



“AN OVERVIEW ON BI-LAYER TABLET TECHNOLOGY AN EMERGING TREND”

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ABSTRACT:

The bi-layer tablet represents a new age in the production of controlled release formulations with a variety of features to ensure effective drug delivery. Bi-layer tablets can be a good way to prevent chemical incompatibilities between APIs and create different drug release profiles by physically separating them. A bi-layer tablet can be used for the sequential release of two drugs in combination, as well as for the continuous release of a tablet in which one layer is for immediate release as a loading dose and the second layer is for the maintenance dose. The following article discusses bi-layer tablet technology, challenges in bi-layer tablet manufacturing, various tablet presses used, quality and GMP specifications for their production, various bi-layer tableting techniques, and recent developments in the field of bi-layer technology.

Keywords: Bi-layer tablet, Incompatibility, multi-layer tablet, sustained release formulation.

INTRODUCTION:

Oral drug delivery has been known for decades as the most appealing route for delivery of drugs. The reason that the oral route achieved such popularity is its ease of administration and the traditional belief that the drug is as well absorbed by oral route as the foodstuffs that are ingested daily. The parenteral route of administration is important in case of emergencies, while the topical route of drug administration recently employed to deliver drug to the specific part of the body for systemic effect. The physical state of most of the drugs being solid, they are administered in solid dosage form. Among the pharmaceutical dosage forms, the conventional tablets seem to be most popular because of its ease of transportability and comparatively lower manufacturing cost.

Tablet: a dosage form: [1-6]

In solid oral dosage forms the tablets and capsules are more commonly employed. The tablets consist of one or more drugs as well as a series of other substances used in the formulation of a complete preparation. In the European Pharmacopoeia, tablets are defined as, “solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles”.

The tablets have advantages than capsules in that they are tamper proof dosage form. The major disadvantage of capsules over tablets is their higher cost. The capsules either hard capsule or soft capsule are susceptible to breakage if they are not stored properly. Topical route is recently developed and is employed for only few drugs like nitro glycerin, scopolamine for systemic effect. Topical route has limitations in its ability to allow effective drug absorption for systemic drug action. Nevertheless, it is possible that at least 90 % of all drugs used to produce systemic effect are administered by oral route.

• General properties of Tablet dosage forms:

- The tablet should include the correct dose of the drug.
- The drug should release from the tablet in a controlled and reproducible way.
- The tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
- Tablet should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- Tablet should have the chemical and physical stability to maintain its physical attributes overtime.
- The tablet should be biocompatible, i.e., not include excipients, contaminants and microorganisms that could cause harm to patients.

• Advantages of tablets as drug delivery system:

- They are unit dosage form, and they offer the capabilities of all oral dosage forms for the dose precision and the least content variability during dosing.
- Their cost is lowest of all oral dosage forms.
- They are the most compact of all oral dosage forms.
- They are in general easier and cheaper to package and ship as compare to other oral dosage forms.
- Product identification is simple and cheap, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They are ease to administer, does not require a specialist.
- They are better suited to large-scale production than other unit oral forms.
- They have the better chemical, mechanical and microbiological stability. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

- **Disadvantages of tablets as drug delivery system:**

- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

Types of Tablets:

Tablets are classified according to their route of administration or function. The following are 5 main classification groups:

Tablets Ingested Orally:

These tablets are meant to be swallowed along with a sufficient quantity of water. Exception is chewable tablet. Over 90% of the tablets manufactured today are administered by orally. It shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards the formulation of tablet.

- Compressed tablets
- Multiple compressed tablets
- Multilayered tablets
- Sustained action tablets
- Enteric coated tablets
- Film coated tablets
- Chewable tablets

- **Tablets Used in the Oral Cavity:**

These tablets are aimed to release drug in oral cavity or to provide local action in this region. The tablet under this category avoids first-pass metabolism and decomposition of drug in gastric environment, nauseating sensations and gives rapid onset of action. The tablets formulated in such a way that fit in proper region of oral cavity.

- Buccal tablets
- Sublingual tablets
- Lozenges
- Dental cone

Multilayer tablet:^[11,12]

Multilayer tablet can be designed and prepared to have separate layers or a core tablet inside a tablet. Multilayer tablets are manufactured by the initial compaction of a portion of fill material in a die cavity followed by additional fill material and compression to form two or more layered tablets depending upon number of separate additional fills.

There are many reasons for choosing a multi-layer tablet form over a conventional mono-layer tablet. These includes to control the delivery rate of either single or two different active pharmaceutical ingredient(s) (API), to separate incompatible 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), to modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release, to administer fixed dose combinations of different APIs.

There are three categories under multilayer dosage forms:

- Layered tablets - Two to three component systems.**fig.no.1**



Figure no.1. A: Bilayer compressed

B: Tri-layer compressed

- Compression coated tablets – Tablet within a tablet.**fig.no.02**
- Inlay tablet – Coat partially surrounding the core.**fig.no.03**

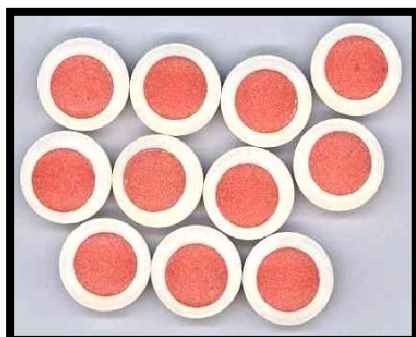


Fig.no.02. Compression coated tablet



Figure no. 3 Inlay tablet

The layered tablet is preferred over compression coated tablet as the surface contact is less and the production is simple and more rapid.

BILAYER TABLET: ^[13-16]

The term Bilayer tablets define as tablets which having two layers that may be either of the same drug or of two different drugs. For these types of drugs, extended-release formulations generally lead to a delayed appearance of effective plasma levels and they cannot provide a prompt disposition of the dose immediately after administration. Bilayer 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. Two-layer tablets may be designed for sustained release – one layer for the immediate release of the drug and second layer for extended release thus maintaining a prolonged blood level. Layers may be colored differently to identify the product

Advantages of bilayer tablet:

- Bi-layer execution with optional single layer conversion kit.
- Low cost compared to other dosage forms.
- Greatest chemical and microbial stability compared to other oral dosage forms.
- Objectionable odour and taste can be masked by coating technologies.
- Flexible concept.
- Offer greatest precision and the least content uniformity.
- Easy to swallow with least hang up problems.
- Fit for large scale production.
- Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
- Bi-layer tablets can be designed in such a manner as to modify release as either of the layers can be kept as extended and the other as immediate release
- Expansion of a conventional technology.
- Maintain physical and chemical stability.
- Product identification is easy.
- Easiest and cheapest to package and strip.

Manufacturing of Bilayer Tablets:

The simplified description of the double-layer manufacturing process can be offered as follows. that are set to apply the right amount of force for achieving the target tablet hardness.

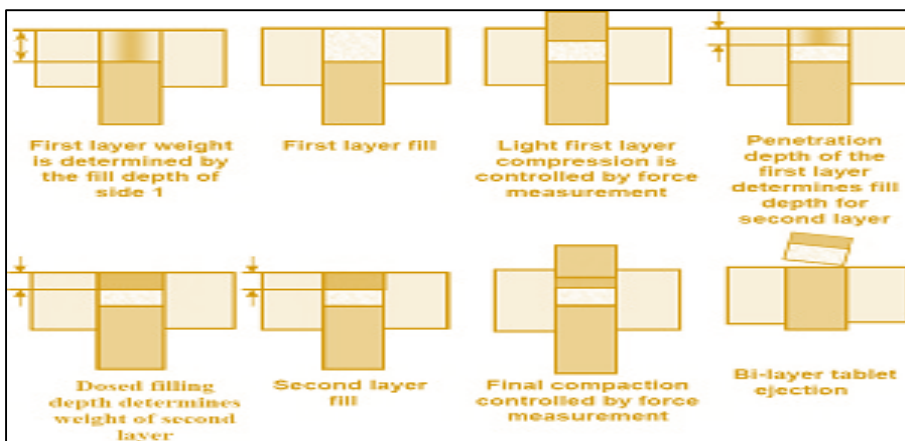


Figure no.4 An overview of bilayer tablet manufacturing process Schematic Presentation for Compression of Bi-Layer Tablet.

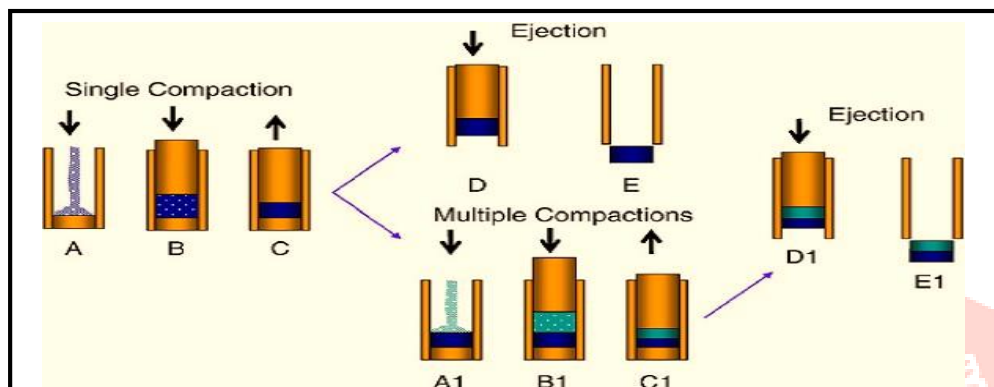


Figure no. 5 Schematic diagram showing the manufacture of single and bilayer tablets utilizing uniaxial compaction.

A- Die filling, B- compression, C- decompression, D- lower punch removal and reapplication of load to the upper punch, E-tablet fully ejected.

Conventional dosage form produces wide range of fluctuation in drug concentration in the blood stream and tissues with subsequent undesirable toxicity and poor efficiency. This dynamic such as repetitive dosing and erratic absorption led to the concept of controlled drug delivery systems.

Critical factors to be considered for bilayer tablet manufacturing

The most common concerns are addressed briefly below.

- Cross-contamination or color “bleeding”

It is imperative in virtually all cases of double-layer manufacturing to ensure that the granulations for the different layers are contained effectively by the feed frames and subsequent scraper assemblies so as to minimize or eliminate the possibility of the colors bleeding together. This is especially important in the case of an uncoated tablet that utilizes different color granulations, and can also be necessitated in cases where mixing the granulations compromise product efficacy.

- Layer binding

A tablet press must have versatile compression force capabilities, so as to foster good binding between layers. If good binding cannot be achieved it may result in lamination of the final tablet, where the two

layers separate from one another after ejection.

- Output capabilities

The press design must effectively meld all engineering characteristics into a package that optimizes output speeds, while ensuring good final tablet characteristics for criteria such as weight, thickness and hardness.

- First-layer sampling

This feature receives more and more attention these days, as it is critical to the overall integrity of the final product. The tablet press must have, at a minimum, the capability of periodically manufacturing layer samples, where the layers are intentionally kept separate in an effort to ensure good weights. The process must also be fast and accurate, as there is the potential for waste during the sampling interval. Novel methods for optimizing this entire process are now being made commercially available.

- “Second-layer-only” tablets

This is the typical problems observed because of the first layer sampling. A partial tablet is the result of such a sampling. To avoid this, a specifically designed discharge chute is necessary.

- Weight control for individual layers

Early double-layer tablet presses were outfitted with weight control systems that would monitor and adjust total weight only, rather than that of the individual layers. But now systems are available which allow for greater accuracy and control in the adjustment of independent layers.

- Compaction principles governing weight control

Unlike conventional tablets, bilayer tablets require three weight controls, namely, individual layers and the final tablet weight control. The complexity in the weight control significantly increases the level of sophistication needed in the rotary press designed for multi-layer tablets. Typically, in closed-loop control systems, two different types of control mechanisms for weight are involved.

- Compression force

Since the material in the die cavity is compressed twice to produce a bilayer tablet, compressed first with layer one followed by both the layers, the compression force affects the interfacial interaction and adhesion between the two layers.

Quality and GMP-requirements: [17-18]

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

- ✚ Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
- ✚ Providing sufficient tablet hardness
- ✚ Preventing cross-contamination between the two layers.
- ✚ Producing a clear visual separation between the two layers.
- ✚ High yield.
- ✚ Accurate and individual weight control of the two layers.

- **Various types of bilayer tablet press:**^[19]

- 1. Single sided tablet press**

- Limitations of single-sided press are:
 - 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.
 - Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight calibration.

- 2. Double sided tablet 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 the main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

IMMEDIATE RELEASE DOSAGE FORM:

Definition: Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong the rate of drug release and/or absorption.^[18,19] Immediate release tablets are one of the tablets prepared by direct compression method.

Immediate release tablets have received ever increasing demand during the last decade and the field has become a rapidly growing area in the pharmaceutical industry because of such tablets readily dissolve or disintegrate in generally less than 60 seconds. As disintegration plays a crucial role, so for development of solid orals, formulators are fascinating towards selection of proper disintegrants / super disintegrants in dosage systems. Disintegrants are substances or mixture of substances added to the drug formulations, which assist dispersion or breakup of tablets and contents of capsules into smaller particles for dissolution. Super disintegrants are those substances, which improves disintegration compared to disintegrants.^[20]

- **Biopharmaceutical Consideration:**^[20,21]

Must that to consider Biopharmaceutical factor like metabolism and excretion.

- **Pharmacokinetics:**

It is the meditation; study has done on absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and

hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

- Pharmacodynamics:

Drug reception interaction impaired in elderly as well as in young adult due to undue Development of organ.

- Decreased sensitivity of -adrenergic agonist and antagonist.
- Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
- Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates. Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.
- Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.
- Immunity is less and taken into consideration while administered antibiotics. Research workers have clinically evaluated drug combination for various classes“ cardiovascular agents, diuretics, anti-hypertensive etc. for immediate release dosage forms. The combination choice depends on disease state of the patient.

Criteria for immediate release drug delivery system:^[22-24]

The case of solid dosage it should dissolve or disintegrate in the stomach within a short period.

- In the case of liquid dosage form it should be compatible with taste masking.
- Be portable without fragility concern.
- It should not leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental condition as humidity and temperature.
- Be manufactured using conventional processing and packaging equipment at low cost.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.

Merits of Immediate Release Drug Delivery System:^[22,25]

- Improved compliance/added convenience.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery.
- Cost-effective.
- Improved solubility of the pharmaceutical composition.
- Decreased disintegration and dissolution times for immediate release oral dosage forms.

Challenges to Developed Immediate Release Drug Delivery System:^[22]

- It should dissolve or disintegrate in the stomach within a short period.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- Should not leave minimal or no residue in the mouth after oral administration.
- Should exhibit low sensitivity to environmental condition as humidity and temperature.

- Be manufactured using conventional processing and packaging equipment at low cost.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.

SUSTAINED RELEASE DOSAGEFORM:

Definition: A Sustained release dosage form is defined as “Any drug or dosage form modification that prolongs the therapeutic activity of the drug”. Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.^[23-26] This delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above the minimum effective concentration to and below the minimum toxic level for an extended period of time.^[27]

Disadvantages of Conventional dosage forms ^[27,28]

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or overmedication.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.
- Recently, several advancements in drug delivery system have been made to overcome the drawback of conventional drug delivery system. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity or targeting the delivery of drug to tissue.

Advantages of Sustained release dosage form: ^[29,30]

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Reduced 'see-saw' fluctuation.
- Drug administration can be made more convenient as well.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced.
- Safety margins of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Improve efficiency in treatment.

Disadvantage of Sustained release dosage form: ^[29,30]

- Dose dumping.
- Reduced potential for dose adjustment.
- Cost is more than conventional tablet.
- Increase potential for first pass metabolism.
- Patient education is necessary for proper medication.
- Systemic availability is decreased in comparison to immediate release conventional dosage forms.
- Poor in vivo and in vitro correlations.

Drug properties, which are suitable for, extended-release formulation**a) Physiochemical Properties of the drug:** ^[31-34]

- Aqueous solubility:(>0.1 mg/ml)
- Partition co-efficient: (1000:1 octanol: water system)
- Drug stability in vivo: (High enough, so drug remain stable during release from system)
- Protein binding: (Drug with high protein binding will not require release modification)
- Drug pKa & ionization at physiological pH: (pKa for acidic API= 3.0 - 7.5, pKa for Basic API = 7.0 -11.0)
- Mechanisms and sites of absorption: (Mechanism of absorption should not be active type and absorption window should not be narrow)
- Molecular size and diffusivity: (Molecule size should be small (100-400 D so it can be easily diffused through polymer matrix)
- Dose size:(<300 mg)

b) Biological Properties of Drug: ^[24,31,32]

- Distribution: (A.P.I. with large volume of distribution is not suitable).
- Metabolism: (A.P.I. should be metabolized with intermediate speed).
- Half-life of drug: (2 - 8hrs).
- Margin of safety: (High enough so dose dumping does not cause any serious side effect).
- Plasma concentration response relationship: (A.P.I. having linear relationship is better candidate).

Type of sustained release formulation ^[24,31,35]

Sustained (zero-order) drug release has been attempted to be achieved, by following classes of sustained drug delivery system.

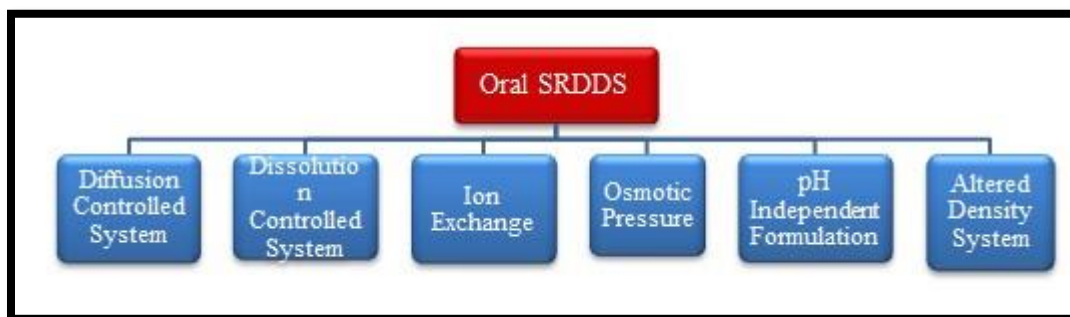


Figure no.6 Types of sustain release formulation

- **Diffusion controlled sustained system:**

Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. In this system the rate controlling step is not the dissolution rate but the diffusion of dissolved drug through a polymeric barrier. The two types of diffusion-controlled system are—

- Matrix System.
- Reservoir System.

- **Dissolution sustained systems:**

In these products, the rate dissolution of the drug (and thereby availability for absorption) is controlled by slowly soluble polymer or by microencapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thicknesses of the coat and its composition, the release rate of drug can be controlled. A drug which having a slow dissolution rate these drugs are naturally sustained and for those drugs with high water solubility, decrease their dissolution rate through appropriate salt or derivative formation. The two types of diffusion-controlled system are –

- Soluble matrix system.
- Soluble reservoir system.



CONCLUSION:

Bi-layer tablets offer an excellent opportunity for manufacturers to separate themselves from their competitors, improve their products' efficacy, and protect against impersonator products. 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. When a quality bi-layer tablet needs to be produced in conjunction with accurate weight control of both layers, compression force-controlled presses are clearly limited because of their insufficient sensitivity and hence lack of accuracy at low compression forces required to secure interlayer bonding. Such problems become even more apparent when the tableting speed is high or increased. Accurate individual layer weight monitoring/control at high speed and in combination with reduced layer separation risk can be achieved with the displacement weight control system-based presses.

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