Development and characterization of floating drug delivery system for the effective management of hyperlipidemia

Dimpal Nageshwar,[1]* Dr. Arun Patel,[2] Dr. Naveen Shivavedi[3]Dr. Adiya Sahu[4]

[1*2,3,4]Shri Ram Group of Institutions, Department of Pharmacy,Jabalpur-482002 M.P.,India.
***Corresponding Author -** Dimpal Nageshwar.
***Gmail:**nageshwardimple@gmail.com

Abstract

Floating systems are systems capable to float over the gastric content for prolonged period of time without affecting gastric emptying rate. The lowering of cholesterol and fat level in blood is shown by the use of rosuvastatin to prevent heart disease. We prepared and characterized floating microspheres using evaluation parameters like micromeritic studies, percentage yield, particle size determination, morphological and microscopical study by SEM, drug loading and drug entrapment efficiency, *in vitro* buoyancy study, *in vitro* release study, and stability studies. There was no significant change observed in the physical appearance, drug entrapment, floating behavior and *in vitro* release study of the microspheres during the stability study time period. There was no significant change observed in the physical appearance, drug entrapment, floating behavior and *in vitro* release study of the microspheres during the stability study time period. It may be due to the characteristics of excipients used in the formulation. The Stability study indicates that the developed formulation is stable at different environmental condition and can be stored at room temperature for long time. The floating microspheres were prepared successfully and remained buoyant for 12 hours. Microspheres of different sizes and improved drug entrapment efficiency were obtained by varying the drug:polymer ratio. The formulations showed good flow properties, suggesting that, in future they could be easily and successfully packed and developed into a capsule dosage form. Thus the prepared floating microspheres may be a potential candidate as a microparticulate controlled release drug delivery device.

Keywords: Floating drug delivery system; Hyperlipidaemia; Rovastatin; Micromeritic studies; *In vitro* buoyancy study; *In vitro* release study.

Introduction

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). **(Allen T.M. *et al.*, (2002)** 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. **(Kulkarni *et al.*, (2011)**

Liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural nontoxic phospholipids. Due to their size and hydrophobic and hydrophilic character (besides biocompatibility), liposomes are promising systems for drug delivery. Liposome properties differ considerably with lipid composition, surface charge, size, and the method of preparation.

Recent scientific and patent literature shows increased interest in academics and industrial research groups regarding the novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT), using gastroretentive drug delivery system (GRDDS) that will

provide us with new and important therapeutic options. (Yeole et al., 2005) Gastroretention is essential for drugs that are absorbed from the stomach, drugs that are poorly soluble or degraded by the higher pH of intestine and the drugs with an absorption which can be modified by changes in gastric emptying time.

Gastroretentive dosage forms are also useful for local as well as sustained drug delivery for certain condition like H.pylori infection which is the cause of peptic ulcers. This dosage form improves bioavailability, therapeutic efficacy and may even also allow a possible reduction in the dose because of steady therapeutic levels of drug, for example furosemide and ofloxacin. The reduction in fluctuations in therapeutic levels minimizes the risk of resistance especially in case of β-lactum antibiotics (penicillins and cephalosporins).(Chawla *et al.,* 2003) A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular portion of the GIT only or are absorbed to a different extent in various segments of the GIT. Such drugs are said to have an absorption window, which identifies the drug's primary region of absorption in the GIT.

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.

Materials and methods

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.

Melting Point:

Melting point determination of the obtained drug sample was done as it is a first indication of purity of the sample.

Table 1: Melting Point Determination

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

Determination of Absorption Maxima:

50 mg 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.

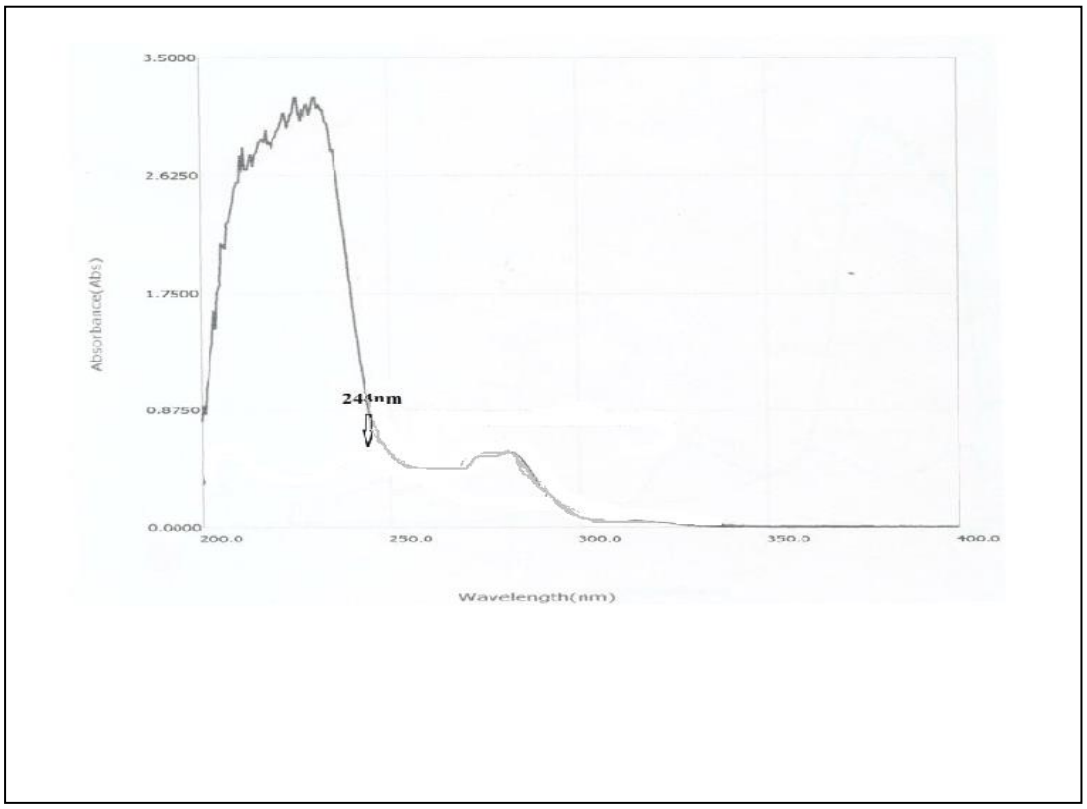

Figure 1: UV Absorption Maxima of Rosuvastatin

Infrared Spectroscopy:

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.

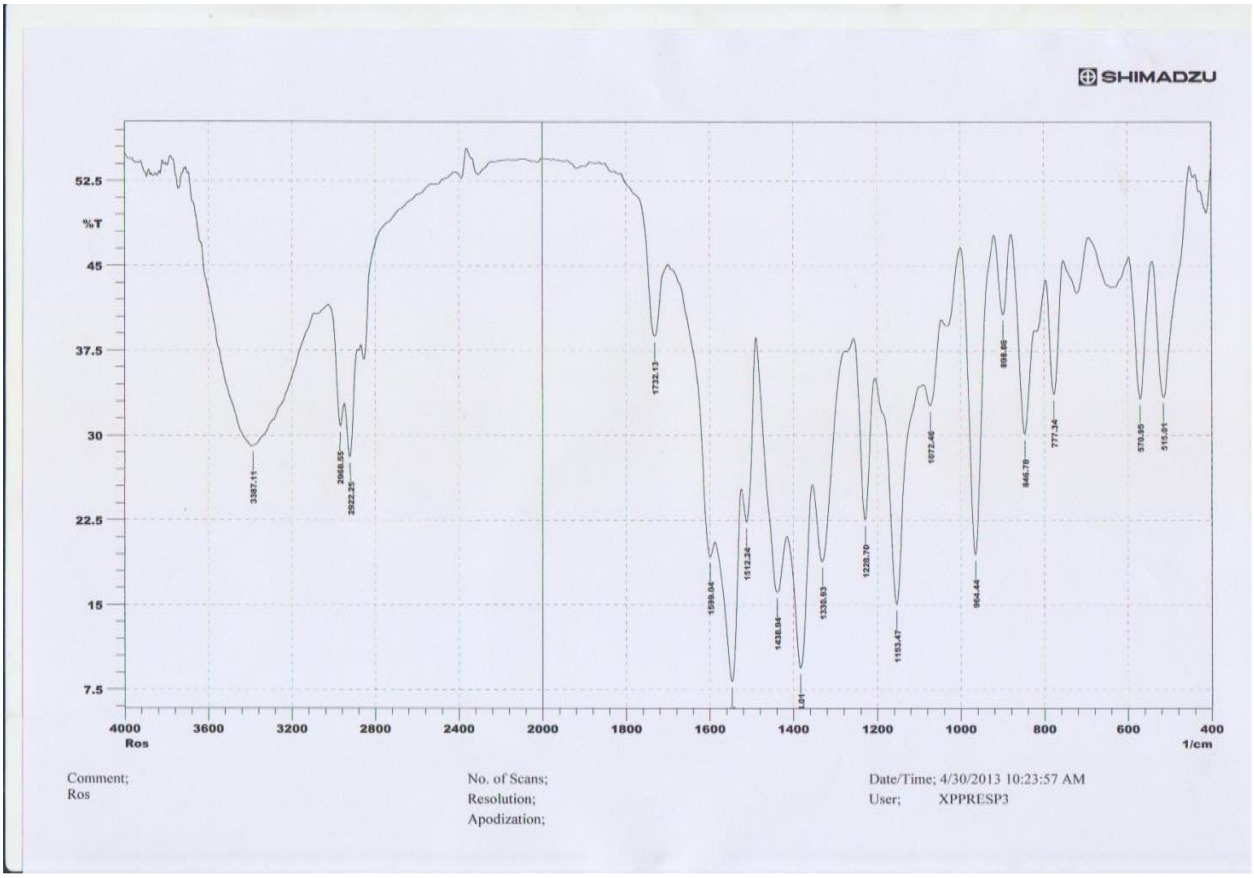

Figure 5.2: Standard FTIR Spectrum of Rosuvastatin

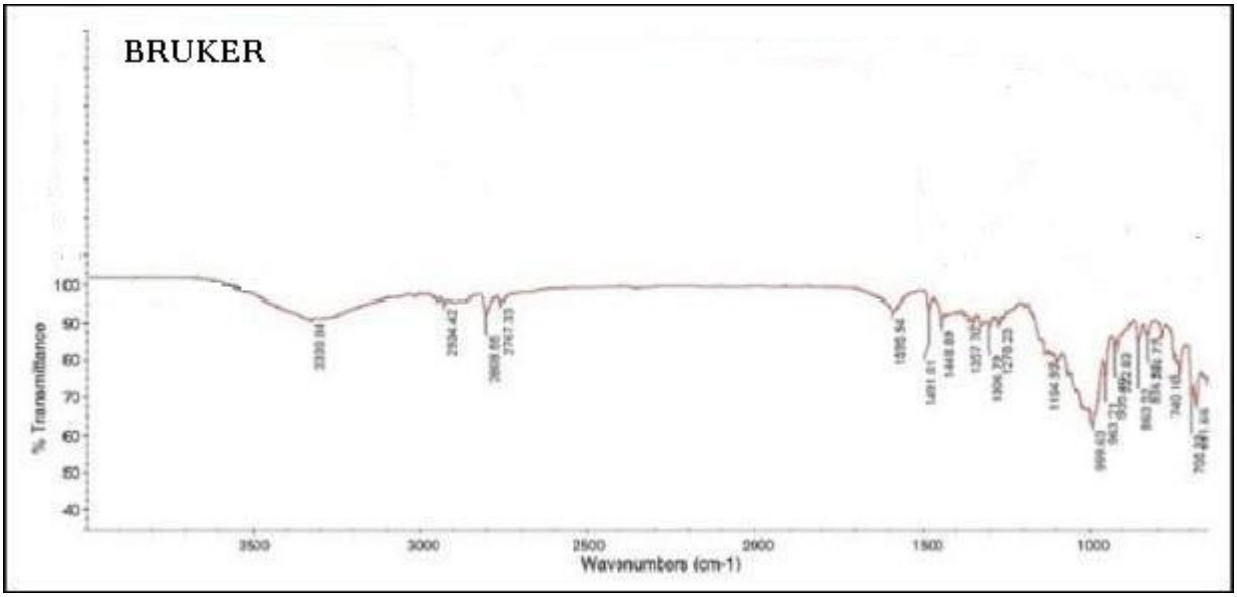

Figure 5.3: FTIR Spectra of Rosuvastain (Sample Drug)

Solubility Profile Studies:

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 **(Martin *et al.*, 1999)**.

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.

Partition coefficient Determination:

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.

Table 5.4: Partition coefficient of Rosuvastatin

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

Preparation of Floating Microspheres of Rosuvastatin

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.

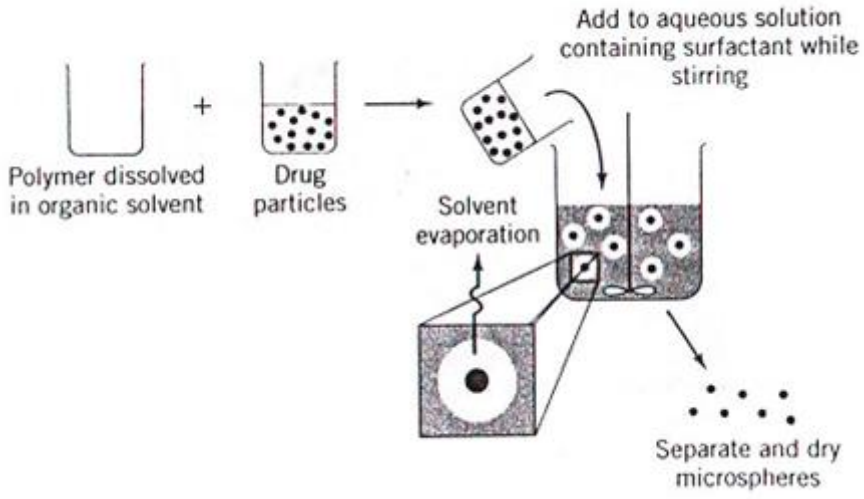

Figure 2: Schematic representation of method of preparation of Floating Microspheres

Table : 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	

Evaluation of Floating Microspheres

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.

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.

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.

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

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

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.

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.

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

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

Where, θ = angle of repose

h = height of the pile and,

r = radius of the powder cone respectively.

Table : 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

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)**.

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

Table : 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%

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)**.

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

Drug Loading and Drug Entrapment:

The floating microspheres equivalent to 100 mg of the drug were taken for evaluation. %

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

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

Table: 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

***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).

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

Where **Qf** and **Qs** are the weight of the floating and settled microspheres respectively.

Table: Buoyancy study of prepared formulation

S. No.	Formulation Code	Weight of Floating Microspheres Taken (mg)	Weight of Micro-spheres 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%

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.

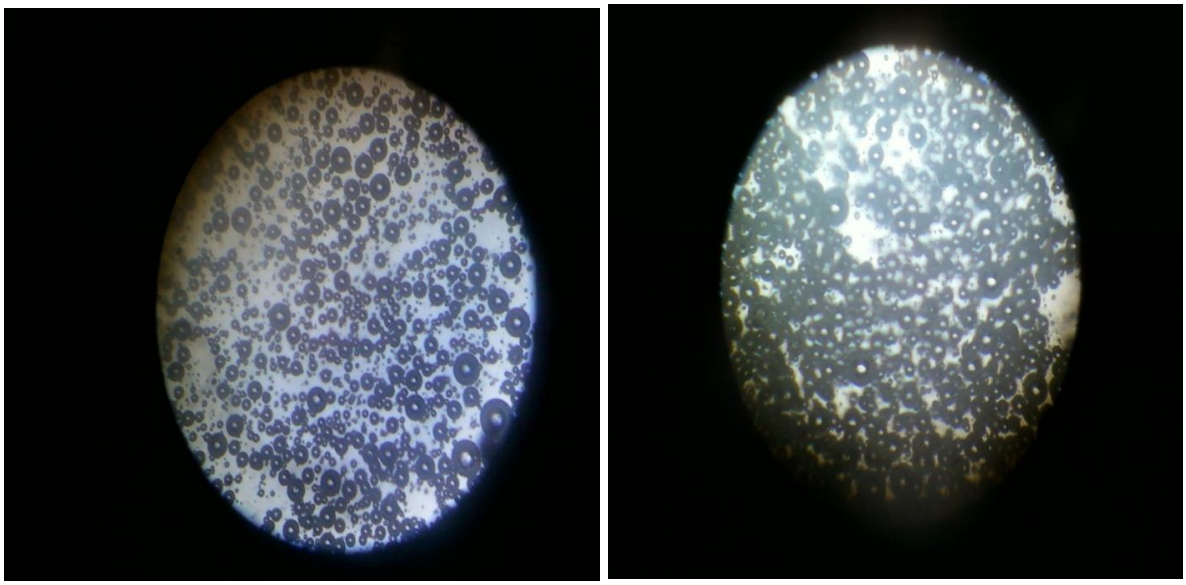

Figure: Photograph of floating microspheres using optical microscope

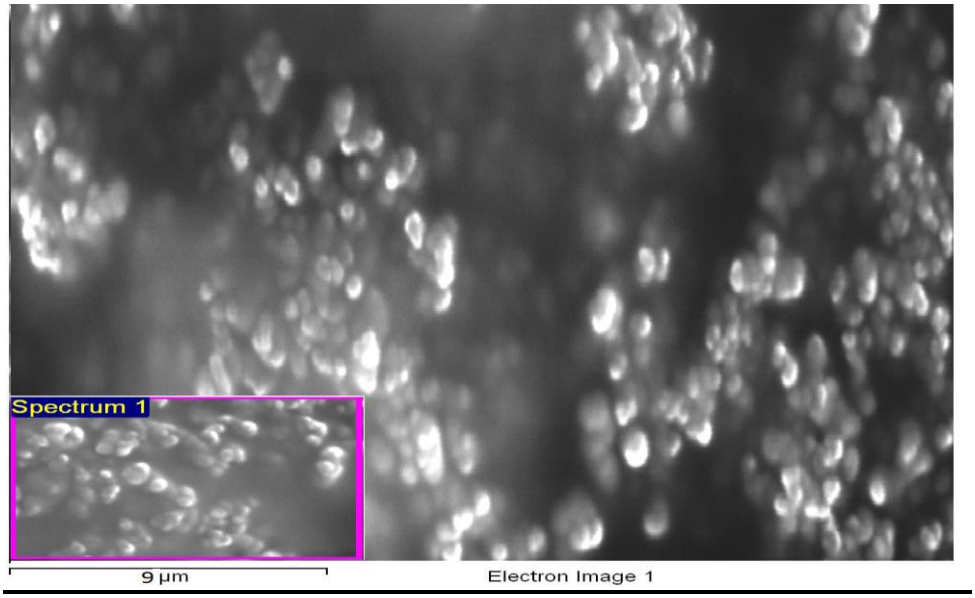

Figure: SEM Photograph of prepared microspheres

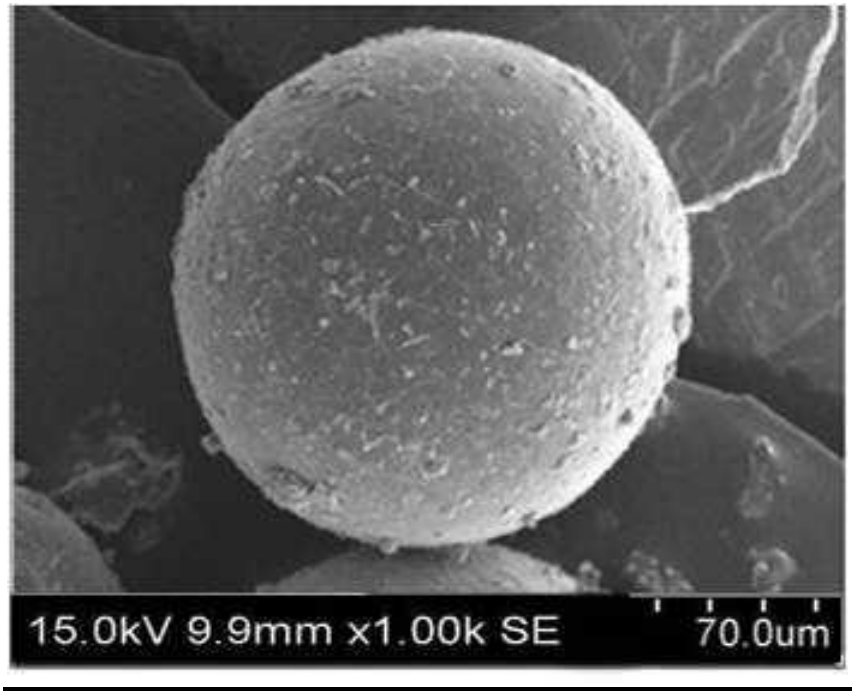

Figure : SEM photograph of prepared microspheres at higher magnification

***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.

Table : *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

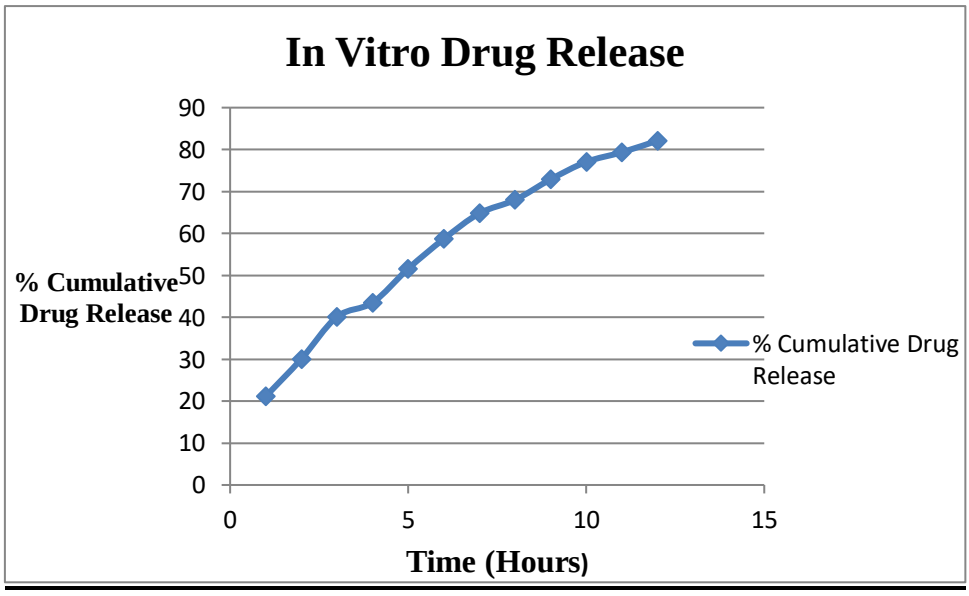

Figure: *In vitro* Drug release of prepared floating microspheres F3

Result and Discussion:

The floating microspheres were prepared by solvent evaporation technique. The polymer ethyl cellulose (EC) and hydroxyl propyl methyl cellulose (HPMC) were dissolved in the mixture of ethanol and dichloromethane. The drug was dispersed in solution of polymers with stirring at 200 rpm for 10 min. The 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 for 1 hour at room temperature (25±2ºC) and allowed to evaporate 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 desiccators.

Various formulations F1 to F4 of Floating microspheres were evaluated for micromeritic parameters such as bulk density, tapped density, % Compressibility index, Hausner's ratio and angle of repose. The results are given in Table 6.4.

The bulk density for the formulations F1, F2, F3, and F4 was found to be 0.46±0.008, 0.48±0.013, 0.46±01012, 0.46±0.011 respectively.

The Tapped density for the formulations F1, F2, F3, and F4 was found to be 0.525±0.012, 0.568±0.009, 0.511±0.007, 0.543±0.006 respectively.

The carr's compressibility index for the formulations F1, F2, F3, and F4 was found to be 11.43±1.895, 15.49±2.042, 10.02±1.918, 14.36±1,720 respectively. It was found to be in the range of 5-15, which shows the excellent flowability.

The Hausner's Ratio for the formulations F1, F2, F3, and F4 was found to be 1.129±0.042, 1.183±0.038, 1.111±0.048, 1.167±0.052 respectively. The value of Hausner's ratio was below 1.25, which indicates good flow property.

The Angle of repose for the formulations F1, F2, F3, and F4 was found to 20.27±1.856, 23.49±2.112, 19.57±1.143, 17.28±1.925 respectively. The angle of repose showed below 25º, which indicate excellent flow of the formulations.

Percentage yield of different formulation F1 to F4 were calculated and the yield was found to be 77.2%, 77.8%, 80.2%, 78.3% respectively.

Average particle size of microspheres was determined by optical microscopy using stage micrometer and ocular micrometer. Results are shown in Table. 5.6. The mean particle size of the floating microspheres was found to be 71.72µm, 88.37µm, 98.82µm, 99.51µm for F1, F2, F3 and F4 formulation respectively. As the concentration of polymer HPMC and ethyl cellulose increases the particle size of microspheres increases for F1 to F4 the respectively. This is because the viscosity of the polymer solution increases with increasing polymer concentration.

The % drug loading for the formulations F1, F2, F3, F4 was found to be 34.36±0.28, 26.74±0.42, 40.12±0.36, 25.84±0.27. The microspheres of formulation F3 showed highest drug loading of 40.42%, while lowest drug loading was observed in formulation F4 25.84%.

The % entrapment efficiency of floating microspheres formulations F1, F2, F3, F4 was found to be 75.72±1.89, 82.23±2.28, 84.38±1.53, 85.81±1.40 respectively.

In vitro buoyancy study for the formulatons like F1, F2, F3 and F4 was found to be 70.6%, 68.3%, 79.0%, 74.6% respectively. Among all the preparations F3 shows the maximum buoyancy. It is due to the size and polymer concentration of prepared floating microspheres.

On the basis of micromeritic parameters, percentage yield, particle size determination, drug loading, entrapment efficiency and in vitro buoyancy, the formulation F3 (Table. 5.1) shown the better results. The floating microspheres, which were prepared by using the formulation F3 were further characterized for the various parameters.

The determination of shape and surface morphology was done by scanning electron microscope HITACHI SU 1500, Japan. SEM analysis of the F3 Formulation revealed that all microspheres prepared were smooth and almost spherical in shape.

In vitro Drug Release on formulation of F3 Rosuvastatin floating microsphere was carried out using a USP dissolution apparatus Type II. 0.1N HCl (pH 1.2) was used as the dissolution medium. The *In vitro* drug release data for formulation is shown in Table.5.9 The cumulative percent drug release after 12 hours was found to be 82.11%. The initial pattern of drug release shows no bursting effect. It means after 1 hour the drug release was recorded 21.13% then after 2 hours drug release was found 30.05%, then after 3 and 4 hours it was found 40.1% and 43.5% respectively. It shows that there is no dose dumping in the drug release of prepared floating microspheres.

Stability Studies

The stability of any pharmaceutical product is defined as the capacity of the formulation to remain within defined limits over a predetermined period of time (shelf life of the product). Durability of a product may be defined as the capability of a particular formulation in a specific container to remain within the physical chemical, microbiological, therapeutic and toxicological specifications. **(Lachman *et al.*,(1987), Kulkarni *et al.*, (2004).** The purpose of stability testing is to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. In addition, product-related factors influence the stability, e.g. the chemical and physical properties of the active substance and the pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container-closure system, and the properties of the packaging materials. Also, the stability of excipients that may contain or form reactive degradation products, have to be considered.

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

Stress Testing:

Stress testing of the active substance can help to identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual active substance and the type of pharmaceutical product involved.

Storege Condition:

In general, an active substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use with due regard to the climatic zone(s) in which the active substance is intended to be stored. (Table 7.1)

Table: Storage Condition

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

In the present study, stability study was carried out (Enviornmental Test Chamber, Dolphin) at 40°C/75% RH for a period up to the 30 days of selected formulations (F3). The

selected formulation F3 was analyzed for the physical appearance, drug entrapment, floating behavior and *in vitro* release study.

Table: Stability Studies of Floating microspheres formulation F3

S.No.	Storage Condition	Time (Days)	Physical Stability		
			Colour	State	Odour
1.	Normal Condition	Initial	NCC	NCC	NCC
2.	Normal Condition	One Week (7^{th} Day)	NCC	NCC	NCC
3.	Normal Condition	Two Week (14^{th} Day)	NCC	NCC	NCC
4.	Normal Condition	Three Week (21^{st} Day)	NCC	NCC	NCC
5.	Normal Condition	Four Week (28^{th} Day)	NCC	NCC	NCC
6.	Stressed Condition	Initial	NCC	NCC	NCC
7.	Stressed Condition	One Week (7^{th} Day)	NCC	NCC	NCC
8.	Stressed Condition	Two Week (14^{th} Day)	NCC	NCC	NCC
9.	Stressed Condition	Three Week (21^{st} Day)	NCC	NCC	NCC
10.	Stressed Condition	Four Week (28^{th} Day)	NCC	NCC	NCC

NC - Normal condition (e.g. room temperature 25ºC ± 2ºC)

SC- Stress condition (40º± 5ºC, %RH- 70± 5)

NCC – No Change

Table : Stability Study for Various Evaluation parameters

S. No.	Formulation Code	Tested After Time (Days)	% Drug Entrapment	% Buoyancy	%Cumulative Drug Release
1.	F3	Initial (0)	84.38±1.53	79.0	82.11
2.	F3	30	83.11±1.13	77.11	81.58

Result and Discussion:

Stability study was conducted for the prepared floating microspheres of formulation F3 at 40°C/75% RH for a period of 30 days. The results of stability studies are shown in the Table 7.2 & 6.3. There was no significant change observed in the physical appearance, drug entrapment, floating behavior and *in vitro* release study of the microspheres during the stability study time period. It may be due to the characteristics of excipients used in the formulation. The Stability study indicates that the developed formulation is stable at different environmental condition and can be stored at room temperature for long time.

Conclusion:

The floating microspheres were prepared successfully and remained buoyant for 12 hours. Microspheres of different sizes and improved drug entrapment efficiency were obtained by varying the drug:polymer ratio. The formulations showed good flow properties, suggesting that, in future they could be easily and successfully packed and developed into a capsule dosage form. Thus the prepared floating microspheres may be a potential candidate as a microparticulate controlled release drug delivery device.

References

- A.J., “Gastroretentive dosage forms”, 1993, Crit Rev Ther Drug Carrier Syst; 10, (2), 193-195.
- A.J., “Gastric retention systems for oral drug delivery”, 2003, Business Briefing. Pharmatech, 157-159.
- Alagusundaram M., Madhu Sudana Chetty C., Umashankari K., Attuluri Venkata Badarinath, Lavanya C. and Ramkanth S., 2009, “Microspheres as a Novel Drug Delivery System - A Review”, *International Journal of Chem. Tech. Research*,1,(3) 526-534.
- Aleksandar Aleksovski, 2012, “Floating Gastro-Retentive Dosage Forms – A Novel Approach for targeted and controlled drug delivery”, 2,(1) 22-30.
- Allen T.M., 2002, “Ligand-targeted therapeutics in anticancer therapy”, Nature Reviews Drug Discovery (2), 750–763.
- Arora S., Ali J., Ahuja A., Khar R.K., Baboota S., 2005, “Floating Drug Delivery System A Review”**,** *AAPS PharmSciTech*, 6,(3) E372–E390.
- Bardonnet P.L., Faivre V., Pugh W.J., Piffaretti J.C., Falson F., 2006, “Gastroretentive dosage forms: overview and special case of Helicibacter pylori”, J Control Release, 111, 1-18.
- Barhate1 Shashikant D., Rupnar Yogesh S., Sonvane Rupesh M., Pawar Kapil R. and Rahane Rahulkumar D., 2009, “Formulation and Evaluation of Floating Microspheres of Ketorolac Trometamol”, *International Journal of Pharmaceutical Research and Development*, 1(9), 1-8.
- Bassam Abdul Rasool Hassan, 2013, “Overview on Hyperlipidemia”, *Chromatography Separation Techniques,* 4,(3)

- Behera A.L., Patil S.V., Sahoo S.K., 2011 "Formulation And Characteristics Of 5-flurouracil Microspheres By Solvent Evaporation Method", *Int J Pharm Pharm Sci*, 3, (1), 32-35.
- Bhardwaj P., Chaurasia H., Chaurasia D., Prajapati S.K., Singh S, 2010, "Formulation and In-vitro Evaluation of Floating Microballoons of Indomethacin", *PubMed,* 67,(3) 291-298.
- Caldwell L.J., Gardner C.R., Cargill R.C., 1988, "Drug delivery device which can be retained in the stomach for controlled period of time", US Patent 473 5804, April 5.
- Caldwell L.J., Gardner C.R., Cargill R.C., Higuchi T., 1988, "Drug delivery device which can be retained in the stomach for a controlled period of time", US Patent 475 8436, July 19.
- Charman W.N., Chan H.-K., Finnin B.C. and Charman S.A., 1999, "Drug Delivery: A Key Factor in Realising the Full Therapeutic Potential of Drugs", *Drug Development Research,* 46, 316-27.
- Chawla G., Gupta P., Koradia V., Bansal A.K., "Gastro-retention. A mean to address regional variability in intestinal drug absorption", Pharm Tech, 2003, 27, (1), 50-68.
- Chen J., Blevins W.E., Park H., Park K., 2000, "Gastric retention of superporous hydrogel composites", J Control Release, 64, (1-3), 39-51.
- Cheng, Y. and X. Tongwen, 2005. "Dendrimers as Potential Drug Carriers. Part I. Solubilization of Non-Steroidal Anti-Inflammatory Drugs in the Presence of Polyamidoamine Dendrimers". *European Journal of Medicinal Chemistry,* 40: 1188-1192.
- Dave Brijesh S., Amin Avani F., and Patel Madhabhai M., 2004, "Gastroretentive Drug Delivery System of Ranitidine Hydrochloride:Formulation and In Vitro Evaluation", *AAPS PharmSciTech,* 5(2), 1-6.
- Desai, S.; Bolton, S., 1993, "A Floating Controlled-Release Drug Delivery Dystem: *In vitro-In vivo* Evaluation". *Pharm. Res.,* 10, 1321-1325.

- Deepa, M.K, Karthikeyan, M., 2009, "Cefpodoxime Proxetil Floating Microspheres: Formulation and In Vitro Evaluation", *Iranian Journal of Pharmaceutical Sciences*, 5, 69-72.
- Deshpande A.A., Rhodes C.T., Shah N.H. and Malick A.W., 1996, "Controlled release drug delivery system for prolonged gastric residence: A Review". *Drug Dev Ind. Pharm.*, 22(6), 531-539.
- Dwivedi, S. and Kumar, V., 2011, "Floating Drug Delivery systems – A Concept of Gastroretention Dosage Forms", *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2(4), 1413-1426
- Faivre V., 2004, Aspects theoriques de la bioadhesion. In: Falson- Rieg V, Faivre V, Pirot F. ed. Nonvelles forms medicamenteuses , Editions Medicales Internationales, Editions TEC and DOC, Cachan.. p. 1-24.
- Fatemeh A., Rudabeh V., Rassoul D., 2004, "Preparation Of Ethylcellulose Coated Gelatin Microspheres As A Multiparticulate Colonic Delivery System For 5-Aminosalicilic Acid", *Iranian J of Pharm.Res*, 3, (2), 81-86.
- Gangadharappa H.V., Pramod Kumar T.M., Shiva Kumar H.G., 2007, "Gastric Floating Drug Delivery Systems". *Indian J Pharm Educ Res*, 41 (4) 295-306.
- Gattani Y.S., Bhagwat D.A., Maske A.P., 2008, "Formulation and evaluation of intragastric floating drug delivery system of diltiazem hydrochloride", *Asian J Pharm*, 2, (4), 228-31.
- Gattani Y.S., 2010, "Floating Multiparticulate Drug Delivery Systems: An Overview", *International Journal of Pharma and Bio Sciences*,(2) 1-14.
- Garg R., Gupta G.D., "Progress in controlled gastroretentive delivery systems", 2008, Trop. J Pharm Res, 7, (3), 1055-1066.

- Girish S., Devendra K., Dhananjay M., 2007, “Preparation and invitro evaluation of bilayer and floating-bioadhesive tablets of Rosiglitazone Ma-leate”. *Asian Journal of Pharmaceutical sciences.,* 2(4), 161-169.
- Goole J., Vanderbist F., Aruighi K., 2007, “Development and evaluation of new multiple-unit levodopa Sustained release floating dosage forms”. *Int J Pharm.,* 334, 35-41.
- Kawatra Monika, Jain Upendra, Ramana Jaspreet, 2012, “Recent Advances in Floating Microspheres as Gastro-Retentive Drug Delivery System: A Review” Int J Recent Adv Pharm Res, 2(3) 5-23.
- Muthuamy K., Govindarajan G., Ravi T.K., 2005, “Preparation and evaluation of lansoprazole floating micropellets”, Indian J. Pharm. Sci., 67, (1), 75-79.
- Naggar V.F., El-Kamel A.H., Sokar M.S., Al Gamal S.S., 2010, “Preparation and Evaluation of Ketoprofen Floating Oral Delivery System”, Int. J. Pharm., 220, 13.
- Rocca D.J.G., Omidian H., Shah K2003, “Progresses in gastroretentive drug delivery systems”, Business Briefing, Pharmatech, 152-156.
- Santini J, Richards A.C., Scheidt R., Cima M.J. and Langer R., 2000, “Microchips as Controlled Drug-Delivery Devices”, Angew. Chem. Int. Ed., 39, 2396-407.
- Tiwari S.B., Murthy T.K., Pai M.R., Mehta P.R., Chowdhary P.B, 2003, “Controlled Release Formulation of Tramadol Hydrochloride Using Hydrophilic and Hydrophobic Matrix System”. AAPS PharmSciTech. 4 (3), E31.
- Vohra S.Y., Patil C.C., 2009, “Development and Characterization of Stavudine Microspheres Prepared using Different Polymers”. J Pharm Res. 2(5) 953-7.
- Vyas S.P., Khar R.K., 2006, “Gastroretentive systems in Controlled drug Delivery”, Vallabh Prakashan, Delhi, India, 197-217.
- Wilson K.R., Waugh A., 1996, “Anatomy and physiology in health and illness”, 9th ed. London: Churchill Livingstone.

- Yamamura, T.; Sudo, H.; Ishikawa, K.; Yamamoto, A. (1979). "Familial type I hyperlipoproteinemia caused by apolipoprotein C-II deficiency". Atherosclerosis 34 (1) 53–65.