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INFORMATIVE REVIEW OF LAYERED TECHNOLOGY OF TABLET- AN EMERGING INNOVATION IN ORAL DRUG DELIVERY SYSTEM

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ABSTRACT

Oral route is most popular method of drug administration. Tablets are designed to deliver a precise dosage to a particular location in the body. They can also be given sublingually, buccally, rectally, or intravaginally. In addition to convenience, it has the benefit of improved absorption. Tablet is the most commonly utilized dosage form because of its durability and patient acceptability. These dosage forms stand out and are preferred over other forms due to their superior aesthetic qualities, such as color, texture, mouth feel, and flavor masking capabilities. Layered tablets typically increase patient compliance and lower production costs in half. Drugs with release boosters, fillers, or numerous dosages of the same drug are all examples of layered technology. This technology usually contains two to three APIs or APIs along with functional or nonfunctional placebo layers. Layered tablets provide more promise for improved patient outcomes and continue to be production-friendly. Comparing multi-layer tablets to conventional immediate-release reveals many significant advantages. By streamlining dosing regimens in combination therapy, the use of such solid oral dose forms increases patient compliance day by day. This study reviews the primary advantages of the layer stressing its key advantages as an oral dosage form as well as outlining its current difficulties and strides in product quality and manufacturing process improvement.

KEYWORDS: Bilayer tablet, combination drugs, incompatible, multi-layered tablet, drug release kinetic.

INTRODUCTION

Oral route is the most common and preferred way to administer medications. There are numerous formulas on the market. They can exist as semi-solids, liquids, or solids. When creating a formulation, one of the most important things to take into account is its pharmacological stability. This route is well-known for its simplicity, self-medication, patient compliance, and diversity in terms of readily available dosage forms.[1] Solid dosage forms are thought to make up about 90% of all dosage types utilized to deliver therapeutic substances to the body systemically. Depending on the patient's administration or presentation technique, pharmaceutical tablet varies. There are many factors that are important for customer acceptance of a tablet, including its general appearance, visual identity, and overall style. Tablets can be found in different sizes, shapes, colors, odors tastes, surface textures, physical flaws, consistencies, and identifying markings.[2] A layered tablet is a combination of one or more APIs (Active Pharmaceutical Ingredients) with auxiliaries, cast in two or more layers into a single whole dosage form. Formulating a combination of drugs into a single dosage form is valuable for treatment. A notable feature is that the drug is released without pharmacokinetic interactions with the individual issue rates. This can greatly help minimize the frequency of dosing and can increase the synergistic effect.[3] Layered tablets are currently being produced by a number of pharmaceutical companies due to the numerous therapeutic benefits of reducing the number of doses required. These tablets also have the added benefit of being more production-friendly. The multilayer tablet is a recent successful idea development of a controlled-release formulation with several properties that provide the opportunity for a successful drug delivery system.[4] They consist of an active matrix core and one or more layers applied during tableting which may act as barriers and regulate drug release.[5] Bi-layer tablet is suitable for the sequential release of two drugs in combination, separate two incompatible substances, and also for sustained-release tablets in which one layer is immediate release as an initial dose and the second layer is the maintenance dose.[6] The design feature provides, unique product performance objectives otherwise not achievable by conventional tablets, but also brings a new set of challenges for formulation design, manufacturing process, controls, and product life performance requirements.[7] Challenges during development include layer weight ratio, first layer tamping force, elastic mismatch of the adjacent layers, and cross-contamination

between layers.[8] Moreover, the other challenges associated here are delamination at the interface between the layers caused by insufficient adhesion, the incomplete separation of tablet portions, the relatively low yield compared to traditional single-layer tablets, and the challenge of achieving the desired weight of individual layers with multilayer tableting. Furthermore, if the compressed layers become excessively soft or too rigid, they will not connect properly with each other, compromising their structural strength.[9] So the purpose of this review was to discuss all things the layered tablet like- objectives, advantages, and limitations of the layered tablet, types, manufacturing technology, and challenges in layered tablet manufacturing.

Layered tablet

A layer tablet is made up of two to three layers of compressed granulation. Each layer's borders are visible, giving them a sandwich-like look. This particular dosage form has the special benefit of putting an inert barrier of separation between two incompatible APIs.[10] There may be a decrease in the need for excipients like fillers when two or more medications are provided in a single dosage form. In the case of long-term care and various pharmacological therapies, layered tablets are strongly desired. To maintain a stable plasma concentration when a mixed-release approach is used a rapid initial release of the medication followed by a slow release is necessary.[11] There are mainly two types of layered tablets used in pharmaceutical industries.[12]

A. Bi-layer tablets

B. Tri-layer tablets.

Rationale of multi-layered tablet[13]

- To regulate the delivery rate of either a single or more different active pharmaceutical ingredients.
- To provide synergistic effects.
- As the layers are typically various colors, these layered tablets also provide high product identification, making it simple for patients to recognize the tablets.
- There may be a decrease in the need for excipients when two or more medications are provided in a single dose form.
- The life cycle of the drug product can be extended by layering active pharmaceutical ingredients with one or more excipients (polymers) to create erodible or swellable barriers for drug release modification. Additionally, different APIs can be administered by fixed-dose combinations.
- To separate incompatible Active pharmaceutical ingredients (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as osmotic property).
- Multi-layered tablet dosage forms are also designed for a variety of reasons: patent extension, efficient pharmacological effect, better patient compliance, etc.

Problems associated with conventional dosage forms[14]

- Repeated dosing
- Poor bioavailability
- Dose dumping
- Poor bioavailability
- Poor absorption
- An early expulsion from the body
- Fluctuation of plasma drug concentration

Ideal properties of layered tablet[15][16]

- It needs to be stable enough chemically and physically to keep its physical properties throughout time.
- The therapeutic components must be capable of controlled, recurrent release.
- Layered tablets must possess a sophisticated brand identity and be devoid of imperfections like chips, fractures, contamination, and color changes.
- It should be strong enough to withstand mechanical shock while being manufactured, stored, transported, and administered.
- Should have a stable chemical composition and shelf life to avoid causing the therapeutic agents to change.

Advantages[17],[18],[19]

- They enable the integration of various release profiles and separate APIs that are incompatible.
- The great advantage is different APIs in combination have proven advantages over single compounds administered separately for therapeutic effect and get a dual release profile so as to reduce dosing frequency and thereby increase patient compliance.
- They are unit dosage forms and provide the best properties of all oral formulations' highest dosage accuracy and the lowest variation of content**.**
- A drug's blood level can be maintained at a therapeutic level for increased drug delivery, safety, accuracy, and side effect reduction.
- Multilayer tablet enables a sustained-release formulation with an immediate-release portion in the first layer and a sustained-release portion in the second layer. A third tier of intermediate releases can be added.
- Compared to other oral dose forms the cost is lower easiest, and least expensive to strip and package.

Limitation[20]

- The layers should be able to bind the formulation together well enough. High throughput pre-formulation and planning are necessary for this.
- Long-term physical and chemical integrity throughout the shelf life.
- Other challenges during development include establishing the order of layer sequences.
- Each layer must have certain properties tested, such as hardness and thickness.

- Layered tablets are more expensive to produce since high work intensity and sophisticated equipment are required.

Bilayer tablet

Bi-layer tablets are medicines that consist of two same or different drugs combined in a single dose for effective treatment of the disease. One of its layers is made to ensure the instant release of the drug and aims to reach a high serum concentration in a brief time. Its second layer is a controlled-release hydrophilic matrix that aims at maintaining an efficient plasma level for a long time.[21]

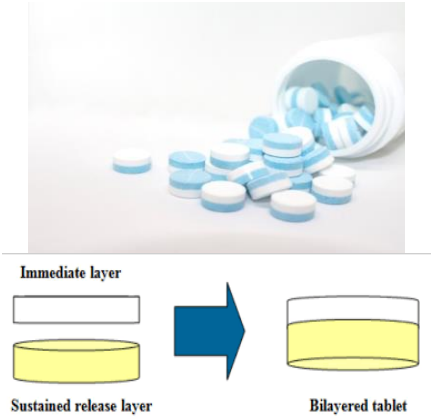

Fig 1: Bi Layered Tablet.

Quality and good manufacturing practice (GMP) requirements of bi-layer tablets

- Avoid capping and separating the two distinct layers that make up the bi-layer tablet. Ensuring adequate tablet hardness.[22]
- Unique and precise weight control for the two layers. Although they appear straightforward, these criteria are more difficult to meet.[23]
- Manufacturing bilayer tablets with no contamination transferring among the two layers.[24]
- Due to the tiny compression roller, the initial layer-dwell time was very short, which might have an impact on de-aeration, capping, and hardness issues. This can be fixed by slowing the turret's spin (to increase the dwell time), but the result will be reduced tablet production.[25]

Classification of bi-layer tablet

The concept of bi-layered tablets refers to tablets that include either the same (homogeneous) or various (heterogeneous) subunits.

A. Homogeneous: Bilayer tablets are preferred when the release patterns of the drugs vary from one another. A layer of the drug in bilayer tablets is meant for immediate release, while a second layer is meant for the medication to be released later, either as a second dosage or in an extended-release form.[26]

B. Heterogeneous: Heterogeneous type bi-layer tablets are fabricated for sequential release of two incompatible drugs in combination.[27]

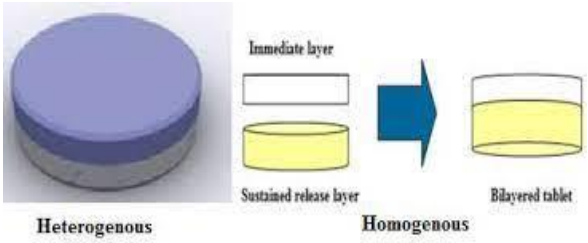

Fig. 2: (With Two Different Drugs- Heterogenous) and (Same Drug with Different Release Pattern-Homogenous).

Types of bilayer tablet press

A. Single-sided tablet press.
B. Double-sided tablet press.
C. Bilayer tablet press with displacement

A. Single-sided tablet press

A single-sided press with the two chambers of the doublet feeder separated is the most basic type. Each chamber is gravity or force-fed with a variable amount of power, resulting in two distinct layers of tablets. When the die passes beneath the feeder, the first layer of powder is filled first, followed by the second layer of powder. The tablet is then compacted in one or two processes.[28]

B. Double-sided tablet press

Compression force is used for tracking and controlling tablet weight in most double-sided tablet presses with automated production control. The control system measures the effective peak compression force applied on each individual tablet or layer during major compression of the layer. When out of tolerance, the control system uses this measured peak compression force to reject it and rectify the die fill depth.[29]

C. Bilayer tablet press with displacement: The principle of bilayer tablet press differs significantly from the principle of compression force. In this situation, when the compression force is lowered, accuracy improves. The danger of capping and separation rises as production speed increases however, it can be mitigated by allowing enough dwell time in tall four compression stages.[30]

VARIOUS TECHNOLOGY FOR BILAYER TABLET

Oros push-pull technology

This system primarily consists of two or three layers, of which one or more layers are necessary for the medication and the remaining layers are push layers. The primary components of the drug layer are drugs and two or more diverse agents. As a result, the medication in this layer is in a relatively insoluble form. Osmotic and a suspending agent have also been added. The tablet core is surrounded by a membrane that is semi-permeable.[31]

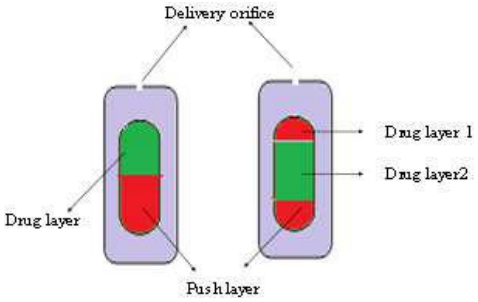

Fig 3: Oros push pull technology.

L – oros Tm technology

This method was used to address the solubility difficulty. Alza created the L-OROS system, in which a lipid soft gel product including medicine in a dissolved condition is first created and then coated with a barrier membrane, an osmotic push layer, and a semi-permeable membrane drilled with an escape hole.[32]

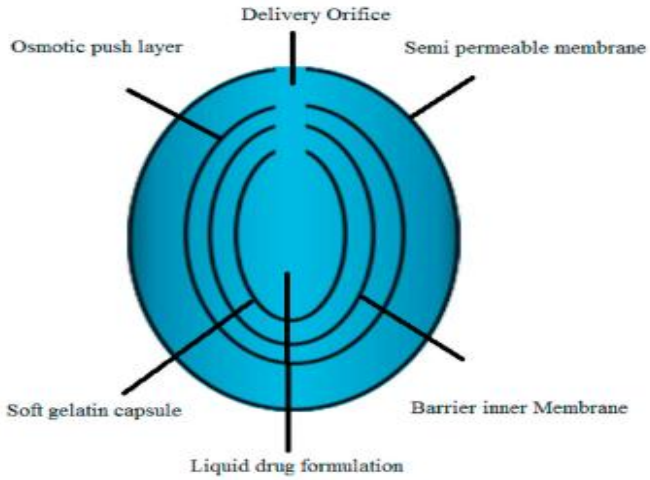

Fig 4: L – oros Tm technology.

En so trol technology

Shire Laboratory uses an integrated strategy for drug delivery with an emphasis on the discovery and implementation of the discovered booster into controlled release technologies to increase solubility by an order larger or to generate optimum dosage forms.[33]

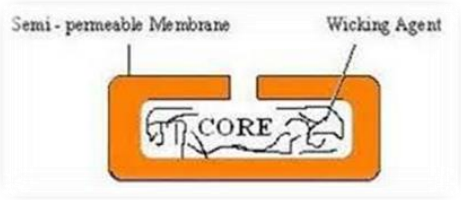

Fig 5: En So Trol Technology.

Duros technology

An exterior cylindrical titanium alloy reservoir makes up the system. High impact strength and enzyme protection are provided by this reservoir. The DUROS technique uses a tiny needle to deliver a continuous stream of concentrated liquid over the course of a year or several months.[34]

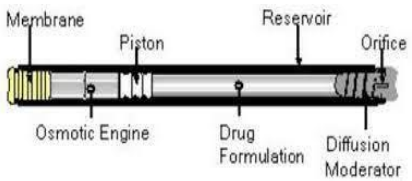

Fig. 6: The duros technology.

Geminex technology

This method significantly improves the therapeutic efficiency of the medications while reducing their adverse effects. It administers one or more medications with various rates of release in a single dosage. Pen West uses it extensively for cardiovascular illnesses, CNS problems, diabetes, cancer, and disorders of the central nervous system (CNS), and it is very advantageous for both patients and the manufacturing sector.[35]

Elan drug technologies' dual-release drug delivery system

The DUREDASTM Technology offers both prolonged release and immediate release of a single medicine, or a mix of sustained release and quick release. This composition combines many controlled-release substances.[36]

Various approaches used in bi-layer tablets[37][38]

Floating drug delivery system

Based on a technical and manufacturing standpoint, floating drug delivery methods are a much simpler and more sensible choice for creating gastro-retentive dosage forms (GRDFs).

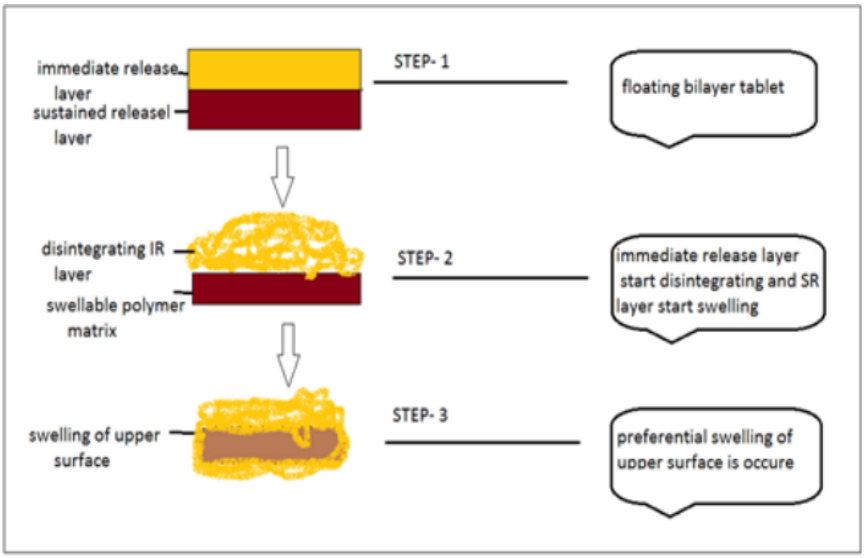

Fig. 7: Release pattern in a floating bilayer tablet.

Polymeric Bio Adhesive System

These are intended to absorb fluid administration such that the outer layer transforms into a viscous, sticky substance that sticks to the mucus layer and gastrointestinal mucosa. While the adhesive forces are being reduced, this should promote stomach retention. One layer of them is designed for quick dosage, and the other layer has a bio-adhesive feature.

Multiple unit type floating pill

These types of systems are made up of two layers around sustained release capsules that act as "seeds." Effervescent agents make up the inner layer while swellable membrane layers make up the outer layer. The system lowers instantly when submerged in dissolving liquid at body temperature, then generates enlarged pills that resemble balloons and float because they have a reduced density.

Swelling System

Tablets are made to be tiny enough when administered that swallowing the dose form won't be challenging. On intake, they expand, break down, or unfold quickly to a size that prevents passage through the pylorus until drug release has reached the necessary stage. It might exit the stomach by gradually eroding away or dissolving into smaller pieces. A basic bilayer tablet may have an instant release layer and a prolonged release layer or a standard release layer between them.

Preparation of bilayer tablets

Bilayer tablets are made with a layer of medication intended for quick release and a second layer intended for delayed or longer release of the medication. It is also possible to produce bilayer tablets with two incompatible medications by compressing individual layers of each drug to reduce the area of contact between the two layers. There may also be a further inert layer added in the middle. Certain conditions, including the required mechanical strength and desirable drug release profile, must be satisfied in order to manufacture an appropriate tablet formulation. Due to the drug's poor flow and compatibility characteristics, it may occasionally be challenging for the formulator to accomplish these parameters, especially when bilayer tablet formulation involves a twofold compression procedure.[38]

Compaction

The method through which a powder's porosity is reduced as a consequence of the granules being compressed together by the force of mechanical methods. Compressibility and consolidation are both factors in a material's compaction.[39]

Compression

It is described as a decrease in bulk volume accomplished by filling voids and bringing particles closer together.[40]

Consolidation

It is a material feature characterized by enhanced mechanical strength as a result of interparticulate contact (bonding). The compression force on layer 1 was discovered to be a significant element determining tablet delamination.[41]

Various steps involved in bilayer tablet formulation are as follows[42]

(1) Filling of the first layer
(2) Compression of first layer
(3) Ejection of upper punch
(4) Filling of second layer
(5) Compression of the second layer
(6) Ejected fully bilayer tablet

Evaluation of bi-layer tablets

The manufactured bilayer tablets from each batch of improved formulation were assessed against the official standard evaluation parameters to ensure proper drug

production and release rate. The following assessment parameters were used:

Size, shape, and thickness
When a compressive load is constant, changes in the die fill, particle size distribution, packing of the particle mix, and tablet weight cause thickness to change, but when a compressive load is variable, thickness changes in response to changes in compressive load. The pill's thickness should remain well within a +5% range of its typical value.

Hardness
The degree of a tablet's hardness indicates how well it can manage mechanical shocks. It is measured (kg/cm^2) using a hardness tester. An average of five duplicate decisions will be calculated.

Friability
A tablet's friability is used to measure its strength. The tumbling apparatus, which rotates at a speed of 25 revolutions per minute and lowers the tablets six inches at a time, will be filled with twenty tablets that have been carefully weighed. After 4 minutes, the tablets will be weighed to determine the amount of weight loss.

Uniformity of Weight
The average weight of twenty tablets will be weighed after a random selection. The weight variance will be determined.

In vitro dissolution studies
The tablet release rate (n=3) will be evaluated using the dissolving testing equipment II (paddle technique) of The United States Pharmacopoeia (USP). The dissolving test will be carried out using 900 ml of dissolution media at 37 ^oC and 75 rpm.

Drug release kinetic
The kinetics of drug release must be assessed since different layers may have different release rates, which can affect the profile. Characterizing sustained release and immediate release patterns is crucial since each layer may display a different rate of release.

Stability studies
The stability of every layer is investigated. There may be varying levels of deterioration between layers. Based on the properties of each layer, shelf life is calculated.

Morphology analysis
Visualization can be used to assess physical attributes. Using cross-section samples, scanning electron microscopy can be used to see the morphological features.

Thermal analysis
The detection of drug-excipient, drug-drug, and excipient-excipient interactions in the formulation is of higher interest when using thermal analysis. Differential Scanning Calorimetry can be used to determine the drug substance's molecular dispersion in the tablet matrix system.

Crystallinity
Drug stability, solubility, and a number of other Physico-chemical properties are directly influenced by the crystalline and amorphous structure of the substance. The X-ray diffractometer (XRD) is used to assess the crystal nature of medicinal compounds at different levels. It is possible to research if the nature of medicine changes from crystalline to amorphous throughout manufacturing or storage.

Challenges in Bilayer Manufacturing[12][43][44]
Bilayer tablets can be conceptualized as a combination of two single-layer tablets. There are various manufacturing difficulties in real life. Such as-

Delamination
When the two tablet parts do not fully join, the tablet will break. When crushed, the two granulations ought to stick together.

Cross-contamination
Cross-contamination happens when the granulation of the first layer mixes with the granulation of the second layer or the other way around. It may defeat the bilayer tablet's fundamental aim. Cross-contamination may be greatly reduced with proper dust collection.

Production yields
Dust removal is necessary to prevent cross-contamination, which results in losses. As a result, single-layer tablets provide higher yields than bilayer tablets.

Cost
For a number of reasons, bilayer tableting is more expensive than single-layer tableting. The tablet press is more expensive, to start. Second, in bilayer mode, the press often operates more slowly. Third, creating two compatible granulations is necessary, which requires extra effort to create, analyze, and validate the formulation. These variables will have an effect on the bilayer compression in general and the quality characteristics of the bilayer tablets (sufficient mechanical strength to retain its integrity and individual layer weight management) in one way or another if they are not effectively regulated or optimized. In order to build a solid product and process, it is crucial to get insight into the underlying reasons.

Individual layer
Inaccurate individual layer weight control and impact of high temperature and humidity on layer adhesion upon storage.

Triple layer tablet

These tablets feature three layers, the first of which indicates an instantaneous release, the second a continuous release, and the third a separation of the two layers that are present in the middle.[45]

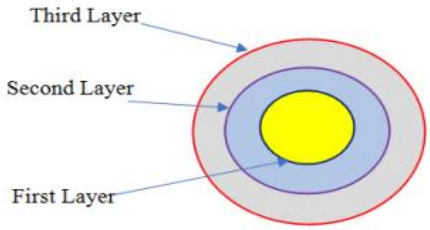

Fig 8: Triple layer tablet.

Typically, controlled-release formulations are used to create three-layer tablets. Such tablets have a drug-filled inner core layer sandwiched between a polymer layer and a barrier layer. Generally, the following geometric adjustments may be used to modulate drug release from the triple-layer matrix system:

- Gradients in drug concentration are created, and the matrix layers are eroded differently.
- Barrier layers restrict the swellable matrix's releasing surface.
- Exterior layers are inflated and differentially eroded to maintain a consistent surface area and continual release.
- Dissolution of the differential layer for pulsatile or quick slow-release applications.[46]

Manufacturing of tri-layer tablets

Tri-layer tablets are made in the same way as bilayer tablets, with the addition of a third hopper used to integrate a third active pharmacological component or a polymer (inert) mix.[47]

Evaluation of prepared three-layered tablets

The uniformity of the tablet thickness, the thickness of the barrier layers, and the in vitro release properties were all assessed for all of the created three-layered tablet formulas.[48]

CONCLUSIONS

Manufacturing of bilayer or tri-layer tablets is one of the great inventions in pharmaceutical technology for oral dosages and it has many advantages. A multi-layered tablet does the same thing better than a single formulation for rapid or long-lasting release. By creating surrounding or multiple swelling layers, multilayer tablet formulations may be utilized to create controlled-release tablet preparations as well as systems for the delivery of incompatible medications. Due to the multilayer technology, there is no need to take multiple tablets at the same time. It is possible to have one or two different functions simultaneously. This technology improves compliance and provides inexpensive capital expenditure and efficient production. Layered tablets continue to be preferred from the standpoints of producers, doctors, and patients. Therefore, more emphasis can be placed on this technology in the future to research this dosage type further.

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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