FORMULATION AND EVALUATION OF BI-LAYERED TABLET OF DIVALPROEX SODIUM

By

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B.Pharm,

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A dissertation Submitted to the

Rajiv Gandhi University of health Sciences

Karnataka Bangalore

In partial fulfillment of the requirements for the

MASTER OF PHARMACY

IN

PHARMACEUTICS

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2015

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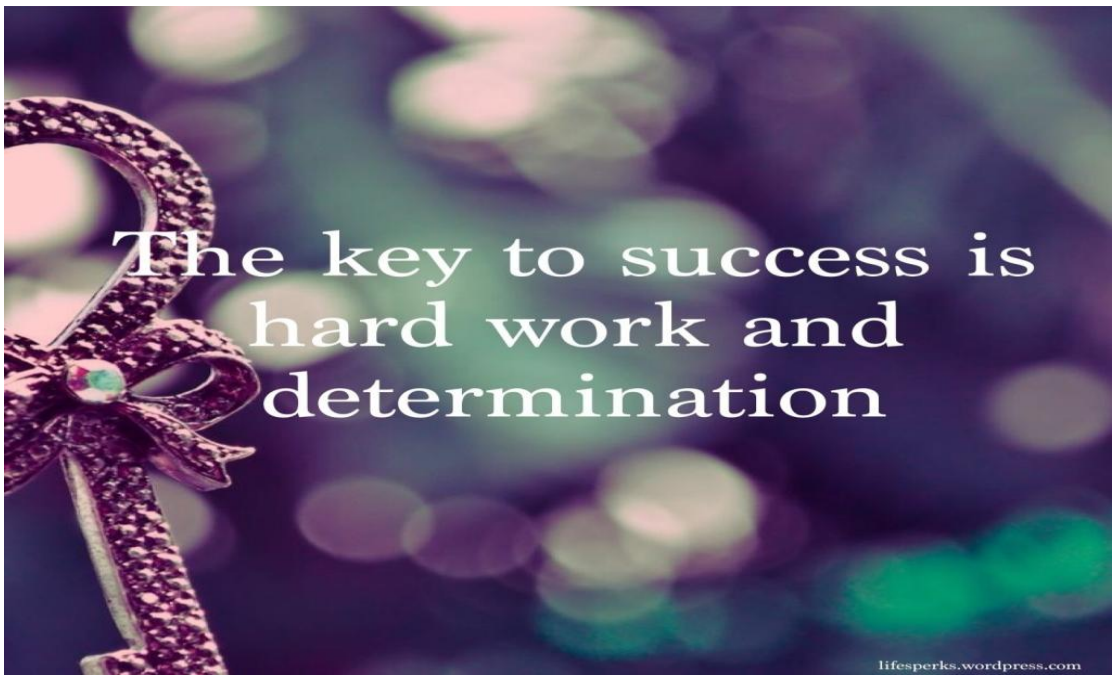

Dedicated to my family members & friends...

ACKNOWLEDGEMENT

Behind every success there are lot many efforts, but efforts are fruitful due to hands making the passage smoother. I express my deep sense of gratitude for the hands people extended to me during my work.

First and foremost I wanted to express my indepth thanks to my father and mother Sri Krishna Prasad Chaudhary and Srimati Sadhana Devi Chaudhary, for all their hard work to bring me up with a high quality education, and a very special thanks to my sisters Sanju Chaudhary and Ranju Chaudhary whose full-hearted co-operation, encouragement, love and moral support made me complete my work successfully.

I would like to give special thanks to my Grandfather Sri Ram Chandra Chaudhary, and grandmother late Srimati Bhangiya Devi Chaudhary for their affection and lovable support.

I take this opportunity to express my deep sincere gratitude, indebtedness and heart-felt thanks to my esteemed research guide, Dr. Mohammed Gulzar Ahmed, Professor and Head, Department of Pharmaceutics for his intellectual supervision, constant guidance, perpetual encouragement and constructive suggestion which helped me immensely throughout my project work. His belief in my abilities and me is deeply treasured.

It's my privilege to thank Dr. B.Ramesh, Principal, S.A.C. College of Pharmacy for providing me the required laboratory facilities and encouragement during my work.

I express my deep and heart-felt thanks to Mr. G.B. Kiran Kumar Associate Professor, Mr. Vedamurthy joshi Asst prof, Mr.Abdul Nasir Kurnool Asst prof, Mr. Senthil Kumar K Asst prof, Mr. Nagesh DR Lecturer, Department of Pharmaceutics and entire staff of Sri Adichunchanagiri College of Pharmacy for their valuable guidance and profound cooperation during the course of study.

I take this opportunity to sincerely thank to all Non-teaching Staff of Sri Adichunchanagiri College of Pharmacy for their timely help.

I would like to express my heartfelt and special thanks to Mr. Jaimin Patel one of the Key Personnel of ROAQ Chemicals Pvt. Ltd Vadodara-391340, Gujarata, India, who provide the drug.

I would like to express my heartfelt thanks to my all classmate Ankit Acharya, Suyash Adhikari, Pramod Kharel, Amrit Timalsina, Promod Dhakal, Guru, Sachin AB, Pavithra G, Chetana SR, Harika, Ashwini G, Hanshiya Sultana, Aksheta RS for their support and generous help for throughout my project work.

I am thankful to my Seniors Purushottam Timilsina, Diwakar Dhadaka, Rakesh Rauniyar, Madhu, Pushkar,Binay for their help during my research work.

I express my whole hearted thanks to my friends Santosh, Rajkumar, Sunil, Ramesh, Bijay, Chintu, Rambinay, Narendra, Prithvi, Braj,Manoj who have always are for me.

Finally I consider this is an opportunity to express my gratitude to all the dignitaries who have been involved directly or indirectly with the successful completion of this dissertation.

Thank you one and all……...

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CONTENTS

ABSTRACT

Divalproex sodium is considered as the most important antiepileptic drug and widely used for treatment of epilepsy and bi-polar disorders and prophylaxis of migraine. The present work has been done to formulate bi-layered tablet of Divalproex sodium containing immediate release layer and sustained release layer. The FTIR study revealed that there was no interaction between drug and polymer and combination can be safely prepared. Both layers were prepared by wet granulation technique as poor flow property exhibited by pure drug. The immediate release layer was formulated by using sodium starch glycolate, croscarmellose sodium as superdisintegrants and evaluated for physical parameters, disintegration time and *in vitro* drug release. The optimized immediate release layer (IF6) with highest in vitro release of 98.11 was selected for bi-layered tablet formulation. HPMC K4M and HPMC K100M polymer used to retard the drug release from sustained release layer in different proportion and combination and evaluated for physical parameter along with in vitro drug release studies.. The optimized sustained release layer (SF8) which extends the Divalproex sodium release more than 18 hrs was selected. *In vitro* drug release studies were performed using USP type II apparatus (paddle method) in 900 ml of phosphate buffer pH 6.8 at 100 rpm. Finally Bi-layered tablets were prepared by double compression of selected sustained release layer and immediate release layer of Divalproex sodium. The tablets were evaluated for hardness, thickness, weight variation, friability, drug content uniformity and *in vitro* drug release. All the physical parameters were in acceptable limit of pharmacopeial specification. The stability studies, shown the bi-layer tablet was stable at 40^0C / 75% RH for a period of 3 months.

KEY WORDS: Bi-layered tablet, epilepsy, wet granulation, Divalproex sodium, immediate release, sustained release.

LIST OF ABBREVIATIONS

Abs	Absorbance
Conc.	Concentration
Cm	Centimeter
˚C	Degree centigrade
FT-IR	Fourier Transform Infrared spectroscopy
G	Gram
GIT	Gastro intestinal tract
Hrs	Hours
HPMC	Hydroxypropyl Methyl Cellulose
IP	Indian Pharmacopoeia
IR	Infra-red
IRL	Immediate release layer
IF	Formulation code for IRL
Mm	Millimeter
Mg	Milligram
MCC	Micro-crystalline cellulose
Min	Minute
Ml	Milliliter
Nm	Nanometer

pH	Negative logarithm of hydrogen ion concentration
RPM	Revolution per minute
RH	Relative humidity
SD	Standard deviation
SSG	Sodium starch glycolate
Sec	Seconds
SRL	Sustained release layer
SF	Formulation code for SRL
$t_{1/2}$	Half life
UV	Ultra violet
Vs	Versus
w/w	Weight by weight
w/v	Weight by volume
λmax	Maximum Wavelength
µg	Microgram
%	Percentage
% CDR	Percentage cumulative drug release

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CHAPTER 1

Introduction

1. INTRODUCITON

Oral route is most commonly employed route of drug administration. Although different route of administration are used for the delivery of drugs, due to flexibility in dosage form design and patient compliance oral route is preferred[1]. The popularity of the oral route is attributed ease of administration, patient acceptance, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product[2].

There are several techniques of conventional drug delivery system where tablets, capsules, pills, liquids, are used as drug carrier. Among them, solid formulation do not require sterile conditions and are therefore, less expensive to manufacture[3].

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing[4]. Tablets are solid dosage forms containing medicinal substances with or without suitable diluents[5]. According to Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents[6]. They are varying in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is most popular dosage form and 70% of the total medicines are dispensed in the form of tablet[7].

Advantage of the tablet dosage form[8]

- They are unit dosage form and great dose precision and the lease content variability.
- Cost is lowest of all oral dosage form.
- Lighter and compact.

- Easiest and cheapest to package and strip.
- Easy to swallow.
- Objectionable odour and bitter taste cab be masked by coating technique.
- Suitable for large scale production.

Disadvantages of tablet dosage form

- Difficult to swallow in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, lower density character.
- Drug with poor wetting, slow dissolution properties, optimum absorption in GIT may be difficult to formulate.

There are different types of tablets are available in market conventional tablet, immediate tablet, fast dissolving tablet, controlled release tablet, sustained release tablet, delayed release tablet[9].

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments[10]. For immediate release formulation, superdisintegrants play key component. Superdisintegrants are used to improve the efficacy of solid dosage form. This achieved by various mechanisms, swelling, porosity and capillary action, heat of wetting, particle repulsion forces, deformation recovery, enzymatic reaction by which the tablets are broken into small particles[11].

Advantages of Immediate Release Drug Delivery System

- Improved compliance
- Improved stability, bioavailability
- Suitable for controlled/sustained release actives
- Allow high drug loading
- Ability to provide advantages of liquid medication in the form of solid preparation
- Adaptable and amenable to existing processing and packaging machinery
- Cost-effective
- Improved solubility of the pharmaceutical composition

Categories of the drug which are preferable for immediate release are analgesic and anti-inflammatory drugs such as Ibuprofen, Diclofenac sodium. Anti-coagulants such as Dicoumarol, Dipyridamol. Anti-Depressants such as Amoxapiine. Anti-diabetic such as Glipizide. Antihypertensive drug such as Amlodipine, Minoxidil, Nifedipine are most preferable for the immediate release[12].

Sustained release systems include any drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled release system. If it is unsuccessful of this day nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged released system[13].

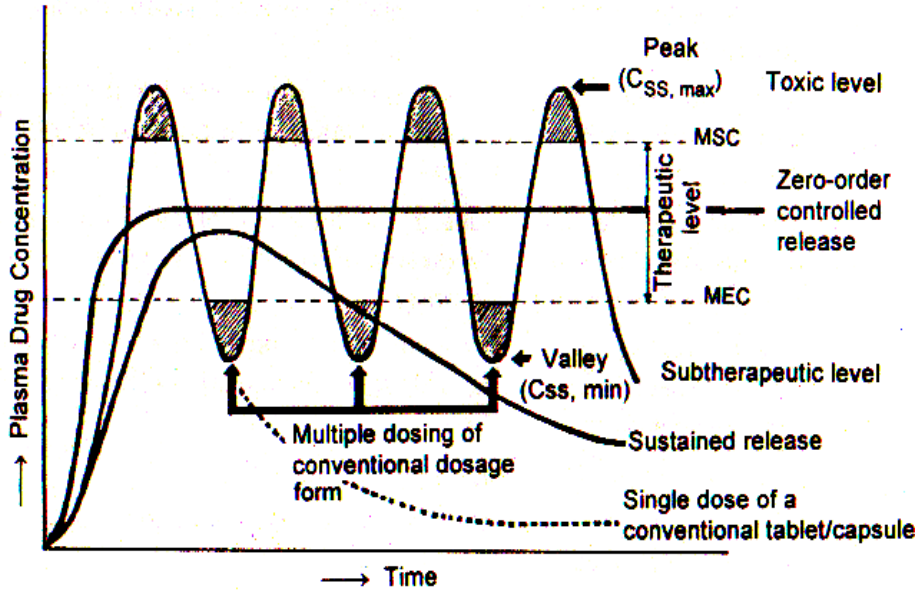


Figure 1: A Hypothetical Plasma Concentration Vs Time Profile

Advantages of sustained release dosage forms[14]

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained.
- The characteristic blood variation due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced thus:
    - Maximizing availability with dose.
    - Minimize or eliminate local side effects.
    - Minimize or eliminate systemic side effects.
    - Minimize drug accumulation with chronic dosing.

- Safety margin of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced and sensitive patients.
- Improve efficiency in treatment.

Disadvantages of sustained release formulation

- Administration of sustained release medication does not permit the prompt termination of therapy.
- Flexibility in adjustment of dosage regimen is limited.
- Controlled release forms are designed for normal population; i.e., on the basis of average drug biological half-lives.
- Economic factors must also be assessed, since more costly process and equipment are involved in manufacturing of many controlled release dosage forms.

Factors Influencing Design of Sustained Release Dosage Forms[15]

Different conditions encountered by the drug molecule while travelling the path of distribution may alter wither the effectiveness of the drug or affect the amount of the drug reaching the receptor site.

A. Pharmaceutical factor

This refers to the development/manufacturing of an efficient delivery system in which the drug has maximum physiological stability and optimum bioavailability.

B. Biopharmaceutics / pharmacokinetics factor

This involves the study of absorption, distribution, metabolism and excretion of the drug, before and after reaching the target site and evaluation of the relationship between delivery system and therapeutic response.

C. Pharmacodynamics/ Clinical Pharmacological factor

It is the study of the mechanism of action and clinical efficacy of a drug administered in dosage form in terms of onset, intensity and duration of pharmacological activity.

Drug properties influencing the design of sustained or sustained release drug delivery system ate classified as:

- Physicochemical properties of the drug: these include dose size, aqueous solubility, protein binding, molecular size, drug stability and partition coefficients.
- Biological factors: These include absorption, distribution, metabolism, duration of action, margin of safety, side effects of drug, disease state and circadian rhythm.

Classification of polymers used in sustained release drug delivery systems (SRDDS)[16]

Table 1: Classification of polymers used in SRDDS

S.No	Polymer characteristics	Material
1.	Insoluble, inert	Polyethylene, Polyvinylchloride, Ethyl cellulose, Methyl acrylates-methacrylate co-polymer.
2.	Insoluble, erodible	Carnauba wax, Stearyl alcohol, Stearic acid, Polyethylene glycol, Castor oil, Monostrarate Triglycerides.
3.	Hydrophilic	Methylcellulose, Hydroxyethylcellulose, HPMC, Sodium CMC, Sodium alginate, Galactomannose, Carboxypolymethylene.

Mechanism of drug release from matrix[17]

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release.
b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;
c) The bathing solution provides sink conditions at all times. The release behavior for the system can be mathematically described by the following equation:

$$DM/Dh = C_O . Dh\text{-}C_S/2 \qquad (1)$$

Where,

DM = change in the amount of drug released per unit area

Dh = change in the thickness of the zone of matrix that has been depleted of drug

C_O = total amount of drug in a unit volume of matrix

C_S = saturated concentration of the drug within the matrix.

Diffusion theory

$$DM = (D. C_S / h).Dt \quad (2)$$

Where, Dm = Diffusion coefficient in the matrix

h = thickness of the drug-depleted matrix

Dt = change in time.

By combining equation 1 and 2 and integrating;

$$M = [C_S. Dm. (2C_O-C_S). t]^{1/2} \quad (3)$$

When the amount of drug is in excess of the saturation concentration, then:

$$M = [2C_S. Dm. C_O. t]^{1/2} \quad (4)$$

Equation 3 and 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores.

The volume and length of the opening must be accounted for in the drug release from a porous or granular matrix:

$$M = [Ds.Ca.p/T.(2C_O - p.C_a) t]^{1/2} \quad (5)$$

Where,

p = Porosity of the matrix, t = Tortuosity, Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium, T = Diffusion path length

For pseudo steady state, the equation can be written as:

$$M = [2D. C_a . C_O (p/T) t]^{1/2} \quad (6)$$

The total porosity of the matrix can be calculated with the following equation :

$$P = pa + Ca/ \rho + Cex/ \rho ex \quad (7)$$

Where,

P = Porosity, ρ = Drug density, pa = Porosity due to air pockets in the matrix

Pex = Density of the water soluble excipients, Cex = Concentration of water soluble excipients

For the purpose of data treatment, equation 7 can be reduced to:

$$M = k. t^{½} \quad (8)$$

Where k is a constant so that the amount of drug released versus the square root of time will be linear if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters.

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer system forming the matrix
- Solubility of the drug

Matrix erosion[18]

The drug release is caused by degradation of the polymer surface.

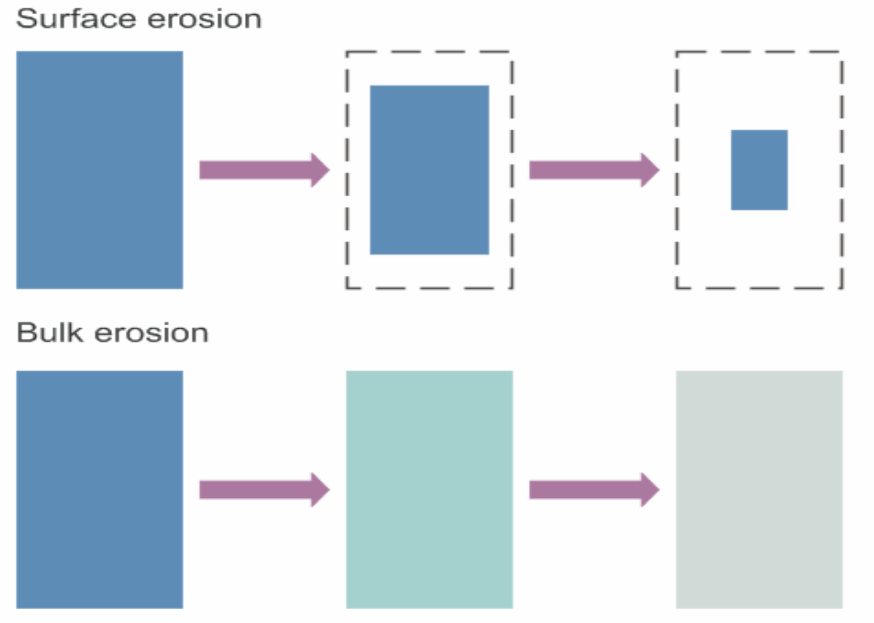


Figure 2: Schematic illustration of surface and bulk erosion

In the last decade, interest in developing a combination of two or more active pharmaceutical ingredients (API) in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bi-layered tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles[19].

Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an extended release manner. Bi-layered tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate

release as initial dose and second layer is maintenance dose. The basic goal of therapy is to achieve a steady state drug in blood level for an extent period of time[20].

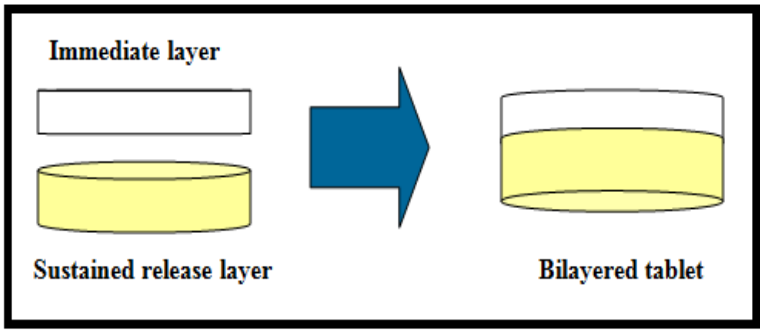


Figure 3: Bi-layered tablet

Advantage of Bi-layered tablets[21]:

1. Bi-layered execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage form.
3. Greatest chemical and microbial stability over all oral dosage form.
4. Objectionable odor and bitter taste can be masked by coating technique.
5. Flexible concept.
6. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
7. Easy to swallowing with least tendency for hang-up.
8. Suitable for large scale production.

Disadvantage of Bi-layered tablets:

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character,

2. Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate as a tablet that will still provide adequate or full drug bioavailability.

Advantage of Bi-layered tablets over conventional tablets:

1. Blood level of a drug can be held at consistent therapeutic level for improved drug deliver, accuracy, safety and reduce side effects.
2. Reduction of adverse effect can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total ddrug content to be reduced.
3. Patient convenience is improved because fewer daily doses are required compated to traditional systems. Patient compliance is enhanced leading to improved drug regimen efficacy.
4. Bi-layered tablets readily lend themselves to repeat action products; where in one layer provide initial dose, the other layer provide maintenance dose.
5. Separate physically or chemically incompatible ingredients.

Types of Bi-layered tablet press[22]

1. Single sided tablet press.
2. Double sided tablet press.
3. Bi-layered tablet press with displacement monitoring.

Single sided tablet press:

The single design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Double sided tablet press:

In most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet of layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

Bi-layered tablet press with displacement monitoring:

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre-compression force.

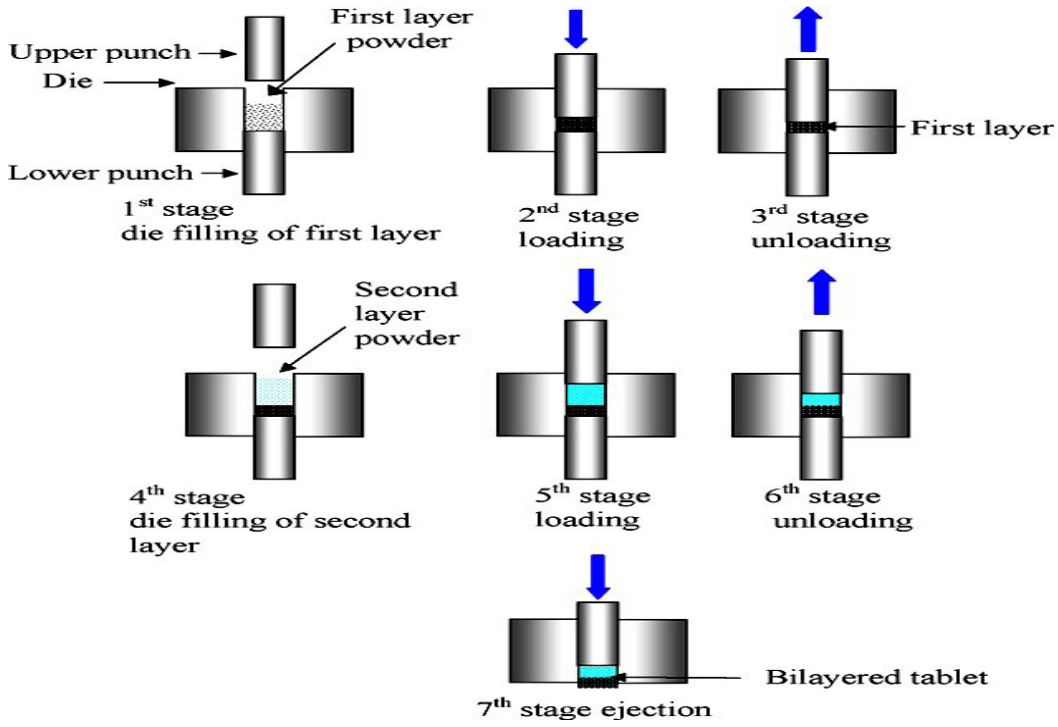


Figure 4: Stages of Bi-layered tablet manufacturing

Ideal characteristics of Bi-layered tablets[23]:

1. A Bi-layered tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
2. It should have sufficient strength to with stand mechanical stock during its production packaging, shipping and dispensing.
3. It should have the chemical and physically stability to maintain its physical attributes over time. The Bi-layered tablet must be able to release the medicinal agents in a predictable and reproducible manner.
4. It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

CHALLENGES IN BI-LAYERED TABLET MANUFACTURING[19]

Conceptually, bi-layered tablets can be seen as two single-layer tablets compressed into one. In practice there are some manufacturing challenges.

- Delamination: tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.
- Cross-contamination: when the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bi-layered tablet. Proper dust collection prevents cross-contamination.
- Production yields: to prevent cross contamination, dust collection is required which leads to losses. Thus, bi-layered tablets have lower yields than single layer tablets.
- Cost: Bi-layered tableting is more expensive than single-layer tableting for several reasons.
    - Tablet press costs more.
    - Tablet press generally runs more slowly
    - Development of two compatible granulation is must, which means more time spent on formulation development, analysis and validation.

Introduction to CNS and it's disorders[24, 25]

Central nervous system is the part of the nervous system consisting of the brain and spinal cord. Any alteration or degeneration of nerves causes CNS disorders. Mainly there are two types of disorders associated with CNS that is neurological and psychological. Neurological disorders

like parkinson's disease, multiple sclerosis, alzheimer's disease, epilepsy, huntington's disease and psychological disorders like anxiety, depression, psychosis, bipolar disorders.

Introduction to epilepsy and bipolar disorders[26, 27]

Epilepsy is abnormal, high frequency electrical discharge in brain characterized by transient episode (seizure) with or without loss of consciousness and characteristic body movement (convulsion). Globally epilepsy is the third most common neurological disorder after cerebrovascular and Alzheimer's disease. About 10 percent of the population will have at lease one seizer in their life time.

Bipolar disorder also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels and the ability to carry out day to day tasks. People with bipolar disorder experience unusual intense emotional states that occur in distinct periods call 'mood episodes'. An overly joyful or overexcited state is called a manic episode, and an extremely sad or hopeless state is called a depressive episode.

Anticonvulsants:[28]

Anticonvulsants (also known as antiepileptic drugs or antiseizure drugs) are a diverse group of pharmacological agents used in the treatment of epileptic seizures. Anticonvulsants suppress the rapid and excessive firing of neurons during seizure. It also prevents the spread of the seizure within the brain. It also used in the treatment of bipolar disorder. They are classified as following

1. Barbiturate : Phenobarbitone
2. Deoxybarbiturate : Primidone
3. Hydantoin : Phenytoin

4. Iminostilben : Carbamazepine
5. Succinamide : Ethisuximide
6. Aliphatic carboxylic acid : Valproic acid, Sodium valproate, Divalproex sodium
7. Benzodiazepine : Clonazepam , Diazepam , Clobazam
8. Phenyltriazine : Lamotriazene
9. Cyclic GABA analogue : Gabapentin
10. Newer drugs : Vigabatrin, Topiramate, Tiagabine, Levetiracetam

Mechanism of action of antiepileptic drugs[29]

Drugs that are effective in seizure reduction accomplish this by a variety of mechanisms, including blockade of voltage-gated channels (Na^+ or Ca^{2+}), enhancement of inhibitory GABAergic impulses, or interference with excitatory glutamate transmission. Some antiepileptic drugs appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined.

CHAPTER 2

OBJECTIVES

2. OBJECTIVES

2.1 Need for the study:

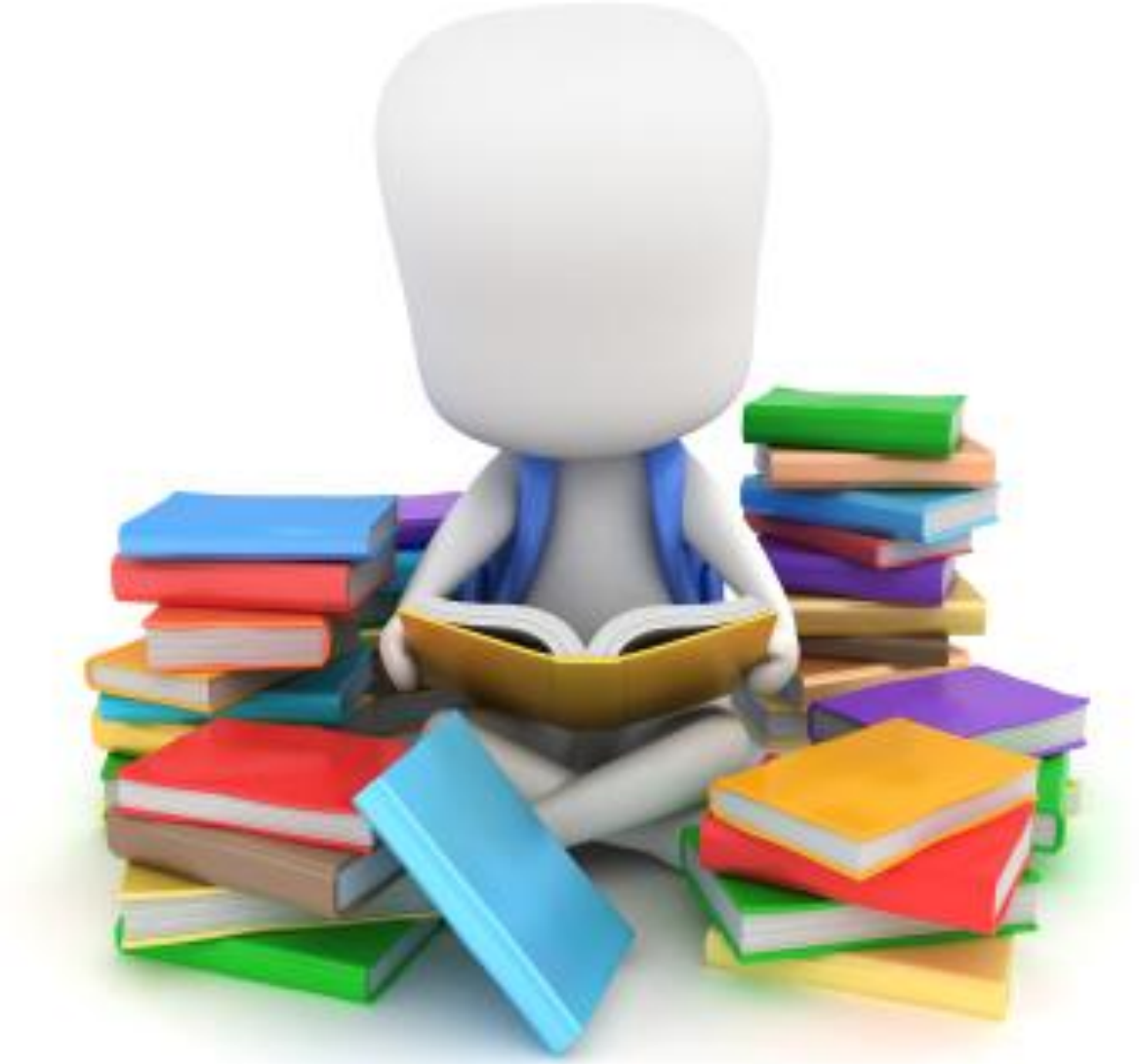
Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost- effective dosage forms[30]. Bi-layered tablet concept has long been utilized to develop sustained released formulation. The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However the blood level is maintained at steady state as the release from sustained layer. Particularly bilayer tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation, and release profile[31]. After stoke and dementias, epileptic seizures constitute the 3rd most frequent neurologic disorders encountered in elderly in developed countries[32]. The aim of the present research work was to develop the different immediate and sustained release formulation of Divalproex sodium and compare their release profile, from above formulation select a best formulation for manufacturing bi-layered tablet.

Hence, in the present research investigation attempt was made to formulate and evaluate bi-layered tablet of Divalproex sodium.

2.2 Objectives of the study:

- To minimize the frequency of administration.
- To study the pre-formulation properties like melting point, solubility of the drug.
- To investigate the drug- excipient interaction studies using FTIR and DSC.
- To formulate the bi-layered tablets of Divalproex sodium.
- To evaluate the formulation with respect to various physical parameters: Hardness, weight variation, thickness, and content uniformity.
- Compare the release profile of different formulation.
- To evaluate either the drug release data will be fit into different kinetic model.
- Stability studies 0f optimized formulation will be carried out according to ICH guide lines.

CHAPTER 3



3. REVIEW OF LITERATURE

Literature survey was carried out on the proposed topic by referring various scientific journals, online and offline also referred various text books available in college library. This survey reveals that no such articles were reported on the proposed work and some related articles are mentioned below.

Lakhani KM et al.,[33] designed an oral Extended release matrix tablet of Divalproex sodium, by a direct compression method using HPMC K100M and Eudragit L100 as matrix forming polymer. Prepared tablet were evaluated for various physiochemical parameters like hardness, thickness, friability, weight variation, content uniformity and *in vitro* drug release. The drug release profile was optimized by using 3^2 full factorial designs where, HPMC K100M and Eudragit L100 were taken as the independent variables. Among all ten formulations, batch F8 containing HPMC K100M 15% and Eudragit L100 10% was found to be optimized formulation as it has almost identical dissolution profile with marketed product.

Vamsy KA et al.,[34] have prepared extended release Tablets of Divalproex sodium, by a direct compression technique. They formulated 5 different formulations using various polymer like HPC-HF, HPMC K4M, HPMC K15M, HPMC K100M in different proportion. FTIR studies shown that the drug and excipients were compatible with each other. Compressed tables were evaluated for weight variation, hardness and *in vitro* dissolution using paddle (USP type II) method. Among the five formulations, batch DERT-V containing 19.5 of HPMC K100M and & % of HPMC K4M taken as ideal formulation of extended release tablets for 18 hours release as it fulfill all the requirements for extended release tablet.

Jadhav RT et al.,[35] have developed bi-layered tablet of Piracetam and Vinpocetine. Both of layers were prepared by wet granulation method using PVP K-30 and maize starch as

granulating agent respectively. Formulated tablets were evaluated for thickness, weight variation, hardness, friability, drug content and *in vitro* drug release. Drug content was evaluated using HPLC method. Among all the formulations, tablets of batch P2 of Piracetam and V2 of Vinpocetine was taken as optimized formula and formulated as bi-layered tablet due to its higher dissolution rate and compiled all official specifications. The selected batches were kept for stability study at 40^{o}C and 75% RH for 3 months.

Kumar S.D et al.,[36] Was formulated the bi-layered floating tablet of ziprasidone Hcl as immediate release and Trihexyphenidyl Hcl as sustained release. HPMC K4M / HPMC K15M used as polymer for sustained release of the drug and sodium bicarbonate as the floating layer. IR shows that no any interaction among the drugs and excipients. The final tablets were evaluated for the different parameter like Hardness, thickness, friability, weight variation, disintegration & dissolution. Release profile of the tablet was carried out by using USP XXIII dissolution apparatus. Among the 20 formulation F1 F2 F11 and F12 are optimized formulation.

Shivanand K et al.,[37] have prepared bi-layer buccal tablets of Tizanidine hydrochloride (TZD HCl), by a direct compression method, using mucoadhesive polymers carbopol 934(CP), HPMC K4M, HPMC K15M and sodium carboxymethylcellulose along with ethyl cellulose as an impermeable backing layer. FTIR and DSC found to be compatible with selected polymers. Bi-layered buccal tablets containing CP and HPMC K4M in the ratio 1:1 (BT1) had the maximum percentage of *in-vitro* drug release in 6 hours. A modified balance method was used for determining the *ex-vivo* mucoadhesive strength. The bioadhesive strength exhibited by the HPMC K4M and Na CMC tablets can be considered satisfactory for maintaining them in the oral cavity.

Remya PN et al.,[38] have prepared Ibuprofen and Methocarbamol bi-layered tablets by wet granulation process by using povidone k-30 as binder. The *in-vitro* disintegration time was found in the range of 3.23 to 7.34 min. sec. Among the formulations tablets of formulation-8 was taken as optimized formula due to its higher rate of dissolution. The percentage drug release for formulation F8 shows the better drug release between 95.1 to 97.2%. It was concluded that Ibuprofen, Methocarbamol bi-layer tablets can be prepared successfully as it satisfies all the criteria as a bi-layered tablet and would be alternative to the currently available conventional tablets.

Patil SS et al.,[39] have developed gastro retentive bi-layer floating tablets of Rosiglitazone maleate by using different super disintegrants and controlled release layer using hydroxypropyl methylcellulose K100M (HPMC K100M) by direct compression method. Among various super disintegrants used, croscarmellose at the concentration of 8% was found sufficient to cause rapid drug release whereas 50% HPMC of the total weight of the tablet effectively controlled the drug release over a period of 24hrs. Sodium bicarbonate at the concentration of 14 %w/w reduced the buoyancy lag time to less than 3 minute for the optimized tablet (F5). The total floating time for different formulations was in the range of 10-28hrs. Release profiles of formulation F5 indicated that, increasing the polymer concentration has drastically retarded the release of rosiglitazone maleate over a period of 24hrs. Tablets followed diffusion controlled first order kinetics. During the stability period optimized formulation was found to be stable with respect to physico-chemical and drug release characteristics.

Patel VM et al.,[40] prepared bi-layer buccal tablets by homogeneously mixing the drug with CP, Na-alginate, PVP K-30, D-mannitol, and PEG 4000 in a glass mortar for 15 minutes and the mixture (100 mg) was then compressed by using a direct compression method. Tablets

containing Na-alginate and CP in the ratio of 5:1 (F2) had the maximum percentage of *in vitro* drug release without disintegration in 12hrs. The formulation F4 was optimized based on good bioadhesive strength (28.9 ± 0.99 g) and sustained *in vitro* drug permeation (68.65% ± 3.69% for 12hrs). The formulation F4 was applied to rabbit oral mucosa for *in vivo* studies. The formulation inhibited Isoprenaline-induced tachycardia. The studies conducted in rabbits confirmed the sustained release as compared with intravenous administration.

Bagde SB et al.,[41] developed ten batches of ER/IR bi-layer tablets of Metoprolol succinate and Ramipril by using wet granulation and dry granulation technique, respectively. Hydroxypropylmethylcellulose K100M and sodium carboxymethylcellulose was used for extended release of Metoprolol succinate. FTIR and DSC studies shown that the drug and excipients were compatible with each other. Compressed tablets were evaluated for weight variation, hardness, and *in vitro* dissolution using paddle (USP type II) method. Among the ten formulations, F_{10} showed compliance with US pharmacopoeial standards, extended the release of drug for 20hrs with 99.6% drug release and subjected to stability studies for 1 month at 40 ^{0}C/75% R.

Jayaprakash S et al.,[42] developed bi-layered tablet of Amlodipine besilate immediate release layer by direct compression method and Metoprolol succinate sustain released layer were prepared by wet granulation method. In the formulation of immediate release sodium starch glycolate and pregelatinised starch were used as super disintegrant and PVP K30 as binder

was used for sustain released layer. An *in-vitro* drug release study shows that optimized formulation showed 9.96%, 35.56%, 52.12%, 90.46% release for Metoprolol succinate in 1, 4, 8, 20hrs respectively. However, Amlodipine besilate released 98.28% at the end of 30 minutes. The

kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows first order kinetics.

Kasid I et al.,[43] developed bi-layer tablets of optimized Gliclazide sustained release layer and Lisinopril fast dissolving layer by double compression method. Lisinopril was formulated as fast dissolving layer using sodium starch glycollate, croscarmellose sodium as super disintegrants. Gliclazide was formulated as sustained release layer using different polymer matrix like hydroxyethylcellulose, hydroxypropylcellulose, and ethylcellulose and evaluated for physical parameter along with *in vitro* release studies. The *in vivo* antidiabetic activity suggested that Lisinopril potentiate hypoglycemic effect of Gliclazide and blood glucose level was constantly maintained up to 24hrs. The FTIR study conducted using a combination of drugs along with excipients and polymers revealed that combination can be safely prepared.

Kulkarni A et la.,[44] developed bi-layer regioselective floating tablets of Atenolol for sustained release and Lovastatin for immediate release by direct compression method. The immediate release layer of Lovastatin comprised sodium starch glycollate as a super disintegrant and the sustained release layer of Atenolol comprised HPMC K100M and xanthan gum as the release retarding. Sodium bicarbonate was used as a gas generating agent was used for formulation of the bilayer tablets. Roentgenography study shows all formulations floated for more than 12hrs. More than 90% of Lovastatin was released within 30 min. The release of Atenolol was found to follow a mixed pattern of Korsmeyer-Peppas, Hixson-Crowell and zero order release models. The optimized formulation was found to be buoyant for 8hrs in stomach. Therefore, biphasic drug release pattern was successfully achieved through the formulation of floating bi-layer tablets in this study.

Brito S.R et al.,[45] Was design a dual retard technique of once daily inlay tablet of atorvastatin calcium as immediate release and Metoprolol tartarate as Sustained release formulation. For immediate release Sodium starch glycolate, cross povidone and croscarmellose are used as the super disintegrants and for the sustained release guar gum, Eudragit, and HPMC are used as the polymer. Differential scanning calorimetry shows no interaction among the drug and the used excipients. Formulated tablet are evaluated for the thickness, Hardness, weight variation, disintegration, swelling erosion behavior, *in vitro* release and stability studies. Six formulations (F1-F6) were prepared among that F4 shows expected release pattern and follows zero order.

Banu H. et al.,[46] Was design acetominophen extended release bilayers tablet containing immediate release layer and sustained release layer. For retard the release different grade of hydroxypropylmethyl cellulose (HPMC 15 cps, HPMC 100 cps and Methacel K4M CR) and sodium starch glycolate is used for immediate release of the drug. FTIR shows no any interaction between the drug and excipients. The tablet was prepared by using wet granulation technique. Six formulation were made for extended release among that formulation ER-4(containing 10% HPMC 100 cps and 1.5% sodium starch glycolate) and ER-6(containing 1.5% Methocel K4M CR and 0.5% sodium starch glycolate) follow compendial specification for drug release profile.

Kumar G.V et al.,[47] Was formulated bilayers tablet of Dicloxacillin sodium and Cefixime trihydrate for oral administration one layer contains sustained release layer of Dicloxacillin sodium and another layer contains immediate release layer of Cefixime trihydrate. Sustained release layer was prepared by using HPMC K4M and HPMC K15M and immediate release layer was prepared by using croscarmellose. Tablet was prepared by wet granulation technique using PVP K30 as binding agent. Tablet was evaluated for all parameters like thickness, hardness, weight variation, disintegration time, drug release. *In vitro* drug release study was carried on the

dissolution apparatus II. Among the nine formulations the F5 formulation was matches with specification.

Musle K et al.,[48] Was prepared bilayer tablet of Diclofenac sodium and paracetamol where Diclofenac sodium as sustained release layer and paracetamol as immediate release layer. Crospovidone incorporated in immediate release layer and hydroxypropylmethylcellullose in sustained release layer. Paracetamol tablet prepared separately using crospovidone and granules of microcrystalline cellulose and diclofenac sodium tablet separately and all parameter are evaluated. The optimized batch of both drug were punched in single punching machine. Bilayered tablets were evaluated for thickness, hardness, friability, weight variation, *in vitro* drug release. Dissolution profile shows 75% of parecetamol released in 30 minute and 92% diclofenac sodium released in 10 hrs.

Gupta B et al.,[49] Was prepared Bilayer tablet of glipizide consist of sustained release layer and immediate release layer. Sustained release layer was prepared by using different concentration of Hydroxypropyl methyl cellulose (HPMC K-100, HPMC K-50 and Ethyl Cellulose. Immediate release layer prepared by using Sodium starch glycolate as super disintegration agent. Tablet was prepared by wet granulation technique. FT-IR shows no interaction between drug and excipients. Tablet was evaluated for all parameters like thickness, hardness, weight variation, *in vitro* drug release. Dissolution was carried out in USP-II paddle type dissolution apparatus. Among six formulation F3 batch show good release behavior in 10 hrs 91.92% of drug released.

Toma N.M et al.,[50] Was prepare floating bilayers tablet of sustained release layer clopidogrel and immediate release layer of Aspirin. Immediate release layer prepared by using super disintegrating agent crosscarmelose and sustained release layer by using hydroxypropyl methyl cellulose, ethyl cellulose, carbapol and combination of same. Tablet is prepared by wet

granulation technique. Sustained and immediate release layer were prepared separately, eleven formulation of sustained release layer were prepared among then the formulation containing HPMC and Carbapol (1:1) show good floating behavior. Three formulations of Aspirin among that A3 having good disintegration time. The best selected batches were punched in bilayers tablet and evaluated for all parameters like thickness, hardness, weight variation, disintegration time, drug content and *in vitro* drug release.

Lakshmi A.P et al.,[51] Has been formulated bilayers tablet, Levofloxacin hemihydrate immediate release and Ambroxol HCL sustained release. HPMC K4M and HPMC K100M were used for retard the release of Ambroxol from Ambroxol layer. Immediate release layer of Levofloxacin were prepared by using sodium starch glycolate. Eleven formulation of Ambroxol HCl and four formulations of Levofloxacin were prepared separately. Among these F11 of Ambroxol HCL and F2 of Levofloxacin are selected as optimum formulation, these formulation punched and evaluated for thickness, hardness, weight variation, friability, disintegration time, drug content uniformity and *in vitro* drug release. Stability studies were conducted for the bilayers tablet for 3 month in normal condition and accelerated condition.

Kasid I et al.,[52] Was prepared bilayer tablet containing fast dissolving Lisinopril layer and sustained release Gliclazide layer. Fast dissolving layer of Lisinopril was prepared by using Sodium starch glycolate, croscarmellose sodium as superdisintegrants and sustained release layer of Gliclazide was prepared by using polymer like hydroxyethylcellulose, hydroxypropylcellulose and ethylcellulose. The FTIR study shows no any interaction between drug and excipients. Optimized formulation of fast dissolving layer of Lisinopril (L-6) and sustained release layer of Gliclazide (G-5) were punched in bilayer tablet by double compression. Tablet was evaluated for hardness, thickness, weight variation, friability, *in vitro* disintegration time, and *in vivo*

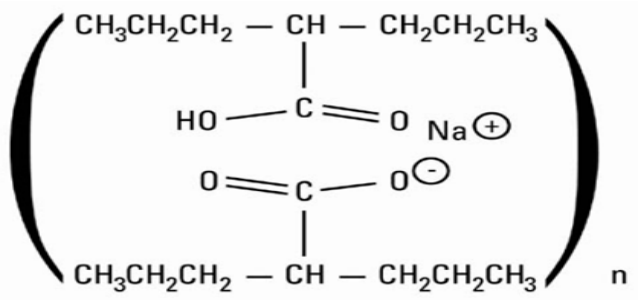
antidiabetic activity using wistar rats. The *in vivo* study suggested that Lisinopril potentiate hypoglycemic effect of Gliclazide and blood glucose level constantly maintained up to 24 hours.

Mohideem S et al.,[53] Was developed a bilayer tablet contain Atorvaststin calcium as an immediate release layer and metformin hydrochloride as sustained release layer. Ten formulations were made, granules of different formulation of both drug were evaluated for bulk density, tapped density, compressibility index and Hausner's ratio. Granules are prepared by wet granulation. Sodium starch glycolate used as superdisintegrants in immediate release layer and HPMC K15M, HPMC K100M and HPMC K100M CR were used as retard the drug release in sustained release layer. Among the all formulations, formulation no. 10 showed good hardness, thickness and low friability. The percentage drug release for this formulation showed the better drug release 96% of Atorvastatin calcium in 45 minutes as immediate release and 102% of Metformin hydrochloride in 12 hours as sustained release.

3.2 DRUG PROFILE:

DIVALPROEX SODIUM[54, 55, 56, 57]

Chemical structure:



Structure of Divalproex sodium

Divalproex sodium contains not less than 98% and not more than 102% of available valproic acid, $C_8H_{16}O_2$.

Chemical Name: 2-propyl-pentanoic acid sodium salt(2:1). Sodium hydrogen bis(2-propylvalerate) oligomer.

CAS Number: 76584-70-8

Brand name: Depakote, Depakote CP, Depakote ER, Epival, Stavzor

Category: Anticonvulsant

Molecular Formula: $C_8H_{16}O_2C_8H_{15}O_2Na$

Molecular weight: 310.41

Description: Odorless, white or off-white crystalline powder.

Melting Point: 222^oC

Solubility: soluble in ethanol (95%), methanol, Isopropyl alcohol, partially soluble in water, ether.

Storage: Store protected from moisture at a temperature not exceeding 30^o C.

MECHANISM OF ACTION:

Divalproex sodium is broad-spectrum anticonvulsant. It increases the availability of gamma-amino butyric acid (GABA), an inhibitory neurotransmitter. It has inhibitory action against GABA transaminase which breakdown GABA, it leads to increased concentration of GABA in the synapses. Other propose mechanisms of action that account for their anticonvulsant properties is it either enhance the action of GABA or mimic its action at postsynaptic receptor

sites. It also block voltage gated sodium channels and T-type calcium channels, and cause inhibitory activity in the brain.

Pharmacokinetics

Absorption: Rapid absorption from gastrointestinal tract.

Distribution: Protein binding 80-90%

Metabolism: Metabolized almost entirely by the liver.

Excretion: Both bile and urine

Half Life: 9-16 hours

Bioavailability (oral): 84%

Pharmacology

Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. It is an anticonvulsant and mood-stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder.it is also used to treat migraine headaches and schizophrenia. In epileptics, divalproex sodium is used to control absence seizures, tonic-clonic seizures (grandmal), complex partial seizures, and the seizures associated with Lennox-Gastaut syndrome. It is believed to affect the function of the neurotransmitter GABA (as GABA transaminase inhibitor) in the human brain. It dissociate to the valproate ion in the gastrointestinal tract.

Contraindications of Divalproex sodium

a) Hepatic disease or significant hepatic dysfunction

b) Urea cycle disorders

c) Hypersensitivity to the drug

Warnings and Precautions

a) Hepatotoxicity

b) Teratogenic

c) Pancreatitis

d) Thrombocytopenia

e) Hyperammonemia and hyperammonemic encephalopathy

Adverse Effects of Divalproex sodium

a) Nausea, Headache

b) Somnolence

c) Dizziness

d) Vomiting

e) Asthenia

f) Abdominal pain

g) Anorexia

h) Weight gain

i) Alopecia

Drug Interactions

a) Hepatic enzyme-inducing drugs: phenytoin, carbamazepine, primidone, phemobarbital, rifampin can decrease valproate clearance.

b) Aspirin, carbapenem antibiotics

c) Topiramate

d) Amitriptyline, warfarin and zidovudine

Table 2: SODIUM STARCH GLYCOLATE[58]

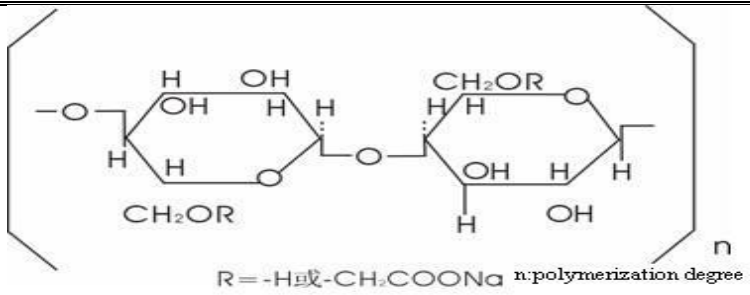
Non-proprietary names	BP: Sodium starch glycollate USP/NF: Sodium starch glycolate PhEur: Carboxymethylamylum natricum
Synonyms	Carboxymethyl starch, sodium salt, Explosol, Explotab, Tablo.
Description	White to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30-100 μm in diameter, with some less-spherical granules ranging from 10-35 μm in diameter.
Structural Formula	
Chemical names **CAS Number**	Sodium carboxymethyl starch 9063-38-1
Empirical formula **Molecular weight**	 $5 \times 10^5 - 1 \times 10^6$
Melting point	Approximately 200^0C
Solubility	Practically insoluble in water, sparingly soluble in ethanol (95%). In water it swells up to 300 times its volume.
Functional Category	Tablet and capsule disintegrant
Stability and storage conditions	It is stable and should be stored in a well-closed container in order to protect it from humidity and temperature, which may cause cracking.
Incompatibilities	Ascorbic acid
Safety	It is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.
Application	It is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet prepared by both direct- compression and wet-granulation process. Usual concentration employed in a formulation is between 2 % and 8%.

Table 3: CROSCARMELLOSE SODIUM[59]

Non-proprietary names	BP: Croscarmellose sodium USPNF: Croscarmellose sodium PhEur: Carmellosum natricum conexum
Synonyms	Ac-Di-Sol, crosslinked carboxymathylcellulose sodium, Explocel, modified cellulose gum, primellose, Solutab
Description	Odorless, white or grayish-white free flowing powder.
Chemical names **CAS Number**	Cellulose, carboxymethyl ether, sodium salt, crosslinked 74811-65-7
Empirical formula **Molecular weight**	$C_{12}H_{10}Ca_3O_{14}.4H_2O$ 570.49
Solubility	Insoluble in water, although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene,
Functional Category	Tablet and capsule disintegrant.
Stability and storage conditions	It is a stable though hygroscopic material and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	The efficacy of croscarmellose sodium may be slightly reduced in tablet formulation prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients.
Safety	It ia mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as nontoxic and nonirritant material.
Application	It is used as a disintegrant for capsules, tablets, and granules. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process. Croscarmellose sodium at concentrations up to 5 % w/w may be used as a disintegrant in tablets prepared by direct compression and 3 % w/w in tablets prepared by a wet-granulation process.

Table 4: LACTOSE[60]

Non-proprietary names	BP: Lactose monohydrate USP/NF: Lactose monohydrate PhEur: Lactosum monohydricum JP: Lactose
Synonyms	Lactochem Coarse Crystals, Lactochem Crystals, Lactochem Powder, Pharmatose 50M, NF Lactose 310.
Description	White to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting.
Chemical names **CAS Number**	O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose 64044-51-5
Empirical formula **Molecular weight**	$C_{12}H_{22}O_{11}.H_2O$ 360.31
Melting point	201-202^{0}C
Solubility	Practically insoluble in chloroform, ethanol and ether, soluble in water.
Functional Category	Binding agent, diluent for dry-powder inhalers, tablet binder, tablet and capsule diluent.
Stability and storage conditions	Mold growth may occur under humid conditions(80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. It should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Primary amine group, amino acids, aminophylline, amphetamines and lisinopril.
Safety	It is widely used in pharmaceutical formulations as a filler and filler-binder in oral capsule and tablet formulation.
Application	It is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method. It is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions.

Table 5: MICROCRYSTALLINE CELLULOSE[61, 62]

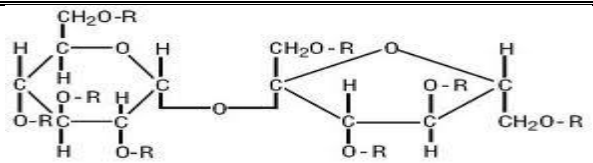
Non-proprietary names	BP: Microcrystalline cellulose USP/NF: Microcrystalline cellolose PhEur: Cellulosum microcristallinum
Synonyms	Avicel PH, Celex, cellulose gel, celphere, crystalline cellulose, E460, Emcocel, Vivapur
Description	White, odorless, tasteless, crystalline powder
Structural Formula	
Chemical names **CAS Number**	Cellulose 9004-34-6
Empirical formula **Molecular weight**	$(C_6H_{10}O_5)_n$ where n ≈ 220 ≈36000
Melting point	260-270
Solubility	Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids, and most of organic solvents
Functional Category	Absorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.
Stability and storage conditions	It is stable though hygroscopic material and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Strong oxidizing agents
Safety	It is widely used in oral pharmaceutical formulations and is generally regarded as a relatively nontoxic and non irritant material.
Application	It is used in tablet or capsule formulation as a binder/diluent in both wet-granulation and direct-compression processes.

Table 6: POLYVINYL PYRROLIDONE[63, 64]

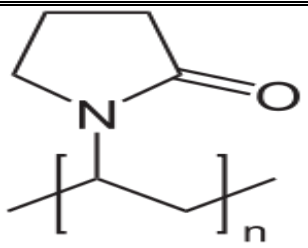
Non-proprietary names	BP: Povidone USP: Povidone PhEur: Povidonum
Synonyms	Plasdone k-30, luviskol k-30, plasdone, povidone, pvp k-30, poly(1-vinyl-2-pyrrolidinone
Description	Fine, white to creamy-white colored, odorless, hygroscopic, amorphous powder.
Structural Formula	
Chemical names **CAS number**	1-Ethenyl-2-pyrrolidinone homopolymer 9003-39-8
Chemical formula	$(C_6H_9NO)_n$
Melting point	150-180^{0}C
Solubility	Soluble in cold water, chloroform, alcohol, chlorinated hydrocarbons, amines and lower weight fatty acids.
Functional Category	Suspending agent, tablet binder
Stability and storage conditions	It darkens to some extent on heating at 150^{0}C, with a reduction in aqueous solubility and should be stored in an airtight container in a cool, dry place.
Incompatibilities	Oxidizing agents.
Safety	It may be regarded as essentially nontoxic and nonirritant.
Application	PVP k series can be used as film forming agent, viscosity enhancement agent and adhesive. In tableting, PVP solutions are used as binders in wet granulation process. PVP solutions may also be used as coating. It is also used as suspending, stabilizing-increasing agents in topical and oral suspensions and solutions.

Table 7: MAGNESIUM STEARATE[65, 66]

Non-proprietary names	BP: Magnesium stearate USP/NF: Magnesium stearate PhEur: Magnesii stearas
Synonyms	Magnesium octadecanoate, octadecanoic acid, magnesium salt
Description	Very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adhere to skin.
Chemical names **CAS Number**	Octadecanoic acid magnesium salt 557-04-0
Empirical formula **Molecular weight**	$C_{36}H_{70}MgO_4$ 591.34
Melting point	117-150^{0}C (commercial samples) 126-130 ^{0}C (high purity magnesium stearate)
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in warm benzene and warm ethanol (95%).
Functional Category	Tablet and capsule lubricant
Stability and storage conditions	It is stable and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Strong acids, alkalis and iron salts.
Safety	It is widely used as pharmaceutical excipient and is generally regarded as being nontoxic.
Application	It is widely used in cosmetic, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. it is also used in barrier creams.

Table 8: TALC[67, 68]

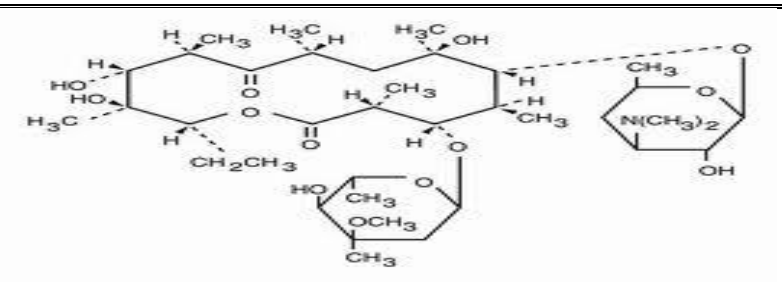
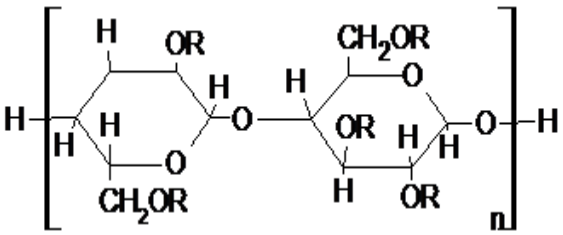
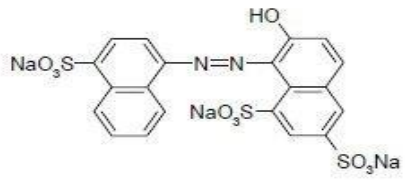
Non-proprietary names	BP: Purified talc USP: Talc PhEur: Talcum
Synonyms	Altalc, E553b, hydrous magnesium calcium silicate, Luzenac Pharma, Purtalc, steatite, purified French chalk.
Description	Very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder.
Structural Formula	
Chemical names **CAS Number**	Talc 14807-96-6
Empirical formula	$Mg_6(Si_2O_5)_4(OH)_4$
Functional Category	Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.
Stability and storage conditions	It is stable material and may be sterilized by heating at 160^0C for not less than 1 hour. It should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Quaternary ammonium compounds.
Safety	
Application	It is widely used oral solid dosage formulations as a lubricant and diluent. It is also used as lubricant in tablet formulation, in a novel powder coating for extended-release pellets and as an adsorbant.

Table 9: HYDROXYPROPYLMETHYL CELLULOSE[69, 70, 71]

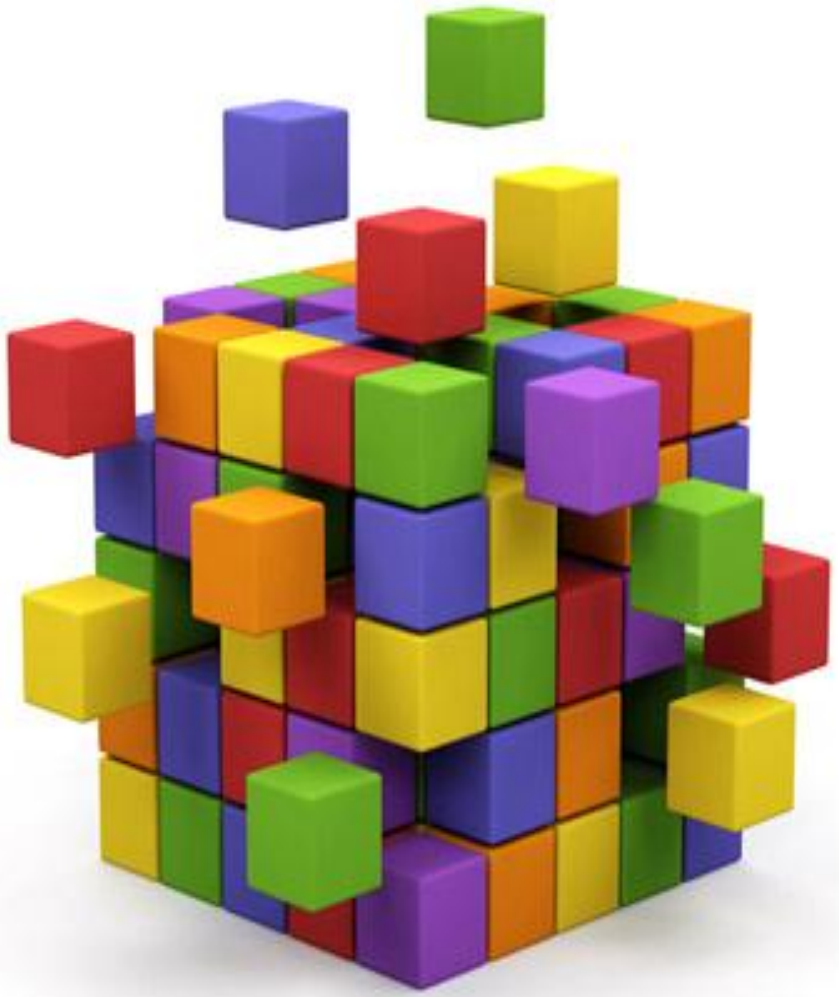
Non-proprietary names	BP: Hypromellose USP: Hypromellose JP: Hydroxypropylmethylcellulose
Synonyms	Benecel MHPC, E464, hydroxypropyl methylcellulose, Methocel, HPMC, Metolose
Description	Odorless and tasteless, white or creamy-white fibrous or granular powder
Structural Formula	
Chemical names **CAS Number**	Cellulose hydroxypropyl methyl ether 9004-65-3
Molecular weight	10 000- 1 500 000
Melting point	Brown at 190-200^{0}C and chars at 225-230^{0}C
Solubility	Soluble in cold water, forming a viscous colloidal solution. Practically in soluble in chloroform, ethanol(95%) and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water and alcohol.
Functional Category	Coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.
Stability and storage conditions	It is a stable material, although it is hygroscopic after daying. Solutions are stable at pH 3-11 and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Oxidizing agents
Safety	It is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products and is generally regarded as a nontoxic and nonirritant material.
Application	It is widely used in oral,ophthalmic and topical pharmaceutical formulations. In oral products, it is primarily used as a tablet binder; concentration between 2% and 5% w/w and as a matrix for use in

	extended release tablet formulations; concentration between 10 to 80%. Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solutions to film-coat tablets. It is also used as a suspending and thickening agent in topical formulations. Concentration between 0.45-1 % w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

Table 10: PONCEAU 4R[72, 73]

Synonyms	C.I. 16255, Cochineal Red A, C.I. Acid Red 18, Brilliant Scarlet 3R, Brilliant Scarlet 4R
Description	Reddish powder or granules
Structural Formula	
Chemical names **CAS Number**	1-(4-sulpho-1-napthylazo)-2-napthol-6,8-disulphonic acid tisodium salt. 2611-82-7
Molecular formula **Molar mass**	$C_{20}H_{11}N_2Na_3O_{10}S_3$ 604.47 g mol^{-1}
Solubility	Soluble in water, sparingly soluble in ethanol
Functional Category	Food additives, pigment
Stability and storage conditions	It is stable to light, heat, and acid but fades in the presence of ascorbic acid. It should be stored in well-closed container in a cool, dry place
Application	Coloring agents in pharmaceutical dosage form.

CHAPTER 4



MATERIALS AND METHODS

4. MATERILS AND METHODS

PLAN OF WORK

1. Literature survey

2. Collection of drug, polymers & other excipients

3. Formulation developments

A. Pre-formulation study

- **Determination of melting**
- **Solubility**
- **Determination of λ_{max}**
- **Standardization of drug**
- **Compatibility study**

B. Formulation design

C. Compression and evaluation of SRL and IRL

D. Selection of best formulation of SRL and IRL

E. Compression of bi-layered tablet from selected formulation

F. Evaluation of bi-layered tablet

4.1 MATERIALS

Table 11: List of materials

Sl No.	Ingredients	Company Name
1.	Divalproex sodium	Gift sample from ROAQ Chemicals Pvt. Ltd. Vadodara
2.	Sodium Starch Glycolate	S.D. Fine Chem. Ltd, Mumbai
3.	Croscarmellose	S.D. Fine Chem. Ltd, Mumbai
4.	HPMC K4M	Yarrow Chem Products, Mumbai
5.	HPMC K100M	Yarrow Chem Products, Mumbai
6.	Lactose	S.D. Fine Chem. Ltd, Mumbai
7.	Micro Crystalline Cellulose	S.D. Fine Chem. Ltd, Mumbai
8.	PVP K 30	S.D. Fine Chem. Ltd, Mumbai
9.	Ponceau 4R	Indian fine chemicals, Mumbai-20
10.	Magnesium Stearate	S.D. Fine Chem. Ltd, Mumbai
11.	Talc	S.D. Fine Chem. Ltd, Mumbai

4.2 LIST OF INSTRUMENTS

Table 12: List of Equipments

Sl No.	Equipment	Model/company
1.	Fourier Transform Infrared spectrophotometer	Thermo Nicolet
2.	UV-Visible spectrophotometer	UV-1800, Shimadzu
3.	Electronic balance	Essae-Teraoke
4.	Hot air oven	Kemi
5.	Multi tablet Punching machine	LAB PRESS, CipMachinaries Ltd. Ahmedabad
6.	Roche Friabilator	PSM Industries, Bangalore
7.	Hardness tester	Monsanto hardness tester
8.	Disintegration test apparatus	DT-1500, Lab India
9.	Dissolution test apparatus	DS-800, Lab India
10.	FTIR- spectrophotometer	Tensor 27 Bruker
11.	DSC Apparatus	DSC-60, Shimadzu
12.	Stability chamber	106 Model/ LabTop, Sky Lab Instruments & Engineering Pvt.Ltd.

4.3 PRE-FORMULATION STUDIES

Pre-formulation testing is the first step in rational development of dosage forms of a drug substance. Pre-formulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the excipients that could affect drug performance and development of as efficacious, stable and safe dosage form. It provides a framework for the drug combination with pharmaceutical excipients in the dosage form.

4.3.1 Determination of λ_{max}[74]

Divalproex sodium was dissolved in methanol further diluted with the same and scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu 1800) in the range from 190 to 380 nm.

4.3.2 Solubility

The solubility of Divalproex sodium was determined in distilled water, methanol, ethanol, acetone, chloroform and pH 6.8 phosphate buffer by shake flask method. An excess amount of Divalproex sodium is added to each vial containing 10 ml of selected solvent till the saturation of the solution. The mixtures were subjected to the mechanical agitation for 48 hours in isothermal shaker at $25^0C \pm 1^0C$ followed by filtration through watmann's filter paper. Absorbance is measured by UV-Visible Spectrophotometer. The drug content is calculated by using the standard graph.

4.3.3 Melting point[75]

Melting point of the Divalproex sodium was determined by capillary method in triplicate.

4.3.4 Standard Curve for Divalproex sodium[74]

100 mg of Divalproex sodium was accurately weighted and dissolved in 100 ml of methanol to prepare first stock solution. 10 ml of above solution was taken and diluted to 100 ml with the same solvent to prepare II stock solution. The aliquot amount of II stock solution was further diluted to get 5, 10, 15, 20, 25 and 30μg of drug per ml of the final solution. Then the absorbance was measured in a UV spectrophotometer at 210 nm against methanol blank.

4.3.5 Compatibility studies

The compatibility studies of the drug with polymers are studies using FT-IR spectroscopy.

- **FT-IR Spectroscopy[76]**

FT-IR spectroscopy was carried out to check the compatibility between drug and excipients. Infrared spectroscopy was conducted using s thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm^{-1}. The sample (drug and drug-excipient mixture in 1:1 ratio) in KBr (200-400mg) was compressed in to discs by applying a pressure of 5 tons for 5 min in hydraulic press. The interaction between drug-excipients was observed from IR-spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug-excipients.

- **DSC Analysis for formulation[77]**

Thermal properties of the pure drug and the physical mixture of drug and excipients were analyzed by Different Scanning Calorimeter -60, Shimadzu limited Japan. The samples were heated in a thermetically sealed aluminium pans. Heat runs for each sample were set from 25 to 350^0C at a heating rate of 10^0C/min, using nitrogen as blanket gas.

4.4 Formulation Design

4.4.1 Calculation of dose[78]

The total dose of Divalproex sodium for once daily formulation was calculated by the following equation, using available pharmacological data.

$Dt = Dose (1+0.693xt/t_{1/2})$

Where, Dt = Total dose of drug,

Dose = Dose of immediate release part.

t = time in hr during which the sustained release is desired (18 hrs)

$t_{1/2}$ = half life of the drug (9 hrs)

Therefore,

$Dt = 125(1+0.693x18/9)$, $Dt \approx 298.25$

Therefore maintenance dose = 298.25-125 = 173.25 mg.

Hence, the formulation should release 125 mg drug within 1 hour and 173.25 mg drug in 18 hours.

A) Formulation of Immediate release layer.

Table 13: Formulation of immediate release layer (IRL)

Sl. No.	Ingredients	IF1	IF2	IF3	IF4	IF5	IF6
1	Divalproex sodium	125	125	125	125	125	125
2	Lactose	82	79.5	82	79.5	82	79.5
3	Croscarmellose sodium	10	12.5	-	-	5	6.25
4	Sodium starch glycolate	-	-	10	12.5	5	6.25
5	Microcrystalline cellulose	25	25	25	25	25	25
6	Ponceau 4R	0.02	0.02	0.02	0.02	0.02	0.02
7	Magnesium stearate	3	3	3	3	3	3
8	Talc	5	5	5	5	5	5
9	Total	250	250	250	250	250	250

B) Formulation of sustained released layer.

Table 14: Formulation of sustained release layer (SRL)

Sl. No.	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9
1	Divalproex sodium	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25
2	Lactose	52.75	45.25	37.75	52.75	45.25	37.75	52.75	45.25	37.75
3	HPMC K4M	45	52.5	60	-	-	-	22.5	26.25	30
4	HPMC K100M	-	-	-	45	52.5	60	22.5	26.25	30
5	Microcrystalline cellulose	20	20	20	20	20	20	20	20	20
6	Magnesium stearate	3	3	3	3	3	3	3	3	3
7	Talc	6	6	6	6	6	6	6	6	6
8	Total	300	300	300	300	300	300	300	300	300

Preparation of IRL

IRL of Divalproex sodium (DS) was prepared by wet granulation by using different Superdisintegrants such as SSG and Croscarmellose sodium. PVP K30 solution with containing coloring agent was used as binding solution. As DS was oily in characteristics, MCC was used as adsorbent. Manufacturing steps-

- Pass all the ingredients though sieve #80.
- Mix Divalproex sodium with MCC geometrically and then mix with lactose.
- Add Superdisintegrants and mix for 10 to 15 min in mortar and pestle.
- Make wet mass using binding agent PVP K 30 solution containing color.
- Pass the cohesive mass through sieve # 16 to get uniform granules.
- Dry the granules at 50^0C for 15 min in hot air oven.
- Lubricate the granules with lubricating agent and compressed into 250 mg each tablet weight by adjusting hardness. The formulations are shown on table no 13.

Preparation of SRL

Accurately weighed Divalproex sodium and polymer and others ingredients were taken in mortar and pestle and mixed well. The powder were mixed with sufficient quantity for PVP K30 solution until wet mass formed. The cohesive mass obtained was passed though sieve # 16 and the granules were dried in a hot air oven at 50^0C for 20 min. The dried granules again passed through sieve # 22 to break the large lumps. Then granules were mixed with talc and magnesium stearate and compressed into 300 mg each tablet by adjusting hardness. The formulations were shown on table no 14.

Preparation of bi-layered tablet

By the study of disintegration and drug release profile of IRL and SRL, best formulations of each layer were chosen and bi-layered tablet were prepared by double compression in single rotatory tableting machine.

4.5 Evaluation of Pre-formulation Parameters:

Angle of Repose:[79]

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel greely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using equation.

$\theta = \tan^{-1}\left(\frac{h}{r}\right)$

Where, θ = the angle of repose

h = height of the heap of the powder

r = radius of the heap of the powder

Table 15: ANGLE OF REPOSE

Sl.No	Angle of Repose(θ)	Type of flow
1	< 25	Excellent
2	25-30	Good
3	30-40	Passable
4	> 40	Very poor

Determination of bulk density and tapped density:[80]

A quantity of 2 g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using following formulas.

$$Db = \frac{Mass\ of\ powder}{Bulk\ volume\ of\ the\ powder}$$

$$Dt = \frac{Mass\ of\ powder}{Tapped\ volume\ of\ the\ powder}$$

Carr's index:[81]

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by

$$\text{Carr's index \%} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \text{ X } 100$$

Table 16: % COMPRESSIBILITY INDEX

Sl.No	% Compressibility index	Property
1	5-12	Free flowing
2	12-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	> 40	Extremely poor

Hausner's ratio:[82]

Hausner's ratio is a indirect index of ease of powder flow. Hausner's ratio was measured by the ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

Table 17: HAUSNER'S RATIO

Sl.No.	Hausner's ratio	Property
1.	0-1.2	Free flowing
2.	1.2-1.6	Cohesive flowing

4.6 Evaluation of prepared formulations

4.6.1 Evaluation of Divalproex sodium IRL, SRL and bi-layered tablet

The tablets prepared were evaluated for the following parameters:

- Weight variation
- Hardness
- Friability
- Drug content
- *In-vitro* Dissolution Studies
- Stability Studies

Weight Variation Test:[83]

To study weight variation, 20 tablets of each formulation were weighted using electronic balance and the test was performed according to the official method.

Table 18: IP standards of Uniformity of weight

S.N.	Avg. Wt of Tablet (mg)	% of Deviation
1	≤80 mg	10
2	> 80 mg – 250 mg	7.5
3	≥250 mg	5

Hardness:[84]

The resistance of tablets to shipping or breakage under condition of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in the terms of kg/cm^2 . 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability:[85]

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. 10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded.

Percentage friability was calculated by using the formula.

$$\% \text{ Friability} = \frac{Weight\ initial - Weight\ final}{Weight\ initial} \text{ X } 100$$

Tablet thickness:[86]

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation. Vernier caliper consists of metric and imperial scales. The main matric scale is read first then

read "hundredths of mm" of imperial scale (count the number of division until the lines concedes with the main metric scale. The imperial scale number is multiply with 0.02. Then that number obtained from imperial scale added with main metric scale to get final measurement.

***In-vitro* dissolution studies of immediate release layer:**[87]

The in-vitro dissolution studies were performed using USP-II (paddle) dissolution apparatus at 100 rpm. Phosphate buffer pH 6.8 dissolution media is maintained at 37±0.50^{0}C. A 5 ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 210 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

***In vitro* dissolution studies of sustained release layer:**[87]

The in vitro release of sustained release layer was carried out for 18 hours using USP type-II apparatus (DT-1200) at 100 rpm for the first 45 minute in 900 ml 0.1N HCL maintaining at 37 ±0.5^{0}C and then at phosphate buffer pH 6.8 in 900ml for another 18 hour. A 5 ml was withdrawn at different time intervals and replaced with an equal volume of fresh medium. The samples were suitably diluted with blank dissolution medium, filtered and analyzed on UV spectrophotometer at 210nm.

Drug Content for IRF, SRF and Bi-layered tablet:[87]

Ten tablets were weight and average weight is calculated. All tablets were crushed and powder equivalent to 100 mg drug was dissolved in pH 6.8 phosphate buffer and the volume was made up to 100 ml with pH 6.8 phosphate buffer. The solution was kept in sonicator for 1 hr. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with pH6.8 phosphate buffer. Solution was filtered and absorbance was measured

spectrophotometrically at 210 nm against pH6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

4.7 Mathematical modeling of drug release profile:[88]

The cumulative amount of Divalproex sodium release from the formulated tablets at different time intervals were fitted to Zero order kinetics, first order kinetics, higuchi model and korsmeyer-peppas model to characterize mechanism of drug release.

1. Zero-order Kinetic model – Cumulative %drug release versus Time.

2. first-order Kenetic medel – Log cumulative % drug remaining versus Time.

3. Higuchi's model – cumulative percent drug released versus square root of time.

4. Korsmeyer equation / peppa's medel- Log cumulative percent drug released versus log time.

Zero order kinetic

It describes the system in which the release rate is independent of its concentration.

$Q_t = Q_0 + K_0 t$

Where, Q_t = amount of drug dissolved in time t

Q_0 = initial amount of drug in the solution

K_0 = zero order release constant

If the zero order drug release kinetic is obeyed, a plot of Q_t versus t will give straight line with a slope of K_0 and an intercept at Q_0.

First Order Kinetic

It describes the drug release from the system in which the release rate is concentration dependent.

$\text{Log } Q_t = \log Q_0 + K_{1t}/2.303$

Where Q_t = amount of drug dissolved in time

Q_0 = initial amount of drug in the solution

K_1 = first order release constant

If the release pattern of drug follows first order kinetics, then a plot of log ($Q_0 - Q_t$) versus t will be straight line with a slope of K_1 /2.303 and an intercept at t= 0 of logQ_0.

Higuchi's Model

It describes the fraction of drug release from a matrix is proportional to square root of time.

$M_t / M\infty = K_H t^{1/2}$

Where,

M_t and $M\infty$ are cumulative amount of drug release at time t and infinite time, and

K_H = Higuchi dissolution constant reflection formulation characteeistics.

If the Higuchi model of drug release is obeyed, then a plot of $M_t /M\infty$ versus $t^{1/2}$ will be straight line with slope of K_H.

Korsmeyer-Peppas Model

The power law describes the fractional drug release is exponentially related to the release rime and adequately describes the release of drug from slabs, cylinders and spheres, as expressed in following equation.

$M_t / M\infty = K\ t^n$

$\text{Log } (M_t / M\infty) = \log K + n \log t$

Table 19: Mechanism of Drug Release as per Korsmeyer Equation/ Peppa's Model

Sl. No	'n' value	Drug release
1	0.45	Fickian release
2	0.45 < n> 0.89	Non-Fickian release
3	0.89	Case II transport
4	Higher than 0.89	Super case II transport

4.8 Stability Studies[89, 90]

The optimized formulation was subjected for two month stability study according to standard guidelines. The selected formulations were packed in aluminum foils, which were in wide mouth bottles closed tightly. They were stored at 40^0C / 75% RH for 3 months and evaluated periodically.

CHAPTER 5

RESULTS

5. RESULTS

5.1 Determination of λ_{max}

The λ_{max} of Divalproex sodium was found to be 210 nm in methanol and phosphate buffer pH 6.8.

5.2 Standard curve of Divalproex sodium.

The absorbance was measured in a UV spectrophotometer at 210 nm against methanol.

Table 20: Spectrophotometric data of Divalproex Sodium

S.no.	Conc. (µg/ml)	Absorbance			Mean ±SD
		Trial 1	Trial 2	Trial 3	
1	0	0.000	0.000	0.000	0.000±0.000
2	5	0.050	0.043	0.046	0.046±0.004
3	10	0.097	0.095	0.098	0.097±0.002
4	15	0.143	0.144	0.146	0.144±0.002
5	20	0.185	0.188	0.187	0.187±0.002
6	25	0.240	0.237	0.237	0.238±0.002

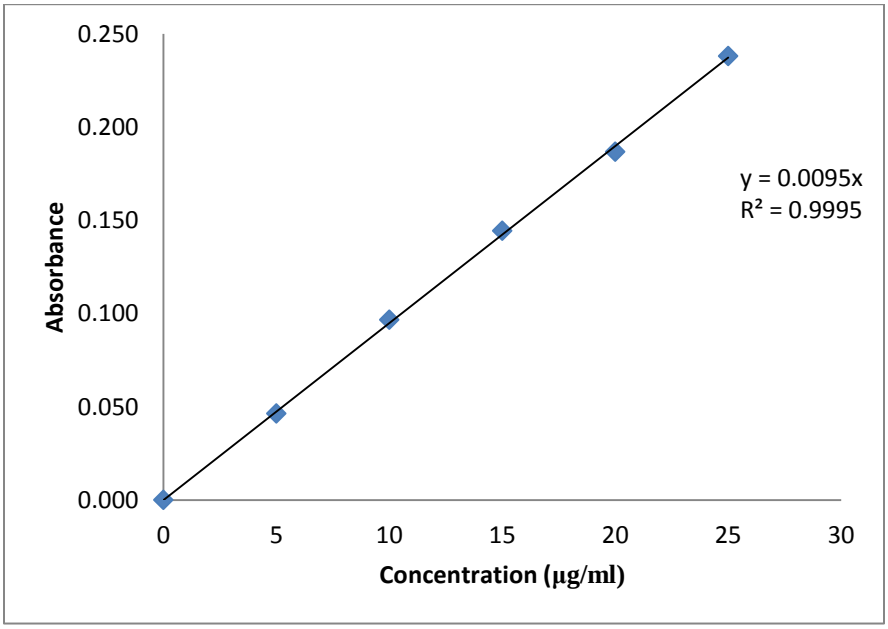


Figure 5: Standard graph of Divalproex sodium

5.3 Drug solubility studies

The solubility studies of drug were done by using various media like distilled water, methanol, chloroform and phosphate buffer pH 6.8. The data for solubility studies in those media are shown in table 5. The result shows maximum solubility in chloroform.

Table 21: Solubility of Divalproex sodium

Solvents	Solubility (mg/ml)
Distilled water	7.35
Methanol	48.45
Chloroform	55.24
Phosphate buffer pH 6.8	29.73

Result showed that Divalproex sodium is more soluble in chloroform in compare to other solvents.

5.4 Melting Point

Melting point of drug was determined by capillary method. The result is found to be **219-223^{0}C.**

5.5 FT-IR spectrum

FT-IR spectrum of pure drug Divalproex sodium and combination of drug with polymers were obtained as shown in figures 6-12. All the characteristic peaks of Divalproex sodium were present in spectrum of drug and polymer mixture, indicating compatibility between drug and polymers. The entire FT-IR spectrum and was tabulated in table 22.

FTIR figure of Drug and Drug with excipients

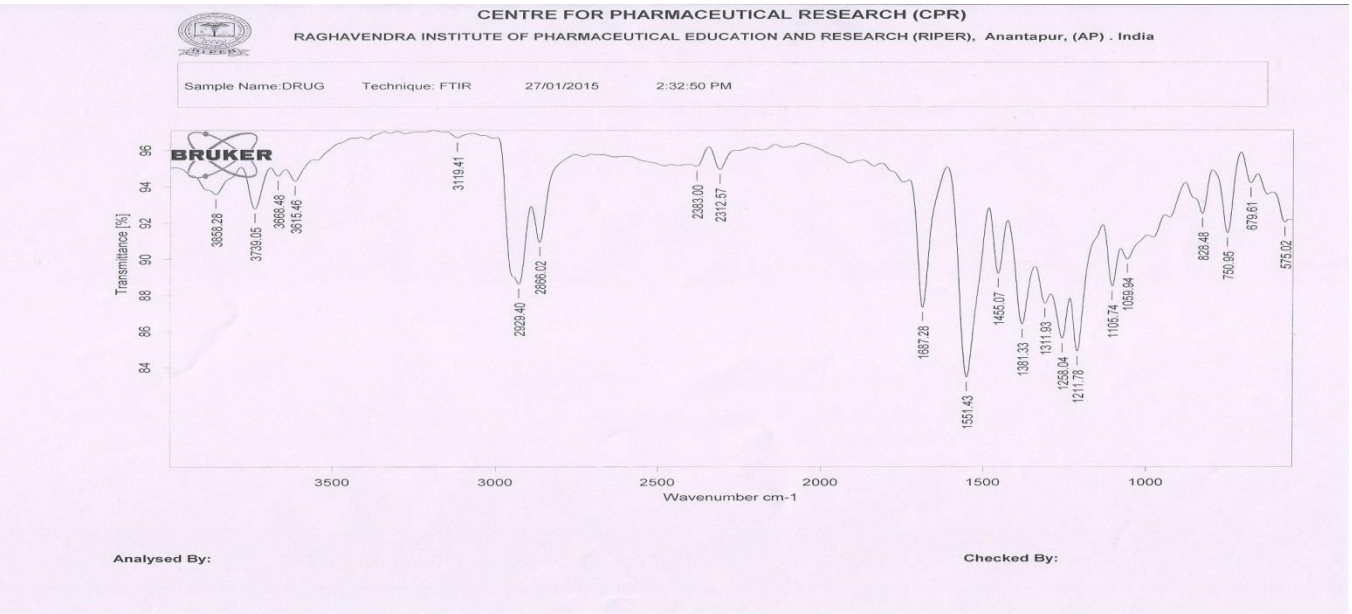


Figure 6: FTIR of Drug Divalproex sodium

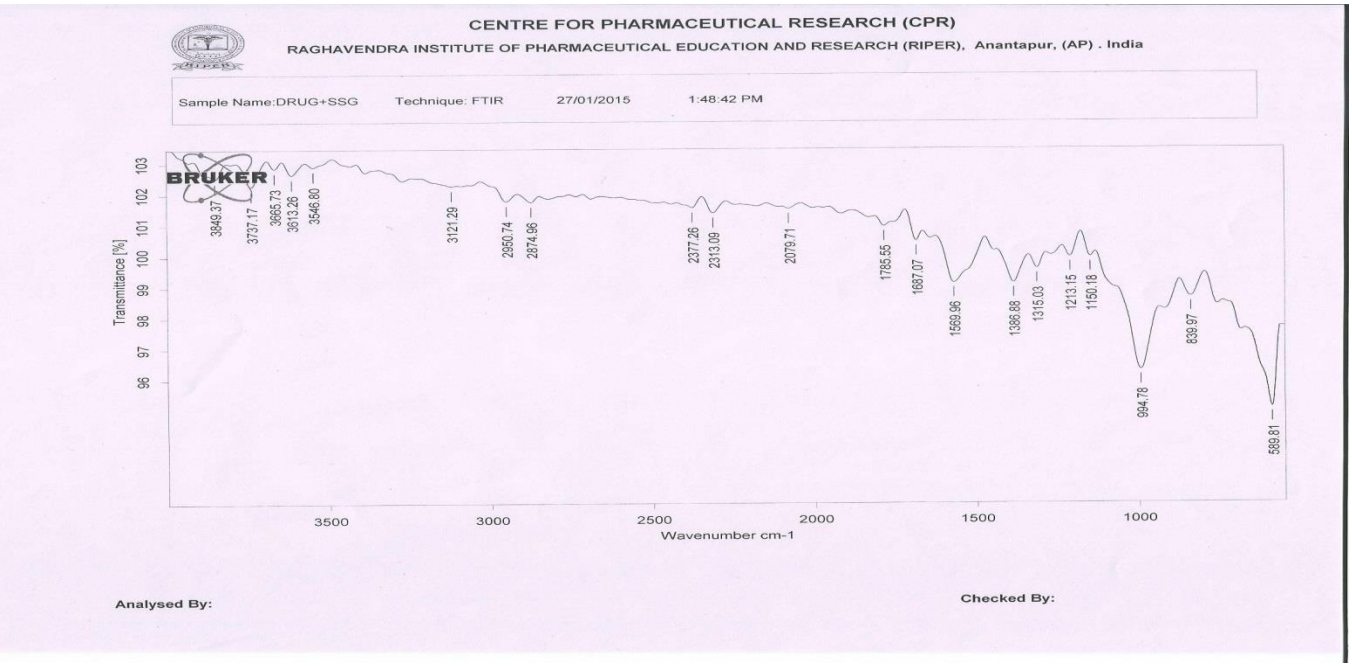


Figure 7: FTIR of Divalproex sodium + Sodium Starch Glycolate (SSG)

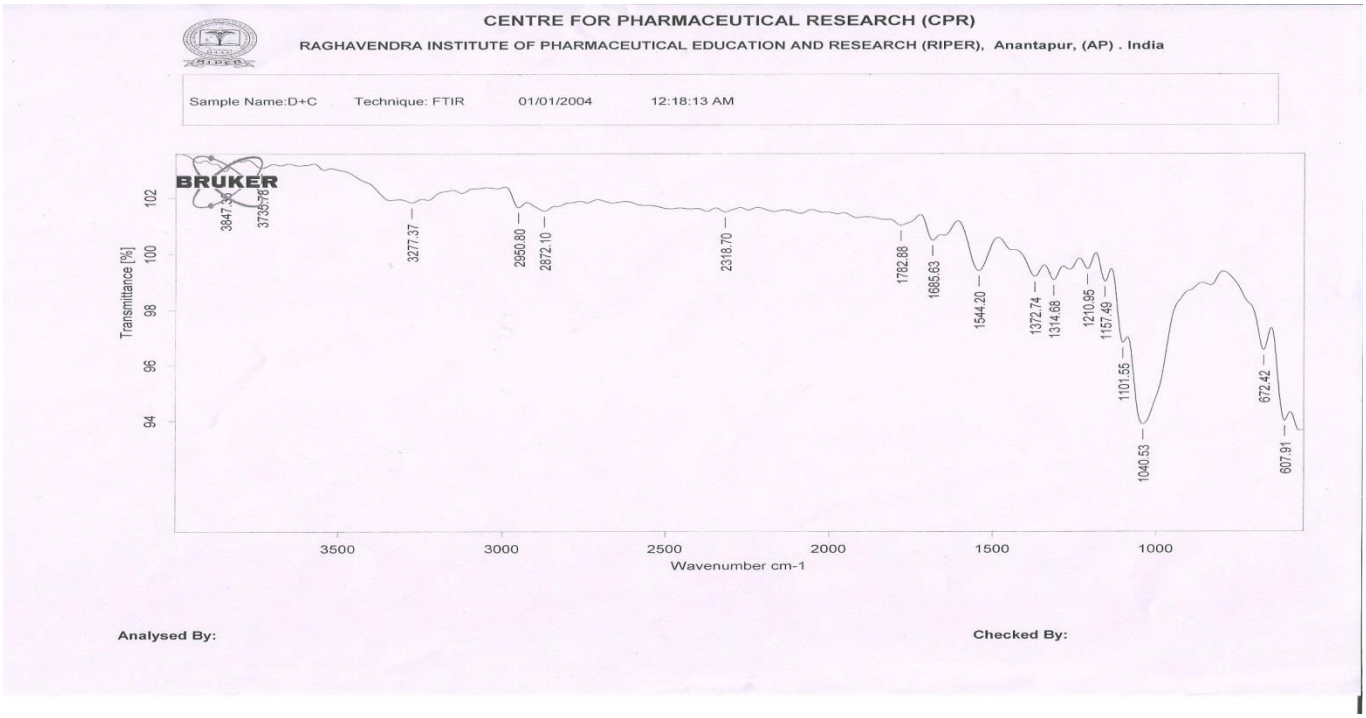


Figure 8: FTIR of Divalproex sodium + Corscarmellose sodium

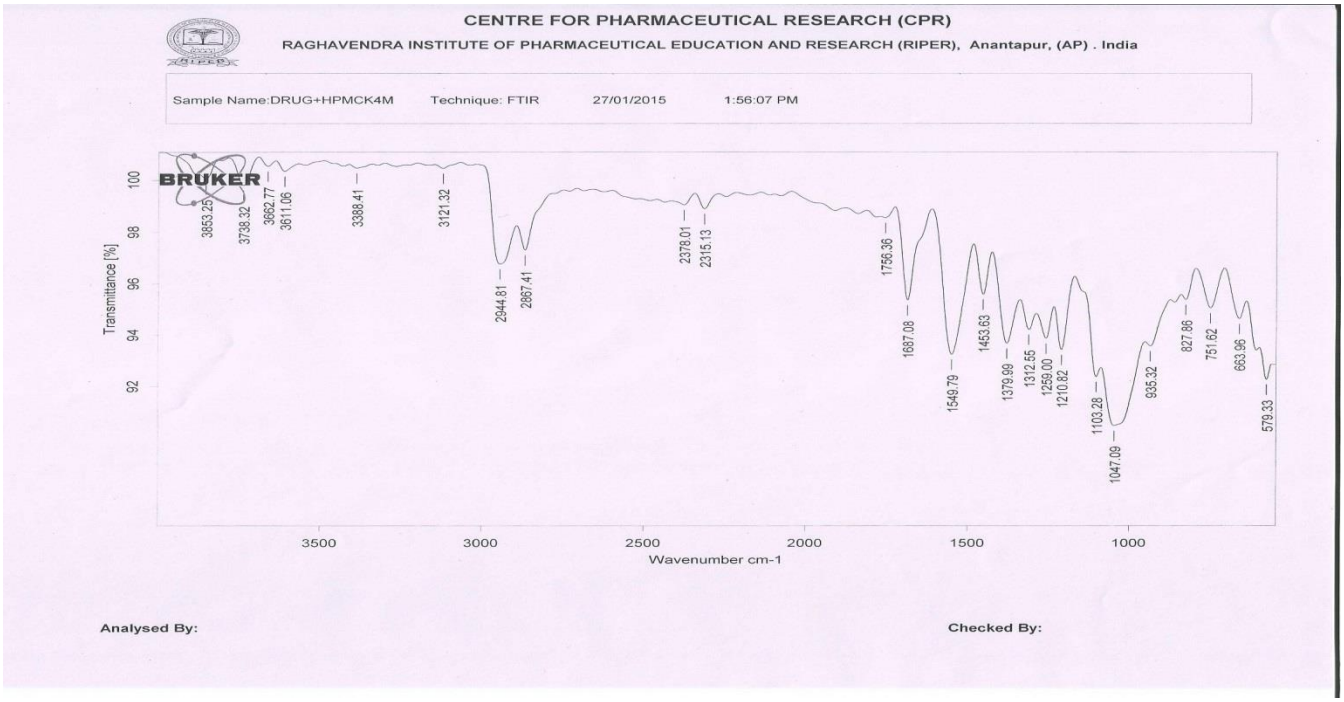


Figure 9: FTIR of Divalproex sodium + HPMC K4M

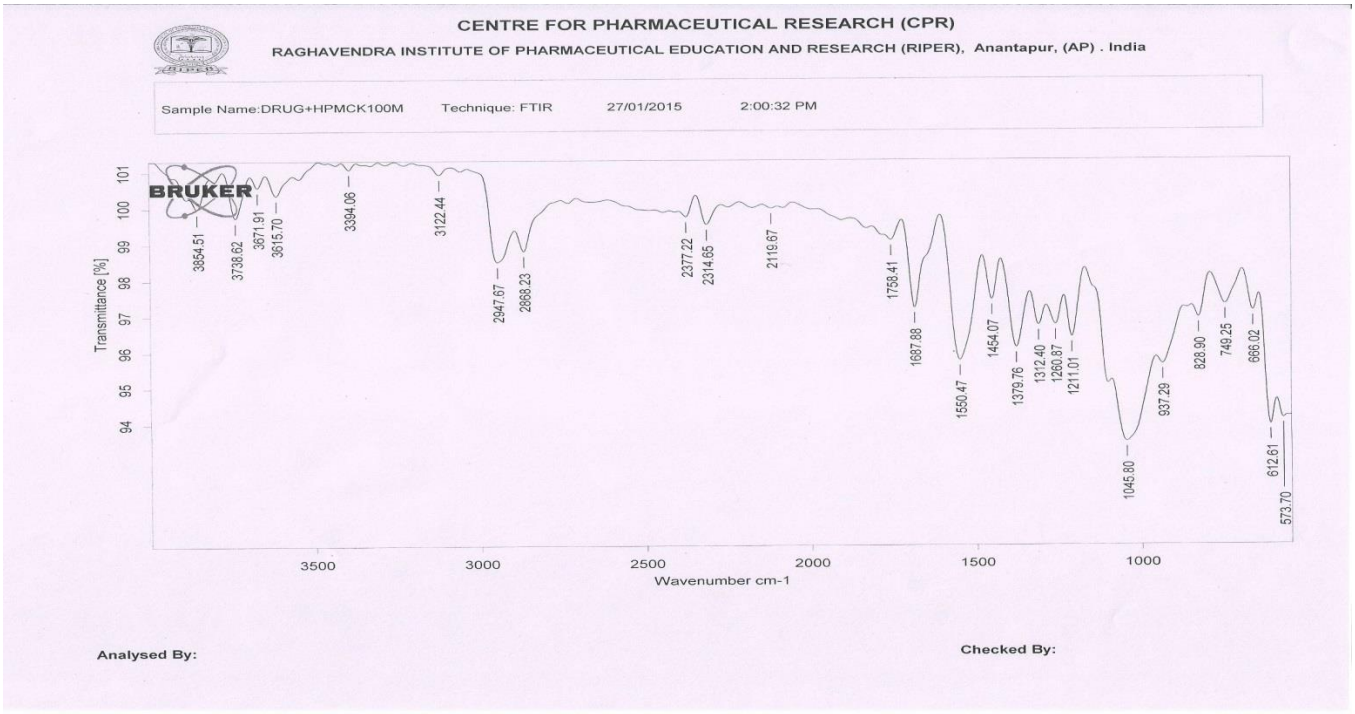


Figure 10: FTIR of Divalproex sodium + HPMC K100M

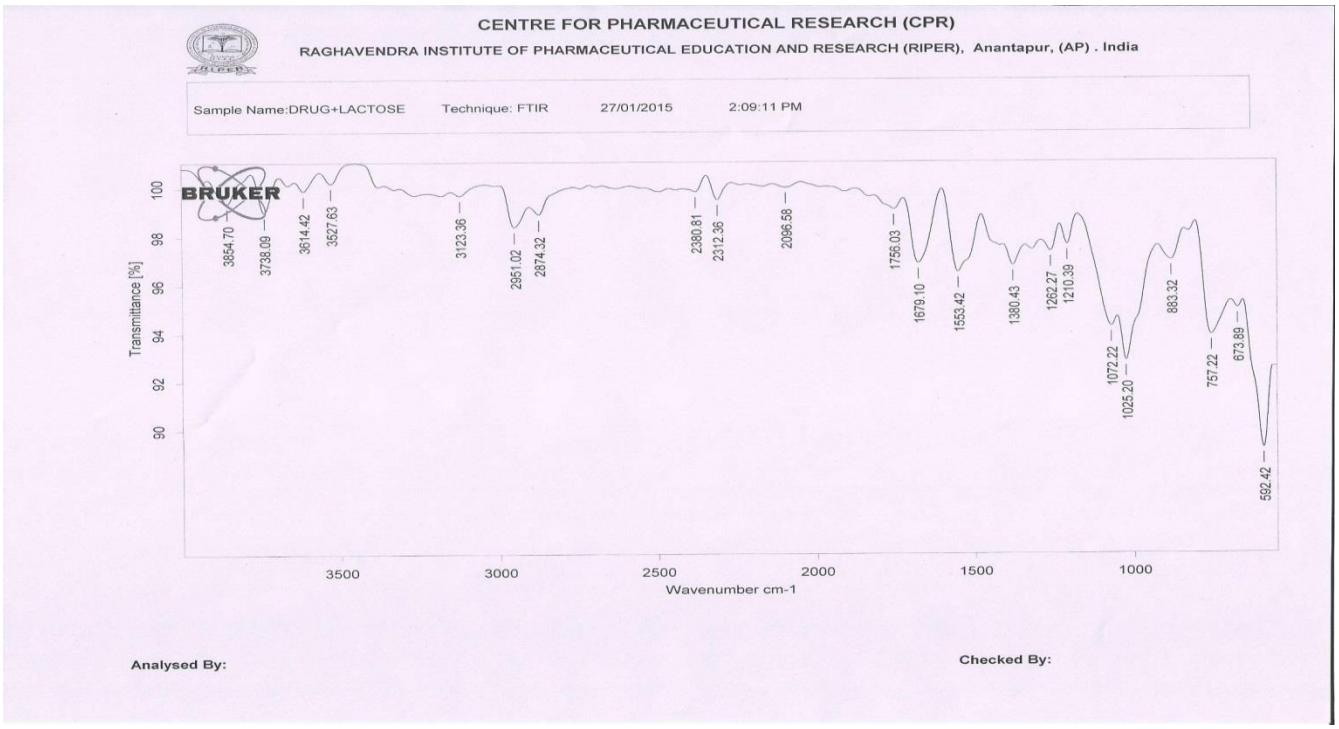


Figure 11: FTIR of Divalproex sodium + Lactose

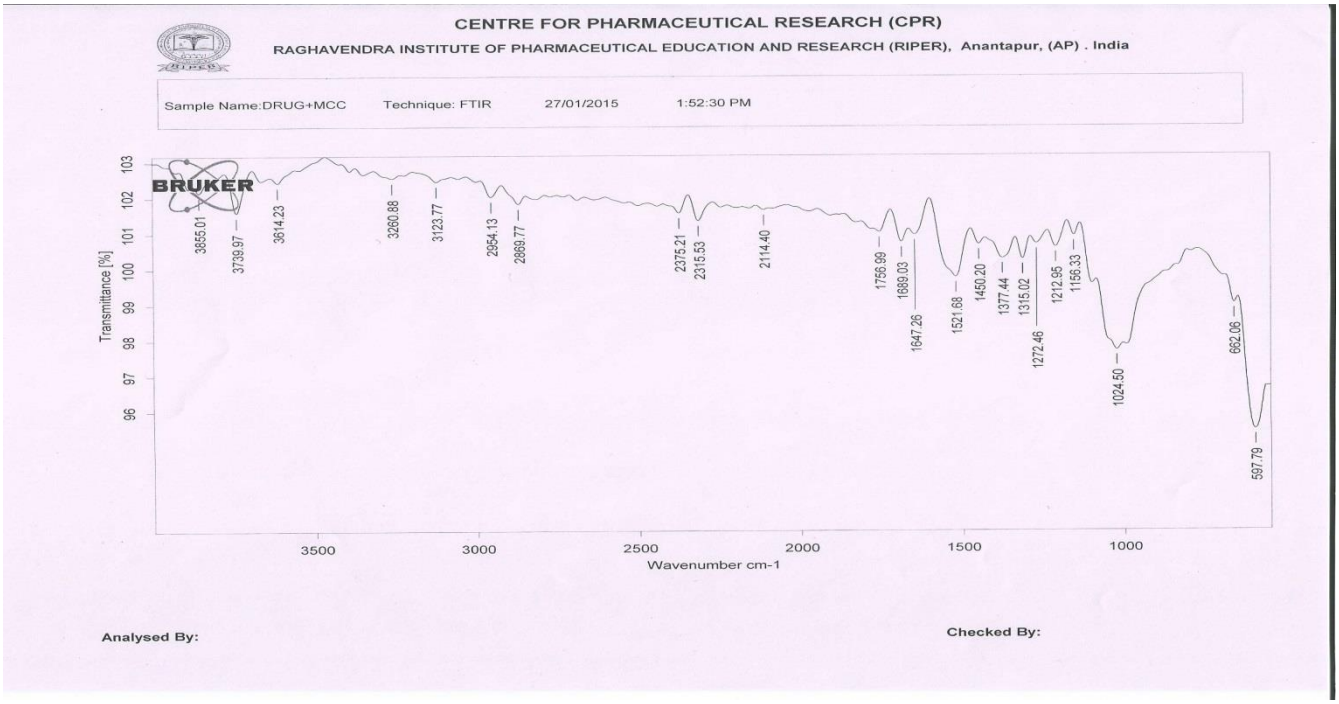


Figure 12: FTIR of Divalproex sodium + Microcrystalline Cellulose (MCC)

Table 22: Compatibility study of drug and excipients using FTIR

Functional group	**Wave number (cm^{-1})**							
	Standard peaks	**Pure drug**	**SSG**	**Croscarmellose**	**HPMC K4M**	**HPMC K100M**	**lactose**	**MCC**
Aliphatic C-H stretch	3300-2500	2919.4	2950.74	2950.80	2944.81	2947.67	2951.02	2954.13
C-H bend	1470-1450	1455	1386.88	1372.74	1453.63	1454.07	1380.43	1450.20
C-H stretch	1300-1000	1211	1213.15	1210.95	1210.28	1211.01	1210.39	1212.95
Carboxylic acid	3100-3300	3119.41	3121.29	3277.37	3121.32	3122.44	3123.36	3123.77
O-H bend	-	1059.94	994.78	1040.53	1047.09	1045.80	1025.20	1024.50

DSC Study

DSC Analysis

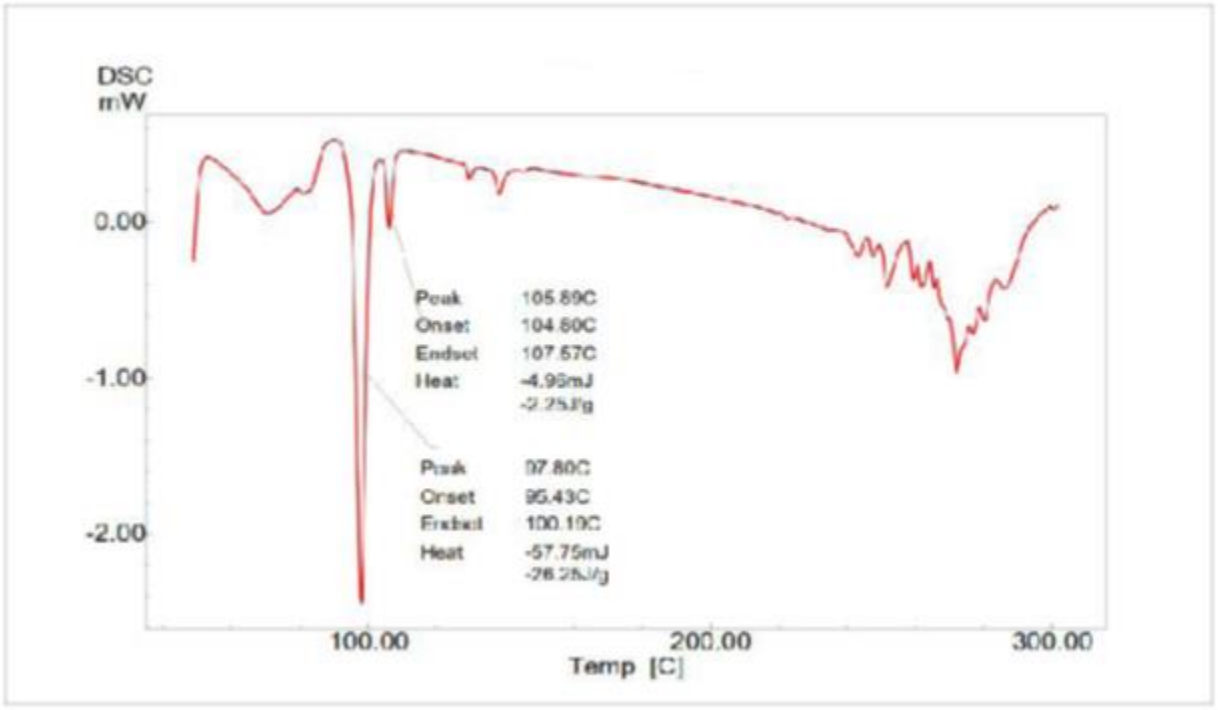


Figure 13: DSC spectrum of Divalproex sodium

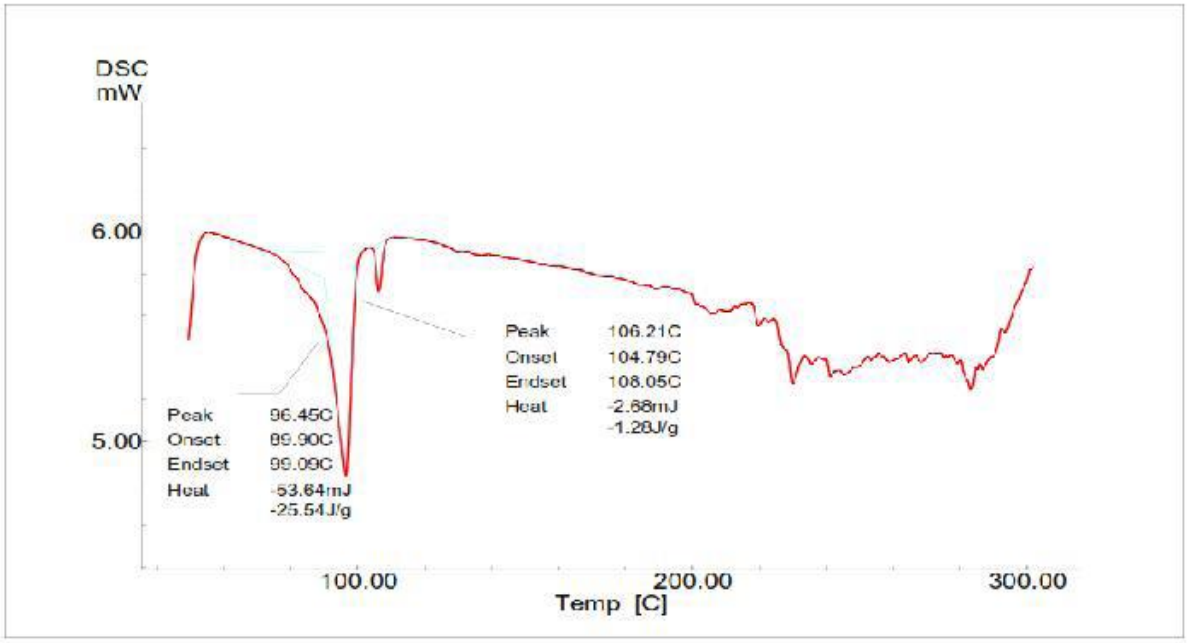


Figure 14: DSC spectrum of Formulation

5.6 EVALUATION OF PRE-COMPRESSION PARAMETERS

Table 23: Pre-compression parameters for IRL and SRL

Formulation	Bulk Density Mean ± SD	Tapped Density Mean ± SD	Car's Index Mean ± SD	Haunsers Index Mean ± SD	Angle of Repose Mean ± SD
IF1	0.557±0.002	0.637±0.005	12.610±0.217	1.145±0.030	16.596±0.356
IF2	0.556±0.005	0.655±0.004	15.084±0.226	1.174±0.020	18.360±0.275
IF3	0.523±0.004	0.626±0.003	15.773±0.109	1.164±0.022	19.421±0.173
IF4	0.585±0.003	0.684±0.003	13.899±0.177	1.163±0.013	20.147±0.156
IF5	0.612±0.010	0.682±0.007	11.767±0.206	1.133±0.009	17.913±0.039
IF6	0.666±0.004	0.755±0.006	11.148±0.157	1.142±0.025	17.101±0.077
SF1	0.592±0.005	0.694±0.003	13.779±0.206	1.154±0.009	19.604±0.279
SF2	0.591±0.008	0.699±0.002	14.494±0.328	1.169±0.017	18.480±0.063
SF3	0.605±0.004	0.681±0.003	11.223±0.186	1.133±0.009	18.201±0.088
SF4	0.623±0.005	0.703±0.002	11.531±0.127	1.132±0.010	22.548±0.280
SF5	0.596±0.004	0.710±0.004	16.144±0.249	1.200±0.028	18.331±0.077
SF6	0.591±0.004	0.727±0.002	18.716±0.397	1.256±0.029	18.168±0.104
SF7	0.615±0.003	0.728±0.004	14.825±0.673	1.174±0.028	18.467±0.091
SF8	0.512±0.001	0.623±0.002	17.564±0.436	1.243±0.024	19.347±0.072
SF9	0.620±0.002	0.693±0.001	10.754±0.181	1.124±0.017	17.396±0.021

5.7 POST-COMPRESSION EVALUATION PARAMETERS:

Table 24: Post-compression parameters for IRL and SRL

Batch code	Weight variation Mean ± SD	Hardness (kg/cm^2) Mean ± SD	Friability (%) Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD	*In vitro* disintegration time (sec) Mean ± SD
IF1	249.9±1.57	5.95±0.05	0.74±0.09	2.87±0.04	98.12±1.19	120.33±1.52
IF2	250.3±1.60	4.18±0.10	0.58±0.04	2.91±0.10	97.65±1.82	91.66±2.08
IF3	250.9±1.60	6.35±0.03	0.56±0.06	2.90±0.07	98.65±1.28	73.33±2.51
IF4	251.55±1.99	6.17±0.07	0.65±0.05	2.87±0.03	99.61±0.94	48.33±3.05
IF5	251.45±2.52	4.14±0.04	0.63±0.03	2.92±0.06	99.43±1.32	59.33±2.08
IF6	250.05±1.81	4.53±0.11	0.69±0.04	2.89±0.09	99.51±1.81	37.33±1.52
SF1	302.6±1.41	5.38±0.10	0.32±0.06	3.34±0.09	99.38±1.19	-
SF2	302.9±2.29	4.33±0.02	0.35±0.02	3.30±0.14	98.61±1.03	-
SF3	302.5±1.59	6.14±0.04	0.43±0.03	3.31±0.03	97.43±1.28	-
SF4	301.75±1.14	6.23±0.06	0.36±0.02	3.28±0.05	98.57±0.85	-
SF5	300.65±1.37	5.14±0.03	0.41±0.06	3.30±0.06	98.43±1.27	-
SF6	302.30±1.31	4.52±0.02	0.48±0.03	3.33±0.03	97.63±0.61	-
SF7	303.20±1.46	6.74±0.04	0.42±0.06	3.28±0.08	99.47±1.04	-
SF8	301.25±1.55	6.16±0.02	0.37±0.04	3.30±0.04	99.51±1.20	-
SF9	302.42±1.04	6.56±0.03	0.31±0.03	3.32±0.07	98.49±0.93	-

Table 25: Post-compression parameters for bi-layered tablet

Formulation	Weight variation Mean ± SD	Hardness Mean ± SD	Friability Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD
BTF	550.75±0.46	7.05±0.15	0.38±0.01	6.28±0.14	99.23±0.53

***In-vitro* dissolution study**

Table 26: *in vitro* dissolution study of IRL

Time in min	% CUMULATIVE DRUG RELEASE					
	IF1	IF2	IF3	IF4	IF5	IF6
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
1	17.056±0.612	21.226±0.872	20.847±0.450	26.532±1.306	30.323±1.125	36.008±1.174
3	31.805±1.075	31.908±1.280	33.738±2.620	54.965±2.391	56.561±0.778	60.653±2.255
5	53.454±2.280	56.489±2.100	56.488±1.288	68.244±0.593	64.455±2.346	68.247±1.723
10	64.837±2.481	68.251±3.001	68.250±1.176	81.525±0.896	77.735±1.791	83.424±2.060
15	71.106±1.634	78.121±1.913	74.141±1.523	89.829±1.107	81.543±0.873	92.918±1.314
20	80.408±1.038	83.445±1.088	82.685±0.582	94.829±0.788	87.246±1.865	98.624±0.722
25	86.676±1.427	92.366±1.472	90.280±1.281	97.497±0.931	92.376±1.325	98.827±1.427
30	91.047±2.031	94.842±1.632	93.135±0.852	98.075±1.265	96.743±1.731	99.404±1.162

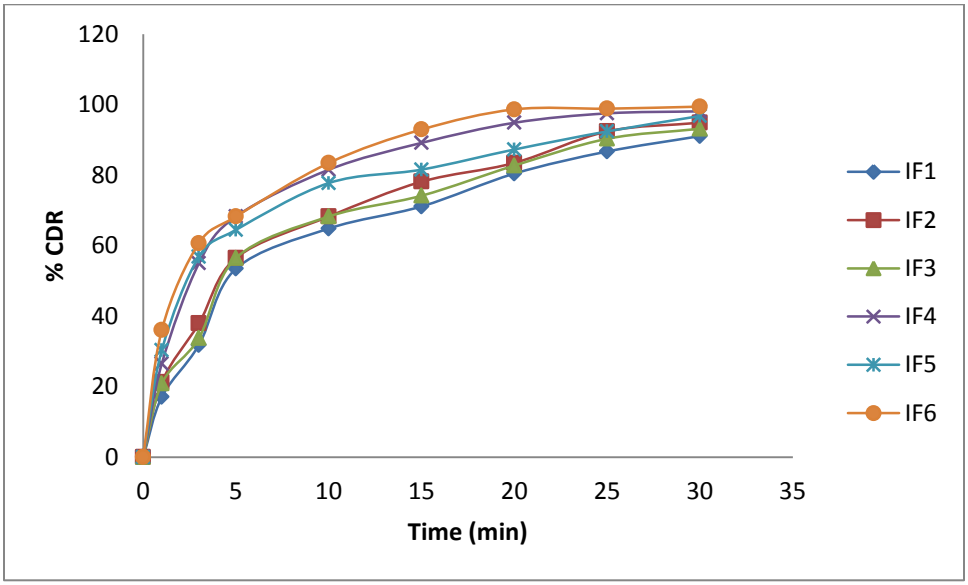


Figure 15: Release profile of immediate release layer

Table 27: *In vitro* dissolution study of SRL

Time in min	% CUMULATIVE DRUG RELEASE							
	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
60	15.408±1.222	7.905±1.234	6.017±1.508	13.469±1.222	6.741±1.281	5.558±1.591	13.006±1.994	5.391±0.882
120	25.634±1.764	19.263±1.532	18.231±1.281	25.637±0.732	18.521±1.421	12.635±0.751	21.351±1.317	17.527±1.114
240	34.323±2.715	24.502±1.083	23.091±1.547	33.235±1.164	25.279±1.003	17.697±1.151	33.589±1.503	24.917±1.426
360	42.342±0.632	31.362±1.321	29.735±0.941	38.852±1.521	33.852±1.835	25.742±1.427	45.247±0.941	36.518±0.831
480	57.151±1.196	43.141±1.974	36.936±1.251	56.674±2.061	47.993±0.539	33.733±2.378	53.869±1.510	46.331±0.891
600	62.342±0.412	48.234±0.826	43.752±1.423	62.316±1.839	50.491±0.694	39.513±1.114	59.523±1.163	52.852±0.792
720	76.620±1.642	56.263±2.227	54.964±2.137	70.315±2.001	65.327±1.779	47.031±1.480	68.215±0.906	64.017±0.710
960	98.183±0.352	82.430±1.267	66.957±1.402	87.123±0.645	86.182±0.467	54.439±2.565	88.053±0.676	77.498±0.918
1080	101.512±1.093	97.816±0.630	84.113±1.317	98.822±1.325	97.692±0.844	67.057±1.191	100.859±2.165	94.298±0.560

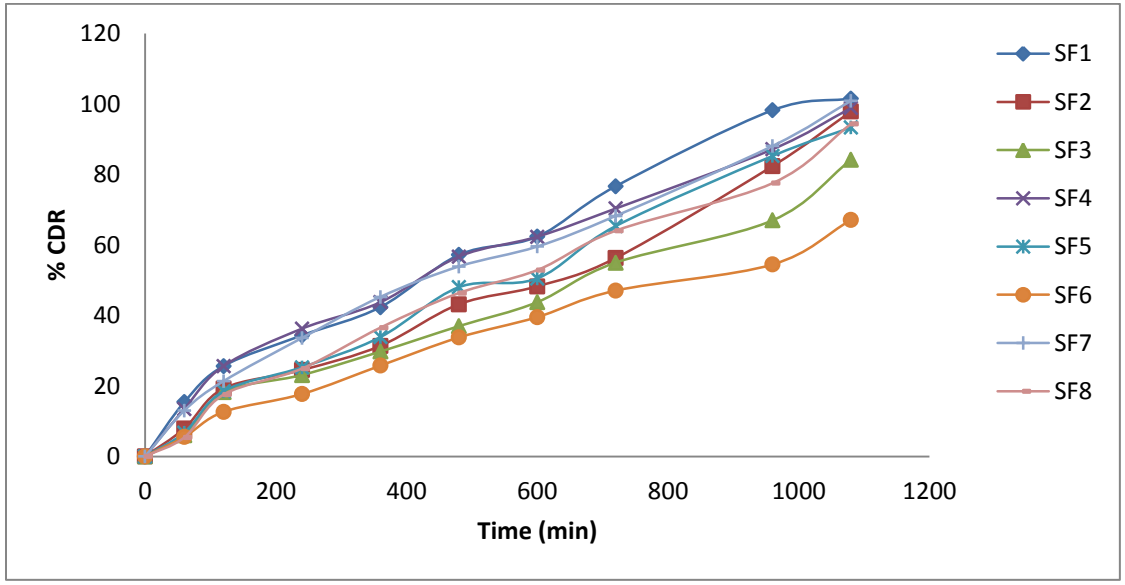


Figure 16: Release profile of sustained release layer

Table 28: Dissolution study of Bi-layered Tablet

Time in min	% CDR	
	BTF	
	IRL	SRL
0	0.000±0.000	0.000±0.000
10	83.424±1.063	-
20	98.351±1.147	-
30	99.413±0.731	-
60	-	5.384±1.032
120		17.512±0.853
240	-	23.483±1.520
360		36.164±0.638
480	-	46.054±0.825
600		52.854±0.841
720	-	64.781±0.527
960	-	76.149±0.952
1080	-	95.823±0.614

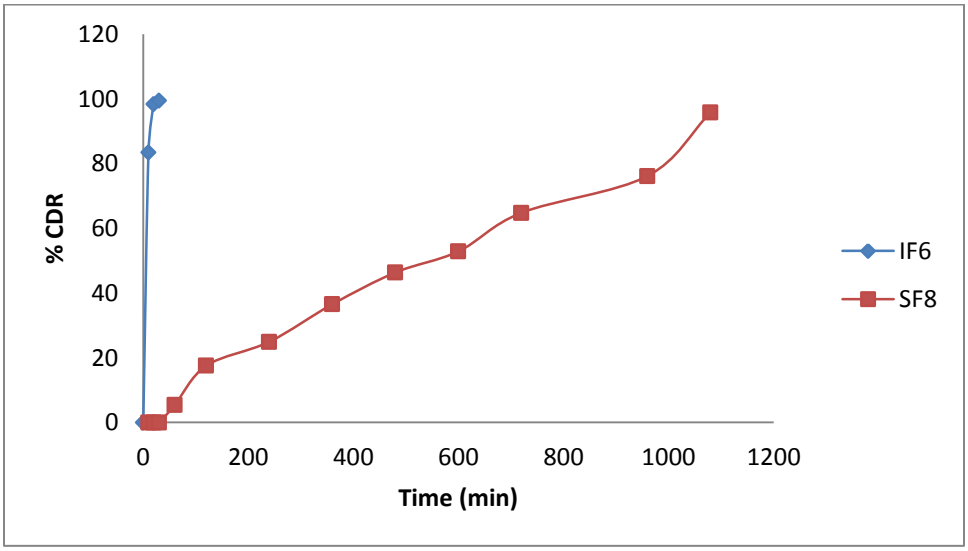


Figure 17: Release profile of Bi-layered Tablet

5.8 Kinetic Release

I) For immediate release tablets

Table 29: Kinetic release for IRL

FORMULATION CODE	KINETIC MODELS				
	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer n	Korsmeyer R^2
IF1	0.8362	0.9816	0.9689	0.8915	0.6657
IF2	0.8228	0.9844	0.9677	0.8694	0.6263
IF3	0.8231	0.9819	0.9643	0.8711	0.6336
IF4	0.7068	0.9850	0.9059	0.8424	0.5642
IF5	0.7101	0.9606	0.9055	0.804	0.5134
IF6	0.6835	0.9792	0.8945	0.8034	0.5129

Zero order Kinetics for IRL

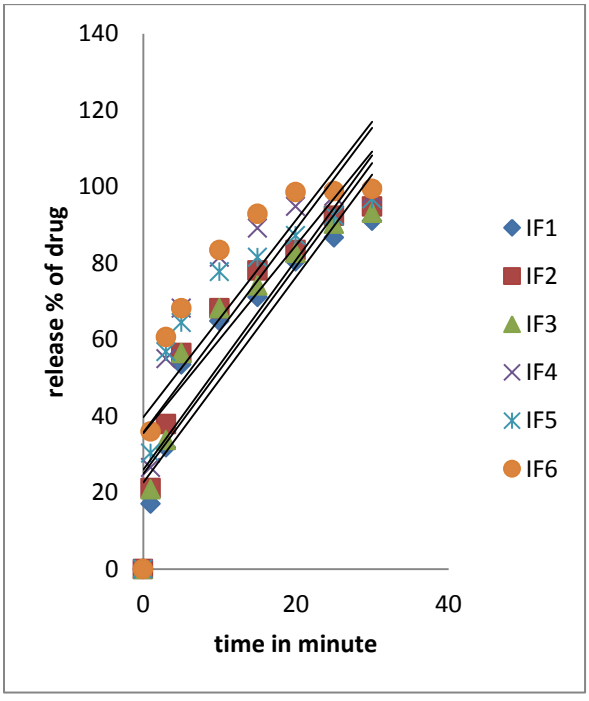


Figure 18: Zero order Kinetics for IRL

First order Kinetics for IRL

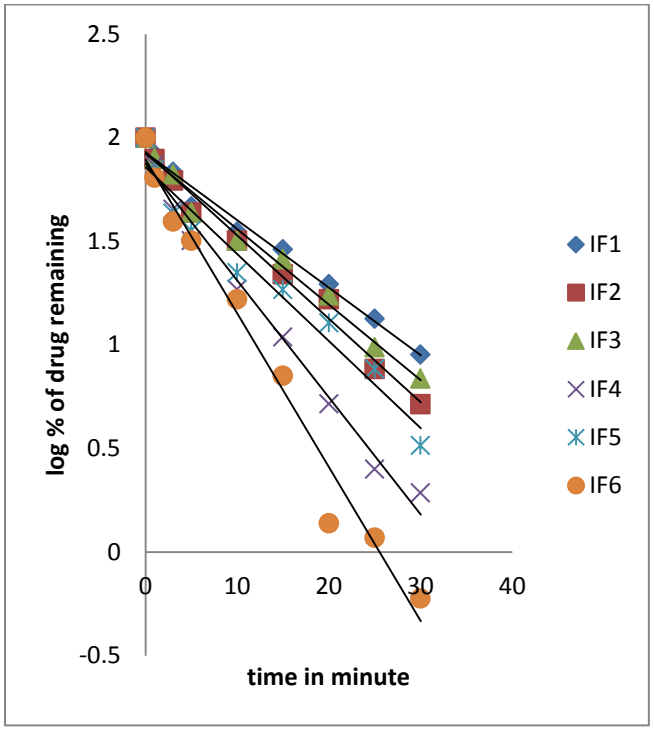


Figure 19: First order kinetics for IRL

Higuchi release kinetic for IRL

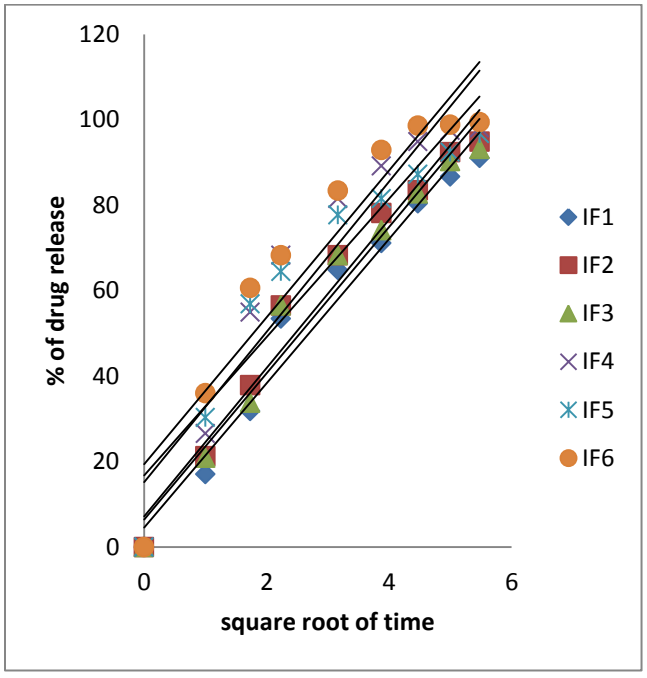


Figure 20: Higuchi release kinetics for IRL

Korsemeyer-peppas release Kinetics of IRL

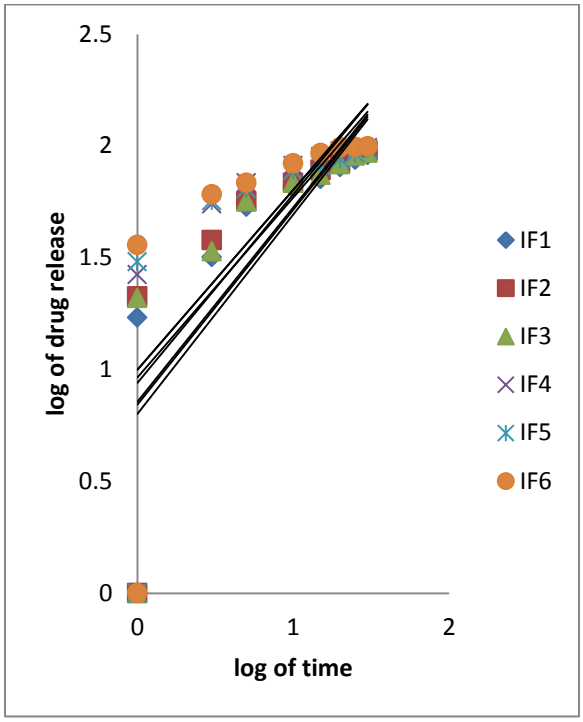


Figure 21: Korsemeyer-peppas release Kinetics for IRL

II) For sustained release layer

Table 30: Kinetic release for SRL

FORMULATION CODE	KINETIC MODELS				
	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer n	Korsmeyer R^2
SF1	0.9821	0.8296	0.9653	0.6549	0.9975
SF2	0.9838	0.7303	0.9074	0.6426	0.9794
SF3	0.9838	0.8986	0.9297	0.6296	0.9699
SF4	0.9736	0.7718	0.9794	0.6510	0.9983
SF5	0.9918	0.8975	0.9404	0.6571	0.9736
SF6	0.9847	0.8975	0.9518	0.6064	0.9692
SF7	0.9827	0.7693	0.9685	0.6528	0.9987
SF8	0.9873	0.7926	0.9427	0.6634	0.9602

Zero order kinetics for SRL

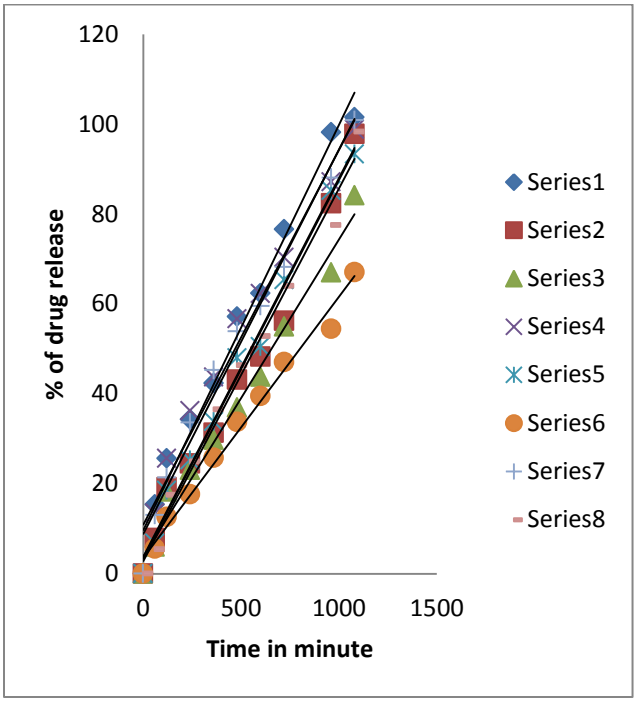


Figure 22: zero order kinetics for SRL

First order kinetics for SRL

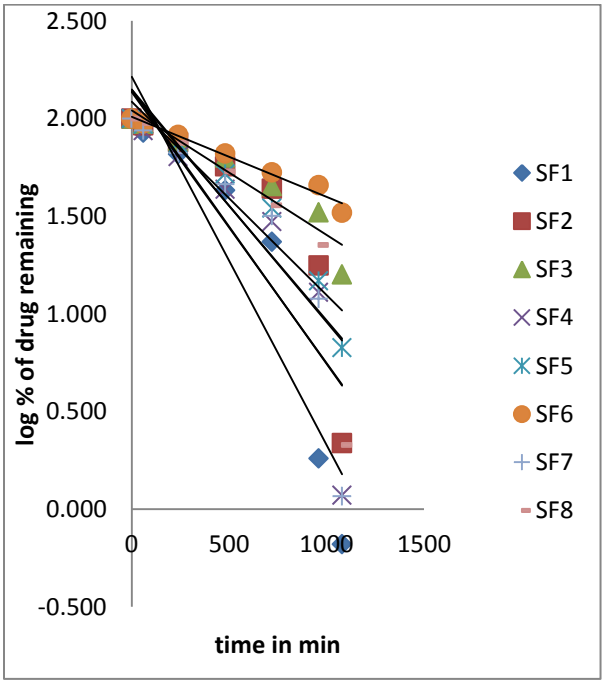


Figure 23: First order kinetics for SRL

Higuchi Model for SRL

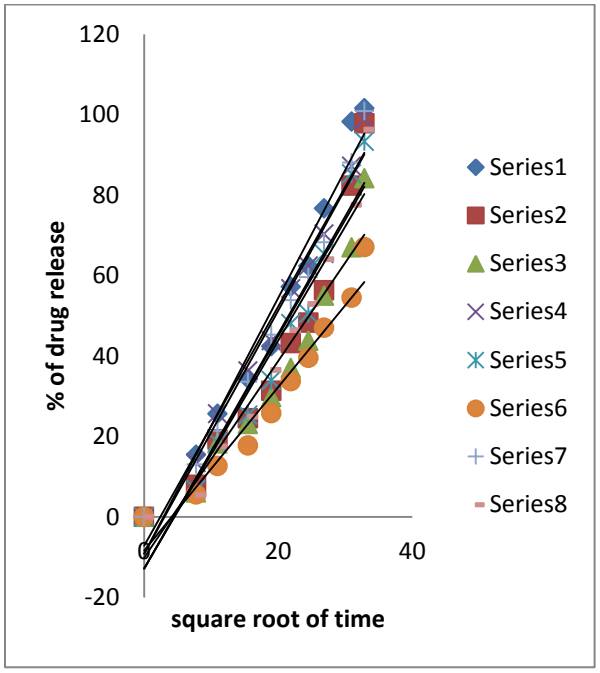


Figure 24: Higuchi Model for SRL

Korsmeyer's peppas release kinetics for SRL

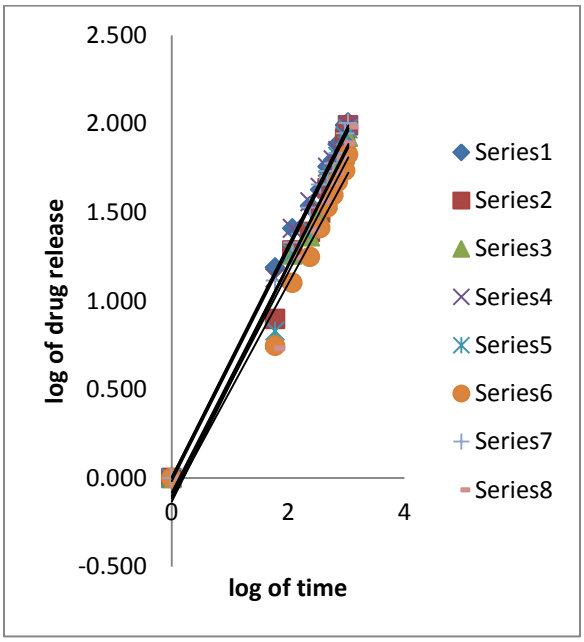


Figure 25: Korsmeyer's peppas release kinetics for SRL

5.9 Stability Studies:

Table 31: Stability data

Stability period	40^0C / 75% RH				
	Hardness Mean ± SD	% Friability Mean ± SD	% Drug content Mean ± SD	Drug release	
				IRL (30 min)	SRL (1080 min)
Initial	7.05±0.67	0.36±0.01	99.23±0.532	99.413	95.823
1 month	7.08±0.49	0.43±0.03	99.35±0.751	99.581	95.421
2 month	6.41±0.49	0.56±0.06	98.96±0.792	99.142	94.736
3 month	5.33±0.60	0.73±0.03	96.94±0.921	98.728	94.381

The bi-layered tablets were subjected to short term stability study, storing the formulation at 40^0C / 75% RH for 3 months. The data for stability studies revealed that no considerable differences in physical parameters, drug content and *in vitro* drug release rate were observed.

CHAPTER 6

DISCUSSION

6. DISCUSSION

In the present work, formulation and evaluation of bi-layered tablet of Divalproex sodium was carried out. In the project, different formulations of immediate release and sustained release layer have been prepared separately. From above formulations best formulation of each immediate and sustained release layers were selected according to the dissolution profile and bi-layered tablet were prepared.

Divalproex sodium a broad spectrum antiepileptic drug was chosen as a model drug as it is a right candidate for immediate as well as sustained release formulations. Divalproex sodium is soluble in 0.1 N NaOH, phosphate buffer pH 6.8, chloroform, methanol, ethanol (95%), and sparingly soluble in water. The result shown that the Divalproex sodium is more soluble in chloroform in compare to other solvents. The absorbance maximum of the Divalproex sodium was found to be at 210 nm when scanned in between 200-400 nm using methanol as well as phosphate buffer pH 6.8 solutions. Calibration curve of Divalproex sodium in methanol measured at 210 nm showed the slope of 0.0094 and regression coefficient of 0.9995 was shown in figure number 5.

Infra-red spectrum of drug and excipients were recorded over KBr disc method and obtained spectra were shown in the figure 6-12. All the characteristic peaks of Divalproex sodium were present in the spectrum of drug and excipient mixture, indicating compatibility between drug and excipients. The spectrum confirmed that there is no significant change in the chemical integrity of the drug. There is no change in functional group peaks (Aliphatic C-H stretch, C-H bend, C-H stretch, O-H bend and Carboxylic acid) of Divalproex sodium in all the IR-spectra and were tabulated in table 22. The DSC thermogram of Divalproex sodium exhibits a

sharp endothermic peak at 97.8^0C within the range 1.0^0C indicating the sample is in the pure form. The peak of formulation containing SSG, CS, HPMC K4M and HPMC K100M showed a wide range of melting process which has started at around 90^0C and completed at around 99^0C with a range 9^0C suggesting that drug in the formulation had remained in a unreacted form. The excipients along with drug in formulation were responsible for prolonged melting range of the formulation. It indicates hat it may not affect the stability of formulation, so it is confirmed that drug is compatible with all excipients.

Both immediate and sustained release formulations were prepared by wet granulation method using PVP K30 solution as binding agent. Six batches (IF1-IF6) of immediate release layer and nine batches (SF1-SF9) of sustained release layer were developed by altering the excipients ratio as given in table number 13 and 14 respectively. Immediate release tablet were prepared by using superdisintegrants such as sodium starch glycolate and croscarmellose sodium and Sustained release tablet were prepared by using polymer like HPMC K4M and HPMC K100M. The tablets were evaluated for weigh variation, friability, thickness, drug content and *in vitro* dissolution parameters using standard procedure as shown in tablet number 24. Best formulations for preparation of bi-layered tablet were selected depending upon the dissolution profile as all the formulation showed good content uniformity, friability, hardness and other physical parameters.

Pre-formulation studies were carried out for all the formulation. Powder properties such as angle of repose, carr's inderx, hausner's ratio, bulk density, tapped density were determined which shown on tablet number 23. Pre-formulation studies for the formulations depicted bulk density 0.512 to 0.66 gm/cm^3 which indicated packing characteristics in dies. The carr's compressibility index was found to be below 18% which suggested good compressibility of

blend. The values of hausner ratio and angle of repose were found in the range of 1.13 to 1.25 and 16.59 to 22.54^{o} respectively suggested excellent flow property of powder blend.

Though the batch size of formulations were limited to 50-80, weight variation was reasonably satisfy the IP Limits as given in table no 18 and the drug content uniformity of all formulations was found to be 97.43-99.61 which indicated uniform distribution of drug in all batches of the formulations. Further hardness and friability was also between 4-6 kg/cm^2 and less 1% respectively indicating stability of tablets against physical shocks.

In vitro drug release profile of the immediate release and sustained release formulations were given in table no 26 and 27 respectively. Among all formulations of immediate release layer, formulation IF1, IF2, IF3 and IF4 showed the least drug release 80.40, 83.44, 82.68 and 94.82 respectively in 20 min as they consist of 5% SSG, 6% SSG, 5% CD and 6% CD respectively. Formulation IF6 releases 98.62% drug in 20 min. The release profile of the formulation IF6 was believed be due to combination of SSG and CD. The result indicated that increase in the concentration of superdisintegrants and combination of superdisintegrants increases the release profile of drug. In sustained release formulation, the formulation SF1 (15% HPMC K4M) showed highest release in 16 hours compare to the formulations SF2 and SF3 (17.5 and 20% HPMC K4M) which showed the drug release of 97.81 and 84.11% in 18 hours. The formulations SF4 and SF5 containing 15% and 17.5% of HPMC K100M showed 98.82 and 97.69% drug release in 18 hours. SF8 was selected as best sustained release formulation based on dissolution profile as they showed more than 90% after 18 hours. The formulations found to contain combination of HPMC K4M and HPMC K100M in ratio 1:1 of the concentration 17.5% of total weight. The formulation SF9 showed floating behavior which consists of polymers in 20% of total weight so withdrawn the batches from the dissolution studies

The selected formulation of immediate and sustained release layer was prepared as bi-layered tablet and the post-compression parameters tabulated in 25. Hardness and friability showed 7.05±0.15 and less than 1% respectively indicating the stability against physical stokes. Thickness was found to be 5.75±1.83 mm and content of uniformity 99.23±0.53 indicate uniform distribution of drug in both layer. In vitro drug release showed in table no 28. The release pattern of the drug from bi-layered tablet showed same as the individual layer tablets of immediate and sustained release.

The release kinetics of immediate release layer formulations (IF1-IF6) was found to following clearly first order kinetics as the values for 'r' is (0.985 to 0.960) and values of 'n' is more than 0.89 shown that Super case II transport. The release kinetics of sustained release layer (SF1-SF8) was found to following zero order kinetics as the value for 'r' is (0.9918 to 0.9736) found to be high in comparison to first order (0.8986 to 0.7303) and Higuchi's square root of time (0.9794 to 0.9074). 'n' values in between 0.6634 to 0.6064 shown non-fickian release.

Stability studies at 40^0C / 75% RH for 3 month for bi-layered tablet tabulated in table no 32 showed that there are no significant loss in drug content, hardness and also no any changes in physical appearance within 2 month of the stability period. But there was slightly change in the hardness and drug content of uniformity in 3 month period stability data which indicates that special care during the storage condition. In *in vitro* drug release pattern no significant change than the initial period.

CHAPTER 7

Conclusion

7. CONCLUSION

In the present work bi-layered tablet of Divalproex sodium were prepared by wet granulation method, using superdisintegrants such as sodium starch glycolate and croscarmellose for immediate release layer and polymer like HPMC K4M and HPMC K100M for sustained release layer.

Best formulations of each layer were selected for bi-layered tablet and bi-layered tablet were prepared. Bi-layered tablet of Divalproex sodium were subjected to hardness, weight variation, friability, drug content uniformity, *in vitro* drug release and drug polymer interaction.

The above studies lids to following conclusions:

- FTIR and DSC studies indicated that the drug is compatible with all the excipients.
- Both immediate and sustained release layer were prepared by wet granulation method and punched separately. The prepared tablets of both layers were evaluated for post compression parameters.
- According to the *in vitro* dissolution profile date one formulation of each layer were selected for bi-layered tablet. IF6 from immediate release formulations as they showed 98.62 % drug release within 20 minute. SF8 from sustained release formulation as they showed 94.29 % drug release within 18 hours.
- The bilayer tablets were prepared using the selected immediate and sustained release layer. The prepared tablets were found to be good and free from chipping and capping.
- The hardness of the prepared tablets was found to be in the range of 5.85 to 7.05 kg /cm^2
- The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared.

- The friability of the prepared tablet was found to be less than 1%.
- The percentage drug content was uniform in all the formulations of prepared bi-layered tablets.
- *In vitro* drug release pattern of the bi-layered tablets were same as individual layer tablets.
- The stability study showed that no significant changes in tablets after 3 months study.

Based on the observations, it can be concluded that the formulated bi-layered tablets of Divalproex sodium using superdisintegrants, release retardant polymers and different excipients was capable of exhibiting all the properties of bi-layered tablet. They are thus reducing the dose intake, minimize dose related adverse effect, cost and ultimately improve the patient compliance and drug efficiency.

CHAPTER 8

SUMMARY

8. SUMMARY

The present work is a formulation and evaluation of bi-layer tablet of Divalproex sodium, which is used in treatment of epilepsy, bipolar disorders and used in prophylaxis of migraine, was carried out.

The formulation known as bi-layered tablet was developed with the aim to deliver the Divalproex sodium as immediate release and extent the drug release for 18 hours for the better and extended clinical effect. Compatibility studies by FTIR indicate that no significant interactions between excipients. Both layer were prepared by wet granulation and punched separately. Six formulations (IF1-IF6) of immediate release tablets were prepared by using sodium starch glycolate and croscarmellose sodium. Nine formulations (SF1-SF9) of sustained release were prepared by using HPMC K4M and HPMC K100M in different ration and combination. All formulations were evaluated for pre-compression and post-compression parameters. Bi-layered tablets were prepared by using selected best formulations of each layer. IF6 from immediate release layer as they showed 98.62 % drug release within 20 minutes. SF8 from sustained release layer as they showed 94.29 % drug release at 18 hours and also the release pattern was within the limit of sustained release tablet. Prepared bi-layered tablet were evaluated for post-compression paramaters. Drug excipient interaction was determined by FTIR. Short term stability studies of formulated bi-layered tablet were carried out at 40^0C / 75% RH for 3 months. The release kinetics of immediate release layer formulations (IF1-IF6) was found to following clearly first order kinetics as the values for ‘r’ is (0.985 to 0.960) and values of ‘n’ is more than 0.89 shown that Super case II transport. The release kinetics of sustained release layer (SF1-SF8) was found to following zero order kinetics as the value for ‘r’ is (0.9918 to 0.9736) found to be high in comparison to first order (0.8986 to 0.7303) and Higuchi’s square root of

time (0.9794 to 0.9074). ‘n’ values in between 0.6634 to 0.6064 shown non-fickian release and drug. Stability studies at 40 ^{0}C / 75 % RH for 3 months for bi-layered tablet batches indicated that there are no significant loss in drug content, release profile and physical appearance. In summary, the release profiles bi-layered tablet formulations were quite promising for once a day formulation.

CHAPTER 9

BIBLIOGRAPHY

9. BIBLIOGRAPHY

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