KASTURBA MEDICAL COLLEGE
MANIPAL
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THE DRUG TIMES

Newsletter from Department of Pharmacology, Kasturba Medical College, Manipal
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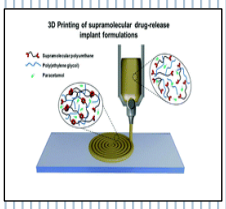
Overview

This edition of the drug times focuses on 3D printing in drug discovery and delivery. This issue also talks about promising results of nasal covid vaccine and artificial pancreas in type 1 diabetes mellitus. Further, accidental discovery of warfarin, new drug approvals and safe use of paracetamol in pregnancy are also highlighted.

3D Printing in Drug Discovery and Delivery



3D printing is a type of manufacturing process in which a physical object is created from a digital design.

Process of 3D printing involves the following steps:

A product is designed in 3D/2D by computer aided design (CAD) → Design is converted into a machine-readable format → Surface is sliced into several distinct printable layers using a software, which then transfers layer by-layer instructions to the printer → Product is 3D printed.

The process involves formation of thin layers of materials in form of liquid or powder and later these layers are fused.

This technique was developed in 1980s and mostly used in automobile industry, however, its scope extended to pharmaceutical industry in 2000s. This was possible due to use of biological materials in 3D printing.

Pharmaceutical applications of 3D printing

Some of the important areas of drug development and usage where 3D printing can be utilized are listed below (Figure 1) -

Drug screening

With the help of 3D printing, biological materials can be used to fabricate living structures, which resembles human organs with similar environment. The routine drug screening methods like use of transgenic animals or 2D cell cultures have their own limitations and do not replicate the same milieu as in real time patients. 3D bio-printing enhances the efficacy of drug screening by providing a natural environment as a diseased patient.

Drug delivery systems

3D printing has helped in developing better drug delivery systems. Since there is precise controlling, it can be used to make tablets of different size, shape, concentrations. It can also manipulate the amount of drug released in the body.

Personalized medicines

3D printing helps in making customized tablets based on patient's requirements. The same drug can produce different responses in different individuals leading to therapeutic failures or toxicities. To overcome this problem, 3D bio-printing can be utilized to design pill size, filling percentage of the active drug, to precisely control the amount of drug required for an individual patient. It may be possible in near future for doctors to be able to print the pills in real time based on the patient's needs (Figure 2).

Patient compliance

3D printing can help overcome some of the difficulties that patients face while taking medicines. For example, it can be used to create more loose and porous tablets, which would be useful in patients having swallowing difficulties. Similarly, with help of 3D printing technology, scientists have developed microneedles to deliver the drug painlessly, which would be a great way to deliver insulin in diabetics.

Current and future perspectives of 3D printing

Current research publications demonstrate infinite possibilities for 3D printing in therapeutics. A 3D printed drug, Spritam (levetiracetam), is already in market since 2015 which proves that it is possible to translate the 3D printing related research ideas into reality.

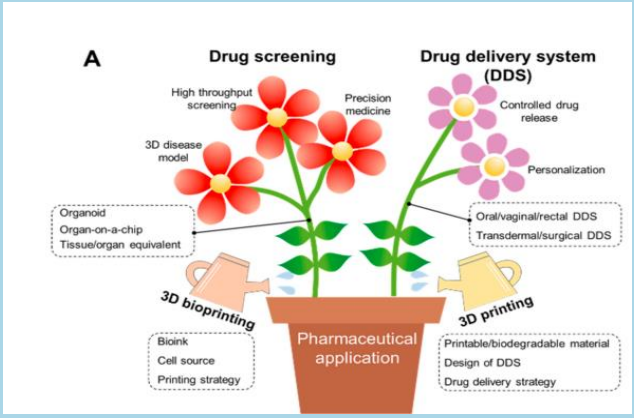


Figure 1: Various pharmaceutical applications of 3D printing

(Figure source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8465948/pdf/pharmaceutics-13-01373.pdf)

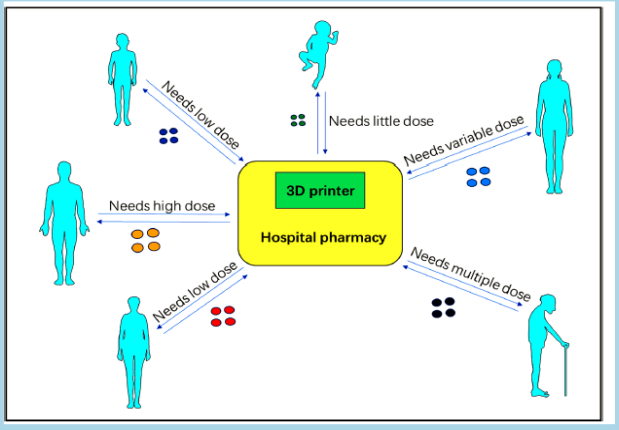


Figure 2: Depending on the requirements of the individual patients, the doctor can get the drugs printed on the spot.

(Figure source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8465948/pdf/pharmaceutics-13-01373.pdf)

References 1. Gao G, Ahn M, Cho WW, Kim BS, Cho DW. 3D Printing of Pharmaceutical Application: Drug Screening and Drug Delivery. Pharmaceutics. 2021 Aug 31;13(9):1373. doi: 10.3390/pharmaceutics13091373. PMID: 34575448; PMCID: PMC8465948.

2. Xiao Zhu , Hongjian Li , Lianfang Huang , Ming Zhang , Wenguo Fan, Liao Cui. 3D printing promotes the development of drugs. Biomedicine & Pharmacotherapy (IF 7.419) Pub Date: 2020-08-24 , DOI:10.1016/j.biopha.2020.110644

Happy accidents (serendipity)in discovery of warfarin

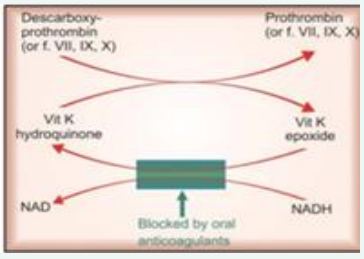
https://www.warf.org/stories/karl-paul-link/

In Prairies of Canada and North America in the year 1920, healthy cattle started dying secondary to internal bleeding. The cattle had grazed on sweet clover hay. The spoiled hay causing this condition was named as sweet clover disease. Frank W. Schofield and Lee M. Roderick showed that sweet clover disease could be reversed by removing the mouldy hay or by fresh blood transfusion.

By 1940, Karl Link, a biochemist and colleagues established that a natural substance called coumarin was oxidized in mouldy hay to produce 3,3′-methylene-bis(4-hydroxycoumarin), which would become better known as dicoumarol. The work was funded by the Wisconsin Alumni Research Foundation (WARF), who were awarded the patent for dicoumarol in 1941.
In 1945, Link considered using a coumarin derivative as a rodenticide. Link and colleagues worked through a list of 150 variations of coumarin, and number 42 was found to be particularly potent. The compound was named ‘warfarin’ after the funding agency and was successfully marketed in 1948 as a rodenticide.

The main advantages of warfarin were high oral bioavailability and high-water solubility; it was more potent than dicoumarol, but its effect could still be reversed by vitamin K. Therefore, warfarin transitioned into clinical use under the trade name Coumadin and was approved for use in humans in 1954. In 1978, John W. Suttie and colleagues demonstrated mechanism of action of warfarin by disrupting vitamin K metabolism by inhibiting the enzyme epoxide reductase. This was a journey from rat poison to clinics.

Reference: Lim, G. Warfarin: from rat poison to clinical use. Nat Rev Cardiol *(2017).*



Nasal spray for acute attack of migraine

Zavegepant is a third-generation calcitonin gene-related peptide (CGRP) receptor antagonist and can be used as nasal spray for the acute treatment of migraine. A single 10 mg dose of zavegepant was more effective than placebo and relieved pain and the related symptoms.

The pain is relieved in 15 minutes and relief lasted for 48 hours. A well tolerated drug and most common adverse events include dysgeusia and nasal discomfort. The New Drug Application (NDA) has been filed for intranasal zavegepant with the U.S. Food and Drug Administration for the acute treatment of migraine in adults. The Prescription Drug User Fee Act (PDUFA) goal date for completion of the FDA review of the NDA is set for 1Q2023.

PEDAP trial: New Artificial pancreas successful in young children in type 1 diabetes

The artificial pancreas is a new diabetes management system that with the help of continuous glucose monitor (CGM) checks blood glucose levels and automatically delivers the insulin when needed using an insulin pump. A trial done on 102 patients aged 2 to 5 years were randomly assigned to either the artificial pancreas group or the standard care comparison group. In this 13-week, it was found that the artificial pancreas group spent 12% more time within their target blood glucose range compared to the standard care group.

In this study, a better control was seen between 10 p.m. and 6 a.m., with artificial pancreas participants spending 18% more time in range than the standard care group. Safety assessment showed similar incidence of hypoglycaemia in two study groups and one event of diabetic ketoacidosis was observed in artificial pancreas secondary to infusion set failure. The study funding was provided by the National Institute of Diabetes and Digestive and Kidney Diseases (grant # U01DK127551).

Reference: https://www.nih.gov/news-events/news-releases/nih-supported-trial-shows-artificial-pancreas-improves-blood-glucose-control-young-children

Thalidomide – A ray of hope in radiation induced brain injury

Thalidomide, the infamous drug known to have cause severe birth defects, has now been found to be effective in treating radiation-induced brain damage. In a phase 2 study conducted by Jinping et al., it is seen that among 58 patients who had hard to treat radiation induced brain injury, 27 of them showed improvement after treatment with thalidomide and there was a reduction in volume of cerebral swelling (overall response rate, 46.6%; 95% CI, 33.3 to 60.1%) . Twenty-five of them had clinical improvement based on the Late Effects Normal Tissues–Subjective, Objective, Management, Analytic (LENT/SOMA) scale, and 36 patients demonstrated cognitive improvement based on the Montreal Cognitive Assessment (MoCA) scores. In a mouse model of RIBI, thalidomide restored the blood-brain barrier and cerebral perfusion, which were attributed to the functional rescue of pericytes secondary to elevation of platelet-derived growth factor receptor β (PDGFRβ) expression by thalidomide. Further studies should be conducted to confirm thalidomide's efficacy in radiation induced brain injury.

Reference- https://www.science.org/doi/10.1126/scitranslmed.abm6543

iNNCOVAC: The nasal COVID vaccine

iNCOVACC®, is a COVID 19 nasal vaccine developed by Bharat Biotech in partnership with a US-based Washington University. It was approved by the Drugs Control General of India as a heterologous booster dose. The nasal vaccine is a recombinant adenoviral vector vaccine.

Administration: This vaccine is formulated as drops for adults (more than 18 years of age) in two doses of 0.5ml or four drops into each nostril four weeks apart. In India, it can be administered as a booster dose to those who have already taken two doses of the Covishield or Covaxin vaccine. It can be booked on the CoWin platform.

Mechanism: The intranasal vaccine stops the virus in the mucosal region by triggering an immune response in the cells and molecules present there. The nasal vaccine stimulates neutralizing IgG, mucosal IgA, and T cells in the mucosal tissues. The immune response at the site of infection (in the nasal mucosa) is essential for blocking both infection and transmission of COVID-19.

Advantages:

- Less cost - can be scaled up for global use
- Painless and no needle-associated infections & injuries
- Easy to administer, with no requirement of trained personnel.
- Easy to store and transport
- Blocks both the infection and the transmission of COVID-19.
- Improved compliance

Side effects: fever, headache, running nose, sneezing, allergic reaction (rarely)

Contraindications: It is avoided in people who have severe allergic reaction to any ingredients of the vaccine or who had a severe allergic reaction after a previous dose of the vaccine and people who currently have an acute infection or fever

Storage: At temperatures between 2 to 8^0Celsius. In addition, it should be used once opened and out of the refrigerator within 6 hours.

Data from clinical studies: Phase 1 and 2 homologous and heterologous clinical trials were conducted and no serious adverse events were reported. A phase III study multi centric was done to compare the immunogenicity and safety of covaxin and iNCOVACC wherein a total of 248 adverse events were reported, 197 in the iNCOVACC® group and 51 in COVAXIN® group

Reference : https://www.bharatbiotech.com/intranasal-vaccine.html

New Drug Approvals

Drug name	Active ingredient	Approval date	Indication
Rezlidhia	olutasidenib	1/12/2022	Acute myeloid leukaemia
Krazati	adagrasib	12/12/2022	KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer
Sunlenca	enacapavir	22/12/2022	HIV infection
Lunsumio	mosunetuzumab-axgb	22/12/2022	Relapsed or refractory follicular lymphoma
Xenoview	hyperpolarized Xe-129	23/12/2022	Evaluation of pulmonary function and imaging
Briumvi	ublituximab-xiiy	28/12/2022	Relapsing multiple sclerosis
NexoBrid	anacaulase-bcdb	28/12/2022	Eschar removal in burns
Leqembi	lecanemab-irmb	6/1/2023	Alzheimer's disease
Brenzavvy	bexagliflozin	20/01/2023	Type 2 diabetes mellitus
Jaypirca	pirtobrutinib	27/1/2023	Mantle cell lymphoma
Orserdu	elacestrant	27/1/2023	Breast cancer
Jesduvroq	daprodustat	1/2/2023	Anaemia caused by chronic kidney disease
Lamzede	velmanase alfa-tycv	16/2/2023	Alpha-mannosidosis
Filspari	sparsentan	17/2/2023	Primary immunoglobulin A nephropathy
Skyclarys	omaveloxolone	28/2/2023	Friedrich's ataxia

Reference - https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2022

Paracetamol use in pregnancy: Safety challenges

A growing body of experimental and epidemiological research suggests that prenatal exposure to paracetamol (*N*-acetyl-*p*-aminophenol (APAP), otherwise known as acetaminophen) might alter fetal development, which could in turn increase the risks of certain neurodevelopmental, reproductive and urogenital disorders.

Acetaminophen is the active ingredient in most of the prescriptions and non-prescription medications used to relieve mild to moderate pain and reduce fever. In the USA, acetaminophen is estimated to be used by up to 65% of pregnant women. Worldwide, more than 50% of pregnant women are estimated to use acetaminophen.

Acetaminophen has been considered by FDA and EMA for use in pregnancy for pain and fever when used as directed, as NSAIDs are contraindicated for use in pregnant women in later pregnancy, Acetaminophen can readily cross the placenta and blood–brain barrier. During pregnancy, changes occur in acetaminophen metabolism, which might make pregnant women and their foetus more vulnerable to toxic effects. The amount of the oxidative metabolite *N*-acetyl-*p*-benzoquinone imine might be increased during pregnancy.

Human observational studies with prenatal acetaminophen usage have been found to be associated with urogenital and reproductive tract abnormalities. Some studies have found an increased risk of cryptorchidism and reduced anogenital distance (AGD). Both reduced AGD and cryptorchidism are indicators of disturbed masculinization and risk factors for reproductive disorders in later life. Prenatal acetaminophen exposure has also been associated with earlier female pubertal development. Additionally, epidemiological studies consistently suggest prenatal acetaminophen exposure might increase the risk of adverse neurodevelopmental and behavioural outcomes, such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder, language delay (in girls), and decreased intelligence quotient. However, it depends on the timing of usage in pregnancy and the duration of use of acetaminophen.

In vivo, in vitro and *ex vivo* studies have shown that acetaminophen directly affects the hormone-dependent processes, which leads to disrupted reproductive development and neurodevelopment in both sexes. Fetal exposure in rodents has been shown experimentally to cause reproductive disorders of the male urogenital tract, including abnormalities in testicular function, sperm abnormalities and sexual behaviour. Experiments have shown disruption of female ovarian development resulting in reduced oocyte number and subsequent early ovarian insufficiency and subsequent reduced fertility. Fetal APAP exposure has been demonstrated to induce changes in neurotransmission in the brain manifesting in altered cognitive function, behaviour, and locomotion.

Hence it has been suggested to design epidemiological studies to reduce confounding factors, control for genetic factors, and accurately capture exposure and outcome. Studies are also required to examine the timing, dosage, and duration of exposure both prenatally and postnatally.

It has been recommended that women be counselled prior to or early in pregnancy not to use acetaminophen unless medically indicated; they should consult the physician before using it on a long-term basis and use it with the lowest possible dose and for the shortest possible time.

Beta 3 agonist - Mirabegron

Beta-3 receptors were initially identified in the adipose tissue. They are also expressed in human heart, gall bladder, gastrointestinal tract, prostate and urinary bladder detrusor, and brain. The table below shows the location of beta3 receptors, agonists, and their probable indications:

Site	Indication	Beta-3 agonist
Brain	Anxiety and depressive disorders	amibegron
Gut	Functional gut disorders, inflammatory bowel disease	solabegron
Urinary bladder	Overactive bladder	Solabegron Mirabegron
Blood vessels	Hypertension	-
Myocardium	Early heart failure Ventricular hypertrophy, Ischemic heart diease , entric	
Myometrium	Preterm labour	
Liver and portal circulation	Portal hypertension	

In 2012, **Mirabegron** was the first β_3-AR agonist to be approved in the United States and Europe for the treatment of overactive bladder (OAB) syndrome. It has been shown to improve storage function and increase maximum cytometric capacity in real-world studies.

Therefore, patients with a small bladder capacity may be more suitable for mirabegron treatment. Mirabegron is used alone or in combination with solifenacin. It is also used to treat neurogenic detrusor overactivity in children 3 years of age and older.
Mirabegron is available as an extended-release (long-acting) tablet and as an extended-release suspension to take by mouth. The tablets are usually taken with or without food once a day in adults and with food once a day in children. The suspension is usually taken with food once a day.

Adverse effects: elevated blood pressure (hypertension) nasopharyngitis, UTI, constipation, QT prolongation, tachycardia.

The future depends on what we do in the present- Gandhi

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