RESEARCH ARTICLE

Formulation, Development and Optimization of Silymarin Loaded Nanoparticle Orodispersible Tablets for its Anti-inflammatory Activity

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ABSTRACT

The objective of this work was to enhance the anti-inflammatory properties of silymarin by developing and refining an orodispersible tablet formulation loaded with nanoparticles. Formulation development and optimization of silymarin-loaded nanoparticle orodispersible tablet for its anti-inflammatory activity is the focus of this research paper. Nanoparticle drug delivery systems can help to overcome these limitations by enhancing solubility and absorption. Disintegration and dissolution of Orodispersible tablets take place in the mouth rapidly without water, providing a faster onset of action. These nanoparticles were then incorporated into orodispersible tablets containing superdisintegrants and sweeteners using direct compression. A Box-Behnken design was utilized to systematically optimize the tablet formulation based on responses including disintegration time, wetting time, hardness and friability. After 15 minutes, SL-NP Formulation -3, which contains 5% crospovidone as a superdisintegrant, demonstrated maximal drug release, or 98.5%. Rats with paw edema caused by carrageenan were used to test the anti-inflammatory potential. Following three hours, the 400 mg/kg dose showed a strong 48% inhibition; the impact grew to 52% after three hours. Overall, the development of silymarin nanoparticle orodispersible tablets shows promise for improving the anti-inflammatory effects of silymarin through a synergistic combination of nanoencapsulation and rapid disintegrating tablet technologies.

Keywords: Orodispersible tablets, Rapid dissolving, Rapid disintegration, Anti-inflammatory activity, Nanoparticles.

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INTRODUCTION

A subtype of an ultrafine particle often called a nanoparticle, has a diameter ranging from 1 to 100 nm. The term "subdivisions" refers to particles less than 100 nm in diameter; in other contexts, it can also refer to tubes or fibers. Smaller than one nanometer, metal particles make up the atomic clusters. One As a result, nanoparticles have different physical and chemical properties to prevent deposition phenomena.[1-3]

Because nanoparticles are separated by visible light wavelengths (400–800 nm), standard optical microscopes cannot observe them. Instead, electron or laser microscopes must be used. In the suspension, scattering of light occurs in larger particles while transparent SL-NP forms dispersion. Additionally, nanoparticles easily flow through standard filters or ceramic candles.[4-6]

There are several advantages of nanoparticles in modern medicine. Undoubtedly, there are certain situations in which nanoparticles enable research and therapies that otherwise would be practically impossible. That being said, there are unique environmental and social issues associated with nanoparticles, particularly with regard to their potential for harm.[5,6] This study aims to enlighten the significant contributions that nanoparticles have made to medicine while also examining the social and natural aspects of their utilization[7,8]

Milk thistle seeds are the primary source of silymarin. The active component of traditional Silybummarianum, milk thistle, is a hepatoprotectant that is used to treat liver disease and also has antiviral as well as anti-inflammatory and antilipidemic properties.[9–11]

These days, pharmacokinetic and pharmacodynamic features of phytotherapeutics are enhanced by their utilization as nanoparticles. The diameters of the nanoparticles range from 1 to 1000 nm, and they differ from their macroscopic counterparts in terms of their characteristics. The drug matrix is integrated in the nanoparticles.[12]

MATERIALS AND METHODS

Silymarin, Polymer-Pluronic F- 68as well as Eudragit gifted from Cipla Pharmaceuticals and Alembic Pharmaceuticals,

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Preparation of Polymeric Nanoparticle Suspension

The microemulsion of nanoparticles of silymarin was prepared by the nanoprecipitation method. Table 1 In this case, the API 50 mg and Eudragit portion were dispersed in methanol (15 mL). Then above mixture was rapidly poured into the solution (30 mL) that already had 10 mL of Pluronic® F-68, and then continued under vigorous stirring for 20 minutes. In addition, I set the stirring and continued to provide heat for 2 hours at 40°C to evaporate methanol completely. Next, concentrate the initial quantity to 40 mL by adding 200 mg of HPMC K-15 dissolved in water that serves as a control. During this process, nanoparticle suspension got optimized and was separated out by freezing and drying at 42°C for a period of 72 hours and then again water was added to get back the aqueous nanoparticle suspension.[13-17] Formulation of silymarin-based nanoparticles:

Results and Analysis

All the evaluation parameter results are illustrated in Table 2. Silymarin calibration curve: An analytical technique that was employed was UV-absorption spectroscopy to examine the content of the drug, entrapment effectiveness as well as *in-vitro* co-relationship of Silymarin drug by means of the methanol and pH 7.4 phosphate buffer saline respectively. Figure 1 The absorption spectra of 20 µg/mL silymarin in methanol and in phosphate buffer saline (pH 7.4) were analyzed based on absorbance values between 400 and 200 nm. The detector sighted for the wavelengths was 287.[18-19]

FTIR Spectroscopy

The figure was followed by the IR spectrum of silymarin Figure 2 and its interpretation of IR frequencies given.[20]

Table 1: Silymarin nanoparticles- Factorial design

Variables	*Coded levels (%w/v)*		
	Low	*Middle*	*High (%w/v)*
Pluronic F-68	0.5	0.6	0.7
Eudragit	0.2	0.35	0.5

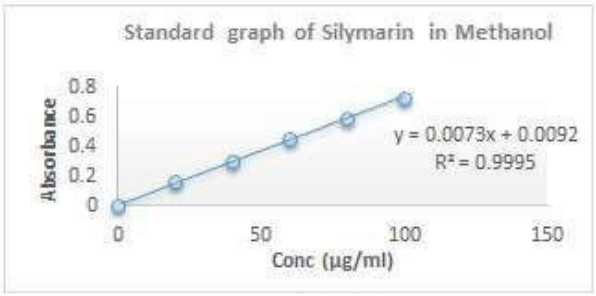

Figure 1: Data of concentration and absorbance for silymarin in methanol

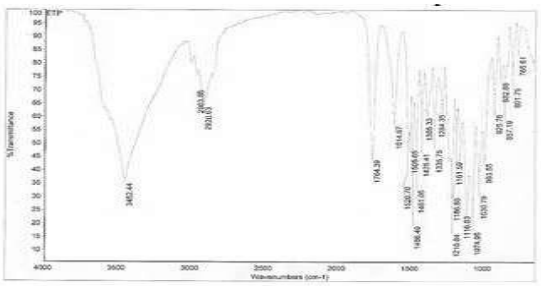

Figure 2: Silymarin-IR spectra

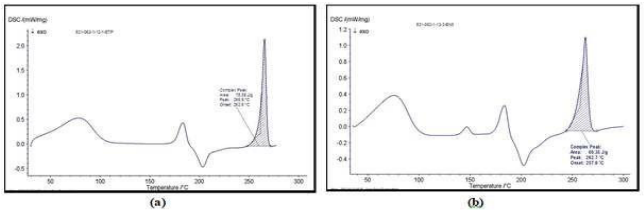

Figure 3: Differential scanning colorimetry (a) drug (b) Silymarin based nanoparticles

DSC Thermogram

DSC analysis has instrumental value in checking the retention and distribution of substances, their cohesion and adhesion characteristics, particle size, coating and other relevant physicochemical properties of the drug molecules in nanoparticles. Figure 3 shows DSC thermograms of drug and polymeric nanoparticles, respectively.[21,22]

Table 2: Evaluation of nanoparticles

S. No.	*Code*	*Percentage yield*	*Percentage drug content*	*Percentage entrapment efficiency*	*Particle size (nm)*	*Polydispersity index*	*Zeta potential (mV)*
1	F1	58.66 ± 0.461	61.86 ± .130	48.96 ± 0.135	114.4 ± 0.305	114.4 ± 0.305	18.30 ± 0.135
2	F2	65.10 ± 0.386	67.43 ± .075	54.40 ± 0.150	125.5 ± 0.862	125.5 ± 0.862	19.46 ± 0.305
3	F3	68.33 ± 0.288	72.87 ± .015	59.97 ± 0.198	134.6 ± 0.200	0.707 ± 0.002	20.2 ± 0.115
4	F4	66.47 ± 0.329	82.21 ± .075	81.82 ± 0.274	128.5 ± 0.100	0.564 ± 0.005	24.6 ± 0.200
5	F5	68.66 ± 0.288	86.25 ± .075	88.23 ± 0.276	129.3 ± 0.100	0.548 ± 0.001	25.6 ± 0.200
6	F6	75.33 ± 0.230	88.36 ± .075	94.28 ± 0.198	131.4 ± 0.057	0.522 ± 0.001	26.2 ± 0.208
7	F7	69.18 ± 0.259	85.90 ± .080	89.95 ± 0.202	134.4 ± 0.115	0.693 ± 0.001	22.3 ± 0.152
8	F8	72.93 ± 0.230	87.66 ± .130	92.42 ± 0.430	135.3 ± 0.152	0.684 ± 0.002	23.6 ± 0.200
9	F9	73.44 ± 0.190	89.50 ± .130	94.10 ± 0.135	136.7 ± 0.100	0.656 ± 0.005	24.60 ± 0.152

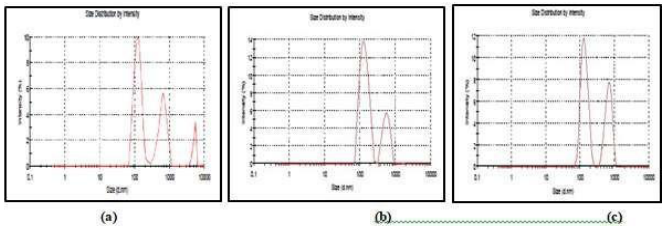

Figure 4: Size distribution of particles (a) F9, (b) F6 (c) F3

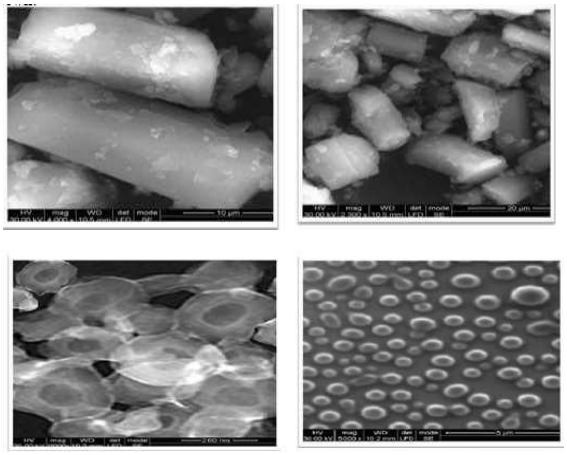

Figure 5: Scanning electron microscopy of pure Silymarin and F9 Formulation

Particle Size Analysis

Among all the evaluation factors of nanocrystals, this item into its particle size. Figure 4 The numbers for the purpose of the particle's dimension and polydispersity quantities were summarized below.[23]

Scanning Electron Microscopy Analysis SEM: The surface word structure and nanoparticle form of samples are examined using the Scanning Electron Microscopy (SEM) technique. Figure 5 was shown at two different magnifications: 50X and 2500X.[24,25]

Measurement of Zeta Potential

Maintaining the consistent stability for nanoparticles was assured by carrying out a potential test. The conclusion leads to the conclusion that there exists the phenomenon of attraction between the particles. Hence, prevents aggregation.[26]

X-ray diffraction study analysis

illustrated in figure 6

Statistical Analysis

illustrated in Figure 7.

Stability Studies

Stability experiments were conducted in order to ascertain the optimal storage conditions as well as the impact of varying storage conditions on the physicochemical properties of nanosuspensions. Therefore, in Table 3 a stability test based on an in-vitro procedure that establishes stability parameters is being conducted on the formulation F6, which was chosen.[27]

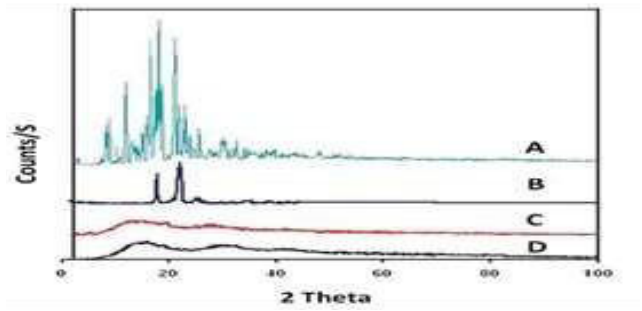

Figure 6: Diffraction spectra of pattern X-ray (A) Silymarin (B) Dispersion of Drug+EPO+F-68(C) SL nanoparticles (Prior lyophilization) (D) SL nanoparticles (completion of lyophilization)

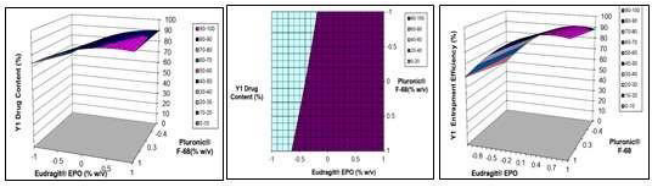

Figure 7: (a) Response surface plot-drug content (b) Response surface plots -entrapment efficiency, and (c) Response surface plot effect on drug content of variables

Table 3: Data of stability on %Drug content

S. No.	*Duration*	*%Drug during stability*		
		T=05 ± 4°C 6% RH	*T=25°T ± 4°C 6% RH*	*T=40° ± 2°C 5 % RH*
1	Initial	88.46 ± 0.075	88.56 ± 0.075	88.36 ± 0.075
2	3 months	88.23 ± 0.020	88.22 ± 0.015	88.15 ± 0.015
3	6 months	88.03 ± 0.152	88.14 ± 0.020	87.94 ± 0.025
4	9 months	87.95 ± 0.026	88.02 ± 0.011	-
5	12 months	87.69 ± .043	87.89 ± 0.005	-

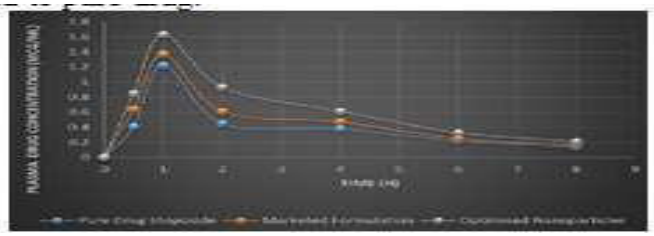

Figure 8: Plasma drug concentration-time curve

Table 4: Bioavailability study

Details	*Silymarin*	*Formulation in market*	*Optimized Nanoparticles*
AUC0	5.77 ± 0.66	6.89 ± 0.37	7.11 ± 0.15*
Fr		119.41	123.22
Tmax	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Cmax	1.23 ± 0.01	1.37 ± 0.01	1.63 ± 0.01*
t1/2	2.60 ± 0.06	2.37 ± 0.37	1.05 ± 0.06*
Ke	0.267 ± 0.005	0.294 ± 0.04	0.652 ± 0.03*

(i) (ii) (iii) (iv)

Figure 9: (i)Spleen (ii) Liver (iii) Kidney (iv) Lungs (v) Brain

Table 5: Tissue distribution

Secluded area	*Percentage drug recovered in tissue**	
	Silymarin	*Optimized nanoparticles*
Liver	29.17 ± 0.041	41.88 ± 0.030
Spleen	17.40 ± 0.080	26.66 ± 0.320
Lung	14.79 ± 0.195	14.82 ± 0.090
Kidney	12.83 ± 0.065	5.52 ± 0.300
Brain	5.63 ± 0.180	5.18 ± 0.49

SL-NP Bioavailability Data

Results are illustrated in Figure 8

Distribution of SL-NP in Tissue Studies: For both the pure medication and the optimized formulation F6, which combines two medications with distinct action mechanisms, an *in-vivo* tissue distribution study in Table 4 was conducted. Using the contrast of free silymarin, a fraction of the silymarin medication in tissues was investigated using NP. The drug silymarin, which is formulated with the maximum drug content and is thought to be a nanoparticle, was compared in different organs, and the results are displayed here in Table 5. This image Figure 9 shows the organs in solitary rats as seen through a collective fluoroscopic view.[28]

Preparation of Tablets

The direct compression technique was used in this work Table 6 to prepare the orodispersible tablets. When compared to the wet granulation approach, direct compression in tableting needs fewer processing stages, is easier to validate, and improves medication stability in addition to being a more cost-effective method. A filler that is directly compressible needs to have good compatibility and flowability. While high compatibility is required to create tablets with enough mechanical strength, good flowability is required to guarantee quick and consistent die-filling.[29-34]

Tablet Evaluation

All evaluator parameters are illustrated in Table 7.[29-34]

Table 6: Formulation of silymarin ODTs

Drug/excipients	*F-1*	*F-2*	*F-3*	*F-4*	*F-5*	*F-6*	*F-7*	*F-8*	*F-9*
Silymarin	52.8	52.8	52.8	52.8	52.8	52.8	52.8	52.8	52.8
Sodium carboxymethoxystarch	-	-	-	-	-	-	3.6	5.4	9
Crosspovidone	3.6	5.4	9	-	-	-	-	-	-
Mannitol	38.4	36.6	33	38.4	36.6	33	38.4	36.6	33
Crosscarmellose sodium	-	-	-		5.4	9	-	-	-
DibasicMagnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Mint flavor	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Talc powder	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Aspartame	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Final amount	100	100	100	100	100	100	100	100	100

Table 7: Evaluation of tablets

Formulation	*Compressibility index*	*Average weight variation*	*Hausner ratio*	*Angle of repose (θ)*	*Hardness (Kg/cm^2)*	*Friability (%)*
F1	12.35 ± 0.09	454 ± 0.12	1.14 ± 0.05	22.5 ± 0.27	3.20 ± 0.27	0.44 ± 0.05
F2	13.40 ± 0.14	451 ± 0.16	1.13 ± 0.04	24.7 ± 0.17	3.30 ± 0.34	0.46 ± 0.08
F3	12.48 ± 0.08	449 ± 0.16	1.06 ± 0.08	25.9 ± 0.21	3.30 ± 0.38	0.44 ± 0.04
F4	13.40 ± 0.11	449 ± 0.09	1.13 ± 0.06	24.6 ± 0.14	3.13 ± 0.29	0.49 ± 0.07
F5	12.50 ± 0.12	455 ± 0.13	1.13 ± 0.04	23.5 ± 0.19	3.20 ± 0.36	0.46 ± 0.06
F6	13.36 ± 0.09	453 ± 0.18	1.10 ± 0.05	26.3 ± 0.28	3.33 ± 0.32	0.46 ± 0.04
F7	13.46 ± 0.07	452 ± 0.09	1.16 ± 0.07	24.2 ± 0.22	3.26 ± 0.28	0.47 ± 0.09
F8	13.58 ± 0.10	454 ± 1.15	1.14 ± 0.09	25.4 ± 0.16	3.36 ± 0.33	0.44 ± 0.06
F9	13.26 ± 0.12	452 ± 1.17	1.18 ± 0.05	26.3 ± 0.23	3.40 ± 0.31	0.46 ± 0.07

CONCLUSION

An efficient and flavonoid-rich loaded nanoparticle of silymarin-containing was already made. A scanning preformulating study for the silymarin drug was also done. The crux of drug development is the beginning of the awesome piece of work with the documentation of drugs. Drug identification was accomplished using assay, infrared spectroscopy, ultraviolet light spectroscopy, melting point determination and solubility study to make tablets with adequate mechanical strength. Nanoparticle loading capacity ranges were within the good limits for all the formulations tested. Compatibility research by FTIR and DSC analysis of nanoparticles demonstrates the absence of incompatibility between drug-active ingredients (APIs) with polymers and surfactants.

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