The most common route of administration used during COVID-19

Mena Raid Khalil*,Ghaidaa S. Hameed*,Dalya Basil Hanna**
**** College of Pharmacy, Mustansiriyah University, Department of Pharmaceutics***
*****College of Pharmacy, Mustansiriyah University, Department of Clinical Laboratory Sciences***

Article Info:

Received Nov 2022
Accepted Jan 2023
Corresponding Author email:
ghaidaahameed@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0003-1470-6808

DOI:

Abstract:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the virus that caused the COVID-19 pandemic. Initial symptoms include fever, cough, and dyspnea. Symptoms include nausea, vomiting, and abdominal pain, GIT involvement is also possible. The COVID-19 outbreak has increased the need for alternative medicine administration routes, particularly in public places. Buccal, sublingual, and rectal administration are all considered transmucosal methods. They are self-administration options for non-invasive systemic distribution. In addition, they are great for use in palliative and end-of-life care because of their quick onset of action and decreased first-pass metabolism. A mucosal atomization device allows for the intranasal administration of a parenteral formulation through nasal spray. Rectal mucosal absorption is comparable to that of the oral route, making the rectal route an extremely versatile and useful method of drug administration for a wide variety of medications. Covid-19 illness is treated with a variety of drugs, including anti-malaria medication (hydroxychloroquine), glucocorticoids (dexamethasone), antibiotics (azithromycin), and antiviral medications (favipiravir). This article discusses the route of drug administration for COVID-19, as well as symptoms, treatments, and the various ways it can be spread.

Key words: COVID-19, Transmission, Symptoms, Treatment, Formulations

استراتيجية صياغة الأدوية المستخدمة خلال كوفيد -19

مينا رائد خليل*،غيداء سليمان حميد*، داليا باسل حنا**
****فرع الصيدلانيات, كلية الصيدلة, الجامعة المستنصرية, بغداد, العراق.***
*****فرع علوم المختبرية السريرية, كلية الصيدلة, الجامعة المستنصرية , بغداد, العراق.***

الخلاصة:

فيروس كورونا المتلازمة التنفسية الحادة الوخيمة هو الفيروس الذي تسبب في جائحة كوفيد-19. تشمل الأعراض الأولية الحمى والسعال وضيق التنفس. تشمل الأعراض الغثيان والقيء وآلام البطن ، ومن الممكن أيضًا تورط الجهاز الهضمي. أدى تفشي مرض كوفيد -19 إلى زيادة الحاجة إلى طرق إدارة الطب البديل ، لا سيما في الأماكن العامة. تعتبر الإدارة الشدقية وتحت اللسان والمستقيم طرقًا عبر الغشاء المخاطي. إنها خيارات الإدارة الذاتية للتوزيع الجهازي غير الغازي. بالإضافة إلى ذلك ، فهي رائعة للاستخدام في الرعاية الملطفة ونهاية العمر بسبب بدء مفعولها السريع وانخفاض التمثيل الغذائي للمرور الأول. يسمح جهاز الانحلال المخاطي بالإعطاء الأنفي لتركيبة الحقن من خلال رذاذ الأنف. يمكن مقارنة امتصاص الغشاء المخاطي في المستقيم بامتصاص الطريق الفموي ، مما يجعل طريق المستقيم طريقة متعددة الاستخدامات ومفيدة للغاية لإعطاء الأدوية لمجموعة متنوعة من الأدوية. يُعالج مرض كوفيد -19 بمجموعة متنوعة من الأدوية ، بما في ذلك الأدوية المضادة للملاريا (هيدروكسي كلوروكوين) ، والجلوكوكورتيكويدات (ديكساميثازون) ، والمضادات الحيوية

(أزيثروميسين) ، والأدوية المضادة للفيروسات (فافيبيرافير). تناقش هذه المقالة مسار تعاطي المخدرات لـكوفيد-19 ، بالإضافة إلى الأعراض والعلاجات والطرق المختلفة التي يمكن أن تنتشر بها.

الكلمات المفتاحية: كوفيد -19 ، انتقال المرض ، الأعراض ، العلاج ، التركيبات

Introduction

The severe acute respiratory syndrome coronavirus (SARS-CoV2), which causes the unique human coronavirus disease (COVID-19), is the primary cause of the global pandemic. That started in late 2019 in Wuhan, in the Chinese province of Hubei, and quickly spread around the globe. There have been 8,128,490 confirmed cases of COVID19 reported from a total of 213 nations and territories worldwide. It spreads over the globe as an unparalleled global epidemic and has an impact on every person, whether they are affected physically, mentally, or financially (1).

The data point to SARS-CoV-2 largely infecting respiratory epithelial cells and spreading from person to person via the respiratory pathway, although the precise viral target cells and organs have not yet been identified (2). Fever and respiratory symptoms like dyspnea and dry cough are some of the most prevalent signs of COVID-19 infections, which are comparable to those of the Middle East respiratory syndrome (MERS) in 2012 and the severe acute respiratory syndrome (SARS) in 2003. Along with respiratory symptoms, there may also be gastrointestinal symptoms such diarrhea, nausea, vomiting, and abdominal discomfort (3). There is growing evidence that COVID-19 patients' stool samples (2, 4, 5), anal swabs (6) , and rectal swabs (7) , contain SARS-CoV-2 RNA, despite the upper respiratory tract and respiratory cells being free of SARS-CoV-2 (2, 6, 8). In addition, the ileum, duodenum, jejunum, caecum, and colon are among the gastrointestinal epithelial cells with the highest expression of the angiotensin converting enzyme-2 (ACE-2) receptor (2, 9). These findings, when combined, imply that SARS-CoV-2 may exhibit fecal-oral transmission in addition to droplet transmission, which has consequences for SARS-CoV-2 transmission as well as infection prevention and management.

Transmission

SARS-CoV-2 can transmit indirectly (through touch) (contaminated objects and airborne contagion) as well as directly (via droplets and human-to-human transfer). The spread of airborne infections may potentially be facilitated by personal protective equipment (PPE) (10). It is believed that the SARS-CoV-2 virus spreads mostly by respiratory droplets, which are created whenever a patient coughs, sneezes, talks, or even sings. In most cases, droplets are only capable of travelling around six feet (almost two meters), and they can only remain suspended in the air for a short amount of time. However, the SARS-CoV-2 virus can remain viable and infectious in droplets for up to three hours if the droplets are allowed to float in the air (less than five microns in diameter) (11).

Anyone who comes into direct contact with SARS-CoV-2-infected surfaces and subsequently touches their own mucous membranes (mouth, eyes, or nose) with their hands is at risk of getting COVID-19 (12).

SARS-CoV-2 can spread from asymptomatic (or incubating) persons without radiological abnormalities (13, 14).

Symptoms

The symptoms of viral respiratory disorders can range from minor to lethal, with the latter being most common in those who are elderly, have impaired immune systems, or are young children (15).

People infected with COVID-19 experience symptoms similar to those of the flu. These symptoms are almost identical to those of its ancestor, SARS. Individuals infected with the virus may experience a wide range of symptoms. However, the virus has a wide range of effects on its human hosts. It's possible that the majority of infected persons will only have mild to moderate symptoms. The symptoms include dry cough, tiredness, and fever (>38 °C) (16, 17). Several people might experience symptoms such as pains and aches, a cold, a stuffy nose, a sore throat, difficulty breathing, and diarrhea. According to recent information provided by the Center for Disease Control (CDC), infected persons may also have other symptoms such as aches, chills and pains in the muscles, shaking, headaches, and a loss of smell and taste. As a result of contact with confirmed patients, more and more studies indicate that a small number of COVID19 pneumonia cases started with conjunctivitis as the primary symptom. Reverse transcriptase polymerase chain reaction (RT-PCR)-based viral RNA detection can aid in the early detection of SARS-CoV-2 infection and the implementation of effective quarantine measures (18).

The infected person may take an average of 5–6 days to begin experiencing symptoms, but in some circumstances, it may take up to 14 days (19, 20). Symptoms start to show up less than a week after being exposed to the virus, and they go away in 10–14 days. Immunocompromised individuals may experience more serious consequences include pneumonia, acute respiratory distress syndrome (ARDS), 29 %, sepsis, thrombosis, shock, and acute renal and/or cardiac failure (21).

It appears that COVID-19 infection can cause gastrointestinal manifestations as part of its natural course, and a patient who presents with symptoms including — but not limited to — diarrhea, nausea and/or vomiting, and abdominal pain should not be dismissed as a minor health concern. It appears that direct viral invasion through the usage of the ACE-2 receptor is connected with at least some of the possible causes of gastrointestinal symptoms (22), changing in the intestinal microflora (22), the use of antibiotics and antiviral medications (23, 24), and the direct or indirect inflammatory response as a result of SARS-CoV-2 causing damage to the digestive system (25)

Treatment

According to Huang et al. (26), anemia, acute heart damage, and secondary infections (27) were the next most frequent complications in COVID-19 patients after acute respiratory distress syndrome (ARDS) (28). In situations of Covid-19 illness, anti-malaria medication (hydroxychloroquine), glucocorticoids (dexamethasone), antibiotics (azithromycin), and antiviral medications (favipiravir) are all recommended due to their efficiency (29).

On the other hand, studies have demonstrated that the combination therapy of lopinavir and ritonavir had no discernible effect on clinical improvement, mortality reduction, or the detection of laryngeal viral RNA in individuals who have severe COVID-19 (30). The therapeutic dose and hazardous dose of chloroquine are close together and can cause fatal cardiovascular symptoms (31). An experimental medication called Remdesivir is being created to treat people who have the Ebola virus (32). The medicine remdesivir has shown promising in vitro action against SARS-COV-2 and is currently undergoing randomized trials, although it has not yet been licensed by the Food and Drug Administration in the United States (33).

Oseltamivir 75 mg BD will be used to treat patients who develop low-grade fever, malaise, cough, rhinorrhea, sore throat, and no shortness of breath, while in patients at high risk for influenza infection, antibiotics such as azithromycin + amoxicillin

/Clavulanic acid along with paracetamol 500 mg are used for symptomatic treatment (1). Through the reduction of inflammatory processes, azithromycin appears to be useful in the treatment of chronic obstructive pulmonary disease. With low adverse effects and the ability to be quickly generated in huge quantities, azithromycin has been utilized for the treatment of infectious disorders. Additionally, progenitor and stem cells may play a significant role in the pulmonary fibrosis caused by COVID-19 (15). In cases that are moderate to severe (any one of the following: Respiratory rate >24/min, Spo2 <94%in room air, confusion, systolic BP <90 mmHg or, diastolic BP<60 mmHg), admission and testing will be advised; if the test is negative, the patient will be managed in accordance with the established protocol; however, if the test is positive, oxygen supplementation will be necessary. Indicated treatments include antipyretic, antitussive, and antibiotics (1).

Depending on how serious their condition is, critically ill patients may require hemodynamic support or mechanical ventilation. In general, aggressive fluid management should be avoided in patients with significant illnesses and those who have a severe acute respiratory infection (34). Systemic corticosteroids should not be used to treat COVID-19 pneumonia or acute respiratory distress syndrome (ARDS).

Antiemetic medicines are used sparingly to treat digestive symptoms including nausea and vomiting. It is advised to conduct additional testing, such as a gastrointestinal pathogen panel and a Clostridium difficile toxin assay, before beginning supportive therapy to rule out other infectious etiologies. Although still debatable, using antibiotics is advised only if a coinfection is discovered (35).

Rotes of administration

Oral transmucosal delivery

For the treatment of breakthrough pain, a variety of oral transmucosal dose forms, including tablets, lozenges, and oral films, are available. The effectiveness of the oral transmucosal route may be diminished in patients undergoing palliative care due to the presence of xerostomia and oral mucositis (36). Additionally, individuals who experience nausea and vomiting find it less appealing. However, it is a crucial route of administration to offer populations receiving palliative care an early commencement of activity.

Table (1): properties of oral transmucosal route (37)

Types	Advantages	Disadvantages
Buccal and sublingual tablet	Easy and self-administration	Small surface area for absorption
Lozenge	Bypass first-pass metabolism	Limited dose and volume
Oral film	Rapid onset of action	May not be suitable in nausea and vomiting

Ophthalmic delivery

The eyes present a number of physiological challenges for ocular medication administration. Blinking, tear washout, nasolacrimal drainage, non-productive losses, and corneal impermeability are all examples (38, 39). In ophthalmology, there are three basic ways to give medication: topically, systemically, or intraocularly, and each has its own set of benefits and drawbacks. Ninety percent of aqueous ophthalmic formulations are administered topically, making it the most popular method of medication delivery. The drugs can be easily injected by the majority of patients, and there are less restrictions on how long they can be stored. The cornea's barrier function, precorneal losses, and the low medication concentration for lipophilic

drugs are all drawbacks (40, 41). To produce a therapeutically effective dose in the eye through systemic distribution, a relatively high drug concentration in circulation is required (42).

In individuals with severe COVID pneumonia, ocular symptoms have been reported, and viral RNA has been detected in the conjunctival sac. Patients with mild cases of COVID-19 do not typically present with conjunctivitis, suggesting that this symptom is not widely shared by the coronavirus (43).

As a result, there is less information on how to best treat COVID-19-related conjunctivitis. During this epidemic, certain antiviral systemic medicines such umefenovir, lopinavir, and ritonavir have been employed (44), but not for the eye condition in particular. Chen et al. reported likelihood that ribavirin eye drops would aid in the treatment of ocular symptoms (44). Cheema et al. recently treated a patient who had pseudodendritic keratoconjunctivitis with moxifloxacin 1 drop once daily to the right eye and oral valacyclovir 500 mg orally three times daily. This treatment was performed under the assumption that the patient had herpetic keratoconjunctivitis; however, the patient's conjunctival swab test result was positive for SARS-CoV-2.

Otic delivery

Otitis media, or middle ear inflammation, can be either acute or chronic. Acute otitis media (AOM) is more common than chronic suppurative otitis media (CSOM) (45). When infections that result in sore throats, colds, or other respiratory or breathing issues travel to the middle ear, the inflammation frequently gets started. These infections may be bacterial or viral (46).

Infectious viral particles, like SARS-CoV-2, have the capacity to migrate from the nasopharynx to the middle ear, which has an impact on how to treat patients who present with AOM during the COVID-19 pandemic (acute otitis media). Viral infection has frequently been linked to AOM, either directly through an irritated nasopharyngeal mucosa that causes Eustachian tube dysfunction and altered immune response, or indirectly through another pathogen that only affects the middle ear (47)

His presentation gave the impression that difficult AOM should be treated with ventilation (large myringotomy and/or tympanostomy tube installation) and broad-spectrum antibiotics, with the latter being determined by microbial culture (48).

Ear drops containing a pharmacological composition of levofloxacin hemihydrate, clotrimazole, dexamethasone sodium phosphate, and moxidectin enable for simultaneous treatment of the etiotropic, pathogenetic, and symptomatic aspects of the condition (49).

4-Pulmonary delivery

A high surface area with rapid absorption due to high vascularization is one of the many systemic advantages offered by the pulmonary route in comparison to other traditional drug delivery systems. Another advantage is that the first pass effect is avoided (50).

Nebulization delivers drugs directly to lung alveoli and pulmonary tissues, allowing for local effects with lesser doses than oral administration. Aerosolized hydroxychloroquine has been described for pulmonary illnesses, and phase 2a clinical tests in asthmatic patients showed no side effects (51). Low dose inhaled or nebulized therapy may confer equivalent or greater drug concentrations in pulmonary tissues, less systemic adverse effects (including cardiotoxicity), and less pressure on the current supply of hydroxychloroquine in critically ill patients. COVID-19 (51).

The simplest and quickest technique of direct pulmonary administration is to inhale 50 mg of remdesivir for 30 minutes (52). First, COVID-19 patients with minor symptoms may self-administer nebulized remdesivir in order to reduce the risk of

aerosol production for medical personnel. Second, it would be challenging to deliver nebulizer inhalation to COVID-19 patients who are using ventilators. Third, as it may not be very helpful for COVID-19 patients with severe pneumonia whose lung function may have been seriously compromised, the antiviral medication should be administered to patients as soon as possible (53, 54).

Use salbutamol (Ventolin), ipratropium bromide (Atrovent), and oral corticosteroids (dexamethasone, prednisone, or prednisolone), as well as intravenous corticosteroids (methylprednisolone or hydrocortisone), when necessary, for severe asthma (55).

Urgent in-clinic therapy of albuterol nebulizer, inhaled budesonide, and intravenous volume expansion with additional parenteral thiamine 500 mg, are recommended for patients with severe symptoms (56).

As a mucolytic and by decreasing NET levels in the lungs, dornase alfa may help patients with severe COVID-19 by increasing lung oxygenation and ventilation (57).

5-Parenteral delivery

Subcutaneous, intramuscular, intravenous, intradermal, and intraarterial parenteral routes of administration, among others, also have strong absorption properties and increase drug bioavailability (58). When oral administration is not an option and prompt onset of action is necessary, such as comatose patients, the method provides many benefits (59). In a hospital or at home, patients who cannot eat or drink on their own must rely on fluids, electrolytes, and nutrients given through a vein (60).

Vaccines must be given by a suitable route, or a route that is ideal in terms of safety, immunogenicity, and practicability. Parenteral immunizations can be given intramuscularly, subcutaneously, or intradermally using hypodermic needles or needle-free injection devices (61).

Rectal delivery

Suppositories for the rectal cavity are one of the standard dose forms. They are preferable to oral dosage forms in some circumstances, such as when a patient has difficulty swallowing, as is common in the elderly and in pediatric patients, as well as when the patient is asleep. Rectal suppositories can be loaded with a variety of medications for the treatment of conditions including nausea, vomiting, inflammation of the intestine, and hemorrhoids (62).

Rectal route offers potential advantages for the delivery of drugs, some of which are as follows: Numerous low molecular weight pharmaceuticals can be absorbed quickly, some first pass metabolism can be avoided, lymphatic system absorption is possible, large amounts can be retained, drug delivery rates can be regulated, and absorption can be improved (63).

A typical suppository is a semisolid dosage form that can be inserted into bodily cavities and either melts or softens when it reaches the internal temperature of the body. This dose type is appropriate for use in newborns, children, and patients who are unconscious (64). The administration of medications in the form of a suppository is preferred due to the advantages that include the following: a) improved enzymatic drug stability; b) higher drug content; c) constant and static environment of rectum; d) avoidance of overdosing; e) improved patient compliance; and f) avoidance of the first pass effect in the gastrointestinal tract and liver (65).

Conclusion

SARS-CoV-2, in conclusion, is a new and highly contagious virus with respiratory effects spanning the spectrum from the common cold to more serious disorders of greater complexity Considering their low toxicity profile, low risk of adverse effects, and capacity to bypass (at least partially) first-pass metabolism, transmucosal routes of administration show promise as

alternatives for the delivery of medications for fast symptom alleviation in palliative and end-of-life treatment. The intranasal and rectal routes can use off-the-shelf medications, but the buccal and sublingual routes necessitate the creation of new dosage forms. Because of this, in times of crisis like the recent COVID-19 outbreak, a quick and safe escape path is essential.

References

1- Ahmad S, Shoaib A, Ali MS, Alam MS, Alam N, Ali M, et al. Epidemiology, risk, myths, pharmacotherapeutic management and socio-economic burden due to novel COVID-19: A recent update. Research Journal of Pharmacy and Technology. 2020;13(9):4435-42.

2- Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. 2020;158(6):1831-3. e3.

3- Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal–oral transmission. Gastroenterology. 2020;158(6):1518-9.

4- Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. New England journal of medicine. 2020.

5- Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. Jama. 2020;323(18):1843-4.

6- Zhang W, Du R-H, Li B, Zheng X-S, Yang X-L, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerging microbes & infections. 2020;9(1):386-9.

7- Xu CL, Raval M, Schnall JA, Kwong JC, Holmes NE. Duration of respiratory and gastrointestinal viral shedding in children with SARS-CoV-2: a systematic review and synthesis of data. The Pediatric infectious disease journal. 2020;39(9): e249-e56.

8- Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nature medicine. 2020;26(4):502-5.

9- Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS letters. 2002;532(1-2):107-10.

10- Yuan L, Zhi N, Yu C, Ming G, Yingle L, Kumar GN, et al. Aerodynamic characteristics and RNA concentration of SARS-CoV-2 aerosol in Wuhan hospitals during COVID-19 outbreak. BioRxiv. 2020.

11- Van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. New England journal of medicine. 2020;382(16):1564-7.

12- McIntosh K, Hirsch M, Bloom A. Coronavirus Disease 2019 (COVID-19), UpToDate. 2020. 2020.

13- Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. New England journal of medicine. 2020; 382(10):970-1.

14- Bai Y, Yao L, Wei T, Tian F, Jin D-Y, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. Jama. 2020;323(14):1406-7.

15- Saber S, Khodir AE, Maghmomeh AO, Nouh NA, El-Baz AM. COVID-19 Pandemic: current Challenges and future Perspectives. Research Journal of Pharmacy and Technology. 2022;15(1):329-37.

16- Ardalan T, Ardalan P, Monajjemi M. Nano theoretical study of a C16 cluster as a novel material for vitamin C carrier. Fullerenes, Nanotubes and Carbon Nanostructures. 2014 ;22(8):687-708.
17- Hafeez A, Ahmad S, Siddqui SA, Ahmad M, Mishra S. A review of COVID-19 (Coronavirus Disease-2019) diagnosis, treatments and prevention. Ejmo. 2020;4(2):116-25.
18- Ozturker ZK. Conjunctivitis as sole symptom of COVID-19: A case report and review of literature. European Journal of Ophthalmology. 2021 ;31(2):NP145-NP50.
19- Jin Y-H, Cai L, Cheng Z-S, Cheng H, Deng T, Fan Y-P, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military Medical Research. 2020;7(1):4.
20- Bonavia A, Zelus BD, Wentworth DE, Talbot PJ, Holmes KV. Identification of a receptor-binding domain of the spike glycoprotein of human coronavirus HCoV-229E. Journal of Virology. 2003;77(4):2530-8.
21- Ahmed MA, Al Jalelli ZN, Alani MA, Mostafa FI, Al-Hamdani AA, Ghanim SM, et al. Two-intervention social distancing strategy to control COVID-19 in Mosul city; A Comparative study. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2020; 20(3):51-7.
22- Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive,cross-sectional, multicenter study. The American journal of gastroenterology. 2020;115.
23- Ye Q, Wang B, Zhang T, Xu J, Shang S. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2020;319(2): G245-G52.
24- Perisetti A, Gajendran M, Goyal H. Putative mechanisms of diarrhea in COVID-19. Clinical Gastroenterology and Hepatology. 2020;18(13):3054-5.
25- Wu Y, Ho W, Huang Y, Jin D-Y, Li S, Liu S-L, et al. SARS-CoV-2 is an appropriate name for the new coronavirus. The Lancet. 2020; 395(10228):949-50.
26- Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance. 2020; 25(3):2000045.
27- Saghazadeh A, Rezaei N. Towards treatment planning of COVID-19: Rationale and hypothesis for the use of multiple immunosuppressive agents:Anti-antibodies, immunoglobulins, and corticosteroids. International immunopharmacology. 2020; 84:106560.
28- Morrow ES, Roseweir A, Edwards J. The role of gamma delta T lymphocytes in breast cancer: a review. Translational Research. 2019; 203:88-96.
29- Raoof IB, Okhti ZA, Abdalah ME. Clinical Signs, Laboratory Diagnosis and Treatments Involved in Corona Viruses-19. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2021;21(1):10-5.
30- Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine. 2020.
31- Delang L, Neyts J. Medical treatment options for COVID-19. European Heart Journal: Acute Cardiovascular Care. 2020;9(3):209-14.
32- Warren TK, Wells J, Panchal RG, Stuthman KS, Garza NL, Van Tongeren SA, et al. Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue

BCX4430. Nature. 2014;508 (7496):402-5.
33- Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. Jama. 2020;323(18):1824-36.
34- Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). Statpearls [internet]. 2022.
35- Patel KP, Patel PA, Vunnam RR, Hewlett AT, Jain R, Jing R, et al. Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19. Journal of Clinical Virology. 2020; 128:104386.
36- Smith H. A Comprehensive Review of Rapid-Onset Opioids for Breakthrough Pain. CNS Drugs. 2012;26(6):509-35.
37- Lam JK, Cheung CC, Chow MY, Harrop E, Lapwood S, Barclay SI, et al. Transmucosal drug administration as an alternative route in palliative and end-of-life care during the COVID-19 pandemic. Advanced Drug Delivery Reviews. 2020; 160:234-43.
38- Tseng C-L, Chen K-H, Su W-Y, Lee Y-H, Wu C-C, Lin F-H. Cationic gelatin nanoparticles for drug delivery to the ocular surface: in vitro and in vivo evaluation. Journal of Nanomaterials. 2013;2013.
39- Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G. Sparfloxacin-loaded PLGA nanoparticles for sustained ocular drug delivery. Nanomedicine: nanotechnology, biology and medicine. 2010;6(2):324-33.
40- Le Bourlais C, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems—recent advances. Progress in retinal and eye research. 1998;17(1):33-58.
41- Abdulrazik M, Behar-Cohen F, Benita S. 24 Drug Delivery Systems for Enhanced Ocular Absorption. Enhancement in drug delivery. 2007.
42- Washington N, Washington C, Wilson C. Physiological pharmaceutics: barriers to drug absorption: CRC Press; 2000.
43- Amesty MA, Alio del Barrio JL, Alió JL. COVID-19 disease and ophthalmology: an update. Ophthalmology and Therapy. 2020;9(3):1-12.
44- Chen L, Liu M, Zhang Z, Qiao K, Huang T, Chen M, et al. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. British Journal of Ophthalmology. 2020;104(6):748-51.
45- Saleh AA, Tektook NK, Rasheed IAAM. Interleukins levels associated with Chronic Otitis Media (CSOM). Research J Pharm and Tech. 2019;12(12):5801-4.
46- Abdullah ZK. The antibacterial activity of Trigonella foenum-graceum extracts against bacteria that causes Otitis media in children. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2013;13 (2):147-54.
47- Heikkinen T, Chonmaitree T. Importance of respiratory viruses in acute otitis media. Clinical microbiology reviews. 2003;16 (2):230-41.
48- Mohan S, Workman A, Barshak M, Welling DB, Abdul-Aziz D. Considerations in management of acute otitis media in the COVID-19 era. Annals of Otology, Rhinology & Laryngology. 2021;130(5):520-7.
49- Arisov MV, Indyuhova EN, Arisova GB. The use of multicomponent ear drops in the treatment of otitis of various etiologies in animals. Journal of advanced veterinary and animal research. 2020;7(1):115.
50- Paul S, Roy T, Bose A, Chatterjee D, Chowdhury VR, Rana M, et al. Liposome mediated pulmonary drug delivery system: An updated review.

Research Journal of Pharmacy and Technology. 2021;14(3):1791-6.
51- Fassihi SC, Nabar NR, Fassihi R. Novel approach for low-dose pulmonary delivery of hydroxychloroquine in COVID-19. British journal of pharmacology. 2020;177(21):4997.
52- Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, et al. Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo [2, 1-f] [triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. ACS Publications; 2017.
53- Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Annals of internal medicine. 2020;173 (5):350-61.
54- Rouhezamin MR, Haseli S. Diagnosing pulmonary thromboembolism in COVID-19: a stepwise clinical and imaging approach. Academic Radiology. 2020;27(6):896.
55- Chan K, Beck C, Chauvin-Kimoff L, Gripp K, Krmpotic K, Thakore S, et al. The acute management of paediatric coronavirus disease 2019 (COVID-19). Can Pediatr Soc JAMA Pediatr[Cited: 2020 Apr 20] Avaliable from URL: https://www cps ca/en/documents/position/the-acute-ma nagement-of-paediatric-coronavirus-disease-2019covid-19. 2021.
56- Flannery AH, Adkins DA, Cook AM. Unpeeling the evidence for the banana bag: evidence-based recommendations for the management of alcohol-associated vitamin and electrolyte deficiencies in the ICU. Critical Care Medicine. 2016;44(8):1545-52.
57- Weber AG, Chau AS, Egeblad M, Barnes BJ, Janowitz T. Nebulized in-line endotracheal dornase alfa and albuterol administered to mechanically ventilated COVID-19 patients: a case series. Molecular Medicine. 2020;26(1):1-7.
58- Gulati N, Gupta H. Parenteral drug delivery: a review. Recent patents on drug delivery & Formulation. 2011;5(2):133-45.
59- Chien YW. Novel drug delivery systems. Drugs and the pharmaceutical sciences. 1992;50.
60- Dornblaser EK, Way SL, Brazeau GA. Dosage Forms: Parenterals. Encyclopedia of Pharmaceutical Science and Technology, Fourth Edition: CRC Press; 2013. p. 884-97.
61- Herzog C. Influence of parenteral administration routes and additional factors on vaccine safety and immunogenicity: a review of recent literature. Expert review of vaccines. 2014;13(3):399-415.
62- Dakhil IA, Mohamed MBM, Abbas AK, Mansour SM. Formulation and Evaluation of Trifluoperazine HCl as rectal suppositories by using different types of surfactants in Cocoa butter. Research Journal of Pharmacy and Technology. 2019;12(10):4934-40.
63- Havaldar VD, Yadav AV, Dias RJ, Mali KK, Survase AB, Ghorpade VS, et al. Screening of Suppository bases for Rectal delivery of Carbamazepine. Research Journal of Pharmacy and Technology. 2017;10(8):2697-703.
64- Havaldar VD, Yadav AV, Dias RJ, Mali KK, Ghorpade VS, Salunkhe NH. Rectal suppository as an effective alternative for oral administration. Research Journal of Pharmacy and Technology. 2015;8(6):759-66.
65- Havaldar VD, Yadav AV, Dias RJ, Mali KK, Kale SS, Pujari PP. Rectal Suppository of Mucoadhesive Microspheres of Alverine Citrate for İrritable Bowel Disease: In vitro Evaluation. Research Journal of Pharmacy and Technology. 2018; 11(7):3091-8.