FORMULATION AND EVALUATION OF SOLID DISPERSIONS OF SILYMARIN BY USING WATER SOLUBLE POLYMERS

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ABSTRACT

Silymarin, a flavolignan from the seeds of Milk thistle (silybum marianum), has been widely used from ancient time because of its excellent hepatoprotective action. It is a mixture of three flavolignans, viz., silybin, silidanin and silychristine with silybin most active silymarin has been widely used medicinally to treat liver disorders including acute and chronic viral hepatitis, toxin/drug induced hepatitis, cirrhosis and alcoholic disorders. It has been reported to be effective in the treatment of certain cancer disorders. It is orally absorbed and it has very poor bioavailability due its solubility. This investigation focuses on the dissolution enhancement of poorly soluble drug silymarin was made by the preparations of solid dispersions by various techniques such as, physical mixture, kneading mixture, co-grinding mixture. A significant improvement in the dissolution was observed in the present investigation having solid mixture with drug, polymer (silymarin,pvp) 1:1 ratio by using physical mixture method. Hence it is proposed to compress the tablets using the mixture and described evaluation tests such as hardness, friability, weight variation, drug content uniformity, disintegration time, dissolution parameters. The review looks at the formulation process that has been done to enhance its solubility and as well as increased its bioavailability and thus its hepatoprotective action.

KEYWORDS: Silymarin, Milk thistle, Solid dispersion, polyvinyl pyrrolidone, Bioavailability, Hepatoprotection.

1.INTRODUCTION:

Silymarin obtained from Silybum marianum (milk thistle), an edible part used for the treatment of liver-related disorders. It is widely prescribed by herbalist and has almost no known side effects. The plant is native to the Mediterranean and grows through the Europe, India and North America (silymarin.com).

Silymarin is a polyphenolic flavonoid, extracted by using 90% ethanol, from the seeds of milk thistle. The most prevalent component of the silymarin complex is silybin (50-60% of silymarin) which is the most active photochemical and it is responsible for hepatoprotection. Besides silybin, which is a mixture of two diastereomers (A&B) in 1:1 proportion silychristin (20%), silydianin (10%), Isosilybin (5%), dehydrosilybin and taxifolin. The seeds also contain betaine, trimethyl glycine and essential fatty acids that may contribute to silymarin's hepatoprotective and anti-inflammatory effects.

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Silymarin is insoluble in water, purely soluble in methanol. And is usually administered in capsules as standard extract (70-80% silymarin). Absorption after oral administration is rather low, with recovery in the bile in rats ranging from 2-3%. Peak plasma concentrations are achieved in 4 to 6hrs, both in animals and in humans. Silymarin is mainly excreted in the bile and lesser extent in urine. Its elimination half life ranges from 6 to 8hrs (Morazzoni,1993; Pepping,1999; Schdandalik,1992)

2. MATERIALS & METHODS

2.1 POLYVINYL PYRROLIDONE (POVIDONE):

Povidone (Hand book of pharmaceutical excipients,1994;I.P.,1996;U.S.P.,1999) is a fine, white to creamy-white coloured, odourless, hygroscopic powder. Povidone with k-value equal to or lower than 30 are manufactured by spray drying and exist as spheres. Povidone k 90 are manufactured by drum drying and exists as flakes. Povidone is chemically, 1-ethenyl-2-pyrrolidone homopolymer and has a molecular formula of $(C_6H_9NO)_n$.It is free soluble in acids, chloroform, ethanol, acetone and water. Practically insoluble in ether, hydrocarbons and mineral oil. Since the powder is hygroscopic, it should be stored

in an air tight container in a cool, dry place. Povidone is used in a variety of pharmaceutical formulations; it is primarily used in solid dosage forms.

2.2. Silymarin:

Silymarin (Dr.Reddy's laboratories Ltd) Hyderabad; Polyvinyl pyrrolidone k 30 Methyl alcohol, Hydrochloric acid , Sodium chloride , Sodium lauryl sulphate (S.D Fine chemical Ltd) Mumbai.

Methods:

Preparations of Solid Dispersions :

Solid dispersion, which was introduced in then early 1970s (Chiou,1971) is a multicomponent system, having a drug dispersed in and around hydrophilic carrier(s).It (solid dispersion technique) has been used for a wide variety of poorly aqueous soluble drugs such as tenoxicam, nimodipine, ursodeoychloricacid and albendazole. "A Solid dispersion is one or more active ingredients in an inert carrier or matrix. These are used to enhance or reduce the dissolution rate of the drugs".

In the present investigation ,solid mixture of selected drug silymarin and carrier polyvinyl pyrrolidone(PVP) were prepared in 1:1,1:3,1:5,1:7 and 1:10 weight ratio by following techniques i.e. , physical mixing, co-grinding & kneading method.

Physical mixture of silymarin were prepared by mixing. Silymarin with PVP in motor untill homogeneous mixture was obtained. The resulting mixture was stored in screw cap bottles at room temperature until further evaluation tests.

Drug content uniformity :

From the prepared tablets five tablets are randomly collected and powdered. Taken 100mg of sample in 100ml volumetric flask dissolved with methanol shaken for 20min and filtered, assayed the drug content uniformity (USP,1999).

Disintegration time :

Disintegration time of tablets was determined in distilled water by using thermonic tablet disintegration test apparatus of USP/IP standard (IP,1985).

Dissolution rate studies:

Dissolution test was carried out by using USP XXI rotating paddle method (Apparatus I) the stirring rate was 100rpm, 900ml of simulated gastric fluid was used as dissolution medium and maintained at 37±0.5°c samples of 5ml were withdrawn at predetermined time intervals and analyzed drug content by spectrophotometric method at 286nm results obtained were compared. The mechanism of dissolution rate improvement from solid dispersion is reviewed by ford (Marshall,1991;Ford,1986).

Tablet preparation and Characterization:

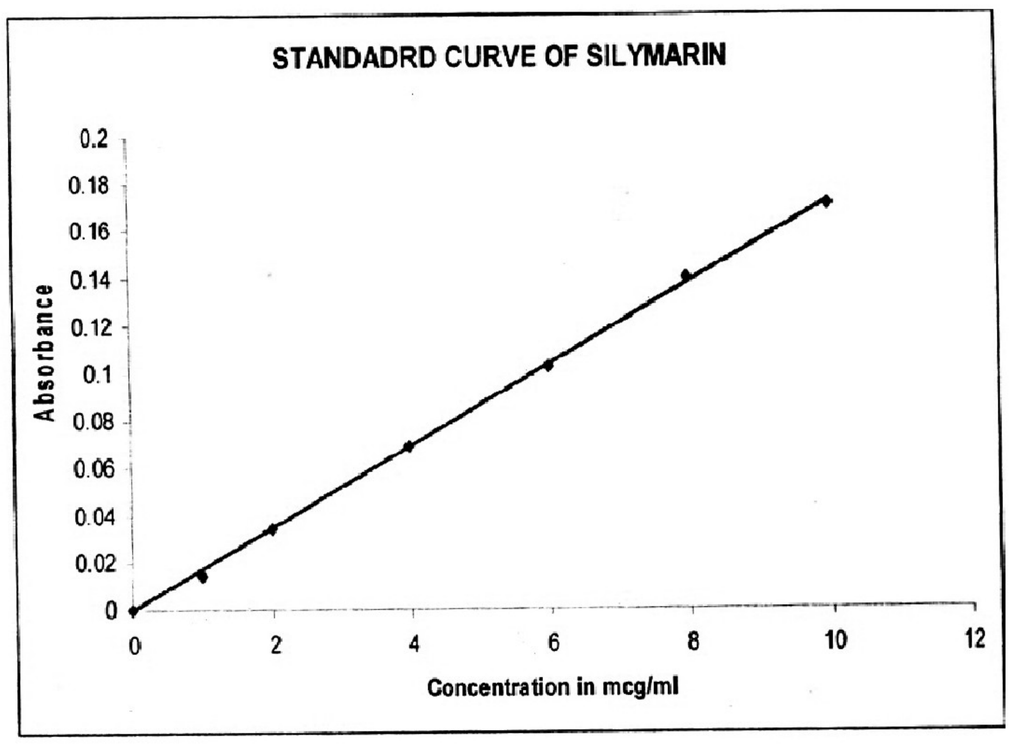
Tablets each containing 5mg of the drug in solid dispersions (PVP) were prepared by wet granulation method as per the formulae given in table3. The blend of powder was compressed in to tablets on a multistation tablet machine (Cadmach) to a hardness of 4-5kg/sq.cm. Prepared tablets were evaluated for hardness (Monosanto hardness tester), friability (Roche friabillator), weight variation and drug content. Estimation of silymarin in phosphate buffer (pH 6.4) was accomplished spectrophotometrically using an double beam UV spectrophotometer. Invitro dissolution studies of tablets containing solid dispersion and commercial tablet of silymarin were carried out in 90ml simulated gastric fluid.

3.RESULTS AND DISCUSSION:

In the present research work poorly water soluble drug silymarin was prepared in to solid mixture with polyvinyl pyrrolidone with the aim to improve their pharmacological properties like solubility & dissolution rate and there by oral bioavailability.

Table-01 ABSORBANCES OF SILYMARIN AT DIFFERENT CONCENTRATIONS

S.NO.	Concentration (mcg/ml)	Absorbance
1	1	0.014
2	2	0.034
3	4	0.069
4	6	0.102
5	8	0.140



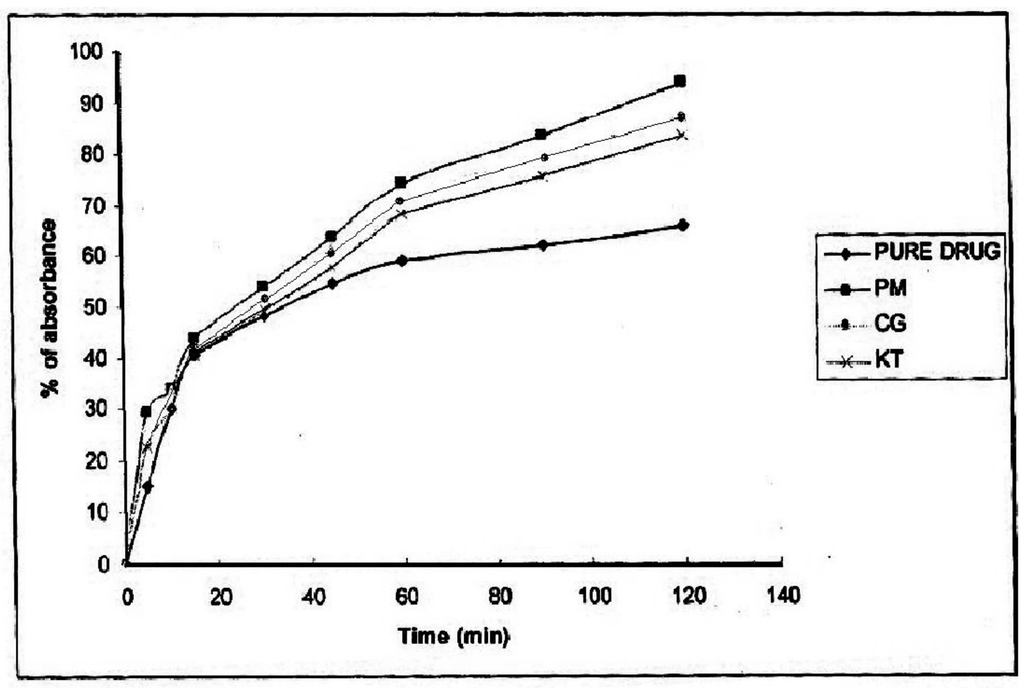
Invitro dissolution profiles of silymarin solid mixtures prepared by PM, CG & KT techniques at 1:1, 1:3, 1:5, 1:7 & 1:10 ratios . The dissolution of pure Silymarin is very slow and only 65.92% was dissolved in 2hrs. Out of the three methods employed to prepare the Silymarin solid mixtures, Physical mixing Method (PM) gave highest Dissolution Efficiency (DE). However all the three methods have significant improvement in the dissolution as compared to that of pure drug. Solid mixtures prepared from SIL: PVP-1:1-PM gave 100% drug release in 120min, Where as SIL: PVP-1:1-CG solid mixture 92% and SIL: PVP-1:1-KT solid mixtures prepared by different methods of preparation are as follows PM>CG>KT and it is shown in the table2 and figure as follows

Table-02

Percent drug dissolved (n=3±SD) from PVP: SIL-1:1

Time(Min)	Pure SIL	PM	CG	KT
5	15..25±1.26	29.47±0.56	26.51±0.85	25.45±0.58
10	30.05±0.85	38.75±0.48	35.22±0.69	33.44±0.77
15	40.63±0.91	46.12±0.72	43.50±0.79	41.41±0.68
30	48.24±1.04	58.25±0.35	55.52±0.49	54.46±0.75
45	54.72±0.28	70.45±0.40	66.52±0.95	65.27±0.84
60	59.01±0.87	80.75±0.73	74.40±0.99	73.55±0.18
90	62.13±1.01	91.25±0.29	83.50±0.89	83.45±0.92
120	65.92±1.15	99.90±0.44	93.25±0.86	91.00±0.47

DISSOLUTION PROFILE FOR THE PERCENT DRUG RELEASE



The higher dissolution for physical mixtures in case of silymarin may be due to its intimate mixing with the polymer in dry state and adsorption of the drug on the polymer, which subsequently expose large surface area of the drug particles to dissolution media. Hence it is proposed to compress the tablets of above solid mixtures to evaluate the efficacy of PVP solid mixture in the tablet dosage form.

To evaluate the effectiveness of the solid mixtures of silymarin, tablets of silymarin with the solid mixtures at the weight ratio 1:1 of PVP prepared by physical mixing method was formulated and studied.

Table-03

Formulae of tablets prepared:

INGREDIENTS(mg/tablet)	SILYMARIN TABLETS
SIL:PVP-1:1-PM	120
Lactose	55
Dicalcium phosphate	27
Talc	2
Starch paste	8
Magnesium state	3
Total weight(mg)	215

The quality control tests such as uniformity of weight, hardness, friability, disintegration time and drug content for the formulation prepared according to the formulae table3 were performed and the results are given in table 4.

Table- 04

Characteristics of formulated and commercial tablets:

Formulation	Weight[a] (mg)	Drug content[a] (%)	Hardness[a] (kg/sq.cm)	Friability[a] (%)	Disintegration Time[a] (min.)
SILT	215.23±1.28	99.89±0.45	3.9±0.80	0.54	5.5±0.51
CT	200.94±1.42	99.61±1.10	4.6±0.75	0.40	7.75±0.24

a: Mean± S.D.

CT: Commercial SILYMARIN Tablet (Silybon, Micro labs).

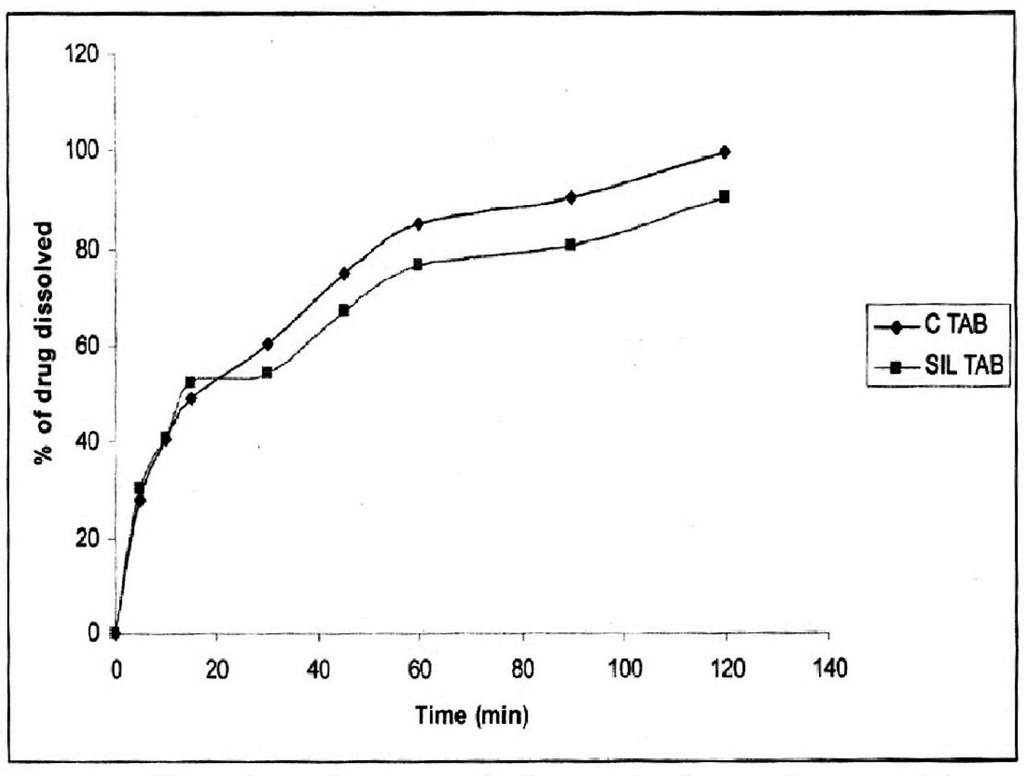
The above formulation prepared complied with compendia standards for uniformity of weight. The hardness for all the formulations was found to be in the range of 3-4.5kg/cm^2 and was satisfactory. The percentage weight loss in the friability test was found to be less than 1% for the batch of tablets. The drug content of the tablets when assayed spectrophometrically was found to be 100±2%.

In vitro dissolution profiles of silymarin prepared tablets with solid mixtures and commercial tablet are shown in table 5.

Table-05
Percent of siymarin drug released from prepared and commercial tablets:

Time(Min)	Mean percent dissolved(n=3±SD)	
	SIT	CT
5	28.12±1.28	30.25±1.11
10	40.50±1.01	40.80±0.98
15	49.25±0.09	52.45±0.85
30	60.60±0.51	54.25±1.01
45	75.10±0.45	67.10±0.56
60	85.00±0.07	76.60±0.51
90	90.23±0.86	80.51±0.87
120	99.58±0.88	90.45±0.4

Comparative studies of dissolution profile for commercial and formulated tablets.



The dissolution of silymarin from these tablets was rapid. Tablets containing silymarin solid mixtures prepared by physical mixing method gave faster and complete release of the drug with in 2hrs. Thus the tablet dosage forms of silymarin made with PVP was found to be of good quality fulfilling the official and other requirements of compressed tablets and the prepared solid mixtures of silymarin can be compressed as tablets without altering the much of dissolution characteristics of solid mixtures.

4. CONCLUSION:

A systematic study involving dissolution enhancement of poorly soluble drug silymarin was made by the preparations of solid dispersions using hydrophilic polymers using various techniques. Among all solid dispersions prepared, physical mixture showing better result. We therefore formulated tablets using solid dispersions prepared by physical mixture method and evaluated which are found to be pharmacopoeial limits and standards.

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