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Formulation, Optimization and Evaluation of Ritonavir Loaded Nano Emulsion

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A B S T R A C T

The present study was undertaken to develop and evaluate nanoemulsion-based transdermal gel formulations of Ritonavir using different polymers. The formulations were systematically assessed through physicochemical and stability studies, including pH, weight/ml, assay, viscosity, sedimentation volume, ease of redispersibility, and particle size analysis. The results demonstrated that all evaluated parameters remained stable throughout the study, confirming the suitability of the developed formulations. Among the different batches, formulation F3 exhibited the most favorable properties, including stability, uniformity, pleasant texture, and good redispersibility. Dissolution studies further revealed that F3 achieved a maximum drug release of 98.89% within 10 hours, designating it as the optimized formulation. Additionally, formulation F8, containing D-Sorbitol at a concentration of 75 mg, was also prepared and evaluated. Overall, the findings highlight formulation F3 as a promising nanoemulsion-based transdermal gel for Ritonavir, offering enhanced drug release and stable characteristics for potential therapeutic application.

Keywords: Assay, viscosity, sedimentation volume, Ritonavir

A R T I C L E I N F O

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1. Introduction

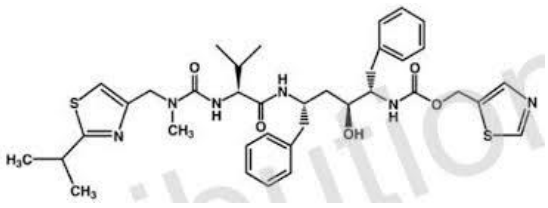

Fig.1: Ritonavir

Molecular Formula: $C_{37}H_{48}N_6O_5S_2$
Molecular Weight: 720.94 g/mol
IUPAC Name: 1,3-thiazol-5-ylmethyl N-[(2S,3S,5S)-3-hydroxy-5-[(2S)-3-methyl-2-[methyl-[(2-propan-2-yl-1,3-thiazol-4-yl)methyl]carbamoyl]amino]butanoyl]amino]-1,6-diphenylhexan-2-yl]carbamate
Chem Spider ID: 54819
Density: ~1.24 g/cm³ (predicted)
Boiling Point: ~947 °C (predicted)
Vapour Pressure: <0.0000001 kPa at 25 °C
Flash Point: ~2 °C
Refractive Index: Not readily available
Polar Surface Area: Not specified, but typically low for lipophilic drugs
LogP (Octanol/Water): High, indicating lipophilicity
Generic Name: Ritonavir

Brand Names: Norvir, Kaletra (when combined with lopinavir)

Drug Category: HIV protease inhibitor; pharmacokinetic enhancer

Indications: Used in combination therapy for HIV-1 infection; also boosts plasma levels of other protease inhibitors

Pharmacology: Inhibits HIV-1 protease, preventing viral replication; also inhibits CYP3A4 enzyme, enhancing other drugs' bioavailability

Potency: High affinity for HIV protease; also a potent CYP3A4 inhibitor

Tolerability: Generally well tolerated but can cause gastrointestinal and hepatic side effects

Contraindications: Co-administration with drugs highly dependent on CYP3A for clearance (e.g., amiodarone, simvastatin)

Adverse Effects: Nausea, diarrhea, hepatotoxicity, vomiting, lipid abnormalities

Availability: Widely available globally in oral tablet and solution forms

2. Materials and Methods

Table.1: List of Materials Used

Name of the material	Source
Ritonavir	Natco LABS
D-Sorbitol	Merck Specialities Pvt Ltd, Mumbai, India
Sodium CMC	Sd fine chemicals Pvt Ltd, Mumbai, India
Citric acid	Sd fine chemicals Pvt Ltd, Mumbai, India
Sodium Lauryl Sulphate	Sd fine chemicals Pvt Ltd, Mumbai, India
Sodium Benzoate	Merck Specialities Pvt Ltd, Mumbai, India
Tween 80	Merck Specialities Pvt Ltd, Mumbai, India

Table.2: List of Equipment's used

Name of the Equipment	Manufacturer
Weighing Balance	Wensar
Diffusion Apparatus	franz
UV-Visible Spectrophotometer	Labindia, Mumbai, India
pH meter	Labindia, Mumbai, India
FT-IR Spectrophotometer	Per kin Elmer, United States of America.
Viscometer	Labman scientific instruments

Determination of UV Absorption maxima:

Ritonavir solution was prepared in 6.8 pH phosphate buffer and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The Solution exhibited UV maxima at 224 nm.

Preparation of Standard Calibration Curve of Ritonavir:

100 mg of Ritonavir was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with 6.8 pH phosphate buffer (pH1.2) to prepare stock solution. The 10 ml of stock solution was further diluted with 6.8 pH phosphate buffer (pH1.2) in 100ml to get 100µg/ml (working standard). Then 0.5, 1, 1.5, 2, 2.5 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N HCl to prepare 5µg,10µg,15µg,20µg, 25µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 224nm against 6.8pH phosphate buffer (pH 1.2) as blank.

Solubility study of Ritonavir in various excipients

The solubility of Ritonavir in various oil, surfactant, co-surfactant was determined. Solubility studies were conducted by placing an excess amount of drug in each vehicle in a 2ml Micro tube (Axygen MCT 200) containing 1.5ml of the vehicle. Then the mixture was vortexed and kept for 48hrs at 25ºC in a Orbital shaking incubator (Remi electrotechnik ltd.) to facilitate the solubilization. The samples were centrifuged at 3000rpm for 15min to remove the undissolved drug. The supernatant was taken and the concentration of drug in each vehicle was quantified by U.V-spectrophotometer.

Construction of Pseudo-ternary phase diagrams

The pseudo-ternary phase diagrams of oil, surfactant: co-surfactant and water were developed using surfactant titration method: The mixtures of oil and water at certain weight ratios were titrated with surfactant: co-surfactant mix in a drop wise manner. Three types of surfactant phases were prepared: Tween 20+ carbitol (1:1,2:1,3:1). For each phase diagram at a specific ratio of surfactant/cosurfactant transparent and homogenous mixture of oil and water was formed under the mixing by cyclomixer. Then, visually observed for phase clarity and flow ability. After the identification of micro emulsion region in the phase diagrams, the micro emulsion formulations were selected at desired component ratios, in order to form the micro emulsion.

Preparation of the dry mixtures for reconstitute nanoemulsion: In the microemulsion formulations, D-sorbitol was used as a polyol. Citric acid and sodium citrate were used as pH modifiers. To produce dry mixture for reconstitution, all the powder components were reduced to more or less the same particle size. Ingredients present in small quantities (buffer components, sodium benzoate and sodium lauryl sulfate) were mixed homogeneously. The same procedure was followed for xanthan gum and Ritonavir -loaded microspheres (equivalent to 200 mg of Ritonavir /dose). Such ingredients were mixed with a portion of D-sorbitol according to the principle of the geometric dilution. The representative formulations for the preparation of dry mixtures are tabulated in Table 1. To prepare the reconstituted microemulsion, 10 mL of water was added to the dry microemulsion powder in two steps and stirred with spoon until a homogenous product was obtained.

Table.3: Formulation of Ritonavir Microemulsion

Ingredient	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Ritonavir	100	100	100	100	100	100	100	100	100
D-Sorbitol	25	50	75						
Methyl cellulose				25	50	75			
Sodium CMC							25	50	75
Citric acid	3	3	3	3	3	3	3	3	3
Sodium lauryl sulphate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium benzoate	2	2	2	2	2	2	2	2	2
Tween 80	5	5	5	5	5	5	5	5	5
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Water	10	10	10	10	10	10	10	10	10

3. Results and Discussion

Standard Calibration curve of Ritonavir: Concentration and absorbance obtained for calibration curve of Ritonavir in 0.1 N hydrochloric acid buffer (pH 1.2**)**

Table.4: Calibration data of Ritonavir

S. No.	Concentration (µg/ml)	Absorbance* (at 230 nm)
1	5	0.227
2	10	0.406
3	15	0.621
4	20	0.824
5	25	0.957
Correlation Coefficient = 0.994 Absorbance y = 0.0376x +0.0436		

It was found that the estimation of Ritonavir by UV spectrophotometric method at λ_{max} 224.0nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml. The regression equation generated was y = 0.0376x +0.0436.

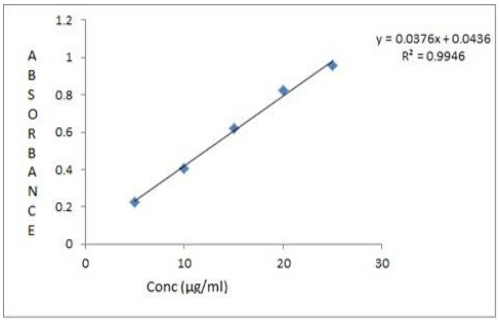

Fig.2: Standard graph of Ritonavir in 6.8 pH phosphate buffer

Solubility study of Ritonavir in various excipients: Selection of right component is important prerequisite for formulation of stable SMEDDS. The drug should have good solubility in components of micro emulsion so as the precipitation of drug during shelf life of formulation and after dilution in GI lumen can be avoided. The solubility of Ritonavir in various vehicles is presented in table below & fig. Tween 20 carbitol, miglyol provided higher solubility than other vehicles and miglyol as oil was selected for the optimal novel emulsion formulation resulting in improved drug loading capabilities. 100mg dose of Ritonavir was selected to prepare formulations.

Table.5: Solubility study of Ritonavir

Vehicle	Tween 20	Carbitol	Miglyol
Solubility(mg/ml)	107.98	118.67	38.12

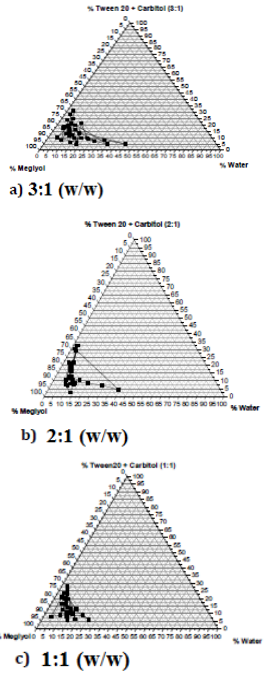

Fig.3: Pseudo ternary phase diagrams indicating the efficient microemulsion region containing (Tween20 /Carbitol) = (a) 3:1(w/w) (b) 2:1(w/w) (c) 1:1(w/w). The shaded area represents O/W microemulsion existence range.

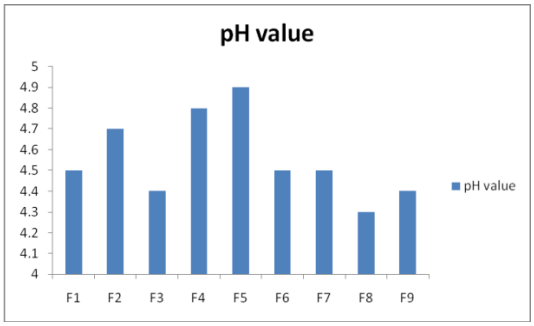

Fig.4: pH value

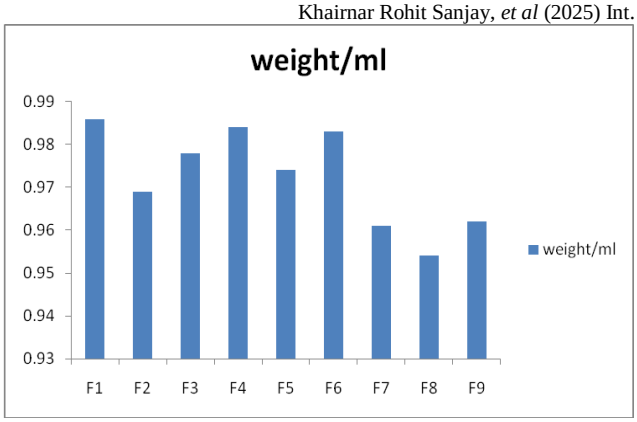

Fig.5: weight/ml

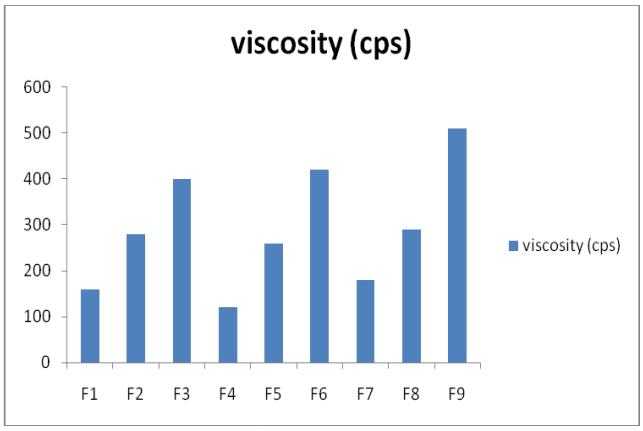

Fig.6: Viscosity

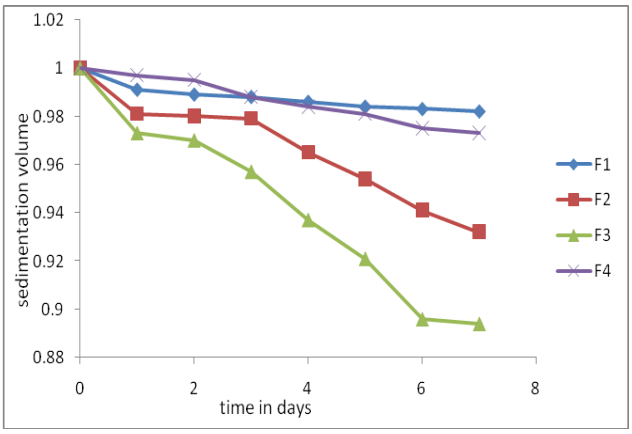

Fig.7

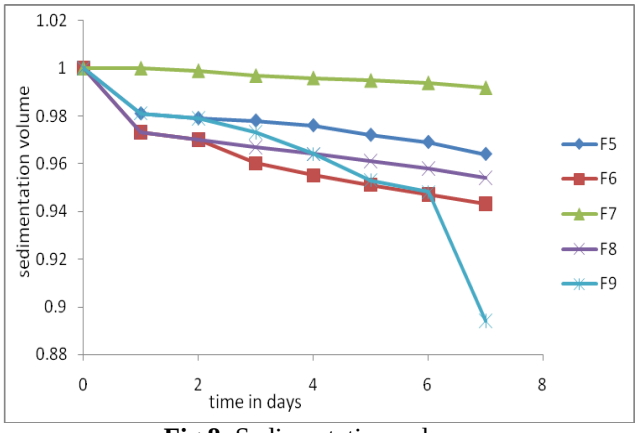

Fig.8: Sedimentation volume

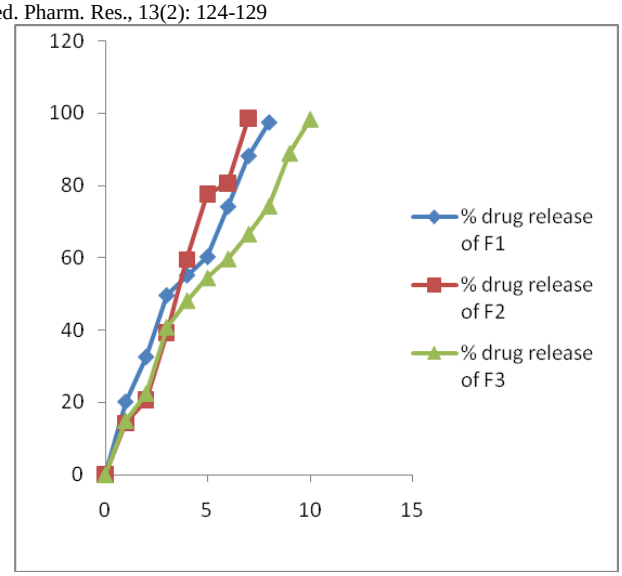

Fig.9: Cumulative drug release of formuations(F1-F3)

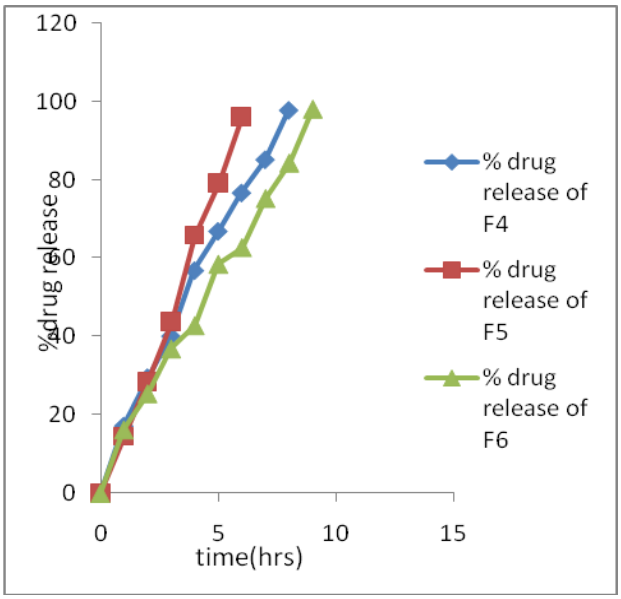

Fig.10: Cumulative drug release of formuations (F4-F6)

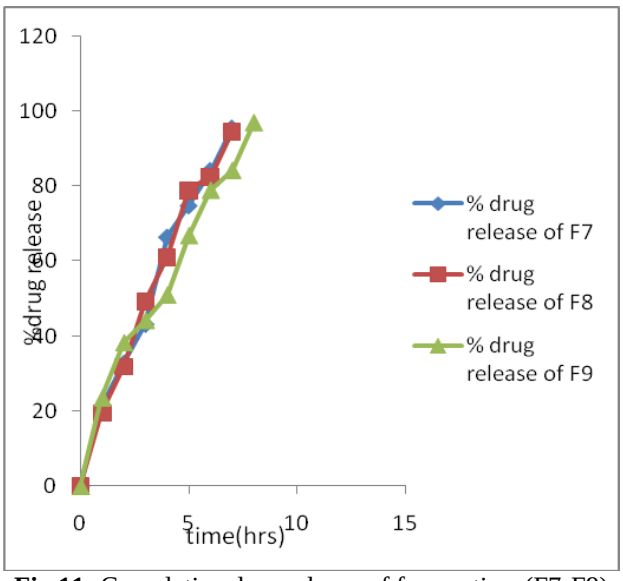

Fig.11: Cumulative drug release of formuations(F7-F9)

Table.6: Pre formulation parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Hausner ratio	Angle of Repose(Ɵ)
F_1	0.45	0.55	1.22	27.91
F_2	0.47	0.55	1.17	28.23
F_3	0.50	0.58	1.16	29.34
F_4	0.46	0.55	1.19	26.71
F_5	0.50	0.58	1.16	29.34
F_6	0.47	0.55	1.17	28.23
F_7	0.50	0.58	1.16	29.34
F_8	0.41	0.50	1.21	26.78
F_9	0.41	0.50	1.21	26.78

Table.7: Physico chemical evaluation parameters of the prepared nanoemulsion gel

Formlation Code	p^H value	Weight/ml	Viscosity
F1	**4.5**	**0.986**	**160cps**
F2	**4.7**	**0.969**	**280cps**
F3	**4.4**	**0.978**	**400cps**
F4	**4.8**	**0.984**	**120cps**
F5	**4.9**	**0.974**	**260cps**
F6	**4.5**	**0.983**	**420cps**
F7	**4.5**	**0.961**	**180cps**
F8	**4.3**	**0.954**	**290cps**
F9	**4.4**	**0.962**	**510cps**

Table.8: Sedimentation volumes

Time in days	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	1	1	1	1	1	1	1	1	1
1	0.991	0.981	0.973	0.997	0.981	0.973	1	0.973	0.981
2	0.989	0.980	0.970	0.995	0.979	0.970	0.999	0.970	0.979
3	0.988	0.979	0.957	0.988	0.978	0.960	0.997	0.967	0.973
4	0.986	0.965	0.937	0.984	0.976	0.955	0.996	0.964	0.964
5	0.984	0.954	0.921	0.981	0.972	0.951	0.995	0.961	0.953
6	0.983	0.921	0.896	0.975	0.969	0.947	0.994	0.952	0.948
7	0.982	0.932	0.894	0.973	0.964	0.943	0.992	0.954	0.894

Table.9: Particle size analysis

Size range (µm)	F1	F2	F3	F4	F5	F6	F7	F8	F9
10-20	**16**	**12**	**14**	**8**	**4**	**8**	**1**	**0**	**3**
20-30	**22**	**23**	**21**	**20**	**15**	**24**	**22**	**23**	**21**
30-40	**35**	**37**	**36**	**39**	**46**	**41**	**43**	**46**	**44**
40-50	**20**	**23**	**21**	**24**	**25**	**21**	**23**	**24**	**20**
50-60	**7**	**5**	**8**	**9**	**10**	**6**	**11**	**7**	**12**
60-70									
70-80									

Table.10: In-vitro dissolution data

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.22	14.26	15.02	17.21	14.66	16.22	21.10	19.50	23.54
2	32.65	20.65	22.55	29.53	28.44	25.45	32.86	31.88	38.33
3	49.68	39.29	40.89	40.12	43.85	36.89	43.24	49.28	44.25
4	55.24	59.55	48.22	56.84	65.88	42.83	66.49	61.11	51.01

5	60.35	77.58	54.48	66.85	79.25	58.46	74.85	78.96	66.86
6	74.24	80.65	59.77	76.63	96.12	62.70	84.25	82.58	78.98
7	88.28	98.63	66.62	85.12		75.23	95.57	94.66	84.26
8	97.55		74.35	97.70		84.26			96.99
9			88.99			97.99			
10			98.89						

4. Conclusion

In the present work, an attempt has been made to develop nanoemulsion transdermal gel formulations of Ritonavir. Different polymers used in the preparation of nanoemulsion transdermal gel. It was observed that during the stability studies, that there was no change in pH, Wt/ ml, Assay, Viscosity, Sedimentation Volume, Ease of redispersibility and even in Particle size analysis. The dissolution data of the formulation were performed. Therefore, the nanoemulsion transdermal gel formulation No. 3 (F3) was considered as stable, uniform, pleasant tasting and readily redispersible Ritonavir nanoemulsion transdermal gel. Among all the formulations F3 formulation showed maximum % drug release i.e., 98.89 % in 10 hrs hence it is considered as optimized formulation. The F8 formulation contains D-Sorbitol in the concentration of 75 mg.

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