Drug & Poison Information Center—Faculty of Pharmacy—Tanta University

Drug & Poison Information Bulletin

WINTER 2019,VOLUME 6, ISSUE 4

Novel drug delivery system for improving chemotherapy efficacy

"In-press, Journal pre-proof"

In this issue:

Tumor cells show acidic conditions compared with normal cells, which further inspires scientists to build nanocarrier responsive to tumor microenvironment (TME) for enhancing tumor therapeutic efficacy. Limited water solubility, nonspecific cytotoxicity, and undesirable adverse effects of traditional chemotherapy drugs lead to poor circulation performance and low tumor tissue-selective accumulation. Stimuli-responsive drug delivery systems have been developed gradually for improving the efficacy of anti-cancer drugs.

Several nanoparticle-based drug delivery systems have been developed to improve the insufficient therapeutic activity of traditional chemotherapy and address the challenges of cancer treatment, including polymeric liposomes and micelles, small molecules prodrug, and inorganic delivery systems. Compared to lipid, stimuli-responsive polymer-based drug-delivery systems exhibited stable structures and selective drug release for cancer therapy.

Generally, the controllable release of drug in tumor can be realized by linking the drug with stimuli-sensitive chemical bonds, such as hydrazone bond , disulfide bond , thioketal,...etc. Furthermore, polymeric drug can be self-assembled into nanoscale micelles in aqueous solution.

Here, a pH-sensitive and biocompatible poly-prodrug based on dextran-doxorubicin (DOXDT) for enhanced chemotherapy was reported.

High-density DOX component was covalently decorated on the nanocarrier and the drug molecules could be effectively released in the acidic tumor tissue/cells, improving chemotherapy efficacy. Compared to lipid-based drug delivery system, the DOXDT prodrug showed higher drug load capacity up to 23.6%. In addition, excellent stability and smaller size of the nanocarrier contributed to better tissue permeability and tumor suppressive effects in vivo. Hence, this amphipathic DOXDT prodrug is promising in the development of translational DOX formulations, which would be widely applied in cancer therapy.

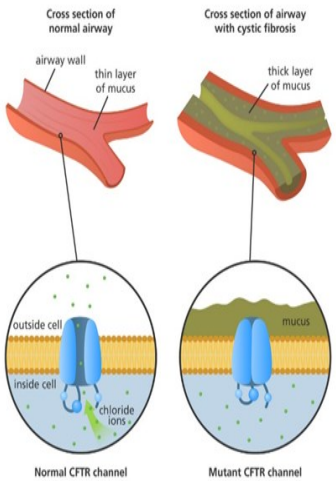
Cite this article as:

Xiaoli Zhang, Tian Zhang , Xianbin Ma, et al. The Design and Synthesis of Dextran-Doxorubicin Prodrug-based pH-Sensitive Drug Delivery System for Improving Chemotherapy Efficacy. AJPC (2019), doi: https://doi.org/10.1016/j.ajps.2019.10.001.

By: Ph/Marwa EL-Sayed, PGCPD

FDA drug approval for cystic fibrosis

Cystic fibrosis, a rare, progressive, life-threatening disease, results in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body. It leads to severe respiratory and digestive problems as well as other complications such as infections and diabetes. This disease is caused by a defective protein that results from mutations in the CFTR gene, which acts to create channels on the cell surface to allow the movement of chloride in and out of the cell. While there are approximately 2,000 known mutations of the CFTR gene, the most common mutation is the F508del mutation.



Approval history:

The U.S. Food and Drug Administration approved Trikafta (elexacaftor/ivacaftor/ tezacaftor), which is a combination of three drugs that target the defective CFTR protein. It helps the protein made by the CFTR gene mutation function more effectively.

The drug is effective for patients of 12 years and older with at least one F508del mutation, which affects 90% of the population with cystic fibrosis or roughly 27,000 people in the United States.

Clinical Data:

The efficacy of Trikafta was demonstrated in two trials. The first trial was a 24-week, randomized, double-blind, placebo-controlled trial in 403 patients who had an F508del mutation and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor or tezacaftor/ivacaftor alone. The second trial was a four-week, randomized, double-blind, active-controlled trial in 107 patients who had two identical F508del mutations. In the first trial, Trikafta increased the mean percent predicted forced expiratory volume (ppFEV1), which is an established marker of cystic fibrosis lung disease progression, by 13.8% from baseline compared to placebo. In the second trial, it increased mean (ppFEV1) by 10% from baseline compared to tezacaftor/ivacaftor.

Safety profile:

The most common adverse drug reactions included:

⇒ Headaches.

⇒ Upper respiratory tract infections, rhinorrhea, rhinitis, influenza, sinusitis, nasal congestion.

⇒ Abdominal pains, diarrhea, rashes.

⇒ Increased liver enzymes (alanine aminotransferase and aspartate aminotransferase).

⇒ Increased blood creatine phosphokinase & blood bilirubin.

Note: The FDA granted this application Priority Review, in addition to Fast Track and Breakthrough Therapy Designation. Trikafta also received orphan drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.

References:

- *Cystic fibrosis. Available at: https://ghr.nlm.nih.gov/condition/cystic-fibrosis#genes. Accessed in November, 2019.*
- *FDA approves new breakthrough therapy for cystic fibrosis. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis. Accessed in November, 2019.*

By: Ph/Mai Mousa, PharmD.

Biotin Safety Alert

The FDA has updated its 2017 safety communication to remind health care providers that biotin (Vitamin B7, often found in dietary supplements), can significantly interfere with certain lab tests and cause incorrect results that may go undetected. While biotin in patient samples can cause falsely high or falsely low results, depending on the type of test, the FDA is particularly concerned about biotin interference causing a falsely low result for troponin, a biomarker to aid in the diagnosis of myocardial infarction, which may lead to a missed diagnosis and potentially serious clinical implications.

Recommendations for Health Care Providers:

- ⇒ Talk to your patients about any biotin supplements or multivitamin supplements they are taking that may contain biotin, including supplements marketed for hair, skin, and nail growth.
- ⇒ Know that biotin is found in multivitamins, including prenatal multivitamins, biotin supplements, and dietary supplements for hair, skin, and nail growth in levels that may interfere with lab tests.
- ⇒ Be aware that many lab tests, including but not limited to cardiovascular diagnostic tests and hormone tests, that use biotin technology are potentially affected, and incorrect test results may be generated if there is biotin in the patient's specimen.
- ⇒ Communicate to the lab conducting the testing, if your patient is taking biotin.
- ⇒ If a lab test result does not match the clinical presentation of your patient, consider biotin interference as a possible source of error.
- ⇒ Report to the lab test manufacturer and the FDA, if you become aware of a patient experiencing an adverse event, following potentially incorrect laboratory test results due to biotin interference.

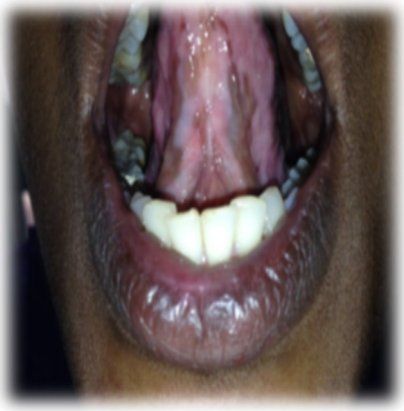
References:

Food & Drug Administration (FDA). Biotin (Vitamin B7): Safety Communication Update- May Interfere with Lab Tests. 2019. Available at https://www.fda.gov/medical-devices/safety-communications/update-fda-warns-biotin-may-interfere-lab-tests-fda-safety-communication. Accessed in November, 2019.

By: Ph/Marwa EL-Hefnawy, M.Sc

Recent case reports to be considered !

Ibuprofen-induced intra-oral fixed drug eruption (FDE)



⇒ **In brief:** A 35-years-old female underwent surgery for anal fissures at a secondary care hospital in India. After surgery, the patient was prescribed ibuprofen 400 mg, t.i.d., for 7 days. On Day 3, the patient complained of a burning sensation, discoloration of the lips and ulcers in the oral cavity. Based on the presenting signs and symptoms, she was diagnosed as experiencing an ibuprofen-induced FDE. Symptoms improved significantly after withdrawal of ibuprofen. The patient was treated with intravenous fluids, prednisolone 40 mg oral tablets and levocetirizine 20 mg. A causality assessment of the reaction was undertaken, indicating a probable relationship between the patient's symptoms and her use of ibuprofen. This report highlights the importance of regular monitoring for adverse drug reactions due to ibuprofen because it is likely to cause an FDE.

⇒ **Source: Pawan A.R.S., Swamy V.H.T. , Mothi S. N. , *et al.* Ibuprofen-induced intra-oral fixed drug eruption. JPPR (2019).https://doi.org/10.1002/jppr.1530.**

Reversible black tongue (BT): A little known side effect of imipenem/ cilastatin and evidence for novel mode of action.

⇒ **In brief:** A 39 years old male patient with Type 2 Diabetes Mellitus (T2DM) presented with a history of ulceration on the right foot for the last two weeks. The ulcer was a manifestation of diabetic foot infection (DFI). Intravenous administration of 500 mg imipenem/ cilastatin every 6 hours/day was started. Prior to this, he had been on stable doses of metformin and insulin aspart 30 for over a year. After five days of treatment with imipenem/cilastatin, the patient complained of a black discoloration of his tongue and teeth and a bitter taste in his mouth.

To be continued

The treatment for antibiotic was performed for two weeks and the BT continued to persist. Within one week of the cessation of the imipenem/cilastatin, the patient's tongue returned to a normal colour. This is the first case of BT induced by imipenem/cilastatin. Withdrawal of the combination is likely to reverse the condition.

⇒ **Source: Zhao S, Fan L, Feng J, Ma P . Reversible black tongue: A little known side effect of imipenem/cilastatin and evidence for novel mode of action. J Clin Pharm Ther. 2019 Oct 17. DOI: 10.1111/jcpt.13066.**

Severe hyperkalemia immediately after Birth

⇒ **In brief:** An interesting clinical case of a newborn male infant was delivered in the 35th week of gestation by urgent C-section after placental abruption suffered from severe hyperkalemia that led to a life-threatening arrhythmia was reported. Such severe hyperkalemia is rarely seen in newborns, especially immediately after birth. Since the newborn in the case had multiple complications during delivery, it was hypothesized that the cause of the severe hyperkalemia was multifactorial. Hyperkalemia accompanied by arrhythmias was treated with calcium gluconate, insulin, Sorbisterit enema, and, finally, by exchange transfusion. Making a decision as early as possible regarding exchange transfusion is essential in patients with hyperkalemia with electrocardiogram changes and hemodynamic instability.

⇒ **Source: Kavčič A, Avčin S, Grosek Š. Severe Hyperkalemia Immediately After Birth. Am J Case Rep. 2019 Oct. DOI: 10.12659/AJCR.916368**

By: Ph/ Marwa EL-Sayed, PGCPD.

How to respond effectively to reviewer's comments?

"Notes for researchers"

One of the Drug and Poison Information Center's activities is research support, and the peer review system is simultaneously rewarding and frustrating, with good suggestions for improving the manuscript often hidden among less useful comments. Therefore, we introduce respectful statements you should use when responding to a reviewer who clearly did not read part of your manuscript or completely misunderstood one of your conclusions.

What you want to say	What you should say
You just did not understand what we wrote!	Several statements that we made were more ambiguous than intended, and we have adjusted the text to be clearer.
You are being so picky about grammar or formatting!	We apologize for this error, and we have corrected the text as suggested.
No one knows the answer to that question.	This is a valid and important question, and we are curious what the results would be. However, we are unaware of any studies that provide the answer.
That experiment would take forever!	The suggested experiment is interesting and would provide additional information about...but we feel that it falls outside the scope of this study.
We are not saying we provided anything that is just our hypothesis!	We agree that this explanation is speculative at this time, and we have edited the text to state that our conclusion is only suggested by our results. Note: Try to make some changes to the text to clarify your thoughts.
You did not even read what we wrote!	We did not intend to indicate [insert reviewer's mistaken assertion here], and we have therefore altered the text to specify that [insert correct conclusion here]. *Note: Change some text to appease the reviewer.*

References:

Responding to Peer Reviewers: You Can't Always Say What You'd Like [Free Guide]. Available at https://www.aje.com/en/arc/responding-reviewers-you-cant-always-say-what-youd/.Accessed in October, 2019 .

By: Ph/Bassant Maher, B.Sc

Test your knowledge!

"From our questions received in 2019"

⇒ **After surgery, a patient has morphine prescribed for postoperative pain. Which parameter is most important to be checked firstly?**

1-Respiratory rate.
2-Heart rate.
3-Pain level.
4-Constipation.

⇒ **In cardiovascular diseases especially ST-Elevation Myocardial Infarction (STEMI) and primary Percutaneous intervention (PCI), which is more recommended, Uncoated or enteric coated salicylic acid?.**

⇒ **For treatment of bed sores (esp. exuding type), what is the suitable dosage form of antibiotics that could be used safely? Why?**

For more contact , we are glad to receive your answers supported by references via our official email:

Tanta_DPIC@pharm.tanta.edu.eg

Editorial Board

Address: **Drug & Poison Information Center, Faculty of Pharmacy, Tanta University.**

E-mail: **Tanta_DPIC@pharm.tanta.edu.eg**

Tel.: **040/3336007(7-241), 3331577 ,** **Hotline:** **090071020**

If you want to receive our bulletin, please check our official website.