Novel Dosage Forms of Nelfinavir Mesylate

Jyothirmayee Devineni, and J.Vijaya ratna

Abstract— The present investigation was undertaken with the objective of formulating liquid fill formulations for soft gelatin capsules of an anti-retroviral drug, nelfinavir mesylate [NLF] to increase rate of absorption and thereby its bioavailability. Liquid fill formulations were formulated using NLF and polyethylene glycol 400(PEG 400), propylene glycol(PG), polyvinyl pyrrolidone( PVP k-30), tween 80, antioxidants, ethanol and purified water. Prepared formulations were evaluated for clarity, pH, drug content percentage, viscosity, stability, water migration studies, in vitro dissolution. Compatability studies between NLF and excipients were studied by FTIR spectra. The filled capsules showed 95.34% to 99.29% of labelled amount, indicating drug content uniformity. Formulation containing 10% PVP k-30, 10%, tween 80 showed superior drug release about 99.79 ± 0.327% within 4 min and optimum gel consistency. From the studies, it can be concluded NLF liquid fill formulations for soft gels were successfully prepared may result in improved bioavailability.

Keywords— Drug content, Soft gel, Stability, Viscosity.

I. INTRODUCTION

Aquired immunodeficiency syndrome, AIDS has no cure or effective therapy even today. Treatment consists of high active antiretroviral therapy (HAART) which slows progression of the disease. HAART is a combination therapy with two kinds of reverse transcriptase inhibitors and a HIV protease inhibitor (PI), that prolongs the survival of AIDS patients.[1] Nelfinavir mesylate,(NLF) a HIV protease inhibitor is currently used alone or in combination with reverse transcriptase inhibitors for the management of HIV infection. All the protease inhibitors (PIs) including nelfinavir mesylate are metabolized via CYP3A and are substrates and/or inhibitors of the membrane efflux transporter, P-glycoprotein (P-gp).[2]-[3]-[4] NLF is a white to off-white powder, freely soluble in methanol, ethanol, isopropyl alcohol and propylene glycol, and is practically insoluble in water.[5]

The oral absorption of NLF is dissolution rate limited because of which it has low and variable oral bioavailability (20-80%).[6]-[7]-[8] NLF is soluble in acidic environment of stomach since it is a weak basic drug and its therapeutic efficacy is limited by its poor aqueous solubility.[6]-[7]-[8] NLF belongs to BCS class-II and IV.[6]-[7]-[8]-[9] NLF is the most lipophilic of the PIs, having a partition coefficient log P value of 4.1.[10]-[11] NLF 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.[12] Presently, NLF is available as immediate release (IR) tablets and powder sachets ([Nelfin-625mg FC tab (Hetero HC), Retronel-250 mg (Alchem), Nelvir-250mg (Cipla), Viracept-250 mg (Agouron)].

Consumers seem to prefer soft gel capsules to other solid dosage forms. The pharmaceutical industry manufactures approximately 75% of its solid dosage forms as compressed tablets, 23% as hard gelatin capsules and 2% as soft gelatin capsules. 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. [13]

A. Advantages [14]

- A soft gel capsule presents the drug to the GIT in the form of a solution or suspension or emulsion. Thus dissolution is no more a rate limiting step in the absorption process. Absorption happens faster, in a more uniform and enhanced manner.
- Soft gel capsules are more easily swallowed, they mask odours, or unpleasant taste and they protect the encapsulated compound against oxygen and light.
- The absorption from soft gel capsules may be higher also due to the fill excipient induced inhibition of P-glycoprotein mediated drug efflux.
- Enhanced absorption may also be due to the enzyme catalyzed degradation of the compound in the lumen of the GIT.
- Soft gels are also used to accurately deliver therapeutic agents that require ultra low doses (e.g., cardiac glycosides, vitamin D-analogues).

B. Challenges [14]

There are two major possibilities against which the soft gel formulations must be protected, one is the physical migration of the components of shell and the fill between themselves, and the migration of the components to the external environment and second is the physical and chemical interactions between the shell components and fill components or within the shell or fill components. Fill formulations must have optimum properties in terms of fill viscosity, blend uniformity, fill weight uniformity, physical stability and
was converted to volume from density values and taken accordingly. The volume of the above liquid ingredients was derived from the available values of density reported in standard literature (density of ethyl alcohol is 1 gm/cm$^3$, propylene glycol is 1.038 gm/cm$^3$, PEG -400 is 1.12 gm/cm$^3$, tween 80 is 1.02 gm/cm$^3$). Empty soft gelatine capsules were incubated at 40$^\circ$C for 10 minutes with an objective of removing moisture taken up by the capsules during storage.[16]

Each oval shaped soft gelatin capsule of size 20 equivalent to 1.232 ml 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. [14] Using a glass syringe the liquid fill was injected into the capsule, which was then sealed by heat. The soft gelatine capsules filled with liquid fill formulations of NLF were then subjected to different tests to evaluate for various parameters. [17]

II. MATERIALS AND METHODS

2.1 Materials

Nelfinavir mesylate was supplied by Lantec pharmaceuticals, Hyderabad, as a gift sample. 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 phamacopoeial and analytical grades.

2.2 Methods

Preparation of liquid filling formulations

Liquid filling formulations were prepared as per the formulae given to a batch size of 6g. Initially propylene glycol, tween 80 and PEG-400 were taken into a small beaker and stirred to dissolve well. PVP K-30 was then added and dissolved. Accurate amount of NLF was then weighed and transferred into this beaker and mixed thoroughly. It was followed by the addition of ethyl alcohol to dissolve the drug completely (evaporation of ethyl alcohol is avoided by covering the beaker during stirring). Nelfinavir base, 10 mg is equivalent to 11.69 mg of nelfinavir mesylate salt. Therefore for 250 mg of nelfinavir base that is required in the formulation, salt equivalent taken was 292.3 mg. BHT was then added and mixed thoroughly. 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 (PG), polyethylene glycol – 400, tween 80

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<td>BHT</td>
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<td>Total wt</td>
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2.3 Evaluation parameters for liquid filling formulations [18]

2.3.1 Appearance

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

2.3.2 pH

The developed NLF liquid fill formulations were evaluated for pH by using Elico LI 120 pH meter and estimations were carried out in triplicate. Soft gel formulations should have a pH range between 2.5 and 7.5.

2.3.3 Drug content uniformity

Drug content was estimated in the liquid fill formulations by weighing approximately 25mg of the fill formulation into a 5 ml volumetric flask. A small volume of methanol was then added, stirred well 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 NLF content by measuring absorbance at 252 nm. The estimations were carried out in triplicate.

2.3.4 Moisture absorption studies

In order to study the effect of liquid fill composition on the water sorption behavior of the softgels, they were subjected to water migration studies. Three capsules from each formula were weighed, transferred to a small dry pre-weighed beaker and kept in a sealed glass humidity chamber containing 100 ml of a saturated aqueous solution of sodium chloride (to provide an atmosphere of 75% relative humidity). The weight of the beaker, with its contents, was recorded every day until it became constant indicating that equilibrated moisture absorption had been achieved. The water content of the prepared softgels was determined at the beginning of the water migration study and after equilibrium 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 softgels and to do this the capsules were cut, inserted into the titration vessel containing dried methanol (Karl-Fisher grade) and titrated with Hydranal Composite 5 reagent (Riedel-de-Haën, Seelze, Germany) after stirring for 2 min. Three capsules were analyzed 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 gelatin capsules was studied.

2.3.5 Rheological studies

Viscosity of all the formulations was measured using a Brookfield DV-II + PRO viscometer. The formulations were taken in the cup of the Brookfield DV-II + PRO viscometer and it was 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.

2.3.6 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. It is a fast process and a very small amount of the sample is needed.

2.3.7 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 ± 0.5°C and a rotation speed of 100/50rpm were maintained. Dissolution studies were performed. As the capsule tends to float in the dissolution medium, sinkers were used. Samples of 5ml were withdrawn at predetermined time intervals over a period 1hr. passed through a 0.45µm nylon membrane. Then the sample was removed with the same volume of fresh dissolution medium in order to maintain constant dissolution medium. The filtered samples were suitably diluted and analyzed at 252nm using UV-Visible Elico SL150 spectrophotometer. Dissolution experiments were conducted in triplicate.

2.3.8 Drug release kinetics & mechanisms

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 NLF from prepared dosage form was analyzed by fitting drug release data into first order release kinetics equation:

\[ \log C = \log C_0 - k t/2.303. \]

Where, \( C_0 \) is the initial concentration of the drug and \( k \) is the first order constant. By plotting log cumulative of % drug unreleased against time and from slope, \( k \) was calculated.

2.3.9 Stability studies on nelfinavir mesylate liquid fill formulations for soft gels

Liquid fill formulations, apart from their other requirements, should be stable with regard to their properties, especially their dissolution characteristics. The stability of nelfinavir liquid fill formulations developed in the present study were evaluated as per ICH guidelines. Stability studies were carried out on the liquid fill formulations, as per ICH guidelines. The capsules were packed in amber coloured bottles and stored at 40°C and 75% RH for 6 months. During storage, the products were monitored for viscosity, pH of the formulation, drug content, appearance, precipitation, dissolution profile studies which were carried out at 3 and 6 months.

III. RESULTS AND DISCUSSION

The formulations prepared were evaluated for various parameters like viscosity, pH, appearance, drug content, water absorption, drug-excipient compatibility and in vitro drug release studies and stability studies.

Appearance

All liquid filling formulations of NLF were visually tested for clarity, colour and precipitation of drug if any. The formulations were clear, homogenous and free of precipitation.

pH

pH is another important parameter for liquid filling formulations. The two areas of critical importance are the effect of pH on solubility and stability. Liquid fill formulations for soft gels should have their pH in the range of 2.5 to 7.5.[18] At pH values below 2.5, gelatin is hydrolyzed causing leakage of the soft gel, whereas at pH values above 7.5, gelatin may be either hydrolyzed or tanned (i.e., cross-linked) resulting in decreased solubility of the gelatin shell.[19] The pH of all the formulations was close to 7.2. The pH of the soft gelatin fill formulation without drug was found to be at 5.4 (placebo). Therefore, all the batches of the formulations are suitable for capsule filling.

Drug content estimation
The drug content was found to be in acceptable range for all formulations indicating uniform distribution of drug. Percent drug content was found to be in the range of 98.89 ± 0.05 - 99.68 ± 0.31.

**Moisture absorption studies**

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

![Figure 1: Percent moisture absorption of liquid fill formulations for soft gels of nelfinav mesylate](image)

**Rheological studies**

Viscosity is one of the important parameters which provides vital information during the optimization of the liquid filling formulation for soft gels. In general, the viscosity of liquid filling formulations for soft gels is in the range of 0.222-3000 cps. [20]

Rheological studies were carried out for all the liquid filling formulations in Brookfield DV-II PRO viscometer. The consistency of F1, F2, F3, and F5 was fluid like, in which 10 percent PVP K-30 was used. Formulation, F6 with 15 percent PVP K-30 had thicker consistency. Formulation F4 with zero percent PVP K-30 showed very less viscosity. The viscosity was measured by plotting the shear stress on x-axis, and shear rate on y-axis. The resultant rheograms were straight lines. From the slope values viscosity was calculated for each formulation. The consistency and viscosity of the liquid fill formulations were related to each other because both are dependent on the concentration of PVP K-30.

All the formulations showed Newtonian type of fluid behaviour. Significant increase in viscosity was observed with increase in PVP K-30 concentration as the system offers more resistance to flow. The decrease in shear viscosity with increasing shear rate is due to tendency of PVP K-30 molecules to orient more in the direction of shear. It is clearly evident that changes in the viscosity and consistency of liquid fill formulations for soft gels were because of change in concentration of PVP K-30. All the liquid ingredients in the formulations are cosolvents to ethanol. Therefore solution form of dosage form results in the liquid fill formulations for soft gels of nelfinav mesylate in the present investigation that shows Newtonian type of fluid behaviour. Dispersion/suspension/emulsion forms show pseudoplastic type of fluid behaviour when PVP K-30, PEG 400, Tween 80 are used. The viscosity of all the formulations was studied.

**FTIR spectrums for liquid fill formulations**

FTIR spectrum of pure nelfinav mesylate showed OH-group bending (alcohols) at 1659.48 cm\(^{-1}\), C=N stretching at 1642.46 cm\(^{-1}\), N-H stretching at 3361.88 cm\(^{-1}\), C-H bending at 836.56 cm\(^{-1}\), S=O stretching at 1375.44 cm\(^{-1}\), C-O stretching at 1358.14 cm\(^{-1}\), N-H bending at 1540.59 cm\(^{-1}\). It indicates that there is no interaction between drug and excipients.

**In vitro drug release studies**

**In vitro dissolution studies** were carried out for both nelfinav mesylate pure drug and liquid fill formulations for soft gels. The dissolution test helps to study the dissolution characteristics of drug and also measures the rate of release of drug from dosage form. For effective absorption of oral solid dosage forms, the dissolution of drug into surrounding medium plays an important role. It can be looked upon as a tool which provides valuable information about the bioavailability of a drug.[21]-[22]-[23]

**In vitro dissolution studies** were carried out in USP type II (paddle method) dissolution apparatus (DISSO 8000, LAB INDIA) in 900mL of 0.1N HCl as a dissolution medium maintained at 37 ± 0.5ºC, with an agitation speed of 50/100rpm for a period of 60 min. In vitro dissolution studies were performed to assess the dissolution parameters like drug percent released at 2 min (DP\(_2\)), at 4 min (DP\(_4\)), and first order release kinetic data for pure drug and its liquid fill formulations (F1 –F6). Initially, dissolution studies were carried out with NLF in powder form at dosage strength of 250 mg. The DP\(_2\) and DP\(_4\) values for pure NLF were 3.6 ± 0.563 and 6.14 ± 0.461. The cumulative percent of NLF dissolved was found to be 33.97 ± 1.407 at the end of 120 min. All the dissolution studies were carried out in triplicate and in each case mean values and standard deviation values were calculated.

**Selection of Apparatus, paddle/basket**

In the present study, the effect of apparatus (Basket and paddle) on drug release from F1 was studied maintaining the speed at 50 rpm. The cumulative percent NLF released was 99.52 ± 0.672 and 99.71 ± 0.88 in the case of basket and paddle methods at the end of 20 min and 15 min respectively. Hence paddle method was selected. When paddle method was used the initial burst release at the end of 10 min was 85.01 ± 1.54 %, whereas it was 69.18 ± 3.22 % for basket method. From the above results it was clear that the initial burst release and cumulative % NLF released in case of paddle with sinker method was higher when compared to basket method. This may be due to the fact that in the paddle apparatus, the drug released has more surface area to get distributed in the entire dissolution bowl. In the basket method, initially the drug released has less surface area in the basket to get uniformly distributed throughout the bowl. This is according to Fick’s law of diffusion.
Therefore keeping in view of the dissolution profile obtained with paddle method, further studies were carried out using paddle method to obtain ideal and reproducible dissolution rates.

Selection of rpm
Agitation speed plays a vital role in drug release characteristics. Agitation speed affects the release of drug from the dosage form and there by its dissolution in the dissolution medium. Therefore agitation speed is one of the crucial variables that affect the dissolution rate of the drug.

In the present investigation, the effect of agitation speed on drug release profiles of F1 and F2 was evaluated. F1 and F2 were evaluated with agitation speeds of 50 and 100 rpm. The cumulative percent NLF release from F1 was 99.71 ± 0.88 and 99.94 ± 0.64 with 50 and 100 rpm respectively. The cumulative % NLF released in the case of F2 was 99.91 ± 0.32 and 99.94 ± 0.64 with 50 and 100 rpm respectively.

When 50 rpm was applied the initial burst release at the end of 5 min from F1 was 44.3 ± 1.94%, whereas it was 78.54 ± 1.47 % at the end of 4 min when 100 rpm was applied for F1 respectively. For formulation F2 when 50 rpm was applied the initial burst release at the end of 4 min was 36.19 ± 1.430, whereas it was 100.79 ± 0.28 % when 100 rpm was applied respectively. Hence, from the above results it was clear that the initial burst release and cumulative % NLF release from F1 and F2 with 100 rpm was higher and faster when compared to values at 50 rpm. This may be due to faster drug release at higher agitation. From the above dissolution profiles obtained with 100 rpm, further studies were carried out with 100 rpm as agitation speed to obtain ideal and reproducible dissolution rates.

Effect of PVP K-30 and Tween 80 on dissolution of NLF
PVP K-30, which inhibits the precipitation of NLF if any and affects the dissolution rate of NLF was used in all the formulations at different concentrations. In all the liquid fill formulations it was majorly used as viscosity modifier to maintain the gel consistency.

In this investigation, the NLF release profiles of formulations containing with and without PVP K 30 were evaluated at 100 rpm agitation speed. In F1, F2 and F3 formulations 10% PVP K-30 was used. In F1 formulation antioxidant was not used. In F2,F3,F4,F5,F6 antioxidant (0.1% BHT) was used. F2 was formulated with 10 percent Tween 80 and F3 with 5 percent Tween 80.Formulation F3 had more percent of propylene glycol compared to F2. The DP 4 and DP 4 values for these liquid fill formulations F1, F2 and F3 were 53.16 ± 3.547, 81.74 ± 2.782, 41.78 ± 1.979 and 78.54 ± 1.477, 100.79 ± 0.287, 71.62 ± 1.755 respectively. Formulation F2 showed more results. F3, even though PG concentration was more, showed prolonged dissolution upto 8 min because of less percent of Tween 80 than F2. Tween 80 is a non-ionic surfactant used as solubility enhancer.

A 12.78, 16.40, 11.65 folds increase in DP 4 values was observed with formulations F1, F2 and F3 respectively, when compared to pure NLF data. Formulation F2 contains ten percent Tween 80. Tween 80 is a non-ionic surfactant used as a solubility enhancer through micellar solubilisation technique. The critical micellar concentration of Tween 80 is 0.03 percent. Above critical micellar concentration, Tween 80 shows solubility enhancing action. The solubilizing action of Tween 80 increases with increase in its concentration. Surfactants are amphiphiles having both lipophilic and hydrophilic portions within the same molecule. At low concentration surfactant molecules exist independently and at high concentration they form aggregates called micelle. The concentration at which micelle are formed is known as critical micellar concentration. At CMC, physical properties of surfactant such as surface tension, interfacial tension, osmotic pressure, electrical conductance change sharply. HLB value of Tween 80 is 15. Tweens are hydrophilic in nature and have high HLB values. Formulation F2 with ten percent Tween 80 got best dissolution release than F3 with five percent Tween 80.

In F4, F5 and F6 formulations, further studies were carried out to study the effect of concentration of PVP, in the range of 0%, 5%, 15% w/w respectively. The DP 4 and DP 4 values for these liquid filling formulations F4, F5, F6 were 70.86 ± 3.363, 89.02 ± 2.365, 40.02 ± 2.618 and 99.04 ± 0.810, 100.18 ± 0.380, 69.79 ± 0.964 respectively. When PVP K-30 concentration was increased in F6 to 15%, the dissolution was prolonged to 10 min even with 100 rpm agitation speed which may be due to high viscosity of the formulation that inhibits drug release.

A 16.11,16.30,11.35 folds increase in DP 4 values was observed with formulations F4, F5 and F6 respectively, when compared to pure NLF data.

From the comparison of the above six formulations, DP 4 values for F2, F4, and F5 have 100 % release. F4 with zero percent PVP K-30 due to low viscosity was eliminated from the study. Formulation F2 (10% PVP K-30) was selected because it showed 100 % drug release within 4 minute interval along with good gel consistency. F5 with only five percent PVP K-30 was also discarded from the study because of lack of optimum gel consistency. Finally F2 was regarded as the test formulation. F2 and F5 were compared for release profiles and release kinetics.
**First order release kinetics**

The dissolution data were analyzed as per zero order and first order kinetics in each case. The $r^2$ values were higher in the first order model than in the zero order models indicating that the release of NLF from these liquid fill formulations followed 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. First order kinetic values were significantly higher for NLF liquid filling formulations compared to NLF. The results are given in Table 5.17. The ‘$k$’ (min$^{-1}$) values for pure NLF and its formulations F1, F2 were 0.018, 0.109, 0.103 at 50 rpm and F1, F2, F3, F4, F5, F6 were 0.375, 0.818, 0.269, 0.614, 0.877, 0.371 at 100 rpm. The effect of agitation speed on ‘$k$’ values was also studied. The ‘$k$’ values for formulations F1 and F2 were 0.109, 0.103 at 50 rpm and whereas at 100 rpm the values were 0.375, 0.818. A 7.9 folds increase in ‘$k$’ value for F2 at 100 rpm compared to F2 at 50 rpm.

A 1.32, 2.2 folds increase in ‘$k$’ value was observed for formulation F2 (10% PVP) when compared to formulations F4 (0% PVP) and F6 (15% PVP) respectively. The ‘$k$’ values are significantly higher for liquid fill formulations containing PVP K-30 when compared to formulations without PVP K-30.

The order of coefficient of determination ($R^2$) values for all the formulations was F2>F4>F6>F3>F1>F5. In F2 formulation the $R^2$ values are higher and it indicates that F2 has superior release characteristics at 100 rpm speed among all the liquid fill formulations and also compared with 50 rpm. This may be due to more uniform release of the drug from the F2 formulation that followed first order because of optimized concentration of excipients.

Finally, the release kinetics showed that F2 best fits the first order release kinetics among all formulations. The viscosity modifier, PVP K-30 was added in this formulation as per the specified limits and better release of NLF was observed compared to remaining formulations.

**IV. CONFLICT OF INTEREST**

The authors declare that they have no conflict of interests.

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