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Research Article

Formulation and Evaluation of Phytosomal Gel of Resveratrol

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Abstract
Phytosomes of resveratrol has been successfully formulated. The preformulation studies helped to determine the organoleptic properties, solubility, λ_{max} at 304 nm, calibration curve and Drug:Excipient Compatibility Studies of resveratrol. Five different type formulations formed using different concentrations of phosphatidylcholine, cholesterol and evaluated under various parameter like yield, drug content, particle size and Encapsulation Efficiency. The Zeta sizer gives phytosome size between 521 to 676nm, potential between -24.6 to 28.5 and PDI 0.299 to 0.443. But on the basis of drug release kinetics F-3 formulation was excellent because its % drug release was 97.91%. With the 92.77 and 95.56% drug release of F-1 and F-2 formulation respectively was also good. Other formulations drug releases were F-4 (81.467) and F-5 (80.018). On the basis of % drug release and regression (R^2) values of all formulations showed that formulation F-3 possessed excellent release profile, so the F-3 Phytosomes, drug release data was converted in different type of kinetic modeling and found best fitted model was zero order. All five phytosome formulations were mix with gel. Phytosomal gels were physically clear, odorless, washable, homogeneous, stable and free from grittiness gel was evaluated under the various parameter, pH of all formulations were observed between 7.0 to 7.4 and Spreadability between 6.6 to 7.6 cm. %drug content between 98% to 101% and viscosity between 98 to 115 centi poice and %permeation between 75% to 91%. Four gel formulations were F-1 to F-4 are stable but F-5was not stable at 4°C and 40 °C and phase separation occurs.

Keyword
Phytosomes, Phytosomal gel, resveratrol, preformulation, phosphatidylcholine

Introduction
Novel herbal drug carriers cure particular disease by targeting exactly the affected zone inside a patient's body and transporting the drug to that area[1]. Phytosomes are phospholipids-based drug delivery system has been found promising for herbal drug delivery[3]. . The term Phytosome relates to 'phyto', which means plant; while 'some' means cell-like[6]. It is able to permeate the hydrophilic botanical extract to be better absorbed in intestinal lumen[7]. Phytosome increases the absorption of active constituents, so its dose size required is small[8]. There is appreciable drug entrapment and improvement in the solubility of bile to herbal constituents, and it can target the liver[9]. In Phytosome, chemical bonds are formed between phosphatidylcholine molecules, so it shows good stability. Phytosome improves the percutaneous absorption of herbal phytoconstituents[10].

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A gel is a two-component, cross linked three-dimensional network consisting of structural materials interspersed by an adequate but proportionally large amount of liquid to form an infinite rigid network structure which immobilizes the liquid continuous phase within. Pharmaceutical and cosmetic industry, gel may be enumerated as delivery systems for orally administered drugs[11]. To deliver topical drug applied directly to the skin, mucous membrane or the eye. It is long acting forms of drug as injected intramuscularly. As binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquid and suppository bases[12].

Resveratrol is a phytoalexin derived from grapes and other food products with antioxidant and potential chemopreventive activities[13]. Resveratrol induces phase II drug-metabolizing enzymes (anti-initiation activity); mediates anti-inflammatory effects and inhibits cyclooxygenase and hydroperoxidase functions (anti-promotion activity); and induces promyelocytic leukemia cell differentiation (anti-progression activity), thereby exhibiting activities in three major steps of carcinogenesis[14]. This agent may inhibit TNF-induced activation of NF-kappa B in a dose- and time-dependent manner.

Material and Method
Resveratrol 98.5 % pure was obtained from Biovia, India. Phosphatidylcholine (PC) (Soya lecithin) and Cholesterol were purchased from Finar Chemical (India) Pvt Ltd Ahmedabad. Carbopol 940and Methyl paraben from HiMedia Laboratories Pvt Ltd., Mumbai and Di sodium EDTA, NaOH and Chloroform were purchased from Oxford Laboratories, Mumbai. All used chemicals blogs to laboratory grade.

(1) Preformulation study

(a) Organoleptic properties: The drug sample was examined for its color, odor and appearance.

(b) Solubility: The solubility of resveratrol was determined by adding excess amount of drug in the solvent (water) at 37°C and kept in sonicator for equilibrium. Solubility was determined by taking supernatant and analyzing it on U.V. spectrophotometer. Repeat the same for dil. HCl, Buffer and Alcohol.

(c) Melting point determination: The Melting point was determined by the capillary method using Digital Melting point apparatus. The capillary tube was fused and filled by pressing the open end gently into pure drug sample and packed by tapping the bottom of the capillary on a hard surface so that the drug packed down into the bottom of the tube. When the drug was packed into the bottom of the tube, the tube was placed into the slot of the apparatus, the apparatus was started and the temperature was noted at which the drug melt.

(d) Partition coefficient: 50mg of drug taken into separating funnel and 50ml of water and 50 ml of n- Octanol mix the solution by shaking then separating funnel stand for 2hrs, separate the two immiscible layers and collect into separate beakers. These separated solutions scanned in UV-Spactrophotometer and obtain its absorbance.

(e) Determination of Wavelength of Maximum Absorbance (λ_{max}): 10 µg/ml solution of was scanned in UV-spectrophotometer range from 200-400nm using double beam visible spectrophotometer.

(f) Calibration Curve of resveratrol in Methanol: Resveratrol (10 mg) was dissolved in 1ml 6.8 pH phosphate buffer and volume was made up to 10 ml volumetric flask using 6.8 pH phosphate buffers (1000 µg/ml). 1 ml of stock solution (1 mg/ml) was further diluted with 6.8 pH phosphate buffer, up to 10 ml. This solution (100µg/ml) was further diluted to 6.8 pH phosphate buffer, to obtain solutions of 10 to 50µg/ml. Absorption of each solution was measured at 304nm using Systronics UV-2203 UV/Vis double beam spectrophotometer and 6.8 pH phosphate buffer, as a reference standard.

(g) Physical compatibility: solubility, color changes, dissolution, sedimentation rate, phase separation or immiscibility and liquefaction.

(h) Chemical compatibility: undesirable reaction between drug and excipients to monitor if compounds undergo oxidation, hydrolysis, reduction, decarboxylation, precipitation and racemization determined by FT-IR Spectroscopy.

(2) Method of Preparation of Phytsomes of Resveratrol

Accurately weighed quantity of phosphatidylcholine and cholesterol were dissolved in 10 ml of chloroform in round bottom flask (RBF) and sonicated for 10 min using bath sonicator. Organic solvent removal is done by Rotary evaporator (45-50°C). After complete removal of solvent thin layer of phospholipids mixture was formed. This film was hydrated with resveratrol in rotary evaporator (37-40°C for 1 hour). After hydration, mixture of lipid and resveratrol was sonicated for 20 minutes in presence of ice bath for heat dissipation. Then prepared phytosomes were filled in amber colored bottle and stored in freezer (2-8 ^{O}C) until used.

(3) Characterization of Phytsomes of resveratrol

(a) Calculation of % yield calculation: During this process, % yield was calculated as mentioned below:

$$\% \text{ Yield } = \frac{\text{Practical yield}}{\text{Theoretical yield}} \text{ X 100}$$

(b) Swelling Index: 20 mg of phytosomes were placed in water and set aside to swell over night. Phytosomes were decanted using filter paper and weighed. The degree of swelling (α) was then calculated from the formula:

$$\text{Swelling Index } (\alpha) = \frac{\{\text{weight of swelled microsomes (Wg)} - \text{Initial weight ofmicrosomes (Wo)}\}}{\text{Initial weight of microsomes (Wo)}}$$

(c) Determination of Size, surface charge and polydispersibility index: The size of phytosomes was measured by dynamic laser light scattering technique using particle size analyzer or Zeta sizer.

(d) SEM analysis: Approximately 5 µL of the phytosomal suspension was transformed to a cover slip, which in turn was mounted on a specimen tab. The samples were allowed to dry at room temperature. Then the particle size of the formulation was viewed and photographed using Scanning Electron Microscope. The particles were coated with gold by using vacuum evaporator and thus coated samples were viewed and photographed in JEOL Field Emission SEM.

(e) Encapsulation Efficiency: 10 mg of the phytosomes from each batch were taken and digested in 100 ml of 0.1N HCl in a 100 ml volumetric flask and kept aside with intermittent shaking for 24 h. Then, the contents of the flask were filtered by using Whatman filter paper no.1. Then 1 ml of the filtrate was diluted with 50 ml of dimethyl sulfoxide (DMSO) in a volumetric flask and sonicated for 10 min so that leave out resveratrol drug from phytosome. This was again filtered by using Whatman filter paper one ml from this solution was further diluted with methanol up to 10 ml and absorbance measured at 304 nm using methanol as blank. After recording the absorbance, the drug content and encapsulation efficiency were calculated. The readings were taken thrice and the average reading was taken for further calculation.

$$\% \text{ Drug Content } = \frac{\text{Amount of drug present in formulation}}{\text{Calculated Amount in formulation}} \text{ X 100}$$

$$\% \text{ Entrapment efficiency } = \frac{(\text{Drug added} - \text{free or unntraped drug})}{\text{Drug added}} \text{ X 100}$$

(f) *In-Vitro* Release Studies

The *in-vitro* dissolution studies were carried using USP - 34 paddle type dissolution apparatus. 10 mg resveratrol loaded phytosomes were placed in a dialysis bag and introduced into 100 ml dissolution medium of buffer solution pH 6.8 maintained at 37± 0.5 ℃ at a rotation speed of 50 RPM. 1 ml of aliquots was withdrawn at predetermined time intervals and an equivalent volume of fresh medium was replaced to maintain sink condition. The aliquots were diluted and analyzed spectrophotometrically at 304 nm to determine the concentration of drug present. The readings were taken thrice and the average reading was taken for further calculation.

(4) Formulation of phytosomes incorporated gel

Accurately, weighed amount of polymers Carbopol 940 (1% w/v) were dispersed in purified water and allowed to swell overnight. After swelling of polymer, the penetration enhancer (Di sodium EDTA) and phytosomes (equivalent to 50 mg of resveratrol) was mixed to the solution with stirring and preservatives were solution also added. Final volume was made up and prepared gels were subjected for further characterization.

(5) Evaluation of phytosomal Gel

(a) Physical examination: The formulation was manually examined to check any variations in the color, odor and texture.

(b) Determination of pH: pH of each formulation was determined by using pH which was calibrated before with buffer solutions of pH 4, 7 and 9.

(c) Determination of Viscosity: Viscosity of each formulation was determined using Brookfield viscometer with spindle at room temperature and at 5, 10, 20, 50 and 100 rpm.

(d) Spreadability: To determine spreadability of the gel formulations, two glass slides of known standard dimensions are selected. Formulation whose spreadability to be determined was place on one slide and then other slide was kept over its top such that the gel is sandwiched between the two slides. The slides were pressed upon each other so as to displace any air present and the adhering gel was wiped off. The two slides were placed onto a stand such that only the lower slide is held firm by the one opposite fangs of the clampclips and allows the upper slide to slip freely over it by the force of weight tied Tie the 20 gm weight to the upper slide carefully. The time taken by the upper slide to completely detach from the lower slide was noted. The spreadability was calculated by using the following formula.

$$s = m.l/t$$

Value s is spreadibility, m is the weight tied to the upper slides, l is the length of glass slide, and t is the time taken.

(e) *In-vitro* permeation study

The diffusion of resveratrol from gel formulations was studied through cellophane membrane using the Franz diffusion apparatus. The donor cell was filled with 300 mg of gel formulation (equivalent to 10 mg of drug). The receptor compartment is filled by phosphate buffer having pH 6.8. The temperature of the receptor compartment was maintained at 37±0.5°C by using circulation of hot water through the jackets of Franz diffusion cell. The samples were removed at predetermined intervals at 0.5,1,2,4,6 hours and replaced immediately with equal volume of receptor solution to maintain sink conditions. The removed samples were analyzed at 304 nm on UV spectrophotometer.

(6) Stability study

Stability study is performed for optimized formulation shows greatest drug release and hence can be termed as 'best formulation' from within those that are developed. Stability study was carried out for 1 month; the formulation was kept in stability chamber at 40°C and at 75% relative humidity and 4 °C. After one month the formulation was checked for parameters like phase separation pH and drug content.

Result and Discussion

The preformulation studies helped to determine the organoleptic properties of resveratrol which was off white amorphous power with characteristic odor. After that solubility determined in various solvents resveratrol was freely soluble in ethanol and methanol, soluble in 0.1N NaOH, 0.1N HCl and buffer pH 6.8, and slightly soluble in Distilled Water. Melting point was 258-260 °C and Partition Coefficient was found 0.868. λ_{max} at 304 nm was determined and also calibration curve was obtained with following linear equation y=0.011x+0.008 and R^2 = 0.995. Drug:Excipient Compatibility Studies also confirmed by FT-IR spectrogram.

Phytosomes of resveratrol has been successfully formulated. The preformulation studies helped to determine the organoleptic properties of resveratrol which was off white amorphous power with characteristic odor. After that solubility determined in various solvents resveratrol was freely soluble in ethanol and methanol, soluble in 0.1N NaOH, 0.1N HCl and buffer pH 6.8, and slightly soluble in Distilled Water. Melting point was 258-260 °C and Partition Coefficient was found 0.868. λ_{max} at 304 nm was determined and also calibration curve was obtained with following linear equation y=0.011x+0.008 and R^2 = 0.995. Drug:Excipient Compatibility Studies also confirmed by FT-IR spectrogram.

Five different type formulations formed using different concentrations of phosphatidylcholine, cholesterol and evaluated under various parameter like yield, drug content, particle size and Encapsulation Efficiency. For all formulation yield was 91% to 94.5%, drug content was 85% to 98% and Encapsulation Efficiency was 86 % to 98.2%. The Zeta sizer gives phytosome size between 521 to 676nm, potential between -24.6 to 28.5 and PDI 0.299 to 0.443. But on the basis of drug release kinetics F-3 formulation was excellent because its % drug release was 97.91%. With the 92.77 and 95.56% drug release of F-1 and F-2 formulation respectively was also good. Other formulations drug releases were F-4 (81.467) and F-5 (80.018). On the basis of % drug release and regression (R^2) values of all formulations showed that formulation F-3 possessed. excellent release profile, so the F-3 Phytosomes, drug release data was converted in different type of kinetic modeling and found best fitted model was zero order.

All five phytosome formulations were mix with gel. Phytosomal gels were physically clear, odorless, washable, homogeneous, stable and free from grittiness gel was evaluated under the various parameter, pH of all formulations were observed between 7.0 to 7.4 and Spreadability between 6.6 to 7.6 cm. %drug content between 98% to 101% and viscosity between 98 to 115 centi poice and %permeation between 75% to 91%. Four gel formulations were F-1 to F-4 are stable but F-5was not stable at 4°C and 40 °C and phase separation occurs.

Conclusion

The prepared phytosomal gel of resveratrol had shown excellent promising results for all the evaluated parameters. On the basis of *in-vitro* drug release and drug content results, **F-3** formulation was excellent drug release as compare to other prepared phytosomal gel formulations which shows higher percentage of drug release.

In- vitro drug release profile was applied on various kinetic models like Zero order, First order, Higuchi and Peppas-Korsemeyer model. The best fit with highest regression coefficient was found with Zero order. The rate constants are calculated from the slop of the respective plots the release mechanism of Multiple Emulsion. **F-3** formulation can be further study for preclinical and clinical evaluations.

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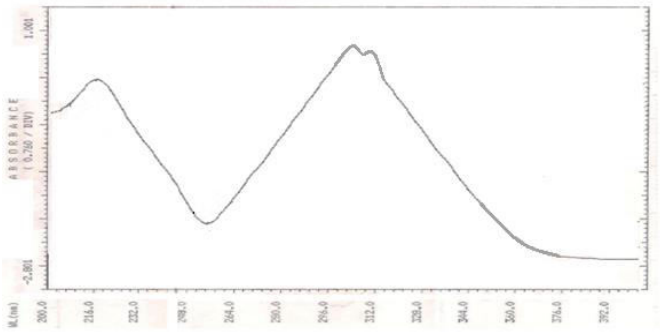

Figure 1: UV spectrogram of Resveratrol scanning from 200- 400

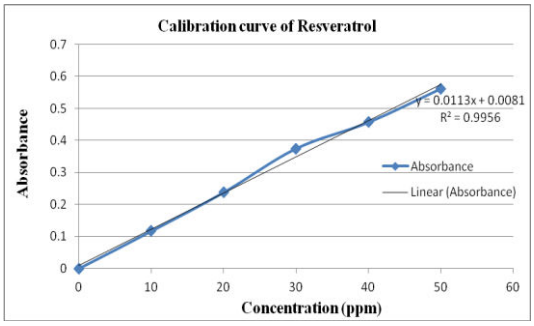

Figure 2: Calibration curve of Resveratrol in 6.8pH buffer

Table 1: Absorbance of drug at different concentrations in water

Concentration (µg/ml)	0	10	20	30	40	50
Absorbance	0.000	0.117	0.238	0.375	0.457	0.562

Table no. 2: Important band frequencies in IR spectrum of Resveratrol

S. No.	**Reported frequency (cm^{-1})**	**Observed frequency (cm^{-1})**	**Peak Assigned**
1.	1275-1200	1249	C-O str. ether
2.	1382-1266	1377	C-N
3	3000-2840	2945, 2875	CH_3 str
4.	3200-3000	3126	OH str.

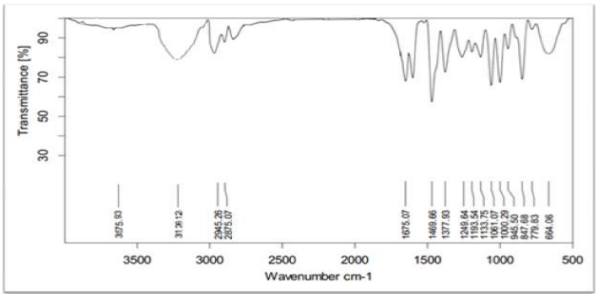

Figure 3: FT-IR spectrogram of Resveratrol

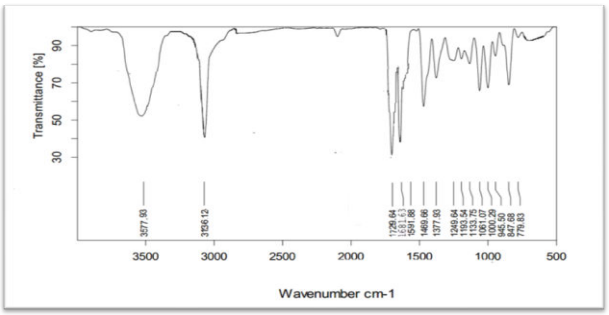

Figure 4: FT-IR spectrogram of Resveratrol with excipients

Table 3: Formulations formed using different concentration of drug and polymer

Formulation code	Resveratrol (mg)	Phosphatidylcholine (PC) in mg	Cholesterol (CL) in mg	Phytosome PC:CL
F-1	100	100	25	4:1
F-2	100	100	50	2:1
F-3	100	100	75	4:3
F-4	100	100	100	1:1
F-5	100	100	125	1:1.25

Table no .4 : General Characterization of Phytosome of resveratrol

Batch code	Yield (%)	Drug Content (%)	Encapsulation Efficiency (%)
F1	94.28±0.045	94.42±1.41	89.80±0.025
F2	92.46±0.038	93.83±1.76	92.70±0.038
F3	91.69±0.052	98.92±1.90	98.20±0.059
F4	93.24±2.106	87.38±2.61	86.2±2.0
F5	94.51±1.125	85.94±3.32	90.9±1.8

All values are mean of triplicate value (n=3) ± S.D

Table no. 5: Characterization of Phytosome of resveratrol by zeta sizer

Formulation Code	Phytosome size (nm) (mean ± SD)	Zeta potential (mV) (mean ± SD)	Poly Dispersity Index (PDI) (mean ± SD)
F1	644 ± 0.016	-27.2 ± 1.42	0.402 ± 0.03
F2	663 ± 0.012	-26.2 ± 1.45	0.329 ± 0.04
F3	676 ± 0.007	-28.4 ± 2.66	0.424 ± 0.01
F4	521 ± 1.004	-24.6 ± 1.37	0.299 ± 0.05
F5	608 ± 2.001	-28.5 ± 1.86	0.443 ± 0.03

All values are mean of triplicate value (n=3) ± S.D

Table no. 6: *In-vitro* cumulative % drug release of Phytosomes of resveratrol formulations

Time (hrs)	Cumulative %drug release of Phytosomes				
	F-1	F-2	F-3	F-4	F-5
0	0	0	0	0	0
1	17.25	19.62	21.61	22.68	24.31
2	32.34	39.68	44.64	41.88	37.40
3	50.93	59.22	60.41	49.93	50.98
4	78.54	82.18	73.72	61.49	60.92
5	84.27	88.56	87.01	72.81	69.17
6	92.77	95.56	97.91	81.53	80.02

Table no 7: R^2 values of all Phytosomes of resveratrol

Model	R^2 (regression coefficient)
F1	$R^2 = 0.975$
F2	$R^2 = 0.969$
F3	**$R^2 = 0.980$**
F4	$R^2 = 0.967$
F5	$R^2 = 0.968$

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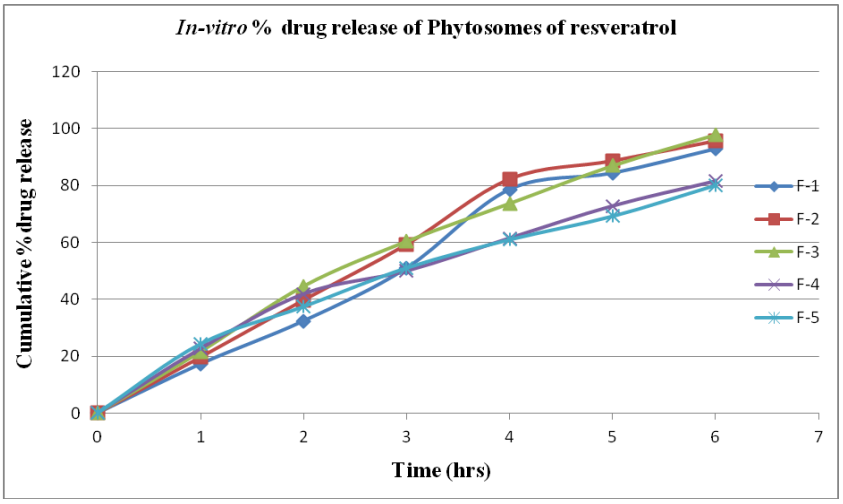

Figure 5: *In-vitro* % drug release of Phytosomes of resveratrol

Table no. 8: *In-Vitro* drug release profile of Phytosomes of resveratrol(F-3)

Time (hr.)	S.R.T.	Log T.	% C.R	Log % C.R	Drug remaining	Log% drug release
0	0	-	0	0	100	2
1	1	0	21.6	1.334	78.4	1.894
2	1.141	0.301	44.64	1.652	55.056	1.74
3	1.732	0.477	60.41	1.781	39.591	1.597
4	2	0.602	73.72	1.86	26.18	1.419
5	2.236	0.686	87.01	1.939	12.989	1.113
6	2.449	0.778	97.91	1.990	2.087	0.319

Figure 6: Zero order kinetic model (F-3)First order kinetic model

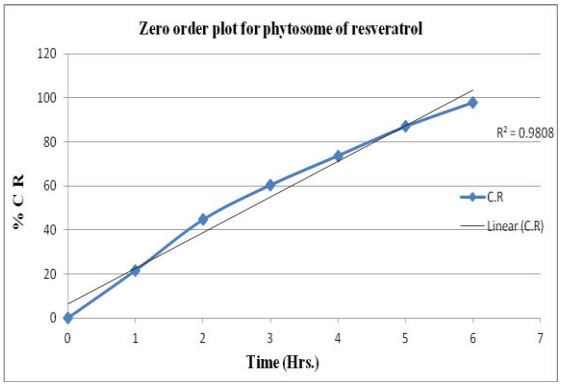

Figure 7: First order kinetic model (F-3)

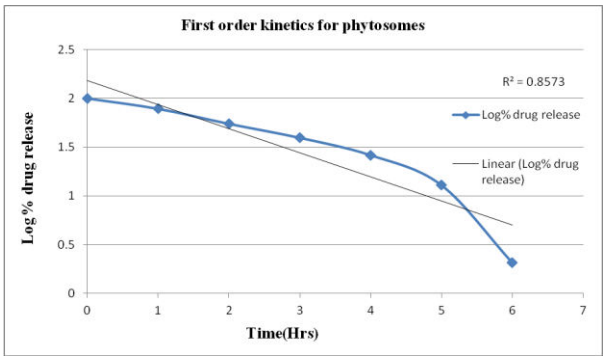

Figure 8: Higuchi model of kinetic model (F-3)

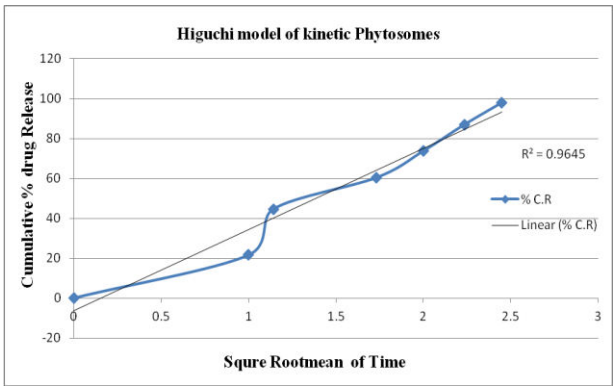

Figure 9: Korsemeyer model of kinetic (F-3)

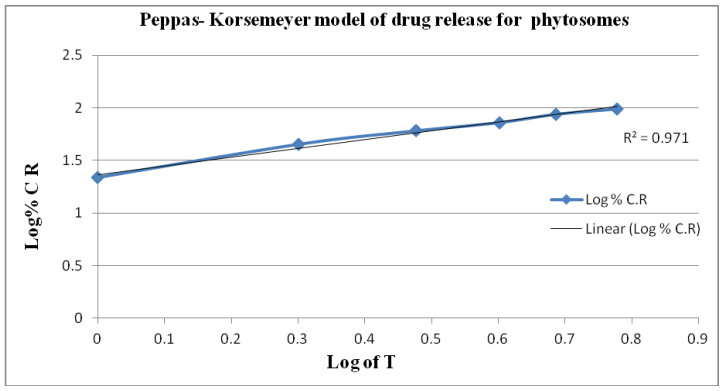

Table no. 9: Formulation of gel of Phytosomes of resveratrol

Formulation	F-1	F-2	F-3	F-4	F-5
Phytosomes (equivalent to 1% of resveratrol)	1.0	1.0	1.0	1.0	1.0
Carbopol 940 (% w/v)	1.0	1.0	1.0	1.0	1.0
Disodium EDTA solution (%w/v)	0.02	0.02	0.02	0.02	0.02
Methyl paraben (%w/v)	0.02	0.02	0.02	0.02	0.02
Distilled water q.s.to 100 ml	100	100	100	100	100

Table no. 10: Physical evaluations of gels of Phytosome of resveratrol

Formulation code	Clarity	Odor	Phase Separation	Wash ability	Homogeneity	Grittiness
F-1	Clear	No	No	Washable	Yes	No
F-2	Clear	No	No	Washable	Yes	No
F-3	Clear	No	No	Washable	Yes	No
F-4	Clear	No	No	Washable	Yes	No
F-5	Clear	No	No	Washable	Yes	No

Table no. 11: Charecterization of gel of Phytosome of resveratrol

Formulation code	pH	Spread-ability	% Drug Content	Viscosity(cp)	% Permeation
F-1	7.1	6.6±0.5	100±1.2	110±1.8	78%
F-2	7.4	7.6±0.0	100±1.3	113±2.0	89%
F-3	7.4	7.0±0.4	99±1.7	100±0.8	91%
F-4	7.2	7.6±0.1	98±2.1	115±1.2	87%
F-5	7.0	7.1±0.3	101±0.6	98±2.6	75%

All values are mean of triplicate value (n=3) ± S.D

Table no. 12: Stability of gels of Phytosome of resveratrol at different conditions

Formulation code	Phase separation		pH		Drug content (%)	
	4ºC	**40 ºC**	**4ºC**	**40 ºC**	**4ºC**	**40 ºC**
F-1	No	No	6.9	7.0	100±1.1	95±2.0
F-2	No	No	7.4	7.3	100±1.8	99±1.9
F-3	No	No	7.4	7.2	98±1.9	98±1.8
F-4	No	No	7.2	7.1	99±0.6	92±1.0
F-5	Yes	Yes	7.1	7.4	101±1.9	97±2.1

All values are mean of triplicate value (n=3) ± S.D