DESIGN AND EVALUATION OF DIFFERENT GASTRORETENTIVE DRUG DELIVERY SYSTEMS OF SOME HMG CO-A REDUCTASE INHIBITORS

A DISSERTATION SUBMITTED TO
SAURASHTRA UNIVERSITY, RAJKOT IN PARTIAL FULFILLMENT FOR THE AWARD OF DEGREE OF

Doctor of Philosophy
IN
PHARMACY

SUBMITTED BY
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DECLARATION

I hereby declare that this dissertation/thesis entitled **"DESIGN AND EVALUATION OF DIFFERENT GASTRORETENTIVE DRUG DELIVERY SYSTEMS OF SOME HMG Co-A REDUCTASE INHIBITORS**" which is submitted herewith to Saurashtra University, Rajkot, for the award of Doctor of Philosophy in the Faculty of Pharmacy is the result of research work carried out by me under the guidance of Dr.T.Y**.** Pasha, Professor**,** Parul Institute of Pharmacy, Vadodara.

I further declare that the result of this work have not been previously submitted for any degree or fellowship.

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CERTIFICATE

This is to certify that the research work embodied in this thesis entitled **"DESIGN AND EVALUATION OF DIFFERENT GASTRORETENTIVE DRUG DELIVERY SYSTEMS OF SOME HMG Co-A REDUCTASE INHIBITORS"** represents the bonafide and genuine research work carried out by **Mr. Patel Sandipkumar Dineshbhai** under my supervision and guidance.

I further certify that the work done by him is of his own and tends to the general advancement of knowledge. For the thesis that he is submitting, he has not been conferred any diploma or degree by either this university or other university according to best of my knowledge. The work is up to my satisfaction.

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Date:

Place: ***Patel Sandipkumar Dineshbhai***

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ABBREVIATIONS

AR	=	Analytical Reagent
BSS	=	British Standard Sieve
CDR	=	Cumulative Drug Release
Conc.	=	Concentration
°C	=	Degree Centigrade
HPMC	=	Hydroxypropylmethylcellulose
Hrs	=	Hour
IR	=	Infrared
LR	=	Laboratory Reagent
mg	=	milligram
ml	=	milliliter
N	=	Normality
n	=	Diffusion coefficient
nm	=	nanometer
rpm	=	Revolution per minute
SI. No.	=	Serial Number
TFT	=	Total Floating Time
USP	=	United States Pharmacopoeia
UV	=	Ultraviolet
Wt	=	weight
w/w	=	Weight by weight
µg	=	microgram

ATS	=	Atorvastatin calcium
SIM	=	Simvastatin
PEO 303	=	Polyethylene Oxide
GIT	=	Gastrointestinal tract
Mg	=	Milligram
λmax	=	Wavelength maxima
%	=	Percente
POLYOX 303	=	Polyethylene Oxide
Veegum	=	magnesium aluminum silicate
C C Sod.	=	Cross Carmellose sodium

1. INTRODUCTION

ATHEROSCLEROSIS AND HYPERLIPIDEMIA[1-3]

Atherosclerosis, a disease which affects large and medium size arteries, is now a leading cause of death in many developed countries. The lesion characteristic of atherosclerosis is a localised plaque in the intima and is composed of cholesterol esters, proliferation of smooth muscle, deposition of fibrous proteins and calcification. Such plaques;

- Narrow the arterial lumen causing distal ischemia.
- Ulcerate in to the arterial lumen, with thrombosis of artery and distal

  embolization; or
- Weaken the arterial wall, leading to formation of aneurysms.

The cause of atherosclerosis is not known although several factors have been blamed in the pathogenesis of atherosclerosis. A lot of experimental and epidemiological evidence suggests a relationship between atherosclerosis and elevated level of plasma lipid.

Table 1.1 Serum lipid levels (mg/dl) and associated risk of Ischemic heart disease

Serum lipid levels (mg/dl) and the risk of IHD*			
Lipid	**Desirable level (Low risk)**	**Borderline level (Moderate risk)**	**Abnormal level (High risk)**
Total cholesterol	< 200	200-240	>240
LDL cholesterol	<130	130-160	>160
HDL cholesterol	>60	40-60	<40
Triglycerides	<200	200-400	>400
* The risk increases further with other risk factors such as smoking, diabetes and hypertension			

In the management of hyperliproteinemia, weight reduction, appropriate modification of diet, abstinence from alcohol, and specific treatment of causative disease, if any such as hypothyroidism and diabetes mellitus, are much more important than lipid-lowering drugs.

Drug therapy is indicated in those:

- In whom the dietary measures are not successful.
- Who find the dietary restrictions irksome; and
- Who are at high risk of pancreatitis.

The main classes of drug used clinically are:

- Statins: HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors
- Fibrates
- Bile acid binding resins.

Statins: HMG-CoA reductase inhibitors

- Lovastatin (Mevacor , Altocor^{Tm}); lovastatin extended release (Atoprev)
- Simvastatin (Zocor); simvastatin + ezetimibe (vytorin)
- Pravastatin (Pravachol)
- Fluvastatin (Lescol, Lescol XL)
- Atorvastatin (Lipitor)
- Rosuvastatin (Crestor)

Mechanism of action of Statins

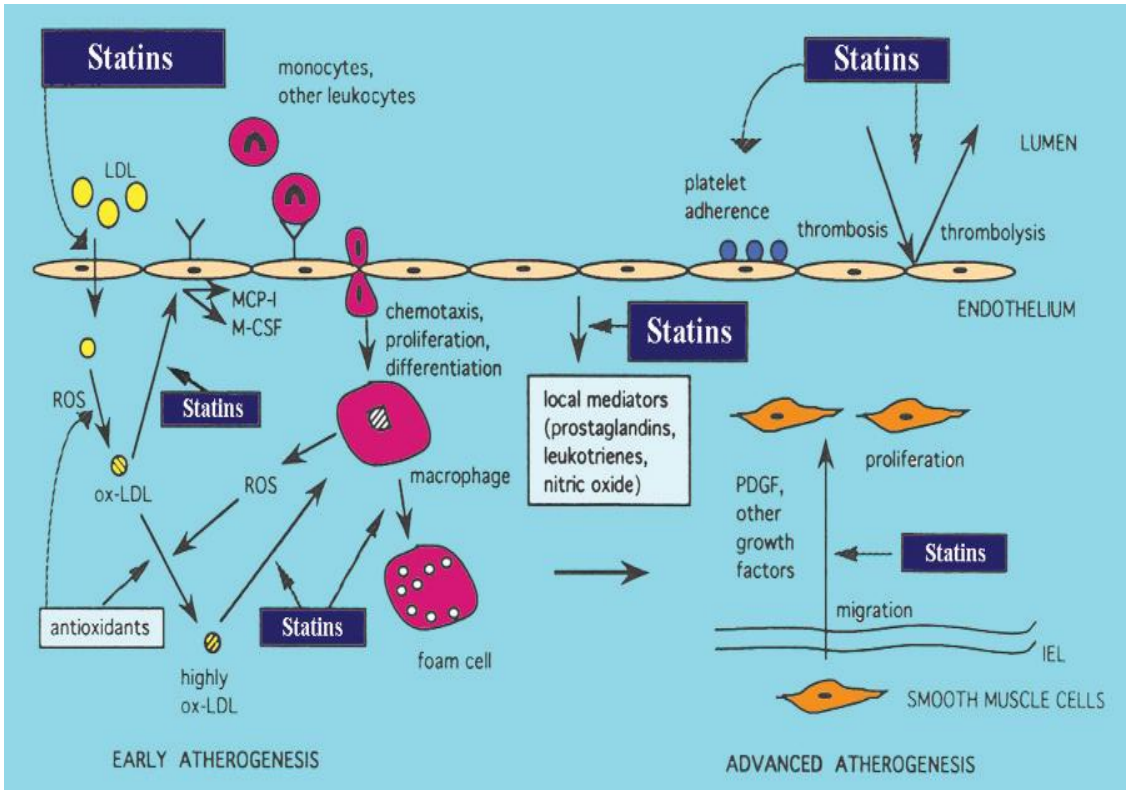

Fig. 1.1 Hypercholesterolemia favors entry of LDL particles into subendothelial space at lesion-prone arterial sites. Monocyte chemotactic protein-1 (MCP-1) and oxidized-LDL act as chemoattractants to direct accumulation of monocytes and their migration to the subendothelial space, where monocytes undergo phenotypic transformation into
macrophages. Concurrently, oxigen free radicals modify LDL. Oxidatively modified LDL is taken up by nondownregulating macrophage receptors to form lipid-rich foam cells. Foam cells develop into fatty streaks, precursor of atherosclerotic plaques. Statins exihibit pleiotropic effects on many components of atherosclerosis that accompany hypercholesterolemia, including platelet coagulation abnormalities, abnormal endothelial function,

and determinants of plaque thrombogenicity such as plaque inflammation and proliferation[13].

Major Secondary Prevention Trials with Statins[1, 4]:

1. Scandinavian simvastatin survival study (4S)
2. cholesterol and Recurrent Events (CARE)
3. Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)

Because patients with established CHD are at very high risk of recurrent CHD, the following studies (Table No. 1.2) demonstrate the reduction in cardiovascular morbidity and mortality and total mortality.

Table 1.2 Major Secondary Prevention Trials with Statins[4]:

study	persons	duration	Statin (dose/ day)	Baseline LDL-C (mg/dl)	LDL-C change	Major Coronary Events	Coronary Mortality	Total Mortality	stroke
4S	4444	5.4 yrs	Simvastatin 10/40 mg	188	-35%	-35%	-42%	-30%	-27%
CARE	4159	5 yrs	Pravastatin 40 mg	139	-27%	-25%	-24%	-9%	-31%
LIPID	9014	5 yrs	Pravastatin 40 mg	150	-25%	-29%	-24%	-23%	-19%

4. The heart protection study[4]

This study showed that simvastatin (40 mg daily) improved outcome in a broadly defined high-risk population, including people with normal/low plasma LDL cholesterol, and that simvastatin was extremely safe.

Lovastatin and simvastatin are members of new class of drug used in the treatment of hypercholesterolemia. Being prodrugs, they hydrolyze *in vivo* to their corresponding β-hydroxyacids which are potent inhibitor of HMG-CoA reductase and, thus, of de novo cholesterol synthesis. As the primary site of cholesterol synthesis and regulation, the liver is the target organ for HMG-CoA reductase inhibitors. Lovastatin and simvastatin were more efficiently extracted by the liver, which is the target organ for both compounds, than their corresponding β- hydroxyacids with subsequent minimization of systemic burden. These suggest that, compared to a conventional dosage form, a sustained/controlled-release dosage form of lovastatin and simvastatin might provide similar or better efficacy. [5-7]

All statins, acts in the liver to demonstrate its lipid-lowering action. It is also noteworthy that plasma concentrations of atorvastatin acid and its metabolites do not correlate with the reduction in LDL cholesterol, indicating that there is a poor pharmacokinetic–pharmacodynamic relationship. This issue has adequately been discussed by Lennernas[7]. Therefore, to improve the therapeutic efficacy of atorvastatin, it is imperative that the effective concentration of atorvastatin be increased in the liver instead of the plasma. Thus, in the case of atorvastatin, increase in the bioavailability does not guarantee improved pharmacodynamics or therapeutic efficacy. Finally, the

ideal delivery strategy for Atorvastatin would be one that would decrease its intestinal and hepatic metabolism and improve its targeting to liver[8].

An ideal dosing scheme would provide therapeutic levels of inhibitor to the liver at a rate that result in a hepatic extraction ratio approaching unity, there by minimizing the systemic HMG-CoA reductase levels. In practice, this may be accomplished by a portal drug infusion.

Hence in the present work, a multi-unit granular dosage form is prepared in the form of capsule, containing swellable hydrogel forming polymer and gas forming agent to float and retard the drug release from the formulation, floating bioadhesive tablet, high density tablet and mucoadhesive tablet.

1.1 Modified Release Oral Drug Delivery Systems

The oral route represents nowadays the predominant and most preferable route for drug delivery. Unlike the majority of parentral dosage forms, it allows ease of administration by the patient and it's the natural, and therefore a highly convenient way for substances to be introduced into the human body.

Oral drug delivery systems (DDS) are divided into immediate release and modified release systems. Immediate release DDS are intended to disintegrate rapidly, and exhibit instant drug release. They are associated with a fast increase and decrease, and hence fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased 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.

Modified release systems, on the other hand, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects[12]. Oral modified release delivery systems are most commonly used for

1) Delayed release (e.g., by using an enteric coating)

2) Extended release (e.g., zero-order, first-order, biphasic release, etc.)

3) Programmed release (e.g., pulsatile, triggered, etc.) and

4) Site specific or timed release (e.g., for colonic delivery or gastric retention). Extended, sustained or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices, with predictability and reproducibility in the drug release kinetics[13]. Delayed release dosage forms are distinguished from the ones mentioned above as they exhibit a pronounced lag time before the drug is released. Oral extended release dosage forms offer the opportunity to provide constant or nearly constant drug plasma levels over an extended period of time following administration. Extended release DDS include single-unit, such as tablets or capsules, and multiple-unit dosage forms, such as minitablets, pellets, beads or granules, either as coated (reservoir) or matrix devices[14].

Extended release DDS offer several advantages compared to conventional DDS[15] including:

I. Avoiding drug level fluctuations by maintenance of optimal therapeutic plasma and tissue concentrations over prolonged time periods, avoiding sub-therapeutic as well as toxic concentrations, thus minimizing the risk of failure of the medical treatment and undesirable side effects;

II. Reducing the administered dose while achieving comparable effects;

III. Reduced frequency of administration leading to improved patients' compliance and subsequently improved efficacy of the therapy and cost effectiveness;

IV. Targeting or timing of the drug action. Hence, it is highly desirable to develop sustained DDS releasing the drug at predetermined rates to achieve optimal drug levels at the site of action.

On the other hand, drugs administered as sustained or extended release oral dosage form should comply with the following parameters:

I. Maintain a constant plasma level over prolonged time periods;

II. Have a broad therapeutic window to avoid health hazard to the patient in case of undesirable burst release of the nominal dose[16].

The maximum achievable sustained drug release is subject to inter individual variations, with an average gastrointestinal (GI) transit time of around 24 h in humans (Davis et al., 1984). The transit time is affected by age, gender, body mass index and the state of health of the individual as well as his emotional state and composition of meals. In addition, drugs affecting gastric motility, such as opioid analgesics or metoclopramide, have to be taken into account.

Numerous oral sustained drug delivery systems have been developed to prolong drug release. The key point in this respect is that the API has to be absorbed well throughout the whole gastrointestinal tract (GIT). Generally, the absorption of APIs from oral DDS is precluded by several physiological difficulties, such as inability to restrain and localize the drug delivery system within desired regions of the GIT and the high variable nature of gastric

emptying process (Rouge et al., 1996). The gastric emptying process can vary from a few minutes to 12 h, depending upon the physiological state of the subject and the design of pharmaceutical formulation. This variation, may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine (Rouge et al., 1996). In addition, the relatively brief gastric emptying time in humans, through the stomach or upper part of the intestine (major absorption zone), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose.

1.1.1 Gastroretentive Dosage Form (GRDF): [17-19]

Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug wastage, and improves solubility for drugs that are less soluble in a high pH environment.

GRDF extend significantly the duration of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

Conventional oral controlled dosage forms suffer from mainly two adversities. The short gastric retention time (GRT) and unpredictable gastric emptying

time (GET), so GRT and GET are important considerations to formulate a controlled release dosage form having required extended GI residence time

Dosage form with prolonged GRT, i.e. gastro retentive dosage forms (GRDF), will bring about new and important therapeutic options such as[10]–

1) This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To overcome this problem, erodible, gastro-retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.
2) GRDF greatly improves the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (e.g. Eradicating *Helicobacter pylori* from the submucosal tissue of stomach) making it possible to treat gastric and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).
3) GRDF can be used as carriers for drugs with so-called absorption windows. These substances for instance antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, tetracyclines etc.), are absorbed only from very specific sites of the GI mucosa.

The design of oral control drug delivery systems (DDS) should be primarily aimed to achieve more predictable and increased bioavailability. The

ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substances. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract, and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the prolong gastric retention. In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailibility, therapeutic efficacy and possible reduction of the dose size. It has been suggested that prolong local availability of antibacterial agents may augment their effectiveness in treating *H.Pylori* related peptic ulcers. Gastroretentive Drug delivery systems (GRDDS) [16-19], however are not suitable for drugs that may cause gastric lesions, e.g., Nonsteroidal anti-inflammatory agents.

1.1.2 Basic physiology of the gastrointestinal tract

The complex anatomy and physiology of the GIT, including variations in acidity, bile salts, enzyme content, and the mucosal absorptive surface, significantly influence the release, dissolution, and absorption of orally administered dosage forms. Two distinct patterns of gastrointestinal (GI) motility and secretion exist, corresponding to the fasted and fed states. As a

result, the BA of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic events, commonly referred to as the *migrating motor complex* (MMC), which regulates GI motility patterns. The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into basal (Phase I), preburst (Phase II), and burst (Phase III) intervals (Figure 1.1) 1. Phase I, the quiescent period, lasts from 30 to 60 min and is characterized by a lack of secretory, electrical, and contractile activity. Phase II exhibits intermittent action for 20–40 min during which contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of Phase II and throughout Phase III. Phase III is characterized by intense, large, and regular contractions, termed *housekeeper waves*, that sweep off undigested food and last 10–20 min. Phase IV is the transition period of 0–5 min between Phases III and I. This series of electrical events originates in the foregut and continues to the terminal ileum in the fasted state, repeating every 2–3 hrs. Feeding sets off a continuous pattern of spike potentials and contractions called *postprandial motility*.

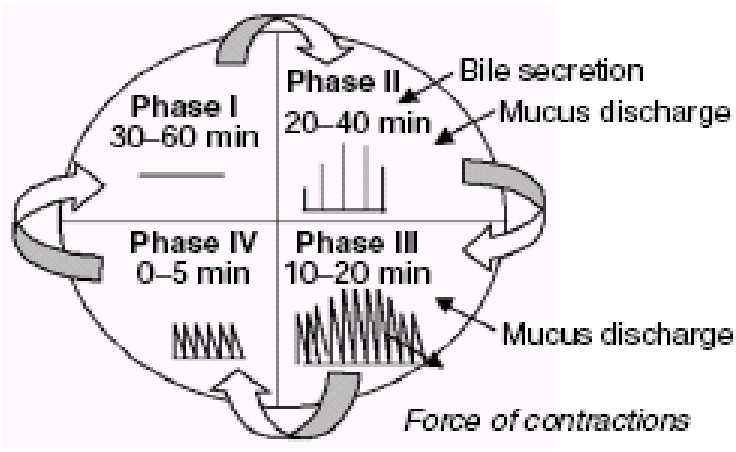

Figure 1.2 ***Motility patterns of the GIT in fasted state***

The particular phase during which a dosage form is administered influences the performance of peroral CRDDS and GRDDS. When CRDDS are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total gastric residence time (GRT) and transit time in the GIT. This assumes even more significance for drugs that have an absorption window because it will affect the amount of time the dosage form spends in the region preceding and around the window. The less time spent in that region, the lower the degree of absorption. Therefore, the design of GRDDS should take into consideration the resistance of the dosage form to gastric emptying during Phase III of the MMC in the fasted state and also to continuous gastric emptying through the pyloric sphincter in the fed state. This means that GRDDS must be functional quickly after administration and able to resist the onslaught of physiological events for the required period of time.

1.1.3 Gastric emptying and problems

It is well recognized that the stomach may be used as a depot for Sustained release dosage forms, both in human and veterinary applications, stomach is anatomically divided in to three parts: Fundus, body and pylorus. The proximal stomach made up of the fundus and body region serves as a reservoir for ingested materials, while the distal region (antrum) is the major site for the mixing motion, acting as a pump to accomplish gastric emptying. The process of the gastric emptying occurs both during fasting and fed stages. Scintigraphy study involving measurement of gastric emptying rates in healthy human subject have revealed that an orally administered Controlled release dosage form is mainly subjected to two physiological adversities,

a) The short GRT (Gastric Residence Time)

b) Variable (unpredictable) GET (Gastric Emptying Time)

Yet another major adversity encountered through the oral route is the first pass effect, which leads to reduce systematic availability of a large number of a drug. These problems can be exacerbated by alteration in the gastric emptying that occur due to factors such as age, race, sex and disease states, as they may seriously affect the release of a drug from DDS. It is therefore desirable to have a controlled release product that exhibits an extended, GI residence and a drug release profile independent of patients' related variables.

1.1.4 Potential drug candidates for stomach specific drug delivery systems

1. Drugs those are locally active in the stomach e.g. misroprostol, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-dopa, para amino benzoic acid, furosemide, riboflavin etc.
3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

1.1.5 Drugs those are unsuitable for stomach specific drug delivery systems

1. Drugs that have very limited acid solubility e.g. phenytoin etc.

2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.

3. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid, corticosteroids etc.

2. APPROACHES TO GASTRIC RETENTION or **MECHANISTIC ASPECTS OF GRDFS** [17- 29]

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include –

Single-unit dosage forms

a) Floating Systems[30]

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system.

b) High Density Systems [31, 32]

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach.

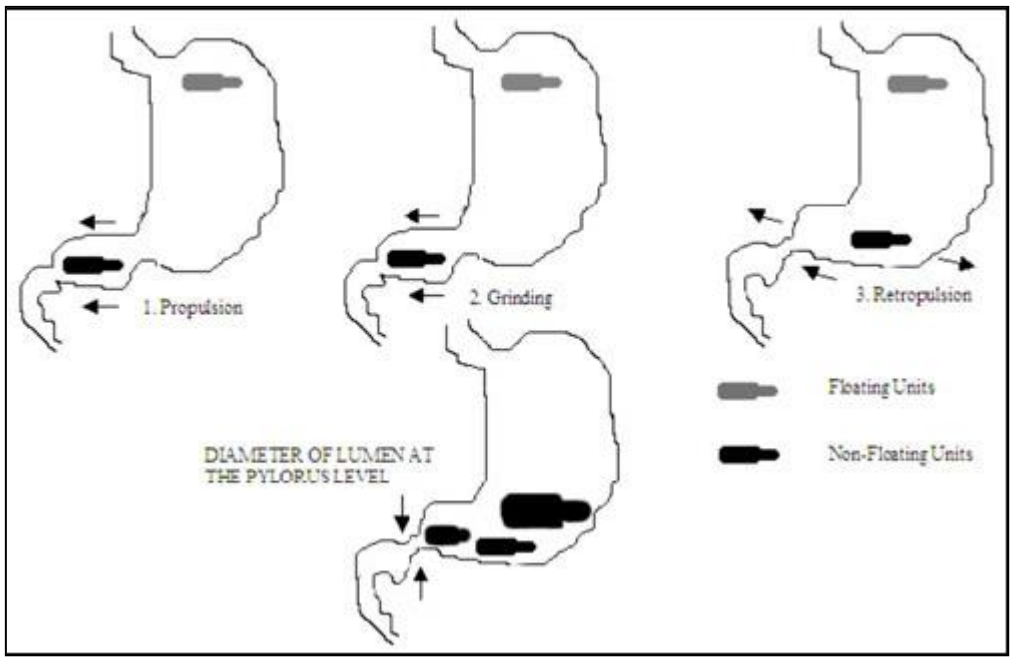

Fig 1.3 Intragastric residence positions of floating and nonfloating units.

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c) Bio/Muco-adhesive Systems: [33-36]

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

d) Swelling and Expanding Systems [37, 38]

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. These systems may be named as "*plug type system*", since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state.

e) Incorporation of Passage Delaying Food Agents [39-42]

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay

in the gastric emptying after meals rich in fat is largely caused by saturated fatty acids with chain length of C_{10}-C_{14}.

f) Ion-Exchange Resins [43]

Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

g) Osmotic Regulated Systems [44, 45]

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio-erodible capsule. In the stomach the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable supports inside forms a deformable hollow polymeric bag that contains a liquid that gasify at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

h) pH-Independent formulation [44]

Most drugs are either weak acids or weak basics and hence pH dependent release is observed in body fluids. However buffers can be added to such formulations to help in maintaining a constant microenvironmental pH to obtain pH independent drug release.

g) Fluid filled floating chamber[19]

These are the dosage forms includes incorporation of a gas-filled floation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein.

h) Multiple-unit dosage forms[46.47]

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of the above mentioned disadvantages of single-unit formulations. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatine, polymethecrylate, polyacrylamine. Spherical polymeric microsponges, also referred to as “microballoons” have been prepared.

2.1 INTRODUCTION TO STOMACH SPCIFIC DOSAGE FORM [48-51]

The floating drug delivery system (FDDS) also called Hydrodynamically Balanced Drug Delivery System (HBS) [51]. FDDS is an oral dosage forms (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. Drug dissolution and release from dosage retained in the stomach fluids occur at the pH of the stomach under fairly controlled condition.

The formulation of the dosage form must comply with major criteria for HBS, like

1) It must have sufficient structure to form a cohesive gel barrier.
2) It must maintain an overall specific gravity less than that of gastric content.
3) It should dissolve slowly enough to serve as a 'Reservoir' for the delivery system.

TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS, which are [17,18, 23]

A. Effervescent System, and
B. Non- Effervescent System.

A. EFFERVESCENT SYSTEM:

These are the matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

I. Gas Generating systems
II. Volatile Liquid/Vacuum Containing Systems.

I. Gas – Generating Systems: [13]

1. **Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced Sysem (HBS) [44, 49]**

These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than

gastric fluids and therefore remain floating in the stomach for a prolonged period.

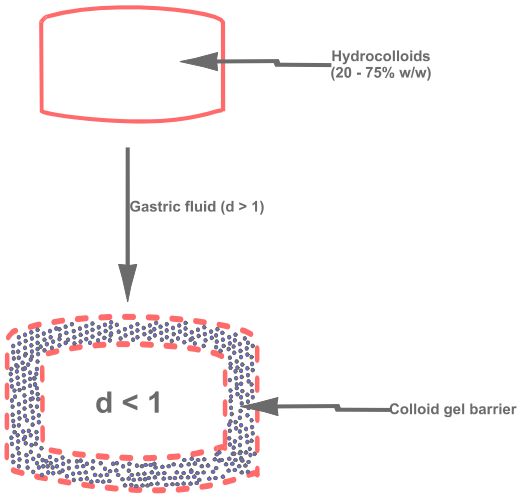


Fig. 1.4 IntraGastric Single Layer Floating Tablet.

2. Intra Gastric Bi-layer Floating Tablets [52]

These are also compressed tablet containing two layers i.e.

i. Immediate release layer and

ii. Sustained release layer.

These are as formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet.

3. Multiple Unit type floating pills [22-24]

The system consists of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

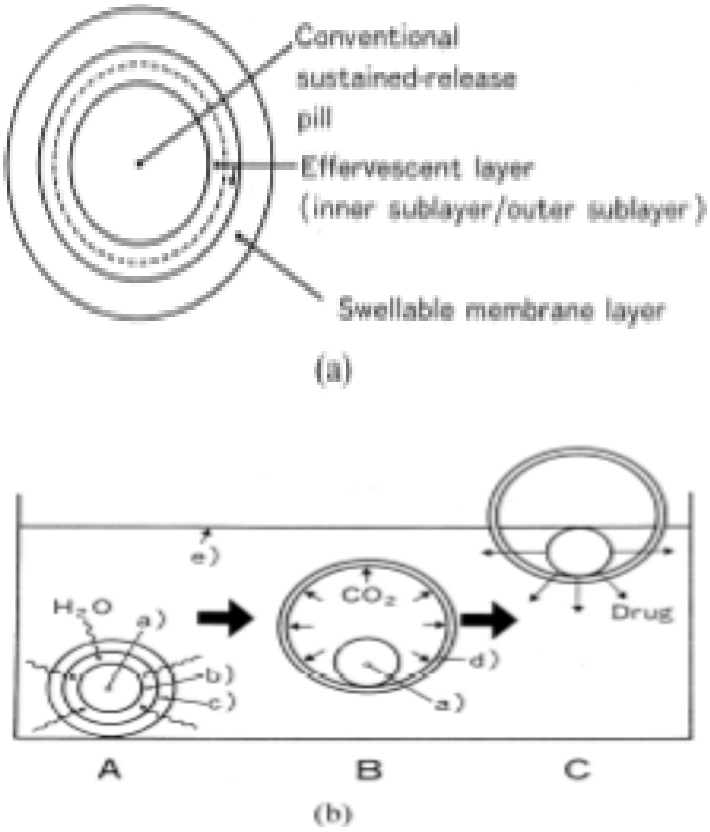


Fig.1.5 (a) A multi-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

II. Volatile Liquid / Vacuum Containing Systems [44, 23]

1. Intra-gastric Floating Gastrointestinal Drug Delivery System:

These system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro-porous compartment.

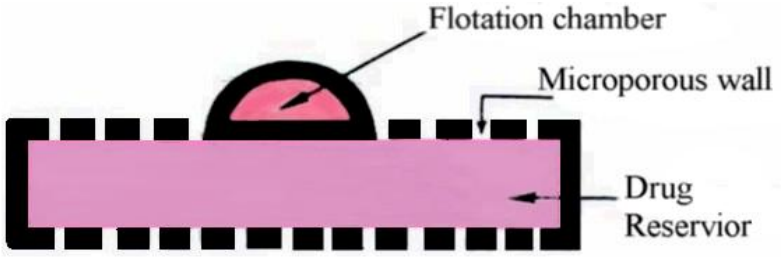


Fig. 1.6 Intra Gastric Floating Gastrointestinal Drug Delivery Device

2. Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

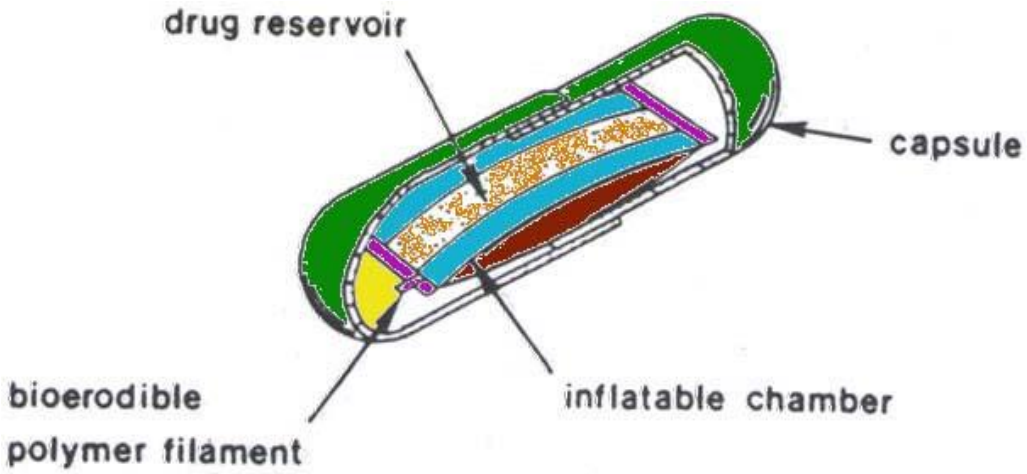


Fig. 1.7 Inflatable Gastrointestinal Delivery System

3. Intra-gastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

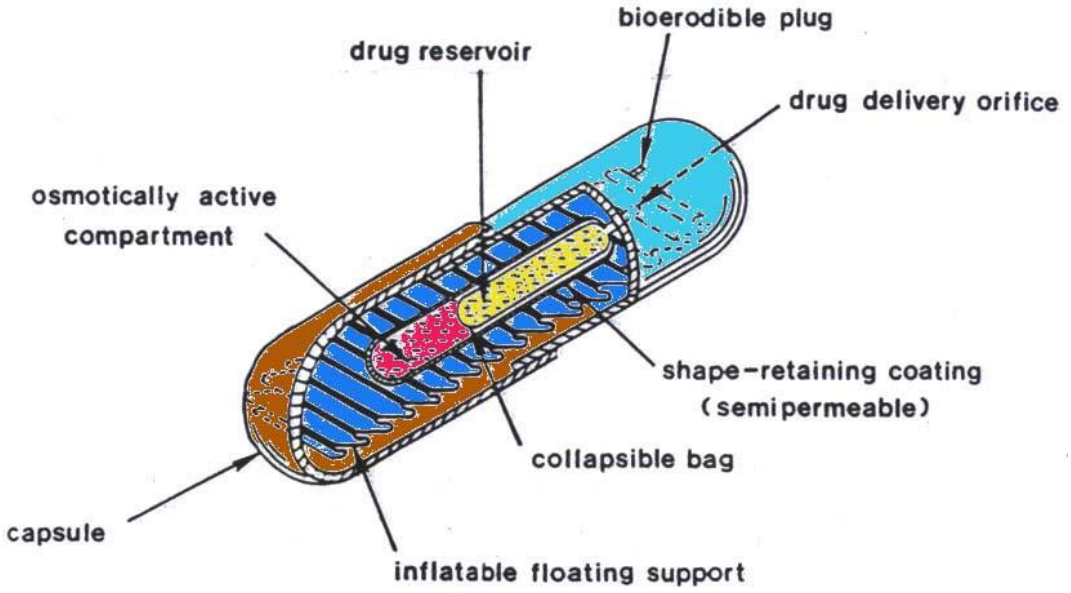


Fig. 1.8 Intragastric Osmotically Controlled Drug Delivery System

B. NON EFFERVESCENT SYSTEMS:

The Non-effervescent FDDS is based on mechanism of swelling of

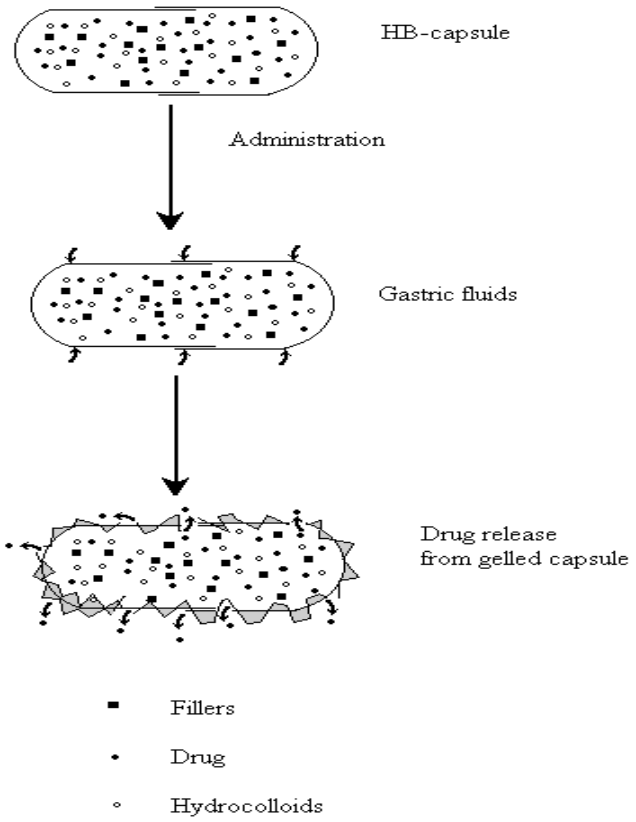


Fig.1.9 Working principle of Non-effervescent type of FDDS

polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol.

ADVANTAGES OF FDDS [13]

Advantages of FDDS can be mainly classified in to four categories.

A) **Sustained drug delivery**

- Administration of a prolonged release floating dosage form will result in dissolution in the gastric fluid. The drug solution will also be available for absorption from small intestine after gastric emptying. It is therefore expected that a drug will be fully absorbed from the floating dosage form.
- Medicaments like aspirin cause irritation to the stomach wall when they come into contact with it, hence FDDS are particularly advantageous and convenient for the administration of such drug, since they remain buoyant in the GI fluid and do not adhere to the walls.

B) **Site specific drug delivery**

- When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances. It may be advantageous to keep the formulation in floating condition in stomach to get a relatively better response.

- The FDDS are advantageous for drugs absorbed through the stomach e.g. ferrous salt and for drugs meant for local action in stomach e.g. antacids.
- FDDS are not restricted to medicament, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments, which are absorb from the intestine e.g. Chlorpheniramine maleate.

C) **Pharmacokinetic advantages**

- Maximizing absorption and improving absolute bioavailability of delivered drugs, which are absorbed mainly in upper GI tract.
- Site-specific absorption and longer GRT could possibly increase the bioavailability of drugs from FDDS e.g. Loop diuretics
- FDDS can reduce fluctuations in the plasma level of drugs due to delayed gastric emptying.

D) **Miscellaneous**

- Ease of administration and better patient compliance.
- Simple and conventional equipment for manufacture.

DISADVANTAGES OF FDDS:

- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted exactly or accurately.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

- Gastric emptying of floating forms in supine subjects may occur at random and become highly dependent on the diameter. Therefore, patients should not be dosed with floating forms just before going to bed.
- High variability in gastric emptying time due to variations in emptying process.
- Drugs such as nifedipine which undergoes first-pass metabolism, may not be desirable.
- Unpredictable bioavailability.

APPLICATIONS OF FDDS

- Because of the increased GRT, FDDS is beneficial in treatment of gastric and duodenal ulcer.
- Floating granules of Indomethacin are superior to the conventional Indomethacin containing dosage form for maintaining desired plasma level of drugs.
- According to recent studies administration of diltiazem floating tablet might be more effective compared to conventional tablet in treatment of hypertension.
- Due to prolonged GRT, it is used to eradicate *H .pylori*, causative organism for chronic gastritis and peptic ulcer.
- FDDS containing 5-fluorouracil is beneficial in treatment of stomach neoplasm.

- Tacrine, in the form of FDDS, provide better drug delivery system with reduced GI side effects in Alzheimer's patients.
- Madopar®HBS- containing L-dopa and benserazide here drug is released and absorbed over a period of 6-8 hr and maintains substantial plasma concentration for Parkinson's patients.
- Cytotec®-containing misoprostol, a synthetic prostaglandin-E1 analog, for prevention of gastric ulcer caused by non-steroidal antiinflammatory drugs (NSAIDS).

Marketed Products of FDDS:

Table 1.3 Marketed Products of FDDS

BRAND NAME	**DRUG**	**Clinical Importance**	**Dosage form**
Madopar®	Levodopa Benserazide	Parkinsonism	Capsule
Cytotec®	Misoprostal	Gastric ulcer	Capsule
Valrelease®	Diazepam	Sedative –hypnotic	Capsule
Conviron	Ferrous sulphate	Pernicious anaemia	Capsule
Liquid Gavison®	Al hydroxide Mg carbonate	Heart burn	Liquid alginate preparation
Topalkan®	Al-Mg antacid	Antacid	Liquid alginate preparation
Cifran OD®	Ciprofloxacin	Urinary tract infection	Tablet
Oflin OD®	Ofloxacin	Genital Urinary, respiratory, Gastro-intestinal infection	Tablet
Prolopa®	Propranolol	Hypertension	Tablet

BIOADHESIVE OR MUCOADHESIVE DRUG DELIVERY SYSTEMS[52]:

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastric retention. The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism.

These mechanisms are:

1. The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.

2. The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.

3. The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.

4. The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material.

Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

2. OBJECTIVES

Oral administration is the most convenient and preferred means of drug delivery to the systemic circulation. In recent years scientific and technological advancements have been made in the research and development of rate controlled oral drug delivery system by overcoming physiological constituents, such as short residence time and unpredictable gastric emptying time.

This goal can be achieved by the development of stomach specific drug delivery system which increases the gastric residence time.

OBJECTIVE OF THE STUDY:-

Following are the objectives of the present study:

The primary objective of this study is to formulate and evaluate a suitable gastroretentive drug delivery system for a model short half-life HMG-CoA reductase inhibitors and comparing the drug release profile for prepared different dosage form and for better management of hyperlipidaemia.

1. To carry out pre-formulation studies for the possible drug/polymer/ excipient interactions by IR/DSC.
2. To design and develop gastro-retentive dosage forms like Floating mucoadhesive tablet, mucoadhesive high density tablet, mucoadhesive Floating capsule, mucoadhesive tablets.
3. Screening of excipients for the envisaged dosage form.
4. Standardizing the process/formulation parameters to manufacture a reproducible dosage form.

5. Evaluating its physicochemical parameters and optimization of dosage form by following experimental design methodology for statistical validation.
6. To carry out short term stability studies on the optimized formulation as per ICH guidelines at 30 ± 2^0C (65 ± 5 %RH) and 40 ± 2^0C (75 ± 5 %RH).
7. Release profile characterization of the final optimized formulation and determine kinetics and mechanism of release.
8. The pharmacodynamic efficacy of the optimized and stable dosage form would be taken up in experimental animal model to establish a meaningful *In Vitro In Vivo* correlation.

3. REVIEW OF LITERATURE

SIMVASTATIN: -

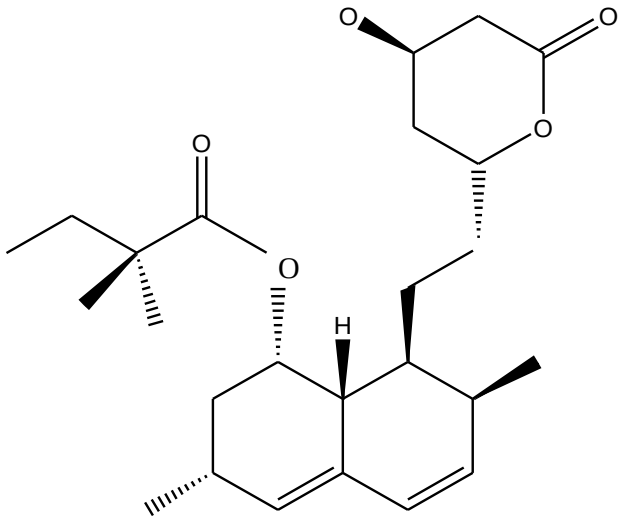
1. DESCRIPTION: [3-5]

1.1 Nomenclature:

- **Generic Name** : Simvastastin
- **Chemical Name** : [(1S,3R,7R,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxo-oxan-2-yl] ethyl]-3-7-dimethyl-1,2,3,7,8, 8a-hexahydronaphthalen-1-yl] 2, 2- dimethylbutanoate
- **Trade Names** : Cholestat, coledis, Simovil, Simvastatin, Simvastatina, Simvastatine, Sinvacor.

1.2 Formula:

- **Empirical Formula** : $C_{25}H_{38}O_5$
- **Structural Formula** :



SIMVASTATIN

1.3 Physical and chemical properties:

- **Molecular weight** : 418.566 g/mol
- **Color** : White or almost-white
- **Nature** : Crystalline powder
- **Odour** : Odourless
- **Melting point** : 135-138 °C
- **Specific rotation** : Between +285° and +300° (t=20°C)
- **LogP** : 4.937
- **Solubility** : Practically insoluble in water; freely soluble in Alcohol, in chloroform, and in methyl alcohol; sparingly soluble in propylene glycol; very Slightly soluble in petroleum spirit.

2. *PHARMOCOKINETICS:* [2, 3, 9-10]

2.1. **Absorption: -**

Simvastatin is absorbed from the gastrointestinal tract after oral administration and is hydrolyzed to its active β-hydroxyacid form. simvastatin undergoes extensive first-pass metabolism in the liver, its primary site of action.

2.2. **Bioavailability:**

Less than 5% of the oral dose has been reported to reach the circulation as active metabolite.

2.3 **Distribution:**

Both simvastatin and its β-hydroxyacid metabolite are about are 95% bound to plasma proteins.

2.4. Elimination:

It is mainly excreted in the faeces via the bile as metabolite. About 10 to 15% is recovered in the urine, mainly in inactive forms.

3. *PHARMACOLOGY*:

3.1. Therapeutic Category: -

Anticholesteremic Agents, HMG-CoA Reductase Inhibitors, Antilipemic agent

3.2. Mechanism of action: [3, 10]

Competitively inhibit 3-hydroxy-3-methyle –glutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. This conversion is an early rate-limiting step in cholesterol biosynthesis.

3.3 Therapeutic/clinical Uses:

- Secondary prevention of myocardial infarction and stroke in patients who have symptomatic atherosclerotic disease.

- Primary prevention of arterial disease in patients who are at high risk because of elevated serum cholesterol concentration, especially if there other risk factors for atherosclerosis.

- In severe drug resistant dyslipidemia (e.g. heterozygous familial hypercholesterolaemia), a bile acid binding resin is added to treatment with a statin.

3.4 Adverse Effects:

Myopathy, rhabdomyolysis, headache, skin rashes, dizziness, blurred vision.

3.5 Toxicity:

Simvastatin is considered to be unsafe in patients with Porphyria because it has been shown to be Porphyrinogenic**.**

3.6 Drug interaction:

- 3A4 substructure: simvastatin, atorvastatin, lovastatin
- 3A4inhibitors: azole antifungls (fluconazole, ketoconazole), grapefruit juice, macrolide antibiotics (erythromycin), protease inhibitors, nefazodone, fluvoxamine, verapamil, amiodarone cyclosporins.
- Drug interaction that increase risk for myopathy: gemofibrozil, fenofibrate &/or niacin (at least 1 g/day) in combination with a statin.

Contraindication: -

Concomitant administration of drugs that inhibit the cytochrome P450 isoenzyme CYP3A4, such as ciclosporin, itraconazole, ketoconazole, erythromycin, clarithromycin, nefazodone, might produce high plasma levels of simvastatin, thus increasing the risk of myopathy.

Use with caution in patients who consumes substantial quantities of alcohol, who have history of liver disease, or have signs suggestive of liver disease. All stains have been associated with myalgia, myopathy (i.e., muscle pain, tenderness, or weakness with creatine phosphokinase [CPK]), and rhabdomyolysis. Uncomplicated myalgia has been reported with drugs in this class.

4. DOSAGE FORM AND DOSE

4.1. Dosage Form:

Tablets

4.2. Dose:

Initial dose of 5 mg to 10 mg in the evening; an initial dose of 20 mg may be used in patients with ischemic heart disease. Maximum up to 80 mg once a day in the evening.

Patients with homozygous familial hypercholesterolaemia may be treated with 40 mg once a daily in the evening, or 80mg daily in three divided doses of 20 mg, 20 mg, and an evening dose of 40 mg.

5. METHOD OF ANALYSIS:

- Elemental analysis
- Spectroscopy like-IR, NMR, Mass and UV-Visible spectroscopy
- Thin Layer Chromatography
- High Performance Liquid Chromatography
- Structural details by X-ray Diffraction
- Thermal methods

6. STORAGE:

Store under nitrogen in airtight containers. Protect from light.

ATORVASTATIN[3, 9-11]: -

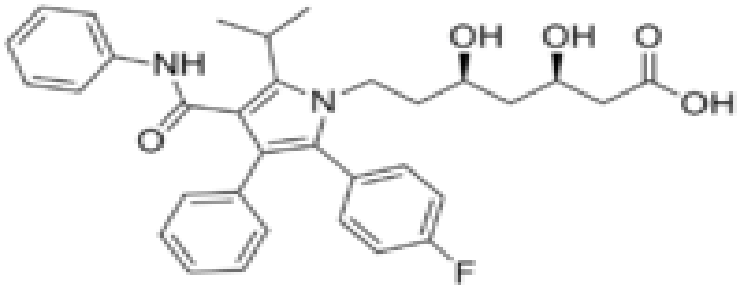
1. DESCRIPTION: [3]

1.1 Nomenclature:

- **Generic Name** : Atorvastatin
- **Chemical Name** : (3*R*,5*R*)-7-[2-(4-fluorophenyl)-3-phenyl-4-phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid
- **Trade Names** : Atogal, Atorpic, Cardyl, Faboxim, Hipolixan, Lipitor, Lipotropic, Lipovastatinklonal, Liprimar.

1.2 Formula:

- **Empirical Formula** : $C_{33}H_{35}FN_2O_5$
- **Structural Formula**:



ATORVASTATIN

1.3 Physical and chemical properties:

- **Molecular weight** : 558.639 g/mol
- **Color** : White or almost-white

- **Nature** : Crystalline powder
- **Odour** : Odourless
- **Melting point** : 159.2-160.7°C
- **Specific rotation** : Between +285° and +300° (t=20°C)
- **LogP** : 5.7
- **Solubility** : Practically insoluble in water; freely soluble in Alcohol, in chloroform, and in methyl alcohol; sparingly soluble in propylene glycol; very Slightly soluble in petroleum spirit.

2. *PHARMOCOKINETICS:*[2, 3, 9-11]

3.1 Absorption: -

Atorvastatin is rapidly absorbed after oral administration with maximum plasma concentrations achieved in 1 to 2 hours. Atorvastatin undergoes extensive first-pass metabolism in the liver, its primary site of action.

3.2 Bioavailability:

The absolute bioavailability of atorvastatin is approximately 14%.

3.3 Distribution:

Atorvastatin is highly protein bound (≥98%) with a blood/plasma concentration ratio of 0.25 indicating a low red blood cell distribution.

3.4 Elimination:

It is primarily eliminated via hepatic biliary excretion with less than 2% of atorvastatin recovered in the urine. Bile elimination follows hepatic and/or extra-hepatic metabolism.

4. *PHARMACOLOGY*:

4.1 Therapeutic Category: -

Anticholesteremic Agents, HMG-CoA Reductase Inhibitors, Antilipemic agent

4.2 Mechanism of action: [3, 10]

Competitively inhibit 3-hydroxy-3-methyle –glutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. This conversion is an early rate-limiting step in cholesterol biosynthesis.

4.3 Therapeutic/clinical Uses:

- Secondary prevention of myocardial infarction and stroke in patients who have symptomatic atherosclerotic disease.
- Primary prevention of arterial disease in patients who are at high risk because of elevated serum cholesterol concentration, especially if there other risk factors for atherosclerosis.
- In severe drug resistant dyslidaemia (e.g. heterozygous familial hypercholesterolaemia), a bile acid binding resin is added to treatment with a statin.

- Myocardial infarction and stroke prophylaxis in patients with type II diabetes.

4.4 Adverse Effects:

Myopathy, rhabdomyolysis, headache, skin rashes, dizziness, blurred vision.

4.5 Toxicity:

Side effects may include myalgia, constipation, asthenia, abdominal pain, and nausea. Other possible side effects include myotoxicity (myopathy, myositis, rhabdomyolysis) and hepatotoxicity.

4.6 Drug interaction:

- 3A4 substructure: simvastatin, atorvastatin, lovastatin
- 3A4inhibitors: azole antifungls (fluconazole, ketoconazole), grapefruit juice, macrolide antibiotics (erythromycin), protease inhibitors, nefazodone, fluvoxamine, verapamil, amiodarone cyclosporins.
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6. METHOD OF ANALYSIS:

- Elemental analysis
- Spectroscopy like-IR, NMR, Mass and UV-Visible spectroscopy
- Thin Layer Chromatography
- High Performance Liquid Chromatography
- Structural details by X-ray Diffraction
- Thermal methods

6. STORAGE:

Store under nitrogen in airtight containers. Protect from light.

HYDROXYPROPYLMETHYLCELLULOSE [53, 54]

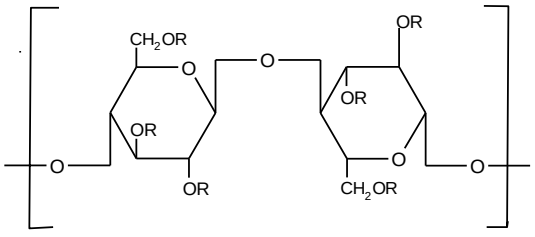
1. DESCRIPTION:

1.1. Nomenclature: -

- **Non-proprietary names :** JP: Hydroxypropylmethylcellulose
  BP: Hypromellose
  Ph Eur: Methylhydroxypropylcellulosum
  USP : Hypromellose
- **Chemical Name :** Cellulose, 2-hydroxypropyl methyl ether
- **Synonyms :** Methyl hydroxypropyl cellulose, Propylene glycol ether of methylecellulose, Methylcellulose,Methylcellulose propylene Glycolether, Methocel, Metolose, E464, Pharmacoat, Culminal MHPC.

1.2 Formula: -

- **Structural Formula :**



Where R is H, CH_3 or CH_3-CH(OH)-CH_2

1.3 Physical and chemical properties:

- **Molecular weight :** 10,000 - 15,00,000

- **Color** : White to creamy-white
- **Nature** : Fibrous or granular powder
- **Odour** : Odourless
- **Taste** : Tasteless
- **Density** : 0.3-1.3 g/ml
- **Specific gravity** : 1.26

Solubility : Soluble in cold water, practically insoluble in Chloroform, ethanol (95%) and ether but Soluble in mixture of ethanol and Dichloromethane

- **Viscosity** : HPMC K4M : 3,000-5600 mPa s

  HPMC K100M: 80,000-1,20,000 mPas
- **Melting point** : Browns at 190-200 °C, chars at 225-230 °C, Glass transition temperature is 170-180 °C

2. FUNCTIONAL CATEGORY: -

Coating agent, film-forming, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

3. APPLICATION: -

- In oral product HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation

process. High viscosity grade may be used to retard the release of water-soluble drug from a matrix.

- ❖ HPMC is widely used in oral and topical pharmaceutical formulation.
- ❖ Concentration of 0.45-1% w/w may be added as a thickening agent to vehicle for eye drop and artificial tear solution.
- ❖ HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products.
- ❖ In addition, HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particle from coalescing or agglomerating thus, inhibiting the formation of sediments.

4 STABILITY AND STORAGE:

It is stable although it is slightly hygroscopic. The bulk material should be stored in an airtight container in a cool and dry place. Increased in temperature reduces the viscosity of the solution.

5. SAFETY:

It is generally regarded as a non-toxic and nonirritant material so it is widely used in many oral and topical pharmaceutical formulations. Excessive consumption of HPMC may have laxative effect.

POLYETHYLENE OXIDE[53, 54]

1. DESCRIPTION:

1.1 Nomenclature: -

- **Non-proprietary names :** USP : Polyethylene oxide
- **Chemical Name :** Polyethylene oxide
- **Synonyms :** Polyox; polyoxiante; polyoxirane; polyoxyethylene

1.2 Formula : $(CH_2CH_2O)n$

1.3 Physical and chemical properties:

- **Molecular weight :** 1,00,000 - 70,00,000
- **Color :** White to creamy-white
- **Nature :** Granular powder
- **Odour :** Slight ammoniacal odor
- **Taste :** Tasteless
- **Density :** 1.3 g/ml (True)
- **Solubility :** Soluble in water and a number of common organic solvents such as acetonitrile, chloroform, and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols
- **Viscosity :** 30 -10000 mPs
- **Melting point :** 65–70°C,

2. FUNCTIONAL CATEGORY: -

Mucoadhesive; coating agent; tablet binder; thickening agent.

4. APPLICATION: -

- Polyethylene oxide used as a tablet binder at concentrations of 5–85%.
- The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach.
- Polyethylene oxide has also been shown to facilitate coarse extrusion for tableting as well as being an aid in hot-melt extrusion.
- Polyethylene oxide has been shown to be an excellent mucoadhesive polymer. Low levels of polyethylene oxide are effective thickeners, although alcohol is usually added to waterbased formulations to provide improved viscosity stability.
- Polyethylene oxide can be radiation crosslinked in solution to produce a hydrogel that can be used in wound care applications
- Polyethylene oxide films demonstrate good lubricity when wet. This property has been utilized in the development of coatings for medical devices.

5. STABILITY AND STORAGE:

Store in tightly sealed containers in a cool, dry place. Avoid exposure to high temperatures since this can result in reduction in viscosity.

6. SAFETY:

Animal studies suggest that polyethylene oxide has a low level of toxicity regardless of the route of administration. It is poorly absorbed from the

gastrointestinal tract but appears to be completely and rapidly eliminated. The resins are neither skin irritants nor sensitizers, and they do not cause eye irritation.

CARBOMER[53, 54]

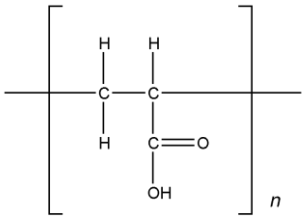
1. DESCRIPTION:

1.1. Nomenclature: -

- **Non-proprietary names** **:** BP : Cabomers
  Ph Eur : Carbomers
  USPNF : Carbomer
- **Synonyms** **:** Acrypol; Acritamer; acrylic acid polymer; carbomera;Carbopol;polyacrylicacid;carboxyvinyl polymer;Pemulen; Tego Carbomer carboxy polymethylene.

Formula: -

- **Structural Formula** **:**



Acrylic acid monomer unit in carbomer resins.

1.2 Physical and chemical properties:

- **Molecular weight** **:** $7*10^5$ to $4*10^9$
- **Color** **:** White
- **Nature** **:** fluffy, hygroscopic powder

- **Odour** **:** slight characteristic odor
- **Viscosity** **:** 20.5-54.5 poise (0.2%)

  305-394 poise (0.5%)
- **Density** **:** 0.3 gm/cm^3
- **Specific gravity** **:** 1.41
- **Solubility** **:** Swellable in water and glycerin and, after neutralization, in ethanol (95%). Carbomers do not dissolve but merely swell to a remarkable extent, since they are three-dimensionally crosslinked microgels.
- **Melting point** **:**Decomposition occurs within 30 min at 260 °C,

  Glass transition temperature is 100-105 °C.

2. FUNCTIONAL CATEGORY: -

Bioadhesive material; controlled-release agent; emulsifying agent; emulsion stabilizer; rheology modifier; stabilizing agent; suspending agent; tablet binder.

3. APPLICATION: -

- Carbomers are used in liquid or semisolid pharmaceutical formulations as rheology modifiers. Formulations include creams, gels, lotions and ointments for use in ophthalmic, rectal, topical and vaginal preparations.
- In tablet formulations, carbomers are used as controlled release agents and/or as binders. In contrast to linear polymers, higher viscosity does not result in slower drug release with carbomers. Lightly

crosslinked carbomers (lower viscosity) are generally more efficient in controlling drug release than highly crosslinked carbomers (higher viscosity). In wet granulation processes, water, solvents or their mixtures can be used as the granulating fluid. The tackiness of the wet mass may be reduced by including talc in the formulation or by adding certain cationic species to the granulating fluid.

- The presence of cationic salts may accelerate drug release rates and reduce bioadhesive properties.
- Carbomer polymers have also been investigated in the preparation of sustained-release matrix beads as enzyme inhibitors of intestinal proteases in peptide-containing dosage forms, as a bioadhesive for a cervical patch and for intranasally administered microspheres, in magnetic granules for site-specific drug delivery to the esophagus, and in oral mucoadhesive controlled drug delivery systems.
- Carbomers copolymers are also employed as emulsifying agents in the preparation of oil-in-water emulsions for external administration. Carbomer 951 has been investigated as a viscosity-increasing aid in the preparation of multiple emulsion microspheres.
- Carbomers are also used in cosmetics. Therapeutically, carbomer formulations have proved efficacious in improving symptoms of moderate-to-severe dry eye syndrome.

4. STABILITY AND STORAGE:

Carbomer powder should be stored in an airtight, corrosion resistant container and protected from moisture. The use of glass, plastic, or resin-lined containers is recommended for the storage of formulations containing carbomer.

5. SAFETY:

Carbomers are generally regarded as essentially nontoxic and nonirritant materials; there is no evidence in humans of hypersensitivity reactions to carbomers used topically.

Incompatibilities

Carbopol is incompatible with phenol, cationic polymers, strong acids and high concentrations of electrolytes, and is discolored by resorcinol. Exposure to light causes oxidation, which is reflected in a decrease in viscosity.

Safety

Acute oral doses of carbopol-934P to rats, mice and guinea pigs produce LD50 values of 4.3, 4.6 and 2.5 g/kg, respectively. In dogs, no fatalities were noted with doses as high as 8g/kg. No primary irritation or any evidence of sensitivity or allergic reaction in humans following topical application of dispersions containing carbopol-934P has been observed. Carbopol-934P in contact with the eye is very irritating.

RIVIEW OF LITERATURE ON DRUG

McClelland GA et al[6] (1991) an extended-release osmotic dosage form was designed for gastrointestinal delivery of the water soluble tromethamine salt of the β-hydroxyacid form of simvastatin, a potent HMG-CoA reductase inhibitor and cholesterol lowering agent. The cholesterol lowering efficacy and systemic plasma drug level resulting from peroral administration of this dosage form, relative to the powder-filled capsule oral bolus, were evaluated in dogs. A twofold improvement in cholesterol lowering efficacy was realized with the controlled release dosage form that was accompanied by a drug AUC and Cmax that were 67 and 16%, respectively, of those achieved with the bolus dosage form. These results suggest that extended release dosage forms have the potential for a dose-sparing advantage in the administration of HMG-CoA reductase inhibitors for the treatment of hypercholesterolemia.

Cheng H, et al[7] (1993) designed seven controlled-release dosage forms for gastrointestinal delivery of Lovastatin or simvastatin, two potent HMG-CoA reductase inhibitors for the treatment of hypercholesterolemia. The *in vivo* performance for these formulations was evaluated in dogs and healthy volunteers in terms of the cholesterol lowering efficacy and/or systemic concentration of HMG-CoA reductase inhibitors. Results from the present and previous studies suggest that, through the controlled release of HMG-CoA reductase inhibitors, sustained lower plasma concentration of HMG-CoA reductase inhibitors may result in an equal or better therapeutic efficacy.

Ballantyne CM et al[55] (2003) previous studies have shown that effects on high-dencity lipoprotein cholesterol may differ among statins. And in this study Simvastatin (80 mg) increased HDL-C and apo A-I significantaly more than did Atorvastatin ((80 mg) in patients with hypercholesterolemia. This advantage was observed regardless of HDL-C level at baseline or the presence of the metabolic syndrome.

Sobal G et al[56] (2005) investigated the influence of simvastatin on oxidation of native and modified LDL as well as high density lipoprotein.(HDL), which plays protective role in atherosclerosis. the influence of simvastatin on lag time (protection from oxidation) by diene conjugation was also investigated. At the highest concentration of simvastatin (1.6 µg/ml), they found a prolongation of lag time from 73 min to 99 min for native LDL, glycoxidated LDL 60 min to 89 min and for HDL 54 min to 64 min. these data shows that simvastatin besides its lipid-lowering action has also significant antioxidative properties.

Pandya P et al [57] (2008) enhanced the solubility and dissolution of poorly aqueous soluble drug simvastatin (SIM) using hydrophilic, low viscosity grade polymer hydroxypropyl methylcellulose (HPMC K3LV). The co-solvent evaporation method was developed for efficient encapsulation of hydrophobic drug in polymer micelles of HPMC K3LV. Spray drying and rotaevaporation method were applied for solvent evaporation. *In vivo* study was conducted on healthy albino rats (Wister strain), and formulations were administered by oral route. The dissolution rate was remarkably increased in co-solvent-evaporated

mixtures compared to SIM. Co-solvent-evaporated mixtures showed better reduction in total cholesterol and triglyceride levels than the SIM.

Maurya D et al [58] (2008) enhanced the solubility and dissolution rate of atorvastatin calcium (ATR) by a solid dispersion technique using poly- (ethylene glycol) 6000 (PEG 6000). Microwave energy was used to prepare an enhanced release dosage form of the poorly water soluble drug ATR with PEG 6000 as a hydrophilic carrier. An *in-vivo* study was performed to determine the lipid-lowering efficacy (cholesterol, high density lipoprotein and triglyceride) of the solid dispersions using a Triton-induced hypercholesterolemia model in rats. An increase in the solubility of ATR was observed with increasing concentration of PEG 6000. The optimized ratio for preparation of solid dispersions of ATR with PEG 6000 was 1: 12 w/w by conventional fusion and the microwave induced fusion method. The *in-vitro* study showed that solid dispersions increased the solubility and dissolution rate of ATR, and thus may improve its bioavailability compared with plain ATR. The solid dispersion formulation prepared by the microwave induced fusion method significantly ($P < 0.05$) reduced serum lipid levels in phases I and II (18 h and 24 h) of the Triton test compared with plain ATR.

Khan F et al [59] (2011) prepared stabilized gastro-retentive floating tablets of ATC to enhance bioavailability. A 3^2 factorial design used to prepare optimized formulation of ATC. The selected excipients such as docusate sodium enhanced the stability and solubility of ATC in gastric media and tablet dosage form. The best formulation (F4) consisting of hypromellose, sodium bicarbonate,

polyethylene oxide, docusate sodium, mannitol, crosscarmellose sodium, and magnesium stearate, gave floating lag time of 56 ± 4.16 s and good matrix integrity with in vitro dissolution of 98.2% in 12 h. After stability studies, no significant change was observed in stability, solubility, floating lag time, total floating duration, matrix integrity, and sustained drug release rates, as confirmed by DSC and powder X-ray diffraction studies. In vivo pharmacokinetic study performed in rabbits revealed enhanced bioavailability of F4 floating tablets, about 1.6 times compared with that of the conventional tablet (Storvas® 80 mg tablet).

Lakshmi NV et al [60] (2011) studied the effect of polyethylene glycol 4000 (PEG 4000) and polyethylene glycol 6000 (PEG 6000) on *in vitro* dissolution of Atorvastatin Calcium (ATC) from solid dispersions. Formulated a physical mixtures and solid dispersions (dropping method) using 1:1, 1:2 and 1:3 ratios of drug and carriers (PEG 4000 & PEG 6000). PEG 6000 in 1: 3 drug to carrier ratio exhibited the highest drug release (89.65%) followed by PEG 4000 (80.03%) in the same ratio formulated as solid dispersions using dropping method. The FT-IR shows the complexation and there were no interactions. Finally solid dispersion of Atorvastatin: PEG 6000 prepared as 1:3 ratio by dropping method showed excellent physicochemical characteristics.

Mohammed A et al[61] (2011) chitosan–atorvastatin (CH–AT) conjugate efficiently synthesized through amide coupling reaction. The formation of conjugate was confirmed by 1H NMR and FT-IR spectrometry. Nano-sized conjugate with a mean size of 215.3 ± 14.2 nm was prepared by the process of high pressure

homogenization (HPH). Scanning electron microscopy (SEM) revealed that CH–AT nano-conjugate possess smooth surface whereas X-ray diffraction (XRD) spectra demonstrated amorphous nature of nano-conjugate. CH–AT nano-conjugate showed solubility enhancement of nearly 4-fold and 100-fold compared to CH–AT conjugate and pure AT, respectively. The plasma-concentration time profile of AT after oral administration of CH–AT nano-conjugate (2574 ± 95.4 ng/mL) to rat exhibited nearly 5-fold increase in bioavailability compared with AT suspension (583 ± 55.5 ng/mL).

Rao M et al[62] (2010) formulated surface solid dispersions (SSD) of simvastatin which improve the aqueous solubility and dissolution rate to facilitate faster onset of action. SSDs of simvastatin with two different superdisintegrants in three different drug–carrier ratios were prepared by a coevaporation method. PXRD study demonstrated that there was a significant decrease in crystallinity of pure drug present in surface solid dispersions, which resulted in an increased dissolution rate of simvastatin.

Taízia DS et al[63] (2010) prepared solid dispersions (SD) of SIM with inert carriers to improve the release profile. SIM SD with polyethylene glycol (PEG 6000) or polyvinylpyrrolidone (PVP K15) in 1:1, 1:2, 1: 3, 1:4, and 1:5 ratios were prepared and their stability and dissolution properties were investigated. Drug release from all SD was significantly improved when compared to their corresponding physical mixture or SIM alone. The tablets gradually released SIM with a final quantity greater than 80% in 60 minutes.

Shen HR et al[64] (2006) prepared self-microemulsifying drug delivery systems (SMEDDS) containing atorvastatin to improve its bioavailability. SMEDDS is a mixture of lipid, surfactant, and cosurfactant, which are emulsified in aqueous medium under gentle digestive motility in the gastrointestinal tract. Droplet size, zeta-potential and long-term physical stability of the formulation was investigated. The release of atorvastatin from SMEDDS capsules was studied using the dialysis bag method in 0.1 M HCl and phosphate buffer (pH 7.4), compared with the release of atorvastatin from a conventional tablet. A pharmacokinetic study was performed in 6 beagle dogs after oral administration of 6mg kg−1 atorvastatin. The bioavailability of atorvastatin SMEDDS capsules was significantly increased compared with that of the conventional tablet. SMEDDS capsules consisting of Labrafil, propylene glycol and Cremophor RH40 provided the greatest bioavailability.

Michael AB et al[65] (2003) studied a multicenter, randomized, double-blind, parallel-dose conducted in 917 hypercholesterolemic patients to compare the efficacy of 80 mg/d simvastatin versus 80 mg/d atorvastatin on HDL-C and apolipoprotein (apo) A-I for 24 weeks. Prespecified subgroups analyzed were patients with low HDL-C levels and with the metabolic syndrome. Simvastatin increased HDL-C and apo A-I values significantly more than did atorvastatin for the mean of weeks 6 and 12 (8.9% vs 3.6% and 4.9% vs -0.9%, respectively) and the mean of weeks 18 and 24 (8.3% vs 4.2% and 3.7% vs -1.4%). These differences were observed across both baseline HDL-C subgroups (<40 mg/dL, ≥40 mg/dL) and in patients with the metabolic syndrome. Low-density lipoprotein

cholesterol and triglyceride reductions were greater with atorvastatin. Consecutive elevations >3* the upper limit of normal in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) occurred in significantly fewer patients treated with simvastatin than with atorvastatin (2/453 [0.4%] vs 13/464 [2.8%]), with most elevations observed in women taking atorvastatin (11/209 [5.3%] vs 1/199 [0.5%] for simvastatin).

REVIEW OF LITERATURE OF GASTRORETENTIVE DOSAGE FORM

Sheth PR et al[66] (1978) formulated sustained release capsules such that they are hydrodynamically balanced so that, upon contact with gastric fluid the formulation acquires and maintain a bulk density of less than one thereby remain buoyant in the fluid and remaining so until substantially all of the active ingredient is released. The formulations comprise adjuvant materials with specific gravity <1 and hydrocolloids. e.g. cellulose derivatives. The % release from capsule containing chlordiazopoxide into simulated gastric fluid (pH 1.2) after 1,2,3,5, and 7 hr are reported 39, 61, 86, 94, and 100% respectively.

Ikura et al[67] (1988) developed a dosage form in the form of a pilule such as subtilized granules and normal granules or a tablet. And they described that pilule and tablet of excessively large size, since they are expected to disintegrate and disperse and then complete releasing the drug while they pass the site of absorption. It is therefore preferable to make the in the form of a pilule whose particle size ranging form 0.5 to 2 mm. this invention was prepared by thoroughly mixing the active drug with lower alkyl ether of cellulose and polyacrylic acid or its salt, and one or more foaming agent, lubricant, binder, and vehicle.

Timmermans J et al[68] (1991) described apparatus for floating dosage form. The apparatus and method are particularly suitable for determining a change in chemical and /or physical properties a material exposed to a fluid and for measurements such as of the floating force produced by buoyant pharmaceutical dosage form.

Krogel I et al[69] (1999) developed and evaluated floating drug delivery system based on effervescent core and a polymeric coating. The mechanical properties (puncture strength and elongation) of acrylic (Eudragit RS, RL and NE) and cellulose (cellulose acetate, ethyl cellulose) polymer, which primarily determined the type of delivery system, a polymer coating with a high elongation value and high water low carbon dioxide permeability was selected (Eudragit RL/ acetyl tributyl citrate 20%w/w) in order to initiate the effervescent reaction and the floating process rapidly. HPMC was also added in the core to retard drug release. The composition and hardness of the tablet core and the composition and hardness of the coating could control the time of flotation.

Li S et al[70] (2003) investigated the effect of formulation variables on the calcium release and floating properties of the delivery system by using 2x3 factorial designs by using different grades of Hydroxypropylmethylcellulose (K100LV and K4M) and carbopol. They reported that by increasing the HPMC viscosity the release rate decreases and floating properties improved as the viscosity of the polymer is increased. Carbopol (CP934) incorporation was found to compromise the floating capacity of floating and release of calcium.

Gohel MC et al[71] (2004) developed a in vitro dissolution method to evaluate a carbamazepine floating drug delivery system. A 100 ml glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 N HCL dissolution medium and allow collection of samples. The performance of the modified dissolution apparatus was compared with USP dissolution apparatus. The drug release followed zero-order kinetics in the proposed method.

Streubel A et al[72] (2003) developed a physicochemically characterize single unit, floating controlled drug delivery systems consisting of polypropylene foam powder, matrix forming polymers, drug and filler. The highly porous foam powder provided low density and, thus, excellent in vitro floating behavior of the tablets. All foam powder containing tablets remained floating for at least 8 h in 0.1 N HCL at 37 °C. The tablet eroded upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion for the resulting release patterns varied significantly with the type of the matrix former.

Chavanpatil M et al[73] (2005) designed the sustained release formulation, with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems. Psyllium husk, HPMC K100M, crospovidone and its combination were used to get sustained release profile over a period of 24 h. it was found that in vitro drug release rate increased with increasing amount of crospovidone.

Baumgartner S et al[74] (2000) prepared the floating matrix tablets with high dose of a freely soluble drug. A tablet containing HPMC, drug and different additives

were compressed. The investigation showed that tablet composition and mechanical strength have the greater influence on the floating propertied and drug release. With the incorporation of a gas-generating agent, beside optimum floating time, 30 sec and duration of floating >8 hr., the drug release was also increased. The drug release was sufficiently sustained (more than 8 hr).

Bodmeier R et al[75] (1999) developed a multifunctional drug delivery system based on HPMC – matrix tablets placed within an impermeable polymeric cylinder (open at both ends). Depending on the configuration of the device, extended release, floating or pulsatile drug delivery systems could be obtained. Release behavior was investigated as a function of HPMC content, HPMC viscosity, position of the matrix within the polymeric cylinder, addition of various fillers and agitation speed of release medium. The release was independent of the agitation rate, the position of the tablet within the cylinder and length of the cylinder.

Gerogiannis VS et al[76] (1993) examined the floating and swelling characteristics of several excipients used in controlled release technology. The floating behavior was evaluated with resultant weight measurements, while a gravimetric method was employed for studying their swelling. The results indicated that higher molecular weight polymers had slower rates of polymer hydration and usually followed by enhanced floating behavior.

Wei Z et al[77] (2001) developed a new kind of two-layer floating tablet for gastric retention with cisapride as a model drug, sodium bicarbonate was used as an effervescent agent in floating layer and the amount of

hydroxypropylmethylcellulose in drug loading layers controls the *in vitro* drug release of cisapride. The *in vitro* drug dissolution in the simulated gastric fluid is more as compared to that of simulated intestinal fluid because cisapride has greater solubility in acid pH. Finally they concluded that this kind of new dosage form could be used as a general model for the design of other tablets for gastric retention, which has separate regulating of buoyancy and drug release.

Talwar N et al[78] (2000) prepared a pharmaceutical composition comprising a drug, a gas generating component, a swelling agent, a viscolying agent and optionally a gel-forming polymer. The swelling agent belonged to a class of compounds known as superdisintegrants (e.g. cross linked PVP, NaCMC). The viscolyzing agent initially and the gel forming polymer thereafter form a hydrated gel matrix which entrap the gas, in the stomach or upper part of the small intestine (spatial control). At the same time the hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug (temporal control).

Chen GL et al[79] (1998) studied the *in vitro* performance of floating sustained release capsule of verapamil. Capsules filled with mixture of verapamil, HPC and effervescent material are proposed to provide floating and sustained release for over 10 hrs. The effects of weight filled in the capsule, amount of HPC and the addition of effervescent material on the dissolution kinetics were studied. They concluded that the release of verapamil from the capsule followed Higuchi release model. However, when effervescent material was added, the system showed a zero-order release

BS Dave et al[80] (2004) prepared a gastroretentive drug delivery system of ranitidine hydrochloride. A 3^2 full factorial design was applied to systemically optimize the drug release profile. The results of the full factorial design indicated that a low amount of citric acid and a high amount of stearic acid favors sustained release of ranitidine hydrochloride from a gastroretentive formulation. No significant difference was observed between the desired release profile and batches F2, F3, F6, and F9. Batch F9 showed the highest f2 (f2 = 75) among all the batches, and this similarity is also reflected in t50 (~214 minutes) and t80 (~537 minutes) values.

Shishu N., et al[81] (2007) developed and evaluated of single unit floating tablets of 5-FU which, after oral administration, are designed to prolong the gastric residence time, increase drug bioavailability and target the stomach cancer. A floating drug delivery system (FDDS) was developed using gas-forming agents, like sodium bicarbonate, citric acid and hydrocolloids, like hydroxylpropyl methylcellulose (HPMC) and Carbopol 934P. The results of the *in vitro* release studies showed that the optimized formulation could sustain drug release for 24 h and remain buoyant for 16 h.

Shah SS et al[82] (2010) developed a system that permits the drug release to be changed freely while maintaining pH-independent drug release (model drug was Domperidone). Powder mixture of drug and HPMC K4M, eudragit L100, sodium bicarbonate (as gas-generating agent) and other excipients were mixed and directly compressed using single-punch tablet compression machine. The linear

regression analysis and model fitting showed that all these formulations followed Higuchi model, which had a higher value of correlation coefficient (r).

Tadros M et al[83] (2010) developed a gastroretentive controlled release drug delivery system with swelling, floating, and adhesive properties. Swelling ability, floating behaviour, adhesion period and drug release studies were conducted in 0.1 N HCl (pH 1.2) at 37 ± 0.5°C. Drug release profiles of all formulae followed non-Fickian diffusion. Statistical analyses of data revealed that tablets containing HPMC K15M (21.42%, w/w), Na alginate (7.14%, w/w) and NaHCO3 (20%, w/w) (formula F7) or CaCO3 (20%, w/w) (formula F10) were promising systems exhibiting excellent floating properties, extended adhesion periods and sustained drug release characteristics. Abdominal X-ray imaging of formula F10, loaded with barium sulfate, in six healthy volunteers revealed a mean gastric retention period of 5.50 ± 0.77 h.

Zate S et al[84] (2010) developed and evaluated the gastroretentive mucoadhesive sustained release tablet of Venlafaxine hydrochloride which releases the drug in a sustained manner over a period of 12 hours, by using Carbopol 971P in combination with eudragit RS-PO and ethyl cellulose as a mucoadhesive and release retardant respectively. Sustained release tablets were prepared by direct compression and were evaluated for bioadhesion time, swelling index and matrix erosion, and in vitro drug release. The tablets of batch F3 and F6 had high swelling behaviors but release of drug is very less and batch F2 having considerable swelling index and in vitro drug release (99.85%). From the experiments they concluded that use of carbopol as a release retardant and

adhesive polymer is very effective; and also it act as strong release retardant in combination with hydrophobic polymers.

Bhisel K et al[85] (2010) developed gastroretentive drug delivery systems (GRDDS) of Ketoconazole, which is having narrow absorption window in gastrointestinal tract. A 3^2 factorial design was used in formulating the buoyant capsule with hydroxypropyl methyl cellulose (HPMC K15 M) and lactose as independent variables. Floating time, swelling index, drug release were the three dependent variables. The floating tablet formulation was developed by taking the optimized capsule formulation as base point. These tablets were evaluated for floating lag time, in vitro floating time and drug release properties. The *in vivo* buoyancy time for tablets and capsules were evaluated by X-ray studies. *In vivo* study showed that the optimum tablet and capsule formulation were retained in stomach for more than eight hours. The percent drug release of capsule formulation was found to be 80.33% and that of tablet formulation was found to be 80.16% in 8 hours.

Prajapati S et al[86] (2011) prepared a floating matrix tablet containing domperidone as a model drug. Polyethylene oxide (PEO) and hydroxypropyl methylcellulose (HPMC) were evaluated for matrix-forming properties. A simplex lattice design was applied to systemically optimize the drug release profile. The amounts of PEO WSR 303, HPMC K15M and sodium bicarbonate were selected as independent variables and floating lag time, time required to release 50% of drug (t50) and 80% of drug (t80), diffusion coefficient (n) and release rate (k) as dependent variables. The amount of PEO and HPMC both had significant

influence on the dependent variables. concluded that the content of PEO had dominating role as drug release controlling factor, but using suitable concentration of sodium bicarbonate, one can tailor the desired drug release from hydrophilic matrixes. The linear regression analysis and model fitting showed that all these formulations followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient (r).

Chandira RM et al[87] (2010) formulated floating tablets of Itopride hydrochloride using an effervescent approach for gastroretentive drug delivery system. Floating tablets were fabricated; using direct compression method containing Itopride hydrochloride, polymers HPMC K100M, HPMC K15M and Carbopol 934 P, along with gas generating agent sodium bicarbonate and citric acid. The addition of Carbopol aided in the reduction of the drug dissolution due to their hydrophobic nature. The concentration of these agents was also optimized to get desired controlled release of drug. The floating tablet formulations were evaluated for physical characterization, assay, swelling index, in-vitro drug release, hardness, friability and weight variation. The drug release pattern of this optimized formulation was found to be non-fickian diffusion mechanism.

Patel JK et al[88] (2010) formulated and evaluated of floating-bioadhesive tablets to lengthen the stay of glipizide in its absorption area. Effervescent tablets were made using chitosan (CH), hydroxypropyl methylcellulose (HPMC), carbopolP934 (CP), polymethacrylic acid (PMA), citric acid, and sodium bicarbonate. The type of polymer had no significant effect on the floating lag time. All tablets floated atop the medium for 23-24 hr. Increasing carbopolP934

caused higher bioadhesion than chitosan ($p < 0.05$). All formulations showed a Higuchi, non-Fickian release mechanism. Tablets with 10% effervescent base, 80% CH/20% HPMC, or 80% CP/20% PMA seemed desirable.

Dias RJ et al[89] (2010) designed and optimized an oral controlled release acyclovir mucoadhesive tablet, in term of its drug release and mucoadhesive strength. A 3^2 full factorial design was employed to study the effect of independent variables like Carbopol-934P and HPMC K100M, which significantly influences like swelling index, ex-vivo mucoadhesive strength and in-vitro drug release. Tablets were prepared by direct compression and evaluated for mucoadhesive strength and in-vitro dissolution parameters. Both these polymers had a significant effect on the mucoadhesive strength of the prepared tablet.

Jagdale SC et al[90] (2009) developed a gastroretentive drug delivery system of propranolol hydrochloride. Hydroxypropyl methylcellulose (HPMC) K4 M, HPMC E 15 LV, hydroxypropyl cellulose (HPC; Klucel HF), xanthan gum, and sodium alginate (Keltose) were evaluated for their gel forming abilities. They were evaluated for physical properties, in vitro release as well as in vivo behavior. floating tablets were formulated with HPMC K4 M and HPC.

Khan F et al[91] (2009) prepared and evaluated of gastroretentive floating tablet of theophylline. Two hydrophilic cellulose derivatives, Methocel K100M and Methocel K15MCR were evaluated for their gel forming and release controlling properties. Sodium bicarbonate and citric acid were incorporated as gas generating agents. Tablets were prepared by direct compression technique. Formulations were evaluated for *in vitro* buoyancy and drug release study. It was

found that polymer content and amount of floating agent significantly affected the mean dissolution time, percentage drug release after 8 hours, release rate constant and diffusion exponent.

Sungthongjeen S et al[92] (2008) Floating multi-layer coated tablets were designed based on gas formation. The system consists of a drug-containing core tablet coated with a protective layer (hydroxypropyl methylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane, respectively. Eudragit RL 30D was chosen as a gas-entrapped membrane due to its high flexibility and high water permeability.

Javed A et al[93] (2007) developed a hydrodynamically balanced system for celecoxib as single-unit floating capsules. The capsules were prepared by physical blending of celecoxib and the polymer in varying ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in citrate phosphate buffer pH 3.0 (with 1% sodium lauryl sulfate). Capsules prepared with polyethylene oxide 60K and Eudragit RL100 gave the best in vitro percentage release and was used as the optimized formulation. For gamma scintigraphy studies, celecoxib was radiolabeled with technetium-99m by the stannous reduction method. Gamma imaging was performed in rabbits to assess the buoyancy of the optimized formulation. The optimized formulation remained buoyant during 5 hours of gamma scintigraphic studies in rabbits.

Krishna SS et al[94] (2006) prepared mucoadhesive dosage form which extend the GI residence time and control the release of rosiglitazone achieve controlled plasma level of the drug which is especially useful after 8 to 12 weeks of

monotherapy using conventional dosage forms. The optimized formulation showed a mucoadhesive strength >40 gm-f, and a mucoadhesion time >12 hours with release profile closer to the target release profile and followed Non-Fickian diffusion mediated release of rosiglitazone maleate.

Singh B et al[95] (2006) designed oral controlled release mucoadhesive compressed hydrophilic matrices of atenolol and to optimized the drug release profile and bioadhesion using response surface methodology. A central composite design for 2 factors at 3 levels each was employed to systematically optimize drug release profile and bioadhesive strength. Carbopol 934P and sodium carboxymethylcellulose were taken as the independent variables. Compressed matrices exhibited non-Fickian drug release kinetics approaching zero-order, as the value of release rate exponent (n) varied between 0.6672 and 0.8646, resulting in regulated and complete release until 24 hours. Both the polymers had significant effect on the bioadhesive strength of the tablets, measured as force of detachment against porcine gastric mucosa ($P < 0.001$).

Srivastava AK et al[96] (2005) developed floating matrix tablets of atenolol to prolong gastric residence time and increase drug bioavailability. The tablets were prepared by direct compression technique, using polymers such as hydroxypropyl methylcellulose (HPMC K15M, K4M), guar gum (GG), and sodium carboxymethylcellulose (SCMC), alone or in combination, and other standard excipients. Tablets were evaluated for physical characteristics viz. hardness, swelling index, floating capacity, thickness, and weight variation. *In vitro* release mechanism was evaluated by linear regression analysis. GG- and SCMC-based

matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium.

Chowdary KPR et al[97] (2003) formulated mucoadhesive tablets of diltiazem as matrix tablets employing sodium carboxymethylcellulose (Sodium CMC), hydroxyl propyl methyl cellulose (HPMC) and ethyl cellulose. Non-Fickian release was observed from most of the formulations. A two layered tablet formulation, an immediately releasing layer consisting of diltiazem and croscarmellose sodium, (a superdisintegrant) and a matrix consisting of diltiazem, sodium CMC and ethyl cellulose as a second maintenance layer, gave release close to the theoretical sustained release (SR) needed for diltiazem.

Abubakr ON et al[98] (2000) prepared captopril floating tablets using two viscosity grades of hydroxypropylmethylcellulose (HPMC 4000 and 15000 cps) and Carbopol 934P. Drug release best fit both the Higuchi model and the Korsmeyer and Peppas equation, followed by first order kinetics. While tablet hardness and stirring rate had no or little effect on the release kinetics, tablets hardness was found to be a determining factor with regard to the buoyancy of the tablets.

Rosa M et al[99](1994) developed utilizing both the concepts of adhesiveness and of flotation, in order to obtain a unique drug delivery system which could remain in the stomach for a much longer period of time. The bioadhesive property of the tablets was determined using rabbit tissue and a modified tensiometer. The new oral controlled-release system shows, at least in vitro, good characetristics in

relation to three parameters: controlled release of the drug, bioadhesiveness in the stomach and intestine of rabbits and buoyancy in an acid medium.

Shoufeng Li et al[100] (2001) composite Box-Wilson design for the controlled release of calcium was used with 3 formulation variables: X1 (hydroxypropyl methylcellulose [HPMC] loading), X2 (citric acid loading), and X3 (magnesium stearate loading). Twenty formulations were prepared, and dissolution studies and floating kinetics were performed on these formulations. All 3 formulation variables were found to be significant for the release properties ($P < 0.05$), while only HPMC loading was found to be significant for floating properties. Experimentally, calcium was observed to release from the optimized formulation with n and T50% values of 0.89 (± 0.10) and 3.20 (± 0.21) hours, which showed an excellent agreement.

Barata P et al[101] developed high-density, gastro retentive controlled delivery system of ranitidine. Four layer tablets containing 150 mg of ranitidine were prepared by manual compression, resulting in a final system consisted by a mucoadhesive layer, a high-density layer, a ranitidine sustained release layer and a ranitidine immediate release layer. The high density layer was obtained by mixing barium sulfate with HPMC K 100 M (90:10). Ranitidine immediate release layer (75 mg) was prepared by mixing ranitidine with 22 mg of lactose and 3 mg of sodium croscarmellose. Tablets density was determined at appropriate time to ensure that it would always be above 2.5 g/cm^3. The immediate release layer disintegrated within 5 minutes and using a 25% level of HPMC K 100 M it is possible to sustain ranitidine release for 6 hours, thus obtaining the desired

release profile. Despite of the swelling of the hydrophilic polymer the system density remained always above 2.5 g/cm^3. It was observed that the addition of the mucoadhesive and of the high density layer significantly ($p<0.05$) increased tablets gastric retention time and ranitidine relative bioavailability.

RIVIEW OF LITERATURE ON POLYMER

Milen D et al[102] (1999) studied Verapamil hydrochloride release from tablets based on high molecular weight poly(ethylene oxide) (PEO). The drug release proceeds as a controlled diffusion (*n* = 0.44–0.47), which rate is dependent on the molecular weight of PEO. The introduction of hydrophilic polymers with pH dependent solubility (Eudragit L, Eudispert hv and Carbopol 934) at concentrations of 10/50% with respect to PEO amount keeping constant the ratio drug: matrix insures relatively complete release both in alkali medium and under the conditions of the Half-change test. Meanwhile drug release kinetics also changes — the release of all models studied runs as a typical abnormal diffusion (*a* = 0.66–0.87), i.e. like a diffusion-relaxation controlled process. The decrease in drug concentration leads not only to retarded release of the drug sample but also to changes in the kinetics of the process. At lower drug concentrations on the matrix from a typical abnormal diffusion it turns into a relaxation controlled diffusion ($n_{10\%} = 1$).

Muhammad AM et al[103] (2011) prepared propranolol hydrochloride-loaded matrix tablets using guar gum, xanthan gum, and hydroxypropylmethylcellulose (HPMC) as rate-retarding polymers. Guar gum alone was unable to control drug

release until a 1:3 drug/gum ratio, where the release pattern matched a Higuchi profile. Matrix tablets incorporating HPMC provided near zero-order release over 12 h and erosion was a contributing mechanism. Combinations of HPMC with guar or xanthan gum resulted in a Higuchi release profile, revealing the dominance of the high viscosity gel formed by HPMC. As the single rate-retarding polymer, xanthan gum retarded release over 24 h and the Higuchi model best fit the data. When mixed with guar gum, at 10% or 20% xanthan levels, xanthan gum was unable to control release. However, tablets containing 30% guar gum and 30% xanthan gum behaved as if xanthan gum was the sole rate-retarding gum and drug was released by Fickian diffusion.

Seyed AM et al[104] (2004) investigated the effect of hydroxyl group containing tablet excipients on the duration of adhesion of mucoadhesive polymers, discs containing Carbopol 934 (C934), polycarbophil (PC), sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose (HPMC), tragacanth and sodium alginate (Na alg.), either alone or in the presence of various amounts of excipients were prepared. All the excipients examined reduced the duration of adhesion and the relative durability of the polymer containing discs. HPMC discs despite showing the longest duration of mucoadhesion, suffered the greatest reduction in adhesive properties in the presence of excipients which were examined. The least reduction in the duration of adhesion was observed with PC and C934. Among the excipients tested, spray-dried lactose produced the greatest reduction in the duration of adhesion, followed by polyethylene glycol 6000 and pregelatinized starch.

Parka JS **et al**[105] **(2010)** evaluated gelling behavior and drug release profiles of PEG, various contents of the polymers were investigated through a robust experimental design method. When exposed to an aqueous environment, the PEO–PEG matrix hydrated slowly and swelled, causing a thick gel layer to form on the surface, the thickness of which increased significantly depending on the PEG contents. The optimal settings of PEO and PEG were 94.26 and 140.04 mg, respectively (PEG rate of 148.57%). Moreover, as the amount of PEG increased, the release rate also increased. When the formulation contained more than 150% of PEG, most of the drug loaded in the tablet was released in about 12 h. When the amount of PEG was less than 100%, the drug release rate was sustained significantly.

Sarojini S et al[106] **(2010)** investigated the floating tablets containing theophylline as a model drug. Formulations were optimized for type of filler and different concentration of polyethylene oxide. Sodium bicarbonate was used as a gas generating agent. A 3^2 randomized factorial design was employed in formulating gastric floating drug delivery system (GFDDS) with content of PEO (X1) and ratio of starch 1500 to lactose as filler(X2) were selected as independent variables. Study revealed that type of filler had significant effect on release of drug and floating property from different concentration of PEO. Lactose gave higher drug release with release mechanism towards zero order compared to starch 1500 which gave slow release with release mechanism towards diffusion based. Optimized formulations were studied for effect of hardness on floating properties

and dissolution medium on drug release. Hardness of tablet had major influence on floating lag time which might be due to decreased porosity.

Panigrahy RN et al[107] (2011) developed combined bioadhesive-floating oral drug delivery system exhibiting a unique combination of bioadhesion and floatation to prolong residence in the stomach using Acyclovir, as a model drug. The *in vitro* drug release, buoyancy lag-time, bioadhesive strength and swelling index were evaluated. The *in vitro* drug release from the tablet was controlled by the amount of HPMC K-15 and other bioadhesive polymers. The release of Acyclovir from the tablets followed the Higuchi matrix model. The swelling properties were increased with increasing polymer concentration and contributed to the drug release from the tablet matrix.

Hongtao Li et al[108] (2008) investigated the effect of drug solubility on polymer hydration and drug dissolution from modified release matrix tablets of polyethylene oxide (PEO). Tablet dissolution was tested using the USP Apparatus II, and the hydration of PEO polymer during dissolution was recorded using a texture analyzer. A multiple linear regression model could be used to describe the relationship among drug dissolution, polymer ratio, hydrogel formation and drug solubility; the mathematical correlation was also proven to be valid and adaptable to a series of study compounds.

Mahalingam R et al[109] (2009) prepared compacts bioadhesive gastroretentive delivery system to deliver water soluble and water insoluble compounds in the stomach. Compacts with 90:10, 75:25, and 60:40 of polyvinylpyrrolidone (PVP) and polyethylene oxide (PEO) were evaluated for swelling, dissolution,

bioadhesion, and in vitro gastric retention. Compacts containing higher PEO showed higher swelling (111.13%) and bioadhesion (0.62±0.03 N/cm2), and retained their integrity and adherence onto gastric mucosa for about 9 h under in vitro conditions.

Shoufeng Li et al[110] (2003) investigated the effect of formulation variables on drug release and floating properties of the delivery system. Hydroxypropyl methylcellulose (HPMC) of different viscosity grades and Carbopol 934P (CP934) were used in formulating the Gastric Floating Drug Delivery System (GFDDS) employing 2 × 3 full factorial design. It was found that both HPMC viscosity, the presence of Carbopol and their interaction had significant impact on the release and floating properties of the delivery system. The decrease in the release rate was observed with an increase in the viscosity of the polymeric system.

RIVIEW OF LITERATURE ON STATASTICAL DESIGN

Dandu R et al[111](2009) prepared 11 formulation and process variables at two levels chosen and randomly assigned to the Plackett-Burman DOE: Ciprofloxacin (unseived vs seived below mesh 35), Avicel® (PH102 vs PH101), Klucel® (EFX vs JF), pregelatinized starch (partially gelatinized vs fully gelatinized), Aerosil® (0% vs 0.25%), Magnesium stearate (vegetable vs animal), mixing time (5 min vs 20 min), roll pressure (80 bar vs 140 bar), feed screw speed to roll speed ratio (5 vs 7), fine granulator (50 rpm vs 25 rpm), and compression force (12kN vs 16kN). Weight variation, tablet hardness, and disintegration time of the resultant tablets was evaluated to elucidate “main effects” among these 11 variables - using only

12 experiments These results demonstrate the feasibility of applying Plackett-Burman DOE to identify the “main effects” in pharmaceutical manufacturing design space with a far fewer number of experiments.

Krzysztof W et al[112] (2011) seven factors of wet granulation process were investigated for criticality. Low and high levels of each factor represented maximal and minimal settings of wide operational ranges. Granulates were produced in line with Plackett-Burman experimental matrix, blended with extra-granular excipients and compressed into tablets. The high shear granulation factors, i.e. quantity of binding solution, rotational speed of impeller and wet massing time were considered of critical importance. Operational ranges of the parameters were optimized.

El-Malah Y et al[113] (2006) Studied the effect of seven factors – POLYOX molecular weight (*X*1) and amount (*X*2); Carbopol (*X*3), lactose (*X*4), sodium chloride (*X*5), citric acid (*X*6); compression pressure (*X*7) – on (1) the release of theophylline from hydrophilic matrices, demonstrated by changes in dissolution rate, and (2) their impact on the release exponent [*n*] indicative of the drug transport mechanism through the diffusion matrix. This objective was accomplished utilizing the Placket–Burman screening design. Theophylline tablets were prepared according to a 7-factor–12-run statistical model and subjected to a 24-h dissolution study in phosphate buffer at pH 7.2. The primary response variable, *Y*4, was the cumulative percent of theophylline dissolved in 12 h. The regression equation for the response was $Y4 = 66.2167 - 17.5833X1 - 3.3833X2 - 9.366X3 - 1.1166X4 - 0.6166X5 + 2.6X6 - 2.783X7$. This polynomial

model was validated by the ANOVA and residual analysis. The results showed that only two factors (*X*2 and *X*3) had significant effect (*p*-value < 0.10) on theophylline release from the hydrophilic polymer matrix. Factors (*X*2 and *X*7) had significant effect (*p*-value < 0.10) on [*n*], the exponent.

Jain SP et al[114](2010) focused on exploiting Plackett–Burman design to screen the effect of nine factors—poly (ethylene oxide) molecular weight (X1), poly (ethylene oxide) amount (X2), ethylcellulose amount (X4), drug solubility (X5), drug amount (X6), sodium chloride amount (X7), citric acid amount (X8), polyethylene glycol amount (X9), and glycerin amount (X11) on the release of drugs from the extended release extrudates, i.e., release rate and release mechanism. The experiments were carried out according to a nine-factor 12-run statistical model and subjected to an 8-h dissolution study in phosphate buffer pH 6.8. The significance of the model was indicated by the ANOVA and the residual analysis. Poly (ethylene oxide) amount, ethylcellulose amount and drug solubility had significant effect on the T90 values whereas poly (ethylene oxide) amount and ethylcellulose amount had significant effect on the n value.

Sastry SV et al[115] (1998) prepared bilayered osmotically controlled Gastrointestinal Therapeutic System of atenolol using cellulose acetate pseudolatex by polymer emulsification method. Various factors such as orifice size, coating thickness, amount and nature of polymeric excipients, and amount of osmotic agent influence the drug release from GITS. Studied a 7-factor, 12-run Plackett–Burman screening design was evaluate the formulation variables for atenolol GITS coated with CA pseudolatex. The variables studied were orifice

size, %coating weight gain, amounts of sodium chloride, Polyox N80 and 303, and Carbopol 934P and 974P on drug release. The screening design has revealed that orifice size, %coating weight gain and amount of Carbopol 934P have prominent influence on in-vitro atenolol release. The response variable was cumulative percent atenolol released (*Y)* in 24 h with constraints on percent release at 2, 6, 12 and 18 h. The polynomial equation obtained was *Y*24=149.82-0.13*X*1- 0.34*X*2+0.06 *X*3-0.13*X*4-0.23*X*5-76.25*X*6-2.46 *X*7. The results indicated that the drug release under constrained conditions was influenced by the factors with decreasing order of importance as %coating weight gain>Carbopol 934P>Polyox N80>Carbopol 974P>Polyox 303>amount of sodium chloride>orifice size.

Zhang Y et al[116](2010) described the (1) development of a software program, called DDSolver, for facilitating the assessment of similarity between drug dissolution data; (2) to establish a model library for fitting dissolution data using a nonlinear optimization method; and (3) to provide a brief review of available approaches for comparing drug dissolution profiles. DDSolver is a program which is capable of performing most existing techniques for comparing drug release data, including exploratory data analysis, univariate ANOVA, ratio test procedures, the difference factor f1, the similarity factor f2, the Rescigno indices, the 90% confidence interval (CI) of difference method, the multivariate statistical distance method, the model-dependent method. Sample runs of the program demonstrated that the results were satisfactory, and DDSolver could be served as a useful tool for dissolution data analysis.

4. METHODOLOGY

The following materials that were either AR/LR grade or the best possible pharma grade available were used as supplied by the manufacturer.

MATERIALS USED:

Table 4.1 List of material used

Sr. No.	Materials	Manufacture
DRUG		
1.	SIMVASTATIN	Biocon limited, Banglore, India., DRL Hyderabad,
2.	ATORVASTATIN	Alembic Pharma Vadodara
EXCIPIENTS		
2.	Cross carmelose sodium	FMC Ireland.
3.	HPMC K4M	Aqualon, USA, Colorcon Asia Pvt Ltd.
4.	HPMC K100M	Aqualon, USA, Colorcon Asia Pvt Ltd.
5.	Gaur Gum	Loba chem. India.
6.	Polyox® WSR 303	Colorcon Asia Pvt Ltd. Goa.
7.	Carbopol 934P	SD Fine Chem. Mumbai.
8.	Micro crystalline cellulose 101	FMC, Ireland.
9.	Sodium bicarbonate	Colorcon, Goa.
10.	Mg Al silicate	Signet, Mumbai.

11.	Sodium starch glycolate	Colorcon, Goa.
12.	PVP K 30	Aqualon, USA.
13.	Hydrochloric Acid	Ranbaxy chemical.
14.	Titanium Dioxide	Merck ltd. Mumbai.

DETAILS OF INSTRUMENTS USED:

Table 4.2 List of instruments used

Sr. No	Instruments	*Manufacture*
1.	Electronic Weighing Balance	Shimadzu Corporation, Japan.
2.	Bulk density apparatus	Erweka, GmbH, Germany
3.	Hardness tester	Dolphin India, Mumbai
3.	Sieve	Techno Instruments comp, Bangalore
4.	Dissolution apparatus	Electrolab, India, Veego lab India.
5.	UV/visible Spectrophotometer	UV-1700 UV/VIS, Shimadzu Corporation, Japan.
6.	FTIR Spectrophotometer (Spectrum RXI)	Perkin Elmer Ltd, USA, Shimandzu, Japan.
7.	Rotary tablet compression machine	Hardik Engg. Ahemedabad.

METHODOLOGY:

1. PREFORMULATION:

Prior to development of the dosage forms with a new drug candidate, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information will dictate many of the subsequent events and possible approaches in formulation development. This first learning phase is known as preformulation.

In this the two sub-phases are:

- ***Analytical*** Involves identification of the active pharmaceutical ingredient, evaluating for pharmacopoeial compliance, and development of analytical procedures.
- ***Formulation,*** the approved material of certain chemical identity and purity can have varied pharmaceutical properties that can have impact over formulations and drug release patterns, so any batch-to batch variations in these characteristics of the material and their effect on the performance of the dosage forms are to be established.

1.1. Analytical phase:

The Preformulation parameter for Simvastatin and Atorvastatin under analytical

aspects is,

1.1.1. UV spectroscopy:

The UV spectra were scanned from 200 to 400 nm at medium scanning speed, with the solution in 1 cm quartz cell. Solution concentration of 100 µg/ml was used, and data were obtained in methanol.

1.1.2. Infrared spectroscopy:

The infrared spectrum of Simvastatin and Atorvastatin were obtained in a KBr pellet using IR spectrophotometer.

1.1.3. Melting point:

The melting point of Simvastatin and Atorvastatin were recorded by using Thiele's apparatus.

1.1.4 Calibration curve of Simvastatin:

Instrument:

Shimadzu UV-Visible spectrophotometer-1700

- **Principle:**

The calibration curve is obtained by dissolving Simvastatin in 0.1N Hydrochloric acid + 0.5% SLS. This solution was treated with manganese dioxide. Absorbance measured spectrometrically at 238 nm, 247 nm, and 257 nm against reagent blank. It obeyed Beer's Law in the concentration range of 2-25μg/ml.

- **Method:**

Standard stock solution: -

The stock solution was freshly prepared by dissolving 20mg Simvastatin in 0.1N hydrochloric acid + 0.5% SLS in a 100ml volumetric flask (Stock-I) for getting 0.2mg/ml strength.

Preparation of Calibration Curve:

The aliquots of 0.2 to 4.0 ml of standard Simvastatin solution (stock-I) were transferred to series of 20 ml volumetric flask. The volume of each volumetric flask was made up to 20ml with 0.1N hydrochloric acid + 0.5% SLS. This solution was treated with manganese dioxide. The absorbance of solution in each volumetric flask was measured at 238 nm, 247 nm, and 257

nm against reagent blank; for standard calibration curves the absorbance was taken as absorbance at 247 nm minus the absorbance at 257 nm against concentration.

Calibration Curve of Atorvastatin:

The calibration curve is obtained by dissolving Atorvastatin in 0.1N Hydrochloric acid + 0.5% SLS. Absorbance measured spectrometrically at 245 nm against reagent blank. It obeyed Beer's Law in the concentration range of 2-26μg/ml.

- **Method:**

Standard stock solution:

The stock solution was freshly prepared by dissolving 50mg Atorvastatin in 0.1N hydrochloric acid + 0.5% SLS in a 100ml volumetric flask (Stock-I) for getting 0.2mg/ml strength.

Preparation of Calibration Curve:

The aliquots of 0.2 to 4.0 ml of standard Atorvastatin solution (stock-I) were transferred to series of 20 ml volumetric flask. The volume of each volumetric flask was made up to 20ml with 0.1N hydrochloric acid + 0.5% SLS. The absorbance of solution in each volumetric flask was measured at 246 nm against reagent blank.

1.2. Formulation phase:

1.2.1. Preformulation study for selection of polymers:

Commonly used pharmaceutical ingredients were screened for the purpose of selecting polymers that can impart floating characteristic to the granules. These include Hydroxypropylmethylcellulose (K100M, K4M), Cross carmellose sodium, sodium starch gycolate, micro crystalline cellulose. The

polymers were passed through a BSS #100 sieve. The dissolution medium used to study the floating behavior was 0.1N HCl. Powder of each polymer (about 100mg) was sprinkled in glass beaker (diameter-6 cm) containing 100ml of a dissolution medium. The floating characteristics were observed at 0, 1, 2, 4, 6, 8, 10 and 12 hr.

2. PREPARATION OF SIMVASTATIN AND ATORVASTATIN GASTRORETENTIVE DOSAGE FORMS:

Procedure for Floating Granules Production:

Floating swellable granules containing Simvastatin/Atorvastatin were prepared by wet granulation technique using varying concentrations of different grades of polymers. Polymers and drugs were mixed homogeneously using glass mortar and pastle. PVP K 30 in isopropyl alcohol was used as granulating agent. Granules were prepared by passing the wet coherent mass through a BSS # 16 sieve. The granules were dried in hot air oven at a temperature of 60 °C; dried granules were sieved through BSS # 20/44 sieves. Dried granules after sieving were mixed with sodium bicarbonate used as a gas-generating agent. Granules were filled in to the '0' size EHGC using hand-filling machine.

Procedure for Tablets (Floating, Mucoadhesive, High density) Production:

In the present study of gastroretentive floating matrix tablets, direct compression method was found the most compatible during the preliminary study because the effervescent mixture is not compatible with wet granulation method as well as low density approach will not be achieved by dry granulation technique.

Dry powder of Simvastatin and Atorvastatin, definite amount of polymer mixture (having various combinations of HPMC K100M, HPMC K4M, Carbopol 934P, Titanium dioxide, Guar gum, Polyox® WSR 303, and Magnesium aluminum silicate) and effervescent agent (Sodium bicarbonate) along with ducusate sodium as a stabilizing agent, Magnesium stearate (as a lubricant) and talc (as a glident) were directly compressed at low pressure and/or high pressure in Rotary Tablet Punching Machine.

2.1. FORMULATION OF FLOATING TABLET*:*

2.1.1 Experimental Design[117-119]

Plackett–Burman factorial designs can identify main factors from the large number of suspected contributor factors for the desired response variables. Therefore, these designs are extremely useful in preliminary studies where the aim is to identify formulation variables that can be fixed or eliminated in further investigation. The model is of the form:

$$Y = \beta 0 + \beta 1\, X1 + \beta 2\, X2 + \beta 3\, X3 + \beta 4\, X4 + \ldots\ldots \beta n\, Xn$$

Where *Y* is the response, β0 is a constant and β1 to β*n* are the coefficients of the response values.

The design analyzes the input data and presents a rank ordering of the variables with magnitude of effect, and designates signs to the effects to indicate whether an increase in factor value is advantageous or not[115]. Below Tables summarizes the formulation variables for screening, and the constraints used. A 7-factor 8-run Plackett–Burman screening design was generated.

Docusate sodium was added in all Atorvastatin formulation as stabilizing agent.

BHA (Butayed Hydroxyl Anisole was added in all Simvastatin formulation as Anti oxidizing agent

Table.4.3 Preliminary trial batches prepared by First line of Plackett-burman design

RUN	Drug	HPMC K100M	Sod Starch Glycolate	$NaHCo^-_3$	PVP	Mg. Stearate	TALC
S1	80	64	20	15	8	4	4
S2	80	48	20	30	8	4	4
S3	80	64	15	30	8	4	4
S4	80	64	20	30	6	4	4
S5	80	64	20	15	6	4	4
S6	80	48	20	15	6	4	4
S7	80	48	15	15	8	4	4
S8	80	48	15	30	6	4	4
S9	80	64	15	15	8	4	4
S10	80	64	15	30	6	4	4
S11	80	48	15	15	6	4	4
S12	80	48	15	15	6	4	4

Table-: 4.4 Formulation design by First line of Plackett-burman design for floating tablet.

RUN	HPMC K100M	HPMC K4M	POLYOX 303	$NaHCO_3$	PVP	Mg. Stearate	TALC
SF1/AF1	+	+	+	-	+	-	-
SF2/AF2	-	+	+	+	-	+	-
SF3/AF3	-	-	+	+	+	-	+
SF4/AF4	+	-	-	+	+	+	-
SF5/AF5	-	+	-	-	+	+	+
SF6/AF6	+	-	+	-	-	+	+
SF7/AF7	+	+	-	+	-	-	+
SF8/AF8	-	-	-	-	-	-	-

Table-: 4.5 Formulation by First line of Plackett-burman design for floating tablet.

RUN	HPMC K100M	HPMC K4M	POLYOX 303	$NaHCO_3$	PVP	Mg. Stearate	TALC
SF1/AF1	48	48	18	12	16	6	3
SF2/AF2	32	48	18	24	8	8	3
SF3/AF3	32	32	18	24	16	6	4
SF4/AF4	48	32	12	24	16	8	3
SF5/AF5	32	48	12	12	16	8	4
SF6/AF6	48	32	18	12	8	8	4
SF7/AF7	48	48	12	24	8	6	4
SF8/AF8	32	32	12	12	8	6	3

2.2. FORMULATION OF HIGH DENSITY TABLET*:*

Table-: 4.6 Formulation design by First line of Plackett-burman design for high density tablet.

RUN	HPMC K100M	HPMC K4M	POLYOX 303	Titanium Dioxide	PVP	Mg. Stearate	TALC
SH1/AH1	+	+	+	-	+	-	-
SH2/AH2	-	+	+	+	-	+	-
SH3/AH3	-	-	+	+	+	-	+
SH4/AH4	+	-	-	+	+	+	-
SH5/AH5	-	+	-	-	+	+	+
SH6/AH6	+	-	+	-	-	+	+
SH7/AH7	+	+	-	+	-	-	+
SH8/AH8	-	-	-	-	-	-	-

Table-: 4.7 Formulation by First line of Plackett-burman design for high density tablet.

RUN	HPMC K100M	HPMC K4M	POLYOX 303	Titanium Dioxide	PVP	Mg. Stearate	TALC
SH1/AH1	48	48	12	16	16	6	3
SH2/AH2	32	48	12	32	8	8	3
SH3/AH3	32	32	12	32	16	6	4
SH4/AH4	48	32	6	32	16	8	3
SH5/AH5	32	48	6	16	16	8	4
SH6/AH6	48	32	12	16	8	8	4
SH7/AH7	48	48	6	32	8	6	4
SH8/AH8	32	32	6	16	8	6	3

2.3 FORMULATION OF MUCOADHESIVE TABLET:

Table-: 4.8 Preliminary trial batches prepared by First line of Plackett-burman design

RUN	Drug	HPMC K100M	Carbopol 934	POLYOX 303	Guar Gum	Mg. Stearate	TALC
S13	80	80	60	15	15	4	4
S14	80	80	40	20	15	4	4
S15	80	60	60	20	15	4	4
S16	80	60	60	20	15	4	4
S17	80	80	40	20	15	4	4
S18	80	60	40	15	15	4	4
S19	80	60	40	20	15	4	4
S20	80	60	60	15	15	4	4

Table-: 4.9 Formulation design by First line of Plackett-burman design for mucoadhesive tablet.

RUN	HPMC K100M	POLYOX 303	CARBOPOL 934P	Guar Gum	PVP	Mg. Stearate	TALC
SM1/AM1	+	+	+	-	+	-	-
SM2/AM2	-	+	+	+	-	+	-
SM3/AM3	-	-	+	+	+	-	+
SM4/AM4	+	-	-	+	+	+	-
SM5/AM5	-	+	-	-	+	+	+
SM6/AM6	+	-	+	-	-	+	+
SM7/AM7	+	+	-	+	-	-	+
SM8/AM8	-	-	-	-	-	-	-

Table-:4.10 Formulation by First line of Plackett-burman design for mucoadhesive tablet.

RUN	HPMC K100M	POLYOX 303	CARBOPOL 934P	Guar Gum	PVP	Mg. Stearate	TALC
SM1/AM1	30	20	40	20	16	6	3
SM2/AM2	15	20	40	40	8	8	3
SM3/AM3	15	10	40	40	16	6	4
SM4/AM4	30	10	20	40	16	8	3
SM5/AM5	15	20	20	20	16	8	4
SM6/AM6	30	10	40	20	8	8	4
SM7/AM7	30	20	20	40	8	6	4
SM8/AM8	15	10	20	20	8	6	3

2.4. FORMULATION OF FLOATING CAPSULE*:*

Table-:4.11 Formulation design by First line of Plackett-burman design for floating capsule.

RUN	C.C Sod	HPMC K4M	MCC 101	VEEGUM	EUDRAGIT RS	HPMC K100M	NaHCO3
SC1/AC1	+	+	+	-	+	-	-
SC2/AC2	-	+	+	+	-	+	-
SC3/AC3	-	-	+	+	+	-	+
SC4/AC4	+	-	-	+	+	+	-
SC5/AC5	-	+	-	-	+	+	+
SC6/AC6	+	-	+	-	-	+	+
SC7/AC7	+	+	-	+	-	-	+
SC8/AC8	-	-	-	-	-	-	-

Table-:4.12 Formulation by First line of Plackett-burman design for floating capsule.

RUN	C.C Sod	HPMC K4M	MCC 101	VEEGUM	EUDRAGIT RS	HPMC K100M	NaHCO3
SC1/AC1	37.5	50	10	25	50	25	12.5
SC2/AC2	25	50	10	37.5	25	37.5	12.5
SC3/AC3	25	25	10	37.5	50	25	25
SC4/AC4	37.5	25	5	37.5	50	37.5	12.5
SC5/AC5	25	50	5	25	50	37.5	25
SC6/AC6	37.5	25	10	25	25	37.5	25
SC7/AC7	37.5	50	5	37.5	25	25	25
SC8/AC8	25	25	5	25	25	25	12.5

*SF, AF, SH, AH, SM, AM, SC, AC were Formulation Code.

(+) = High level amount

(–) = Low level amount

Docusate sodium was added in Atorvastatin formulation as stabilizing agent.

All quantities given are in mg.

BHA (Butayed Hydroxyl Anisole was added in all Simvastatin formulation as Anti oxidizing agent

3. *EVALUATION OF GASTRORETENTIVE DOSAGE FORM: -*

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

3.1. TABLET THICKNESS:

Thickness of tablets was important for uniformity of tablet size. Thickness was measured using Vernier Calipers on 3 randomly selected samples.

3.2. TABLET HARDNESS:

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester.

3.3. FRIABILITY:

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Friability was done as per USP specification.

$$\%\text{Friability} = \frac{(\text{Initial wt. of tablets} - \text{Final wt. of tablets}) \times 100}{\text{Initial wt. of tablets}}$$

3.4. WEIGHT VARIATION:

Twenty tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation as per USP. The average weight of 20 tablets was calculated for each formulation.

3.5. TEST FOR CONTENT UNIFORMITY:

Tablet and capsule containing 80 mg of drug was dissolved in 200 ml of 0.1N HCl with 0.5% SLS (sodium lauryl sulphate) taken in volumetric flask. The drug was allowed to dissolve in the solvent and sonicate for 2 to 3 hr. after, this solution was treated with manganese dioxide then centrifuge for 10 min, filtered it, this filtered solution was measured at 238 nm, 247 nm, and 257 nm against reagent blank. The absorbance taken for calculating concentration was absorbance at 247 nm minus the absorbance at 257 nm for simvastatin and for Atorvastatin was measured at 246 nm against reagent blank. The concentration of Simvastatin/Atorvastatin in mg/ml was obtained by using standard calibration curve of the drug. Claimed drug content was 80 mg per tablet. Drug content studies were carried out in triplicate for each formulation batch.

3.6. BUOYANCY / FLOATING TEST:

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT). The lag time was carried out in beaker containing 250 ml of 0.1N HCl (pH 1.2) as a testing medium maintained at 37 $^{\circ}$C.

3.7. MEASUREMENT OF *IN VITRO* MUCOADHESION TIME/ STRENGTH

These were measured by ‘modified balance method. Briefly, a balance was taken and its left pan was replaced with a weight to the bottom of which a tablet was attached. Both sides were balanced with weight. Rat gastric

mucosa having a thick layer of mucus was fixed to a rubber cork, which was already attached to the bottom of the beaker containing corresponding medium with a level slightly above the mucosa. The weight, which was attached to the tablet, was brought into contact with the porcine mucosa, kept undisturbed for 5 minutes and then the pan was raised. Weights were continuously added on the right side pan in small increments and the weight at which the tablet detached from the mucosa was recorded as the mucoadhesive strength. For measuring mucoadhesion time a 10-gram weight was put on right side pan after raising it and the detachment time was noted. The time period throughout which the tablet remained attached to the mucosa is mucoadhesion time.

The force of adhesion was calculated using following formula;

Force of adhesion (N) = Mucoadhesive strength/100 × 9.81

3.8. *IN VITRO* SWELLING STUDIES

The degree of swelling of bio-adhesive polymers is an important factor affecting adhesive. For conducting the study, a tablet was weighed and placed in a beaker containing 100 ml of 0.1 N HCl for 24 hrs, the tablets were taken out from the beaker and excess water was removed carefully by using filter paper. The swelling Index was calculated using the following formula,

Swelling Index (SI) = (Wt-Wo)/Wo X 100

Where SI= Swelling index.

Wt = Weight of tablets after time at‘t’.

Wo = Weight of tablet before placing in the beaker.

3.9. DISSOLUTION STUDIES:

5.9.1 Dissolution Study of floating capsule: -

Apparatus	:	Dissolution test apparatus (USP XXIII)
Method	:	USP type 2 apparatus (paddle)
Dissolution medium	:	0.1N HCl + 0.5% SLS
Volume of DM	:	900 ml
Temperature	:	37 ± 0.5 °C
Speed	:	50 rpm

Procedure:

The capsule was placed inside the dissolution vessel. 10 ml of sample were withdrawn at time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24 hr. The volume of dissolution fluid adjusted to 900 ml by replacing 10ml of dissolution medium after every sample. Each sample was analyzed at 238 nm, 247 nm, 257 nm using double beam UV and Visible Spectrophotometer against reagent blank. The absorbance taken for calculating concentration was absorbance at 247 nm minus the absorbance at 257 nm for the simvastatin and for Atorvastatin was measured at 246 nm against reagent blank. The drug concentration was calculated using standard calibration curve.

3.9.2 Dissolution Study of Tablets: -

Apparatus	:	Dissolution test apparatus (USP XXIII)
Method	:	USP type 2 apparatus (paddle)
Dissolution medium	:	0.1N HCl + 0.5% SLS
Volume of DM	:	900 ml
Temperature	:	37 ± 0.5 °C
Speed	:	50 rpm

Procedure:

The tablet was placed inside the dissolution vessel. 10 ml of sample were withdrawn at time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24 hr. The volume of dissolution fluid adjusted to 900 ml by replacing 10ml of dissolution medium after every sample. Each sample was analyzed at 238 nm, 247 nm, 257 nm using double beam UV and Visible Spectrophotometer against reagent blank. The absorbance taken for calculating concentration was absorbance at 247 nm minus the absorbance at 257 nm for the simvastatin and for Atorvastatin was measured at 246 nm against reagent blank. The drug concentration was calculated using standard calibration curve.

4. MECHANISM OF DRUG RELEASE[116, 120-122.] :

Various models were tested for explaining the kinetics of drug release.

To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, Hixon-Crowell model and Korsmeyer-Peppas release model. Drug release rate kinetic of dosage form was calculated by using DDSover, A Microsoft Excel Add-in.

- **Zero order release rate kinetics*: -***

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_o.t$$

Where ‘F’ is the drug release, ‘K’ is the release rate constant and‘t’ is the release time.

The plot of % drug release versus time is linear.

- **First order release rate kinetics:**

The release rate date are fitted to the following equation

Log (100-F) = kt

A plot of log % drug release versus time is linear.

- **Higuchi release model:**

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$F = k\, t^{1/2}$$

Where 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

- **Korsmeyer and Peppas release model:**

The release rate data were fitted to the following equation,

$$M_t / M_\infty = K.t^n$$

Where, M_t / M_∞ is the fraction of drug released,

'K' is the release constant,

't' is the release time.

'n' is diffusion exponent, if n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or nonfickian diffusion (swellable & cylinder Matrix).

In this model, a plot of log (M_t/M_∞) versus log (time) is linear.

The dissolution data of plackett-burman design batches of Simvastatin/Atorvastatin gastroretentive tablets and capsule were fitted to Zero-order, First-order, Higuchi, and Korsmeyer-Peppas model to study the kinetics of drug release.

4.2.3 Optimization of gastroretentive formulation using Plackett-burman design

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = \beta0 + \beta1X1 + \beta2X2 + \beta3X3 + \beta4X4 + \beta5X5 + \beta6X6 + \beta7X7$$

Where, Y is the dependent variable, β0 is the arithmetic mean response of the eight runs, and βi is the estimated coefficient for the factor *Xi*. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative. The high values of correlation coefficient for the dependent variables indicate a good fit. The equation may be used to obtain estimate of the response because small error of variance was noticed in the replicates. Regression analysis was calculated by using the Microsoft Excel.

4. *In Vivo* Evaluation Of Gastrointestinal Residence Time

in vivo evaluation of gastrointestinal residence time of gastroretentive dosage form to confirm the spatial and temporary placement of gastroretentive drug delivery system, a variety of techniques have been used like string technique, endoscopy, gamma scintigraphy [25-29]. Of these techniques, X-ray technique was used to determine the gastric residence time of the tablets. For in vivo testing, healthy volunteers were selected. Volunteer was asked to swallow the placebo tablet with sufficient water after meal in the afternoon under the supervision of registered doctor. This was noted as zero time reading. The successive images were then recorded at regular intervals over a period of 4–8 h. The X-ray of the tablet in the volunteers was recorded at intervals of 1, and 8 h.

4.1. Tablet Preparation for In Vivo Studies[29]

Tablets with diameter 8 mm and 226 mg in weight were prepared. All the ingredients used in this study are transparent to X-ray, and therefore, to make the tablets X-ray opaque, the incorporation of BaSO4 was necessary. Barium sulfate has a high relative density (4.4777 g/cm^2) and poor floating properties. For in vivo tests, tablets with the following composition were compressed: 40 mg barium sulfate, and other ingredient as per the formula without the drug. Hardness was adjusted to 4.2 kg/cm^2.

5. STABILITY STUDY:

Introduction

In any rational design and evalution of dosage forms for drugs, stability of the active component must be a major criterion in determining their acceptance or rejection. Stabitily of the drug can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.

OR

Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

The international conference on Harmonization (ICH) guidelines titled ‘stability testing of New Drug substance and products’(Q1A) describes the stability test requirements for drug registration applications in the European union, japan and the USA.

ICH specifies the length of the study and storage conditions,

Long-Term Testing: 25°C ± 2°C / 60% RH ± 5% for 12 months.

Accelerated Testing: 40°C ± 2°C / 75% RH ± 5% for 6 months.

Stability studies were carried out at 40°C / 75% RH for the selected formulation for six months.

Method

The selected formulaton were packegd in air tight plastic container. They were then stored at 40°C / 75% RH, forn six month and evaluated for their physical appearance, drug content, and drug release at at specific interval of time per ICH guidelines.

6. ANIMAL STUDY:

Experimental animals

Male albino Wister rats weighing between 200-250 gm was used. Institutional Animal Ethics Committee approved the experimental protocol; animals were maintained under standard conditions in an animal house approved by Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA).

Selection of dose and treatment period for models:

The treatment period consisted of 40 days in all the models.

The following doses were administered once daily for duration mentioned above.

6.1 Evaluation of Total Cholesterol:

Experimental animals

Female adult albino rats (Wister strain) weighing between 190-240 gms body weighs were selected for the experimental study. They were divided into

3 groups, each group consisting of 6 rats and kept under standard laboratory conditions.

Treatment protocol

Group 1: Control group: Animal of this group received 0.5% Sod. CMC solution, p.o. 2.85 ml/Kg daily for forty days.

Group 2: Pure drug group: Animals of this group received Pure Drug (Simvastatin/Atorvastatin), 11.42mg/Kg/day p.o. for forty days.

Group 3: Optimized Formulation group: Animals of this group received Last Optimized Formulation of Simvastatin, 11.42mg/Kg/day, p.o. for forty days.

Blood samples were collected at 18^{th} day and 40^{th} day by retro orbital puncture method and serum was used for assay of Total cholesterol.

Estimation of Total cholesterol:

Principle:

Cholesterol esters are hydrolysed by Cholesterol Esterase (CE) to give free cholesterol and fatty acids. In subsequent reaction, Cholesterol Oxidase (CHOD) oxidizes the 3-OH group of free cholesterol to liberate Cholest-4-en-3-Peroxide couples with 4-Aminoantipyrine (4-AAP) and phenol to produce red Quinoneimine dye. Absorbance of colored dye is measured at 505 nm and is proportional to amount of Total Cholesterol concentration in the sample.

6.2 Assay Parameters:

Mode of reaction	End point
Wavelength	505 nm (490-510 nm)
Flow-cell temperature	37º c

Optical path length	1 cm
Blanking	Reagent blank
Sample volume	10 µl
Reagent volume	100 µl
Incubation time	10 min at 37º C or 30 min
	At room temperature
Concentration of Standard	200 mg/dL
Stability of final colour	1 hour
Linearity	750 mg/dL
Units	mg/dL

Laboratory Procedure:

	Sample Blank	Test
Total Cholesterol reagent	1000 µL	1000 µL
Serum	---	10 µL

Mixed well and incubated for exactly 10 minutes. Measured the absorbance of the sample against respective sample blank at 505 nm.

Statistical analysis

The statistical significance was assessed using one-way analysis of variance (ANOVA) followed by Dunnett's comparison test. The values are expressed as mean $\pm$ SEM and $p<0.05$ was considered significant.

5. RESULT

1. Preformulation: -

1.1. Analytical Phase:

1.1.1. UV spectroscopy:

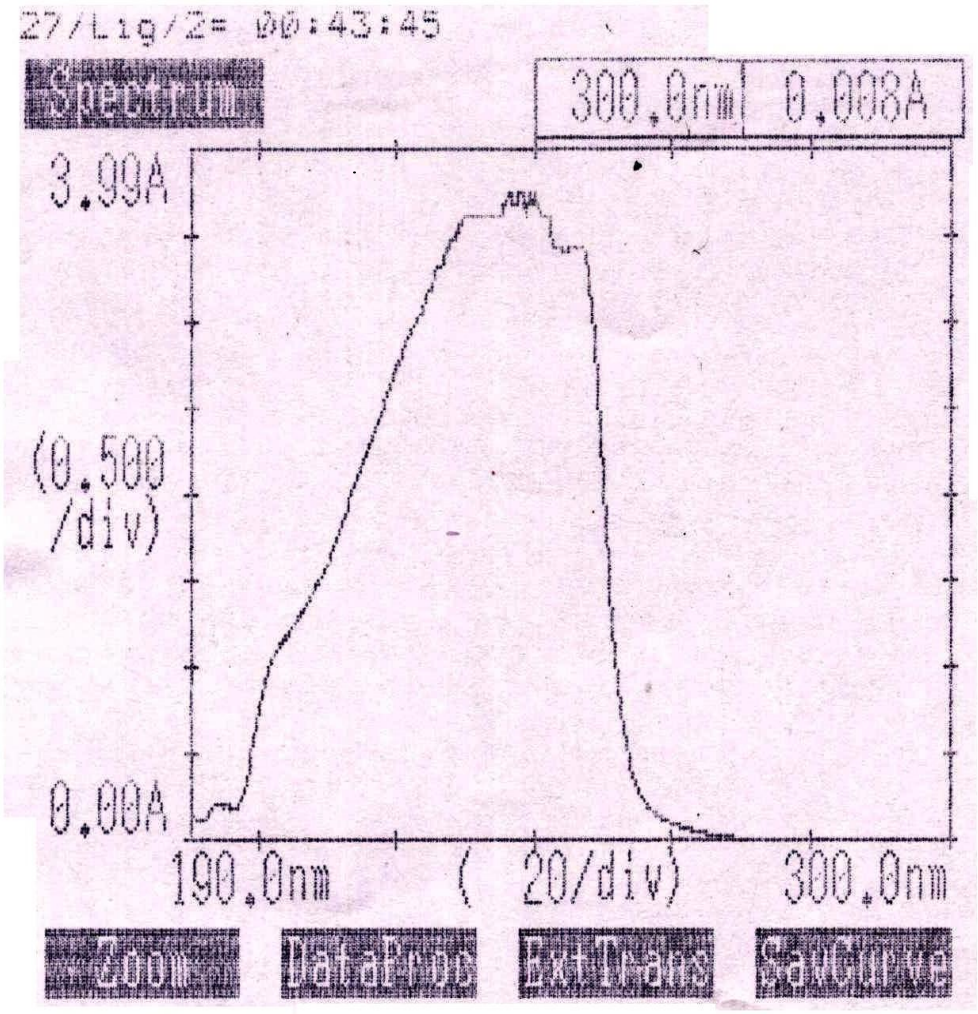


Fig. 5.1 Simvastatin UV Spectrum

In 0.1 N HCl solution of Simvastatin spectral maxima was observed at 238 nm.

1.1.2. Infrared spectroscopy:

Figure 5.2 and 5.3 shows IR spectrum of Simvastatin and drug with all excipients which used in formulation having characteristic absorption band in the following region.

The characteristic peaks of drug appear in the spectra of mixture of drug and excipient same wave number, indicating no modification or interaction between the drug and the excipients.

From that it can conclude that the drug has maintained its identity without losing its characteristic properties.

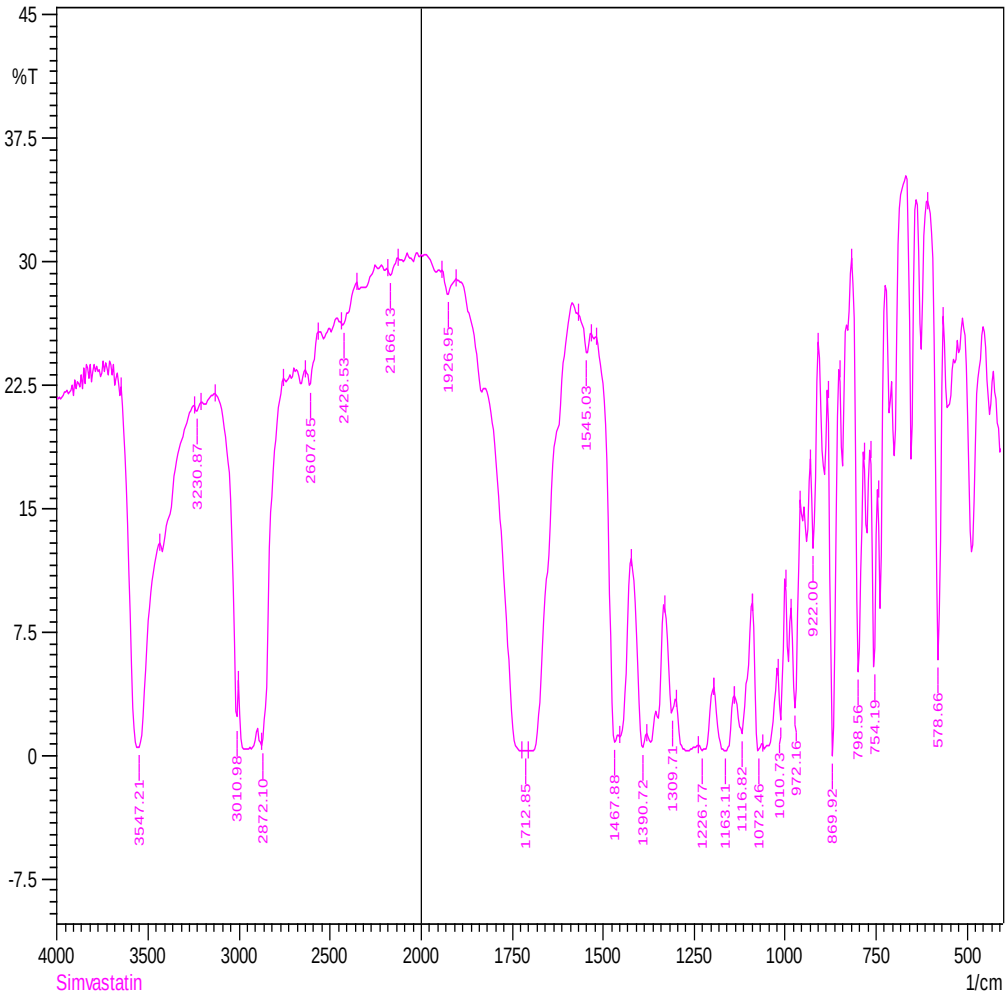


Fig. 5.2 Simvastatin IR Spectrum

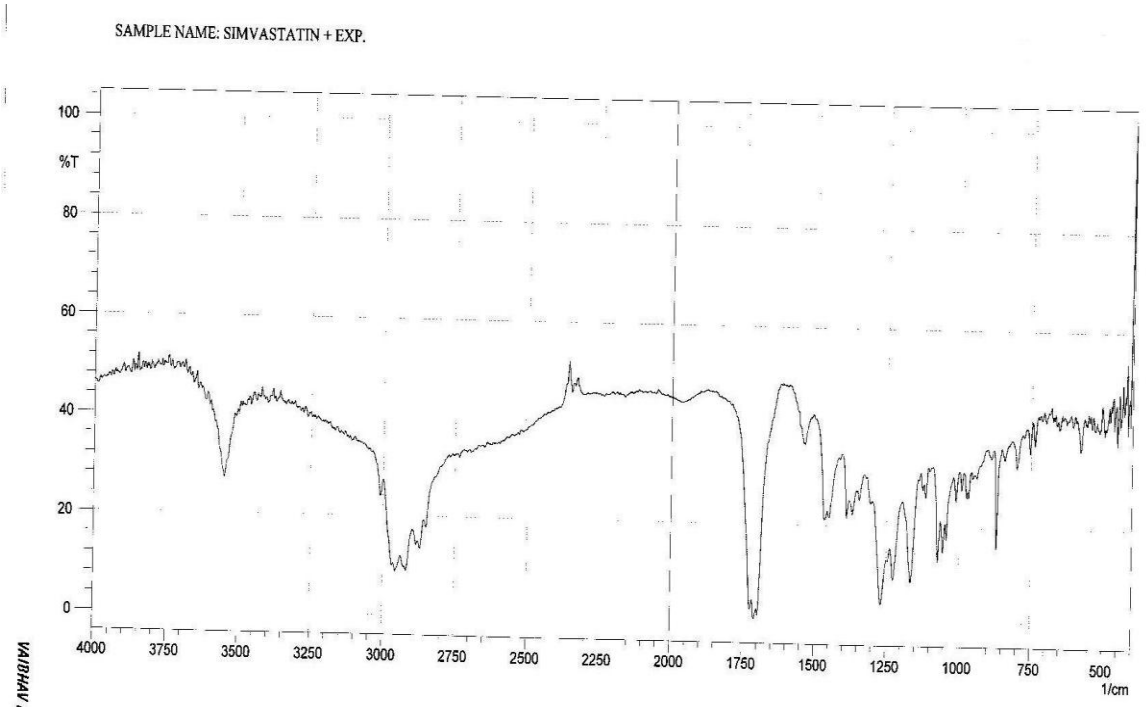


Fig. 5.3 Simvastatin+ Excipients IR Spectrum

1.1.3. Melting point:

Melting point of simvastatin was found to be 135 °C which is in accordance with the standard melting point of simvastatin.

Table 5.1 Data of simvastatin melting point

Parameter	Reported	Observed
Melting point	135-138 °C	133-136 °C

1.1.4 Calibration curve of Simvastatin:

The table shows the absorbance value of different concentration of simvastatin in 0.1 N HCl at 247 nm minus the 257 nm.

The calibration curve was plotted as shown in Fig 5.4 in concentration range of 2-12 μg/ml after regression analysis of data as shown in table 5.2 the value of R^2 was found to be 0.9992 which indicate the accuracy of results.

Table 5.2 Data of the standard calibration curve of Simvastatin

Conc. μg/ml	Absorbance			
	Set1	**Set2**	**Set3**	**Average**
00	0.000	0.000	0.000	0.000
2	0.071	0.071	0.071	0.071
4	0.140	0.139	0140	0.140
6	0.208	0.208	0207	0.208
8	0.270	0270	0.271	0.270
10	0.348	0.348	0.347	0.348
12	0.419	0.418	0.419	0.419
Regression output				
Intercept = 0.0000 **Slope =** 0.0347		**Correlation coefficient (R^2) =** 0.9992		

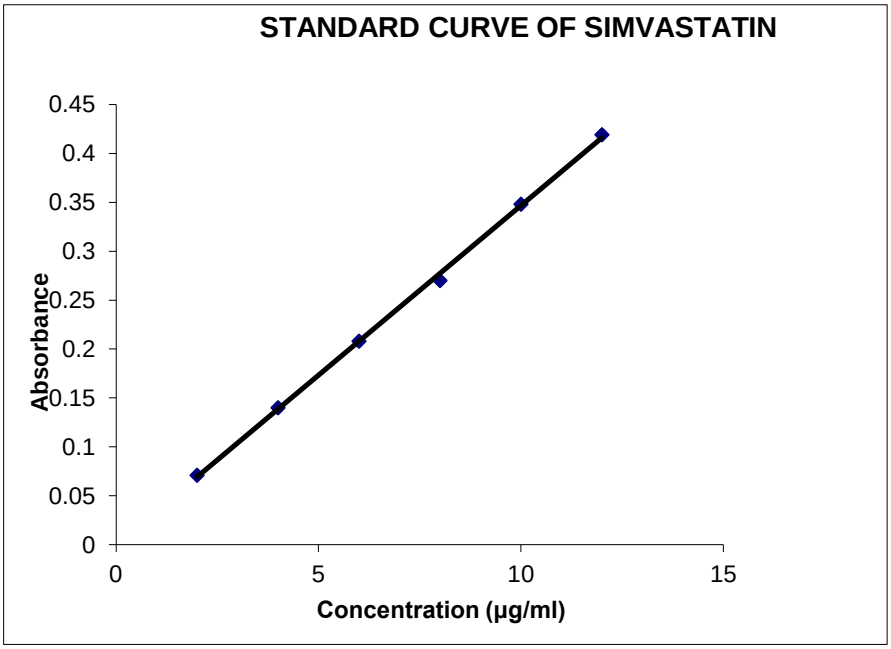


Fig. 5.4 Standard curve of Simvastatin

1.2. Analytical Phase:

1.2.1. UV spectroscopy:

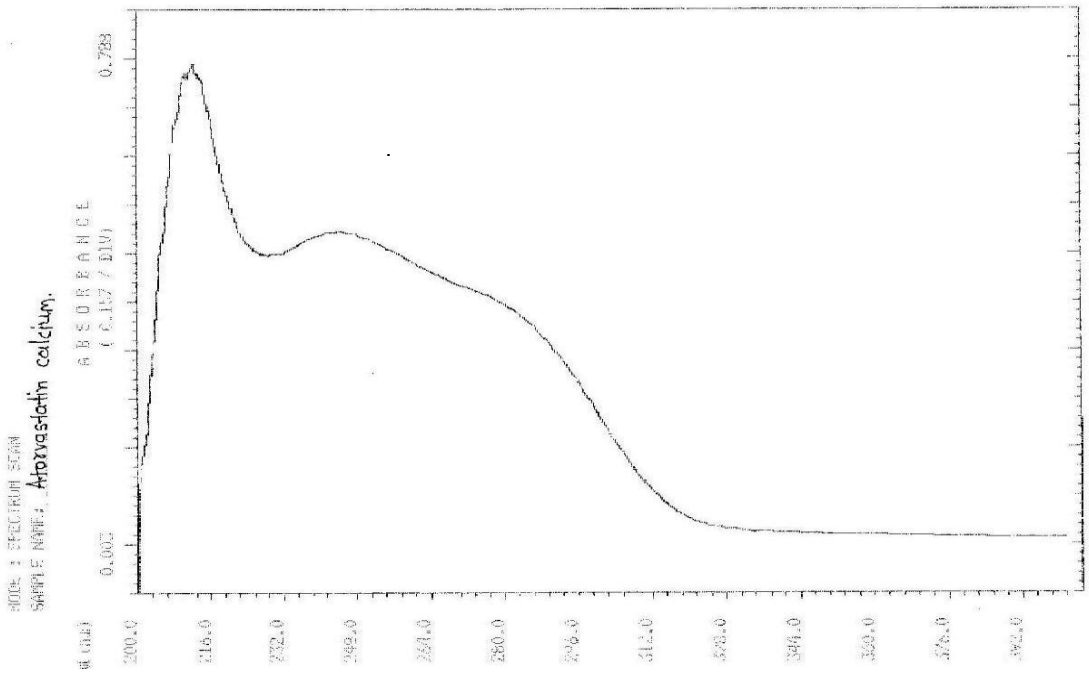


Fig. 5.5 Atorvastatin UV Spectrum

In 0.1 N HCl solution of Atorvastatin spectral maxima were observed at 246 nm.

1.2.2 Infrared spectroscopy:

Figure 5.6 and 5.7 shows IR spectrum of Atorvastatin and drug with all excipients which used in formulation having characteristic absorption band in the following region.

The characteristic peaks of drug appear in the spectra of mixture of drug and excipient same wave number, indicating no modification or interaction between the drug and the excipients.

From that it can conclude that the drug has maintained its identity without losing its characteristic properties.

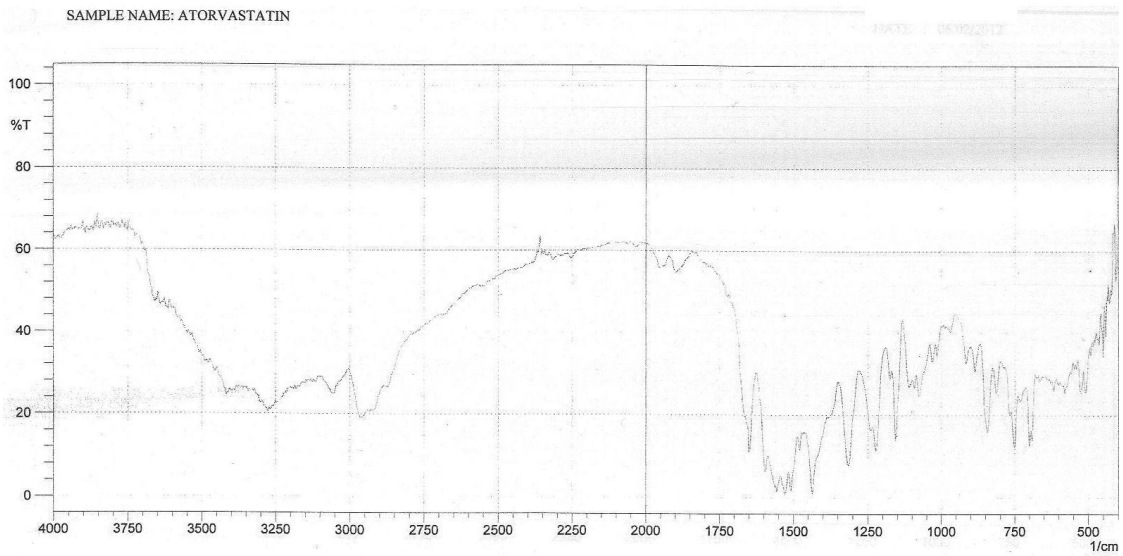


Fig. 5.6 Atorvastatin IR Spectrum

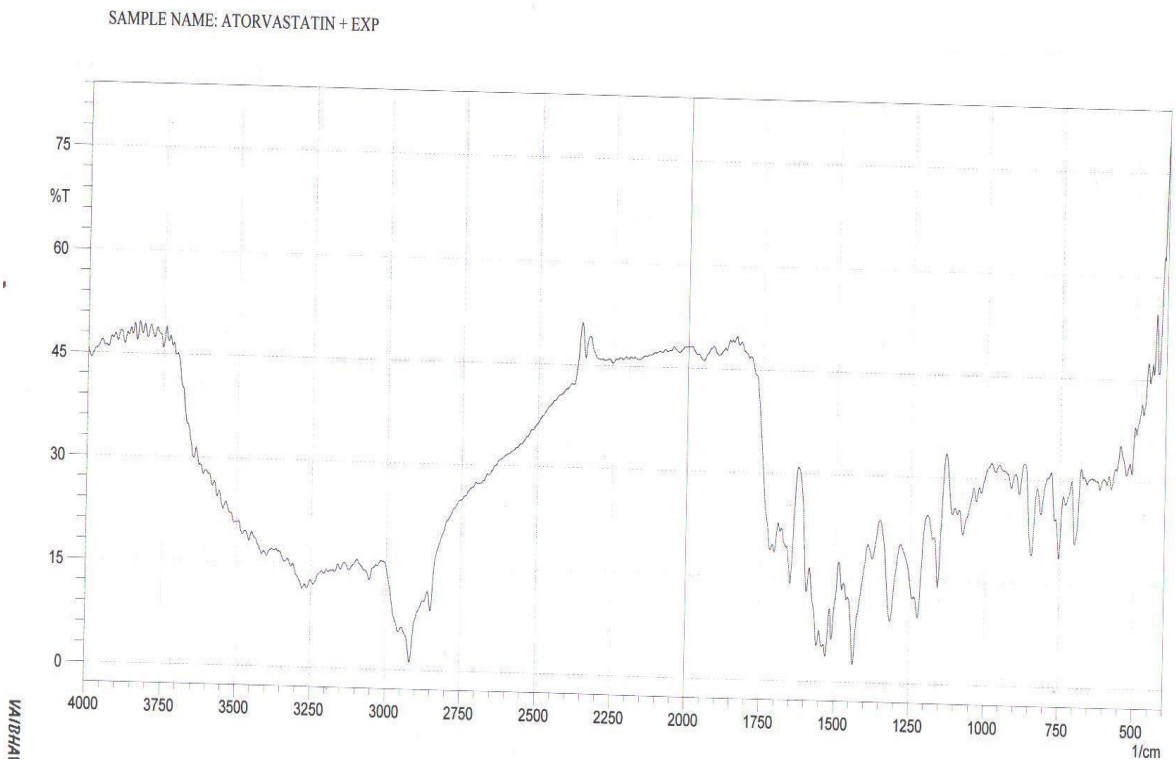


Fig. 5.7 Atorvastatin+ Excipient IR Spectrum

1.2.3 Melting point:

Melting point of atorvastatin was found to be 159 °C which is in accordance with the standard melting point of atorvastatin.

Table 5.3 Data of atorvastatin melting point

Parameter	Reported	Observed
Melting point	159.2-160.7 °C	159-160 °C

1.2.4 Calibration curve of Atorvastatin:

The table shows the absorbance value of different concentration of simvastatin in 0.1 N HCl at 246 nm. The calibration curve was plotted as shown in Fig 5.8 in concentration range of 5-50 μg/ml after regression analysis of data as shown in table 5.4 the value of R^2 was found to be 0.9993 which indicate the accuracy of results.

Table 5.4 Data of the standard calibration curve of Atorvastatin

Conc. μg/ml	Absorbance			
	Set1	**Set2**	**Set3**	**Average**
00	00	00	00	00
5	0.177	0.177	0.177	0.177
10	0.347	0.348	0.347	0.347
15	0.510	0.511	0.511	0.511
20	0.697	0.698	0.697	0.697
25	0.825	0.825	0.825	0.825
50	1.687	1.687	1.687	1.687
Regression output				
Intercept = 0.0000 **Slope =** 0.0338		**Correlation coefficient (R^2) =** 0.9993		

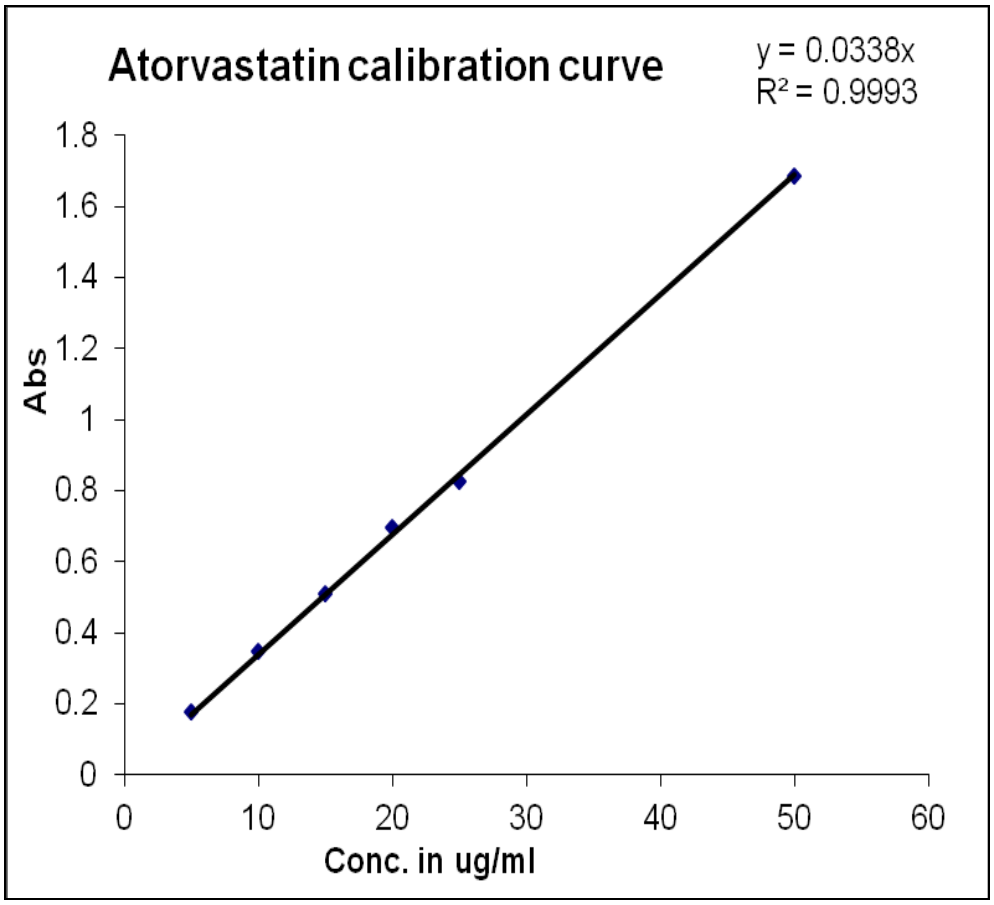


Fig. 5.8 Standard curve of Atorvastatin

2. EVALUATION OF GASTRORETENTIVE DOSAGE FORM OF SIMVASTATIN :

2.1. EVALUATION OF FLOATING CAPSULE

2.1.1 Filling capsule evaluation:

Table 5.5 The values of various evaluation parameters of the formulations SC made at formulation stage

Response	FORMULATION CODE							
	SC1	**SC2**	**SC3**	**SC4**	**SC5**	**SC6**	**SC7**	**SC8**
Bulk density (gm/ml)	0.333	0.335	0.439	0.380	0.363	0.389	0.391	0.387
Tapped density (gm/ml)	0.384	0.393	0.537	0.459	0.430	0.448	0.438	0.461
Angle of repose (^{o})	29.74	31.32	29.74	32.93	35.92	32.52	33.31	30.46
Friability (%) (granules)	0.98	0.45	0.89	1.4	0.67	0.62	0.88	0.91
% Fine	15	12	9	13	11	21	9	16
Wt variation (%)	2.34	1.56	3.12	3.67	0.93	1.30	0.84	0.06
TFT (hr)	24	25	8	8	28	9	22	12
Drug content (%)	99.17	99.57	102.2	99.55	101.7	97.23	102.6	103.4

2.1.2 Dissolution Study or drug release testing of floating Capsule: -

Table 5.6 Data of the release profile of the SC1 – SC8.

Time (Hrs)	Cumulative drug release (%)							
	SC1	**SC2**	**SC3**	**SC4**	**SC5**	**SC6**	**SC7**	**SC8**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	12.32	5.19	14.78	18.16	11.61	12.02	8.09	10.45
1	17.21	10.39	19.48	34.08	20.52	19.90	13.05	20.83
2	21.14	15.60	28.09	43.88	27.56	28.72	16.50	38.45
3	34.15	19.20	46.07	55.98	31.47	53.57	18.65	42.19
4	43.31	23.13	58.80	65.50	37.69	59.11	25.67	51.46
5	46.65	28.04	72.80	76.12	43.34	70.51	27.30	55.35
6	61.34	39.45	77.95	89.04	48.58	89.14	32.49	60.58
7	66.34	44.73	88.94	99.15	52.83	92.55	35.49	69.43
8	72.32	52.28	97.83	99.95	60.03	97.28	51.10	77.41
9	75.40	54.34			66.59	103.70	57.51	82.69
10	81.07	59.98			74.79		67.55	90.61
12	90.33	71.13			86.48		80.51	100.25
24	100.25	101.4			99.47		98.19	

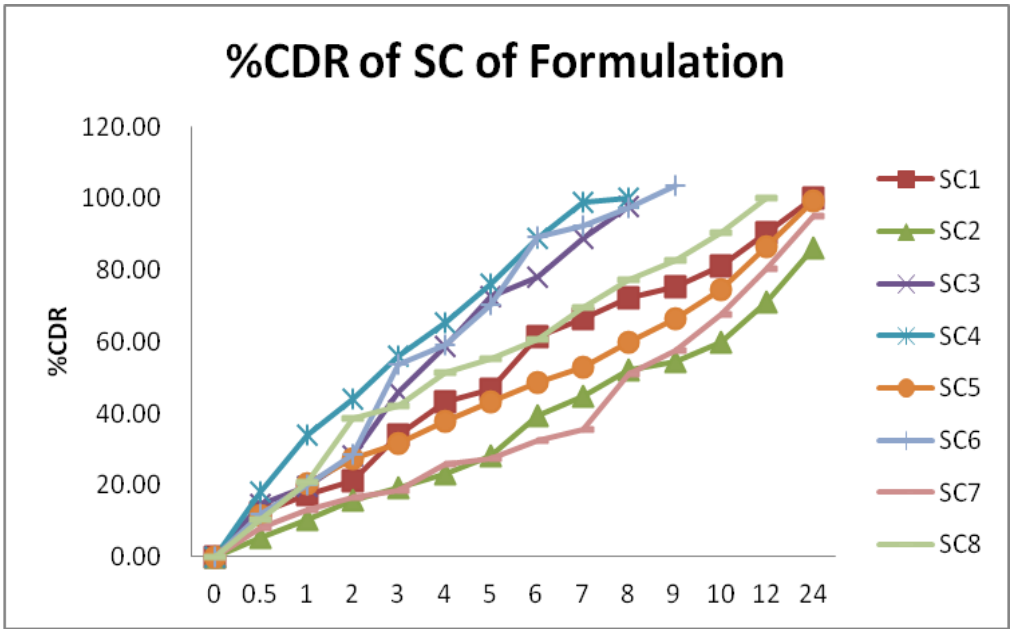


Fig. 5.9 *In vitro* release profile of Designed formulation SC1 –SC8

2.1.3 Mechanism of Drug Release: -

Table 5.7 R^2 & k values of the release profiles of each formulation made at formulation stage corresponding to Zero order, First order, and higuchi kinetics.

Form	Zero-order		First order		Higuchi	
	R^2	k_o	R^2	k_1	R^2	kH
SC1	0.5231	6.302	**0.9858**	0.167	0.9433	23.200
SC2	0.7907	4.808	**0.9818**	0.086	0.9192	17.077
SC3	0.1635	7.527	0.9614	0.333	0.8477	28.619
SC4	0.8845	14.538	0.9689	0.601	0.9833	34.802
SC5	0.6176	5.842	0.9700	0.178	0.9655	21.270
SC6	0.9472	13.067	0.9549	0.359	0.9402	32.685
SC7	0.8295	5.104	0.9343	0.114	0.8734	17.882
SC8	0.8943	9.512	**0.9725**	0.195	0.9759	26.893

NOTE: R^2 = Coefficient of determination, k_o = Zero-order release constant, k_1 = First-order release constant, kH = Highchi release constant,

Table 5.8 R^2, n & kKP values of the release profiles of each formulation made at formulation stage corresponding to Korsmeyer – peppas models

Formulation	Korsmeyer-peppas		
	R^2	**kKP**	**N**
SC1	0.9434	17.077	0.669
SC2	0.9533	9.262	0.771
SC3	0.8682	21.039	0.726
SC4	**0.9939**	29.671	0.598
SC5	0.9680	18.206	0.569
SC6	**0.9862**	19.920	0.789
SC7	0.9304	11.178	0.685
SC8	**0.9934**	19.554	0.669

2.1.4 Polynomial equation

Table 5.9 Polynomial equation of the various dependent variables in SC Formulation

Simvastatin Floating capsule	kH of Higuchi	*Y1=25.503+0.294X1-0.436X2+0.037X3-0.113X4+0.134X5+0.185X6-0.030X7*
	'n' of Korse-Peppas	*Y1=0.621+0.0001X1-0.000878X2+0.022X3+0.002X4-0.004X5-0.00045X6+0.001X7*
	log(K) Korse-Peppas-	*Y1=1.3898+0.00422X1-0.0088X2-0.0125X3-0.0055X4 +0.0068X5+0.0021X6-0.0006X7*
	k_1 of 1st order	*Y1=0.199-0.009X1+0.009X2+0.007X3-0.005X4-0.005X5-0.008X6+0.001X7*
	k_0 of zero order	*Y1=7.265+0.226X1-0.226X2-0.165X3-0.055X4+0.017X5+0.196X6-0.072X7*
	R^2 of zero order	*Y1=0.962+0.014X1-0.001X2-0.040X3-0.006X4-0.013X5+0.017X6-0.011X7*

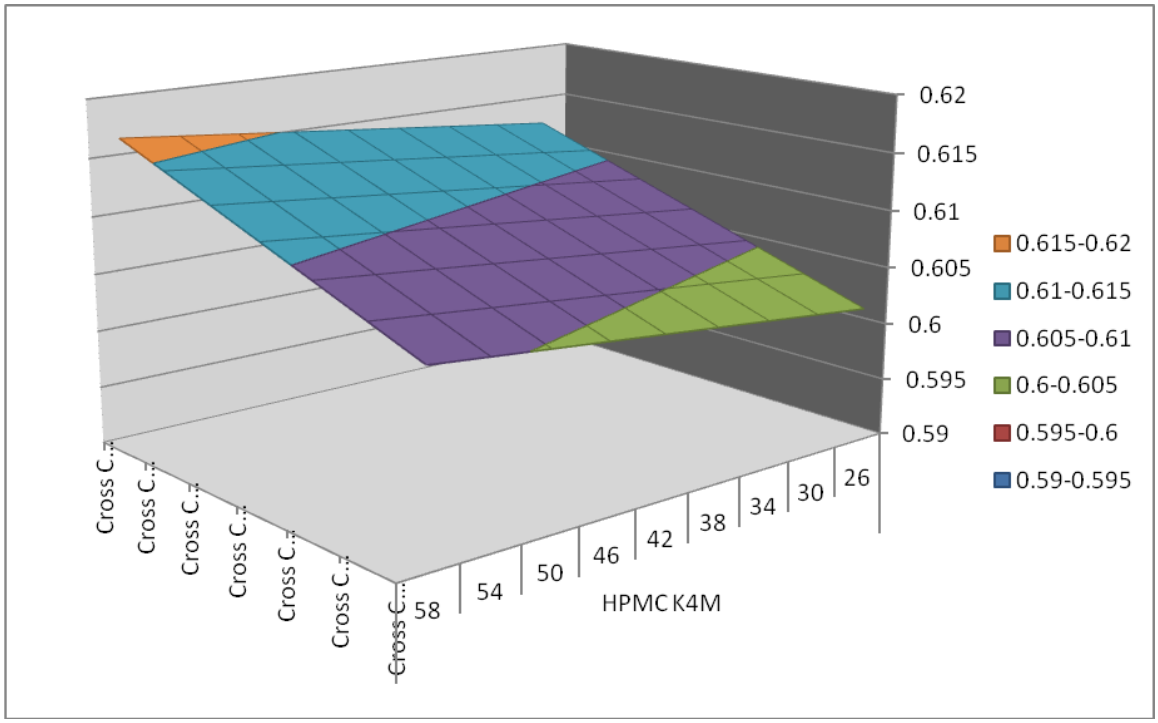


Fig 5.10 Effect of HPMC K4M and Cross carmellose sodium on 'n' of Korsemeyer-peppas

For tablets of a known geometry (in this case a slab) n = 0.5 means Fickian diffusion, 0.5 < n < 1.0 non-Fickian diffusion, and n = 1.0 Case II diffusion. Considering the n values calculated for the studied tablets (Table 5.9), almost in most cases a non-Fickian mechanism is dominant. In this case the non- Fickian or anomalous diffusion shows also a relaxation of the polymeric chains, and influences the drug release. Release from initially dry, hydrophilic glassy polymers that swell in contact of water and become rubbery show anomalous diffusion as a result of the rearrangement of macromolecular chains. The thermodynamic state of the polymer and the penetrate concentration are responsible for the different types of the diffusion. A third class of diffusion is case II diffusion, which is a special case of non-Fickian diffusion. The results of

the calculated *n* (Table 5.9) reveal a non-Fickian type of drug diffusion, which means that the process of diffusion and relaxation run at comparable rates. On the basis of polynomial equation for 'n' of Korsemeyer-peppas equation Cross carmelose sod., HPMC K4M, Veegum, HPC, Klucel HF having positive effect, and Veegum have the maximum effect on the 'n' value.

2.1.5 Stability studies:

Table 5.10 Stability data of optimized SC2 formulation stored at 45 ºC **/** 75% RH

Sampling interval	Optimized Formulation			
	PA	**%DC**	**%CDR at 24 Hr.**	**TFT (Hr)**
0	**++**	100.43	89.51	25
1 Week	**++**	101.65	88.52	24
2 week	**++**	101.33	89.64	25
3 Week	**++**	101.95	88.14	24
4 week	**++**	101.23	87.75	25
2 month	**++**	100.56	88.34	25
3 month	**++**	100.34	87.56	25

PA- Physical appearance, DT**-** Disintegration time, **% DC-** Percent Drug Content. **%CDR-** Percent cumulative drug Release. ++: same as initial, TFT- Total Floating Time

2.1.6 Animal study:

Table 5.11 Total cholesterol level in treated group.

Treatment	Total cholesterol level in mg/dL		
	0 Day	**18th Day**	**40th Day**
Control	25.85±1.609	25.26±1.668	25.85±1.399
Pure Drug	25.93±2.003	13.11±1.166	10.55±0.607***
Formulation	27.35±3.123	13.46±1.785	10.23±0.951***

All values are mean ± SEM, n = 6. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ when compared to control group

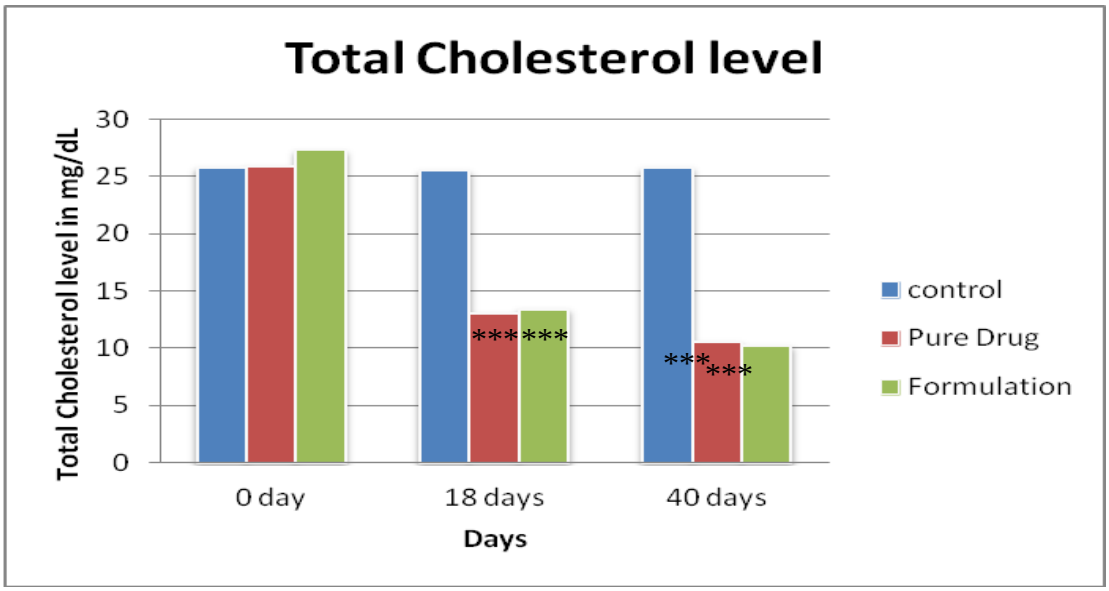


Fig. 5.11 Total cholesterol level in treated group.

2.2. EVALUATION OF FLOATING TABLET

2.2.1 Floating tablet evaluation:

Table 5.12 The values of various evaluation parameters of the formulations made at formulation stage

Response	FORMULATION CODE							
	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
Bulk density (gm/ml)	0.435	0.436	0.376	0.388	0.391	0.403	0.431	0.423
Tapped density (gm/ml)	0.489	0.478	0.434	0.456	0.432	0.487	0.465	0.489
Angle of repose	28.43	34.1	32.12	28.34	30.34	31.45	32.45	29.65
Friability (%)	0.23	0.45	0.49	0.73	0.72	0.82	0.48	0.54
Hardness (kg/cm^2)	4-5	4-5	4	4	5	4	4	4
Wt variation (%)	1.44	1.87	2.52	2.76	0.89	0.54	0.71	0.24
Floating Lag Time (Sec)	65	209	165	180	90	245	720	1

TFT (hr)	24	24	28	31	30	28	30	24
Swelling Index (24 Hr)	572.4	578.5	580.8	559.5	611.6	602.8	602.5	692.5
Drug content (%)	98.37	98.23	101.3	99.37	100.3	99.34	97.23	100.3

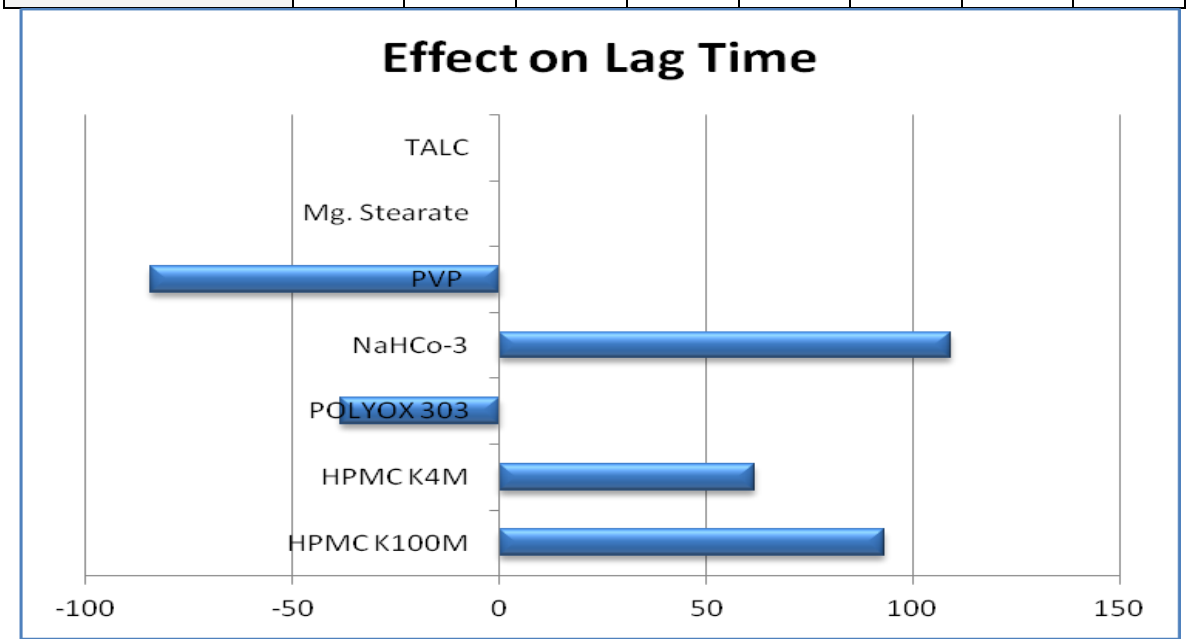


Fig 5.12 Pareto Chart showing the effect on Floating lag time of tablet[112,123]

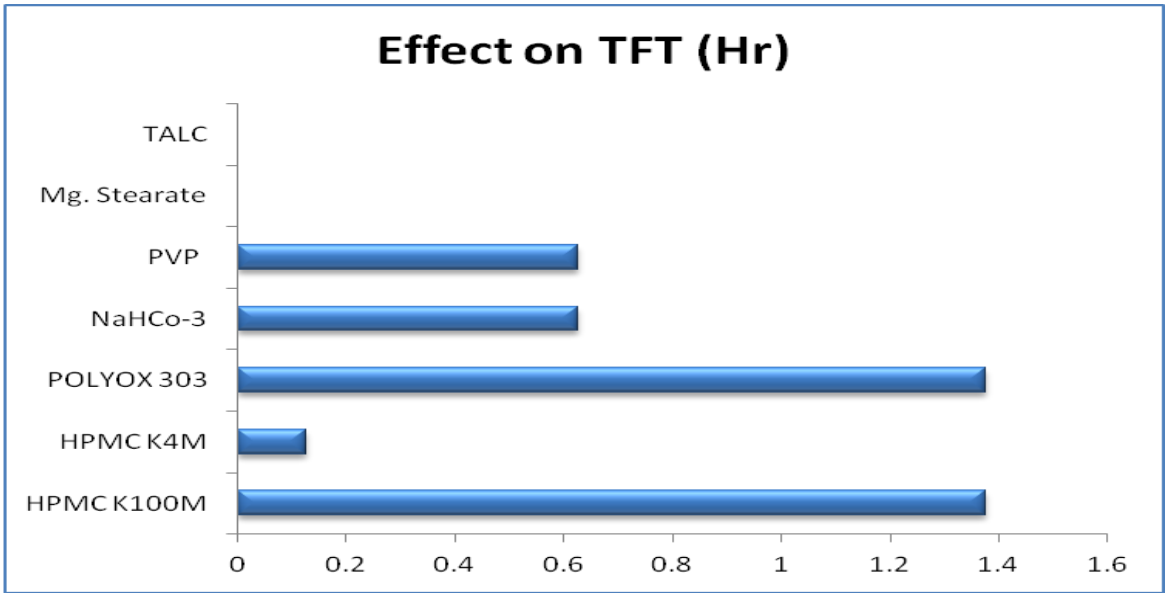


Fig 5.13 Pareto Chart showing the effect on Total Floating time of tablet

2.2.2 Dissolution Study or drug release testing of floating Tablet: -

Table 5.13 Data of the release profile of the SF1 – SF8.

Time (Hrs)	Cumulative drug release (%)							
	SF1	**SF2**	**SF3**	**SF4**	**SF5**	**SF6**	**SF7**	**SF8**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	3.89	2.92	6.16	8.11	8.11	7.46	3.89	10.05
1	7.14	5.19	11.04	10.07	11.37	11.36	9.73	18.18
2	11.05	10.07	17.22	23.38	19.17	15.28	16.24	24.05
3	14.31	13.33	30.88	36.40	28.29	21.15	24.71	38.70
4	23.42	21.14	42.94	45.24	42.62	34.81	33.51	48.83
5	34.50	34.48	52.11	53.77	53.41	42.35	48.50	56.40
6	49.49	48.18	60.01	60.05	63.58	52.81	58.98	64.95
7	61.59	61.90	69.22	67.64	71.50	59.09	67.54	72.88
8	75.99	76.63	79.10	74.27	77.82	68.30	77.74	81.79
9	83.94	81.33	86.08	82.86	85.12	75.26	88.94	89.10
10	93.53	88.00	92.76	90.18	91.80	82.23	96.27	97.73
12	97.95	98.24	99.12	93.29	96.21	89.55	100.04	102.48
24				98.36		99.79		

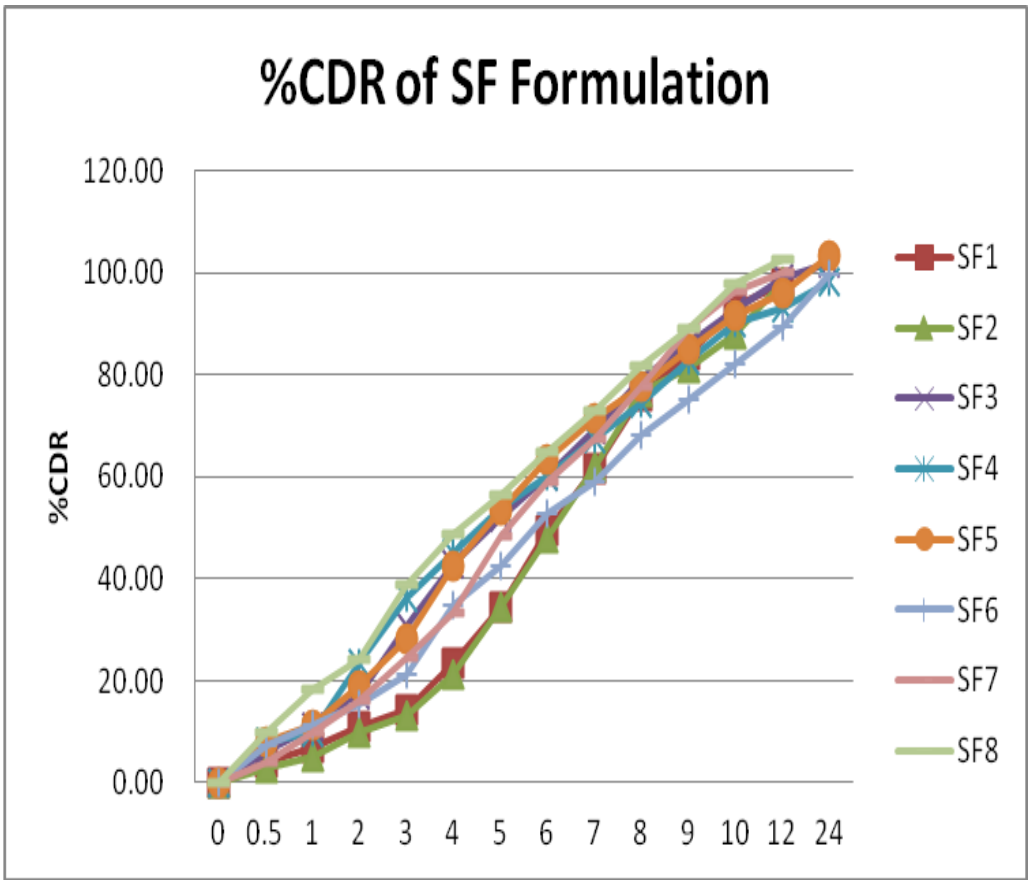


Fig 5.14 *In vitro* release profile of Designed formulation SF1 –SF8

2.2.3 Swelling Studies of floating tablets

Table 5.14 Data of the Swelling index of the SF1 – SF8

Swelling Index (%)								
Time (Hr)	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
1	177.7	182.5	180.3	180.4	183.7	186.3	175.8	213.8
3	304.3	310.7	320.0	310.4	320.9	324.5	301.2	368.6
6	361.1	376.7	399.0	376.8	388.8	390.5	367.6	445.2
12	476.4	489.2	475.2	497.7	488.3	463.2	469.3	545.2
24	572.4	578.5	580.8	559.5	611.6	602.8	602.5	692.5

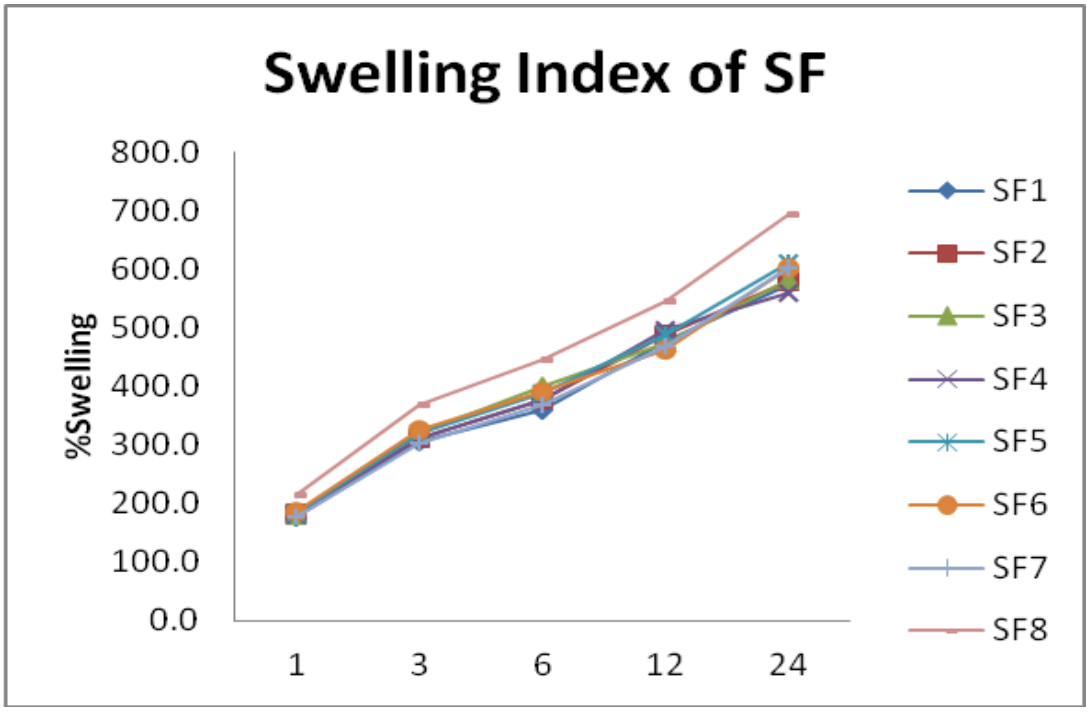


Fig 5.15 Swelling index of the SF1 – SF8

2.2.4 Mechanism of Drug Release: -

Table 5.15 R^2 & K values of the release profiles of each formulation made at formulation stage corresponding to Zero order, First order, and higuchi kinetics.

Form	Zero-order		First order		Higuchi	
	R^2	k_o	R^2	k_1	R^2	R^2
SF1	0.9649	8.583	0.8650	0.220	0.7788	23.116
SF2	0.9632	8.408	0.8654	0.210	0.7715	22.594
SF3	0.5562	6.683	0.9591	0.254	0.8912	24.516
SF4	0.4870	6.492	**0.9830**	0.183	0.9126	24.016
SF5	0.5536	6.693	0.9647	0.219	0.9013	24.564
SF6	0.6801	6.068	0.9635	0.209	0.9030	21.891
SF7	0.9851	9.272	0.9190	0.219	0.8602	25.402
SF8	0.9541	9.878	0.9630	0.249	0.9450	27.625

NOTE: R^2 = Coefficient of determination, k_o = Zero-order release constant, k_1 = First-order release constant, kH = Highchi release constant,

Table 5.16 R^2, n & kKP values of the release profiles of each formulation made at formulation stage corresponding to Korsmeyer – peppas models

Formulation	Korsmeyer-peppas		
	R^2	K	N
SF1	**0.9766**	8.588	0.964
SF2	**0.9814**	7.037	1.054
SF3	0.9462	14.631	0.752
SF4	0.9562	16.771	0.685
SF5	0.9487	16.195	0.703
SF6	0.9345	14.003	0.703
SF7	**0.9873**	11.020	0.923
SF8	**0.9951**	20.312	0.660

2.2.5 Polynomial equation

Table 5.17 Polynomial equation of the various dependent variables in SF tablet formulation

Simvastatin Floating Tablet	kH of Higuchi	*Y1=42.917-0.076X1-0.037X2-0.395X3-0.014X4-0.041X5-0.949X6-0.245X7*
	'n' Of Korse-Peppas	*Y1=0.226+0.002X1+0.013X2+0.021X3+0.008X4-0.007X5-0.019X6-0.071X7*
	Log(k) of Korse-Peppas-	*Y1=1.176+0.0033X1+0.0079X2+0.0069X3+0.0075X4+0.0114X5-0.0156X6-0.1271X7*
	k_0 of 1^{st} order	*Y1=-0.374+0.002X1+0.0004X2-0.001X3+0.001X4+0.0003X5+0.015X6-0.010X7*
	k_1 of zero order	*Y1=19.817-0.019X1+0.060X2-0.108X3-0.008X4-0.162X5-0.844X6-1.162X7*
	R^2 of zero order	*Y1=1.745+0.001X1+0.012X2+0.008X3-0.003X4-0.032X5-0.097X6-0.149X7*
	Floating Lag Time (sec)	*Y1=-917.5+11.64X1+7.7X2-12.79X3+18.18X4-21.09X5-28.37X6-191.1X7*

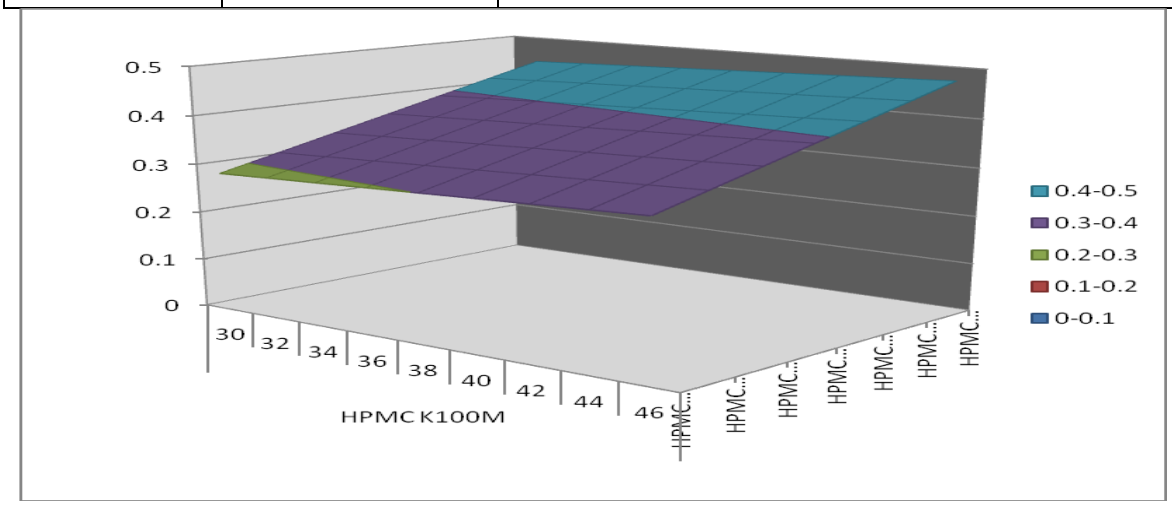


Fig.5.16 Effect of HPMC K100M and HPMC K4M on 'n' of Kors-peppas

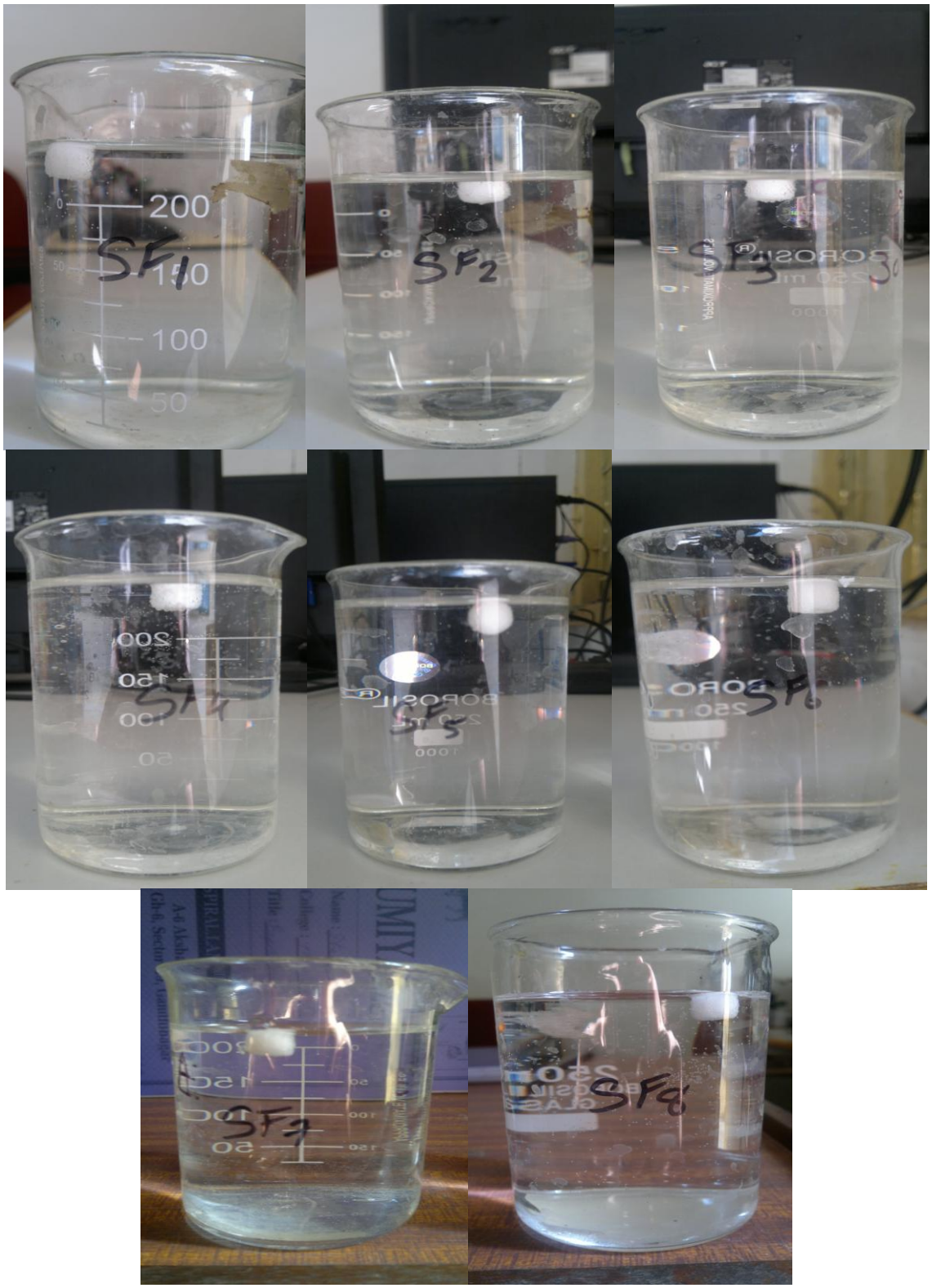


Fig. 5.17 Floating Tablet after 1 Hour

Fig. 5.18 Floating tablet after 24 Hour

2.2.6 Stability studies:

Table 5.18 Stability data of optimized **SF8** formulation stored at 45 ºC **/** 75% RH

Sampling interval	Optimized Formulation			
	PA	**%DC**	**%CDR at 24 Hr.**	**TFT (Hr)**
0	**++**	99.34	98.23	24
1 Week	**++**	99.23	98.56	25
2 week	**++**	99.76	99.67	24
3 Week	**++**	99.12	98.34	24
4 week	**++**	98.78	99.63	24
2 month	**++**	99.67	99.48	24
3 month	**++**	99.21	99.23	24

PA- Physical appearance, DT**-** Disintegration time, **% DC-** Percent Drug Content. **%CDR-** Percent cumulative drug Release. ++: same as initial, TFT- Total Floating Time

2.3. *EVALUATION OF HIGH DENSITY TABLET*

2.3.1 High Density Tablet Evaluation:

Table 5.19 The values of various evaluation parameters of the formulations made at formulation stage

Response	FORMULATION CODE							
	SH1	**SH2**	**SH3**	**SH4**	**SH5**	**SH6**	**SH7**	**SH8**
Bulk density (gm/ml)	0.367	0.373	0.339	0.360	0.373	0.378	0.389	0.339
Tapped density (gm/ml)	0.401	0.423	0.378	0.394	0.410	0.418	0.421	0.353
Angle of repose	28.45	29.24	35.64	38.12	31.56	34.39	29.65	30.91
Hardness(kg/cm^2)	7	7	7	7	7	7-8	7-8	7
Friability (%)	0.18	0.08	0.18	0.14	0.15	0.15	0.12	0.11
%Mass Remain at 24 Hr	35	40	56	37	43	51	47	33
Wt variation (%)	1.34	2.03	1.10	1.07	1.43	1.43	1.04	0.2
Drug content (%)	98.27	97.17	100.1	100.5	101.5	99.63	101.2	100.4

2.3.2 Dissolution Study or drug release testing of High density tablet: -

Table 5.20 Data of the release profile of the SH1 – SH8.

Time (Hrs)	Cumulative drug release (%)							
	SH1	**SH2**	**SH3**	**SH4**	**SH5**	**SH6**	**SH7**	**SH8**
0.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	28.53	23.67	22.05	18.16	12.32	16.21	18.16	12.64
2	32.81	26.31	25.01	23.38	16.56	26.95	21.11	19.16

3	41.31	35.13	31.55	27.65	23.73	31.54	26.02	27.63
4	48.21	43.31	39.40	33.22	28.00	35.83	31.92	35.15
5	57.26	52.16	48.57	39.46	35.19	42.39	38.47	42.68
6	67.90	62.32	54.19	44.73	41.43	48.65	43.42	50.88
7	73.88	67.97	62.41	49.69	47.36	52.32	48.70	58.13
8	82.15	70.39	64.49	54.34	50.38	57.95	52.70	65.71
9	90.11	76.38	71.45	59.32	55.03	62.29	57.68	75.58
10	98.09	84.66	78.09	63.99	59.04	68.59	61.37	84.18
12		93.27	84.42	77.10	73.76	80.41	69.94	91.17
24		97.37	95.30	98.21	99.89	92.90	98.82	97.86

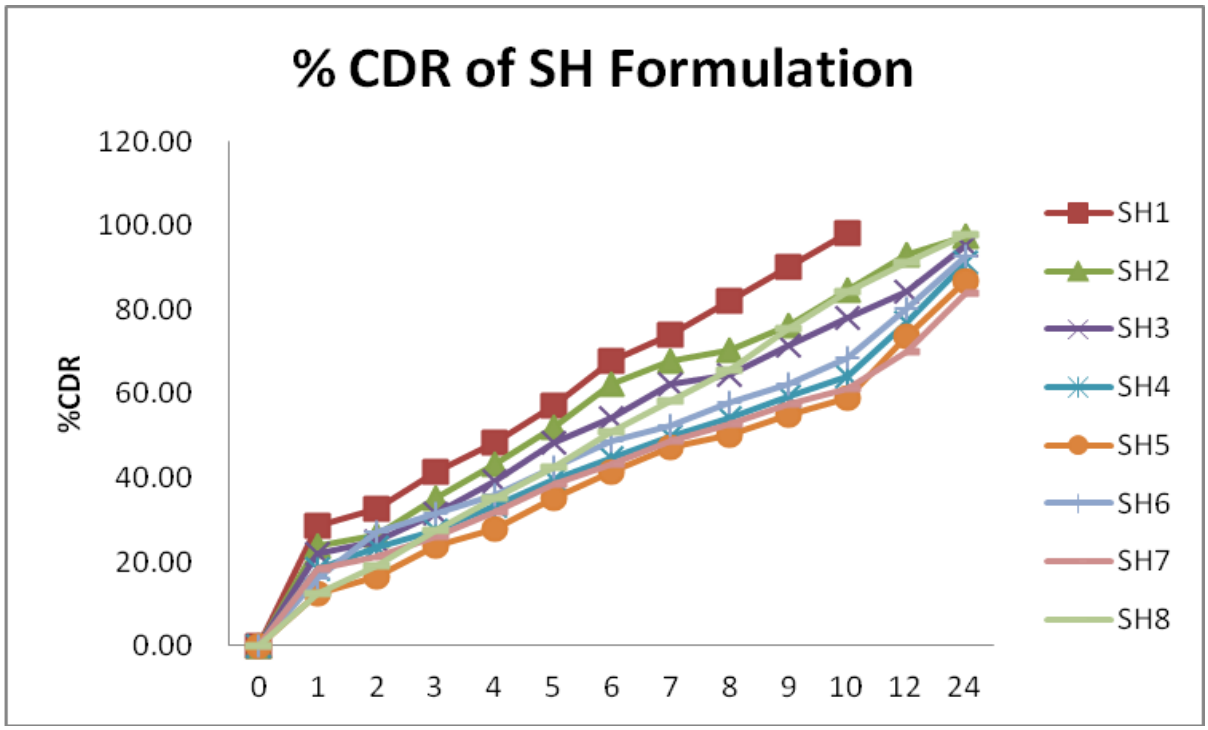


Fig. 5.19 In vitro release profile of Designed formulation SH1 –SH8.

2.3.3 Mechanism of Drug Release: -

Table 5.21 R^2 & K values of the release profiles of each formulation made at formulation stage corresponding to Zero order, First order and higuchi kinetics.

Form	Zero-order		First order		Higuchi	
	R^2	k_o	R^2	k_1	R^2	kH
SH1	0.0891	6.881	0.9622	0.220	0.8737	26.001
SH2	0.3132	6.352	**0.9805**	0.166	0.9269	23.665
SH3	0.4150	5.945	**0.9853**	0.135	0.9510	21.982
SH4	0.6040	5.264	**0.9814**	0.104	0.9700	19.152
SH5	0.7048	4.927	**0.9890**	0.090	0.9469	17.734
SH6	0.5356	5.505	**0.9839**	0.114	0.9711	20.157
SH7	0.5435	4.951	**0.9792**	0.086	0.9726	18.113
SH8	0.5899	6.055	**0.9642**	0.161	0.9054	22.041

NOTE: R^2 = Coefficient of determination, k_o = Zero-order release constant, k_1 = First-order release constant, kH = Highchi release constant,

Table 5.22 R^2, n & kKP values of the release profiles of each formulation made at formulation stage corresponding to Korsmeyer – peppas models

Formulation	Korsmeyer-peppas		
	R^2	kKP	N
SH1	0.8990	26.691	0.494
SH2	0.9319	21.592	0.546
SH3	0.9518	19.719	0.552
SH4	0.9737	16.423	0.567
SH5	0.9638	11.623	0.688
SH6	0.9716	17.051	0.578
SH7	0.9734	15.968	0.556
SH8	0.9122	12.934	0.743

2.3.4 Polynomial equation

Table 5.23 Polynomial equation of the various dependent variables in SH Formulation

Simvastatin High density	kH of Higuchi	*Y1=30.326-0.031X1+0.034X2+0.615X3-0.063X4 +0.028X5-0.929X6-3.218X7*
	'n' of Korse-Peppas	*Y1=1.238-0.005X1-0.002X2-0.016X3-0.006X4 -0.004X5+0.004X6+0.006X7*
	Log(K) of Korse-Peppas-	*Y1=0.82106+0.00423X1+0.00274X2+0.02881X3 +0.004432X4+0.00378X5-0.024X6-0.073X7*
	k_0 of 1^{st} order	*Y1=-0.385+0.004X1-0.004X2- 0.008X3+0.001X4-0.001X5+0.016X6+0.056X7*
	k_1 of zero order	*Y1=9.282-0.011X1+0.005X2+0.145X3-0.013X4 +0.005X5-0.223X6-0.806X7*
	R^2 of zero order	*Y1=0.718-0.004X1-0.008X2-0.045X3-0.001X4- 0.005X5+0.065X6+0.151X7*

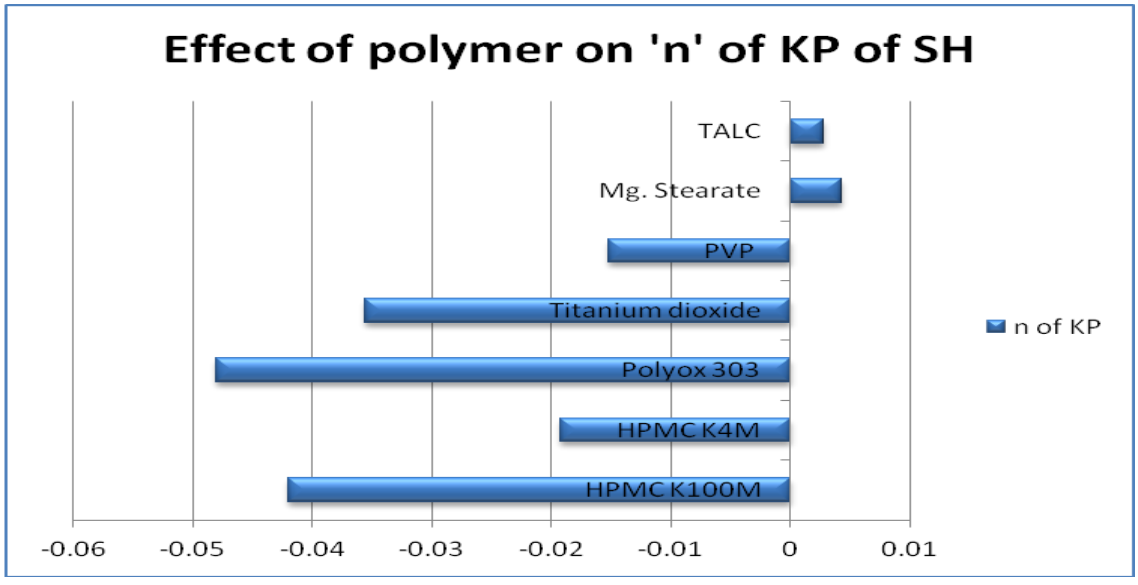


Fig 5.20 Pareto chart showing the effect of polymer on 'n' of Kors-Peppas of SH

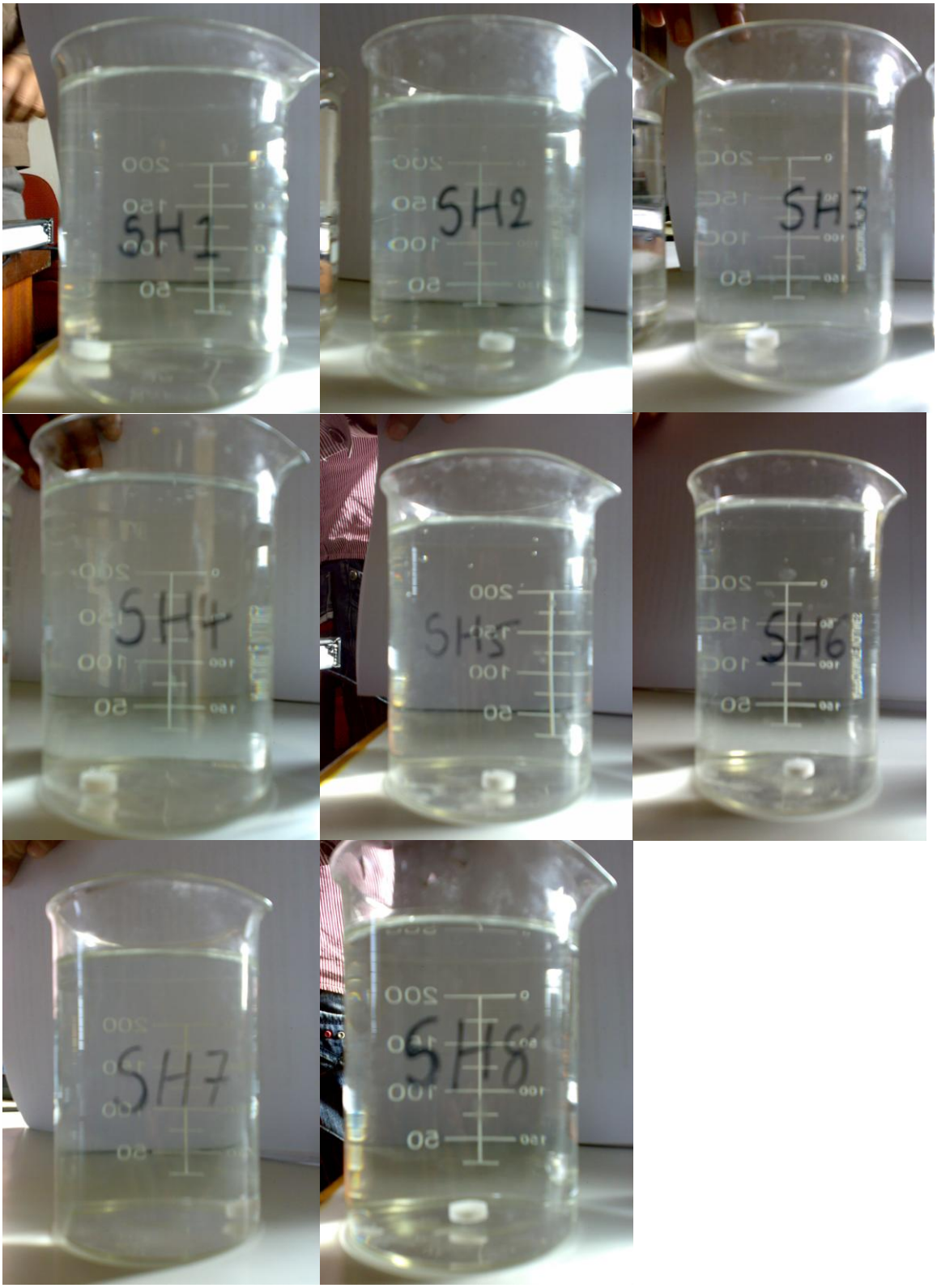


Fig. 5.21 High Density Tablet at 0 Hour

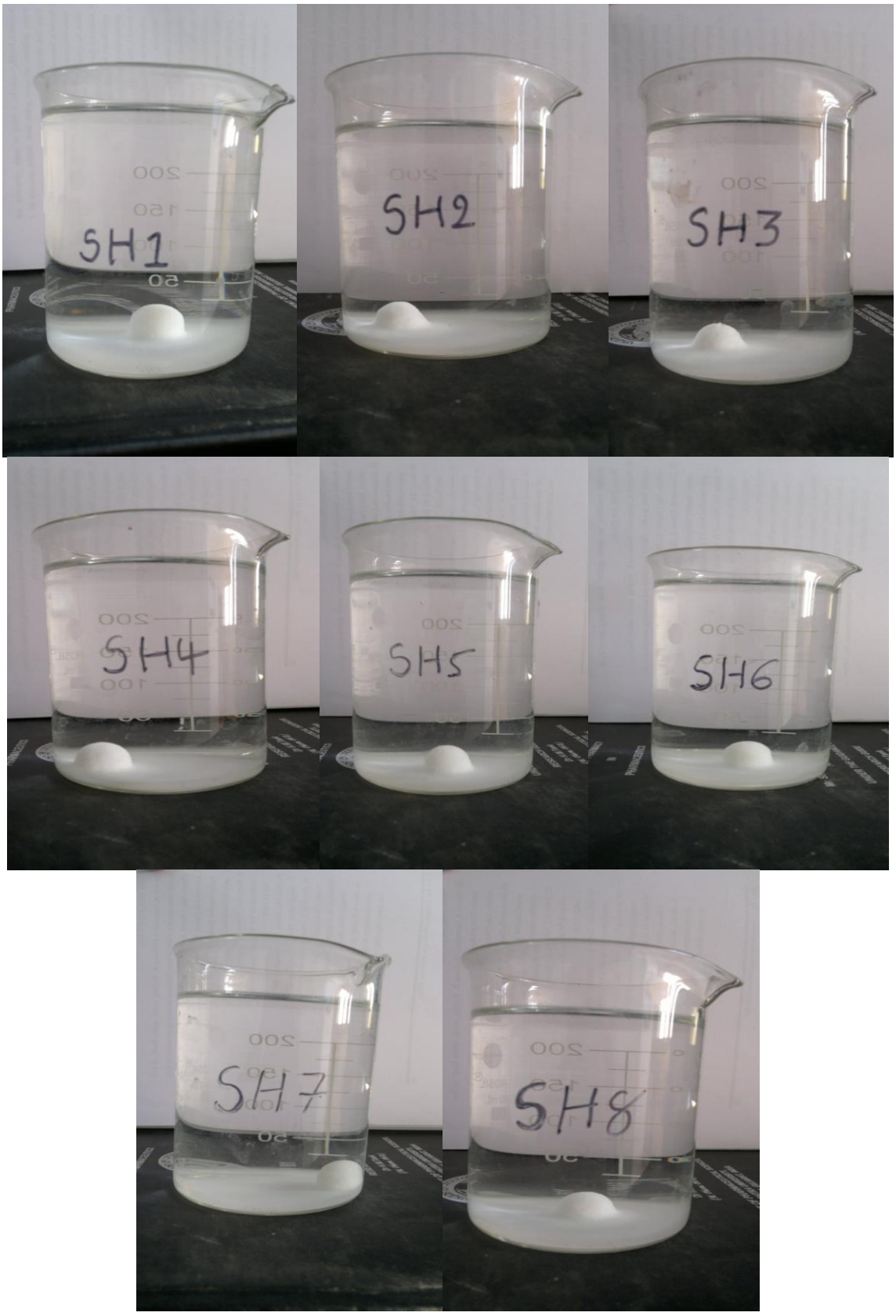


Fig. 5.22 High Density Tablet at 27 Hour

2.3.5 Stability studies:

Table 5.24 Stability data of optimized SH4 formulation stored at 45 ºC **/** 75% RH

Sampling interval	Optimized Formulation		
	PA	**%DC**	**%CDR at 24 Hr.**
0	**++**	100.23	92.34
1 Week	**++**	100.45	93.56
2 week	**++**	100.34	92.45
3 Week	**++**	100.12	92.78
4 week	**++**	100.23	93.01
2 month	**++**	100.11	93.42
3 month	**++**	99.34	93.04

PA- Physical appearance, DT**-** Disintegration time, **% DC-** Percent Drug Content. **%CDR-** Percent cumulative drug Release. ++: same as initial, TFT- Total Floating Time.

2.4 *EVALUATION OF MUCOADHESIVE TABLET*

2.4.1 Evaluation of Mucoadhesive Tablet.

Table 5.25 The values of various evaluation parameters of the formulations made at formulation stage

Response	FORMULATION CODE							
	SM1	**SM2**	**SM3**	**SM4**	**SM5**	**SM6**	**SM7**	**SM8**
Bulk density (gm/ml)	0.321	0.341	0.339	0.350	0.333	0.410	0.389	0.391
Tapped density (gm/ml)	0.374	0.383	0.547	0.419	0.360	0.448	0.428	0.422
Angle of repose	29.34	28.65	30.12	29.67	35.34	38.23	31.48	34.53
Hardness(Kg/cm^2)	4	4	5	5	4	4	4-5	4
Friability (%)	0.56	0.64	0.78	0.55	0.78	0.63	0.92	0.92
Wt variation (%)	1.46	1.34	1.1	2.63	5.92	3.40	1.84	0.21
Swelling Index (24 Hr)	767.9	791.4	797.6	813.4	927.3	884.6	810.3	1045.4

Mucoadhesive Strength (gm)	25	27	23	21	22	23	22	18
Mucoadhesion Time (Hr)	18	15	19	26	24	21	25	24
Drug content (%)	99.17	99.57	102.2	99.55	101.7	97.23	102.6	103.4

2.4.2 Dissolution Study or drug release testing of mucoadhesive tablet: -

Table 5.26 Data of the release profile of the SM1 – SM8.

Time (Hrs)	**Cumulative drug release (%)**							
	SM1	**SM2**	**SM3**	**SM4**	**SM5**	**SM6**	**SM7**	**SM8**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	13.29	8.75	12.32	19.13	6.48	7.78	4.86	7.78
1	17.86	19.80	21.75	21.44	12.33	17.20	9.41	11.69
2	28.92	23.08	35.74	31.21	17.55	24.05	13.32	16.58
3	33.20	29.29	40.03	38.74	26.67	30.26	18.87	31.85
4	36.84	32.92	50.17	46.61	31.91	35.51	23.77	38.73
5	44.70	38.83	51.26	48.33	36.85	40.46	31.93	44.65
6	47.07	44.11	53.96	58.49	41.14	46.06	40.10	51.24
7	51.39	49.39	60.56	62.83	46.10	52.97	48.62	56.21
8	55.39	51.12	62.32	72.37	50.41	61.84	51.00	61.85
9	60.70	58.69	70.56	79.02	55.39	66.84	56.95	68.47
10	66.02	63.03	75.58	84.70	59.72	75.09	64.85	76.72
12	73.95	69.33	81.90	93.64	68.61	82.71	72.45	84.02
24	96.76	98.94	98.27	99.03	97.73	99.89	98.96	99.12

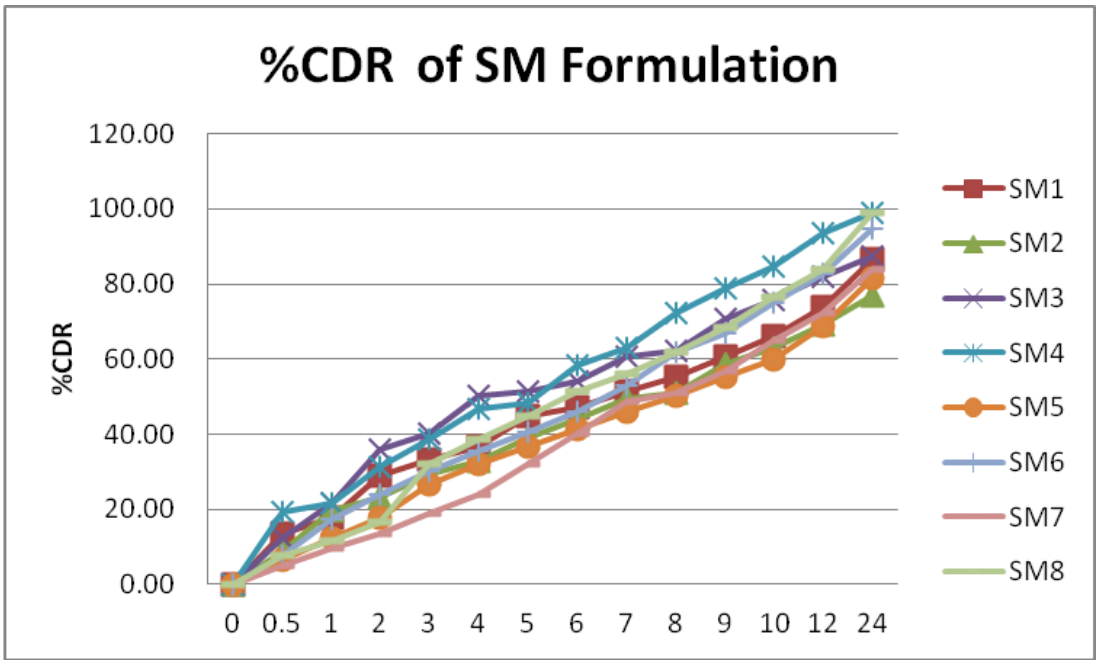


Fig. 5.23 *In vitro* release profile of Designed formulation SM1 –SM8.

2.4.3 Swelling Studies of floating tablets

Table 5.27 Data of the Swelling index of the SM1 – SM8

	Swelling Index(%)							
Time (Hr)	SM1	SM2	SM3	SM4	SM5	SM6	SM7	SM8
1	132.6	136.2	137.2	141.3	167.8	156.9	140.1	194.5
3	311.6	318.6	314.4	328.8	382.0	356.4	323.6	441.2
6	328.4	340.5	334.4	349.5	406.0	378.5	345.8	458.2
12	535.8	571.4	592.6	520.2	738.8	766.7	586.8	715.2
24	767.9	791.4	797.7	813.5	927.3	884.6	810.4	1045.5

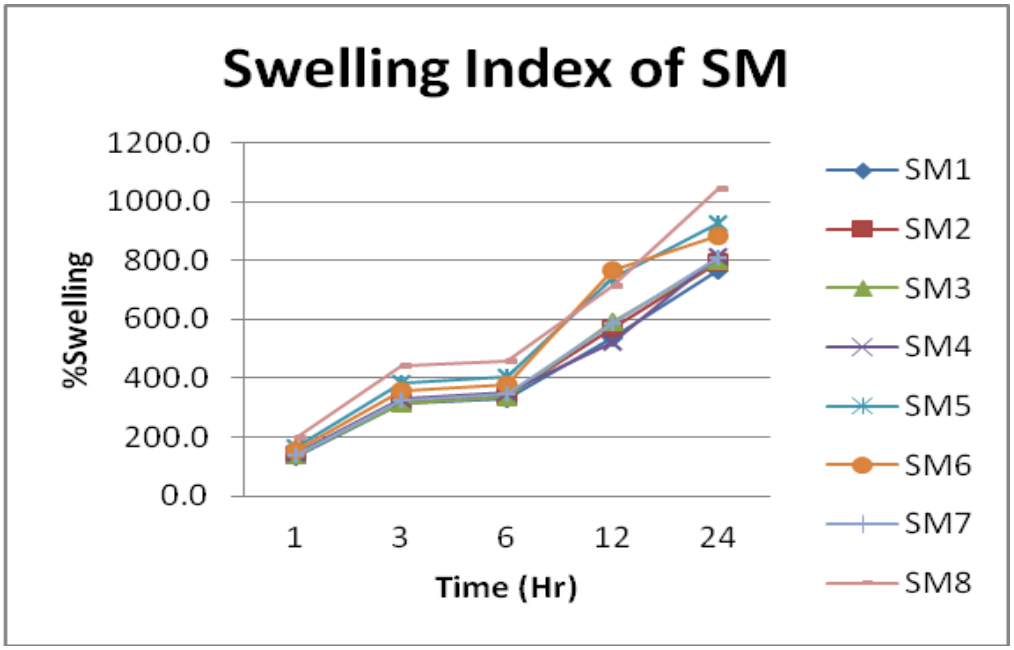


Fig 5.24 Swelling index of the SM1 – SM8

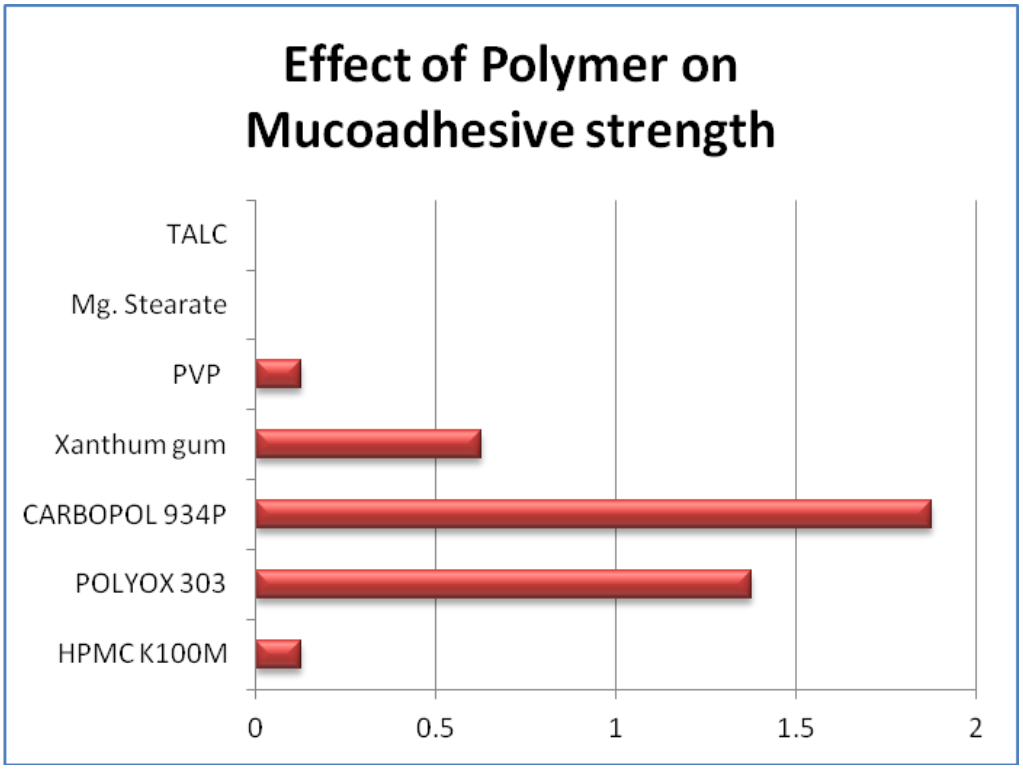


Fig. 5.25 Pareto Chart showing the effect of polymer on Mucoadhesive strengh of tablet

2.4.4 Mechanism of drug release: -

Table 5.28 R^2 & K values of the release profiles of each formulation made at formulation stage corresponding to Zero order, First order, and higuchi kinetics.

Form	Zero-order		First order		Higuchi	
	R^2	k_o	R^2	k_1	R^2	kH
SM1	0.4545	5.261	0.9614	0.096	0.9800	19.447
SM2	0.4402	4.832	0.9467	0.079	0.9592	17.900
SM3	0.1834	5.782	0.9504	0.111	0.9328	21.813
SM4	0.3782	6.393	**0.9687**	0.188	0.9438	23.783
SM5	0.6557	4.791	**0.9887**	0.081	0.9666	17.405
SM6	0.6318	5.671	**0.9824**	0.126	0.9527	20.632
SM7	0.7485	4.872	**0.9790**	0.086	0.9102	17.406
SM8	0.6697	5.871	**0.9891**	0.167	0.9480	21.278

NOTE: R^2 = Coefficient of determination, k_o = Zero-order release constant, k_1 = First-order release constant, kH = Highchi release constant.

Table 5.29 R^2, n & kKP values of the release profiles of each formulation made at formulation stage corresponding to Korsmeyer – peppas models

Formulation	Korsmeyer-peppas		
	R^2	kKP	n
SM1	**0.9821**	19.005	0.515
SM2	**0.9611**	15.885	0.563
SM3	**0.9593**	21.710	0.517
SM4	0.9485	23.817	0.501
SM5	0.9720	11.778	0.685
SM6	0.9570	14.705	0.659
SM7	0.9364	8.720	0.810
SM8	0.9564	12.779	0.737

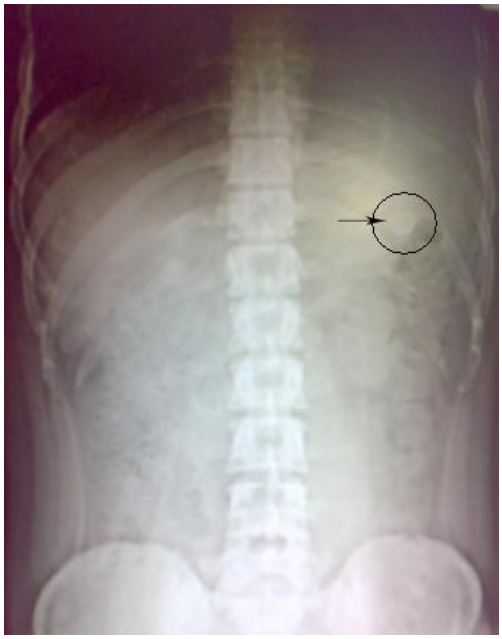
2.4.5 Polynomial equation

Table 5.30 Polynomial equation of the various dependent variables in SM Formulation

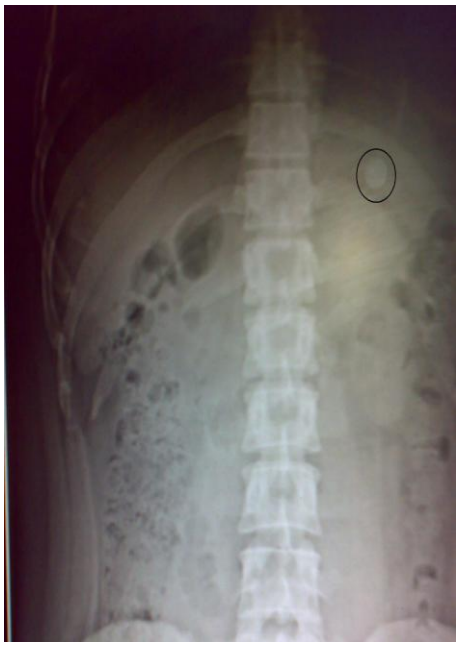
Simvastatin Mucoadhesive Tablet	kH of Higuchi	*Y1=21.903+0.048X1-0.384X2-0.001X3 +0.027X4+0.163X5+0.028X6-1.288X7*
	'n' of Kors-Peppas	*Y1=1.034-0.0003X1+0.004X2-0.006X3-0.003X4-0.017X5+0.022X6+0.089X7*
	log(k) of Kors-Peppas	*Y1=-0.348-0.00096X1 +0.00628X2 +0.00138X3+0.00007X4-0.00058X5 +0.00165X6+0.0316X7*
	k_1 of 1^{st} order	*Y1=-0.348-0.001X1+0.006X2+0.006X3 +0.000073X4-0.001X5+0.002X6+0.032X7*
	k_0 of zero order	*Y1=7.243+0.015X1-0.099X2-0.005X3+ 0.004X4+0.031X5+0.012X6-0.310X7*
	R^2 of zero order	*Y1=0.892+0.004X1+0.011X2-0.009X3 -0.008X4-0.026X5+-0.006X6+0.069X7*
	Mucoadhesive strength	*Y1=15.5+0.017X1+0.275X2+0.188X3 +0.063X4+0.031X5-0.625X6-0.250X7*

2.4.6 *In vivo* studies

in vivo evaluation of gastrointestinal residence time of gastroretentive dosage form to confirm the spatial and temporary placement of gastroretentive drug delivery system. X-ray technique was used to determine the gastric residence time of the tablets.



(a)



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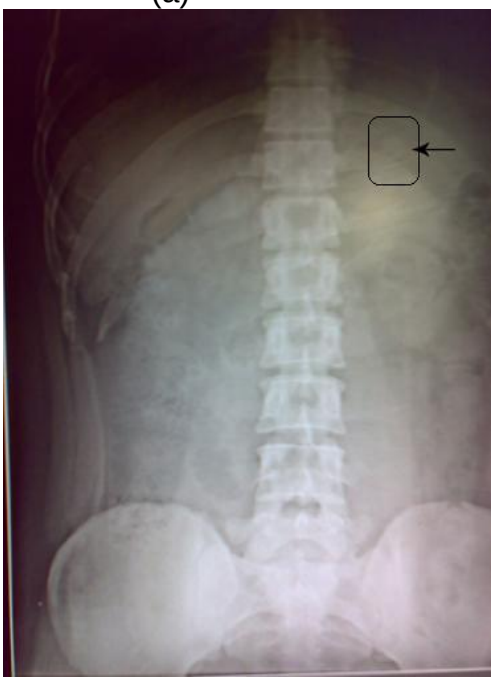


(c)

Fig. 5. 26 X-ray images shows the placing of placebo table, (a) At 5 Min. (b) 3 hr (c) 12 hr

2.4.7 Stability studies:

Table 5.31 Stability data of optimized SM5 formulation stored at 45 ºC **/** 75% RH

Sampling interval	Optimized Formulation				
	PA	**%DC**	**%CDR at 24 Hr.**	**Mucoadhesion Time (Hr)**	**Mucoadhesive Strength (gm)**
0	**++**	101.84	81.34	24	21.98
1 Week	**++**	101.65	83.45	24	21.83
2 week	**++**	101.45	85.31	24	22.03
3 Week	**++**	101.69	83.56	24	21.45
4 week	**++**	101.34	84.83	24	22.10
2 month	**++**	101.45	83.40	24	21.49
3 month	**++**	101.23	84.98	24	21.45

PA- Physical appearance, DT**-** Disintegration time, **% DC-** Percent Drug Content. **%CDR-** Percent cumulative drug Release. ++: same as initial, TFT- Total Floating Time

3. EVALUATION OF GASTRORETENTIVE DOSAGE FORM OF ATORVASTATIN :

3.1. EVALUATION OF FLOATING CAPSULE

3.1.1 Filling capsule evaluation:

Table 5.32 the values of various evaluation parameters of the formulations made at formulation stage

Response	FORMULATION CODE							
	AC1	**AC2**	**AC3**	**AC4**	**AC5**	**AC6**	**AC7**	**AC8**
Bulk density (gm/ml)	0.346	0.324	0.367	0.327	0.378	0.339	0.398	0.388
Tapped density (gm/ml)	0.401	0.398	0.478	0.445	0.480	0.427	0.456	0.487
Angle of repose (^{o})	28.34	33.45	28.34	35.98	33.45	33.45	33.23	29.34
Friability (%) (granules)	0.11	0.21	0.39	0.34	0.23	0.63	0.49	0.86
% Fine	12	15	15	16	18	20	13	21
Wt variation (%)	2.21	1.46	2.13	2.56	1.23	1.34	0.68	0.23
TFT (hr)	20	26	8	7	21	7	18	9
Drug content (%)	99.1	99.4	99.3	101.2	102.7	99.8	100.6	101.3

3.1.2 Dissolution Study or drug release testing of floating Capsule: -

Table 5.33 Data of the release profile of the AC1 – AC8.

Time (Hrs)	Cumulative drug release (%)							
	AC1	AC2	AC3	AC4	AC5	AC6	AC7	AC8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	9.65	3.66	11.65	17.97	12.65	15.64	8.31	12.98
1	14.37	13.00	21.70	27.73	17.38	23.05	13.42	19.38
2	19.44	18.73	24.48	40.53	26.46	30.84	17.01	29.80
3	29.86	23.83	32.27	51.73	30.60	45.32	19.28	38.95
4	41.68	30.28	39.44	63.67	37.43	55.22	26.55	45.49
5	48.90	34.78	48.98	72.01	45.29	66.17	28.31	54.40
6	57.15	44.29	62.56	81.72	50.19	75.52	33.73	63.01
7	66.12	47.86	72.22	88.16	58.79	85.26	36.92	74.01
8	69.81	55.44	82.27	95.96	67.76	94.71	53.07	81.73
9	80.17	66.39	94.69	104.47	78.12	101.54	59.82	90.17
10	82.60	72.74	102.20		84.86		70.32	98.64
12	92.70	75.80			92.31		83.85	103.17
24	102.19	98.20			104.13		99.20	

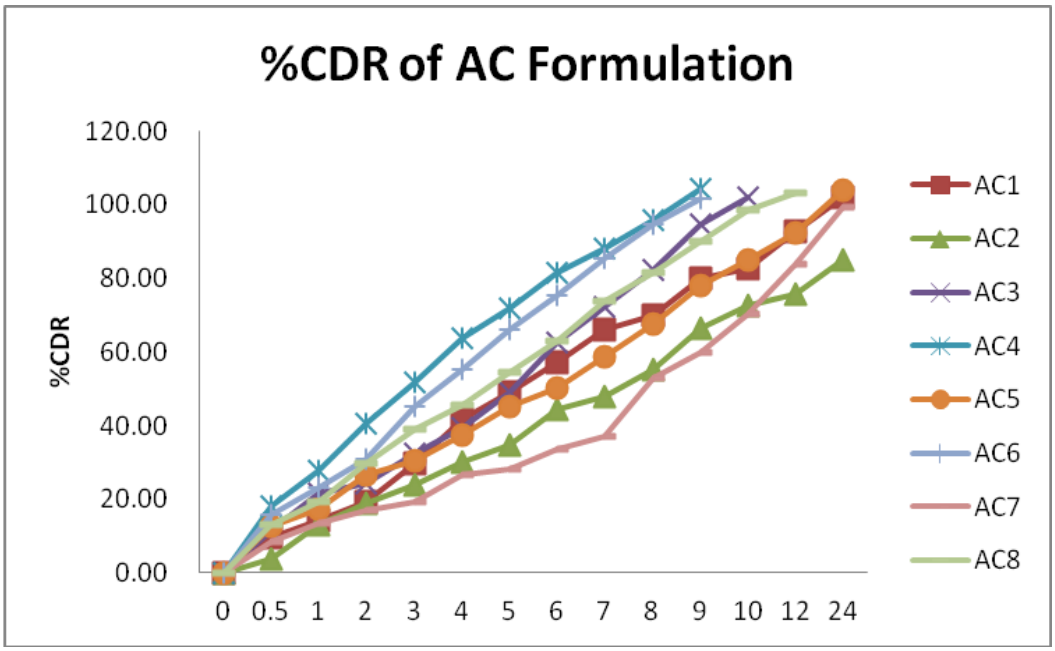


Fig. 5.27 *In vitro* release profile of Designed formulation AC1 –AC8.

3.1.3 Mechanism of Drug Release: -

Table 5.34 R^2 & K values of the release profiles of each formulation made at formulation stage corresponding to Zero order, First order, and higuchi kinetics.

For m	Zero-order		First order		Higuchi	
	R^2	k_o	R^2	k_1	R^2	kH
AC1	0.5926	6.366	**0.9792**	0.176	0.9315	23.267
AC2	0.6538	5.195	**0.9749**	0.095	0.9170	18.828
AC3	0.4832	7.004	**0.9266**	0.219	0.8787	25.843
AC4	0.0107	7.720	**0.9697**	0.318	0.8561	29.555
AC5	0.6220	6.295	**0.9631**	0.169	0.9401	22.903
AC6	0.1834	7.426	**0.9635**	0.278	0.8664	28.155
AC7	0.8318	5.312	0.9276	0.157	0.8721	18.599
AC8	0.4112	6.988	**0.9599**	0.264	0.9069	25.994

NOTE: R^2 = Coefficient of determination, k_o = Zero-order release constant, k_1 = First-order release constant, kH = Highchi release constant.

Table 5.35 R^2, n & kKP values of the release profiles of each formulation made at formulation stage corresponding to Korsmeyer – peppas models

Formulation	Korsmeyer-peppas		
	R^2	**kKP**	**n**
AC1	0.9344	14.318	0.757
AC2	0.9263	9.709	0.812
AC3	0.8788	17.850	0.688
AC4	0.9026	27.257	0.604
AC5	0.9445	17.306	0.642
AC6	0.8857	22.767	0.659
AC7	**0.9303**	11.503	0.690
AC8	0.9083	19.324	0.678

3.1.4 Polynomial equation

Table 5.36 Polynomial equation of the various dependent variables in AC Formulation

Atorvastatin Floating Capsule	kH of Higuchi	*Y1=28.33+0.120X1-0.260X2-0.048X3 -0.150X4+0.100X5+0.115X6-0.043X7*
	'n' of Kors-Peppas	*Y1=0.688-0.002X1+0.002722X2+0.015X3 +0.001X4-0.001X5-0.002X6-0.003X7*
	Log(K) of kors-peppas	*Y1=1.363+0.005X1-0.009X2-0.013X3 -0.006X4+0.004X5+0.005X6+0.001X7*
	k_1 of 1^{st} order	*Y1=-0.341-0.004X1+0.005X2+0.007X3 +0.002X4-0.001X5-0.001X6+0.001X7*
	k_0 of zero order	*Y1=7.772+0.027X1-0.060X2-0.016X3 -0.037X4+0.025X5+0.019X6-0.005X7*
	R^2 of zero order	*Y1=0.594-0.011X1+0.016X2+0.002X3 +0.003X4-0.004X5-0.017X6+0.009X7*

3.1.5 Stability studies:

Table 5.37 Stability data of optimized AC2 formulation stored at 45 ºC **/** 75% RH

Sampling interval	Optimized Formulation			
	PA	**%DC**	**%CDR at 24 Hr.**	**TFT (Hr)**
0	**++**	102.34	101.2	20
1 Week	**++**	102.45	100.45	21
2 week	**++**	102.67	99.45	22
3 Week	**++**	101.45	99.82	22
4 week	**++**	101.53	99.83	21
2 month	**++**	101.83	99.64	21
3 month	**++**	102.77	99.62	21

PA- Physical appearance, DT**-** Disintegration time, **% DC-** Percent Drug Content. **%CDR-** Percent cumulative drug Release. ++: same as initial, TFT- Total Floating Time

3.1.6 Animal study:

Table 5.38 Total cholesterol level in treated group

Treatment	Total cholesterol level in mg/dL		
	0 Day	**18th Day**	**40th Day**
Control	27.71±3.20	27.82±3.68	27.15±3.48
Pure Drug	28.8±1.93	12.5±1.68	9.2±0.96
Formulation	26.08±4.49	12.8±2.32	7.95±1.01

All values are mean ± SEM, n = 6. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ when compared to control group

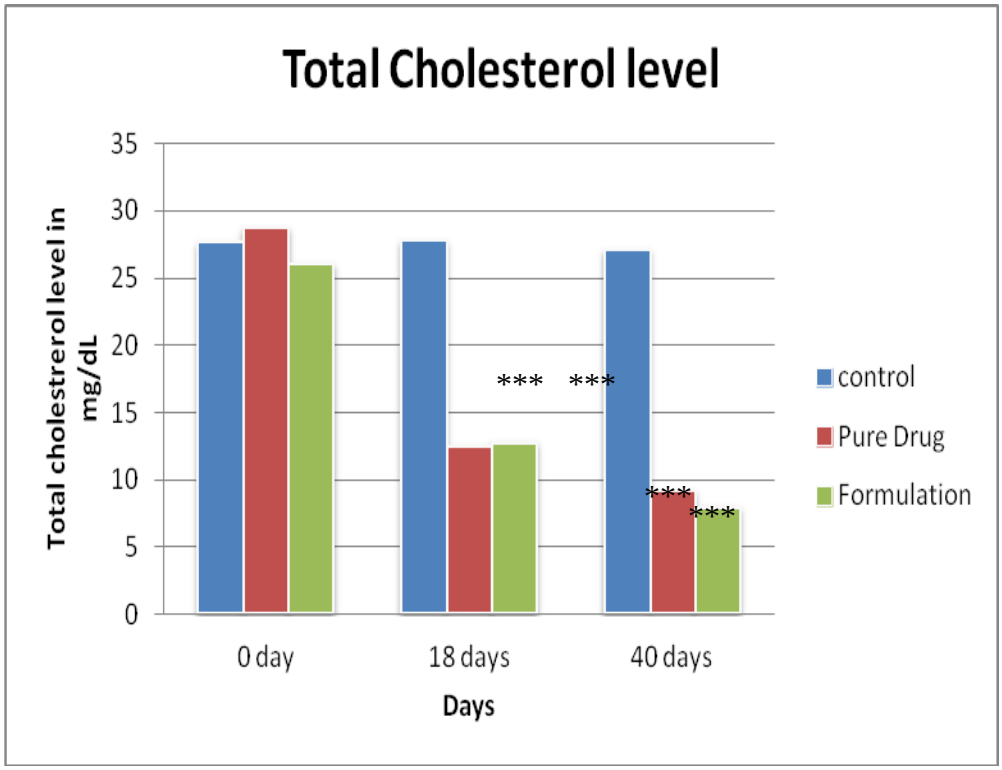


Fig. 5.28 Total cholesterol level in treated group.

3.2. EVALUATION OF FLOATING TABLET

3.2.1 Floating tablet evaluation**:**

Table 5.39 The values of various evaluation parameters of the formulations AF made at formulation stage

Response	FORMULATION CODE							
	AF1	**AF2**	**AF3**	**AF4**	**AF5**	**AF6**	**AF7**	**AF8**
Bulk density (gm/ml)	0.323	0.345	0.382	0.389	0.364	0.383	0.399	0.401
Tapped density (gm/ml)	0.364	0.391	0.437	0.421	0.401	0.418	0.438	0.442
Angle of repose(^{o})	27.34	29.45	32.45	33.67	29.95	34.76	32.86	31.78
Hardness(Kg/cm^{2})	4	4	4	4	4	4-5	4	4
Friability (%)	0.28	0.25	0.29	0.76	0.63	0.73	0.21	0.92
Wt variation (%)	1.83	2.06	1.74	1.93	1.98	2.20	4.04	1.74

Floating Lag Time (Sec)	78	167	112	195	110	185	550	3
TFT (hr)	28	21	28	17	29	28	30	21
Swelling Index (24 Hr)	571.6	578.3	580.3	556.1	614.3	602.8	604.3	691.6
Drug content (%)	99.17	99.57	102.2	99.55	101.7	97.23	102.6	103.4

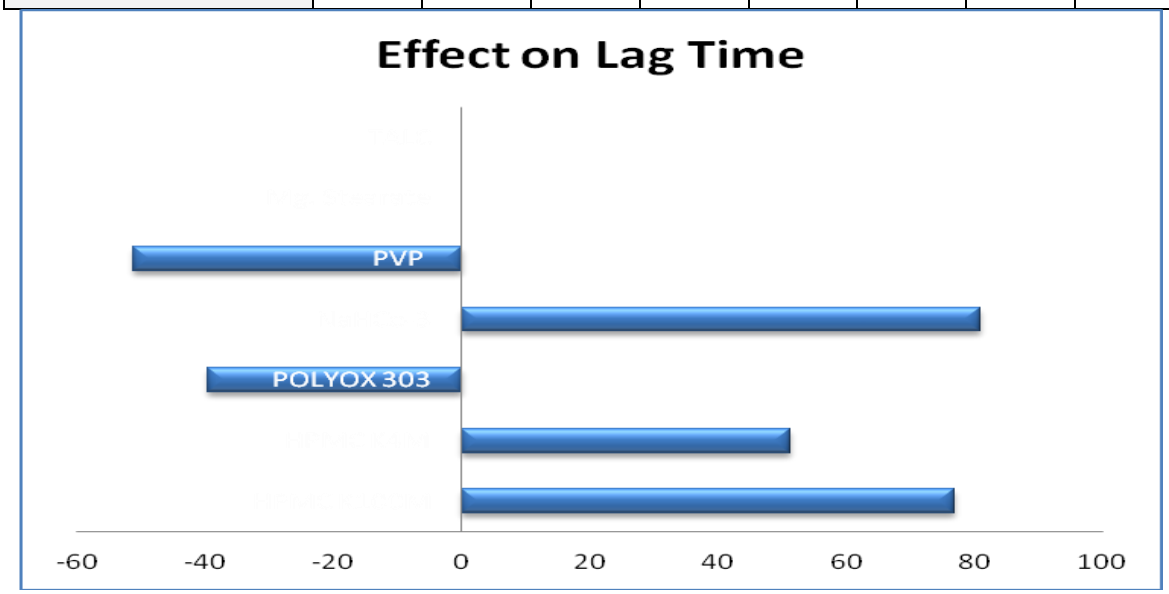


Fig 5.29 Pareto chart showing the effect of polymer on floating lag time of AF

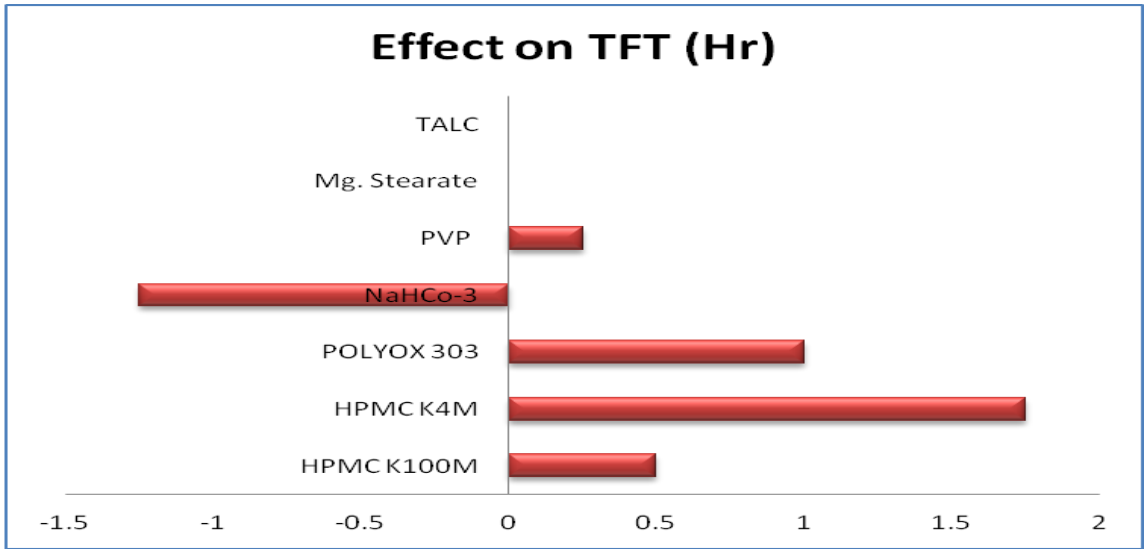


Fig 5.30 Pareto chart showing the effect of polymer on Total floating time of AF

3.2.2 Dissolution Study or drug release testing of Floating Tablet: -

Table 5.40 Data of the release profile of the AF1 – AF8.

Time (Hrs)	Cumulative drug release (%)							
	AF1	**AF2**	**AF3**	**AF4**	**AF5**	**AF6**	**AF7**	**AF8**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	5.99	4.66	8.32	9.65	3.00	11.65	9.99	12.65
1	8.69	7.68	13.69	13.70	7.67	15.38	13.70	20.71
2	10.73	12.38	19.09	19.43	13.71	20.45	25.43	29.47
3	17.12	14.45	26.52	24.53	19.11	31.88	32.89	35.96
4	21.87	19.52	34.99	32.99	29.20	38.71	41.39	45.48
5	29.64	27.28	43.50	41.83	37.68	44.59	50.27	61.04
6	36.80	32.76	48.07	52.37	48.87	57.14	64.20	69.03
7	45.32	38.60	53.66	62.98	63.78	63.78	74.53	78.39
8	52.89	46.13	58.94	69.64	75.78	72.12	81.93	86.81
9	59.84	54.04	68.91	79.68	86.85	80.16	90.36	91.94
10	69.15	62.98	76.94	85.10	96.31	88.92	98.51	103.42
12	83.50	72.65	81.68	97.21	102.16	94.39	102.37	
24	99.27	98.76	89.11	102.73	103.37	104.55		

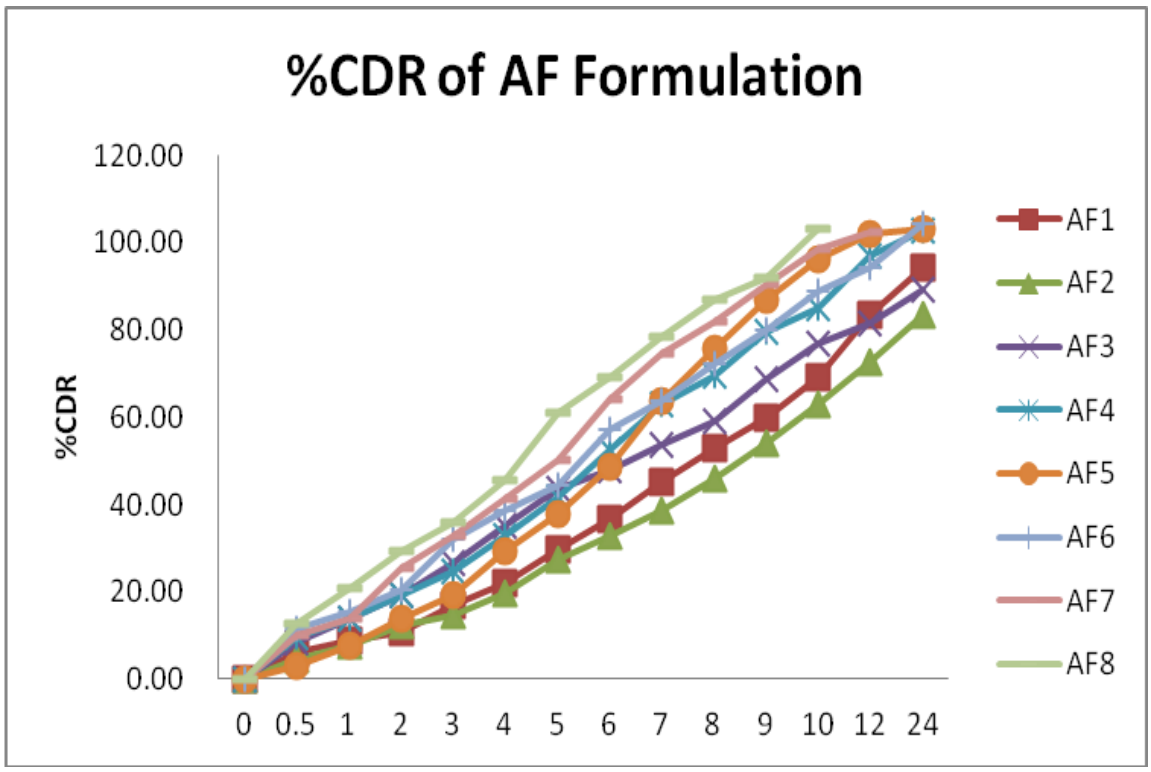


Fig. 5.31 *In vitro* release profile of Designed formulation AF1 –AF8.

3.2.3 Swelling Studies of floating tablets

Table 5.41 Data of the Swelling index of the AF1 – AF8

	Swelling Index (%)							
Time (hr)	**AF1**	**AF2**	**AF3**	**AF4**	**AF5**	**AF6**	**AF7**	**AF8**
1	174.5	180.4	182.5	178.3	185.3	187.3	178.3	206.9
3	304.3	310.4	315.5	311.4	321.6	324.3	301.0	369.6
6	360.4	378.3	398.3	376.3	389.4	392.5	369.3	445.7
12	480.3	490.3	477.3	498.4	492.2	462.5	470.2	547.8
24	571.6	578.3	580.3	556.1	614.3	602.8	604.3	691.6

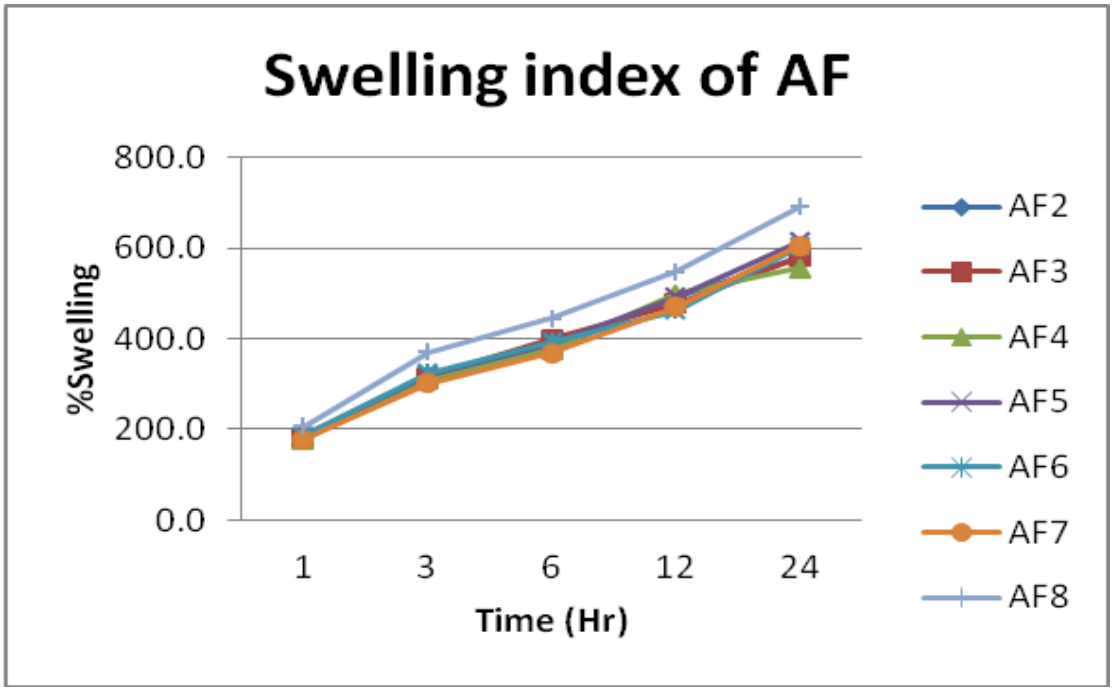


Fig 5.32 Swelling index of the AF1 –AF8

3.2.4 Mechanism of Drug Release: -

Table 5.42 R^2 & K values of the release profiles of each formulation made at formulation stage corresponding to Zero order, First order, and higuchi kinetics.

Form	Zero-order		First order		Higuchi	
	R^2	k_o	R^2	k_1	R^2	kH
AF1	0.8204	5.226	0.9451	0.115	0.8661	18.324
AF2	0.8189	4.637	0.9578	0.081	0.8709	16.277
AF3	0.5944	5.553	0.9826	0.110	0.9294	20.282
AF4	0.6604	6.319	0.9488	0.195	0.8998	22.842
AF5	0.6797	6.511	0.8959	0.204	0.8286	23.313
AF6	0.6100	6.473	0.9643	0.190	0.9256	23.590
AF7	0.9726	9.777	0.9425	0.260	0.9153	27.145
AF8	0.9721	10.902	0.9505	0.232	0.9347	28.576

NOTE: R^2 = Coefficient of determination, k_o = Zero-order release constant, k_1 = First-order release constant, kH = Highchi release constant.

Table 5.43 R^2, n & kKP values of the release profiles of each formulation made at formulation stage corresponding to Korsmeyer – peppas models

Formulation	Korsmeyer-peppas		
	R^2	**kKP**	**n**
AF1	0.9232	8.397	0.830
AF2	0.9259	7.426	0.837
AF3	0.9326	13.569	0.687
AF4	0.9120	13.302	0.768
AF5	0.8542	6.527	1.143
AF6	0.9301	15.640	0.712
AF7	**0.9903**	14.991	0.797
AF8	**0.9945**	19.410	0.693

3.2.5 Polynomial equation

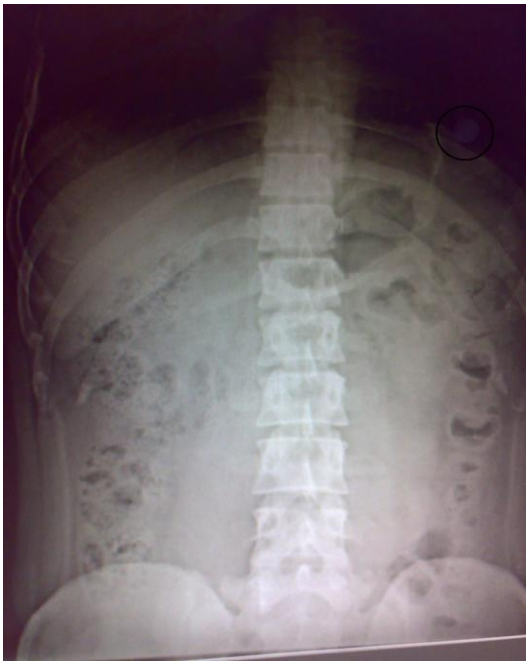
Table 5.44 Polynomial equation of the various dependent variables in AF Formulation

Atorvastatin Floating tab	kH of Higuchi	*Y1=48.183+0.054X1-0.160X2-0.975X3-0.151X4-0.338X5-1.038X6+2.077X7*
	'n' Of Korse-Peppas	*Y1=0.089-0.004X1+0.012X2-0.014X3-0.006X4+0.012X5+0.057X6+0.053X7*
	log(k) of Korse-Peppas-	*Y1=2.167+0.005X1-0.015X2-0.012X3 +0.002X4-0.017X5-0.065X6-0.065X7 +0.028X7*
	k_0 of 1^{st} order	*Y1=-0.3841-0.0021X1+0.0010X2+0.0164X3 + 0.0020X4+0.0044X5+0.0058X6-0.0351X7*
	k_1 of zero order	*Y1=25.632+0.003X1-0.048X2-0.484X3 -0.059X4-0.256X5-0.940X6+0.307X7*

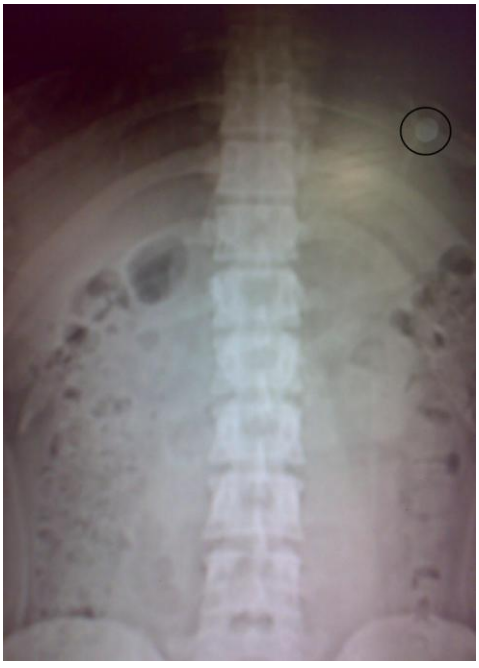
	R^2 of zero order	*Y1=1.643-0.014X1+0.009X2-0.004X3-0.010X4 -0.011X5-0.142X6+0.212X7*
	Floating Lag Time (sec)	*Y1=-732+9.62X1+6.40X2-13.64X3+13.5X4 -12.81X5-10.75X6+128.5X7*

3.2.6 *In vivo* studies

in vivo evaluation of gastrointestinal residence time of gastroretentive dosage form to confirm the spatial and temporary placement of gastroretentive drug delivery system. X-ray technique was used to determine the gastric residence time of the tablets.



(a)



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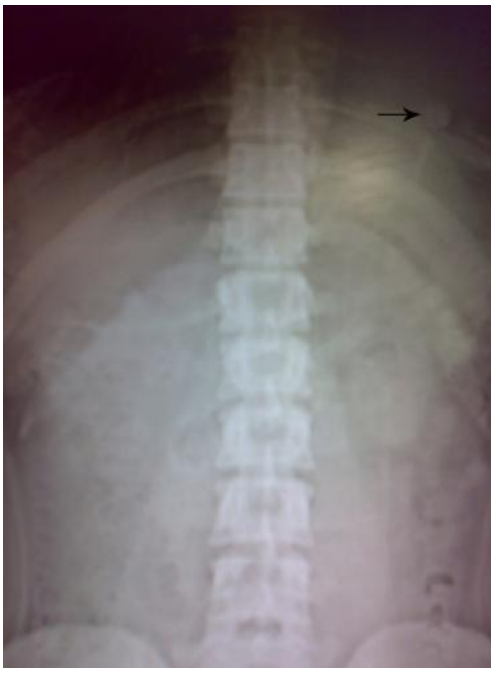


(c)

Fig. 5.33 X-ray image shows the placing of placebo table, (a) At 5 Min. (b) 3 hr (c) 8 hr

3.2.7 Stability studies:

Table 5.45 Stability data of optimized AF1 formulation stored at 45 ºC **/** 75% RH

Sampling interval	Optimized Formulation			
	PA	**%DC**	**%CDR at 24 Hr.**	**TFT (Hr)**
0	**++**	99.40	84.34	24
1 Week	**++**	99.57	85.84	24
2 week	**++**	99.23	89.95	24
3 Week	**++**	99.10	88.47	24
4 week	**++**	99.64	88.83	26
2 month	**++**	99.42	83.78	22
3 month	**++**	99.43	85.21	24

PA- Physical appearance, DT**-** Disintegration time, **% DC-** Percent Drug Content. **%CDR-** Percent cumulative drug Release. ++: same as initial, TFT- Total Floating Time.

3.3 *EVALUATION OF HIGH DENSITY TABLET*

3.3.1 High Density Tablet Evaluation:

Table 5.46 The values of various evaluation parameters of the formulations made at formulation stage

Response	FORMULATION CODE							
	AH1	**AH2**	**AH3**	**AH4**	**AH5**	**AH6**	**AH7**	**AH8**
Bulk density (gm/ml)	0.382	0.362	0.385	0.401	0.373	0.384	0.399	0.381
Tapped density (gm/ml)	0.424	0.402	0.435	0.485	0.412	0.412	0.450	0.421
Angle of repose	36.89	32.74	32.77	37.76	27.67	29.49	30.54	31.96
Friability (%)	1.57	1.83	1.43	0.21	0.23	0.32	0.42	0.49
Wt variation (%)	1.43	2.95	3.39	3.85	1.39	1.94	0.57	1.93
Hardness(Kg/cm^2)	6-7	6-7	7-8	7-8	7-8	7-8	7-8	7-8
Drug content (%)	99.17	99.57	102.2	99.55	101.7	97.23	102.6	103.4
%Mass remain	35	40	56	23	46	56	45	17

3.3.2 Dissolution Study or drug release testing of high density tablet: -

Table 5.47 Data of the release profile of the AH1 – AH8.

Time (Hrs)	Cumulative drug release (%)							
	AH1	**AH2**	**AH3**	**AH4**	**AH5**	**AH6**	**AH7**	**AH8**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	5.33	11.98	3.66	14.98	4.33	8.65	5.99	16.31
2	8.68	21.04	7.68	31.70	6.35	12.03	8.69	25.72
3	16.05	27.14	10.71	47.19	8.38	24.08	13.06	34.18

4	22.47	34.28	14.77	56.10	11.09	33.20	15.46	42.69
5	29.58	45.45	20.17	62.40	16.48	42.37	17.88	54.24
6	35.40	53.36	27.94	70.73	18.56	46.93	20.64	63.20
7	48.24	61.31	33.09	74.78	23.66	60.17	24.75	68.20
8	57.16	67.30	38.93	82.84	26.45	69.48	29.54	76.56
9	70.79	72.33	47.79	87.62	30.92	78.18	33.70	83.63
10	80.83	78.38	55.04	99.08	36.75	85.93	35.88	98.40
12	94.91	87.79	65.33	103.94	41.94	97.38	44.72	
24	101.42	103.57	86.98		84.13	102.23	89.60	

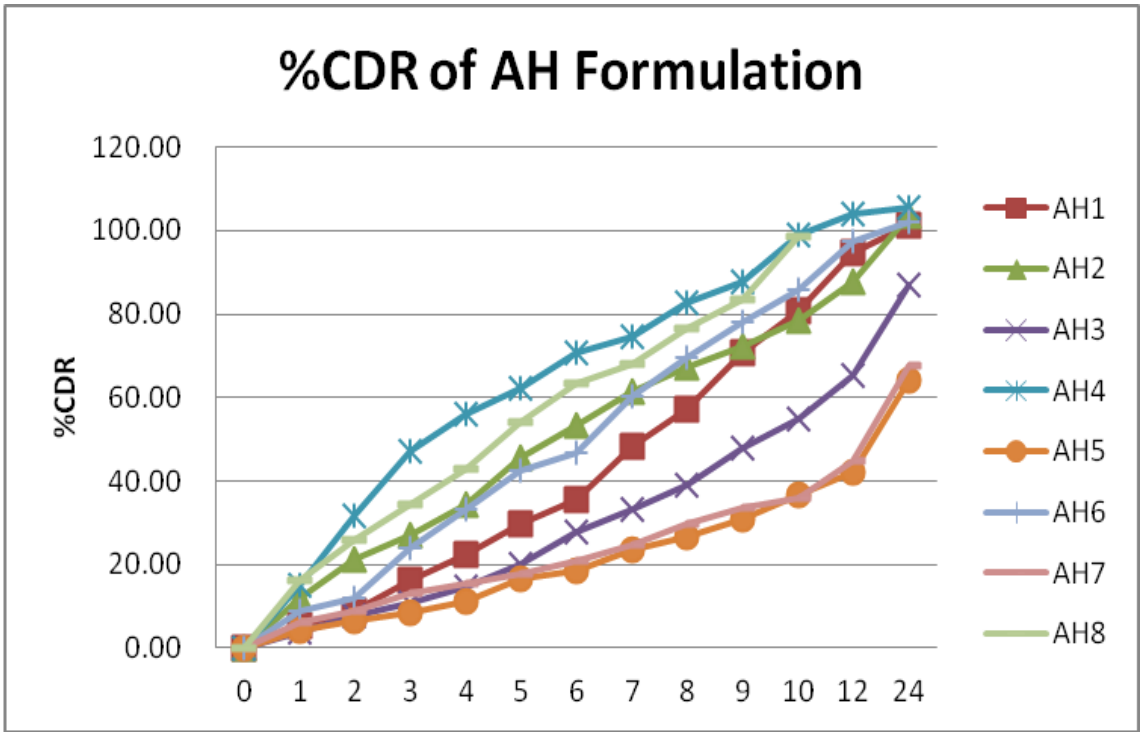


Fig. 5.34 *In vitro* release profile of Designed formulation AH1 –AH8.

3.3.3 Mechanism of Drug Release: -

Table 5.48 R^2 & K values of the release profiles of each formulation made at formulation stage corresponding to Zero order, First order, and higuchi kinetics.

Form	Zero-order		First order		Higuchi	
	R^2	k_o	R^2	k_1	R^2	kH
AH1	0.7830	5.733	**0.8869**	0.153	0.8062	20.067
AH2	0.6436	6.119	**0.9779**	0.148	0.9369	22.182
AH3	0.9124	4.320	0.9420	0.078	0.8177	14.766
AH4	0.2200	7.172	**0.9744**	0.280	0.9019	26.943
AH5	0.9547	3.028	**0.9822**	0.042	0.8365	10.309
AH6	0.6638	6.238	**0.9314**	0.193	0.8674	22.457
AH7	0.9442	3.229	**0.9911**	0.046	0.8767	11.121
AH8	0.9804	9.917	0.9557	0.237	0.9198	26.044

NOTE: R^2 = Coefficient of determination, k_o = Zero-order release constant, k_1 = First-order release constant, kH = Highchi release constant.

Table 5.49 R^2, n & kKP values of the release profiles of each formulation made at formulation stage corresponding to Korsmeyer – peppas models

Formulation	Korsmeyer-peppas		
	R^2	kKP	n
AH1	0.8730	4.362	1.228
AH2	0.9468	11.693	0.827
AH3	**0.9431**	3.649	1.102
AH4	0.9136	17.538	0.768
AH5	0.9771	3.586	0.945
AH6	0.8880	7.491	1.052
AH7	0.9886	5.335	0.808
AH8	**0.9953**	15.362	0.776

3.3.4 Polynomial equation

Table 5.50 polynomial equations of the various dependent variables in AH Formulation

Atorvastatin High density	kH of Higuchi	*Y1=57.814+0.114X1-0.415X2+0.211X3-0.060X4-0.304X5+1.237X6-9.145X7*
	'n' of Kors-Peppas	*Y1=0.380+0.003X1+0.002X2+0.038X3-0.008X4+0.018X5-0.040X6+0.077X7*
	log(k) of Kors-Peppas-	*Y1=-0.313+0.001235X1+0.00079X2+0.017X3-0.003498X4+0.007X5-0.016X6+0.041X7*
	k_1 of 1^{st} order	*Y1=0.631+0.003X1-0.006X2-0.001X3-0.001X4-0.002X5+0.019X6-0.115X7*
	k_0 of zero order	*Y1=27.333-0.016X1-0.149X2-0.039X3-0.064X4-0.164X5-0.080X6-3.031X7*
	R^2 of zero order	*Y1=1.643-0.014X1+0.009X2-0.004X3-0.010X4-0.011X5-0.142X6+0.212X7*

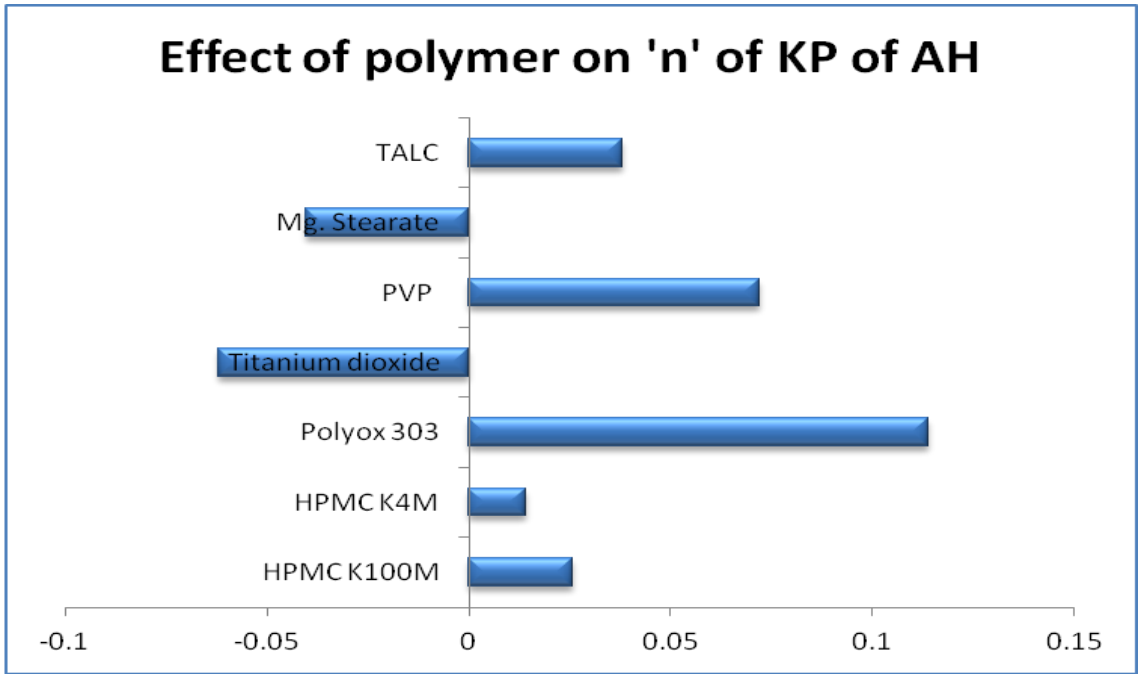
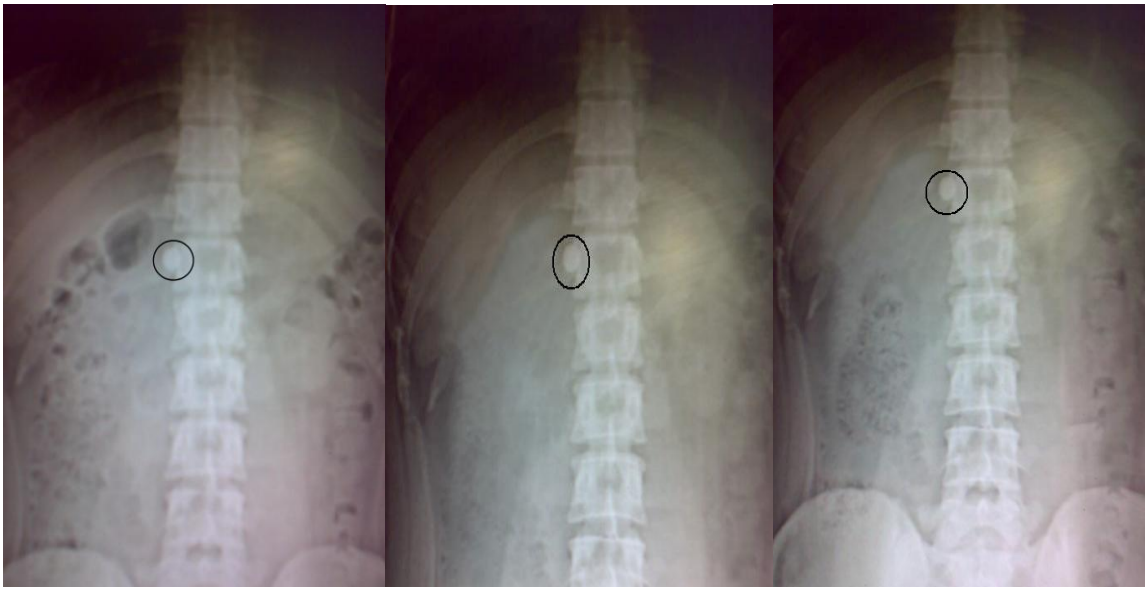


Fig 5.35 Pareto chart showing the effect of polymer on 'n' of Kors-Peppas of AH

3.3.5 *In vivo* studies



(a) **(b)** **(c)**

Fig. 5.36 X-ray image shows the placing of placebo table, (a) At 5 Min. (b) 3 hr (c) 6 hr

3.3.6 Stability studies:

Table 5.51 Stability data of optimized AH7 formulation stored at 45 ºC **/** 75% RH

Sampling interval	Optimized Formulation		
	PA	**%DC**	**%CDR at 24 Hr.**
0	**++**	101.33	86.81
1 Week	**++**	102.04	83.32
2 week	**++**	101.44	85.74
3 Week	**++**	101.56	85.64
4 week	**++**	101.54	87.55
2 month	**++**	101.89	88.94
3 month	**++**	100.93	88.12

PA- Physical appearance, DT**-** Disintegration time, **% DC-** Percent Drug Content. **%CDR-** Percent cumulative drug Release. ++: same as initial, TFT- Total Floating Time

3.4. EVALUATION OF MUCOADHESIVE TABLET

3.4.1 Mucoadhesive Tablet Evaluation:

Table 5.52 The values of various evaluation parameters of the formulations AM made at formulation stage

Response	FORMULATION CODE							
	AM1	**AM2**	**AM3**	**AM4**	**AM5**	**AM6**	**AM7**	**AM8**
Bulk density (gm/ml)	0.333	0.335	0.439	0.380	0.363	0.389	0.391	0.387
Tapped density (gm/ml)	0.384	0.393	0.537	0.459	0.430	0.448	0.438	0.461
Angle of repose	29.74	31.32	29.74	32.93	35.92	32.52	33.31	30.46
Friability (%)	0.98	0.45	0.89	1.4	0.67.	0.62	0.88	0.91

Wt variation (%)	2.34	1.56	3.12	3.67	0.93	1.30	0.84	0.06
Hardness (Kg/cm^2)	4-5	4	4	4-5	5	4-5	4-5	4-5
Swelling Index (24 Hr)	767.9	791.4	797.6	813.4	927.3	884.6	810.3	1045.4
Mucoadhesive Strength	25.2	27	23	20.8	22	23	22.3	18
Mucoadhesion Time (Hr)	27	15	20	26	14	24	25	24
Drug content (%)	99.77	98.23	101.6	98.4	99.5	97.43	102.2	99.8

3.4.2 Dissolution Study or drug release testing of mucoadhesive tablet: -

Table 5.53 Data of the release profile of the AM1 – AM8.

Time (Hrs)	**Cumulative drug release (%)**							
	AM1	**AM2**	**AM3**	**AM4**	**AM5**	**AM6**	**AM7**	**AM8**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	11.65	8.65	9.99	19.30	7.66	10.65	7.66	3.66
1	17.37	19.02	13.70	25.07	16.35	20.36	16.35	12.34
2	28.45	22.45	22.43	31.87	19.77	29.79	24.76	25.38
3	33.27	30.23	28.55	41.36	26.87	37.61	33.89	33.51
4	37.45	35.06	35.36	46.91	30.68	40.82	38.40	39.02
5	44.64	39.25	42.21	50.17	39.50	45.70	43.60	43.57
6	49.88	47.12	48.10	60.76	43.05	52.94	47.84	45.80
7	54.14	51.37	56.68	69.41	44.61	59.55	51.43	48.38
8	56.43	56.31	62.65	77.11	49.51	65.87	53.37	56.30
9	59.40	63.27	71.31	83.85	55.11	73.21	56.32	60.93
10	64.05	69.60	80.35	88.96	56.74	80.60	58.95	62.92
12	69.39	76.97	88.78	96.43	59.70	85.69	63.26	70.25
24	99.05	101.01	100.90	102.61	98.32	103.46	98.23	99.59

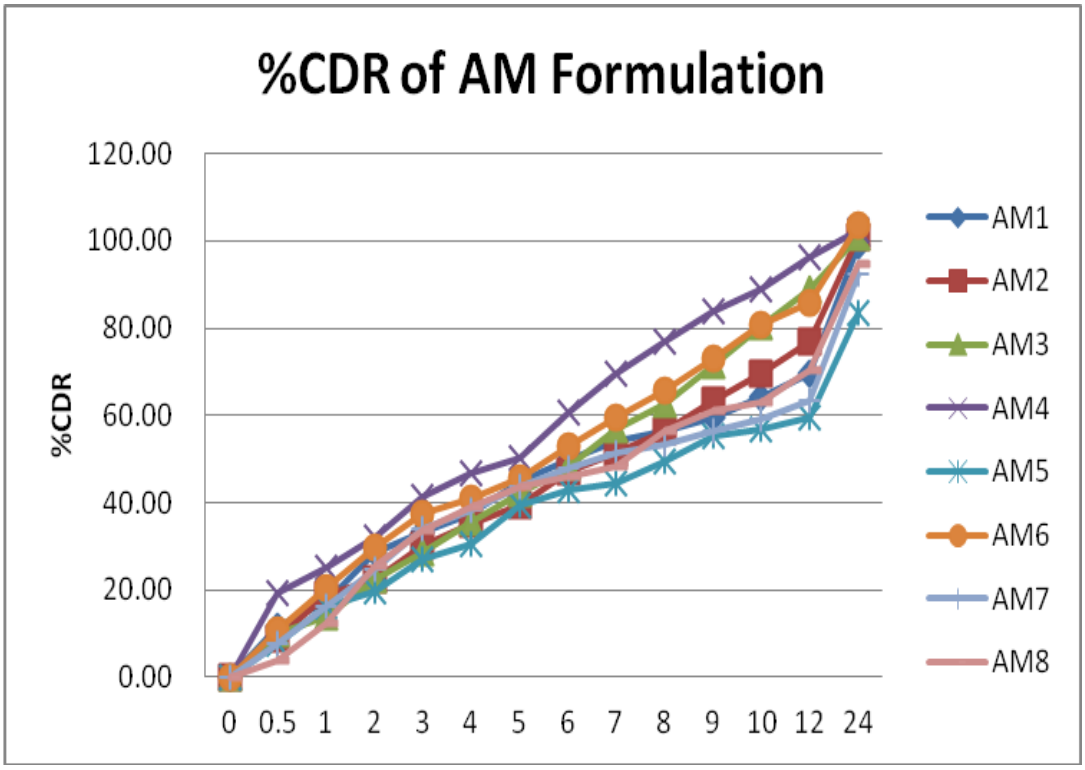


Fig. 5.37 In *vitro* release profile of designed formulation AM1 –AM8.

3.4.3 Swelling Studies of floating tablets

Table 5.54 Data of the Swelling index of the AM1 – AM8

	Swelling Index(%)							
Time (Hr)	**AM1**	**AM2**	**AM3**	**AM4**	**AM5**	**AM6**	**AM7**	**AM8**
1	133.4	135.5	138.3	140.3	165.3	157.2	140.3	193.3
3	311.6	315.0	310.4	330.3	382.5	360.2	330.4	449.4
6	328.7	345.5	340.4	355.3	402.4	380.3	350.3	475.3
12	535.9	563.3	595.4	524.4	745.3	770.4	599.1	734.9
24	771.3	800.4	801.5	815.3	950.2	884.2	818.4	1050.6

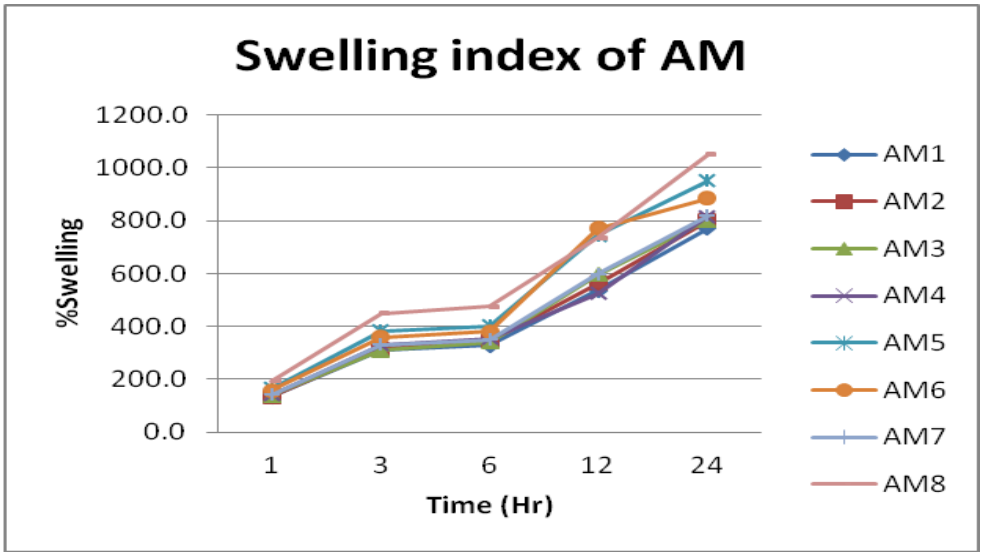


Fig 5.38 Swelling index of the AM1 –AM8

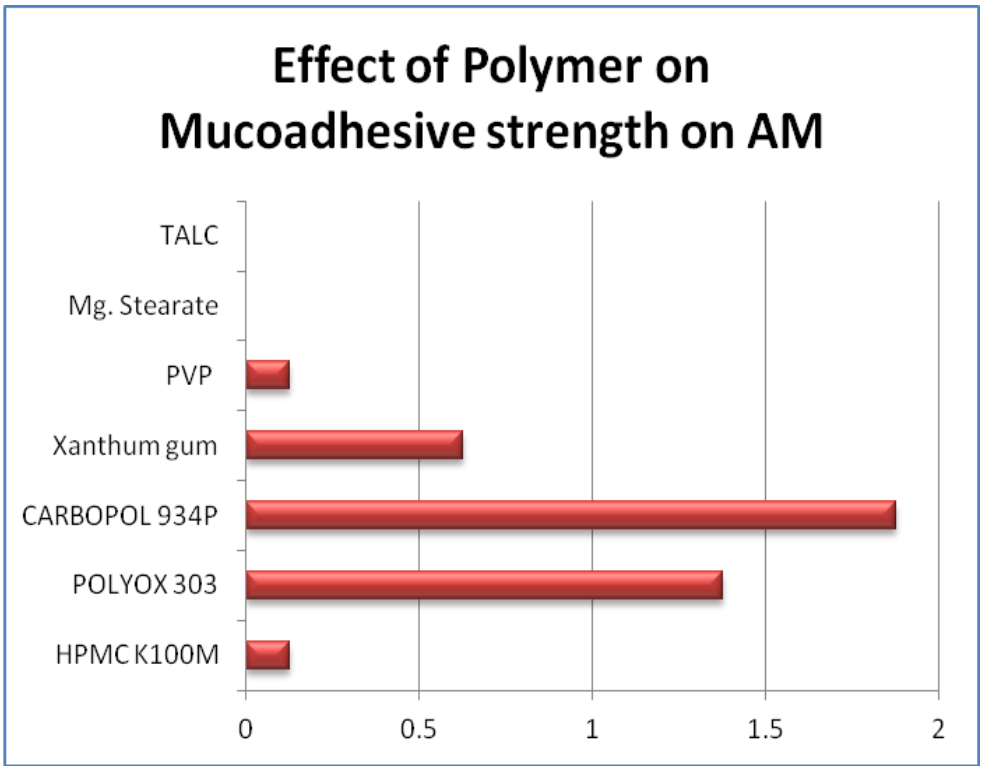


Fig. 5.39 Pareto Chart showing the effect of polymer on Mucoadhesive strengh of tablet of AM

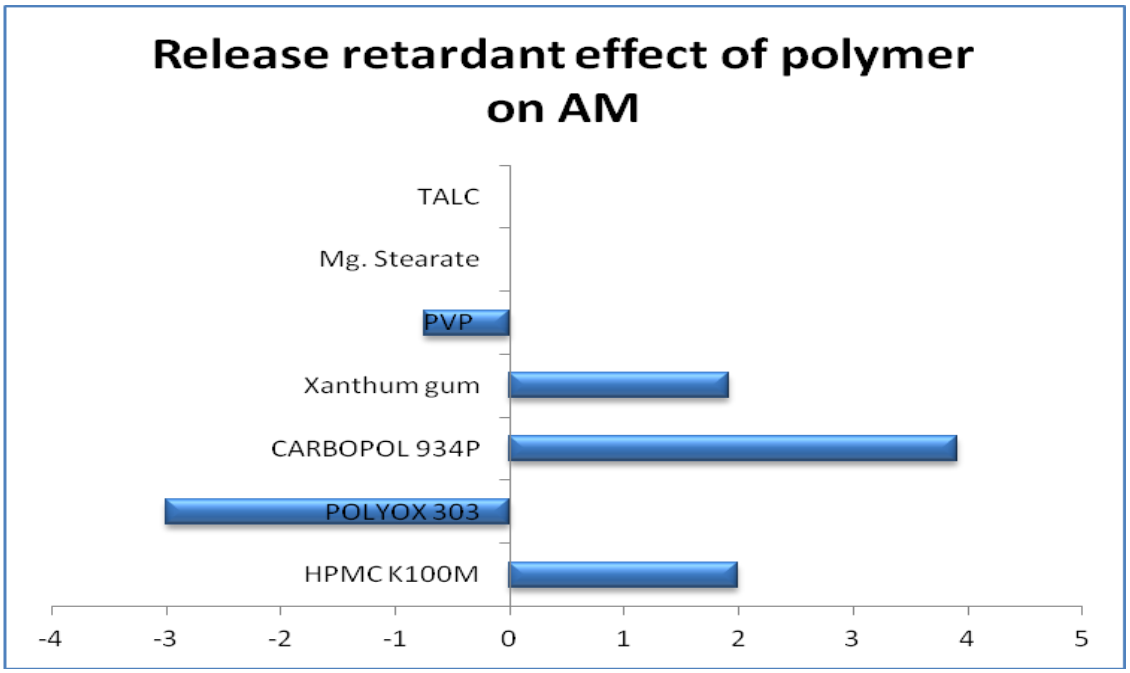


Fig. 5.40 Pareto Chart showing the release retardant effect of polymer on tablet of AM

3.4.4 Mechanism of Drug Release: -

Table 5.55 R^2 & K values of the release profiles of each formulation made at formulation stage corresponding to Zero order, First order, and higuchi kinetics.

Form	Zero-order		First order		Higuchi	
	R^2	k_o	R^2	k_1	R^2	kH
AM1	0.3907	5.157	0.9553	0.090	0.9771	19.176
AM2	0.5800	5.343	0.9823	0.102	0.9637	19.549
AM3	0.6767	5.990	**0.9739**	0.147	0.9387	21.660
AM4	0.3501	6.688	**0.9644**	0.213	0.9384	24.936
AM5	0.4486	4.465	0.9315	0.068	0.9662	16.544
AM6	0.4750	6.018	**0.9809**	0.142	0.9574	22.239
AM7	0.1628	4.631	0.8662	0.071	0.9209	17.536
AM8	0.5190	5.094	**0.9737**	0.089	0.9648	18.781

NOTE: R^2 = Coefficient of determination, k_o = Zero-order release constant, k_1 = First-order release constant, kH = Highchi release constant.

Table 5.56 R^2, n & kKP values of the release profiles of each formulation made at formulation stage corresponding to Korsmeyer – peppas models

Formulation	Korsmeyer-peppas		
	R^2	kKP	n
AM1	**0.9831**	18.233	0.532
AM2	**0.9646**	15.536	0.609
AM3	0.9488	14.272	0.709
AM4	0.9449	24.587	0.526
AM5	**0.9680**	13.963	0.588
AM6	0.9580	18.755	0.586
AM7	0.9490	15.605	0.575
AM8	0.9648	11.071	0.767

3.4.5 Polynomial equation

Table 5.57 Polynomial equation of the various dependent variables in AM Formulation

Atorvastatin Mucoadhesive tablet	kH of Higuchi	*Y1=26.113+0.123X1-0.370X2+0.060X3 +0.087X40.132X5-0.764X6-1.115X7*
	'n' Of Korse-Peppas	*0.725-0.0076X1-0.007X2+0.00024X3 -0.001X4-0.006X5+0.034X6+0.006X7*
	log(K) of Kors-Peppas-	*Y1=-0.23065-0.00184X1+0.00650X2- 0.00049X3-0.00179X4-0.00361X5 +0.01617X6 +0.01655X7*
	k_1 of 1^{st} order	*Y1=-0.231-0.002X1+0.006X2-0.00049X3 -0.002X4-0.004X5+0.016X6+0.017X7*

	k_0 of zero order	*Y1=7.078+0.027X1-0.105X2+0.020X3 +0.024X4+0.038X5-0.205X6-0.295X7*
	R^2 of zero order	*Y1=0.825-0.014X1-0.011X2+0.008X3 -0.001X4+0.004X5-0.013X6-0.019X7*
	Mucoadhesive strength	*Y1=14.4+0.022X1+0.293X2+0.189X3 +0.061X4+0.022X5-0.538X6-0.175X7*

3.4.6 Stability studies:

Table 5.58 Stability data of optimized AM1 formulation stored at 45 ºC **/** 75% RH

Sampling interval	Optimized Formulation				
	PA	**%DC**	**%CDR at 24 Hr.**	**Mucoadhesion Time (Hr)**	**Mucoadhesive Strength (gm)**
0	**++**	99.45	99.77	27	35.23
1 Week	**++**	99.39	99.23	27	33.67
2 week	**++**	99.5	98.45	27	34.59
3 Week	**++**	99.34	99.84	28	35.93
4 week	**++**	99.89	99.52	28	34.82
2 month	**++**	99.11	98.51	27	35.83
3 month	**++**	98.49	98.23	26	34.73

Note: PA- Physical appearance, DT**-** Disintegration time, **% DC-** Percent Drug Content. **%CDR-** Percent cumulative drug Release. ++: same as initial, TFT- Total Floating Time

6. DISCUSSION

Oral drug delivery system represents one of the frontier areas of controlled drug delivery system. Such a dosage form has major advantage of patient compliance. Gastroretentive drug delivery system belongs to oral controlled drug delivery system group, which are capable of retain in the stomach.. The release rate will be controlled depending upon the type and concentration of the polymer, which swells, leads to diffusion and erosion of the drug.

The main objective of the present research work is to formulate a multi-unit granular dosage form dispense, in the form of capsule, mucoadhesive floating tablet, Mucoadhesive tablet and high density tablet. It also aims at studying the effects of formulation variable on the release, floating properties, mucoadhesive properties, retention time of gastroretentive drug delivery system.

To achieve the above objectives, various formulations were prepared by using data of trial batches, First line of Plackett-burman design. Simvastatin and Atorvastatin were identified and checked for purity by melting point, UV-Visible scanning and IR spectroscopy.

The Preformulation study constitutes standardization of the analytical procedure for the estimation of the drug content from the formulations. Standard calibration curve of Simvastatin and Atorvastatin were prepared using 0.1 N HCl + 0.5% SLS and then this solution was treated with manganese dioxide 10mg/ml and the absorbance was noted for different concentration at 238 nm, 247 nm, 257 nm for simvastatin and 246 nm for atorvastatin. This method has good reproducibility, correlation between the concentration and the absorbance was found to be

0.9992, with slope = 0.0347 for simvastatin and correlation between the concentration and the absorbance was found to be 0.9993, with slope = 0.0338 for atorvastatin.

The same procedure was applied to the estimation of drug from the prepared gastroretentive dosage form. Docusate sodium was used in all the formulation of atorvastatin as stabilizing agent and BHA (Butylated hydroxyanisole) was used in all the formulation of simvastatin as anti oxidizing agent.

The next step in the Preformulation study was the preparation and *in vitro* evaluation of the gastroretentive dosage form containing simvastatin and atorvastatin by considering the various formulation variables (such as drug to polymer ratio, and polymer to polymer ratio).

Floating capsule of simvastatin and atorvastatin

Initial trials were taken to check the floating characteristics, gel forming capacity, extent of swelling and buoyancy of different polymers like sodium starch glycolate, cross carmellose sodium, HPMC K4M, HPMC K100M. Trial batch was prepared by using HPMC K4M, cross carmellose sodium, Mg. Al. silicate (Veegum), MCC 101, HPC LH 11, Eudragit RS, with $NaHCO_3$. These prepared formulations were evaluated mainly for percent weight variation, percent drug content, floating lag time and *In vitro* release pattern. At that time proper floating lag time with 45 to 50% CDR at 4 hrs of the formulation was obtained.

After Preformulation study, the formulations of floating capsule containing

simvastatin/atorvastatin were done by taking into consideration the formulation variables like HPMC K4M, cross carmellose sodium, Mg. Al. silicate (Veegum), MCC 101, HPMC K100M, Eudragit RS, with $NaHCO_3$ using "First line of Plackett-burman design". By applying this design eight formulations were prepared and parameters like weight variation, drug content floating lag time, Total floating time and *in vitro* drug release of prepared floating capsule were evaluated.

The mechanism of release, followed by the above formulations was determined by finding the R^2 value and release constant for each kinetic model viz. Zero-order, First-order, Higuchi, Korsmeyer-Peppas and diffusion coefficient of korsmeyer-peppas model corresponding to the release data of each formulation. For most of the simvastatin formulations the R^2 value of First order and korsmeyer-peppas model is very near to 1 than the R^2 values of other kinetic models. Thus it can be inferred that the drug release follows First order and korsmeyer-peppas mechanism. The n values of Korsmeyer-Peppas model of all formulations are 0.569 to 0.789. It indicate the almost in most cases a non-Fickian mechanism is dominant. Whereas in atorvastatin formulation R^2 value of First order and korsmeyer-peppas model is very near to 1 than the R^2 values of other kinetic models. Thus it can be inferred that the drug release follows first order and korsmeyer-peppas mechanism. The n values of Korsmeyer-Peppas model of all formulations are 0.604 to 0.814. It indicate the almost in most cases a non-Fickian mechanism is dominant

The linear model generated for 'n' value of Korsmeyer-Peppas was found to be insignificant with an *F*-value of 29.02 ($p<0.05$) and R^2 value of 0.9864. From the

polynomial equation of simvastatin concluded that the polymer having the significant effect on the "n" value of Korsemeyer-Peppas constant (Y1) = 0.621+0.0001X1-0.000878X2+0.022X3+0.002X4-0.004X5-0.00045X6+0.001X7. From the above equation conclude that HPMC K4M (X2), EUDRAGIT RS (X5) and HPMC K100M (X6) had negative effect so that we can conclude that polymers were responsible for the diffusion of drug and drug release is by swelling and erosion and polynomial equation of atorvastatin for 'n' value of Korsmeyer-Peppas was found to be significant with an *F*-value of 1.173 ($p<0.05$) and R^2 value of 0.8756 concluded that the polymer having the significant effect on the "n" value of Korsemeyer-Peppas coefficient (*Y1) = 0.688-0.002X1 +0.00272X2 +0.015X3 +0.001X4-0.001X5-0.002X6-0.003X7* From the equation Cross Carmelose sodium (X1), EUDRAGIT RS (X5) and HPMC K100M (X6) had negative effect means the polymers were responsible for the diffusion of drug.

From the eight formulation of simvastatin, the formulation number SC2 was chosen as it had 71% release at 12 hr and near to 100% release at 24 hr, and total floating time (TFT) 25 hr, which gives the first order release kinetic. And from the eight formulation of Atorvastatin, the formulation number AC2 was chosen as it had 75.80% release at 12 hr and near to 98.2% release at 24 hr, and total floating time (TFT) 26 hr, which gives the first order release kinetic.

The final optimized formulation were kept for stability study at 40ºC / 75% RH condition and after every week drug content and drug release were estimated. After 3 month of stability data there was no significant change in drug content and drug release.

Carry out the animal studies for the above optimized formulation. The Total cholesterol was estimated in treated animal group. Animal study data shows the there was significant difference in control and formulation treated group but there was insignificant difference in pure drug and formulation treated group.

Floating tablet of Simvastatin and Atorvastatin

Initial trials were taken to check the floating characteristics, gel forming capacity, extent of swelling and buoyancy of different polymers like sodium starch glycolate, cross carmellose sodium, HPMC K4M, HPMC K100M. Trial batch was prepared by using HPMC K4M, HPC LH 11, and POLYOX 303, with $NaHCO_3$. These prepared formulations were evaluated mainly for percent weight variation, percent drug content, floating lag time, total floating time (TFT) and *In vitro* release pattern.

After Preformulation study, the formulations of floating tablet containing simvastatin/atorvastatin were done by taking into consideration the formulation variables like HPMC K4M, HPMC K100M, POLYOX 303, with $NaHCO_3$ using "First line of Plackett-burman design". By applying this design eight formulations were prepared and parameters like weight variation, drug content floating lag time, total floating time (TFT) and *in vitro* drug release of prepared floating capsule were evaluated.

The mechanism of release, followed by the above formulations was determined by finding the R^2 value and release constant for each kinetic model viz. Zero-order, First-order, Higuchi, Korsmeyer-Peppas and diffusion coefficient

of korsmeyer-peppas model corresponding to the release data of each formulation. For most of the simvastatin formulations the R^2 value of First order and korsmeyer-peppas model is very near to 1 than the R^2 values of other kinetic models. Thus, it can be inferred that the drug release follows first order and korsmeyer-peppas mechanism. The n values of Korsmeyer-Peppas model of all formulations are 0.660 to 1.052. It indicate the almost in most cases a non-Fickian mechanism is dominant. Whereas in atorvastatin formulation R^2 value of First order and korsmeyer-peppas model is very near to 1 than the R^2 values of other kinetic models. Thus it can be inferred that the drug release follows first order and korsmeyer-peppas mechanism. The 'n' values of Korsmeyer-Peppas model of all formulations are 0.687 to 1.143. It indicate the almost in most cases a non-Fickian mechanism is dominant.

The linear model generated for floating lag time was found to be significant with an *F*-value of 1.325 (p<0.05) and R^2 value of 0.7681. From the polynomial equation of floating lag time of simvastatin floating dosage form concluded that the polymer having the significant effect on the Floating lag time (*Y1)*=-*917.5+11.64X1+7.7X2-12.79X3+18.18X4-21.09X5-28.37X6-191.1X7,* From the equation HPMC K100M (X1), HPMC K4M (X2), $NaHCO_3$(X4) have positive effect on floating lag time, From this $NaHCO_3$(X4) having the maximum effect on the Floating lag time and polynomial equation of atorvastatin floating lag time was found to be significant with an *F*-value of 1.81 (p<0.05) and R^2 value of 0.8197 and from the polynomial equation concluded that the polymer having the significant effect on the Floating lag time *Y1=-732 + 9.62X1 + 6.40X2-*

13.64X3+13.5X4-12.81X5-10.75X6+128.5X7 From the equation HPMC K100M (X1), HPMC K4M (X2), $NaHCO_3$(X4) have positive effect on floating lag time.

From the eight formulation of simvastatin, the formulation number SF8 was chosen as it has 100% release at 12 hr, Floating lag time 1 to 2 second, and total floating time (TFT) 24 hr, which gives the non-fickian drug release. And from the eight formulation of Atorvastatin, the formulation number AF1 was chosen as it had 83.50% release at 12 hr and near to 99.2% release at 24 hr, Floating lag time 78 to 85 second and total floating time (TFT) 26 hr, which gives the first order release kinetic.

The final optimized formulation were kept for stability study at 40ºC / 75% RH condition and after every week drug content and drug release were estimated. After 3 month of stability data there was no significant change in drug content and drug release.

In vivo study carried out on healthy volunteer, In vivo study showed that the optimized tablet formulation was retained in stomach for more than eight hours

High density tablet of simvastatin and atorvastatin

Initial trials were taken to check the density of tablet, gel forming capacity, extent of swelling. Trial batch was prepared by using HPMC K4M, HPMC K100M, barium sulphate, Titanium dioxide, POLYOX 303, POLYOX 301, Mg. Al. silicate (Veegum), Eudragit RS. These prepared formulations were evaluated mainly for percent weight variation, percent drug content and *In vitro* release pattern.

After Preformulation study, the formulations of High density tablet containing simvastatin/atorvastatin were done by taking into consideration the formulation variables like HPMC K4M, HPMC K100M, Titanium dioxide, POLYOX 303 using “First line of Plackett-burman design”. By applying this design eight formulations were prepared and parameters like weight variation, drug content, and *in vitro* drug release of prepared high density tablet were evaluated.

The mechanism of release, followed by the above formulations was determined by finding the R^2 value and release constant for each kinetic model viz. Zero-order, First-order, Higuchi, Korsmeyer-Peppas and diffusion coefficient of korsmeyer-peppas model corresponding to the release data of each formulation. For most of the simvastatin formulations the R^2 value of First order is very near to 1 than the R^2 values of other kinetic models. Thus it can be inferred that the drug release follows first order mechanism. The n values of Korsmeyer-Peppas model of all formulations are 0.494 to 0.743. It indicate the almost in most cases a non-Fickian mechanism is dominant. Whereas in atorvastatin formulation R^2 value of First order and korsmeyer-peppas model is very near to 1 than the R^2 values of other kinetic models. Thus it can be inferred that the drug release follows first order and korsmeyer-peppas mechanism. The n values of Korsmeyer-Peppas model of all formulations are 0.768 to 1.228. It indicate the almost in most cases a non-Fickian mechanism is dominant.

The linear model generated for ‘n’ value of Korsmeyer-Peppas was found to be insignificant with an *F*-value of 88.04 ($p<0.05$) and R^2 value of 0.9954. From the

polynomial equation of simvastatin concluded that the polymer having the significant effect on the 'n' value of Korsmeyer-Peppas constant (Y1) = *1.238-0.005X1-0.002X2-0.016X3-0.006X4-0.004X5+0.004X6+0.006X7*. From the equation HPMC K100M (X1), HPMC K4M (X2), POLYOX 303 (X3) and Titanium dioxide (X4) had negative effect so that we can conclude that polymers were responsible for the diffusion of drug and drug release is by swelling and erosion, PVP (X5) have insignificant effect on drug release and polynomial equation of atorvastatin for 'n' value of Korsmeyer-Peppas was found to be significant with an *F*-value of 2.95 ($p<0.05$) and R^2 value of 0.8807 concluded that the polymer having the significant effect on the 'n' value of Korsemeyer-Peppas coefficient (*Y1) = 0.380+0.003X1+0.002X2+0.038X3-0.008X4+0.018X5-0.040X6 +0.077X7.* From the equation *HPMC* K100M (X1), HPMC K4M (X2), POLYOX 303 (X3) and Titanium dioxide (X4) all the term have insignificant value.

From the eight formulation of simvastatin, the formulation number SH7 was chosen as it has 70% release at 12 hr, near to 100% release at 24 hr which gives the first order release kinetic and from the eight formulation of Atorvastatin, the formulation number AH1 was chosen as it had 44.50% release at 12 hr and near to 89.2% release at 24 hr, which gives the first order release kinetic.

The final optimized formulation were kept for stability study at 40ºC / 75% RH condition and after every week drug content and drug release were estimated. After 3 month of stability data there was no significant change in drug content and drug release.

Mucoadhesive tablet of simvastatin and atorvastatin

Initial trials were taken to check the mucoadhesion strength, gel forming capacity, extent of swelling different polymers like HPMC K4M, HPMC K100M, POLYOX 303, POLYOX 301, Xanthum gum, Gaur gum, and Carbopol 934P based on Mucoadhesion strength trial batches were prepared. Trial batch was prepared by using HPMC K4M, HPMC K100M, POLYOX 303, and POLYOX 301. These prepared formulations were evaluated mainly for percent weight variation, percent drug content, Mucoadhesion strength, Mucoadhesion time and *In vitro* release pattern.

After Preformulation study, the formulations of Mucoadhesive tablet containing simvastatin/atorvastatin were done by taking into consideration the formulation variables like, HPMC K100M, POLYOX 303, Carbopol 934P and Guar Gum, using “First line of Plackett-burman design”. By applying this design eight formulations were prepared and parameters like weight variation, percent drug content, Mucoadhesion strength, Mucoadhesion time and *In vitro* release pattern of prepared Mucoadhesive tablet were evaluated.

The mechanism of release, followed by the above formulations was determined by finding the R^2 value for each kinetic model viz. Zero-order, First-order, Higuchi and Korsmeyer-Peppas corresponding to the release data of each formulation. For most of the simvastatin formulations the R^2 value of First order and korsmeyer-peppas is very near to 1 than the R^2 values of other kinetic models. Thus it can be inferred that the drug release follows first order mechanism. The n values of Korsmeyer-Peppas model of all formulations are

0.501 to 0.810. It indicate the almost in most cases a non-Fickian mechanism is dominant.

Whereas in atorvastatin formulation R^2 value of First order and korsmeyer-peppas model is very near to 1 than the R^2 values of other kinetic models. Thus it can be inferred that the drug release follows first order and korsmeyer-peppas mechanism. The n values of Korsmeyer-Peppas model of all formulations are 0.526 to 0.767. It indicate the almost in most cases a non-Fickian mechanism is dominant.

The *in-vitro* mucoadhesion test showed that the mucoadhesion of tablet of all the batches of the plackett burman design, were good enough to adhere to gastric mucosa. The linear model generated for mucoadhesion strength was found to be significant with an *F*-value of 5.738 ($p<0.05$) and R^2 value of 0.9348: for Simvastatin dosage form Mucoadhesion strength (SIM) = *15.5+0.017X1 +0.275X2+0.188X3+0.063X4+0.031X5-0.625X6-0.250X7.* The linear model generated for mucoadhesion strength was found to be significant with an *F*-value of 8.242 ($p<0.05$) and R^2 value of 0.9537: for Atorvastatin dosage form, Mucoadhesion strength (ATS) = *14.4 +0.022X1 +0.293X2 +0.189X3+ 0.061X4 +0.022X5-0.538X6-0.175X7.*

It can be concluded from the above equation that HPMC K4M (X1), POLYOX 303 (X2), Carbopol 934P (X3), Guar Gum (X4), exhibited positive effect on Mucoadhesion strength on increasing the concentration of POLYOX and CARBOPOL 934P. In the above polynomial equation showed that the maximum mucoadhesion was achieved by the POLYOX 303. From the results, it can be

concluded that some variables have to be minimized and some variables have to maximize to have desirable responses.

From the eight formulation of simvastatin, the formulation number SM5 was chosen as it has 68.6% release at 12 hr, near to 100% release at 24 hr, good mucoadhesive strength and good mucoadhesion time which gives the first order release kinetic and from the eight formulation of Atorvastatin, the formulation number AM5 was chosen as it had 59.7% release at 12 hr and near to 98.3% release at 24 hr, High mucoadhesive strength and high mucoadhesion time, which gives the first order release kinetic.

The final optimized formulation were kept for stability study at 40ºC / 75% RH condition and after every week drug content and drug release were estimated. After 3 month of stability data there was no significant change in drug content and drug release.

7. CONCLUSION

The main aim the present dissertation was to minimize the liver extraction ratio by controlling the release of drug from the dosage form. Thus gastroretentive dosage form was formulated to achieve the above aim. These systems proved to give better efficacy by minimizing extraction ratio.

Thus from the data obtained, it can be concluded that:

- Gastroretentive dosage form of an antihyperlipidemic drug simvastatin/atorvastatin formulated as an approach to increase gastric residence time and thereby minimizing hepatic extraction ratio.
- Among the polymers used to improve the gastric residence, cellulose polymers HPMC K4M, HPMC K100M, showed better control over drug release, and POLYOX 303, Carbopol 934P showed good control on mucoadhesive strength.
- Formulated capsules and tablets gave satisfactory results for various physicochemical evaluation for capsules like Weight variation, Floating lag time, Content uniformity, Total floating time, Mucoadhesion time, mucoadhesive strength and *in vitro* drug release.
- Formulated gastroretentive dosage form best fitted to Korsmeyer-peppas and First-order model rate kinetics.
- Further it is concluded that, by the application of optimization technique,

  Optimized formulation can be obtained with minimum expenditure of time and money.
- *In vivo* study showed that optimized tablet and capsule formulation were retained in stomach for more than eight hours.

- Thus the objective of the work of formulating a gastroretentive dosage form of Simvastatin and atorvastatin to minimize hepatic extraction has been achieved with success.

8. SUMMARY

In the present study Gastroretentive delivery systems of simvastatin/atorvastatin has been successfully developed in the form of Hydrodynamically Balanced Tablet, Mucoadhesive Tablet, High Density Tablet and Hydrodynamically Balanced capsule to improve local action.

Initial trials were for checking the effect of various ingredients on the floating, mucoadhesive characteristics of the dosage form.

First line of Plackett-burman design is an experimental design technique, by which the factors involved and their relative importance can be assessed. The tablets and capsule were formulated using different grades of polymers (HPMC K4M, HPMC K100M, Cross carmellose sod., Sod Starch glycolate, MCC 101, Mg. Al. silicate, Eudragit RS) and effervescing agent ($NaHCO_3$), POLYOX 303, carbopol 934P, Guar Gum, for mucoadhesive polymer and titanium dioxide for the high density material.

The evaluation parameters like content uniformity were within the limits for various batches formulated. Another most important parameter like *in vitro* drug release was also performed. Formulations subjected to curve fitting analysis showed to best fit Korsmeyer-peppas and first order equation.

Optimized formulations were obtained using constraints on drug release at 12 hr (% CDR), at 24 hr (%CDR), Floating lag time, total floating time, Mucoadhesive strength and ‘n’ of korsmeyer-peppas coefficient.

The optimized formulations were evaluated for the responses. The actual response values were in accordance with the predicted values.

The final optimized formulation were kept for stability study at 40ºC / 75% RH condition and after every week drug content and drug release were estimated. After 3 month of stability data there was no significant change in drug content and drug release.

Animal study was carried out for the above suitable optimized formulation. The Total cholesterol was estimated in treated animal group. Animal study data shows the there was significant difference in control and formulation treated group but there was no significant difference in pure drug and formulation treated group.

In vivo buoyancy time for tablet and capsule were evaluated by X-ray studies. In vivo study showed that the optimized tablet formulation was retained in stomach for more than eight hours.

9. BIBLIOGRAPHY

1) D.R.Laurence, P.N.Bennett. “Clinical pharmacology”. Churchill Livingstone NY. 8th edition: 482.

2) H.P. Rang, M.M. Dale. “pharmacology”. Churchill Livingstone NY. 3rd edition: 306.

3) Shen Danny, Thummel Kenneth. Goodman and Gilman’s “The pharmacological basis of therapeutics”. 2007.

4) Gable KN. Hyperlipidemia drug class formulary review. Statewide pharmacy and therapeutics committee. March 17, 2006.

5) Michael Schachter. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update, Fundamental & Clinical Pharmacology 2004; 19:117–125.

6) McClelland GA, Stubbs RJ, Fix JA. Enhancement of 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitor Efficacy Through administration of a controlled porosity osmotic pump. Pharma Res 1991; 8(7):873-6.

7) Cheng H, Sutton SC, Pipkin JD, Zetner GM. Evaluation of sustained/controlled-release dosage forms of 3-hydroxy-3-methylglutararyl-coenzyme A (HMG-CoA) reductase inhibitorsin dogs and humans. Pharma Res 1993; 10(11):1683-7.

8) Date A and Nagarsenker M. Novel delivery systems of atorvastatin should be evaluated for pharmacodynamics instead of pharmacokinetics. 2007; JPP, 59: 1583–1584.

9) Camelia Stancu, Anca Sima. Statins: mechanism of action and effects. J.Cell.Mol.Med. 2001; 5(4):378-387.

10) http://repoll.pharmacy.ulberta.ca/drug_bank/ (accessed date June 11 2011).

11) Lennernas, H. (2003) Clinical pharmacokinetics of atorvastatin.

Clin. *Pharmacokinet***.** 42: 1141–1160.

12) Eisen, S.A., Miller, D.K., Woodward, R.S., Spitznagel, E., Przybeck, T.R.,. The effect of prescribed daily dose frequency on patient medication compliance. 1990, Arch. Intern. Med. 150, 1881-188.

13) Longer, M.A., Robinson, J.R., 1990. Sustained-release drug delivery systems, in: A.R. Gennaro (Ed.), Remington's Pharmaceutical Sciences, 18th ed. Mark Easton Publishing Company, New York, p. 1676.

14) Kumar, M.N., Kumar, N., 2001. Polymeric controlled drug-delivery systems: perspective issues and opportunities. Drug Dev. Ind. Pharm. 27, 1-30.

15) Siepmann, J., Siepmann, F., 2008. The Modified-Release Drug Delivery Landscape: Academic Viewpoint, in: Rathbone, M.J., Hadgraft, J., Roberts, M.S., Lane, M.E. (Eds.), Modified release drug delivery technology, Second ed. Informa Healthcare USA, Inc., New York, pp. 17-34.

16) Hoichman, D., Gromova, L.I., Sela, J., 2004. Gastroretentive controlled-release drugs. Pharmaceutical Chemistry Journal 38, 621-624.

17) Rocca DJG, Omidian H, Shah K. Progresses in gastroretentive drug delivery systems. Business briefing Pharmatech 2003; 152-6.

18) Garg S, Sharma S. Gastroretentive drug delivery systems. Business Briefing Pharmatech 2003; 160-66.

19) Arora S, Ali J, Ahuja A, Khar RK. Floating drug delivery system: A review. AAPS PharmsciTech.2005; 6:E47.

20) Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur J Pharm Biopharm 2003; 18: 37-45.

21) Swarbrick J, Boylan JC. Encyclopedia of pharmaceutical technology. vol.3 (NY and Basel): Marcel Dekker, INC; 1990.

22) Ichikawa M, Watanabe S, Miyake Y. A New multiple-unit oral floating dosage system. I: Preparation and in-vitro evaluation of floating and sustained-release characteristics. J Pharma Sci 1991;80 (11):1062-6.

23) Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Contr Rel 2000; 63: 235-59.

24) Kim CJ. Controlled Release Dosage Form Design, Lancaster (Basel): Technomic Pub; 2000.

25) Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for floating drug delivery system: effects of CO_2 gas-forming agents. Int J Pharm 2002; 239: 81-91.

26) Murthy RSR, Reddy LHV. Floating dosage system in drug delivery. Crit Rev Ther Drug Carrier Sys 2000; 19 (6): 98-134.

27) Desai S, Bolton S. A floating controlled-release Drug Delivery system: In-vitro – in vivo Evaluation. Pharma Res. 1993; 10:1321-5.

28) Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a Novel controlled-release system for gastric retention. Pharma Res 1997; 14(6): 815-9.

29) Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int J Pharm 1996; 136: 117-39.

30) Whitehead L, Collett JH, Fell JT. Amoxycillin release from a floating dosage form based on alginates. Int J Pharm 2000; 210: 45-9.

31) Davis SS, Stockwell AF, Taylor MJ, Hardy JG, Whalley DR, Wilson CG et al. The effect of density on the gastric emptying on single and multiple unit dosage forms. Pharma Res 1986; 3: 208-13.

32) Bechgaard H, Ladefoged K. Distribution of pellets in the gastrointestinal tract: The influence on transit time excreted by the density or diameter of pellets. J Pharma Pharmacol 1978; 30: 690-92.

33) Lenaerts VM, Gurny R. In: Bioadhesive drug delivery system. Boca Raton (FL): CRC Press; 1990.

34) Lehr CM. Bioadhesion technologies for the delivery of peptide and protein drugs to the gastrointestinal tract. Crit Rev Ther Drug Carrier Syst 1994; 11: 119-60.

35) Jimenez-Castellanos MR, Zia H, Rhodes CT. Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm1994; 105: 65-70.

36) Chitnis VS, Malshe VS, Lalla JK. Bioadhesive polymers synthesis, evaluation and application in controlled release tablets. Drug Dev Ind Pharm 1991; 17: 879-92.

37) Urquhart J, Theeuwes F. Drug delivery system comprising a reservoir containing a plurality of tiny pills. US Patent 4,434,153. 1984 Feb 28.

38) Mamajek RC, Moyer ES. Drug-dispensing device and method. US Patent 4,207,890. 1980 June 17.

39) Groning R, Heun G. Dosage forms with controlled gastrointestinal passage-studies on the absorption of nitrofurantoin. Int J Pharm 1989; 56: 111-16.

40) Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Dev Ind Pharm 1984; 10: 527-39.

41) Todd RS, Fryers GR. Cholestyramine compositions and method for treating biliary gastritis. US Patent 4,172,120. 1979 Oct 23.

42) Kopitar Z, Vrhovac B, Povsic L, Plavsic F, Francetic I, Urbancic J. The effect of food and metoclopramide and side effects of bromocriptine. Eur J Drug Metab Pharmacokinet 1991; 16: 177-81.

43) Atyabi F, Sharma HL, Mohammad HAH, Fell JT. In vivo evaluation of a novel gastroretentive formulation based on ion exchange resins. J contr Rel 1996; 42: 105-13.

44) Chein YW. Novel drug delivery systems. 2nd ed. (NY): Marcel Dekker, INC; 1992.

45) Clarke GM, Newton JM, Short MB. Comparative gastrointestinal transit of pellet system of varying density. Int J Pharm 1995; 114: 1-11.

46) Kawashima Y, Niwa H, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci 1992; 81: 135-40.

47) Sato Y, Kawashima Y, Takeuchi H. In vitro in vivo evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans. Int J Pharm. 2004;275:97-107.

48) Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J contr Rel 2003; 90: 143-62.

49) Sheth PR, Tossounian JL. Novel sustained release tablet formulation. US Patent 4,167,558. 1979 Sep 11.

50) Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int J Pharm 1996; 136: 117-39.

51) Sheth PR, Tossounian J. The hydrodynamically balanced system (HBS™): a novel drug delivery system for oral use. Drug Dev Ind Pharm 1984; 10: 313-39.

52) Ponchela G., Iracheb JM Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. Advanced Drug Delivery Reviews 34 (1998) 191–219.

53) Raymond CR, Qaul LS and Qaul LM. Handbook of pharmaceutical excipients.4th Edn., Published by the Pharmaceutical Press, Royal Pharmaceutical Society of Great Britain.89-110.

54) Dow chemical company. Technical literature: 2011.

55) Ballantyne CM, Blazing MA. Effect on high-density lipoprotein cholesterol of maximum dose simvastatin and atorvastatin in patient with hypercholesterolemia : Result of the comparative HDL efficacy and safety study (CHESS). Am Heart J 2003;146:862-9.

56) Sobal G., Sinzinger H. Effect of simvastatin on the oxidation of native and modified lipoproteins. Bioche Pharmaco. 2005;70:1185-1191

57) Pandya P, Gattani S, Jain P, Khirwal L, Surana S. Co-solvent Evaporation Method for Enhancement of Solubility and Dissolution Rate of Poorly Aqueous Soluble Drug Simvastatin: In vitro–In vivo Evaluation. AAPS PharmSciTech, 2008; 9(4).

58) Maurya, D, Belgamwar V, Tekade A. Microwave induced solubility enhancement of poorly water soluble atorvastatin calcium. JPP 2010; 62: 1599–1606.

59) Khan, Furquan, Dehghan, Mohamed. Enhanced Bioavailability of Atorvastatin Calcium from Stabilized Gastric Resident Formulation. AAPS PharmSciTech 12(4): 1077-1086.

60) Lakshmi NV, Bhaskar.J, Venkateswarlu.G, Kanakam V B. Enhancement of dissolution rate of atorvastatin calcium using solid dispersions by dropping method. International Journal of PharmTech Research 2011; 3(2):652-659.

61) Mohammed A , Musarrat H W, Mallick N , Akhter S , Gahoi S et al. Enhanced bioavailability of nano-sized chitosan–atorvastatin conjugate after oral administration to rats. Eur J Pharm 2011.

62) Rao M, Mandage Y, Thanki K, Bhise S. Dissolution Improvement of Simvastatin by Surface Solid Dispersion Technology. Dissolution Technologies 2010.

63) Taízia D S, Valquíria T A, Jackson A L C, Nivaldo L. S et al. Preparation and characterization of solid dispersion of simvastatin. Drug Dev Ind Pharm 2010; 36(11): 1348–1355.

64) Shen H R , Zhong M K. Preparation and evaluation of self-microemulsifying drug delivery systems (SMEDDS) containing atorvastatin. JPP 2006; 58: 1183–1191.

65) Michael A B ,Christie M B, Donald B H, Michael H D. Effect on high-density lipoprotein cholesterol of maximum dose simvastatin and atorvastatin in patients with hypercholesterolemia: Results of the Comparative HDL Efficacy and Safety Study (CHESS). Am Heart J 2003; 146:862–9.

66) Sheth PR, Tossounian JL. Sustained release Pharmaceutical capsules. US Patent 4,126,672. 1978 Nov 21

67) Ikura; Suzuki; Nagai; Yoshiki. Oral sustained release pharmaceutical preparation. US Patent 4,777.033 October 1988.

68) Timmermans J, Moes AJ. Apparatus and method for resultant-weight measuring system. US Patent 5,076,107. 1991 Dec 31.

69) Krogel I, Bodmeier R. Development of a multifunctional matrix drug delivery

system surrounded by an impermeable cylinder. J Contr Rel 1999; 61: 43-50.

70) Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int J Pharm 2003; 253: 13-22.

71) Gohel MC, Mehta PR. A more relevant dissolution method for evaluation of floating drug delivery system. Dissolution Technologies. 22-25, 2004.

72) Streubel A, Siepmann J Bodmeire R. Floating matrix tablets n low density foam powder: effect of formulation and processing parameters on drug release. Eur J Pharm 2003;18:37-45.

73) Chavanpatil M, Jain P, Chaudhari S. Development sustained release gastroretentive drug delivery system for ofloxacin: In viro and in vivo evaluation. Int J Pharm. 2005;304:178-84.

74) Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000; 195: 125-35.

75) Krogel I, Bodmeier R. Floating or pulsatile drug delivery system based on coated effervescent cores. Int J Pharm 1999; 187: 175-84.

76) Gerogiannis VS, Rekkas DM, Dallas PP, Choulis NH. Floating and swelling characteristics of various excipients used in controlled release technology. Drug Dev Ind Pharm 1993; 19 (9): 1061-81.

77) Wei Z, Yu Z, Bi D. Design and evaluation of a two-layer floating tablet for gastric retention using cisapride as a model drug. Drug Dev Ind Pharm 2001; 27 (5): 469-74.

78) Talwar N. Orally Administered Controlled Drug delivery System providing temporal and spatial control. WO 00/15198. 2000 Mar 23.

79) Chen GL, Hao WH. In Vitro performance of floating sustained-release capsule of verapamil. Drug Dev Ind Pharm 1998; 24 (11): 1067-72.

80) Dave B. S., Amin A F., and Patel.M M. Gastroretentive Drug Delivery System of Ranitidine Hydrochloride: Formulation and In Vitro Evaluation. *AAPS PharmSciTech* 2004; 5 (2)**:** Article 34.

81) Shishu, NG, Aggarwal N. A gastro-retentive floating delivery system for 5-fluorouracil. Asian Journal of Pharmaceutical Sciences 2007, 2 (4): 143-149

82) Shah SS, Pandya SJ, Waghulade MK. Development and investigation of gastroretentive dosage form of weakly basic drug. Asian J Pharm 2010;4:11-6

83) Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro–in vivo evaluation in healthy human volunteers. European Journal of Pharmaceutics and Biopharmaceutics 2010; 74:332–339.

84) Zate SU, Kothawade1 PI, Rathi MN, Shitole MH. Development and characterization of gastroretentive mucoadhesive tablets of venlafaxine hydrochloride. International Journal of Drug Delivery 2010; 2: 299-303.

85) Bhise K, Rub R A, Rahil M G, Shah S K et al. Development of Gastroretentive Drug Delivery System for Ketoconazole: *In-Vitro* and *In-Vivo* Evaluation. Inventi Impact: NDDS Vol. 1(1).

86) Prajapati,S Patel L Patel C Floating Matrix Tablets of Domperidone Formulation and Optimization Using Simplex Lattice Design. Iranian Journal of Pharmaceutical Research (2011), 10 (3): 447-455

87) Chandira R M , Bhowmik D, Chiranjib, Jayakar B. Formulation And Evaluation Of Gastroretentive Drug Delivery System Of Gastroprokinetic Drug Itopride Hydrochloride. International Journal Of Pharmacy And Pharmaceutical Sciences 2010; 2(1).

88) Patel JK, Chavda JR. Formulation and Evaluation of Glipizide Floating-Bioadhesive Tablets. Brazilian Archives of Biology and Technology 2010; 53(5):1073-1085.

89) Dias R J, Sakhare S S, Malic K K. Design and Development of Mucoadhesive Acyclovir Tablet. Iranian Journal of Pharmaceutical Research (2009); 8 (4): 231-239.

90) Jagdale S C, Agavekar A J, Pandya S V, Bhanudas S. Formulation and Evaluation of Gastroretentive Drug Delivery System of Propranolol Hydrochloride .AAPS PharmSciTech 2009; 10(3).

91) Khan Fs, Razzak S M Ibn, Khan Z R, Kalam Azad M A. Theophylline Loaded Gastroretentive Floating Tablets Based On Hydrophilic Polymers: Preparation And *In Vitro* Evaluation. Pak. J. Pharm. Sci. 2009;.22(2):155-161.

92) Srisagul S , Sriamornsak P , Puttipipatkhachorn S. Design and evaluation of floating multi-layer coated tablets based on gas formation. European Journal of Pharmaceutics and Biopharmaceutics 2008;69: 255–263.

93) Ali Javed, Arora S, Ahuja A, Babbar A K, Sharma R K. Formulation and Development of Floating Capsules of Celecoxib: In Vitro and In Vivo Evaluation. AAPS PharmSciTech 2007; 8 (4) Article 119.

94) Krishna S S, Ray S, Thakur R S. Formulation And Evaluation Of Mucoadhesive Dosage Form Containing Rosiglitazone Maleate**.** Pak. J. Pharm. Sci. 2006;19(3):208-213.

95) Singh B, Kaur S C, Ahuj N. Formulation and Optimization of Controlled Release Mucoadhesive Tablets of Atenolol Using Response Surface Methodology. AAPS PharmSciTech 2006; 7 (1).

96) Srivastava A K, Wadhwa S, Ridhurkar D, Mishra B. Oral Sustained Delivery of Atenolol from Floating Matrix Tablets-Formulation and In Vitro Evaluation. Drug Dev Ind Pharm 2005; 31:367–374.

97) Chowdary, K P R, Suresh B, Sangeeta B, Reddy G K. Design And Evaluation Of Diltiazem Mucoadhesive Tablets For Oral Controlled Release. Saudi Pharmaceutical Journal 2003; 11(4).

98) Nur AO, Zhang J S. Captopril Floating and/or Bioadhesive Tablets: Design and Release Kinetics. Drug Dev Ind Pharm 2000; 26(9):965–969.

99) Cnez-Castellanos M. R, Zia H, Rhodes C T. Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm 1994; 105:65-70.

100) Li S, Lin S, Chien Y W, Daggy B P, Mirchandani H L. Statistical Optimization of Gastric Floating System for Oral Controlled Delivery of Calcium. AAPS PharmSciTech 2001; 2 (1) article 1.

101) Barata P, Múrias I, Bettini R, Oliveira R. Production and Evaluation of a high-density gastroretentive delivery system of ranitidine.

102) Milen Dimitrov, Nikolai Lambov. Study of Verapamil hydrochloride release from compressed hydrophilic Polyox-Wsr tablets. Int J Pharm 189 (1999) 105–111

103) Muhammad AM, Zafar Iqbal, Steven HN. Guar Gum, Xanthan Gum, and HPMC Can Define Release Mechanisms and Sustain Release of Propranolol Hydrochloride. AAPS PharmSciTech, 2011; 12(1).

104) Seyed Am The Effect Of Hydroxyl Containing Tablet Excipients On The Adhesive Duration Of Some Mucoadhesive Polymers. DÁRU 2004;12,(1): 11.

105) Parka J S, Shima J Y. A pharma-robust design method to investigate the effect of PEG and PEO on matrix tablets. Int J Pharm 2010; 393:79–87.

106) Sarojini S, Arivazagan D, Manavalan R, Jayanthi V. Buoyant Sustained Release Tablets Based On Polyethylene Oxide. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2l (1).

107) Panigrahy R N, Mahale A M, Sakarkar D M. Design development and *in vitro* testing of a combined bioadhesive-floating oral drug delivery system. Journal of Pharmacy Research 2011; 4(7):2212-2215.

108) Hongtao Li, Robert J. Hardy, Xiaochen Gu. Effect of Drug Solubility on Polymer Hydration and Drug Dissolution from Polyethylene Oxide (PEO) Matrix Tablets. AAPS PharmSciTech 2008; 9(2).

109) Mahalingam R, Jasti B, Birudaraj R, Stefanidis D et al. Evaluation of Polyethylene Oxide Compacts as Gastroretentive Delivery Systems. AAPS PharmSciTech 2009; 10(1).

110) Li S, Lin S., Daggy B P, Mirchandani H L, Chien Y W. Effect of HPMC and Carbopol on the release and floating properties of Gastric Floating Drug Delivery System using factorial design. Int J Pharm 2003; 253:13–22.

111) Dandu R., Kona R, . Fahmy R, Bensley D, Hoag S. Application of Plackett-Burman design of experiments (DOE) to describe product design space: Identification of critical formulation and process variables. AAPS Annual Meeting and Exposition 2009.

112) Orlewicz K W, Jachowicz R. Analysis Of Wet Granulation Process With Plackett-Burman Design- Case Study. Acta Poloniae Pharmaceutica and Drug Research 2011; 68(5): 725-733.

113) El-Malah Y, Sami N. Hydrophilic matrices: Application of Placket–Burman screening design to model the effect of POLYOX–carbopol blends on drug release. Int J Pharm 2006; 309:163–170.

114) Jain S P, Singh P P, Javeer S, Amin P D. Use of Placket–Burman Statistical Design to Study Effect of Formulation Variables on the Release of Drug from Hot Melt Sustained Release Extrudates. AAPS PharmSciTech, 2010; 11(2).

115) Sastry S V, Khan M A. Aqueous based polymeric dispersion: Plackett–Burman design for screening of formulation variables of Atenolol

Gastrointestinal Therapeutic System. Pharmaceutical Acta Helvetiae 1998; 73: 105–112.

116) Zhang Y, Huo M, Zhou J, Zou A, Li W. DDSolver: An Add-In Program for Modeling and Comparison of Drug Dissolution Profiles. The AAPS Journal 2010; 12(3).

117) Lewis G. Didier M. Pharmaceutical Experimental Design. 3rd ed (NY): Marcel Dekker, INC; 1990;

118) Bolton S, Bon C. Pharmaceutical Statastics, Practicle and clinical application. 3rd ed (NY): Marcel Dekker, INC; 2004: 535-337.

119) Maximo C. Gacula, Design and analysis of sensory optimization. food & nutrition press Trumbull, connecticut USA.

120) Martin A, Bustamante P, Chun AHC. Physical Pharmacy. 4th ed. B.I.Waverly Pvt Ltd New Delhi: 1999.

121) Higuchi WI. Diffusional models useful in biopharmaceutics-drug release rate processes. J Pharm Sci 1967; 56 (3): 315-24.

122) Peppas NA, Ritger PL. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J Control Release. 1987;5 (1):37-42.

123)Pund S, Joshi A, Vasu K, Nivsarkar M, Shishoo C, Multivariate optimization of formulation and process variables influencing physico-mechanical characteristics of site-specific release isoniazid pellets. Int J Pharm 2010; 388: 64–72.