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REVIEW ARTICLE

Novel Approach of Bilayer Tablet Technology: A Review

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ABSTRACT

Over the past 30 years stated that the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Controlled release dosage forms have been extensively used to improve therapy with several important drugs. Use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. In the case of bilayered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper nonadhesive layer its delivery occurs into the whole oral cavity.

KEYWORDS

Bilayer Tablets, API, OROS Push Pull Technology, DUROS Technology

INTRODUCTION

The bilayer tablet is a concept utilized by Skye Pharma PLC in their Geomatrix tablet, which is composed of different layers. The system allows the incorporation of more than one drug into the dosage form. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependant polymers. There are clearly a number of issues of concern to the production of bilayered tablets.

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While the mechanical strength of layered tablets has been observed not to be a controlling factor in drug release the determination of this property could be beneficial in understanding the adhesion between various layers and provide an improved characterization of the systems.

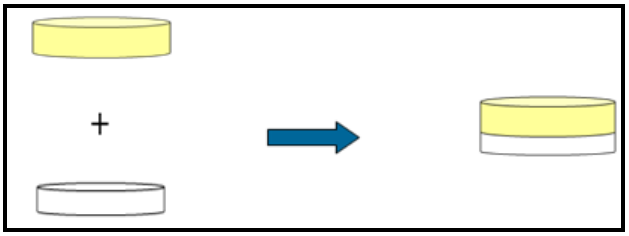

Figure 1: Bilayer Tablet

Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. Bi-layer tablet is suitable for sequential release of two

drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.[1] The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. Control release systems that have been proposed for providing controlled release formulations showing how the different designs can be used to control the drug release profile such as constant, delayed pulsatile and multi modal release profiles.[2] Several different geometries are described and to prepare these by compression will require various strategies.

Advantages of Layered Tablet

1. The administration of sustained release preparation as one layer with the immediate release preparation as the second layer is possible.
2. The separation of two incompatible substances with addition of any barrier layer between them is possible.
3. The widths of each layer can be accurately controlled.
4. Preventing of cross-contamination between two layers.
5. Producing a clear visual separation between two layers.
6. Accurate and individual weight control of two layers.[3,4,5]

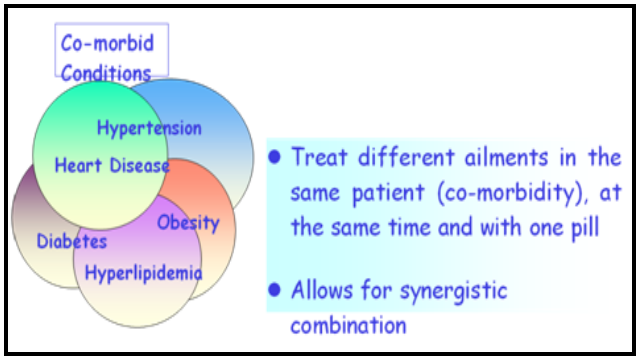

Figure 2: Co-Morbid Condition

Limitations of Layered Tablet

1. Capping.
2. Hardness problem.
3. Layer Separation.[4]

Bilayer Tablets: Quality and GMP Requirements

To produce a quality bilayer tablet in a validated and GMP way it is important that the selected press is capable of,

1. Preventing capping and separation of the two individual layers that constitute the bilayer tablet.
2. Providing sufficient tablet hardness.
3. Preventing cross-contamination between the two layers.
4. Producing a clear visual separation between the two layers.
5. High yield
6. Accurate and individual weight control of the two layers.[5]

Various Techniques for Bilayer Tablet

OROS® Push Pull Technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.[6]

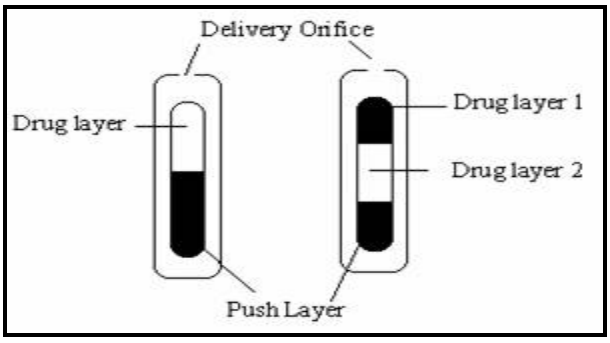

Figure 3: Bilayer And Trilayer OROS Push Pull Technology

L-OROS ™ Technology

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice.[6]

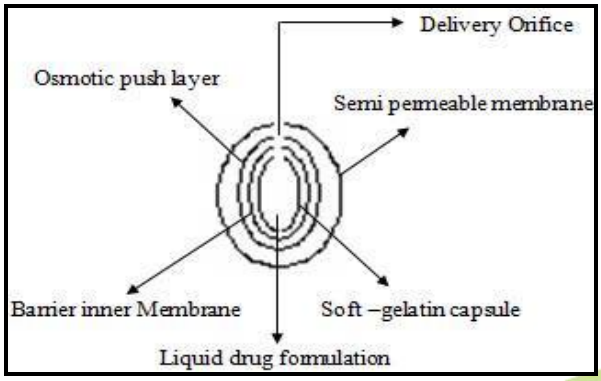

Figure 4: L-OROS ™ Technology

EN SO TROL Technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.[6]

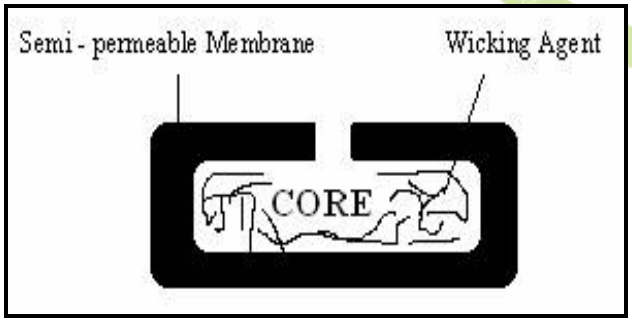

Figure 5: EN SO TROL Technology

DUROS Technology

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or year.[7]

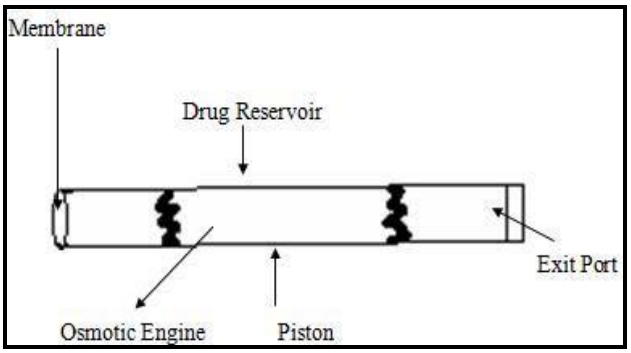

Figure 6: DUROS Technology

Elan Drug Technologies' Dual Release Drug Delivery System

(DUREDAS™ Technology) is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tabletting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.[6]

Benefits Offered by the DUREDAS™ Technology Include

1) Bilayer tabletting technology
2) Tailored release rate of two drug components
3) Capability of two different CR formulations combined
4) Capability for immediate release and modified release components in one tablet
5) Unit dose tablet presentation

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bilayer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be achieved. Typically an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet. This gives the characteristic bilayer effect to the final dosage form. A further extension of the DUREDAS™

technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers and drug release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are possible. A number of combination products utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of a number of OTC controlled release analgesics. In this case a rapid release of analgesic is necessary for a fast onset of therapeutic effect. Hence one layer of the tablets is formulated as immediate releases granulate. By contrast, the second layer of the tablet, through use of hydrophilic polymers, releases drug in a controlled manner. The controlled release is due to a combination of diffusion and erosion through the hydrophilic polymer matrix.[7]

Types of Bilayer Tablet Press

1. Single sided tablet press.
2. Double sided tablet press or "compression force" controlled tablet press.
3. Bilayer tablet press with displacement monitoring.

1. Single Sided Tablet Press

The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or force fed with different powers, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Limitations of Single Sided Tablet Press

- No weight monitoring/control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor de aeration, capping and hardness problems. This may be corrected by reducing the turret- rotation speed (to extend the dwell time) but with the consequence of lower tablet output.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

2. Double Sided Tablet Presses

A double sided press offers an individual fill station, pre-compression and main compression for each layer. In fact the bi-layer tablet will go through four compression stages before being ejected from the press. Most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablet and correct the die fill depth when required.

Advantages

1. Displacement weight monitoring for accurate and independent weight control of the individual layer.
2. Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
3. Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
4. Maximum prevention of cross contamination between two layers.
5. Maximized yield.

Limitations

Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression. Bonding

is too restricted if first layer is compressed at a high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with "compression force measurement". Most of the double sided tablet presses with automated production control use compression force to monitor and control tablet weight. Compression force control system is always based on measurement of compression force at main compression but not at pre-compression.

3. Bilayer Tablet Press With Displacement Monitoring

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre compression force. In fact the lower the pre-compression force, the more the monitoring control system and this ideal for good interlayer bonding of the bi-layer tablet.

Advantages

- Weight monitoring/ control for accurate and independent weight control of the individual layers.
- Low compression force extends on the first layer to avoid capping and separation of the two individual layers.
- Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between the two layers.[8,9]

Bilayer Compression Basics

A. Initial layer die filling and compaction.

B. Initial layer compaction showing the predominant stress transmission profile.

C. Density profile of initial layer before die filling of the final layer.

D. Final layer die filling and compaction.

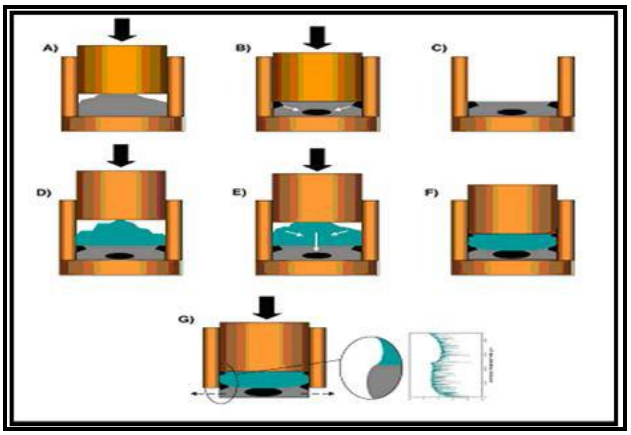

Figure 7: Schematic Diagram Showing the Different Stages Occurring During Bilayer Tablet Uniaxial Compaction

E. Final layer compaction showing the predominant stress transmission profile.

F. Density profile of bilayer tablet before ejection.

G. Ejection of a bilayer tablet.

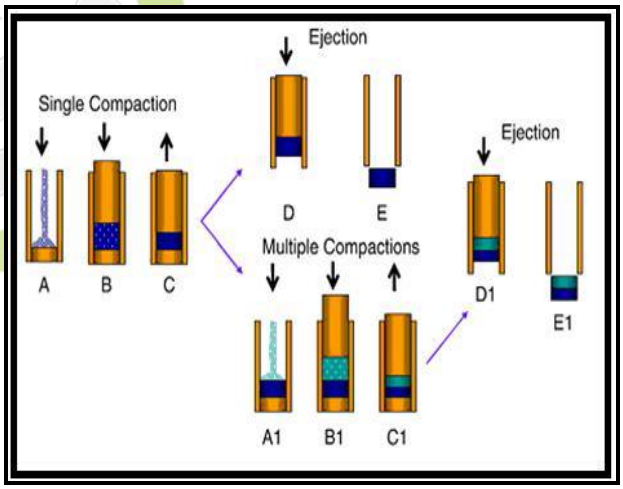

Figure 8: Schematic Diagram Showing the Manufacture of Single and Bilayered Tablets Utilizing Uniaxial Compaction

Dashed arrows show the postulated radial expansion due to energy dissipation. Black areas correspond to regions of localized high density. Arrows show the direction of the applied stress.[10,11]

Manufacturing Process of Bilayer Tablet

Manufacturing processes such as wet granulation/roller compaction and addition of

binders increases the level of complexity in understanding the critical factors governing compression and tablet breaking force. Thus, the tablet breaking force and the tablet's propensity for delamination/capping either during manufacturing or during storage need to be carefully observed.

Apart from the critical material attributes of individual components and final blend, the tablet press has large influence on the manufacture of multilayer tablets. The level of precompression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have significant effect on the critical quality attributes of the tablet.

For instance, the extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity.[12]

Compaction

To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met.

At times, this may be difficult task to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

Compression

It is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation

It is the property of the material in which there is increased mechanical strength due to interparticulate interaction (bonding). The compression force on layer one was found to be major factor influencing tablet delamination.

Compression Force for Bilayer Tablets

Since the material in the die cavity is compressed twice to pro- duce a bi-layer tablet, compressed first with layer one followed by both the layers, the compression force affects the interfacial interaction and adhesion between the two layers. A certain amount of surface roughness of the initial layer is required for particle interlocking and adhesion with the second layer. As the surface roughness of the first layer is reduced, the contact area for the second layer is significantly reduced at the interface and makes the adhesion weaker. Immediately after final compaction, the compressed second layer may release the stored elastic energy unevenly and may produce crack on the first layer which could act as a stress concentrator and eventually making the tablet interface weaker. This may result in capping or de-lamination of the tablet along the interface either during manufacturing or immediately after the level of compression force used in the first layer compaction determines the degree of surface roughness of the first layer.

The higher the first layer compression force, the lesser the surface roughness resulting in reduced adhesion with the second layer. Therefore, for a given final compression force the strength of interfacial adhesion decreases with the increasing first layer compression force. It implies that the extent of plastic/elastic deformation of the first layer has profound effect on the strength of the interface. Thus, understanding the interaction and adhesion behavior between different layers composed of various ingredients with differing physico-chemical properties during compaction is critical to understand the failure mechanisms of bi-layer tablets. Understanding of material attributes of the excipients and API that undergo

compression and compaction is decisive in predicting the interaction.[13]

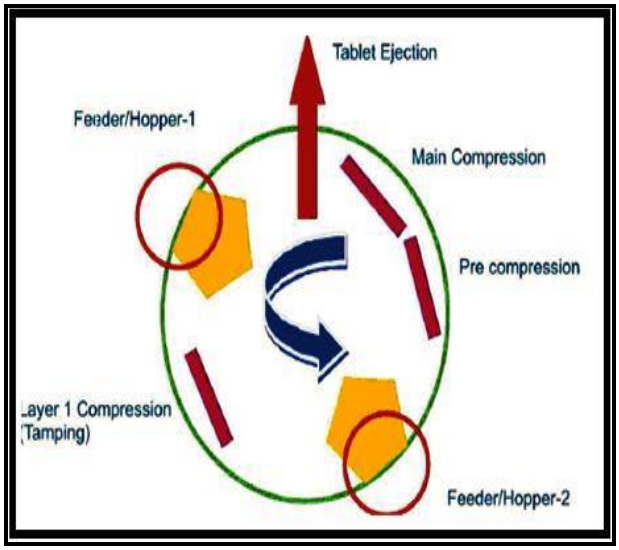

Figure 9 : Bilayer Compression Process

Evaluation of Bilayer Tablets

General Appearance

The general appearance of a tablet, its visual identity and overall 'elegance' is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.[13,14]

Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.[14]

Tablet Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.[13]

Weight Variation

Standard procedures are followed as described in the official books.

Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress the loss in the weight of tablet is the measure of friability and is expressed in percentage as[13,14]

% Friability = 1- (loss in weight / Initial weight) X 100

Hardness (Crushing Strength)

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. It is now designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrally to the tablet. The Strong-Cobb Pfizer and Schleuniger apparatus which were later introduced measures the diametrically applied force required to break the tablet. Hardness, which is now more appropriately called crushing strength determinations are

made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10-20 kg).Tablet hardness have been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression.[13,14]

Stability Study (Temperature Dependent)

The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation.[13,14]

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. Bi-layer tablet quality and GMP-requirements can vary widely. This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single-sided presses to highly sophisticated machines such as the Courtoy-R292F. Whenever high quality bi-layer tablets need to be produced at high speed, the use of an 'air compensator' in combination with displacement control appears to be the best solution.

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