DESIGN, DEVELOPMENT AND *IN VITRO* EVALUATION OF CHRONO-MODULATED DRUG DELIVERY SYSTEM OF ASPIRIN AND SIMVASTATIN

A Dissertation submitted to

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY
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In partial fulfillment of the requirements for the award of the degree of

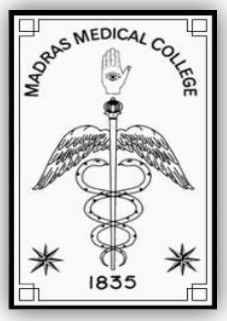
MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by
Reg. No. 261211254

Under the Guidance of

Prof. K. Elango, M.Pharm., (Ph.D.)

Professor and Head
Department of Pharmaceutics



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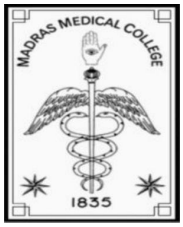

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DATE:

This is to certify that the Dissertation entitled "**DESIGN DEVELOPMENT AND *IN VITRO* EVALUATION OF CHRONOMODULATED DRUG DELIVERY SYSTEM OF ASPIRIN AND SIMVASTATIN** submitted by the candidate with **Reg. No. 261211254** for The Tamil Nadu Dr. M.G.R. Medical University examinations is evaluated.

Evaluated.

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CERTIFICATE

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Place: Chennai-03.

Date: (Dr. A.Jerad Suresh)

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Place: Chennai-03.

Date: (Prof. K.Elango)

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"Gratitude makes sense of our past, brings peace for today and creates a vision for tomorrow"

I consider this as an opportunity to express my gratitude to all the dignitaries who have been involved directly or indirectly with the successful completion of this dissertation. The satisfaction that accompanies the successful completion of any task would be incomplete without mention of the people who made it possible with constant guidance, support and encouragement that crows all effort with success.

Many Thanks to **ALMIGHTY**, for it, He who began this work in me and carried it to completion. It is He who has blesses me with the people whose names I feel privileged to mention here.

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Dedicated to My
Family and My Profession
℞

LIST OF ABBREVIATIONS USED

ACE	Angiotensin-converting enzyme
API	Active Pharmaceutical ingredient
AUC	Area under the curve
BP	British Pharmacopoeia
C	Celsius
CAD	Coronary artery disease
CHD	Coronary Heart disease
Cm	Centimetre
CMC	Carboxy methyl cellulose
CNS	Central Nervous system
COX	Cyclo oxygenase
CrCl	Creatinine clearance
CRP	C-reactive protein
CVD	Cardio vascular disease
DDS	Drug delivery system
DR	Delayed release
et al	and others
Fig.	Figure
FTIR	Fourier Transform Infra-Red

g	gram
GIT	Gastro-intestinal tract
GMP	Good Manufacturing Practices
HCl	Hydrochloric acid
HDL	High density lipoprotein
HMG-CoA	hydroxymethylglutaryl CoA
HPMC	Hydroxy propyl methyl cellulose
ICH	International Conference on Harmonization
IR	Immediate release
JP	Japanese Pharmacopoeia
KBr	Potassium bromide
Kg	kilogram
LD	Lethal dose
LDL	Low density lipoprotein
LFT	Liver function test
LOD	Loss on drying
M	Molar
MCC	Micro crystalline cellulose
mg	milligram
Min	Minute
ml	millilitre
NaOH	Sodium hydroxide

NC	No Change
NSAID	Non-steroidal anti-inflammatory drug
pH	Negative logarithm of hydrogen ion concentration
Ph Eur	European Pharmacopoeia
ppm	parts per million
Psi	pound per square inch
RH	Relative Humidity
rpm	revolutions per minute
S.D	Standard deviation
SiO_2	Silicon dioxide
SS	Steady state
SSG	Sodium starch glycolate
USP	United States Pharmacopoeia
UV	Ultra Violet
W	weight
µg	microgram

Contents

Introduction

1. INTRODUCTION

Oral solid dosage forms[1]

From various current methods for treating illness and diseases, chemotherapy (treatment with drugs) is the most frequently used technique. It has the broad range of applications over the greatest variety of disease states and is frequently the preferred treatment method. For many decades, treatment of acute disease or chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectable as drug carriers.

However, if it is a viable option, oral drug delivery will be chosen in all but the most exceptional circumstances. Moreover, if the oral route is not immediately viable, pharmaceutical companies will often invest resources in making it viable, rather than plumping for an alternative delivery system. Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms and is the most convenient and preferred route for systemic effects due to its ease of dosing administration, pain avoidance, accurate dosage, patient compliance and flexibility in formulation

Conventional dosage form are accused of repetitive dosing and unpredictable absorption window that cause wide range of fluctuation in drug concentration in the blood stream and tissues with subsequent undesirable toxicity and poor therapeutic efficiency. This dynamic such as repetitive dosing and erratic absorption led to the concept of controlled drug delivery systems.

Formulation of layers from different polymers allows manipulation over more than one rate controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependant polymers.

The aim in designing sustained or controlled delivery systems is to decrease the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or provide uniform drug delivery. The main objective of

sustained release drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance. But often this controls drug delivery system fails to achieve the stated advantages due to lack of releasing the initial bolus dose, dose dumping and failure to achieve site specific drug delivery.

Immediate release drug delivery system is intended to disintegrate rapidly, and exhibit instant drug release. It is associated with fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increase incidence of side effects. Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract. On the basis of these considerations, I have proposed a bilayer tablet.

Tablets[2]

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the 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. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet. All medicaments are available in the Tablet form except where it is difficult to formulate or administer.

Advantages of Tablet dosage forms

- 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.
- Cost is lowest of all oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.

- Easy to swallowing with least tendency for hang-up.
- Sustained release product is possible by enteric coating.
- Objectionable odour and bitter taste can be masked by coating technique.
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of Tablet dosage forms

- Difficult to swallow in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.

General properties of Tablet dosage forms

- A tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time
- The tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- Must have a chemical stability over time so as not to follow alteration of the medicinal agents.

Different types of Tablets

(A) Tablets ingested orally:

1. Compressed tablet
2. Multiple compressed tablet
3. Repeat action tablet
4. Delayed release tablet
5. Sugar coated tablet
6. Film coated tablet
7. Chewable tablet

(B) Tablets used in oral cavity:

1. Buccal tablet
2. Sublingual tablet
3. Troches or lozenges
4. Dental cone

(c) Tablets administered by other route:

1. Implantation tablet
2. Vaginal tablet

(D) Tablets used to prepare solution:

1. Effervescent tablet
2. Dispensing tablet
3. Hypodermic tablet
4. Tablet triturates

Layer Tablets[3]

Layer tablets are composed of two or three layers of granulation compressed together. As the edges of each layer are exposed, they have the appearance of a sandwich. This dosage form has the advantage of separating two incompatible substances with an inert barrier between them. It makes possible sustained release preparations with the immediate-release quantity in one layer and the slow release portion in the second. A third layer with an intermediate release might be added.

Multi-layer tablet dosage forms are designed for variety of reasons which are as follows:

- To control the delivery rate of either single or two different active pharmaceutical ingredient(s)
- To separate incompatible active pharmaceutical ingredients from each other, to control the release of active pharmaceutical ingredient from one layer by utilizing the functional property of the other layer (such as, different active pharmaceutical ingredients, to prolong the drug product life cycle and osmotic property).
- To modify the total surface area available for active pharmaceutical ingredients layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release
- To administer fixed dose combinations
- To fabricate novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems and floating tablets for gastro-retentive drug delivery

The goal to designing bilayer tablets

- To Control the delivery rate of either single or two different API'S.
- To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).
- For the administration of fixed dose combinations of drugs, Prolong the drug product life cycle, buccal/mucoadhesive delivery systems, manufacture novel drug delivery

systems such as chewing device and floating tablets for gastro-retentive drug delivery systems.

- To adapt the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for controlled release.

Quality and GMP Requirements[4]

To produce a quality bilayer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
- Providing sufficient tablet hardness
- Preventing cross-contamination between the two layers
- Producing a clear visual separation between the two layers
- Producing high yield
- Accurate and individual weight control of the two layers.

Ideal characteristics of bilayer tablets

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

Challenges in bilayer manufacturing[5]

Conceptually, bilayer 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 bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

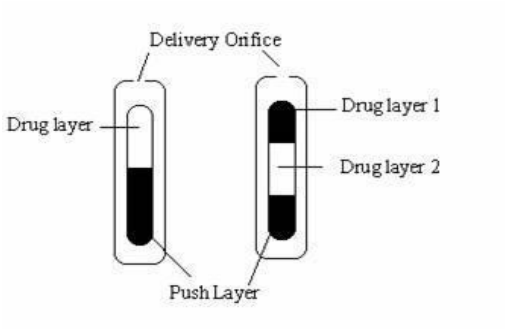
Production yields: To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets.

Cost: Bilayer tableting is more expensive than single-layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per sec and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

Various techniques for bilayer tablet[6]

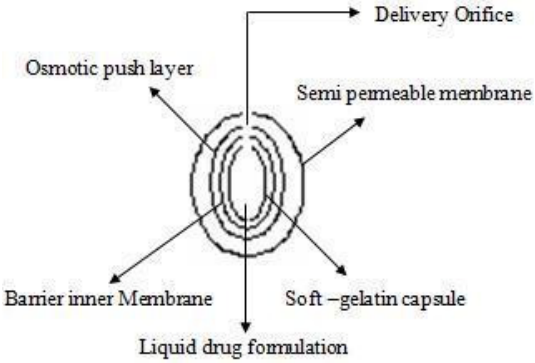
OROS push pull technology:

This system consist of mainly two or three layers among which one or more layers are essential of the drug and other layers are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.



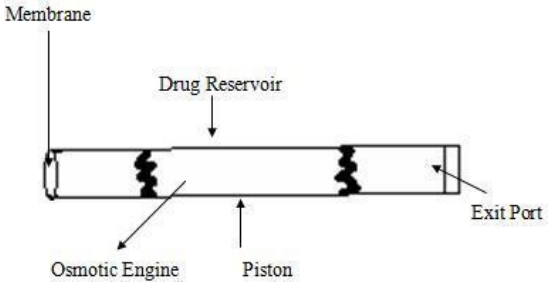
L-OROS Technology

This system used for the solubility issue. Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then osmotic push layer and then a semi permeable membrane, drilled with an exit orifice.



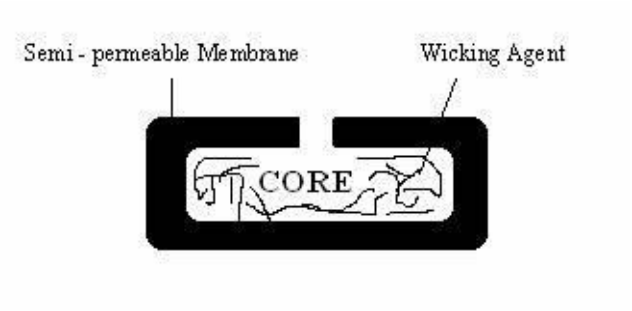
DUROS TECHNOLOGY:

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or year.



EN SO TROL technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.



DUREDAS Technology

It is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tabletting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

Types of bilayer tablet press

1. Single sided tablet press
2. Double sided tablet press
3. Bilayer tablet press with displacement monitoring

1. Single sided press

The simplest 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.

2. 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 or 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.

3. Bilayer tablet press with displacement

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 precompression force.

Immediate release

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption.[7]

When it comes to immediate-release tablet formulations, the choice of disintegrant can have a significant effect on the rate and extent of drug dissolution. Once a tablet disintegrates, the characteristics of the API, either alone or assisted by other formulation ingredients, determine the dissolution rate and extent of the API. Thus, the choice of superdisintegrant is important, especially with poorly soluble APIs.

It is important to consider the impact of the superdisintegrant with respect to the performance of the final dosage form. As drug dissolution is essential for absorption by the body, formulators no longer select disintegrants based on the lowest disintegration time because it is important to also consider the effect of the superdsintegrant on dissolution. Additionally, the ionic nature of both the API and the superdisintegrants must also be considered. Anionic superdisintegrants, such as croscarmellose sodium and sodium starch

glycolate, can interact with cationic APIs and retard dissolution. Thus, nonionic superdistegrants are preferred when working with cationic APIs. Formulators also consider the impact of the superdisintegrant on physical tablet characteristics, such as tablet breaking force and friability. In today's high-speed tablet presses, superdisintegrants that provide tablets with high breaking force and low friability, while maintaining fast disintegration, are particularly important.[8]

Modified Release[9]

Modified Release (MR) formulations have a modification in the release mechanism. Modified release dosage forms are developed by altering drug absorption or the site of drug release in order to achieve predetermined clinical objectives.

Modified drug release from dosage forms is complemented by the allied processes of drug design, of dosage administration, and of membrane transport and absorption of drug to the biological site of action. Modified-release drugs have complex formulations that can offer an advantage over standard medication for some patients.

Types of Modified Release Drug System

1. Extended release dosage forms
2. Sustained release
3. Controlled release
4. Delayed release dosage forms
5. Targeted release dosage forms
6. Repeat action dosage forms
7. Prolonged action dosage forms

Delayed Release

Delayed Release preparations are pharmaceutical preparation that releases the drugs at a time other than promptly after administration. Typically, Delayed-release tablets are intended to resist gastric fluid but disintegrate in intestinal fluid.

This is achieved by using coating substances such as cellacefate (cellulose acetate phthalate) and anionic copolymers of methacrylic acid and its esters. It is sometimes necessary to apply more than one layer.

The design of such systems involves release of drug only at specific site in the GIT.

The drugs contained in such a system are those that are:

- Destroyed in the stomach or by intestinal enzymes
- Known to cause gastric distress
- Absorbed from a specific intestinal site
- Meant to exert local effect at a specific GI site

The two types of delayed release systems are intestinal release systems and colonic release systems.

Chronotherapeutics[10]

Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed in relation to repetitive rhythms of drug related biological phenomena to produce the maximum health benefit and minimum harm to the patient.

Chronotherapy decisions are based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and the risk factors, pharmacologic sensitivity and pharmacokinetics of many drugs. The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness.

Theoretically, optimum therapy is more likely to result when the right amount of the drug is delivered to the correct target organ at the most appropriate time. In contrast many side effects can be minimized if a drug is not given when it is not needed. Chronotherapeutic formulations may use various release mechanisms eg., time-delay coatings, Osmotic pump mechanisms, Matrix systems that provide for varying levels throughout the day.

Various groups of drugs and its Chronotherapies

CLASS	EXAMPLES
Cardiovascular drugs	Verapamil, Propanolol, Diltiazem, Nifidipine, Enalapril
Antiasthmatic drugs	Methylpredisolone, Predisolone, Albuterol, Terbutaline, Theophylline
Anticancer drugs	Cisplatin, Oxaliplatin, Doxorubicin, 5-Fluorouracil, Folinic acid, Methotrexate, Mercaptopurine
NSAIDs	Ibuprofen, Ketoprofen, Indomethacin, Tenoxicam. Acetylsalicylic acid
Anti-ulcer agents	Cimetidine, Ranitidine, Famotidine, Pirenzipine, Omeprazole
Anticholesterolemic agents	Simvastatin, Lovastatin
Others	Vitamin D3, Diazepam, Haloperidol

Review of Literature

2. REVIEW OF LITERATURE

- **Preeti Karwa et al.**[11] developed bilayer tablet of Zolpidem Tartrate (ZT) for biphasic release and in vitro evaluation of the same. Bilayer tablets comprised two layers, i.e. immediate release and controlled release layer. The immediate release layer comprised Cros carmellose sodium as a super disintegrant and the controlled release layer comprised HPMC K100M as the release retarding polymers. Direct compression method was used for formulation of the bilayer tablets.

- **Dileep Kumar Gattu et al.**[12] formulated immediate release tablets containing Aspirin and Clopidogrel in which Aspirin was prepared by direct compression method using Microcrystalline cellusose as diluent and the formulation showed maximum release at the end of 60 mins.

- **Prabhakar Shirse**[13] formulated and evaluated the bilayered tablets containing Diclofenac Sodium in the sustained release (SR) portion and Ranitidine HCl in the immediate release (IR) portion. The sustained release layer of Diclofenac Sodium was prepared by using different grades of HPMC like, HPMC E15, HPMC K4M, K100M, and Ethyl Cellulose with cross carmellose along with other excipients like Magnesium stearate, Microcrystalline cellulose & PVP by wet granulation technique. The Immediate release layer of Ranitidine HCl was prepared by direct compression method. The release rate of Ranitidine HCl was studied for 45 min using water as media and that of Diclofenac Sodium was studied for 2 h in 1.2pH buffer followed by 6 h in pH 6.8 phosphate buffer media. The release rate of ranitidine HCl from all the formulations was more than 80% at 45 mins.

- **Rajalakshmi R et al.**[14] developed a stable formulation of antihypertensive drugs of Telmisartan and Amlodipine Besylate as an immediate release bilayer tablet and evaluate their pre-compression and post-compression parameters. The formulation of the developed work was initiated with wet granulation method for Telmisartan and direct compression for Amlodipine Besylate. Microcrystalline cellulose pH102 and manifold were used as diluents. The sodium starch glycolate (SSG) was used as the disintegrant. The immediate release layer showed above 95% drug release at the end of 40 mins.

- **Oyeniyi YJ et al.**[15] evaluated the *in-vitro* formulation properties of sawdust microcrystalline cellulose with a poorly compressible active pharmaceutical ingredient, by direct compression. All the tablets produced by direct compression show acceptable pharmacopeia standard and superior tableting properties. The accelerated stability studies reveals, that the formulation under consideration is very stable as the percentage decrease in acetylsalicylic acid content after six months was less than 0.1% w/w while other tested parameter remain the same.

- **Na Zhao et al.**[16] compared the disintegration efficiency and developed a discriminating test model for the 3 classes of superdisintegrants represented by Ac-Di-Sol (Cros carmellose sodium), Primojel (Sodium starch glycolate), and Polyplasdone XL10 (Crospovidone). Ac-Di-Sol was found to disintegrate tablets rapidly into apparently primary particles; Primojel also apparently disintegrated tablets into primary particles but more slowly; Polyplasdone XL10 disintegrated tablets rapidly but into larger masses of aggregated particles.

- **Subramaniam Kannan et al.**[17] develop delayed release stable tablet formulation of Aspirin. The delayed release tablet is intended to release the drug after some delay or after tablet pass GI tract. Micro crystalline cellulose, maize starch, cros carmellose Sodium are used and the tablets are prepared using direct compression method

- **Malay Patel R**[18] formulated Doxycycline hydrochloride delayed release tablets using hydroxy propyl methylcellulose phthalate and cellulose acetate phthalate. The dissolution for all the formulations was carried out according to US Pharmacopoeia [13] for 2 h in 0.1N HCl and then media was changed into phosphate buffer pH 6.8. The tablet shows no release upto 2 hours and release completely at the end of 45 minutes.

- **Viral Patel**[19] formulated and evaluated pantoprazole Delayed release tablets of pantoprazole by wet granulation method using HPMC, Cassava starch and polyvinyl pyrrolidine as polymer. The in vitro release study revealed that the prepared tablets were able to sustain release drug in to the intestine.

- **Pankaj Jadhav et al.**[20] formulated simvastatin sustained release bilayer tablet by wet granulation method. The formulated uncoated tablet of simvastatin is evaluated

successfully within the evaluation parameters which suggest that the tablet have better therapeutic level in systematic circulation.

- **Aisha Khanum et al**.[21] formulated Bi-layer Tablets of Propanolol hydrochloride by direct compression method using super-disintegrant such as Sodium starch glycolate for fast releasing layer and hydrogels like hydroxyl propyl methyl cellulose (HPMC K4M) and sodium carboxy methyl cellulose alone and in combination for sustained release layer. The formulations were subjected to in-vitro drug release in simulated gastric fluid and simulated intestinal fluid which revealed that dissolution kinetics followed a first order release for formulations containing HPMC (or) Na CMC alone, whereas formulations containing combination of polymers followed zero order kinetics. Thus, it was concluded that in bilayer tablets it is possible to have a fast releasing layer and a sustaining layer so as to achieve zero order release of water soluble drugs like Propanolol.

- **Abdul Althaf S et al.**[22] formulated immediate release bilayer tablets of Clopidogrel bisulphate and Aspirin using Solid dispersion technique for the solubility enhancement of Clopidogrel bisulphate. Different disintegrants like Sodium starch glycollate, Crospovidone and Croscarmellose sodium were selected for this study and the release profiles showed 97% drug release at the end of 45 minutes.

- **Shajan A et al.**[23] formulated bilayer tablets containing Doxofylline HCl as sustained release (SR) layer and Montelukast sodium as immediate release (IR) layer. The sustained release layer of Doxofylline HCl was developed by wet granulation technique using polymers HPMC K100M and Eudragit RL100 and the immediate release layer of Montelukast sodium by direct compression method using superdisintegrant crosscarmellose sodium. The results suggested that the developed bilayer tablets can be used as an alternative to the conventional dosage form.

- **Aarti Jogiya P et al.**[24] formulated and evaluated Sustained Release Tablets of Aspirin and Atorvastatin which release the drug in a sustained manner over a period of 12 hours by using various polymer and studied their effect on release pattern of both the drugs.

- **Shailesh Kumar et al**.[25] formulated and evaluated bi-layer tablets of Atorvastatin Calcium and Nicotinic acid by direct compression method using super-disintegrant

such as Lactose monohydrate, Microcrystallince cellulose 114, and Sodium starch glycolate for fast releasing layer and polymer such as HPMC K100M for sustaining layer. In the study HPMC was found to play a great role in controlling release of Nicotinic acid from the matrix system.

- **Ajit Kulkarni et al.**[26] formulated and evaluated bilayer floating tablets of Atenolol as sustained release layer and Lovastatin as immediate release layer. Tablets were prepared by direct compression using sodium starch glycolate as a superdisintegrant and HPMC K100M and Xanthan gum as the release controlling polymer

- **Atram SC, et al**.[27] worked on Formulation of bilayer tablets containing Metoprolol Succinate as sustained release layer using polymers such as HPMC K4M and Starch 1500 and Amlodipine besylate as immediate release layer using super-disintegrants Sodium starch glycolate and Microcrystalline Cellulose, by wet granulation method.

- **Basuvan Babu et al.**[28] developed oral immediate release and Sustained release dosage form of Simvastatin and evaluated its Pharmacokinetic parameters. AUC values for the SR tablets were higher than the marketed IR tablets indicating more efficient and controlled drug delivery, which would maintain plasma SS levels better. This was also evident by the lower elimination rate and higher $t_{½}$ values.

- **Prasad Tandale et al.**[29] developed Extended Release Solid Dispersions Conatining Simvastatin using Polyethylene glycol 4000 as the hydrophilic carrier and Methocel K15M as the release retardant. The combination of the drug with a hydrophilic polymer such as methocel K15M was effective in adequately modulating the drug release rate. Release experiments demonstrate that the extended release effects can be obtained by simply varying the relative amounts of the polymer in the dispersion.

- **Brahmaiah B et al.**[30] formulated and evaluated extended release mucoadhesive microspheres of Simvastatin using polymers such as HPMC (K 100 M), carbopol 940P, sodium CMC, guar gum, sodium alginate, ethyl cellulose, methyl cellulose and xanthan gum. The *in vitro* release profile which shows an extended drug release of 97.11% upto 8 hours in phosphate buffer of pH 7.0.

Aim and plan of work

3. AIM AND PLAN OF WORK

Aim of the work

- To provide effective, safe and stable pharmaceutical, chronomodulated oral formulation containing antiplatelet drug Aspirin as immediate release layer and antihyperlipidemic drug Simvastatin as delayed release layer for effective treatment of coronary artery disease.
- To optimise immediate release tablets of Aspirin by direct compression method using various concentration of sodium starch glycolate as super disintegrant.
- To optimise delayed release tablets of Simvastatin by wet granulation method using HPMC K100 in different ratios.
- To formulate and evaluate the bilayer tablets from the optimised batches of immediate and delayed release formulations

Plan of work

- Preformulation studies
    - Raw material analysis
    - Physical and Chemical compatibility studies
- Construction of calibration curve
- Precompression studies of the drug, blend and IR granules
    - Bulk density
    - Tapped density
    - Angle of repose
    - Carr's index
    - Hausner's ratio
- Formulation of Aspirin immediate release (IR) tablets

- Post compression studies of IR tablets for physical parameters like
    - Uniformity of weight
    - Physical appearance
    - Thickness, hardness and diameter
    - Friability
    - Determination of drug content of IR tablets
    - Disintegration time of IR tablets
    - Evaluation of *in vitro* dissolution study of IR tablets
- Pre compression studies of the drug, blend and DR granules
    - Bulk density
    - Tapped density
    - Angle of repose
    - Carr's index
    - Hausner's ratio
- Formulation of Simvastatin delayed release (DR) tablets
- Post compression studies of DR tablets for physical parameters like
    - Uniformity of weight
    - Physical appearance
    - Thickness, hardness and diameter
    - Friability
    - Determination of drug content of DR tablets
    - Evaluation of *in vitro* dissolution study of DR tablets

- Formulation of bilayer tablets from the optimized batches of IR and DR layer
- Post compression study of bilayer tablets for physical parameters like
    - Uniformity of weight
    - Physical appearance
    - Thickness, hardness and diameter
    - Friability
    - Determination of drug content
    - Evaluation of *in vitro* dissolution study of bilayer tablets
    - Determination of stability of bilayer tablets as per ICH guidelines

Rationale of the study

4. RATIONALE OF THE STUDY

RATIONALE FOR SELECTION OF SIMVASTATIN OVER OTHER STATINS

- The average percent reduction in LDL cholesterol with usual starting dose of Simvastatin is 35% which is more than Lovastatin (24%), Pravastatin (24%) and Fluvastatin (16%) and comparable to Atorvastatin (37%).[31]
- Simvastatin 40 mg increase HDL-C twice as much as atorvastatin 40 mg (9.6% vs 4.8%)[32]

RATIONALE FOR SELECTION OF ASPIRIN OVER OTHER ANTIPLATELET AGENTS

- Aspirin is primarily first choice anti-platelet drug since it is more effective in preventing symptoms in CHD than Clopidogrel, Prasugrel and Ticlopidine[33]
- Aspirin is recommended for all apparently healthy individuals who are at a risk of coronary heart disease.

RATIONALE FOR SELECTION OF ASPIRIN AND SIMVASTATIN FOR FORMULATING BILAYER TABLETS

- The anti-inflammatory effects of both Aspirin and Statins contribute to beneficial effects on CVD.[34]
- Co-administration of Aspirin and Statin show additional effects in decreasing cardiovascular mortality.
- Aspirin therapy provides an additive effect of 24% relative risk reduction of cardiovascular events in addition to Statin monotherapy.
- Statin therapy provides an additional 13% relative risk reduction of cardiovascular events in addition to Aspirin monotherapy.[35]
- Platelet response to aspirin therapy is linearly reduced with increased cholesterol plasma levels. The presence of dyslipidemia is partly responsible for lower efficacy of Aspirin. The concomitant use of Statins could restore the normal platelet sensitivity to Aspirin by reducing cholesterol levels.[36]

RATIONALE FOR FORMULATING ASPIRIN AS BUFFERED TABLETS

- It is found that low dose Aspirin increases a patient's chance for developing ulcer without any warning symptoms[37] and henceforth Aspirin is formulated here as buffered tablets.

CHRONOPHARMACOLOGY

- Simvastatin is probably best taken at night because concentrations of total cholesterol and of low density lipoprotein are significantly greater when it is taken in the morning.[38]
- Therapeutic compliance is significantly higher when statins were taken at bed time (87.7%) as when compared to midday (78.6%).[39]
- Small dose of aspirin taken at night could reduce the risk of heart attack or stroke in people with high blood pressure – more so than if aspirin were taken in the morning.[40]

Disease profile

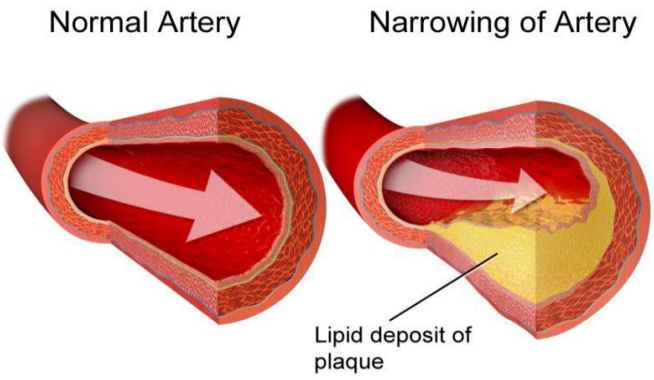
5. DISEASE PROFILE[41]

CORONARY ARTERY DISEASE

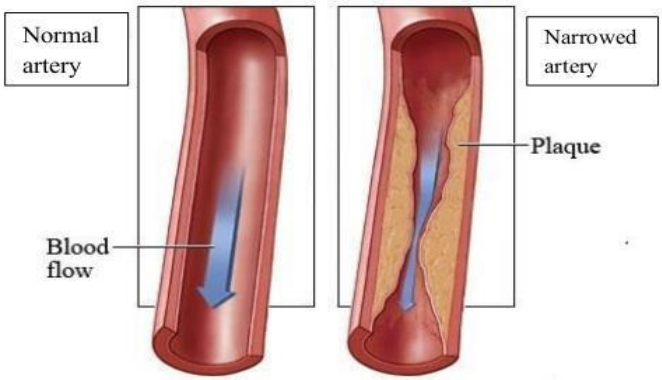
Coronary artery disease (CAD) also known as atherosclerotic heart disease, coronary heart disease, or ischemic heart disease (IHD), is the most common type of heart disease and cause of heart attacks.

Coronary artery disease develops when your coronary arteries, the major blood vessels that supply your heart with blood, oxygen and nutrients become damaged or diseased. Cholesterol-containing deposits (plaque) on your arteries are usually to blame for coronary artery disease. When plaques build up, they narrow your coronary arteries, causing your heart to receive less blood. Eventually, the decreased blood flow may cause chest pain (angina), shortness of breath, or other coronary artery disease signs and symptoms. A complete blockage can cause a heart attack.

Fig 1: Pathophysiology of CAD



Coronary Artery Disease



Because coronary artery disease often develops over decades, it can go virtually unnoticed until you have a heart attack. But there's plenty you can do to prevent and treat coronary artery disease start by committing to a healthy lifestyle.

Symptoms

If coronary arteries become narrowed, they can't supply enough oxygen-rich blood to your heart — especially when it's beating hard, such as during exercise. At first, the decreased blood flow may not cause any coronary artery disease symptoms. As the plaques continue to build up in your coronary arteries, however, it may develop coronary artery disease symptoms, including:

- **Chest pain (angina).** Feeling of pressure or tightness in chest. The pain, referred to as angina, is usually triggered by physical or emotional stress. It typically goes away within minutes after stopping the stressful activity. In some people, especially women, this pain may be fleeting or sharp and noticed in the abdomen, back or arm.
- **Shortness of breath.** If the heart can't pump enough blood to meet the body's needs, it may develop shortness of breath or extreme fatigue with exertion.
- **Heart attack.** If a coronary artery becomes completely blocked, it leads to heart attack. The classic signs and symptoms of a heart attack include crushing pressure in chest and pain in shoulder or arm, sometimes with shortness of breath and sweating. Women are somewhat more likely than men are to experience less typical signs and symptoms of a heart attack, including nausea and back or jaw pain. Sometimes a heart attack occurs without any apparent signs or symptoms.

Causes

Coronary artery disease is thought to begin with damage or injury to the inner layer of a coronary artery, sometimes as early as childhood. The damage may be caused by various factors, including:

- Smoking
- High blood pressure
- High cholesterol
- Diabetes

- Radiation therapy to the chest, as used for certain types of cancer

Once the inner wall of an artery is damaged, fatty deposits (plaques) made of cholesterol and other cellular waste products tend to accumulate at the site of injury in a process called atherosclerosis. If the surface of these plaques breaks or ruptures, blood cells called platelets will clump at the site and to try to repair the artery. This clump can block the artery, leading to a heart attack.

Risk factors

Risk factors for coronary artery disease include:

- **Age.** Simply getting older increases risk of damaged and narrowed arteries.
- **Sex.** Men are generally at greater risk of coronary artery disease. However, the risk for women increases after menopause.
- **Family history.** A family history of heart disease is associated with a higher risk of coronary artery disease, especially if a close relative developed heart disease at an early age. The risk is highest if ones father or a brother was diagnosed with heart disease before age 55, or ones mother or a sister developed it before age 65.
- **Smoking.** Nicotine constricts your blood vessels, and carbon monoxide can damage their inner lining, making them more susceptible to atherosclerosis. The incidence of heart attack in women who smoke at least 20 cigarettes a day is six times that of women who've never smoked. For men who smoke, the incidence is triple that of non-smokers.
- **High blood pressure.** Uncontrolled high blood pressure can result in hardening and thickening of the arteries, narrowing the channel through which blood can flow.
- **High blood cholesterol levels.** High levels of cholesterol in the blood can increase the risk of formation of plaques and atherosclerosis. High cholesterol can be caused by a high level of low-density lipoprotein (LDL), known as the "bad" cholesterol. A low level of high-density lipoprotein (HDL), known as the "good" cholesterol, also can promote atherosclerosis.
- **Diabetes.** Diabetes is associated with an increased risk of coronary artery disease. Both conditions share similar risk factors, such as obesity and high blood pressure.

- **Obesity.** Excess weight typically worsens other risk factors.
- **Physical inactivity.** Lack of exercise also is associated with coronary artery disease and some of its risk factors, as well.
- **High stress.** Unrelieved stress in life may damage the arteries as well as worsen other risk factors for coronary artery disease.

Risk factors often occur in clusters and may build on one another, such as obesity leading to diabetes and high blood pressure. When grouped together, certain risk factors put you at an ever greater risk of coronary artery disease. For example, metabolic syndrome — a cluster of conditions that includes elevated blood pressure, high triglycerides, elevated insulin levels and excess body fat around the waist — increases the risk of coronary artery disease.

Sometimes coronary artery disease develops without any classic risk factors. Researchers are studying other possible factors, including:

- **Sleep apnoea.** This disorder leads to repeatedly stop and start breathing while one is sleeping. Sudden drops in blood oxygen levels that occur during sleep apnea increase blood pressure and strain the cardiovascular system, possibly leading to coronary artery disease.
- **C-reactive protein.** C-reactive protein (CRP) is a normal protein that appears in higher amounts when there's swelling somewhere in the body. High CRP levels may be a risk factor for heart disease. It's thought that as coronary arteries narrow, one will have more CRP in the blood.
- **Homocysteine.** Homocysteine is an amino acid the body uses to make protein and to build and maintain tissue. But high levels of homocysteine may increase the risk of coronary artery disease.
- **Fibrinogen.** Fibrinogen is a protein in the blood that plays a central role in blood clotting. But too much may increase clumping of platelets, the type of blood cell largely responsible for clotting. That can cause a clot to form in an artery, leading to a heart attack or stroke. Fibrinogen may also be an indicator of the inflammation that accompanies atherosclerosis.

- **Lipoprotein (a).** This substance forms when a low-density lipoprotein (LDL) particle attaches to a specific protein. Lipoprotein (a) may disrupt body's ability to dissolve blood clots. High levels of lipoprotein (a) may be associated with an increased risk of cardiovascular disease, including coronary artery disease and heart attack.

Complications

Coronary artery disease can lead to:

- **Chest pain (angina).** When coronary arteries narrow, the heart may not receive enough blood when demand is greatest — particularly during physical activity. This can cause chest pain (angina) or shortness of breath.
- **Heart attack.** If a cholesterol plaque ruptures and a blood clot forms, complete blockage of heart artery may trigger a heart attack. The lack of blood flow to heart may damage the heart muscle. The amount of damage depends in part on how quickly you receive treatment.
- **Heart failure.** If some areas of heart are chronically deprived of oxygen and nutrients because of reduced blood flow, or if the heart has been damaged by a heart attack, heart may become too weak to pump enough blood to meet the body's needs. This condition is known as heart failure.
- **Abnormal heart rhythm (arrhythmia).** Inadequate blood supply to the heart or damage to heart tissue can interfere with heart's electrical impulses, causing abnormal heart rhythms.

Tests and diagnosis

- Electrocardiogram (ECG)
- Echocardiogram
- Stress test
- Cardiac catheterization or angiogram
- CT scan
- Magnetic resonance angiography (MRA)

Treatments and drugs

Treatment for coronary artery disease usually involves lifestyle changes and, if necessary, drugs and certain medical procedures.

Lifestyle changes

Making a commitment to the following healthy lifestyle changes can go a long way toward promoting healthier arteries:

- Quit smoking.
- Eat healthy foods.
- Exercise regularly.
- Lose excess weight.
- Reduce stress.

Drugs

Various drugs can be used to treat coronary artery disease, including:

- **Cholesterol-modifying medications.** By decreasing the amount of cholesterol in the blood, especially low-density lipoprotein (LDL, or the "bad") cholesterol, these drugs decrease the primary material that deposits on the coronary arteries. This includes statins, niacin, fibrates and bile acid sequestrants.
- **Aspirin.** Taking a daily aspirin or other blood thinner drug can reduce the tendency of blood to clot, which may help prevent obstruction of coronary arteries. If one have had a heart attack, aspirin can help prevent future attacks.
- **Beta blockers.** These drugs slow heart rate and decrease blood pressure, which decreases heart's demand for oxygen. If one has had a heart attack, beta blockers reduce the risk of future attacks.
- **Nitroglycerin.** Nitroglycerin tablets, sprays and patches can control chest pain by opening up your coronary arteries and reducing heart's demand for blood.

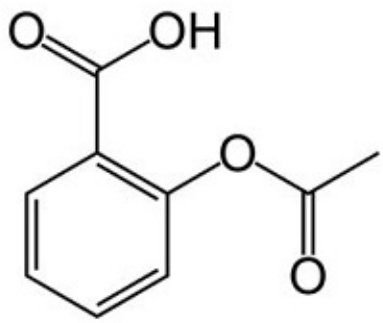
- **Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).** These similar drugs decrease blood pressure and may help prevent progression of coronary artery disease. If one has had a heart attack, ACE inhibitors reduce the risk of future attacks.
- **Calcium channel blockers.** These medications relax the muscles that surround your coronary arteries and cause the vessels to open, increasing blood flow to the heart. They also control high blood pressure.

Drug profile

6. DRUG PROFILE

ASPIRIN[42,43,44]

Chemical Structure



CAS Number 50-78-2

Chemical formula $C_9H_8O_4$

IUPAC Name 2-(acetyloxy)benzoic acid

Molecular weight 180.1574

Melting point 135 °C

Boiling point 140 °C

Description

Colourless or white crystals or white crystalline powder or granules;

Odourless or almost odourless with a slight acid taste

Solubility

Soluble 1 in 300 of water, 1 in 5 - 7 in alcohol, 1 in 17 of chloroform and 1 in 20 of ether; soluble in solutions of acetates and citrates and, with decomposition, in solutions of alkali hydroxides and carbonates.

Stability

Acetylsalicylic acid is stable in dry air, but gradually hydrolyses in contact with moisture to acetic and salicylic acids. In solution with alkalis, the hydrolysis proceeds rapidly and the clear solutions formed may consist entirely of acetate and salicylate.

Acetylsalicylic acid decomposes rapidly in solutions of ammonium acetate or of the acetates, carbonates, citrates or hydroxides of the alkali metals.

Pharmacology

Pharmacodynamics

Acetylsalicylic acid is an analgesic, antipyretic, antirheumatic, and anti-inflammatory agent.

Acetylsalicylic acid's mode of action as an antiinflammatory and antirheumatic agent may be due to inhibition of synthesis and release of prostaglandins.

Acetylsalicylic acid appears to produce analgesia by virtue of both a peripheral and CNS effect. Peripherally, acetylsalicylic acid acts by inhibiting the synthesis and release of prostaglandins. Acting centrally, it would appear to produce analgesia at a hypothalamic site in the brain, although the mode of action is not known.

Acetylsalicylic acid also acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilation and increased peripheral blood flow. Acetylsalicylic acid's antipyretic activity may also be related to inhibition of synthesis and release of prostaglandins.

Mechanism of action

The analgesic, antipyretic, and anti-inflammatory effects of acetylsalicylic acid are due to actions by both the acetyl and the salicylate portions of the intact molecule as well as by the active salicylate metabolite.

Acetylsalicylic acid directly and irreversibly inhibits the activity of both types of cyclooxygenase (COX-1 and COX-2) to decrease the formation of precursors of prostaglandins and thromboxanes from arachidonic acid. This makes acetylsalicylic acid

different from other NSAIDS (such as diclofenac and ibuprofen) which are reversible inhibitors. Salicylate may competitively inhibit prostaglandin formation.

Acetylsalicylic acid's antirheumatic (nonsteroidal anti-inflammatory) actions are a result of its analgesic and anti-inflammatory mechanisms; the therapeutic effects are not due to pituitary-adrenal stimulation.

The platelet aggregation-inhibiting effect of acetylsalicylic acid specifically involves the compound's ability to act as an acetyl donor to cyclooxygenase; the nonacetylated salicylates have no clinically significant effect on platelet aggregation. Irreversible acetylation renders cyclooxygenase inactive, thereby preventing the formation of the aggregating agent thromboxane A2 in platelets. Since platelets lack the ability to synthesize new proteins, the effects persist for the life of the exposed platelets (7-10 days). Acetylsalicylic acid may also inhibit production of the platelet aggregation inhibitor, prostacyclin (prostaglandin I2), by blood vessel endothelial cells; however, inhibition prostacyclin production is not permanent as endothelial cells can produce more cyclooxygenase to replace the non-functional enzyme.

Absorption

Absorption is generally rapid and complete following oral administration but may vary according to specific salicylate used, dosage form, and other factors such as tablet dissolution rate and gastric or intraluminal pH.

Protein binding

Highly bound (99.5%) to albumin. It decreases as plasma salicylate concentration increases, with reduced plasma albumin concentration or renal dysfunction, and during pregnancy.

Metabolism

Acetylsalicylic acid is rapidly hydrolysed primarily in the liver to salicylic acid, which is conjugated with glycine (forming salicyluric acid) and glucuronic acid and excreted largely in the urine.

Bioavailability

After oral administration, 80 - 100% will be absorbed in the stomach and in the small intestine. However, bioavailability is lower because partial hydrolysis occurs during absorption and there is a "first-pass" effect in the liver.

The non-protein bound fraction of salicylate increases with the total plasma concentration, and the binding capacity of albumin is partially saturated at therapeutic concentrations of salicylate.

Half life

The plasma half-life is approximately 15 minutes; that for salicylate lengthens as the dose increases: doses of 300 to 650 mg have a half-life of 3.1 to 3.2 hours; with doses of 1 gram, the half-life is increased to 5 hours and with 2 grams it is increased to about 9 hours.

Toxicity

Oral, mouse: LD_{50} = 250 mg/kg;

Oral, rabbit: LD_{50} = 1010 mg/kg;

Oral, rat: LD_{50} = 200 mg/kg.

Effects of overdose include: tinnitus, abdominal pain, hypokalemia, hypoglycemia, pyrexia, hyperventilation, dysrhythmia, hypotension, hallucination, renal failure, confusion, seizure, coma, and death.

Indications

As an analgesic for the treatment of mild to moderate pain,

As an anti-inflammatory agent for the treatment of soft tissue and joint inflammation,

As an antipyretic drug,

In low doses salicylate is used for the prevention of thrombosis.

Therapeutic dosage

Adult Dose

For Ankylosing Spondylitis, Osteoarthritis, Rheumatoid Arthritis, Systemic Lupus Erythematosus

3 grams per day in divided doses (spondyloarthropathies may require up to 4 grams per day in divided doses).

For Fever and Pain

325 to 650 mg orally or rectally every 4 hours as needed, not to exceed 4 g/day.

For Rheumatic Fever

80 mg/kg/day orally in 4 equally divided doses, up to 6.5 g/day.

For Myocardial Infarction

160 to 162.5 mg orally once a day beginning as soon as an acute myocardial infarction is suspected and continuing for 30 days. If a solid dose formulation is used, the first dose should be chewed, crushed, or sucked. Long-term aspirin therapy for secondary prevention is recommended after 30 days.

For Ischemic Stroke

50 to 325 mg orally once a day. Therapy should be continued indefinitely.

For Angina Pectoris

75 mg to 325 mg orally once a day beginning as soon as unstable angina is diagnosed and continuing indefinitely.

For Angina Pectoris Prophylaxis, Thromboembolic Stroke Prophylaxis, Myocardial Infarction – Prophylaxis and Ischemic Stroke - Prophylaxis

75 mg to 325 mg orally once a day, continued indefinitely.

For Revascularization Procedures - Prophylaxis

For coronary artery bypass graft (CABG):
325 mg orally once a day beginning 6 hours after the procedure and continuing for 1 year or indefinitely as needed.

For percutaneous transluminal coronary angiography (PTCA):
325 mg orally once 2 hours prior to procedure, then 160 to 325 mg orally once a day indefinitely.

For carotid endarterectomy:
80 mg orally once a day up to 650 mg orally twice a day beginning prior to surgery and continuing indefinitely.

Pediatric Dose

For Fever and Pain

2 to 11 years: 10 to 15 mg/kg orally or rectally every 4 to 6 hours as needed, not to exceed 4 g/day.

12 years or older: 325 to 650 mg orally or rectally every 4 hours as needed, not to exceed 4 g/day.

For Juvenile Rheumatoid Arthritis

2 to 11 years or less than or equal to 25 kg:
Initial: 60 to 90 mg/kg/day orally in equally divided doses.
Maintenance: 80 to 100 mg/kg/day orally in equally divided doses; higher dosages, up to 130 mg/kg/day, may be necessary in some cases, not to exceed 5.4 g/day.

12 years or older or greater than 25 kg:
Initial: 2.4 to 3.6 g/day orally in equally divided doses.
Maintenance: 3.6 to 5.4 g/day orally in equally divided doses; higher dosages may be necessary in some cases.

For Kawasaki Disease

Initial (acute febrile period): 80 to 100 mg/kg/day orally or rectally in 4 equally divided doses every 4 to 6 hours for up to 14 days (until fever resolves for at least 48 hours).

For Rheumatic Fever

90 to 130 mg/kg/day in equally divided doses every 4 to 6 hours, up to 6.5 mg/day.

Renal Dose Adjustments

Detailed information concerning the pharmacokinetic disposition of aspirin in patients with renal dysfunction is not available. Aspirin should be used with caution in chronic renal insufficiency, since it may cause a transient decrease in renal function. The use of aspirin in patients with severe renal impairment (CrCl less than 10 mL/minute) is not recommended due to the potential for increased risk of salicylate toxicity.

Liver Dose Adjustments

The use of aspirin in patients with severe hepatic impairment is not recommended due to the potential for increased risk of clinically significant bleeding and other adverse effects.

Precautions

The use of aspirin is contraindicated in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm in these patients.

The risk of bleeding is increased in patients receiving aspirin. Inhibition of platelet function occurs even at low doses of aspirin. Aspirin should not be given to patients with inherited or acquired bleeding disorders or in patients with a recent history of gastrointestinal (GI) bleeding.

Aspirin should not be used in children or adolescents with chickenpox or influenza symptoms due to the association with Reye's syndrome.

Contraindications

Active peptic ulcer

Febrile/post-febrile illness in children

Haemostatic disorders, including anticoagulant and thrombolytic treatment

Hypoproteinemia

Hypersensitivity

Asthma induced by acetylsalicylic acid or other NSAIDs.

Caution is indicated in patients with:

A history of peptic ulceration or gastro-intestinal haemorrhage

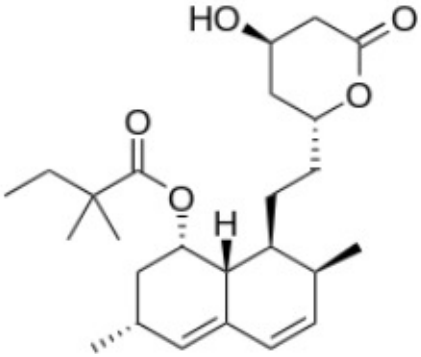
Hepatic or renal insufficiency

Asthma

Children < 2 years, especially in those who are dehydrated

SIMVASTATIN[45,46]

Chemical structure



CAS number	79902-63-9
Chemical formula	$C_{25}H_{38}O_5$
IUPAC Name	(1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl2,2-dimethylbutanoate
Molecular mass	418.566 g/mol
Melting point	139^0C
Description	white powder
Solubility	very soluble in dichloromethane freely soluble in ethanol (95%)

Pharmacology

Indication

For the treatment of hypercholesterolemia

Pharmacodynamics

Simvastatin, the methylated form of lovastatin, is an oral antilipemic agent which inhibits HMG-CoA reductase. simvastatin is used in the treatment of primary hypercholesterolemia and is effective in reducing total and LDL-cholesterol as well as plasma triglycerides and apolipoprotein B.

Mechanism of action

The 6-membered lactone ring of simvastatin is hydrolysed in vivo to generate the beta, delta-dihydroxy acid, an active metabolite structurally similar to HMG-CoA (hydroxymethylglutaryl CoA). Once hydrolysed, simvastatin competes with HMG-CoA for HMG-CoA reductase, a hepatic microsomal enzyme. Interference with the activity of this enzyme reduces the quantity of mevalonic acid, a precursor of cholesterol.

Absorption

Absorption of simvastatin, estimated relative to an intravenous reference dose, in each of two animal species tested, averaged about 85% of an oral dose. In animal studies, after oral dosing, simvastatin achieved substantially higher concentrations in the liver than in non-target tissues.

Protein binding

Both simvastatin and its b-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins.

Metabolism

Hepatic, simvastatin is a substrate for CYP3A4.

Route of elimination

Following an oral dose of 14C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces.

Half life

3 hours

Adult Dose

For Hyperlipidemia, Cardiovascular Risk Reduction

Initial dose: 10 to 20 mg orally once a day in the evening.
Maintenance dose: 5 to 40 mg orally once a day in the evening.

For patients at high risk for a CHD event due to existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg orally once a day.

For Heterozygous familial hypercholesterolemia:

Adolescents 10 to 17 years: 10 mg once daily in the evening
May increase dose in intervals of 4 weeks or more to a maximum of 40 mg/day

Pediatric Dose

For Heterozygous Familial Hypercholesterolemia

10 to 17 years:

Initial dose: 10 mg orally once a day in the evening.
Maintenance dose: 10 to 40 mg/day (the maximum recommended dose is 40 mg/day).
Dosage increases should be done at intervals of 4 weeks or more.

Renal Dose Adjustments

CrCl less than 25 mL/min: Initial dose: 5 mg once a day in the evening. Maintenance dose: Dosage increases should be done with careful monitoring for adverse reactions.

Liver Dose Adjustments

The use of this drug is contraindicated in patients with liver dysfunction.

Dose Adjustments

Adjustments in dosage should be made in intervals of 4 weeks or more.

The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant therapy with verapamil, diltiazem, or amiodarone.

The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant therapy with amlodipine or ranolazine.

The benefits of the use of simvastatin in patients receiving other lipid-lowering drugs (other fibrates or greater than 1 g/day of niacin), amiodarone, verapamil, diltiazem, amlodipine, or ranolazine should be carefully weighed against the risks of these combinations.

Precautions

Simvastatin is associated with elevations in liver function tests (LFTs greater than 3 times the upper limit of normal) in 1% of patients. Baseline liver function tests, followed by periodic re-evaluations during the first year of therapy are recommended.

More frequent evaluations may be needed in those patients who have elevated values, an increase in simvastatin dose or the addition of interacting drugs that may increase serum levels. Simvastatin should be discontinued in patients who develop persistent, significant (three times normal values) elevations in LFTs.

Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80 mg dose of simvastatin should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity.

Patients who are currently tolerating the 80 mg dose of simvastatin who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for interaction.

Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 80 mg dose of simvastatin, patients unable to achieve their LDL-C goal utilizing the 40 mg dose of simvastatin should not be titrated to the 80 mg dose, but should be placed on alternative LDL-C lowering treatment.

Interactions

Grapefruit contains furanocoumarins, notably bergamottin and 6',7'-dihydroxybergamottin, which inhibit the intestinal cytochrome P450 3A4 isoform. This, in turn, slows metabolization of simvastatin and a large number of other drugs, resulting in higher plasma levels of the drug. Due to the risk of toxicity, patients taking simvastatin should avoid intake of grapefruit and grapefruit-containing products.

Notable interactions with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone.

Patients taking 10 mg of simvastatin should not take it with gemfibrozil, cyclosporine, or danazol. If taking 20 mg of simvastatin, do not take it with amiodarone or verapamil. Diltiazem should not be taken with 40 mg of simvastatin.

These drugs mentioned are CYP3A4 inhibitors which decrease the metabolism of simvastatin, therefore increasing the plasma activity of simvastatin, which leads to higher risk of developing rhabdomyolysis and myopathy.

Contraindications

Simvastatin is contraindicated with pregnancy, breast feeding and liver disease.

Pregnancy must be avoided while on simvastatin due to potentially severe birth defects. Patients cannot breast feed while on simvastatin due to potentially disrupting the infant's lipid metabolism.

Simvastatin is also contraindicated with Amlodipine and should not exceed a dosage greater than 20 mg/day when taken alongside Amlodipine.

Excipients profile

7. EXCIPIENTS PROFILE

Hydroxy propyl methyl cellulose[47]

Nonproprietary Names

BP: Hypromellose, JP: Hypromellose, PhEur: Hypromellose, USP: Hypromellose

Synonyms

Benecel MHPC ; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.

Chemical Name and CAS Registr y Number

Cellulose hydroxypropyl methyl ether and 9004-65-3

Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Functional Category

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder, in film coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film coat tablets.

Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypro-mellose produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%.

Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling respectively. The gelation temperature is 50–908 C, depending upon the grade and concentration of material. For temperatures below the gelation temperature, viscosity of the solution decreases as temperature is increased. Beyond the gelation temperature, viscosity increases as temperature is increased.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Lactose, Monohydrate[47]

Nonproprietary Names

BP: Lactose, PhEur: Lactose Monohydrate, JP: Lactose Hydrate, USP-NF: Lactose Monohydrate

Synonyms

CapsuLac; GranuLac; Lactochem ; lactosum monohydricum; Monohydrate; Pharmatose; PrismaLac; SacheLac; SorboLac; SpheroLac ; SuperTab 30GR; Tablettose.

Chemical Name and CAS Registr y Number

O-β- D-Galactopyranosyl-(1, 4)-α- D-glucopyranose monohy-drate & 5989-81-1

Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}.H_2O$ & 360.31

Description

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous, and α -lactose anhydrous. The stable crystalline forms of lactose are a-lactose monohydrate, β-lactose anhydrous and stable α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odourless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β -lactose is 40% as sweet.

Functional Category

Dry powder inhaler carrier; Lyophilisation aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler and diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry-powder inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when

milling during processing is carried out, since the fine size allows better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion.

Lactose is also used in combination with sucrose (approximately 1: 3) to prepare sugar-coating solutions. It may also be used in intravenous injections.

Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions.

Direct-compression grades of lactose monohydrate are available as granulated/agglomerated α-lactose monohydrate, containing small amounts of anhydrous lactose. Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation. Other directly compressible lactose are spray-dried lactose and anhydrous lactose.

Stability and Storage Conditions

Mould 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. The purities of different lactoses can vary and color evaluation may be important, particularly if white tablets are being formulated. The color stabilities of various lactoses also differ. Solutions show mutarotation. Lactose should be stored in a well-closed container in a cool, dry place.

Incompatibilities

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. The Maillard interaction has also been shown to occur between lactose and secondary amine. However, the reaction sequence stops with the formation of the imine, and no yellow-brown coloration develops. Lactose is also incompatible with amino acids, amphetamines and lisinopril.

Microcrystalline Cellulose[47]

Nonproprietary Names

BP: Microcrystalline Cellulose, JP: Microcrystalline Cellulose, PhEur: Cellulose, Microcrystalline, USP-NF: Microcrystalline Cellulose

Synonyms

Avicel PH; Cellets ; Celex; Cellulose gel; Hellulosum microcristalli-num; Celphere ; Ceolus KG ; crystalline cellulose; Fibrocel; MCC Sanaq; Pharmacel; Tabulose ; Vivapur.

Chemical Name and CAS Registry Number

Cellulose & [9004-34-6]

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_{220}$ & 36 000

Description

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles.

Functional Category

Adsorbent; Suspending agent; Tablet and capsule diluent; Tablet disintegrant

Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule. In addition to its use as a binder/diluent, micro-crystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Stability and Storage Conditions

It should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

Sodium starch glycolate[47]

Nonproprietary Names

BP: Sodium Starch Glycolate, PhEur: Sodium Starch Glycolate, USP-NF: Sodium Starch Glycolate

Synonyms

Carboxymethyl starch, sodium salt; carboxymethylamylum natri-cum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

Chemical Name and CAS Registr y Number

Sodium carboxymethyl starch & 9063-38-1

Description

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The granules show considerable swelling in contact with water.

Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. The usual concentration employed in a formulation is between 2% and 8%. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Stability and Storage Conditions

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.

Croscarmellose Sodium[47]

Non-proprietary Names

BP: Croscarmellose Sodium, JP: Croscarmellose Sodium, PhEur: Croscarmellose Sodium, USP-NF: Croscarmellose Sodium

Synonyms

Ac-Di-Sol; carmellosum natricum conexum; cross-linked carbox-ymethylcellulose sodium; Explocel ; modified cellulose gum; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt, cross-linked & 74811-65-7

Functional Category

Tablet and capsule disintegrant

Description

Croscarmellose sodium occurs as an odourless, white or greyish-white powder.

Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant.

Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30^0C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Aluminium hydroxide[48]

Non-proprietary Names

BP: Dried Aluminium hydroxide, PhEur: Hydrated Aluminium Oxide

Synonyms

Aluminic acid**,** Aluminic hydroxide, Aluminium(III) hydroxide, Aluminium hydroxide, Hydrated alumina**,** Orthoaluminic acid

Chemical Name and CAS Registry Number

Aluminium (3+) trioxanide & 21645-51-2

Empirical Formula and Molecular Weight

$Al(OH)_3$ & 78.00 g/mol

Description

Aluminium hydroxide occurs as a white amorphous powder. It is insoluble in water, but soluble in strong acids and bases.

Functional Category

Antacid

Applications in Pharmaceutical Formulation or Technology

Pharmaceutical grade Aluminium hydroxide is widely used in medicine production of antacids and laxatives.

Stability and Storage Conditions

In an airtight container, at a temperature not exceeding 30 °C

Uses

It is used as an antacid. The hydroxide reacts with excess acid in the stomach, reducing its acidity which may help to relieve the symptoms of ulcers, heartburn or dyspepsia. It can also cause constipation. This compound is also used to control phosphate levels in the blood of people suffering from kidney failure.

Magnesium hydroxide[49]

Non-proprietary Names

BP: Magnesium hydroxide, IP: Magnesium hydroxide, PhEur: Magnesium hydroxide

Synonyms

Milk of magnesia, Phillips' Milk of Magnesia, Cream of Magnesia, Magnesium Hydroxide Mixture,

Chemical Name and CAS Registry Number

Magnesium hydroxide & 1309-42-8

Empirical Formula and Molecular Weight

$Mg(OH)_2$ & 58.3197

Description

Magnesium hydroxide occurs as a white hexagonal crystal or amorphous powder which is slightly soluble in water.

Functional Category

Antacid, Osmotic laxative

Applications in Pharmaceutical Formulation or Technology

Pharmaceutical grade magnesium hydroxide is widely used in medicine production of antacids, laxatives, stomach acid can be neutralize fastly, and strongly, lasting effect, does not produce carbon dioxide, protect the ulcer.

Stability and Storage Conditions

Store protected from moisture.

Uses

Medicinally Magnesium hydroxide, in the form of a mixture is used as an antacid or a laxative to neutralize stomach acid. It therefore relieves stomach upset.

Colloidal Silicon Dioxide[47]

Non-proprietary y Names

BP: Colloidal Anhydrous Silica, JP: Light Anhydrous Silicic Acid, PhEur: Silica, Colloidal Anhydrous, USP-NF: Colloidal Silicon Dioxide

Synonyms

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; fumed silicon dioxide; hochdisperses silicum dioxid; SAS; silica colloidalis anhydrica; silica sol; silicic anhydride; silicon dioxide colloidal; silicon dioxide fumed; synthetic amorphous silica; Wacker HDK.

Chemical Name and CAS Registr y Number

Silica & 7631-86-9

Empirical Formula and Molecular Weight

SiO_2 & 60.08

Functional Category

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling.

Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations.

In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles.

Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.

Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate.

Colloidal silicon dioxide is also used as an adsorbent during the preparation of wax microspheres, as a thickening agent for topical preparations; and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

Stability and Storage Conditions

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container.

Incompatibilities

Incompatible with diethylstilboestrol preparations.

Stearic Acid[47]

Non-proprietary y Names

BP: Stearic Acid, JP: Stearic Acid, PhEur: Stearic Acid, USP-NF: Stearic Acid

Synonyms

Acidum stearicum; cetylacetic acid;Crodacid ; Cristal G ; Cristal S; Dervacid ; E570; Edenor; Emersol; Extra AS; Extra P; Extra S; Extra ST; 1-heptadecanecarboxylic acid; Hystrene ; Industrene ; Kortacid 1895; Pearl Steric ; Pristerene; stereophanic acid; Tego-stearic .

Chemical Name and CAS Registr y Number

Octadecanoic acid & 57-11-4

Empirical Formula and Molecular Weight

$C_{18}H_{36}O_2$ & 284.47

Functional Category

Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

Description

Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odour (with an odour threshold of 20 ppm) and taste suggesting tallow.

Applications in Pharmaceutical Formulation or Technology

It is mainly used in oral formulations as a tablet and capsule lubricant, although it may also be used as a binder or in combination with shellac as a tablet coating. It has also been suggested that stearic acid may be used in enteric tablet coatings and as a sustained-release drug carrier.

In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams.

Stability and Storage Conditions

Stearic acid is a stable material; an antioxidant may also be added to it. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Stearic acid is incompatible with most metal hydroxides and may be incompatible with bases, reducing agents, and oxidizing agents.

Magnesium Stearate[47]

Non-proprietary Names

BP: Magnesium Stearate, JP: Magnesium Stearate, PhEur: Magnesium Stearate, USP-NF: Magnesium Stearate

Synonyms

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

Chemical Name and CAS Registr y Number

Octadecanoic acid magnesium salt & 557-04-0

Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$ & 591.24

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Functional Category

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, 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.

Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities

It is incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing some vitamins, and most alkaloidal salts.

Materials and methods

8. MATERIALS AND METHODS

Table 1: List of materials and their applications in formulation

S.No.	Name of the material	Manufacturer/Supplier	Use in formulation
1	Aspirin	Kwality Pharmaceuticals, Chennai	Active ingredient
2	Simvastatin	Orchid chemicals, Chennai	Active ingredient
3	Magnesium hydroxide	Kwality Pharmaceuticals, Chennai	Buffering agent
4	Aluminium hydroxide	Kwality Pharmaceuticals, Chennai	Buffering agent
5	Microcrystalline cellulose	Kwality Pharmaceuticals, Chennai	Diluent
6	Lactose	Kwality Pharmaceuticals, Chennai	Diluent
7	Hydroxy propyl methyl cellulose	Kwality Pharmaceuticals, Chennai	Retardant
8	Pregelatinised starch	Kwality Pharmaceuticals, Chennai	Binder
9	Sodium starch glycolate	Kwality Pharmaceuticals, Chennai	Super-disintegrant
10	Magnesium stearate	Kwality Pharmaceuticals, Chennai	Lubricant
11	Stearic acid	Kwality Pharmaceuticals, Chennai	Lubricant
12	Colloidal silicon dioxide	Kwality Pharmaceuticals, Chennai	Glidant
13	Sunset yellow	Kwality Pharmaceuticals, Chennai	Colouring agent

Table 2: List of instruments/Equipments used

S.No.	Equipments/Instruments	Manufacturer/Supplier
1	Electronic Weighing Balance	Asha Scientific Company, Mumbai
2	Sieve set	Pharma Spares, Mumbai
3	10 Station Rotary Compression Machine	Rimek, India
4	Vernier Caliper	Mitutoyo, Japan
5	Monsanto Hardness Tester	Erweka, Mumbai
6	Friabilator	Electrolab, India
7	Disolution Test Apparatus	Veego, Mumbai
8	UV-Visible Spectrophotometer	Shimadzu, Japan
9	FT-IR Spectrophotometer	Nicolet
10	Stability Chamber	Technico, India

METHODOLOGY

PREFORMULATION STUDIES[50]

A preformulation study is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation studies is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

A. Organoleptic properties

The colour, odour and taste of the drugs were studied.

B. Particle size and shape

Particle size and shape of the drugs were studied by Optical microscopic method.

C. Melting point

Melting points of the drugs were confirmed by Capillary tube method.

D. Solubility Analysis

Solubility is an important parameter for preformulation studies because

1. It affects the dissolution of the drug.
2. Bioavailability of drug is directly affected by oral administration and also by dissolution.
3. Particle size, shape, surface area may affect the dissolution characteristics of drug hence it should be determined during preformulation.

Method: Weighed quantity of drug was added to the suitable volume of solvent and solubility is determined.

E. Loss on drying (%)

1g of drug was accurately weighed and dried in an oven at 105ºC for 3 hours. By gentle sidewise shaking, the sample was distributed at the specified temperature for constant

weight. The drug sample was allowed to come to room temperature in a desiccator before weighing.

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{W3 - W2}{W2 - W1} \times 100$$

Where,

W1 –Weight of empty weighing bottle

W2 –Weight of weighing bottle + sample

W3 –Weight of weighing bottle + dried sample

DRUG EXCIPIENT COMPATIBILITY STUDY

The drug and the excipients chosen for the formulation were screened for compatibility by physical methods and Fourier Transform infrared (FTIR) spectroscopic studies.

Physical compatibility study[51]

The physical compatibility studies were conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drugs and the excipients and kept at room temperature and at 40^0C and 75% RH. Any change in colour of the physical mixture was observed visually.

Chemical compatibility study by FTIR[52]

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drugs, polymers, excipients, drug excipient mixture was subjected to FTIR studies to investigate the Drug-excipient interactions. The IR spectra of test samples were obtained by Pressed Pellet Technique using Potassium bromide.

PREPARATION OF BUFFER AND REAGENTS[53]

Preparation of 0.1N Hydrochloric acid

8.5ml of concentrated hydrochloric acid was taken and dissolved in water and made up to 1000 ml to get 0.1N Hydrochloric acid**.**

Sodium hydroxide solution (0.2 M)

8 g of Sodium hydroxide was dissolved in distilled water and volume was made up to 1000 ml with distilled water.

Potassium dihydrogen phosphate solution (0.2 M)

50.0 ml of 0.2 M Potassium dihydrogen phosphate was taken in a 100 ml volumetric flask, to which 22.4 ml of 0.2 M sodium hydroxide was added and volume was made up to the mark with distilled water.

Phosphate buffer (pH 6.8)

50.0 ml of 0.2 M Potassium dihydrogen phosphate was taken in a 1000 ml volumetric flask, to which 22.4 ml of 0.2 M sodium hydroxide was added and volume was made up to the mark with distilled water.

Standard Curve for Aspirin[54]

100 mg of Aspirin was weighed, transferred to a 100 ml standard flask. It was dissolved in ethanol and made up to the volume with 0.1 M Hydrochloric acid, to get a concentration of 1 mg/ml. From the stock solution 10 ml was taken and diluted to 100 ml with 0.1 M Hydrochloric acid to get a concentration of 100µg/ml. The above solution was further diluted with 0.1 M Hydrochloric acid to get concentrations of 2, 4, 6, 8, 10 µg/ml. The absorbance of resulting solutions was measured at 230 nm using UV-Visible Spectrophotometer taking 0.1 M Hydrochloric acid as blank.

Standard curve for Simvastatin[55]

100 mg of Simvastatin was weighed, transferred to a 100 ml standard flask. It was dissolved in methanol and made up to the volume with phosphate buffer pH 6.8, to get a concentration of 1 mg/ml. From the stock solution 10 ml was taken and diluted to 100 ml with phosphate buffer pH 6.8 to get a concentration of 100µg/ml. The above solution was

further diluted with phosphate buffer pH 6.8 to get concentrations of 2, 4, 6, 8, 10 µg/ml. The absorbance of resulting solutions was measured at 230 nm using UV-Visible Spectrophotometer taking 0.1 M Hydrochloric acid as blank.

PRECOMPRESSION STUDIES OF DRUG AND BLEND

FLOW PROPERTY MEASUREMENTS[56]

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. The flow property measurements include Bulk Density, Tapped Density, Compressibility index, Hausner's ratio and Angle of Repose. The flow property measurements of drug and blend were determined to select the type of granulation technique to be carried out for the formulation.

A. Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and initial weight was noted. The initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$\rho_b = M/V_b$$

where **M** and V_b are mass of powder and bulk volume of the powder respectively.

B. Tapped density

It is the ratio of total mass of powder to the tapped volume of powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for 500 times on a wooden surface at a 2 sec interval and the volume attained is the tapped volume. From this the tapped density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$\rho_t = M/V_t$$

where **M** and V_t are mass of powder and bulk volume of the powder respectively.

C. Angle of repose

The flow properties were characterized in terms of angle of repose, Carr's index and Hausner's ratio. For the determination of angle of repose (Θ), the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The drug or the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using the following equation.

$$\Theta = \tan^{-1}(h/r)$$

Where, **h** = height of pile in cm; **r** = radius of pile in cm.

D. Carr's index (or) % Compressibility

It indicates powder flow properties. It is measured for determining the relative importance of interparticulate interactions. It is expressed in % and is given by

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

E. Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the formula given below.

$$HR = \rho_t / \rho_b$$

Where, ρ_t and ρ_b are tapped and bulk density respectively.

Table 3: Values of Angle of Repose, Compressibility Index and Hausner's Ratio

Flow property	Angle of Repose (Ɵ)	Compressibility Index (%)	Hausner's Ratio
Excellent	25 - 30	<10	1.00 – 1.11
Good	31 – 35	11- 15	1.12 – 1.18
Fair	36 - 40	16 – 20	1.19 – 1.25
Passable	41 – 45	21 – 25	1.26 – 1.34
Poor	46 – 55	26 - 31	1.35 – 1.45
Very poor	56 -65	32 – 37	1.46 – 1.59
Very Very poor	>65	>38	>1.60

Formulation development

9. FORMULATION DEVELOPMENT

Formulation of Immediate release powder blend of Aspirin

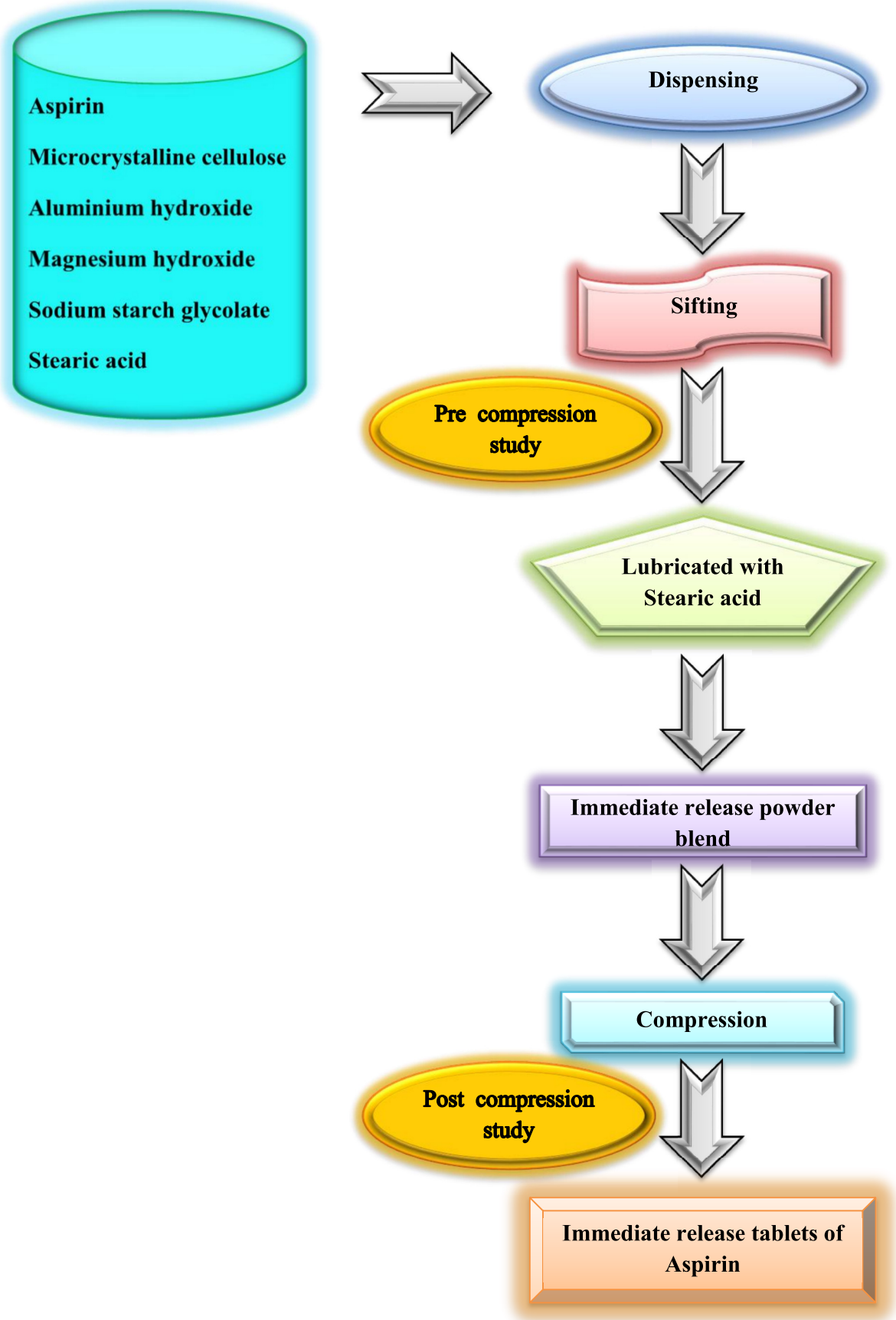
The immediate release powder blend was prepared using Microcrystalline cellulose as diluent. Aluminium hydroxide and Magnesium hydroxide were used as buffering agents[57]. Sodium starch glycolate was used as super disintegrant at 6% concentration to improve the disintegration of the formulation. The powder blend was compressed by 10 station (D tooling) tablet compression machine using 12/32 punches.

Table 4: Composition of immediate release granules

S.No.	INGREDIENTS	A1(mg)	**A2(mg)**	A3(mg)	A4(mg)
1	Aspirin	75	**75**	75	75
2	Magnesium hydroxide	40	**40**	40	40
3	Aluminium hydroxide	40	**40**	40	40
4	Micro crystalline cellulose	75	**75**	70	80
5	Cros carmellose sodium	15	**-**	-	-
6	Sodium starch glycolate	-	**15**	20	10
7	Stearic acid	5	**5**	5	5
Total weight		250	**250**	250	250

The immediate release tablet of Aspirin was formulated and optimized. The optimized formulation was used for the final bilayer tablets.

Flowchart for formulation of immediate release Aspirin tablets



Formulation of delayed release granules of Simvastatin

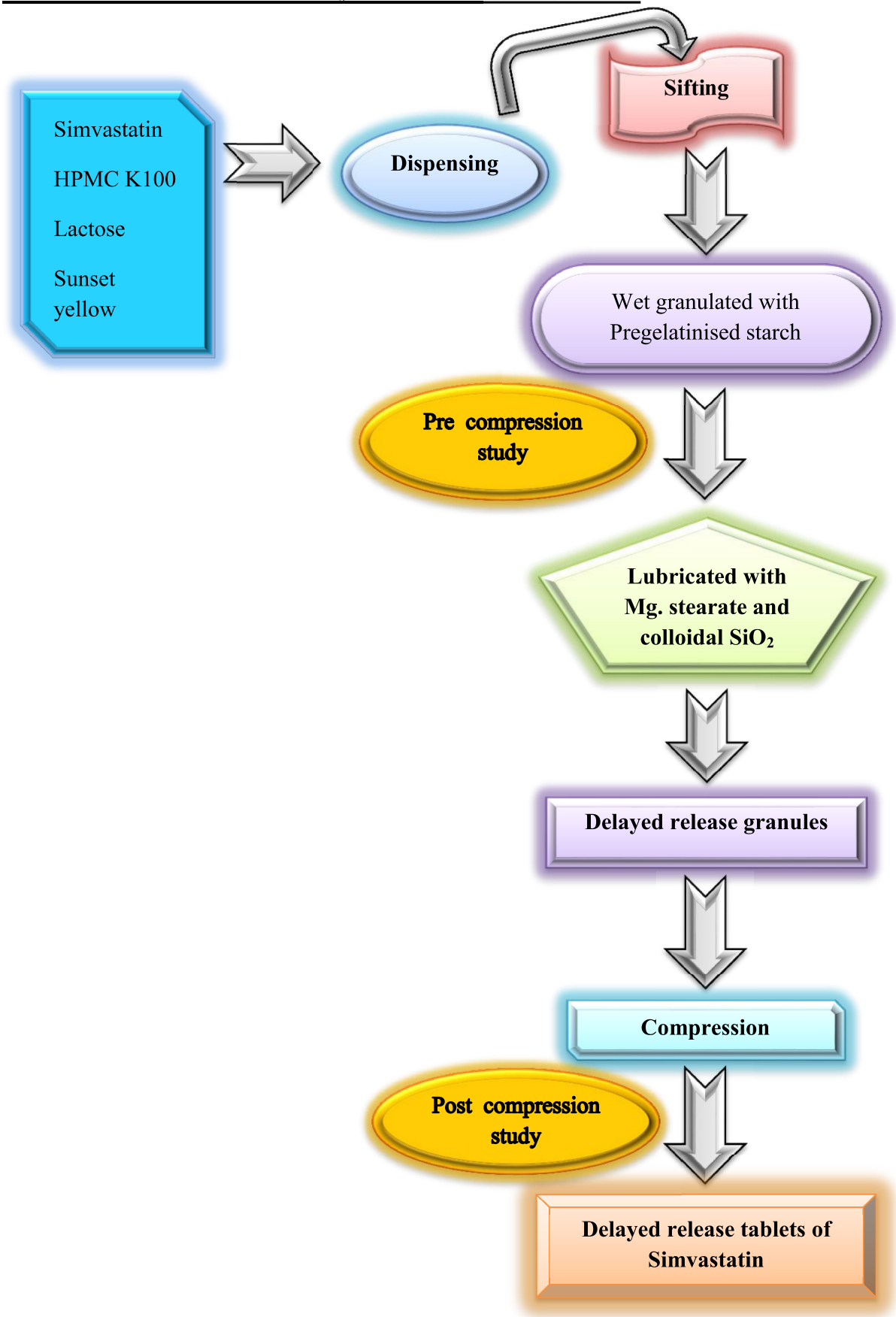
The delayed release granules were prepared by wet granulation technique. HPMC K100 was used as polymer in different concentrations. The tablets were compressed by 10 station (D tooling) tablet compression machine using 9/32 punches. The optimized batch of Delayed release granules of Simvastatin was then compressed with the optimized batch of immediate release powder blend of Aspirin to get bilayer tablets.

Table 5: Compostion of delayed release granules

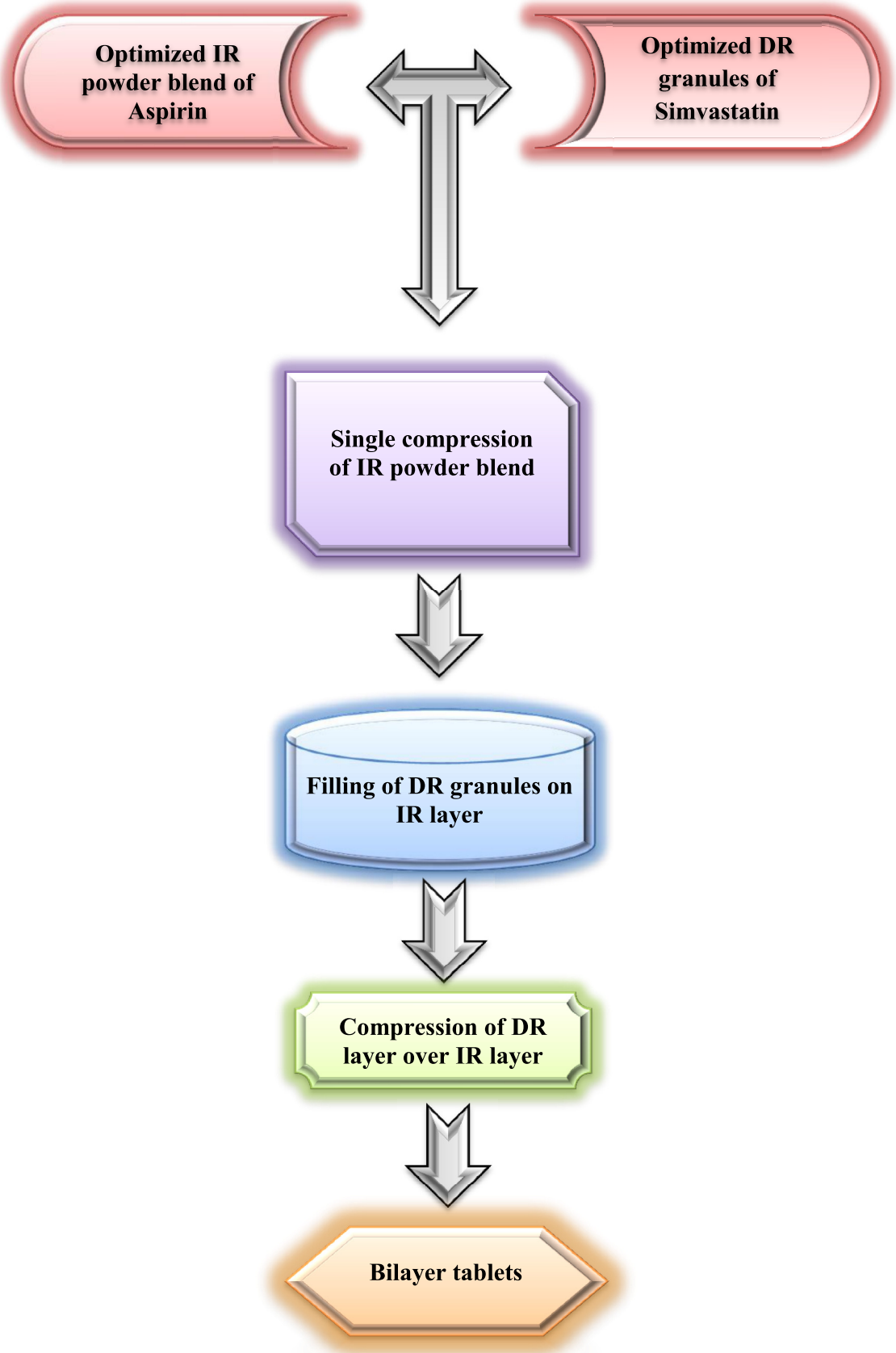
S.No.	INGREDIENTS	S1(mg)	S2(mg)	**S3(mg)**	S4(mg)	S5(mg)	S6(mg)
1	Simvastatin	40	40	**40**	40	40	40
2	Lactose	73	78	**83**	88	93	98
3	HPMC K100	15	10	**5**	15	10	5
4	Pregelatinized starch	30	30	**30**	15	15	15
5	Magnesium stearate	1.5	1.5	**1.5**	1.5	1.5	1.5
6	Silicon dioxide	0.5	0.5	**0.5**	0.5	0.5	0.5
Total weight		160	160	**160**	160	160	160

The delayed release tablet of Simvastatin was formulated and optimized. The optimized formulation was used for the final bilayer tablets.

Flowchart for formulation of Delayed release Simvastatin tablets



Flowchart for bilayer tablets of Aspirin (IR) and Simvastatin (SR)



I. POST COMPRESSION STUDIES

A. PHYSICAL PARAMETERS [58]

1. General appearance

The general appearance of the tablets from each formulation batch was observed. The general appearance parameters such as shape, colour, presence or absence of odour and taste were evaluated visually.

2. Uniformity of Weight

Twenty tablets were selected at random and weighed individually. The average weight was also calculated. The percentage deviation of tablets was calculated and compared with the standard specifications.

3. Thickness and diameter

Thickness and diameter of the tablets were measured using vernier caliper.

4. Hardness

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared formulations was determined using Monsanto hardness tester. It was expressed in Kg/cm^2.

5. Friability

Friability of the prepared formulations was determined using Roche friabilator. Pre-weighed sample of tablets was placed in the friability tester, which was then operated for 100 revolutions, tablets were dedusted and reweighed. The friability of the tablets was calculated using the formula mentioned below.

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Final weight of the tablets}} \times 100$$

DRUG CONTENT

1. FOR IR TABLETS CONTAINING ASPIRIN

Twenty tablets were selected randomly, weighed and finely ground. An accurately weighed quantity of powder equivalent to 100 mg of Aspirin was transferred to a 100 volumetric flask and dissolved in 10 ml of ethanol and the volume was made upto the mark with 0.1M HCl. The solution was kept overnight. The solution was filtered and 10 ml portion of the filtrate was further diluted with 0.1M HCl in a 100ml volumetric flask. The absorbance of the resulting solution was measured at 230 nm taking 0.1M HCl as blank using UV-Visible Spectrophotometer. The concentration was obtained from the calibration graph.

2. FOR DR TABLETS CONTAINING SIMVASTATIN

Twenty tablets were selected randomly, weighed and finely grounded. An accurately weighed quantity of powder equivalent to 100 mg of Simvastatin was transferred to 100ml volumetric flask and shaken with 10ml of ethanol for 15 minutes, then it was made upto the mark with phosphate buffer pH 6.8 solution. The solution was kept overnight. The solution was filtered and 10 ml portion of the filtrate was diluted with pH 6.8 phosphate buffer solution in a 100ml volumetric flask. From the above solution 10 ml portion was further diluted upto the mark with pH 6.8 phosphate buffer solution in a 100ml volumetric flask. The absorbance of the resulting solution was measured at 238 nm taking 6.8 pH phosphate buffer solution as blank using UV-Visible Spectrophotometer. The concentration was obtained from the calibration graph.

3. BILAYER TABLETS OF ASPIRIN AND SIMVASTATIN (SIMULTANEOUS EQUATIONS METHOD)[59]

Simultaneous estimation of Aspirin and Simvastatin was carried out using UV-Visible spectrophotometer

Procedure

The following equation were used to determine the contents

$$C_x = \frac{A_2 a_{y1} - A_1 a_{y2}}{a_{x2}\, a_{y1} - a_{x1}\, a_{y2}}$$

$$C_y = \frac{A_1 a x_2 - A_2 a_{x1}}{a_{x2}\, a_{y1} - a_{x1}\, a_{y2}}$$

Where a_{x1} and a_{x2} - The absorptivity of drug X at λ_1 and λ_2 respectively

a_{y1} and a_{y2} - The absorptivity of drug Y at λ_1 and λ_2 respectively

A_1 and A_2 – The absorbance of sample at λ_1 and λ_2 respectively

$$\frac{A_1 / A_2}{a_{x1} / a_{x2}} \quad \text{and} \quad \frac{a_{y1} / a_{y2}}{A_1 / A_2}$$

The ratios should lie outside the range of 0.1 – 2.0 for the precise determination of X and Y drugs. This criterion is satisfied only when the λmax of the two components is reasonably dissimilar and the components should not interact chemically.

Preparation of standard stock solution of Aspirin

Aspirin equivalent to 100 mg was accurately weighed and dissolved using 10 ml of ethanol. The volume was made upto mark with 0.1M HCl in a 100 ml volumetric flask. 10 ml of the resulting solution was diluted to 100 ml with 0.1M HCl. Again10 ml of the resulting solution was diluted to 100 ml with 0.1M HCl.

Preparation of standard stock solution of Simvastatin

Simvastatin equivalent to 100 mg was accurately weighed and dissolved using 10 ml of ethanol. The volume was made upto mark with 0.1M HCl in a 100 ml volumetric flask. 10 ml of the resulting solution was diluted to 100 ml with 0.1M HCl. Again10 ml of the resulting solution was diluted to 100 ml with 0.1M HCl.

Preparation of sample solution:

Twenty tablets were selected randomly, weighed and finely ground. Powder equivalent to 100mg of Aspirin was weighed and transferred to a 100ml standard flask. The powder was then dissolved in ethanol. The volume was made upto the mark using 0.1M HCl. 10 ml of the resulting solution was diluted to 100 ml with 0.1M HCl. Again10 ml of the

resulting solution was diluted to 100 ml with 0.1M HCl. The absorbance of the resulting solutions was measured at 278 and 238 nm respectively.

IN VITRO DISINTEGRATION STUDIES FOR IR TABLETS

The disintegration time was determined using disintegration test apparatus. The tablets were placed in each of the six tubes of the basket. The assembly was suspended in 0.1M HCl maintained at a temperature of 37^0C $\pm 2^0$C and the apparatus was switched on. The time taken to disintegrate the tablets completely was noted.

IN VITRO DISSOLUTION STUDIES

For IR tablets

The release of Aspirin was determined using USP Type II (paddle) dissolution apparatus under sink condition. 900ml of 0.1M HCl was used as dissolution medium at a temperature of 37^0C $\pm 0.5^0$C. The paddle was stirred at a speed of 50 rpm. The release studies were carried out for 45 mins. The absorbance of the solution was measured at 230nm taking 0.1M HCl as blank using UV- Visible Spectrophotometer.

For DR tablets

In vitro drug release studies of the DR tablets were carried out using USP type II dissolution test apparatus at 37°C (± 0.5°C) and 50 rpm speed in 900 ml of 0.1 N hydrochloric acid (gastric simulated fluid, pH 1.2) as a dissolution medium for first 2 hours and in intestinal simulated fluid (buffer solution, pH 6.8) for the next 4 hours.

Buffer stage:[60] After 2 hours operation in the acid stage, 20 ml NaOH (25%) was added to the previous fluid. The pH (6.8 ± 0.05) was adjusted with the addition of 1.2 ml ortho-phosphoric acid. The operation was continued for 4 hours. After each 30 mins interval 10 ml of dissolution solution was sampled and the released drug assayed by using UV spectrophotometer at 238 nm. At each withdrawal 10 ml of fresh dissolution medium was added. The dissolution study was continued for 4 hours to get a simulated picture of the drug release and the percentage of drug release was plotted against time.

For bilayer tablets

The release of bilayer tablets was determined using Type II (paddle) dissolution apparatus under sink condition. 900ml of 0.1M HCl was used as dissolution medium for first

two hours followed by pH 6.8 phosphate buffer solution for next two hours maintained at a temperature of 37^0C ±0.5^0C. The paddle was stirred at a speed of 50rpm. The release studies were carried out for four hours. The absorbance of the solution was measured at 230 nm and 238 nm taking respective buffer solutions as blank using UV-Visible Spectrophotometer and the calculations were done by simultaneous equations method.

STABILITY STUDY

Stability studies of optimized bilayer tablets were carried out according to ICH guidelines. All the tablets were packed in blisters and kept in a humidity chamber at 40 ± 2^0C and 75 ± 5% RH for 3 months. Samples were withdrawn at monthly intervals and analyzed for physical characteristics, hardness and *in vitro* dissolution.

Results and discussion

10. RESULTS AND DISCUSSION

The present work was aimed to formulate bilayer tablets containing Aspirin for Immediate release and Simvastatin for Delayed release. The therapy with these drugs offers a good quality of life for patients who are suffering from Coronary artery disease.

PREFORMULATION STUDIES

DRUG CHARACTERIZATION

ASPIRIN

Aspirin raw material obtained from Kwality Pharmaceuticals was tested and the results are listed in table 6.

Table 6: Identification of Aspirin

S.No	Test	Specification	Results
1	Description	White or almost white, crystalline powder or colourless crystals or granules	White granules
2	Loss on drying	Not more than 0.5 % w/w	0.12 % w/w
3	Solubility	Slightly soluble in water, freely soluble in ethanol	Complies
4	Melting point	143^0C	143^0C

SIMVASTATIN

Simvastatin raw material was obtained from Orchid Chemicals was tested and the results are listed in table 7.

Table 7: Identification of Simvastatin

S.No	Test	Specification	Results
1	Description	A white or almost white, crystalline powder	A white crystalline powder
2	Loss on drying	Not more than 0.5% w/w	0.25% w/w
3	Solubility	Insoluble in water, very soluble in methylene chloride, freely soluble in ethanol	Complies
4	Melting point	135^0C - 138^0C	136^0C

DRUG -EXCIPIENT COMPATIBILITY STUDY

Physical compatibility study

The compatibility studies were carried out to study the possible interactions between active ingredients (Aspirin & Simvastatin) and inactive ingredients. Physical mixtures of both API and excipients were prepared separately and kept for stability at 40^0C and 75% RH for one month. Samples were taken out after every 10 days and were subjected to physical and chemical compatibility tests. The physical compatibility of drug and excipients are given in table 8.

Table 8: Physical compatibility study drugs and excipients

S.No.	Drug & Excipient	Description and condition				Comments
		Initial	Room temperature & 40^0C/75% RH in days			
			10^{th}	20^{th}	30^{th}	
01	Aspirin	White coloured granules	NC	NC	NC	Compatible
02	Simvastatin	White powder	NC	NC	NC	Compatible
03	Aspirin + Simvastatin	White blend	NC	NC	NC	Compatible
04	MCC	White crystalline powder	NC	NC	NC	Compatible
05	SSG	White or almost white hygroscopic powder	NC	NC	NC	Compatible
06	Lactose	White to off white crystalline powder	NC	NC	NC	Compatible
07	HPMC K100	White or creamy white powder	NC	NC	NC	Compatible
08	Pregelatinized starch	White or off white powder	NC	NC	NC	Compatible
09	Aluminium hydroxide	White powder	NC	NC	NC	Compatible
10	Magnesium hydroxide	White powder	NC	NC	NC	Compatible
11	Stearic acid	White or yellowish white crystalline powder	NC	NC	NC	Compatible
12	Magnesium stearate	White or almost white crystalline powder	NC	NC	NC	Compatible
13	SiO_2	White powder	NC	NC	NC	Compatible

14	Sunset yellow	Yellowish orange coloured powder	NC	NC	NC	Compatible
15	Aspirin + MCC	White crystalline powder	NC	NC	NC	Compatible
16	Aspirin + $Al(OH)_2$	White powder	NC	NC	NC	Compatible
17	Aspirin + $Mg(OH)_3$	White powder	NC	NC	NC	Compatible
18	Aspirin + SSG	Creamy white crystalline powder	NC	NC	NC	Compatible
19	Aspirin + Stearic acid	White crystalline powder	NC	NC	NC	Compatible
20	Simvastatin + Starch	White powder	NC	NC	NC	Compatible
21	Simvastatin + Lactose	Creamy white powder	NC	NC	NC	Compatible
22	Simvastatin + HPMC K100	White crystalline powder	NC	NC	NC	Compatible
23	Simvastatin + Magnesium stearate	White crystalline powder	NC	NC	NC	Compatible
24	Simvastatin + Colloidal SiO_2	White powder	NC	NC	NC	Compatible

NC – No Change

Chemical compatibility study

All the samples were scanned at the wave number region of 4000-400 cm^{-1} using KBr disc method. This KBr discs were formed by taking Drug and KBr in a ratio of 1:100 respectively. Then this mixture was mixed well in mortar for three to five mins. A very small amount of this mixture was uniformly spread and sandwiched between the disks and pressed using KBr pellet press at a pressure of 20,000 psi for 1 min. The pressure was then released and pellet was placed into the pellet holder and thus scanned in the IR region. The results are given below.

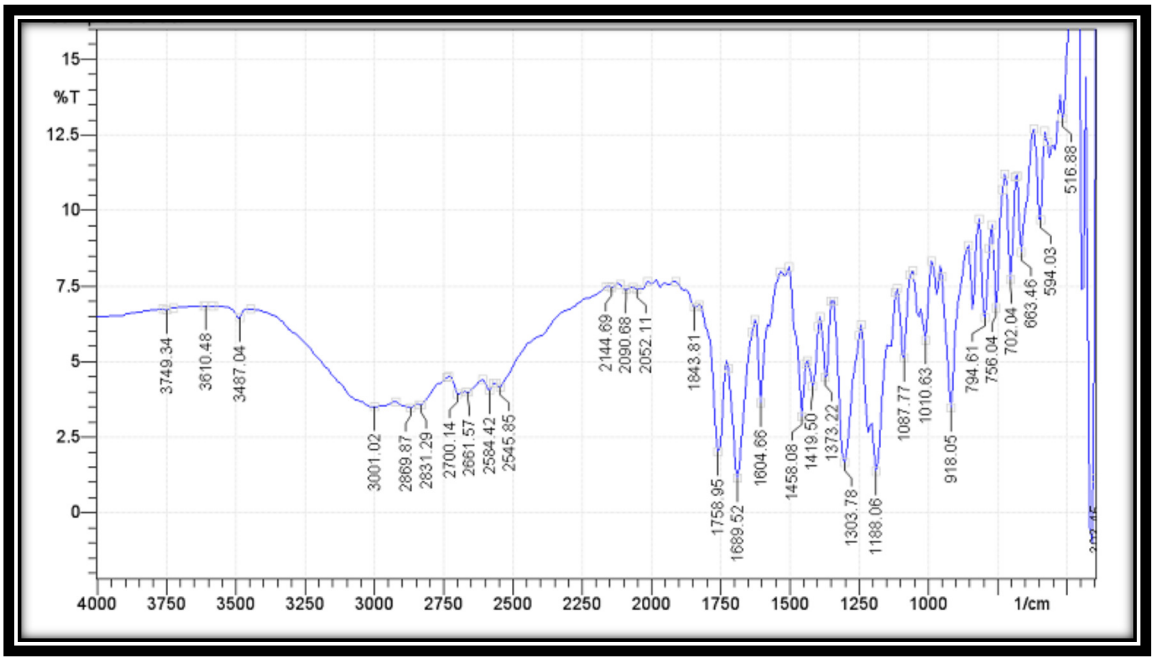


Fig 2. FTIR of Aspirin

Table 9: IR spectral Interpretation of Aspirin

Functional group	Characteristic peak (cm^{-1})		Observed peak(cm^{-1})	
	Stretching	Bending	Stretching	Bending
C=C (Aromatic)	--	1700 – 1500	--	1689
C=O (Carboxylic acid)	1780 – 1700	--	1758	--
C-H (Alkane)	2950 – 2850	--	2869	--
O-H (Carboxylic acid)	3000 – 2500	--	2700	--
C-H (Aromatic)	3100 – 3000	--	3001	--

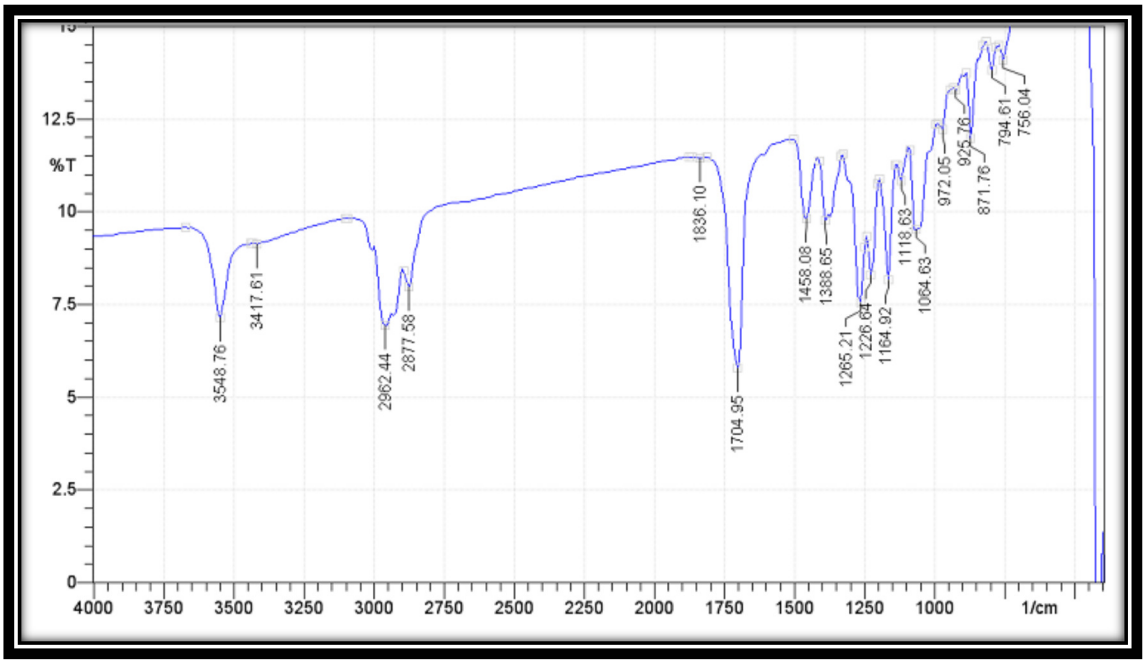


Fig 3: FTIR of Simvastatin

Table 10: IR spectral Interpretation of Simvastatin

Functional group	Characteristic peak (cm^{-1})		Observed peak(cm^{-1})	
	Stretching	Bending	Stretching	Bending
C-O	1320 – 1000	--	1265	--
C=O (Carboxylic acid)	1780 – 1700	--	1704	--
C-H (Alkane)	2950 – 2850	--	2877	--
O-H (Alcohols)	3550 – 3200	--	3548	--

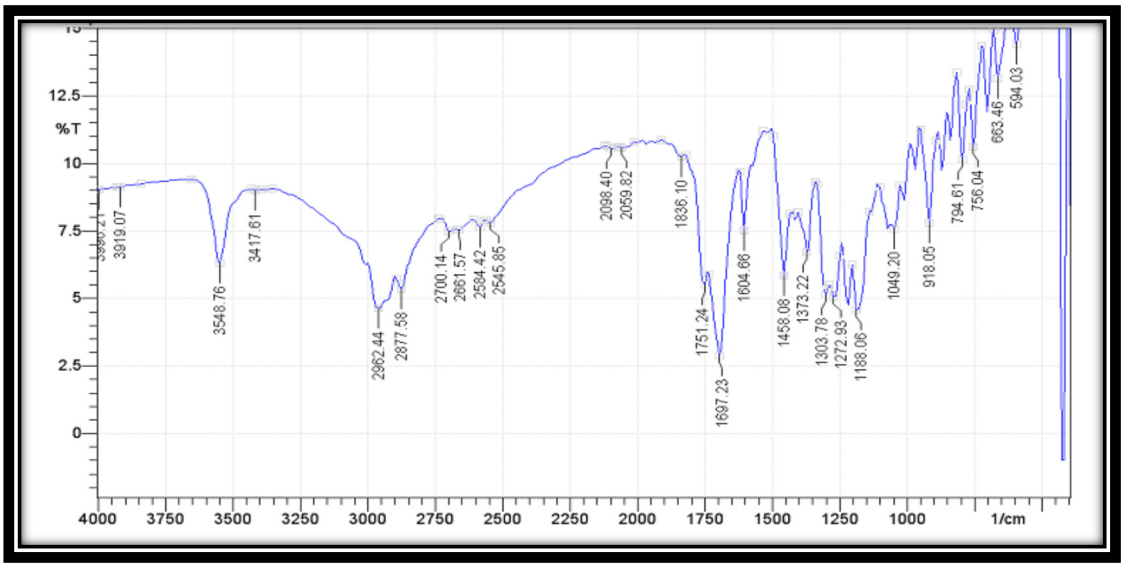


Fig 4: FTIR of Aspirin and Simvastatin

Table 11: IR spectral Interpretation of Aspirin and Simvastatin

Functional group	Characteristic peak (cm^{-1})		Observed peak(cm^{-1})	
	Stretching	Bending	Stretching	Bending
C-O	1320 – 1000	--	1272	--
C=C (Aromatic)	--	1700 – 1500	--	1697
C=O (Carboxylic acid)	1780 – 1700	--	1751	--
C-H (Alkane)	2950 – 2850	--	2877	--
O-H (Carboxylic acid)	3000 – 2500	--	2700	--
OH (Alcohols)	3550 – 3200	--	3548	--

INFERENCE

Characteristic peaks were observed in the spectrum. There is no interaction between the two drugs.

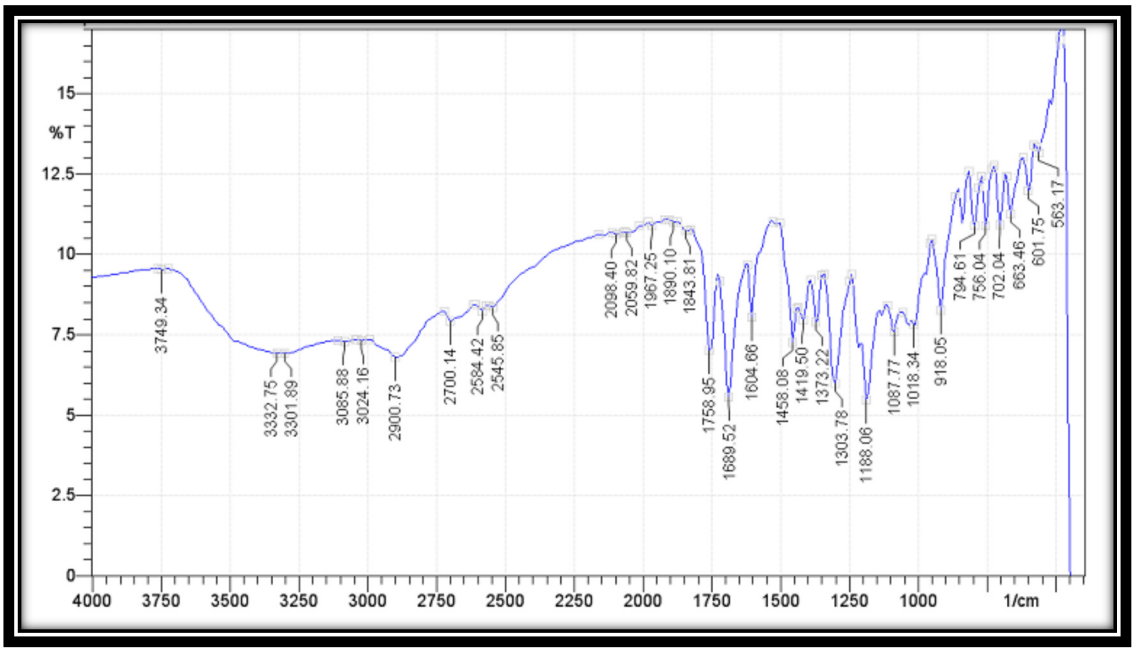


Fig 5: FTIR of Aspirin & Micro crystalline cellulose

Table 12: IR spectral Interpretation of Aspirin & Micro crystalline cellulose

Functional group	Characteristic peak (cm^{-1})		Observed peak(cm^{-1})	
	Stretching	Bending	Stretching	Bending
C=C (Aromatic)	--	1700 – 1500	--	1689
C=O (Carboxylic acid)	1780 – 1700	--	1758	--
C-H (Alkane)	2950 – 2850	--	2900	--
O-H (Carboxylic acid)	3000 – 2500	--	2700	--
C-H (Aromatic)	3100 – 3000	--	3024	--

INFERENCE

Characteristic peaks were observed in the spectrum. There is no interaction between Aspirin & Micro crystalline cellulose.

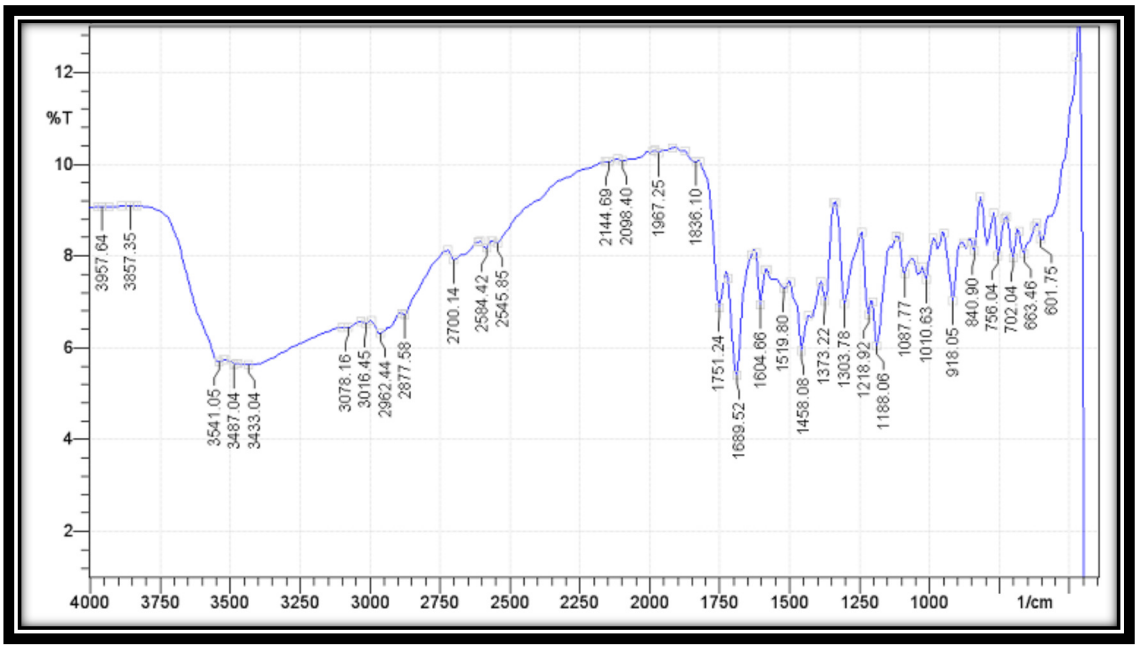


Fig 6: FTIR of Aspirin & Aluminium hydroxide

Table 13: IR spectral Interpretation of Aspirin & Aluminium hydroxide

Functional group	**Characteristic peak (cm^{-1})**		**Observed peak(cm^{-1})**	
	Stretching	**Bending**	**Stretching**	**Bending**
C=C (Aromatic)	--	1700 – 1500	--	1689
C=O (Carboxylic acid)	1780 – 1700	--	1751	--
C-H (Alkane)	2950 – 2850	--	2877	--
O-H (Carboxylic acid)	3000 – 2500	--	2700	--
C-H (Aromatic)	3100 – 3000	--	3016	--

INFERENCE

Characteristic peaks were observed in the spectrum. There is no interaction between Aspirin & Aluminium hydroxide.

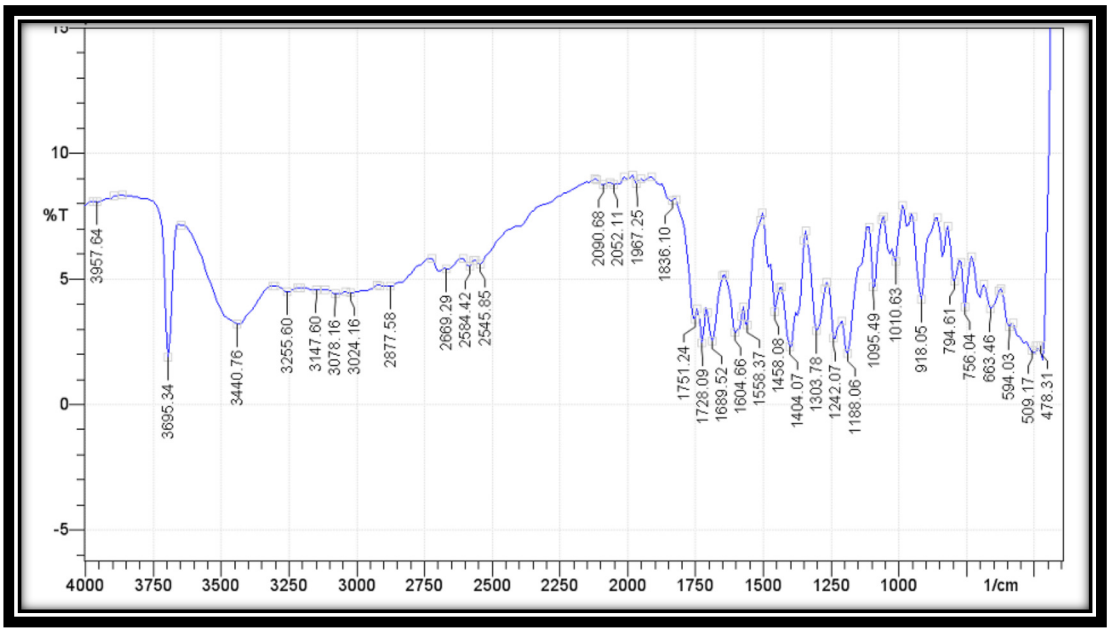


Fig 7: FTIR of Aspirin & Magnesium hydroxide

Table 14: IR spectral Interpretation of Aspirin & Magnesium hydroxide

Functional group	**Characteristic peak (cm^{-1})**		**Observed peak(cm^{-1})**	
	Stretching	**Bending**	**Stretching**	**Bending**
C=C (Aromatic)	--	1700 – 1500	--	1689
C=O (Carboxylic acid)	1780 – 1700	--	1751	--
C-H (Alkane)	2950 – 2850	--	2877	--
O-H (Carboxylic acid)	3000 – 2500	--	2669	--
C-H (Aromatic)	3100 – 3000	--	3024	--

INFERENCE

Characteristic peaks were observed in the spectrum. There is no interaction between Aspirin & Magnesium hydroxide.

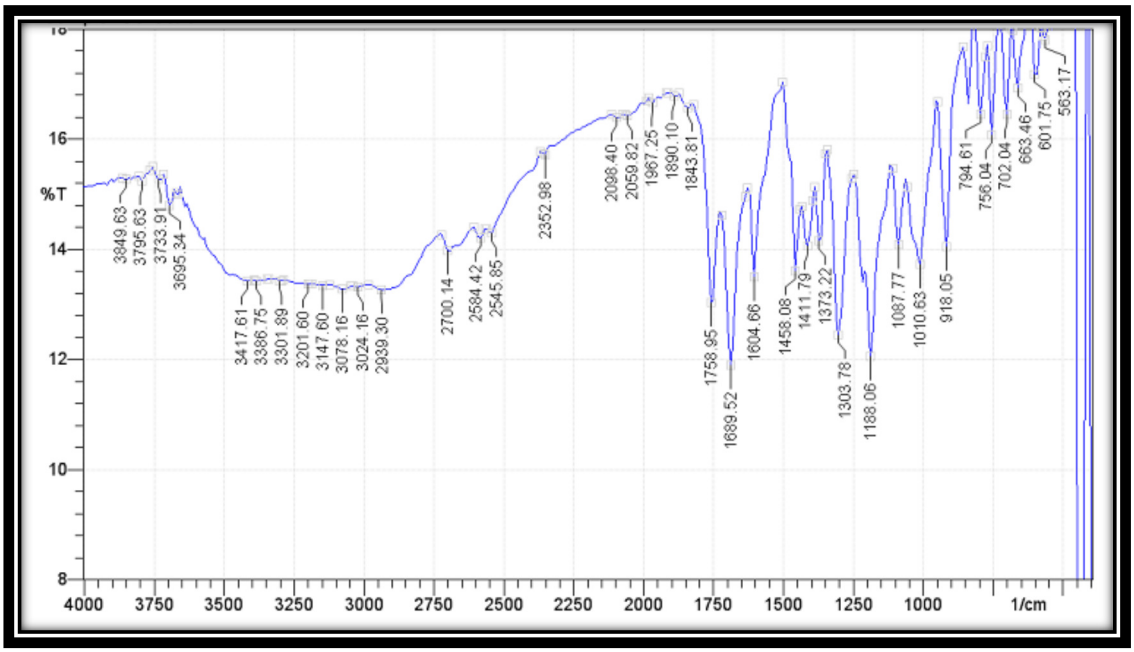


Fig 8: FTIR of Aspirin & Sodium starch glycolate

Table 15: IR spectral Interpretation of Aspirin & Sodium starch glycolate

Functional group	Characteristic peak (cm^{-1})		Observed peak(cm^{-1})	
	Stretching	Bending	Stretching	Bending
C=C (Aromatic)	--	1700 – 1500	--	1689
C=O (Carboxylic acid)	1780 – 1700	--	1758	--
C-H (Alkane)	2950 – 2850	--	2939	--
O-H (Carboxylic acid)	3000 – 2500	--	2700	--
C-H (Aromatic)	3100 – 3000	--	3024	--

INFERENCE

Characteristic peaks were observed in the spectrum. There is no interaction between Aspirin & Sodium starch glycolate.

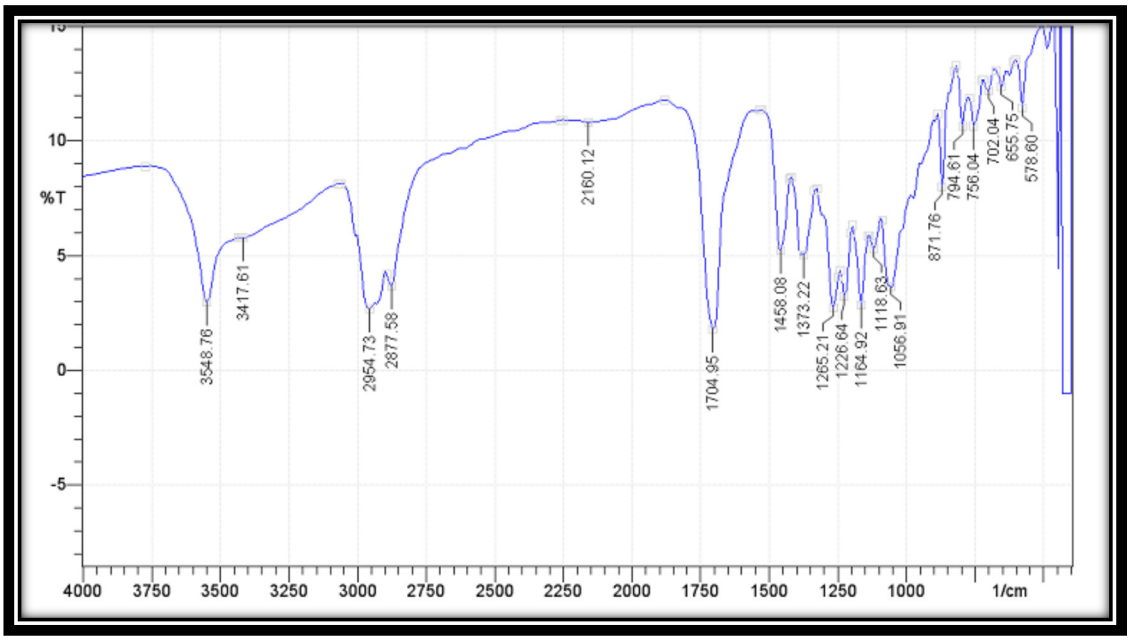


Fig 9: FTIR of Simvastatin & HPMC K100

Table 16: IR spectral Interpretation of Simvastatin & HPMC K100

Functional group	**Characteristic peak (cm^{-1})**		**Observed peak(cm^{-1})**	
	Stretching	**Bending**	**Stretching**	**Bending**
C-O	1320 – 1000	--	1265	--
C=O (Carboxylic acid)	1780 – 1700	--	1704	--
C-H (Alkane)	2950 – 2850	--	2877	--
O-H (Alcohols)	3550 – 3200	--	3548	--

INFERENCE

Characteristic peaks were observed in the spectrum. There is no interaction between Simvastatin & HPMC K100.

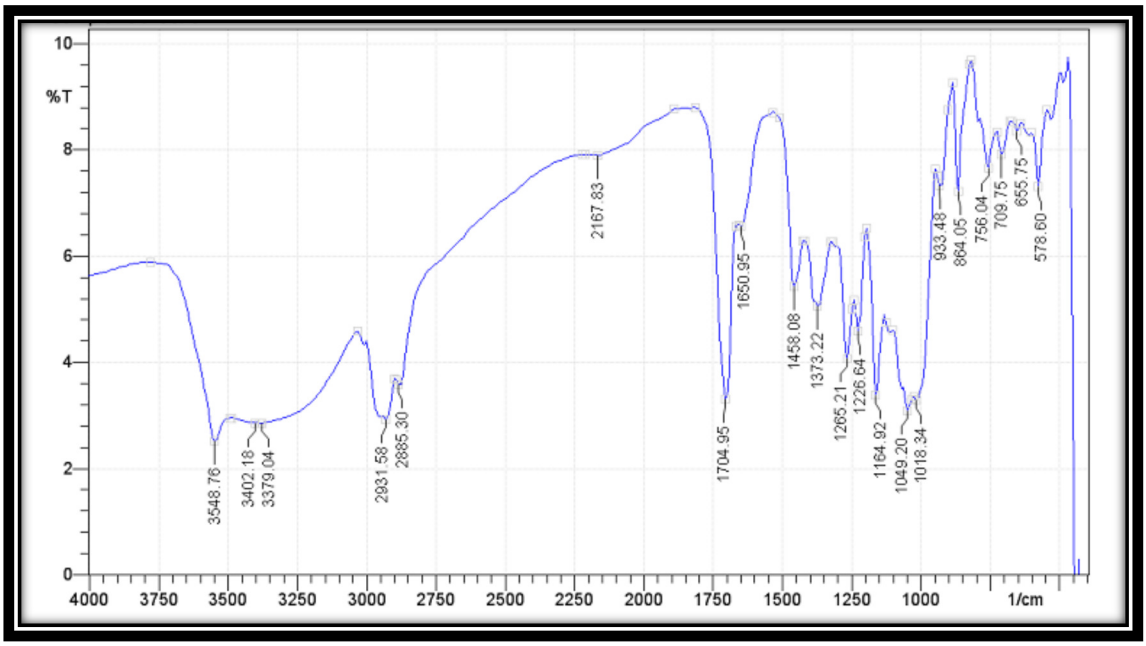


Fig 10: FTIR of Simvastatin & Starch

Table 17: IR spectral Interpretation of Simvastatin & Starch

Functional group	Characteristic peak (cm^{-1})		Observed peak(cm^{-1})	
	Stretching	Bending	Stretching	Bending
C-O	1320 – 1000	--	1265	--
C=O (Carboxylic acid)	1780 – 1700	--	1704	--
C-H (Alkane)	2950 – 2850	--	2885	--
O-H (Alcohols)	3550 – 3200	--	3548	--

INFERENCE

Characteristic peaks were observed in the spectrum. There is no interaction between Simvastatin & Starch.

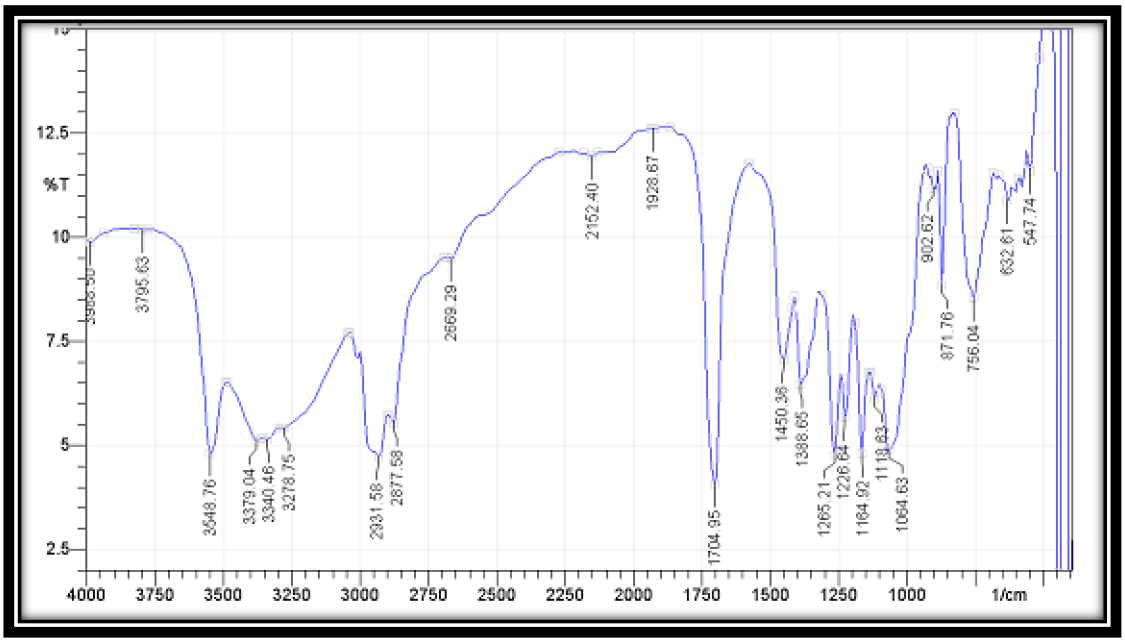


Fig 11: FTIR of Simvastatin & Lactose

Table 18: IR spectral Interpretation of Simvastatin & Lactose

Functional group	**Characteristic peak (cm^{-1})**		**Observed peak(cm^{-1})**	
	Stretching	**Bending**	**Stretching**	**Bending**
C-O	1320 – 1000	--	1265	--
C=O (Carboxylic acid)	1780 – 1700	--	1704	--
C-H (Alkane)	2950 – 2850	--	2877	--
O-H (Alcohols)	3550 – 3200	--	3548	--

INFERENCE

Characteristic peaks were observed in the spectrum. There is no interaction between Simvastatin & Lactose.

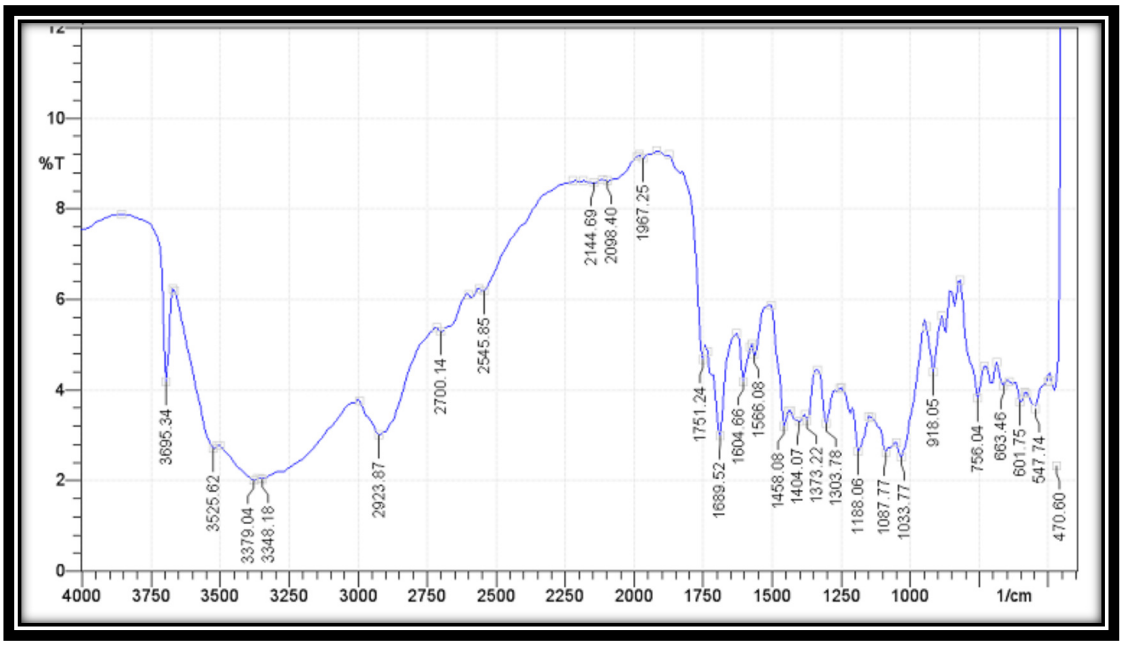


Fig 12: FTIR of Optimised Bilayer formulation

Table 19: IR spectral Interpretation of Optimised Bilayer formulation

Functional group	Characteristic peak (cm^{-1})		Observed peak(cm^{-1})	
	Stretching	Bending	Stretching	Bending
C-O	1320 – 1000	--	1188	--
C=C (Aromatic)	--	1700 – 1500	--	1689
C=O (Carboxylic acid)	1780 – 1700	--	1751	--
C-H (Alkane)	2950 – 2850	--	2923	--
O-H (Carboxylic acid)	3000 – 2500	--	2700	--
OH (Alcohols)	3550 – 3200	--	3525	--

INFERENCE

Characteristic peaks were observed in the spectrum. There is no interaction between the drugs and excipients.

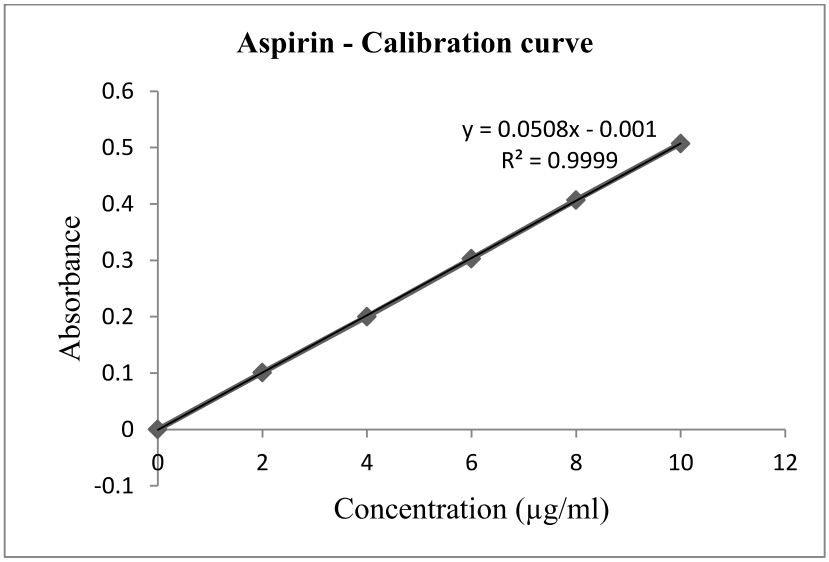
CALIBRATION CURVE FOR ASPIRIN

The data for calibration curve of Aspirin is shown in Table 20 and the calibration curve shown in Fig. 13.

Table 20: Data for calibration curve of Aspirin in 0.1M HCl

Concentration (µg/ml)	Absorbance at λ_{230nm}
0	0
2	0.101
4	0.2
6	0.303
8	0.407
10	0.507

Fig 13: Calibration curve of Aspirin



It was found that the solution of Aspirin in 0.1M HCl show linearity (R^2= 0.9999) at concentrations of 2 -10 (µg/ml) and obey Beer Lambert Law.

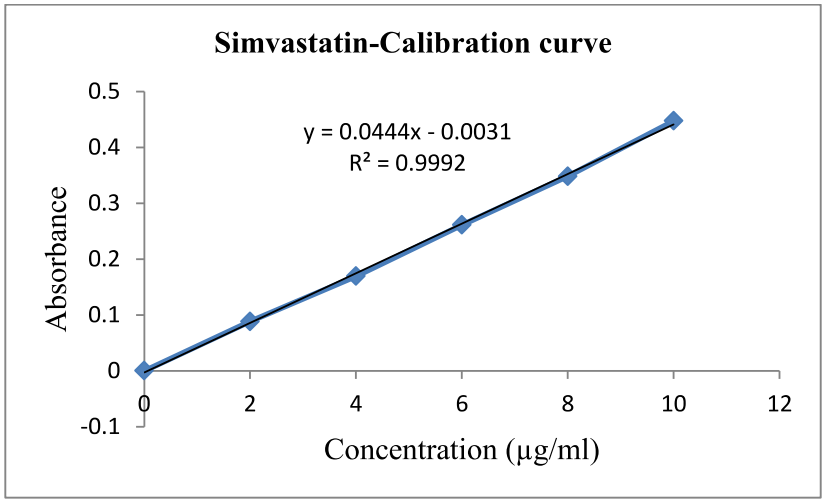
CALIBRATION CURVE FOR SIMVASTATIN

The data for calibration curves of Simvastatin in 0.1M HCl and pH 6.8 phosphate buffer is shown in Tables 21 & 22 and the calibration curves are shown in Fig. 14 & 15.

Table 21: Data for calibration curve of Simvastatin in 0.1M HCl

Concentration (µg/ml)	Absorbance at λ_{238nm}
0	0
2	0.088
4	0.169
6	0.261
8	0.348
10	0.447

Fig 14: Calibration curve of Simvastatin in 0.1 M HCl

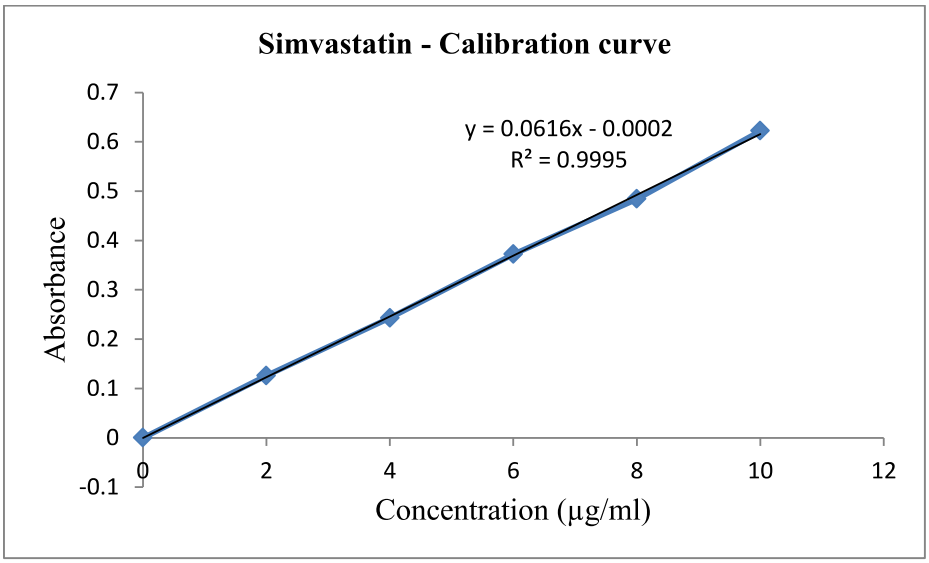


It was found that the solution of Simvastatin in 0.1M HCl show linearity (R^2= 0.9992) at concentrations of 2 -10 (µg/ml) and obey Beer Lambert Law.

Table 22: Data for calibration curve of Simvastatin in phosphate buffer pH 6.8

Concentration (µg/ml)	Absorbance at λ_{238nm}
0	0
2	0.126
4	0.243
6	0.372
8	0.484
10	0.622

Fig 15: Calibration curve of Simvastatin in phosphate buffer pH 6.8



It was found that the solution of Simvastatin in phosphate buffer pH 6.8 show linearity (R^2= 0.9995) at concentrations of 2 -10 (µg/ml) and obey Beer Lambert Law.

PRECOMPRESSION STUDY - IR FORMULATION

The API and the formulated blends were evaluated for precompression parameters. The results are given in Table 23.

Table 23: Precompression study of API and formulated blends

API and Formulation	Bulk density g/cm^3*	Tapped density g/cm^3*	Compressibility index (%)*	Hausner's ratio*	Angle of repose (Degree)*
Aspirin	0.625 ± 0.2548	0.714 ± 0.1472	12.4642 ± 0.1513	1.1424 ± 0.0485	$35^0 23' \pm 0.1368$
A1	0.4762 ± 0.2354	0.625 ± 0.0214	23.8081 ± 0.1254	1.3125 ± 0.2135	$45^0 14' \pm 0.1247$
A2	0.4545 ± 0.0214	0.5882 ± 0.5461	22.6964 ± 0.1864	1.2942 ± 0.1523	$48^0 23' \pm 0.0245$
A3	0.4761 ± 0.8412	0.6061 ± 0.9462	21.4486 ± 0.4862	1.2731 ± 0.7724	$49^0 72' \pm 0.2441$
A4	0.4651 ± 0.3541	0.6061 ± 0.3543	23.2635 ± 0.5454	1.3032 ± 0.4215	$48^0 49' \pm 0.0219$

* Mean ± S.D (n = 3)

The bulk density of IR blends ranged from 0.4545 – 0.4762 g/cm^3 and the tapped density ranged from 0.5882 – 0.625 g/cm^3. The compressibility index of IR blends ranged from 21.4486 – 23.808 and Hausner's ratio ranged from 1.2731 – 1.3125. The angle of repose of the IR blends ranged from $45^0 14' - 49^0 72'$. The formulated blends showed passable flow property, so direct compression technique was used for preparing IR blend of Aspirin

FORMULATION DEVELOPMENT

Preparation of IR tablets of Aspirin

Direct compression technique was employed for the formulation of IR blend of Aspirin.

Four formulations of immediate release layer of Aspirin (A1, A2, A3, A4) were prepared using Croscarmellose sodium and Sodium starch glycolate (super disintegrant). The

tablets were compressed using 10 Station (D tooling) tablet compression machine using 12/32 punches.

POST COMPRESSION STUDY FOR TABLETS

UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated tablets is given in table 24.

Table 24: Uniformity of weight of the formulated tablets

Formulation	Uniformity of weight (mg)*
Specified limit	237.5 - 262.5
A1	251.4 ± 0.0452
A2	253.3 ± 0.0052
A3	255.1 ± 0.0111
A4	248.3 ± 0.0031

* Mean ± S.D (n = 3)

The tablet complies with the test for uniformity of weight.

TABLET THICKNESS AND DIAMETER

The thickness and diameter of the formulated tablets is given in table 25.

Table 25: Thickness and diameter of the formulated tablets

Formulation	Thickness (mm)*	Diameter (mm)*
A1	9.5 ± 0.0	4.0 ± 0.0
A2	9.5 ± 0.0	4.0 ± 0.0
A3	9.5 ± 0.0	4.0 ± 0.0
A4	9.5 ± 0.0	4.0 ± 0.0

* Mean ± S.D (n = 3)

The tablets were found to be uniform in thickness and diameter.

HARDNESS

The hardness of the formulated tablets is given in table 26.

Table 26: Hardness of the formulated tablets

Formulation	Hardness (Kg/cm^2)*
A1	5.47 ± 0.3298
A2	4.97 ± 0.1247
A3	4.36 ± 0.2399
A4	5.20 ± 0.2944

* Mean ± S.D (n = 3)

All the formulated tablets showed sufficient mechanical strength to resist the transportation.

FRIABILITY

The friability of the formulated tablets is given in table 27.

Table 27: Friability of formulated tablets

Formulation	% friability*
Specified limit	Not more than 1.0 %
A1	0.214 ± 0.0124
A2	0.321 ± 0.0211
A3	0.117 ± 0.0713
A4	0.183 ± 0.0318

* Mean ± S.D (n = 3)

The percentage friability of all the formulations was within the acceptable limits. i.e. not more than 1%.

DRUG CONTENT

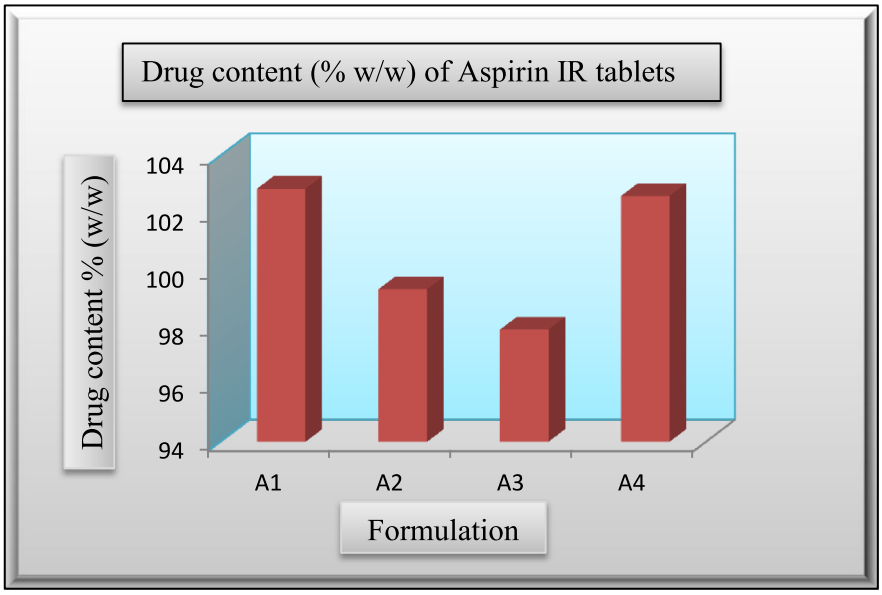
The drug content of the formulated tablets is given in fig. 16 and table 28.

Table 28: Drug content of formulated IR tablets

Formulation	Drug content (% w/w)*
Specified limit	95 – 105
A1	102.84 ± 0.6547
A2	99.33 ± 0.2318
A3	97.92 ± 0.0024
A4	102.59 ± 0.1183

* Mean ± S.D (n = 3)

Fig 16: Drug content of formulated IR tablets



The drug content of all the IR formulations was found to be within the limit. i.e. the drug content was not less than 95% and not more than 105%.

DISINTEGRATION TIME

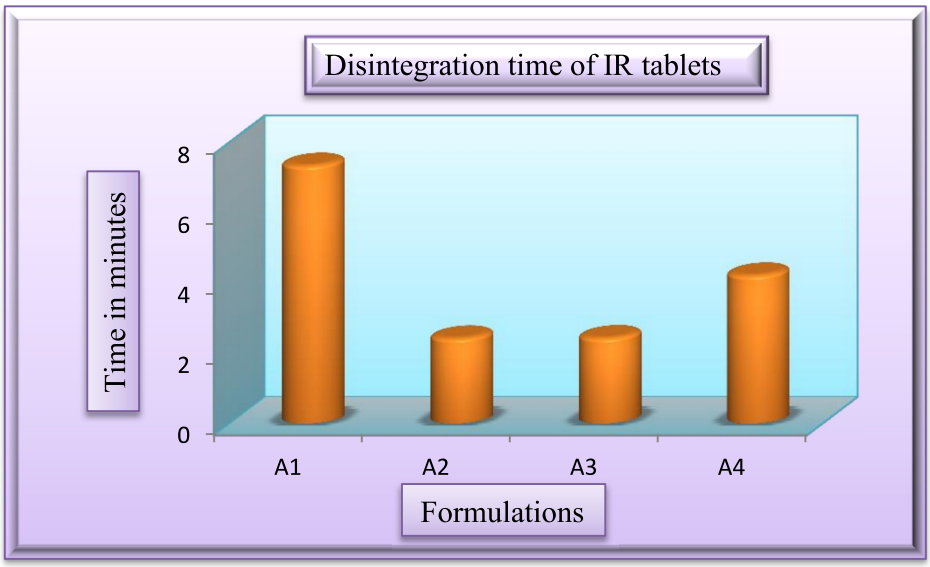
The disintegration time of the IR tablets is given in table 29 and fig. 17.

Table 29: Disintegration time of IR tablets

Formulation	Disintegration time (mins)*
A1	7.33 ± 0.0042
A2	2.42 ± 0.1248
A3	2.43 ± 0.4112
A4	4.21 ± 0.0472

* Mean ± S.D (n = 3)

Fig 17: Disintegration time of IR tablets



The disintegration time of IR tablets ranged from 7.33 to 2.42 mins. The disintegration time of formulation A2 containing 2% Sodium starch glycolate was found to have optimum disintegration time for IR tablets.

IN VITRO DISSOLUTION STUDY

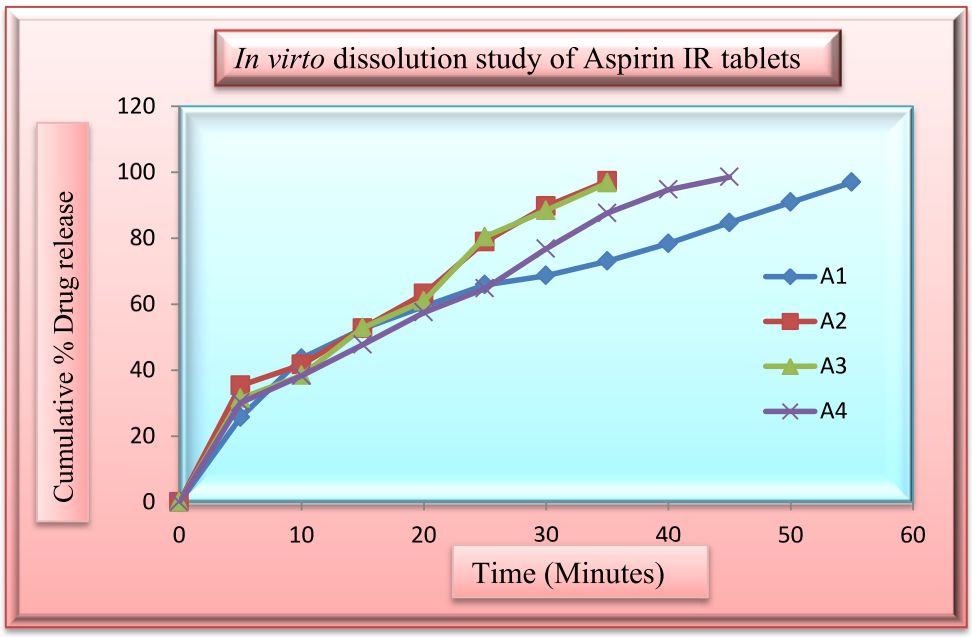
The *in vitro* dissolution study of IR formulations of Aspirin is shown in table 30 and fig. 18.

Table 30: *In vitro* dissolution study of IR tablets

Time (mins)	Cumulative % drug release*			
	A1	A2	A3	A4
0	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000
5	25.67 ± 0.2415	35.38 ± 0.0014	31.45 ± 0.4512	30.14 ± 0.2152
10	43.6 ± 0.0214	41.67 ± 0.0482	38.41 ± 0.1520	38.29 ± 0.4128
15	52.55 ± 0.2451	52.73 ± 0.2145	52.86 ± 0.0415	47.73 ± 0.1247
20	59.31 ± 0.1548	63.21 ± 0.1243	60.99 ± 0.7115	57.5 ± 0.5412
25	65.91 ± 0.4715	78.98 ± 0.4157	80.46 ± 0.2541	64.76 ± 0.7116
30	68.68 ± 0.2418	89.74 ± 0.1248	88.45 ± 0.8421	76.84 ± 0.1774
35	73.08 ± 0.5472	97.36 ± 0.5421	96.82 ± 0.2751	87.63 ± 0.6521
40	78.43 ± 0.2176			94.73 ± 0.4189
45	84.75 ± 0.4152			98.57 ± 0.4127
50	90.91 ± 0.0245			
55	96.97 ± 0.0214			

* Mean ± S.D (n = 3)

Fig 18: *In vitro* dissolution study of IR tablets of Aspirin



The in vitro dissolution study of IR tablets showed that 6% concentration of SSG was found to be optimum for immediate release of Aspirin.

The 6% concentration of SSG released 97.36 % at the end of 35mins.

Therefore formulation A2 was optimized and selected for final bilayer tablets.

FOR DR TABLETS

PRECOMPRESSION STUDY

The API, formulated blends and granules were evaluated for precompression parameters. The results are given in Table 31.

Table 31: Precompression study of API and formulated blends

API and Formulation	Bulk density g/cm^3*	Tapped density g/cm^3*	Compressibility index (%)*	Hausner's ratio*	Angle of repose (Degree)*
Simvastatin	0.1786 ± 0.1478	0.2778 ± 0.1593	35.71 ± 0.1349	1.56 ± 0.1558	$57^0 26' \pm 0.1245$
S1	0.5000 ± 0.5471	0.7100 ± 0.4961	29.57 ± 0.6442	1.42 ± 0.1279	$55^0 03' \pm 0.1444$
S2	0.5281 ± 0.5632	0.7314 ± 0.4972	27.79 ± 0.4192	1.39 ± 0.4457	$51^0 23' \pm 0.2456$
S3	0.5136 ± 0.2549	0.7211 ± 0.3118	28.77 ± 0.4572	1.40 ± 0.1149	$53^0 19' \pm 0.2421$
S4	0.5311 ± 0.6324	0.7439 ± 0.8221	28.60 ± 0.5472	1.40 ± 0.2245	$51^0 31' \pm 0.2147$
S5	0.5416 ± 0.2178	0.7792 ± 0.3172	30.49 ± 0.6219	1.44 ± 0.5434	$52^0 68' \pm 0.0412$
S6	0.5384 ± 0.5419	0.7419 ± 0.4253	27.43 ± 0.5661	1.38 ± 0.5486	$51^0 29' \pm 0.1749$

* Mean ± S.D (n = 3)

The bulk density of DR blends ranged from 0.5 – 0.5416 g/cm^3 and the tapped density ranged from 0.71 – 0.7792 g/cm^3. The compressibility index of DR blends ranged from 27.436 – 30.493 and Hausner's ratio ranged from 1.378 – 1.439. The angle of repose of the DR blends ranged from $51^0 23'$ - $55^0 03'$.

The formulated blends showed poor flow property so wet granulation technique was used for preparing DR granules of Simvastatin. The DR granules were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and Angle of Repose. The results are given in the Table 32.

Table 32: Precompression study of formulated granules

Formulation	Bulk density g/cm^3*	Tapped density g/cm^3*	Compressibility index (%)*	Hausner's ratio*	Angle of repose (Degree) *
S1	0.4719 ± 0.0145	0.5449 ± 0.0478	13.40 ± 0.0148	1.15 ± 0.0587	$23^0 43' \pm$ 0.0112
S2	0.4721 ± 0.1248	0.5318 ± 0.1654	11.23 ± 0.0125	1.13 ± 0.1258	$24^0 57' \pm$ 0.0184
S3	0.4793 ± 0.0225	0.5431 ± 0.0457	11.74 ± 0.0651	1.13 ± 0.2547	$23^0 10' \pm$ 0.1291
S4	0.4619 ± 0.1985	0.5307 ± 0.2017	12.96 ± 0.0632	1.15 ± 0.3657	$25^0 24' \pm$ 0.0245
S5	0.4528 ± 0.2871	0.5114 ± 0.2941	11.46 ± 0.3614	1.13 ± 0.0547	$24^0 41' \pm$ 0.2248
S6	0.4624 ± 0.0945	0.5426 ± 0.1118	14.78 ± 0.1367	1.17 ± 0.0246	$24^0 57' \pm$ 0.0157

* Mean ± S.D (n = 3)

The bulk density of DR granules ranged from 0.4528 – 0.4793 g/cm^3 and the tapped density ranged from 0.5114 – 0.5449 g/cm^3. The compressibility index of DR granules ranged from 11.23 – 14.78 and Hausner's ratio ranged from 1.13 – 1.17. The angle of repose of the DR blends ranged fom $23^0 10'$ - $25^0 24'$. The formulated granules showed good flow property.

FORMULATION DEVELOPMENT

Wet granulation technique was employed for the formulation of DR granules of Simvastatin. Six batches of DR granules were prepared by using hydrophilic polymer HPMC K100. The formulations were compressed on a 10 station (D tooling) tablet compression machine using 9 × 32 mm inch punches.

POST COMPRESSION STUDY FOR TABLETS

UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated tablets is given in table 33.

Table 33: Uniformity of weight of the formulated tablets

Formulation	Uniformity of weight (mg)*
Specified limit	148.00 – 172.00
S1	162.79 ± 0.2496
S2	161.23 ± 0.0248
S3	162.18 ± 0.1542
S4	162.40 ± 0.2764
S5	159.11 ± 0.8162
S6	160.90 ± 0.3814

* Mean ± S.D (n = 3)

The tablet complies with the test for uniformity of weight.

TABLET THICKNESS AND DIAMETER

The thickness and diameter of the formulated tablets is given in table 34.

Table 34: Thickness and diameter of the formulated tablets

Formulation	Thickness (mm)*	Diameter (mm)*
S1	8.0 ± 0.0	2.5 ± 0.0
S2	8.0 ± 0.0	2.5 ± 0.0
S3	8.0 ± 0.0	2.5 ± 0.0
S4	8.0 ± 0.0	2.0 ± 0.0
S5	8.0 ± 0.0	2.0 ± 0.0
S6	8.0 ± 0.0	2.0 ± 0.0

* Mean ± S.D (n = 3)

The tablets were found to be uniform in thickness and diameter.

HARDNESS

The hardness of the formulated tablets is given in table 35.

Table 35: Hardness of the formulated tablets

Formulation	Hardness (Kg/cm^2)*
S1	5.17 ± 0.2357
S2	4.83 ± 0.6236
S3	5.66 ± 0.2357
S4	5.23 ± 0.7587
S5	5.43 ± 0.4922
S6	5.60 ± 0.5657

* Mean ± S.D (n = 3)

All the formulated tablets showed sufficient mechanical strength to resist the transportation.

FRIABILITY

The friability of the formulated tablets is given in table 36.

Table 36: Friability of formulated tablets

Formulation	% friability*
Specified limit	Not more than 1.0 %
S1	0.877 ± 0.0020
S2	0.008 ± 0.0031
S3	0.369 ± 0.0061
S4	0.414 ± 0.0065
S5	0.049 ± 0.0772
S6	0.493 ± 0.0080

* Mean ± S.D (n = 3)

The percentage friability of all the formulations was within the acceptable limits. i.e. not more than 1%.

DRUG CONTENT

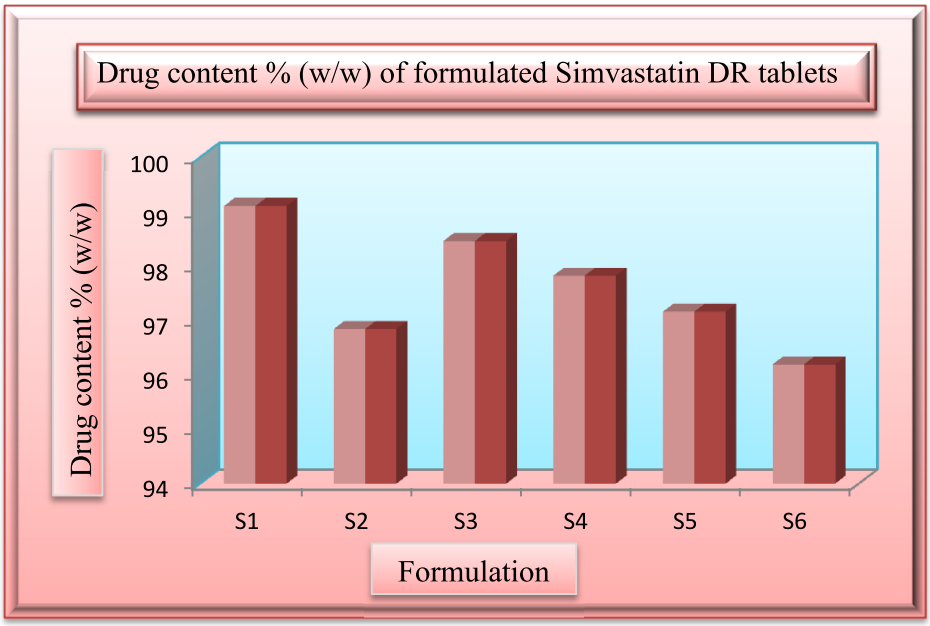
The drug content of the formulated tablets is given in fig. 19 and table 37.

Table 37: Drug content of formulated DR tablets

Formulation	Drug content (% w/w)*
Specified limit	90 – 110
S1	99.1 ± 0.2451
S2	96.84 ± 0.1475
S3	98.46 ± 0.0524
S4	97.82 ± 0.2247
S5	97.16 ± 0.3147
S6	96.19 ± 0.0814

* Mean ± S.D (n = 3)

Fig 19: Drug content of formulated DR tablets



The drug content of all the IR formulations was found to be within the limit. i.e. the drug content was not less than 90 % and not more than 110 %. (as per I.P. 2010).

IN VITRO DISSOLUTION STUDY

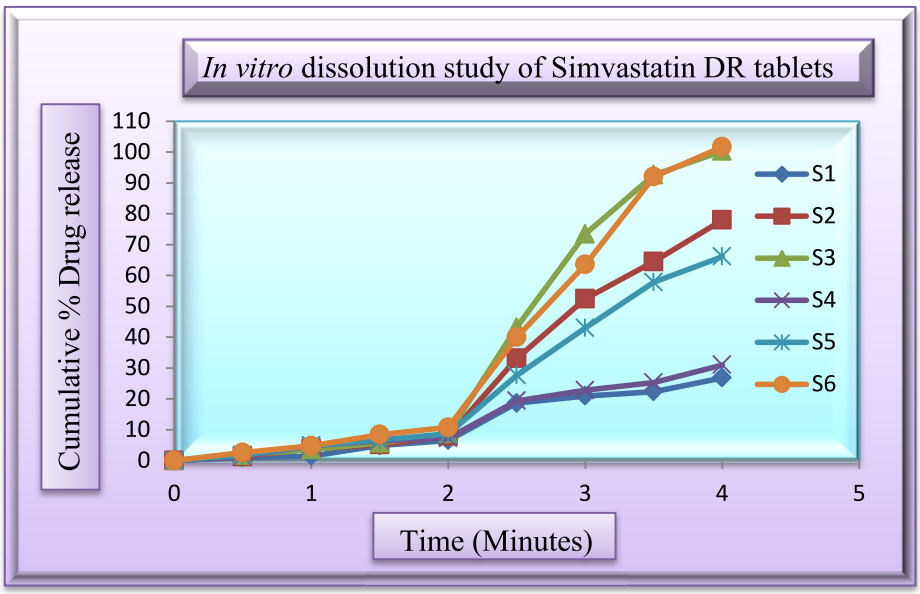
The *in vitro* dissolution study of the formulated DR tablets is given in table 38 and fig. 20.

Table 38: *In vitro* dissolution study of DR tablets

Time (hours)	Cumulative % drug release*					
	S1	**S2**	**S3**	**S4**	**S5**	**S6**
0	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000
0.5	0.96 ± 0.5124	1.27 ± 0.2485	1.68 ± 0.2547	1.31 ± 0.2101	1.71 ± 0.0024	2.58 ± 0.2471
1.0	1.44 ± 0.0148	3.77 ± 0.2541	3.58 ± 0.0021	4.75 ± 0.6325	4.78 ± 0.2147	4.75 ± 0.5524
1.5	4.89 ± 0.2454	5.12 ± 0.2147	5.67 ± 0.6324	6.41 ± 0.2104	6.68 ± 0.2887	8.41 ± 0.2179
2.0	6.51 ± 0.2489	7.91 ± 0.5214	8.68 ± 0.2014	7.28 ± 0.3327	8.67 ± 0.0179	10.76 ± 0.2274
2.5	18.61 ± 0.2147	33.09 ± 0.2147	43.18 ± 0.2019	19.33 ± 0.0024	27.62 ± 0.7961	39.95 ± 0.4417
3.0	20.92 ± 0.8452	52.42 ± 0.3549	73.45 ± 0.2219	22.77 ± 0.0782	42.96 ± 0.4128	63.54 ± 0.6361
3.5	22.35 ± 0.4152	64.46 ± 0.0217	92.57 ± 0.2199	25.27 ± 0.0214	57.81 ± 0.7114	91.98 ± 0.0019
4.0	26.81 ± 0.2489	77.95 ± 0.2314	100.3 ± 0.0029	30.99 ± 0.5224	66.11 ± 0.4172	101.72 ± 0.0742

* Mean ± S.D (n = 3)

Fig 20: *In vitro* dissolution study of DR tablets



The results of *in vitro* dissolution study of DR tablets showed that

- The formulation S3 containing 5 % of HPMC K100 showed only 8.68 % of drug at the end of 2 hours and thus met the IP specifications and it showed a complete release of drug at the end of 4 hours.
- The formulation S6 showed 10.76 % drug release at the end of 2 hours and thus it failed to meet the IP specifications.
- The formulations S1, S2, S4, and S5 met the IP specifications at the end of 2 hours but to achieve the complete drug release it took more time.
- Based on the comparative release profile, formulation S3 was selected for final bilayer tablets.

FORMULATION DEVELOPMENT

PREPARATION OF BILAYER TABLETS

- Optimized immediate layer of Aspirin was prepared by direct compression method.
- Optimized delayed release layer of Simvastatin was prepared by wet granulation method. The granules were compressed on 10 station (D-tooling) tablet compression machine using 12/32 punches.

POST COMPRESSION STUDY OF BILAYER TABLETS

The compressed bilayer tablets were evaluated for the following parameters and the values are given in table 39.

Table 39: Post compression study of Bilayer tablets

Parameters*	Bilayer tablet*
Uniformity of weight (mg)*	401.27 ± 0.0684
Thickness (mm)*	4.00 ± 0.0000
Diameter (mm)*	9.5 ± 0.0000
Hardness (kg/cm^2)*	5.83 ± 0.2357
Friability (%)*	0.182 ± 0.4119
Drug content (Simultaneous estimation method) 1. Aspirin (% w/w) 2. Simvastatin (% w/w)	 103.24 ± 0.0289 102.49 ± 0.0874

* Mean ± S.D (n = 3)

IN VITRO DISSOLUTION STUDY

The *in vitro* dissolution study of drugs in bilayer tablets is given in tables 40 & 41 and fig. 21 & 22.

Table 40: *In vitro* dissolution study of Aspirin in Bilayer tablets

Time (mins)	% Drug release*
0	0 ± 0.0000
5	38.93 ± 0.5208
10	44.46 ± 0.7598
15	54.65 ± 0.9294
20	68.01 ± 0.0356
25	82.15 ± 0.8706
30	92.81 ± 0.7041
35	99.9 ± 0.8991

* Mean ± S.D (n = 3)

Fig 21: *In vitro* dissolution study of Aspirin in Bilayer tablets

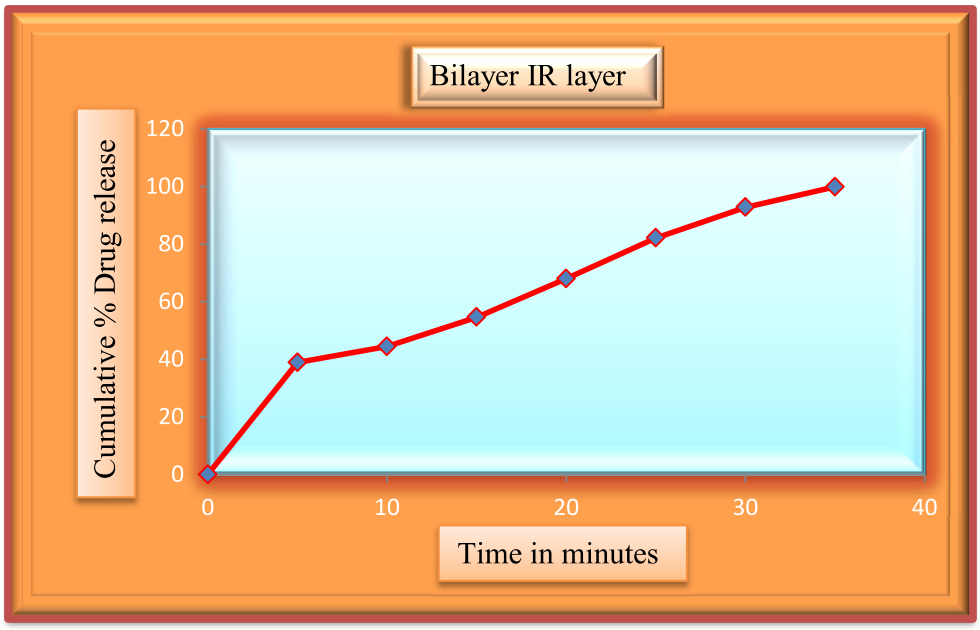
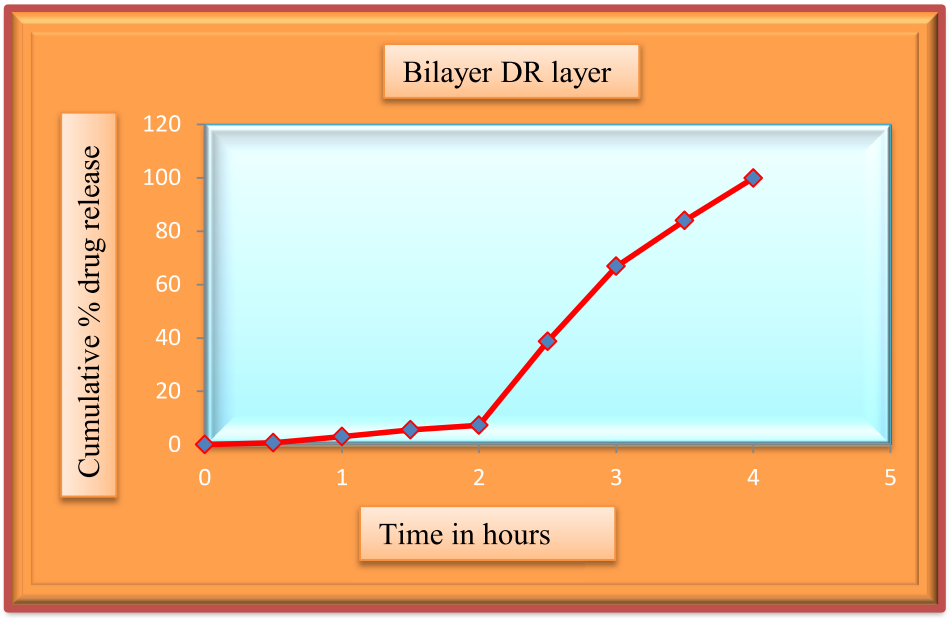


Table 41: *In vitro* dissolution study of Simvastatin in Bilayer tablets

Time (mins)	% Drug release*
0	0 ± 0.0000
0.5	0.69 ± 0.1078
1.0	3.03 ± 0.2491
1.5	5.53 ± 0.2502
2.0	7.24 ± 0.1438
2.5	38.66 ± 0.7654
3.0	66.74 ± 0.8152
3.5	83.93 ± 0.3967
4.0	99.84 ± 0.1236

* Mean ± S.D (n = 3)

Fig 22: *In vitro* dissolution study of Simvastatin in Bilayer tablets



POSTCOMPRESSION STUDIES OF BILAYER TABLETS:

- The bilayer tablets fulfilled the official requirements of uniformity of weight. The average percentage of deviation of 20 tablets was less than ± 3%.
- The thickness of all the formulations of bilayer tablet was 4.0 mm. The hardness and percentage friability were 5.83 kg/cm^2 and 0.182 % respectively.
- The percentage drug content of the IR and SR formulations were found to be within the limits.
- The release profile of Aspirin from the immediate release layer was found to be satisfactory.
- The release profile of Simvastatin from the delayed release layer was found to be satisfactory, where the release of the drug were within the limits.

Stability study

Stability study

The optimized bilayer tablets were subjected to stability studies and the results are given in Table 42.

Table 42: Stability study of physical parameters of the optimized bilayer tablets

Parameters	**Initial**	**1st month**	**2nd month**	**3rd month**
Uniformity of weight (mg)*	401.27 ± 0.06	401.89 ± 0.01	402.11 ± 0.32	401.21 ± 0.02
Thickness (mm)*	4.0 ± 0.00	4.0 ± 0.00	4.0 ± 0.00	4.0 ± 0.00
Diameter (mm)*	9.5 ± 0.00	9.5 ± 0.00	9.5 ± 0.00	9.5 ± 0.00
Hardness (Kg/cm^2)*	5.83 ± 0.23	5.21 ± 0.02	5.63 ± 0.28	5.91 ± 0.49
Friability (%)*	0.182 ± 0.41	0.097 ± 0.04	0.118 ± 0.15	0.216 ± 0.22

*Mean ± S.D (n=3)

Table 43: Assay and Dissolution profile of bilayer tablets

Time interval (month)	**Drug content (%w/w)***		**Cumulative % release***	
	Aspirin	**Simvastatin**	**Aspirin (At the end of 35 mins)**	**Simvastatin (At the end of 4 hrs)**
Initial	103.24 ± 0.02	102.49 ± 0.08	99.9 ± 0.89	99.84 ± 0.12
1 month	101.18 ± 0.25	101.82 ± 0.62	100.21 ± 0.52	98.38 ± 0.42
2 month	102.59 ± 0.54	101.52 ± 0.22	97.12 ± 0.19	99.27 ± 0.47
3 month	101.88 ± 0.87	102.17 ± 0.29	99.24 ± 0.47	98.31 ± 0.51

*Mean ± S.D (n=3)

Fig.23: Photograph of Bilayer tablets

Summary and conclusion

11. SUMMARY AND CONCLUSION

SUMMARY

The present work involves the formulation development, optimization and *in-vitro* evaluation of bilayer tablet containing Aspirin in the immediate release layer and Simvastatin in the delayed release layer, using sodium starch glycolate as a super disintegrant for the immediate release layer and the hydrophilic polymer HPMC K100 for the delayed release layer. The developed formulation shows an alternative to the conventional dosage form for the treatment of Coronary artery disease.

- The polymer and other excipients were selected based on the satisfying results produced during drug-excipient compatibility studies to develop the final formulation.
- Immediate release tablets were formulated by direct compression method. Delayed release tablets were formulated by wet granulation method because of the poor flow property of the blends.
- The formulated granules were evaluated for precompression parameters which showed that the flow property was good.
- The formulated tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, diameter and friability.
- The disintegration time of IR tablets containing SSG 6% was found to be optimum.
- The drug content of the formulated IR and DR tablets were found to be within the limits.
- Based on the *in vitro* dissolution studies of IR tablets, formulation A2 was optimised and selected for final bilayer tablets.
- Based on the *in vitro* dissolution studies of DR tablets, formulation S3 met the IP specifications at the end of 2 hours. Thus the formulation S3 was optimised and selected for bilayer tablets.
- The optimised IR and DR formulations were compressed into bilayer tablets.
- The formulated bilayer tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, diameter and friability.
- The drug content of the bilayer tablets were estimated by simultaneous estimation method and it was found to be within the Pharmacopoeial limit.

- The *in vitro* dissolution studies of the optimised bilayer tablets met the IP specifications at the end of 2 hours.
- Stability studies of optimized bilayer tablets were carried out according to ICH guidelines. It indicated that the bilayer tablets are stable and does not show any significant changes in the physical characteristics, drug content and dissolution. The results obtained were found to be within the limits.

CONCLUSION

- Combination of Aspirin as an immediate release layer and Simvastatin as a delayed release layer reduces polytherapy to monotherapy and improves the patient compliance.
- From the results, formulated bilayer tablet provides better *in vitro* release from immediate release layer as well as delayed release layer.
- The stability studies indicated that the bilayer tablets are stable and does not show any significant changes during storage.
- Success of the *in vitro* drug release studies recommends the product for further in vivo studies, which may improve patient compliance.

FUTURE PLAN

- Scale up studies of the optimized formulation.
- *In-vivo* studies and *in vitro- in vivo* correlation studies.
- Bioequivalence studies with the marketed formulations.

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