Design and Evaluation of Silymarin-HP-ß-CD Solid Dispersion Tablets

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Since solubility is the main constraint for oral bioavailability of silymarin, an attempt has been made to design tablet formulations of silymarin-HP-β-CD solid dispersion in order to improve oral bioavailability. Tablet formulations were prepared by direct compression technique using superdisintegrants such as crosscarmellose sodium, sodium starch glycolate and polyplasdone XL in different concentrations. Developed formulations were evaluated for various pharmaceutical characteristics viz. hardness, % friability, weight variation, drug content, disintegration time and *in vitro* dissolution profiles. Amongst different batches, formulations containing crosscarmellose sodium showed superior disintegration and dissolution profiles compared to other formulations. However all the formulations showed improved dissolution over marketed formulation reflecting vital role of HP-β-CD dispersion in promotion of silymarin oral bioavailability. Moreover, optimized formulation showed stability at varying temperature and relative humidity.

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Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability[1]. Silymarin is a hepatoprotective and hepatogenerative drug which is the standarised seed extract rich in flavanolignans. The main flavanolignans in silymarin are isomers silybin, silydianin and silychristin[2]. Silybin is the main active component and basically silybin is silymarin[3]. It is regarded as the single most important component in silymarin and has been subjected to numerous biochemical and pharmacological studies. The hepatoprotective activity of silymarin rests with strong antioxidant, free radical scavenging activity and hepatogenerative activity is due to the ability of silybin to accelerate protein synthesis, and mitosis via activation of DNA-dependent RNA-Polymerase which leads to regeneration of hepatocytes[2]. However silybin is a water insoluble drug and shows poor dissolution characteristics[3]. The water insolubility leads to poor bioavailability of the drug with only 23-47% bioavailability and time taken to reach plasma concentration is about 1.3-4 hours[2,4]. Silymarin has the solubility in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8) 0.209±0.65 mg/ml and 0.148±0.88 mg/ml, respectively.

In light of above facts, solid dispersions of silymarin were prepared, with β-CD or HP-β-CD in various ratios (1:1, 1:2, and 1:3 w/w) of drug to polymer, by kneading method using hydroalcoholic solvent (1:1). Among these ratios, drug to HP-β-CD (1:3 w/w) ratio showed best dissolution characteristics and thus, in the present study conventional tablets of silymarin-HP-β-CD (1:3) dispersion were prepared by using superdisintegrants in various concentrations[5,6].

Tablets of silymarin-HP-β-CD solid dispersions were prepared by using different disintegrants in 4, 6 and 8%. Microcrystalline cellulose was used as a diluent and magnesium stearate (2%) was used as a lubricant. The compositions of various formulations are as shown in Table 1. All the ingredients were passed through sieve No.100, weighed and blended. The lubricated formulations were compressed by direct compression technique using 12 mm concave faced punches.

All prepared tablets and the marketed preparation were evaluated for drug content, friability, hardness, thickness and weight variation[7]. Friability was determined using Roche friabilator[8]. Hardness was measured using Pfizer hardness tester. Thickness was measured using Vernier caliper. The drug content was estimated at 286 nm (Shimadzu UV spectrophotometer 2401 PC, Japan). *In vitro* disintegration test was performed for tablets at 37 ± 1^0 using the disintegration test apparatus (Tablet Disintegration Tester ED-2L (USP), Electrolab, Mumbai). The study was conducted in triplicate.

In vitro drug release study was done using USP II (paddle) apparatus with 900ml of dissolution medium maintained at 37±2° for 2 h at 75 rpm. Simulated gastric fluid (without pepsin)[9] was used as a dissolution medium. Ten ml of sample was withdrawn after every 15 min and was replaced by equal volume of fresh medium maintained at 37±2°. Samples were analyzed spectrophotometrically at 286 nm and cumulative % drug release was calculated. The study was performed in triplicate. Optimized formulation A3 was tested for stability at ambient temperature (R.T.) and 45±2° at 75%±5% R.H. for a span of three months.

The study of physical parameters of the formulations revealed that all the tablets were acceptable in regard to silymarin content, weight variation, hardness and thickness (Table 2). Among the three disintegrants used, Crosscarmellose sodium demonstrated best disintegration power as compared to other two disintegrants. This might be again attributed to their mechanism, which may comprise capillary action with a secondary burst effect. The result also showed decrease in disintegration time as the concentration of superdisintegrants increases from 4% to 8%. This can be correlated to tablet matrix pore size

TABLE 1: COMPOSITION OF SILYMARIN CONVENTIONAL TABLETS

Ingredients (mg)	Formulation code								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
Solid dispersion equal to 70 mg of drug	280	280	280	280	280	280	280	280	280
Crosscaremellose sodium	16.8	25.2	33.6	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	16.8	25.2	33.6	-	-	-
Polyplasdone-XL	-	-	-	-	-	-	16.8	25.2	33.6
Microcrstalline cellulose	114.8	106.4	98	114.8	106.4	98	114.8	106.4	98
Magnesium stearate	8.4	8.4	8.4	8.4	8.4	8.4	8.4	8.4	8.4

Formulae for the preparation of silymarin-HP-β-CD solid dispersion tablets.

TABLE 2: CHARACTERISTICS OF TABLETS CONTAINING SILYMARIN

Formulation code	Drug content* (%)	Friability (%)	Hardness* (Kg/cm^2)	Thickness* (mm)	Dissolution		D.T.(Sec)
					t50% (Min)	t75% (Min)	
A1	100.45±0.52	0.23	3.66±0.81	5.30±0.10	25	>120	78
A2	99.87±0.28	0.26	3.80±0.45	5.46±0.06	18	94	60
A3	100.16±0.14	0.31	3.40±0.40	5.33±0.15	14	80	42
A4	100.04±0.98	0.33	3.33±0.60	5.26±0.05	30	>120	90
A5	101.58±0.40	0.28	3.20±1.20	5.50±0.00	25	120	74
A6	99.34±1.02	0.25	3.30±0.76	5.46±0.05	20	105	59
A7	100.45±0.74	0.46	3.80±0.98	5.26±0.16	28	>120	88
A8	98.86±0.16	0.37	3.40±0.36	5.30±0.08	24	115	70
A9	99.28±0.35	0.32	3.50±1.08	5.34±0.06	18	98	54
Marketed	100.42±0.72	0.26	6.80±1.06	3.53±0.14	>120	>120	126

* Each value represents mean±S.D. (n = 6).

distribution created by the use of superdisintegrants. Higher levels of disintegrants probably made larger pores with continuous network or skeleton providing enough pressure within a matrix for faster disintegration.[5]

All the formulations showed improved dissolution as compared to marketed preparation (Table 2). The attributes for these findings are dispersion of silymarin in HP-β-CD which increases the solubility and the superdisintegrants which cause swelling leading to sufficient hydrodynamic pressure to induce complete disintegration.

The accelerated stability study revealed that the tablets of optimized batch A3 showed no significant changes in both physicochemical properties and dissolution profiles (P>0.05). Thus, it could be concluded that oral bioavailability of silymarin can be improved by the way of HP-β-CD solid dispersions.

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