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LIQUISOLID TECHNIQUE: A REVIEW

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ABSTRACT: Dissolution of drug and its release from the dosage form have basic impact on bioavailability. Bioavailability depends on solubility of drug. Solubility is major challenge for the pharmaceutical industry with the developments of new pharmaceutical products. There are several approaches for solubility enhancement which includes micronization, Nanonisation, use of salt forms, use of surfactant, solid dispersion, and supercritical fluid recrystalization etc. Liquisolid technique is novel and efficient approach for solubility enhancement. According to this method the conversion of water insoluble drug into dry looking, non adherent, free flowing and acceptably compressible powder by incorporating into suitable non volatile solvents, carrier material and coating materials. This free flowing powder is than subjected to Preformulation studies like Fourier transformed infrared spectroscopy, differential scanning Calorimetry for compatibility studies , angle of slide, flow properties, solubility studies, calculation of liquid load retention potential, liquid load factor etc. These free flowing powders are subjected to compression for tablet or filled in capsules. The mechanism for solubility enhancement includes increase in wettability and surface of drug available for dissolution. This method is efficient, economic, viable for industrial production, also useful in control drug delivery system. Hence due to above reasons liquisolid technique is most efficient and novel approach for solubility enhancement.

INTRODUCTION: Solubility of drug is one of the important parameter for bioavailability of drug. In recent years, approximately 70% of new drugs candidate and 40% of marketed new drugs in oral immediate release dosage form exhibits low aqueous solubility. [1] Mainly oral route is preferred for administration of the drugs because of patient compliance, convenience and low cost factor. When oral route for administration of the drug is chosen then that drug should be sufficiently dissolved in gastric fluids for its proper absorption.

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If the drugs have less solubility in the gastric fluids then it will be less available for its absorption and due to this its bioavailability will be less. Thus, one of the greatest challenges the pharmaceutical industries faces today is the application of technological strategies towards improving the dissolution performance of drugs, producing formulations with adequate bioavailability and therapeutic effectiveness.

Several methods are studied for increasing dissolution performance and bioavailability including micronization, Nanonisation, complexation with cyclodextrins, solid dispersion, self emulsifying system, liquisolid systems etc.

Various methods used for enhancing solubility and thus bioavailability of drug are: [2, 3]

1. Micronization: This process involves reducing the size of the drug particles to 1 to 10 microns commonly by spray drying or by use of air attrition methods (fluid energy or jet mill).The process is also called as micro milling. *e.g.* micronization of griseofulvin.

2. Nanonisation: It is the process in which drug powder is converted in to nanocrystals of sizes 200-600nm. *e.g.* amphotericin B.

There are three basic technologies currently in use to prepare nanoparticles.

- Pearl milling
- Homogenisation in water (wet milling as in a colloid mill)
- Homogenisation in non aqueous media

3. Use of surfactants: Surfactants are very useful as absorption enhancers and enhance both dissolution rate as well as permeability of drug. They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles.

4. Use of salt forms: Salts have improved solubility and dissolution as compared to the original drug. Alkali metal salts of acidic drugs like penicillin and strong acid salts of basic drugs like atropine are more water soluble than parent drugs.

5. Supercritical fluid recrystalization: Supercritical fluids (*e.g.* carbon dioxide) are the fluids whose temperature and pressure are greater than their critical temperature (Tc) and critical pressure (Tp), allowing it to assume properties of both liquid and gas. At near critical temperature, SCFs are highly compressible allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that determines its solvent power. Once drug particles solubilised in SCFs, they may be greatly recrystallised at greatly reduced particle sizes.

4. Solid dispersion: These are generally prepared by solvent or co precipitation method whereby both the guest solute and carrier solvent are dissolved in common volatile solvent system such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which result in amorphous precipitation of guest in a crystalline carrier.

5. Complex with cyclodextrins: The beta and gamma cyclodextrins and their several derivatives have unique ability to form molecular inclusion complexes with hydrophobic drugs having poor aqueous solubility. *e.g.* thiazide diuretics, barbiturates, benzodiazepines and number of NSAIDs.

6. Use of Amorphous, Anhydrates, Solvates and Metastable Polymorphs: Depending upon internal structure of solid drugs, selection of proper form of drug is with greater solubility is important. In general amorphous are more soluble than metastable polymorphs, anhydrates are more soluble than hydrates and solvates are more soluble than non-solvates.

Liquisolid technique: A liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents, into dry, non-adherent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials.

Need of liquisolid technique: The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. Thus, one of the major challenges to drug development today are poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. The dissolution rate of these drugs can be improved by decreasing particle size, decreasing crystallinity, and/or increasing the surface area. Several studies have been carried out to increase the dissolution rate of drugs by decreasing the particle size, by creating nanoparticles and microparticles. However, the fine drug particles have high tendency to agglomerate due to Vander Waals attraction or hydrophobicity, which both result in a decrease in surface area over time. Another way of increasing the dissolution rate is adsorption of the drug onto a high-surface area carrier. In this technique, the drug is dissolved in an

organic solvent followed by soaking of the solution by a high surface area carrier such as silica. Here, agglomeration of the drug particles is prevented due to the binding of drug to the carrier. However, due to the presence of the residual solvent in the drug formulation, it is disadvantageous to use toxic solvents. To overcome the problem, the technique of 'liquisolid compacts' is a new and promising approach towards dissolution enhancement.

Concept of liquisolid technique: When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibres in its interior as cellulose, both absorption and adsorption take place; *i.e.* the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.

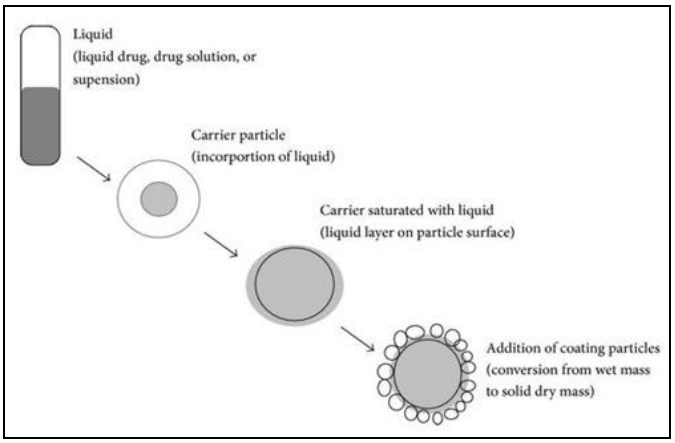

FIG. 1: SCHEMATIC REPRESENTATION OF LIQUISOLID SYSTEMS

Mechanism of enhancement of solubility: [1, 15]
The wettability of the compacts in the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non-volatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. Thus, due to substantial increase in wettability and effective surface area for dissolution, liquisolid compacts may be expected to reveal enhanced release profiles of water-insoluble drugs. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. However, the drug release profile entirely depends on the characteristics of drug, carrier and vehicle used. Thus by altering these variables, liquisolid technique can be used for enhancing or retarding the drug release.

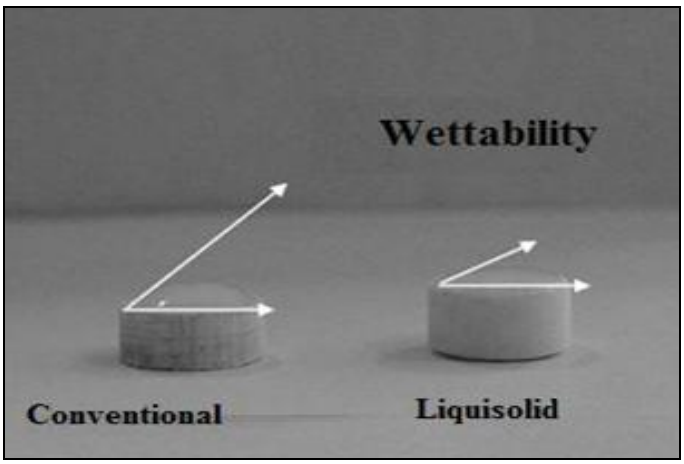

FIG. 2: COMPARISON OF WETTABILITY OF CONVENTIONAL AND LIQUISOLID TABLETS. [15]

Merits of liquisolid techniques: [8, 9]

- Number of water-insoluble solid drug can be formulated into liquisolid systems.
- Can be applied to formulate liquid medication such as oily liquid drugs.
- Simplicity.
- Better availability of an orally administered water insoluble drug.
- Lower production cost than that of soft gelatin capsules.
- Production of liquisolid system is similar to that of conventional tablets.
- Viability of industrial production.
- Can be used for formulation of liquid oily drugs.
- Exhibits enhanced in-vitro drug release as compared to commercial counterparts, including soft gelatin capsule preparations.
- Can be used in controlled drug delivery.
- Optimized sustained release, liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates (zero order release).

- Drug can be molecularly dispersed in the formulation.

Demerits of liquisolid techniques: [9]

- Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique.
- In order to achieve acceptable flowability and compactability for liquisolid powder formulation, high levels of carrier material and coating materials should be added. This will increase the weight o tablets to above one gram which makes them difficult to swallow.

Classification of liquisolid techniques: [15]

Based upon liquid medication used:

- Powdered drug suspension.
- Powdered liquid drug
- Powdered drug solutions.

Based upon technique of formulation:

- Liquisolid Microsystems.
- Liquisolid compacts.

Components of Liquisolid formulations and selection criteria:

Drug candidate: Mainly liquisolid technique is used for drug candidates comes under class II and class IV drugs. These drugs has low solubility and low dissolution rate. By using liquisolid technology dissolution rate of such poorly soluble drugs get improved by improving their solubility. *e.g.* Digitoxin, Digoxin, Prednisolone, Hydrocortisone, Famotidine, Spironolactone, Indomethacin, Carbamazepine, Piroxicam, Naproxen, Polythiazides, Chlorpheniramine. etc.

Non volatile solvent:

Ideal characteristics:

- It should be inert.
- It should have high boiling point.
- It should be preferably water miscible.
- It should not be highly viscous organic solvent system.
- It should be compatible with having ability to solubilise the drug.
- The non volatile solvents used in the liquisolid system mainly acts as binding agent.
- *e.g.* PEG 200, PEG 400, Polysorbate 80, Propylene glycol, Glycerine etc.

Carrier materials: Carrier materials should be sufficiently porous so that can enhance absorption properties and hence can absorb liquid sufficiently to enhance the solubility. *e.g.* Avicel PH 102 and 200, Eudragit RL and RS, starch, cellulose, lactose, sorbitol etc.

Disintegrant: Mainly superdisintegrants increases rate of drug release, its wettability and increases solubility of drug particles within short period of time. *e.g.* Sodium Starch Glycolate (SSG), Crosspovidone etc.

Coating material: Coating material should be with high adsorptive property so that when used for coating the carrier particles can absorb the excessive non volatile solvent layer over the carrier particles and can give dry solid appearance to the saturated carrier particles having liquid external layer of non volatile solvent. Hence can give dry, non adherent, free flowing powder particles. *e.g.* Silica of various grades like Cab-o-Sil M5, Aerosil 200, Syloid 244 FP etc.

Formulation of Liquisolid:

It is mainly divided into two categories:

1. Preformulation studies
2. Formulation of liquisolid compacts.

Preformulation studies:

1. Solubility of drug: It is carried out by preparing saturated solution of drug in different solvents. This saturated solution is prepared by adding excess amount of drug in non solvent. This solution is shaken with shaker for specific period of time than it is filtered and analyzed under UV spectrophotometer.

2. Determination of angle of slide: Angle of slide is used as a measure of the flow properties of powders. Determination of angle of slide is done by weighing the required amount of carrier material and placed at one end of a metal plate with a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as angle of slide. Angle of 33º is regarded as optimum.

3. Determination of flowable liquid retention potential (Φ value): The term "flowable liquid-retential potential" (Φ-value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ-value is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably flowing liquid/powder admixture.

The Φ values are calculated according to equation
Φ value = weight of liquid / weight of solid

4. Calculation of liquid load factor (Lf): Different concentrations of non-volatile solvents are taken and the drug is dissolved. Such liquid medication is added to the carrier coating material admixture and blended. Using equation (2) drug loading factors are determined and used for calculating the amounts of carrier and coating materials in each formulation.

Lf = weight of liquid medication / weight of carrier material… (2)

5. Liquisolid compressibility test (LSC): Liquisolid compressibility test is used to determine Φ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid or powder admixtures, compressing each liquid or powder admixtures to tablets, assessing average hardness, determination of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Φ value and LF.

Formulation of liquisolid compacts: It is one of the novel techniques which is used for solubility enhancement and bioavailability of poorly water soluble drug. It is first described by Spires. It is also called as "Powdered Solution Technology". [4]

Steps involved in formulation: [9]

- Suitable drug candidate is dispersed in suitable non volatile solvent like Polysorbate 80, PEG 200 etc. having different Drug: Solvent ratios.
- In this step suitable carrier material with other excipients are added into initial mixture of drug and non volatile solvent. During this continuous mixing in the mortar should be going on.
- In the third step suitable superdisintegrants like sodium starch Glycolate or Crosspovidone is added in the prepared mixture with continuous shaking in a mortar.
- In this step suitable coating material is added which adsorbs the layer of excess non volatile solvent over the carrier material. Due to this the liquid layer gets converted in the solid layer and this gives the dry, non adherent, free flowing powder particles.
- The final mixture is then allowed to compress by using tablet compression machine.
- The prepared liquisolid tablet is then evaluated for its solubility, dissolution, compressibility

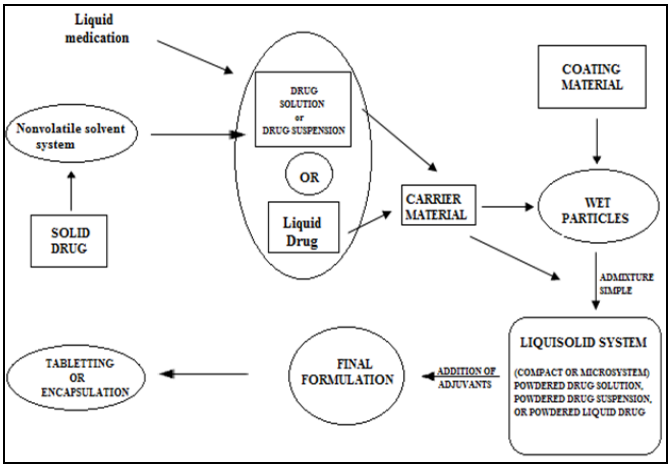

FIG. 3: GENERAL METHOD FOR FORMULATION OF LIQUISOLID COMPACT

Evaluation of liquisolid compacts:

Flow behavior: [8] The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations. Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid systems.

Angle of repose: The angle of repose physical mixtures of liquisolid compacts were determined by fixed funnel method. The accurately weighed physical mixtures of liquisolid compacts were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely into the surface. The height and diameter of the powder cone was measured and angle of repose was calculated.

$$\tan \theta = h/r$$

Where, θ is the angle of repose, h is the height in cms, r is the radius in cms

Bulk Density: The loose bulk density and tapped density were determined by using bulk density apparatus apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$$Db=M/Vb$$

Where, M is the mass of powder
Vb is bulk volume of powder

Tapped Density: The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the. Formula:

$$Dt= M/Vt$$

Where, M is the mass of powder
Vt is tapped volume of powder

Carr's Index (%): The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because all of these ca influence the compressibility index. The simplest way for measurement of free flow of powder is Carr's Index, a indication of the ease with which a material can be induced to flow is given by Carr's index (CI) which is calculated as follows:

CI (%) = [(Tapped density – Bulk density) / Tapped density] x 100

The value below 15% indicates a powder with usually gives rise to good flow characteristics, where as above 25% indicates poor flow ability.

Hausner's Ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's Ratio=Tapped density (ρt) / Bulk density (ρb)

Where ρt is tapped density and ρb is bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones, between 1.25 to 1.5 showing moderate flow properties and more than 1.5 poor flow.

2. Precompression studies of the prepared liquisolid Powder systems: In order to ensure the suitability of the selected excipients, Fourier Transform Infra Red Spectroscopy, Differential scanning Calorimetry, X-ray Diffraction and Scanning Electron Microscope studies are to be performed. In addition, flowability studies are also to be carried out to select the optimal formulae for compression, prior to the compression of the powders the dosage forms such as into tablets and capsules.

3. Fourier transformed infra red spectroscopy: FT-IR spectra of prepared melt granules are recorded on FTIR-8400 spectrophotometer. Potassium bromide (KBr) pellet method is employed and background spectrum is collected under identical situation. Each spectrum is derived from single average scans collected in the region 400 - 4000cm^{-1} at spectral resolution of 2cm^{-2} and ratio against background interfereogram. Spectra are analyzed by software.

4. X-ray diffraction: For the characterization of crystalline state, X-ray diffraction (XRD) patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts. Absence of constructive specific peaks of the drug in the liquisolid compacts in X-ray diffractogram specify that drug has almost entirely converted from crystalline to amorphous or solubilised form. Such lack of crystallinity in the liquisolid system was understood to be as a result of drug solubilisation in the liquid vehicle *i.e.*, the drug has formed a solid solution within the carrier matrix. This amorphization or solubilization of drug in the liquisolid compacts it may contribute to the consequent improvement in the apparent solubility and enhancement of dissolution rate of the drug.

5. Scanning electron microscopy: Scanning electron microscopy shows that there is presence or absence of crystal form of the drug or excipients in the formulation. If SEM shows that there is absence of crystal form of the drug then it shows that now the drug is completely solubilised in to carrier system. After complete formulation liquisolid tablets also get evaluated for wt. variation, thickness, friability, moisture content (by using

Karl Fischer's method), disintegration test, dissolution test and content uniformity.

6. Contact angle measurement: For assessment of wettability, contact angle of liquisolid tablets is measured according to the imaging method. The commonly used method is to measure contact angle directly for a drop of liquid resting on a plane surface of the solid, the so-called imaging method. A saturated solution of the drug in dissolution media is prepared and a drop of this solution is put on the surface of tablet. The contact angles are calculated by measuring height and diameter of sphere drop on the tablet.

7. Stability studies: In stability studies drug content is determined by charging up the crystals of the drug to accelerated stability conditions according to ICH guidelines Q1 R2. In this study samples are taken after each specific interval of the time. These samples are then analyzed by using infra red spectrophotometer or differential scanning Calorimetry.

***8. In vitro* release:** *In vitro* release of liquisolid tablets is carried out by using USP II apparatus at 37 ^{o}C ± 2 ^{o}C. During this study many researchers observed that if there is low drug concentration in liquid formulation then there is rapid drug release from the formulation. If *In vitro* release rates for liquisolid tablets are higher than the absorption rate will also be higher which enhances drug bioavailability.

***9. In vivo* study:** This liquisolid technology is a promising tool for the enhancement of drug release of poorly soluble drugs. The absorption characteristics of Hydroclorothiazide liquisolid compacts in comparison with commercial tablets were studied in beagle dogs. Significant differences in the area under the plasma concentration time curve, the peak plasma concentration and the absolute bioavailability of the liquisolid and the commercial tablets were observed. However, for the mean residence time, the mean absorption time, and the rate of absorption no significant differences were found. The absolute bioavailability of the drug from liquisolid compacts was 15% higher than that from the commercial formulation.

10. Estimation of drug content: The liquisolid compacts are powdered well and equivalent to 10mg of the drug powder is weighed and diluted using suitable solvent. The drug content is analyzed using UV-Visible spectrophotometer. [6]

Storage and packaging: [17]

1. The quality of the packaging of pharmaceutical products plays a very important role in the quality of such products. It must:

- protect against all adverse external influences that can alter the properties of the product, *e.g.* moisture, light, oxygen and temperature variations.
- protect against biological contamination
- protect against physical damage
- carry the correct information and identification of the product

.

2. The kind of packaging and the materials used must be chosen in such a way that:

- the packaging itself does not have an adverse effect on the product (*e.g.* through chemical reactions, leaching of packaging materials or absorption);
- the product does not have an adverse effect on the packaging.

For liquisolid tablet: blister or strip package.
For capsules: hard gelatin shell
Storage: store at cool and dry place.

Application:

- It is used for enhancing rate of dissolution of the many poorly soluble drugs by enhancing their solubility.
- Bioavailability of many class II and class IV drugs get enhanced by using liquisolid technique.
- Release rates of many poorly water soluble drugs get increased by using liquisolid system.
- It is also used for designing controlled drug delivery system.
- Liquisolid technique is also successfully used for the formulation of many water insoluble or liquid lipophilic drugs.
- It is also used to formulate sustained release dosage form

CONCLUSION: Various methods are studied to improve water solubility and drug release, among which the liquisolid technology is one of the most promising approaches. With this technology liquids such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders by simple physical blending with selected excipients named the carrier and the coating material. As highest drug release rates are observed with liquisolid compacts containing a drug solution as liquid portion, liquisolid compacts may be optimized by selection of the liquid vehicle and the carrier and coating materials. The addition of Disintegrant may further accelerate drug release from liquisolid compacts. The liquisolid technology may also be used for the preparation of sustained release formulations with zero order release pattern. Thus, a constant plasma level will be reached, which is maintained throughout the dosing interval. For sustained release liquisolid compacts, the selection and the concentration of the excipients such as liquid vehicle, retarding agent (matrix forming material) as well as carrier and coating material play an important role. The liquisolid approach is a promising technology because of the simple manufacturing process, low production costs and the possibility of industrial manufacture due to the good flow and compaction properties of liquisolid formulation.

CONFLICT OF INTEREST: We have no conflict of Interest.

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