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Research Article

Technologies in Pulsatile Drug Delivery System

Supriya. Shidhaye*, Ashwini. Dhone, Tejal. Budhkar and Chaitali. Surve

Department of Pharmaceutics, Vivekanand Education Society's College of Pharmacy

Mumbai, India.

ABSTRACT

Pulsatile drug delivery system (PDDS) has developed because of their multiple advantages over conventional dosage forms. These systems are designed according to the circadian rhythm of the body, and the drug is released rapidly and completely as a pulse after a lag time or an off release phase. These systems are beneficial for drugs with chronopharmacological behaviour, where nocturnal dosing is required, and for drugs that show the first-pass effect. They deliver the drug at the right time, at the right site of action and in the right amount, which provides more benefit than conventional dosages and increased patient compliance.

The aim of this review is to introduce the concept of chronopharmaceutics, to cover the technologies that have been developed to achieve pulsatile delivery such as Pulsincap®, Diffucaps®, CODAS®, and PULSYS™; which follow the above mechanism to render a sigmoidal drug release profile. Diseases wherein PDDS are promising include asthma, peptic ulcers, cardiovascular ailments, arthritis and attention deficit syndrome in children and hypercholesterolemia. Therefore, pulsatile drug delivery systems have the potential to bring new developments in the therapy of many diseases.

Keywords: Chronopharmacological behaviour, circadian rhythm, lag time, Chronopharmaceutics.

INTRODUCTION[1-4]

Oral drug delivery is one of the widest segment of the total drug delivery market. Oral dosage forms are known to provide a zero order or first order release in which the drug is released at a substantially steady rate of release per unit of time. There are certain conditions for which constant release pattern i.e. a zero-order release is not suitable and that demand release of a drug after a lag time. In other words, they require pulsatile drug delivery system. Pulsatile drug delivery is time and site-specific drug delivery, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body.

Chronopharmacotherapy

"Chronopharmaceutics" consist of two words chronobiology and Pharmaceutics.

Pharmaceutics is the discipline of pharmacy that deals with the process of turning a new chemical entity (NCE) into a medication to be used safely and effectively by patients. It is also called the science of dosage form design and deals with the formulation of a pure drug substance into a dosage form.

Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body, they are:

a) **Circadian**
"Circa" means about and "dies" means day.

b) **Ultradian**
Oscillation of shorter duration is termed as Ultradian (more than 1 cycle per 24 hrs).

c) **Infradian**
Oscillations those are longer than 24 h (less than one cycle per day).

Table 1: Targets for pulsatile drug delivery

Disease	Chronological behaviour	Drugs used
Asthma	Precipitation of attacks during night or at early morning	Antihistamines, B2 agonist
Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate
Arthritis	Pain increases in early morning caused by the marked release of inflammatory cytokines, including interleukin-6 in the early hours of the morning.	NSAIDs, Glucocorticoids
Cancer	Blood flow to tumour is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase	Vinca alkaloids, Taxans
Duodenal ulcers	Gastric acid secretion is highest at night,bowel motility& gastric empting are slower at night	Proton pump inhibitors
Peptic ulcers	Acid secretion is high in afternoon & at night	H2 Blockers
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitor
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, Insulin
Neurological disorder	Central pathophysiology of epilepsy and behavioural classification of convulsive events	MAO-B inhibitor
Cardiovascular disease	BP is at its lowest during sleep cycle.	Nitro-glycerine, CCBs, ACE inhibitors

CLASSIFICATION OF PULSATILE DRUG DELIVERY TECHNOLOGIES

This review classifies the technologies in PDDS based on the main routes of drug administration.

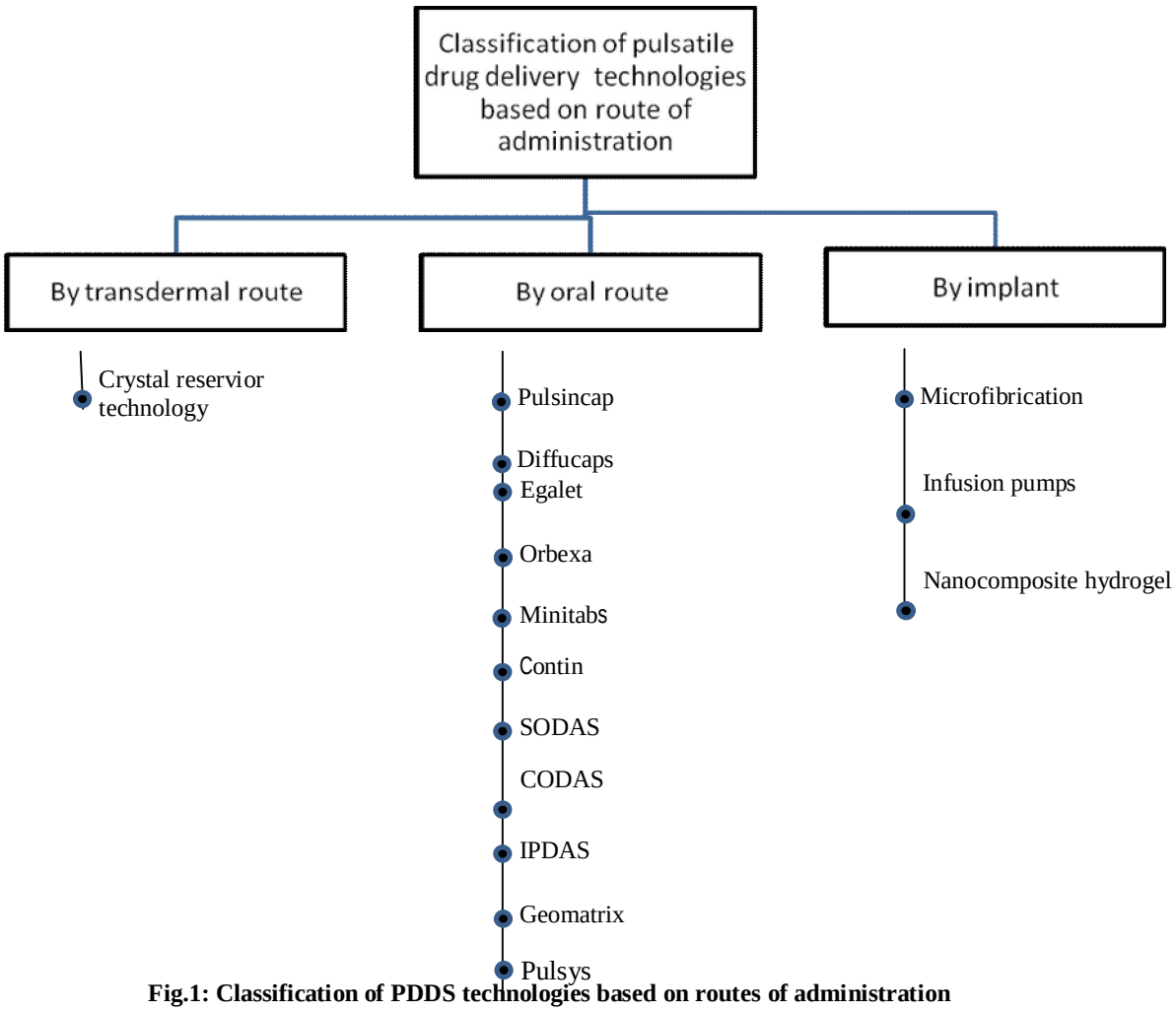

Fig.1: Classification of PDDS technologies based on routes of administration

Benefits of these technologies

- Once daily dose resembling multiple daily doses by releasing drugs in discrete bursts.
- Constant drug levels at the site of action and prevent the peak-valley fluctuations.
- Chance of development of drug resistance and tolerance can be reduced.
- Rate of release independent of pH, food and minimal potential for dose dumping.
- Facility to produce combination dosage forms, ease of combining pellets with different compositions or release pattern.
- Protection of mucosa from irritating drugs.
- Delivery profile designed to compliment circadian pattern.
- Drug loss by extensive first pass metabolism is prevented.
- Reduced dose frequency, dose size and cost, which ultimately reduces side effects and local irritation, thereby improving patient compliance.

Limitations

- Multiple manufacturing steps.
- Homogenicity of the coated barrier is mandatory to assure the predictability of the lag time.
- Rupture time cannot be always adequately manipulated as it depends on the physicochemical properties of the polymer.
- Pulsatile delivery drugs are costly, raw material is not easily available.
- Dosage form design requires highly educated professionals.
- Technologies employed and the equipment used are complicated.

CHRONOMODULATED SYSTEMS FOR ORAL ROUTE

Pulsincap® Technology[5-7]

Pulsincap was developed by R.R.Scherer International Corporation (Michigan).

This device consists of a non-disintegrating half capsule body sealed at the open end with a hydrogel plug that is covered by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When this capsule comes in contact with the dissolution fluid, it swells, and after a lag time the plug pushes itself outside the capsule and rapidly releases the drug. The time lag can be controlled by manipulating the dimension and the position of the plug. For water insoluble drugs, a spontaneous release can be ensured by inclusion of effervescent agents or disintegrants.

The plug material consists of insoluble but permeable and swellable polymers (polymethacrylates), erodible compressed polymers (hydroxypropylmethylcellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (saturated polyglycolated glycerides) and enzymatically controlled erodible polymer (pectin).

Diffucaps® Technology[9]

Developed by Eurand Pharmaceuticals Ltd, USA**.** Diffucaps is a multiparticulate bead system comprised of multiple layers of drug, excipients, and functional polymer membrane to control the rate of drug release. Diffucaps beads are <1.5 mm in diameter and can be filled into capsules. The beads contain a layer of organic acid or alkaline buffer to control the solubility of a drug by creating an optimal pH microenvironment for drugs that exhibit poor solubility in intestinal pH, in environments with pH greater than 8.0, or in physiological fluids. Alternatively, the beads can contain a solid-solution of drug and crystallization inhibitor to enhance bioavailability by maintaining the drug in its amorphous state. Advantages of Diffucaps ® are

- Ideal for drugs exhibiting poor solubility in lower intestinal pH, in environments with pH above 8.0, or in physiological fluids.
- Can combine multiple drugs and/or multiple release profiles in the same dosage form.
- Can minimize food effect.

CONTIN ® Technology[10]

Developed by Purdue Pharma. This technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of their disease (particularly at night), and reducing unwanted side effect.

Molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and react the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations since it has a uniform porosity (semi permeable matrixes) that may be varied**.** This technology has leads to the development of tablet forms for aminophylline, theophylline, morphine, and other drugs.

CODAS® (Chronotherapeutic oral drug absorption system)[14]

Elan Corporation, USA, developed CODAS® technology. Delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads. The release-controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer-coated beads, the water soluble polymer

slowly dissolves, and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of the drug.

Advantages of the CODAS technology include a delivery profile designed to complement circadian pattern, controlled onset, an extended release delivery system, rate of release essentially independent of pH, posture and food, "sprinkle" dosing by opening the capsule and sprinkling the contents on food, reduction in effective daily dose and drug exposure, gastrointestinal tract targeting for local effect and reduced systemic exposure to achieve a target profile.

Egalet® Technology[31]

Developed by Egalet Ltd, Denmark. System consists of an impermeable shell with two lag plugs; active drug is sandwiched between the plugs. After the inert plugs have eroded, the drug is released, thus a lag time occurs. Time of release can be modulated by the length and composition of the plugs. This system shows erosion control drug release. The shells are made of slowly biodegradable polymers (such as ethylcellulose) and include plasticizers (such as cetostearyl alcohol), while the matrix of the plugs is made up of a mixture of pharmaceutical excipients including polymers like polyethylene oxide (PEO). Several opioid products are developed using this technology.

IPDAS® (Intestinal protective drug absorption system)[15]

A new oral drug delivery approach that is applicable to gastrointestinal (GI) irritant drugs, including the non-steroidal anti-inflammatory drug (NSAID) class. The IPDAS technology is composed of numerous high-density, controlled-release beads, which are compressed into a tablet form. Once an IPDAS tablet is ingested, it disintegrates and disperses beads containing a drug in the stomach, which subsequently passes into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state. Release of active ingredient is controlled by the polymer system used to coat the beads and/or the micromatrix of polymer/active ingredient formed in the extruded/spheronised multiparticulates. The intestinal protection by this technology is due to the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the gastrointestinal tract.

Geoclock® [16]

Developed by SkyePharma. It is in form of chronotherapy focused press-coated tablets. Geoclock tablets have an active drug [core] inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a pre-determined release rate. This dry coating approach is designed to allow the timed release of both slow release and immediate release active cores by releasing the inner tablet first, after which time, the surrounding outer shell gradually disintegrates. In addition to controlled release, the Geoclock technology also has applications for the improved release of colonic drug delivery as well as for multiple pulse drug delivery to deliver doses of a drug at specific times throughout the day.

Geomatrix® [17-18]

Developed by Skye Pharma Plc., USA. It is multi-layered tablet which consists of a hydrophilic matrix core, containing the active ingredient and one or two impermeable or semi-permeable polymeric coatings (films or compressed barriers) applied on one or both bases of the core which act as surface controlling barriers.

Advantages of the Geomatrix technology are: can achieve simultaneous release of two different drugs and different rates from a single tablet, their ability to be easily incorporated into the production line, can be manufactured by readily available equipment, reproducibility, controlled release of poorly soluble drugs, timed release of drugs, pulsed release of drugs and safety of use. Some of the drugs that are marketed based on this technology are Diltiazem hydrochloride, Nifedipine, and Diclofenac sodium.

Diffutab®[19]

This technology is useful for sustained and targeted pulsed delivery.

The Diffutab technology incorporates a blend of waxes and hydrophilic polymers that control drug release through diffusion and erosion of a matrix tablet. Diffutabs are particularly useful for high-dose products. This technology is applies to both soluble and insoluble products.

Advantages of Diffutabs

- Matrix tablet utilizes a combination of water soluble particles and active drug
- Suitable for high drug loading
- Supports sustained-release, once-a-day dosing

Pulsys™[20-21]

Developed by MiddleBrook Pharmaceuticals, this enables pulsatile delivery or delivery in rapid bursts of certain drugs and provides the prolonged release and absorption of a drug. The rationale behind designing such a system is that it has been reported that antibiotics are more effective against fast-growing bacteria. When an immediate release antibiotic is administered, bacteria respond to it by going into a dormant stage, while the administration of a pulsatile system in such a case is more effective because the regular release of

increased pulses of antibiotic does not let defence system of the bacteria to go into a dormant stage. The preclinical studies have shown that pulsatile approach of delivering antibiotic is more effective.

SODAS® (spheroidal oral drug absorption system[23]

Developed by Elan Corporation. Multiparticulate drug delivery system, consist of uniform spheroidal beads of 1-2mm in diameter. Each bead begins as an inert core onto which the drug is applied, followed by a number of layers of soluble and insoluble polymers combined with other excipients to produce the rate-controlling layer. Drug release from these beads occurs by a diffusion process. Within the GI tract, the soluble polymers dissolve, leaving pores within the outer membrane. Fluid then enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the *in vivo* dissolution and absorption phases. The immediate environment of the drug within the seed core can be manipulated by use of excipients to ensure optimal stability and solubility. These controlled-release beads can be packaged into a capsule or compressed into a tablet to produce the final dosage form. Based on the production of controlled release beads, the SODAS® technology is characterized by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs.

Orbexa® [24]

Developed by Aptalis Pharmaceutical Technologies**.** Orbexa technology is a multiparticulate system that enables high drug loading and is suitable for products that require granulation. This technology consists of beads of a controlled size and density using granulation/extrusion and spheronization techniques. These beads provide higher drug concentration, can be coated with functional polymer membranes for additional release rate control and can also be used for sensitive drugs such as proteins, enzymes.

This technology can be used for gastric protection, delayed release, sustained release, site-specific delivery, pulsatile delivery, complex release pattern, separation of incompatibles and combination products. Orbexa beads can be filled into capsules or single-dose sachets.

Minitabs® [25]

Developed by Aptalis Pharmaceutical Technologies. It consists of tiny (2 mm x 2 mm) cylindrical tablets coated with a functional membrane to control the rate of drug release. They contain gel-forming excipients that control drug release rate. Additional membranes may be added to further control release rate. The tablets are filled into capsules, allowing a combination of multiple drugs and/or multiple release profiles in the same dosage form. Minitabs can be formulated as matrix tablets prior to further coating.

Advantages of Minitabs are: They combine the simplicity of tablet formulation with the sophistication of multiparticulate systems, suitable for high drug loading, and can be used as a sprinkle for pediatric and geriatric patients who have difficulty swallowing tablets.

CHRONOMODULATED SYSTEMS FOR TRANSDERMAL ROUTE[26-27]

Crystal reservoir system

Crystal Reservoir Technology is small patches, which shows controlled and sustained drug release. Release of a drug is based on the oversaturation of an adhesive polymer with drug, thus forcing a partial crystallization of the drug. The presence of both molecular solute and solid crystal forms allow for a considerably higher concentration and consistent supply of drug. As the skin absorbs the molecular solute, crystals re-dissolve to maintain maximum thermodynamic activity at the site of contact. By modifying the concentration of crystals to solute, various patterns of drug release are achieved.

Chrononomodulated delivery systems by implant route

Chronomodulated infusion pumps[30]

These pumps are usually characterized by a light weigh (300–500 g) for easy portability and precision in drug delivery. Implantable infusion pumps used in Insulin therapy containing a reservoir of insulin may be surgically placed within the subcutaneous tissue of the abdomen in the left upper or lower quadrant (above or below the belt). A catheter leads from the pump through the muscle layers into the peritoneal cavity where it floats freely and insulin delivery is by intraperitoneal route. The insulin reservoir is refilled after 1 or 3 months by inserting needle through skin into pump. Doses adjustments are made by the patient--within ranges established by the physician--using radio elementary and an electronic device that is held over the pump. Examples of infusion pumps are Melodie®- The Melodies pump has been used successfully in cancer chemotherapy indicating that the chronopharmaceutical systems for the parenteral route are important alternatives for effective and safe cancer therapy further studies showed that the major material cost of chronochemotherapy devices was balanced by a better tolerability profile, other are programmable Synchromed®, Panomat® V5 infusion and the Rhythmic® pumps. Possible drawbacks of this approach include eventual formation of fibrous tissue pocket and local skin erosion.

Microfabrication[28]

These devices contain small reservoirs loaded with drugs and separated from outside environment by thin membrane. The active silicon-based microchip membrane is thin layer of gold. In order to release the drug the voltage need to be applied**.** The release mechanism is based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. Here a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand. A study for release have been conducted with a prototype microchip using gold and saline solution as a model electrode material and release medium, and demonstrated controlled, pulsatile release of chemical substances with this device.

Magnetic nanocomposite hydrogel[29]

Magnetic nanocomposite of temperature responsive hydrogel was used as remote controlled pulsatile drug delivery. Nanocomposites were synthesized by incorporation of superparamagnetic Fe3O4 particles in negative temperature sensitive poly (N-isopropyl acrylamide) hydrogels along with model drug. High frequency alternating magnetic field was applied, the beads oscillate within the matrix, creating compressive and tensile forces, and hydrogel temperature increases results into accelerated collapse of gel. This in turn acts as a pump to push an increased amount of the drug molecule out the matrix to produce on demand pulsatile drug release from nanocomposite hydrogel.

Also magnetic particle like magnetite, iron, nickel, cobalt and steel can also be incorporated.

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Obstacles in PDDS research and development[30-31]

Currently there are three major hurdles for the successful transition of PDDS from laboratory to Market. These include the challenges to identify adequate rhythmic biomaterials and systems, rhythm engineering and modelling, and regulatory issues.

a) Rhythmic biomaterials and systems- There have been good progress in development of systems intended for chronotherapy but the true breakthrough in this field will only be possible with smarter biomaterials. Advances in microfabrication, nanotechnology, and polymer chemistry in near future will make development of such material possible.
b) Rhythm engineering and modelling- The second major hurdle to chronopharmaceutical drug formulation is ability to engineer rhythm and use reliable models, to predict the complex physicochemical properties of these novel delivery systems as well as their biological responses.
c) Regulatory issues- Regulatory is another big question.As a whole, developing a commercially successful NDDS poses many challenges. In preapproval phase it is sometimes difficult to show chronotherapeutic advantage in clinical settings. In postapproval phase causal recreational drug abuse along with on a much larger scale, by the criminal diversion of these modified formulations for profit have arisen problems. The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow an approval of a drug to go forward while exercising some restrictions.

Table 2: Example of FDA approved pulsatile drug delivery systems in market

S. No	API	Proprietory name,dosage form	Chronopharmace-utical technology used	Diseases
1.	Theophyline	Uniphyl®: extended release tablets	CONTIN®	Asthma/increased bronchoconstriction in morning
2.	Verapamil HCl	CoveraHS: extended release tablets	OROS®	Hypertension/increased BP in early morning
3.	Verapamil HCl	Verelan® PM: extended release capsules	CODAS®	Hypertension
4.	Methylphenidate HCl	Concerta® tablet	OROS®	Attention deficit syndrome
5.	DiltiazemHCl	Cardizem®LA: extended release tablets	CEFORM®	Hypertension
6.	Propranolol HCl Verapamil HCl	Innopran® XL: extended release capsules	DIFFUCAPS®	Hypertension
7.	Dofetilide	PulsincapTM	PulsincapTM	Hypertension
8.	Tulobuterol	Hokunalin® tape	Transdermal chrono-delivery system.	Asthma
9.	Amoxicillin	MOXATAG®: extended-release tablets	PULSYS™	Antibiotic

CONCLUSION

Rapid advancement and newer developments in the field of drug delivery have led to the formulation of the pulsatile drug delivery system, which can be formulated with ease and, provides a significant amount of therapeutic benefits.The market for drug delivery systems has come a long way and will continue to grow at an impressive rate.

The circadian disorders generally require Chronopharmacotherapy, which can be easily accomplished by pulsatile drug delivery system in a very organized manner. With the advent of pulsatile drug delivery, one can remain assured of accomplishment of goal for safe and effective therapy. Although several milestones have been reached in this respect, there are still some unexplored facets of pulsatile drug delivery that can open new vistas through better engineering of the same. Today's drug delivery technologies enable the incorporation of drug molecules into new delivery systems, thus providing numerous therapeutic and commercial advantages. A large number of companies are involved in the development of new drug delivery systems, which is evident by an increased number of products in the market and the number of patents granted in the recent past.

Tomorrow's drugs definitely will be more challenging in terms of the development of delivery systems, and pharmaceutical scientists will have to be ready for a difficult task ahead.

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