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FORMULATION AND EVALUATION OF LIQUID FILL FORMULATIONS FOR SOFT GELS OF LOPINAVIR AND RITONAVIR

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ABSTRACT

The present investigation includes preparation and evaluation of liquid fill formulations for soft gels using combination of anti-retro viral drugs of Lopinavir (LOPI) and Ritonavir (RIT), in order to improve its dissolution properties and thereby it's bioavailability. Liquid fill formulations were prepared by using excipients like Poly ethylene glycol (PEG-400), Propylene glycol (PG), Dimethyl sulphoxide (DMSO), Poly vinyl pyrrolidine (PVPK-30) and Ethanol. The prepared formulations were evaluated for appearance, pH, drug content, *in-vitro* dissolution studies, viscosity and stability studies. The compatibility between the drug and excipients were determined by FTIR spectra. The drug content of the liquid fill formulations were found to be in the range of 97.53 to 99.60 for LOPI and 97.64 to 99.35 for RIT and viscosity was found to be in the range of 39-138cps The formulation containing PEG/PG/DMSO/Ethanol/SLS system showed better drug release compared to other formulations. Formulation F7 is having superior drug release (100% drug release in 3 min for LOPI and 4 min for RIT) when compared to formulations with PEG/PG/DMSO/Ethanol and PVPK-30 systems. Hence F7 was selected as optimized formulation. The stability studies were conducted for all the formulations for a period of 6 months at room temperature. From these studies it can be concluded that Lopinavir and Ritonavir liquid fill formulations showed superior *in-vitro* drug release when compared to Lopinavir and Ritonavir tablets.

KEYWORDS: Anti-retro viral drugs, Liquid fill formulation, Soft gel, Lopinavir, Ritonavir, poly ethylene glycol-400.

INTRODUCTION

Acquired immunodeficiency syndrome, AIDS has no cure or effective therapy even today. Lopinavir is an antiretroviral of the protease inhibitor class. It is used against HIV infections as a fixed-dose combination with another protease inhibitor, Ritonavir, under the trade names Kaletra (high-income countries) and Aluvia (low-income countries). It was first approved by the FDA on 15 September 2000.All the protease inhibitors (PIs) are metabolized via CYP3A and are substrates and/or inhibitors of the membrane efflux transporter, P-glycoprotein (P-gp). The oral absorption of LOPI and RIT are dissolution rate limited because of which it has low and variable oral bioavailability. Both LOPI and RIT shows low and variable bioavailability because of P-glycoprotein efflux system, which can be avoided by modifying its release to occur more in the stomach where P-glycoprotein content is lowest. Presently, LOPI and RIT combination is available as immediate release (IR) tablets (Kaletra-200mg, 50 mg). Lopinavir[1,2,4] belongs to BCS CLASS II. It is practically insoluble in water 1.92 -0.3 gm/lt, freely soluble in methanol and ethanol, soluble in isopropanol and melting Point is 124 -127°C. Ritonavir[2,4,9] belongs to BCS CLASS II. It is practically insoluble in water, freely soluble in methanol and ethanol, soluble in isopropanol and melting Point is 120-122ºc. Kaushal P. Patel ***et al.,*** studied on Formulation, Development and *In-vitro* evaluation of Lopinavir loaded solid lipid nanoparticles.S.Prakash ***et al.,*** studied on Development and characterization of Ritonavir Nanosuspension for oral use. Dalal V ***et al.,*** studied on Preparation and Evaluation of Lopinavir Mucoadhesive thermo reversible gels for intranasal delivery for anti-retroviral therapy. K.Sai Saran ***et al.,*** studied on Enhancement of solubility of Ritonavir by using solid dispersion technique, but there were no works reported on liquid fill formulation of LOPI and RIT. Soft gels facilitated a higher absorption of poorly soluble compounds when compared to that from other conventional dosage forms not only due to solubilization of the compounds in the fill formulation but also due to fill excipients induced inhibition of P-glycoprotein-mediated drug efflux and reduced enzyme catalyzed degradation of the compound in the lumen of GIT.[3,5,6,7]

Soft gels can be an effective oral drug delivery system, especially for poorly soluble drugs.[10] This is because they offer several advantages in delivering the liquid matrix designed to increase the solubility or permeability of the drug across the membranes in the body.

MATERIALS AND METHODS

Lopinavir and Ritonavir were supplied by Lantec pharmaceuticals, Hyderabad, as a gift sample. Dimethyl sulphoxide(DMSO), Poly vinyl pyrrolidine (PVPK-30), Ethanol, Sodium lauryl sulphate, Hydrochloric acid, PVP K-30 (gift sample from ISP Pharmaceuticals), PEG-400 (gift sample from S.D Fine chemicals Ltd, Mumbai), Propylene glycol (gift sample from Central drug house, Bombay), Tween 80 (gift sample from Central drug house, Bombay), Ethyl alcohol of HPLC grade (gift sample from Changshu Yang chemicals, China), Butylated Hydroxy toulene (gift sample from Merck specialities Ltd, Mumbai), Empty soft gelatine capsules (gift sample from Kahira pharm.chem.co, Cairo, Egypt), Distilled de-ionized water. All the materials used were of pharamcopoeial and analytical grades.

Method used in present research work

An UV-VIS Spectrophotometric method based on the measurement of simultaneous estimation of LOPI at 258 nm and 245 nm for RIT in methanol stock solution was used in the present research work.

For the estimation of LOPI and RIT in 0.1N Hcl solution, the stock solution was subsequently diluted to get a series of dilutions 10,15,20,25 and 30µg/mL for LOPI and 2,4,6,8 and 10µg/ml for RIT and the absorbance was measured at 258 nm for LOPI and 245 nm for RIT (Schimadzu Double beam U.V. Visible spectrophotometer) against the same dilution as blank. The calibration curves of LOPI and RIT at different concentrations in 0.1N Hcl were shown in Fig.1&2.

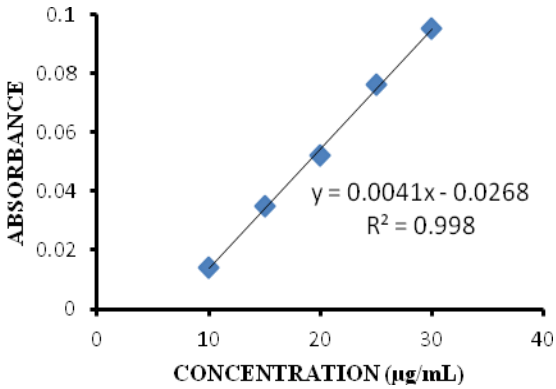

Fig.1: Calibration curve of LOPI.

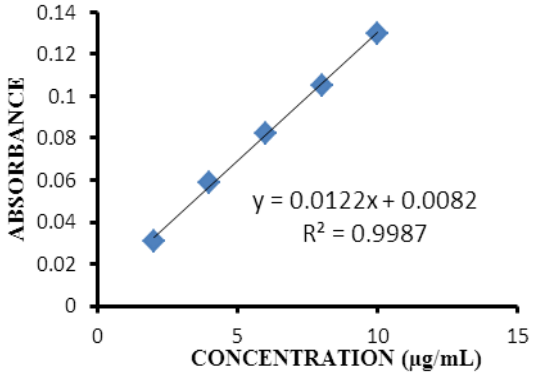

Fig.2: Calibration curve of RIT.

Procedure for liquid fill formulations

Liquid fill formulations were prepared as per the formulae given in Table 1 to a batch size of 6g. Initially Propylene glycol, PEG-400 and DMSO were taken into a small beaker and was mixed thoroughly. Now accurate amount (200mg) of LOPI was weighed and transferred into this beaker and mixed thoroughly followed by the addition of pvpk-30 and ethyl alcohol to dissolve the drug completely. To this RIT (50 mg) was added. The prepared formulation was sonicated for 3 minutes in order to remove any entrapped air. The weight of the liquid ingredients like Ethyl alcohol, propylene glycol, poly ethylene glycol-400 and DMSO was converted to volume from density values and taken accordingly. The volume of the above ingredients derived from the available values of density reported in standard literature (density of ethyl alcohol is 1gm/cm^3, propylene glycol is 1.038gm/cm^3,PEG-400 is 1.12gm/cm^3 , DMSO is 1.100g/cm^3). Empty soft gelatin capsules were incubated at 40ºC for 10 minutes with an objective of removing moisture taken up by the capsules during storage. Each oval shaped soft gelatin capsule of size 20 equivalent to 1.232mL was taken for filling. Each capsule was filled by injection with 1.0 mL of each of the formulation. Each capsule should be filled up to 75 percent of its total volume. Using a glass syringe the liquid fill was injected into the capsule, which was then sealed by heat. The soft gelatin capsules filled with liquid fill formulations of LOPI and RIT were then subjected to different tests to evaluate for various parameters.[11,12,13,14]

Evaluation parameters for liquid fill formulations

Appearance

Appearance is one of the most important parameter of liquid fill formulations. All the formulations were evaluated for clarity by visual appearance.

pH

The developed formulations were evaluated for pH by using Elico LI 120 pH meter and estimations carried out in triplicate.

Table.1: Formulae of Liquid Fill Formulations for soft gels of LOPI and RIT.

FORMULATION(mg/capsule)	F1	F2	F3	F4	F5	F6	F7
DRUG (LOPI)	200	200	200	200	200	200	200

DRUG (RIT)	50	50	50	50	50	50	50
PEG-400	100	200	100	100	200	200	200
PG	100	100	200	50	50	-	100
PVPK-30	-	-	-	50	50	50	-
DMSO	150	150	150	150	150	150	150
SLS	-	-	-	-	-	-	1
ETHANOL	400	300	300	400	300	350	299
TOTAL	1000	1000	1000	1000	1000	1000	1000

Drug content uniformity

Drug content was estimated in the liquid fill formulation by weighing approximately 50mg of the fill formulation into a 5 mL volumetric flask. Few ml of methanol was added and the volume was made up to 5 mL with remaining methanol. Samples were suitably diluted with 0.1N Hcl and the samples were analysed for LOPI and RIT content by measuring absorbance at 258nm and 245nm. The estimations were carried out in triplicate.

Rheological studies

Viscosity of all formulations was measured using a Brookfield DV-II + PRO viscometer. The formulations were taken in a cup of Brookfield DV-II + PRO viscometer rotated with CP52 spindle. The angular velocity was fixed at 10-100 rpm. The viscosity measurements were made in triplicate using fresh samples each time at room temperature.

FTIR studies

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000–500 cm−1 at a resolution of 1.0 cm^{-1}. The powder or film sample is simply placed onto the ATR crystal and the sample spectrum is collected. The sample is then cleaned from the crystal surface and the accessory is ready to collect additional spectra. ATR analysis is less complicated than using KBr pellets is fast and a very small amount of the sample is needed.

***In-vitro* drug release studies**

In vitro dissolution studies were conducted using 900mL of 0.1N Hcl, as dissolution medium using USP XXI type I/II (paddle method) dissolution apparatus (DISSO 8000, LAB INDIA). A temperature of 37 ± 0.5ºC and a rotation speed of 50 rpm were maintained. Liquid formulations containing 200mg of LOPI and 50mg of RIT were filled into empty soft gelatin capsules (size 1) and dissolution studies were performed. As the capsule tends to float in the dissolution medium, sinkers were used. 5mL samples were withdrawn at predetermined time intervals over a period of 0,30,60,90,120,180,240,300 and 360 seconds and then replaced with same volume of fresh dissolution medium. The filtered samples were suitably diluted and analyzed at 258nm for LOPI and 245nm for RIT using Schimadzu U.V -1800 Double beam U.V. Visible spectrophotometer. Dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

Appearance

All liquid fill formulations of LOPI and RIT were visually tested for clarity, color and precipitation of drug if any and the results were given in Table.2 and shown in Fig.7 (a), 7(b), and 7(c).

Table.2: Morphological characters of liquid fill formulations.

Formulations	Morphological character
F1	Homogeneous, clear, no color change.
F2	Homogeneous, clear, no color change
F3	Homogeneous, clear, no color change.
F4	Homogeneous, clear, no color change.
F5	Homogeneous, clear, no color change.
F6	Homogeneous, clear, no color change.
F7	Homogeneous, clear, no color change.

pH

The pH of liquid fill formulations should be in the range of 2.5-7.5.The prepared formulations pH were given in Table.3 And shown in Fig .8(a).

Table.3: pH values for Liquid fill formulations (0-6 Months).

Formulations	pH
F1	5.98
F2	6.01
F3	6.04
F4	5.94
F5	5.97
F6	6.06
F7	6.04

Drug content

All the liquid fill formulations were estimated for drug content and the active ingredients were found to be with in the labeled claim limits. Both the drugs are uniformly distributed and the percent drug content values are satisfactory. The drug content values were given in Table.4 and shown in Fig. 8(b).

Table.4: Drug content profile for liquid fill formulations.

Formulations	Drug content							
	Trail-1	Trail-2	Trail-3	Mean ± SD				
	LOPI	RIT	LOPI	RIT	LOPI	RIT	LOPI	RIT
F1	98.62	99.13	99.04	99.46	98.84	98.79	98.83±0.21	99.12±0.33
F2	99.24	98.09	98.97	99.48	99.34	98.46	99.18±0.19	98.67±0.71
F3	97.18	98.04	97.39	98.36	98.04	97.85	97.53±0.44	98.08±0.25
F4	99.36	97.48	98.89	98.06	99.17	97.38	99.14±0.23	97.64±0.36
F5	98.79	99.16	99.03	98.94	98.64	99.63	98.82±0.19	99.24±0.35
F6	99.02	98.64	98.89	98.93	99.46	99.31	99.12±0.29	98.96±0.33
F7	99.98	99.32	99.84	99.76	98.99	98.97	99.60±0.53	99.35±0.39

Rheological studies

Viscosity is one of the important parameters which provide vital information during the optimization of the liquid fill formulation for soft gels. Rheological studies were carried out for all the liquid fill formulations in Brookfield DV-II PRO viscometer. F1, F2, F3, and F7 had fluid like consistency, whereas F4, F5 had thicker consistency. But formulation F2 had very less viscosity and was like a very clear solution. The viscosity was measured by plotting the shear stress on x-axis, and shear rate on y-axis which gave a straight line. From the slope values viscosity was calculated for each formulation. The viscosities of all formulations were studied. The viscosity of moderately concentrated solutions of PVPK-30 has been studied in PEG 400, PG, and ethanol at different shear rate conditions in concentration range of 5-10%w/w. The study showed that PVP K-30 solutions are Newtonian at high shear rates and non-Newtonian fluid in the low shear rate region. The rheological data for the formulations (F1- F7) were given in Table.5 and shown in Fig.8(c).

Table.5: Rheological data of LOPI and RIT.

Formulations	Viscosity (cps)
F1	39
F2	64
F3	65
F4	132
F5	138
F6	128
F7	53

Drug-excipient compatibility studies

The IR spectra of Lopinavir and Ritonavir pure drug and all the formulations were obtained by KBR pellet method by ATR-FTIR spectra (Bruker, Germany). The characteristic spectrums were all within the range for all the formulations and it indicated that there was no interaction between the drugs and excipients. The IR spectra were shown in Fig.3-5.

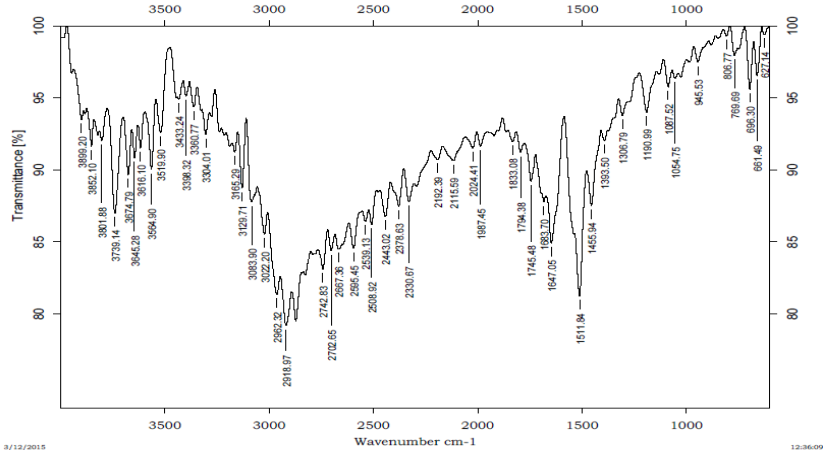

Fig.3: FTIR spectrum of pure Lopinavir.

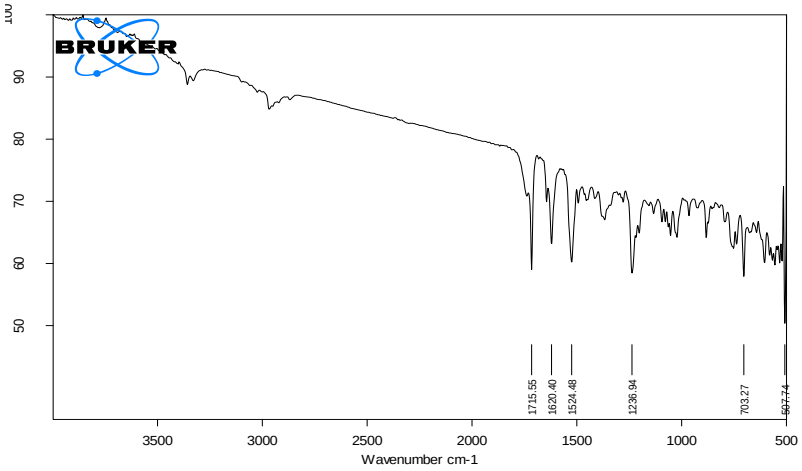

Fig.4: FTIR spectrum of pure Ritonavir.

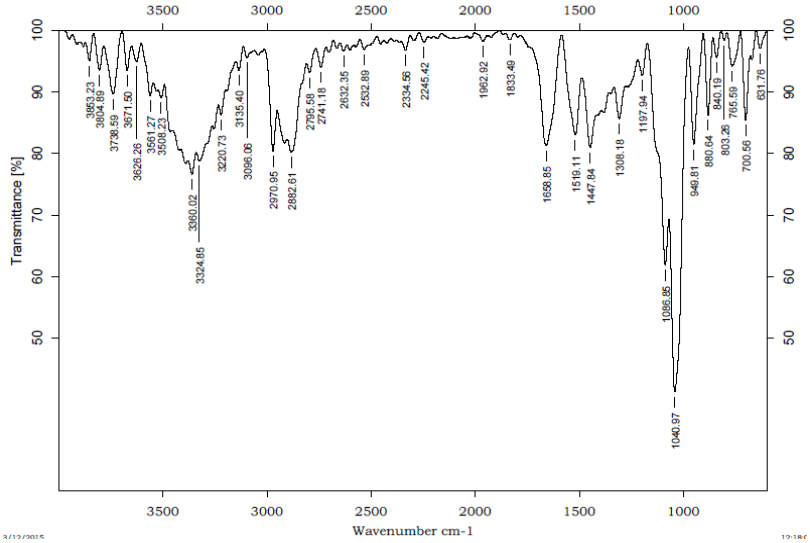

Fig.5: FTIR spectrum of formulation 7.

***In-vitro* release studies**

In- vitro release studies were carried out for liquid fill formulations and the prepared tablet. The dissolution helps to study the dissolution characteristics of drug and also measures the rate of release of drug from dosage form. The dissolution studies were conducted in 900 mL of 0.1 N Hcl at 50 rpm and 37.5±0.5ºc and the comparative profiles were shown in Fig.6 (a)-6(d).

In formulation F1 ethyl alcohol at 40% along with PEG-400(10%), PG (10%) and DMSO (15%) were used instead of PVPK-30 and the percent drug release was found to be 100% in 300 seconds for LOPI and RIT. Hence ethyl alcohol is the best co-solvent for PEG-400, PG and DMSO for LOPI and RIT drug release.

In F2 formulation ethyl-alcohol was used at 30%, PG at 10%, PEG-400 at 20%, DMSO at 15% instead of PVPK-30 then the percent drug release was found to be 100% in 300 seconds for LOPI and in 240 seconds for RIT. This may be attributed to the compatibility of ethyl-alcohol with PEG-400, PG and DMSO.

In F3 formulation ethyl alcohol (30%) was used PG at 20%, PEG-400 at 10%, DMSO at 15% was used and percent drug release was found to be 100% at the end of 300 seconds for LOPI and RIT. This may be due to the increase in the concentration of PG.

In F4 formulation, PVPK-30 (5%) was used and percent drug release was found to be 100% at the end of 360seconds for LOPI and RIT. This may be due to the increase in the concentration of PVPK-30.

In F5 formulation PVPK-30(5%) was used and the percent drug release was found to be 99% for LOPI and 100% for RIT in 360 seconds. This may be due to the PVPk-30.

In F6 formulation ethyl alcohol (35%) was used PEG-400(20%), DMSO(15%), PVPK-30(5%) was used instead of PG and percent drug release was found to be 98% in 360 seconds for LOPI and RIT. This may be due to the increase in the concentration of PVPK-30 when compared to F5 formulation.

In F7 formulation , ethyl alcohol at 29% and PEG-400 at 20% PG at 10% DMSO at 15% and 1% SLS were used and the percent drug release was found to be 100% at the end of 180 seconds for LOPI and 240 seconds for RIT. This showed that there is an increased effect of the surfactant on the drug release of LOPI and RIT.

In F7 formulation (using basket) , ethanol at 29% and PEG-400 at 20%,PG at 10%,DMSO at 15% and 1% SLS were used and the percent drug release was found to be 100% at the end of 90 seconds for LOPI and 120 seconds for RIT. This showed that there is an increased effect of the surfactant on the drug release of LOPI and RIT.In F2 formulation (1% SLS+0.1NHCl was used as dissolution medium) and the percent drug release was found to be 100% at 120 seconds for LOPI and 180 seconds for RIT. This may be due to the addition of surfactant to the dissolution medium.

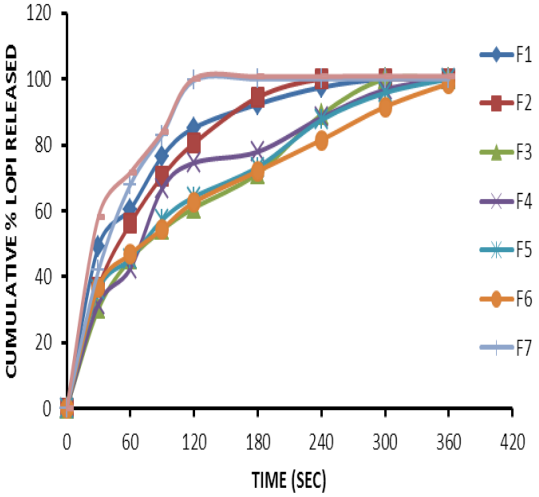

Fig.6(a):Comparative dissolution profile of F1-F7 of LOPI.

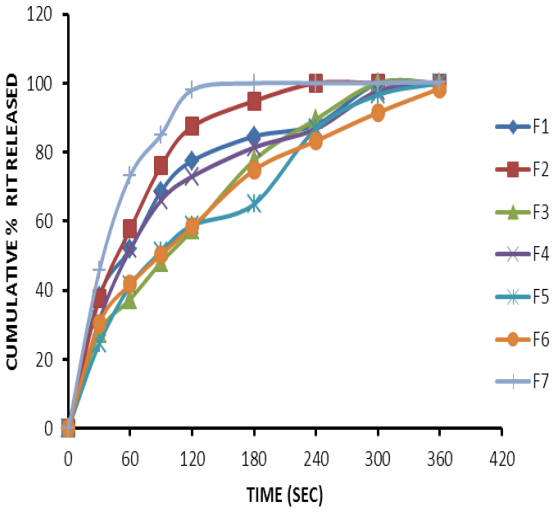

Fig.6(b): Comparative dissolution profile of F1-F7 of RIT.

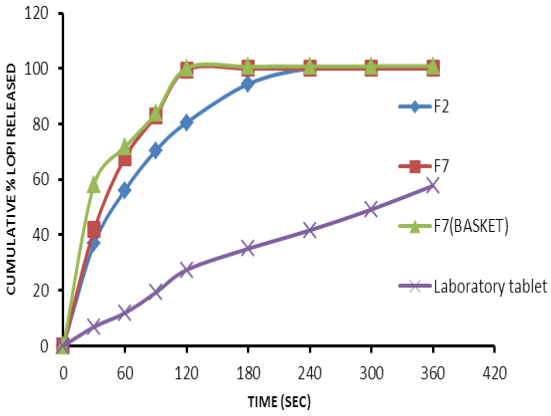

Fig.6(c): Comparative dissolution profile of F2,F7,F7(Basket) of LOPI,Tablet.

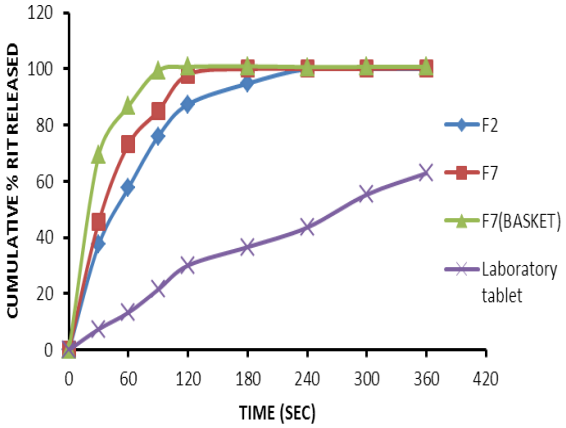

Fig.6(d): Comparative dissolution profile of F2,F7,F7(Basket) of RIT,Tablet.

The laboratory prepared tablet percent drug release was found to be 57.78 % for LOPI and 62.90% for RIT at the end of 360 seconds(Fig 6(c)). This may be due to the disintegration as a rate limiting step. Formulation F2, prepared using Ethanol/PEG/PG/DMSO system showed superior drug release when compared to formulation F4, F5, F6 prepared using ethanol/PEG/PG/DMSO/ PVPK-30 system. This may be attributed due to increase in the viscosity of liquid fill formulation (F4, F5, F6) because of PVPk-30.

Formulation F7, prepared using Ethanol/PEG/PG/DMSO/SLS system showed superior drug release when compared to formulationF1, F3, prepared using ethanol/PEG/PG/DMSO system. This may be attributed due to incorporation of surfactant (1%SLS) in F7 which increased the solubility of liquid fill formulation.

Formulation, F2(1%SLS+0.1N Hcl as dissolution medium), prepared using Ethanol/PEG/PG/DMSO system showed superior drug release when compared to formulation F2 using 0.1N Hcl as dissolution medium. This may be due to the addition of surfactant (1%SLS) to the dissolution medium.

Formulation prepared with SLS (F7), showed rapid drug release when compared to formulations (F4, F5, F6) prepared with PVPk-30, and laboratory prepared tablet.

Formulation F7 is having superior release properties, hence F7 was selected as optimized formulation. This confirms that Ethyl alcohol/PEG/PG/DMSO/SLS system is better for LOPI and RIT release than Ethanol/PEG/PG/DMSO/PVPK-30 and Ethanol/PVP/PEG/DMSO systems. Finally, the release kinetic was studied and showed that F7 better fits the first order release kinetics among all formulations.

First order release kinetics

The dissolution data were analyzed as per zero order and first order kinetics for each formulation. The R^2 values were higher in the first order model than in zero order models indicating that the releases of LOPI and RIT from these liquid fill formulations follow first order kinetics. The first order rate constant 'K' (min^{-1}) values for liquid fill formulation were calculated from dissolution data by fitting the data into first order equation. The first order plot for LOPI and RIT of formulation F7 (optimized) were shown in Fig.6(e).The results were given in Table.6. The comparative plot of 'R^2' values for LOPI and RIT and its formulations F1, F2, F3, F4, F5, F6, F7, were shown in Fig.6 (f).

The order of regression coefficient (R^2) values for all the formulations were in the order of F1>F2>F7>F6>F3>F5>F4 for LOPI and F2>F6>F7>F1>F1>F5>F4 for RIT. Finally, the release kinetics was studied and F1 formulation better fits the first order release kinetics among all other formulations.

Table 6: First order kinetics data for LOPI and RIT liquid fill formulations.

Formulation	K value		R^2	
	LOPI	RIT	LOPI	RIT
F1	0.014	0.008	0.992	0.952
F2	0.015	0.016	0.985	0.995
F3	0.008	0.008	0.955	0.977
F4	0.010	0.010	0.952	0.926
F5	0.0094	0.007	0.954	0.940
F6	0.007	0.007	0.971	0.990
F7	0.017	0.018	0.980	0.978
Laboratory Tablet	0.0025	0.002	0.990	0.984

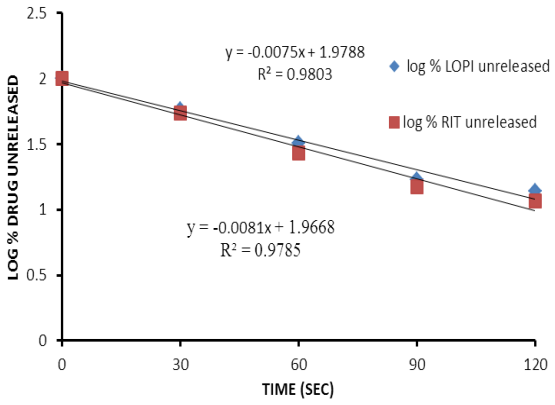

Fig. 6(e): First order plot of F7(Optimized formulation).

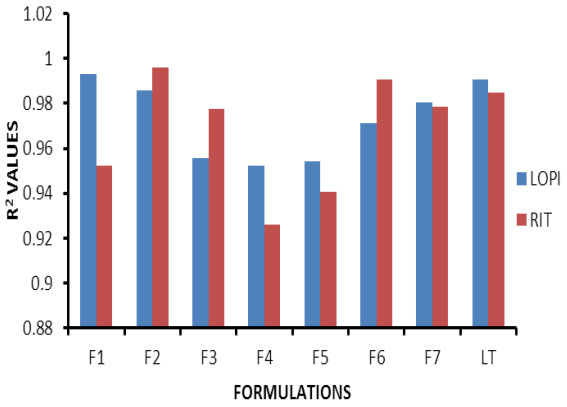

Fig. 6(f): Comparative R^2 values for all the formulations (F1-F7) & tablet.

Stability studies

Liquid fill formulations were subjected to stability studies at room temperature for a period of 6 months. Samples were observed for clarity, color change and precipitation at 0, 3 and 6 months' time periods. The results were given in Table.7 and shown in Fig.7 (a), 7(b), 7(c).

Table.7: Comparative stability data for LOPI and RIT liquid fill formulations (0-6 M).

Formulations	Appearance			Precipitation			Viscosity			pH			Drug content		
	0	3	6	0	3	6	0	3	6	0	3	6	0	3	6
F1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

F2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

X- No Change.

The stability studies showed that all the formulations (F1-F7) have no significant changes and were stable at room temperature without any degradation. Stability studies were conducted for the evaluation of various parameters such as pH, drug content and viscosity for a period of 6 months.

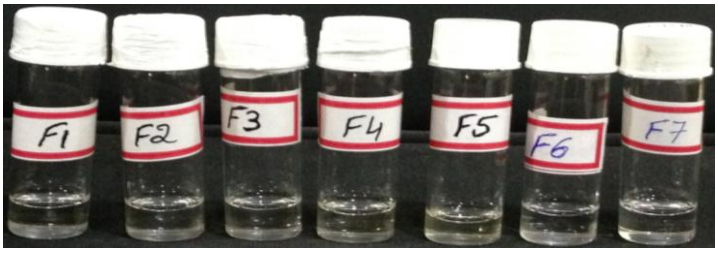

Fig.7 (a): Appearance at zero months.

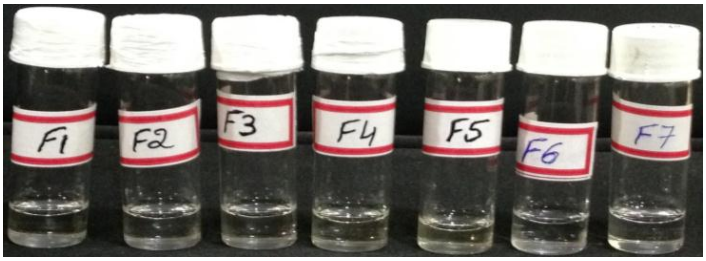

Fig.7 (b): Appearance at three months.

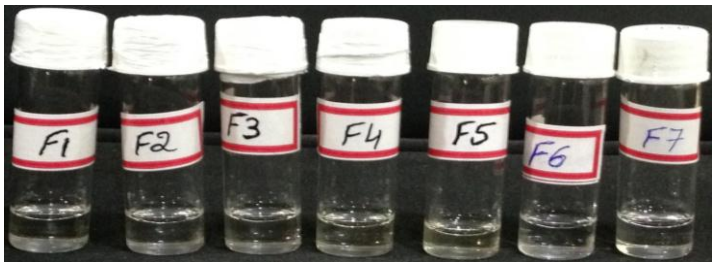

Fig.7(c): Appearance at six months.

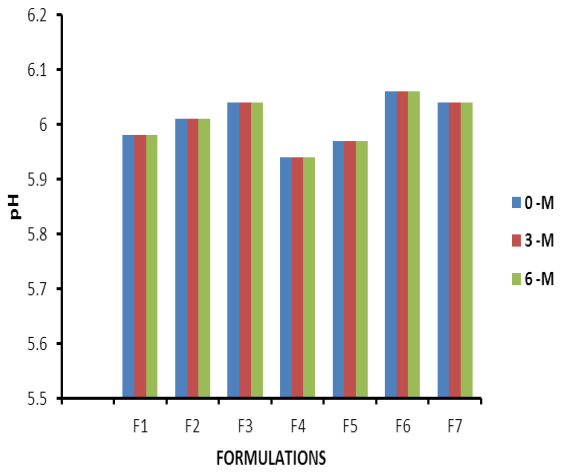

Fig.8 (a): Comparative profiles of pH at 0, 3, 6 months.

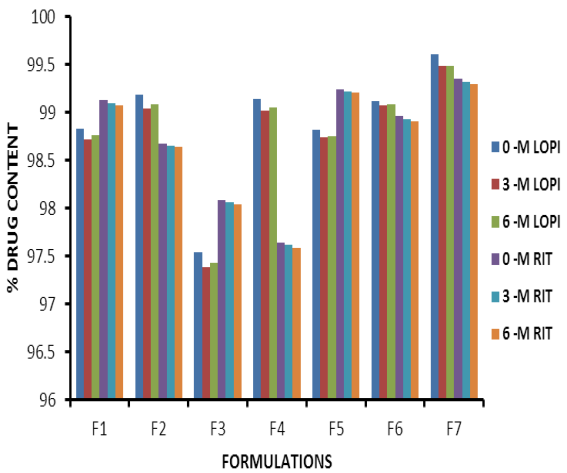

Fig.8 (b): Comparative profiles of drug content at 0, 3, 6 months.

CONCLUSION

The poorly soluble anti-retro viral drugs Lopinavir and Ritonavir can be solubilized by using the co-solvents like PEG-400/PG/DMSO/Ethanol systems and showed superior dissolution property when compared to tablet formulation. The liquid fill formulation containing PEG-400/PG/ DMSO/ Ethanol/SLS system showed superior drug release characteristics compared to PEG-400/PG/DMSO/Ethanol/PVPK-30 systems. All the formulations were stable for a period of 6 months without undergoing any degradation.

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