International Journal of Science and Research Archive

eISSN: 2582-8185

Cross Ref DOI: 10.30574/ijsra

Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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Overview on pulsatile drug delivery system

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International Journal of Science and Research Archive, 2022, 05(02), 110–118

Publication history: Received on 19 February 2022; revised on 27 March 2022; accepted on 29 March 2022

Article DOI: https://doi.org/10.30574/ijsra.2022.5.2.0067

Abstract

Traditionally, drugs are released in an immediate or extended fashion. However, in recent years, pulsatile drug release systems are gaining growing interest. Pulsatile drug delivery systems are developed to deliver drug according to circadian behavior of diseases. The product follow a sigmoidal drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. Pulsatile release systems can be classified in multiple-pulse and single-pulse systems. A popular class of single-pulse systems is that of rupturable dosage forms. Other systems consist of a drug-containing core, covered by a swelling layer and an outer insoluble, but semipermeable polymer coating or membrane. The potential benefits of chronotherapeutics have been investigated and established for number of diseases like asthma, arthritis, cancer, diabetes, epilepsy, hypertension, ulcer, hypercholesterolemia etc.

Keywords: Pulsatile Delivery; Osmosis; Membrane Erosion; Solubilization

1. Introduction

Oral controlled drug delivery system represents the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. But there are certain conditions which demand the release of drug after a lag time. i.e. chronopharmacotherapy of diseases which show circadian rhythms in their pathophysiology. Recent studies have been revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. There are many conditions that demand pulsatile release like:

- Many body functions that follow circadian rhythm e.g. Secretion of hormones, acid secretion in stomach, gastric emptying and gastrointestinal blood transfusion.
- Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer and hypertension.
- Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase as this tends to reduce their therapeutic effect.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g. peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.

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- Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.
- The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite and potential food drug interactions require delayed release of the drug to the extent possible.

All of these conditions demand for a time controlled therapeutic scheme releasing the right amount of drug at the right time. This essential requirement is fulfilled by Pulsatile Drug Delivery Systems. Today, a vast amount of literature reports that biological processes are not constant but vary according to time. Although much of drug delivery research has focused on constant drug release rate due to limitations of delivering drug according to disease rhythmicity, clinical studies show that magnitude of rhythmic differences can be to a great extent and a strong determinant of when during 24 hour most morbid and mortal event will occur. For many drugs constant release system is not suitable. Drugs not suitable for constant release are used in disease condition that exhibit rhythmic variation within a circadian cycle. Such systems release the drug with constant or variable release rates. The oral controlled release system shows atypical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action [1].

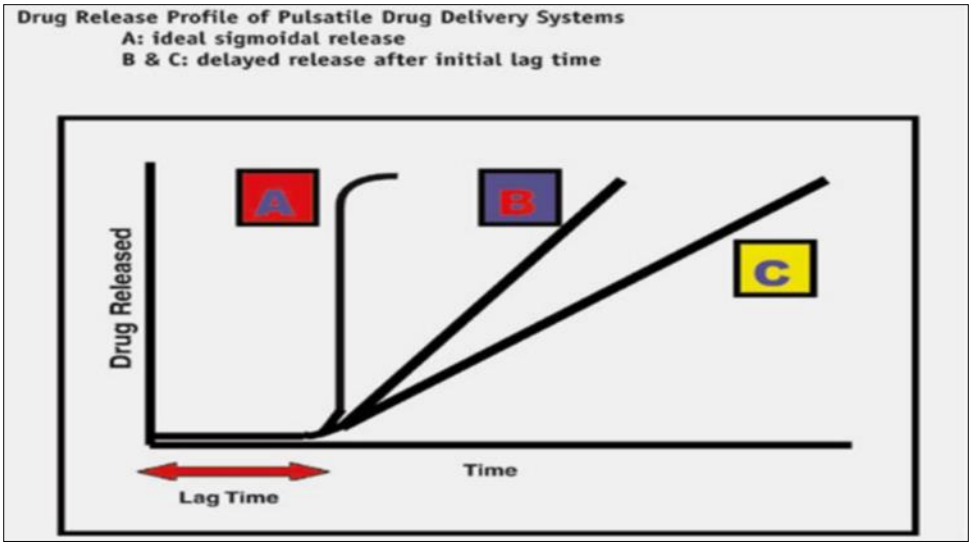

Figure 1 Drug release profile of pulsatile drug delivery system [2]

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- The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite, and potential fooddrug interactions require delayed release of the drug to the extent possible [3].

1.1. Advantages of Pulsatile Delivery

- Reduced dosage frequency.
- Improved patient compliance.
- Reduction in dose.

- Drug targeting to specific site.
- Drug loss is prevented by extensive first pass metabolism [4].

2. Pulsatile drug delivery system

Pulsatile drug delivery system is the most interesting time and site specific system. This system is designed for chronopharmacotherapy which is based on circadian rhythm. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e. a zero-order release is not desired. *(*Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug within a short time period immediately after a predetermined off-release period, i.e., lag time*)* (Fig. 1) Various systems like capsular systems, osmotic systems, pulsatile system based on the use of soluble or erodible polymer coating, use of rupturable membranes and pulsatile system based on membrane permeability are beneficial for the drugs having chronopharmacological behavior [4] where night time dosing is required and for the drugs having high first-pass metabolism and having specific site of absorption in gastrointestinal tract.

Pulsatile systems are gaining a lot of interest as the drug is released completely after defined lag time. Pulsatile drug delivery system is time and site specific drug delivery system, thus providing special and temporal delivery and increasing patient compliance. Such a novel drug delivery has been attempted for the following:

- Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology.
- Avoiding degradation in upper gastrointestinal tract, e.g., proteins and peptides.
- For time-programmed administration of hormones and many drugs such as isosorbide dinitrate to avoid suppression of hormones in the body that can be hampered by constant release of hormone from administered dosage form and development of resistance.
- For drugs which develop biological tolerance, for the drug with extensive first pass metabolism and for drugs targeted to specific site in the intestinal tract, e.g. colon.

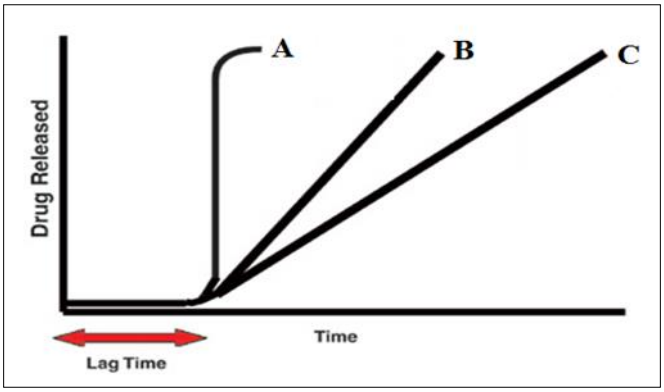

Figure 2 Drug release profile of pulsatile drug delivery systems-Ideal sigmoidal release (A), Delayed release after initial lag time (B & C)

2.1. Chronopharmacotherapy

Recent studies have revealed that diseases have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions. “Chronopharmaceutics” consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in ourbody [5]. They are:

2.1.1. Circadian

This word comes from Latin word “circa” means about and “dies” means day.

2.1.2. Ultrdian

Oscillations of shorter durations are termed as ultrdian (more than one cycle per 24 h).

2.1.3. Infradian Oscillations that is longer than 24 h (less than one cycle/day).

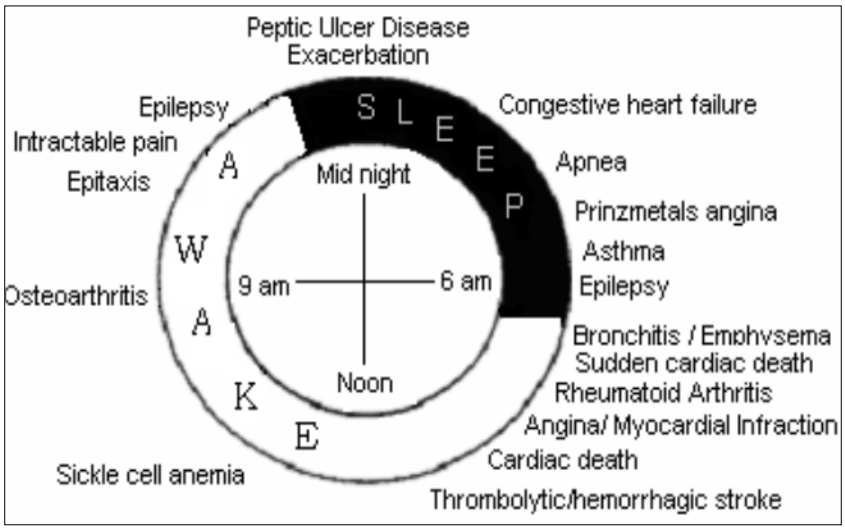

Figure 3 Cycle of circadian rhythm

2.2. Diseases Required For Pulsatile Technology

There are number of diseases which required to be formulated as PDDS as like: hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases (e.g. hypertension and acute myocardial infarction) and colonic delivery. The rationale for chronotherapy of pulsatile release for each of these diseases will be briefly reviewed in tabular and text form in table 1.

Table 1 Diseases requiring pulsatile drug delivery [6]

Diseases	Chronological behaviour (category of drugs used)
Arthritis	Pain in the morning and more pain at night (NSAIDs, Glucocorticoids)
Asthma	Precipitation of attacks during night or at early morning hour (Antihistamines andβagonist)
Cardiovascular disease	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period (Nitroglycerine, calcium channels blockers)
Diabetes mellitus	Increase in the blood sugar level after meal (sulfonyl urea, biguanide, insulin)
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time(HMGCo-Areductase enzyme)
Peptic ulcer	Acid secretionis high (H^2 blockers)

3. Methods for Pulsatile Drug Delivery

3.1. Single unit systems

3.1.1. Capsular system

Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body. e.g.: Pulsincap® system. In this system a water insoluble body containing the drug formulation, system is closed with a swellable hydrogel as shown in fig 4. Plugged (insoluble but permeable & swellable) at open end. Upon contact with, gastrointestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position & dimensions of plug, control lag-time. For rapid release of water insoluble drug effervescent or disintegrating agents is added [8] Plug material is generally made up of following:

- Swellable materials coated with but permeable polymer (polymethacrylates).
- Erodible compressed polymer (HPMC,polyvinyl alcohol).
- Congealed melted polymer (glyceryl mono oleate).
- Enzymatically controlled erodible polymer (pectin)

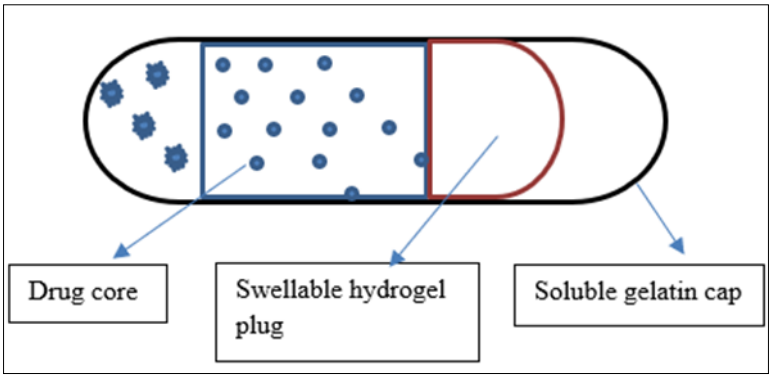

Figure 4 Design of Pulsincap® system[9]

3.1.2. Pulsatile Delivery by Osmosis

This system consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. This system shows good *in-vivo* and *in-vitro* correlation in humans and used to deliver methylphenidate to school age children for the treatment of Attention Deficit Hyper activity Disorder (ADHD), **e.g**.: Port® System. Another system is also based on expendable orifice that contain capsular system in which liquid drug is absorbed on highly porous particles. Drug releases through orifice of a semi permeable capsule supported by an expending osmotic layer after the barrier layer is dissolved. The Port® System (Port Systems, LLC) consists of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g.lipidic) and an osmotically active agent along with the drug formulation (Figure 3).When in contact with the aqueous medium, water diffuses across the semipermeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness [10,11]

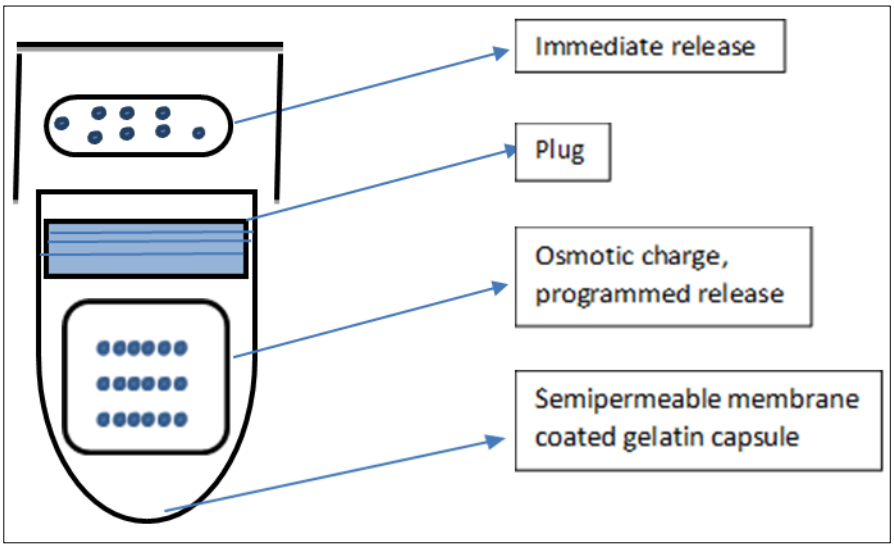

Figure 5 Design of Port® system [13]

3.1.3. Pulsatile Delivery by Solubilisation (or) Erosion of Membrane

These systems are based up on a drug reservoir surrounded with a soluble or erodible barrier layer that dissolves with time and the drug releases at once after the lag time. e.g. time clock® system. The Time Clock system consists of solid dosage form coated with lipid barriers such as carnauba wax & beeswax along with surfactants like Polyoxyethylene sorbitan monooleate [12]. When this system comes in contact with the aqueous medium the coat emulsifies or erodes

after the lag-time depending on the thickness of coat. The lag time of system is independent of the gastrointestinal motility, PH, enzyme & gastric residence[14,15].

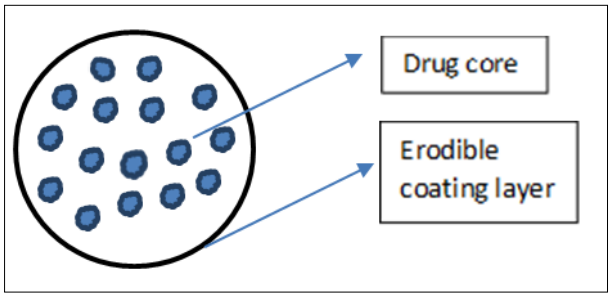

Figure 6 Erosion of membrane system [17]

3.1.4. Pulsatile Delivery by Rupture of Membrane

System coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents (or) swelling agent. Citric acid & sodium bicarbonate is incorporated as effervescent mixture in tablet core coated with ethyl cellulose, when system comes in contact with water it produces carbon dioxide gas which exerts pressure & after lag time rupture the membrane & rapid release of drug occurs [13,16]. A reservoirsystem with a semi permeable coating is proposed especially with drugs with high first pass effect in order to obtain in-vivo drug pattern similar to the administration of several immediate release doses croscarmellose sodium starch glycollate or low substituted hydroxy propyl cellulose were used as swelling substances, which resulted in complete film rupture followed by rapid drug release. The lag time is controlled by composition of outer polymeric membrane[17,18].

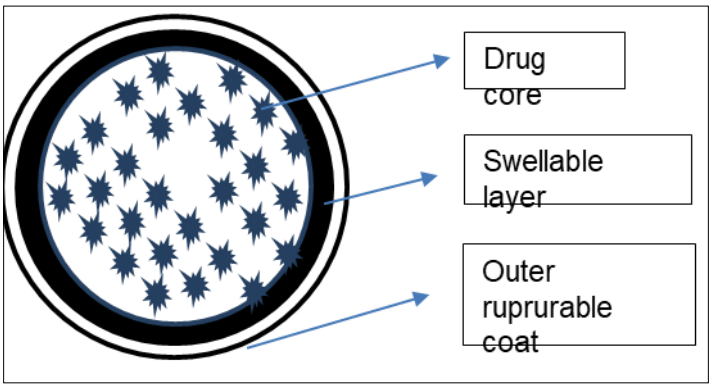

Figure 7 Delivery systems with rupturable coating layer [20]

3.2. Multiple unit systems

Multiparticulate systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar seeds these granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The active pharmaceutical ingredient may also be blended or granulated with polymers before coating to provide an additional level of control. However, drug loading in this type of system is low due to higher need of excipients[19,20]

3.2.1. Pulsatile Delivery by Rupturable Coating

Similar to single unit system, the rupturing effect is achieved by coating the individual units with effervescent (or) swelling agents. Drug delivery was controlled by the rupture of the membrane. The timing of release was controlled by the thickness of coating and the amount of water soluble polymer to achieve the pulsed release. [21] The swelling agent includes superdisintegrents like carboxymethylcellulose, sodium starch glycollate, and L-hydroxy propyl cellulose. Polymers like polyacrylic acid, polyethylene glycol etc. alternatively comprising of a mixture oftartaric acid & sodium bicarbonate that used as effervescent agent. The commercial products of pulsatile drug delivary system are present in table 1[22,23]

Table 2 Commercial products of pulsatile drug delivery system

Technology	Mechanism	Proprietary name and dosage form	API	Disease
OROS*	OROS* Osmotic	Covera-H5*; XL tablet	Verapamil HCL	Hypertension
Three dimentional printing*	Externally Regulated system	Their Form*	Diclofenac sodium	Inflammation
DIFFUCAPS*	Multiparticulate system	Innopran*; XLtablets	Verapamil HCL, Propranolo lHCL	Hypertension
Pulsincap TM	Pulsincap TM	PulsincapTM	Dofetilide	Hypertension

4. Evaluation parameters for pulsatile release tablets

4.1. The Percentage Weight Variations Test

The weight of the core tablet being made was routinely determined to ensure that a tablet contains the proper amount of drugs. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit [24].

4.2. Hardness Test

The resistance of core tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet should be checked by using Monsanto hardness tester according to IP. The hardness is measured in terms of kg/cm^2 [25].

4.3. Disintegration Test

Tablet disintegration is an important step in drug absorption. The test for disintegration can be carried out in the Electro lab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of core tablets, one tablet to be placed in each tube and the basket rack is to be positioned in a 1 liter beaker containing 6.8 phosphate buffer solution at 37 °C ± 1 °C such that the tablet remains 2.5 cm below the surface of the liquid [26,27]

4.4. Friability Test

20 core tablets should be weighed and the initial weight of these tablets is to be recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets should be removed from the friabilator, dusted off the fines and again weighed and the weight was recorded. Friability should be NMT 1% [28]

4.5. Thickness Test

Thickness of the tablet is important for uniformity of tablet size. Thickness is measured using Vernier Calipers. It should be determined by checking the thickness of ten tablets of each formulation [29].

4.6. Release Kinetics

As a model-dependent approach, the dissolution data of best formulation fitted to four popular release models such as zero-order, first-order, Higuchi and KorsmeyerPeppa's equations. The order of drug release from matrix systems was described by using zero-order kinetics or first-order kinetics. The mechanism of drug release from the matrix systems was studied by using the Higuchi equation and Koresmeyer Peppa's equation.

- Q = kot (zero order release kinetics)
- In (1-Q) = - K1t (First order release kinetics)
- Q = K2t½ (Higuchi equation)
- Mt /M0 = K.tn KoresmeyerPeppa's equation (Power Law)
- Where Q is the amount of drug released at time t,

- K0 = zero-order rate constant,
- K1 = first-order rate constant,
- K2 = Higuchi rate constant,
- Mt is the amount of drug released at time t
- M0 is the amount released at time 0,

Thus, the Mt/M0 is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent [30].

5. Conclusion

Although sustained and controlled drug delivery systems have gained a lot of success and application in field of medication, these systems fail to deliver drug according to circadian behavior of diseases for which pulsatile systems are beneficial. For successful development of chronotherapeutic dosage form, knowledge of circadian time structure, rhythm in disease pathophysiology or 24 hour pattern in symptom intensity of chronic medical conditions and chronopharmacology of medication is needed. Significant progress has been made towards achieving pulsatile drug delivery system that can effectively treat diseases with non-constant dosing therapy.

Compliance with ethical standards

Acknowledgments

The authors are thankful to the Principal of R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur for providing the necessary facilities, support and encouragement.

Disclosure of conflict of interest

The authors have no conflicts of interest regarding this investigation.

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