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Formulation and Characterization of Mucoadhesive Microparticulate Drug Delivery System Encapsulated With Silymarin

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ABSTRACT

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface and increase the residence time of the dosage form at the absorption site. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. Silymarin (SLM) is an effective hepatoprotective drug used in therapeutic practice today. However, its absorption is in stomach and needs to be retained in the same for prolonged period. So SLM is suitable candidate to develop into mucoadhesive drug delivery system. The objective of the present study was to formulate mucoadhesive microspheres of Silymarin and carryout evaluation of the formulated microspheres. In the present study, five formulations of microspheres with variable concentrations of mucoadhesive polymer and film forming polymer (HPMC & EC) were prepared by Emulsification solvent evaporation method and evaluated for physico-chemical, preformulation and formulation parameters. Compatibility studies proved that there was no interaction between Silymarin and polymers used. Silymarin microspheres were smooth and spherical in nature, which was confirmed by SEM. The *in vitro* performance of SLM microspheres showed controlled release depending on the concentration of mucoadhesive polymer. Finally it can be concluded that mucoadhesive microspheres encapsulated with optimum concentration of mucoadhesive polymer and film forming polymer showed better results in all the evaluated parameters making it a potential candidate for controlled release drug delivery system.

Keywords: Mucoadhesive Microspheres, Controlled Release, HPMC, EC.

INTRODUCTION

Oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation in the body. However oral administration of most of the drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastrointestinal tract. In order to circumvent this problem, it has been proposed, to associate drugs to polymeric particulate systems because of their propensity to interact with the mucosal surface. This property is not only used for the local targeting of drugs but also for a better control of systemic delivery.

Thus the real issue in the development of oral controlled release drug delivery systems is to provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, through the predominantly controlled release profiles

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by special technological construction and design of the system itself. The idea of using bioadhesive polymers to prolong the contact time in the mucosal route of drug delivery was introduced in early 1980s, and since then it has attracted considerable attention from pharmaceutical scientists. The concept of mucoadhesive drug delivery is based on the bioadhesive property of certain polymers that becomes adhesive on hydration and hence can be used for localizing the drugs to a particular region of gastrointestinal tract and to extend the gastric residence time. Once the dosage form sticks to the mucosal surface of gastric tissue, it will reside there until removed by turnover of mucins. Recent advances pertaining to drug delivery systems incorporate different type of polymers within the matrix of drug delivery systems to protect the active ingredient and to induce slow release characteristics. [1-6]

There has been considerable interest in the field of mucoadhesive drug delivery systems since the immobilization of drug carrying particles at mucosal surface would result in:

1. A prolonged residence time at the site of drug action or absorption. [7]
2. A localization of drug action of the delivery system at a given target site. [8-9]
3. An increase in the drug concentration gradient due to the intense contact of particles with the mucosal. [10]
4. A direct contact with intestinal cells that is the first step before particle absorption.

Microspheres form an important part of novel drug delivery systems. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres. [11-16]

Bioadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site. Mucoadhesive microspheres that are retained in the stomach would increase the drug absorption and decrease dosing frequency which provides better patient compliance as compared to conventional dosage forms. [17-19]

In the present work Silymarin (SLM) was chosen as the drug to formulate the gastro retentive drug delivery system like mucoadhesive microspheres. Silymarin (SLM) is one of the most powerful drugs for the hepatic diseases. It is known for its hepatoprotective action against hepatic glutathione depletion induced by ethyl alcohol and paracetamol in animal studies. Silymarin degrades as the pH increases. Hence it is necessary to dissolve it in less pH for the protection of the drug and to reduce the gastric disturbance and more over, the site of absorption of SLM is in the stomach pH. Hence it is suitable to formulate silymarin as mucoadhesive microspheres to reduce frequency of dosing, prevent the drug from degradation in the intestinal pH and increases its shorter biological half life. [20-21]

The SLM is degraded as the pH increases so it is necessary to dissolve in the less pH for the protection of the drug and to reduce the gastric disturbance and more over, the site of absorption of SLM is in the stomach pH. Hence it is suitable to formulate SLM as mucoadhesive microspheres to reduce frequency of dosing and to prevent the drug from degradation in the intestinal pH. To overcome inherent drawbacks associated with conventional dosage forms of Silymarin, an attempt is being made to develop an alternative drug delivery system in the form of mucoadhesive microspheres which increases its stability, biological half life and bioavailability in stomach.

MATERIALS & METHODS

Preparation of Mucoadhesive Microspheres of Silymarin: [22-23] For present study, variable concentrations of film coating polymer ethyl cellulose combined with mucoadhesive polymer hydroxy propyl methyl cellulose are used with the active ingredient for preparation of mucoadhesive microspheres.

Accurately weighted amount of the Mucoadhesive polymer hydroxy propyl methyl cellulose and film forming polymer ethyl cellulose as shown in Table 1 were dissolved in 50 ml of acetone to form a homogenous polymers solution. Silymarin was then dispersed in it and mixed thoroughly. This organic phase containing drug was slowly poured at 150°C into liquid paraffin (50 ml) containing 1% (w/w) of Span-80 with stirring at 1000 rpm to form a uniform emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth-walled, rigid and discrete microspheres were formed. The microspheres were collected by decantation and the product was washed with petroleum ether or n- hexane and dried at room temperature for 3 hours. The microspheres were then stored in a desiccators over fused calcium chloride.

Evaluation of Drug Loaded Mucoadhesive Microspheres

Drug polymer interaction (FTIR) study: [24] Drug polymer interactions were studied by FT-IR spectroscopy. One to 2 mg of Silymarin alone, mixture of drug and polymer, drug loaded microspheres were weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR- spectrum of the pellet from 500–4000 cm^{-1} was recorded taking air as the reference and compared to study any interference.

Scanning Electron Microscopy (SEM): [25] Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. Dry Silymarin mucoadhesive microspheres were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of Silymarin microspheres were taken by random scanning of the stub.

Frequency distribution analysis: [26] The diameter of a sample of mucoadhesive microspheres (300 no) of each formulation was determined using optical microscopy. In order to be able to define a frequency distribution or compare the characteristics of particles with many different diameters, the frequency distribution can be broken down into different size ranges, which can be presented in the form of a histogram.

Percentage yield: [27] Percentage practical yield of Silymarin microspheres was calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Silymarin microspheres recovered from each batch in relation to the sum of starting material.

The percentage yield of Silymarin microspheres prepared was determined by using the formula.

Percentage Yield = Actual weight of product / Total weight of drug and polymer × 100

Drug Content: [28] To determine the drug content and encapsulation efficiency of the mucoadhesive microspheres, 200 mg microspheres were crushed using a porcelain mortar and a pestle, and dispersed in suitable solvent (methanol). The dispersion was sonicated for 15 minutes and left overnight for 24 hrs, then the dispersion was filtered. A 1 ml sample was taken and diluted with suitable solvent (methanol), and drug content assayed using a UV-visible spectrophotometer at λ_{max} of 287 nm. The drug content of each formulation was recorded as mg / 200 mg of microspheres.

Drug Entrapment Efficiency: [29] The drug entrapment efficiency of prepared microspheres was determined by using the following equation.

EE (%) = [Actual Drug Content / Theoretical Drug Content] × 100

Drug Loading was calculated as:

DL (%) = [Actual Drug Content / Weight of Powdered Microspheres] × 100

Degree of Swelling: [30] The swell ability of microspheres in physiological media was determined by swelling them in the PBS pH 6.4. Accurately weighed 100 mg of microspheres were immersed in little excess of PBS pH 6.4 for 24 hrs and washed.

The degree of swelling was calculated using following formula:

$$\alpha = (W_s - W_o) / W_o$$

Where α is the degree of swelling; W_o is the weight of microspheres before swelling; W_s is the weight of microspheres after swelling.

Table 1: Formulation Design of Silymarin Mucoadhesive Microspheres

S. No.	Ingredients	Formulation Code				
		F_1(g)	F_2(g)	F_3(g)	F_4(g)	F_5(g)
1	Silymarin (SLM)	1	1	1	1	1
2	HPMC	0.1	0.15	0.2	0.25	0.3
3	Ethyl Cellulose	0.8	0.75	0.7	0.65	0.6
4	Liquid Paraffin (ml)	50	50	50	50	50
5	Span 80 (ml)	1	1	1	1	1

Table 2: Percentage Yield, Particle Size, Percent Encapsulation, Percent Drug Loading

Code	Percentage Yield	Particle Size (μm)	Percent Encapsulation	Percent Drug Loading
F_1	74.28	289.43	94.35	25.06
F_2	76.73	310.54	91.71	23.23
F_3	81.98	320.45	88.91	20.35
F_4	88.86	346.07	86.88	18.14
F_5	94.54	387.75	84.25	16.17

Table 3: Degree of swelling and Percent Mucoadhesion

S. No	Formulation Code	Degree of Swelling	Percentage Mucoadhesion
1	F_1	1.03	81.23
2	F_2	1.26	85.42
3	F_3	1.47	89.18
4	F_4	1.59	93.67
5	F_5	1.74	98.91

***In vitro* Mucoadhesion Studies:** [31] *In vitro* mucoadhesion studies of microspheres were assessed using falling liquid film technique. A small portion of the sheep intestinal mucosa was mounted on a glass slide and accurately weighed microspheres were sprinkled on the mucosa. This glass slide was kept in desiccator for 15 min to allow the polymer to interact with the membrane and finally placed in the cell that was attached to the outer assembly at an angle of 45°. Phosphate buffer solution pH 6.4, previously warmed to 37 ± 5°C was circulated all over the microspheres and membrane at the rate of 1 ml/min. Washings were collected at different time intervals and microspheres were collected by centrifugation followed by drying at 50°C. The weight of washed out microspheres was determined and percent mucoadhesion was calculated by following formula:

$$\% \text{ Mucoadhesion} = (W_a - W_l) \times 100 / W_a$$

Where, W_a = weight of microspheres applied; W_l= weight of microspheres leached out.

***In vitro* dissolution studies:** [32-34] The release rate of Silymarin mucoadhesive microspheres was determined by employing USP XXIII apparatus II (Rotating basket method). The dissolution test was performed using 900 ml 0.1N HCL, in 37 ± 0.5°C at 50 rpm. Silymarin mucoadhesive microspheres equivalent to 100 mg of Silymarin was used for the study. At various time points (hourly) 5 ml of the sample solution was withdrawn from the dissolution apparatus for up to 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at 287nm. Dissolution profiles of the formulations were analyzed by plotting cumulative percentage drug release versus time. The data obtained were also subjected to kinetic treatment to understand release mechanism.

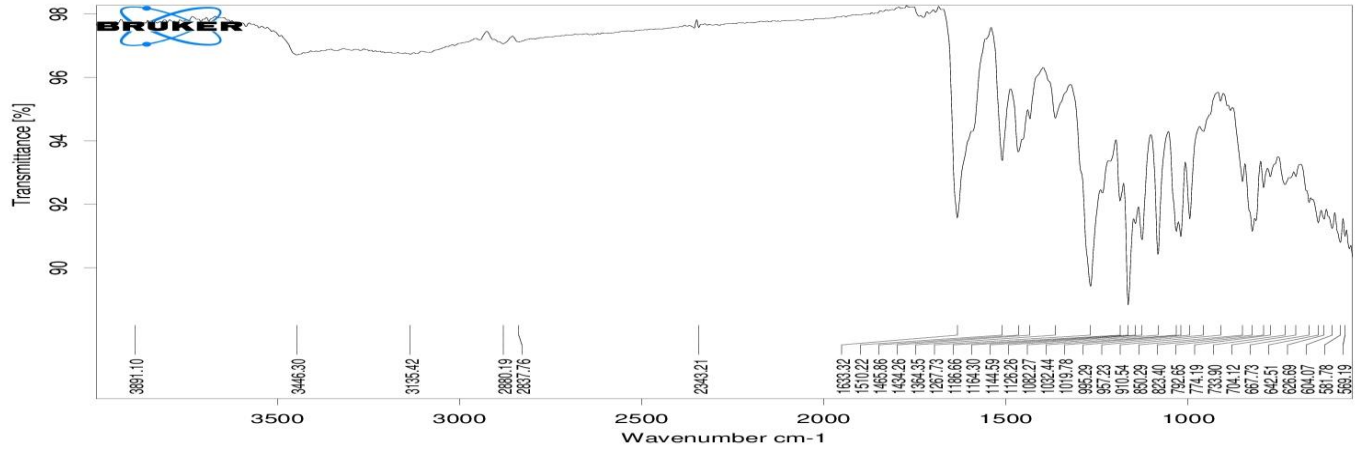

Fig. 1: FTIR spectrum of pure Silymarin

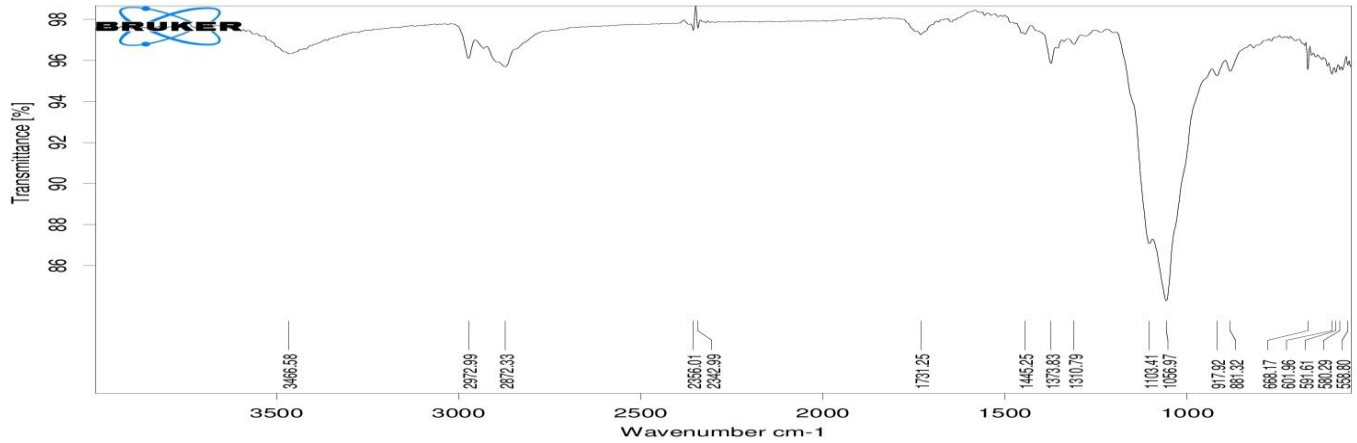

Fig. 2: FTIR spectrum of Ethyl Cellulose

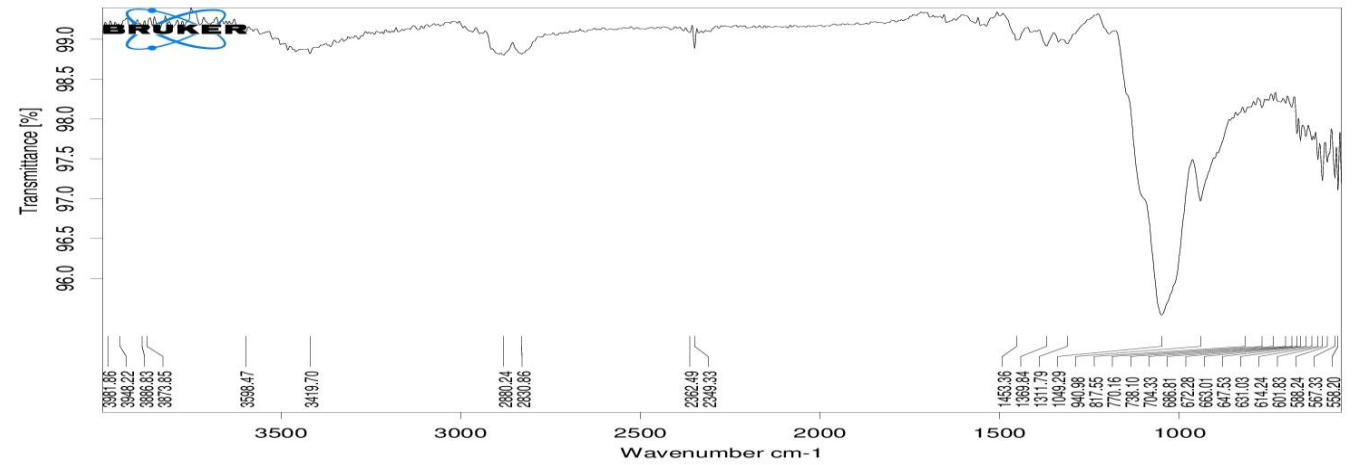

Fig. 3: FTIR spectrum of HPMC

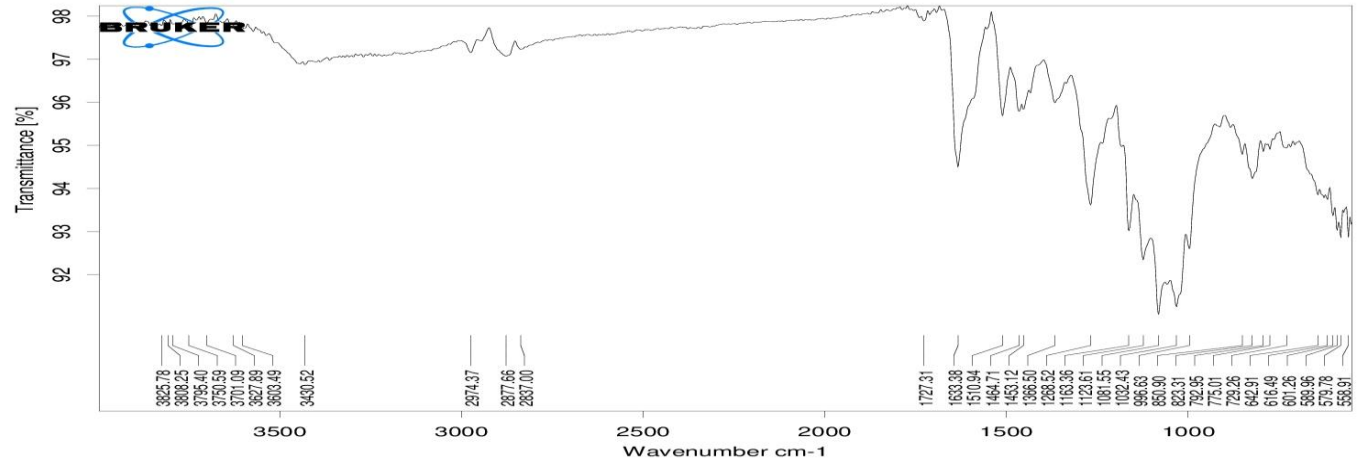

Fig. 4: FTIR spectrum of physical mixture of Drug + Ethyl Cellulose + HPMC

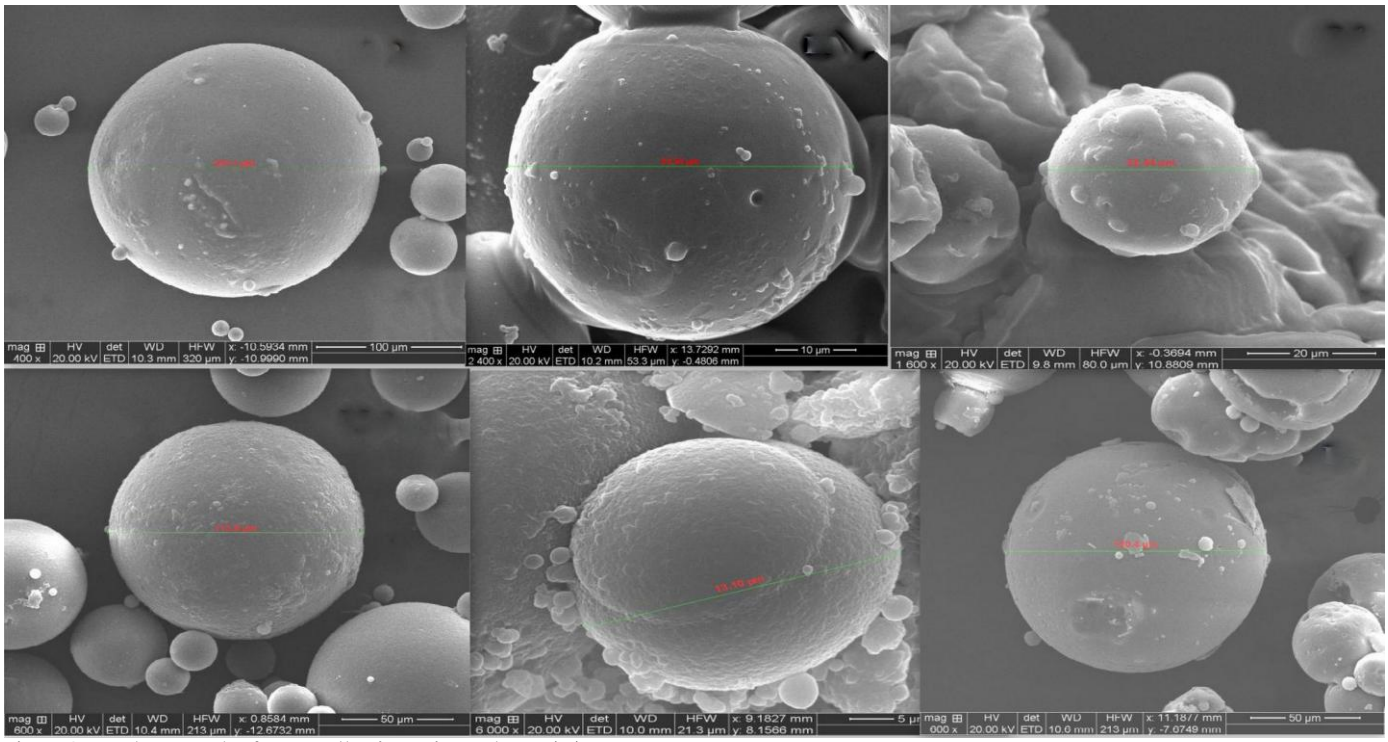

Fig. 5: SEM Photograph of Mucoadhesive Microspheres (F_3)

RESULTS & DISCUSSION

In the current research, mucoadhesive microspheres encapsulated with Silymarin were formulated using emulsification solvent evaporation method and evaluated.

FTIR Studies: The physical mixture of drug and polymers showed identical spectrum with respect to the spectrum of the pure silymarin, indicating there is no chemical interaction between the drug molecule and polymers used. (Fig. 1-4)

Scanning Electron Microscopy (SEM): Scanning electron microscopy confirms the outer surface of the formulations was smooth and dense, while the internal surface was porous. The shell of microspheres also showed some porous structure which may be caused by evaporation of solvent entrapped within the shell of microspheres after forming smooth and dense layer.

Particle Size and Frequency Distribution Analysis: The mean particle size of mucoadhesive microspheres was in range of 289.43-387.75µm (Table 2 & Fig. 6). As the ratio of HPMC was increased, the mean particle size of SLM microspheres had also increased. The significant increase may be due to the increase in the viscosity of the droplets. SLM mucoadhesive microspheres having a size range of 200 to 500 µm (Fig 7) with normal frequency distribution was obtained.

Percentage Yield: For different formulations percentage yield was calculated by weighing the microspheres after drying. The percentage yield of mucoadhesive microspheres was in range of 74.28 – 94.54% (Table 2 & Fig. 8).

Percent Encapsulation Efficiency and Percent Drug loading: Entrapment efficiency decreased with increase in the mucoadhesive polymer concentration. From the results it can be inferred that there is a proper distribution of SLM in the microspheres and the deviation were within the acceptable limits. The percent of drug content in the formulations were found to be in the range of 16.17% to 25.06%. The percentage entrapment efficiency was found to be 84.25% to 94.35%. The results obtained are given in Table 2 and their histograms are shown in Fig. 8.

Degree of swelling and Percent Mucoadhesion: Degree of swelling and percentage mucoadhesion of the formulations were carried out and were found to be within the range between 1.03 to 1.74 and 81.23 to 98.91%. Both parameters increased with increase in the concentration of mucoadhesive polymer.

***In vitro* Dissolution Studies:** The *in vitro* performance of SLM microspheres showed prolonged and controlled release of SLM. The results of the *in vitro* dissolution studies showed controlled release in a predictable manner. As the mucoadhesive polymer concentration was increased, the drug release from the mucoadhesive microspheres was found to decrease. However, all the formulations had an optimum release at the end of 12th hour. The *in vitro* release profiles of all the formulations (F_1 to F_5) are shown in Table 4 and Fig. 9.

Release kinetics of Silymarin Mucoadhesive Microspheres: The slopes and the regression co-efficient of determinations (r^2) were listed in Table 5. The co-efficient of determination indicated that the release data was best fitted with zero order as-well-as first order kinetics. Higuchi equation explains the diffusion controlled release mechanism. The diffusion exponent 'n' values of Korsemeyer-Peppas model was found to be in the range of 0.5 to 0.6 for the SLM mucoadhesive microspheres indicating Non-Fickian release of drug.

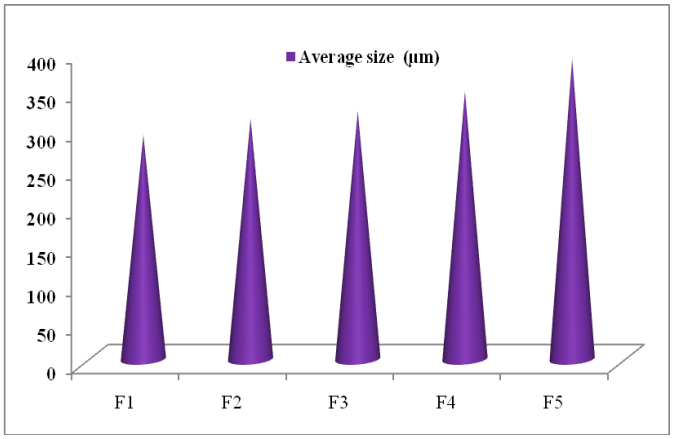

Fig. 6: Average diameter of Silymarin Mucoadhesive microspheres

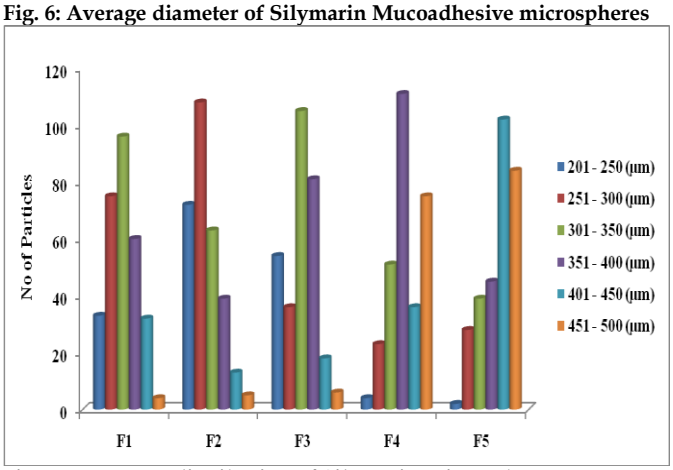

Fig. 7: Frequency distribution of Silymarin Microspheres

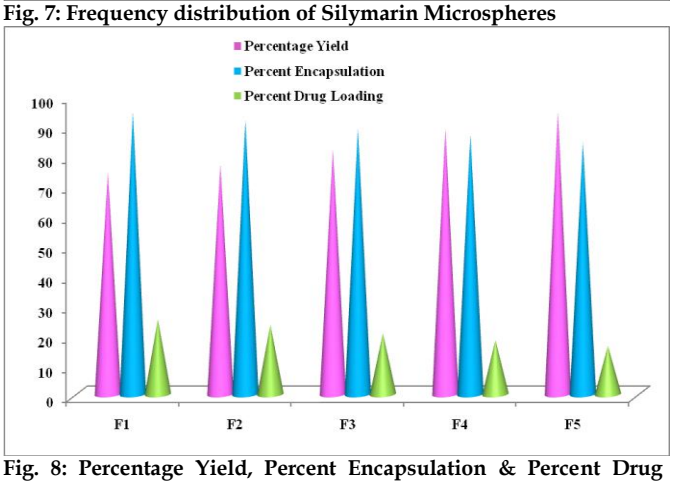

Fig. 8: Percentage Yield, Percent Encapsulation & Percent Drug Loading

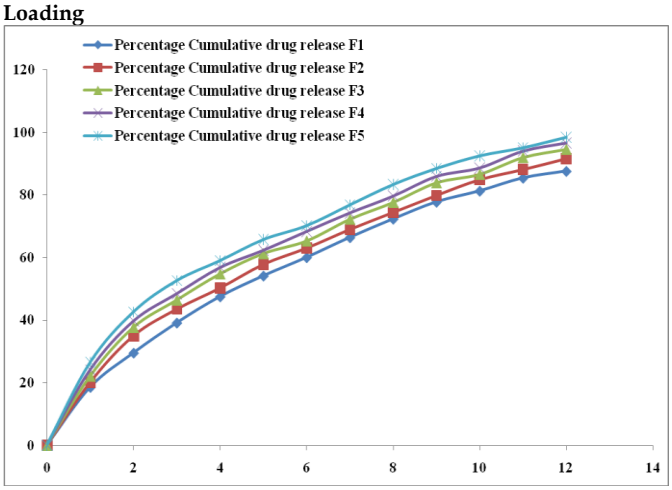

Fig. 9: Comparative *in vitro* release profile of Silymarin loaded microspheres

Table 4: *In vitro* release data of Silymarin Mucoadhesive Microspheres

Time (hrs)	Percentage Cumulative drug release				
	F_1	F_2	F_3	F_4	F_5
0	0	0	0	0	0
1	18.57	20.12	22.1	24.1	26.5
2	39.54	34.96	37.67	39.67	42.67
3	29.15	43.53	46.43	48.43	52.69
4	47.54	50.28	54.78	56.78	59.09
5	54.18	57.83	61.27	62.27	65.82
6	60.07	63.06	65.3	68.3	70.26
7	66.46	69.03	72.24	74.24	76.91
8	72.36	74.46	77.61	79.61	83.42
9	77.81	79.9	83.89	85.89	88.58
10	81.33	84.94	86.61	88.61	92.61
11	85.47	88.18	91.97	93.97	95.19
12	87.66	91.66	94.58	96.58	98.55

Table 5: Regression co-efficient (r^2) values of different kinetic models and diffusion exponent (n) of Peppas model for Silymarin Microspheres

Formulation	Zero order	First order	Higuchi Matrix	Peppas plot	
				R^2 value	'n' value
F_1	0.888	0.953	0.990	0.970	0.599
F_2	0.935	0.903	0.997	0.996	0.537
F_3	0.908	0.911	0.996	0.989	0.522
F_4	0.920	0.971	0.997	0.991	0.550
F_5	0.936	0.984	0.997	0.996	0.578

From the study it is evident that mucoadhesive microspheres are more promising for controlled release dosage forms. By studying all the results, mucoadhesive microspheres encapsulated with Silymarin can be successfully formulated by emulsification solvent evaporation method. By incorporating mucoadhesive polymer such as HPMC and film forming polymer like ethyl cellulose in the shell of microspheres, the rate of drug release can be modulated in a controlled manner. Therefore formulation F_3 containing optimum concentration of mucoadhesive polymer and film forming polymer showed the best appropriate balance between mucoadhesion and controlled release and is considered as the ideal batch of formulation.

REFERENCES

1. Khan GM. Controlled release oral dosage forms: Some recent advances in matrix type drug delivery systems. The Science 2001; 1(5): 350-354.
2. Ponchel G, Irache Jaun M. Specific and non-specific bioadhesive particulate systems for oral delivery to gastrointestinal tract. Advanced Drug Delivery Reviews 1998; 34: 191-219.
3. Ahmed A, Bonne C, Desai AT. Bioadhesive microdevices with multiple reservoirs: a new platform for oral drug delivery. Journal of Controlled Release 2002; 81: 291-306.
4. Lee TW, Robinson JR. Controlled release drug delivery systems: In Gennaro, A.R. (ed.) Remington Pharmaceutical Sciences, Edn 20, Lippincott Williams and Willkins, Philadelphia. 2000, 903-929.
5. Sachan NK, Bhattacharya A. Basics and Therapeutic Potential of Oral Mucoadhesive Microparticulate Drug Delivery Systems. IJPCR. 2009; 1(1): 10-14
6. Bernkop SA. Mucoadhesive systems in oral drug delivery. Drug discovery today: Technologies 2005; 2 (1): 83-86.
7. Jasti DrsB, Li X, Cleary G. Recent advances in mucoadhesive drug delivery systems. Business briefing: Pharmtech. 2003: 194-197.

8. Ben HL, Leeuw BJ, Perrad D. Bioadhesive polymers for the per-oral delivery of peptide drugs. Journal of Controlled Release 1994; 29: 329-338.
9. Ben HL, Leeuw, BJ, Perrad D. Mucoadhesive excipients for the per-oral delivery of peptide drugs. European Journal of Pharmaceutics and Biopharmaceutics 1996; 4: 117-128.
10. Longer MA, Cheng HS, Robinson JR. Mucoadhesive materials for controlled release dosage forms. Journal of Pharmaceutical Sciences 1985; 74: 406-410.
11. Dhakar RC, Maurya SD, Aggarwal S, Kumar G, Kumar Tilak VK. Design and Evaluation of SRM Microspheres of Metformin Hydrochloride. Pharmacie Globale IJCP. 2010; 1(1): 1-5.
12. Rajput G, Majumdar F, Patel J, Thakor R, Rajgor NB. Stomach Specific mucoadhesive microspheres as a controlled drug delivery system. Sys Rev Pharm. 2010; 1(1): 70-78.
13. Capan Y, Jiang G, Giovagnoli S, DeLuca PP. Preparation and characterization of poly (D, L-lactide-co-glycolide) microsphere for controlled release of human growth hormone. AAPS Pharm Sci Tech. 2003; 4: E28.
14. Gohel MC, Amin AF. Formulation optimization of controlled release diclofenac sodium microspheres using factorial design. J Control Release. 1998; 51: 115-122.
15. Nagai T, Nishimoto Y, Nambu N, Suzuki Y, Sekine K. Powder dosage form of insulin for nasal administration. J Control Release. 1984; 1: 15-22.
16. Ilium L, Farraj NF, Critchley H, Davis SS. Nasal administration of gentamicin using a novel microsphere delivery system. Int J Pharm. 1988; 46: 261-265.
17. Wang J, Tabata Y, Bi D, Morimoto K. Evaluation of gastric mucoadhesive properties of aminated gelatin microspheres. J Control Release. 2001; 73(2–3):223–231.
18. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. *In vitro* evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int J Pharm. 1992; 78: 43-48.
19. Chowdary KPR, Rao YS. Design and *in vitro* and *in vivo* evaluation of mucoadhesive microcapsules of glipizide for oral controlled release: a technical note. AAPS Pharm Sci Tech. 2003; 4: E39.
20. Gavini V, Murthy MS, Kumar PK, Radhika DL. Formulation and *In vitro* Evaluation of Mucoadhesive Microspheres loaded with Stavudine using Hydrophilic Macromolecular Polymers. RJPDFT. 2014; 6(2): 99-104.
21. Gavini V, Ganesh NS. Formulation & Evaluation of Mucoadhesive microspheres of macromolecular polymers using Flurbiprofen as model drug. Der pharmacia Lettre. 2012; 4(5): 1560-1566.
22. Boddupalli BM, Mohammad ZNK, Ramani R, Anisetti RN, Banda K, Mudium NM, Banji D. Formulation and evaluation of mucoadhesive microspheres of venlafaxine hydrochloride. Journal of Pharmacy Research 2010; 3(11): 2597-2600.
23. Arya RKK, Singh R, Juyal V. Mucoadhesive Microspheres of Famotidine: Preparation, Characterization and *In vitro* Evaluation. International Journal of Engineering Science and Technology 2010; 2(6): 1575-1580.
24. Yadav P, Katewa J, Singh A, Kumar A. Formulation development and evaluation of mucoadhesive microspheres of diltiazem hydrochloride. Novel Science International Journal of Pharmaceutical Science 2013; 2(3-4): 78-87.
25. Patel JK, Patel RP, Amin AF, Patel MM. Formulation and Evaluation of Mucoadhesive Glipizide Microspheres. AAPS Pharm Sci Tech. 2005; 6(1): E49-E55.
26. Kalyankar TM, Rangari NT, Khan M, Hosmani A, Sonwane A. Formulation & Evaluation of Mucoadhesive Pioglitazone Hcl Microspheres. IJPWR. 2010; 1(3): 1-14.
27. Gavini V, Murthy MS. Formulation and *In vitro* Evaluation of Buoyant Drug Delivery system of Glipizide using Acrylic polymer. Journal of Drug Delivery and Therapeutics 2014; 4(6): 107-113.
28. Bhalekar M, Patil KP, Kshirsagar SJ, Mohapatra S A. Formulation, Optimization and *in vivo* evaluation of mucoadhesive Xyloglucan microspheres. Pharmaceutical Chemistry Journal 2011; 45(8):503-508.
29. Jain SK, Nitin K Jain, Gupta Y, Jain A, Jain D, Chaurasia M. Mucoadhesive Chitosan microspheres for non-invasive and improved nasal delivery of insulin. Ind. J. Pharm. Sci 2007; 69(4): 498-504.
30. Dandagi PM, Masthiholimath VS, Gadad AP, Iliger SR. Mucoadhesive microspheres of Propranolol hydrochloride for nasal delivery. Ind. J. Pharm. Sci. 2007; 69(3): 402-07.
31. Gavini V, Ragini B, Kaumudi K. Mucoadhesive Microspheres-A Novel Approach of Drug Targeting. World Journal of Pharmacy and Pharmaceutical Sciences 2014; 3(10): 310-335.
32. Ascentiis AD, Grazia JL, Bowman CN, Colombo P, Peppas NA. Mucoadhesion of poly (2- hydroxyethyl methyl methacrylate) is improved when linear poly (ethylene oxide) chains are added to the polymer network. J. Control. Release. 1995; 33: 197-201.
33. Ping He, Stanley S, Davis, Lisbeth Illum. *In vitro* evaluation of the mucoadhesive properties of Chitosan microspheres. International Journal of Pharmaceutics 1998; 166: 75-68.
34. Chowdary KPR, Annamma Devi GS. Preparation and Evaluation of Mucoadhesive Microspheres of Efavirenz for Enhancing Its Dissolution Rate and Bioavailability. RJPBCS. 2012; 3(2): 119-124.

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