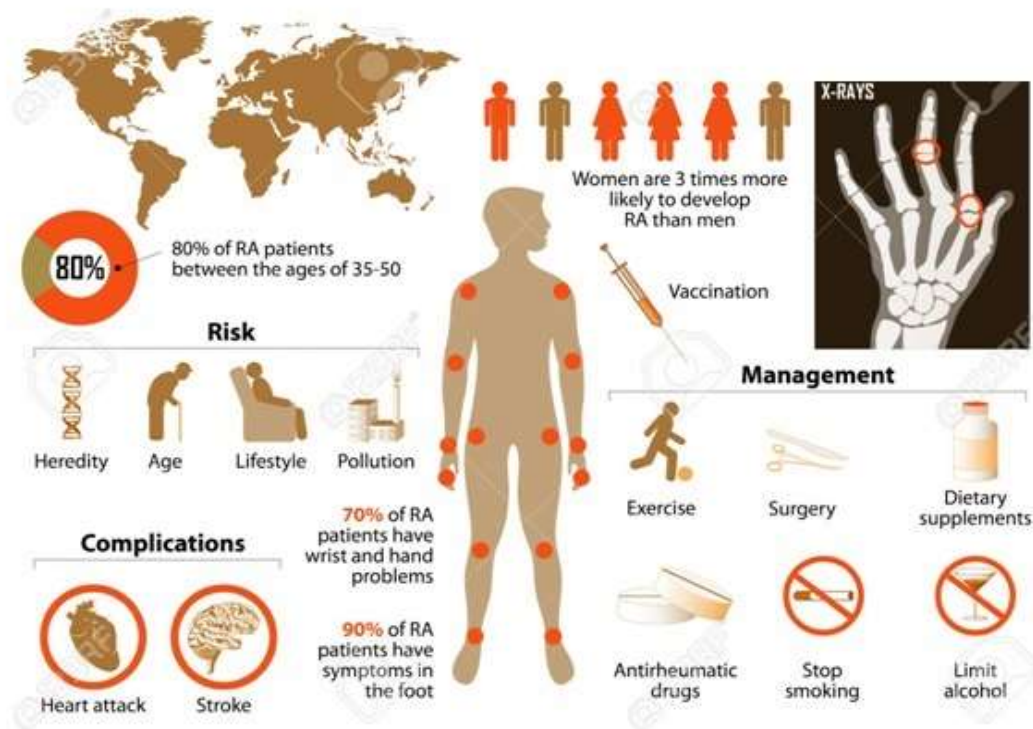


Figure 1.3 Rheumatoid arthritis

1.3 Osteoporosis

Osteoporosis is defined as the disease where there is the loss of the strength of the bone and which leads to the cause of the fractures and fragile bones. (Raisz *et al.*, 2005) The word 'osteoporosis' can easily be understood as 'osteo' means bones, and 'porosis' stands for porous, which leads to weakness. Osteoporosis is a most common disorder these days, which is generally characterized by a reduction in bone mineral density (BMD) along with the micro-

architectural and cellular deterioration. (Stewart *et al.*, 2000) Osteoporosis is a severe health problem, which worsens with age.



Figure 1.4 Stages of Osteoporosis

Osteoporosis is the disorder of the skeletal system in which the bone strength is decreased with time and therefore risk for fracture is increased. There are two aspects, which influence the bone strength; one of them is quality of the bone while other is the density of the bone. (Raisz *et al.*, 2005) As we know bone is made up of calcium, protein and collagen, which all together makes the bone strong. In case of the osteoporotic patient the chances of the breakage of the bone is more as compared to the normal human bones due to some injury or accident. The fracture can be of any type like it can be cracking of the bone or also there can be collapsing of the bone. For instance hip fracture is the type of the cracking in the bone while compression of the spinal vertebrae is the collapsing one. (Kanis *et al.*, 2007) If we talk about the osteopenia it is the condition in which there is the strength and density of the bone decreases slightly as compared to the normal bone and it is worse condition than the pertinent bone. Half of the women of the world above 50 years of age are more likely to suffer from osteoporosis, which is lesser as compared to the ratio in the men. (Abrahamsen *et al.*, 2010) Although wrist, hip and back are the most common sites of the fractures in the osteoporosis.

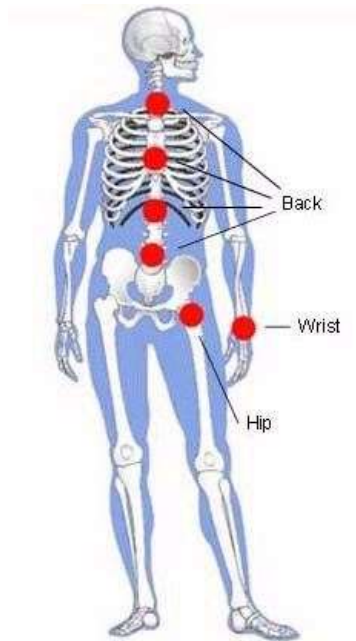


Figure 1.5 Common sites of fractures in osteoporosis

With osteoporosis, trivial slip-and-fall accidents can typically result as hip fractures. After surgical repair during hip fracture there may be slow or poor heal because the healing of the bone is too slow. The two reasons due to which people tend to get osteoporosis is that at the time of the skeletal maturity there is low peak bone mass and at the time of the menopause there is increased bone loss. The time period of skeletal maturity of a person is the best time for the development of the healthy and strong bones as that is the time where one can achieve the maximum bone mass therefore special attention should be paid therefore towards the healthy eating and adequate healthy lifestyle. (Bliuc *et al.*, 2009)

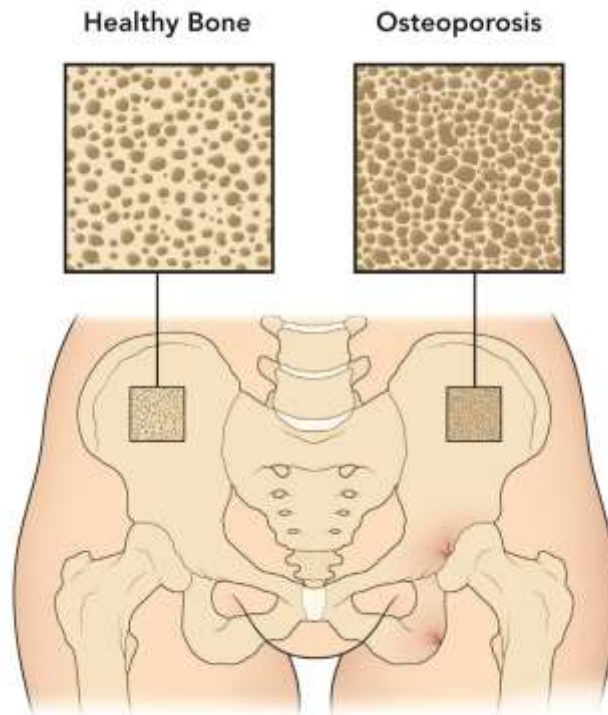


Figure 1.6 Osteoporotic bone

It is a big problem that once the bone loss begins the rate of the bone loss is not slow which should be avoided in any of the situation. During the period of the menopause the rate of the bone loss increases which leads to the increased risk of the osteoporosis although this can be decreased to some extent with the help of the proper medication. (Harvey *et al.*, 2010) There is the destruction of the architectural structure of the bone and its tissue, which makes the bone more fragile. And thus the patient is then more susceptible to the fractures. More of the patient's do not realize that they are suffering from the osteoporosis until they got the easy fracture because osteoporosis has no symptoms in its early stages. (Geel *et al.*, 2009) Osteoporosis in actual is spreading all over the world without being noticed which is the serious problem. It can be compared in the same manner, as we know that hypertension is the serious risk factors the stroke and other heart diseases. It was surveyed and concluded that after the age of the 50s half of the women and 20 percent of the men are suffering from the disease of the osteoporosis. Some parts of the body are really susceptible to the bone fractures as like distal forearm femur (proximal), vertebrae. Those of the vertebrae, proximal femur and distal

forearm. But still osteoporosis can be easily treated and even prevented if it properly diagnosed on the time and proper care and treatment should be taken. (**Gaines *et al.*, 2010**)

1.4 Pathophysiology

If we talk about the pathophysiology of the osteoporosis it is difficult to understand. The perfect time for the growth of the healthier bones is the adolescence and the childhood as this is the time when density and the size of the bones increases. With the age this process is slowed down and thus the bones start to become weaker. In general cases the bone loss is increased to great extent at menopause time and which is still continued for many years therefore ladies are more susceptible for the osteoporosis and other bone disorders. (**Sipos *et al.*, 2009**) The primary reason for the bone loss is the genes also but there are other factors responsible too for the same some of them are like alcohol and smoking habits, improper intake of the calcium and other mineral and vitamins, various medications that effects the skeletal system of the body. (**Bono *et al.*, 2003**) Still studies are going on for the appropriate estimation of the bone mass at the puberty. As we know childhood the adolescence is the optimum time for the bones to grow and to get stronger and as the age increases it goes on decreases and is least in the old age. Various hormones and vitamin D is also responsible for the proper growth of the bones. As with age and after menopause the bone loss exceeds the level of formation of the bones therefore fractures are most common in this stage of life. (**Szulc *et al.*, 2011**)

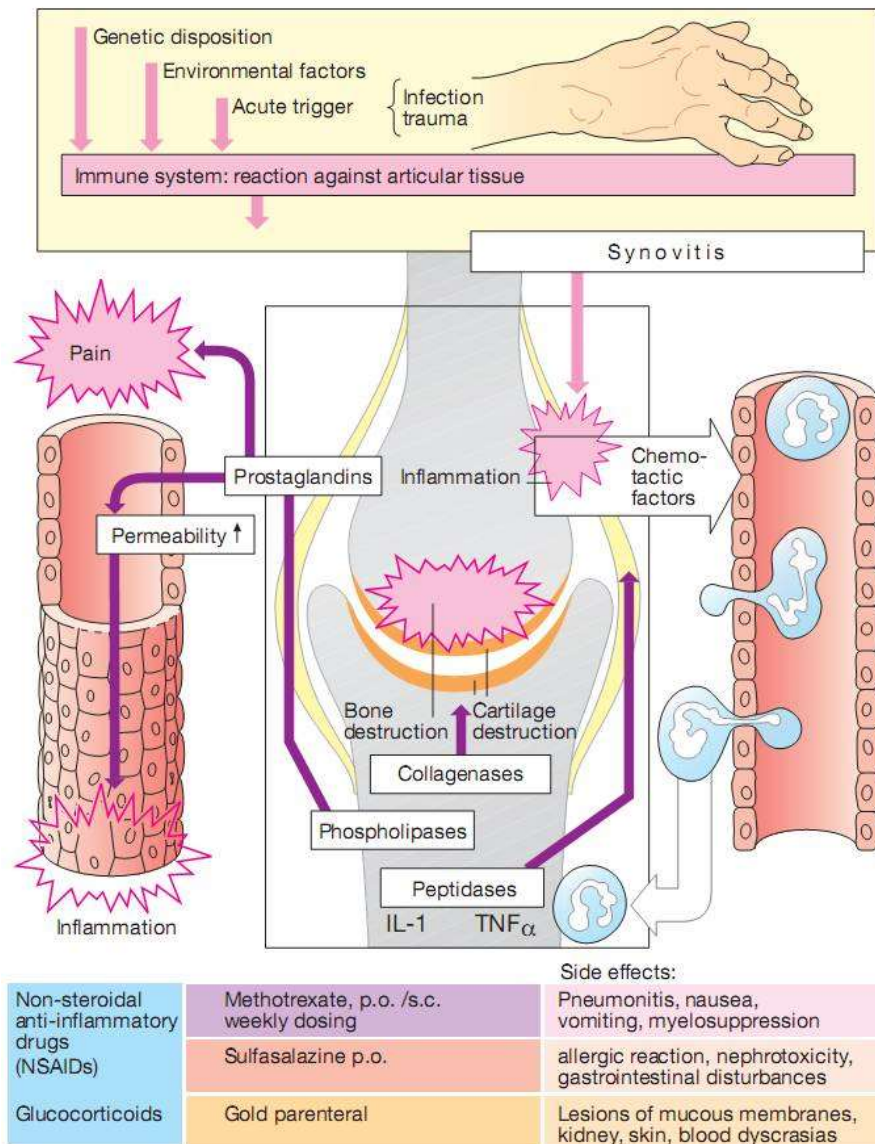


Figure 1.7 Explaining the pathophysiology of rheumatoid arthritis

When there is the typical imbalance between osteoblasts and osteoclasts that leads to the loss of the bone mass. However the susceptibility to the fractures can be determined to some extent by determining the bone tissue quantity of the bones which is also defined as the peak bone mass . Peak bone mass can determined by various methods now a days but the accuracy varies from method to method's.(Stetzer *et al.*, 2011) As we has discussed earlier the proper balance between the osteoclastic and osteoblastic functioning is very much important because this is the primary factor responsible for the bone formation and bone loss.

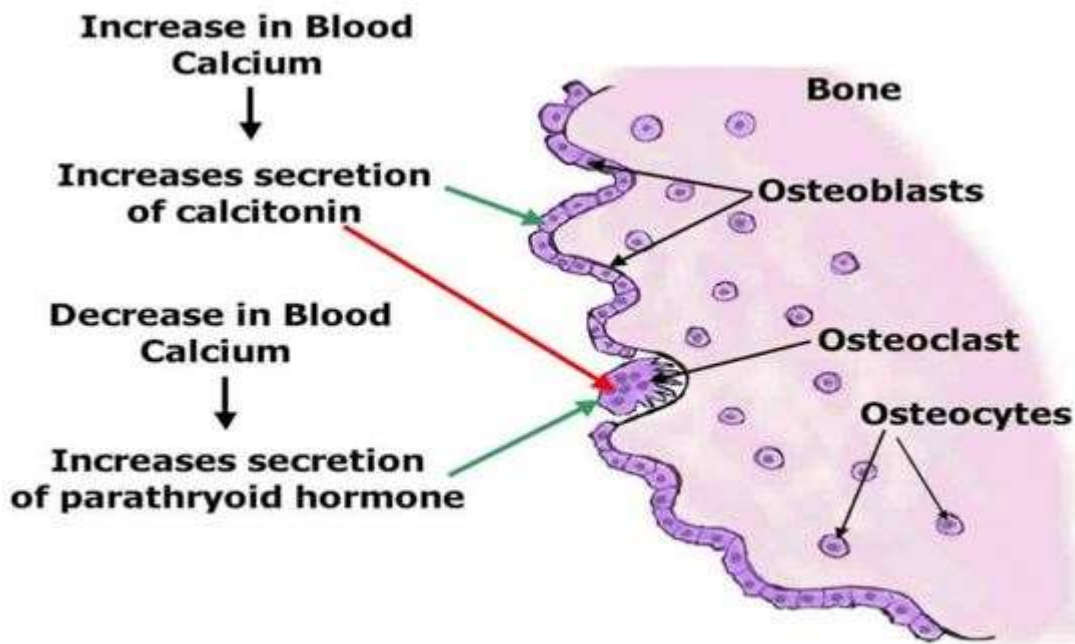


Figure 1.8 Process of osteoclastic and osteoblastic condition

The problem is that if one such fracture happens then there are increased chances of the other fractures too. Studies reveal that women who had previously suffered from the fracture is more susceptible to the fractures in life. (Kamau *et al.*, 2011)

1.5 Signs and symptoms

Osteoporosis is such a disease, which cannot be recognized by the patient himself for many years until the patient suffers from fractures or breakage of bone. Therefore, this disease cannot be prevented unless patient experience or suffers from painful fracture. Although there are many symptoms of osteoporosis, which is discussed as under:

The spine fracture generates like “band-like” pain in which the patient feels the pain running from the back the body sides. If the spinal fractures are repeated the patient may also suffer from the pain of the lower back which can even cause the curving of the spine and thus patient suffers from decrease in height.

The fracture, which occurs in normal conditions, is known as minimal trauma, which is also known as stress fracture. It is seen in various patients who are suffering from osteoporosis has pain or stress on their feet when they walk. The fracture that occurs after falling is generally hip fracture. Due to slipping and falling accidents hip fractures can easily take place in the patients

that suffer from osteoporosis. The worst thing is that the healing of the hip fracture is very slow even after the surgical repair of the bone. (Szulc *et al.*, 2011)

There can be other fractures that are non-vertebra, which are generally symptomatic but in some cases it can be asymptomatic too.

If we talk about the fracture of the vertebra compression the patient suffers from the minor pain, which is generally ignored by the patients but is gradually increased with the weight and time. It may be felt by the patients in weeks and may be experienced for months.

Sometimes anomalous stress is felt by the patients on the muscles of the spinal cord and their ligaments that lead to the pain and aching generally in the lower back part of the body.

Osteoporosis is also linked with the respiratory system, because of the compression of the ribs and the abdominal cavity. The respiratory system gets disturbed and the patients suffer from shortness of breath.

If we talk about the further symptoms of osteoporosis, when a person starts getting stooped posture which means his body is getting shrinks symptomize that the person is suffering from spontaneous fracture or indirectly the osteoporosis. (Sipos *et al.*, 2009).

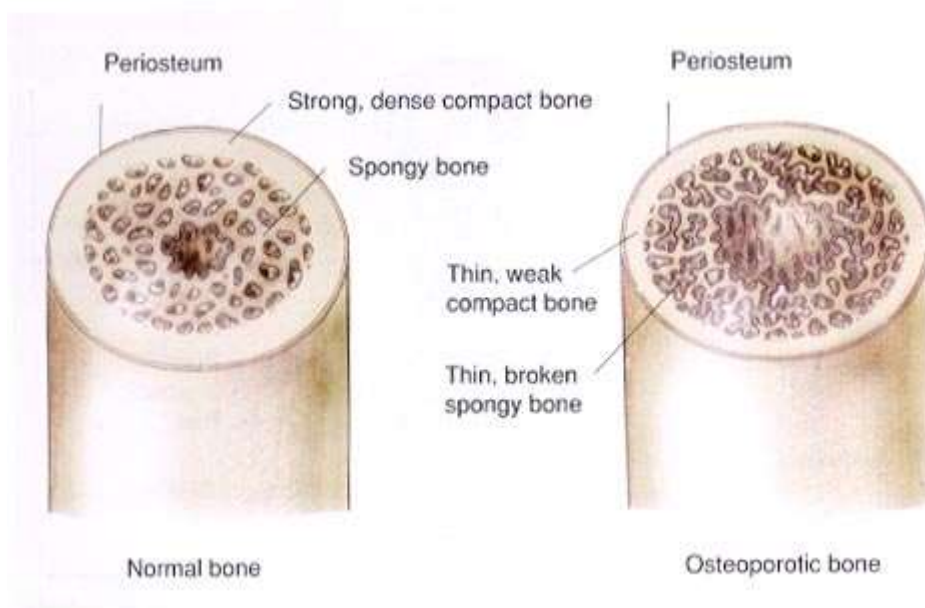


Figure 1.9 Normal vs. osteoporotic bone

1.6 Risk factors

According to the NOF the risk factors of osteoporosis are those factors, which ascend the

chances of causing osteoporosis and leading to the breakage of bones. Lesser is the bones mass there are more chances of fractures occurring or breaking of the bone to occur. If the osteoporosis has caused the fracture then it's also called as established osteoporosis. Osteoporosis can be transferred from generations to generations, although it is not necessary in all cases. For instances, the daughter has higher chances of the osteoporosis whose mother that has already suffered from hip fracture or osteoporosis. Therefore, children of the parents who suffer from osteoporosis should be alert and aware for themselves as they have chances of getting the same. **(Raisz et al., 2011)** Also the long-term medications for various other diseases can also lead to the risk of osteoporosis, as there are many medications, which cause the loss of calcium in the body, which indirectly is the cause of osteoporosis although there is no evidence or proof. A study revealed that the regular intake of the oral corticosteroids leads to the increase chances of the osteoporosis. Therefore, a person who knows that he may have risk of osteoporosis genetically should take the corticosteroids with proper guidance. Age is another major risk facture for the osteoporosis. A survey was for the women of the age between 60-90 and it was observed that the percentage of the fracture is increase with the ages of the patient. Although there are innumerable risk factors for the osteoporosis, but some of them are: Age of the patient, race of the patient, genetic history of the patients, personal history of the patients, intake of the steroids and related medications, other disorders affecting the osteoporosis, transplantation of the bone marrow or any other organ of the bones, the habit of smoking and alcoholism, thyroid problems, various kidney and liver diseases, lifestyle and eating habits of the patients, disorders of the gonads. **(Stetzar et al., 2011)**



Figure 1.10 Increasing risk factor of osteoporosis with age

1.7 Ubiquity of osteoporosis

It was surveyed that 30 to 50 percent of the women and half of that males suffers from osteoporosis, although statics varies from survey to survey. As we already know with the increase of the age the chances of the osteoporosis increases as under:

- 35 percent of the female between the ages of the 50 to 60
- 50 percent of the female between the ages of 60 to 70
- 75 percent of the female between the ages of 70 to 80
- 87 percent of the female at the ages of 80 and above

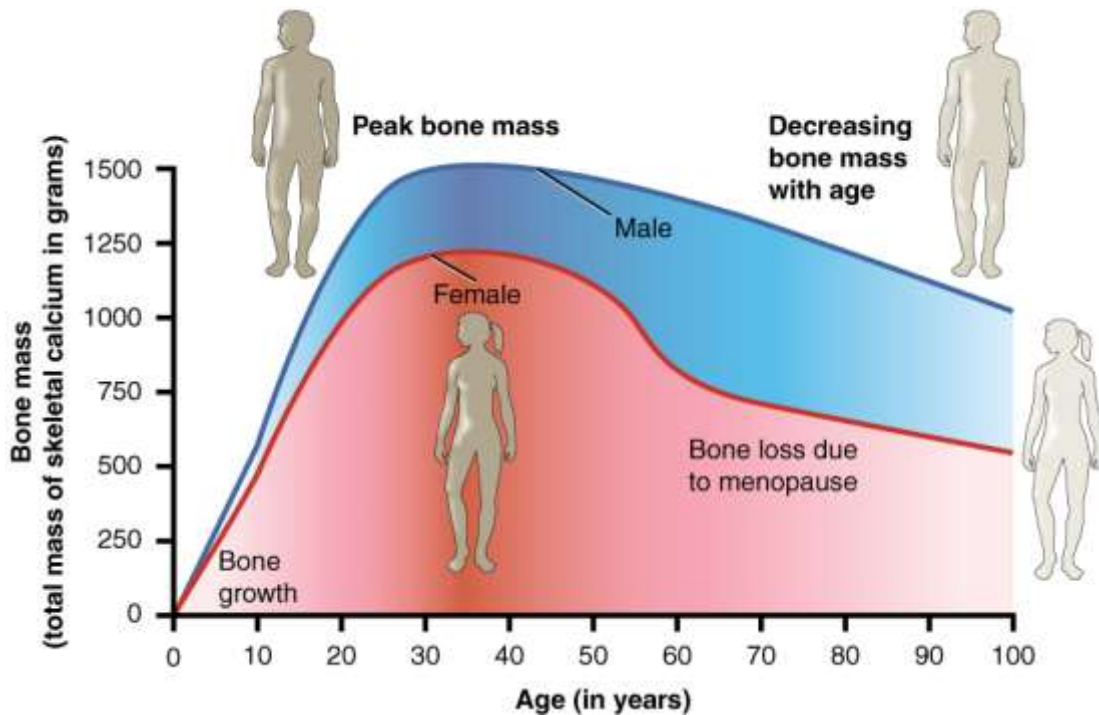


Figure 1.11 Showing Relationship Between Age and Bone Mass

1.8 Remedial treatments for osteoporosis

In the patient suffering from the osteoporosis should have the following therapeutic aims and goals: He should prevent and avoid fractures by increasing the strength of the bones and descending the risk of injury and falling down.

- To be aware of the fractures symptoms and deformity of the skeletal system.
- He should do some regular exercises so that physical functioning of the skeletal system should be kept good.
- If the patient keeps in mind the above points and choose a proper health care then he can get rid of the osteoporosis sooner as compared to others. (**Barrett *et al.*, 2011**)

The current available treatment of osteoporosis comprises of:

- Antiresorptive treatments
- Anabolic treatments.

Antiresorptive treatments generally include the bisphosphonates, which activates the receptors of the RANKL antibody, which is the nuclear factor and SERM. They have different mechanisms of action but at the end they all inhibit Bisphosphonates and RANKL antibody are the most widely used antiresorptive treatments. They are both generally well tolerated, but if

we talk about the jaw and femur osteonecrosis of the jaw and atypical femur fractures are very rare side effects that have gained much attention and are causing much concern.

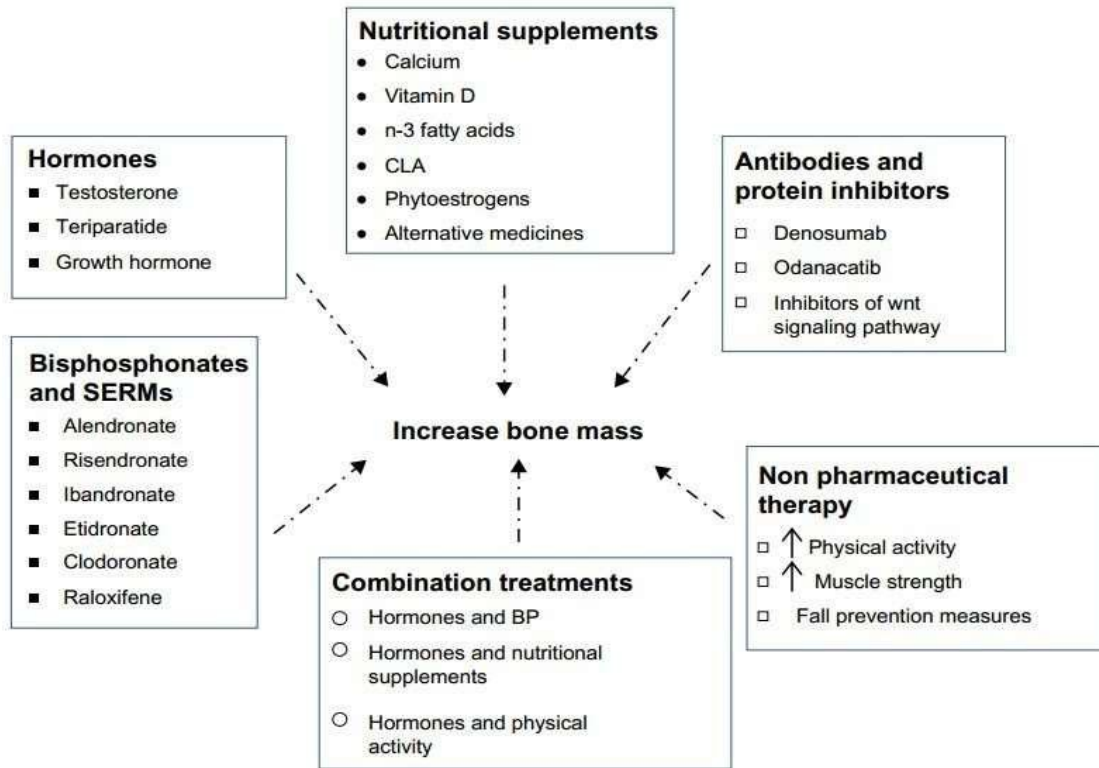


Figure 1.12 Different aspects to increase bone mass

1.9 Medication for the osteoporosis

Pharmacologically the antiresorptive agents can treat osteoporosis, which decreases the resorption of the bones for instance bisphosphonates, like SERMs, raloxifene, denosumab, and the calcitonin. Various anabolic steroids are all also helpful for the osteoporosis patient like teriparatide along with therapies that are provided, which includes the calcium and vitamin D supplementation. Various treatments and therapies available for the osteoporosis are described below:

- Derivatives of Estrogen
- Fat-Soluble and Vitamins
- Progestin/ Estrogens
- Salts of Calcium

- Modifiers of the Calcium Metabolism
- Endocrinal Monoclonal Antibodies
- Analogues of the Parathyroid Hormone
- Progestin-HRT/ Estrogens
- SERMs
- Derivatives of Estrogen

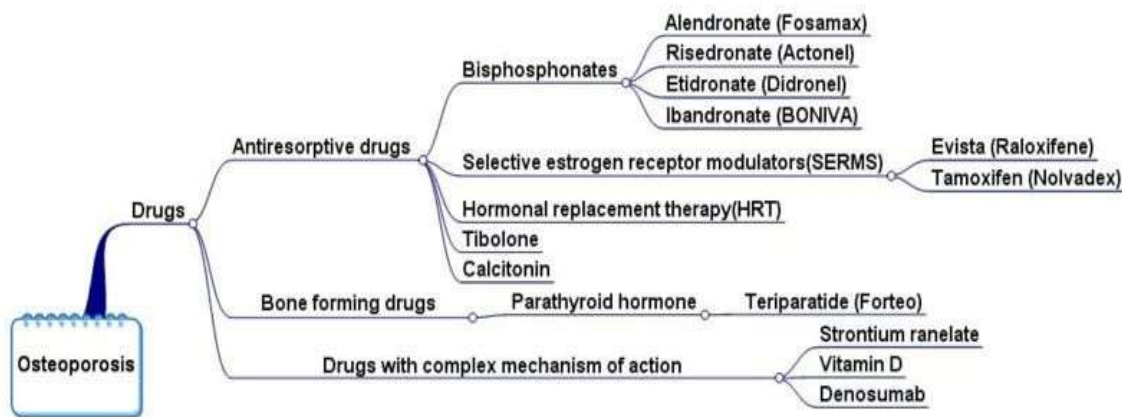


Figure 1.13 Various drugs employed for the management of osteoporosis

1.10 Selective Estrogen Receptor Modulator (SERMs) and its mechanism of action

The mechanism of the SERMs is that it affects the various receptors, which are stimulated by the estrogen, but the advantage is that it can be selectively available as agonist or antagonist as per the organs. They are also the antiresorptive agents. The advantage of the selective action is that it minimizes the adverse affects of the estrogen as it screens off the therapeutic effects. The estrogenic pathways are activated in various tissues and disruptions of the various pathways in other tissues are the prime reason for the reasons therapeutic and biological actions of the raloxifene hydrochloride. (Jochemms *et al.*, 2008)BMD at the hip and spine is elevated by the raloxifene hydrochloride therefore the chances of the fractures of the spine are lower down by the 32 to 50 percent. Raloxifene hydrochloride is the well approved medication for the treatment and prevention of the osteoporosis especially in the post-menopausal women. The dose available

in the market is 60 mg tablets. Although, no serious side effects has been observed but still the adverse reaction like flu syndrome, sweating, craps in the legs, edema, and hot flashes can be experienced in some patients. **(Vestergard *et al.*, 2012)**

1.11 Organogels

Organogels are the type of formulations that are semi-solid in nature comprising of the apolar solvent that acts as the liquid phase. Organogels are generally thermo-reversible, but some physical interactions between the components of the organogels may occur. **(Sahoo *et al.*, 2014)** Organogels are found to be thermostable up to a certain temperature, which is less than gellation temperature. They are used for the topical preparations due to their viscoelastic properties. On changing the compositions of the organogels, the drug release can also be changed. There are the large numbers of surfactants and co-surfactants that can be used for the formulation of the organogels. **(Motulsky *et al.*, 2015)** The good surfactants enhance the quality of the organogels and also increase the penetration power of the organogels reducing the irritation of the skin. **(Pieve *et al.*, 2011)** Water is also one of the important components of the organogels, as with the change in composition of water the properties of organogels alter. Lecithin is one of the important surfactants which is used globally due to its various advantageous properties. Using the lecithin as surfactant also increases. Viscoelasticity of the organogels. **(Bhatia *et al.*, 2013)** There are varieties of helpful properties of the organogels due to which they can be incorporated into the novel drug delivery system. Viscoelastic is important property which makes the preparation both elastic and viscous. Organogels are generally non-birefringent, which means they do not allow the passage of polarized light through it. Although organogels are themostable but on heating more than critical temperature the organogels loses its properties. Organogels are generally optically clear or transparent in nature, although it depends upon the color of the surfactant and the drug used. Chirality effects also plays important role in the formation of the organogels. It was found that gelators having the chiral centre form the better organogels as compared to others. Now days, biocompatible ingredients are widely used for the preparation of the organogels. **(Han *et al.*, 2013)** Depending upon the gelators and surfactants used, organogels are of seven types: lecithin, pluronic lecithin organogels, premium lecithin organogels, limonene organogels, gelatin stabilized micro emulsion based organogels, fatty acids derived sorbitan organogels, and poly (ethylene) organogels. **(Kuentz *et al.*, 2012)** The interest in the formation of the organogels has been seen

in last few decades due to its advantages properties. Many drugs have very less bioavailability if given through the parietal route or oral route, which can be overcome by using the topical route and administered in the form of organogels. **(Kuwahara *et al.*, 2014)** It also increases the transport rate of the drugs due to its high penetration property. Organogels are widely accepted by the patients, as it is a better way of administering the drug. Also, it bypasses the first pass metabolism in the liver and therefore having the lesser side effects. **(Wang *et al.*, 2014)** This can also be used for the delivery of various vaccines. Therefore, we can say that organogels are easy to prepare having the faster release rate, biocompatible, good viscosity, and spread ability, it can be used as the administration mode for the various drugs. **(Baseeth *et al.*, 2011)**

LITERATURE REVIEW

CHAPTER 2

Literature Review

The detailed survey of all these literature was performed and topics relevant to present work were collected to design the project work.

2.1 Literature review of disease:

Joshi et al., (2012) explained the pathophysiology and treatment of the rheumatoid arthritis as we all know that a lot of people suffered from this disease in the past 2-3 decades. Most of the patients do not know that there lies the hormonal factor behind the cause of the arthritis as mostly women suffer from this disease. Also it is difficult to diagnose the same in its early stage because it does not have any specific symptoms. He studied the various patients of the arthritis and concluded that it can be treated more effectively if diagnosed in its prematuring stage.

Lain et al., (2012) discussed about the rheumatoid arthritis is the disease which is related to the systemic complications and disability of the patient. Although the proper cause of the arthritis is unknown as it may be due to the various factors. If we study about the disease pathogenically then it can help in the formulation of the various new molecules for the treatment of the arthritis and osteoporosis.

Ishimi Y. et al., (2015) discussed that formation of the skeletal muscles takes place mainly in the first 20 years of life after that the bone mass is maintained constantly for the 20 or more years. As the age increases the bone mass decreases gradually especially after the age of 70's. As the definition given by The National Institute of Health Consensus conference osteoporosis can be defined as the disorder in which the bone strength is decreased and thus increasing the risk of fractures which one of the problem faced by the elders these days.

Stetzer E. S. et al., (2011) discussed that osteoporosis is the one the serious disease these days which is affecting the life of the millions of people at present. Also the treatment of the same is not very cheap. In many cases patient even becomes the bed ridden. Mostly the elderly patients are affected by the osteoporosis but the main causing factors can be controlled from the childhood or young age only.

Mcleod K. M. et al., (2011) explained and evaluated that mostly the people in the elderly age is most affected by the osteoporosis. . The Osteoporosis Health Belief Scale (OHBS) and Osteoporosis Self-efficacy Scale (OSES) discussed in detail various factors causing the osteoporosis and also the various obstacles faced in the efficient treatment of the osteoporosis.

Sipos W. et al., (2009) demonstrated that osteoporosis is the disease which attacks the patient in the elderly age when there is decrease in the bone mass and women are the one which are more affected as compared to the men. In 1941 Albright and colleagues discussed that osteoporosis is also caused by the deficiency of the estrogen hormone. However the exact disease mechanism is still unrevealed.

Malhotra N. et al., (2007) discussed that it is not necessary that osteoporosis is but in the several western parts of the India many of the younger patients were found. It is also been revealed that many of the Indians suffers from the vitamin D which leads to the decrease in the bone mass density. If we compare to the western countries Indians people have the lower BMD.

Prentice A. et al., (2004) discussed that the thousands of people are added up every day in the line of the osteoporotic patients. There is the micro deterioration of the of the bone tissue along with the decrease in the bone mass and increasing the risk of the osteoporosis.

2.2 Literature review of drugs (raloxifene hydrochloride):

Akhila C R. et al., (2015) discussed that Raloxifene hydrochloride (RLX) is a drug used for the arthritis and which comes under the category lies in the class of benzothienopyridines. Raloxifene hydrochloride is wide accepted and used for the prevention and the treatment of the osteoporosis, arthritis and other fractures.

Maheswara Rao U. V. et al., (2015) studied that raloxifene hydrochloride is very effective in the treatment of the fracture of the bone tissue and it also has the effect on the bone formation cycle. It mainly shows its action by the production of the estrogen like effects which causes the increase in the bone mineral density and decrease in the resorption of the bones.

Reddy R. B. et al., (2012) studied that raloxifene hydrochloride comes under the category of the SERMs and along with the osteoporosis it can be also used for the treatment of the breast cancer. Also the selective action of the raloxifene hydrochloride increases the therapeutic effects and decreases the side effects of the drug.

Pickar H. J. et al., (2011) explained very nicely the working mechanism of the SERMs and the raloxifene hydrochloride. Depending on the target tissues they interact with the antagonists or the agonists. SERMs can be used in combination with the various other drugs for the enhanced effect for the treatment of the osteoporosis.

Arango B. A. et al., (2009) studied that if we compare the raloxifene with the various other SERMs it has the best effects with lesser side effects and thus so many trials have been already been done on the raloxifene hydrochloride for the treatment of the osteoporosis. The study also revealed the raloxifene hydrochloride is also beneficial for the treatment of the breast cancer.

Prakash et al., 2013 discussed the formulation of the nano preparation of the raloxifene HCl. As we know raloxifene comes under the second category of the biopharmaceutics classification system (BCS).He tried to prepare the nanoparticles with the help of the biopolymer called the gellan. Raloxifene HCl was encapsulated with the gellan. Various tests were performed for the efficacy and the pharmacokinetics of the drug.

Patil et al., 2013 discussed the various properties of the raloxifene HCl and solubility and dissolution of the same. As it lies under the second category of the BCS classification therefore it has the low solubility in the water therefore, here HPMC was used for increasing the solubility of the drug. Being an hydrophilic in nature it was completely mixed with drug and also was converted into the amorphous state of the drug. Different tests were performed for the analysis of

the various properties of the drugs which finally gave the significant results that HPMC aids in increasing dissolution rate and thus bioavailability of the drug.

Peter et al., discussed the various advantages of the drug raloxifene HCl. If we compared with calcium and vitamin D supplementation, raloxifene hydrochloride has the more effects in reducing the risk of the fractures in postmenopausal women. He also discussed the rare side effects of the drugs which were observed in very few patients for instance fatal strokes and thromboembolic events. No other major side effect of the drug was observed tested on the different patients.

Foster et al., 2013 studied that raloxifene HCL with the combination of the alendronate can be helpful both in the prevention and also the treatment of the disease osteoporosis. No doubt that it has another major advantage for the breast cancer patients. He explained in the working mechanism of the raloxifene HCl along with its various side effects.

2.3 Literature review of drug delivery system:

Sahoo et al., (2014) discussed that organogel is defined as the system which is viscoelastic in nature, also it is a formulation of semi solid nature having the which external phase apolar and immobilized in nature The immobilization of the apolar phase with the spaces of the 3D structure of gelators .This proven the stability of the organogels thermodynamically and can be used for the delivery of the various therapeutic agents

Motulsky et al., (2015) studied the on the formulation of simple, efficient and effective drug delivery system for the various proteins and peptides and also the hydrophilic molecules having the lesser molecular weight. He tried to formulate the implant which was biodegradable in nature with the help of different pharmaceutical oils and amphiphilic organogelators. Thermo reversible method of gelation was used for the formulation.

Pieve et al., (2011) studied the effect on the structure of organogel due to the cod liver oil. Firstly the monoglycerides were taken in increasing proportions and was mixed with the cod liver oil which itself is natural fatty acid. It was noticed that on increasing the concentration of the monoglycerides macroscopic changes were observed in the structure of the organogels. It was found that it was helpful in preventing the oxidation of the formulated product.

Bhatia et al., (2013) studied about the organogels and proved its various properties. According to him the organogels are usually semi-solid system which has the immobilized liquid phase usually organic in nature entrapped in the network of the gelators. After the formulation of the lecithin organogel and studying and researching the various properties of the organogels it was concluded that biocompatible, easy for application and more safer thus which was a motivating step for the efficacious and more safer delivery system of the drug.

Esposito et al., (2013) studied and was quite successful in the preparation of the fenretinide organogel with help of the lecithin which was quite stable and has enough efficacies. The type and quantity of the oils, lecithin and hyaluronic acid. Various properties like viscosity of the gels with the help of the Franz diffusion cells. Finally the bioavailability of the fenretinide was studied which was found to be more as compared to the other dosage forms of the fenretinide.

Han et al., (2013) studied and tried to formulate the organogel food grade with the help of the lecithin and sitosterol with the help of the edible food oil. Sunflower was used which was rich in trilinolein and organogel was prepared by changing the different concentrations and storing at the different temperatures. Then he evaluated the organogels after ten days found that the physical properties were slightly altered such as the viscosity, storage temperature and microstructure etc.

Iwanaga et al., (2012) formulated the organogel with help of the soybean oil and as a gelators he used the 12-hydroxy stearic acid. Ibuprofen was the drug used which is highly lipophilic in nature. Also he tried the same procedure for the ofloxacin and theophylline but they showed the lower releasing rates. At end also the drugs were tested on the rats which were administered through the intraduodenal route which showed the rapid absorption. Although the bioavailability was not up to the expectations but it was quite higher than the same administered through the suspension form.

Kuentz et al., (2012) discussed that different excipients shows the different effects on the properties of the organogels. Here the lipid based excipients were used for the preparation of the organogel and significant results were observed in case of the pharmacodynamics. But still it requires the more changes in the formulation processes to achieve the significant and desired results. Also this technique was useful for the formulations of the various other lipid base formulations.

Kuwahara et al., (2014) demonstrated that polyaniline can be used successfully for the preparation of the organogels. Here the organogelating agents used were 1, 10-diaminodecane and cholesterol hydrogen succinate. Poly aniline used here showed the thixotropic behavior and also the thermal reversibility. The various physiochemical properties of the organogel were studied. The thermal conductivity of the organogel showed the various changes with the addition of the different excipients.

Gabriele et al., 2013 formulated the organogels with the help of the policosanol which is generally the mixture of the various fatty alcohols along with which olive oil was used. Also it comes under the food grade category of the additives. Different tests were performed at the different temperatures.

Raut et al., 2011 studied that the organogels can play the vital role in the formulation of the cosmetics and various anti-aging products. Organogels which are biodegradable and biocompatible in nature are used for the incorporation of the various anti-aging ingredients. Lecithin was used here as organogelators for the formulation of the organogel. As we all know that lecithin has the excellent gelation properties which general derived from the eggs or the soybeans. It is not only safe and effective also it can dissolve the both hydrophobic and hydrophilic drugs. Due to its various properties it is widely used in the preparation of the various organogels.

Wang et al., 2014 discussed that method for the preparation of the organogel by using the different pharmaceutical oils. As we know the organic solvent causes the tissue irritation

therefore the use of it was avoided in the preparation of the organogel. Thermo-reversible procedure of the gelation was used and different fatty acids were used along with the soybean oil. The pharmacokinetic study was done by injecting the organogels into the rats. The results obtained were quite fruitful which showed the gradual absorption of the drug thus showing that it is a good platform for the synthesis of the newer drug delivery system.

Hailong Yu *et al.*, 2012 studied and formulated the organogel consisting of the curcuminoids. Medium chain triglycerides and the span 20 were used for the synthesis of the curcumin loaded organogel. For the formulation of this food grade organogel monostearin was used which comes under the category of the GRAS (safer category) of the organogelators. This organogel can be either used by the oral as well as by the topical route of administration.

Baseeth *et al.*, 2011 studied organogel compositions consisting of the various compositions of the phospholipids. He explained the various methods for the preparation of the organogels. Furthermore, he explained that how these organogels can be incorporated into the various pharmaceutical and cosmaceutical products.

RESEARCH ENVISAGED

CHAPTER 3

Research Envisaged

3.1 Rational for disease selection

Although osteoporosis is the disease related to the post-menopausal women, which is also observed in other women and men. Although there are advancement in the treatment and the diagnoses of the osteoporosis still in many regions in the world it is under treated and under diagnosis. A survey revealed that 5 to 50 percent of women suffers from the osteoporosis are not being treated correctly. Osteoporosis fractures disturbs the life quality, cost of the health care and rate of mortality. In the past years, awareness had been seen in the public and the various healthcare providers which has lead to improve the efforts done for the treatment of the osteoporosis. Patient counseling and clinical information plays an important role in the treatments of the osteoporosis. It was surveyed that if the person suffers from a fracture he has never been diagnosed for the osteoporosis as no one has knowledge about the symptoms of the osteoporosis. So, to get advanced management of osteoporosis with improved patient's compliance we recommended the organogel including raloxifene hydrochloride.

3.2 Rational for selecting raloxifene hydrochloride as organogel

Organogel concept has not been long utilized to develop sustained release formulations. Organogels usually are the systems, which are semisolid in nature having the liquid phase, which is organic in nature and is immobilized by 3D network of gelators. Although major composition is of liquid still they have behavior and morphology of the solids. Although keen has been shown in the field of the organogels but still attention is required for the updation of the system to achieve the better and expected results. Organogel provide dual advantage of same dosage form provide immediate as well as sustained action. This delivery maintains plasma drug concentration for whole body that is much more as compared to available conventional dosage form. The pharmacokinetic advantage leads to sudden rise in blood concentration.

Organogel includes some important features, discussed below:

- Ability to combine different release rate
- Promoting patient convenience and compliance
- Increase therapeutic effect with lesser side effects and more safety and accuracy

- Reduced incompatibilities
- Bypass of the first passed mechanisms
- Increased stability as compared to other formulations
- Maintains the accuracy and potency of the drug

3.3 Scope of study and rationale for selecting drug

Raloxifene hydrochloride:

- It is not well absorbed from oral route
- The protein binding of drug is 95%, so it will distribute in body for longtime.
- The half-life of drug is high i.e. 27-32hrs.

The faster onset of action hence immediate-release Raloxifene is associated with rapid absorption and rapid onset of estrogen modulator action. To overcome the drawbacks of the current available dosage forms of the raloxifene hydrochloride like much lesser bioavailability (which is only 2%), lower drug retention level, and degradation of the drug before reaching the target sites, difficulties in achieving the optimum results. Organogels have the various advantages over the tablets as the first pass metabolism is by-passed, therefore they will increase the therapeutic performance of the drug molecules.

The other advantage of the organogel over the tablets is that it protects the drug from the various problem creating biological conditions. Also they have the better skin penetration properties thus can increased the bioavailability drugs showing the poor bioavailability through the oral route. Being non-invasive also this method has the advantage of better patient compliance. Also all the excipients that will be used for the formulation preparation are biodegradable and biocompatible therefore decreases the chances of the toxicity. Dosing frequencies and the side effects of the drugs are also reduced by administration of the drug by the skin route. Thus, delivering raloxifene hydrochloride using the organogel as a drug delivery system can show the improvement in the pharmacodynamics and pharmacokinetics of the raloxifene hydrochloride with the reduced toxicity.

3.4 Aim and objectives

3.4.1. Aim

To develop, optimize and characterize raloxifene hydrochloride bearing organogels for topical delivery.

3.4.2 Objectives

The primary aim of the formulation of the raloxifene organogel is to treat the postmenopausal osteoporosis in the better way showing the higher rate of the bioavailability. As we know that till now raloxifene HCl is available in the form of the tablets, which has the very less bioavailability. This is fact that organogel will increase the pharmacokinetics and pharmacodynamics of the raloxifene hydrochloride. Thus the objective is to deliver the maximum possible amount of the drug to the targeted area with the maximum bioavailability and minimum side effects.

3.5 Scope of study

To overcome the drawbacks of the current available dosage forms of the raloxifene hydrochloride like much lesser bioavailability (which is only 2%), lower drug retention level, and degradation of the drug before reaching the target sites, difficulties in achieving the optimum results. Organogels have the various advantages over the tablets as the first pass metabolism is by-passed, therefore they will increase the therapeutic performance of the drug molecules. The other advantage of the organogel over the tablets is that it protects the drug from the various problem creating biological conditions. Also they have the better skin penetration properties thus can increased the bioavailability drugs showing the poor bioavailability through the oral route. Being non-invasive also this method has the advantage of better patient compliance. Also all the excipients that will be used for the formulation preparation are biodegradable and biocompatible therefore decreases the chances of the toxicity. Dosing frequencies and the side effects of the drugs are also reduced by administration of the drug by the skin route. Thus, delivering raloxifene hydrochloride using the organogel as a drug delivery system can show the improvement in the pharmacodynamics and pharmacokinetics of the raloxifene hydrochloride with the reduced toxicity

PLAN OF WORK AND EXPERIMENTAL WORK

CHAPTER 4

Plan of work and Experimental Work

4.1 Materials used

Table 4.1 List of the materials used

S.No.	Chemicals	Manufactures
1	Carbopol 934	BB chemicals
2	Span 40	BB chemicals
3	Tween 80	BB chemicals
4	Glycerol	BB chemicals
5	Ethylene glycol	BB chemicals
6	Propylene glycol	BB chemicals
7	Methyl paraben	BB chemicals
8	Palm oil	Gokul refoils & solvent ltd
9	Soya lecithin	CDH
10	Sodium alginate	BB chemicals
11	Pluronic f68	Thermo fischer scientific

4.2 Equipments used

Table 4.2 List of the equipments used

S.No.	Instruments	Manufacturers
1.	Electronic weighing balance	Shimadzu Co.Ltd., Japan
2.	FTIR spectrometer	Shimadzu Co.Ltd. Japan
3.	UV Spectrophotometer	Shimadzu Co. Ltd. Japan
4.	General glasswares	Tarsons Products Pvt. Ltd.
5.	Hot air oven	Navyug, Mumbai, India
6.	Heated/Magnetic stirrer	Remi, Pvt. Ltd. Mumbai, India
7.	pH meter	Systronic, μ pH system, India
8.	Optical microscope	Kyowa, Gentner, Japan
9.	Hot plate	Popular, India
10.	Viscometer	Brookfield viscometer
11.	Borosilicate	Tarsons Products Pvt. Ltd.
12.	Franz Diffusion Cell Assembly	M/s Permegear, Inc., USA
13.	SEM	Carl Zeiss, Germany
14.	Software Design xpert [®]	Licenced to StatEase, USA (www. Statease.com)

4.3 Drug Profile

Raloxifene HCl is the drug, which is widely used for the preventions and treatment of the osteoporosis especially for the post-menopausal women. Along with the calcium and vitamin D raloxifene HCl plays a very vital role for the treatment of osteoporosis and fractures. Raloxifene HCl is basically an estrogen agonist or antagonist, which is also called SERM. (Foster *et al.*, 2013) Some of the properties of the Raloxifene Hcl are discussed below.

Type: small molecule

Groups: approved, investigational

Description: It lays under category of SERM which is helpful in the treatment of osteoporosis. It shows both estrogen agonist and estrogen antagonist effects and therefore is helpful for both osteoporosis and breast cancer.

Structure:

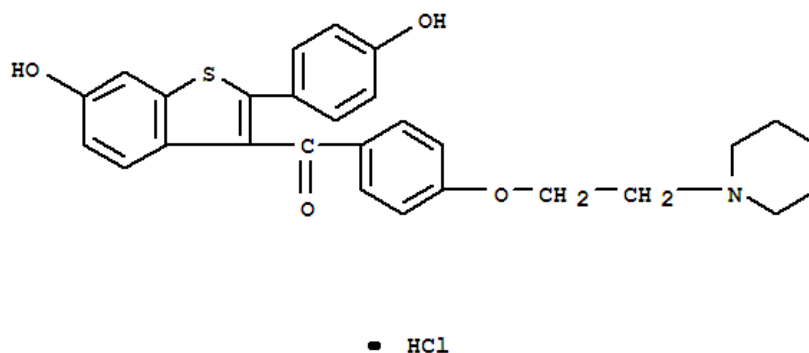


Figure 4.1 Chemical structure of raloxifene hydrochloride

Synonyms: Keoxifene

Raloxifeno

RAL

Raloxifenum

2-(4-Hydroxyphenyl)-6-hydroxybenzo(b)thien-3-yl) (4-(2-(1-piperidinyl)ethoxy)phenyl)
methanone

PLAN OF WORK AND EXPERIMENTAL WORK

Approved prescription products:

Table 4.3 Approved prescription products of raloxifene hydrochloride

Name	Dosage	Strength	Route	Manufacturer
Act raloxifene	tablet	60mg	oral	Actavis pharma company
Evista	tablet	60mg	oral	Eli lily and company
Evista	tablet	60mg	oral	Pd Rx pharmaceuticals inc.
Evista	tablet	60mg	oral	Lake Erie Medical & Surgical Supply DBA Quality Care Products LLC
Evista	tablet	60mg	oral	Physicians total care, Inc.
Optruma	Film coated tablet	60mg	oral	Eli lily Nederland B.V.

Weight: Average: 473.583

Monoisotopic: 473.166079047

Chemical formula: C₂₈H₂₇NO₄S

IUPAC name: 2-(4-hydroxyphenyl)-3-{4-[2-(piperidin-1-yl)ethoxy]benzoyl}-1-benzothiophen-6-ol

Indication: It is used for the treatment prevention of the osteoporosis and arthritis in the post-menopausal women. It is also helpful in various other bone loss disorders. It has shown the significant results in various patients suffering from the breast cancer. **(Rey et al., 2009)**

Structured Indications: Osteoporosis

Invasive breast cancer

Pharmacodynamics: Raloxifene comes under the category of SERM that is selective estrogen and receptor modulator and belongs to the benzothiopenes class. Its agonist effect is helpful for the treatment of osteoporosis were has its antagonist effect is used for the treatment for breast cancer. Raloxifene HCl is different from the estrogen that occurs naturally. As we know, estrogen has the significant role in cardiovascular, central nervous system, skeletal, reproductive system in females. **(Bhatia et al. 2013)** It shows the effect by the regulation of gene expression. On binding of estrogen to its receptor the therapeutic activity of the drug starts due to the gene transcription. Different signally pathways and response elements are responsible for the gene transcription. It therefore helps in the reduction of bone loss in the post-menopausal women. **(Nanetti et al., 2007)**

PLAN OF WORK AND EXPERIMENTAL WORK

Absorption: 60 percent of the drug absorbed by the oral route but due to the conjugate form during metabolism the bioavailability is only 2 percent.

Volume of distribution: 2348 L/kg [single doses of 30 to 150 mg orally]

Protein binding: 95%

Metabolism: It is metabolized by the liver therefore it undergoes first-pass metabolism and forms conjugates as there metabolites raloxifene-6-glucuronide, raloxifene-4'-glucuronide, and raloxifene-6, 4'-diglucuronide. It is studied that cytochrome P450 pathways plays no role in the metabolism of raloxifene. (**Jochemms *et al.*, 2008**)

Route of elimination: Feces is the main route of elimination while 0.2 percent is eliminated in urine unchanged.

Half life: 27.7

Clearance: 44.1 L/kg/hr [Postmenopausal Woman with Single Dose]

47.4 L/kg/hr [Postmenopausal Woman with Multiple Dose]

Oral cl=44.1 L/kg/hr

Toxicity: no record

Affected organisms: all humans beings and mammals

Drug Interactions: Various drugs diminishes the metabolism of Raloxifene HCl such as fluconazole, rifampicin, atazanavir, imatinib, clotrimazole, amiodarone, phenytoin, cyclosporine, amodiaquine, efavirenz, verapamil, dexamethasone etc.

Mechanism of action: The mechanism of the SERMs is that it affects the various receptors, which are stimulated by the estrogen, but the advantage is that it can be selectively available as agonist or antagonist as per the organs. They are also the antiresorptive agents. The advantage of the selective action is that it minimizes the adverse affects of the estrogen as it screens off the therapeutic effects. The estrogenic pathways are activated in various tissues and disruptions of the various pathways in other tissues are the prime reason for the reasons therapeutic and biological actions of the raloxifene hydrochloride. (**Jochemms *et al.*, 2008**) BMD at the hip and spine is elevated by the raloxifene hydrochloride therefore the chances of the fractures of the spine are lower down by the 32 to 50 percent. Raloxifene hydrochloride is the well approved medication for the treatment and prevention of the osteoporosis especially in the postmenopausal women. The dose available in the market is 60 mg tablets. Although, no serious side effects has been observed but still the adverse reaction like flu syndrome, sweating, craps

in the legs, edema, and hot flashes can be experienced in some patients. (Vestergard *et al.*, 2012)

4.1 Preformulation studies

The preformulation is initial step towards the development of the dosage form of the drug alone and when mixed with the excipients. The main goals of preformulation are as under:

To establish the physical characteristics.

To establish the physiochemical parameter of the new drug substances.

To establish the physical characteristics. (Bhatia *et al.* 2013)

- Physical appearance
- Melting point
- Phase separation
- UV visible spectrophotometry
- FTIR

4.1.1 Physical Appearance

The checking of the physical appearance of the drug and formation is the primary step of the evaluation. All the organoleptic properties are analyzed like color, taste, odor, texture, etc of the drug. The standard terminology should be used for the description of the various properties of the formulation so that there should be no confusion among different scientist. Various other parameters like homogeneity and clarity of the formulation are also inspected. (Baran *et al.* 2013)

4.1.2 Melting Point: The melting point of the drug was performed by capillary method. In this, drug was filled in the capillary tube sealed at one end to a height of 3 mm from closed end and capillary was introduced into digital melting point apparatus. The temperature range at which drug melt was noted down. (Penzes *et al.* 2015)

4.1.3 Phase separation: Phase separation is the conversion of a single-phase system into a multi-phase system; especially the separation of a solution into two immiscible liquids. Therefore, the organogel was evaluated for the phase separation. (Oliver *et al.* 2012)

4.1.4 Estimation of RLX using UV- visible spectrophotometer

Determination of absorbance maxima (λ_{max}) of raloxifene hydrochloride

For the standardization of the drug by using UV spectroscopy, the drug is firstly subjected to wavelength scan for determination of absorbance maxima (λ_{max}). A stock solution (1000 μ g/ml) of drug was prepared by dissolving 50 mg drug in 50 ml methanol, in 50 ml volumetric flask and volume was made up to 50 ml with respective dissolution media (phosphate buffer or distilled water). The samples were scanned between range of 200-400 nm by using UV-visible spectrophotometer. The wavelength at which maximum absorbance observed was selected as the analytical wavelength of the drug for that particular buffer media.

(Pavithra *et al.* 2006)

Calibration curve of the raloxifene

The Calibration curve of the drug was plotted in phosphate buffer saline (pH 5.5) using 0.1 NaOH as a co solvent to dissolve the drug. A stock solution of drug was prepared and was serially diluted with phosphate buffer saline pH 5.8 to obtain the concentration range of 100-800 μ g/ml respectively. The dilutions were analyzed spectrophotometrically at λ_{max} using phosphate buffer saline (pH 5.8) as a blank.

4.2 Drug Excipients Interaction Studies

Characterization of RLX was done by FTIR spectroscopy. The drug was mixed with KBr & pressed into a very thin pellet which was then observed under IR spectrophotometer and the spectrum obtained was interpreted. **(Baran *et al.* 2013)**

4.3 Design and Optimization of Formula

Optimization of organogel

4.4 Evaluation after formulation of organogel

- Uniformity of content
- Grittiness
- Measurement of pH
- Gellation time
- Homogeneity
- Invitro diffusion study
- Viscosity study

4.4.1 Uniformity of content

This is one of the very important parameter which should be analyzed for the formulation as it is the important part of the quality control and insurance. Different and multiple samples of the organogels are picked up randomly and assay of the content of the API of the drug is analyzed individually. Here we took suitable amount of raloxifene hydrochloride gel in the test tubes. The tubes were kept for few hours and concentration of the API was determined. (Peive *et al.*, 2011)

4.4.2 Grittiness

As organogels is the topical formulation therefore the grittiness of the gel was checked so that it does not irritate the skin. It was evaluated visually as well as under microscope. (Rakesh *et al.*, 2013)

4.4.3 Measurement of pH

As we know the pH of the human skin is 5.5, thus the pH of raloxifene hydrochloride organogel was analyzed with the help of digital PH meter. The observations and the readings were repeated 3 times and concordant values were noted down. (Sahoo *et al.*, 2013)

4.4.4 Gellation time

After the mixing of the last ingredient that was water the time required to form the gel was noted down which is called the gellation time. The test tube or the beakers are continuously tested by tilting them to ensure the proper gellation. Then the proper gellation is confirmed by inverting the beaker or tube and total time required is noted down which is the gellation time. (Peive *et al.*, 2011)

4.4.5 Homogeneity

The Homogeneity of the organogels was checked visually by the observing the gels in the container. The aggregation and appearance of the organogels was also tested. (Bhatia *et al.*, 2013)

4.4.6 Invitro diffusion studies

Invitro diffusion studies of the different formulations of the organogels were performed with the helped of Franz diffusion cell in which the fresh inner egg membrane was used. Phosphate

buffer was used in the receptor compartment and gel was applied uniformly over the egg membrane the donor compartment and the receptor compartment was attracted with each other at 37 ± 0.50 temperature. The receptor compartment solution was continuously stirred at different time intervals. 5ml solution was driven out for sample and fresh 5 ml phosphate buffer was added. Spectrophotometrically the concentration of the drug was determined and same was repeated 3 times. (Pavithra *et al.* 2009)

4.4.7 Viscosity study

Viscosity is one of the important parameter of the organogels therefore it was analyzed with the help of Brookfield Viscometer. Different rpm and spindle were used as per the monographs. (Bhatia *et al.*, 2013)

**RESULTS
AND
DISCUSSIONS**

CHAPTER 5

Results and Discussion

5.1 Identification and characterization of raloxifene hydrochloride

5.1.1 Physical Description

The organogels raloxifene hydrochloride was characterized organoleptically and colour of the drug was found to be slight yellow. The drug was in solid state in the form of fine powder. The drug was also odourless. (Bhattacharya *et al.* 2012)

Table 5.1 Organoleptic evaluation of the drug.

Morphological Parameters	Observation
Colour	Slight yellow
Odour	Odourless
State	Solid
Texture	Fine powder

5.1.2 Melting point analysis

Melting point for the drug was performed using the capillary method. In this, drug was filled in the capillary tube sealed at one end to a height of 3 mm from closed end and capillary was introduced into digital melting point apparatus. The temperature range at which drug melt was noted down which gave the concordant reading of 252°C which was similar as described in the Indian pharmacopeia 2014. (Penzes *et al.* 2015)

5.1.3 Identification of the raloxifene hydrochloride by FTIR spectra

FTIR spectroscopy of the raloxifene hydrochloride was performed and observed.

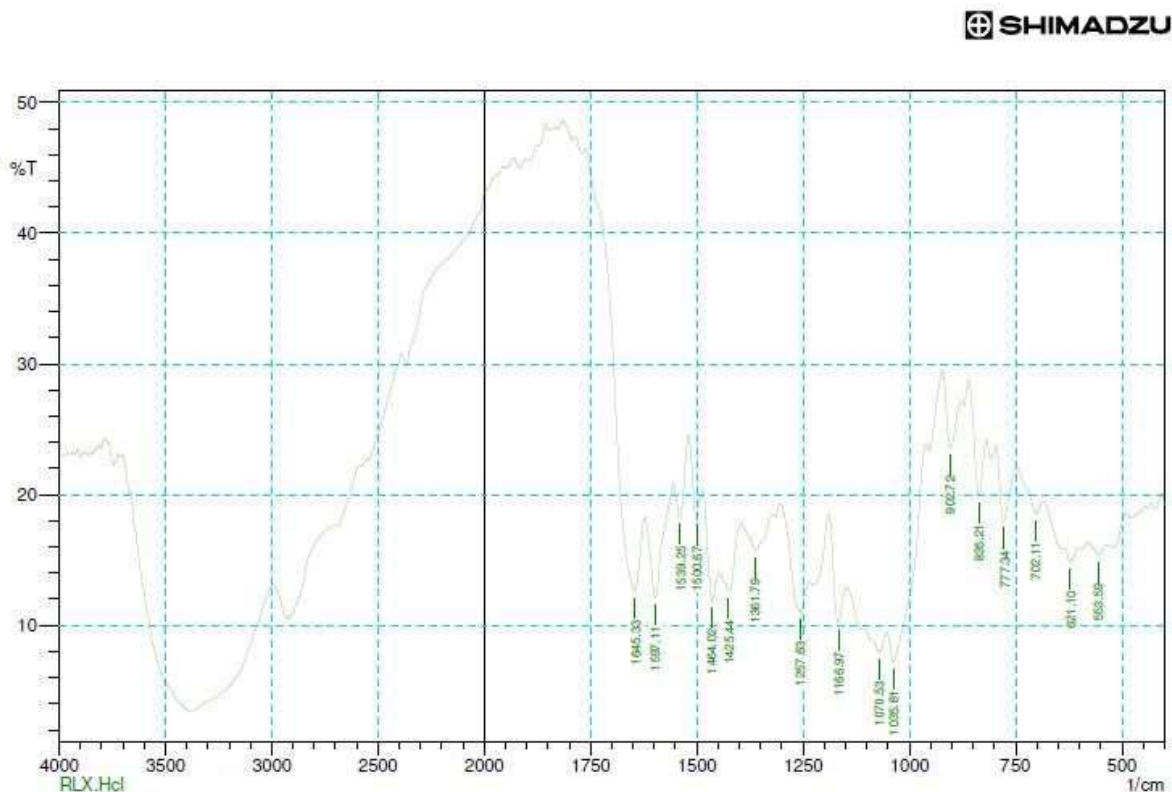


Figure 5.1 IR graph for Raloxifene hydrochloride

Below given is the chemical structure of the raloxifene hydrochloride which can be related with its FTIR spectra.

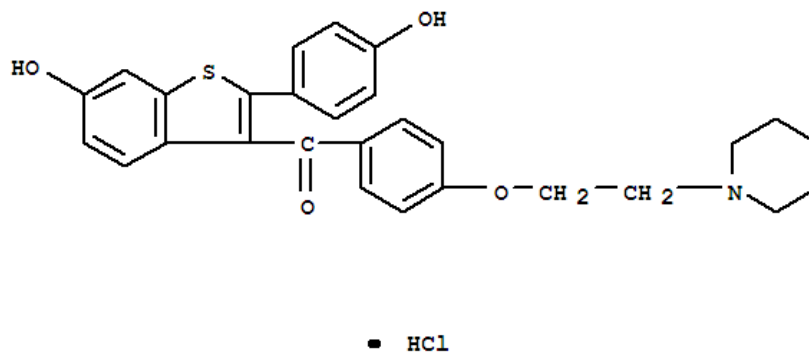


Figure 5.2 Chemical structure of raloxifene hydrochloride

From the FTIR spectra of the raloxifene hydrochloride characteristic peaks were observed at the 1645.33 which is due to C=O stretching. Peak at 1597.11 recognizes the C-O-C stretching whereas peak at 1464.02 is for the S-benzothiofuran and also the peak at 902.72 indicates the presence of benzene ring. (Pavia *et al.*, 2009)

5.1.4 Scanning for absorption maxima and calibration curve of the raloxifene hydrochloride.

UV spectroscopy of the drug was observed using the Shimadzu's UV spectrophotometer. Samples for the different concentrations were prepared and were analysed.

Experiment :

1. 5 mg of the raloxifene was dissolved in the 50 ml of the methanol.
2. The solution was then filtered through the whatman filter paper, which gives us the stock solution having the concentration of 1mg/ml or 1000 µg/ml.
3. Now from the stock solution further dilutions were made using the distilled water having the concentration of 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml, 5µg/ml and 10 µg/ml.
4. With methanol as the blank solution all the solutions were scanned for the maximum wavelength by Shimadzu's UV Spectrophotometer and the common maximum wavelength came out to be 285 nm.
5. With methanol as the blank solution absorbance was measured at the λ_{\max} 285 nm for all the solutions by Shimadzu's UV Spectrophotometer.
6. All the λ_{\max} values were analysed and absorbance of all the solutions were measured at the common wavelength.
7. The graph was plotted for the same and regression and equation was calculated for the same. (Pavithra *et al.* 2006)

The following contains the data for the above discussed experiment:

Table 5.2 Readings of the samples from the UV spectrophotometer

Sr no.	Concentration ($\mu\text{g/ml}$)	Absorbance
1.	0	0
2.	10	0.104
3.	20	0.231
4.	30	0.338
5.	40	0.408
10.	50	0.509

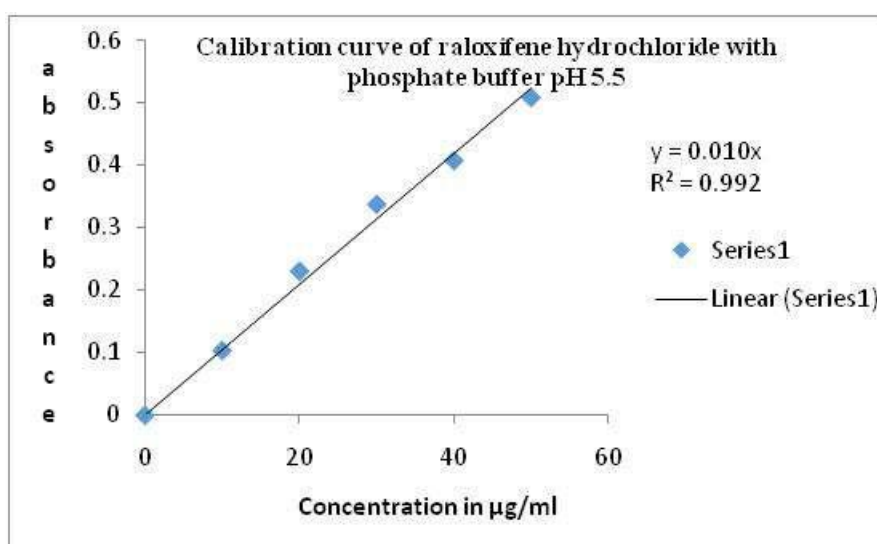


Figure 5.3 Calibration curve of raloxifene hydrochloride with phosphate buffer pH 5.5

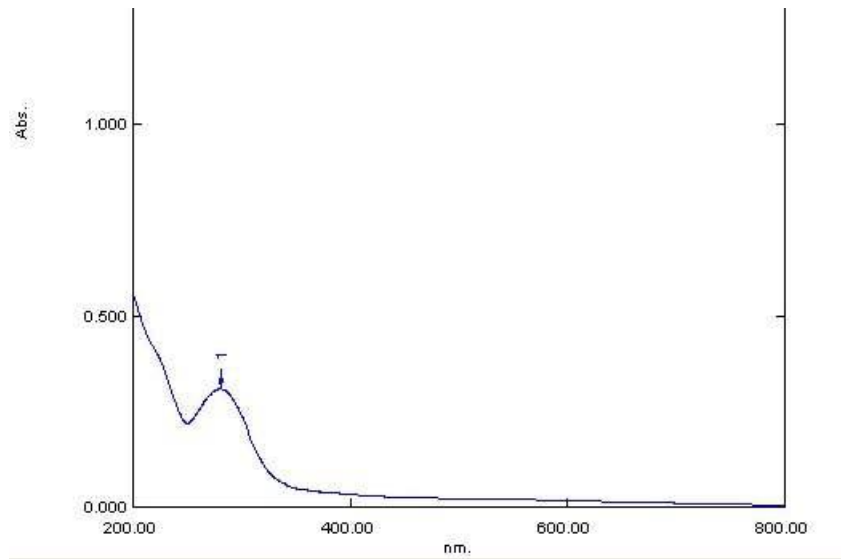


Figure 5.4 UV Graph of concentration 30 µg/ml observed in UV spectrophotometer.

5.2 Preformulation Studies

5.2.1 Drug excipients compatibility

No physical and chemical incompatibilities were observed the results gathered from the compatibility studies of the raloxifene hydrochloride and other excipients under stressed conditions. No change in the colour, odour, and appearance was observed during the study. Also the FTIR spectra were done with different excipients and drug. There was no change observed in the main peaks drugs when mixed with the excipients. Therefore we can say that dug and excipients are compatible with each other.

Table 5.3 Drug and excipients in 1:1 ratio for compatibility studies

Sr. no	Ingredients	Colour	Appearance	State	Lumps
1.	RaloxifeneHcl	Light yellow	crystalline	solid	No
2.	Soya lecithin	cream	crystalline	solid	No
3.	Carbopol 934	white	crystalline	solid	No
4.	RlxHcl :S.lecithin	Light yellow	crystalline	solid	No
5.	RlxHcl :carbopol 934	Light yellow	crystalline	solid	No
6.	RlxHcl :S.lecithin : carbopol 934	Light yellow	crystalline	solid	No

Table 5.4 Drug and excipients in 1:1 ratio at different time intervals

Ingredients	1st day	2nd day	3rd day	4th day	5th day
RaloxifeneHCl	√	√	√	√	√
Colour	√	√	√	√	√
Appearance	√	√	√	√	√
State	√	√	√	√	√
Lumps	√	√	√	√	√
Soya lecithin	√	√	√	√	√
Colour	√	√	√	√	√
Appearance	√	√	√	√	√
State	√	√	√	√	√
Lumps	√	√	√	√	√
Carbopol 934	√	√	√	√	√
Colour	√	√	√	√	√
Appearance	√	√	√	√	√
State	√	√	√	√	√
Lumps	√	√	√	√	√
RlxHCl :S.lecithin	√	√	√	√	√
Colour	√	√	√	√	√
Appearance	√	√	√	√	√
State	√	√	√	√	√
Lumps	√	√	√	√	√
RlxHCl :carbopol 934	√	√	√	√	√
Colour	√	√	√	√	√
Appearance	√	√	√	√	√
State	√	√	√	√	√
Lumps	√	√	√	√	√
RlxHCl :S.lecithin : carbopol 934	√	√	√	√	√
Colour	√	√	√	√	√

Appearance	√	√	√	√	√
State	√	√	√	√	√
Lumps	√	√	√	√	√

From the above drug excipients study it was found that all the excipients are compatible with the drug as they showed the no change in the physical properties even after 15 days.

5.2.2 FTIR of Soya lecithin, carbopol and drug with excipients

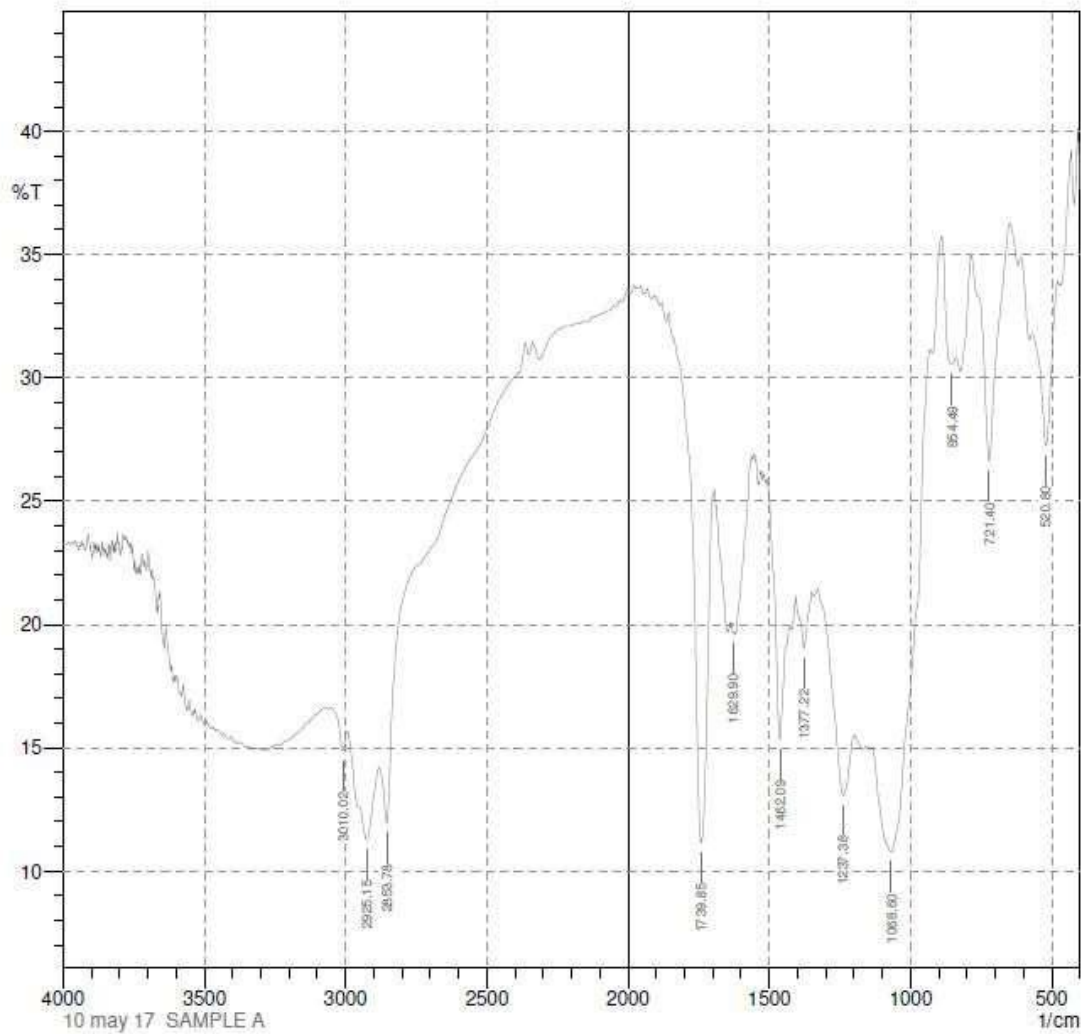


Figure 5.5 IR graph for soya lecithin

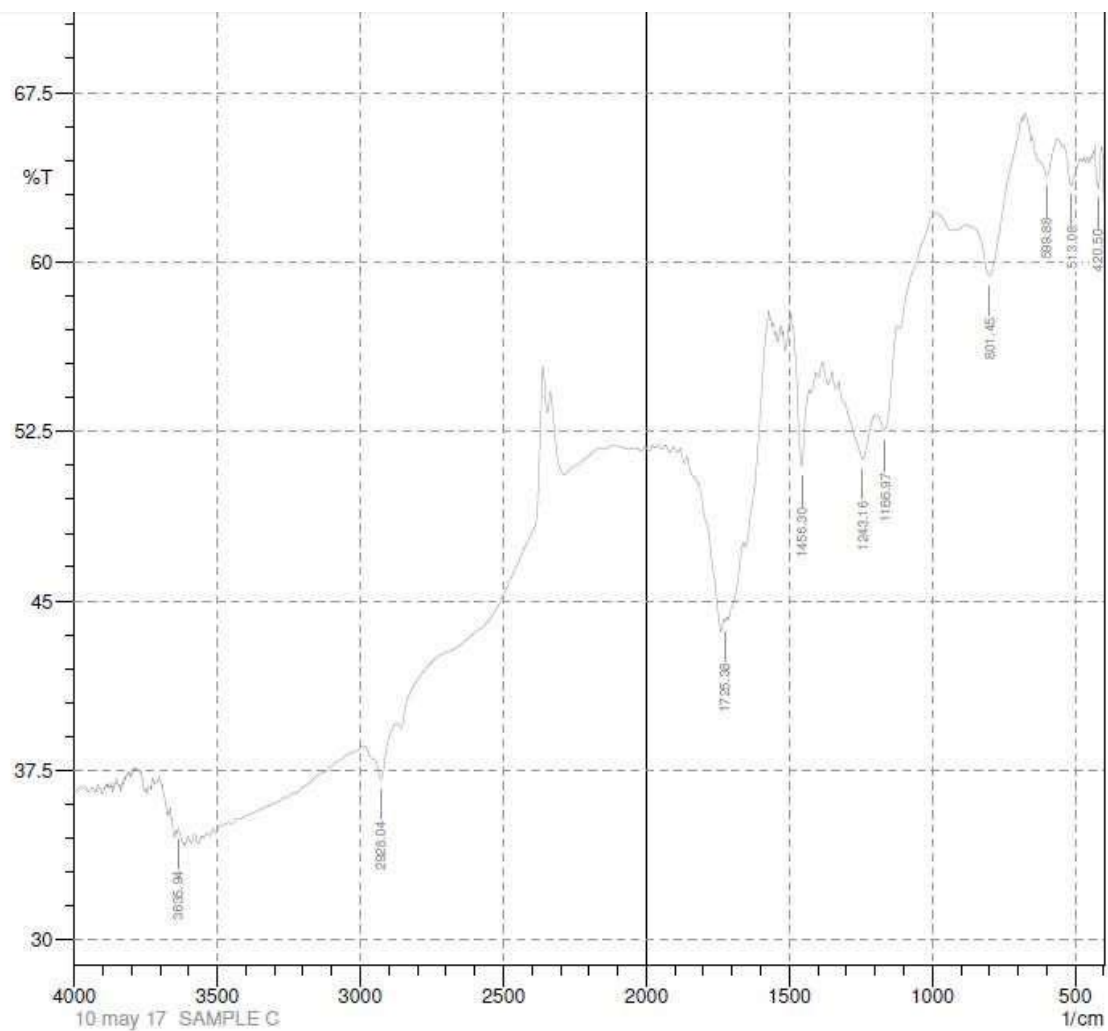


Figure 5.6 IR graph for carbopol 934

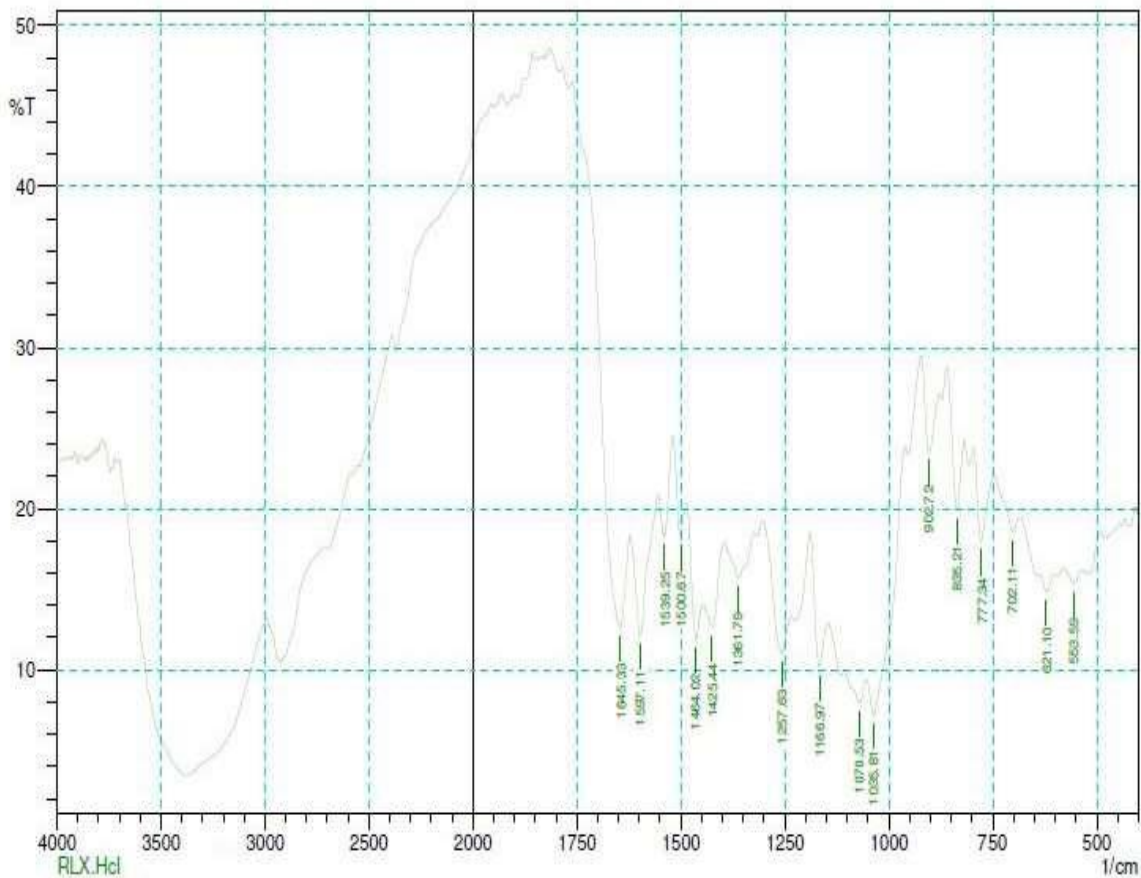


Figure 5.7 IR graph for raloxifene hydrochloride

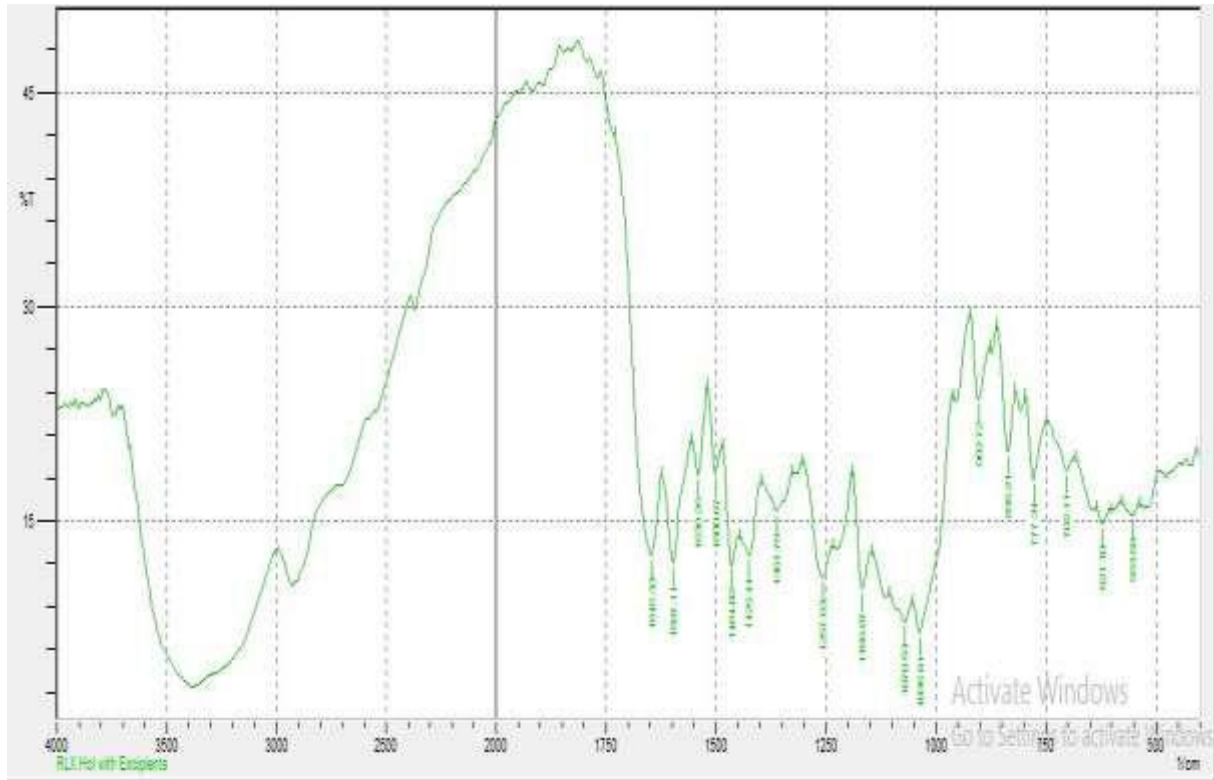


Figure 5.8 IR graph for drug mixed with excipients

From the above FTIR study of the drug and excipients we found that there is not much difference between the FTIR of the drug individual and drug mixed with the excipients. Almost all the peaks were observed in the drug and when mixed with excipients. Therefore we can say that drug is compatible with excipients. (Pavia et al. 2009)

5.3 Preparation of the organogel

Palm oil based organogel was prepared with help of the soya lecithin by using the different proportions of the surfactant soya lecithin, co-surfactant tween 80, distilled water and palm oil. Here fluid fibre mechanism was used for the preparation of the organogel. Different oils and different concentrations of the ingredients were used for the preparation of the organogel but the palm oil was suitable for the organogel in all aspects. (Baran et al. 2013)



Figure 5.9 Different oils used for the preparation of the organogels

Not all the oils are suitable for the preparation of the organogel as the emulsions were formed instead of the organogels with various other oils.



Figure 5.10 Formation of the emulsion instead of organogel with other oils.

Palm oil formed the best organogel while others formed the emulsions too. The colour obtained of the organogel whitish yellow to yellow. The organogel was checked by the tube inversion method for the stability. (Baran *et al.* 2013)



Figure 5.11 Formation of the stable organogel with palm oil.

Table 5.5 Composition of organogel with palm oil, surfactant and co surfactant

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Palm oil	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml
Soya lecithin	0.5gm	1gm	0.5gm	1gm	0.5gm	1gm	0.5gm	1gm
RaloxifeneHcl	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
Tween 80	2.5 ml	4ml	2.5ml	4ml	2.5ml	4ml	0	0
Carbopol (1%)	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Methyl paraben	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%

As here we have used the soya lecithin as the main surfactant therefore the organogel could be formed either by solid fibre or fluid filled structure mechanisms. As we are using the tween 80 as the co-surfactant here thus the increased amount of the tween 80 may lead to the formation of the microemulsion based organogel. On the other hand the viscosity of the organogel can be increased with help of the soya lecithin. Therefore the optimum amount of the soya lecithin and tween 80 are very much necessary for the formation of the stable organogel. (Penzes *et al.* 2015)

5.4 Organoleptic Evaluation

The organogels formed were characterized organoleptically and colour of the organogel was found to be slight yellow, consistency was stable which was verified by the tube inversion method. On touching the preparation it was oily in nature and the organogel formed as odourless in odour. (Baran *et al.* 2013)

Table 5.6 Morphology of the organogel prepared

Morphological Parameters	Observation
Colour	Slight yellow
Odour	Odourless
State	Gel
Texture	Greasy and oily

5.5 Stability Studies

The accelerated stability test was performed for the formed organogels by freeze-thaw method to ensure the stability of the organogels for long period of time. All the samples were analyzed for the changes like change in colour, change in odour and other changes like degradation and phase separation. All the samples of the palm oil based organogels passed the stability test. (Sahoo *et al.* 2011)



Figure 5.12 Samples which passed the stability test

5.6 Microscopic Studies

The microscopic study of the organogel was performed using the optical microscope. The microscopy was performed by using the organogels of the different concentrations. With the increase in the amount of the surfactant that is soya lecithin the spherical globules were observed where as the crystals were observed with the lesser amount of the surfactant. Usually we observed the spherical shaped droplets. The test tubes were then allowed to dried and again

observed under the microscope again upon which the crystal like structures of the organogel was observed. (Bhatia *et al.* 2013)



Figure 5.13 (a) Microscopic study of the organogel comprising the high concentration of surfactant

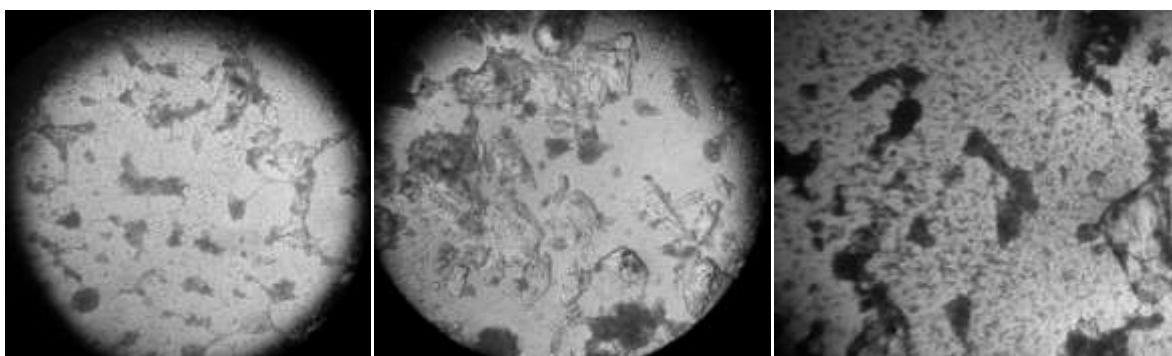


Figure 5.13(b) Microscopic study of the organogel comprising the lower concentration of surfactant

5.7 SEM analysis

The organogel was observed under the SEM (scanning electron microscope) and the results analyzed. It was observed that the concentration of the surfactant alters the microscopic structures of the organogel. In organogel comprised of the lesser amount of the surfactant showed the non fibrous structure of the organogel whereas the organogel sample comprised of the more concentration of the surfactant leads to the fibrous structure under the scanning electron transmission microscope. (Penzes *et al.* 2015)

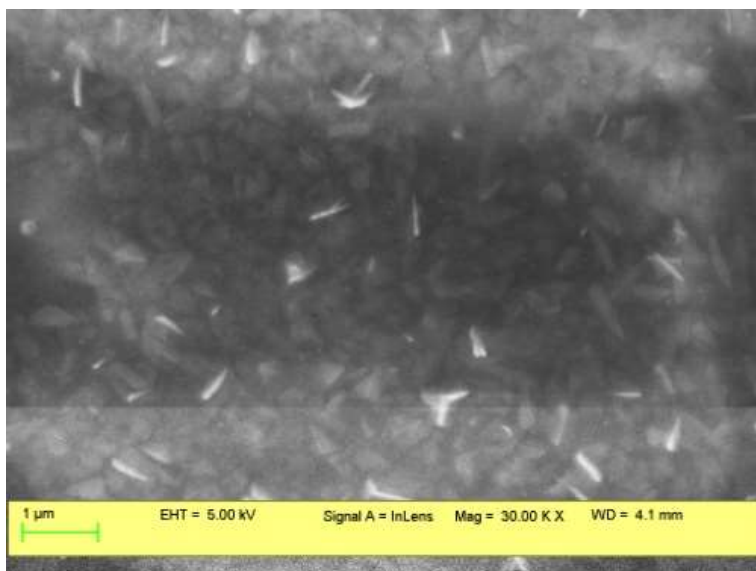


Figure 5.14 (a)

In the above picture we can see the non fibrous structure of the organogel.

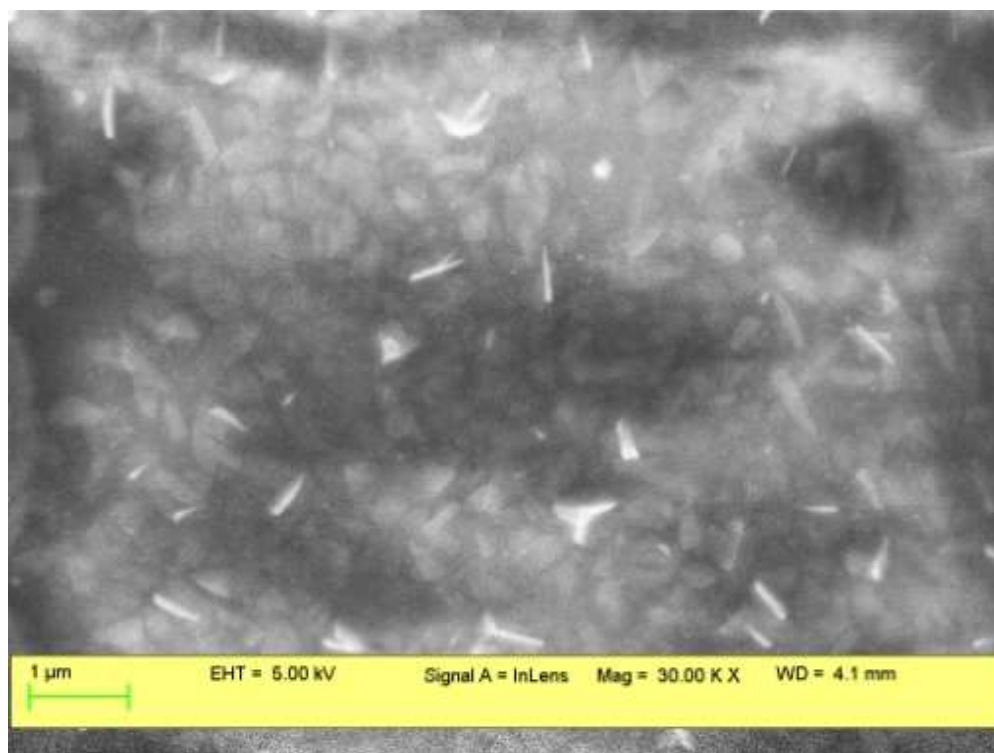


Figure 5.14 (b)

Figure 5.14 (a,b) SEM graphs showing the structure of organogel consisting of the lower amount of the surfactant

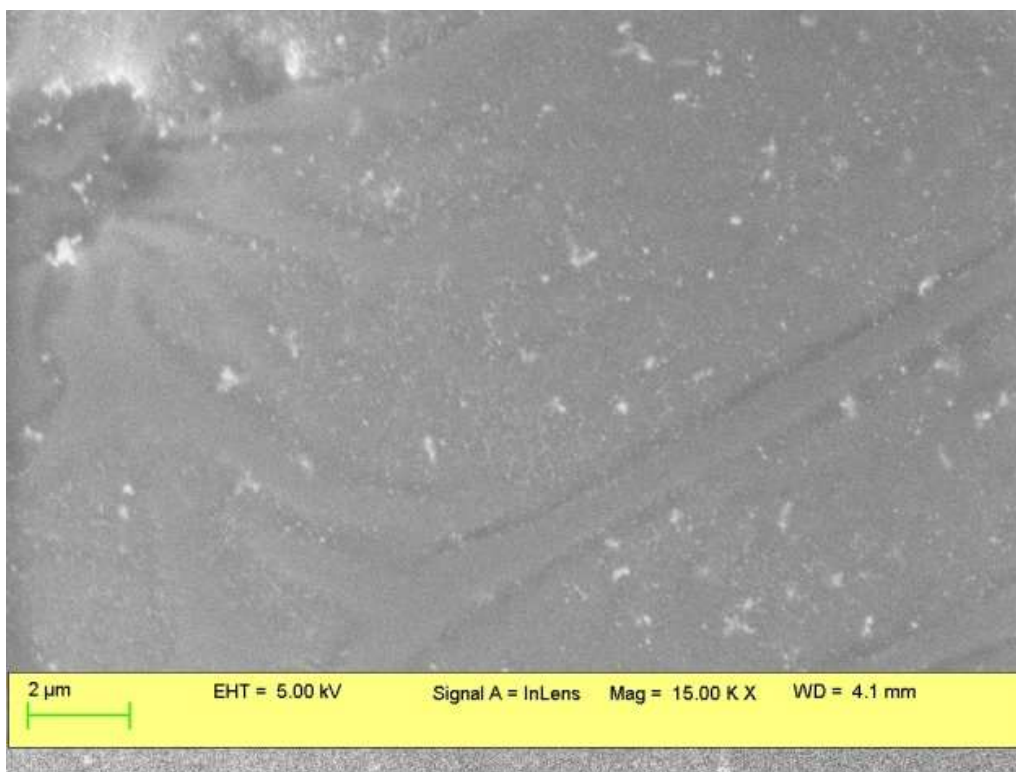


Figure 5.15 (a)

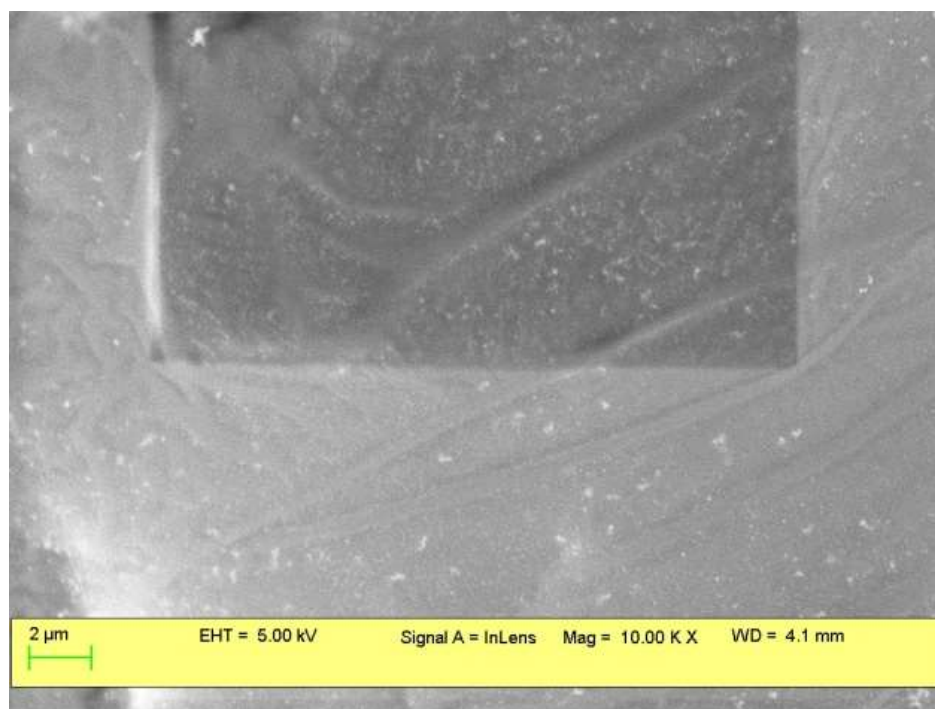


Figure 5.15 (b)

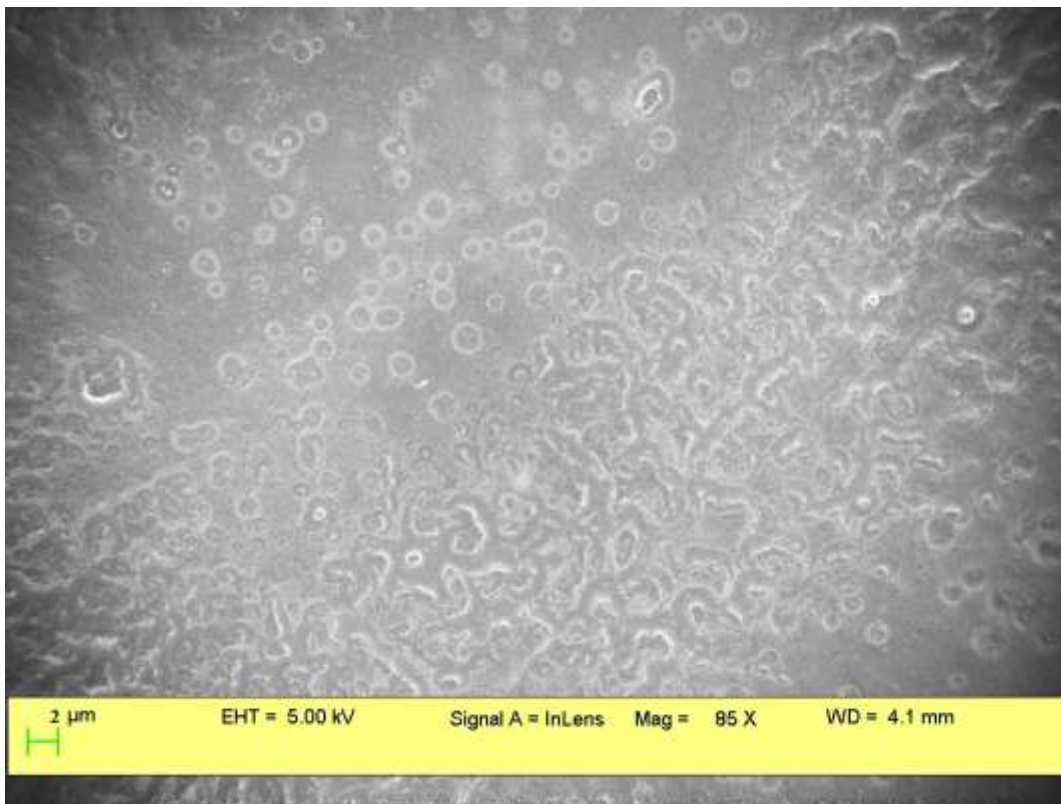


Figure 5.15 (c)

Figure 5.15 (a,b,c) SEM graphs showing the structure of the organogel at the different concentrations of the surfactant.

Here we can see the non-fibrous structure of the organogels which is due to the lesser concentration of the surfactant and co surfactant. Increasing the concentration of the surfactant and co surfactant the heterogeneous network become more dense and fibrous. With the increase in the concentration of the surfactant the tubules like structures were absorbed which were connected to each other and similar to rod like structure. Thus we can say that the concentration of the surfactant alters the structure and properties of the organogels. As it was clearly indicated that how the droplet like structure changes to the fiber like structures with the alteration in the concentration of the soy-lecithin. (Penzes *et al.* 2015)

5.8 Macroscopic Studies

The macroscopic study of the prepared organogels was also performed using the solution of rhodamine B as the aqueous phase. It is clear from the figure below that aqueous phase of the organogel is comprised of the internal phase which ensures that organogel prepared is w/o

emulsion. Also we observed that self arrangement was done by the molecules of the surfactant into the spherical structures later on which formed network type structure. Upon which the immobilization took place of the oil phase which ensures the formation of the organogel. The texture of the organogel formed was oily indicating the apolar nature of the external phase. (Bhattacharya *et al.* 2012)



Figure 5.16 Morphological observation of the organogels

5.9 pH measurement

As we know that human skin has the normal pH of 5.5 to 7.0. The organogels prepared here showed the pH in between this range therefore it can be safely used for the topical application on the human skin. (Tarun *et al.* 2011)

Table 5.7 Values of the pH observed for the different formulations

Sr. no.	Formulations	pH observed
1.	F1	5.6
2.	F2	5.5
3.	F3	5.7
4.	F4	5.8
5.	F5	5.5
6.	F6	5.7
7.	F7	5.6
8.	F8	5.5

5.10 Occlusiveness: As we know water and oil are the essential parts of the gel formulation. The oil part consist of hydrocarbons like various mineral oils. Therefore on checking the texture of organogel was found to be greasy and occlusive which was checked by rubbing on the hand. (Iwanaga *et al.* 2012)

5.11 Phase separation: Phase separation is the conversion of a single-phase system into a multi-phase system; especially the separation of a solution into two immiscible liquids. Therefore, the organogel was evaluated for the phase separation. All the preparations of the organogels were allowed to stand at different temperatures and at different intervals of time. All the preparations passed the test and in none of them phase separation was observed. (Rakesh *et al.* 2014)

5.12 Homogeneity: The Homogeneity of the organogels was checked visually by the observing the gels in the container. The aggregation and appearance of the organogels was also tested. All the organogels formed passed the homogeneity test. (Tarun *et al.* 2011)

5.13 Grittiness

As organogels is the topical formulation therefore the grittiness of the gel was checked so that it does not irritate the skin. It was evaluated visually as well as under microscope. All the prepared organogels were found to be fine and passed the test as no grittiness was observed and felt in any of the prepared organogel. (Iwanaga *et al.* 2012)

5.14 Viscosity study

Viscosity is one of the important parameter of the organogels therefore it was analyzed with the help of Brookfield Viscometer. Different viscosity was observed for the different formulated organogels which are described in the table below. (Sahoo *et al.* 2011)

Table 5.8 Readings of the viscosity measured for different formulations at different RPM.

RPM	Viscosity in cps							
	F1	F2	F3	F4	F5	F6	F7	F8
0.3	65460	67350	74560	68730	62340	59760	58370	58180
0.5	63580	65420	72450	66340	58760	55430	55370	54870
0.6	59350	61450	70560	63450	54630	52460	52630	51620
1	54980	57890	65340	61230	49870	49870	49870	47860
1.5	48560	53450	62350	59780	44890	44320	44530	42370

2	42530	48970	59080	56760	40620	40620	40390	39760
2.5	38760	44900	56780	53290	36420	37650	36780	36720
3	34230	40980	51320	49870	31270	32450	31450	31870
4	31250	36740	47850	42360	28760	29850	27650	27760
5	29870	32980	41980	39640	26540	24350	24350	21780
6	27540	28760	35640	35380	24350	21370	21450	19670
10	25450	26570	29730	27450	21890	18490	17560	17120

5.15 Invitro Drug Release Studies

The profiles of drug release for raloxifene hydrochloride were studied. It was observed that the composition of the organogels effects the release of the drug to large extent. Franz diffusion cell used for the invitro diffusion studies. Egg membrane was used as it resembles to the human membrane and also it is friendly with the animals and environment as there is no need of the animals. The hole was made in the egg very carefully and whole of the material inside the egg was taken out without cracking the egg shell. Now it was washed with the water. This egg was now dipped in the beaker containing the 0.1N HCl for 20 mins. (**Bhattacharya et al. 2012**) After the 20 mins the inside membrane of the egg was easily taken out which was further used for the diffusion studies. It was then soaked in the phosphate buffer for the 24 hours before the use. 1gm of the organogel was placed in the donor compartment whereas phosphate buffer 7.4 was filled in the receptor compartment. The surface of the donor compartment was in contact with the receptor and continuous stirring was done with the maintenance of the temperature of $37\pm 1^{\circ}\text{C}$. Then the samples were withdrawn after the time period of 30 mins for 8 hours and same amount was replaced for the maintenance of the sink conditions. The samples were analyzed at 285nm using the UV spectrophotometer. Here the 8 different formulations were prepared using the different concentrations and their drug release study was performed in the detail. (**Esposito et al. 2013**)

RESULTS AND DISCUSSION

Table 5.9 Drug release values for the different formulations.

TIME (mins)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)
0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0
30	4.3±0.02	3.2±0.03	9±0.05	7.2±0.04	6.2±0.03	9.2±0.02	3.1±0.5	3.40±0.03
60	6.2±0.03	5.8±0.02	16.3±0.04	14.9±0.06	12.6±0.05	15.3±0.03	6.8±0.4	7.1±0.05
90	10.1±0.02	11.3±0.05	21.4±0.06	19.7±0.03	16.6±0.03	20.4±0.06	11.5±0.6	12.4±0.06
120	13.7±0.04	13.8±0.07	26.8±0.03	24.8±0.02	23.1±0.06	25.9±0.03	17.7±0.8	18.4±0.02
150	15±0.06	16.2±0.04	29.1±0.05	26.1±0.07	24.8±0.02	28±0.05	20.4±0.2	21.5±0.03
180	20.3±0.03	18.5±0.09	33.9±0.07	31±0.04±0.08	29.7±0.08	32.4±0.01	27.8±0.7	29.3±0.07
210	26.8±0.07	22.8±0.06	39±0.09	40.2±0.05	36.8±0.04	37.7±0.06	36.5±0.5	35.5±0.03
240	30.7±0.02	29.9±0.08	45.2±0.02	46.1±0.09	43.7±0.06	43.8±0.09	43.5±0.3	44±0.08
270	36.3±0.04	38.1±0.05	49.1±0.06	50.8±0.07	48.2±0.09	47.7±0.02	49.9±0.8	50.8±0.06
300	44.1±0.05	47.9±0.03	56.7±0.05	54.5±0.02	53.3±0.05	57±0.08	58.3±0.5	57.7±0.09
330	53.9±0.03	55.7±0.09	62.1±0.08	61±0.07	59.1±0.07	63.9±0.06	61.1±0.9	62.2±0.03
360	62.1±0.10	64.9±0.20	67.9±0.30	65.7±0.40	63.6±0.30	66.8±0.10	67.2±0.20	68.8±0.40
390	68.4±0.30	66.2±0.09	72.2±0.10	70.3±0.10	71.1±0.40	71.9±0.40	73.9±0.40	74.3±0.20
420	74±0.20	76±0.10	79.2±0.40	76.3±0.30	76.9±0.10	78.8±0.20	76.2±0.10	79.9±0.10
450	81.2±0.10	80.9±0.30	88.6±0.30	83.9±0.20	83.7±0.20	86.3±0.30	80.1±0.20	81±0.50
480	86±0.30	85±0.08	96±0.10	89±0.40	87±0.30	92±0.10	84±0.50	86±0.10

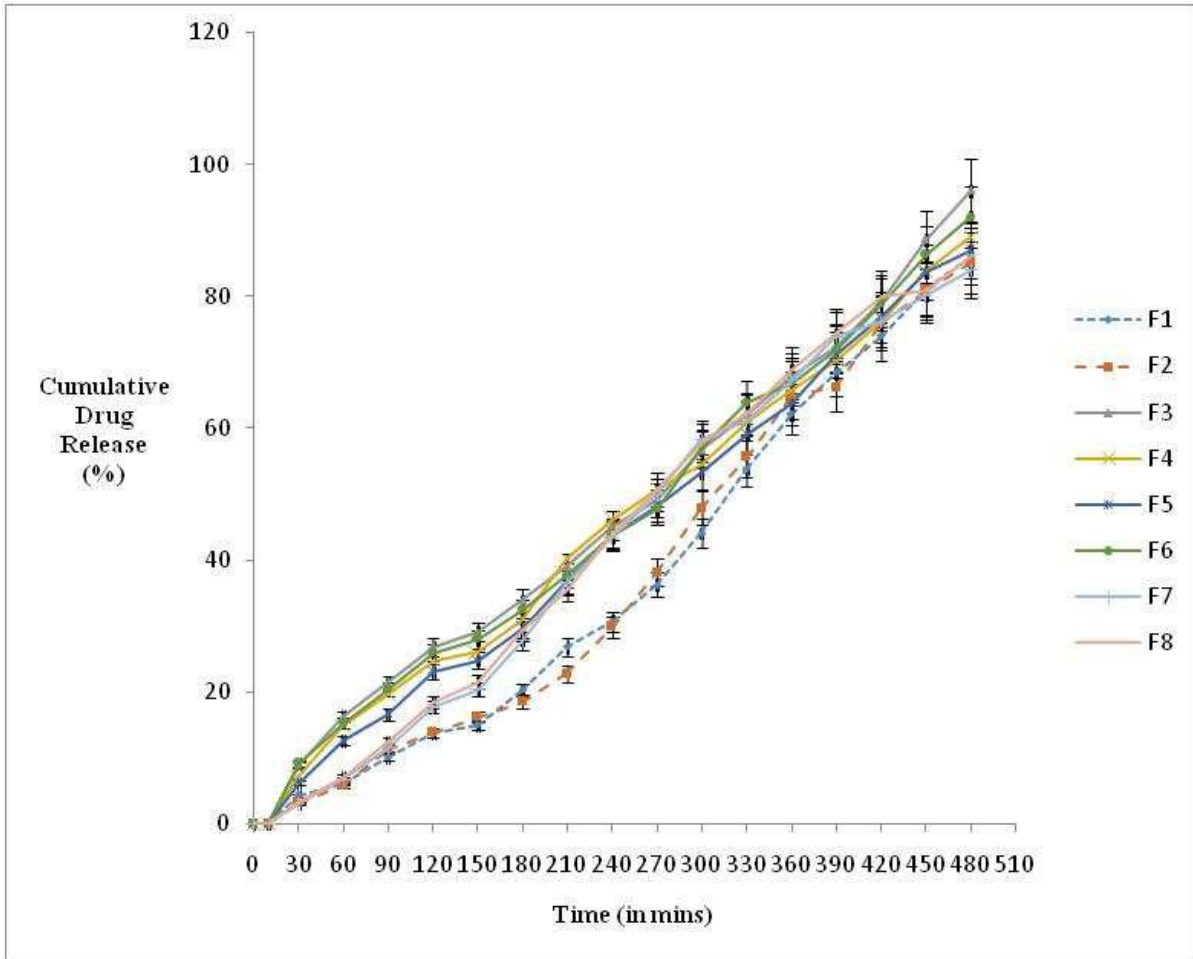


Figure 5.17 Graph showing the drug release of all the 8 formulations (F1-F8)

After this the different graphs were plotted for all of the different formulations like zero order, first order, huguchi model, Hixson and Korspeppas.

Formulation F1

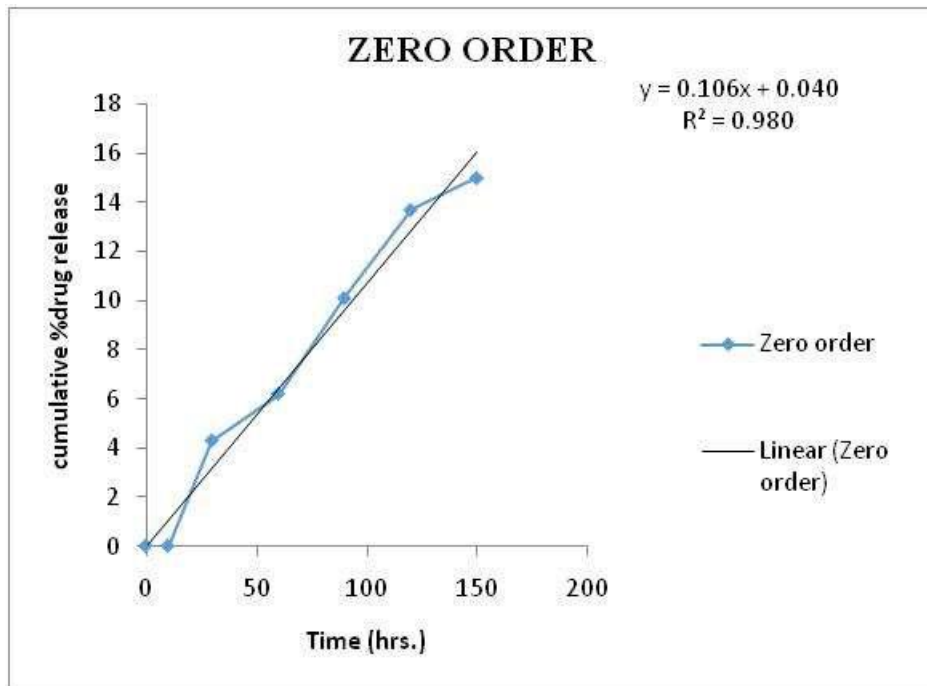


Figure 5.18 Zero order kinetics for formulation F1

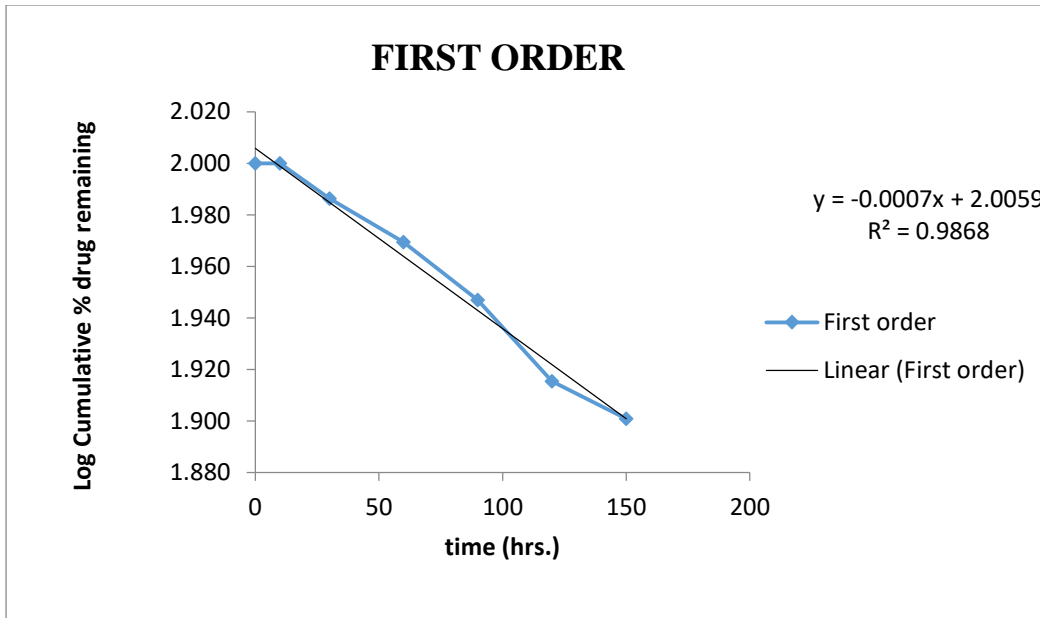


Figure 5.19 First order kinetics for formulation F1.

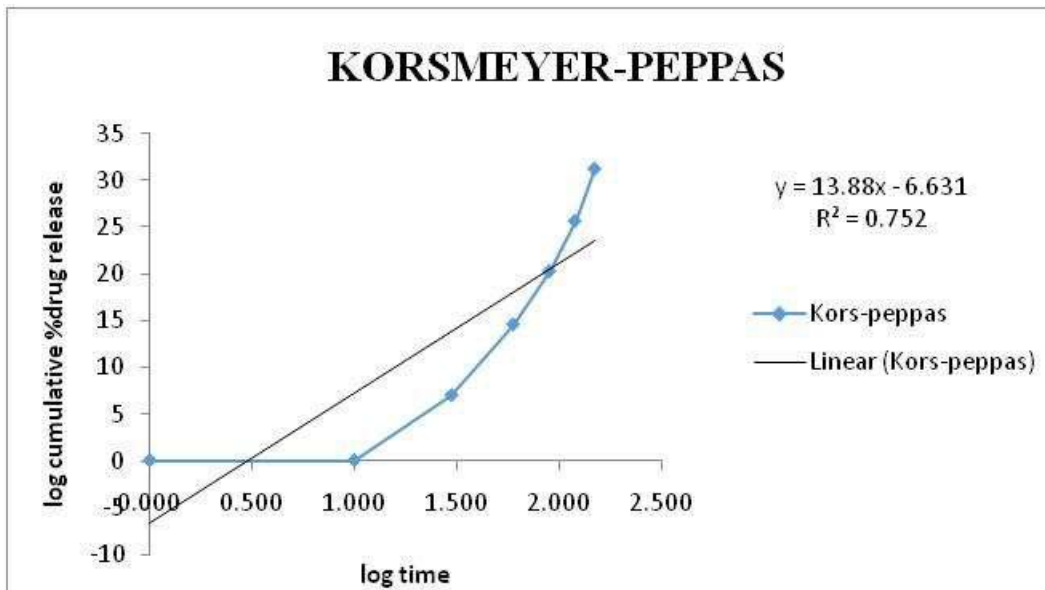


Figure 5.20 Korsmeyer-Peppas model for formulation F1.

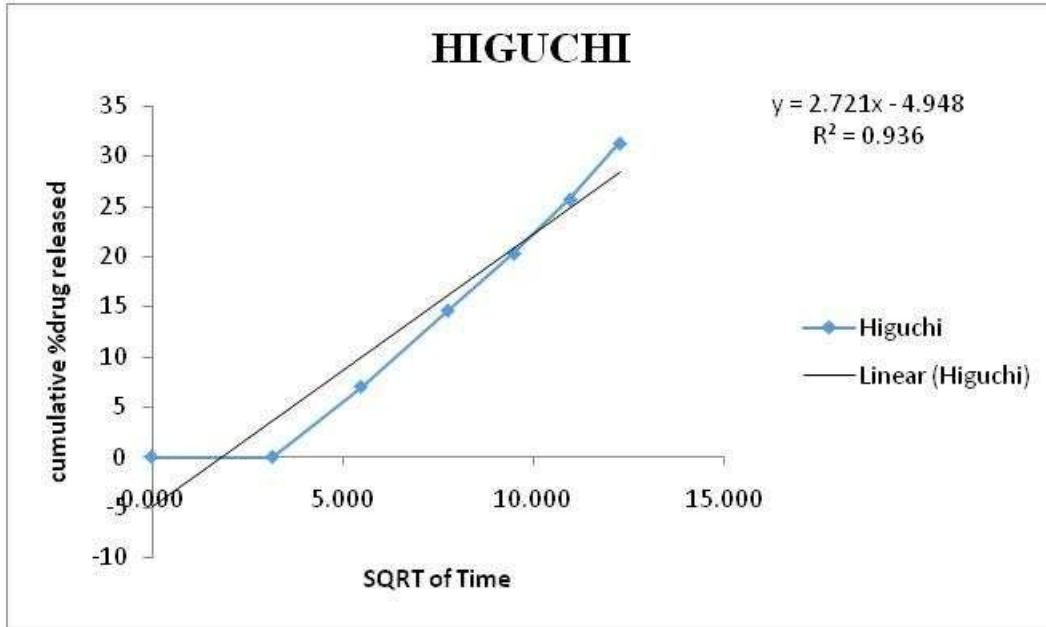


Figure 5.21 Higuchi model for formulation F1.

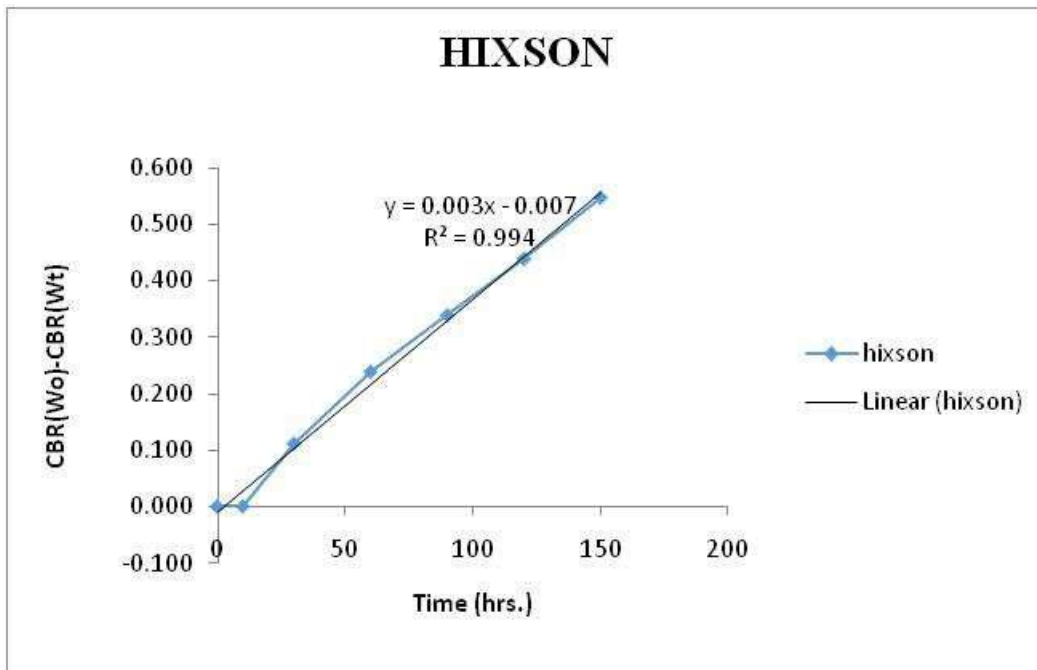


Figure 5.22 Hixson model for formulation F1.

Formulation F2

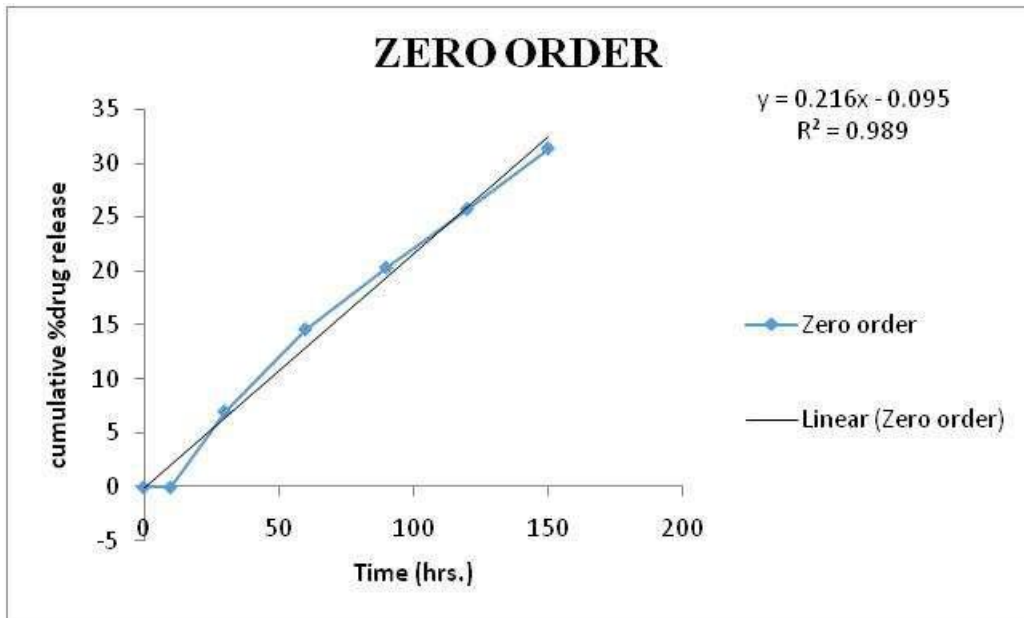


Figure 5.23 Zero order kinetics for formulation F2

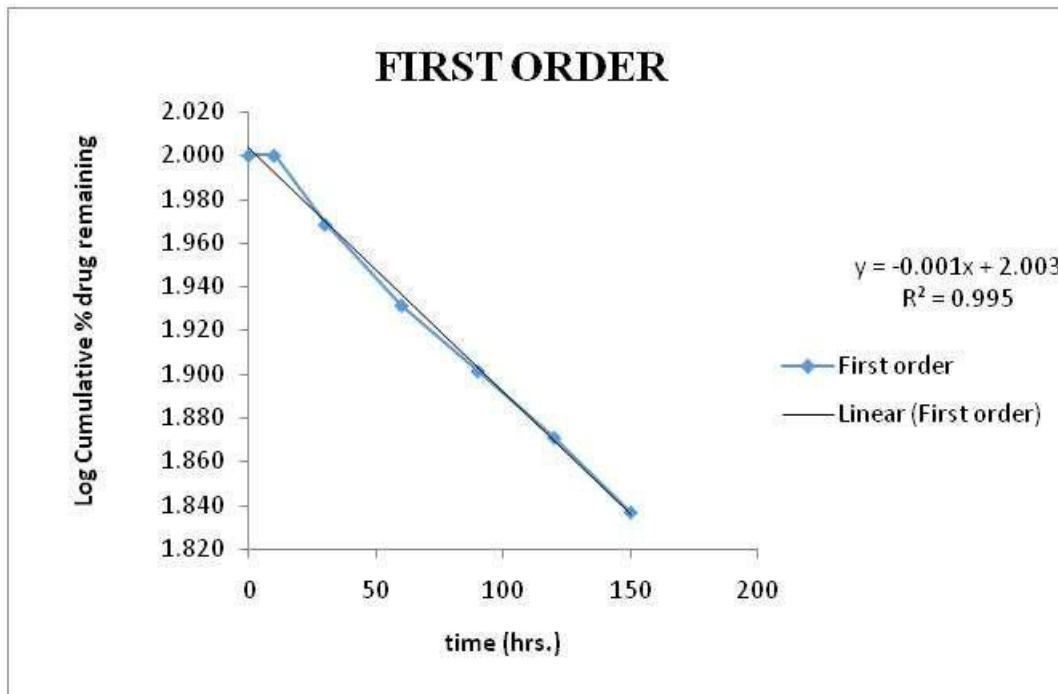


Figure 5.24 First order kinetics for formulation F2

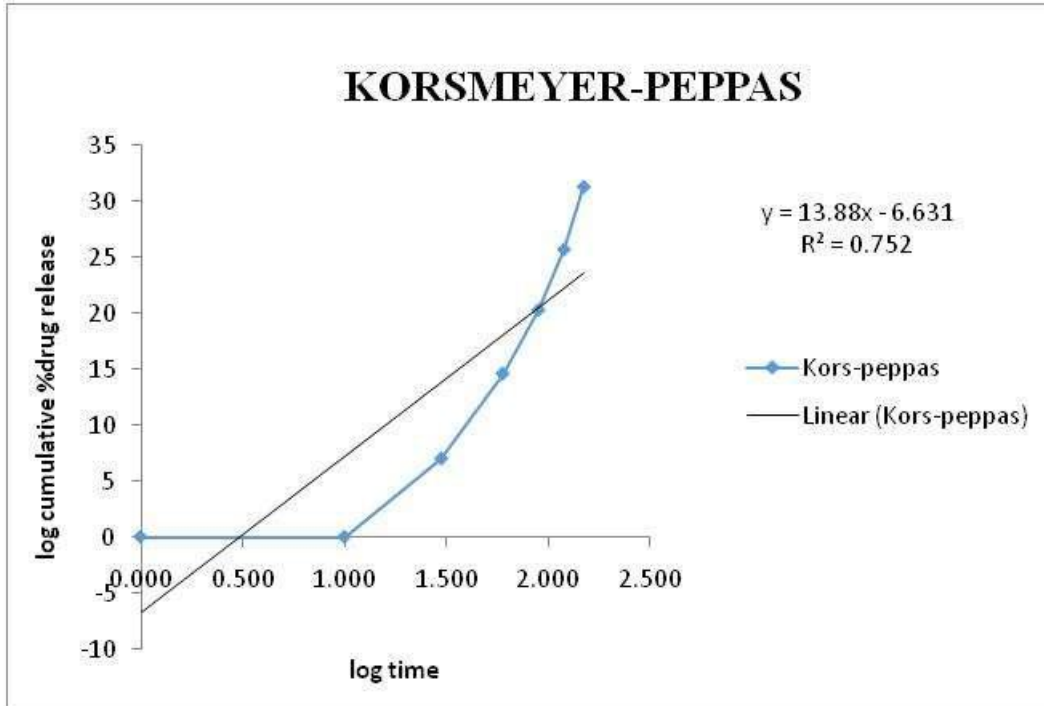


Figure 5.25 Korsmeyer-peppas model for formulation F2

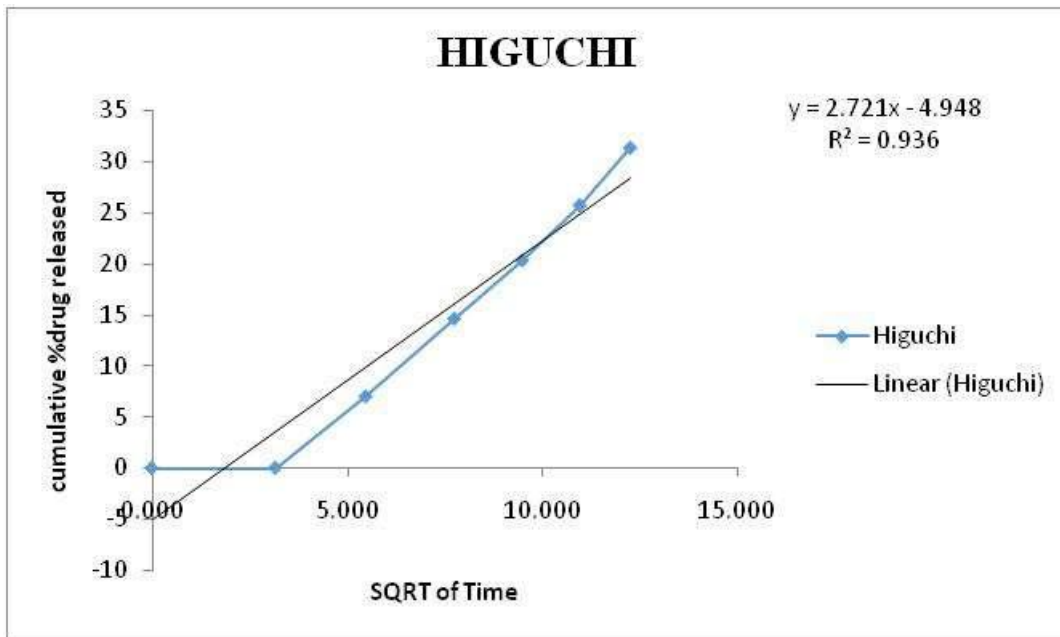


Figure 5.26 Higuchi model for formulation F2

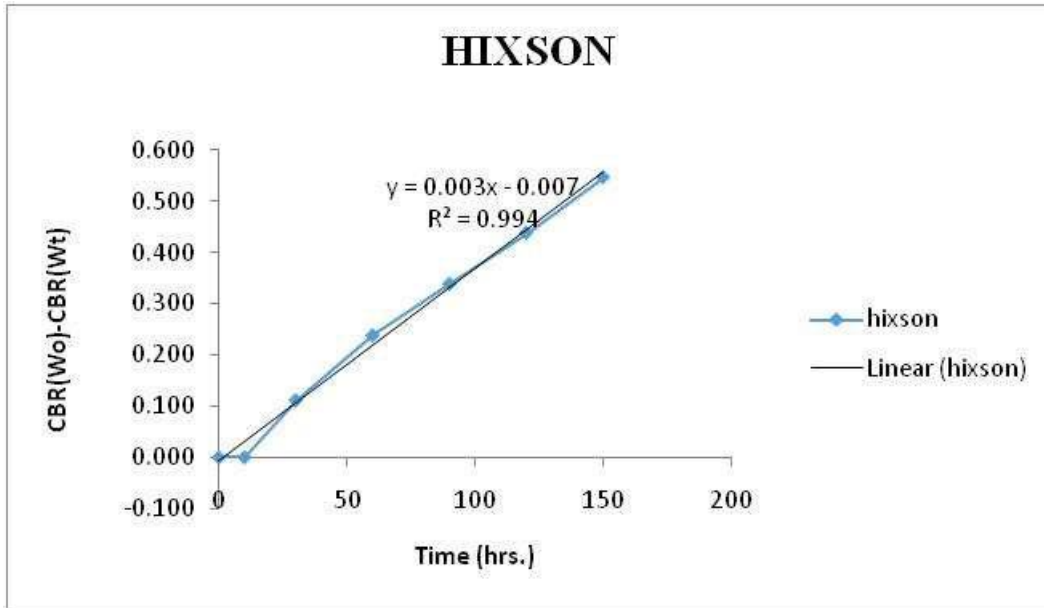


Figure 5.27 Hixson model for formulation F2

Formulation F3

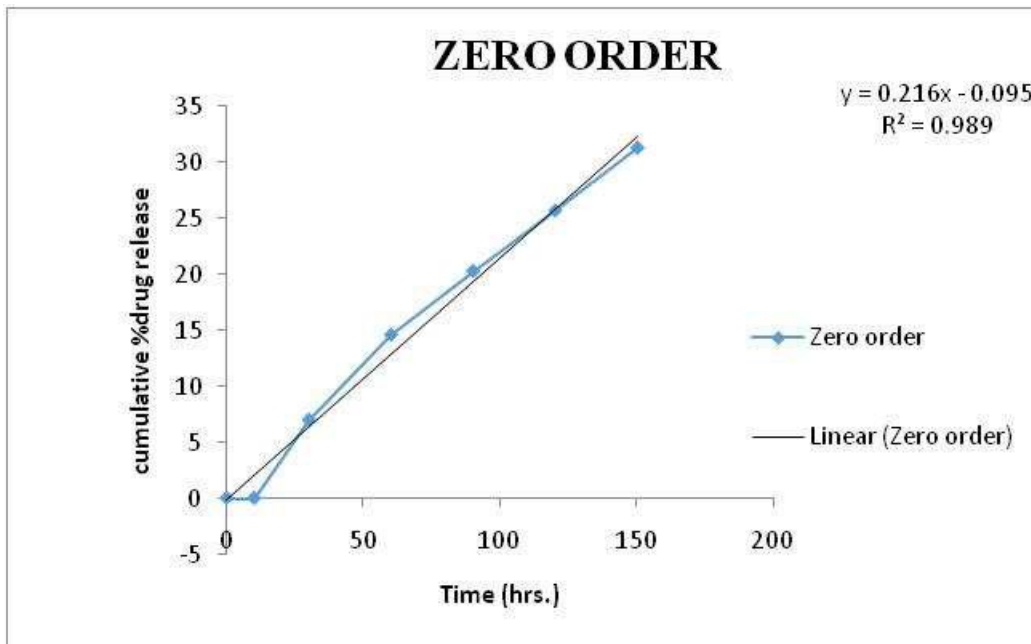


Figure 5.28 Zero order kinetics for formulation F3

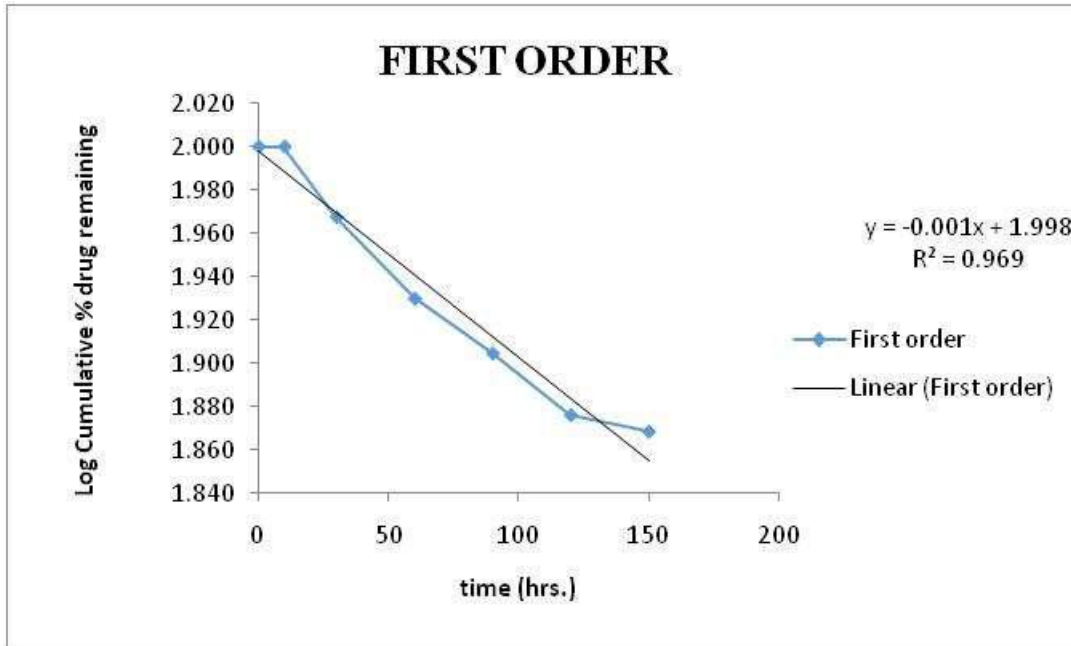


Figure 5.29 First order kinetics for formulation F3

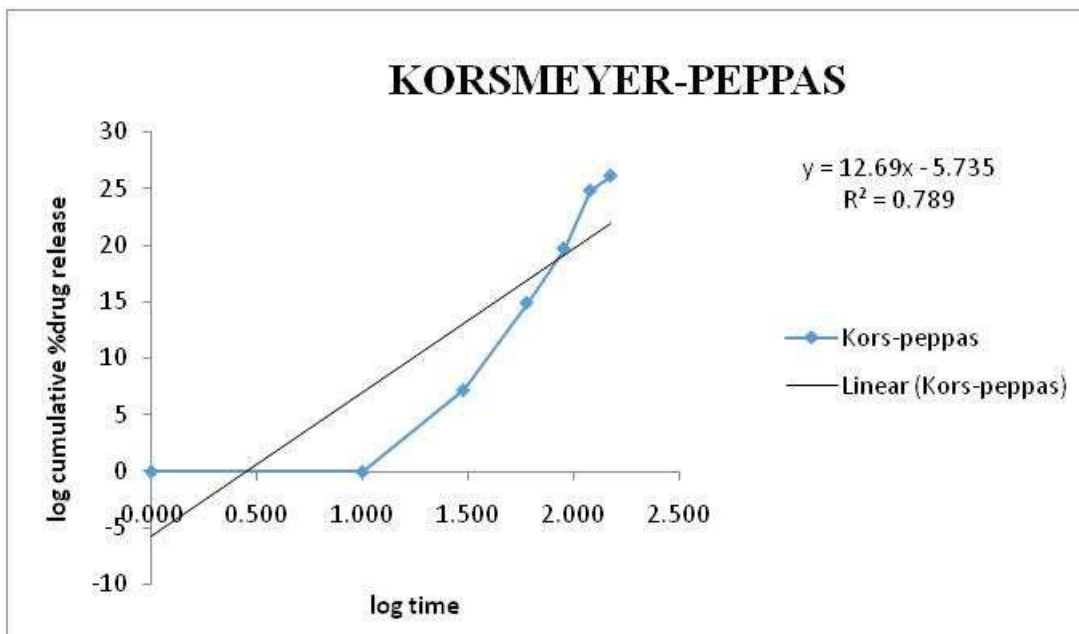


Figure 5.30 Korsmeyer-peppas model for formulation F3

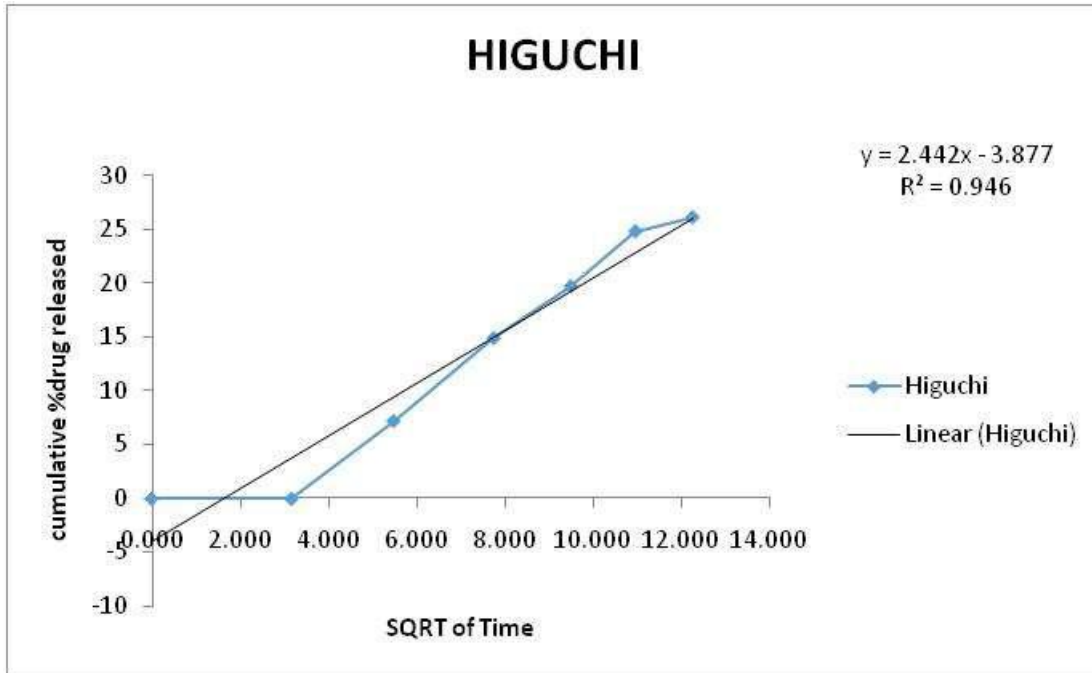


Figure 5.31 Higuchi model for formulation F3

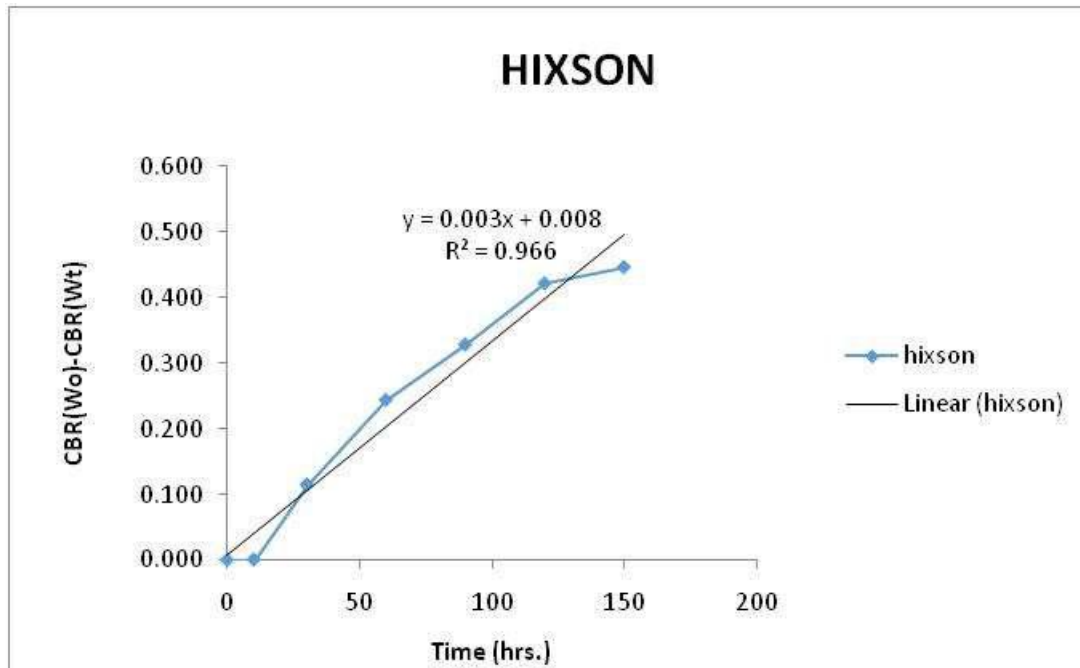


Figure 5.32 Hixson model for formulation F3

Formulation F4:

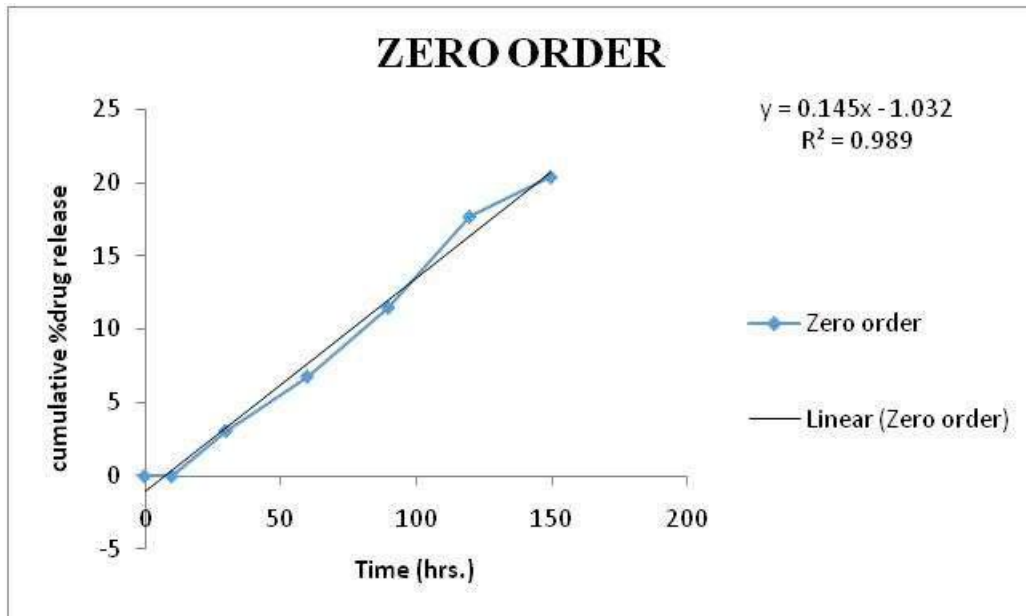


Figure 5.33 Zero order kinetics for formulation F4

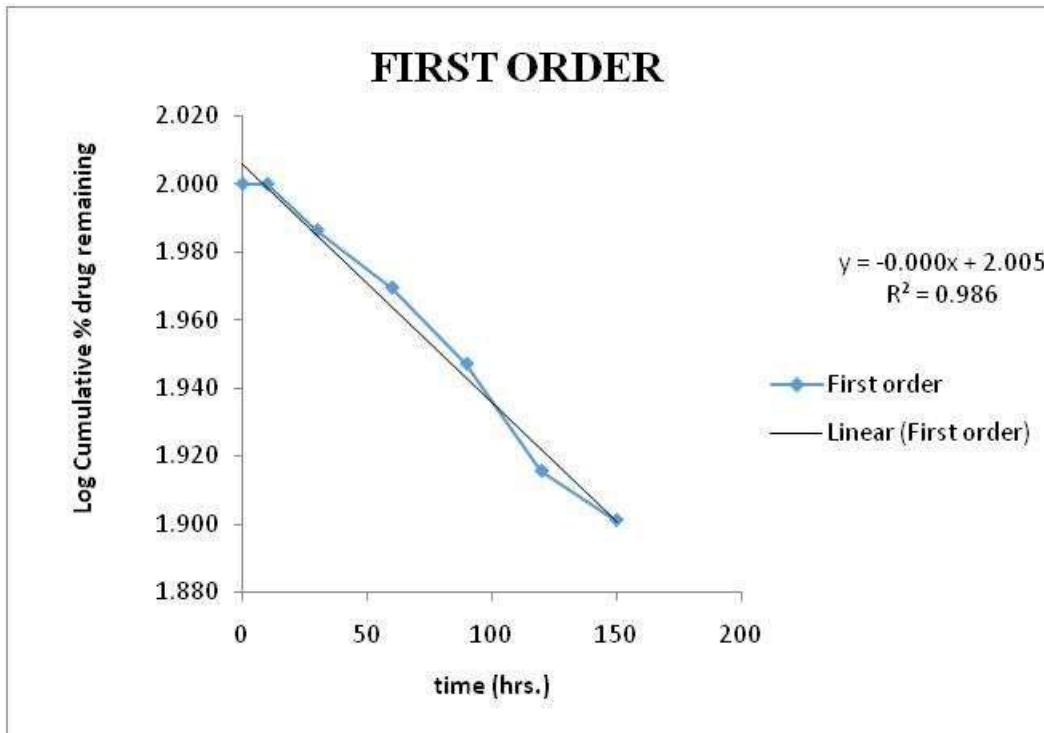


Figure 5.34 First order kinetics for formulation F4

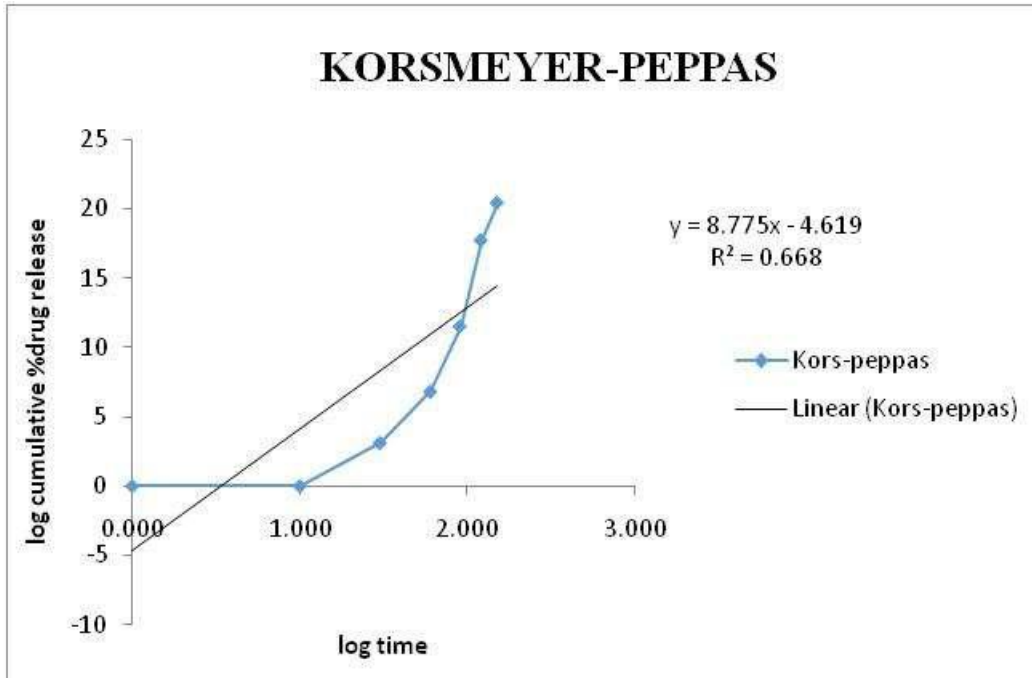


Figure 5.35 Korsmeyer-Peppas model for formulation F4

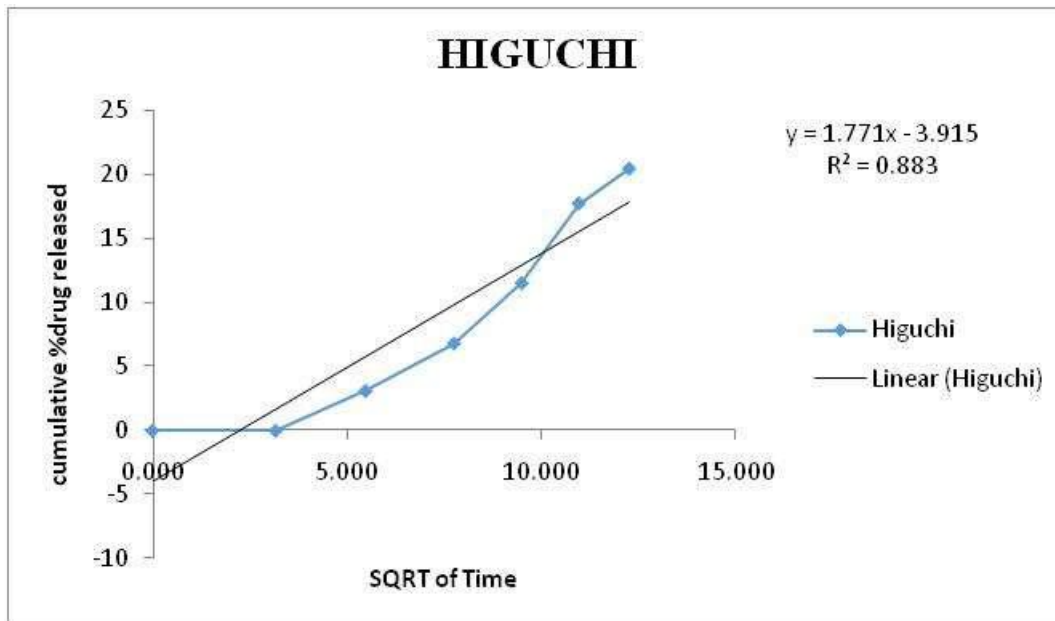


Figure 5.36 Higuchi model for formulation F4

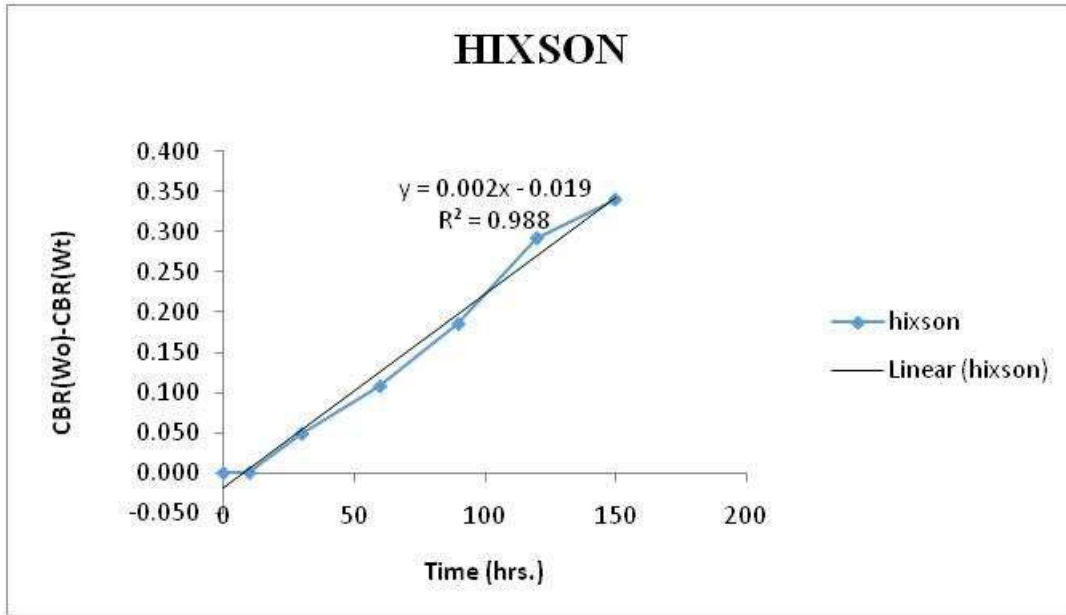


Figure 5.37 Hixson model for formulation F4

Formulation F5

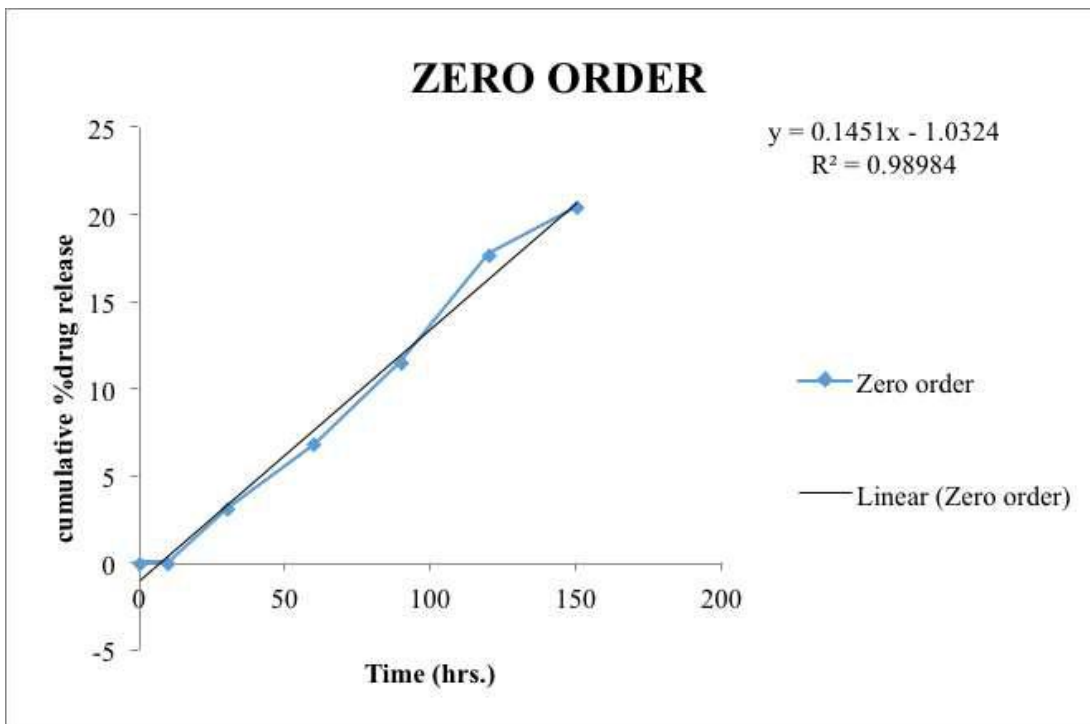


Figure 5.38 Zero order kinetics for formulation F5

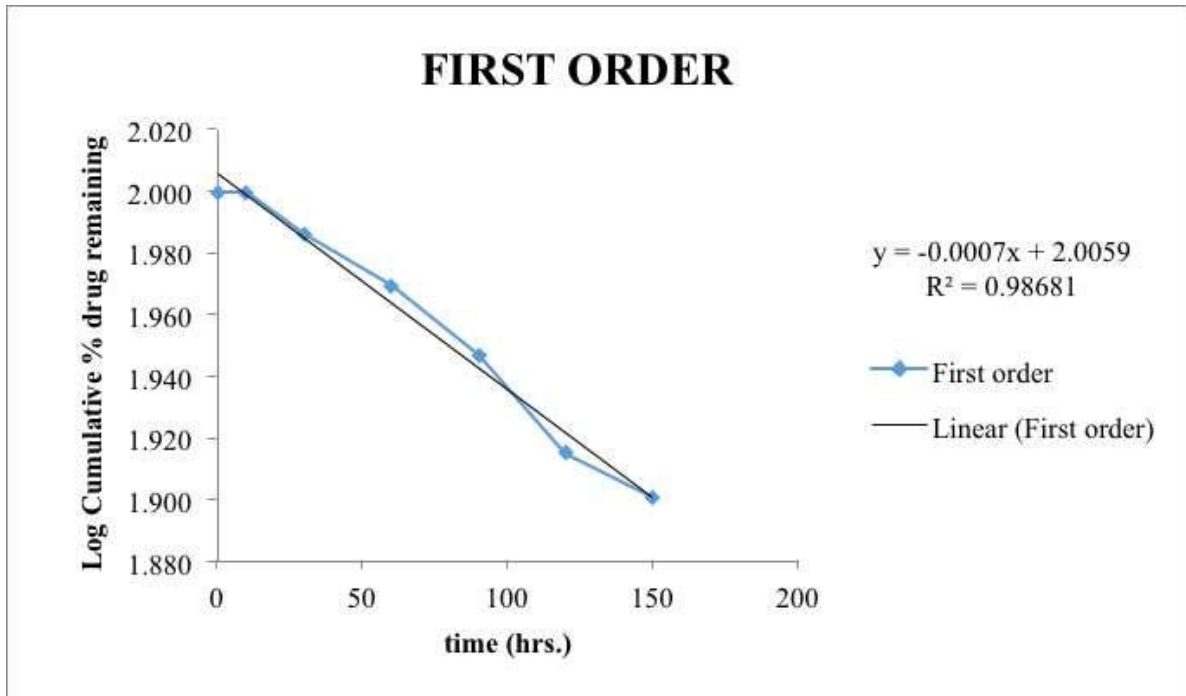


Figure 5.39 First order kinetics for formulation F5

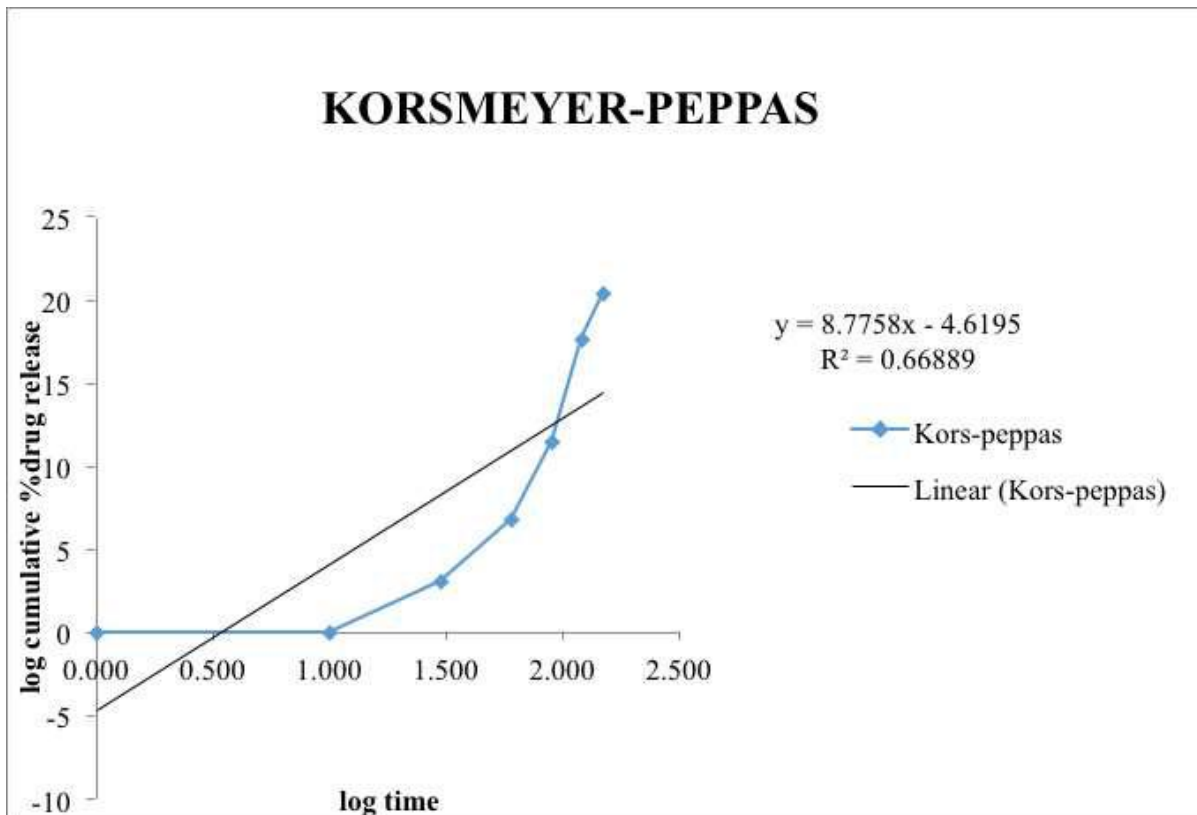


Figure 5.40 Korsmeyer-Peppas model for formulation F5

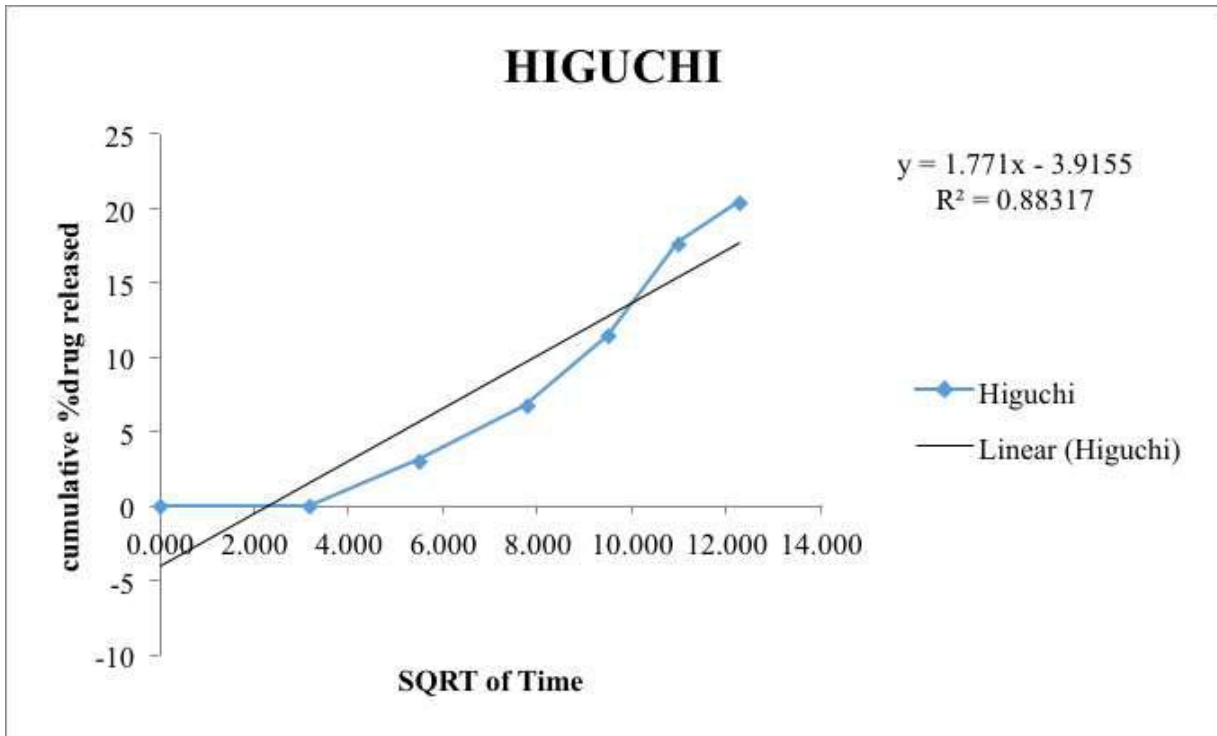


Figure 5.41 Higuchi model for formulation F5

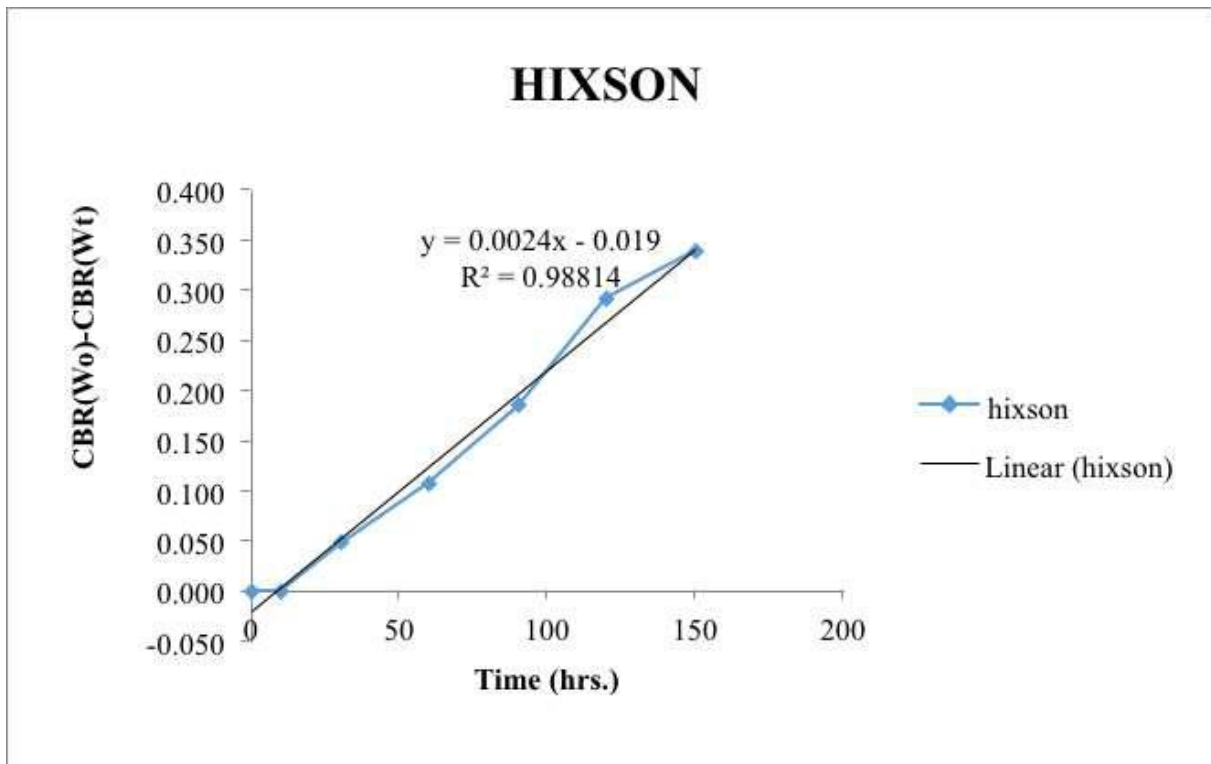


Figure 5.42 Hixson model for formulation F5

Formulation F6

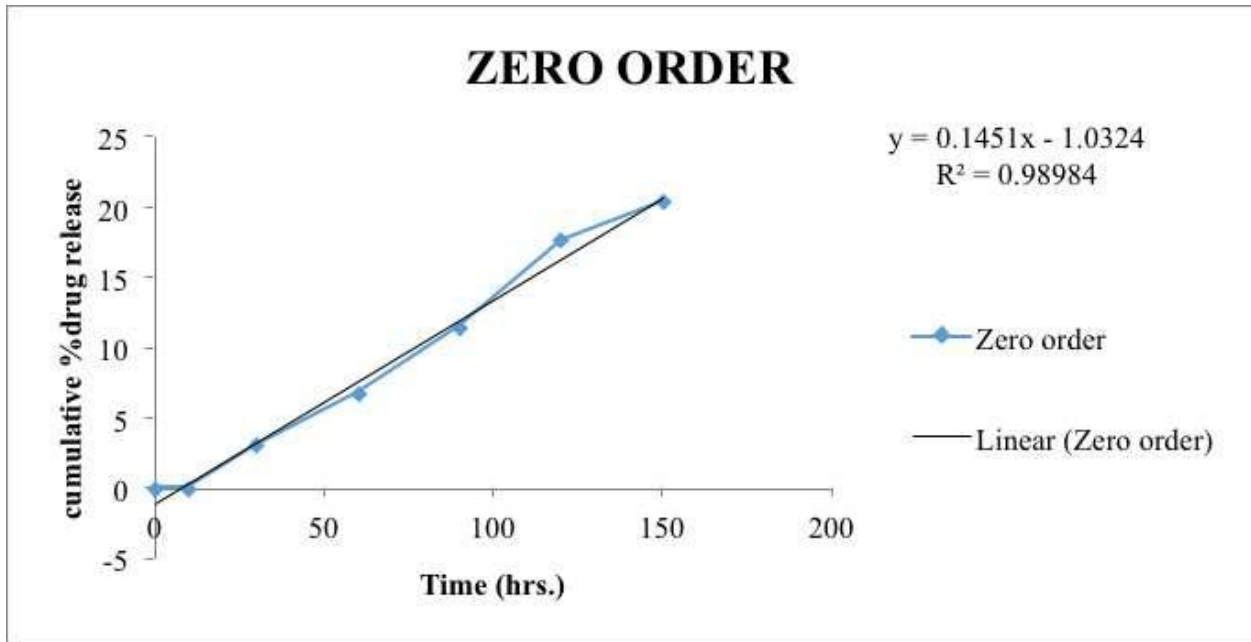


Figure 5.43 Zero order kinetics for formulation F6

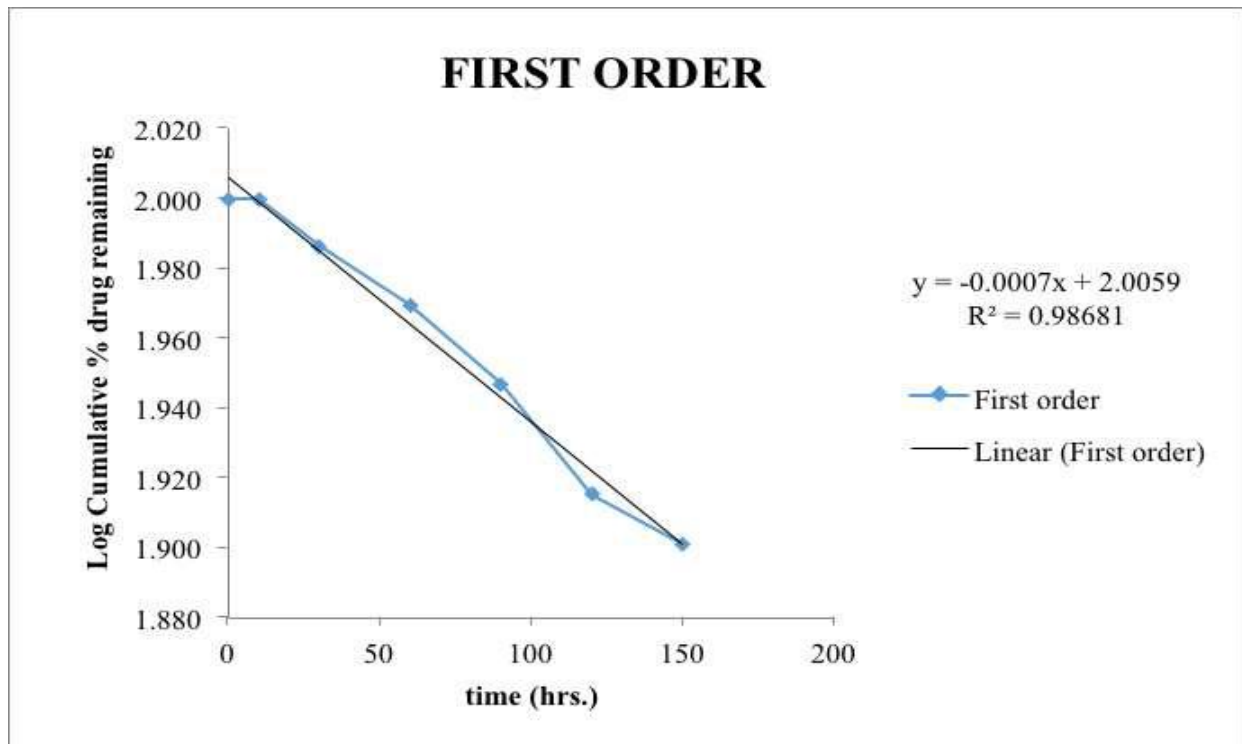


Figure 5.44 First order kinetics for formulation F6

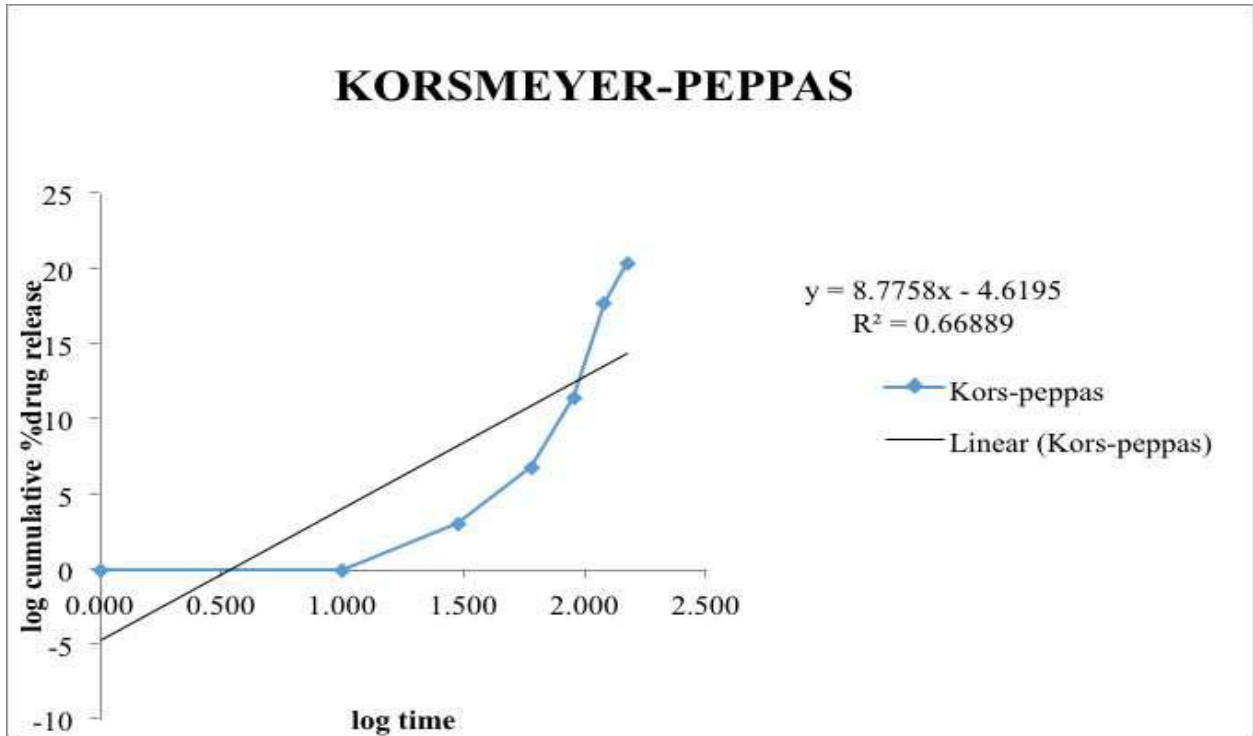


Figure 5.45 Korsmeyer-peppas model for formulation F6

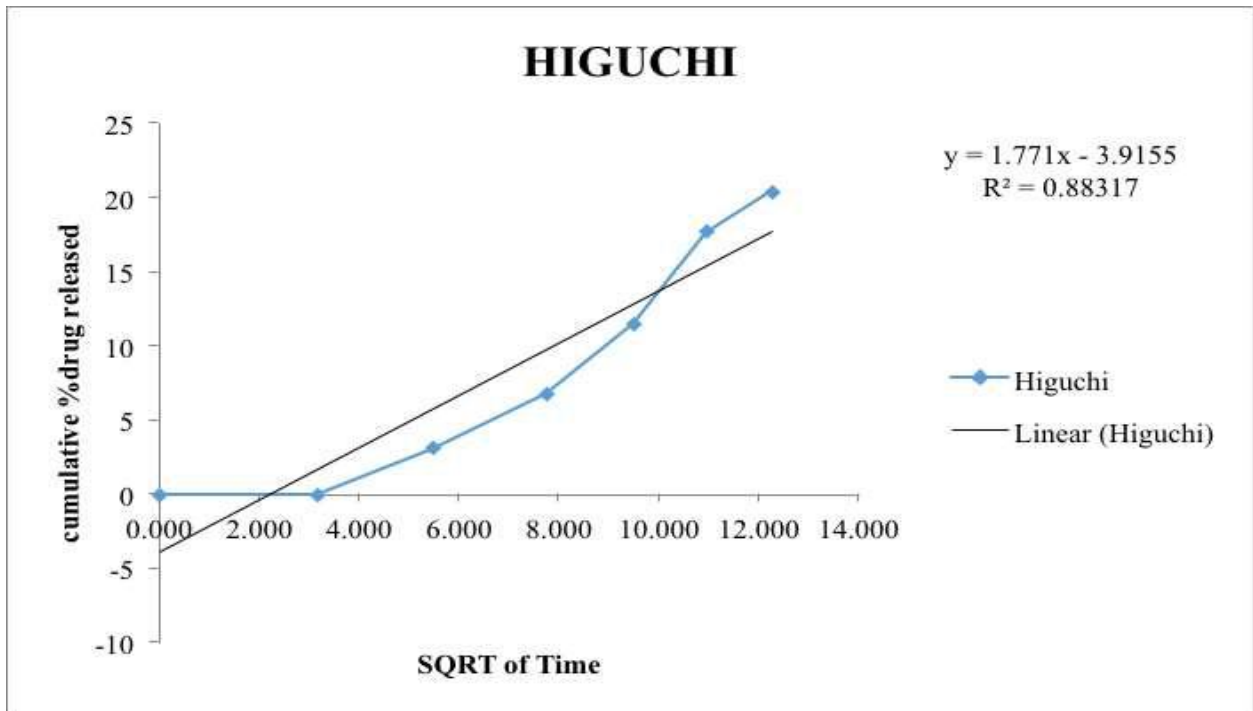


Figure 5.46 Higuchi model for formulation F6

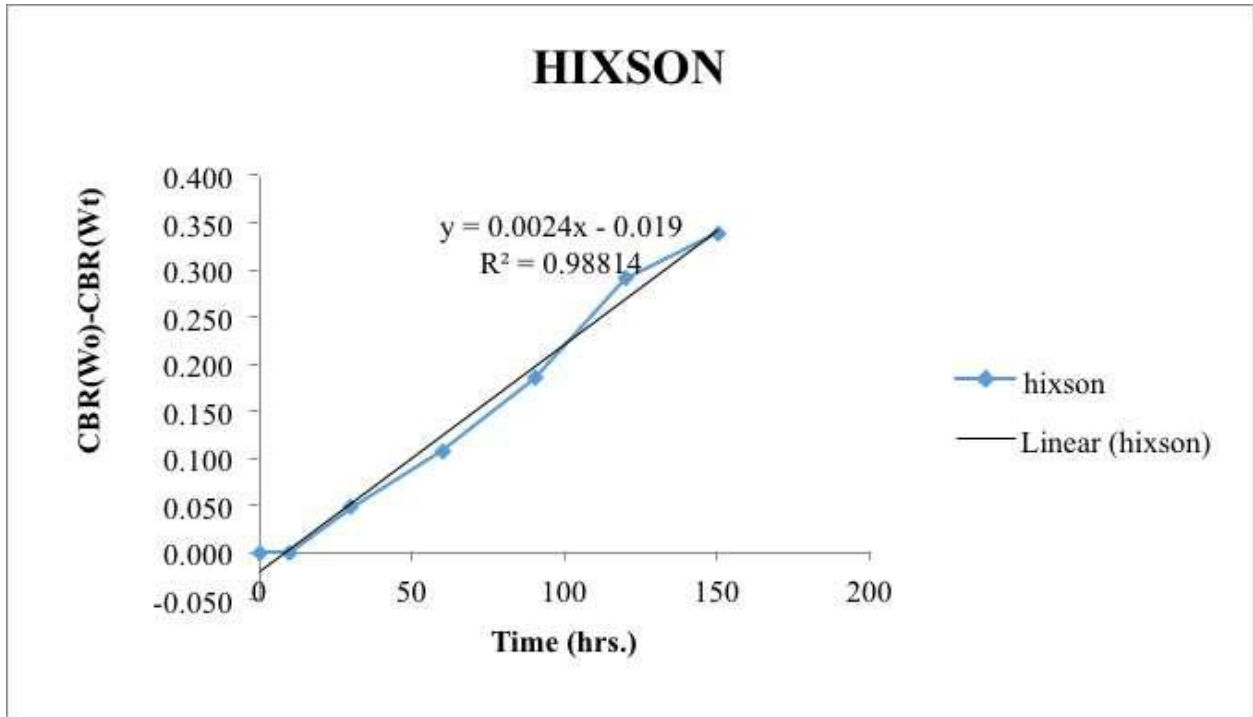


Figure 5.47 Hixson model for formulation F6

Formulation F7

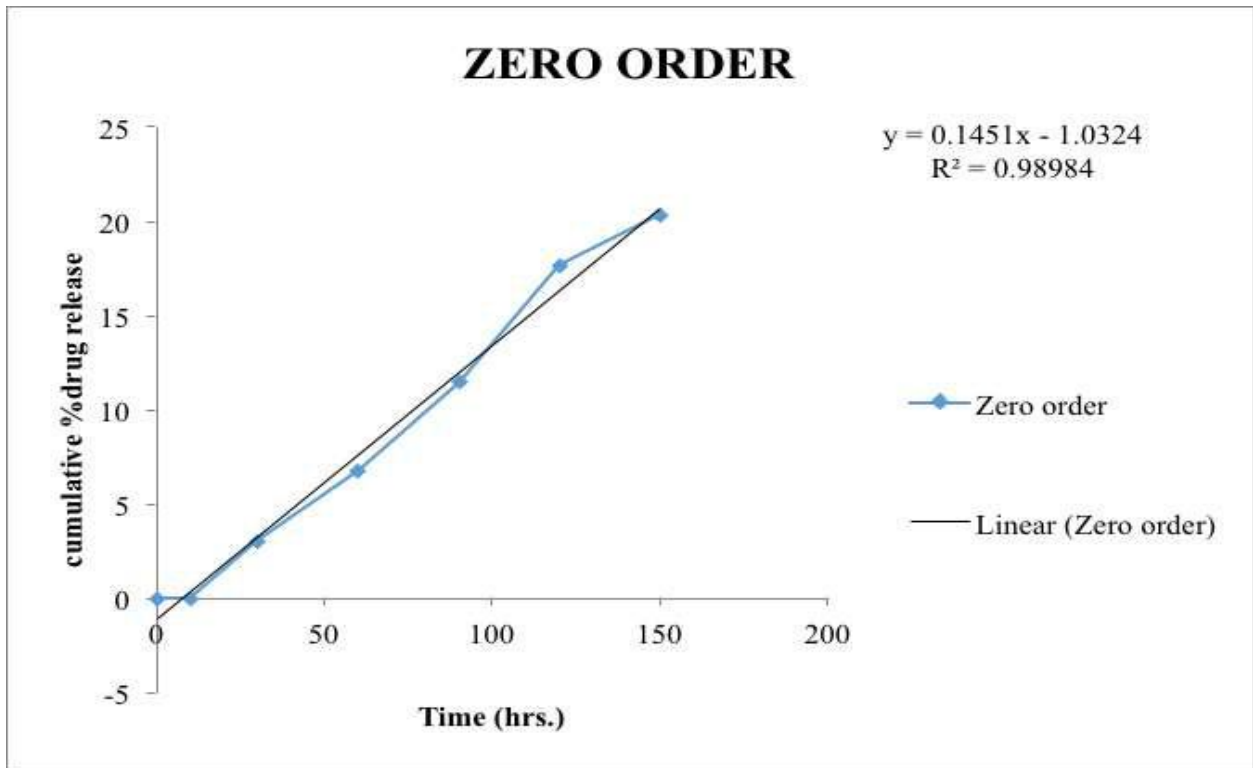


Figure 5.48 Zero order kinetics for formulation F7

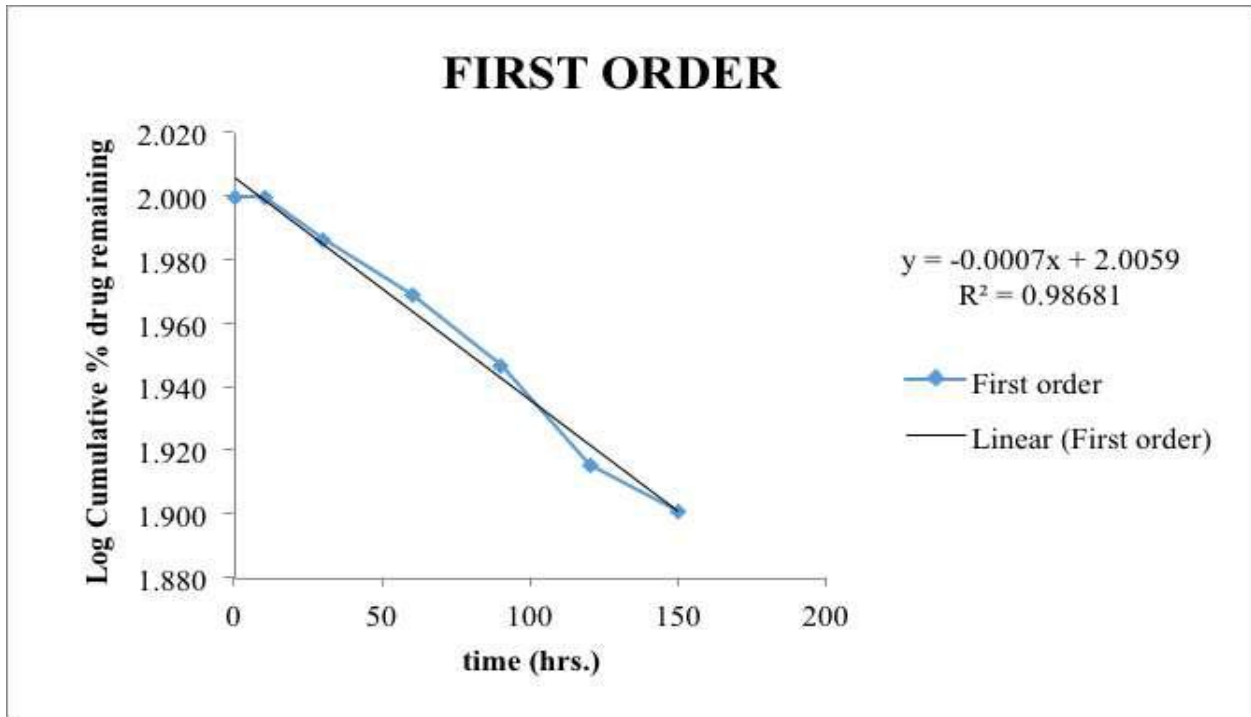


Figure 5.49 First order kinetics for formulation F7

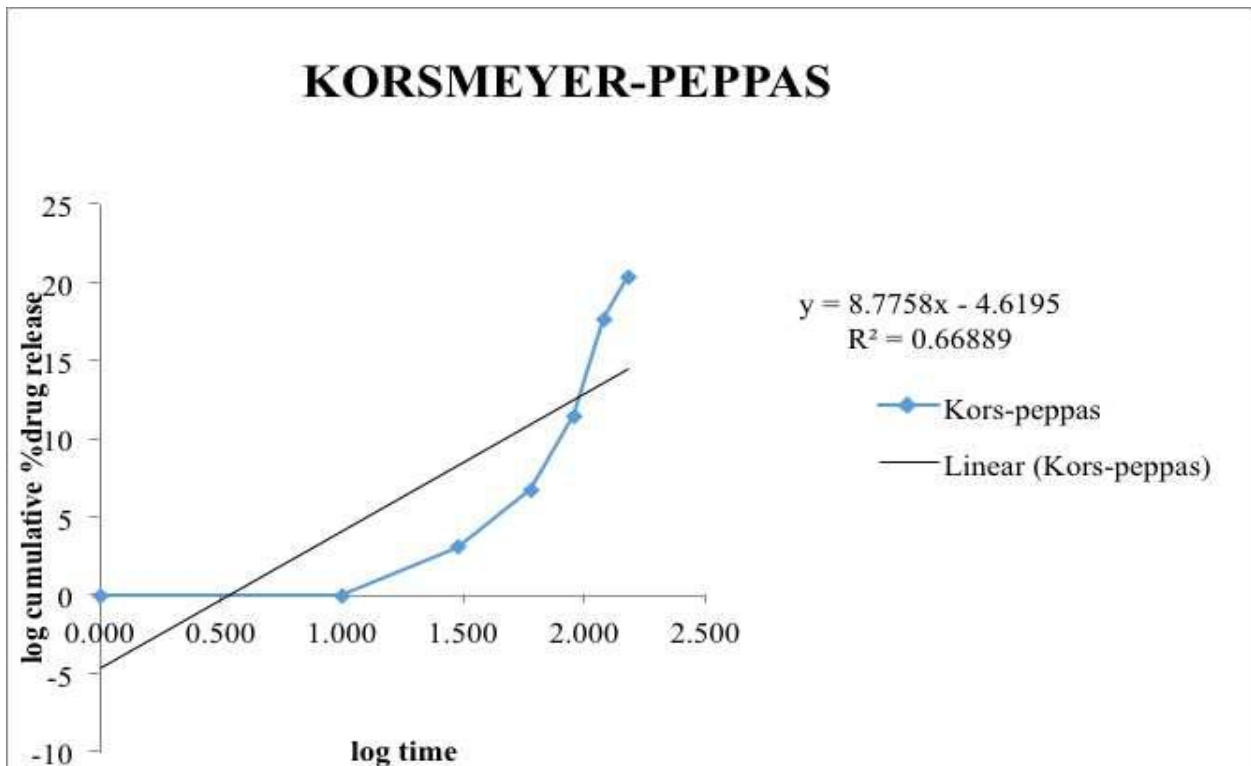


Figure 5.50 Korsmeyer-peppas model for formulation F7

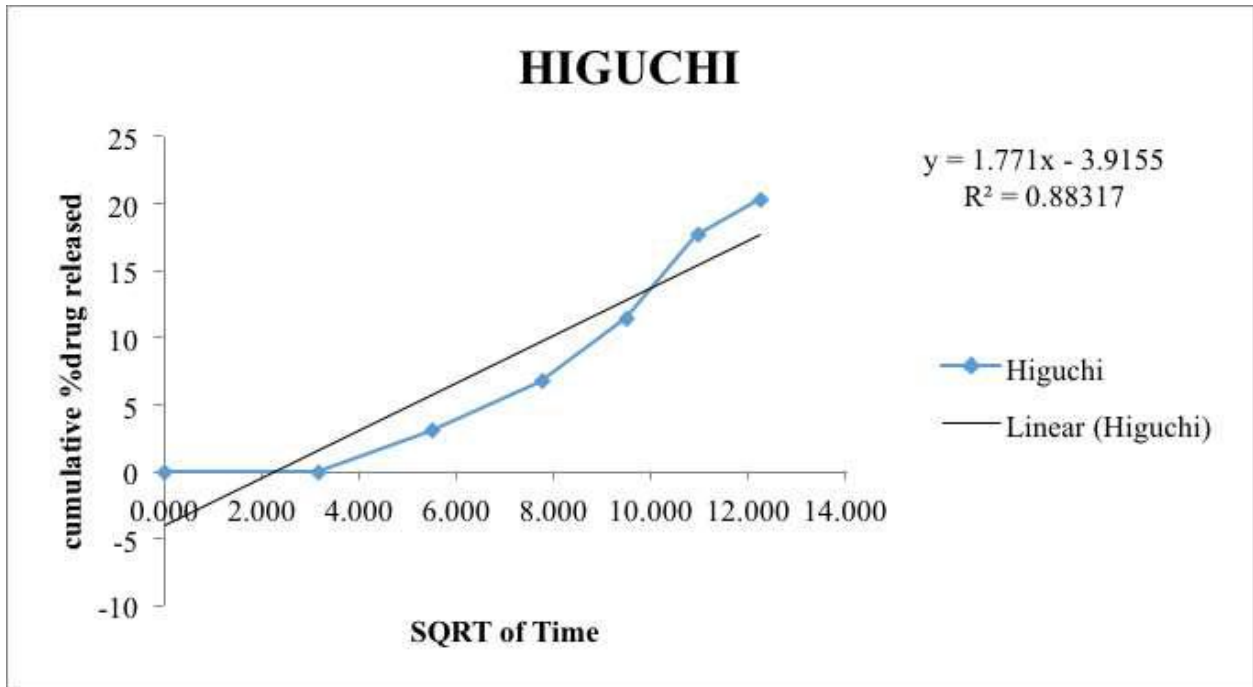


Figure 5.51 Higuchi model for formulation F7

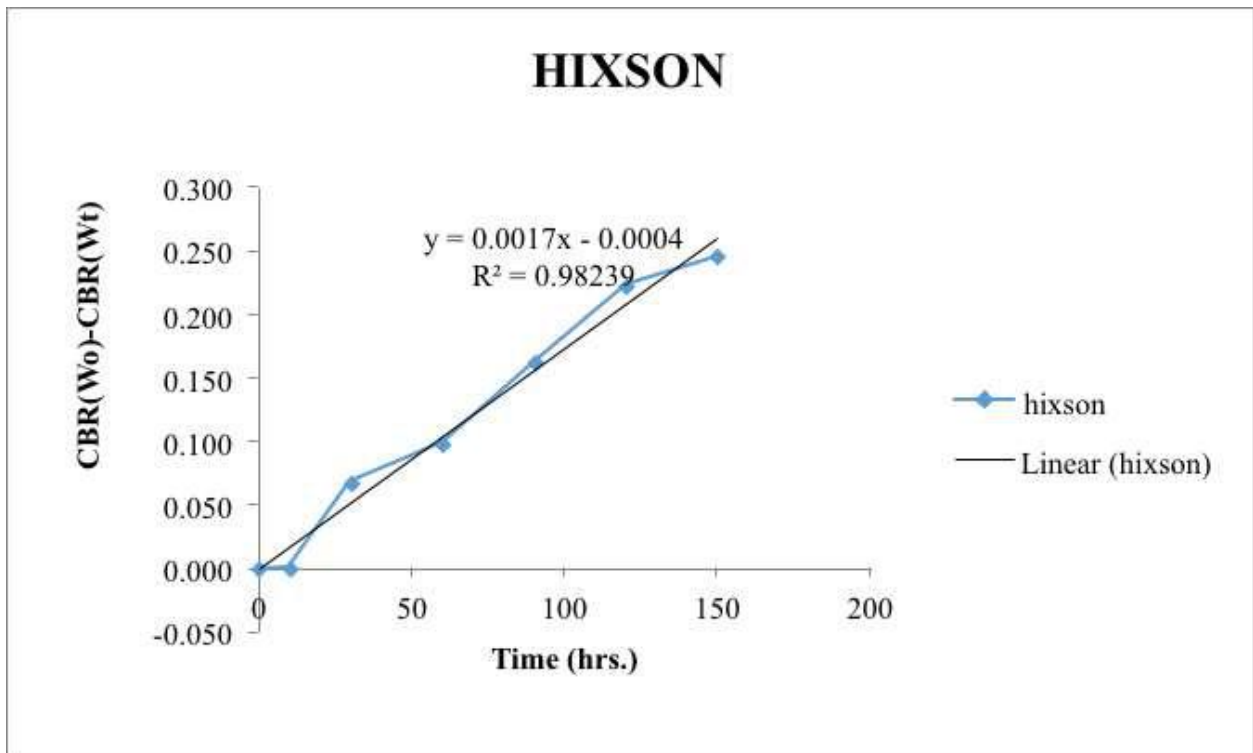


Figure 5.52 Hixson model for formulation F7

Formulation F8

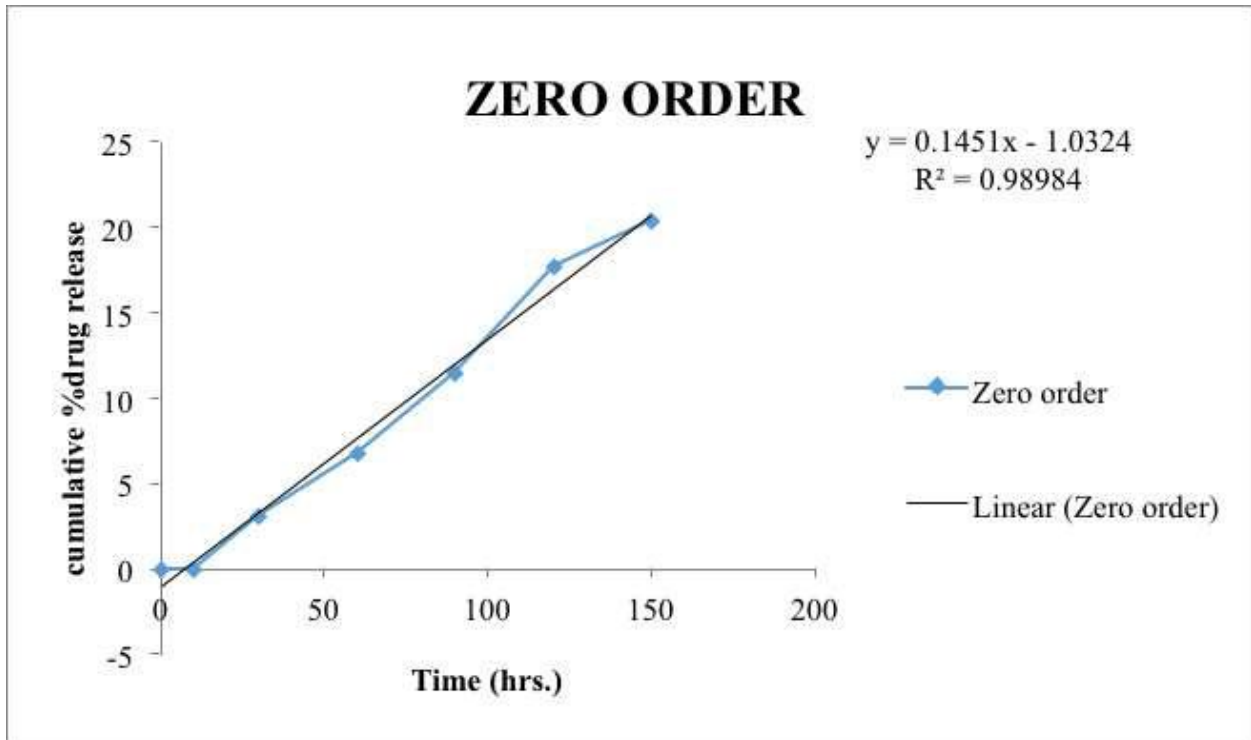


Figure 5.53 Zero order kinetics for formulation F8

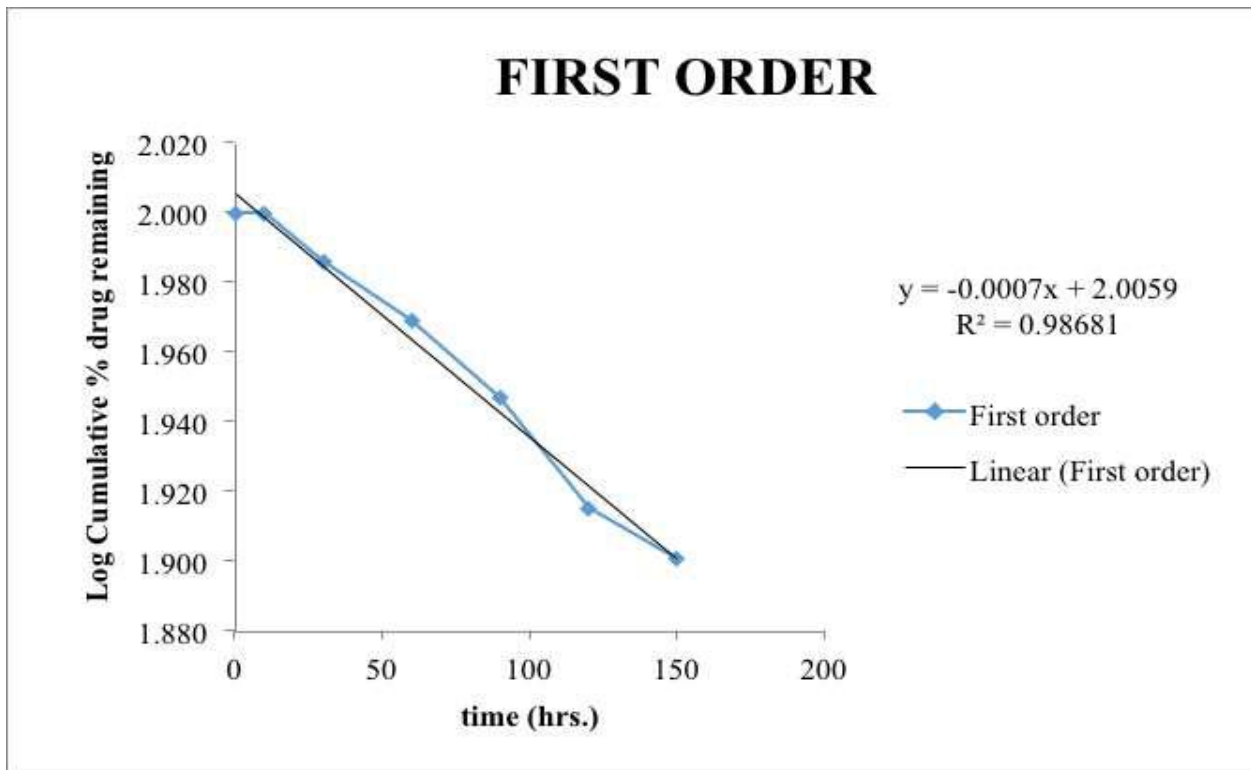


Figure 5.54 First order kinetics for formulation F8

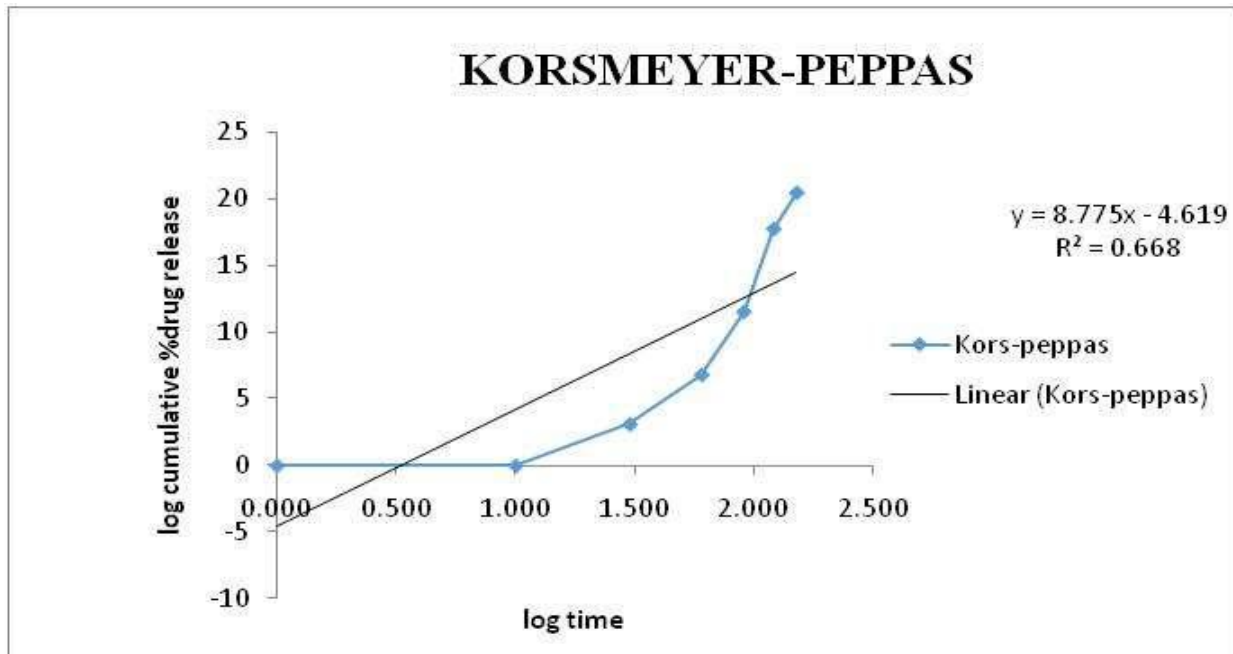


Figure 5.55 Korsmeyer-peppas model for formulation F8

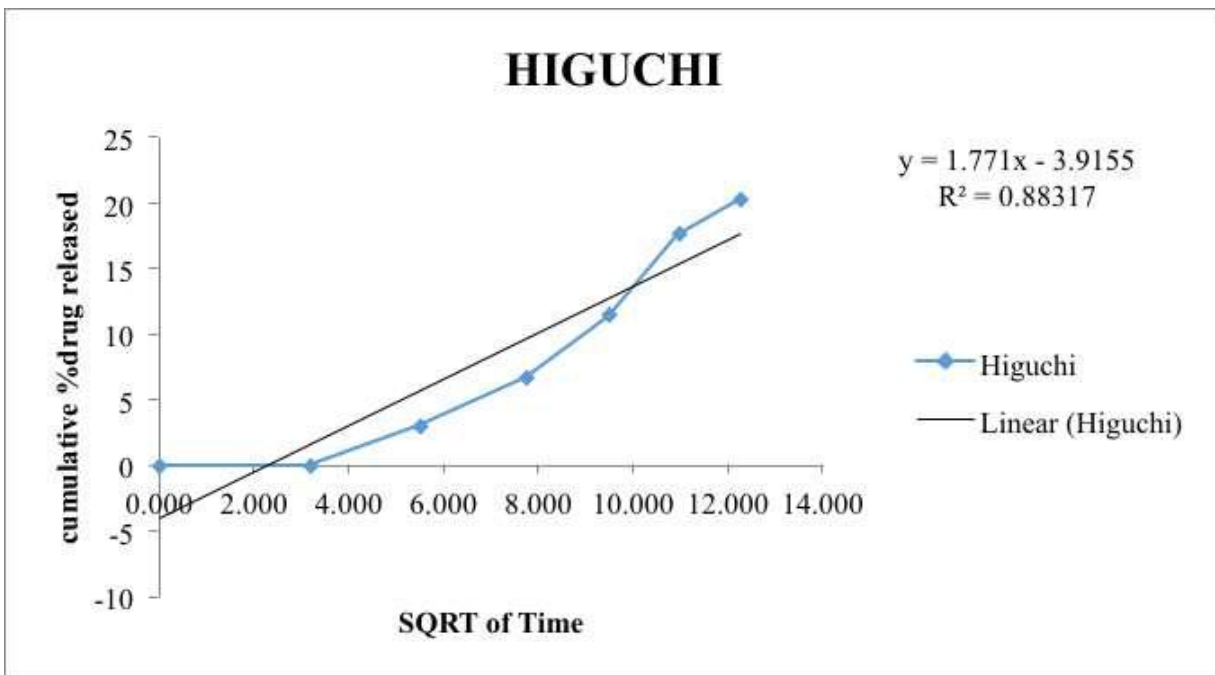


Figure 5.56 Higuchi model for formulation F8

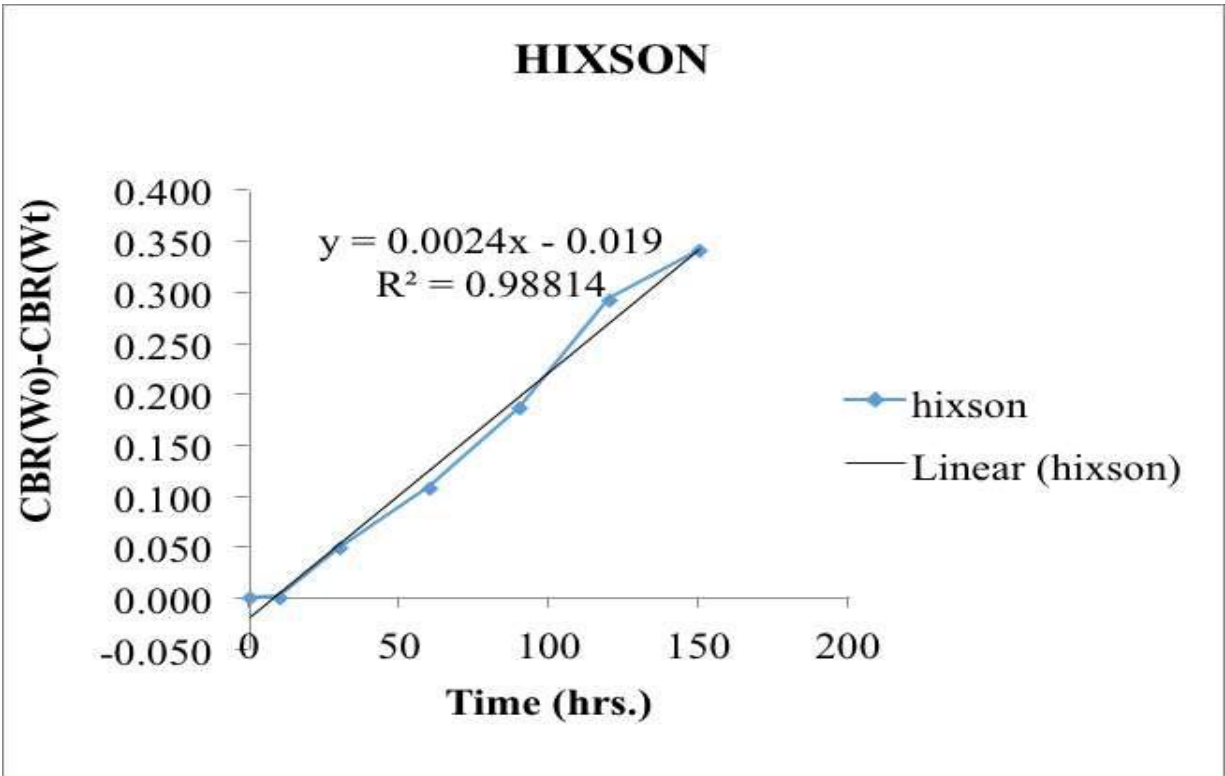


Figure 5.57 Hixson model for formulation F8

Table 5.10 Representing R² values of different formulations for different graphs.

Formulations	R ² Values				
	Zero Order	First Order	Kors peppas	Higuchi	Hixson
F1	0.980	0.983	0.750	0.929	0.982
F2	0.986	0.987	0.711	0.910	0.987
F3	0.989	0.995	0.752	0.936	0.994
F4	0.958	0.969	0.789	0.946	0.966
F5	0.977	0.984	0.763	0.938	0.982
F6	0.959	0.973	0.801	0.953	0.969
F7	0.989	0.986	0.668	0.883	0.988
F8	0.991	0.988	0.673	0.886	0.990

From all of the above graphs we conclude that different formulations showed the different regression values for the zero order kinetics, first order kinetics, kors peppas, higuchi model and hixson graph. They can be compared on the different factors but after the overall analysis we found the F3 as the best formulation as it gave better results in all others tests and also it follows the first order kinetics here.

5.16 Discussion and Conclusion

From the above study we concluded that soya lecithin and palm oil based organogels can be formulated successfully. We have prepared here the 8 different formulations of the organogels with the different concentrations of the ingredients. If we talk about the morphology all of the 8 formulations passed the test. Similarly pH of all the eight formulations was found to be within the range. In case of the viscosity formulation F1 to F5 showed the better viscosity as compared to the other three formulations, however formulation F3 was found to be most viscous. The release of the formulated organogels was also very good. Different formulation followed the different models for instance F1 followed both zero order and first order kinetics in same manner. Amongst all of them formulation F3 showed the best result which followed the first order kinetics and Hixson model. The microscopy and the SEM of the formed organogels were studied and it was found that some of the organogel showed the spherical droplets in the structures while others showed fiber like structure. This all is dependent on the concentration of the surfactant and the co surfactant. The mechanism of the organogellation also varies with the change in the concentration of the various ingredients. Some of the organogels forms the fibre filled mechanism for the organogel formation while changing the concentration of the surfactant the mechanism changes to the microemulsion based organogellation which can be confirmed from the different images of the SEM which was showing spherical droplets in some cases while fiber like structures in others. Therefore by comparing the all of the other parameters also formulation F3 was found to be optimum and best for the formulation of the raloxifene hydrochloride bearing organogel. One of the advantages is that it is easy to manufacture. From the one of the preliminary study we can say that organogels can be used as potential carriers for the therapeutic agents. The thermal stability of the organogels was also found to be good. The composition of the organogel plays an important role in the therapeutic action of the organogel. Here soya lecithin was used as the surfactant, the concentration of which largely affects the action and properties of the organogels. All the evaluation parameters were passed by the formulated organogel which ensures that various other drugs like raloxifene can be incorporated into the organogels as the novel drug delivery system. The organogel prepared possess good viscosity and also the biocompatibility of the organogel was found to be very good. Last but not the least it may be summarized that organogels may be the very good carriers for the various drugs and thus can be administered through the topical route with the enhanced bioavailability.

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CHAPTER 6

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