



Original Article

Design and *In-vitro* Evaluation of Silymarin Bilayer Tablets

Thorata V Sai Krishna*, M Venkata Anjaneyulu, JN Suresh Kumar, Chandan Kumar Brahma,
A Vivekananda

Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet-522601, Andhra Pradesh

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A B S T R A C T

In the present study an attempt was made to study the effect of formulation variables on bilayered floating tablet of Silymarin. Immediate release layer was formulated by using various super disintegrants such as sodium starch glycolate, cross carmellose sodium, crospovidone and sustained release layer was formulated with different grades of hydrophilic polymers like HPMCK4M, HPMCK5M and HPMCK100M by wet granulation method. The influence of polymer and their concentrations were also investigated. The prepared tablets were characterized and rate of drug release from an immediate release layer was 98.3% were found at the end of 15 minutes followed by sustained the drug release for 12hrs from sustained release layer. The dissolution data were fitted into zero order, first order, Higuchi and Peppas equations. Results revealed that the drug release from the formulation F17 followed zero order kinetics and exhibited Peppas transport mechanism.

Key Words: Silymarin, Bilayer tablets, combined tablet, HPMC, SSG

1. INTRODUCTION

The oral route is considered as the most promising and predominant route of drug delivery¹. Effective oral drug delivery may depend upon the factors such as GI transit time of dosage form, gastric emptying process, drug release from the dosage form and site of absorption of drug. Most of the oral dosage forms possess several physiological limitations such as variable GI transit, because of variable gastric emptying, leading to incomplete drug release, nonuniform absorption profiles and shorter residence

Corresponding author *

Thorata V Sai Krishna, Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet-522601, Andhra Pradesh, Email: saikrishna.thorata@gmail.com

time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed.

To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the GI tract. Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability.

One of the novel approaches in the area of sustained drug delivery was Gastro retentive drug delivery systems (GRDDS). Several techniques have been proposed to increase the Gastric residence time of dosage forms such as floating systems, swelling systems, hydro dynamically balanced systems and low density systems etc. In the present investigation Silymarin was selected as drug which is a hepato protective agent and is widely used in the treatment of hepato cellular damage like hepatitis. The drug has short biological half life 6 hrs, low bioavailability and narrow absorption window in upper part of GIT. Multi layer concepts have been utilized in this present investigation. Bi-layered floating tablets having immediate release layer and sustained release layer, the drug was released within 15 minutes from the IR layer leads to a sudden raise in blood concentration, blood level was maintained at steady state as the drug was released from the sustained release layer.

2. MATERIALS & METHODS

The preparation of Bilayer floating tablets involved two steps prepared by wet granulation method. The

excipients used in the formulation are superdisintegrants such as SSG, Croscarmellose sodium, Crospovidone, PVP in isopropyl alcohol as binding solution, HPMCK4M, HPMCE5 and HPMCK100M as polymers, lactose as diluent, and talc and magnesium stearate as glidant and lubricant. The immediate release dose was considered as 100mg and the maintenance dose was considered as 200mg.

Preparation of the immediate release layer:

The immediate release layer was prepared as per the formula given in table 1. The damp mass was passed through sieve no 12. The granules thus obtained were dried in an oven at 50°C. The dried granules were sieved through sieve no16 and lubricated with talc and magnesium stearate.

Preparation of the floating sustained release layer:

The SR layer was prepared as per the formula shown in table2. The damp mass was passed through sieve no 12 to obtain granules. The granules thus obtained were dried in an oven at 50°C. The dried granules were sieved through sieve no 16 and lubricated with talc and magnesium stearate.

Compression of bilayer floating tablets:

The required quantity of granules of SR layer was compressed slightly using 16 station rotary tablet machine with 10mm punches. After that upper punch was lifted and the required amount of granules of IR layer were placed over the above compact, both the layers were compressed tablet using 12.5 mm flat punches, with the hardness of 4.5 Kg/cm² to obtain the bilayer tablet as shown in figure number 1. ^{1,2}

Evaluation of Silymarin bi-layered floating tablets

All the prepared bi-layered floating tablets were evaluated for following parameters.

Weight Variation: Formulated tablets were tested for weight uniformity, in which 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent

weight variation was calculated by using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Hardness: The hardness of tablets was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm².

Friability: The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Drug content:

For determination of drug content three tablets from each formulation were weighed Individually and powdered. The quantity of powder was equivalent to 10 mg. The equivalent weight Silymarin was transferred into 100 ml volumetric flask diluted to 100ml with sufficient amount of 0.1N HCL. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 282nm against blank.³

Floating characteristics

Floating characteristics were determined using USP dissolution apparatus at 100rpm using 900 ml of 0.1 N HCl, temperature was maintained at 37°C.

Floating lag time: The tablet was placed in dissolution apparatus and the time taken to float on the dissolution medium was noted.

Floating time: The total duration of the time that the tablet float on dissolution medium was noted.

In-vitro dissolution studies:

In-Vitro Dissolution rate was studied by using USP type II paddle dissolution apparatus in 900ml of 0.1N Hydrochloric acid at 37±0.5° at 50 rpm. 5ml of aliquot

of dissolution medium was withdrawn at regular time intervals, the same volume of pre-warmed (37±0.5°) fresh dissolution medium was replaced. The samples were filtered and drug content of Silymarin in each sample was analyzed after suitable dilution by Shimadzu UV-spectrophotometer at 282 nm.

3. RESULTS AND DISCUSSION

Micromeritic properties for formulations were evaluated, the results revealed that IR layer and SR layer granules exhibited good flow properties; it was also further supported by Carr's Index and Hausner's ratios values. The formulated tablets were subjected to various quality control tests and the results were shown in table 3. The obtained results were found to be within limits of pharmacopoeia. The % drug content in all bilayer formulations were observed in the range of 98.6±0.03% to 99.±0.02%. The floating lag time for the prepared formulations were found to be decreased while increasing the concentration of polymer and also total floating time of SR layer formulations were increased by increasing the concentration of polymer.

The formulations of immediate release layer were shown in table 1. ^{4, 5} In vitro release profiles were shown in fig 2 & 3, *in-vitro* release data were fitted into various kinetic models i.e. First order and zero order, drug release from formulations exhibited the first order kinetics, the order of drug release from the formulations were in the following order F6>F5>F3>F1>F2>F9>F4>F8>F7 i.e. increasing the concentrations of SSG, Croscarmellose sodium and Crospovidone in formulations the drug release rate was found to be increased. Finally F6 was optimized for development of the bi layer Silymarin tablets.

In vitro drug release profiles for bilayer tablets were shown in fig 4 and 5, percentage of drug release for the formulations F10, F11, F12, F13, F14, F15, F16, F17 and F18 are 96.47 ± 0.34, 94.12 ± 0.34, 91.24 ± 0.34, 94.66 ± 0.34, 94.68±0.34, 95.87±0.34,

91.68±0.34, 98.63±0.34 and 93.68±0.34 observed at the end of 7, 9, 11, 7, 9, 11, 12, 12 and 12 hours

Table 1: Composition of Immediate release layer for bi-layered floating tablets of Silymarin formulated with SSG, Croscarmellose sodium, Crospovidone

Ingredients	Quantity per single tablet (mg)								
	F1	F2	F3	F4	F5	F6*	F7	F8	F9
Silymarin	100	100	100	100	100	100	100	100	100
Crosscarmellose Sodium	4	6	8	-	-	-	-	-	-
Sodium Starch Glycollate	-	-	-	4	6	8	-	-	-
Cross Povidone	-	-	-	-	-	-	4	6	8
PVP K30	4	4	4	4	4	4	4	4	4
Lactose	88	86	84	88	86	84	88	86	84
Talc	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Colour	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
IPA	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total tablet weight (mg)	200	200	200	200	200	200	200	200	200

respectively. Among all the formulations F17 retarded the drug release for 12 hrs. So tablets formulated with HPMCK 100M (F17) was found satisfactory.^{6, 7}

Table 2: Composition of bi-layered floating tablets of Silymarin formulated with HPMC K4M, HPMC K5M and HPMC K100M

Ingredients	Quantity per tablet (mg)								
	F10	F11	F12	F13	F14	F15	F16	F17*	F18
Immediate Release Layer									
Silymarin	100	100	100	100	100	100	100	100	100
Sodium Starch Glycollate	8	8	8	8	8	8	8	8	8
PVP K30	4	4	4	4	4	4	4	4	4
Lactose	84	84	84	84	84	84	84	84	84
Talc	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Colour	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
IPA	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Sustain Release Layer									
Silymarin	200	200	200	200	200	200	200	200	200
HPMC K4M	35	52.5	70	-	-	-	-	-	-
HPMC K15M	-	-	-	35	53	70	-	-	-
HPMC K100M	-	-	-	-	-	-	35	53	70
PVP K30	7	7	7	7	7	7	7	7	7

Lactose	48.5	31	13.5	48.5	31	13.5	48.5	31	13.5
Na ₂ CO ₃	52.5	52.5	52.5	52.5	53	52.5	52.5	53	52.5
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
IPA	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total tablet weight (mg)	550	550	550	550	550	550	550	550	550

Table 3: Physico-chemical evaluation of the for bi-layered floating tablets of Silymarin

Formulation code	Thickness (mm)	Weight Variation (n=20)	Hardness ± S.D (kg/cm ²) (n=5)	Friability (%)	Content uniformity (%)	Floating lag time (sec)	Total Floating time (hrs)
F10	4.8±0.02	551±0.611	6.4±0.30	0.72±0.12	99.28	65	More than 9 hours
F12	4.9±0.08	554±0.54	6.3±0.20	0.68±0.08	97.1	74	More than 9 hours
F13	4.8±0.06	548±0.91	6.7±0.25	0.69±0.09	101.18	95	More than 9.5 hours
F14	4.8±0.04	549±0.58	6.6±0.10	0.66±0.15	97.68	72	More than 10 hours
F15	4.8±0.01	551±0.46	6.7±0.40	0.68±0.14	99.41	70	More than 10.5 hours
F16	4.7±0.02	548±0.50	6.9±0.25	0.65±0.06	98.19	79	More than 10.5 hours
F17	4.9±0.06	550±0.20	7.1±0.10	0.68±0.16	99.31	66	More than 12 hours
F18	4.8±0.04	552±0.10	7.2±0.30	0.67±0.08	102.6	62	More than 12 hours

Table 4: Concentration and absorbance of Silymarin in 0.1N HCL P^H 1.2.

Concentration in mcg	Absorbance
0	0
10	0.086
20	0.173
30	0.266
40	0.346
50	0.443
60	0.532

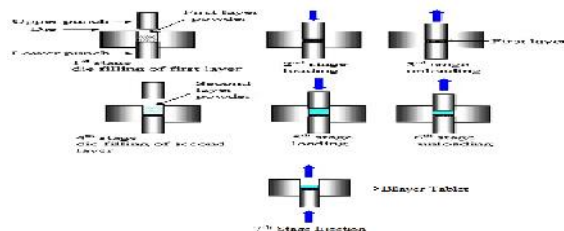


Fig 1: Showing various steps in compression

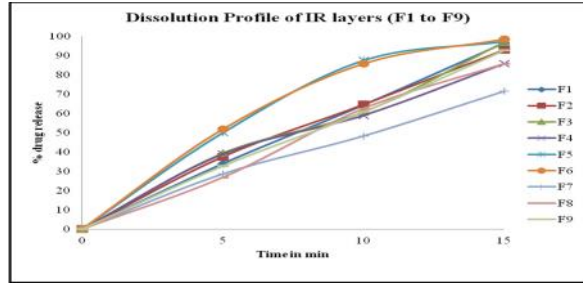


Fig 2: Dissolution profile of formulations F1-F9

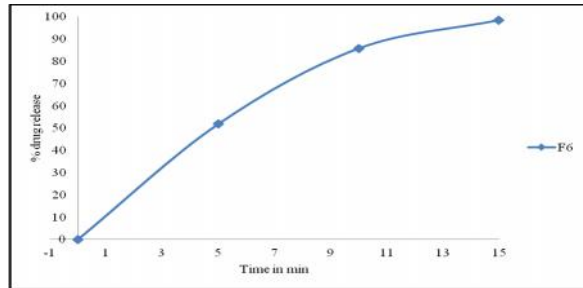


Fig 3: Dissolution profile of formulation F6

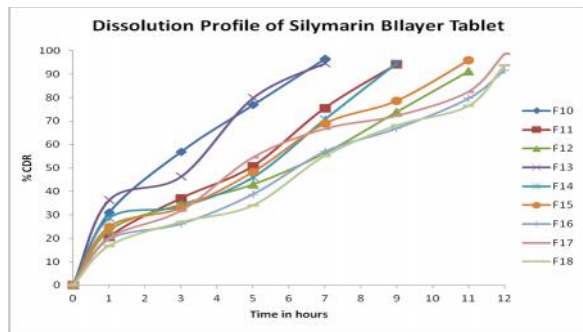


Fig 4: Dissolution profile of formulations F10-F18

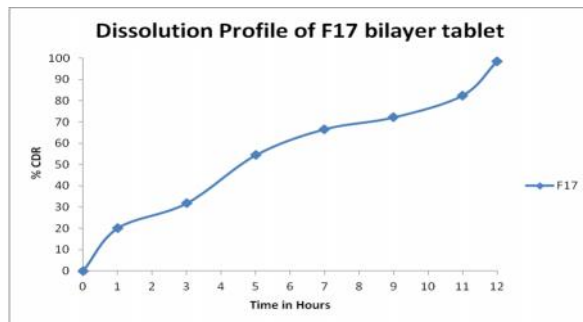


Fig 5: Graphical representation of F17 Formulation

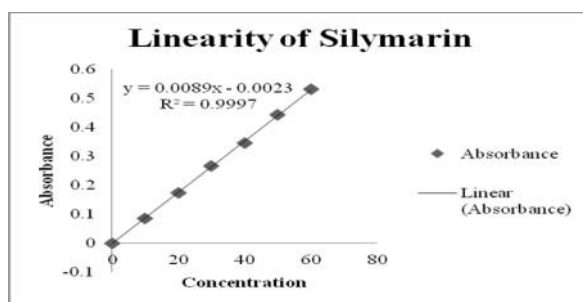


Fig 6: Beer-Lambert's plot for Silymarin in P^H 1.2

The *In-vitro* release data were fitted into various kinetic models i.e. First order, zero order, Higuchi and Peppas equations, drug release from formulations exhibited zero order kinetics and exhibited the Higuchi transport mechanism. The exponential coefficient from the Higuchi plots was found to be 0.972 indicating Fickian diffusion transport mechanism, the order of release retardant was as follows HPMCK100M>HPMCK5M>HPMCK4M, from the results it indicated that release rate was retarded by increasing the concentration of the polymer.

In- vitro buoyancy studies revealed that tablets of hardness 2-4 Kg/cm² after immersion into the floating media floated immediately, tablets with hardness of 4-5 Kg/cm² sank for 3-4minutes, and then floated on to the surface. Tablets with different hardness remained floating for 8-12 hrs. The buoyancy of the tablets is governed by both the swelling of the poly hydrocolloid particles in the tablet surface when it the contacts the gastric fluids and presence of the internal voids in the centre of the tablet, hence altering a bulk density <1.

The formulation F17 formulated with HPMC K 100 M sustained the release for 12 hrs, when compared with formulations made with HPMC K4 M and HPMC K5M grade of polymers this may be due to the viscosity of the polymer i.e. formation of gel structure. Finally concluded that, results of the studies based on the *in- vitro* performance clearly suggested that, sustained release floating bilayer tablets can be prepared by immediate release layer of drug with Sodium Starch Glycollate and SR layer comprises the sodium bicarbonate, with HPMC K 100 M for achieving the sustained action and restricted the drug release in the stomach.

4. CONCLUSION

The drug and excipients were found to be compatible; it can be confirmed by FTIR spectral analysis. The characteristics of the granules such as angle of repose,

bulk density, tapped density, carr's index, hausner's ratio were studied, found to be good flow properties. Evaluation parameters of the tablets such as weight variation, hardness, friability, drug content, swelling index, floating characteristics, was found to be satisfactory. The buoyancy lag time was found to be satisfactory. The optimised formulation F17 was found to sustain the drug release for 12 hrs and also investigated the effect of various grades of HPMC on release rate of drug. The optimized tablet formulations showed a satisfactory dissolution profile and floating characteristics. The *in-vitro* drug release from all formulations followed zero order kinetics and Fickian diffusion. In the present investigation, successfully developed the bilayer floating tablets of Silymarin by wet granulation method using super disintegrants Sodium starch glycollate for IR layer and HPMCK100M for SR layer.

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