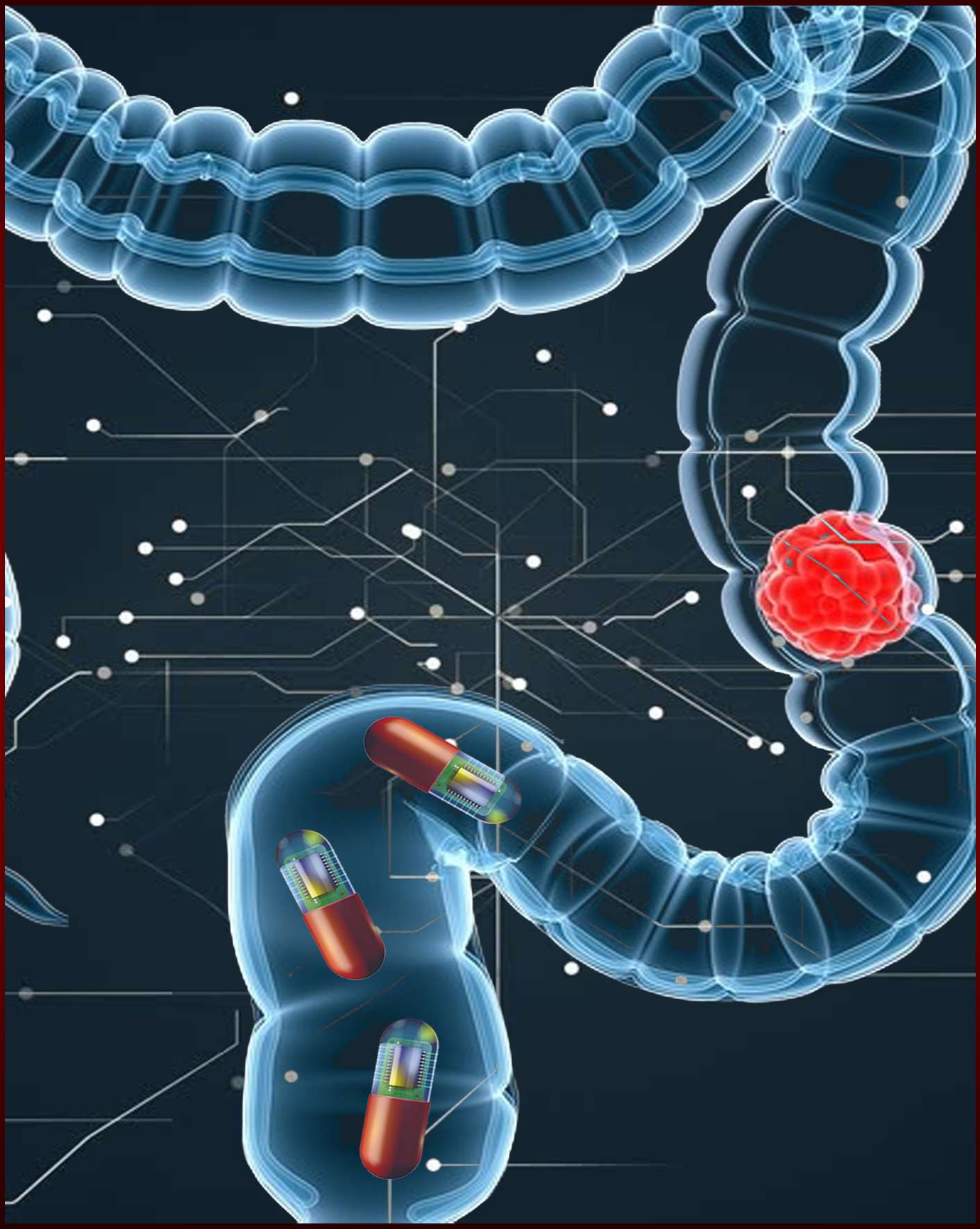
Kuwait Pharmacy Bulletin

DRUG INFORMATION FOR THE HEALTH PROFESSIONAL



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Orally targeted drug delivery to the colon

Colon-specific drug delivery systems (CDDS) are desirable for the treatment of a range of diseases including ulcerative colitis, Crohn's disease, irritable bowel syndrome, chronic pancreatitis, inflammatory bowel disease, colonic pancreatitis, colon and rectal cancer. CDDSs reduce the incidence of systemic side effects and require lower doses. Several factors need to be considered for the success of CDDS: physico-chemical properties of the drugs, type of delivery system, the degree of interaction between the drug and the GI tract and the drug carrier. Also, the chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen (1). The colon is an ideal region for drug delivery; the colonic content provides longer retention time (up to 5 days) and the mucosa of the colon, which facilitates the absorption of several drugs, appears to be highly responsive to poorly absorbed agents to enhance their resolution. These drugs may have minimal systemic absorption in the upper GI tract, thus a high amount of the drug will reach the colon. Examples of colon-targeting drugs are sulfasalazine, dexamethasone, hydrocortisone, metronidazole and prednisolone (2).

Dosage forms for colon delivery

For orally absorbed drugs to be released in the target site, various pharmaceutical formulation technologies are available (Table 1) (2).

Rectal drugs are used to treat specific parts of the colon only as this depends on the spreading capacity and the retention time, so reaching the proximal part of colon via rectal administration is difficult (3).

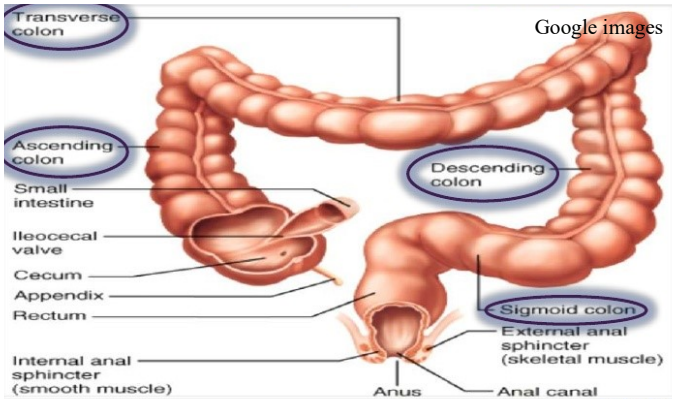
The spread of rectal dosage forms is volume dependent; for instance, spread of hydrophobic suppositories is confined to the rectum only, whereas hydrophilic drugs may spread upward to the colon parts. Enemas and foams may spread to the descending colon and may reach the proximal part of the small intestine and distal part of the colon. Additionally, drug delivery through rectum is uncomfortable for patients (4).

Limitations of colon targeted delivery

In order to reach the colon, a drug has to pass through the entire GI tract to reach this distal portion; during this time it may be absorbed or metabolised in a different area. Drug absorption may be affected by the acidic environment in the stomach. Fluid volume and transient time are other limitations facing these delivery systems.

Furthermore, a drug's solubility is the rate limiting factor for colonic absorption as some drugs will be soluble in the stomach or small intestine before reaching the colon.

Thus, the drugs of this delivery system should be soluble in the colon only in order to exert a local effect (2). Disease status (5) as well as physical properties such as appearance, crystallization, solubility, disintegration rate, pH, viscosity and



palatability may affect drug absorption and metabolism (2). Colonic bacteria may secrete enzymes such as nitroreductase and β-galactosidase that are capable of degrading drug molecules (6).

Factors influencing colonic-specific drug targeting & colonic bioavailability

These factors are anatomy and physiology, transit time, pH, fluid volume, and viscosity of the colon. Colonic enzymes and metabolism also affect targeting systems, in addition to formulation factors (4). The intestinal surface of the colon (approximately 1.5 m in length) is large because of the colonic folds; this will affect movement of drugs and food products, and their absorption or metabolism.

Variation in GI contents will also affect the delivery of drugs to the colon. Gastric enzymes, such as pepsin, lipase and gastrin that are not found in the colon, will influence

In this issue

Table 1. Approaches for targeted delivery (2, 3, 4)

Type of formulation	Description	Examples
Immediate release	Drugs are released immediately when they reach a specific area so they need some excipients, such as diluents and binders.	**Azathioprine (Azasan®)** **Mercaptopurine (Purinethol®)** **Rifaximin (Xifaxan®)**
Extended release	Drugs are released slowly over a specific time period.	**Metronidazole (Flagyl ER®)** **Hyoscyamine (Levbid®)**
Delayed release	Drugs having slow dissolution and absorption rates in the upper GIT, are not released in the stomach but in the intestine (enteric coating).	**Mesalazine (Asacol®)** **Doxycycline (Doryx®)**
Timed release	The lag time for onset of release has to exceed the transit time through the stomach and the small intestine, then release occurs when the drug reaches the colon.	**Mesalazine (Pentasa®)**

absorption of some food products and drugs.

Colonic contents such as enteric bacteria, vitamins, mucus, food residues and gases may affect CDDS performance (2). The colon is responsible for several physiological functions including storage of fecal content, expulsion of the contents of the colon at a suitable time, absorption of water and sodium ions from the lumen, and secretion of potassium and bicarbonate ions. Furthermore, the colon provides a suitable environment for the growth of colonic micro-organisms and microflora (7).

The rate of delivery to the colon depends on the rate of gastric emptying and transit time (8). Colonic transit time is influenced by various factors, such as the presence of food, gender, size of the dosage forms, excipients, disease state and stress condition. Gastrointestinal transit time is dependent on the presence or absence of food. In the fasting state, the drug will pass out of the stomach within 1h, while in the presence of food it may take longer time (7).

Because of steroid hormones, women have longer transit time than men (9). Larger dosage forms (capsules) transit faster than smaller ones (dispersed particles). Additionally, the colonic disease state may influence transit time; patients suffering from ulcerative colitis will have shorter colonic times compared with healthy individuals (4). In addition, transit time in patients with diarrhea is shorter than in patients with constipation. Stress conditions will reduce transit time.

Drugs acting on sympathetic or parasympathetic nervous systems will affect motor activity and thus will influence transit time (7). Laxatives increase motility, so decrease the transit time, whereas anti-spasmodic drugs do the opposite (9). Gastric emptying rate may affect drug entry to the colon, so this will affect the transit time. The emptying rate is lower in females, in the presence of food, and in depression states. Other factors that slow down emptying rate are high acidity and high osmolarity (7). Colonic transit times have been reported between 6-48 h depending on disease state, gender, presence of food, action of the drugs, and stress (9).

Drug disintegration, dispersion, dissolution and absorption depend on the volume and composition of the gastrointestinal fluid (9). The higher water content in the distal colon will increase the chance of the drug mixing with luminal content, favoring drug dispersion (9). Because of its high water-absorbing capacity, the colonic lumina have higher viscosity compared to the upper GI tract contents, which will affect the dissolution rate of CDDSs. In addition, the viscosity increases from the ascending colon towards the descending colon, and this will reduce drug dissolution and mucosal absorption. Depending on the disease state, colonic viscosity will vary (2).

Diets rich in carbohydrates and polysaccharide-based drugs such as laxatives will influence colonic pH; due to fermentation of polysaccharides by colonic bacteria and subsequent formation of short chain fatty acids (10, 11). Crohn's disease and acute

ulcerative colitis may reduce the pH value. Therefore, pH-sensitive drug delivery systems may be used as an approach to ensure the release of the active ingredient in the targeted region (12).

There are more than 400 aerobic and anaerobic micro-organisms in the colon such as *Bacteroids, Bifidobacterium, Eubacterium, Peptococcus*, and *Clostridium*. They are responsible for producing hydrolytic and reductive metabolizing enzymes such as β-glucuronidase, β-xylosidase, β-galactosidase and α-L-arabinosidase.

On the other hand, nitroreductase, deaminase, urea dehydroxylase, and azoreductase are reductive enzymes produced by colonic micro-flora (13). Colonic micro-flora can be affected by polysaccharide rich diets, disease state and drug therapy. For instance in Crohn's disease, *Bacteroids, Eubacteria, and Peptostreptococcus* increase, while the number of *Bifidobacteria* decrease (9).

Polysaccharide based drugs are one of the colon-specific delivery systems because of their resistance to gastric and intestinal enzymes, but they are metabolised by colonic micro-flora. Additionally, the metabolism of some drugs by colonic enzymes can result in the formation of pharmacologically active or inactive metabolites (13). Using pro-drugs is one CDDS approach which relies on activation by colonic micro-flora enzymes (Table 2) (9).

Table 2. Some pro-drugs activated by colonic enzymes (9)

Pro-drug	Active form in the colon
Calcium folinate (Leucovorin®)	5-methyltetrahydrofolate
Balsalazide (Colazal®)	5-aminosalicylic acid
Olsalazine (Dipentum®)	5-aminosalicylic acid
Loperamide oxide	loperamide

Solubility and dosage are important for colonic bioavailability; for example, budesonide (9 mg), which is a highly potent drug for ulcerative colitis, has low water solubility but is well absorbed in the colon. On the other hand, mesalamine (4.8 g) has a higher water solubility and requires higher dose so it may not be absorbed well in the colon. Dosage forms of some drugs will also influence drug delivery and bioavailability. For instance, Uceris® is a multi-matrix-based delayed release tablet, enhancing absorption in the colon for ulcerative colitis treatment, whereas Entocort® is a capsule used to treat Crohn's disease, and is released in the ileum (14, 15).

Biodegradable & polysaccharide delivery systems

Biodegradable colon delivery systems focus on coating drugs with polymers that are released specifically in the colon by the action of bacterial species such as bacteriodes, eubacteria, clostridia and enterobacteria. Thus, new formulations are designed to protect certain drugs from digestive enzymes that are found in stomach and small intestine.

As a result the drugs will be released in the colon through degradation by colonic enzymes (16) leading to bond cleavage, extraction or reduction in the molecular weight of polymers, and these changes will result in defects of the surface resulting in the degradation of drug molecules (17). Azo-polymer is released after the reduction of azo bonds by azo-reductase enzyme predominantly found in the colon (16).

Several polymeric drugs targeted to the colon by CDDS are designed based on azo-linkages for instance coating systems, hydrogels, polymeric pro-drugs and redox sensitive polymers (13). Metronidazole capsules were coated with azo-aromatic polymer beside polymers sensitive to pH for release in the colon. Proteins and peptides were coated with azo-aromatic polymers in order to be protected from gastric and intestinal peptidases (18). In addition, peptides are mostly destroyed by first pass metabolism in the liver, so by coating with azo-polymers, the drug will be released specifically in the colon. Hydrogels are degraded in the colon because of cross-linkage with aromatic azo-groups (17).

Some colonic bacteria are responsible for synthesis of reductive and hydrolytic enzymes that degrade polysaccharides such as chitosan, guar gum and amylose. Polysaccharide coating is important for them to be released in the colon. Chitosan can be used as a polysaccharide carrier for development of orally targeted drug delivery to the colon as it is degraded by colonic bacteria and soluble in slightly acidic environment, it will be protected from stomach acidity and enzymatic activity.

5-fluorouracil (5-FU) is one of the drugs that can be coated with chitosan to be released in the colon. 5-amino-salicylic acid can be formed by combination of hydroxyl-propylmethyl-cellulose (HPMC) and chitosan acetate (CSA), which is degraded by colonic β-glycosidase and by this combination the drug will be released in the colon. Additionally, oxaliplatin, which targets colon tumors can be coated with enteric-coated hyaluronic acid (HA)-coupled chitosan nanoparticles. Uncoated drugs will be released in the upper GI tract (13).

Another natural polysaccharide is guar gum used as a polymer to coat active drug forms to be released in the colon as it is degraded by colonic enzymes. To make a hydrogel of bovine serum albumin, the acetyl derivative of guar gum is used as a polymer as it is hydrolysed by β-mannase (19). Amylose-ethyl-cellulose has been used for enteric coating to prevent premature release of drugs through simple diffusion (7). Some of the drugs coated with amylose ethyl-cellulose contain corticosteroids (prednisolone sodium metasulphobenzoate; COLAL-PRED®), and have reached phase III clinical trials for treatment of moderate to severe ulcerative colitis (20, 21).

Matrix based systems

Formulating drugs with pH-sensitive or biodegradable polymer matrices is another approach for colon-targeting drug delivery systems. Metronidazole coated with starch is an example. *In vitro* studies using 0.1M HCl, phosphate buffer (pH 7.4), and goat cecal content showed sustained release of the drug in the alkaline condition because of erosion and dissolution of starch polymer. (22).

Timed-release systems

The concept of this approach is to delay drug release until reaching the colon, so drug release takes place after a fixed lag time, which is usually 3-5 h. Pulsincap is the first formulation that was designed using this approach (7, 23, 24).

Another preparation is tinidazole in which both pH and timed release systems are used to deliver drug mainly in the colon. This preparation is designed in three parts, which are the core of the tablet containing drug, an outer enteric film-coating layer, and inner press coating layer. These two coating layers will affect gastric emptying time so the core will be released in the colon (25).

Bio-adhesive systems

Bio-adhesive systems remain in contact with the colon for an extended period of time. This approach will improve uptake of poorly absorbed drugs. Examples are polycarbophils, polyurethanes and polyethylene oxides (7). Metronidazole with bio-adhesive microsphere (BAM) was developed for colon targeting. The advantages include increased retention time and absorption improving therapeutic effect (22).

Multiparticulate systems

Multiparticulate delivery systems mean that the active drug is designed to be divided into multiplicity of small spherical units, and the drug filled in a sachet and encapsulated or compressed into a tablet. The smaller size of particles allows easier movement through the GI tract.

The advantages are higher bioavailability, better distribution so lower risk of irritation, less dependence on gastric emptying and less side effects.

Some of the multiparticulate formulations that are designed to be released in the colon are pellets, granules, microparticles and nanoparticles.

Stabilised pellet delivery system is an approach in which the drug is formulated by using single or combination of functional polymers and additives to be released specifically in the colon as sustained release system. The active drug is coated with beads or pellets with pH dependent/independent polymers designed as protective polymeric membranes for unstable drugs and then released in the colon (26).

Calcium alginate-carboxymethyl cellulose (CA-CMC) beads are used in colon-specific oral drug delivery, as in case of 5-flurouracil, in order to extend the duration of drug release (27). Microsphere is another example of multiparticulate delivery system. Metronidazole consisting of cross-linked chitosan microspheres coated with Eudragit® pH sensitive polymers is an example (28).

Another formulation of metronidazole, in which microsphere of pectin polysaccharide coated with pH sensitive polymer, showed that the drug was released in the neutral to slightly alkaline condition of the colon and not released in the acidic environment of the stomach (29). Nanoparticles are used as multiparticulate systems to improve drug bioavailability as they have higher surface area and this will allow more time for the drug to be in contact with biological surfaces.

Nanoparticles have a good therapeutic effect as they are taken up by macrophages in the inflamed area of the colon. One challenge facing the nanoparticle system is degradation by GI enzymes before reaching the colon. New nanoparticle technologies were successfully applied to overcome degradation by GI tract enzymes by formulating metronidazole with K10-montmorillonite, which is an additive that allows longer drug duration time in the colon (30).

Colon delivery by coatings

One of the most common pH dependent polymers is methacrylic-acid copolymer, which is commonly used as Eudragit S® and Eudragit L®. Combination of these two copolymers in different ratios is useful to

overcome pH variations as each one has its own pH optimum for dissolution, and this will facilitate the release of the drug to the colon and at a specific period of time (16). Eudragit S® is soluble at pH >7, while Eudragit L® is soluble at pH >5.5, and they are widely used in IBD (31). Mesalazine tablet is designed to be coated with Eudragit L100-55® and Eudragit S100® to be used as colon targeting delivery. Another example is budesonide which can be formulated by combining two approaches to be specifically released in the colon. Coating with pH sensitive polymer Eudragit S® and with cellulose acetate butyrate provides controlled release of budesonide (16).

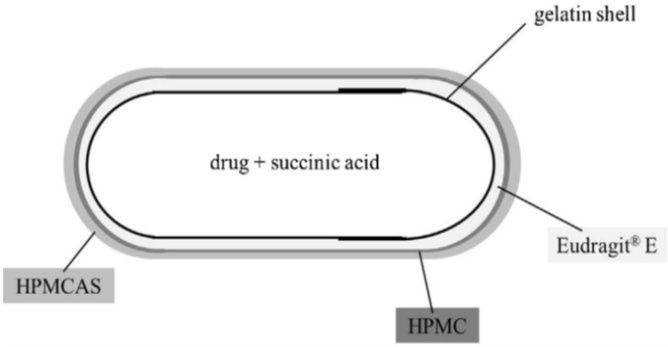


Figure 1: Triple coating layers of Eudragit E polymer (32)

Eudragit E® is an acid soluble coating polymer that can be used for colon targeting capsules; it consists of three layers containing an organic acid such as succinic acid and active drug. The three coating layers are Eudragit E100®, enteric soluble hypromellose acetate succinate (HPMCAS) and low viscosity hypromellose (HPMC); Fig 1 (32). Dexamethasone tablet is coated with Eudragit E dissolved in pH 2-5 buffer to allow rapid release within 10-15 min such as in ulcerative colitis where pH can drop to 2.3-4.7(33).

Coating the active ingredient of drugs with pulsatile systems is another approach. Pulsatile systems include rupturable, permeable and semi-permeable film coatings (34). Rupturable film coatings depend upon drug release after disruption by hydrostatic pressure within the core. Permeable film coatings consist of insoluble polymeric coating; however, water can pass through the drug and dissolve its core. As these coatings are resistant to dissolution, the drug with these coatings will not rupture after exposure to water. Thus, the core of the drug will take longer to be released (32, 34). Semi-permeable film coating depends on both osmotic and hydrostatic pressure. When hydrostatic pressure exceeds osmotic pressure within the system, small orifices will be formed, so the drug dissolves in the aqueous medium and the core is pumped out after a specific period of time (35).

Evaluation of the integrated approaches

Pressure controlled delivery

The concept of pressure-controlled delivery capsules is based on the luminal pressure of the colon which is higher than in the small intestine. The capsule is made of ethyl-cellulose (EC), a water insoluble coating polymer, and released in the lumen because of its high pressure. Two factors are important for disintegration of the formulation in the colon; capsule size and thickness. Coating mesalamine capsules with ethyl-cellulose is one example of pressure controlled delivery resulting in drug release after 3 to 5 h which is the colon arrival time (1).

Osmotic controlled systems

Osmotic controlled Release Oral delivery System (OROS) (Fig 2) can be single or 5 to 6 units encapsulated in a hard gelatin capsule. Each unit is enteric coated in order to dissolve in the small intestine and prevent drug release in the acidic gastric environment. A semi-permeable membrane within the enteric coating is composed of an osmotic push compartment and a drug compartment. After the enteric coat is dissolved in the small intestine, water enters the units so the push compartment swells and forms a gel in the drug compartment. Swelling of the push compartment forces the drug gel out of the orifice at a rate based on the rate of water entry through a semi-permeable membrane. In order to target the colon, each push unit is designed to give action 3-4 h post gastric delay (1, 16).

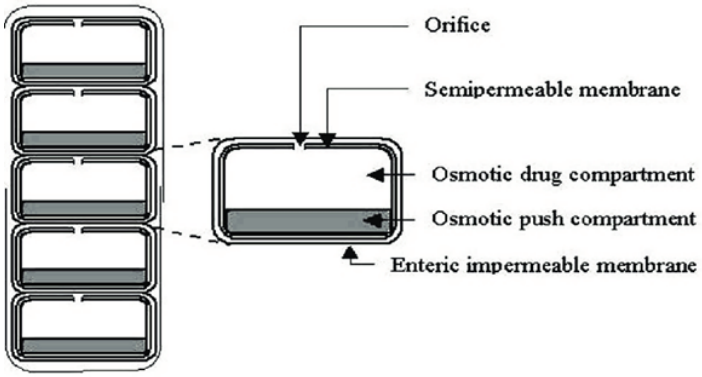


Figure 2. Cross-section of the OROS-CT colon targeted drug delivery system. (16)

Pulsincap approach

Pulsincap consists of a water insoluble cap as body compartment, which contains active drug, and hydro-

gel plug that is coated with water soluble cap. The capsule is coated with insoluble acidic coat to prevent the drug from being released in the stomach. The enteric coat dissolves in the small intestine, so the hydrogel plug begins to swell; this will allow lag time before drug release. Different formulations with different polymers were used as pulsincap system, and they were tested at pH 1.2 for 2 h to stimulate gastric fluid, pH 7.4 for 3 h to stimulate intestinal fluid, and pH 6.8 for 7 h to stimulate colon conditions. The results showed that there was no significant release of the drug within the first 5 h, and this pulsincap system can be successfully used to formulate metronidazole as a colon-targeted drug (36). (Fig 3)

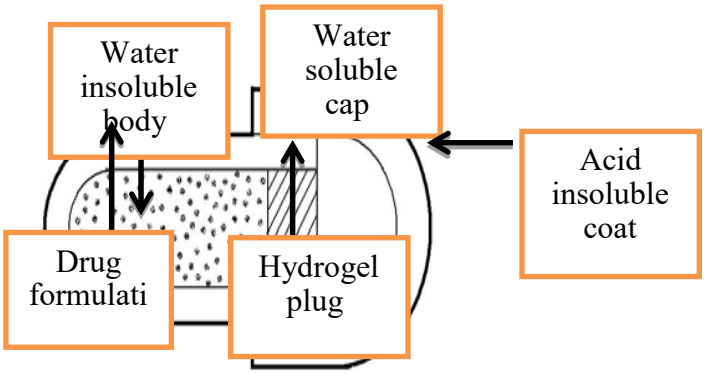


Figure 3. Schematic diagram of Pulsincap (7)

Table 3. Summary of conventional approaches for colonic delivery

Delivery system	Comments
Biodegradable delivery system	Drug release takes place after degradation of coating polymer by colonic bacteria.
Polysaccharide-based delivery system	Polysaccharides are ideal materials for colon delivery because they are degraded by colonic enzymes.
Matrix-based system	Embedding the drug in polymer matrices, which can be pH sensitive or biodegradable, for trapping and release in the colon.
Timed-release system	Drug release takes place after fixed lag time between 3-5 h.
Bio-adhesive system	Drug coated with bio-adhesive polymers adhere to the colonic mucosa to be released in the colon.
Multiparticulate system	Formulation of drug in smaller particle size to allow easier movement through GI tract.
Colon delivery by coating	Coating drugs with pH sensitive polymers to prevent release in the acidic environment of the stomach and small intestine.

In conclusion, absorption, bioavailability and targeted drug delivery can be enhanced by applying advanced and versatile pharmaceutical technologies.

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TEST YOUR KNOWLEDGE

Answers on back page

1) The factors that influence colonic-specific drug targeting and colonic bioavailability are

a) Fluid volume
b) Transit time
c) pH
d) All of the above

2) The first formulation that was designed using a timed-release system for the colon:

a) Pulsincap
b) Azasan
c) Purinethol
d) Xifaxan

3) Which of the following is an immediate release formulation?

a) Levbid
b) Doryx
c) Xifaxan
d) Pentasa

Is there a problem?

A patient is given the prescription below to treat his newly diagnosed hypothyroidism. Is there any major error with the prescription?

ROX HOSPITAL

Patient Name: Joseph Age: 32 years
Address: Street No: 15

Rx

Levothyroxine tablets
50mg once a day
Send one packet

Dr. John
Signature Date: 15/12/18

Answer (Prescription Exercise)

The unit is wrong. It should be 50 mcg and not mg)

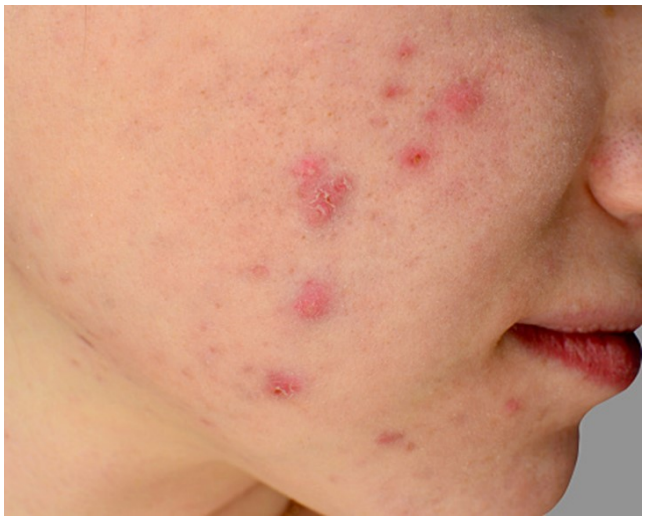
Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

Pharmacy management of acne vulgaris

Although acne is considered as a trivial disease that adolescents grow out of, research suggests that the impairment in quality of life is comparable to the impact of other chronic diseases such as asthma, epilepsy and arthritis.

Pharmacists have an important role to play in facilitating effective self-care for those with mild to moderate-severity acne because over-the-counter topical treatments are licensed for the management of this level of disease.(1)



Causes

There are at least four factors: altered sebum excretion; abnormal keratinocyte proliferation and

differentiation (comedogenesis); proliferation of *Propionibacterium acnes* (*P. acnes*) in functionally blocked follicles; and a host-induced inflammatory response.

Acne is a disease of the pilosebaceous follicle and during adolescence there is an increase in the production of sex hormones (mainly androgens) that cause sebaceous gland hyperplasia with a corresponding increase in the output of sebum giving the skin a greasy appearance. There is also an increase in the production and desquamation (shedding) of the keratinocyte cells lining the pilosebaceous follicle. These cells become unusually cohesive and block the follicular opening.

If the blockage occurs close to the surface of the skin, pigment in the desquamated cells reacts with the atmosphere and turns black. This produces an open comedone or blackhead; if the blockage occurs further down the lumen of the canal, the increased pressure from sebum trying to escape raises the skin to produce a flesh-coloured lump, which is known as a closed comedone or whitehead.

Once comedones are formed, *P. acnes* thrives in the oxygen-deficient and sealed environment and hydrolyses the sebum into glycerol and free fatty acids. These are released into the surrounding epidermis and provoke an immune response that leads to the formation of inflammatory lesions.

Types of acne lesions

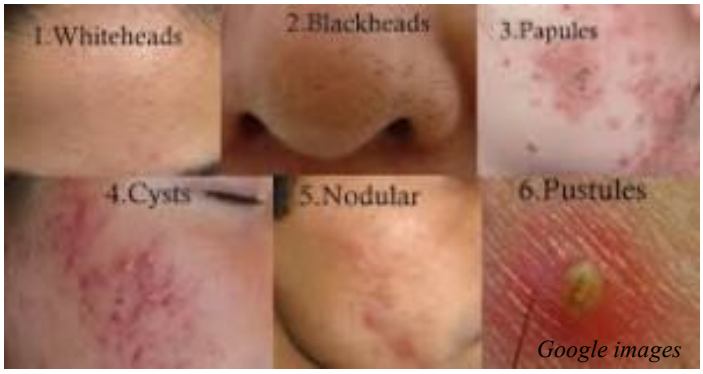
Typically, a patient with acne presents with the following lesions:

Non-inflammatory lesions

* Open comedones (blackheads).
* Closed comedones (whiteheads)

Inflammatory lesions

* Papules – small, pink or red inflamed lesions that can be tender to touch
* Pustules – inflamed papules with white or yellow pus-filled tops
* More severe forms of acne will be more widespread with lots of inflammatory lesions as well as:
* Nodules – large and painful solid lesions deep within the skin
* Cysts – like nodules but filled with pus, which can lead to scarring.



Classification

While there are various grading systems for acne, none have been universally accepted

In primary care, the following classification is used:

* Mild acne, a limited number of non-inflammatory comedones.
* Moderate acne, a mixture of both inflamed and non-inflamed lesions.
* Severe acne, widespread and extensive, affecting the face, chest and back and characterised by a larger number of both non-inflamed and inflamed lesions together with nodules and cysts.

Treatment options in the pharmacy

If acne affects the chest and back, unless it is mild, referral to the GP is advisable, since treating these areas with topical agents is more difficult. Patients who have evidence of scarring should also be referred.

Acne responds very slowly to treatment and all products should be used for at least six weeks before giving up. Furthermore, topical agents should be applied to all acne-prone areas of the skin rather than to individual lesions.

Facial washes

Lipo-hydroxy acids, glycolic acid, linoleic acid and alpha-hydroxy acids might help but further work is needed to provide more convincing evidence. One agent used in facial washes is salicylic acid, which is a keratolytic and is of benefit in comedonal acne.

Benzoyl peroxide

The most commonly used topical anti-acne drug is benzoyl peroxide (BPO) and its clinical efficacy has been demonstrated in many studies.

BPO has both comedolytic (breaking down blackheads and whiteheads) and powerful bacteri-cidal effect. In fact, twice daily application of 5% BPO gel can reduce the population of *P. acnes* by more than 95% after five days, There is currently no known resistance to BPO. This is due to its mode of

action. Once in the skin, BPO degrades to benzoic acid and hydrogen peroxide, generating free radicals, which destroy *P. acnes*.

The two main problems with BPO are, first, that it is a powerful bleaching agent that will discolour clothes, pillows, bedding etc. Also, it is potentially irritant. One way to reduce the irritancy is to initially apply BPO products for limited periods of time (say, 15 min) before washing off and to gradually increase the contact time.(2,3)

Nicotinamide

This vitamin B3 compound has anti-inflammatory and bacteriostatic properties and there is evidence that it can reduce the rate of sebum excretion. Randomised trials suggest that nicotinamide can significantly improve acne and that the improvement is comparable to the topical antibiotic clindamycin.(4)

Topical vehicles

Acne products are available in gels and creams and there is little evidence that either is more effective. While some authorities argue that patients with greasy skin benefit from using a gel (because of the drying effect) and those with dry skin are better with a cream, there is little evidence to support this. It is more important that the patient finds a formulation they are happy to use. Both dryness and irritation are common with all topical therapies and patients should be advised to use non-comedogenic (oil-free) moisturisers to combat these adverse effects. If the active topical agent such as BPO is used at night, an oil-free moisturiser can be used in the morning after washing or showering.

Lifestyle factors affecting acne

Diet

One factor that has attracted a great deal of attention in acne is diet. The Western diet with a high glycaemic load (highly refined carbohydrates such as white bread and cakes) leads to an increased production of androgens, which then worsens acne. In fact, a randomised, controlled, low glycaemic index dietary trial, emphasising fresh fruits and vegetables and avoiding refined carbohydrates, did show a significant reduction in acne lesions after three months. The role of diet in managing acne remains controversial and patients should be advised to adopt a healthy diet.(5)

Hygiene and sunlight

Poor hygiene (lack of washing) as a causative agent and lack of exposure to sunlight are often cited as lifestyle factors in acne. However, there is little evidence that either has a noticeable effect. (6)

Patients also like to use facial washes that contain particulates (exfoliants) and believe that these unclog the pores. However, vigorous scrubbing is more likely to irritate the skin and worsen acne.

Make-up

People with acne who wish to use make-up should look for the term non-comedogenic (oil free) on the label. Heavy make-up products can block pilosebaceous follicles, exacerbating acne. Other factors that appear to aggravate acne include emotional stress, smoking and picking at lesions.

Talking to patients

Pharmacists should discuss the treatment options available in the pharmacy and how each therapy should be used. The importance of perseverance should be emphasised because treatments are slow to work. Likely side-effects, such as dryness and irritation, and how these can be managed should also be explained to the patient.

Conclusion

Pharmacists should understand that acne can have a huge psychological impact on sufferers, who are likely to be embarrassed when seeking help. Nevertheless, pharmacists should reassure patients that acne is very treatable if therapies are used correctly. The retinoid adapalene has been approved for over-the-counter use and has become an additional treatment option for pharmacists.

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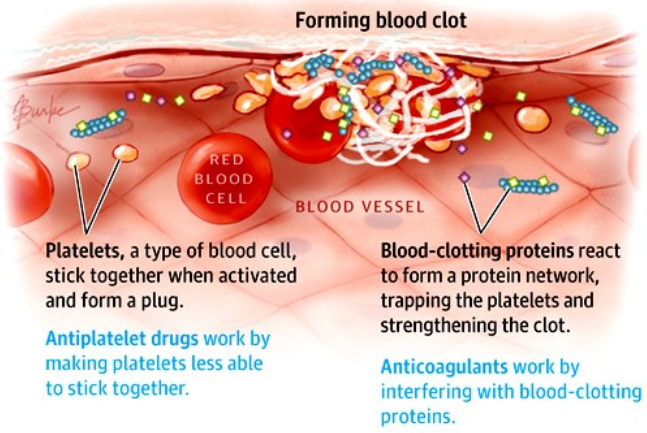
Gene test to predict those who won't benefit from blood thinner Clopidogrel

A new study suggests that stent patients with a certain gene mutation may need to consider alternatives to clopidogrel, a commonly prescribed blood thinner. They reported that mutation-carrying patients are much less likely to have or die from a heart attack, stroke or other major complication within a year if they take a substitute blood thinner. The findings, published in *Circulation: Genomic and Precision Medicine,* indicate a genetic test may help patients who are receiving a heart stent to avoid complications.

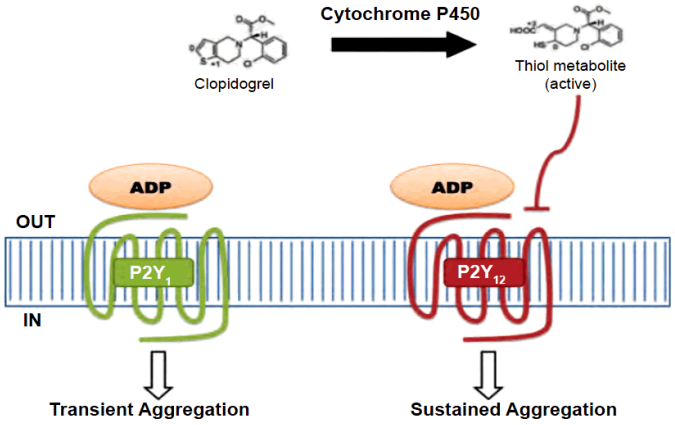
Atherosclerosis is a condition in which fatty deposits or plaque fill up the blood vessels. This is usually treated with an angioplasty, a procedure that widens the blood vessels. Sometimes, a special tube, called a stent, is also inserted to help keep the vessel open. Some patients who receive a stent are advised to take two drugs, aspirin, and another blood thinner, to reduce the risk of developing life-threatening heart problems.



From: https://jamanetwork.com/journals/jama/fullarticle/1790897

One of the commonly prescribed blood thinners is clopidogrel, marketed under the brand name Planix. But studies have found the drug doesn't metabolise as well and may be less effective in patients who have mutations in a gene called CYP2C19. These CYP2C19 mutations are found in about 2% of Caucasians, 4% of African-Americans and 14% of Chinese. Currently, however, testing is not routine, and not all physicians agree on who should be tested. The test costs $100 to $350 and is covered by most insurers in the United States, with various co-pay requirements.

The University of North Carolina, in 2012, began



From: http://www.ijddr.in/drug-development/efficacy-of-clopidogrel-drug-and-response-prediction-with-special-reference-to-recent-paradigm-shift.php?aid=11137

testing CYP2C19 of patients scheduled to receive a stent who were at high risk for complications. The new study looked at how the test was used and the complications that developed. The study was a single-center observational study conducted in 1193 patients who underwent percutaneous coronary intervention and received dual antiplatelet therapy (DAPT) after using an algorithm that recommended *CYP2C19* testing in patients at high risk and alternative DAPT (prasugrel or ticagrelor) in LOF allele carriers. The primary implementation endpoints were the frequency of genotype testing and alternative DAPT selection.

Patients with the mutation were less likely to die or have a heart attack, stroke or other major complication within one year after treatment if they received an alternative drug to clopidogrel. Eight percent of mutation carriers who took an alternative drug had a major complication compared to 27% who took clopidogrel. These findings back up a previous study that found a higher risk of major cardiovascular complications in patients with a CYP2C19 mutation who took clopidogrel.

According to the study's senior author and co-director of McAllister Heart Institute at UNC, physicians are already using CYP2C19 genetic testing to assist in making decisions for drug prescribing.

Prasugrel (Effient) and ticagrelor (Brilinta) are the two drugs researchers used instead of clopidogrel. They cost more than clopidogrel and carry a higher risk for internal bleeding. Because the new study used data collected after treatment, definitive answers about what exactly led to the better

outcomes are lacking. But clopidogrel already carries a boxed warning from the US FDA that it may not be as effective in patients with CYP2C19 mutations, a warning physicians need to be aware of, according to the study's lead author at the UNC Eshelman School of Pharmacy.

The study authors conclude that it is feasible and sustainable to implement *CYP2C19* genotype-guided DAPT in a real-world setting, which will improve clinical outcomes but will be challenging to maintain at a consistently high level of accuracy.

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NEWS from the FDA

Myths and realities about FDA approval

Some marketers may say their products are "FDA approved," but how can one be sure what the U.S. FDA really does approve?

FDA is responsible for protecting public health by regulating human drugs and biologics, animal drugs, medical devices, tobacco products, food (including animal food), cosmetics, and electronic products that emit radiation.

But not all those products undergo premarket approval, that is, a review of safety and effectiveness by FDA experts and agency approval before a product can be marketed. In some cases, FDA's enforcement efforts focus on products after they are already for sale. That is determined by Congress in establishing FDA's authorities.

Even when FDA approval is not required before a product is sold, the agency has regulatory authority to act when safety issues arise. Here is a guide to how FDA regulates products -and what the agency does (and doesn't) approve.

FDA doesn't approve companies

FDA does not "approve" health care facilities, laboratories, or manufacturers. FDA does have authority to inspect regulated facilities to verify that they comply with applicable good manufacturing practice regulations.

Owners and operators of domestic or foreign food, drug, and most device facilities must register their facilities with FDA, unless an exemption applies. Blood and tissue facilities also must register with the agency.

FDA approves new drugs and biologics

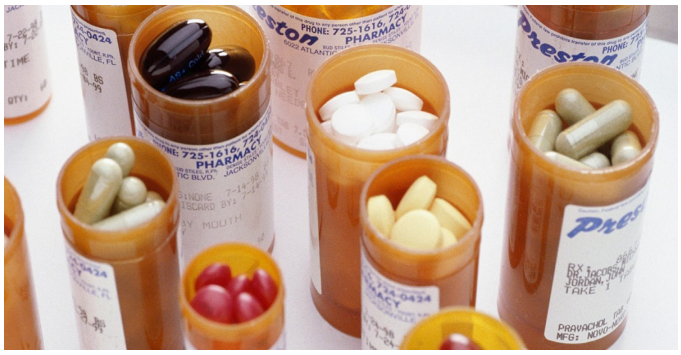
New drugs and certain biologics must be proven safe and effective to FDA's satisfaction before companies can market them in interstate commerce. Some examples of biologics that require approval are therapeutic proteins, vaccines, cellular therapies, and blood and blood products. Manufacturers must also prove they are able to make the drug product according to federal quality standards.

FDA does not develop or test products before approving them. Instead, FDA experts review the results of laboratory, animal, and human clinical testing done by manufacturers. If FDA grants an approval, it means the agency has determined that the benefits of the product outweigh the known risks for the intended use.

FDA doesn't approve compounded drugs

Compounding is generally a practice in which a pharmacist or a doctor combines ingredients to create medications that meet the needs of individual patients, including those who are allergic to ingredients in FDA-approved medicines or who cannot swallow an FDA-approved pill. But consumers need to be aware that compounded drugs are not

FDA approved. This means that FDA does not review applications for compounded drugs to evaluate their safety, effectiveness, or quality.



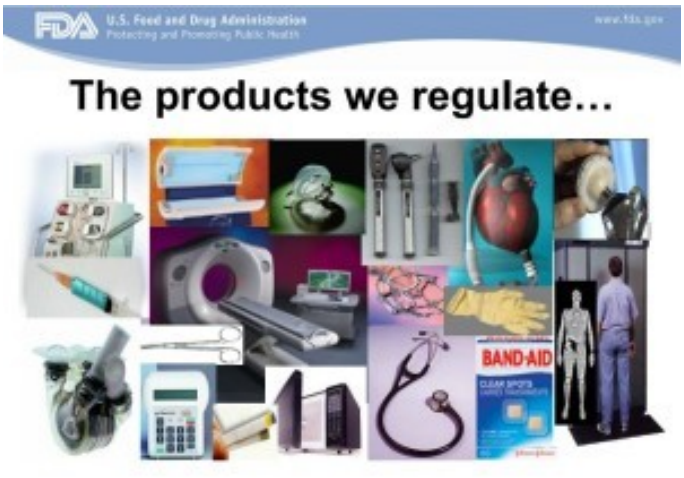
From: http://eureka.criver.com/compounding-and-unapproved-drugs/

FDA uses a risk-based, tiered approach for regulating medical devices

FDA classifies devices according to risk. The highest-risk devices (Class III), such as mechanical heart valves and implantable infusion pumps, generally require FDA approval of a pre-market approval application before marketing.

Generally, FDA "clears" moderate-risk medical devices (Class II) (for example dialysis equipment and many types of catheters) for marketing once it has been demonstrated that the device is substantially equivalent to a legally marketed predicate device that does not require premarket approval.

Devices that present a low risk of harm to the user (Class I) (for example non-powered breast pumps, elastic bandages, tongue depressors, and exam gloves) are subject to general controls only, and most are exempt from premarket notification requirements.



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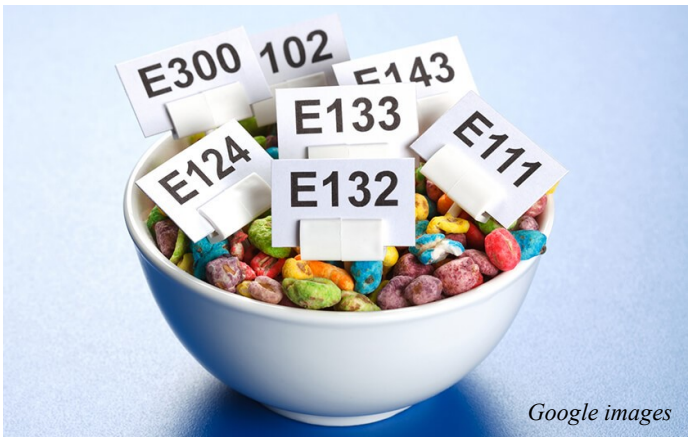
FDA uses a risk-based approach for human cells and tissues

All human cells and tissues intended for use in humans -collectively referred to as human cells, tissues, and cellular and tissue based products -are regulated to prevent the transmission of infectious disease. Examples of cells and tissues include bone, skin, corneas, ligaments, tendons, dura mater, heart valves, and reproductive tissue.

FDA approves food additives in food for people

Although FDA does not have premarket approval of food products, it has the authority to approve certain ingredients before they are used in foods. Those include food additives, such as substances added intentionally to food, and color additives.

FDA approves colour additives used in FDA-regulated products



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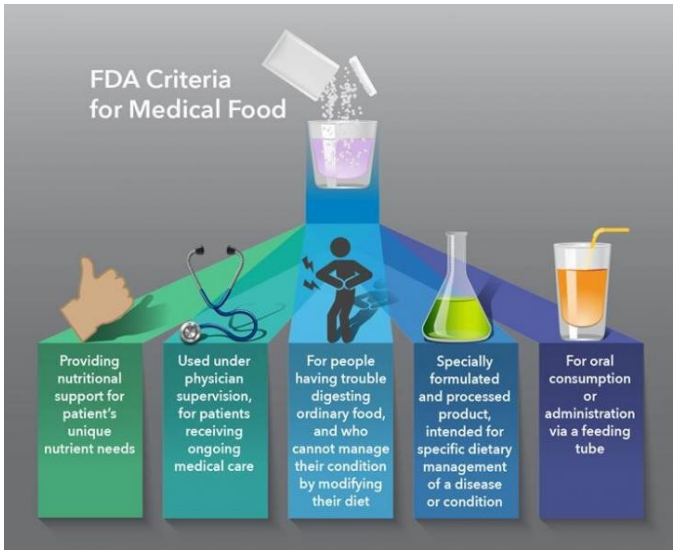
This includes those used in food (including animal food), dietary supplements, drugs, cosmetics, and some medical devices. These colour additives (except coal-tar hair dyes) are subject by law to approval by the agency, and each must be used only in compliance with its approved uses, specifications, and restrictions.

FDA does not approve cosmetics

Examples of cosmetics are perfumes, makeup, moisturisers, shampoos, hair dyes, face and body cleansers, and shaving preparations. Cosmetic products and ingredients, and their labeling, do not require FDA approval before they go on the market. There's one exception: color additives (other than coal-tar hair dyes).

FDA doesn't approve medical foods

A medical food is used for the dietary management of a disease or health condition that requires special nutrient needs. An example of a medical food is a food for use by persons with phenylketonuria, a genetic disorder. A person with this disorder may need medical foods that are formulated to be free of the amino acid phenylalanine. A medical food is intended for use under the supervision of a physician.



FDA doesn't approve infant formula

FDA does not approve infant formulas before they can be marketed. But manufacturers of infant formula are subject to FDA's regulatory oversight.

FDA doesn't approve dietary supplements

Unlike new drugs, dietary supplements are not reviewed and approved by FDA based on their safety and effectiveness.

FDA doesn't approve the food label, including the Nutrition Facts panel

FDA does not approve individual food labels before food products can be marketed. But FDA regulations require nutrition information to appear on most foods, including dietary supplements. Also, any claims on food products must be truthful and not misleading, and must comply with any regulatory requirements for the type of claim.

Reference

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IN THE NEWS

New drug test for detection of cocaine in fingerprint in seconds

A team of researchers has developed a simple paper-based test that can detect whether a person has recently been using cocaine in a matter of seconds. The method can potentially be applied to various substances. The researchers claim the technique to be safe, rapid and highly accurate as a method of running a variety of drug tests in the real world. The team, from institutions in the Netherlands and the UK, published their findings in the journal *Clinical Chemistry*.

The technique involves a method called paper spray mass spectrometry. This allows researchers to determine the identity of a substance by measuring the mass of its molecules. Since molecules of cocaine have a unique mass, the spectrometer can detect their presence. The test can also detect the metabolites that result from the body processing cocaine.

According to lead researcher Catia Costa, a researcher at the University of Surrey in the UK, in an interview with CNBC, the test can detect cocaine and metabolites of which is further proof that cocaine has gone through the body and is excreted.

The team tested 39 people, some known users of cocaine and some non-users. The test was 99% effective. A sample can be analysed in 30 seconds, which is extremely fast. Most conventional lab-based drug tests take several hours to days to return results. The new test also does not involve taking samples of blood, hair or urine, making it less invasive and safer.

It works like this: first, a fingerprint is collected on a small triangular piece of paper. Then the paper is placed on a mass spectrometer, the instrument that measures the various masses of different molecules and atoms. The researchers then pour a solvent on the paper and send a small electrical charge through the paper, which releases the molecules and sends them into the spectrometer's analyser and detector, which measure and record the mass of the molecules.

The method could, in theory, be used to test a variety of drugs. The team has already been able to detect heroin. They have also added a fingerprint identification step to the process, which in a real-world application would ensure the sample came from the person meant to take the test. The test could potentially be used in any of the usual situations where drug tests are needed, such as workplaces, legal situations, hospitals and treatment centers. The test could also be used in emergency situations, such as overdoses. Rapidly running a few tests could allow paramedics or doctors to determine what sorts of substances might be responsible for an overdose. Finally, doctors might be able to use it to ensure patients are taking prescribed medications.

The researchers claim to spend three months talking to people in industry, health care and other areas to explore the business case for the product. The research was funded by a company called Intelligent Fingerprinting, a company that does other fingerprint-based drug tests, and the UK's National Institute for Health Research.

Reference

https://www.cnbc.com/2017/09/22/new-drug-test-can-detect-cocaine-in-a-fingerprint-in-seconds.html

FDA approves 2nd gene therapy Yescarta

Last year the FDA approved a new treatment, Yescarta (axicabtagene ciloleucel), for diffuse large B-cell lymphoma (DLBCL),the most common type of non-Hodgkin lymphoma in adults.

Known as chimeric antigen receptor (CAR) T cell therapy it is only the second such therapy sanctioned by the FDA. In August 2017, the agency approved a similar CAR-T cell therapy for a childhood leukemia.

With CAR-T cell therapy, clinicians can take patients' own cells and turn them into a powerful weapon to attack cancer. It's a highly personalised, innovative therapy that hopefully will prove to be effective against many different types of cancer.

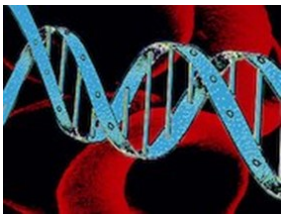
Each dose of Yescarta is a customised treatment created using a patient's own immune system to fight the lymphoma. The patient's T-cells, are collected and genetically modified to include a new gene that targets and kills the lymphoma cells. Once the cells are modified, they are infused back into the patient.

The FDA approval is based on a multicenter clinical trial of >100 patients. The complete remission rate after treatment with Yescarta was 51%.

Like all treatments, Yescarta comes with risk. Potentially serious side effects may include cytokine release syndrome (CRS), which can cause high fever and flu-like symptoms, and neurologic toxicities, both of which can be life-threatening.
Other potential side effects include serious infections, low blood cell counts and a weakened immune system.

Reference

www.drugs.com/news/fda-approves-2nd-gene-therapy-yescarta-67427.html



Answers to: Test your knowledge

Correct answers:
1-d; 2-a; 3-c

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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