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A Review on Discosomes

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ABSTRACT

Drug delivery refers to approaches, formulations, technologies and systems for transporting a pharmaceutical compound in the body as required to safely achieving its desired therapeutic effect, in the past few decades, considerable attention has been focused on the development of novel drug delivery system (NDDS). Due to the intricately sensitive anatomy and physiology of the eye pharmacologist find the ocular delivery system to be more involuted than other routes. Pre-corneal, static and dynamic is the 3 types of ophthalmic barriers, which along with the inflow and outflow of lacrimal fluids, nasolacrimal drainage, are some of the germane factors that affect bioavailability. Discosomes are giant, disc-shaped structures modified from niosomes by arresting the vesicles at the discosome phase. Due to their idiosyncratic size, it provides all due benefits compared to other ocular drug delivery systems. From the review, it can be concluded that discosomes are a potential subject of opposition and opportunities in the area of safe and effective ocular drug delivery.

INTRODUCTION

A Novel Drug Delivery System (NDDS) can be defined as a new approach that combines innovative development, formulation, new technologies, and novel methodologies for delivering pharmaceutical compounds in the body as needed to safely achieve its desired pharmacological effects[1]. The field of nanomedicine employs novel drug delivery system (NDDS) to overcome the limitations of traditional dosage forms. Conventional formulations are associated with poor drug solubility, toxic side effects, lack of site selectivity, uncontrollable release profile, and low bioavailability. Furthermore, the frequent administration rates of conventional formulations lead to poor patient compliance. Recently, NDDS have gained much attention mainly in cancer therapy and immunodeficiency diseases due to their high efficacy and stability. The nanocarrier-based delivery systems and extended controlled release DDS which maintain the concentration of the drug within the therapeutic window for a longer time, thereby lowering the frequency of administration[2].

VESICULAR DRUG DELIVERY SYSTEM

Vesicles have become the choice in drug delivery system called Vesicular Drug Delivery System. Vesicular drug delivery system is of great latitude in immunology, modelling of biologic membranes, diagnostic techniques, genetic engineering, transport of active pharmaceutical moiety, etc. It is a combination of new dosage forms and advanced techniques that have proved to be far more efficient than conventional dosage forms. This commendatory outlook overthrows the issues of drugs having poor bioavailability and rapid elimination from the body. The biological origin of vesicles in the delivery of drugs dates back to 1995 by Bingham and was thus named “Bingham bodies”. The incorporation of a drug into vesicular structures in a system extends the bioavailability of the drug in systemic circulation and boosts its efficacy. One of the most prominent examples of such natural carriers is extracellular vesicles (EV). EVs are cell-derived membranes particles which play important roles in intercellular communication. EVs possess a number of characteristics that quality them as promising vehicles for drug delivery[3].

The chief benefit of lipid vesicular system is its ability to target drugs to the tissue in the body. Enhanced delivery of bioactive molecules through the skin by means of vesicular carrier opens new opportunities for the development of novel improved therapies.

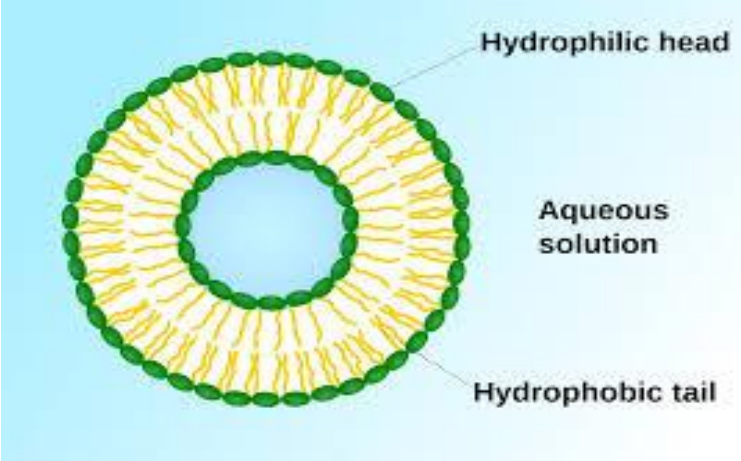

Fig no 1: Structure of vesicle

ADVANTAGES

- Prolong the existence of the drug in systemic circulation, and perhaps reduces the toxicity if selective uptake can be achieved due to the delivery of drug directly to the site of action.
- Delays elimination of rapidly metabolized drugs and thus functions as sustained release systems.
- Reduces the cost of therapy.
- Improves bioavailability.
- Hydrophilic-lipophilic drugs can be incorporated.
- Sustained release system function.
- Delayed elimination of rapidly metabolized drugs.

DISADVANTAGES

- Drugs passively, which may lead to low drug loading efficiency and leakage in preparation, preservation and transport in vivo.
- Need of intensive sonication, leads to leakages of drug during storage.

TYPES

1. LIPOIDAL BIOCARRIERS

- Liposomes
- Emulsomes
- Enzymosomes
- Sphingosomes
- Ethosomes
- Transferosomes
- Pharmacosomes

2. NON-LIPOIDAL BIOCARRIERS

- Niosomes
- Bilosomes
- Aquasomes

DISCOSOMES

Disc shaped Niosomes are known as discosomes. Discosomes are considered as modified niosomal formulations. Discosomes are large structures formed by solubilisation of niosomes with a non-ionic surfactant. Interestingly, their large size (12-16μm) thus prevents their drainage into the systemic circulation. Furthermore, their disc shape guarantees better fitting into the conjunctival sac. Discosomes were reported to entrap larger quantity of drug compared with niosomes, thus increasing ocular bioavailability[4].

In vivo studies showed that discosomes released the contents in a biphasic profile as the drug was loaded using a pH gradient technique. Discosomes may act as potential drug delivery carriers as they released drug in a sustained manner. Their size varies from 12 to 16μm. Discosomes differ from niosomes in that the former contain the addition of non-ionic

surfactant, Solulan C24, a derivate of lanolin, which is a mixture of ethoxylated fatty alcohols (ether of cetyl alcohol and polyethylene glycol). The size of discosomes is their advantage, because of which they do not enter the general circulation.

STRUCTURE OF DISCOSOMES

The discosomal structure consists of a bilayer formed by non-ionic surfactants and the assimilation of cholesterol which functions as an excipient. The self-assembly of non-ionic surfactants in aqueous media is the provoking factor that leads to the evolution of this bilayer. Discosomes can entrap drug molecules with a broad range of solubility due to the presence of amphiphilic moieties in the structure. To form the enclosed bilayer structure, a source of mechanical energy such as thermal energy or physical agitation is essential[5].

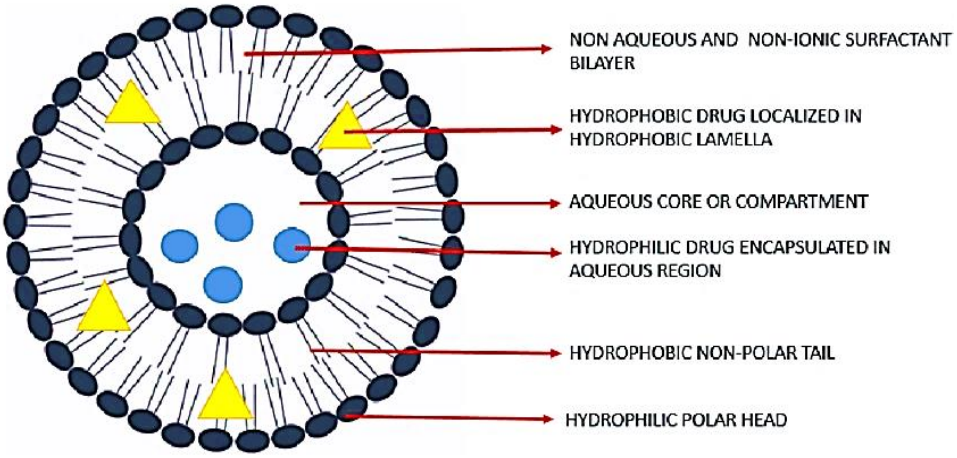

Fig no 2: Structure of discosomes

The surfactant molecules tend to organize themselves in a system where the hydrophilic heads of non-ionic surfactants that are polar and are oriented outwards, whereas the hydrophilic tails, which are non-polar face each other to form a bilayer. The centre of the discosome consists of an aqueous core in which the hydrophilic drugs are assimilated. The sandwiched area between the hydrophobic (lipophilic) non-polar tails envelopes hydrophobic drugs. Various repulsive forces are accountable for maintaining the integrity of the discosomal structure[6]. The high interfacial tension between the aqueous medium and lipophilic tails of the amphiphilic is the associating factor of this system. Recently it was validated that the intercalation of cholesterol in bilayers reduces the volume for entrapment during formulation in niosomes, which has a structural resemblance to that of discosomes[7].

CHARACTERIZATION OF DISCOSOMES

➢ Discosomes are compact disc shaped modified forms of niosomes and provide better ocular localization. Their size conventionally varies from 12 to 16μm.

➢ This drug delivery system comprises of non-ionic surfactants, Solulan C24 which is a derivative of lanolin.

➢ Their large size is an added advantage in the case of ophthalmic preparations which helps in impeding its drainage into the systemic pool and the disc-shaped structure also determines the superior and closer fitting of a discosome into the conjunctival sac.

➢ Discosomes are osmotically active, stable, biodegradable, biocompatible and cost-effective. They entrap solutes and are carriers of both hydrophobic and hydrophilic drugs.

ADVANTAGES

❖ Enhanced corneal permeability.

❖ Prolonged shelf life.

❖ They showed reduced toxicity.

❖ As discosomes are non-ionic surfactants, they can incorporate both hydrophilic (di-hydro streptomycin) and lipophilic (tri-aminolone acetonide) drugs in the aqueous layer or lipid bilayers.

❖ They are capable of entrapping water-soluble drugs.

❖ Their large faceted structure is likely to prevent their drainage and absorption into systemic circulation via the nasolacrimal duct.

❖ Discosomes showed a sustained drug release pattern and systemic absorption was minimized to a negligible level[8].

DISADVANTAGES

❖ During the preparation of discosomes, high temperature is needed which may influence the chemical stability of some thermolabile therapeutic agents.

❖ Discosomes also have limited drug loading capacities[9].

❖ The movement of this drug delivery device in pre-corneal space may cause some anxiety to the patient.

❖ The preparation and preservation of discosomes requires specialized equipment have increased production cost and is time-consuming.

❖ There are possibilities of inefficient drug loading, and leakage in the preparation, preservation, and transportation of discosomes.

APPLICATIONS

➢ Discosomes are used in the effective targeting of ophthalmic drugs and to preserve the therapeutic moiety in ocular blood circulation. It helps to improve the stability and physical properties of an ophthalmic drug.

➢ Discosomes are comprised of cholesterol and hence they withhold a more stable membrane than polyhedral ones. It plays an important role in improving the medication adherence of a patient as it condenses the need for frequent administration[10].

➢ Discosomes do not interfere with oxygen permeability in the eye and also significantly reduce the visual and systemic adverse effects that may materialize during the administration of a drug when compared to other ocular drug delivery system.

➢ It is also practical to intend to ocular diseases in hypersensitive patients, as the exclusion of complex preservation makes discosomes relatively safe from causing anaphylactic reactions.

➢ Discosomes are used in some pharmacokinetic studies to analyse the reproducibility of drug release kinetics (zero-order drug delivery). Timolol maleate is a drug used to improve ophthalmic pressure to treat diseases like ocular hypertension and glaucoma. This drug in discosomal form captures a substantial quantity of active drug components and hence elevates its bio-availability.

➢ Discosomes are used to treat diabetic keratopathy. Diabetic keratopathy refers to the abnormalities in the cornea caused by high blood sugar, characterized by kerato-conjunctivitis, delayed healing of a corneal wound, and diminished corneal nerve sensation.

➢ Naltrexone hydrochloride is an opioid antagonist in discosomal form that is used in the treatment of opioid dependence and alcoholism.

➢ It also normalizes the secretion of lacrimal fluids in diabetic patients, advances the renewal of the wound in the cornea, and rejuvenates the sensitivity of ocular nerves. Some drugs are used in discosomal forms to analyse their extend of irritation potential.

➢ Discosomes may also be used in the treatment of inherited retinal diseases (IRD) that consequently results in the degeneration of retinal cells in the eye due to the mutation of retinal layers[11].

➢ It is used to treat conjunctivitis, which can be defined as the inflammatory condition of the conjunctiva. The conjunctiva is a translucent mucous membrane that is situated in the sclera, where the drug is directly released on placing the discosomes. The causes of conjunctivitis may be bacterial, fungal, viral, parasitic, certain allergens, toxicities, or irritants depending on the contagiously of the disease.

➢ Keratitis, the inflammation of the cornea produced by pathogenic microbes that causes redness in the sclera, pain, blurred vision, and excessive lacrimal discharge, can be relieved instantaneously by the administration of discosomes.

➢ The use of discosomes as ocular anaesthetics in eye surgeries is under analysed studies.

PREPARATION

METHOD OF PREPARATION OF DISCOSOMES

Discosomes are prepared in two stages. They are,

➢ Step 1: Preparation of Niosomes.

➢ Step 2: Preparation of Discosomes from Niosomes.

Step 1: Preparation of Niosomes.

Niosomes can be prepared by a number of methods which are as follows:

- Sonication method

- Ether Injection method
- Hand Shaking Method
- Reverse Phase Evaporation Technique
- Transmembrane pH gradient drug uptake process
- The Bubble method

SONICATION METHOD

It is the conventional method to produce small uniform size niosomes. This process includes mixing a sample of drug solution with a lipid mixture of surfactant and cholesterol and subjected to sonication by using titanium probe at a temperature of 60 °C for 3 min to get niosomes.

ETHER INJECTION METHOD:

In this method, a solution of surfactant is made by dissolving it in diethyl ether. This solution is injected into warm water or aqueous media containing the drug maintained at 60°C. Vaporization of the ether leads to the formation of single layered vesicles. The particle size of the niosomes formed depend on the conditions used, and can range anywhere between 50-1000µm.

HAND SHAKING METHOD (THIN FILM HYDRATION TECHNIQUE):

In this method a mixture of the vesicle forming agents such as the surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether or chloroform in a round bottom flask. The organic solvent is removed at room temperature using a rotary evaporator, which leaves a thin film of solid mixture deposited on the walls of the flask. This dried surfactant film can then be rehydrated with the aqueous phase, with gentle agitation to yield multilamellar niosomes. The multilamellar vesicles thus formed can further be processed to yield unilamellar niosomes or smaller niosomes using sonication, micro fluidization or membrane extrusion techniques.

REVERSE PHASE EVAPORATION TECHNIQUE:

This method involves the creation of a solution of cholesterol and surfactant (1:1 ratio) in a mixture of ether and chloroform. An aqueous phase containing the drug to be loaded is added to this, and the resulting two phases are sonicated at 4-5°C. A clear gel is formed which is further sonicated after the addition of phosphate buffered saline (PBS). After this the temperature is raised to 40°C and pressure is reduced to remove the organic phase. This results in a viscous niosome suspension which can be diluted with PBS and heated on a water bath at 60°C for 10 mins to yield niosomes.

TRANS MEMBRANE PH GRADIENT (INSIDE ACIDIC) DRUG UPTAKE PROCESS (REMOTE LOADING):

In this method, a solution of surfactant and cholesterol is made in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask, similar to the hand shaking method. This film is then hydrated using citric acid solution (300mM, pH4.0) by vortex mixing. The resulting multilamellar vesicles are then treated to three freeze thaw cycles and sonicated. To the niosomal suspension, aqueous solution containing 10mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 using 1M disodium phosphate (this causes the drug which is outside the vesicle to become non-ionic and can then cross the niosomal membrane, and once inside it is again ionized thus not allowing it to exit the vesicle). The mixture is later heated at 60°C for 10 minutes to give niosomes.

THE "BUBBLE" METHOD:

It is a technique which has only recently been developed and which allows the preparation of niosomes without the use of organic solvents. The bubbling unit consists of a round bottom flask with three necks, and this is positioned in a water bath to control the temperature. Water-cooled reflux and thermometer are positioned in the first and second neck, while the third neck is used to supply nitrogen. Cholesterol and surfactant are dispersed together in a buffer (pH 7.4) at 70°C. This dispersion is mixed for a period of 15 seconds with high shear homogenizer and immediately afterwards, it is bubbled at 70°C using the nitrogen gas to yield niosomes.

Step 2: Preparation of Discosomes from Niosomes.

The previously prepared niosomes undergoes incubation with soluble poly-oxy-ethylene cholesteryl ether and Solulan C24, at 74 °C for 1 hour. The vesicles that were developed within the discosome phase, were found to be large (volume distribution mean diameter which is about 12-60 mm). The inherent large size is considered to prevent discosomes from being rapidly washed out by tear dynamics. They also showed a gradual increase in its dimension instantly after sonication[12]. Also, their non-uniform spherical structure can render a better fit on the ocular surface and they have also achieved higher encapsulation efficiency (EE %). Discosomes were shown entrapping water-soluble solutes. Discosomes of 5(6) - carboxy- fluorescein were developed and started in retaining 50% of entrapped carboxy-fluorescein over a 24-hour period at room temperature. Discosomes are voluminous discoidal structures that subsist under definite conditions of this phase of non-ionic surfactant vesicle formation.

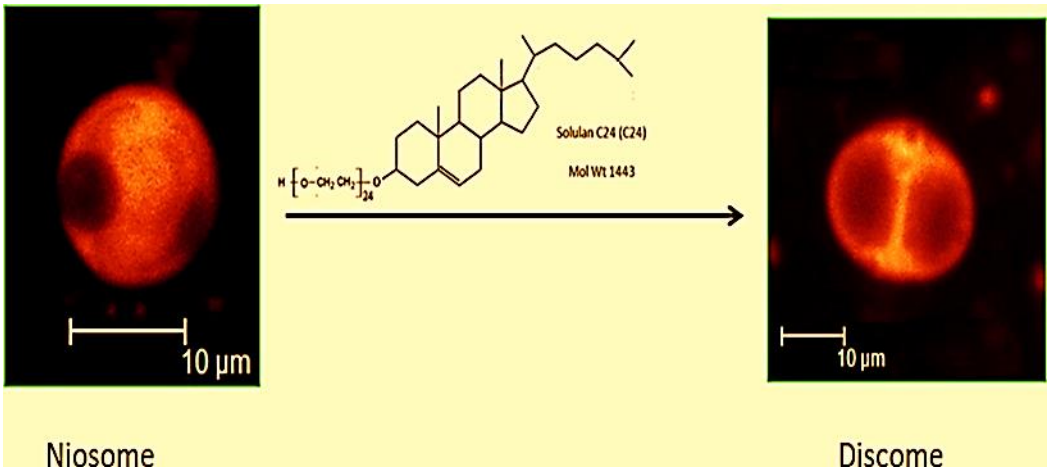

Fig no 3: Preparation of discosome from niosomes

MECHANISM OF ACTION OF DISCOSOMES

Discosomes can be referred to as non-ionic surface-active agents, which are niosomes solubilized with non-ionic surfactant solutions, predominantly from the class of poly-oxyethylene-cetyl ether[13]. They have a size of 12-16 µm with a progressive potential for the exclusive drug administration of water-soluble drugs into the ocular cavity with negligible reduction in the systemic absorption of drug compounds[14]. They have bi-layers that can incorporate both hydrophilic and lipophilic drugs in the aqueous core and within the bi-layer shell of the particle, respectively.

Non-ionic surfactants own both polar and non-polar segments and manifest a high interfacial activity. It carries no particular charge and comprises a hydrocarbon chain which is the main integral of a discosomal structure. However, the tail may be branched, linear or aromatic. The choice of surfactant to be used may depend upon many salient factors like Hydrophilic-lipophilic balance (HLB) preferably between 16-17, Critical Packing Parameter (CPP), Critical Micelle Concentration (CMC) values[15]. These non-ionic surfactants also accelerate the rate and extent of drug absorption by the envelopment of the therapeutic drug molecule, facilitates the easy penetration through the ocular barrier, and nullifies the irritant effect of the drug. Additionally, it can also alter the rigidity of bi-layer, along with cholesterol molecules that serve this complementary function. The addition of a surfactant may mitigate the formation of the micellar structure by the dose-dependent breakdown of vesicles into a giant disc-like structure which further contributes to better contact time with the cornea and amplifies bio-availability. Mucoadhesive polymers like chitosan and carbapol-coated discoidal niosomes improve bio-availability and pre-corneal retention too.

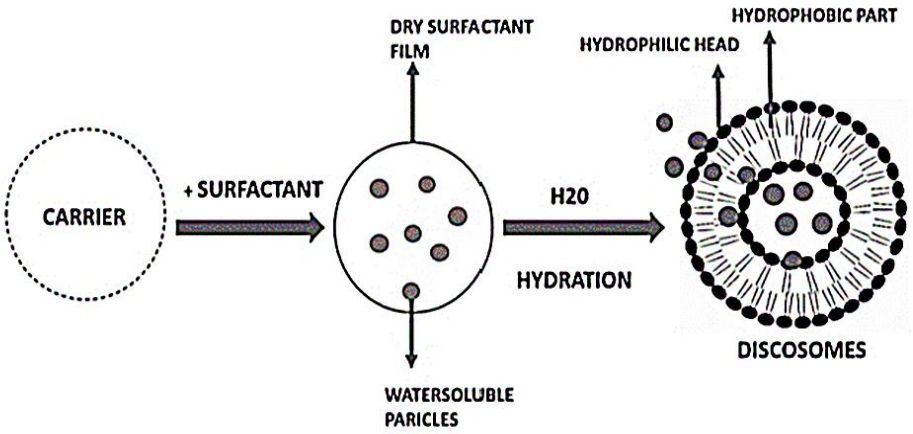

Fig no 4: Mechanism of action of Discosomes

Upon administration into the ocular cavity, the particles reside at the site of delivery and then diffuse into the membrane through the ligand-gated mechanism. The residence time of the drug is associated to the corresponding spreading coefficient of the vehicle and the ability of polymer to drag aqueous fluid as the vehicle spreads over the surface with each blink. Discosomes cause thermodynamic activity gradient of drug which acts as the perforating stimulant for lipophilic drugs transverse across the cell membrane. Rarely penetration enhancers are added to multiply the bio-availability of drug by promoting the permeability. Examples of some penetration enhancers are actin filament inhibitors, chelators, etc.

EVALUATION OF DISCOSOMES

- **Thickness of the film**

The thickness of the film is estimated by a dial calliper at different points of the discosome, followed by the calculation of its mean value.

- **Uniformity of drug content**

The uniformity of drug content is determined by the use of a cast film, cut at discrete places and tested for active drug.

- **Uniformity of weight**

Uniformity of weight is analysed using three patches, weighed randomly and any patch crossing the Known threshold difference in weight is disqualified[16].

- **Drug encapsulation**

To obtain high drug encapsulation efficiency, respective principal Components consisting of the shape of the selected surfactant, lipid level, content of cholesterol, and drug content must be optimized.

- **Entrapment efficiency**

Entrapment efficiency evaluation involves the split out of residual drug that is not entrapped by dialysis, centrifugation, or even by gel filtration, and the amount of drug remaining entrapped is determined using complete vesicle disruption[17].

- **Vesicle diameter**

The vesicular diameter of discosomes can be measured due to their spherical shape, which is an added perk. The breadth can be assessed using photon correlation microscopy, light microscopy, and freeze-fracture electron microscopy[18].

- ***In vitro* release.**

The method of in vitro release study encompasses the use of dialysis tubing wherein a dialysis sac is scrubbed and immersed in distilled water. The vesicle suspension made up of

tubing is pipetted into a bag and sealed. The bag restraining the vesicles is set in 200 ml of buffer solution in a 250 ml beaker combined with continuous shaking at 25 °C. The buffer is inspected for drug content by a suitable assay method at various time intervals[19].

CONCLUSION

The novel drug delivery system is of more than the conventional system of medicine. The use of discosomes in the case of diseases like diabetic retinopathy, age-related muscular degeneration etc. can be very useful where drug delivery to the target site has become an uphill assignment. Discosomes are found to be more site-specific and show considerable patient acceptance in clinical studies. A study was conducted which showed results as discosomes were found to entrap timolol maleate way better than niosomes and thus it also has better in vivo bioavailability. The use of drug delivery system like discosomes enhance drug permeation and provide optimal drug delivery. The current momentum in new drug delivery invention holds a promise for much progressed ocular therapies in the future to cure diseases that are vision-threatening.

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