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Formulation and in-vitro evaluation Rutin Phytosomes

Adity Sen Pal[1], Sweta Goel[2], Manmeet Singh Saluja[2]

[1]Research Scholars, SunRise University, Alwar, Rajasthan, India
[2]Research Supervisor, SunRise University, Alwar, Rajasthan, India

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Corresponding author: Adity Sen Pal
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Abstract:

Rutin, a naturally occurring bioflavonoid with potent antioxidant and therapeutic properties, suffers from poor water solubility and limited bioavailability, restricting its clinical applications. To overcome these limitations, the present study aimed to develop and evaluate rutin-loaded phytosomes using a lyophilization technique. Rutin phytosomes were formulated using different molar ratios of rutin and soy phosphatidylcholine (SPC) and characterized for particle size, polydispersity index (PDI), zeta potential, drug content, and in-vitro drug release. The optimized phytosomal complex showed improved particle uniformity, stability, and high drug entrapment efficiency. Characterization techniques such as FTIR, DSC, XRD, SEM, TEM, AFM, and [1] H-NMR were employed to confirm the formation and morphological properties of the complex. The in-vitro release study demonstrated a sustained and enhanced release profile of rutin from the phytosomal system compared to pure rutin. These results suggest that rutin phytosomes may serve as an effective delivery system for improving the solubility, stability, and therapeutic efficacy of rutin.

Keywords: Rutin, Phytosomes, Bioavailability, Drug delivery, Soy phosphatidylcholine

Introduction

Flavonoids, particularly rutin, are widely recognized for their remarkable pharmacological effects, including antioxidant, anti-inflammatory, vasoprotective, and anticancer activities. However, rutin's clinical potential is significantly hampered due to its poor aqueous solubility and low oral bioavailability. Conventional delivery systems fail to adequately address these issues, resulting in suboptimal therapeutic outcomes. Phytosomes are novel drug delivery carriers formed by complexation of plant-based active compounds with phospholipids, which improve the lipid solubility, permeability, and bioavailability of poorly soluble compounds. The unique amphiphilic nature of phytosomes allows better integration into biological membranes, thereby enhancing drug delivery across gastrointestinal and cellular barriers. In this study, rutin phytosomes were developed using soy phosphatidylcholine via lyophilization, and evaluated for various physicochemical characteristics and in-vitro release behavior. The use of design of experiments (DoE) helped in optimizing the formulation parameters for maximum drug incorporation and improved release profile. Multiple analytical and imaging techniques

were employed to confirm the complex formation and assess the surface morphology and thermal behavior of the rutin phytosomal system. The goal of this work is to establish a stable and efficient phytosomal formulation of rutin that can enhance its therapeutic efficacy through improved delivery and sustained release.

Materials and method

Materials

Rutin (98%pure) was procured from Yucca Enterprises, Mumbai. Soybean phosphatidylcholine and Lecithin soya-30% were purchased from Lipoid®, Ludwigshafen, Germany and HiMedia Laboratories, Mumbai. All the chemicals were of analytical grade.

Method

Preparation of Rutin phytosomes

First, rutin and SPC were weighed accurately in 1:1, 1:2, and 1:3 molar ratios. Rutin was dissolved in DMSO, and SPC was dissolved in t-butyl alcohol. Then, the rutin solution was added to the SPC solution, followed by 3 hours of stirring on a magnetic stirrer for the formation of the phytosomal complex.

The solution containing the phytosomal complex was then isolated by lyophilization with the addition of mannitol as a cryoprotectant in 0.5 to 1.5% w/v concentration. Before lyophilization, the solution was sonicated for 3 minutes.

This solution was filled into vials, and the vials were frozen at –80 ºC by placing them in an ultra-low temperature freezer for 4 hours. These frozen vials were then placed in a lyophilizer with a condenser temperature of –70 ºC. Lyophilization was carried out at 40 mbar pressure and a shelf temperature of –40 ºC for 24 hours, followed by secondary drying at 25 ºC for another 24 hours.

The dried rutin phytosomal complex product was removed from the freeze drier, filled into amber-coloured glass containers, and placed in a desiccator over fused calcium chloride at room temperature (20 ± 2 ºC) until further use. [1]

Evaluation of phytosomes

Average Particle Size, Particle Size Distribution (PDI), and Zeta Potential

The mean particle size (PS), and size distribution as polydispersity index (PDI) of all the rutin phytosome formulations generated by DoE software, including the optimized rutin phytosomes, were determined by dynamic light scattering (DLS) technique. The zeta potential (ZP) of the optimized rutin phytosomes was measured by electrophoretic light scattering (ELS) technique using Malvern Zeta Nano Sizer at a settled scrambling point of 90º at 25 ± 0.5 ºC. The samples were diluted with distilled water in a 1:10 ratio and sonicated using a probe sonicator before the measurement. Measurements were performed in triplicates, and the results are expressed as mean size ± SD. [2]

Extent of Rutin Incorporation in Rutin Phytosomes (Drug Content)

The rutin amount in the phytosomes was estimated by the spectroscopic method described by Tan Q et al. An accurately weighed amount of rutin phytosomes (~10 mg of rutin added) was dispersed in 5 ml of chloroform. The complex and pure SPC dissolve in chloroform, and free, uncomplexed rutin precipitates out. The dispersion was then filtered using Whatman® filter paper (ashless, grade 41, Sigma Aldrich). The free rutin residue was dried, dissolved in methanol, and diluted suitably. [3] This was analyzed using UV-VIS spectrophotometer at λmax 360 nm. Drug content (percentage incorporated drug) was determined for all the rutin phytosome

formulations generated by DoE software, including the optimized rutin phytosomes.

The percentage incorporated drug was calculated by the following equation:

$$\% \, Incorporated \, drug = \frac{W(Addeddrug) - W(Freedrug)}{W(Addeddrug)} X100$$

Differential Scanning Calorimetry (DSC)

The thermal response of optimized rutin phytosomes was evaluated using differential scanning calorimetry. The samples were taken in an aluminum crimp cell and sealed, then heated at a speed of 10 °C/min from 25 °C to 500 °C in a nitrogen atmosphere (60 ml/min). Thermograms of pure rutin, SPC (Lipoid® S100), physical mixture of rutin:SPC (1:2), and optimized rutin phytosomes were obtained using a thermal analyzer.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra matching approach was used to determine the possible chemical interactions between the rutin and SPC using an FTIR spectrometer. ATR method was employed in which a small quantity of the sample was placed below the FTIR spectrophotometer probe. Then the probe was tightly fixed and scanned in the wavenumber region 4000–500 cm^{-1} to obtain the spectrum of samples. [4] Samples assessed included pure rutin, SPC (Lipoid® S100), physical mixture of rutin:SPC (1:2), and optimized rutin phytosomes.

Surface Morphology

Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) were used to determine the surface characteristics of the formulated optimized rutin phytosomes.

Scanning Electron Microscopy (SEM)

SEM study was carried out using a scanning electron microscope. The samples for SEM were prepared by lightly sprinkling the pure rutin and optimized rutin phytosomes on a double-sided carbon adhesive tape, which was stuck on an aluminum stub. The samples were observed under a scanning electron microscope, and the photographs were taken. [5]

Transmission Electron Microscopy (TEM)

Transmission electron microscopy was also used to determine the morphological characteristics of optimized rutin phytosomes. The optimized rutin phytosome sample was diluted with distilled water in a 1:20 ratio and sonicated for 3 minutes. One drop of the diluted solution was placed on a carbon-coated copper grid to form a fine liquid film. The film was negatively stained by the addition of one drop of ammonium molybdate (2% w/w) in ammonium acetate buffer (pH 6.8). Excess stain was removed with a filter paper. The stained film was dried in air and observed under a transmission electron microscope with operating voltage of 200 kV, and photographs were taken. [6]

Atomic Force Microscopy (AFM)

The 3D surface morphology of the optimized rutin phytosomes was visualized using an atomic force microscope. The sample powder was converted into a thin pellet, deposited onto Mica Discs, and visualized in contact mode using AFM tips at 267–328 kHz resonance frequency with a scan speed of 1.2 Hz. In contact mode, the AFM tip had direct contact with the sample. While the tip was scanned along the surface, the sample topography induced vertical deflection of the cantilever. This deflection was measured by a fiber-optical interferometer. AFM analysis was also carried out after dilution of optimized rutin phytosomes with distilled water in a 1:20 ratio followed by 3-minute Sonication. [7]

Proton NMR (^{1}H-NMR)

^{1}H-NMR spectra of pure rutin, SPC (Lipoid® S100), and optimized rutin phytosomes were taken to compare the carbon-hydrogen framework of individual components. Samples were dissolved in DMSO, transferred to NMR tubes, and analyzed using an NMR spectrometer. [8]

X-ray Powder Diffractometry (XRD)

To study molecular crystallinity, X-ray diffraction patterns of pure rutin, SPC (Lipoid® S100), and optimized rutin phytosomes were obtained using an X-ray diffractometer. The operational specifications were: 40 kV tube voltage, 40 mA tube current, Kα lines of copper as radiation source, scanning angle range 0º–50º of 2θ in step scan mode with 1º/min step width. [9]

Solubility and Partition Coefficient

To determine the saturation solubility of pure rutin and optimized rutin phytosomes in water and n-octanol, excess amount of sample was added to 10 ml of solvent in a glass vial. The vial was capped and stirred at 100 rpm using a magnetic stirrer to achieve uniform mixing at room temperature (25–30 °C) for 24 h. The resultant solution was centrifuged at 5000 rpm for 30 min using a compact cooling centrifuge. The supernatant was filtered through a 0.2 µm membrane filter and, after suitable dilutions, analyzed using UV-VIS spectrophotometer at λmax 360 nm. [10]

The partition coefficient of pure rutin and optimized rutin phytosomes in n-octanol–phosphate buffer (pH 7.4) system was also determined by the conventional method using a separating funnel and calculated using the following equation:

$$K=C1/C2$$

Where:
C_1 = concentration of the drug in the oil phase
C_2 = concentration of the drug in the aqueous phase
K = equilibrium constant

In Vitro Drug Release

In vitro drug release from the optimized rutin phytosomes was determined using the dialysis method. The dialysis sacks were washed as per manufacturer instructions. After proper pre-treatment, one end of the sack was tied, and a known amount (10 mg) of pure rutin and optimized rutin phytosomes (~10 mg of rutin) was placed inside the sacks. The other end was tied and suspended vertically into a beaker placed on a magnetic stirrer with hot plate. The beaker contained 500 ml of buffer solution of pH 1.2 initially for 2 h, followed by replacement with pH 7.4 phosphate buffer to mimic the pH of the stomach and distal part of the small intestine. The content of the beaker was stirred at 100 rpm at 37 °C. Samples (5 ml) were withdrawn at specific time intervals, and the apparatus was immediately replenished with an equal quantity of fresh buffer to maintain sink conditions. [7] Samples were filtered and analyzed by UV-

VIS spectrophotometer at λmax 360 nm after the required dilutions.

Results and discussion

Average particle size, particle size distribution (PDI) and zeta potential

The PS and ZP obtained for all the rutin phytosome formulations generated by DoE software are given in Table 3.4. The PS, PDI, and ZP of optimized rutin phytosomes was foundtobe272.6±2.48nm, 0.376±0.02 and-28.2±0.10mV.

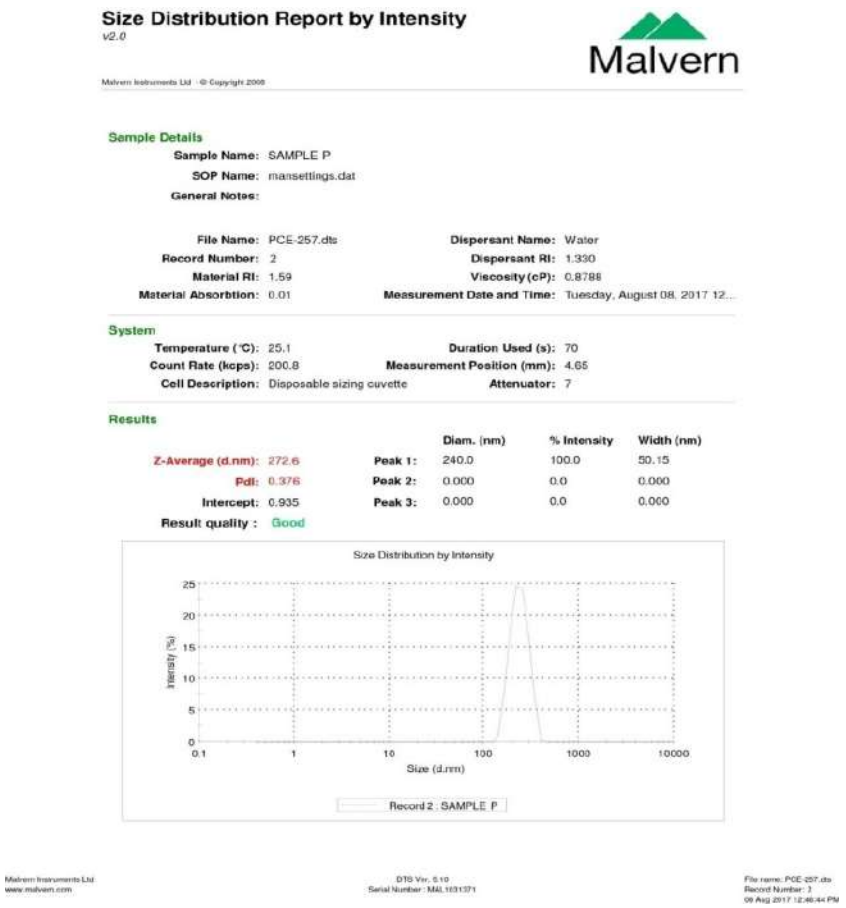

Fig.1.Average particle size and polydispersity index of optimized rutin phytosomes

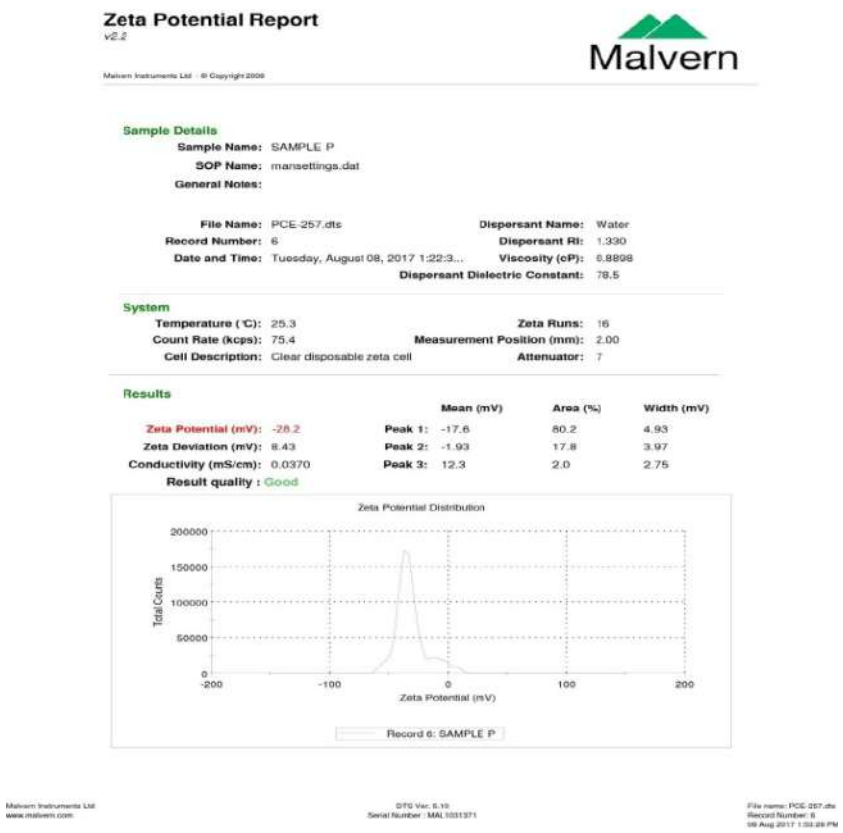

Fig. 2. Zeta potential of optimized rutin phytosomes

Extent of rutin incorporation in rutin phytosomes (drug content)

The drug content of all the rutin phytosome formulations generated by DoE software is given in Table 3.4. The rutin content in the optimized rutin phytosomes was found to be 91.38±0.24%w/w

Differential scanning calorimetry (DSC)

Thermal analysis was carried out to investigate solid-state interactions, especially phytosomal complex. DSC thermograms of pure rutin, SPC, physical mixture of rutin:SPC (1:2), and optimized rutin phytosomes. The thermogram of pure rutin showed a sharp endothermal peak at 242 ºC. Two endo thermal peaks were observed at 67.7ºCand 164.8 ºC in the thermogram of SPC. Thermogram of a physical mixture of rutin:SPC (1:2) showed the endothermal peaks at 233 ºC and 138 ºC. DSC thermogram of optimized rutin phytosomes showed a broad endothermal peak at 163 ºC.

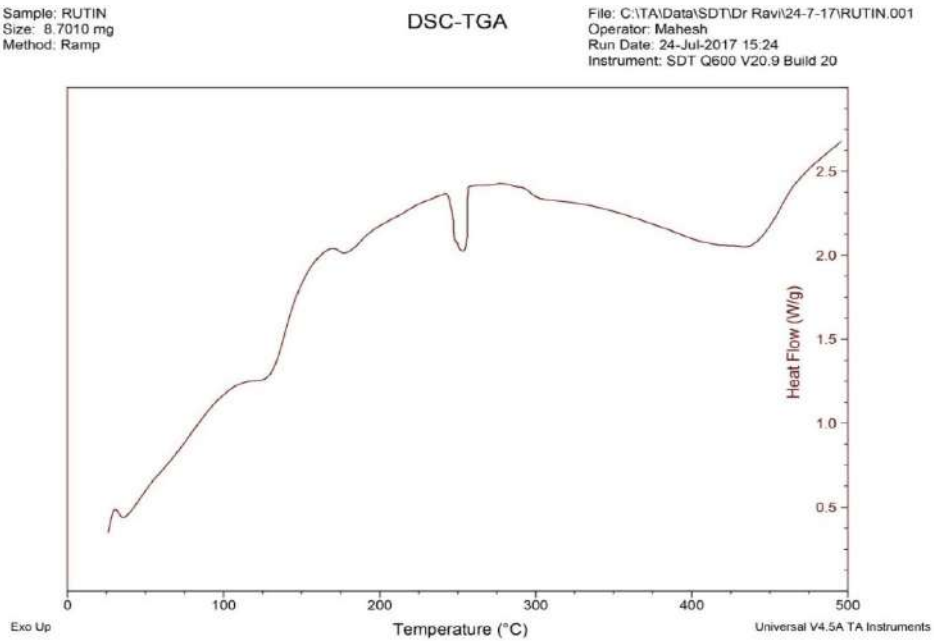

Fig.3. DSC thermogram of pure rutin

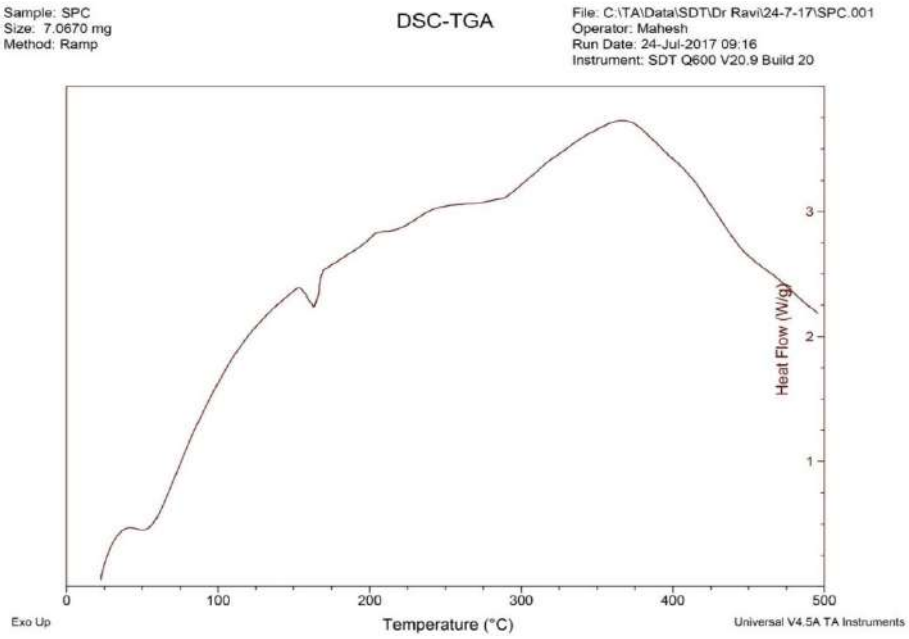

Fig.4. DSC thermogram of SPC

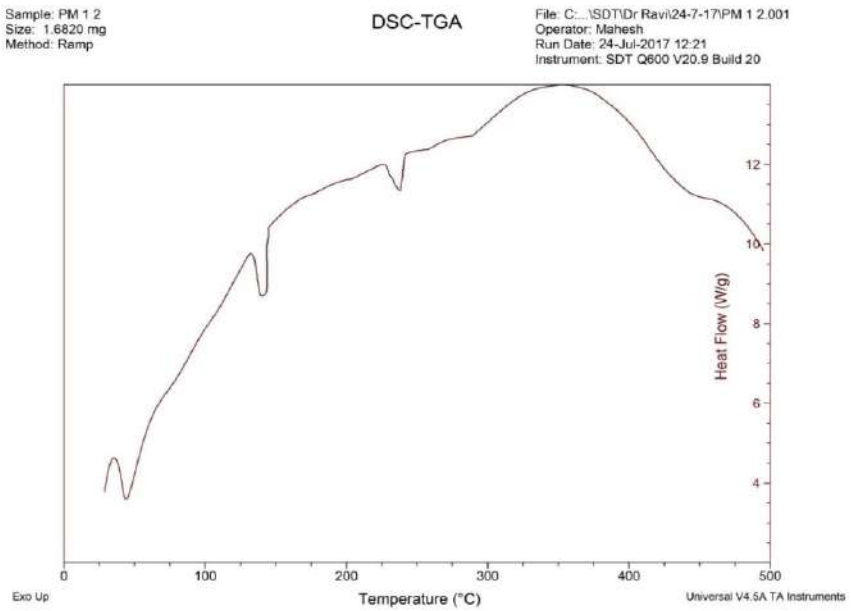

Fig.5.DSC thermogram of physical mixture of rutin:SPC (1:2)

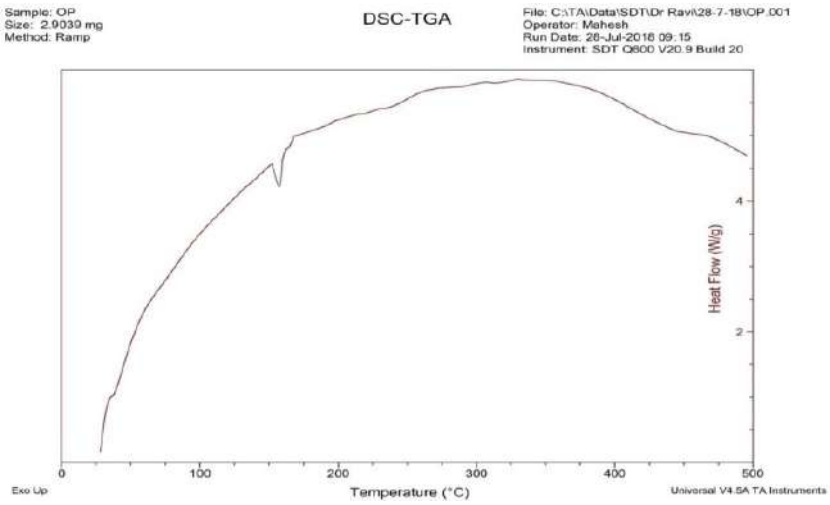

Fig. 6.DSC thermogram of optimized rutin phytosomes

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of the pure rutin, SPC, physical mixture of rutin:SPC (1:2), and optimized rutin phytosomes. The changes were observed between the physical mixture and optimized rutin phytosomes in the wave number ranges from 1231 cm^{-1} to 942 cm^{-1}. Broadening of the phenolic (–OH) band of rutin at 3637 $cm^{-1}$was also observed. The spectra of the physical mixture 1:2 and the optimized rutinphytosomes showed the absorption peaks at 1651 $cm^{-1}$and 2852 cm^{-1}, respectively.

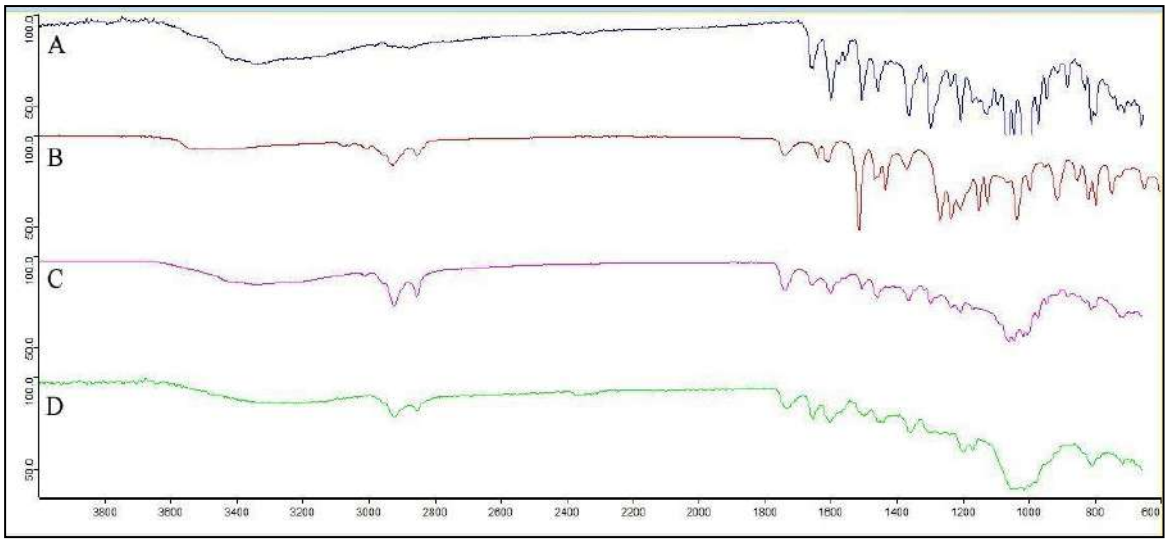

Fig. 7 IR spectra of rutin(A), SPC(B), physical mixture of rutin:SPC (1:2) (C), and optimized rutin phytosomes (D)

Surface morphology

Scanning electron microscopy (SEM)

The SEM image of the pure rutin revealed the crystalline nature of the drug rutin whereas optimized rutin phytosomes showed the amorphous nature and fluffy, porous and rough surface.

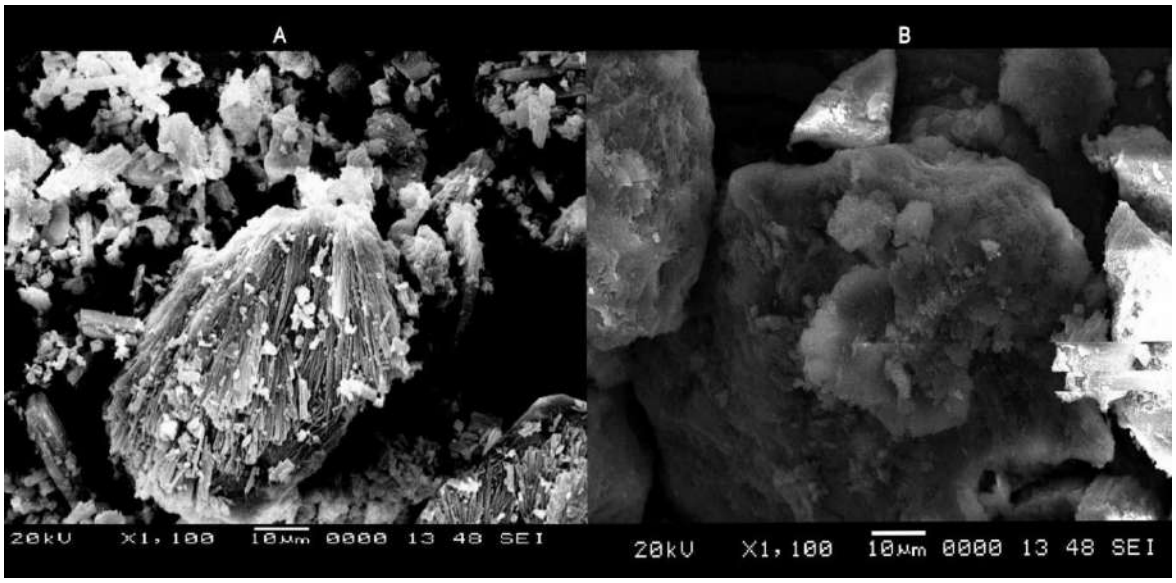

Fig. 8 SEM image of pure rutin (A) and optimized rutin phytosomes (B)(X1100).

Transmission electron microscopy (TEM)

The TEM image of the optimized rutin phytosomes showed well formed, discrete vesicles with no evidence of aggregation or decomposition.

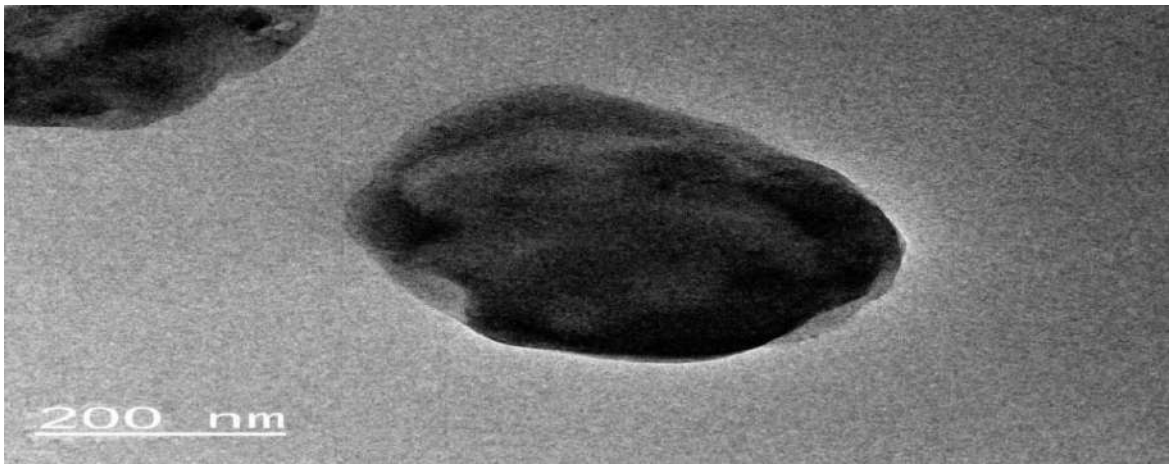

Fig. 9.TEM image of optimized rutin phytosomes with 20-fold dilution in distilled water.

Atomic force microscopy (AFM)

The optimized rutin phytosomes exhibited the porous and rough surface. The diluted sample of optimized rutin phytosomes with distilled water exhibited vesicular structure with fairly uniform sized, evenly distributed vesicles with almost no sign of the aggregation.

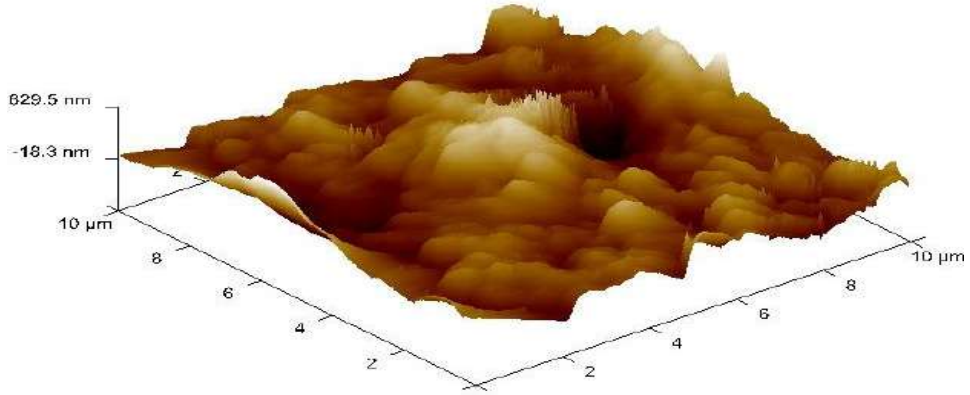

Fig. 10 AFM image of the optimized rutin phytosomes.

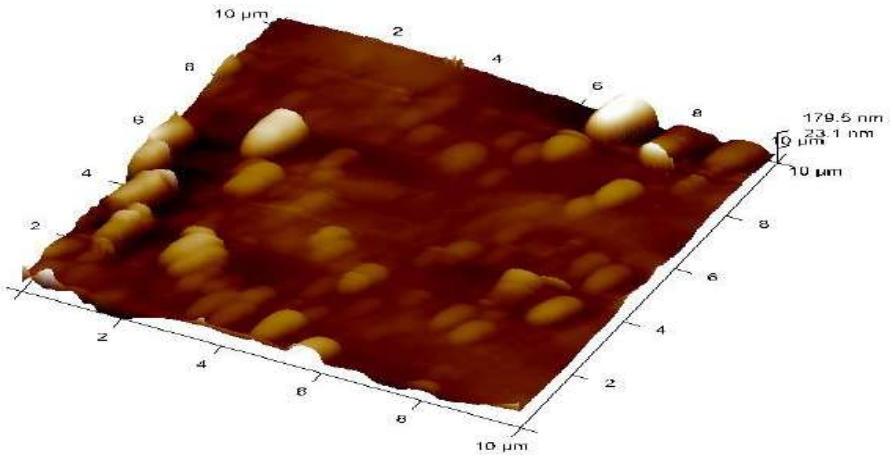

Fig.11 AFM image of the optimized rutin phytosomes dispersed in distilled water.

Proton NMR(^{1}H-NMR)

The ^{1}H-NMR spectrum of pure rutin (Fig. 3.32A) exhibited the characteristic chemical shiftvalues (δ, ppm; d6DMSO) as follows: δ12.493 (s, 1H, OH at C5,7), δ10.775 (s, 2H,

OHat C3'and4'), δ9.586(s,1H,OHat C4''), δ9.361(d, J=24.4Hz,4H,OHatC2, 3''and 2,3'''),δ7.679-7.673(d,J=2.4Hz,2HatC2'and6'-H),δ7.547-7.526(dd,J=2.0Hz,4H,

H at C2, 3''and 2, 3'''), δ6.894-6.873 (d, 1H at C¬5'), δ6.408-6.403 (d, 1H at C8),δ6.189-6.184(d,1H atC6-H),δ3.336(s,2H,H atCH2bridge),δ2.508-2.500(t,J=1.6Hz,

2H, H at C4''). The ^{1}H-NMR spectrumofSPC (Lipoid® S100) (Fig. 3.32B) exhibited the characteristic chemicalshift values (δ, ppm;d6DMSO) as follows: δ 5.331 (2H, t, J=3.2), δ3.342(4H,s,-OCH2),δ2.516(3H,s,CH3),δ2.288(t,J=3.2,16 H),δ2.050(d,J=6.4

Hz,8H),δ2.018(d,J=6.8,1H,CH2),δ1.510(s,2 3H),δ1.270(s,3H,).the^{1}H-NMR spectrum of optimized rutin phytosomes (Fig. 3.32C) showed the characteristic chemical shift values at δ12.491 (s, 1H, OH at C5,7), δ7.562-7.545 (d, J=6.8Hz, 2H, H at C2'and 6'-H),δ6.868 6.846(d,J=8.8Hz,1HatC¬5'),δ6.407-6.404(d,J=1.2Hz,1HatC8),

δ6.210 (s, 1H at C6-H), δ5.362-5.344 (d, J=7.2Hz, 1H Glu), δ5.201-5.192 (d, J=3.6Hz,2H Phos), δ5.087(s, 1H Rham), δ4.397 (s, 1H, CH, Rham), δ4.099-4.085 (d, J=5.6Hz, HatGlu),δ3.732-3.705(d,J=10.8Hz,HatCH2,Glu),δ3.573-3.110(s,d,dd,HofPhos)

δ3.349(s,3H,HatCH3),δ3.306(s,2H,H at CH2 bridge).

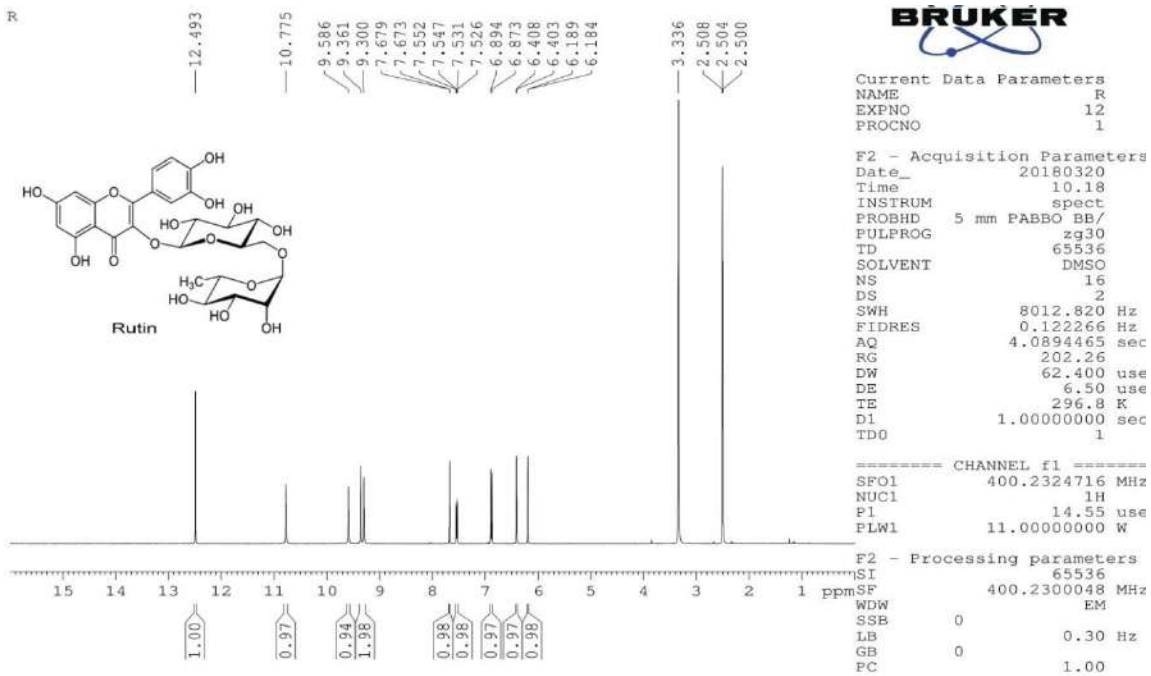

Fig.12 ^{1}H-NMR spectrum of pure rutin.

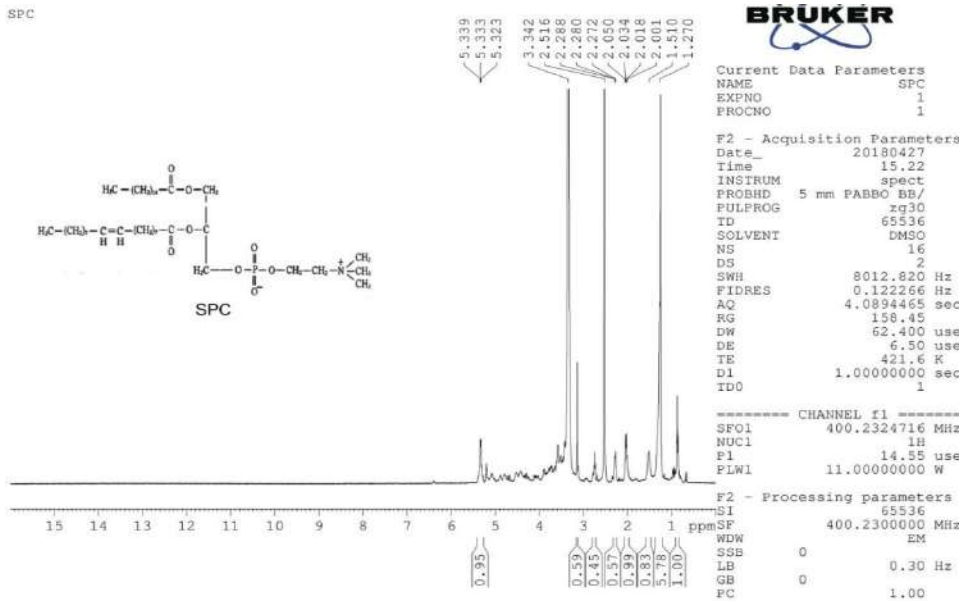

Fig.13 [1]H-NMR spectrum of SPC

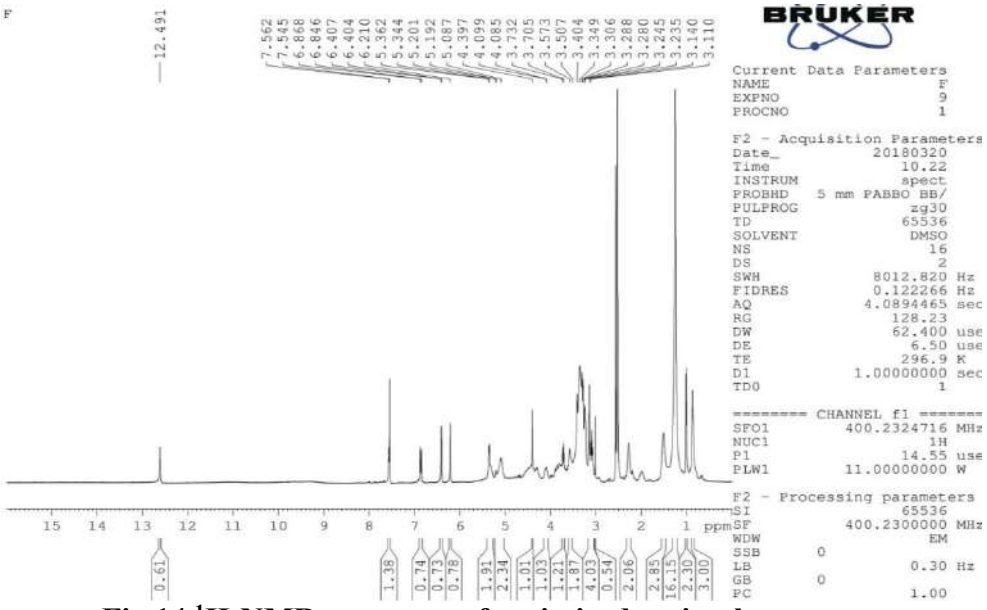

Fig.14.[1]H-NMR spectrum of optimized rutin phytosomes.

X-ray powder diffractometry (XRD)

The X-ray diffractogram of pure rutin (Fig. 3.33A) showed the intense and sharp diffraction peaks of crystallinity at 2θ = 12.0769º, 15.5618º, 23.4592º, and 27.0049º. The X-ray diffractogram of SPC (Lipoid® S 100) (Fig. 3.33B) showed a single, relatively broad diffraction peak at 2θ = 19.567º. The X-ray diffractogram of optimized rutin phytosomes exhibited a single broad peak at 2θ = 20.9873º.

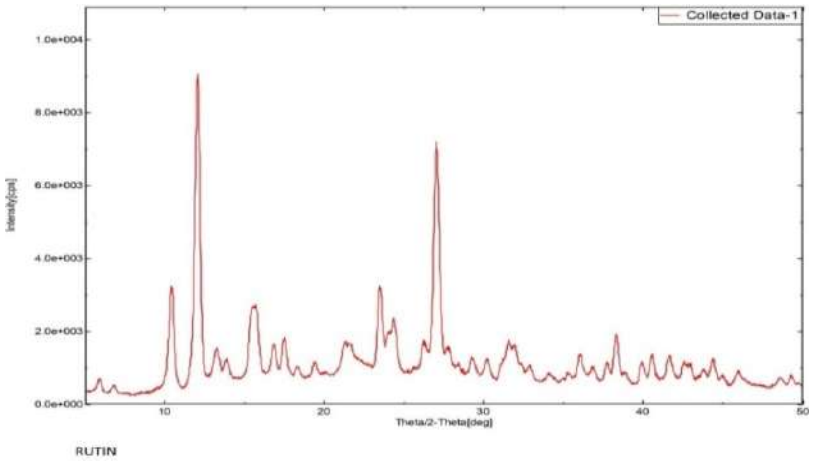

Fig. 15. X-ray diffractogram of pure rutin.

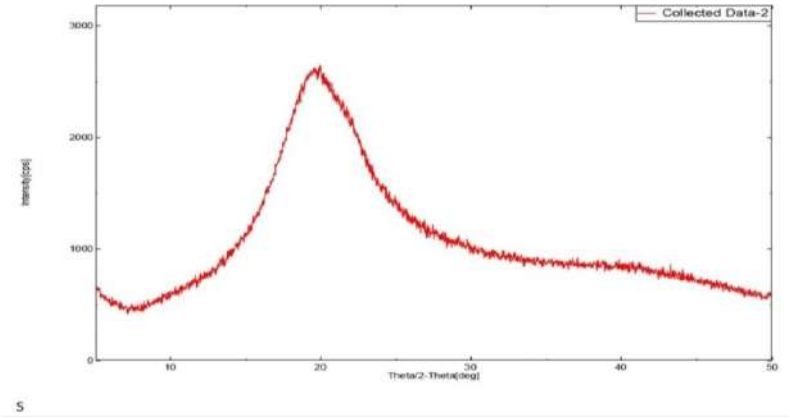

Fig. 16. X-ray diffractogram of SPC.

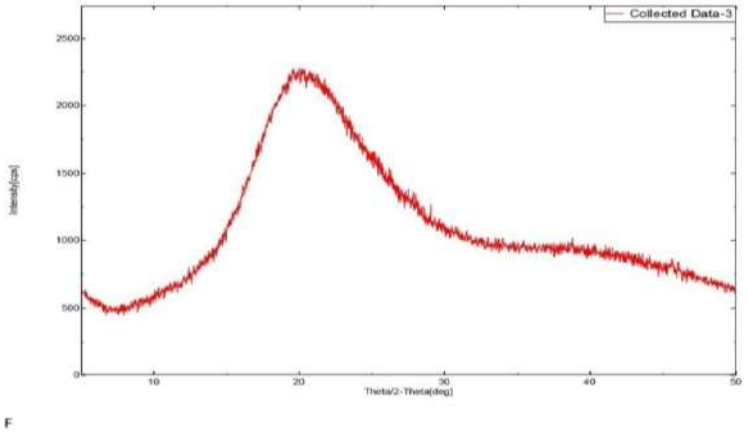

Fig. 17 .X-ray diffractograms of optimized rutin phytosomes.

Solubility and partition coefficient

The results of the solubility study of pure rutin and optimized rutin phytosomes in water and n-octanol.The aqueous solubility of rutin was found to be 1.76±0.21 µg/ml and relatively higher solubility was observed in n-octanol (126.18±1.75µg/ml) whereas,

optimized rutin phytosomes showed the solubility 44.58±0.20 µg/ml and 210.86±0.99 µg/ml in water and n- octanol, respectively. The partition coefficient of pure rutin and optimized rutin phytosomes in n-octanol/phosphate buffer pH 7.4 was found to be 2.59±0.539 and 0.67±0.073, respectively.

Table no. 1. Solubility of pure rutin and optimized rutin phytosomes in water and n-octanol at 37 ºC.

Medium	Solubility(µg/ml)	
	Purerutin	Optimized rutinphytosomes
Water	1.76±0.21	44.58±0.20
n-octanol	126.18±1.75	210.86±0.99

Values are mean±SD (n=6).

Invitro drug release

In vitro drug release profile ofpure rutin and optimized rutin phytosomes in acidic buffer pH1.2 (upto2h) and phosphate buffer pH 7.4 (2-24h). The pure rutin showed 10.4±0.09% drug release at the end of 2 h in acidic pH 1.2 and 19.13±0.96% drug release at the end of 24 h after reaching maximum value 34.35±0.86 in 12 h in phosphate buffer pH 7.4. Unlike pure rutin, the optimized rutin phytosomes showed high drug release of 74.4±0.99 % at the end of24 h, but in acidic pH the drug release was less than that of the pure rutin.

Table 2 In vitro drug release profile of pure rutin and optimized rutin phytosomes in acidic buffer pH 1.2 (upto 2 h) and phosphate buffer pH 7.4 (2-24 h).

Time(h)	Pure Rutin	Optimized rutin phytosomes
0	0.00	0.00
2	10.4±0.09	9.7±0.23
4	18.1±0.73	23.5±1.20
6	24.59±0.54	26.8±1.35
8	29.33±0.87	28.6±1.01
10	33.24±0.21	35.4±1.12
12	34.35±0.86	42.6±1.87
14	33.19±0.38	51.5±1.72
16	30.34±0.98	56.7±1.60
18	28.88±0.61	59.8±1.27
20	26.36±1.18	63.7±2.18
22	23.77±0.78	67.1±1.18
24	19.13±0.96	74.4±0.99

Values are mean± SD(n=6).

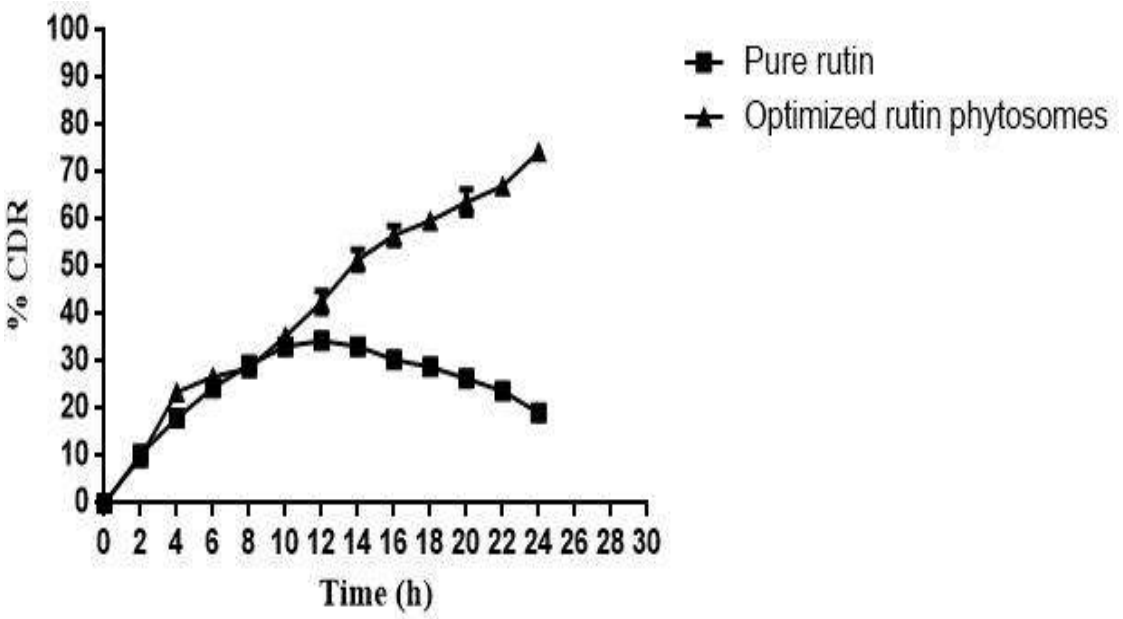

Fig. 18. Invitro drug release profile of pure rutin and optimized rutin phytosomes in acidic buffer pH 1.2 (upto 2 h) and phosphate buffer pH 7.4 (2-24 h).

Conclusion

Phytosomes technology gained much importance from the researchers in the recent past, especially for superior delivery of the phytoconstituents, which lack promising bioavailability. Despite having potential biological activities, the clinical use of the phytoconstituents such as flavonoids is limited due to their poor bioavailability. The effectiveness of any herbal formulation depends on its potential to deliver a therapeutic level of active component to the desired site for the desired period of time. Phytosomes technology meets this challenge by markedly enhancing the delivery of phytoconstituents. The rationale behind the development of rutin pytososmes was to improve the rutin deliverybyenhancing its bioavailabilityand thereby to increase its therapeutic use.

In the present research work an attempt was made to develop rutin phytosomesby various methods, optimize statistically, formulate the optimized rutinphytosomes, characterize in vitro, and to evaluate the impact of optimized rutin phytosomes

The particle size of optimized rutin phytosomes was found to be appropriate for the oral delivery with narrow range of particle size distribution, and ZP value suggested excellent physical stability of the optimized rutin phytosomes.

DSC and FTIR studies on optimized rutin phytosomes provided the initial confirmation on the complexation between rutin and SPC. Surface morphology study of the optimized rutin phytosoemes by SEM, TEM,and AFM confirmed the fluffy, porous, and rough surface of the optimized rutin phytosomes which on dispersion in distilled water formed vesicular nanostructures with no evidence of aggregation or decomposition. Proton NMR study of the optimized rutin phytosomes confirmed the interaction of phosphate group of the SPC with the negative oxygen of labile –OH group of the rutin and formation of intramolecular hydrogen bonding. X-ray powder diffractometry study

confirmed the conversion of crystalline rutin into amorphous form after the complexation with SPC. The aqueous solubility of the rutin improved after complexation with the SPC, confirmed from the solubility study. The improved release of rutin from optimized rutin phytosomes with diffusion-controlled drug release mechanism was seen.

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