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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF SILYMARIN FLOATING MATRIX TABLET

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ABSTRACT

A Gastroretentive floating controlled drug delivery system containing Silymarin was prepared in the form of tablets and evaluated for its processing parameters, in vitro release in 0.1 N HCl. Eight formulations were prepared by using rate controlling polymers such as HPMC K4M and Eudragit RS100, alkalizing agent sodium bicarbonate and solubilizing agent poly vinyl Pyrrolidone (PVP K30). Floating tablets were prepared by direct compression method. The preformulation studies and tablet evaluation tests were performed and results were within the limits. Tablets remained buoyant over 20 hours in the release medium and the amount of sodium bicarbonate found to be significant for not only to remaining buoyant without causing disintegration of the tablet. The different ratios of polymers 15% and 20% showed the significant difference in the drug release with increasing in the concentration of solubilizing agent PVP K30. Stability studies for all formulations were conducted for a period of 60 days at 4º±2ºC, 27º±2ºC and 45º±2ºC respectively and the formulations showed no significant changes in physical appearance, drug content and in-vitro drug release even after 60 days. All the formulations exhibited diffusion dominant drug release.

Keywords: Floating drug delivery system, Controlled drug release, Low-density polymers, Alkalizing agent, Silymarin.

INTRODUCTION

Silymarin, a flavonolignan from 'milk thistle' (Silybum marianum) is used in the treatment of liver diseases. The half-life of Silymarin is 4-6 hrs. Since, it has a very low bioavaliability of 20%-50% and poor water solubility; multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. To overcome these problems, Silymarin has been formulated as floating drug delivery system (FDDS) to increase the gastric retention time which in turn improve the bioavailability of drug. It releases the drug over an extended period in the stomach and upper gastrointestinal tract (GIT), thus enhancing the opportunity for absorption.

Various approaches have been proposed to control the gastric residence of drug delivery system in the upper GIT including FDDS, high density DDS, mucoadhesive systems, swelling and expanding DDS, modified shape systems and other delayed gastric devices [1,2].

FDDS is a gastro retentive dosage form (GRDF), which can prolong the gastric residence time (GRT) to produce an acceptable drug bioavailability. FDDS is suitable for drugs having absorption window in the stomach or upper small intestine and for drugs that are poorly soluble or unstable in the intestine in the intestinal fluid. FDDS should have lower bulk density than gastric fluid and thus it floats on gastric fluid for a prolonged period of time and releases the drug slowly at controlled manner. Therefore it was proposed to develop Silymarin as FDDS to enhance the absorption of drug using two polymers namely Hydroxy propyl methyl cellulose K4M (HPMC K4M) and Eudragit RS100 with different concentrations.

MATERIAL AND METHODS

Materials

Silymarin, Hydroxy propyl methyl cellulose (HPMC K4M) and Eudragit RS100 were obtained as gift sample from Micro labs, Hosur. Polyvinyl pyrrolidone (PVP K30) was obtained from Granules India Ltd., Hyderabad. Other reagents and solvents were of analytical grade.

Method

Preparation of Silymarin floating tablets

The drug, polymers (at different ratios), PVP K30, sodium lauryl sulfate (SLS), sodium bicarbonate ($NaHCO_3$) and lactose were blended thoroughly in a motor and pestle and then passed through sieve no. 100. The powder blend was mixed with talc (2%) and tablets were prepared by direct compression method using a single punch-tableting machine (Minipress-I) with hardness 6 kg/cm^2 [3]. Eight formulations were prepared and coded them from F1 to F8. The details of composition of each formulation are given in **Table-1**.

Table 1: Formulations of Silymarin floating tablets

S. No.	Ingredients	Formulations of Silymarin floating tablets							
		F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
01.	SILYMARIN	280	280	280	280	280	280	280	280
02.	HPMC K4M	75	100	100	--	--	--	50	50
03.	EUDRAGIT RS 100	--	--	--	75	100	100	50	50
04.	$NaHCO_3$	70	70	70	70	70	70	70	70
05.	PVP K30	20	20	40	20	20	40	20	40
06.	SLS	3	3	3	3	3	3	3	3
07.	TALC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
08.	LACTOSE	45	20	--	45	20	--	20	--

* Weight of one tablet is 500mg.

F1 - HPMC K4M (15%w/w) and PVP K30 (4%w/w); F2 - HPMC K4M (20%w/w) and PVP K30 (4%w/w); F3 - HPMC K4M (20%w/w) and PVP K30 (8%w/w); F4 – Eudragit RS100 (15%w/w) and PVP K30 (4%w/w); F5 – Eudragit RS100 (20%w/w) and PVP K30 (4%w/w); F6 – Eudragit RS100 (20%w/w) and PVP K30 (8%w/w); F7 – HPMC K4M (10%w/w), Eudragit RS100 (10%w/w) and PVP K30 (4%w/w); F8 – HPMC K4M (10%w/w), Eudragit RS100 (10%w/w) and PVP K30 (8%w/w)

Evaluation of Granules (OR) Powder Blend

Preformulation studies such as angle of repose (n=5), bulk density (n=5), tapped density (n=5), compressibility index (n=5) and

Hausner's ratio (n=5) were determined for their micromeritic properties.

Evaluation of floating tablets

To design tablets and tablets production quality, the formulated tablets were evaluated for Hardness test (n=5) (using Monsanto Hardness Tester) [4], friability test (n=5) (using Roche Friabilator) [5] and weight variation test (n=5) [6].

Buoyancy / Floating test

The time interval between introduction of tablet into the dissolution medium and its floatation to the top of the dissolution medium was termed as buoyancy lag time (BLT). The duration upto which the tablet floats on the dissolution medium was taken as duration of buoyancy (DB). Both BLT and DB were determined using USP 24 type II dissolution apparatus in 900ml of 0.1N HCl at 37°±1°C [7].

Drug content

Five tablets from each formulation were taken and grinded in to fine powder. From this 0.100gm equivalent weight of Silymarin was weighed and dissolved in sufficient quantity of methanol and diluted with 0.1 N HCl. The samples were analysed spectrophotometrically at 286nm (n=5) [3].

Drug-polymers interaction studies

Drug-polymers interactions was studied by using FTIR (Shimadzu, Japan, Model-8400s) [8].

Dissolution studies

In vitro drug release of all the formulations were carried out using USP–type II dissolution apparatus (paddle type). The dissolution medium, 900 ml 0.1N HCl solution, was placed into the dissolution flask maintaining the temperature of 37 + 0.5°C and rpm of 50. One Silymarin tablet was placed in the dissolution apparatus. The apparatus was allowed to run for 7 hours. Samples measuring 10 ml were withdrawn every 30mts intervals upto 7 hours. The fresh dissolution medium (37°C) was replaced every time with the same quantity of dissolution medium to maintain the same volume of dissolution medium. Collected samples were diluted upto 100ml with 0.1N HCl and analyzed at 286nm using 0.1N HCl as blank. The cumulative percentage drug release was calculated [3].

Drug release kinetics (Curve Fitting Analysis)

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were fitted into zero order, first order, Higuchi's model and Korsmeyer's equation release models. The model with the highest correlation coefficient was considered to be the best model. The value of 'n' in the Korsmeyer's model indicates the release mechanism [9,10,11].

Stability studies

It was carried out to evaluate the stability of the drug. All the formulations were stored at 4°±2°C, 27°±2°C and 45°+2°C (RH 75+5%) temperatures for 60 days. Two tablets were taken from all the stored samples at the intervals of 15th, 30th, 45th and 60th days. The drug content analysis and in vitro release studies were carried out to determine the percentage of Silymarin released using U.V. spectrophotometrically at 286nm. Stability studies are used to find out whether any chemical degradation of Silymarin formulations taken place or not [3].

RESULTS AND DISCUSSIONS

The Silymarin floating tablets using two polymers and in combination of polymers with different ratios were prepared by direct compression method. Before compression of the powder, preformulation studies such as Bulk density, Tapped density, Angle of repose, Compressibility index and Hausner's ratio were determined for all formulations. Angle of repose and Compressibility index (Carr's index) (%) ranged from 29.05° to 33.27° and 11.57 to 13.73 respectively. The results of bulk density and tapped density were ranged from 0.314 to 0.416 and 0.352 to 0.470 respectively **(Table-2)**. These ranges are acceptable limits for powder bled to show good flow properties while formulating tablets.

Table 2: Evaluation of Silymarin powder blend

S. No.	Parameters	Physical Characteristics of silymarin powder blend							
		F1	F2	F3	F4	F5	F6	F7	F8
01.	Bulk Density* (gm/cc)	0.358± 0.025	0.314± 0.039	0.374± 0.018	0.380± 0.076	0.357± 0.104	0.393± 0.085	0.416± 0.067	0.376± 0.068
02.	Tapped Density* (gm/cc)	0.400± 0.017	0.352± 0.054	0.425± 0.062	0.424± 0.098	0.402± 0.087	0.447± 0.064	0.470± 0.015	0.427± 0.057
03.	Bulkiness* (cc/gm)	2.79± 0.019	3.18± 0.064	2.67± 0.095	2.63± 0.108	2.80± 0.095	2.54± 0.038	2.40± 0.044	2.66± 0.014
04.	Angle of Repose* (θ)	29º58'± 0.534	33º23'± 0.351	33º27'± 0.259	30º96'± 0.190	29º05'± 0.251	29º35'± 0.483	31º26'± 0.604	30º96'± 0.365
05.	Compressibility Index* (%)	11.73± 0.794	12.10± 0.542	13.63± 0.387	11.57± 1.054	12.60± 0.864	13.74± 0.573	12.98± 0.652	13.56± 1.004
06.	Hausner's Ratio*	1.11± 0.154	1.12± 0.288	1.13± 0.121	1.11± 0.854	1.12± 0.432	1.13± 0.548	1.12± 0.742	1.13± 0.240

* All values are expressed as mean ± standard deviation, n =5

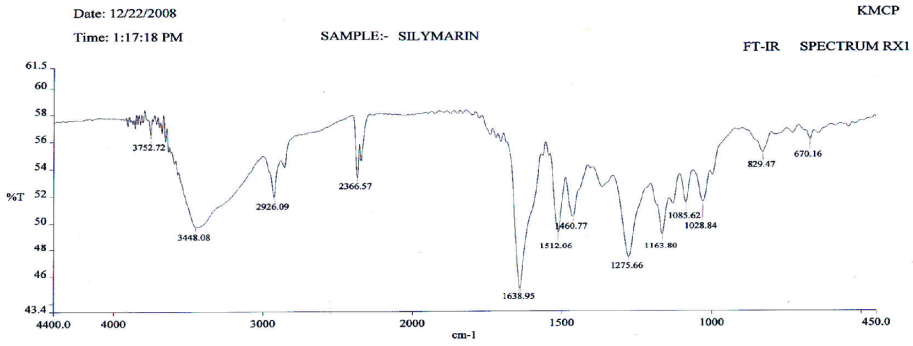
Table 3: Evaluation of Silymarin floating tablets

S. No.	Parameters	Physical charecteristics of Silymarin floating tablets							
		F1	F2	F3	F4	F5	F6	F7	F8
01.	Hardness* (kg/cm^2)	6.1± 0.4	6.0± 0.2	6.2± 0.3	6.1± 0.3	6.1± 0.7	6.0± 0.5	6.0± 0.3	6.2± 0.1
02.	Friability* (%)	0.29± 0.12	0.20± 0.18	0.26± 0.21	0.17± 0.11	0.20± 0.15	0.28± 0.11	0.20± 0.17	0.22± 0.20
03.	Uniformity of weight* (mg)	0.500± 0.21	0.500± 0.43	0.499± 0.30	0.498± 0.42	0.500± 0.34	0.499± 0.26	0.499± 0.17	0.499± 0.29
04.	Drug Content* (%)	99.10± 0.255	100.0± 0.498	99.40± 0.352	99.70± 0.647	100.21± 1.205	98.80± 0.654	98.80± 0.354	100.0± 0.412
05.	Buoyancy Lag Time* (sec)	113± 4.58	129± 2.68	174± 3.47	150± 5.10	165± 5.02	140± 1.65	96± 2.84	109± 3.00
06.	Duration of Buoyancy (hrs)	>20	>20	>20	>20	>20	>20	>20	>20

* All values are expressed as mean ± standard deviation, n =5

The tablets were prepared and evaluated for the hardness, friability, weight variation, buoyancy determination and drug content. The hardness of the tablets ranged from 6.0 to 6.2 respectively. The friability, weight variation and percentage of drug content for all the formulations were found to be within the acceptable range. The buoyancy lag time of all formulations was ranged from 96 to 174 sec. and duration of buoyancy was more than 20 h **(Table-3)**. These results exhibited satisfactory floatable ability because of their low density and internal voids.

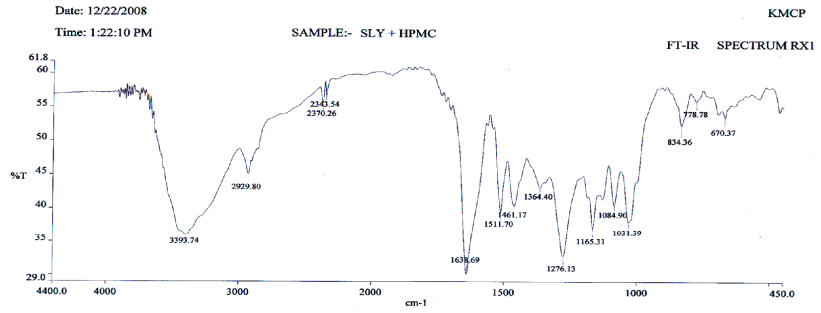
IR spectrum of pure Silymarin and Silymarin with combination of polymers showed no significant interactions between the drug and polymers and they are compatible with each other **(Figure-1A, 1B, 1C and 1D)**.



SLY.PK

SLY.002 1976 4400.00 450.00 45.11 58.37 4.00 %T 1 1.00
12 nov 2008 external polystyrene
REF 4000 57.76 2000 57.98 600
3752.72 56.50 3677.10 56.66 3448.08 49.73 2926.09 51.97 2366.57 53.35
2341.67 54.59 1638.95 45.08 1512.06 49.31 1460.77 50.44 1275.66 47.40
1163.80 49.15 1085.62 51.48 1028.84 51.58 829.47 55.18 670.16 56.08

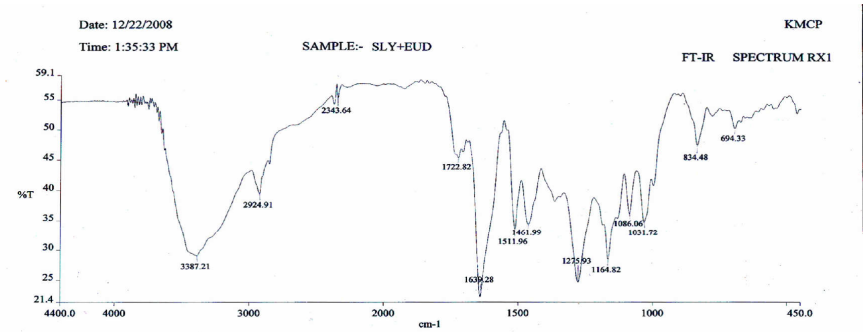
Fig. 1A: IR spectrum of pure Silymarin



SLYC.PK

SLYC.002 1976 4400.00 450.00 30.11 61.02 4.00 %T 1 1.00
12 nov 2008 external polystyrene
REF 4000 57.20 2000 60.19 600
3907.72 56.33 3856.24 56.02 3840.93 56.45 3822.52 56.62 3805.65 56.74
3752.49 55.89 3692.09 55.87 3676.98 54.51 3652.09 53.12 3393.74 36.03
2929.80 45.10 2370.26 55.66 2343.54 56.71 1638.69 30.09 1511.70 39.48
1461.17 40.40 1364.40 43.00 1276.13 32.79 1165.31 37.09 1084.90 40.51
1031.39 37.98 834.36 52.27 778.78 55.88 670.37 53.50

Fig. 1B: IR spectrum of Silymarin +HPMC K4M



SED.PK

SED.002 1976 4400.00 450.00 22.28 58.36 4.00 %T 1 2.00
12 nov 2008 external polystyrene
REF 4000 54.68 2000 57.62 600
3387.21 29.10 2924.91 39.54 2343.64 55.33 1722.82 45.41 1639.28 22.25
1511.96 33.58 1461.99 34.43 1275.93 24.70 1164.82 28.55 1086.06 36.18
1031.72 34.76 834.48 47.41 694.33 50.18

Fig. 1C: IR spectrum of Silymarin +Eudragit RS 100

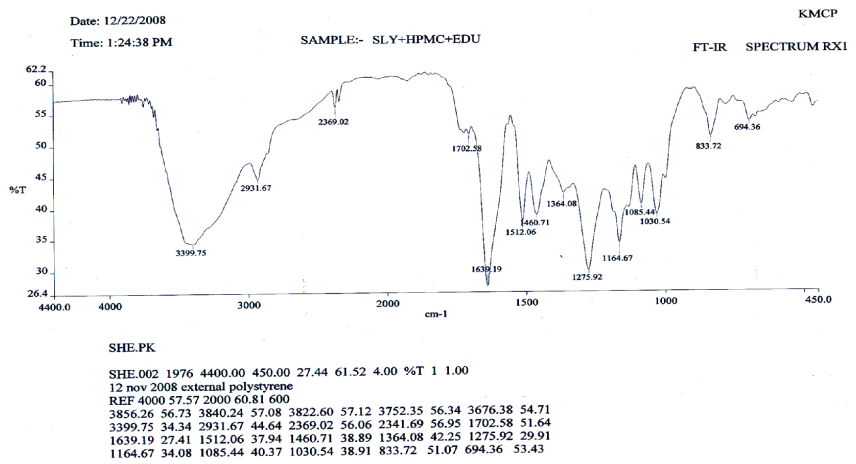


Fig. 1D: IR spectrum of Silymarin +HPMC K4M +Eudragit RS100

The in-vitro dissolution studies of all the formulations are performed and shown in Table-**4**. The percentage drug release at the end of 7 h from F1, F2, F3, F4, F5, F6, F7 and F8 were found to be 40.26%, 36.16%, 45.21%, 39.67%, 34.15%, 43.95%, 35.29% and 44.43% respectively. As the ratio of the polymers (HPMC K4M and Eudragit RS100) increased from 15% to 20%, the percentage drug release was decreased that is in formulation F2 (36.16%) and F5 (34.15%) when compared to the formulations F1 (40.26%) and F4 (39.67%). The formulations F3, F6 and F8 (i.e., 45.12%, 43.95% and 44.43%) showed slightly higher percentage drug release when compared to the formulations F2, F5 and F7 (i.e., 36.16%, 34.15% and 35.29%) due to solubilization property of PVP K30 and increased concentration of PVP K30 from 4% to 8% [12]. However, when the drug release of F1 and F2 (using HPMC K4M) is compared with the F4 and F5 (using Eudragit RS100) showed less drug release due to the less water permeability of Eudragit RS100 when compared with HPMC K4M .

Four kinetics models namely zero order equation, first order equation, Higuchi's equation and Korsmeyer's equation and results are presented in the Table-5. All formulations follow the first order release rate (R^2: 0.8814 to 0.9423). Higuchi's equation describes that all formulations follow the diffusion is the dominant mechanism (R^2: 0.9544 to 0.9829) [10]. From the Korsmeyer's plot it was known that the drug release shows the shows the n (slope) <0.45 for all the formulations. Hence it follows the Fickian release mechanism [11].

Stability studies were performed for all the formulations. All the formulations were stored at 4°±2°C, 27°±2°C and 45°+2°C (RH 75+5%) for 60 days. After an interval of 15th, 30th, 45th and 60th, the samples were withdrawn and tablet evaluation tests were conducted. There was no colour change and there were no deviations in the percentage of drug release also. It showed that all formulations remain stable for 60 days.

Table 4: Cumulative percentage of drug release from the Silymarin formulations

S. No.	Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
01.	0.5	19.12±1.21	14.72±1.56	18.28±1.22	17.89±1.24	12.50±1.69	17.87±1.02	13.72±1.04	17.51±1.15
02.	1.0	20.97±1.65	16.61±1.64	20.79±1.45	19.82±1.65	14.72±1.24	20.40±1.04	15.53±1.05	19.91±1.08
03.	1.5	22.16±1.42	18.38±1.51	23.22±1.61	21.48±1.84	16.78±1.65	22.93±1.12	17.84±1.34	22.05±1.22
04.	2.0	23.33±1.24	20.02±1.20	25.36±1.07	23.23±1.77	18.74±1.31	24.59±1.64	19.21±1.54	24.29±1.54
05.	2.5	24.79±1.65	22.06±1.64	27.79±1.54	24.88±1.22	19.97±1.08	26.73±1.35	21.36±1.42	26.53±1.02
06.	3.0	27.01±1.35	23.52±1.84	29.65±1.24	26.63±1.35	21.63±1.08	28.19±1.55	22.80±1.94	28.77±1.20
07.	3.5	28.68±1.02	25.27±1.77	31.79±1.36	28.10±1.54	23.48±1.65	31.00±1.92	24.77±1.02	31.00±1.31
08.	4.0	30.43±1.06	26.73±1.64	33.44±1.62	29.94±1.20	24.61±1.55	32.28±1.34	25.63±1.31	32.57±1.54
09.	4.5	31.89±1.92	28.29±1.55	35.10±1.54	31.21±1.14	26.27±1.33	34.41±1.75	27.35±1.45	34.03±1.22
10.	5.0	33.16±1.08	30.04±1.32	37.23±1.20	32.57±1.05	28.21±1.42	36.55±1.98	29.80±1.20	36.07±1.31
11.	5.5	34.81±1.35	31.31±1.20	39.57±1.00	34.22±1.06	29.78±1.65	38.11±1.44	30.34±1.05	38.49±1.64
12.	6.0	36.46±1.11	33.05±1.04	41.61±1.64	35.49±1.00	31.33±1.33	40.15±1.35	32.17±1.34	40.35±1.20
13.	6.5	38.69±1.25	34.61±1.24	43.08±1.08	37.62±1.84	32.70±1.20	42.29±1.08	33.42±1.24	42.01±1.05
14.	7.0	40.26±1.09	36.16±1.64	45.21±1.34	39.67±1.15	34.15±1.61	43.95±1.95	35.29±1.64	44.43±1.84

* All values are expressed as mean ± standard deviation, n =5

Table 5: Curve Fitting Analysis

Formulation	Zero order	First order	Higuchi's plot	Korsmeyer's plot	
	R^2	R^2	R^2	R^2	n
F1	0.8383	0.8814	0.9544	0.3302	0.176
F2	0.8867	0.9224	0.9810	0.3890	0.296
F3	0.8841	0.9284	0.9814	0.3720	0.312
F4	0.8459	0.8926	0.9641	0.3443	0.272
F5	0.9100	0.9423	0.9877	0.5385	0.384
F6	0.8840	0.9256	0.9795	0.3709	0.240
F7	0.8961	0.9145	0.9844	0.5207	0.256
F8	0.8930	0.9335	0.9829	0.3820	0.336

R^2= regression coefficient; n= slope

CONCLUSION

The present study was carried out to develop the floating drug delivery system using HPMC K4M and Eudragit RS100 polymers as carriers. The results of experimental studies of Silymarin floating tablets proved that the powder blend showed good flow properties, tablet evaluation tests are within the acceptable limits, IR spectral analysis proved that there was no drug-polymer interaction, percentage drug release was controlled and the formulations were stable after storing at different temperatures for 60 days. Thus, results of the current study clearly indicates, a promising potential of the Silymarin floating system as an alternative to the conventional dosage form.

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