



Pulsatile drug delivery system

Introduction

Traditional drug delivery system, or TDDS, is the classical method of delivering a drug to the body without controlling the rate or time of drug release.

On the other hand, modified drug delivery system, or MDDS, is a more recent method to introduce a drug into the body with the adjustment of time, rate, and site of medication liberation. An important type of MDDS is pulsatile drug delivery systems, PDDS, in which the drug is released from its formulation after a pre-determined off-release period or into a specific body site under certain conditions. This period is called lag time and defined as the time needed to release a drug from the dosage form after placing it in an aqueous environment. In an ideal pulsatile drug delivery system, the drug is released completely and rapidly after a lag time; however, drug release can be in a sustained or delayed fashion.

Certain diseases such as arthritis, cardiovascular diseases, peptic ulcer and hypercholesterolemia can be targeted by PDDS.

These are good targets for PDDS due to their unique daily rhythmic activity, and the pulsatile release of the drugs mimics the activity patterns of these disorders. For instance, colon-specific release has been achieved by PDDS to manage irritable bowel disease.

Many pharmaceutical companies have become more interested in PDDS, which follows the same physiological release pattern of the endocrine system. Moreover, many physiological functions are affected by the body's rhythm, including gastric and urinary pH, GI motility, blood pressure and body temperature[1]. In addition, some conditions follow a certain rhythm in their activity, and constant release of the drug is not suitable for these conditions because of increased side effects. PDDS target these conditions only when they are active, minimising side effects.

Advantages (2-6)

- Best option for conditions that follow a circadian

rhythm in terms of their daily activity.

- Better absorption and bioavailability in comparison to TDDS and sustained release, because of complete release of the drug from the formulation.
- Ability to target specific organs or tissues increases the bioavailability of poorly bioavailable drugs.
- Drug frequency and dose used in PDDS is lower than in TDDS. This will reduce side effects and will increase patient compliance and decrease the cost.
- First pass metabolism can be avoided, leading to less drug-drug interactions.
- Risk of local GI irritation is lowered.
- No risk of dose dumping effect.
- Reduced chance of developing biological tolerance.
- Reduced intra- and inter-patient variability.
- Many solid dosage forms have been successfully made as PDDS, including tablets, capsules, microspheres, and pellets.

Disadvantages

- Low medication loading limit and incomplete discharge of medication
- Higher expense of formulation
- Huge number of procedure variables
- Absence of creation reproducibility and efficacy
- Erratic *in vitro-in vivo* correlation
- Complex equipment needed in manufacturing [7]

Classification

PDDS can be classified based on their target release, including time-controlled, site-specific or stimuli-induced systems in which the drug is released under gastrointestinal pH or enzymatic control, and externally regulated

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systems where the active components are liberated in response to irradiation, ultrasound, magnetism and electrical effect. The other classification depends on the technology used to prepare PDDS, consisting of both single and multiple unit systems.

Classification based on target release

Time-controlled pulsatile release

Time-controlled pulsatile release dosage forms are used to liberate the medication after a predetermined lag time. This delayed release is not affected by gastric pH, enzymes or motility. However, it is influenced by the delivery system, in which the active agent is released by different mechanisms depending on the type of barrier coating [8].

In formal techniques, water-soluble coatings were used in order to achieve slow dissolution in the intestine to liberate the active ingredient. Another technique is to surround an osmotic agent and drug molecules by a water-permeable but insoluble coat. Once the tablet reaches the GI tract, water diffuses gradually through the coat into the core, where the osmotic agent swells until the coat bursts to liberate drug molecules. In addition to these two techniques, a water-impermeable film with a controlled opening can be used to enclose the active ingredient. As water from GI tract enters the tablet through this opening, core release occurs once the film bursts [9].

Stimuli or site specific delivery system

A. Gastrointestinal pH dependent release

Different sites of the GI tract have different pH conditions. One example of a pH dependent release is enteric coated oral dosage forms. Enteric coating usually consists of weakly acidic polymers that maintain their non-ionized form at gastric pH; however they are ionized at intestinal pH and therefore soluble in the intestine [9]. One formulation example is theophylline, which is designed to relieve symptoms of nocturnal asthma. The inner core consists of micro-encapsulated theophylline coated with eudragit L-100 and S-200, which are pH sensitive co-polymers. This core is capped by a hydrogel plug followed by an insoluble hard gelatin and a soluble cap. The whole dosage form is enteric coated in order to achieve pH dependent release [10].

B. Intestinal enzymes dependent release

Many bacterial species present in the colon undergo vitamin K synthesis, releasing some enzymes, and immunity function. Sulfasalazine is a pro-drug consisting of sulfapyridine and mesalamine, which is the active moiety. Sulfasalazine is the first pro-drug that utilises bacterial enzymes called azoreductases which break the azo bond between sulfapyridine and mesalamine in the colon in order to exert their pharmacological action in patients with rheumatoid arthritis or irritable bowel syndrome. Many side effects have been experienced by patients due to the presence of sulfapyridine in the formulation, so newer dosage forms have replaced it with dextran, pectin or other natural polysaccharides [2].

C. GI transit time/pressure dependent release

Different parts of the GI tract have different transit times. Gastric transit time is not constant between individuals, and it depends on the type of diet, mobility, diseases and drugs. However, it can be utilised to deliver the drug to the large intestine after a lag time of around 5-6 h. In addition to transit time, the difference in the pressure of different regions in the GI tract can also be useful to achieve site specific drug delivery. A good example is the use of ethyl cellulose coated dosage forms [11]. The molecular weight of ethyl cellulose can be controlled in order to withstand gastric and small intestinal pressure. High molecular weight results in higher resistance to GI pressure. In comparison to other GI regions, the pressure in the colon is the highest and ethyl cellulose will rupture in the colon, achieving colon specific delivery [12].

D. Inflammation-induced pulsatile release

Numerous mediators such as hydroxyl radicals are released from immune cells during inflammation. Hyaluronic acid is a drug that is degraded by these radicals and also by hyaluronidase enzymes, to exert the anti-inflammatory action. Hyaluronic acid is often indicated to be injected into the affected joint in patients with rheumatoid arthritis [11].

E. Antibody dependent release

Intelligent gels were developed to release the drug in response to antibody concentration. They are able to change their swelling/de-swelling properties by which drug permeation changes. The basic design is to incorporate polymerized antigen-antibody complex in the gel network, and in the presence of the same free antigen, the antibody in the antigen-antibody complex will bind to the free antigen leading to gel swelling and subsequently drug release [11].

F. Glucose-responsive insulin release devices

A novel device that consists of a pH sensitive hydrogel incorporating glucose oxidase and insulin has been used to replace insulin injections. At high blood glucose levels, glucose will be converted to gluconic acid by glucose oxidase. The acidity of gluconic acid causes swelling of the hydrogel, leading to release of the integrated insulin [11].

Externally regulated systems

The advantages of using an external stimulus include choosing the dose, duration and time of drug release. External stimuli used in pulsatile release systems involve electric and magnetic field, as well as ultrasound.

A. Electric field

Preparations using this technique usually contain polyelectrolytes, so they are responding to pH changes and electric field. On application of external electric field to a hydrogel that contains polyelectrolytes, hydroxyl ions will be generated at the cathode, and the local pH will increase. This leads to hydrogel erosion and drug release [13].

B. Magnetic field

Magnetically induced pulsatile release system consists of magnetic beads incorporated in a dosage form, and external magnetic field. The basic mechanism of this approach is to control the movement of oral drugs in the GI tract by magnetic attraction. This can change the onset and the amount of drug absorption through the intestine or stomach [14].

C. Ultrasound

This technique enhances the absorption of topical, inhaled and oral dosage forms. In addition, it may be used to improve drug release from formulations. This idea was applied to an ethylene and vinyl acetate matrix that contains 5-fluorouracil, an anti-cancer drug used to interfere with DNA synthesis to treat various solid cancers. The release of 5-fluorouracil from this matrix is reported to be 27-fold higher than conventional dosage forms [15].

Classification based on technology used

Single unit system

A. Capsular system

An example of capsule based system is Pulsincap[®], (figure 1). This capsule is composed of water-impermeable capsule body, drug core, swellable hydrogel plug and a water-soluble gelatin cap. When the gelatin cap dissolves in GI fluid, the plug

Drug release mechanism from pulsincap system

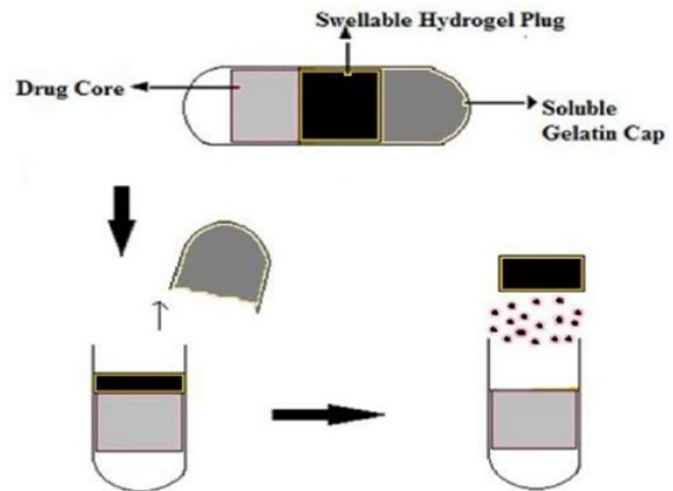


Fig 1. Pulsincap[®] design [16]

swells slowly during a defined lag time and pushes itself outside the capsule to release the drug [16].

B. Osmotic based dosage forms

Various preparations of PDDS, such as PORT system, rely on osmosis to release drugs. The PORT system is composed of drug molecules mixed with an osmotically active agent and capped with an insoluble plug. The whole system is covered with a semi permeable film that allows GI fluid entry, which leads to the expansion of the osmotic agent, and the plug will be pushed out to liberate the drug after a pre-determined time. This system was applied to methylphenidate, used in the management of attention deficit hyperactivity disorder [17].

C. Erodible or soluble barrier system

In this system the lag time will be determined by the thickness of the soluble or erodible coat. Time clock system is an example of a soluble barrier system in which the outer-most layer is composed of a water soluble adhesion coat. The second layer consists of an aqueous dispersion of a hydrophobic surfactant coat, with drug molecules located in the core. Upon exposure to GI fluid, the outer layer dissolves followed by rehydration and re-dispersion of the second layer after a lag time. After that, the drug core is released rapidly and completely [18].

D. Rupturable coating

In formulations with rupturable coating, effervescent ingredients, swellable agents or osmotic driving force are commonly added to the core to rupture the outer layer, which is mainly composed of non-

flexible ethyl cellulose. The lag time depends on the thickness of the coat and core hardness [4].

Multiple units

Systems providing multiple doses are more convenient for patients with chronic conditions. One of the multiple units systems is a capsule consisting of three pellet populations; each population has a different coat to control the time of drug release through controlling water permeability. However, the core of the three pellet groups contains the same active ingredient with a swellable agent to rupture the coat when an adequate amount of water enters the pellet. This system is illustrated in figure 2 [11].

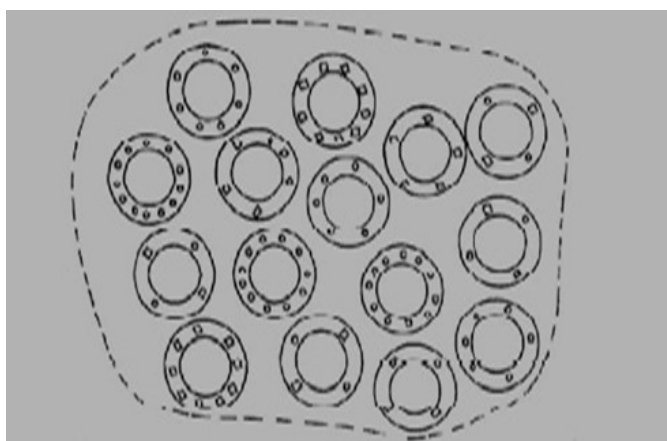


Fig 2. Three pellet populations with different coating surrounded by a capsule [11].

Targeted diseases for PDDS

Many body functions and some disease conditions are regulated by infradian, circadian or ultradian rhythm. One cycle of infradian rhythm usually ends in less than 24 h, while a cycle of circadian rhythm is completed in 24 h. On the other hand, one cycle of ultradian rhythm is the longest and is completed in more than 24 h. Based on chronobiology, there has been much interest in developing chronopharmaceuticals, drug delivery systems such as PDDS matching the rhythmic activity of some medical conditions [19]. Some examples of conditions that follow rhythmic cycles in their activity and can be targeted for PDDS are shown in Table 1.

Applications and recent technologies

DIFFUCAPS®

Gastrointestinal pH is one of the most important

factors that can affect drug solubility and absorption, and it differs in each anatomical region. The slightly alkaline small intestine is the best site for drug release, dissolution and absorption. Basic drugs such as carvedilol and dipyridamole are unable to dissolve in the small intestine to be absorbed; therefore these drugs will have low bioavailability. To overcome this problem, EurandCompany developed Diffucaps technology which incorporates an acid or a crystallization-inhibiting polymer on an inner core. The benefit of the incorporated acid is to maintain the soluble form of the basic drug. The outer layer of the formulation consists of drug-layered beads, and the entire preparation is coated with a functional polymer and filled in a capsule or compressed into a tablet. ARMIX is a preparation that was developed using Diffucaps technology[23].

OROS® technology

OROS technology is mainly used to enhance the absorption of poorly water soluble drugs. It consists of a two or three layer core comprising of one push layer in addition to one or more drug layers. The main components of the push layer include an osmotic agent and water swellable polymers. The drug layer mainly consists of the poorly water soluble drug, a suspending agent and an osmotic agent. This two or three layer core is surrounded by a semi-permeable film. As fluids from the GI tract enter this preparation, a suspension that contains the drug, GI fluids and the suspending agent will be formed in the core. In addition, the push layer will swell to push the suspension outside the dosage form after a pre-determined time. Many preparations, such as Procardia XL®, Ditropan XL® and Concerta® have been developed by applying OROS® technology[6].

The intestinal protective drug absorption system (IPDAS®)

NSAIDs may cause GI irritation. To avoid this problem, IPDAS® has been recently developed as a tablet containing beads that are coated with a controlled release polymer system. After tablet ingestion, the beads will disperse widely in the stomach, and the drug will be released slowly by virtue of the controlled release polymers. This tablet protects the GI tract from irritant drugs by the wide dispersion of the drug containing beads, instead of local accumulation of drug molecules.

The basic concept of IPDAS® was extended and modulated by Elan Drug Technology Company to formulate Naprelan®, which contains naproxen as the active ingredient. The intention was to administer naproxen once daily, so it will be released over an extended period. In addition to extended release, an immediate release was desired for pain relief within

Table 1. Targeted conditions for PDDS and their chronobiological behaviour

Medical condition	Chronobiological behavior
Bronchial asthma	Release of inflammatory mediators and airway resistance peak at night, leading to nocturnal asthma symptoms. At early morning, disease activity is also high due to exposure to antigens such as pollen [20].
Hypercholesterolemia	Hepatic enzymes responsible for cholesterol synthesis, such as 3-hydroxy-3-methyl-glutaryl-CoA reductase, are more active during the night [11].
GI ulcer	Acid secretion from the gastric parietal cells is highest at night and during the presence of food in the stomach [21].
Cancer	Cancer cells usually divide and proliferate faster than other cells. This is an advantage because chemotherapy administration at specific times can result in more efficacy and less toxicity to normal cells [11].
Pain	In osteoarthritis, pain peaks at night, while pain associated with rheumatoid arthritis peaks in the morning [22].
Diabetes mellitus	In healthy individuals, insulin is released in a pulsatile pattern after carbohydrate rich meals. In addition, low amount of insulin is released from B cells in the pancreas to prevent blood glucose fluctuations during the day. Patients with type 1 diabetes mellitus and some type 2 patients have low or no insulin release. To mimic the physiological pattern, insulin therapy is given as basal and after meals [13].
Cardiovascular system	In hypertensive patients, the highest blood pressure is achieved during the morning because of the high vascular resistance, while the lowest one is attained during sleep. In addition, patients with myocardial infarction are at high risk of death during the morning because the hypercoagulability state of the blood is attained in the morning [11].
Glaucoma	Many patients with glaucoma suffer from high intraocular pressure that peaks between 2-4 am.[22]

30 min. This system was well-tolerated by patients and successfully studied and tested to achieve a biphasic release profile[15].

Geoclock[®] technology

Geoclock[®] technology produces compressed tablets. The core contains the active ingredient, and the outer film is made up of wax with brittle material to provide a pH-independent lag time. In addition to time-controlled release, this basic design was utilized to produce tablets that target the colon. Geoclock[®] technology was applied on prednisone to formulate Lodotra[™] tablets in order to control rheumatoid arthritis. These tablets are taken at night before sleeping, and the active component will be released after 4-6 h, which is the optimal timing to relieve sharp morning pain [15].

Controlled-onset-extended-release (COER-24[™]) technology

One of the currently approved preparations to control hypertension and angina pectoris is Covera-HS tablet, which contains verapamil hydrochloride as the active ingredient. This unique tablet was made by using COER-24[™] technology to mimic circadian fluctuations in heart rate and blood pressure. Covera-HS tablet is taken at night to achieve the peak plasma concentration in the early morning hours for the purpose of targeting the highest blood pressure and heart rate during that time [15].

Diffutab[®] technology

Diffutab[®] This allows control of the time and site of drug release. High doses of a drug can be incorporated into the core of the preparation, and it is covered by a combination of hydrophilic and hydrophobic poly-

mers to control drug release. The whole preparation can be covered by an enteric coat. Erosion of the polymers and diffusion of the active ingredient allow once-a-day dosing (Fig 3) [6].

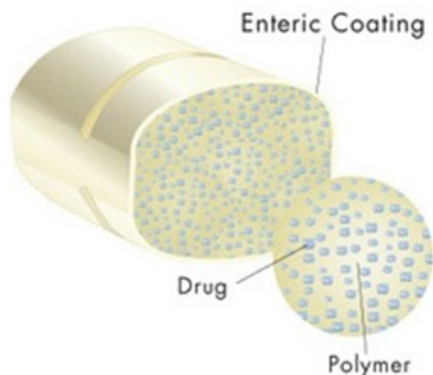


Fig 3. Diffutab technology [6].

Chronotherapeutic oral drug absorption system

The main advantages of Chronotherapeutic oral drug absorption system (CODAS) technology are food and pH independent drug release, extended release pattern after a lag time and site-specific drug release.

This technology was applied on verapamil to produce a preparation named Verelan[®]PM taken at bedtime to be released 4-5 h after ingestion to target the highest blood pressure during the day, which is usually early morning. In order to achieve this delay in drug release, a combination of water soluble and insoluble polymers were used to coat drug-loaded beads that were filled in a capsule. In the presence of GI fluids, the water soluble polymers will dissolve gradually to form pores through which the active ingredient will be released over an extended period. The rate of verapamil release has been shown to be independent of pH, food and GI motility [24].

Covera-HS

One of the currently approved preparations to control hypertension and angina pectoris is Covera-HS. This unique tablet was made by using COER-24[™] technology to mimic circadian fluctuation in heart rate and blood pressure [7].

Orbexa[®] technology

For high-dose products, Orbexa technology can be used. It is a multi-particulate system used to produce special beads with specific size and density, and these beads are filled in a capsule or single-dose sachets. Orbexa technology can be useful in achieving time-controlled, site-specific or sustained drug release [25].

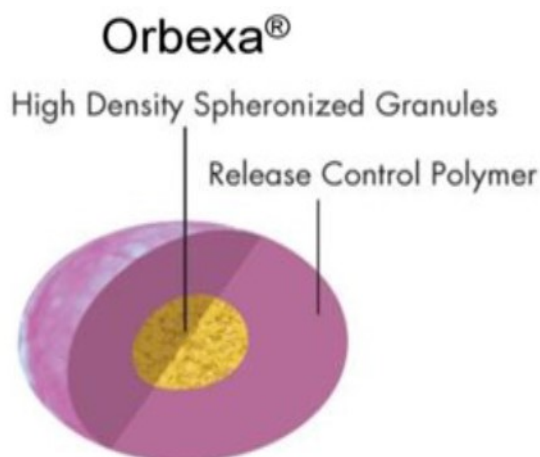


Fig 4. Orbexa technology [7]

Minitabs[®]

Minitab[®] is a capsule containing minute cylindrical tablets of one or more active ingredients. Each small tablet is coated with one or more membranes to control drug release rate. In addition, gel forming excipients or a matrix can be added inside each tablet in order to control medication release rate [6].

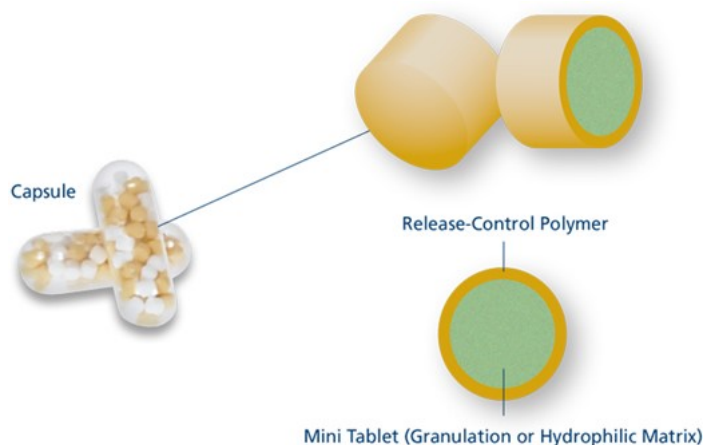


Fig 5. Minitabs[®] technology [6].

Comparison between traditional and pulsatile-release prednisone available in the market

Glucocorticoids are very effective as anti-inflammatory drugs to control rheumatoid arthritis, eczema, bronchial asthma and other local and systemic conditions but with serious side effects. To improve their safety profile, local dosage forms were developed to be applied at the inflamed site in order to reduce systemic exposure. Furthermore, new glucocorticoids have been developed with lower miner-

alocorticoid activity. A novel modified-release oral tablet has been formulated and studied in human beings. It contains prednisone as the active ingredient, which will be released 4 h after dosage form ingestion. It is designed to be taken at bedtime, so prednisone will reach its plasma therapeutic levels in the early morning.

The main purpose of this preparation is to target the circadian rhythms of endogenous pro-inflammatory cytokines, cortisol, pain and stiffness of rheumatoid arthritis which reach their highest intensities early morning.

To assess the efficacy and safety of the new prednisone tablet, it was compared with a conventional immediate-release prednisone tablet in a study called Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA-1).

In this double-blind, randomised controlled trial, one group of patients were randomly assigned to take an immediate-release prednisone tablet in the early morning for 12 weeks. The second group was assigned to take the new modified-release prednisone tablet at bedtime for the same duration. Both groups were diagnosed with rheumatoid arthritis according to the criteria of the American College of Rheumatology. Morning stiffness and pain experienced by the two groups were similar in terms of intensity before the study. These patients were receiving disease-modifying anti-rheumatic drugs, or DMARDs, for 3 months or more before they were enrolled in the trial.

During the study, full patient assessment and evaluation were done at baseline and after 2, 6 and 12 weeks of therapy initiation. The assessment in-

volves erythrocyte sedimentation rate, C-reactive protein and interleukin 6, which are good indicators of prednisone therapy effectiveness. Moreover, patients recorded on a daily basis the duration of morning stiffness and pain frequency during the day. Morning stiffness improvement was noticed after 2 weeks of therapy. In the 7th week and until the 12th week, the difference in morning stiffness improvement increased and plateaued at 38% (figure 6).

Future perspectives

The pulsatile drug delivery system is a good approach to improve drug efficacy and safety as well as patient compliance. With the assistance of chronobiology, this system can be designed to deliver a drug when the targeted disease is in the highest activity state during the day.

In addition, PDDS can be intended to target a certain site in the body, such as the colon. Moreover, drug resistance in pulsatile release formulations is lower compared to conventional and sustained release dosage forms. Consequently, many preparations have been approved by the FDA, and they are available in the market.

However, many drawbacks are limiting the progression of PDDS. Despite that, controlled, sustained and other drug delivery systems have so far failed to deliver drugs in response to the circadian activity of some diseases for which PDDS are the most effective.

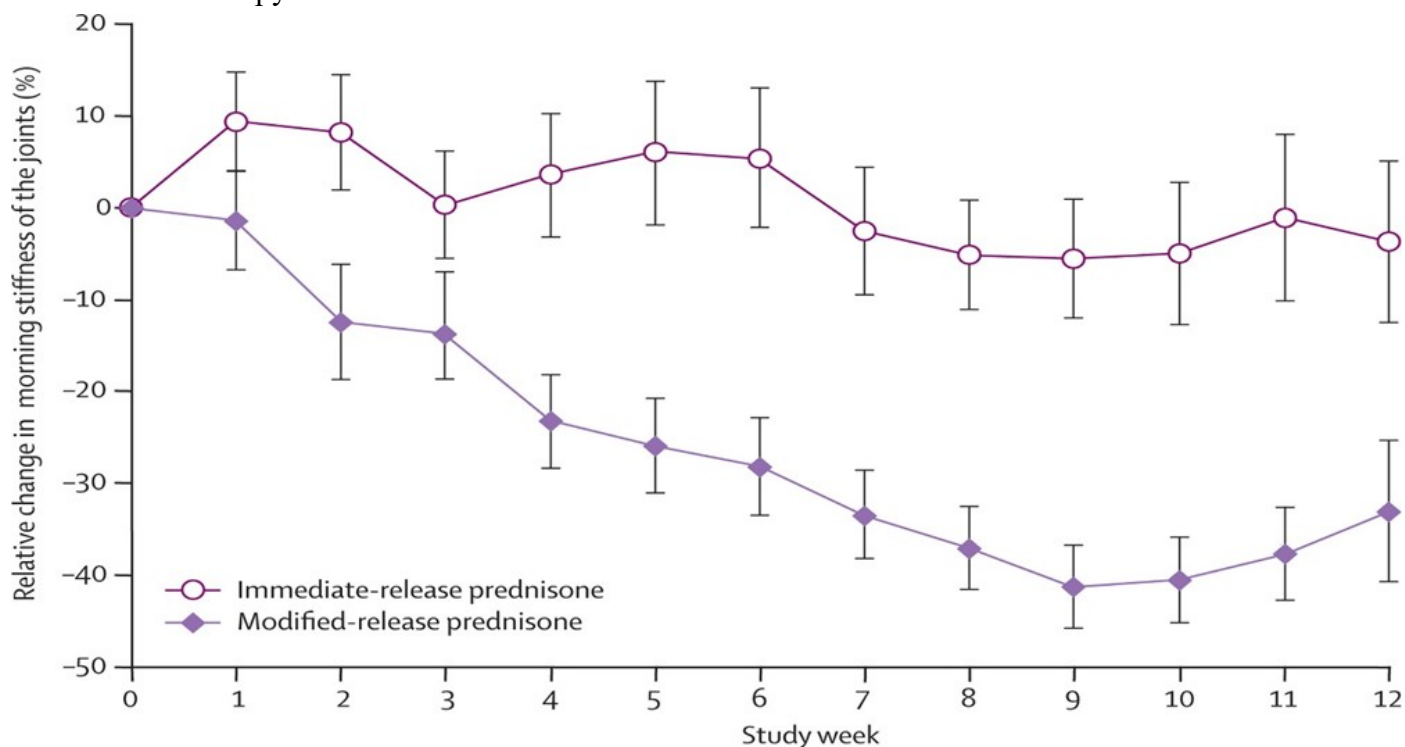


Fig 6. Changes in morning stiffness in patients using immediate release and modified release prednisone from

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TEST YOUR KNOWLEDGE

Answers on back page

1) Which of the following is an advantage of PDDS?

- Low medication loading limit
- Higher expense of formation
- Absence of creation reproducibility
- No risk of dose dumping effect
- Huge number of procedure variables

2) The Covera-HS tablet, based on COER-24™ technology is currently approved to control:

- Asthma
- Multiple Sclerosis
- Hypertension
- Diabetes
- GERD

3) Which of the following PDDS technologies had been applied to develop Procardia XL®, Ditropan XL®, and Concerta®?

- OROS
- IPDAS
- DIFFUCAPS
- Geoclock
- COER-24

Is there a problem?

A 35 year old female patient was given the following prescription for her acute uncomplicated cystitis. Is there any major error with the prescription?



YAX HOSPITAL	
Patient Name: Aaleyah	Age: 35 years
Address: Street No.15	
Rx	
	Ciprofloxacin tablets 500mg once daily x 3 days Send one pack
Dr. Ahmad Signature	Date: 8/09/16

Answer (Prescription Exercise)

The initial dose is incorrect. Should be initially 1 mg at bedtime and slowly titrated to maximum 10mg, depending on response, to avoid hypotension.



Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

Ebola's immune escape

The Ebola virus can persist in several tissues where the immune system is less active. Researchers are working to better understand this phenomenon and how it can stall the clearing of Ebola in survivors.

Even when a person has recovered from Ebola and his or her blood is Ebola-free, the virus can linger in the body. It can remain in semen for months after the initial infection. It was found replicating in the eye of Ebola survivor Ian Crozier, an American physician who helped treat patients in Sierra Leone, nine weeks after he recovered from the illness. It has been detected in swabs of the bodies, amniotic fluid, and placentas of stillborn babies whose mothers were infected with and recovered from Ebola while pregnant. Most recently, the virus was detected in the nervous system of Scottish nurse Pauline Cafferkey, who recovered from Ebola about a year ago, but became very ill and developed meningitis, an inflammation of the membranes around the brain and spinal cord.

A commonality among these cases is that they involve the recurrence of Ebola in sites where the immune system is known to be less active; sites of immune privilege. Immune privilege helps protect tissues in which, for various reasons, an immune response could be harmful. Sites of immune privilege include the placenta, the testes, the eye, and the brain.

Doctors have hypothesized that, after a person recovers from an Ebola infection, the virus can hide in these immune-privileged sites and, as in the cases of Crozier and Cafferkey, later flare up. In such instances, especially when the infected person could not have been infected a second time, the only way that we could surmise that the virus could be present is that it was seeded from the acute original infection and persisted. There is increasing evidence that the virus can persist in some of these sites of immune privilege.

The immune system, meant to protect the body, can sometimes cause it harm. In the delicate tissues of the brain and eye, infection-related inflammation could do serious damage. Once damaged, tissues of the eye can be slow to heal, and scarring can impede vision. Meanwhile, immune privilege of the testes and placenta seems to keep the immune system from destroying the body's own cells.

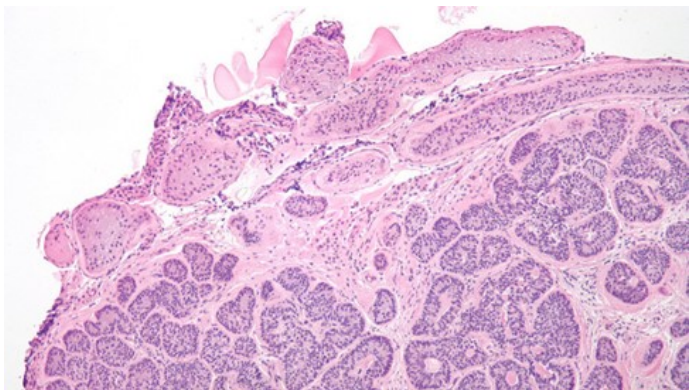
Immune privilege involves three general components: a structural barrier between the blood, which



www.google.com.kw/search?q=enola+virus&biw=1704&bih=870&source=lms&ibm=isch&sa=X&ved=0ahUKewiYnO256uHOAhVB5xoKHeNwDYMQAUIBigB#imgrc=65pGLkbEv9JVom%3A

carries immune cells, and the immune-privileged tissue; the production of immunosuppressive molecules; and the conversion of immune cells that could mount an immune response into ones that keep the immune system in check.

In the testes, for example, sperm begin their lives in and around a network of tubes, called seminiferous tubules, lined by what are called Sertoli cells. The Sertoli cells are connected by tight junctions that let no cells or molecules through, except the developing germ cells, forming a blood-testis barrier. These undifferentiated germ cells, called spermatogonia, begin outside the Sertoli cells; then, as they develop into sperm, they pass through the Sertoli-cell barrier and move toward the center of the tubule.



Sertoli cell nodule (WIKIMEDIA, NEPHRON)

Yet these tight junctions alone are not enough to protect developing germ cells, which form outside the blood-testis barrier, where immune cell-rich blood flows. A second layer of protection is provided by molecules produced by Sertoli cells, such as prostaglandins, which destroy activated T cells that could otherwise mount an immune response. As a third means of protection, molecules secreted by testicular cells, such as TGF- β , help convert immune cells, both T cells and macrophages, from

those that could spur an immune response to those that are immune-regulatory.

Similar mechanisms of immune suppression also exist in the brain, the eye and the placenta. The only difference is that each immune-privileged tissue has a different set of cells that are actually making the factors; the cells that are regulating the immune response. The end result comes out the same.

Another source of variation among immune-privileged sites lies in their structural barriers. The blood-brain barrier exists at the level of the blood vessel, which has tight junctions in its epithelium. Testicular blood vessels, on the other hand, do not have tight junctions; the blood-testis barrier is formed instead by the tight junctions of the Sertoli cells.

That a system set up to protect the body from its

own immune system can serve as a hideout for Ebola may be distressing; however, in the study of Ebola persistence in semen, the frequency of Ebola-positive samples decreased with time. These and other data suggest that the body eventually defeats the pathogen. It's just that these are sites where it's harder for the immune system to get into and so it takes longer for it to get cleared. Over time, everyone who survives Ebola will be completely Ebola-free.

Meanwhile, the WHO recommends that Ebola survivors abstain from sex or use condoms until their semen has twice tested negative for Ebola.

Source:

www.the-scientist.com/?articles.view/articleNo/44403/title/Ebola-s-Immune-Escape/

World Alzheimer's Report 2015: global impact of dementia

About 9.9 million new cases of dementia will be diagnosed in 2016 around the world- that's 1 case every 3 seconds. Globally, the number of people now living with dementia is expected to rise from the current 46 million to 131.5 million by 2050.

Costs to treat dementia are estimated at about \$818 billion US but are expected to soar to \$1 trillion by 2018 and to a whopping \$2 trillion by 2030.

About half of the projected increases in costs due to dementia can be attributed to growth in the numbers of people with dementia and half to increases in per capita costs, particularly in low- and middle-income countries.

Despite interest in the possibility that the age-specific prevalence of dementia may be declining in high-income countries because of public health improvements, "the evidence to support this is currently weak and inconclusive," said the report.

Global challenge

There's no doubt that dementia, including Alzheimer's disease, is one of the biggest global public health and social care challenges facing people today and in the future. If dementia care were a country, it would be the world's 18th largest economy, more than the market values of companies such as Apple (US\$ 742 billion), Google (US\$ 368 billion), and Exxon (US\$ 357 billion).

About 94% of people living with dementia in low- and middle-income countries are cared for at

home. In many regions, health and care systems provide limited or no support to people living with dementia or to their families.

National dementia plans are the first step toward ensuring all countries are equipped to enable people to live well with dementia and help to reduce the risk for dementia in years to come.

The report authors said a global dementia action plan needs clear targets and deliverables. Providing a better quality of life for people with dementia can be a reality, but only if governments and societies make it an urgent priority, they write.

New Cases

Alzheimer's and other dementias are an expanding crisis for families and national economies around the world. The Alzheimer's Association calls on the US Congress to continue its commitment to the fight against Alzheimer's by increasing funding for research by at least \$300 million in fiscal year 2016. In the US, the Health Outcomes, Planning, and Education for Alzheimer's Act (known as the HOPE Act) would provide Medicare coverage for comprehensive care planning services, for both people with Alzheimer's and caregivers following a diagnosis.

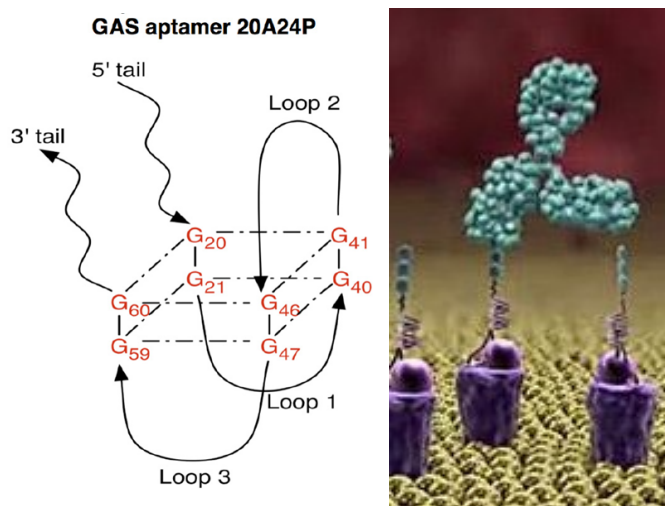


Google images

Can alphamers replace antibiotics?

Antibiotic-resistant bacteria constitute a substantial and growing medical threat. As researchers scramble to squeeze new life from existing antibiotics and identify novel ones, a team at Altermune Technologies in Irvine, CA, is pursuing an alternate therapeutic strategy: “alphamers.”

Alphamers are sugar-conjugated DNA aptamers that bind bacteria and mark them for recognition by naturally occurring anti-sugar antibodies. Using these molecules, the team targeted group A *Streptococcus* (GAS) in culture, demonstrating that they could increase phagocytosis by white blood cells and reduce bacterial cell viability in whole blood. The team members suggest that additional pathogens could likewise be targeted as long as suitably selective aptamers can be identified.



This is a new proof of concept of neutralizing path-

ogens, as opposed to the traditional use of vaccination to elicit pathogen-specific antibodies. And it's a clever approach, novel, and potentially very high-impact.

Many mammals and bacteria produce the trisaccharide, galactose- α -1,3-galactosyl- β -1,4-N-acetylglucosamine (α -Gal). Humans do not, but they are routinely exposed to the antigen and have naturally occurring antibodies that target it. As many as 1% of the antibodies in human sera target α -Gal.

The team started with an aptamer called 20A24P, which binds the M1 protein of GAS. They then added the α -Gal moiety to the aptamer's 5' end and a fluorescent tag to its 3' end, and tested its ability to bind the bacteria and elicit an immune response.

The 5'- α -Gal-20A24P alphamers recruited mouse and human antibodies to the bacterial cell surface, while random alphamer sequences and 20A24P aptamer without the α -Gal epitope did not. When mixed with human neutrophils, the 5'- α -Gal-20A24P alphamer elicited “opsonophagocytosis”—phagocytosis induced by antibody decoration of the bacterial cells—and reduced bacterial viability.

In conclusion, antibodies can be recruited out of blood onto the bacteria in a fashion that depends on the sequence of the aptamer and the presence of the α -Gal modification. Those antibodies can help recruit antimicrobial complement factors to the bacterial surface or engage white blood cell surface receptors to promote phagocytosis killing.

Reference

Kristian SA et al., *J Mol Med*, 93:619–31, 2015.

IN THE NEWS

Sweeping changes to opioid policies unveiled by FDA

In response to the ongoing opioid abuse epidemic, top officials at the US FDA announced plans to reassess the agency's approach to opioid medications.

They are determined to help defeat this epidemic through a science-based and continuously evolving approach. The plan contains real measures the agency can take to make a difference in the lives of so many people who are struggling under the weight of this terrible crisis. The plan is further outlined in a recently published article (*N Engl J Med* 2016; 374:1480-1485). In the US, the annual

number of deaths from opioid overdoses now exceeds the number of deaths caused by motor vehicle accidents.

Regardless of whether these issues are viewed from the perspective of patients, physicians, or regulators, the status quo is clearly not acceptable. As the public health agency responsible for oversight of pharmaceutical safety and effectiveness, the FDA recognizes that this crisis demands solutions, and urges all concerned to join them in this area. The multicomponent plan will focus on policies aimed at reversing the epidemic, while still providing pain

patients access to effective medication. Specifically, the FDA plans to:

- * Re-examine the risk-benefit paradigm for opioids and ensure that the agency considers their wider public-health effects
- * Convene an expert advisory committee before approving any new drug application for an opioid that does not have abuse-deterrent properties
- * Assemble and consult with the Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before any new labeling is approved
- * Develop changes to immediate-release opioid labeling, including additional warnings and safety information that incorporate elements similar to those of the extended-release/long-acting (ER/LA) opioid analgesics labeling that is currently required
- * Update Risk Evaluation and Mitigation Strategy requirements for opioids after considering advisory committee recommendations and review of existing requirements
- * Expand access to, and encourage the development of, abuse-deterrent formulations of opioid products;
- * Improve access to naloxone and medication-assisted treatment options for patients with opioid-use disorders
- * Support better pain-management options, including alternative treatments.

The FDA says they will seek guidance from outside experts in the fields of pain management and drug abuse. The agency has already asked the National Academy of Medicine to assist in developing a framework for opioid review, approval, and monitoring that balances an individual's need for pain control with considerations of the broader public-health consequences of opioid misuse and abuse. They will convene independent advisory



committees made up of physicians and other experts when considering approval of any new opioid drug that does not contain abuse-deterrent properties. The agency will also convene a meeting of its standing Pediatric Advisory Committee to provide advice on a framework for pediatric opioid labeling and use of opioid pain medications in children.

The FDA also plans to tighten requirements for drug companies to generate post market data on the long-term impact of using ER/LA opioids, an action, they say, that will generate the "most comprehensive data ever collected in the field of pain medicine and treatments for opioid use disorder. The data will further the understanding of the known serious risks of opioid misuse, abuse, overdose and death".

Drug overdose deaths, driven very frequently by overdose from prescription opioids and illicit drugs like heroin and illegally-made fentanyl, are now the leading cause of injury death in the US. The FDA is a vital component to combating this epidemic, and the innovation and modernization they have committed to undertaking is an important part of the overall efforts at HHS. The HHS had announced a major initiative to address the opioid abuse epidemic in the US. The initiative focuses on informing opioid prescribing practices, increasing the use of naloxone, and using medication-assisted treatment to move people out of opioid addiction. The FDA says it will provide updates on progress with the goal of sharing timely, transparent information on a regular basis.

Source: <http://www.medscape.com/viewarticle/858411>

Once-weekly diabetes drug dulaglutide wins EU approval

The European Commission has granted marketing approval to Eli Lilly and Co's injectable drug Trulicity (dulaglutide) for adults with type 2 diabetes. The once-weekly drug belongs to a family of diabetes treatments called GLP-1 receptor agonists, which includes Novo Nordisk's widely used daily treatment Victoza (liraglutide). They act like GLP-1, a natural hormone, in prodding the body to release insulin when patients eat.

Trulicity can be taken any time of day, with or without meals, and either by itself or with other treatments for type 2 diabetes, which is highly linked to obesity. Like other diabetes drugs, including insulin, Trulicity can cause hypoglycemia, a potentially dangerous decline in blood sugar that can cause fainting, nausea and other symptoms.

Source: www.medscape.com/viewarticle/835441?nlid=71186_1842&src=wnl_edit_medp_wir&uac=118197BN&spn=17

ISLAMIC CONTRIBUTIONS TO MEDICINE

Biography of Jabir ibn Hayyan

Jabir ibn Hayyan was a natural philosopher who lived mostly in the 8th century. He was born in Tus, Khorasan, in Persia, now known as Iran, then ruled by the Umayyad Caliphate.

Jabir in the classical sources has been entitled differently as al-Azdi al-Barigi or al-Kufi or al-Tusi or al-Sufi. There is a difference of opinion as to whether he was a Persian from Khorasan who later went to Kufa or whether he was, as some have suggested, of Syrian origin and later lived in Persia and Iraq. His ethnic background is not clear, but most sources reference him as a Persian. In some sources, he is reported to have been the son of Hayyan al-Azdi, a pharmacist of the Arabian Azd tribe who emigrated from Yemen to Kufa (in present-day Iraq) during the Umayyad Caliphate.

He is known to have promoted alchemy as a career and profession. Jabir became an alchemist at the court of Caliph Harun al-Rashid, for whom he wrote the *Kitab al-Zuhra* ("The Book of Venus", or "the noble art of alchemy"). Hayyan had supported the Abbasid revolt against the Umayyads, and was sent by them to the province of Khorasan (present day Afghanistan and Iran) to gather support for their cause. He was eventually caught by the Umayyads and executed. His family fled to Yemen, where Jabir grew up and studied the Quran, mathematics and other subjects. Jabir's father's profession may have contributed greatly to his interest in alchemy.

After the Abbasids took power, Jabir went back to Kufa. He began his career practicing medicine, under the patronage of a Vizir (from the noble Persian family Barmakids) of Caliph Harun al-Rashid. His connections to the Barmakid cost him dearly in the end. When that family fell from grace in 803, Jabir was placed under house arrest in Kufa, where he remained until his death. Some scholars have asserted that Jabir was a student of the sixth Imam Ja'far al-Sadiq and Harbi al-Himyari; however other scholars have questioned this theory.

In total, nearly 3,000 treatises and articles are credited to Jabir ibn Hayyan. Following the pioneering work of Paul Kraus, who demonstrated that a corpus of some several hundred works ascribed to Jābir were probably a medley from different hands, mostly dating to the late 9th and early 10th centuries, many scholars believe that many

of



15th-century European portrait of "Geber", Codici Ashburnhamiani 1166, Biblioteca Medicea Laurenziana.

these works consist of commentaries and additions by his followers.

The scope of the corpus is vast: cosmology, music, medicine, magic, biology, chemical technology, geometry, grammar, metaphysics, logic, artificial generation of living beings, along with astrological predictions, and symbolic Imāmi myths.

Jabir's alchemical investigations ostensibly revolved around the ultimate goal of *takwin* — the artificial creation of life. The *Book of Stones* includes several recipes for creating creatures such as scorpions, snakes, and even humans in a laboratory environment, which are subject to the control of their creator. What Jabir meant by these recipes is unknown.

Jabir's alchemical investigations were theoretically grounded in an elaborate numerology related to Pythagorean and Neoplatonic systems. The nature and properties of elements was defined through numeric values assigned the Arabic consonants present in their name, a precursor to the character notation used today.

By the time of Jabir, Aristotelian physics had become Neoplatonic. Each Aristotelian element was composed of these qualities: fire was both hot and dry, earth, cold and dry, water cold and moist, and air, hot and moist. This came from the elementary qualities which are theoretical in nature plus

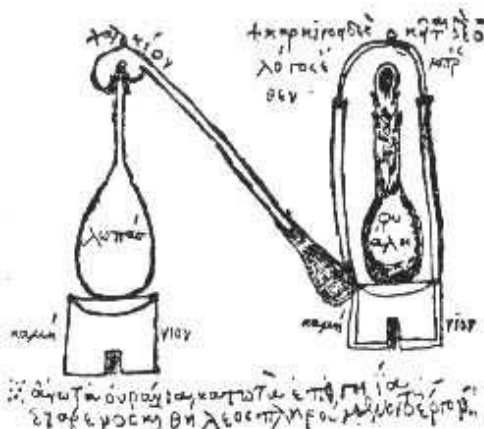
substance. In metals two of these qualities were interior and two were exterior. For example, lead was cold and dry and gold was hot and moist. Thus, Jabir theorized, by rearranging the qualities of one metal, a different metal would result. Like Zosimos, Jabir believed this would require a catalyst, an al-iksir, the elusive elixir that would make this transformation possible — which in European alchemy became known as the philosopher's stone.

According to Jabir's mercury-sulfur theory, metals differ from each in so far as they contain different proportions of the sulfur and mercury. These are not the elements that we know by those names, but certain principles to which those elements are the closest approximation in nature. Based on Aristotle's "exhalation" theory the dry and moist exhalations become sulfur and mercury (sometimes called "sophic" or "philosophic" mercury and sulfur). The sulfur-mercury theory is first recorded in a 7th-century work, *Secret of Creation*, credited (falsely) to Balinus (Apollonius of Tyana). This view becomes widespread.

Laboratory equipment and material

The Jabirian corpus is renowned for its contributions to alchemy. It shows a clear recognition of the importance of experimentation, "The first essential in chemistry is that thou shouldst perform practical work and conduct experiments, for he who performs not practical work nor makes experiments will never attain to the least degree of mastery."

He is credited with the use of over twenty types of now-basic chemical laboratory equipment, such as the alembic and retort, and with the description of many now-commonplace chemical processes such as crystallization, various forms of alchemical "distillation", and substances like citric acid (the sour component of lemons and other unripe fruits), acetic acid (from vinegar) and tartaric acid (from various wine-making residues), arsenic, antimony and bismuth, sulfur,



and mercury that have become the foundation of today's chemistry.

Legacy

Jabir paved the way for most of the later alchemists, including al-Kindi, al-Razi, al-Tughrai and al-Iraqi, who lived in the 9th–13th centuries. His books strongly influenced the medieval European alchemists and justified their search for the philosopher's stone.

In the Middle Ages, Jabir's treatises on alchemy were translated into Latin and became standard texts for European alchemists. These include the *Kitab al-Kimyā* (titled *Book of the Composition of Alchemy in Europe*), translated by Robert of Chester (1144); and the *Kitab al-Sab'een* (*Book of Seventy*) by Gerard of Cremona (c1187). Marcelin Berthelot translated some of his books under the fanciful titles *Book of the Kingdom*, *Book of the Balances*, and *Book of Eastern Mercury*. Several technical Arabic terms introduced by Jabir, such as alkali, have found their way into various European languages and have become part of scientific vocabulary.

Max Meyerhoff states the following on Jabir ibn Hayyan: "His influence may be traced throughout the whole historic course of European alchemy and chemistry." The historian of chemistry Erick John Holmyard gives credit to Jabir for developing alchemy into an experimental science and he writes that Jabir's importance to the history of chemistry is equal to that of Robert Boyle and Antoine Lavoisier.

Sources

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Copyright: <http://creativecommons.org/licenses/by-sa/3.0/>
- 2) David T. *Short history of Islamic Pharmacy*
<http://www.ishim.net/ishimj/3/03.pdf>

News from FoP Kuwait University



A new look for Pharmacy Practice teaching

Competency-based education requires a change in the teaching model that we are accustomed to. Lectures have to make room for more active learning methods designed to allow students to use the acquired knowledge in a context that mimics the professional environment. The laboratories then become the intermediate space between theory and the real world, allowing students to explore, experiment and make mistakes in a controlled environment that provides guidance and feedback.

In line with our commitment to provide competency-based education, we are currently re-designing some of our current student laboratories. The new layout will be composed of several cubicles to allow students to practice different facets of pharmacy practice in small groups under the supervision of their instructors. The cubicles will also serve to evaluate students and administer OSCE (objective structured clinical evaluations) to ensure that they have reached the expected level of competency. These new rooms will be equipped with cameras so that students can review their performance and assessors can evaluate the students in all of the dimensions required by the professional practice.

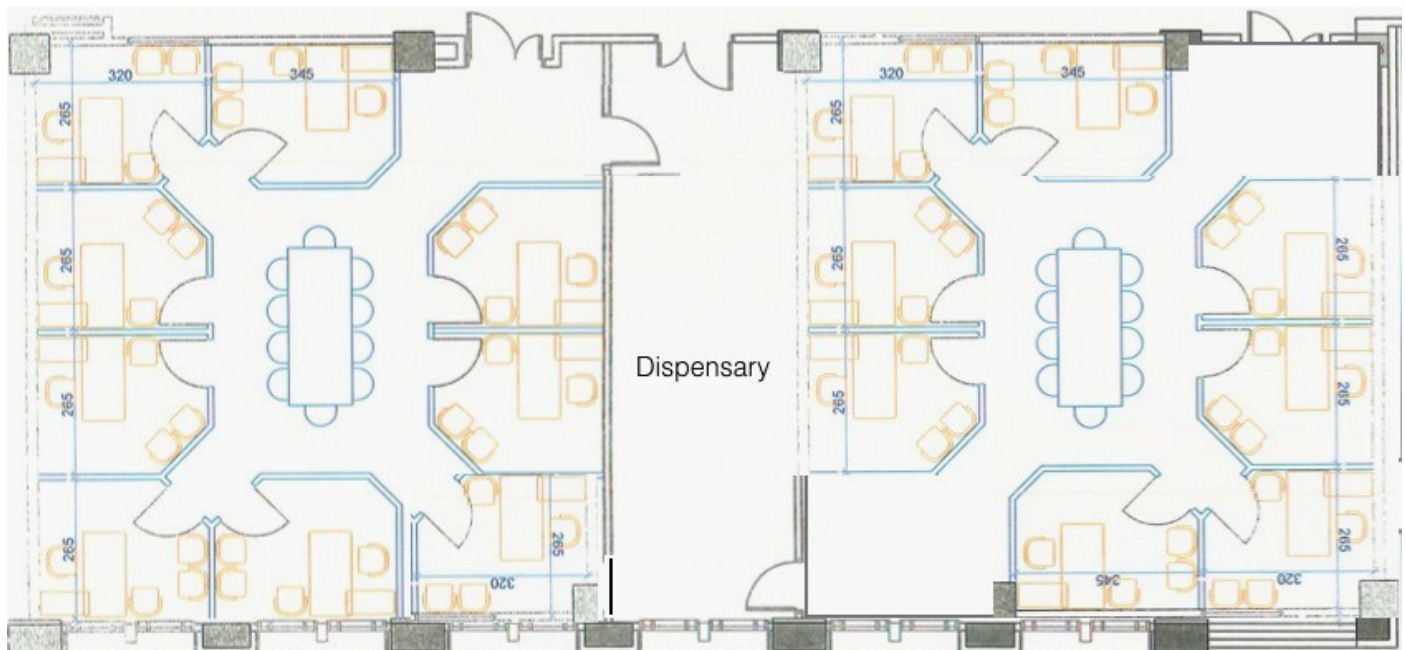
Several models of pharmacy practice laboratories exist. Some try to reproduce a real pharmacy, while others focus on dispensaries with counseling areas. Several schools have opted for an open space design with several "stations" in one room, but this normally creates a noisy environment,

making it difficult for students to concentrate. We have chosen a cubicle-style design that will allow small groups of students to practice together in a quieter atmosphere. They can double up as counseling areas, as students engage in role-playing activities. In fact, these cubicles can accommodate several active learning techniques that are the cornerstone of competency-based education. The cubicles are linked by a common area where students can receive instructions and guidance to proceed with their learning activities.

We have also created a dispensary area that students will be able to use to practice this important pharmaceutical service. Again, our goal is to familiarize students with the professional practice to build their competence and improve their confidence before going to different clinical site rotations. By better preparing them for the professional environment, we believe that they will gain more from their practice experience courses within the healthcare system by engaging at a more advanced level with patients.

We are grateful to Kuwait University for their support for this re-modelling initiative and we surely hope that this rather simple transformation will have all the positive impact on the profession that we expect.

P Moreau,
Faculty of Pharmacy, Kuwait University



STATE OF KUWAIT**Pharmaceutical & Herbal Medicines Control and Registration Administration*****New Pharmaceutical products approved from June to August 2016***

- Anoro Ellipta Inhalation Powder 62.5/25mcg; Umeclidinium (as bromide) – 62.5mcg Vilanterol (as trifenale) – 25mcg; Glaxo Group Limited/U.K.
- Axcel Betamethasone Cream 0.1%; Betamethasone (as 17-valerate) – 0.1g; Kotra Pharma (M) SDN BHD/Malaysia
- Axcel Miconazole Cream; Miconazole Nitrate – 20mg; Kotra Pharma (M) SDN BHD/Malaysia
- Bemfola Solution for Injection 150IU/0.25ml, 225IU/0.375ml, 300IU/0.5ml, 450IU/0.75ml 75IU/0.125ml PFP; Follitropin alfa (rDNA) – 150, 225, 300, 450 and 750 IU, Finox Biotech AG/Switzerland
- Ciprexel Melts 10, 20mg; Escitalopram – 10, 20mg; H. Lundbeck A/S /Denmark
- Deltacef Powder for Solution for Injection 1, 2g; Cefepime (as dihydrochloride monohydrate – 1, 2g; Medochemie Ltd./Cyprus
- Desloratidine/Genepharma Orodispersible Tablets 5mg; Desloratidine – 5mg; Genepharma S.A./Greece
- Desogest Tablets 0.075mg; Desogestrel – 0.075mg; Oman Pharmaceutical Products Co. L.L.C. (ZYNOVA)/Sultanate of Oman
- Elitan Solution for Injection 10mg/2ml; Metochlopramide HCl Anhydrous (as monohydrate) –10mg; Medochemie Ltd. Cyprus
- Endolet Tablets 30, 60mg; Cinacalcet (as HCl) – 30mg; Tabuk Pharmaceutical Man.Co/Saudi Arabia
- Eperzan Powder and Solvent for Solution for Injection 30, 50mg P.F. Pen; Albiglutide (rDNA) – 30, 50mg; Glaxosmithkline Trading Sciences Ltd./Ireland
- Hi-Quin Cream 2, 4% w/w; Hydroquinone – 20, 40mg; Jamjoom Pharma/Saudi Arabia
- Ipramax Tablets 100mg; Topiramate – 100mg; Tabuk Pharmaceutical Manufacturing Co./Saudi Arabia
- Lejam Tablets 30, 60mg; Dapoxetine (as HCl) – 30, 60mg; Spimaco/Saudi Arabia
- Leupro-Sandoz 1, 3 month Depot Implant; Leuprorelin (as acetate) – 5, 3.6mg; Hexal AG/Germany
- Lorine Fast Melting Tablets 10mg; Loratidine (micronized) – 10mg; Spimaco/Saudi Arabia
- Merotinib Medpharma Tablets 400mg Imatinib (as mesylate) – 400mg; Med Pharma Group Europe S.L/Spain
- Novo Eight Powder and Solvent for Solution for Injection 250, 500, 1000, 1500, 2000, 3000 IU/Vial Turoctocog alfa (rDNA) – 250, 500, 1000, 1500, 2000, 3000 IU Sodium Chloride 0.9% - 4ml; Novo Nordisk A/S / Denmark
- Pamidronato Azevedos Powder for Solution for Infusion 90mg; Pamidronate Disodium – 90mg; Laboratorios Azevedos Industria Farmaceutica S.A./Portugal
- Pandiol Solution Infusion 10mg/ml; Paracetamol – 10mg; P.T. Novell Pharmaceutical Laboratories /Indonesia
- Portazza Injection for IV Infus 800mg/5ml; Necitumumab (rDNA) – 16mg; Eli Lilly & Company/USA
- Pregamax Capsules 75, 150mg; Pregabalin – 75, 150mg; Nasila Pharma Ltd./U.K.
- Rabeprazol Azevedos Gastro-Resistant Tablets 10, 20mg; Rabeprazole Sodium – 10, 20mg; Laboratorios Azevedos-Industria Farmaceutica S.A./Portugal
- Rebif Solution for Injection PFP 22, 44mcg; Interferon beta-1a (rDNA) -22mcg (6MIU), 44mcg (12MIU); Merck Serono Europe Ltd./U.K.
- Redex Tablets 5, 10, 30mg; Tadalafil – 5, 10,30mg; Al-Taqaddom Pharmaceutical Industries/Jordan
- Rinofed Plus Syrup; Triprolidine HCl -1.25mg Pseudoephedrine HCl – 25mg Paracetamol – 125mg; Jazeera Pharmaceutical Industries/Saudi Arabia
- Somatostatin Lyomark Lyophilisate for Solution for Infus3mg; Somatostatin (as acetate) – 3mg; Lyomark Pharma GmbH/Germany
- Spedra Tablets 100, 200mg; Avanafil – 100, 200mg; Sanofi-Aventis Groupe/France
- Super Amp Sterilised Water for Inj. B.P – 1ml; Claris Lifesciences Ltd./India
- Tagrisso Tablets 40, 80mg; Osimertinib (as Mesylate) – 40, 80mg; AstraZeneca AB/Sweden
- Talerin Solution for iv Infus 5mg/ml; Levofloxacin (as hemihydrate) – 500mg; Demo S.A. Pharmaceutical Industry/Greece
- Triaxone Powder for Solution for IV Infus 2g; Ceftriaxone (as sodium) – 2g; Gulf Pharmaceutical Industries (Julphar)/UAE
- Vancomicina Azevedos Powder for Solution for Infus 500, 1000mg; Vancomycin – 500, 1000mg; Laboratorios Azevedos

Answers to: Test your knowledge**Correct answers:****1-D; 2-C; 3-A**

The Kuwait Pharmacy Bulletin (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs from the MOH. It aims to provide instructive reviews and topical news items on a range of drug related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

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