Research Article

"Formulation and Evaluation of Oral Soluble Film of *Silybum marinum* seed extract"

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Abstract

Given that *Silybum marinum* seed extract is a medication with limited solubility, the goal of the current work was to develop oral soluble films of *Silybum marinum* seed extract to maximize patient convenience during administration, give faster onset of action, and improve bioavailability. By adding the medication to a film made of Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol (PEG400), Sodium Starch Glycolate, glycerin, etc., using the solvent casting process, the rate of dissolution can be increased. The physicochemical characteristics of the films, such as disintegration time, surface pH, thickness, weight, percentage moisture absorption, folding endurance, drug content, and stability tests, were assessed. The solubility of the drug increased more by using Polyethylene Glycol 400 than Propylene Glycol and Isopropyl Alcohol; the release rate indicates that adequate concentration of Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol 400 and the solvent evaporation method gave good results.

Keywords: Solvent casting method, Oral Soluble Film, *Silybum marinum* seed extract

INTRODUCTION:

The oral route is one of the most popular medication administration methods since it is more practical, and economical, and results in a high level of patient compliance. The oral route presents challenges since elderly and pediatric patients who are afraid of choking have trouble swallowing. The research focused on compliance and patient convenience has led to the development of safer and more modern drug delivery methods. Fast-dissolving drug delivery systems are one such example that has just begun to acquire popularity and acceptability because of improved customer choice, rapid disintegration or dissolution, and self-administration even without water or chewing.[1]

Silybum marinum belonging to family Asteraceae is well known for hepatoprotective action. It is used to treat a variety of conditions, including cancer, inflammation, and neurodegeneration, in addition to its liver-protective characteristics; Silymarin's outstanding antioxidant capability is

primarily responsible for this drug's broad pharmacological efficacy. [3]

MATERIAL AND METHODS:

Silybum marinum seed extract was obtained from Sun pure extract, New Delhi, and the other chemicals used were of analytical grade

Preformulation Studies

Organoleptic properties

The drug was tested for organoleptic properties such as appearance, color, odor, taste, etc.

Solubility Analysis:

The solubility study of the drug is carried out in 4 different non–volatile solvents like PEG 400, PG, and Tween 80, by preparing saturated solutions of the drug and analyzed by UV spectro -photometer at wavelength of 288 nm.

Melting Point Determination: The melting point of Silymarin was determined by the capillary tube method.

Spectroscopic study for Silymarin:

Determination of λmax by Spectroscopy:A solution equivalent to 100 mg of drug in100ml 6.8 phosphate buffer was prepared and analysed by UV -Spectrophotometer (Jasco V -630) against respective blank to confirm λmax of *Silybum marinum.*

FTIR Study:

FTIR spectrometer simultaneously collects spectral data in a wide spectral range. The Infrared absorption spectrum of pure Silymarin is carried out for identification of the drug. The absorption spectra are obtained in the range of 500 to 4000cm $^{-1}$using FTIR (8400, Shimadzu, Japan).

Preparation of Oral soluble film of *Silybum marinum* seed extract:

The solvent casting method was used for the preparation of films. The required amount of Hydroxy Propyl Methyl Cellulose (HPMC) was allowed to hydrate using minimum amount of water to get clear solution of film forming polymer. After that the required amount of Propylene Glycol (PG), Polyethylene Glycol (PEG400), Mannitol, and other respective ingredients were added to solution. Citric acid as saliva stimulating agent is added with constant stirring to form clear aqueous solution. The aqueous solution was kept aside till entrapped bubbles were removed. This is labelled as Solution A and then drug is dissolved in adequate solvent and labelled as Solution B. Solution B is added to Solution A to form homogenous mixture and the solution is casted on glass Petri dish and kept until dry. The dried film was carefully removed from the Petri dish and cut into 2x3 cm size for testing.

Trial batches F1-F5 were rejected due to physical parameters. Batches F6-F8 were found ok and were evaluated for their physicochemical parameters.

TableNo.1; Formulation of trial batches:

	Ingredients	**Formulation Trials (g)**							
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
1	Silymarin	-	0.789	0.789	0.789	0.789	0.789	0.789	0.789
2	HPMC K4	-	0.400	-	-	-	-	-	-
3	HPMC K15	0.300	-	0.400	0.500	0.600	0.712	0.712	0.712
4	SSG	-	-	-	-	-	0.019	-	0.019
5	PEG 400	0.127	0.127	0.127	-	-	1.12	-	-
6	Propylene Glycol	-	-	-	-	-	-	1.12	-
7	Citric acid	0.033	0.033	0.33	0.033	0.033	0.011	0.011	0.011
8	Mannitol	0.024	0.024	0.024	0.024	0.024	0.024	0.024	0.024
9	Tween 80	-	0.5	0.9	-	0.5	-	-	-
10	PEG 6000	-	-	-	0.200	-	-	-	-
11	Isopropyl alcohol	-	-	10ml	-	-		-	10ml
12	Glycerin	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
13	Water	Up to 15ml	Up to 20ml	Up to 30ml	Up to 35ml	Up to 35ml	Up to 35ml	Up to 35ml	Up to 35ml

Evaluation and Characterization:

Preliminary attributes: A polymer's ability to form films that can be detached from the surface they are cast on is known as film-forming capability. Depending on their capacity to create films, the films were rated as extremely poor, poor, average, good, better, and best.

Weight variation of the film: To ensure consistency of film preparation as well as the amount of drug in the film, weight variation is done.**;** each strip was cut into 2x3 cm and the weight of each strip was taken and average weight variation was calculated.

The thickness of film: The thickness of oral soluble film was measured by a digital Vernier caliper with least count of 0.01mm at different spots of the film and an average was taken.

Folding endurance: For the ready films, the folding durability was manually measured by carefully folding film in the middle repetitively. The value of folding endurance was calculated as the amount of folds on a single crease needed to cause a crack in the film

Test for disintegration: USP disintegration device was used for the disintegration test. The medium was simulated salivary fluid (PH 6.8). The discs were positioned on top of the films, which were inserted into the container's tubes. Six films from each formulation were used and average disintegration time recorded.

Surface pH analysis For this, a mixed pH electrode was employed. Water was used to help moisten the oral strip just a little. By placing the electrode against the oral film's surface, the pH was determined. The trials were carried out three times, and average results were presented.

Dissolution: The dissolution profile of the oral soluble film of *Silybum marinum* seed extract is carried out in dissolution apparatus containing 900ml of phosphate buffer of pH 6.8 as dissolution medium maintained at 37 ^{0}C. The paddle speed is set at 100 rpm. 5ml solution was withdrawn at 2,4,6,8,10 min intervals, and the same amount was replaced with fresh medium. The percentage of the drug dissolved at various time intervals were calculated and plotted against the time.

Drug Content: Three oral soluble film strips of 2x3 cm size were taken and dissolved in 100 ml Phosphate buffer of 6.8 individually and further 10 ml were withdrawn from each and diluted to 100ml separately and absorbance was measured by UV spectroscopy at 286 nm and drug content was determined as average of 3 tests .

Stability study: The formulation was sealed in aluminum foil and packed into bottles separately, sealed, and placed in a humidity chamber maintained at 25 ± 5^{0}C / 40% RH and 40 ± 5^{0}C /75 %RH in accordance with ICH guidelines. After each month sample was scrutinized for physical features, color, drug content, and characteristics of drug release were for changes.

RESULTS AND DISCUSSION :

The batches where in the film is formed are evaluated for appearance, weight variation, thickness, tackiness, folding endurance, disintegration, dissolution, drug content, and stability studies.

Calibration curve of *Silybum marinum* seed extract :

The calibration graph was plotted from the data obtained from concentrations of 10ppm to 50ppm.The solvent used was Phosphate Buffer pH 6.8 .The peak was observed at 286 nm and its equation is given as y= 0.0191+0.0488 ; R^2= 0.9786

Fig.no.4 Calibration curve of *Silybum marinum* seed extract

FT-IR Spectra:

IR spectra of pure *Silybum marinum* seed extract and excipients is shown in given figures 5 & 6. *Silybum marinum* seed extract has characteristics peak which are not affected along the combination with excipient combination .

Fig.No.5 IR Spectra of *Silybum marinum* seed extract **Fig.No.6 IR Spectra of Formulation**

Evaluation Parameters: Evaluation parameters of trail batches F6,F7, F8 are discussed in Table no.2

Table No.2 Evaluation parameters of oral soluble films of optimized trial batches

Parameter	F6	F7	F8
Physical Appearance	Glossy Transparent	Glossy Transparent	Glossy Transparent
Surface Texture	Smooth	Smooth	Smooth
Thickness(mm)	0.55±0.04	0.76±0.016	0.78±0.02
Weight (mg)	56±0.003	61±0.01	231±0.05
Time taken to solubilize (sec)	65	120	72
Folding endurance	120	108	117
pH of film	6.09	6.06	6.11
Drug Content	98%	95.71%	97.28%

Dissolution studies :

The in vitro drug release profile of F6 –F8 depicted below, F6 shows best release. The combination of PEG 400, Sodium Starch Glycolate(SSG), HPMC K15 gave good results.

Table No.3 : Determination of In vitro Drug Release for different formulations of Silymarin Oral soluble film (F6 – F8)

Time	F6	F7	F8
0	0	0.00%	0.00%
2	27.50%	23.58%	19.19%
4	63.64%	57.52%	48.34%
6	78.78%	75.01%	59.90%
8	85.11%	82.41%	75.34%
10	96.30%	93.67%	85.42%

Fig.no.7 In Vitro Drug Release of formulation F6 to F8

Stability studies:

The best batch F06 is subjected to stability study for thickness,folding endurance,surface pH,drug content ,disintegration ,dissolution and the results showed that film remain stable without any changes.

Table no.4 Stability study results of *Silybum marinum* seed extract oral soluble film

Parameter	Initial	1month	2Month	3Month
Thickness(mm)	0.55	0.54	0.53	0.52
Folding endurance	120	118	117	118
Surface pH	6.09	6.09	6.08	6.09
Drug content	98 %	98%	98%	97%
Disintegration	65	65	66	67
Dissolution	96.30%	95.30%	95.45%	95.42%

CONCLUSION:

Silybum marinum seed extract is widely used as a Hepatoprotective agent. They are formulated as suspensions, tablets, and capsules which show conventional dosage forms.

Based on various studies carried out we arrived at the following conclusions:

The solvent casting method was the preferred technology for the preparation of oral soluble film. Based on the preliminary studies various formulation trials(F06-F08) were carried out with different concentrations of, film forming agents, disintegrants, and solubilizing agents. From the various formulations, it was concluded that the formulation batch of F6 was finalized as the optimized formula. Formulation F6 showed satisfactory results with various physicochemical evaluation parameters like Weight variation test, Disintegration time, Dissolution profile, Drug content when data compared to other batches. (12,13)

Refrences:

1. Sandip D.Firke:Method development and validation of silymarin in bulk and pharmaceutical formulation by UV- spectrophotometric area under curve method (AUC), Analytical Chemistry an Indian Journal 2015,pg no 101
2. Yan H, Liang M, Jianga M, Sieslerb HW. Non-destructive determination of silymarin in Silybum marianum extracts with a handheld near-infrared spectrometer. In Proceedings of the 18th International Conference on Near Infrared Spectroscopy 2019 Feb 19 (pp. 135-141). IM Publications Open.
3. Kolling WM. Handbook of pharmaceutical excipients. American Journal of Pharmaceutical Education. 2004;68(1-5):BF1
4. Skoog D.A, HollerF and Nieman S. Principles of instrumental analysis, 5th edition, ThomsonAsiaPvt.Ltd.,Singapore,1996,410-413.
5. Husain M, Agnihotri VV, Goyal SN, Agrawal YO. Development, optimization, and characterization of hydrocolloid-based mouth dissolving film of Telmisartan for the treatment of hypertension. Food Hydrocolloids for Health. 2022 Dec 1;2:100064.Kammali Lavanya, V. Senthil, and Varun Rathi.
6. Meghreji. Moin.: Validated method for Silymarin by Spectrophotometry in Bulk drug and Pharmaceutical formulations, Journal of Chemical and Pharmaceutical Research , 2010 , pg no.39
7. Buchi. N et.al 'Development and evaluation of fast dissolving films of sumatriptan succinate for better therapeutic efficacy' Jr App PhSci, Aug 2013 vol 3 (8), p.no 161-166
8. Deepthi KS, Goutam K, Sharma A, Khushal S. Formulation and characterization of atenolol fast dissolving films. Indian Journal of Pharmaceutical Science & Research. 2012;2(2):58-62.
9. Dixit N, Baboota S, Kohli K, Ahmad S, Ali J. Silymarin: A review of pharmacological aspects and bioavailability enhancement approaches. Indian journal of pharmacology. 2007 Jul 1;39(4):172
10. Javed S, Kohli K, Ali M. Reassessing bioavailability of silymarin. Alternative medicine review. 2011 Sep 1;16(3):239.
11. Shimoda H, Taniguchi K, Nishimura M, Matsuura K, Tsukioka T, Yamashita H, Inagaki N, Hirano K, Yamamoto M, Kinosada Y, Itoh Y. Preparation of a fast dissolving oral thin film containing dexamethasone: a possible application to antiemesis during cancer chemotherapy. European journal of pharmaceutics and biopharmaceutics. 2009 Nov 1;73(3):361-5.

12 Nalanda Rangari, Rushikesh Palkar, Sonia Singh, Ajit Gund, Sonali Patil Solubility enhancement of Luliconazole by solid dispersion 2022,

20(9) 5050-5058

13. Sonia Singh, Rushikesh Shinde, Nalanda Rangari, Kunal Gahukar, Shubham Ingawale Formulation and evaluation of mouth dissolving tablets of sitagliptin phosphate with enhanced permeability Neuro Quantology 2022 20(9), 5091-5098