



CONTROLLED AND SUSTAINED RELEASE APPROACHES IN DEVELOPING SUITABLE DOSAGE FORMS FOR THE ANTIRETROVIRAL DRUG LAMIVUDINE

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ABSTRACT

Lamivudine is a Nucleoside Reverse Transcriptase Inhibitor (NRTI), licensed for the treatment of HIV, and chronic Hepatitis B. The pharmacokinetic data of Lamivudine shows that, frequent administration for a prolonged period of time (lifelong in AIDS and for one year in hepatitis patients) is necessary to maintain constant therapeutic drug levels in the body, in case of AIDS-the dose is 150 mg twice daily (i.e. multiple times a day) in the form of conventional oral tablets. But the long-term AIDS therapy with the conventional tablets of Lamivudine found to have some drawbacks, such as adverse side effects (sometimes severe) resulting from accumulation of drug in multi-dose long-term therapy; poor patient compliance; and high cost. Designing of controlled and sustained release once-daily formulations of Lamivudine can overcome these problems, and maintaining of systemic drug levels consistently above its target antiretroviral concentration throughout the course of the treatment (which is crucial for the success of AIDS therapy) is also possible with these approaches. This review briefly discusses about the novel dosage forms like controlled release matrix tablets, floating tablets, nanoparticles, microparticles, liposomes, and niosomes; which may possibly suitable for the controlled and/or sustained release of Lamivudine and thus, useful in developing the more effective AIDS therapy with very less or no adverse side effects.

Keywords: Lamivudine, Controlled Release, AIDS, HIV, NRTIs, and Novel Drug Delivery Systems.

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). As of 2009, AVERT (also known as the AIDS Education and Research Trust) estimated that there are 33.3 million people worldwide living with HIV/AIDS, with 2.6 million new HIV infections per year and 1.8 million annual deaths due to AIDS¹.

When HIV infects a cell, a viral enzyme, reverse transcriptase copies the viral single stranded RNA genome into a double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which then allows host cellular processes, such as transcription and translation to reproduce the virus². Reverse Transcriptase Inhibitors blocks the reverse transcriptase's enzymatic function and prevent completion of synthesis of the double-stranded viral DNA, thus preventing HIV from multiplying.

Lamivudine comes under the class - Nucleoside Reverse Transcriptase Inhibitors (NRTIs). It is a nucleoside analogue, which was originally licensed for the treatment of HIV. It is now additionally licensed for the treatment of chronic hepatitis B with evidence of viral replication. For the treatment of AIDS, the dosage of conventional oral formulations of Lamivudine is 300mg per day (i.e. 150 mg twice daily, multiple times a day)³.

PHARMACOKINETICS OF LAMIVUDINE

Absorption: As the aqueous solubility profile (70 mg/ml at 20°C) of Lamivudine is good, it dissolves easily in gastric fluids. Lamivudine is well absorbed from the gut, and the bioavailability of oral Lamivudine is normally between 86% ± 16%. Following oral administration the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour.

Distribution: From intravenous studies, the mean volume of distribution is 1.3 L/kg. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding to albumin. Limited data show relatively low penetration of Lamivudine into the central nervous system.

Metabolism: Lamivudine is predominately cleared by renal excretion of unchanged drug. No evidence of first pass effect. The likelihood of metabolic drug interactions with Lamivudine is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Elimination: The mean systemic clearance of Lamivudine is approximately 0.3 L/h/kg. The observed half-life of elimination is 4 to 6 hours. The majority of Lamivudine is excreted unchanged in the urine via glomerular filtration and active secretion (organic cationic transport system). Renal clearance accounts for about 70% of Lamivudine elimination⁴.

The above mentioned pharmacokinetic data shows that, Lamivudine is rapidly absorbed after oral administration



with an absolute bioavailability of $86\% \pm 16\%$, peak serum concentration of Lamivudine (C_{max}) of 1.5 ± 0.5 mcg/mL and mean elimination half-life ($t_{1/2}$) of 4 to 6 hours, thus necessitating frequent administration for a prolonged period of time (lifelong in AIDS and for one year in hepatitis patients) to maintain constant therapeutic drug levels. The pronounced fluctuations resulting from the conventional drug administration are likely to yield period of no therapeutic effects when the concentration falls below the minimum therapeutic drug concentration⁵, and can be controlled within the narrow therapeutic range by use of controlled and sustained release systems⁶ (Table 1). This will minimize the severity of side effects. It is crucial for the success of AIDS therapy to maintain systemic drug levels consistently above its target antiretroviral concentration throughout the course of the treatment⁷.

Another major issue is, long-term therapy for the treatment of chronic diseases like AIDS by using conventional formulations of Lamivudine is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multi-dose therapy, poor patient compliance, and high cost. Controlled and sustained release once-daily formulations of Lamivudine can overcome some of these problems⁸.

List of some common side effects associated with Lamivudine:

- Headache; neuropathy; dizziness; sleep disturbances; depression; insomnia and other sleep disorders; depressive disorders.
- Nausea; vomiting; diarrhea; anorexia; abdominal pain/cramps; dyspepsia; stomatitis.
- Anemia; neutropenia; hyperglycemia; weakness; lactic acidosis; lymphadenopathy; splenomegaly; lactic steatosis.
- Malaise; fatigue; fever; chills; myalgia; arthralgia; pancreatitis; elevated liver enzymes; musculoskeletal pain; anaphylaxis; urticaria; rhabdomyolysis; peripheral neuropathy; hepatic steatosis; muscle weakness with CPK elevation; post treatment exacerbation of hepatitis; redistribution/accumulation of body fat⁹.

Therefore the ultimate objective in designing the Lamivudine control and sustain release dosage forms is to modify the drug release from the dosage form, thus to maintain the blood levels of the Lamivudine for a prolonged period of time and to minimize the adverse side effects resulting from accumulation of drug in the body.

Now a days numerous controlled and sustained drug release novel dosage forms are available in market for different drugs. The rationale for control drug delivery is to alter the pharmacokinetics and pharmacodynamics of drug substance in order to improve the therapeutic efficacy and safety through the use of novel drug delivery

system. Here the selection/design of a particular suitable dosage form for a drug is majorly depends on that drug's specific properties/characteristics.

Table 1: Beneficial characteristics of controlled-release drug delivery systems¹⁰:

Benefit	Reason
Therapeutic advantage	Reduction in drug plasma level fluctuations; maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.
Reduction in adverse side effects and improvement in tolerability.	Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release dosage forms. This greatly reduces the possibility of side effects.
Patient comfort and compliance	Reduction in dosing frequency enhances compliance.
Reduction in healthcare cost.	The total cost of therapy of the controlled release product could be comparable or lower than the immediate-release product. With reduction in side effects, the overall expense in disease management also would be reduced.

Based on these specific physicochemical, pharmacokinetic and pharmacodynamic properties of Lamivudine, designing of controlled and sustained release dosage form for this drug is possible. These novel dosage forms may overcome the drawbacks associated with the conventional Lamivudine tablets. In this review, we discussed in detail about the possible novel dosage forms which are suitable for controlled and sustained release of Lamivudine. These dosage forms include, controlled release matrix tablets, floating tablets, nanoparticles, microparticles, and liposomes.

CONTROLLED RELEASE MATRIX TABLETS

Numerous approaches are available for oral controlled and sustained release. Matrix tablets are an interesting option when developing an oral controlled release formulation. The matrix system of dosage form proves to be potential because of its simplicity, ease of manufacturing, low cost, high level of reproducibility, stability, ease of scale up, and process validation. Development of this dosage form particularly depends on chemical nature of the drug/polymers, matrix structure, swelling, diffusion, erosion, release mechanism and the in vivo environment^{11,12}.

Fast release drug generally causes toxicity if not formulated as extended release dosage form. Among various formulation approaches, in controlling the release of water-soluble drugs, the development of controlled release matrix tablets has a unique advantage of lessening the chance of dose dumping. Most of the researchers have worked on matrix tablets and



multilayered matrix tablets. The matrix tablets can be prepared by wet granulation or by direct compression methods¹³. The drug release from the matrix tablets usually occurs by two mechanisms: drug diffusion through swelling and erosion of swollen polymer¹⁴.

Reports were found on usage of hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), methylcellulose, sodium carboxymethylcellulose, carbopols, and polyvinyl alcohol for the purpose of Controlled release matrix formulations of different drugs¹⁵. Matrix tablets prepared by using HPMC on contact with aqueous fluids gets hydrated to form a viscous gel layer through which drug will be released by diffusion and/or by erosion of the matrix. The release of the drug from the CR matrices is influenced by various formulation factors, such as polymer viscosity, polymer particle size, drug-to-polymer ratio, drug solubility, drug particle size, compression force, tablet shape, formulation excipients, processing techniques, and dissolution medium¹⁶. The drug release from the polymer matrix can be due to disentanglement or diffusion, depending on the polymer molecular weight and the thickness of the diffusion boundary layer. Polymer dissolution plays an important role in regulating the drug release.

As the Lamivudine is a highly soluble drug, use of single hydrophilic polymer is not justified here, because it diffuses out rapidly through the water-filled pores of matrix. Hydrophobic polymers like glycerides, ethyl cellulose (EC) are suitable in combination for this type of drugs⁶.

The experimental studies has shown that, matrix tablets of Lamivudine containing HPMC 4000 cps were found to show good initial release (26% in first hour) and extended the release up to 16-20 hours. In another study, matrix tablets of Lamivudine containing a natural polymer Guar Gum were found to show good initial release (21.34% in first hour) and extension of release for more than 12 hrs. This can overcome the disadvantages associated with conventional tablet formulations of Lamivudine¹⁵.

Hydrophilic and hydrophobic polymer matrix system are widely used for designing oral controlled drug delivery dosage form because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory acceptance¹⁷. Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The matrix tablets formulation by direct compression method is most acceptable in large scale production.

FLOATING DRUG DELIVERY SYSTEMS

Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time¹⁸. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the

residual system is emptied from the stomach. A better control of the fluctuations in plasma drug concentration is possible here. Floating systems offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin of Lamivudine.

Floating drug delivery systems are classified depending on the use of 2 formulation variables: effervescent and non-effervescent systems. In case of Lamivudine, effervescent Systems are more useful. These effervescent type floating systems are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid¹⁹. They are formulated in such a way that when in contact with the acidic gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

Ichikawa et al²⁰ developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO₂ was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/mL. It was found that the system had good floating ability independent of pH and viscosity and the drug released in a sustained manner. This approach can be useful for the drug Lamivudine.

Lactic acidosis, steatosis, including fatal cases, has been reported with the long-term use of nucleoside analogues alone or in combination, including Lamivudine and other antiretrovirals²¹. Use of Sodium bicarbonate (IV and/or Oral) is one of the treatments of lactic acidosis²². In the preparation of effervescent floating systems, if we use Sodium Bicarbonate as the effervescent agent for floating purpose, it may also helpful for the prevention of Lactic Acidosis.

The recent studies conducted on Lamivudine proved the possibility of obtaining prolonged (up to 12hrs), relatively constant effective levels of Lamivudine from floating drug delivery systems. So these floating drug delivery systems may more useful than conventional tablets²³.

The only disadvantage of the floating systems is, Lamivudine causes nausea and vomiting, so a little patient in compliance may occur. But this problem occurs with all the oral dosage forms.



NANOPARTICLES AND NANOSPHERES

Nanoparticles are submicron (< 1 μ m) level colloidal particles. This definition includes monolithic nanoparticles (nanospheres) in which the substances are adsorbed, or dissolved, or dispersed throughout the matrix and nanocapsules in which the drug is confined to an aqueous or oily core surrounded by a shell-like wall. Alternatively, the drug can be covalently attached to the surface or into the matrix²⁴.

Nanoparticles are made from biocompatible and biodegradable materials such as polymers, either natural or synthetic, or solid lipids²⁵. In the body, the drug loaded in nanoparticles is usually released from the matrix by diffusion, swelling, erosion, or degradation. For decades pharmaceutical sciences have been using nanoparticles to reduce toxicity and side effects of drugs.

In recent years, several research reports are available regarding the development of polymeric nanocarrier system with the aim to have better cellular targeting, overcoming the pharmacokinetic problems, and enhancing the activities of drugs for the treatment of HIV infection and AIDS²⁶. Polymeric nanoparticles with entrapped drug represent an exciting approach to control the release of drugs like Lamivudine.

Their smaller size may facilitate their capture by the intestinal lymphoid tissue cells. As the HIV is very active in the lymph nodes, these nanoparticle systems are useful for targeting the Lamivudine to lymph nodes. Another targeting approach: Mononuclear (macrophages) and polymorphonuclear leucocytes cells play an important role in the immunopathogenesis of AIDS. The uptake of PLA and PLA/PEG blend nanoparticles into polymorphonuclear leucocytes were studied *in vitro*²⁷. Thus, this approach is also useful in drug targeting.

The slow and constant release of Lamivudine from polymethacrylic acid nanoparticles was observed in some studies, these nanoparticles maintained a constant drug plasma concentration thereby increased the therapeutic efficacy. Coating of lipid nanoparticle formulations with a chitosan layer can also confer beneficial effects like sustained release of hydrophilic drugs²⁸. Thus, this approach may be suitable for the Lamivudine sustained and controlled release²⁹.

The important technological advantages of nanoparticles used as drug carriers are high stability, increased bioavailability, high carrier capacity, site specific drug delivery, feasibility of incorporation of both hydrophilic and hydrophobic substances, and feasibility of variable routes of administration, including oral application and inhalation. Nanoparticles can also be designed to allow controlled (sustained) drug release from the matrix over longer period of time, retention of dosage form in entire length of gastrointestinal tract and convenient to patient due to reduction in frequent dosing²⁵.

Recently, increasing attention has been focused on solid lipid Nanoparticles (SLN), because it offers following advantages- possibility of controlled drug release and drug targeting, increased drug stability, high drug payload, no biotoxicity of the carriers, avoidance of organic solvents, no problems with respect to large scale production, cost effective and easy sterilization. Furthermore, incorporation of hydrophilic Lamivudine in SLN carriers results in decrease bone marrow toxicity, increased bioavailability and enhanced antiviral activity³⁰. Another advantage of SLNs is, brain targeting also possible.

MICROPARTICLES, MICROCAPSULES AND MICROSPHERES

The term "microcapsule" is defined, as a spherical particle the size varying in between 50nm to 2mm containing a core substance. Microspheres are in strict sense, spherically empty particles. However the terms are often used synonymously. In addition, some related terms also used as well³¹. For example, microparticles and microbeads.

Micro encapsulation (MEC) has been the subject of massive research efforts since its inception around 1950's of all sustained release systems. The advantages of MEC include longer duration of action, control of content release, increased therapeutic efficiency, and protection of drug from biological environment, reduction of toxicity, bio compatibility, sterilizability, release stability, water solubility and targeting.

The microsphere's polymer matrix is formed from at least two highly water soluble biodegradable polymers, selected for example from starch, crosslinked starch, ficoll, polysucrose, polyvinyl alcohol, gelatine, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-ethyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxymethyl cellulose, cellulose acetate, sodium alginate, polymaleic anhydride esters, polyortho esters, polyethylenimine, polyethylene glycol, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide, poly(1,3 bis(p-carboxyphenoxy) propane-co-sebacic anhydride, N,N-diethylaminoacetate, block copolymers of polyoxyethylene and polyoxypropylene. The microspheres are coated with a (d,l lactide-glycolide) copolymer. The coating makes the microspheres more resistant to enzymatic degradation and also controls the drug release pattern³². Thus, prolonged drug release is possible.

MEC provides more efficient drug delivery because it increases the ability of drug to interact with the body. The active ingredient of a drug is encapsulated into particle that may be as small as one micron. Within a normal tablet, there may be millions of these microcapsules and each able to release the drug in the body. Compared to normal tablet, the microcapsules have much greater surface area, which increases the solubility and



effectiveness. Perhaps the greater future of microsphere is the control provided by the choice of coating³³.

A recent study has shown the possibility of obtaining prolonged, relatively constant effective levels of Lamivudine from microspheres using Eudragit polymers, which gave pH independent release from the formulations. In another study lamivudine loaded microspheres were prepared by using polymers like Acrylacoat, L30D and S100. This study concluded that, a better control over 3TC (Lamivudine) plasma concentration profile was obtained after oral administration of Lamivudine loaded microspheres to rabbit (New Zealand white species) with respect to that of Lamivir tablet³⁴.

The Lamivudine micro capsules prepared with Cellulose acetate phthalate (CAP), cellulose acetate butyrate (CAB), ethyl cellulose (EC), hydroxy propyl methyl cellulose acetate phthalate (HPMCP) and combination of CAP: CAB gave prolonged drug release for 12 hours or longer. The microspheres could be administered as prepared or could be compressed into tablet or filled in capsule shell. The entire process is feasible in an industrial scale and demands pilot study. They were capable of reducing the frequency of administration and the dose-dependent side effects associated with the repeated administration of conventional Lamivudine tablets³⁵.

LIPOSOMES

Liposomes are microscopic spheres with an aqueous core surrounded by one or more outer shell(s) consisting of lipids arranged in a bilayer configuration³⁶. Liposomes can be composed of naturally-derived phospholipids with mixed lipid chains (like egg phosphatidyl ethanolamine) or other surfactants³⁷. Majorly, there are three types of liposomes - MLV (multi lamellar vesicles): SUV (Small Unilamellar Vesicles) and LUV (Large Unilamellar Vesicles). These are used to deliver different types of drugs and their physical properties depend on the composition of the lipids that form the lipid bilayer or multilayer. Using lipid combinations that enhance acid and enzyme resistance, liposomes can be tailored to suit for oral delivery of drugs³⁸.

Liposomes are used for drug delivery due to their unique properties. A liposome encapsulates a region on aqueous solution inside a hydrophobic membrane; dissolved hydrophilic solutes cannot readily pass through the lipids. Hydrophobic chemicals can be dissolved into the membrane, and in this way liposome can carry both hydrophobic molecules and hydrophilic molecules³⁷.

To deliver the molecules to sites of action, the lipid bilayer can fuse with other bilayers such as the cell membrane, thus delivering the liposome contents. By making liposomes in a drug solution (which would normally be unable to diffuse through the membrane) they can be (indiscriminately) delivered past the lipid bilayer³⁹.

In a study, Liposomes were targeted to HIV-1 infected cells via covalently coupled soluble CD4. An HIV-1 protease inhibitor encapsulated in conventional negatively charged multilamellar liposomes was about 10-fold more effective than the free drug inhibiting HIV-1 production in human monocyte derived macrophages. The drug encapsulated in stearically stabilized liposomes was as effective as free drug. These studies concluded that liposomes can be used to facilitate the intracellular delivery of certain anti-HIV agents and to enhance their therapeutic effects⁴⁰.

The liposomal Lamivudine formulation, for transdermal administration was successfully prepared by Roopa Pai S. et al. These liposomes were stable and have shown appreciably controlled skin permeation as well as minimal retention of drug molecules in the skin. Also by achieving controlled release of Lamivudine across the skin, these studies concluded that, it is possible to achieve a reduction in dose, while maintaining the required drug concentration. Thus the dose dependent side effects, which generally result in cessation of the therapy, can be reduced. These results advocate a further development of suitable transdermal formulations incorporated with these Lamivudine liposomes⁴¹.

Lamivudine is a highly water soluble drug, so the permeation of this drug through the lipid membranes may be a problem, thus if we use the liposomal drug delivery for the drug Lamivudine, it may helpful in permeation through different biological layers/membranes including blood brain barrier (BBB). Liposomes are the very promising drug carriers for the drug targeting. Including the oral drug delivery, various other routes for the drug administration are also possible with the liposomes. If we formulate the Lamivudine liposomes carefully, they could sustain the release of the drug by increasing residence time and, could reduce its dose-related systemic toxicity.

NIOSOMES

Niosomes are organized nonionic surfactant based vesicles formed from the self-assembly of non-ionic amphiphiles in aqueous media resulting in closed bilayer structures⁴². The assembly into closed bilayers is rarely spontaneous and usually involves some input of energy such as physical agitation or heat. The result is an assembly in which the hydrophilic head groups enjoy maximum contact with the aqueous solvent and hydrophobic parts of the molecule are shielded from the same⁴³. Since the structure of the niosome offers place to accommodate hydrophilic, lipophilic as well as amphiphilic drug moieties, they can be used for a variety of drugs⁴⁴.

Niosomes exhibit more chemical stability than liposomes (a phospholipids vesicle) as non-ionic surfactants are more stable than phospholipids⁴⁵.



Advantages with the niosomes include:

- The niosomal vesicles can act as a depot to release the Lamivudine slowly and offer a controlled release. Thus, the adverse effects due to the drug accumulation can be minimized/ prevented.
- They increase the stability of the entrapped drug.
- Handling and storage of surfactants do not require any special conditions.
- Can increase the oral bioavailability of drug.
- Can enhance the skin penetration of drugs.
- They can be used for oral, parenteral as well topical use.
- The surfactants are biodegradable, biocompatible, and non-immunogenic.
- Improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug.
- The niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to control the release rate of the drug and administer normal vesicles in external non-aqueous phase⁴⁶.

Niosomes can be formulated by proper adjustment of process parameters to enhance Lamivudine entrapment and sustainability of release. These improvements in Lamivudine formulation may be useful in developing a more effective AIDS therapy.

CONCLUSION

A lot of work is running to develop different types of controlled and sustained drug release systems of various drugs. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapies including Lamivudine therapy. However, large scale production needs more simplicity in the formulation with economic and cheapest dosage form.

Patients always expect the pharmacist to keep abreast of technological and scientific developments in the field and it is the responsibility of pharmacists/ formulators/ manufacturers to improve, even to overturn the current approaches to the drug(s) treatment by reducing adverse reactions and increasing drug(s) efficacy. So, it is mandatory to a pharmacist to gain access to the recent advances in drug delivery systems. As the treatment with Lamivudine has gained immense popularity in AIDS therapy in the present era, the concerns about this drug are also increased enormously to minimize the adverse effects. Thus, by designing a suitable novel controlled and/or sustained release dosage form, we may successfully overcome the disadvantages associated with conventional formulations of Lamivudine.

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