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FORMULATION AND EVALUATION OF ATENELOL LIQUID FILL FORMULATIONS FOR SOFT GELS

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ABSTRACT
The present investigation was under taken with the objective of enhancing the permeability of Atenolol (ATL), a β1 selective receptor antagonist through the preparation of liquid fill formulations for soft gels. Liquid fill formulations for ATL(25mg) soft gels were prepared using excipients such as dimethyl sulfoxide(DMSO), Ethanol, hydrophilic vehicles like Propylene glycol (PG), polyethylene glycol(PEG-400) and HP-β-CD, Water. The prepared formulations were evaluated for Appearance, pH, content uniformity, viscosity, drug excipient compatibility and *in vitro* drug release parameters. Stability of the optimised formulation was evaluated by storing for six months, at 40^0C and 75% RH. Among all the prepared formulations, formulation F3 containing 40% DMSO, 23.75% PEG-400 and 23.75% PG showed superior drug release (100% within 75sec) with definite physical and chemical stability. The results provide surveillance for developing soft gel capsule of ATL that give better rate of absorption, than existing dosage form and provide quick onset of action with better patient compliance.

KEYWORDS: Atenolol, *In vitro* dissolution, Liquid fill formulations, Stability, Viscosity.

INTRODUCTION
Atenolol (ATL) is a selective β1 receptor antagonist, a drug belonging to the group of beta blockers[1], without membrane stabilizing or intrinsic sympathomimetic activities.[2] ATL was introduced in 1976. It was developed as a replacement for propranolol in the treatment of hypertension.[3] Approved by US FDA in1981, whereas generic products of atenolol were available since 1988.[4] It has lower absorption window in the GIT.[5] Thus, it seems that an increase in gastric residence time may increase the absorption and bioavailability of drug.[6] The objective was to enhance its rate of absorption by formulating into soft gels.

Hypertension is the most common risk factor for Cardiovascular diseases and affects nearly two-thirds of adults aged 60 years or older. It is estimated that uncontrolled HTN is responsible for 7.5 million deaths per year worldwide and in USA alone accounts for over 47 billion dollars spent in health care services, medications and absent workforce. Despite various advances in the field it is projected that 1.56 billion people will suffer from HTN by 2025. 3 various randomized controlled trails have demonstrated that even slight blood pressure decreases such as 10mmHg reduces patients risk of stroke related mortality by 40%. ATL reduces renal vascular resistance in hypertensive patients.[7] Hence, ATL was chosen because of its anti-hypertensive activity, in order to increase its absorption.

Atenolol is white powder, freely soluble in methanol, DMSO and is practically insoluble in Acetonitrile, Chloroform.[8] ATL is used in the management of hypertension, angina pectoris, cardiac arrhythmias and myocardial infraction. It may also be used for the prophylaxis of migraine.[9] ATL is rapidly, but incompletely absorbed from the GIT, the oral bioavailability being about 50-60%.[10] ATL belongs to BCS class-III.[11] It has poor permeability in the lower GIT due to its hydrophilic nature.[12] The permeability is enhanced by addition of penetration enhancers like DMSO.[13] The originator brand name of ATL is TENORMIN where it is manufactured by AstraZeneca pharmaceuticals.[4] The dosage forms available in the market are tablets (25,50,100mg) and injection (0.5mg/ml). CATENOL (25,50,100mg), ATEN (25,50,100mg). ATL is mostly used in combination with Amlodipine ABITEN-A (Atenolol (50mg) + Amlodipine (5mg)).[14]

The pharmaceutical industry manufactures approximately 75% of its solid dosage form as

compressed tablets, 23% as hard gelatin capsules and 2% as soft gelatin capsules.[15] A market survey on consumer preferences has indicated that 44.2% consumers prefer soft gelatin capsules, 39.6% prefer tablets and 19.4% prefer hard gelatin capsules. Soft gels improve the stability of loaded drugs as they do not allow oxygen permeability.[16] The present liquid fill formulations for soft gels contain a vehicle, solubility enhancer, permeation enhancer and complexing agent as fill excipients along with selected drug ATL.

From the literature review, it is clearly evident that works were published with muco adhesive patches (Monica ghalwat, 2013)[17], Oral disintegrating tablets (P. Sandhya *et al.*,2013)[18], transdermal patches (Mohd. Amjad *et al.,* 2011)[19], floating matrix tablets (Sanjay Dey *et al.*,2012)[20], U.V method for atenolol in bulk and pharmaceutical formulation (Shital Shridhar Gite *et al.,* 2013)[21] for improving the dissolution, bioavailability of ATL. However, no reports were published on the liquid fill formulations for soft gels dosage form in order to improve the *invitro* dissolution and oral bioavailability of ATL.

MATERIALS AND METHODS

Materials

Atenolol was supplied by life line formulations, Vijayawada, as a gift sample. DMSO (Gift sample from Roquette (France)), PEG (Gift sample from S.D. Fine chemicals Ltd, Mumbai), Propylene glycol (gift sample from central drug house, Bombay), Ethanol of HPLC grade (gift sample from changshu yang chemicals, china). Empty soft gelatin capsules (gift sample from kahira pharm.chem.co, cario, Egypt), Distilled de-ionized water. All the materials used were of Pharmacopeial and analytical grades.

Method used in present research work

An UV-VIS spectrophotometric method based on measurement of absorbance at 280nm in methanol stock was used in the present research work for the estimation of ATL in *in vitro* studies.

Preparation of liquid fill formulations

Liquid fill formulations were prepared as per the formula given in Table. 1 to a batch size of 1000mg. Initially PEG-400 and Propylene Glycol were taken into a small beaker and was mixed thoroughly. Accurate amount of 25mg of atenolol was weighed and transferred into the separate beaker containing water and mix thoroughly to dissolve the drug. In the formulations 25mg of Atenolol was taken because label claim of Atenolol available in market is 25mg.the drug solution was transferred into PEG-400 and PG mixture and mixed thoroughly. Then finally add DMSO/Ethanol to dissolve the drug completely. The prepared formulation was sonicated for 3 minutes in order to remove any entrapped air. The weight of 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 was 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 1.12g/cm^3, DMSO is 1.100gm/cm^3). Empty soft gelatin capsules were incubated at 40^0C for 10 minutes with an objective of removing moisture taken up by the capsules during storage.[15] Each oval shaped soft gelatin capsule of size 20 equivalent to 1.232ml was taken for Filling. Each capsule was filled by injection with 1.0ml of each of the formulation. Each capsule should be filled by injection with 1.0ml of each of the formulation. Each capsule should be filled up to 75 percent of its total volume.[22] 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 Atenolol were then subjected to different tests to evaluate for various parameters.

Table 1: Formulae for liquid fill formulations of soft gels for Atenolol.

Ingredients (mg/capsule)	F1	F2	F3	F4	F5	F6
Drug	25	25	25	25	25	25
PEG-400$	237.5	237.5	237.5	237.5	237.5	237.5
PG#	237.5	237.5	237.5	237.5	237.5	237.5
Ethanol*	250	400	-	250	250	250
DMSOˆ	-	-	400	-	-	-
HP-β-CD	-	-	-	25	50	75
Water	250	100	100	225	200	175
Total wt. (mg)	1000	1000	1000	1000	1000	1000

**=0.25ml, $=0.21ml, #=0.22ml, ˆ=0.3ml*

Evaluation parameters for Atenolol liquid fill formulations

Appearance

Appearance is one of the most important characteristic parameter of liquid fill formulations. All the formulations were evaluated for clarity and colour change by visual observation against a black background.

pH

pH is one of the most important parameter in the liquid fill formulations. The developed liquid fill formulations

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

Drug content uniformity

Drug content of developed Liquid Fill Formulations was estimated by weighing approximately 50 mg of fill formulation into a 5 mL of volumetric flask. To the flask few mL of methanol was added and mix thoroughly to dissolve the formulations and the volume was made up to the mark with remaining methanol. Samples were suitably diluted with 4.6 Acetate buffer and the samples were analyzed for Atenolol content by measuring absorbance at 280nm. The estimation was carried out in triplicate.

Moisture absorption studies

In order to study the effect of liquid fill composition on the water sorption behavior of the soft gels, they were subjected to water migration studies. Three capsules from each formula were weighed, transferred to a small dry pre-weighed beaker and kept sealed glass humidity chamber containing 100ml of a saturated aqueous solution of sodium chloride (to provide an atmosphere of 75% RH). The weight of the beaker, this beaker with its contents was recorded every day until it became constant indicating that equilibrated moisture absorption has been achieved. The water content of the prepared soft gels was determined at the beginning to calculate the weight of water gained by each formula at equilibrium, and this was expressed as a percentage of the initial capsule weight. A Karl Fischer titrator (Veego, Matic-Md, Veego Instruments Corporation, India) was used to determine the moisture content of the gels and to do this the capsule were cut, inserted into the titration vessel containing dried methanol (Karl-Fischer grade) after stirring for 2 minutes. Three capsules were analysed from each formula and the results were presented as a mean value ± SD. For comparison, the water sorption behaviour of empty capsule shells and filled soft gelatine capsules was studied.

Gastric stability studies

Gastric stability studies were carried out on REMI-Orbital shaking incubator over a period of 1hr and the prepared drug solution was incubated at 37^0C. The samples were withdrawn at predetermined time intervals and analysed in UV-Visible spectrophotometer at 280nm.

Rheological studies

Viscosities of all the developed formulations were measured by using Brookfield DV-II+PRO Viscometer. The formulations were taken in 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 4000-500cm^{-1} at a resolution of 1.0cm^{-1}. The powder or liquid fill sample is simply placed on to 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.

***In vitro* drug release studies**

In vitro dissolution studies were conducted by using 900ml of pH 4.6 Acetate buffer as medium using USPXXI type I/II (paddle method) dissolution apparatus (DISSO 8000, LAB INDIA). A temperature of 37±0.5^{o}C and a rotation speed of 50 rpm were maintained and dissolution studies were performed. As the capsule tends to float in the dissolution medium, sinkers were used. The samples were withdrawn at predetermined time intervals over a period of 0,5,10,15,30,45,60,75,90,105,120,240 seconds and then replaced with same volume of fresh dissolution medium to maintain constant dissolution medium. The filtered samples were suitably diluted and analyzed at 280nm using UV-Visible Elico SL 150 spectrophotometer. Dissolution experiments were conducted in triplicate.

Drug release kinetics and studies

There are a number of kinetic models, to describe the overall release of drug from the dosage form. Because qualitative and quantitative changes in a formulation may alter drug release and *in vivo* performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. The rate of release of Atenolol from prepared dosage form was analysed by fitting drug release data into first order release kinetics equation.

Log C=Log Co-k t/2.303

Where, Co is the initial concentration of the drug and k is the first order rate constant. By plotting, Log cumulative of % drug unreleased against time a line was obtained and from its slope was calculated.

Stability studies

Stability testing is performed to ensure that drug products retain their fitness for use until the end of their expiration dates. Liquid fill formulations(F1-F6) were observed for clarity, colour, change, drug content, pH, viscosity and precipitation for a period of 6 months at room temperature (~30^{o}C/65% RH). The samples were withdrawn after 1,3 and 6 months and evaluated for following parameters such as appearance, pH and drug content.

RESULTS AND DISCUSSION

All the formulations were evaluated for appearance, pH, Drug content uniformity, Rheological studies, *In vitro* studies, drug excipient compatibility studies, Stability.

Appearance

All liquid formulations of Atenolol were visually tested for clarity, colour and precipitation of drug. The formulations were clear, homogeneous and free of precipitation and the results were shown in Figure 1.

Fig. 1: Appearance of liquid fill formulations (0-6M).

pH

pH is another important parameter for liquid filling formulations. The two areas of critical importance are the effect of pH in the range of 2.5-7.5.[21] At pH values below 2.5, gelatin is hydrolysed causing leakage of the soft gel, whereas at pH values above 7.5, gelatin may be either hydrolysed or tanned (i.e., crosslinked) resulting in decreased solubility of the gelatin shell. pH of all the formulations were close to 6. The pH of the soft gelatin fill formulation without drug was found to be at 5.4. Therefore, all the batches of formulations are suitable for capsule filling and the results were shown in Figure 2.

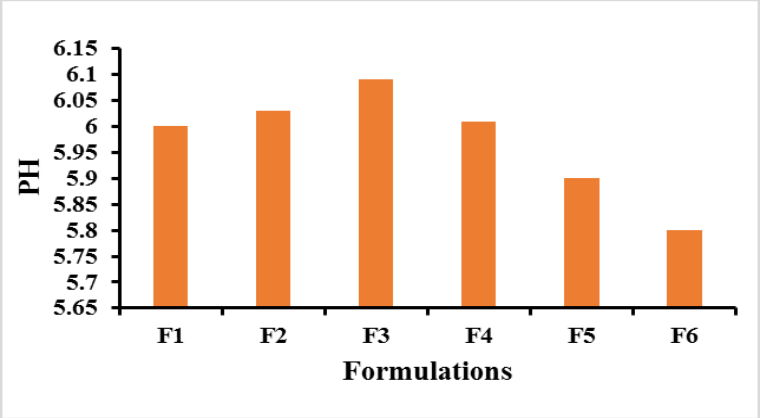

Fig. 2: pH of liquid fill formulations.

Drug content estimation

The drug content for all developed formulations was found to be in acceptable range that indicating uniform distribution of drug. The percent drug content was found to be in the range of 97.81± 0.47 to 99.63±0.22 and the results were shown in Figure 3.

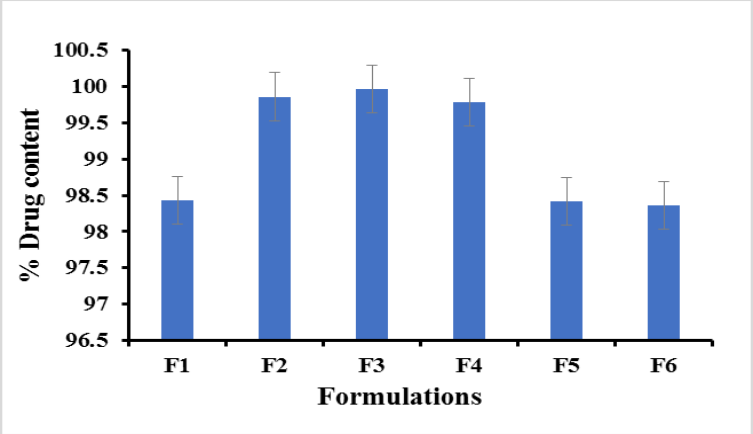

Fig. 3: Drug content of liquid fill formulations.

Moisture absorption studies

The moisture absorption was found to be in the acceptable range for all the formulations indicating their stability. Percent moisture absorption as found to be in the range of 1.17±0.95-4.83±0.64.

Rheological studies

Viscosity is one of the important parameters, which provides vital information during the optimization of the liquid filling formulations for soft gels in the range of 0.222-3000cps.[23]

Rheological studies were carried out for all the liquid filling formulations in Brookfield DV-II PRO viscometer. The formulation F2, F3, F4 has thick consistency and F1, F5, F6 has thin consistency. The viscosity was measured by plotting the shear stress on X-axis, and shear rate on Y-axis. From the slope values viscosity was calculated for each formulation.

All the formulations showed Newtonian type of fluid behaviour. Therefore, solution form of dosage form that show Newtonian type of fluid behaviour, results in the liquid fill formulations for soft gels of Atenolol and the results were shown in Figure 4.

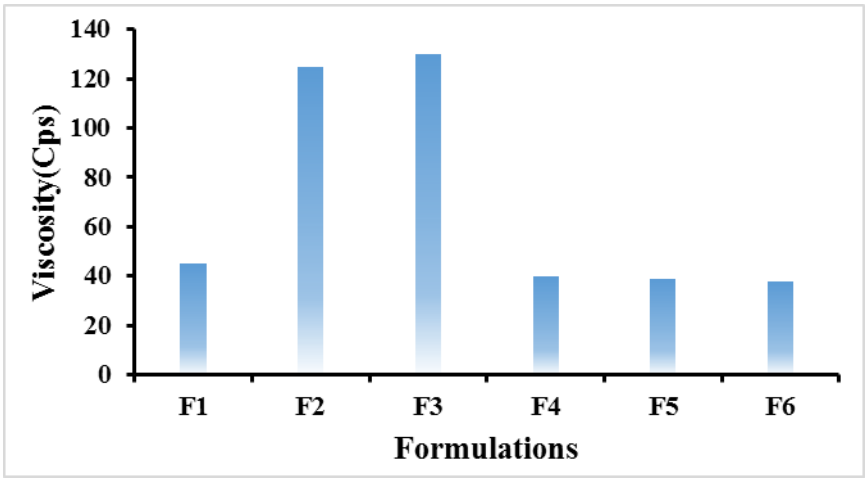

Fig. 4: Viscosity of all the Liquid fill formulations.

Drug-excipient compatibility study

The IR spectra of Atenolol 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 drug and excipients. The IR spectra were shown in Figure 5-7.

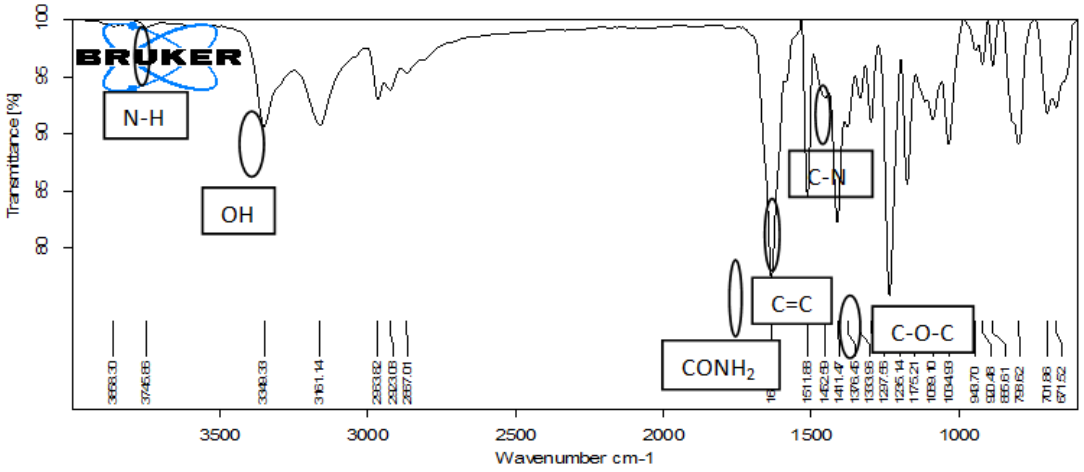

Fig. 5: FTIR Spectra of pure drug.

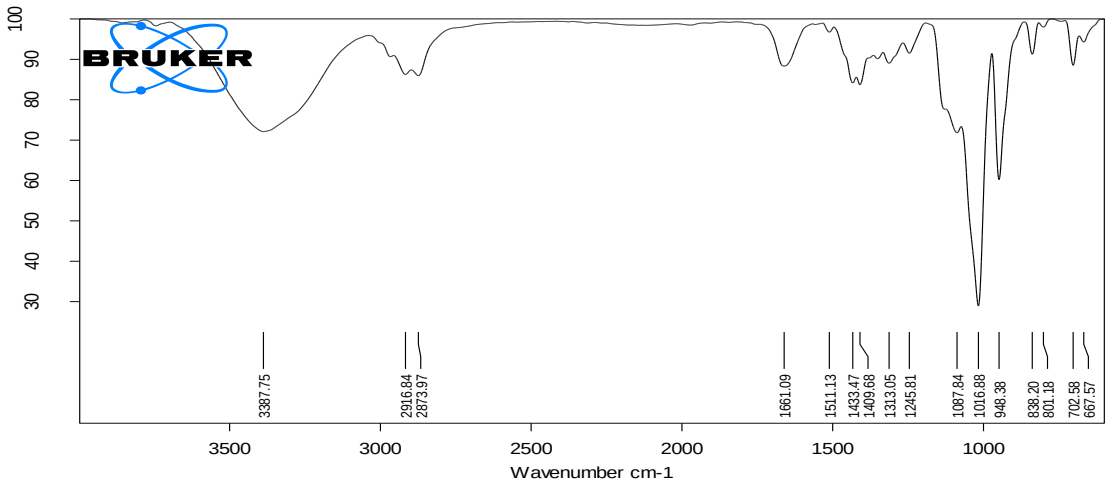

Fig. 6: FTIR Spectra of optimized formulation (F3).

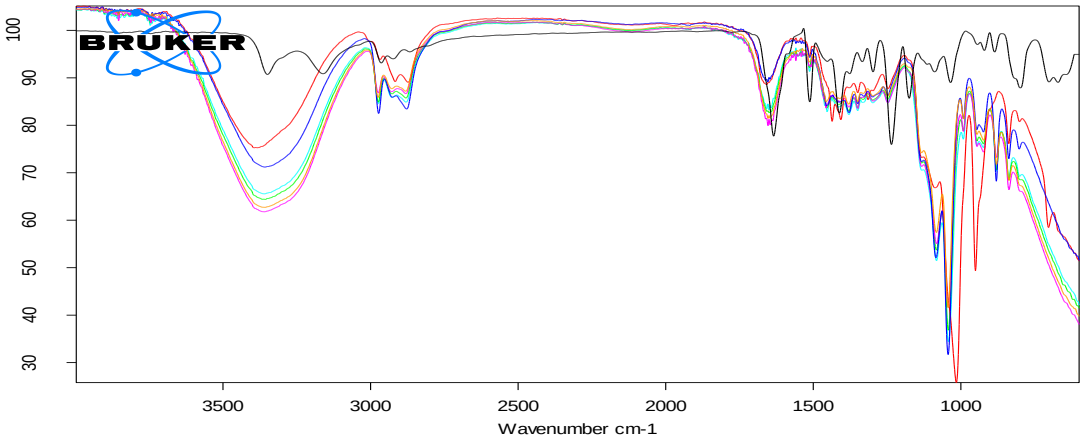

Fig. 7: Overlay of all liquid fill formulations and pure drug.

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

In-vitro release studies were carried out for liquid fill formulations and the pure drug. 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 900ml of pH 4.6 Acetate buffer at 50rpm and 37.5±0.5°C and the comparative *in vitro* dissolution profiles were shown in Figure 8.

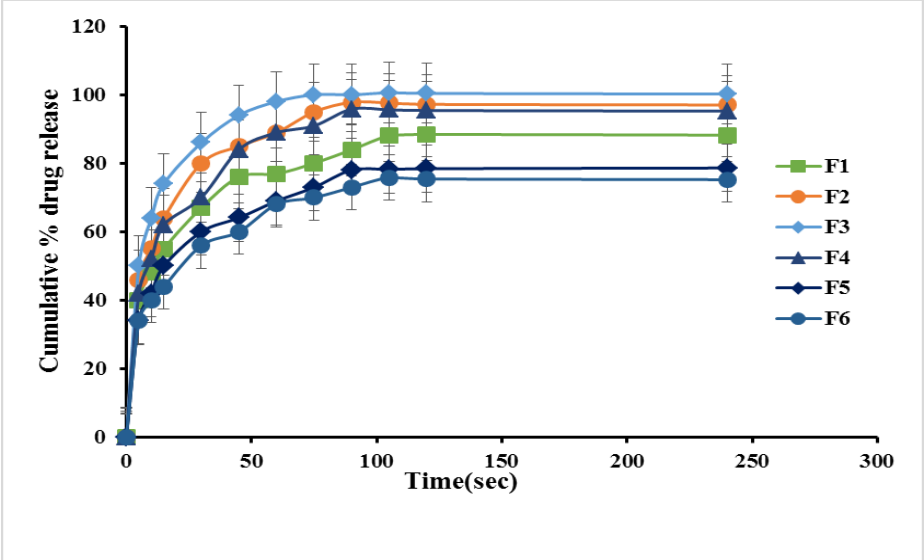

Fig. 8: Comparative *In vitro* dissolution profile of F1-F6.

In F1 formulation, PEG-400 at 23.75%, PG at 23.75% and Ethanol at 25%, water at 25% were used and the drug release was found to be 80.07 % at 75sec. This may be due to the use of ethanol.

In F2 formulation PEG-400 at 237.5%, PG at 23.75%, Ethanol at 40% and water at 10% were used and the drug release was found to be 95.07% at the end of 75sec. this may be due to increased co-solvency used.

In F3 formulation PEG-400 at 23.75%, PG at 23.75%, DMSO at 40%, water at 10% were used. The drug release was found to be 100% at 75sec. hence DMSO is considered the best co-solvent of PEG-400 and PG for the efficient ATN drug release.

Formulation F3 prepared using DMSO/PEG-400/PG/Water showed better drug release (100% at 75sec) than F1&F2 prepared using Ethanol/PEG-400/PG/Water. This may be due to ATN is having higher solubility in case of DMSO and better compatible with the ATN drug release.

Hence F3 was further studied with the inclusion of cyclodextrins (HP-β-CD) in the ratios of 1:1,1:2,1:3. β-cd are used in order to increase the permeability of the drug.

In formulation F4 PEG-400 at 23.75%, PG at 23.75%, Water at 22.5% and Ethanol at 25%, HP-β-CD (25mg) were used. The drug release was found to be 95% at 75 sec. This may be due to good complexation efficiency of carrier with the drug and has compatibility with the ratio of 1:1 of HP-β-CD.

In F5 formulation PEG-400 at 23.75%, PG at 23.75%, Ethanol at 25%, water at 22.5% and HP-β-CD (50mg) were used. The drug release was found to be 73.02% at 75sec. this may be due to less compatibility of the drug with carrier.

In formulation F6 PEG-400 at 23.75%, PG at 23.75%, water at 17.5%, Ethanol at 25% and HP-β-CD(75mg) were used. The drug release was found to be 70.02% at 75sec; this may be due to no proper compatibility of the drug with the carrier.

Formulation F4 has better dissolution profile than F5, F6, due to good compatibility with the carrier ratio of 1:1. Formulation F6 has poor compatibility due to increase in the concentration of carrier.

When compared to the Formulations (F4, F5, F6) prepared with HP-β-CD and without HP-β-CD (F1, F2, F3) those prepared with HP-β-CD i.e., F5, F6 showed less drug release than other formulations. F3 is having superior dug release compared to other formulations, this may be due to increased concentration of co-solvent drug release.

Pure drug of 25mg was taken and conducted dissolution studies the drug release was found to be 92.07% at 75sec. The comparative study of pure drug with all the 6 formulations were shown in Figure 9.

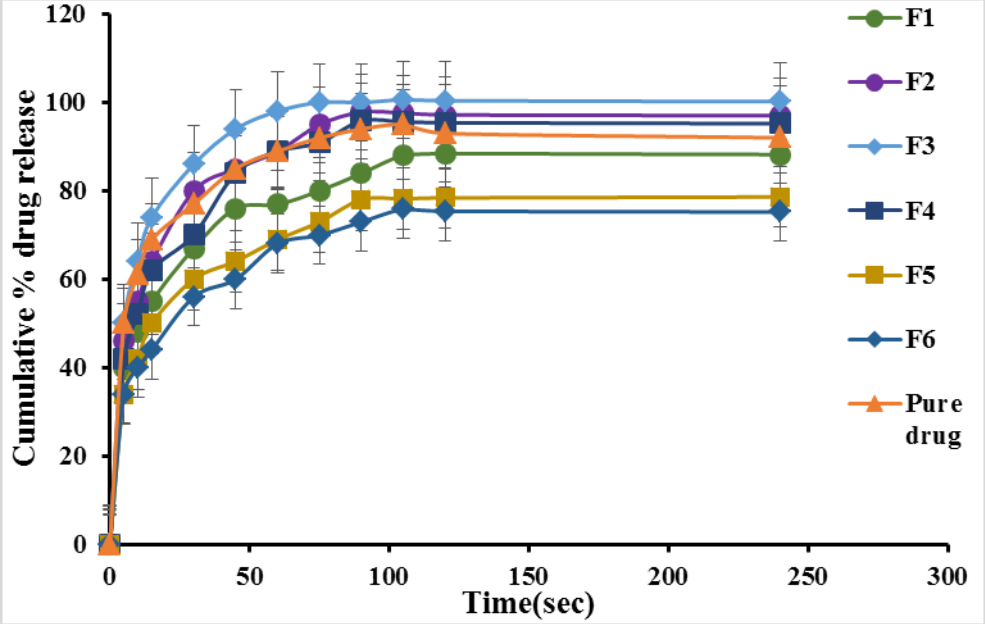

Fig.9: Comparative *In vitro* dissolution profiles of all formulations and pure drug.

The formulation F3(100% at 75sec) is having superior drug release properties compared to F1, F2, F4, F5, and F6. When compared with the pure drug the drug release is superior in the optimised formulation (F3). Hence F3 was selected as optimized formulation. The comparative study of pure drug with optimized formulation were shown in Figure 10.

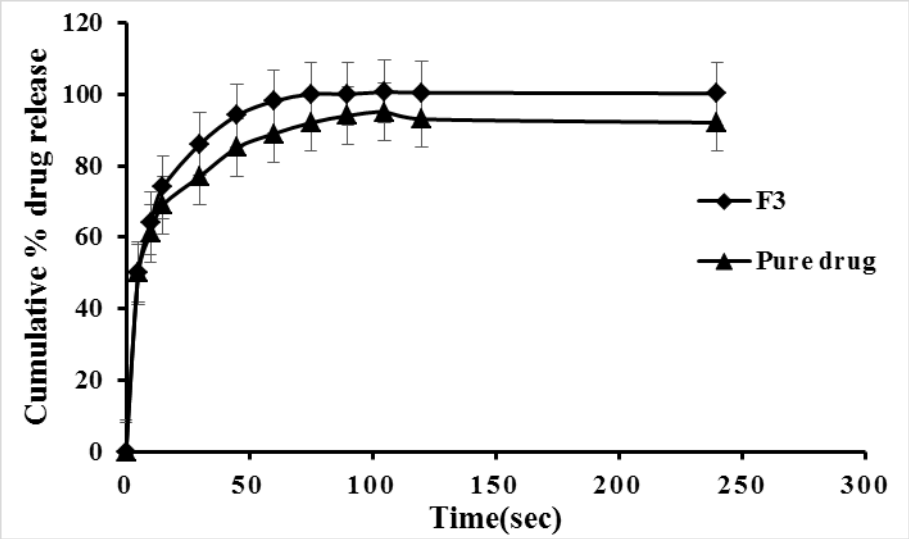

Fig.10: Comparative *in vitro* dissolution profile of F3 and pure drug.

First order release kinetics

The dissolution data were analysed as per zero order and first order kinetics in each case. The r^2 values were higher in the first order model indicating that the release of ATL from these liquid fill formulations followed first order kinetics. The first order rate constant 'K' (sec^{-1}) values for liquid fill formulation were calculated from dissolution data by fitting the data into first order equation. Both liquid fill and tablet formulations followed by first order release kinetics. The first order kinetics data for liquid fill formulations was shown in Fig 11, 12 and 13.

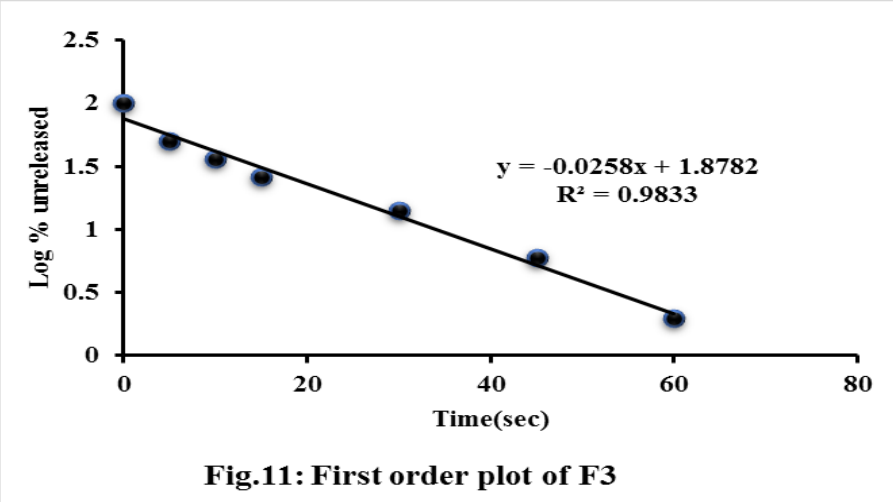

Fig.11: First order plot of F3

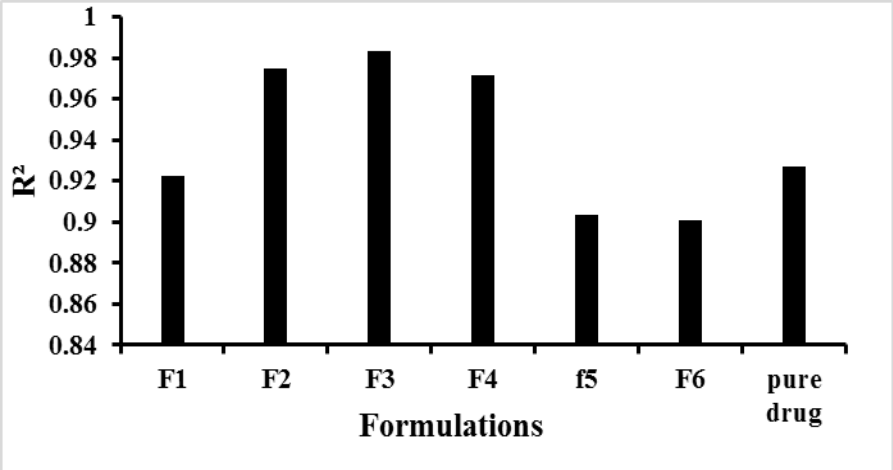

Fig. 12: Comparative R^2 values of all liquid fill formulation (F1-F6) and pure drug.

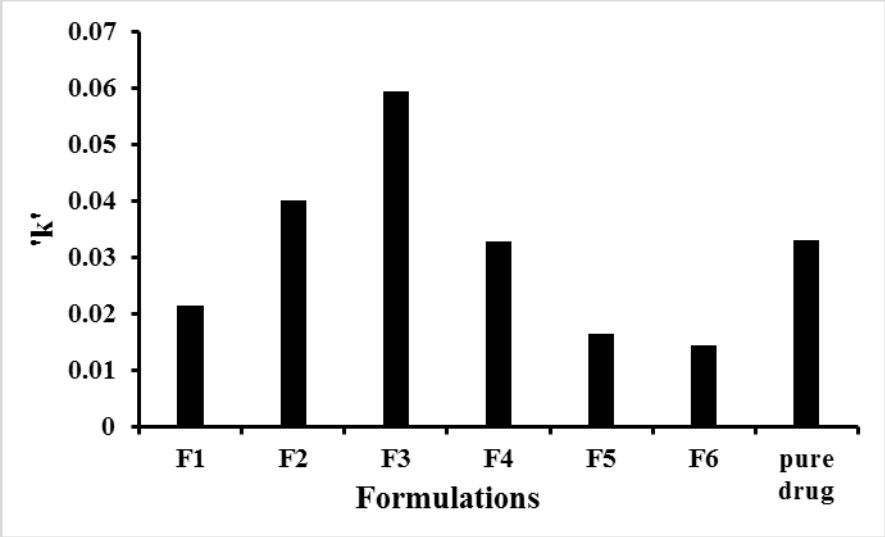

Fig. 13: Comparative K value of all the liquid fill formulations(F1-F6) and pure drug.

The order of coefficient of determination (R^2) values for all the formulations were in the order F3>F2>F4>F1>F5>F6**.**

In F3, R^2 values are higher and it indicates that F3 has superior release characteristics among all the liquid fill formulations. Finally, the release kinetics showed that F3 best fits the first order release kinetics among all the formulations.

Stability studies

The optimized liquid fill formulation (F3) was observed in triplicate for accelerated stability studies and monitored for appearance, pH, percent drug content, Viscosity, *in vitro* dissolution studies for 6 months. The results indicated that there is no significant variation in appearance, pH, Percent drug content, Viscosity, *in vitro* dissolution profile studies up to three and six months.

CONCLUSION

For Atenolol, the best co-solvent system (Water/PEG-400/PG/DMSO) in liquid fill formulations for the better atenolol drug release than other systems (Water/Ethyl alcohol/PEG-400/PG), (water/Ethyl alcohol/PEG-400/PG) and pure drug. Hence, Atenolol was chosen in order to increase its rate of absorption and to have a rapid onset of action for a hypertensive patient. All the liquid fill formulations showed good physico-chemical properties. The formulations were stable up to 6 months without undergoing any degradation.

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