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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING MICROSPHERES OF ACYCLOVIR

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ABSTRACT

The aim of present work is to prepare Gastroretentive floating microspheres of Acyclovir using Ethyl Cellulose and Eudragit L 100 as Polymer. Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time in stomach and to sustain the release of acyclovir. Floating microspheres of acyclovir were prepared. Acyclovir is Antiviral drug. The floating microspheres of acyclovir prolong the residence time by emulsion diffusion method using ethyl cellulose and eudragit L 100 as polymer. The floating microspheres was evaluated such as micrometric properties, particle size, Percentage yield, invitro buoyancy, entrapment efficiency, drug polymer compatability(IR study), SEM and drug release of microspheres. The micrometric properties was found to be good and SEM confirmed their hollow structure with smooth surface. Formulation F4 prepared with Ethyl cellulose drug:polymer ratio(1:4) which exhibited excellent micrometric properties, percentage yield, invitro buoyancy, entrapment efficiency and %drug release 99.36% for a period of 12hrs. Results show that as increase in drug:polymer ratio affects particle size, percentage yield, invitro buoyancy and drug release of microspheres. The data obtained in this study thus suggest that floating microspheres of acyclovir are promising for sustained drug delivery which can reduce dosing frequency.

INTRODUCTION

Oral route of drug administration is the most convenient and commonly used method of drug delivery but this route usually produces gastric emptying rate that varies from person to person with a short stomach transit time and the existence of large absorption window in the upper small intestine for several drug. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. 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. [1] Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. [2] 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 waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro

retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion modified shape systems or by the simultaneous administration of pharmacological agent, that delay gastric emptying. This review focuses on the principal mechanism of floatation to achieve gastric retention. [3-7]

The main objectives of these drug delivery systems are:

1. It would be single dose which releases the active ingredient over an extended period of time.
2. It should deliver the active entity directly to the site of action thus minimizing or eliminating the side effects. [8]

Acyclovir is an antiviral drug, effective in the treatment of herpes simplex Type I and II (HSV I and HSV II) and varicella zoster infections. Absorption of orally administered acyclovir is variable and incomplete, with a bioavailability of Ca.15-30%. The drug is absorbed in the duodenum after oral administration and hence preparation of a floating drug delivery system(FDDS) for acyclovir may increase oral absorption of the drug. [9]

MATERIALS: Acyclovir was purchased from KP Laboratories Ltd., Hyderabad, India. Ethyl cellulose, Eudragit L 100, Ethanol, Dichloromethane, Polyvinyl alcohol, and all other chemicals used were laboratory reagent grade.

METHOD: Floating microspheres were prepared by Emulsion solvent diffusion method. Weighed amount of acyclovir was mixed with ethyl cellulose (Drug:polymer ratio) (1:1, 1:2, 1:3, 1:4, 1:5) and eudragit L 100 (Drug:polymer ratio) (1:6, 1:7, 1:8, 1:9, 1:10) in a solution of ethanol:dichloromethane(1:1) at room temperature. The drug polymer solution was poured slowly glass tube in 200ml of water containing 0.75% w/v Polyvinyl alcohol maintained at constant temperature of 40°c and preparation was stirred at 300rpm for 1hour. The finely developed microspheres were then filtered, washed with water and sieved between 50 and 30 mesh size and dried overnight at 40°c.

DRUG-EXCIPIENTS COMPATIBILITY STUDIES

Fourier transform infrared (FTIR) spectroscopy: FT-IR studies were carried out on individual samples of ethyl cellulose, eudragit L 100, acyclovir and optimized formulation of microspheres (F4). The samples were mixed with IR grade KBr in the ratio of 1:100 and compressed using a hydraulic press under a pressure of 15000 lb. The pellets were scanned in an inert atmosphere over a wave number range of 4000-400 cm^{-1}.

EVALUATION TESTS

Micrometritic Properties: The microspheres were characterized by their micrometric properties, such as particle size, tapped density, compressibility index and flow properties.

Particle Size: The particle size of the microspheres was determined with an optical microspheres under regular polarised light, and mean particle size was calculated by measuring 100 microspheres (n=3) with the help of a calibrated oculometer.

Angle of repose: Angle of repose (θ) of floating microspheres measures the resistance to particles flow, and is calculated according to fixed funnel standing cone method. Where, (θ) is angle of repose, H/D is surface area of the free standing height of the microspheres heap that is formed on a graph paper after making microspheres flow from glass funnel.

Bulk Density: Bulk density of formulated microspheres was determined by taking a known mass of microspheres in a 5ml graduated measuring cylinder. The cylinder was dropped three times from a height of one inch at an interval of two seconds and the bulk density was calculated.

Tapped Density: Tapping method was used to calculate tapped density. Tapped density is the volume of powder determined by tapping using measuring cylinder containing weighed amount of sample and the tapped density was calculated.

Carr's (Compressibility) Index: This parameter was calculated from bulk density (the ratio of weighed quantity of microspheres to its volume), and tapped density.

Drug Content: The drug content of ethyl cellulose microspheres was determined by dispersing 50mg formulation (accurately weighed) in 10ml ethanol followed bt agitation with a magnetic stirrer for 12hr to dissolve the polymer and to extract the drug. After fitration through a 5µm membrane filter(Millipore), the drug concentration in the ethanol phase was determined spectrophotometrically at 243nm.

Percentage yield: The percentage yields of microspheres were calculated as the weight of the final product after drying to the initial weight of the drug and polymer used for the preparation of microspheres.

Entrapment Efficiency: The drug content of acyclovir loaded microspheres was determined by dispersing 100mg microspheres in 10ml of ethanol, which was stirred with a magnetic bead for 8hrs to extract the drug. The samples were diluted and analysed spectrometrically at 254nm and the percentage drug entrapment was calculated.

Floating behavior and *In vitro* buoyancy: 50mg of the microspheres were placed in 100ml of simulated gastric fluid(PH 1.2) containing 0.02% w/v tween20. The mixture was stirred at 100rpm on a magnetic stirrer. After 12hrs, the layer of buoyant microspheres was pipette and separated by filtration. Particles in the sinking particulate layer were also separated by filtration. Particles of both types were dried in desicators. Both the fraction of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

***In vitro* drug release study:** *In vitro* drug release studies of floating microspheres were performed using USP type I dissolution apparatus in 900ml of 0.1N HCL(PH 1.2) dissolution media at 100rpm and 37°C. At each specified interval 5ml of the sample was withdrawn and was replaced by equal volumes of fresh dissolution medium on each occasion. The sample was analyzed by UV Spectrophotometer at 286nm.

RESULTS AND DISCUSSION

Formulation of microspheres: Microspheres were prepared by using different concentration ratio of ethyl cellulose, drug and polymers, as shown in below **Table 1.**

DRUG-EXCIPIENTS COMPATIBILITY STUDIES

Fourier transform infrared (FTIR) spectroscopy: Drug and polymers identified by FTIR spectroscopy. The FTIR spectrum given below show that the peaks of the drug, polymer and optimized formulation 4.

FTIR Study showed that there was no major change in position of peaks obtained in alone and formulation, which shows that there was no interaction between drug and polymers.

EVALUATION TESTS

Microscopy: Microspheres were examined by optical Microscope to determine the particle size.

Morphology: Morphology of the microspheres was performed with the help of a Scanning Electron Microscope (SEM).

Evaluation of floating microspheres of Acyclovir: An attempt was made to prepare gastroretentive floating microspheres of acyclovir by using emulsion solvent diffusion method using polymers like ethyl cellulose and eudragit L 100 achieve an oral controlled release of the acyclovir. In the present study ten formulations were formulated by using ethtyl cellulose and eudragit L 100 in various proportions. All the formulations were subjected to evaluation. FTIR, Optic microscopy, particle size, percentage yield, percentage drug entrapment, in vitro buoyancy, and in vitro dissolution studies had shown satisfactory results. FTIR spectra were obtained for acyclovir pure drug, physical mixture of acyclovir and polymer and acyclovir floating microspheres **(Fig: 4,5,6)** were represented in the figure, the characteristics peaks of the acyclovir were compared with the obtained formulation. The principle peaks for the formulation were almost similar to that of drug.

Determination of Yield (%) and Drug Entrapment (%): The percentage yield of different formulation was in range 49-92% (as shown in **Table 2**)**.** The maximum percentage yield was found in F4. The drug Entrapment efficiency of the formulations (F1-F10) was estimated and the results were in the range of 61-91%.The drug Entrapment determination also showed that the drug was uniformly distributed throughout the preparation.

Table 1: Formulations with different Ratio of drug and polymers (Drug:Polymer)

Formulation Code	Ingredients		
	Drug	Ethyl Cellulose	Eudragit L 100
F1(1:1)	500mg	500mg	---
F2(1:2)	500mg	1g	---
F3(1:3)	500mg	1.5g	---
F4(1:4)	500mg	2g	---
F5(1:5)	500mg	2.5g	---
F6(1:1)	500mg	---	500mg
F7(1:2)	500mg	---	1g
F8(1:3)	500mg	---	1.5g
F9(1:4)	500mg	---	2g
F10(1:5)	500mg	---	2.5g

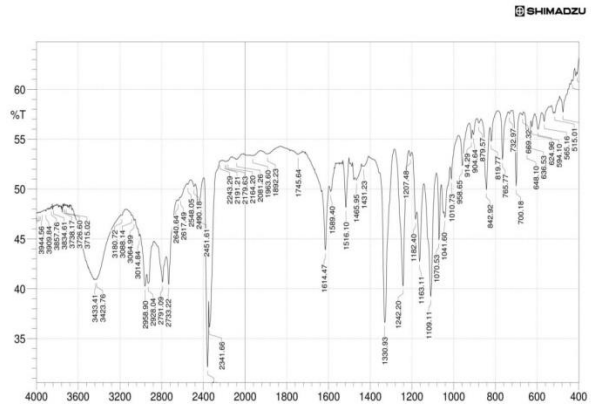

Figure No.1: FTIR spectrum of acyclovir

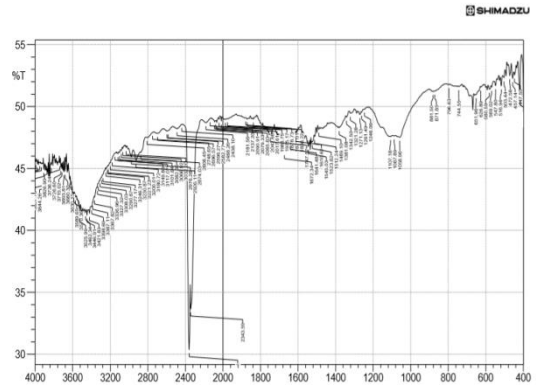

Figure No.2: FTIR spectrum of ethyl cellulose

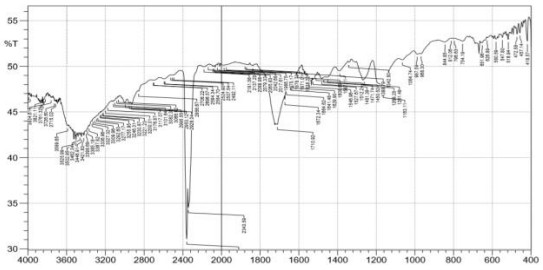

Figure No.3: FTIR spectrum of formulation

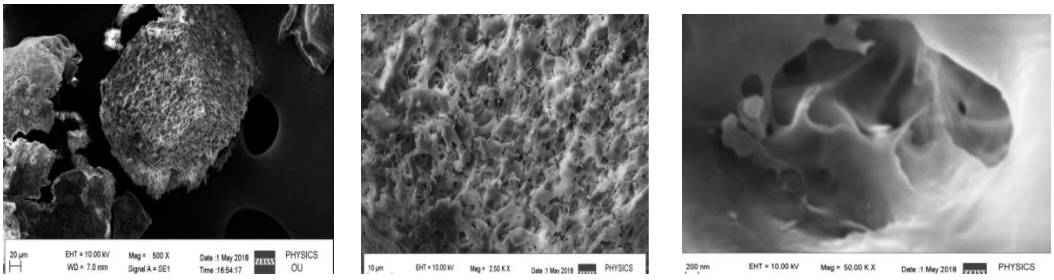

Figure No.4,5,6: SEM images of acyclovir microspheres

Formulation No	Percentage yield	Drug content in %	Entrapmet Efficiency (%)	% drug release	% buoyancy
F1(1:1)	49.20	39.20	61.09	94.86	68.51
F2(1:2)	76	47.50	72.27	95.76	80.80
F3(1:3)	84	58.50	86.72	87.60	87.92
F4(1:4)	92.50	91.50	91.50	99.36	92.40
F5(1:5)	94	88.90	81.56	94.08	87.50
F6(1:1)	40.60	50.10	70.07	87.66	70.58
F7(1:2)	51.20	62.50	81.06	84.42	83.89
F8(1:3)	75	69.50	85.56	97.32	86.72
F9(1:4)	82	82.50	89.27	96.10	89.28
F10(1:5)	88.80	90.70	90.06	93.52	80.80

Table 2: Percentage yield, Drug Content, Entrapment efficiency, Drug release, In vitro buoyancy of floating microspheres of Acyclovir

Table 3: Micrometric properties of floating microspheres of Acyclovir.

Formulation No	Particle size(µm)	Tapped density (gm/cm3)	Bulk density (gm/cm3)	Angle of repose (degree)	Compressibility Index (%)
F1(1:1)	118.06	0.262	0.123	2.6	35
F2(1:2)	128.06	0.258	0.127	2	30
F3(1:3)	133.06	0.255	0.129	2.2	30.8
F4(1:4)	114.04	0.251	0.108	1.7	25
F5(1:5)	121.01	0.254	0.180	1.7	40
F6(1:1)	122.08	0.265	0.138	2.2	28
F7(1:2)	136.09	0.267	0.135	2	34
F8(1:3)	123.08	0.259	0.137	2	39.5
F9(1:4)	124.02	0.302	0.136	1.7	40.9
F10(1:5)	193.02	0.263	0.152	1.7	60

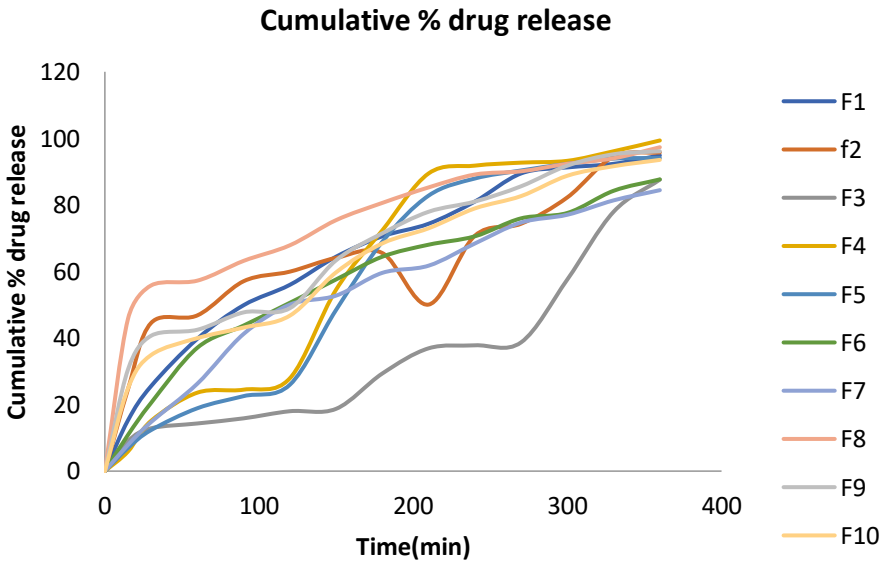

Figure No.7: In vitro release profile of Acyclovir floating microspheres for formulations F1-F10 in 0.1N HCl

Determination of percentage Buoyancy (%): The *in vitro* buoyancy test was carried out to investigate buoyancy of prepared microspheres. The microspheres formulations F1 to F10 showed good floating ability range from 68-92% (as shown in **Table 2**). The results also showed a tendency that, larger size longer the floating time.

Drug Content: The drug content of different formulation was in range 39% -91% the maximum drug content was found in F4.

***In vitro* drug release study:** The in vitro performance of acyclovir gastroretentive floating microspheres showed prolonged and controlled release of drug. The drug release of floating microspheres was in the range 94-99% as shown in **Table 2**.The maximum drug content was found in F4. The result of in vitro dissolution studies shows controlled manner as the polymer concentration increases the drug release from the floating microspheres decreases. The in vitro dissolution data described in **Table 2** and percent cumulative drug release profile (was showm in **figure 7**).

MICROMERITIC PROPERTIES: The angle of repose of different formulation was in range 2.6-1.7, Bulk and tapped densities showed good pack ability of floating microspheres. The particle size of different formulation was in range 118-122%. The tapped density of different formulation was in range 0.20-0.25. The bulk density of different formulation was in range 0.23-0.152 (as shown in **Table 3).**

Scanning Electron Microscopy (SEM): Morphology of floating microspheres was examined by scanning electron microscopy. The view of the microspheres showed hollow structure with a rough surface morphology(**fig.4,5,6)** exhibited ranges of sizes within each batch. The outer surface of microspheres was smooth and dense, while the internal surface was porous. The shell of microspheres also showed some porous structure it may be caused by the evaporation of solvent entrapped within the shell of microsphere after forming smooth and dense area.

Particle size: The particle size of different formulation was in range 118-114%(as shown in **Table 3**)**.** The tapped density of different formulation was in range 0.262-0.251. The bulk density of different formulation was in range 0.123-0.108. The angle of repose of different formulation was in range 2.6-1.7.

***IN VITRO* DRUG RELEASE STUDY:** *In vitro* drug release studies of floating microspheres were performed using USP type I dissolution apparatus in 900ml of 0.1N HCL (PH 1.2) dissolution media at 100rpm and 37°C. At each specified interval 5ml of the sample was withdrawn and was replaced by equal volumes of fresh dissolution medium on each occasion. The sample was analyzed by UV Spectrophotometer at 286nm. Formulation with different ratio(F4) showed high release of drug when compared to formulations with other ratio(F1,F2,F3,F5,F6,F7,F8,F9,F10). The plot of cumulative percentage V/s time (min) for all formulations was plotted and depicted in Figure: **7** respectively.

CONCLUSION

Floating microspheres of acyclovir with acrylic polymers such as Eudragit L 100 and Ethyl cellulose were successfully prepared by the emulsion solvent diffusion method. The formulation F4 with drug: polymer ratio (1:4) was found to be satisfactory in in terms of excellent micrometric properties, yield of microspheres (88.00%), drug entrapment efficiency(91.50%), drug content(91.50%), invitro buoyancy (92.40%), and highest invitro drug (99.36%) in sustained manner with constant fashion over extended period of time for 12hrs. From the results it was observed that Drug: Polymer ratio influences the particle size, in vitro buoyancy, as well as drug release pattern of floating microspheres.

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REFERENCES

1. Yasunori Sato, Yoshiaki Kawashima, Hirofumi takeuchi, hiromitsu yamamoto. In vitro evaluation of floating and drug releasing behaviour of hollow microsphers (microballoons)

prepared by emulsion solvent diffusion method. European journal of pharmaceutics and biopharmac eutics 2004; 57: 235– 243.

2. Varshosaz, Tabbakhian, M.Zahrooni. Development and Characterization of floating microballoons for oral delivery of cinnarazine by a factorial design. Journal of microencapsulation 2007; 24 (3): 253–262.

3. Kumaresh S. Soppimath, Anandrao R Kulkarni, Tejraj M Aminabhavi. Development of Hollow Microspheres as Floating Controlled-Release Systems for Cardiovascular Drugs: Preparation and Release Characteristics. Drug Development and Industrial Pharm acy 2001; 27(6): 507-515.

4. Martindale,the complete drug refrence, 3 3 rd edition, edited by sean c.sweetman, published by pharmaceutical press, londo n, 2002:11:65: 47-48.

5. Klaus Florey. Analytical profiles of drug substances. Elsevier, New Delhi, 2006; 443-471.

6. Basavaraj BV, Deveswaran R, Bharath S, Sindhu Abraham, Sharon Furtado, Madvan V. Hollow microspheres of diclofenac sodium – A gastroretentive controlled drug delivery system. Pakistan journal of pharmaceutical sciences 2008; 21(4):451- 454.

7. Yogesh S Gattani, Durgacharan A Bhagwat, Akhil P Maske. Formulation and evaluation of intragastric floating drug delivery system of dilitiazem hydrochloride. Asian journal of pharmaceutics 2008; oct-dec:228-231

8. Asha Patel, Subhabrata Ray, Ram Sharangat Thakur. In vitro evaluation and optimization of controlled release floating drug delivery system of metformin hydrochlor ide. DARU 2006; 14(2): 57–64.

9. Yuveraj Singh Tanwar, Pushpendra Singh Naruka, Garima Rani Ojha. Development and evaluation of floating microspheres of verpamil hydrochloride. Brazilian Journal of Pharmaceutical Sciences 2007; 43 (4): 529–534.

10. Shashikant P Bharate, Yogesh S rupnvar, Rupesh M Sonvane, Kapil R. Pawar, Rahulkumar P Rahane. Formulation and evaluation of floating microspheres of ketrolac trometamol. International journal of pharmaceutical research and development online 2009; 1(9): 1-8

11. Parul trivedi, AML verma, N garud. Preparation and characterization of aceclofenac microspheres . Asian journal of pharmaceutics 2008; APRIL: 110-115.

12. Saravanan, K.Bhaskar, G.Srinivasa Rao and M.D. Dhanaraju. Ibuprofen loaded ethylcellulose / polystyrene microsphers an approach to get prolonged drug release with reduced burst effect and low ethylcellulose content. J.Microencapsulation 2003; 20 (3): 289–302.

13. R D kale, P T Tayade. A multiple unit floating drug delivery system of piroxicam using eudragit as pol ymer. Indian journal of pharmaceutical sciences 2007:jan-feb: 12 0-123.

14. Ashishkumar jain, C P Jain, Y S Tanwar, P S Naruka. Formulation, characterization and in vitro evaluation of floating microspheres of famotidine as a gastroretentive dosage form. Asian journal of pharmaceutics 2009; jul-sep: 222-226

15. Haznedar, B Portune. Preparation and in vitro evaluation of eudragit microspheres containing acetazolamide. International journal of pharmaceutics 2004;269: 131-140

16. Mostafa Safari, Malihe Shahbazi, Shafee ardestani. Formulation and in vitro evaluation of eudragit L 100

micropshere of piroxicam. Nature preceddings 2008:1-5.

17. Amol Pahuri, aweshik yadav, sunil k jain, shyam s Panholi, govind agrawal. Eudragit coated pectin microspheres of 5- flurouracil for colon targeting. AAPS pharscitech 2007;8(1): E87-E93.

18. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv. 2006; 3: 217-233.

19. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery viagastric retention. J. Control. Release. 2000; 63: 235-239.

20. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: An in vivo study demonstrating prolonged gastric retention. J Control Release. 1998; 55: 3-12.

21. Rouge N., Leroux J C, Cole E T, Doelker E, Buri P. Prevention of the sticking tendency of floating minitablets filled into hard gelatin capsules. Eur. J. Pharm. Biopharm. 1997; 43: 165-171.

22. Muriel P, Mourelle M. Prevention by siymarin of membrane alterations in acute CCl4 liver damage. J Appl Toxicol. 1990; 10: 275.

23. Sonnenbichler J, Zetl I. Biochemical effects of the flavonolignan silibinin on RNA, protein and DNA synthesis in rat liver. Progr Clin Biol Res. 1986; 213: 319-31.

24. Kawashima Y, Niwa T, 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: 135-140.

25. Martin A. Micromeritics. Physical Pharmacy, fourth ed. Lea Feiger, Philadelphia, 1993: 431-432.

26. Lin S, Kao Y. Solid particulates of drug bcyclodextrin inclusion complexes directly prepared by a spray drying technique. Int J Pharm. 1989; 56: 249-259.

27. Sinha VR, Agarwal MK, Kumaria R. Influence of formulation and excipients variables on the pellet properties prepared by extrusion spheronization. Curr. Drug Delivery. 2005; 2: 1-8. 28. The United State Pharmacopoeia XXIV, United state Pharmacopoeial Convention, Rock Ville 2000: pp 1941-1943.

28. Okor RS, Obi CE. Drug release through aqueous based film coatings of acrylate-methacrylate, a water insoluble copolymer. Int J Pharm. 1990; 58: 89-91.

29. Li CL, Martini LG, Ford JL, Roberts M. The use of hypromellose in oral drug delivery. J Pharm Pharmacol. 2005; 57: 533-546.

30. Moldenhauer M, Nairn J. The control of ethyl cellulose microencapsulation using solubility parameters. J Control Release. 1992; 22: 205- 218.

31. Bramhankar et al. Biopharmaceutics and pharmacokinetics. Vallabh prakashan. (2009) 434-438. 2. A. Sharma et al. Gastroretentive drug delivery system: an approach to enhance gastric retention for prolonged drug release. International journal of pharmaceutical sciences and research, 5,4 (2014) 1095-1106.

32. Vadaliya et al. Gastro-Retentive Floating Drug Delivery System Containing Anti-Diabetic Drug - An Overview. International journal of pharmaceutical and chemical sciences. 1, 4 (2012) 1322.

33. Gholap et al. Hollow microsphere: a review. International Journal of Pharmaceutical Sciences Review and Research, 1, 1 (2010) 74-77.

34. Yadav et al. The Need of Floating Drug Delivery System: A Review. Res J Pharm Bio Chem. Sci., 1, 2 (2010) 396-402.

35. Anne et al. Anatomy and Physiology in Health and Illness. Elsevier, 128 (2006) 293-297.