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DEVELOPMENT AND CHARACTERIZATION OF A FLOATING DRUG DELIVERY SYSTEM FOR THE EFFECTIVE MANAGEMENT OF HYPERLIPIDEMIA

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1.1 ABSTRACT

Hyperlipidemia is one of the major risk factors responsible for cardiovascular diseases, affecting millions of people worldwide. Conventional oral dosage forms of antihyperlipidemic drugs often exhibit limited gastric residence time, resulting in reduced bioavailability and therapeutic efficacy. Floating Drug Delivery Systems (FDDS), classified under gastroretentive drug delivery systems, have emerged as an effective strategy to prolong gastric residence time and improve drug absorption in the upper gastrointestinal tract. The present study aims to formulate and characterize a floating drug delivery system containing an antihyperlipidemic drug to enhance gastric retention, sustain drug release, improve patient compliance, and maximize therapeutic outcomes. Various formulation approaches involving hydrophilic polymers, gas-generating agents, and controlled-release excipients are evaluated. The prepared formulations are characterized for physicochemical properties, buoyancy behavior, swelling index, in vitro drug release, release kinetics, stability studies, and compatibility using advanced analytical techniques. The optimized formulation is expected to demonstrate prolonged floating duration, controlled drug release over 12–24 hours, improved bioavailability, and better lipid-lowering efficacy compared to conventional formulations.

KEYWORDS: Floating Drug Delivery System, Hyperlipidemia, Gastroretentive Drug Delivery, Sustained Release, Buoyancy, Controlled Drug Delivery.

INTRODUCTION

Novel drug delivery system is a system for delivery of drug other than conventional drug delivery system. It is advanced drug delivery system which improve drug potency, control drug release to give a sustained therapeutic effect, provide greater safety, finally it is to target a drug specifically to a desired tissue.

A system that formulates or device that delivers therapeutic agent(s) to desired body location(s) and/or provides timely release of therapeutic agent(s), such a system by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called Drug Delivery Systems (DDS).

To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development.

The therapeutic benefits of novel drug delivery system include

- Increased efficacy of the drug.
- Site specific delivery.
- Decreased toxicity/side effects.
- Increased convenience
- Viable treatments for previously incurable diseases
- Potential for prophylactic applications
- Lower healthcare costs - both short and long term
- Better patient compliance.

1.2. Floating Drug Delivery Systems:- Floating systems (hydro-dynamically balanced systems) are systems capable to float over the gastric content for prolonged period of time without affecting gastric emptying rate **(Kawatra *et al.*, 2012).** This feature is due to the lower bulk density these systems poses compared with gastric fluids. By remaining buoyant these systems prolong the gastric residence time and also release the active compound in a slow and controlled manner which leads to better control over the plasma concentration levels (**Kumar *et al.*, 2011**). Usually floating systems are prepared from different kinds of hydrophilic polymers. When introduced into aqueous medium they swell and form outer cohesive gel layer, which improves system's floatability. Because of the hydrophilic nature these polymers allow controlled drug release both by diffusion and erosion. After releasing active compound the residual system is removed from the stomach area by contractile forces. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach **(Singh *et al.*, 2000).** Hollow microspheres (micro-balloons) are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200µm. Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration **(Patel *et al.*, 2011).**

Several conditions should be accomplished in order buoyancy to occur: **(Nayak *et al.*, 2010)**

- The system should have lower bulk density than the gastric content (<1.004 g/cm3).
- The stomach should contain at least minimal gastric content.
- The system should poses sufficient floating force in order to remain buoyant over the gastric fluids.

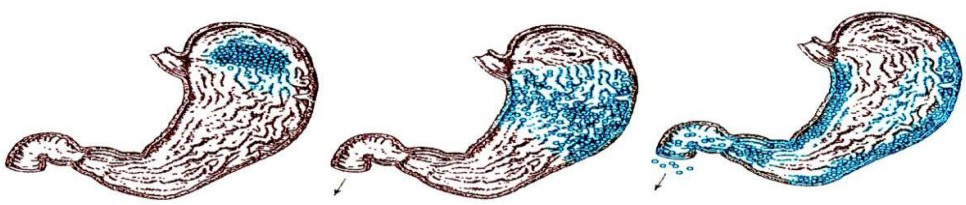


Figure 1.1: (A) Microspheres Float On Stomach Contents (B) & (C) Micropsheres Adheres To Stomach Wall during Gastric Emptying.

Floating systems could be designed and produces both as single and multiple unit dosage forms. Single units are represented by floating tablets and capsules, while multiple units could be designed in systems such as hollow microspheres, mini tablets, pellets, granules, alginate beads etc. Multiple unit systems show advantages over single unit systems since they overcome problems such as irreproducible and unreliable drug release, they reduce intra- and inter-subject variability in drug release and absorption and decrease the possibility of dose dumping.

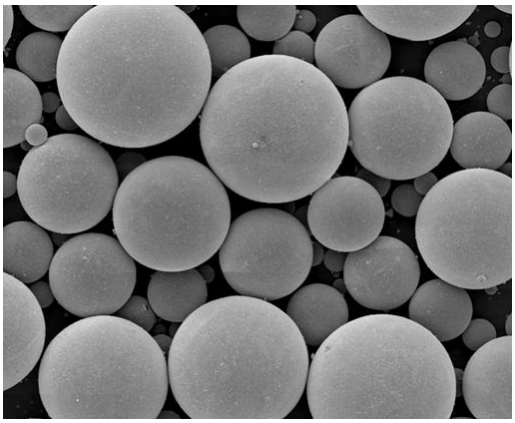


Figure 1.2: Floating Microspheres.

1.3 Advantages of Floating Microspheres (Mayavanshi *et al.*, 2008)

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration.

- It releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.
- Improved receptor activation selectivity.
- Extended time over critical (effective) concentration.
- Extend patent protection, globalize product, and provide new business opportunities.
- Site-specific drug delivery to stomach can be achieved.

1.4 Method of Preparation of Floating Microspheres

1.4.1 Solvent Evaporation Method

Floating multiparticulate dosage form can be prepared by solvent diffusion and evaporation

methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing suitable additive (surfactants / polymer) to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring **(Streubel *et al.*, 2002), (Kale *et al.*, 2001).** The solvent removal leads to polymer precipitation at the oil/water interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, Eudragit, Acrycoat, Methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide and polycarbonates.**(Muthuamy *et al.*, 2005).**

1.4.2 Ionotropic Gelation Method

Ionotropic gelation is based on the ability of poly electrolytes to cross link in the presence of counter ions to form beads. Since, the use of alginates, gellan gum, chitosan and carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose**(Streubel *et al.*, 2002).** The natural poly electrolytes in spite, having property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations.

1.4.3 Emulsion Solvent Diffusion Method

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse in to the droplets by which drug crystallizes.

1.5 Classification of Floating Drug Delivery System

Based on the mechanism of buoyancy, floating systems can be classified into two distinct categories *viz*. non-effervescent and effervescent systems.

1.5.1. Non-Effervescent systems

1.5.1.1 Colloidal gel barrier systems

Hydrodynamically balanced system (HBS) of this type contains drug with gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers. They help prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption. These systems incorporate high levels (20 to 75 % w/w) of one or more gel forming highly swellable cellulose type hydrocolloids e.g. hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC) hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (NaCMC) incorporated either in tablets or capsules. When such a system comes in contact with the gastric fluid, the hydrochloride in the system hydrates and forms a colloidal gel barrier around its surface. This gel barrier controls the rate of the fluid penetration into the device and consequent release of drug from it. As the exterior surface of the dosage form goes in to the solution, the adjacent hydrochloride layer becomes hydrated and thus maintains the gel layer. The air trapped inside the swollen polymer maintains the density less than unity and confers buoyancy to these dosage forms. **(Reddy *et al*., (2002) (Bardonnet P.L *et al*., (2006)**

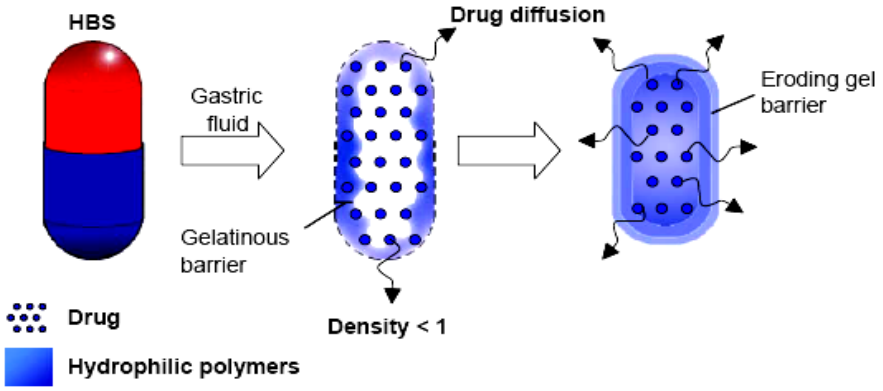


Figure 1.7: Hydrodynamically balanced system.

The HBS must comply with following three major criteria

1. It must have sufficient structure to form cohesive gel barrier.
2. It must maintain an overall specific density lower than that of gastric contents.
3. It should dissolve slowly enough to serve as reservoir for the delivery system.

1.5.1.2 Microballoons/ Hollow microspheres

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods to prolong

the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours **(Garg *et al.*, (2008)**. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

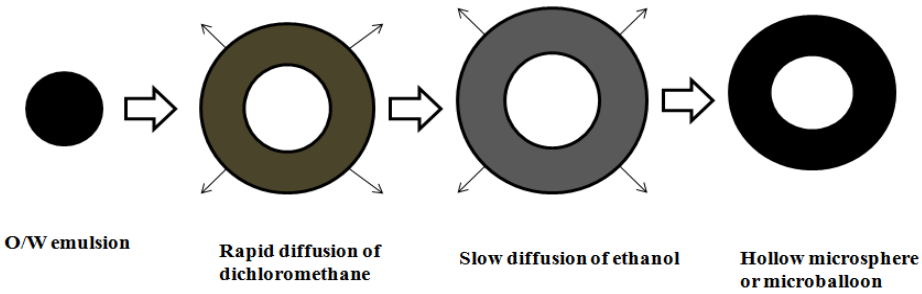


Figure 1.8: Formulation of floating hollow microsphere or microballoon.

1.5.2 Effervescent (gas generating) systems

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid) **(Harrigan *et al.*, (1977).** Bilayer or multilayer system has also been designed. **(Ingani *et al.*, (1987).** Drugs and excipients can be formulated independently and the gas generating material can be incorporated in to any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of the polymers.

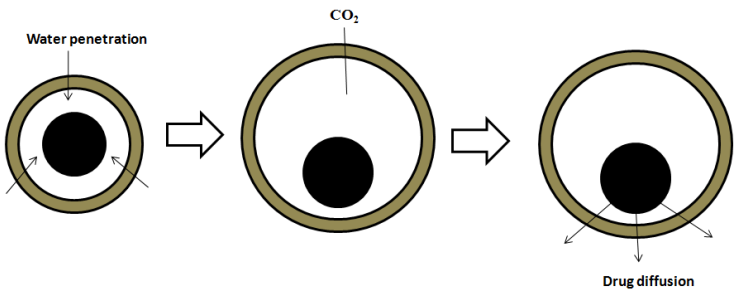


Figure 1.9: Drug release from effervescent (gas generating) systems.

1.5.3 Bio adhesive or Mucoadhesive drug delivery Systems

Bio adhesive 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.

1.5.4 Expandable, unfoldable and swellable systems

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations **(Klusner *et al.*, (2003)** are required to develop an expandable system to prolong gastric retention time (GRT):

1) A small configuration for oral intake,
2) An expanded gastroretentive form, and
3) A final small form enabling evacuation following drug release from the device.

Thus, gastroretentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery.

1.6 Hyperlipidemia

Hyperlipidemia, hyperlipoproteinemia, or hyperlipidaemia involves abnormally elevated levels of any or all lipids and/or lipoproteins in the blood. It is the most common form of dyslipidemia (which includes any abnormal lipid levels). It is a heterogeneous group of disorders characterized by an excess of lipids in the bloodstream. These lipids include

cholesterol, cholesterol esters, phospholipids, and triglycerides. Lipids are transported in the blood as large 'lipoproteins.[1]

Lipoproteins are divided into five major classes, based on density: chylomicrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Most triglyceride is transported in chylomicrons or VLDL, and most cholesterol is carried in LDL and HDL.

Primary hyperlipidemias are probably genetically based, but the genetic defects are known for only a minority of patients. Secondary hyperlipidemia may result from diseases such as diabetes, thyroid disease, renal disorders, liver disorders, and Cushing's syndrome, as well as obesity, alcohol consumption, estrogen administration, and other drug-associated changes in lipid metabolism. **(Bassam Abdul Rasool Hassan., 2013).**

Table 1.1: Classification of LDL and Total Cholesterol Levels in Adolescents.

Lipid Profile	Acceptable	Borderline	High
Total Cholesterol	<170mg/dl	170 – 199mg/dl	≥200mg/dl
LDL Cholesterol	<110mg/dl	110 – 129mg/dl	≥130mg/dl

1.6.1 Diagnosis of Hyperlipidemia

In this part the patients have to fast for at least 12 hours before taking the blood sample, the main reason for this is that chylomicron clearance required at least 10 hours. The laboratory test for this case mainly focuses on the lipid profile i.e., measure lipid profile which include total plasma cholesterol, HDL, LDL, VLDL and triglycerides levels. The mathematical way to calculate the VLDL is by dividing triglyceride value by 5, while for LDL it can be calculated by subtracting HDL cholesterol and VLDL cholesterol from total plasma cholesterol value.

1.6.2 Managements for Hyperlipidemia

The major treatment used for hyperlipidemia divided into three parts which are:

• **Dietary control:** This point focus on reducing intake of foods that contain high amount of saturated fat and cholesterol i.e., foods of animal origin. On the other hand this point will encourage intake of food or supplements that include fish oil or olive oil which include a very low concentration of saturated fat focusing on intake of vegetarian foods which are free of cholesterol. These types of food will significant play role in reducing elevated triglyceride levels.

• **Lifestyle change:** This will include focusing on daily exercises, since regular exercises will lead to an improvement within lipid concentrations i.e., daily walking will reduce triglyceride level by an average of 10 mg/dL and elevation within HDL level by 5 mg/dL.

• **Medical treatments**: These treatments will be indicated for those patients who suffer from hyperlipidemia since early childhood i.e., familial hyperlipidemia. These medications include: HMG CoA reductase inhibitors (first line treatment for elevated LDL levels), Fibrates (first line treatment for triglyceride elevation), Bile acid sequestrants (second line treatment for elevated LDL levels), Nicotinic acid (niacin) (second line treatment for all lipid disorders) and Ezetimibe and colesevelam (second line treatments to reduce absorption of cholesterol through gastrointestinal tract).

1.6.3 Classification of Antihyperlipidemic Drugs

Antihyperlipidemic agents promote reduction of lipid levels in the blood. Some antihyperlipidemic agents aim to lower the levels of low-density lipoprotein (LDL) cholesterol, some reduce triglyceride levels, and some help raise the high-density lipoprotein (HDL) cholesterol. By reducing the LDL cholesterol, they can prevent both the primary and secondary symptoms of coronary heart disease. Antihyperlipidemic Drugs may be classified as following:

1. **Bile Acid Sequestrants**

- Cholestyramine
- Colestipol HCl
- Colesevelam HCl

2. **HMG-CoA Reductase Inhibitors**

- Atorvastatin
- Fluvastatin
- Lovastatin

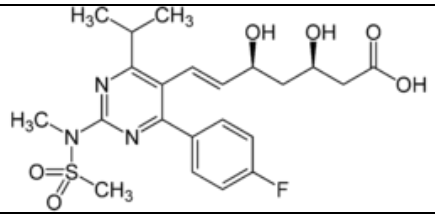
3. **Fibric Acid Derivatives**

- Clofibrate
- Fenofibrate
- Gemfibrozil

4. Miscellaneous Preparations

- Niacin

2.1 DRUG PROFILE

Name	**Rosuvastatin**
Type	small molecule
Structure	
Categories	• Anticholesteremic Agents • HMG-CoA Reductase Inhibitors • Hydroxymethylglutaryl-CoA Reductase Inhibitors
Molecular Weight	481.538
Melting Point	151-156ºC
Chemical Formula	$C_{22}H_{28}FN_3O_6S$
IUPAC Name	(3R,5S,6E)-7-[4-(4-fluorophenyl)-2-(N-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid
Absorption	Bioavailability is approximately 20%
Protein binding	90% bound to plasma proteins
Route of Administration	oral
Half life	19 hours
Indication	Used as an adjunct to dietary therapy to treat primary hypercholesterolemia (heterozygous familial and nonfamilial), mixed dyslipidemia and hypertriglyceridemia. Also indicated for homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering therapies
Pharmacodynamics	Rosuvastatin is a synthetic, enantiomerically pure antilipemic agent. It is used to lower total cholesterol, low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apoB), non-high density lipoprotein-cholesterol (non-HDL-C), and trigleride (TG) plasma concentrations while increasing HDL-C concentrations. High LDL-C, low HDL-C and high TG concentrations in the plasma are associated with increased risk of atherosclerosis and cardiovascular disease. The total cholesterol to HDL-C ratio is a strong predictor of coronary artery disease and high ratios are associated with higher risk of disease.
Mechanism of action	Rosuvastatin is a competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Rosuvastatin acts primarily in the liver. Decreased hepatic cholesterol concentrations stimulate the upregulation of hepatic low density lipoprotein (LDL) receptors which increases hepatic uptake of LDL. Rosuvastatin also inhibits hepatic synthesis of very low density lipoprotein (VLDL). The overall effect is a decrease in plasma LDL

	and VLDL.
Toxicity	Generally well-tolerated. Side effects may include myalgia, constipation, asthenia, abdominal pain, and nausea. Other possible side effects include myotoxicity, and hepatotoxicity.
Dose	5 – 40 mg
State	Solid
water solubility	Sparingly soluble in water (8.86e-02 g/l)
pKa (strongest acidic)	4
pKa (strongest basic)	-2.8
Refractivity	121.44
Storage	Stored at room temperature between 2-25º C (36-77 F).

3.1 Preformulation Studies

Preformulation is an exploratory activity that begins early in drug development. Preformulation studies are designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical, and analytical investigation in support of promising experimental formulations. Data from preformulation studies provide the necessary groundwork for formulation attempts.

Preformulation studies strengthen the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, improve public safety standards, enhance product quality, facilitate the implementation of new technologies, and facilitate policy development and regulatory decision making.

(a) Selection of the drug candidate itself,

(b) Selection of formulation components,

(c) API and drug product manufacturing processes,

(d) Determination of the most appropriate container closure system,

(e) Development of analytical methods,

(f) Assignment of API retest periods

(g) The synthetic route of the API,

(h) Toxicological strategy.

3.2 Drug Identification

Rosuvastatin was identified by the procedures described in Indian Pharmacopoeia 2009.

3.3 Physical Appearance

The drug Rosuvastatin was supplied by Glenmark Pharmaceutical Ltd. Mumbai, as a gift sample. It was odourless, white crystalline powder.

3.4 Melting Point

Melting point determination of the obtained drug sample was done as it is a first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range. The melting point of Rosuvastatin was determined by capillary melting point apparatus (Biotechnics, India) by filling in one sided sealed capillary.

The melting point of the obtained drug sample was found to be 154ºC± 1ºC which is within the reported range of 151-156ºC. It complies with the purity of the drug sample.

Table 5.1: Melting Point Dtermination.

Drug	Temperature (ºC)
Rosuvastatin (I.P.)	151 - 156ºC
Rosuvastatin (Observed)	154ºC ± 1ºC

3.5 Determination of Absorption Maxima

Organic molecules when exposed to light in ultraviolet region of the spectrum absorb light of particular wavelength depending on the type of electronic transition associated with the absorption. The ultraviolet spectrophotometry was used for structural validation of the drug in the present study.

50mg of Rosuvastatin was dissolved in 100 ml with 0.1N HCl (pH-1.2) (Conc. 500 µg/ml). From this solution 1ml was pipetted out in to 50 ml volumetric flask and volume was made up to with 0.1N HCl (pH-1.2) (Conc.10 µg/ml). The solution containing 10 µg/ml of Rosuvastatin in 0.1N HCl (pH-1.2) was scanned over the range of 200 to 400 nm against 0.1N HCl (pH-1.2) as blank using double beam UV spectrophotometer (EI Model No. 1372). The maximum obtained in the graph was considered as λmax for the pure drug.

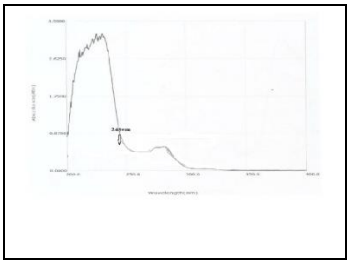


Figure 5.1: UV Absorption Maxima of Rosuvastatin.

3.6 Infrared Spectroscopy

Fourier Transform Infrared Spectroscopy is a technique utilized for the characterization of organic materials (including Polymers) and certain inorganic compounds. This provides information about the presence of specific molecular structure.

Infrared spectrum of any compound gives information about the groups present in that particular compound. Drug (5 mg) was mixed with potassium bromide (100mg) and compressed as pellets. These pellets were further processed for IR spectra. IR spectra were taken in Bruker IR spectrophotometer. The observed peaks were compared with standard spectra of rosuvastatin as per given in Indian Pharmacopeia 1996 and inference recorded.

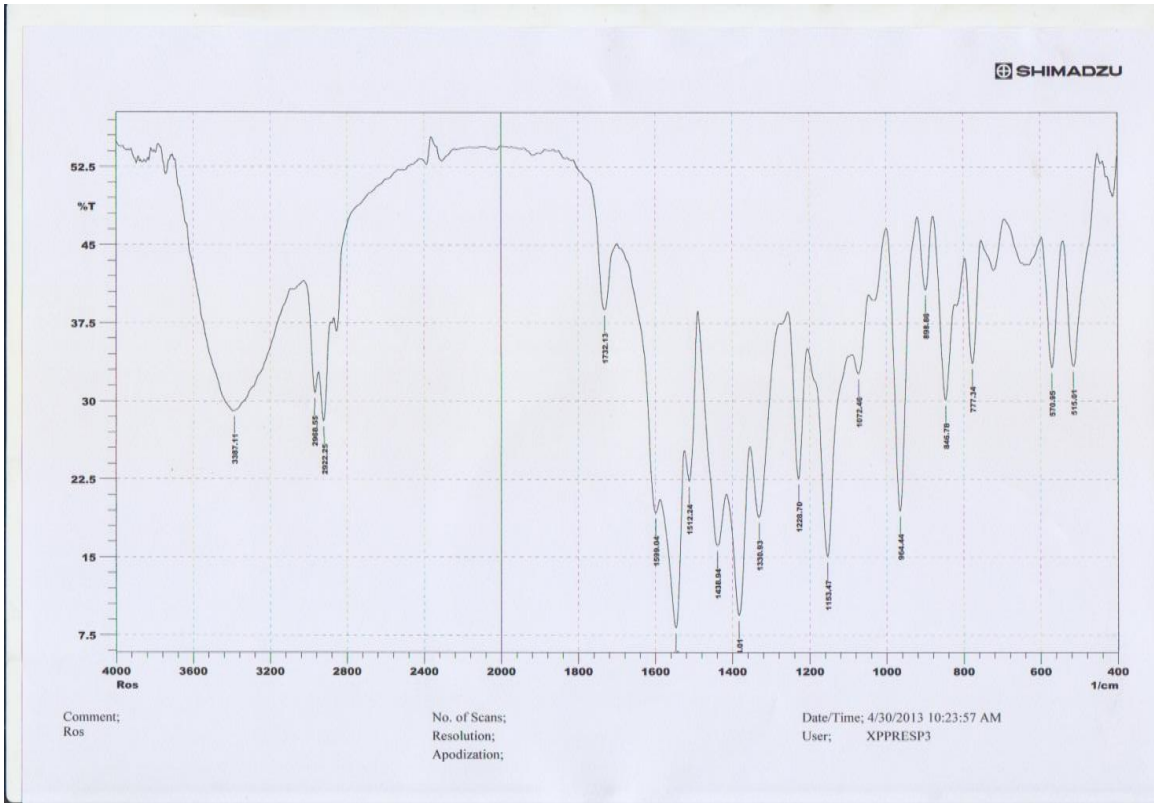


Figure 5.2: Standard FTIR Spectrum of Rosuvastatin.

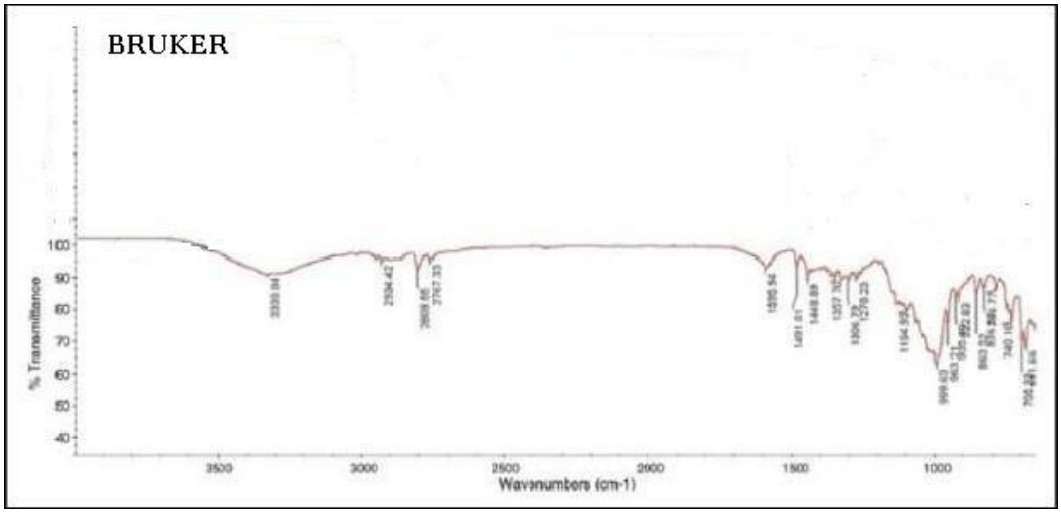


Figure 5.3: FTIR Spectra of Rosuvastain (Sample Drug).

Table 5.2: IR Interpretation of Rosuvastatin.

S. No.	IR Spectrum	Wave Number (Cm^{-1})	Groups	Stretching/Deformation
1.	Rosuvastatin Standard	3387.11	O-H	Stretching
		2958.55	C-H	Stretching
		1732.13	C=O	Stretching
		1438.94	C-F	Stretching
		1330.93	C-N	Stretching
		1153.47	S=O	Stretching
2.	Rosuvastatin (Sample Drug)	3398.04	O-H	Stretching
		2934.42	C-H	Stretching
		1448.09	C-F	Stretching
		1270.23	C-N	Stretching
		1154.97	S=O	Stretching

3.7 Solubility Profile Studies

Solubility is a maximum amount of solute that dissolves in a solvent under condition of equilibrium at certain temperature. It is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature and in qualitative terms it may be defined as the spontaneous interaction of two or more substances to form a w/v homogenous molecular dispersion. Drug (10mg approx.) was added separately to a series of solvents (2 ml) in capped test tube at room temperature. These tubes were shaken mechanically for about 6 hrs using wrist action shaker and solubility was recorded.

The Rosuvastatin sample was found to be freely soluble in ethanol, soluble in methanol, dichloromethane and acetone. It was also soluble in 0.1N HCl (pH 1.2) and 0.1 N NaOH. It is sparingly soluble in water and chloroform.

Table 5.3: Solubility Profile of Rosuvastatin.

S. No.	Solvent	Solubility
1.	Distilled water	+ +
2.	Ethanol	+ + + +
3.	Methanol	+ + +
4.	Dichloromethane	+ + +
5.	Acetone	+ + +
6.	Chloroform	+ +
7.	Toluene	-
8.	0.1 N HCl	+ + +
9.	0.1 N NaOH	+ + +

Keys:

+ + + + : Freely soluble = 1-10 part of solvent.

+ + + : Soluble = 10-30 part of solvent.

+ + : Sparingly Soluble = 30-100 part of solvent.

+ : Slightly soluble = 100-1000 part of solvent.

- : Insoluble = <10,000 part of solvent.

3.8 Partition coefficient Determination

The partition coefficient is defined as the ratio of unionized drug distributed between the organic and aqueous phases at equilibrium.The value of partition coefficient indicates the polar and non-polar nature of the drug which is responsible for its *in-vivo* performance, i.e. transport of drug across cellular barriers depends on lipophilicity of the drug.

10 mg of rosuvastatin was accurately weighed and transferred to a volumetric flask of 25ml capacity containing 10ml each of two immiscible phases, n- octanol and aqueous phase distilled water. The flask was shaken using wrist action shaker for 24hrs. Two phases were separated using a separating funnel and aqueous phase was analysed spectrophotometricaly at 244nm for the amount of drug after suitable dilution.

The partition coefficient was calculated using the following equation:-

$$Po/w = \frac{Coil}{Cwater}$$

Partition coefficient was found to be same as reported.

Table 5.4: Partition coefficient of Rosuvastatin.

Solvent System	Partition Coefficient	
	(Reported)	(Observed)
n- octanol: water	0.13	0.13

3.9. Quantitative Estimation of Drug

Preparation of Standard Calibration Curve of Rosuvastatin

Rosuvastatin (100 mg) was accurately weighed and dissolved in 100 ml 0.1N HCl to form a stock solution (1000 µg/ml). The stock solution was further diluted suitably with 0.1N HCl to get a working standard solution of concentration 100 µg/mL. Aliquots (0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, and 2.0) mL of working standard solution corresponding to 2-20 µg were taken in a series of 10 ml volumetric flask and volume made up with 0.1N HCl. The absorbance measurements of these solutions were carried out against 0.1N HCl as blank at 244 nm (Table 5.5). A calibration curve of Rosuvastatin was plotted (Figure 5.4).The curve was found to be linear in the range of 2-20 µg/ml at λmax 244nm. The regression value was found to be 0.998.

Table 5.5: Calibration Curve of Rosuvastatin.

S. No.	Concentration (µg/ml)	Absorbance	Regression Analysis
1.	2	0.276	Y = 0.091x + 0.096 R^2 = 0.998
2.	4	0.459	
3.	6	0.642	
4.	8	0.812	
5.	10	1.015	
6.	12	1.213	
7.	14	1.402	
8.	16	1.611	
9.	18	1.725	
10.	20	1.895	

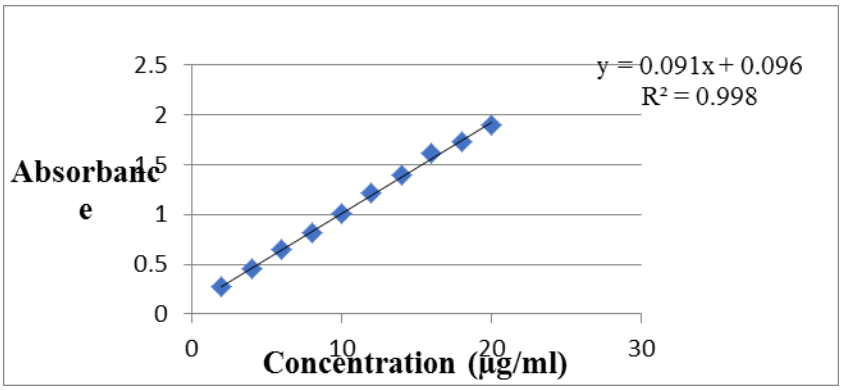


Figure 5.4: Standard curve of Rosuvastatin.

4.1 RESULT AND DISCUSSION

Identification studies showed that the drug supplied by Glenmark Pharmaceuticals Ltd, Mumbai, matches with the standard as prescribed in Indian Pharmacopeia (2009). The drug is odorless, white crystalline powder.

Melting point is the first sign of purity of the drug. It was found to be 154ºC±1ºC.

The absorption maxima of the drug Rosuvastatin in 0.1N HCl was measured through EI (1601) UV/Visible spectrophotometer and was found to be 244nm. The above maxima matched with standards given in Indian Pharmacopeia (2009).

Infra red spectrum of Rosuvastatin confirms the presence of different groups. The various peaks obtained in the IR spectrum matched with the reported IR spectrum.

Solubility profile of the drug in different solvents at room temperature indicates that the drug rosuvastatin was found to be freely soluble in ethanol, soluble in methanol, dichloromethane and acetone. It was also soluble in 0.1N HCl (pH 1.2) and 0.1 N NaOH. It was sparingly soluble in water and chloroform. The results obtained in solubility studies matched with the reported profile.

Partition coefficient value of rosuvastatin revealed that it is hydrophilic in nature and it was found to be 0.13 in n-octanol/water system.

The standard curve of Rosuvastatin was prepared in 0.1N HCl (pH 1.2). The equation of the line was y = 0.091x + 0.096. The curve was found to be linear in the range of 2-20 µg/mL. The correlation coefficient calculated was found to be 0.998.

4.2. Preparation of Floating Microspheres of Rosuvastatin

The present work was proposed to prepare and evaluate the Floating Microspheres for the site-specific delivery of an HMG CoA Reductase inhibitor drug i.e. Rosuvastatin for effective management of Hyperlipidemia.

The floating microspheres were prepared by solvent evaporation technique. The polymers, ethyl cellulose (EC) and hydroxyl propyl methyl cellulose (HPMC) were dissolved in the mixture of ethanol and dichloromethane in the ratio 1:1. The drug was dispersed in the solution of polymers for 10 minutes under stirring at 200 rpm. The resulting dispersion was poured slowly under stirring into distilled water (dispersion medium) containing 0.01% of Tween 80. The stirring speed was maintained at 1000 rpm and temperature was maintained at 30-40ºC. Stirring was continued for 1 hour and allow evaporation of dichloromethane and ethanol completely. After evaporation of dichloromethane and ethanol, the prepared microspheres were collected by filtration using filter paper, then washed 3 to 4 times with

distilled water and dried at room temperature for 24 hours and stored in a desiccator. **(Nixon *et al.*, 1984).**

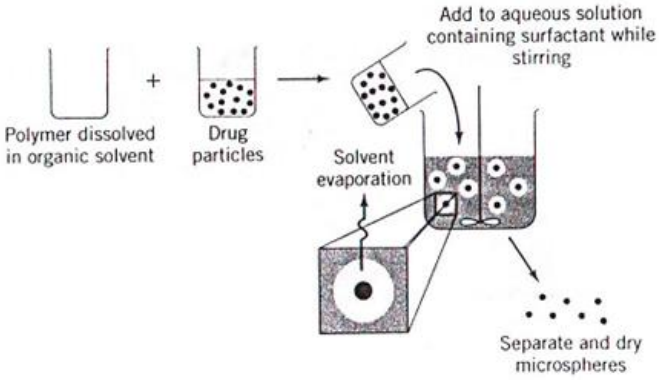


Figure 6.1: Schematic representation of method of preparation of Floating Microspheres.

Following this procedure we have prepared the various formulations of F1-F4.The quantity of Ethyl cellulose (polymer) was varied in the formulations. Table 5.1

Table 6.1: Formulation Design.

Formulation Code	Dispersed Phase				Continuous Phase
	Drug (mg)	HPMC (mg)	EC (gm)	Ethanol :Dichloromethane (ml)	
F1	300	500	0.50	1:1	100 ml water containing 0.01% of Tween 80
F2	300	500	1.0	1:1	
F3	300	500	1.5	1:1	
F4	300	500	2.0	1:1	

Figure 6.2: Preparation of Floating Microspheres.

4.3 Evaluation of Floating Microspheres

The floating microspheres prepared and evaluated for the following-

4.3.1 Micromeritic Studies

The prepared microspheres were characterized by their micromeritic properties, such as microsphere size, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose. **(Jain S.K. *et al.*, (2006), (Behera *et al.*, (2011).**

4.3.1.1 Bulk Density

Bulk density is a property of powders, granules. It is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume, and internal pore volume. The bulk density of a powder is determined by measuring the volume of a known mass of powder sample,that may have been passed through a sieve, into a graduated cylinder, or by measuring the mass of a known volume of powder that has been passed through a volumeter into a cup or a measuring vessel. The formulation F1 to F4 were evaluated for bulk density and it was calculated using the below given formula. The results are given in Table. 6.4

$$\text{Bulk Density} = \frac{\text{Mass of Microspheres}}{\text{Volume of microspheres before tapping}}$$

4.3.1.2 Tapped Density

The Tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample. After observing the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped, and volume or are taken until little further volume or mass change is observed. Tapped density is the volume of powder determined by tapping by using a measuring cylinder containing weighed amount of sample. The cylinder containing known amount of microspheres was tapped for about 1 minute on a tapped density apparatus until it gives constant volume. The formulation F1 to F4 were evaluated for tapped density and it was calculated using the below given formula. The results are given in Table. 6.4

$$\text{Tapped Density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

4.3.1.3 Carr's Compressibility Index

The Carr's index is an indication of the compressibility of a powder. A volume of powder is filled into a graduated glass cylinder and repeatedly tapped for a known duration. The volume of powder after tapping is measured. This is an important property in maintaining uniform weight. The formulation F1 to F4 were evaluated for carr's compressibility index and it was calculated using the below given formula. The results are given in Table. 5.4

$$\% \text{ Compressibility Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}}$$

Lower the compressibility values indicate better flow.

Table 6.2: Compressibility Index.

% Compressibility Index	Flowability
5 – 15	Excellent
12 -16	Good
18 -21	Fair to Passable
23 -35	Poor
33 – 38	Very Poor
>40	Extremely Poor

4.3.1.4 Hausner ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. it is not an absolute property of a material; its value can vary depending on the methodology used to determine. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability. The formulation F1 to F4 were evaluated for Hausner ratio and it was calculated using the below given formula. The results are given in Table. 6.4.

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

4.3.1.5 Angle of Repose

Good flow properties are critical for the development of any pharmaceutical tablet, capsules or powder formulation. It is essential that an accurate assessment of flow properties be made as early in the development process as possible so that an optimum formulation can be quickly identified. Inter particle forces between particles as well as flow characteristics of powders are evaluated by angle of repose. Angle of repose is defined as the maximum angle possible between the surface and the horizontal plane.

The angle of repose of each powder blend was determined by glass funnel method.

Powders were weighed accurately and passed freely through the funnel so as to form a heap. The height of funnel was so adjusted that the tip of the funnel just touched the apex of the heap. The diameter of the powder cone so formed was measured and the angle of repose was calculated using the following equation,

$$\tan \theta = h/r$$

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

Where, θ = angle of repose

h = height of the pile and,

r = radius of the powder cone respectively.

Angle of repose affects particle size distribution, as larger the particle size, it will flow freely and vice-versa. It is a helpful parameter to monitor quality of powdered or granular pharmaceutical formulations. For good flowing materials, angle of repose should be less than 30°. The formulation F1 to F4 were evaluated for bulk density and it was calculated using the below given formula. The results are given in Table 6.4.

Table 6.3: Angle of Repose.

Angle of Repose	Flowability
< 25	Excellent
25-30	Good
30-40	Passable
>40	Poor

Table 6.4: Micromeritic Parameters of the formulation.

S. No.	Formulation Code	Bulk Density	Tapped Density	Compressibility Index	Hausner's Ratio	Angle of Repose
1.	F1	0.46±0.008	0.525±0.012	11.43±1.895	1.129±0.042	20.27±1.856
2.	F2	0.48±0.013	0.568±0.009	15.49±2.042	1.183±0.038	23.49±2.112
3.	**F3**	**0.46±0.012**	**0.511±0.007**	**10.02±1.918**	**1.111±0.048**	**19.57±1.143**
4.	F4	0.46±0.011	0.543±0.006	14.36±1.720	1.167±0.052	17.28±1.925

The value of Hausner's Ratio was below 1.25 it indicates that the formulations having good flow property. The value of angle of repose was below 25º, it indicates excellent flow of the microspheres.

4.3.2 Percentage Yield

The percentage yield of the product is the measured weight of prepared microspheres divided by the total amount of all the excipients and drug used in the preparation of the microspheres, which gives the total percentage yield of floating microspheres. **(Bhardwaj *et al.*, (2010),**

(Singhal *et al.*, (2011). It was calculated by using following equation, and the results are recorded in table 6.5.

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipients and drug}} \times 100$$

Table 6.5: Percentage yield of formulated microspheres.

S. No.	Formulation Code	Theoretical Weight (mg)	Practical Yield (mg)	% Yield
1.	F1	1000	772	77.2%
2.	F2	1000	778	77.8%
3.	**F3**	**1000**	**802**	**80.2%**
4.	F4	1000	783	78.3%

4.3.3 Particle Size Determination

The size of floating microspheres was determined by using an optical microscope under regular polarized light, and the mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer **(Tanwar *et al.*, (2007), (Manju *et al.*, (2007)**. The results are shown in Table. 6.6.

Table 6.6: Particle size determination of formulated microspheres.

S. No.	Formulation Code	Average Particle Size (µm)
1.	F1	71.72±9.45
2.	F2	88.37±8.35
3.	**F3**	**98.82±6.85**
4.	F4	99.51±5.47

In the determination of particle size the result showed that the particle size was found in the increasing order, it is due to variation in polymer concentration. As the polymer concentration increases, the particle size of floating microsphere increased.

4.3.4 Drug Loading and Drug Entrapment

The floating microspheres equivalent to 100 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl (pH-1.2) repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using 0.1N HCl (pH-1.2). The solution was filtered and the absorbance was measured after suitable dilution spectrophotometricaly (EI, UV Model No. 1372,) at 244 nm against appropriate blank. **(Gatti *et al.*, (2008), (Fatemeh *et al.*, (2004).** The amount of drug loaded and entrapped in the microspheres was calculated by the following formula and the results are recorded in Table 6.7.

$$\% \text{ Drug Loading} = \frac{\text{Weight of the drug loaded in the microspheres}}{\text{Total weight of the microspheres}} \times 100$$

$$\% \text{ Drug Entrapment} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

Table 6.7: Drug Loading & Drug Entrapment.

S. No.	Formulation Code	% Drug Loading	% Drug Entrapment
1.	F1	34.36±0.28	75.72±1.89
2.	F2	26.74±0.42	82.23±2.28
3.	**F3**	**40.12±0.36**	**84.38±1.53**
4.	F4	25.84±0.27	85.81±1.40

4.4.5 *In vitro* Buoyancy Study

Various floating microspheres (300mg) were spread over the surface of a USP dissolution apparatus type I filled with 900 ml of 0.1 N HCl (pH-1.2). The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. **(Patil *et al.*, (2009), (Shrivastava *et al.*, (2005).** The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres. The results are recorded in Table 6.8

% Buoyancy = Qf / (Qf + Qs) X 100

Where **Qf** and **Qs** are the weight of the floating and settled microspheres respectively. It was clearly observed that the microspheres of prepared formulation remain buoyant. Fig. 5.6.

Figure 6.3: Photograph showing the buoyant microspheres of prepared formulation.

Table 6.8: Buoyancy study of prepared formulation.

S. No.	Formulation Code	Weight of Floating Microspheres Taken (mg)	Weight of Microspheres Floated (mg)	% Buoyancy
1.	F1	300	212	70.6%
2.	F2	300	205	68.3%
3.	**F3**	**300**	**237**	**79.0%**
4.	F4	300	224	74.6%

4.3.6 Morphological Study using Scanning Electron Microscopy

Examining the surface of a polymeric drug delivery system can provide vital information on the porosity and microstructure of the systems. The most common technique used for characterizing the surface morphology of drug delivery systems is Scanning Electron Microscopy (SEM). This method offers several advantages, by its versatility of the method, simplicity of sample preparation and ease of operation. The sample sizes, which can be analyzed using this method, range from nanometers to micrometers to centimeters. Sample prepared for this method should be sufficiently dehydrated since, a vacuum field is necessary for image generation in SEM. Prior to loading the samples for taking the photomicrograph, samples were coated (20-30nm in thickness) with electron-dense coating materials like gold, palladium or combination of both, to enhance the signal emitted by the sample by providing heavy metal atoms with incident beam of electron and, to conduct the accumulated sample charge and heat to the sample holder. **(Singhal *et al.*, (2011)**. The coating process wass either carried through sputter-coating or thermal vacuum evaporation. The surface morphology of the formulated floated microspheres before and after dissolution studies was observed by Scanning Electron Microscope (HITACHI SU 1500, Japan) The microspheres were placed on steel surface and coated with gold using an ion sputter and were observed. The formulation F3 was selected for the morphological study. The photographs are shown in Figure. 6.4, 6.5.

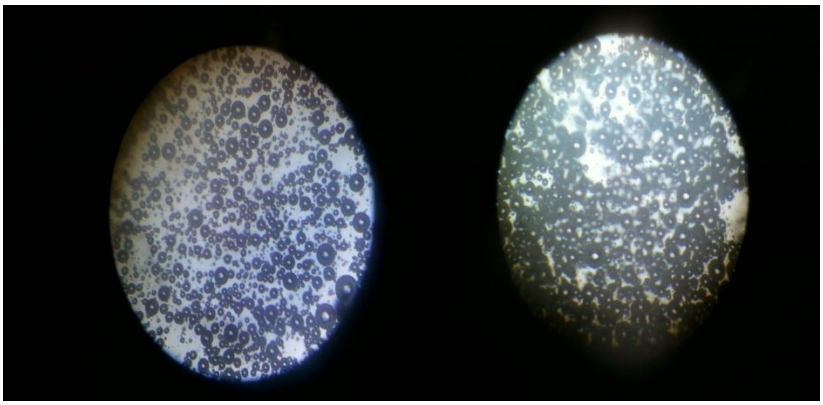


Figure 6.4: Photograph of floating microspheres using optical microscope.

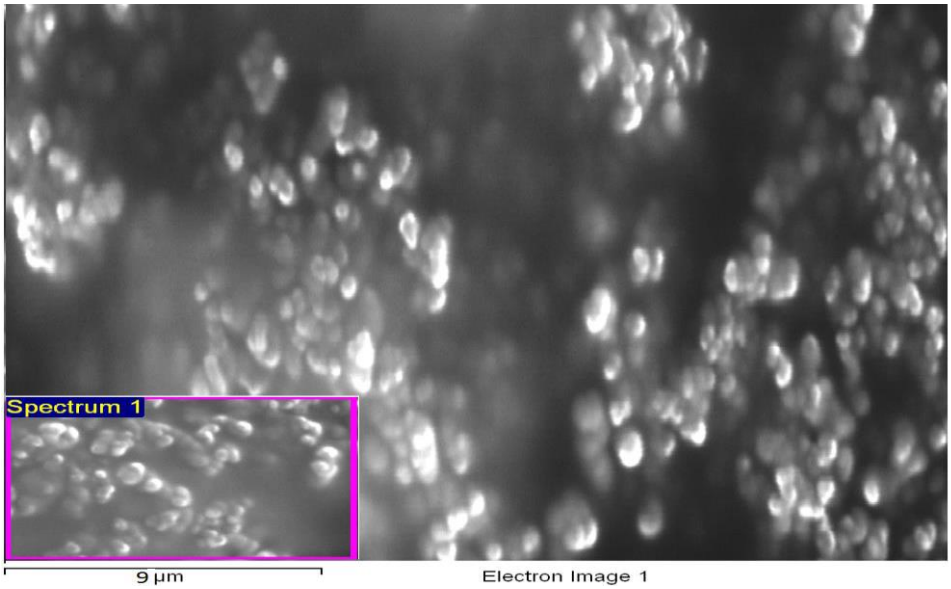


Figure 6.5: SEM Photograph of prepared microspheres.

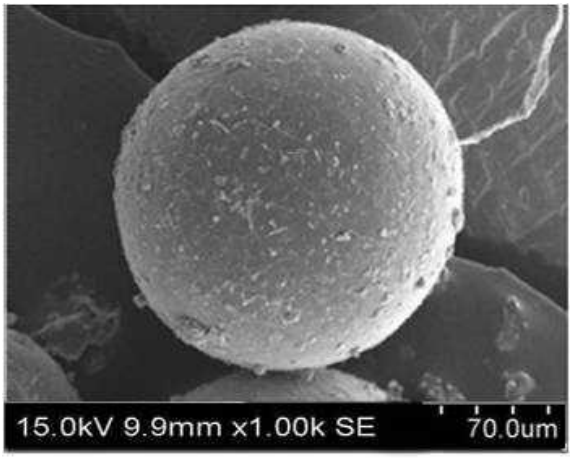


Figure 6.6: SEM photograph of prepared microspheres at higher magnification.

6.2.7 *In-vitro* Release Study

The drug release study was performed for selected formulation F3. The floating microspheres equivalent to 100 mg was weighed and studied by using USP dissolution apparatus Type II (Rolex Tablet Dissolution Test Apparatus) in 900 ml of 0.1N HCl dissolution media (pH-1.2) at 100 rpm and 37ºC temperature. 1 ml of sample was withdrawn at predetermined time interval for 12 hours and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were assayed spectrophotometrically at 244nm. **(Gatti *et al.*, (2008)**, **(Shrivastava *et al.*,(2005).** The cumulative % drug release was calculated using standard calibration curve (Table.6.9)

Table 6.9: *In vitro* drug release of floating microspheres F3.

S. No.	Time (Hours)	Absorbance	% Cumulative Drug Release
1.	1	0.000	21.13
2.	2	0.301	30.05
3.	3	0.477	40.1
4.	4	0.602	43.5
5.	5	0.699	51.58
6.	6	0.778	58.68
7.	7	0.845	64.79
8.	8	0.903	67.98
9.	9	0.954	72.89
10.	10	1.000	77.05
11.	11	1.041	79.35
12.	12	1.109	82.11

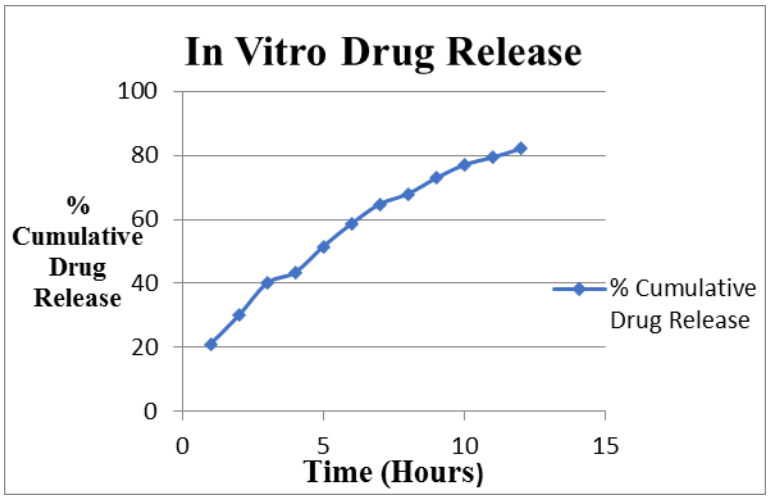


Figure 6.7: *In vitro* Drug release of prepared floating microspheres F3.

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