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RESEARCH ARTICLE

FORMULATION AND INVITRO EVALUATION OF SOLID DISPERSION TABLETS OF SILYMARIN

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Abstract

Objective: The research aims to formulate and evaluate Solid Dispersion tablets of Silymarin.

Methods: Solid dispersions of Silymarin were prepared with various concentrations of carriers by using solvent evaporation method. The prepared solid dispersions were compressed into tablets by using 8 mm punch rotary tablet punching machine, with the hardness of 3.5kg/cm². The formulated tablets were evaluated for various quality control parameters.

Results: Silymarin was mixed with various proportions of excipients which showed no drug-excipients interactions. The precompression blend of Silymarin solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blend of all the batches indicated good to fair flowability and compressibility.

Conclusion: The tablet passed all the tests. Among all the formulations F4 formulation containing, Drug and PEG 4000 in the ratio of 1:4 showed good result that is 94.95 % in 60 minutes. As the concentration of polymer increased the drug release was increased. While the formulations containing PEG 6000 showed less release. Hence from the dissolution data it was evident that F4 formulation is the better formulation.

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Introduction:-

Solid dosage form such as tablets and capsules hold the highest share in the pharmaceutical market despite the advancement in innovative dosage forms such as liposome, transdermal delivery system etc. The drug's concentration at the site of action affects the therapeutic effect of the drug. The crucial factors solubility and dissolution determine the amount of drug absorbed since only dissolved drug can pass the gastrointestinal membrane. Dissolution depends on the solubility of the surrounding medium. Other factors which may reduce the bioavailability are drug metabolism in the intestinal lumen, liver and the intestinal wall. Therefore the onset and extent of clinical effect can be determined by the dissolution of the drug and subsequently transporting through the intestinal membrane and passage to the liver. These two suspect forms the basis of Biopharmaceutical Classification System {BCS} which is incorporated in the guidelines of Food and Drug Administration {FDA}.

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One of the most challenging tasks in drug development is to improve the dissolution and solubility of poorly and practically water in-soluble drugs. Various methods are available to increase dissolution rate, oral absorption and bioavailability of such drugs. One such method is Solid dispersion. Solid dispersion was defined as dispersion of one or more active ingredients in an inert carrier at solid-state to achieve increased dissolution rate and bioavailability of poorly and practically insoluble drugs [1, 2].

Silymarin belongs to BCS class II drugs that are characterized by low solubility and high permeability. Silymarin is practically insoluble in water; upon oral administration, its absorption rate in the gastrointestinal tract is low with 20 to 40 % bioavailability. Therefore, the enhancing of its solubility and dissolution profile was expected to significantly improve its bioavailability and reduce its side effects [3, 4].

Materials and Methods:-

Silymarin was given as a gift sample by Matrix Laboratories, Hyderabad. PEG 4000, PEG 6000, Sodium Starch Glycollate, Aerosil, Microcrystalline Cellulose and magnesium stearate were procured from Asian Scientifics, Hyderabad.

Drug excipients interaction study and identification

Fourier Transform Infrared Spectroscopy (FTIR)

An IR spectrum was routinely analyzed for drug-polymer interaction. FTIR spectra were taken for pure drug Silymarin and a physical mixture of drug and polymers to check the compatibility. The samples were prepared in KBr discs at a hydrostatic pressure of 5 tonnes/cm² for 2 min. To identify any chemical interaction any change in the spectrum pattern of the drug due to the polymers presence was investigated.

UV spectroscopy (determination of lambda max)

A spectrum of the working standards was obtained by scanning from 200-400 nm against the reagent blank to fix absorption maxima on Elico double beam UV visible spectrophotometer.

Preparation of standard curve

100 mg of Silymarin was dissolved in methanol 5 ml volumetric flask and made up to 100 ml with phosphate buffer of pH 7.4. From this primary stock 10 ml was transferred to another volumetric flask made up to 100ml with phosphate buffer of pH 7.4; from this secondary stock was taken separately and made up to 10 ml with phosphate buffer of pH 7.4, to produce 10,20,30,40 and 50 µg/ml respectively. The absorbance was measured by using a UV spectrophotometer. A calibration curve was plotted. The Slope, regression coefficient and equation for the line were determined.

Preparation of Silymarin solid dispersion

Solid dispersion of Silymarin was prepared by solvent evaporation method by using methanol as the solvent. Silymarin dose was taken as 140 mg. Silymarin was taken in a china dish and dissolved in 5 ml of methanol. Water soluble polymers such as PEG 4000 and PEG 6000 were selected as carriers for formulation F1 to F4 and F5 to F8 respectively. To the methanol solution, carriers in 1:1, 1:2, 1:3 and 1:4 ratios were added and the mixtures were evaporated at room temperature for 24 hrs. Then the mixtures were collected and packed in amber-colored glass containers, hermetically sealed and then stored at ambient conditions. Drug and polymers were taken in different ratios stated in the formulation chart (Table 1). To get uniform sized particles the prepared solid dispersions were passed through the sieve no 20. The blends were evaluated for precompression parameters [5, 6].

Preparation of Silymarin tablets

All the ingredients were weighed and passed through sieve no. 44. The powder blends were lubricated with Magnesium stearate and Talc and mixed for two to three minutes. These lubricated blends were compressed into tablets using 8 mm flat-faced round tooling on a multiple punch rotary tablet machine.

Table 1:- Formulation table showing various compositions.

Formulation	Ingredients	Ratio
F1	Drug: PEG 4000	1:1
F2	Drug: PEG 4000	1:2
F3	Drug: PEG 4000	1:3

F4	Drug: PEG 4000	1:4
F5	Drug: PEG 6000	1:1
F6	Drug: PEG 6000	1:2
F7	Drug: PEG 6000	1:3
F8	Drug: PEG 6000	1:4

Pre-compression evaluation

The granules were evaluated for flow property i.e., angle of repose, bulk density, tapped density, compressibility index (Carr's index) and Hausner's ratio using standard procedures [7].

Post-compression evaluation

The prepared tablets were evaluated for their physical parameters like thickness, weight variation, friability, hardness and drug content [8, 9].

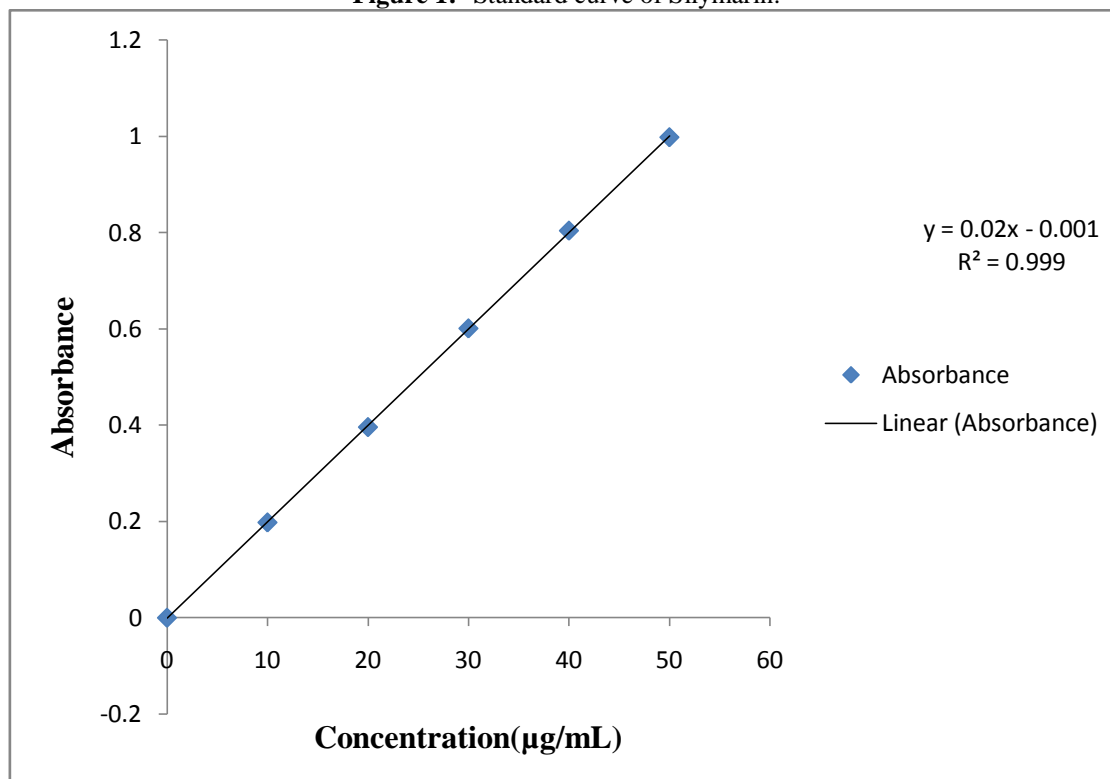
Drug release from Silymarin tablets was determined by using dissolution test United States Pharmacopoeia (USP) type II (paddle). The dissolution study was carried out by using 900 ml of pH 7.4 phosphate buffer. The dissolution study was carried out at a temperature of 37⁰ C and at a speed of 50 rpm. At suitable time interval 5ml aliquots of dissolution media was withdrawn (5, 10, 20 minutes.) and replaced with fresh medium. Samples were filtered and analyzed after appropriate dilution by UV spectrophotometer at 288 nm. The concentration of the drug was calculated using the standard calibration curve [10].

Results:-

Determination of lambda max

The maximum absorbance was obtained at 288 nm. The calibration curve was in the range of 0 to 50 µg /ml and a straight-line equation was obtained having the regression coefficient value of 0.999.

Figure 1:- Standard curve of Silymarin.



Drug excipients interaction and identification

Silymarin mixed with various proportions of excipients showed no drug-excipients interactions.

Figure 2:- FTIR spectra of Silymarin.

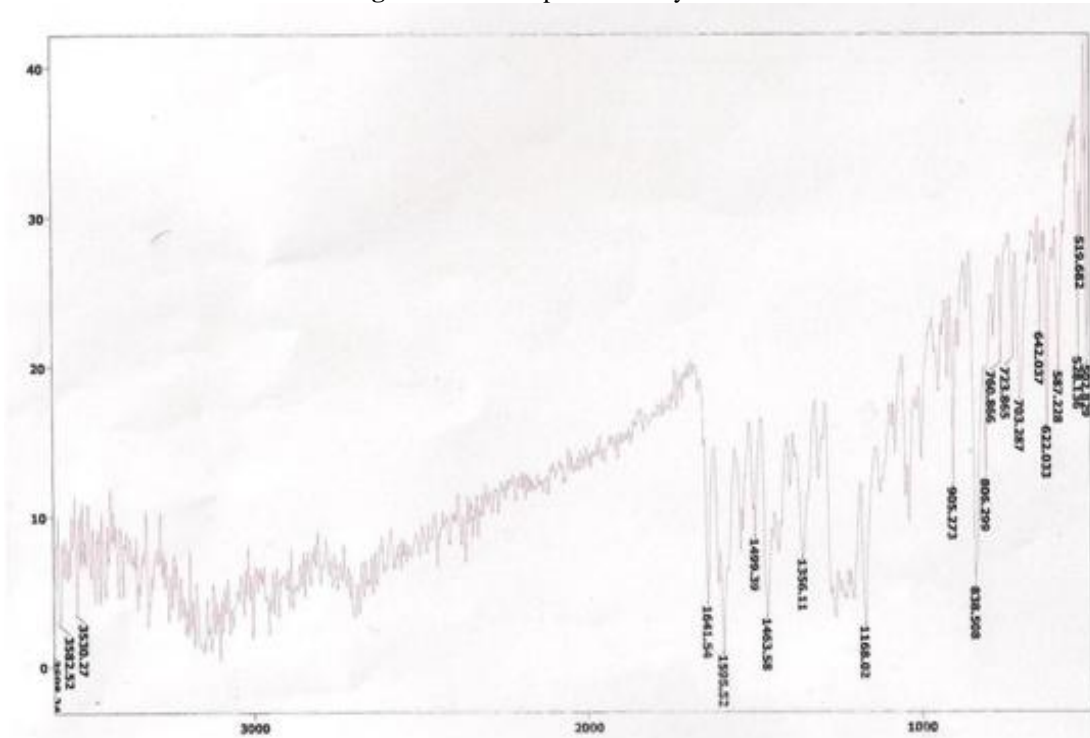
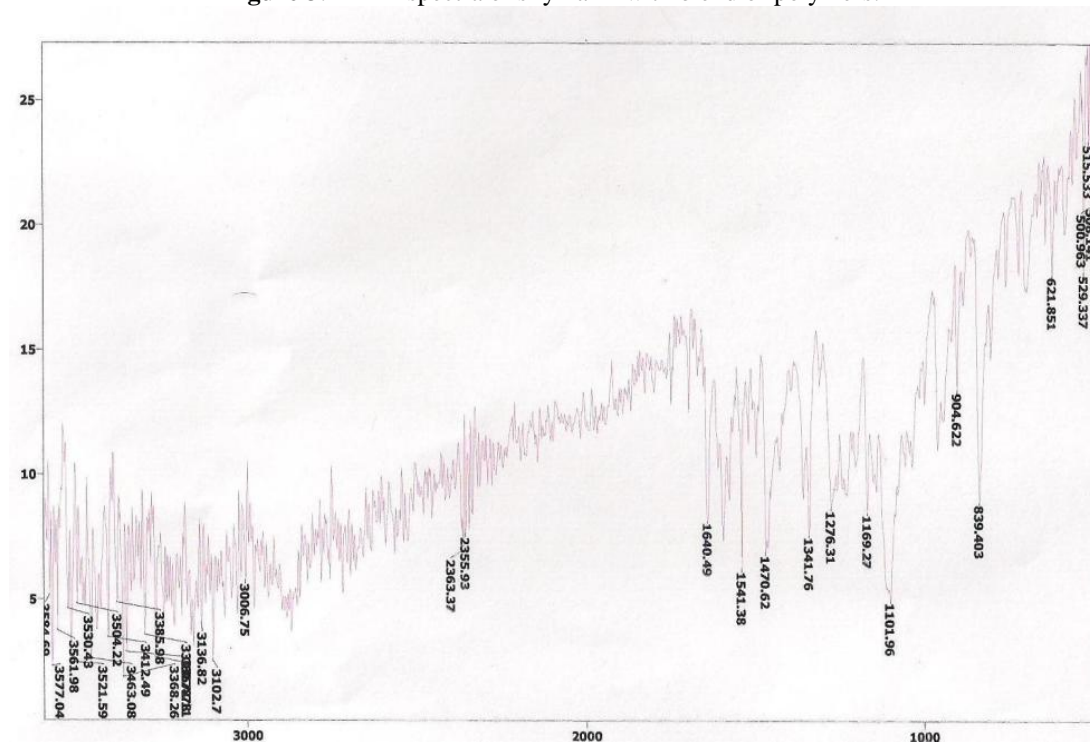


Figure 3:- FTIR spectra of silymarin with blend of polymers.



Physical characteristics

The precompression blend of Silymarin solid dispersions were evaluated with the parameters angle of repose, bulk density, tapped density, Carr’s index and Hausner’s ratio. Precompression blend showed good to fair flowability and

compressibility since the angle of repose of all the formulations were within 25.15° to 27.12°, Carr's index values were less than 11. Hausner's ratio was less than 1.17 for all the batches indicating good flow properties.

Table 2:- Physical properties of precompression blend.

Formulation Code	Angle of repose (Θ)	Bulk density (gm/cm ³)	Tapped density (gm/cm ³)	Carr's Index (%)	Hausner's ratio
F1	25.15°	0.53±0.01	0.59±0.01	9.43±0.12	1.09±0.02
F2	26.43°	0.54±0.03	0.60±0.02	9.40±0.13	1.10±0.01
F3	25.31°	0.54±0.02	0.58±0.03	10.01±0.19	1.13±0.06
F4	25.40°	0.51±0.01	0.61±0.06	10.11±0.02	1.16±0.01
F5	27.12°	0.58±0.03	0.63±0.03	10.34±0.13	1.17±0.03
F6	25.31°	0.59±0.03	0.64±0.04	10.12±0.34	1.11±0.06
F7	26.21°	0.56±0.01	0.63±0.01	9.93±0.11	1.13±0.03
F8	26.45°	0.53±0.03	0.58±0.03	10.13±0.02	1.12±0.01

All the values were mean ± Standard deviation (SD), n=3

Physical Evaluation of Silymarin solid dispersion tablets:

The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 3. All the tablets of different batches pass the limits of weight variation and hence complied with the official requirement of weight variation. The hardness of the tablets ranged from 3.2 to 3.8 kg/cm² and the friability values ranges from 0.341 % -0.561% which is less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 4.71±0.01cm to 4.81±0.04 cm. The disintegration time of all the tablets was found to be less than 60 sec. All the formulations showed good uniformity in drug content as they contained 98±0.9 to 100±0.3 of Silymarin. Thus physical evaluation of the prepared Silymarin tablets were found to be practically within control limits.

Table 3:- Important parameters of evaluation for tablets.

Formulation code	Weight variation (mg)	Thickness (cm)	Diameter	Hardness (Kg/cm ²)	Friability (%)	Content uniformity (%)
F1	351±1	4.76±0.01	8.12±0.01	3.5±0.7	0.420	99±0.12
F2	350±2	4.74±0.04	8.14±0.02	3.2±0.5	0.341	99±0.3
F3	350±1	4.71±0.01	8.01±0.01	3.6±0.6	0.363	100±0.1
F4	349±2	4.80±0.06	8.03±0.03	3.8±0.5	0.561	100±0.3
F5	350±3	4.81±0.04	8.04±0.04	3.8±0.4	0.482	99±0.6
F6	350±1	4.74±0.05	8.09±0.05	3.4±0.6	0.513	99±0.4
F7	350±1	4.76±0.03	8.11±0.03	3.5 ± 0.1	0.412	98±0.9
F8	349±2	4.71±0.04	8.09±0.06	3.6±0.2	0.432	99±0.1

In vitro drug release

The drug release rate from tablets was evaluated at 288 nm using UV-Visible spectrophotometer. The invitro dissolution data of formulations F1 – F4 by using PEG 4000 polymer were showed in figure-4 and formulations F5– F8 by using PEG 6000 were showed in figure-5 respectively.

Figure 4:- Invitro dissolution data for formulations F1 – F4 by using PEG 4000 Polymer.

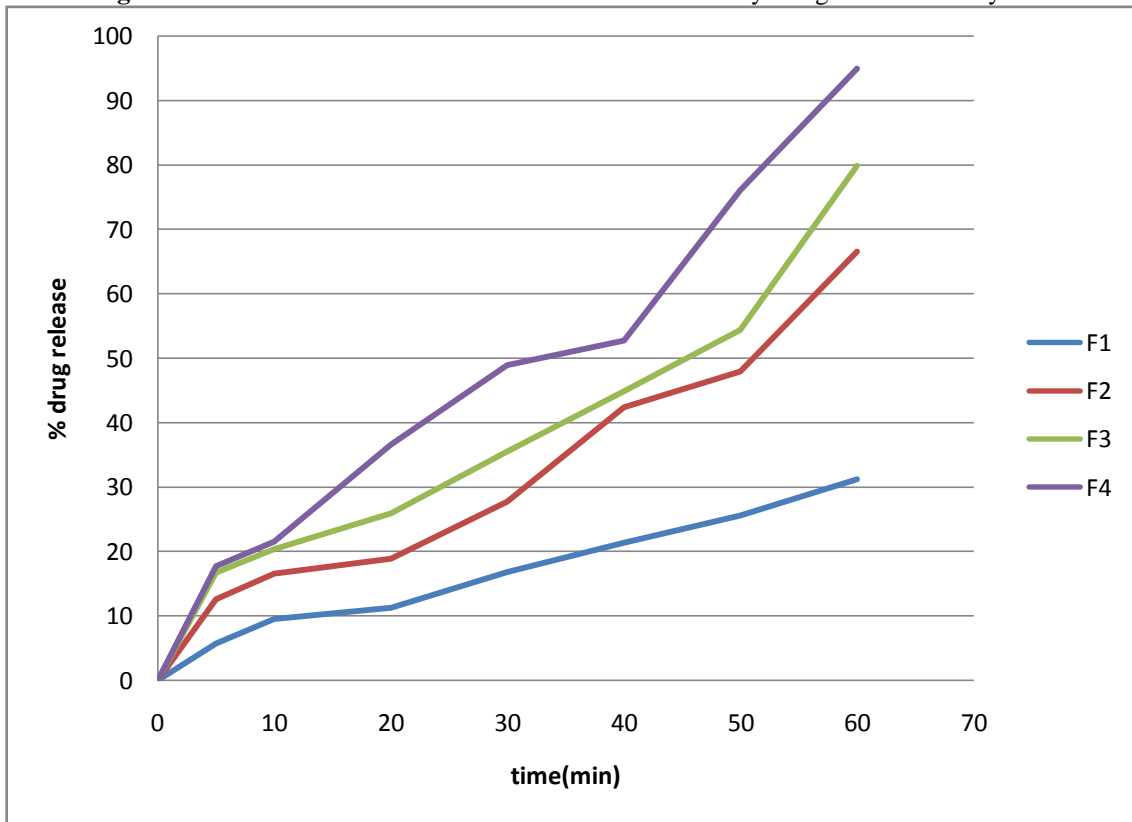
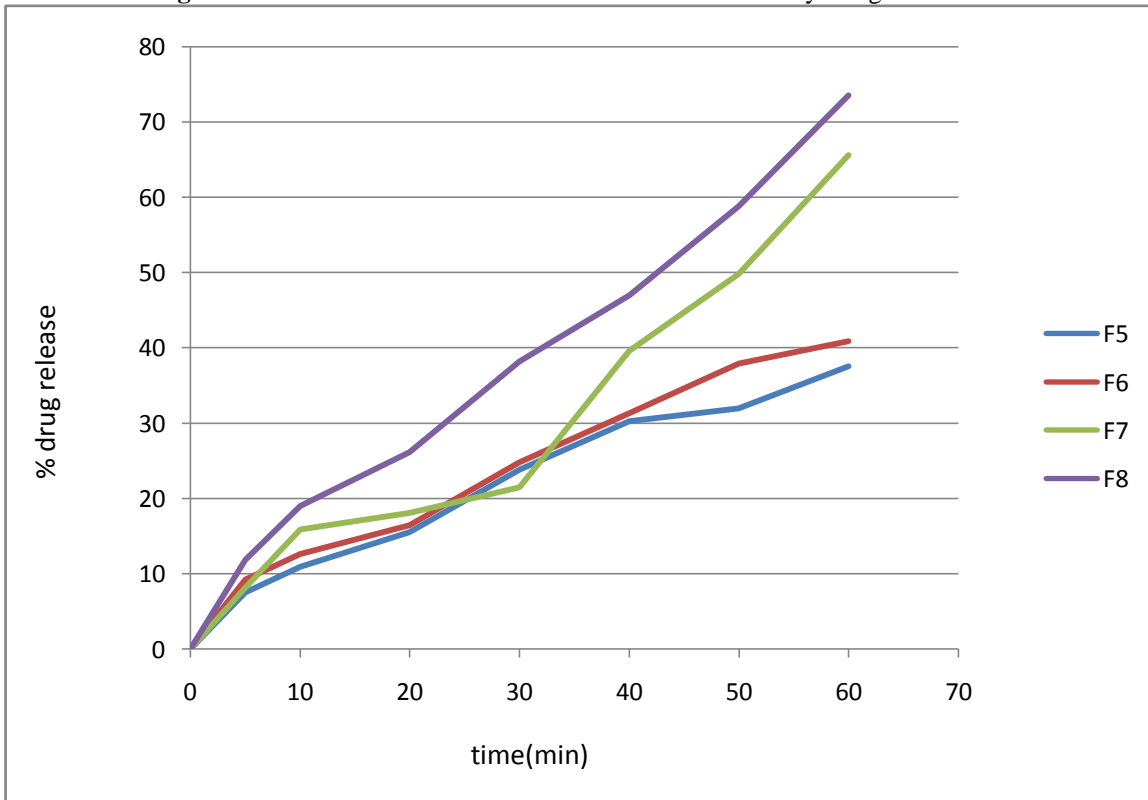


Figure 5:- Invitro dissolution data for formulations F5– F8 by using PEG 6000.



Discussion:-

The studies were conducted on the different concentrations of polymers. Among all the formulations F4 formulation containing, Drug and PEG 4000 in the ratio of 1: 4 showed good result that is 94.95 % in 60 minutes. As the concentration of polymer increased the drug release was increased. While the formulations containing PEG 6000 showed less release. It was evident from the dissolution data that F4 formulation is the better formulation. The solubilization effect of PEG 4000, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wettability and dispersibility and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of Silymarin from its Solid Dispersion.

Conclusion:-

The results showed that among all the formulations F4 formulation containing, Drug and PEG 4000 in the ratio of 1:4 showed the good release of 94.95 % in 60 minutes. While the formulations containing PEG 6000 showed less release. Hence from the dissolution data it was evident that F4 formulation is the better formulation. Thus the solubility and dissolution rate of Silymarin was enhanced by solid dispersion.

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Authors Contribution

The authors of the research have equally contributed for this work.

Conflicts Of Interest

There remains no conflict of interest.

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