

The potential of ODFs as carriers for drugs/vaccines against COVID-19

Maram Suresh Gupta  and Tegginamath Pramod Kumar 

Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research (JSSAHER), Mysore, India

ABSTRACT

COVID-19 has spread out its wings across the globe and is taking away many lives. Millions of people are (self) quarantined to prevent the spread of this viral disease. World Health Organization (WHO) has affirmed that there is not any medicine for COVID-19. Besides, there is also no single drug that is approved by any regulatory agency for usage against this dangerous disease. Researchers across the globe are working tirelessly to fix an end to this virus and to save precious lives. While the research is in full swing, one is not sure whether they would come up with a chemical/herbal drug or a vaccine. Irrespective of the type of active ingredient for COVID-19, one needs to have a proper system to deliver the identified active ingredient to subjects/patients across the globe. Orodispersible films (ODFs) are excellent and attractive drug delivery carriers that have the potential to deliver drugs, herbal extracts, and vaccines. They are apt for patients who have a problem consuming traditional drug products such as tablets or capsules. The beauty of this dosage form is that it does not need water to consume by the subjects and can be readily administered to the tongue. The present review highlights the true potential of ODFs to act as a carrier for the delivery of various antiviral drugs/herbs/vaccines.

ARTICLE HISTORY

Received 5 November 2020
Accepted 16 November 2020

KEYWORDS

Vaccines; herbal extracts;
antiviral drugs; carrier;
ODFs; WHO

Introduction

During the fag end of 2019, Wuhan – the most densely populated city and capital of Hubei Province – China was witnessing pneumonia whose etiology was unknown. At the beginning of 2020, the pathogen was successfully identified and was named as the 2019 novel corona virus (2019-nCoV) [1,2]. Later, on 20 February 2020, the International Committee on Taxonomy of Viruses (ICTV) named it as Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2), a new variant of SARS-CoV, and the disease caused was corona virus disease 2019 (COVID-19) [3]. Since then the whole world is on 'High Alert' due to this new viral threat. Millions of people have been (self) quarantined to prevent it from further spreading [4]. Nonetheless, the individuals infected by corona virus are augmenting everyday [5]. There are absolutely no drugs that are approved by regulatory agencies across the globe. In India, the Indian Council of Medical Research (ICMR) strongly recommended the usage of hydroxychloroquine for asymptomatic purposes [6]. Followed by this development, emergency use authorization was granted by United States Food and Drug Administration (USFDA) to promote the usage of chloroquine phosphate or hydroxychloroquine sulfate for treating COVID-19 [7]. World Health Organization (WHO) identified and recommended usage of remdesivir, lopinavir–ritonavir with or without interferon, immunotherapy, and recuperative sera. WHO also launched SOLIDARITY trials for the above-prescribed drugs to support that they are effective in treating COVID-19 [8]. In addition, novel chemical entities against the corona virus protease were also proposed by some researchers [9] and some have proposed various integrated Chinese and Western medicines for treating this pandemic [10].

While the research is going on to identify an active agent for COVID-19. Identifying the mode of delivering the active moieties

to patients and healthy subjects cannot be ignored. At present, there are several drug delivery systems, whereas the most novel and transformative drug delivery/carrier system is orodispersible films (ODFs). European Pharmacopoeia (Ph. Eur.) defines ODFs as 'single or multilayered sheets of suitable materials, to be placed in the mouth where they disperse rapidly' [11]. They are a type of oromucosal preparations which are ultra-thin, elegant, stamp sized, portable, patient friendly, and attractive dosage forms across all the age groups [12]. Clinical Data Interchange Standards Consortium (CDISC) defines ODFs as 'A thin layer or coating which is susceptible to being dissolved when in contact with a liquid' [13]. On the contrary, United States Pharmacopoeia (USP) employs a different terminology and called them as 'Oral Films' and defined as 'Thin sheets that are placed in the oral cavity. They contain one or more layers. A layer might or might not contain API' [14]. ODFs undergo rapid disintegration/dissolution and are usually swallowed along with saliva and a small amount of the drug gets absorbed via the oral mucosa due to its high vasculature [15,16].

ODFs are excellent and attractive carriers for delivery of various over the counter (OTC) or prescription drugs [17], herbal extracts [18–21], vaccines [22], probiotics [23], and vitamins [24]. Drugs are either directly introduced [25–28] in the formulation of ODFs or size reduced and converted to solid dispersions [29] or nanoparticles [30,31] or solid lipid microparticles [32] or micronized and surface modified using silica [33] which not only help in enhancing the amount of drug that could be loaded on to ODFs but also help in enhancing the release rate and, bioavailability of the drug. At present, ODFs are used as an excellent carrier system for delivering various therapeutically active agents. The composition of ODFs includes a drug substance (natural or synthetic), a film-forming agent and plasticizer. Additionally, it also includes saliva

stimulating agent, organoleptic agents, and stabilizers [12]. The critical quality characteristics of ODFs are its appearance, stability, water content, uniformity of the active agent, color, taste, after-taste, and mouthfeel. Most importantly, it shall not cause irritation of mucosa when administered [34]. The authors provided an overview on characterization of ODFs to determine various quality parameters of ODFs and also introduced a 3D printed disintegration test apparatus for testing the disintegration time of ODFs using sensor technology [35]. ODFs are capable for drug delivery in patients with swallowing problems, mentally retarded patients, subjects with Parkinson's disease, bed-ridden patients, oral cancer patients, and uncooperative patients [36–38]. The present review is focused on critically analyzing the potential of ODFs as carriers for delivering antiviral drugs/herbs/vaccines with a potential for treatment of COVID-19, the global pandemic.

ODFs as carriers for antiviral drugs

At present, there are no regulatory approved drugs for treatment of COVID-19. Current recommendations include supportive care, ventilator based assistance for respiration, usage of anti-infectives, antivirals, and glucocorticoid therapy [39]. National Health Commission of the People's Republic of China has provided some preferred drugs for treatment of COVID-19 that include interferon alpha, lopinavir/ritonavir, chloroquine phosphate, ribavirin, and arbidol. Some of the drugs that are presently at clinical trials stage are chloroquine, arbidol, remdesivir, and favipiravir [40,41]. Of all these drugs lopinavir/ritonavir, chloroquine phosphate, and arbidol are administered via oral route. However, favipiravir appears to be the most potent and promising drug when compared to lopinavir/ritonavir. In India, Glenmark Pharmaceuticals has initiated phase III clinical trials for favipiravir and is expected to complete

the trials by end of August 2020 [42]. The solubility of this drug is very poor in water and is necessary to convert it into its salt version (sodium or meglumine) and formulate it as an injection. A Chinese company by name Chengdu Xinhengchuang Pharmaceutical Co., Ltd. developed a tablet formulation that helps in overcoming the dissolution problem and achieved desired clinical results [43]. Table 1 provides a list of antiviral agents that are currently being developed by various investigators in the world for treating COVID-19. From the table, it is evident that researchers focus is on both small molecules [55] and biologics [45,46, 48]. Further, proteins such as brilacidin [44] and recombinant protein AT-100 [50] are being developed by Innovation Pharmaceuticals and Airway Therapeutics, respectively.

The drugs that are being developed, mentioned in Table 1, could face many challenges when it comes to delivering to the subject. For instance, favipiravir is associated with poor water solubility and demands an injection formulation. A potential alternative to such a disadvantage of favipiravir and other similar drugs is to formulate them as ODFs. Table 2 provides a list of antiviral drugs that were successfully formulated as ODFs. It is evident from Table 2 that drugs with low solubility, bioavailability, and dose are excellent candidates for formulating as films. The most conventional method used to prepare ODFs is solvent casting method and the modern methods include printing technologies using inkjet printing, wherein antiviral drugs are printed either alone or in combination with other drugs, for instance, anticancer drugs printed alongside antiviral drugs [64,65]. In addition, antiviral ODFs can be prepared as a single layered or multi-layered dosage forms, example: entecavir [67]. Drugs could either be directly loaded onto ODFs or converted into nanoparticles before loading onto ODFs. The key ingredients include a film-forming material (polymer) and plasticizer.

Table 1. Antiviral drugs in pipeline for treating COVID-19.

Name of the company	Details of antiviral drugs under development	Ref.
Innovation Pharmaceuticals	Brilacidin – a defensin (protein) mimetic drug candidate	[44]
CytoDyn	Leronlimab – CCR5 antagonist	[45]
Roche	Tocilizumab – Roche initiated phase III clinical trials	[46]
Biocryst Pharma	Galidesivir – adenosine nucleoside analogue acts by blocking viral RNA polymerase	[47]
Roivant Sciences	Gimsilumab – monoclonal antibody targets pro-inflammatory cytokine 'granulocyte macrophage-colony stimulating factor (GM-CSF)' which is high in corona virus patients.	[48]
I-Mab Biopharma	TJM2 – acts by neutralizing high GM-CSF in corona virus infected patients	[49]
Airway Therapeutics	AT-100 – developing human recombinant protein. It has collaborated with Celonic Group for producing AT-100	[50]
Tiziana Life Sciences	TZLS-501 – a monoclonal antibody and are planning to deliver it using its proprietary formulation technology, which are patent protected	[51–53]
OyaGen	OYA1 – is a broad spectrum antiviral compound which is more effective than chlorpromazine HCl in inhibiting corona virus	[54]
Beyond Spring	BPI-002 – a small molecule, acts as an adjuvant when combined with a vaccine. This small molecule is protected by a provisional US patent application (yet to be published)	[55]
Algenon Pharmaceuticals	Ifenprodil – small molecule that can be delivered via oral route. Filed a pre-IND application with USFDA. Ifenprodil is a generic drug originally developed by Sanofi	[56]
APEIRON Biologics	APN01 – Recombinant form of human angiotensin convertase enzyme 2. Dr. Josef Penninger, University of British Columbia, has carried out extensive research on APN01 in collaboration with various companies and academic institutes	[57]
Lattice Biologics Limited	AmnioBoost – is an amniotic fluid concentrate obtained from subjects during cesarean delivery	[57]
Synaigen Research	SNG001 – is nothing but interferon β – 1a administered as an inhalation to COVID patients	[58]
Emanta Pharmaceuticals	It is testing various known and new small molecule drug candidates that have the potential to act against COVID 19.	[59]
Vir Biotechnology	VIR-7831 and VIR-7832 are two monoclonal antibodies that target the spike protein of the corona virus and enter via ACE2 cell receptor. Vir has collaborations for development of these antibodies	[60]
Columbia University	Received a research grant of 2.1 million USD from Jack Ma foundation to develop various drugs for treatment of corona virus. They are developing antiviral drugs and an antibody that has the potential to neutralize the virus	[61]

Table 2. Antiviral drugs formulated as ODFs.

Drug name – technique employed to load to ODFs	Reason for choosing the drug or API to formulate as an ODFs	Polymer	Plasticizer	Method	Key highlight(s)	Ref.
Herpetrione (HPE) – extracted from <i>Herpetospermum caudigerum</i> . HPE nanoparticles were prepared using sodium dodecyl sulfate and PVP K-30	Poor water solubility and low bioavailability	Hydroxypropyl methylcellulose (HPMC), microcrystalline cellulose (MCC), and L-hydroxypropyl cellulose (HPC)	PEG-400	Solvent casting method (SCM)	Studies established that ODFs are suitable for delivery of poorly water-soluble drugs SCM is modified to prepare drug nanosuspension Oral bioavailability of HPE nanoparticles was higher when compared HPE coarse suspension	[62]
Herpetrione (HPE) Nanoparticles were prepared and optimized using the Box–Behnken design response surface methodology	Poor water solubility and low bioavailability	HPMC, MCC, L-HPC	PEG-400	SCM	ODFs formulation of HPE nanoparticles was successfully optimized using the Box–Behnken design response surface methodology	[63]
Cidofovir Nanoparticles were prepared using poly(ethylene glycol)–polycaprolactone (PEG–PCL)	To achieve its controlled release and also due to its wide spectrum anti-viral activity	HPC	^a	Printed using inkjet printer	Combination of complexed anti cancer drug (Paclitaxel) and complexed anti viral drug (Cidofovir) were printed onto ODFs Mechanical properties of film were enhanced due to drug printing	[64,65]
Acyclovir – solid dispersion was prepared	Poor water solubility and low bioavailability	HPMC	Glycerol	SCM	Oral administration of ODFs of acyclovir instead of intravenous route of administration	[66]
Entecavir (single or multi-layered ODFs)	Low dose – 0.5–1 mg per day	Starch, carrageenan, pullulan and many others	Acetyl triethyl citrate or propylene glycol or citrate ester or triacetin	SCM	Multi-layered ODFs were disclosed	[67]

^aNothing found.

Table 3. Patent protected herbs for preventing/treating COVID-19.

Name of the player	Drug name and details	Ref.
Biostandard Inc	Fermented Isatidis Radix Extract	[82]
Bioniche Life Sciences Inc	Pyranocoumarin enriched composition (free from furanocoumarins) obtained from <i>Zanthoxylum americanum</i> (Prickly Ash)	[83]
The University of Hong Kong	Baicalin – compound extracted from <i>Scutellaria baicalensis</i>	[84]
Seoul National University Industry-Academic Cooperation Foundation	Extract of <i>Angelica dahurica</i>	[85]
Amazon Biotech Inc.	Herbal composition comprising ' <i>Boswellia carterii</i> stem resin, <i>Styrax benzoin</i> stem resin, <i>Cinnamomum zeylanicum</i> bark, <i>Curcuma zedoaria</i> root, <i>Syzygium aromaticum</i> fruit, <i>Nardostachys chinensis</i> root, <i>Betula alba</i> bark, <i>Impatiens balsamina</i> bark, <i>Costus spicatus</i> root, <i>Allium sativum</i> bulb <i>Cyperus rotundus</i> root and <i>Hyssopus officinalis</i> '	[86]
Biopharmacopae Inc.	Extracts of ginger and/or goldenrod (<i>Solidago</i>)	[87]

Table 4. Antiviral herbs formulated as ODFs.

Name of the herb and technique employed, if any, to load to ODFs	Reason for choosing/ selecting the herb to formulate as an ODFs	Polymer	Plasticizer	Method	Key highlight(s)	Ref.
Ginger extract	Existing formulations (capsules and liquids) of ginger suffer with problems of wettability of contents and inaccuracy in dosing.	Hydroxypropyl methylcellulose (HPMC) or maltodextrin or pullulan	Polyethylene glycol (PEG)	Solvent casting method (SCM)	HPMC based ODFs were found to be ideal with low disintegration time and stable at high temperature	[21]
Indonesian herbal extracts of <i>Phaleria macrocarpa</i> and <i>Zingiber officinale</i>	Selected based on the herbal extracts popularity, reproducibility and well established scientific support (clinical evidence)	HPMC with carbomer 947p (or) hydroxypropyl cellulose (HPC)	Glycerol	SCM	Stable ODFs were obtained and benzalkonium chloride was employed as a stabilizer and also for spreadability	[92]
Foeniculum officinalis extract	– ^a	HPMC	Glycerol	SCM	Employed super disintegrating agent (sodium starch glycollate) to achieve low disintegration time of ODF	[93]
Garlic extract	– ^a	Hypromellose	Glycerol	SCM	Menthol was used as a flavoring agent	[94]

^aNothing found.

ODFs as carriers for antiviral and immunity boosting herbs

WHO said 'To date there is no specific medicine recommended to prevent or treat the novel coronavirus' [68]. In view of the fact that there are no drugs and vaccines, that are approved, for treating COVID-19, many are turning toward herbal medicines that are either of the Indian or Chinese origin. There are many herbs in Indian Ayurveda that have the potential for prophylaxis and treatment of corona virus infection. For instance, Rastogi et al. reported a 'pragmatic and plausible plan of action for Ayurvedic intervention' of various Ayurvedic drugs that have the potential to be used in mild to severe COVID-19 symptoms [69]. Subjects who are not yet exposed and asymptomatic group can use Ayurvedic 'Swarna Prashana' and 'Rasayana' as potential immunity boosting agents [70–73]. This in combination with social distancing helps in preventing the spread of disease [74].

Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH), Government of India recommends three immunity boosting measures. First and foremost is taking 10g of Chyavanprash every day (not suitable to formulate as ODFs due to its heavy dose), second: drinking golden milk (milk with turmeric) twice a day, and lastly drinking herbal tea or a drink prepared by boiling tulsi, cinnamon, black pepper, dry ginger and raisin taken either by adding jiggery (natural sweet) or lemon juice for taste, if

required – to be taken once a day or twice in a day [75]. The Ministry of AYUSH has also confirmed that clinical trials are initiated on AYUSH-64, a polyherbal anti-malarial Ayurvedic formulation [76]. Indian Institute of Delhi in collaboration with National Institute of Advanced Industrial Science and Technology, Japan has reported the potential of Ashwagandha against COVID-19 [77]. CSIR (Council of Scientific and Industrial Research) in collaboration with Sun Pharma are working on a phytopharmaceutical composition that is found to be effective in treatment of COVID-19 [78]. Very recently, Sun Pharma received approval for clinical trials of AQCH from Drugs Controller General of India (DCGI) [79].

Chinese National Health Commission announced, dated 14 April 2020, three patented Chinese herbal drugs for treatment of COVID-19 which include namely: 'Lianhuaqingwen capsules and Jinhuaqinggan granules for mild conditions, and Xuebijing (injectable) for severe conditions' [80]. Luo et al. carried out an excellent review on Chinese herbal medicines that have the strong potential for usage in prevention of COVID-19. They have also reported the highly used herbs for preventing COVID-19 infections [81]. A Korean company by name, Biostandard Inc, reported usage of fermented Isatidis Radix Extract and claim to be effective against corona virus infections and they have protected the same by a Korean patent application [82]. Few other companies/academic institutions that have patent protected herbal extracts effective in preventing COVID-19 are provided in Table 3.

Table 5. Antiviral vaccines in pipeline for treating COVID-19.

Name of the player	Details of antiviral vaccines under development	Ref.
Migal Galilee Research Institute, Israel	Developing an oral (mucosal) vaccine, wherein the viral antigen is delivered via mucosa tissues by self-activated endocytosis	[104]
Entos Pharmaceuticals	Fusogenix – DNA vaccine is being developed based on its patent protected platform, proteo-lipid vehicle (PLV). It uses a new mechanism for delivering genetic material into the cells	[105,106]
Vaxart Inc	Oral recombinant vaccine in tablet formulation using its VAAST platform. It has protected its vaccine tablet formulation by US patent applications	[107–109]
University of Oxford – Jenner Institute	ChAD0X1 nCoV-19 – prepared from cold virus (weakened) – initiated Phase III trials	[110]
Altimmune	AdCOVID – vaccine delivered via intranasal route platform technologies NasoVAX and NasoShield	[111,112]
Medicago	Developing a vaccine and also an antibody. It was successful in producing virus like particles of coronavirus. It is developing antibodies in collaboration with Laval University	[113]
Inovio Pharmaceuticals	INO-4800 – vaccine that is developed in collaboration with Beijing Advaccine Biotechnology Company. It is proposing to deliver the vaccine using the device called as CELLECTRA [®] which works by creating a pulse for transferring the plasmids across the cell. It is also developing INO 4700 in collaboration with GeneOne Life Sciences company	[114]
Moderna	mRN 1273 – recently received fast track designation from USFDA. It vaccine basically targets spike protein of corona virus	[115]
Tonix Pharmaceuticals	TXN-1800 – developed based on its horsepox virus vaccine platform. It has filed a provisional patent application with USPTO	[116]
Clover Biopharmaceuticals	Subunit vaccine developed using trimeric spike protein developed using its patented technology	[117]
Novavax, Inc	Middle East Respiratory Syndrome (MERS) vaccine was developed using recombinant nanoparticle based vaccine technology. The vaccine showed positive results in inhibiting the virus when administered along with its patented adjuvant formulations	[118–121]
Predictive oncology (PO)	Introduced artificial intelligence for development of a vaccine using Inventa Biotech's HSC [™] technology which deals with chromatographic system of high throughput screening. In addition, PO is also developing a new vaccine based on nanoparticle (NSP-10: non specific protein) platform technology developed by Dr. Daniel Carter	[122]

A decoction of various Ayurvedic herbs namely: *Tinospora cordifolia*, *Zingiber officinale*, *Curcuma longa*, *Ocimum sanctum*, *Glycyrrhiza glabra*, *Adhatoda vasica*, *Andrographis paniculata*, *Swertia chirayita*, *Moringa oleifera*, *Triphala* and *Trikatu* have broad antiviral activity and protease inhibitor activity [88–90]. This decoction could be very useful in COVID-19 patients who are quarantined.

Turning now to ODFs of herbal extracts, Cure pharmaceuticals published US patent on herbs ((agrimony, andrographis paniculata, bistort, fenugreek, ginger, myrrh, solanum, etc.) tree and plant extracts ((licorice, shitake, sarsaparilla, slippery elm, etc.), and essential oils (clove, camphor, cinnamon, lemon, spearmint, etc.) that are formulated as multilayered edible oral thin films for management of cough/Pharyngitis [91]. Table 4 provides a list of ODFs formulated using herbal extracts. From the table, it is evident that solvent casting method is the most preferred method to fabricate herbal ODFs. Zim laboratories limited, a leading Indian company in the domain of oral thin films has published a research article on oral dissolving films of ginger [21]. Visser et al. reported ODFs of five Indonesian medicinal plants extracts namely: *Lagerstroemia speciosa*, *Phyllanthus niruri*, *Cinnamomum burmannii*, *Zingiber officinale*, and *Phaleria macrocarpa* [92] were prepared by solvent casting method [95]. Of these plant extracts, *Phaleria macrocarpa* and *Zingiber officinale* are associated with antiviral activity [96,97]. Song et al. evaluated antiviral activity of quercetin-7-glucoside isolated from *Lagerstroemia speciosa* [98]. Sri Wahyuni et al. reported antiviral activity of *Phyllanthus niruri*, particularly they reported its activity against hepatitis C virus [99]. Verma et al. reported ODFs of *Piper betel* and *Foeniculum officinalis* [93]. *Foeniculum officinalis* is reported to possess antiviral and antioxidant activity [100].

Similarly, Pawar and Butle reported ODFs of *Allium sativum* [94], a potent antiviral agent [101].

Generally speaking, ODFs are well known to act as carriers for various herbal extracts [18–21]. But, from the above explanation, it is particularly evident that they have the potential to act as carriers to aid in the delivery of various antiviral herbs.

ODFs as carriers for antiviral vaccines

The Center for Disease Control and Prevention defines vaccines as 'A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease. Vaccines are usually administered through needle injections, but can also be administered by mouth or sprayed into the nose' [102]. Vaccination is considered as one of the most effective ways of preventing cause of a disease [103]. At present, there are several companies, academic institutes that are actively working to develop a vaccine against COVID-19. Vaccines that are currently under development are provided in Table 5.

Primarily, vaccines pose extreme challenges vis-a-vis its handling, (cold) storage and shipping, all expensive propositions. For instance, one of the studies reported that 38 billion USD would be spent on transportation and administration of 18 vaccines in 94 countries [123,124]. Therefore, there is a need for alternate dosage forms that can help reducing the cost. For instance, Vaxart Inc is developing recombinant vaccine for COVID-19 in tablet formulation using its patent protected technology called VAAST [107–109]. RP Scherer Technologies LLC is also developing a tablet formulation (fast dissolving) for influenza vaccine with starch as immune stimulating agent [125]. Tablets are highly traditional and

Table 6. Antiviral vaccines that are formulated as ODFs.

Name of the player	Name of vaccine formulated as ODFs	Polymer	Plasticizer	Method employed	Key highlight(s)	Ref.
The Johns Hopkins University	Several live-attenuated viruses were proposed, including the corona virus. Provided methodology to prepare rotavirus vaccine	Eudragit	Polyethylene glycol (PEG) and polyvinyl alcohol (PVA)	Double emulsion solvent evaporation	Prepared as monolayered or bilayered ODFs	[126]
Brian Pulliam (single applicant and inventor)	Rotavirus vaccine along with an antacid namely magnesium hydroxide or aluminum hydroxide nanoparticles for digestion purpose	Polyvinyl pyrrolidone + hydroxypropyl cellulose (HPC)	PEG	Solvent casting method (SCM)	Antacid successfully combined with a vaccine in layered fashion	[22]
Nitto Denko Corporation	Cancer vaccine comprising WT1 peptide or Db126 along with a promoter namely lipopolysaccharide or quercetin or ioxoprofen	Mannitol, PEG, and HPC	PEG, mannitol	SCM	Composition successfully induces cellular immunity in cancer patients	[127]
Nasir Uddin from Larkin University	Gonorrhoea microparticulate vaccine	^a	^a	SCM	Microparticulate vaccine particles were obtained by spray drying Bilayered ODFs can be prepared, outer layer acts as protection layer	[128]
Aridis Pharmaceuticals	Rotavirus vaccine	^a	^a	^a	Patent protected vaccine stabilization technology and plasticized glass stabilization technology were employed in preparing the vaccine film	[129–131]

^aNothing found.

conventional dosage forms that are difficult to administer to patients who have dysphagia or Parkinson's disease and are extremely difficult to administer to pediatrics and geriatrics. Therefore, ODFs remain as an alternate choice of administration as they do not need water to consume. Most importantly, they are easy to transport from one place to another. Israel's Migal Galilee Research Institute is actively developing a vaccine that is administered via oromucosal route [104]. Some of the vaccine preparations that are successfully formulated as ODFs are provided in Table 6.

Administration of vaccines using fast dissolving buccal films is the most optimized form of administration as it has plethora of advantages when compared with parenteral route of administration [132]. Research suggests that vaccines administered via oral route are as good as or even better than those that are administered via parenteral route. For instance, Bajrovic et al. demonstrated that oral administration (sublingual and buccal routes) of influenza virus vaccine as a thin film formulation has shown good or better results than the vaccine that is administered via intramuscular route [133]. From Table 6, it is evident that ODFs comprising vaccines can be prepared as mono or bilayered using the most popular solvent casting method. Tian et al. prepared influenza virus vaccine by using trehalose and pullulan to maintain the stability and antigenicity of the vaccine. They also employed hypromellose that further helped in enhancing the stability of the

film [134]. ODFs remain an excellent option for delivery of vaccines to subjects across all the age groups. They are easily portable and maintain stability of the vaccine during transportation till it reaches to the subject for consumption. All these strongly suggest that ODFs are cost-effective carriers and easy to consume dosage forms.

Conclusion

In light of the above, ODFs are a novel oromucosal carriers that could be used to deliver a new active agent (drug/vaccine) against COVID-19. ODFs have already proven its potential to act as a carrier for delivery of drug/herb/vaccine. But, more research is still needed vis-a-vis loading vaccines onto ODFs. Research in the domain of corona virus infections has taken the front seat across the globe and companies are heavily investing in R&D. Hopefully, soon the world will witness a new active entity for treating COVID-19 and the life of all the human beings will come to normalcy – from unusual to life as usual.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ORCID

Maram Suresh Gupta  <http://orcid.org/0000-0002-3435-7900>
 Tegginamath Pramod Kumar  <http://orcid.org/0000-0002-5994-831X>

References

- [1] Su L, Ma X, Yu H, et al. The different clinical characteristics of corona virus disease cases between children and their families in China – the character of children with COVID-19. *Emerg Microbes Infect.* 2020;9(1):707–713.
- [2] World Health Organization. Pneumonia of unknown cause – China', emergencies preparedness, response, disease outbreak news; 2020; [cited 2020 May 29]. Available from: <https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/>
- [3] Gorbalenya AE, Baker SC, Baric RS, et al. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* 2020;5:536–544.
- [4] Carlos WG, Dela Cruz CS, Cao B, et al. Novel Wuhan (2019-nCoV) coronavirus. *Am J Respir Crit Care Med.* 2020; 201(4):P7–P8.
- [5] WHO coronavirus disease (COVID-19) dashboard; 2020; [cited 2020 May 29]. Available from: https://covid19.who.int/?gclid=EAlalQobChMlzdXi__HY6QIVFbeWCh03Rg67EAAAYASAAEgltSPD_BwE
- [6] Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis.* 2020; 71(15):732–739.
- [7] Georgiev T. Coronavirus disease 2019 (COVID-19) and anti-rheumatic drugs. *Rheumatol Int.* 2020;40(5):825–826.
- [8] Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun.* 2020;11(1):222.
- [9] Choudhury C. Fragment tailoring strategy to design novel chemical entities as potential binders of novel corona virus main protease. *J Biomol Struct Dyn.* 2020;1–15.
- [10] Liu M, Gao Y, Yuan Y, et al. Efficacy and safety of integrated traditional Chinese and western medicine for corona virus disease 2019 (COVID-19): a systematic review and meta-analysis. *Pharmacol Res.* 2020;158:104896.
- [11] Ph.Eur 9.3. Oromucosal preparations. In: European Pharmacopoeia Commission (Ed.), European Pharmacopoeia. Strasbourg, France: European Directorate for the Quality of Medicines & Healthcare (EDQM); 2018.
- [12] Gupta MS, Pramod Kumar T, Vishakante Gowda D. Orodispersible thin films: a new patient centered innovation. *J Drug Deliv Sci Technol.* 2020;59. DOI:10.1016/j.jddst.2020.101843
- [13] [cited 2020 May 12]; 2020. Available from: https://ncitthesaurus.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=ncit&code=C42984
- [14] Anon. Pharmaceutical dosage forms. United States Pharmacopoeia, 40-NF35; 2017.
- [15] Hoffmann EM, Breitenbach A, Breitzkreutz J. Advances in orodispersible films for drug delivery. *Expert Opin Drug Deliv.* 2011;8(3):299–316.
- [16] Preis M, Woertz C, Schneider K, et al. Design and evaluation of bilayered buccal film preparations for local administration of lidocaine hydrochloride. *Eur J Pharm Biopharm.* 2014;86(3):552–561.
- [17] Tian Y, Orlu M, Woerdenbag HJ, et al. Oromucosal films: from patient centricity to production by printing techniques. *Expert Opin Drug Deliv.* 2019;16(9):981–993.
- [18] Cannabinoid oral dispersible film strip. International PCT publication no.: WO2020014776. 2020.
- [19] Oral thin films comprising plant extracts and methods of making and using same. International PCT publication no.: WO2018094037. 2020.
- [20] Gopi S, Amalraj A, Kalarikkal N, et al. Preparation and characterization of nanocomposite films based on gum arabic, maltodextrin and polyethylene glycol reinforced with turmeric nanofiber isolated from turmeric spent. *Mater Sci Eng C Mater Biol Appl.* 2019;97:723–729.
- [21] Daud AS, Sapkal NP, Bonde MN. Development of *Zingiber officinale* in oral dissolving films: effect of polymers on in vitro, in vivo parameters and clinical efficacy. *Asian J Pharm.* 2011;5(3):183–189.
- [22] Oral thin film vaccine preparation. International patent publication no.: WO2012/103464. 2020.
- [23] Saha S, Tomaro-Duchesneau C, Daoud JT, et al. Novel probiotic dissolvable carboxymethyl cellulose films as oral health biotherapeutics: in vitro preparation and characterization. *Expert Opin Drug Deliv.* 2013;10(11):1471–1482. [cited 2020 May 10]; 2020. Available from: <https://www.curepharmaceutical.com/cure-products/vitamin-d/>
- [24] Han X, Yan J, Ren L, et al. Preparation and evaluation of orally disintegrating film containing donepezil for Alzheimer disease. *J Drug Deliv Sci Technol.* 2019;54: 101321.
- [25] El-Setouhy DA, Abd El-Malak NS, El-Malak NSA. Formulation of a novel tianeptine sodium orodispersible film. *AAPS PharmSciTech.* 2010;11(3):1018–1025.
- [26] Manda P, Popescu C, Juluri A, et al. Micronized zaleplon delivery via orodispersible film and orodispersible tablets. *AAPS PharmSciTech.* 2018;19(3):1358–1366.
- [27] Talekar SD, Haware RV, Dave RH. Evaluation of self-nanoemulsifying drug delivery systems using multivariate methods to optimize permeability of captopril oral films. *Eur J Pharm Sci.* 2019;130:215–224.
- [28] Łyszczarz E, Hofmanová J, Szafraniec-Szczęsny J, et al. Orodispersible films containing ball milled aripiprazole-poloxamer[®]407 solid dispersions. *Int J Pharm.* 2020;575: 118955.
- [29] Bharti K, Mittal P, Mishra B. Formulation and characterization of fast dissolving oral films containing buspirone hydrochloride nanoparticles using design of experiment. *J Drug Deliv Sci Technol.* 2019;49:420–432.
- [30] Chonkar AD, Rao JV, Managuli RS, et al. Development of fast dissolving oral films containing lercanidipine HCl nanoparticles in semicrystalline polymeric matrix for enhanced dissolution and ex vivo permeation. *Eur J Pharm Biopharm.* 2016;103:179–191.
- [31] Musazzi UM, Dolci LS, Albertini B, et al. A new melatonin oral delivery platform based on orodispersible films containing solid lipid microparticles. *Int J Pharm.* 2019;559: 280–288.
- [32] Zhang L, Li Y, Abed M, et al. Incorporation of surface-modified dry micronized poorly water-soluble drug

- powders into polymer strip films. *Int J Pharm.* 2018; 535(1–2):462–472.
- [34] Borges AF, Silva C, Coelho JFJ, et al. Oral films: current status and future perspectives. *J Control Release.* 2015.
- [35] Gupta MS, Kumar TP. Characterization of orodispersible films: an overview of methods and introduction to a new disintegration test apparatus using LDR-LED sensors. *J Pharm Sci* 2020;3549(20):30324–30325.
- [36] De Caro V, Giandalia G, Siragusa MG, et al. New prospective in treatment of Parkinson's disease: studies on permeation of ropinirole through buccal mucosa. *Int J Pharm.* 2012;429(1–2):78–83.
- [37] Visser JC, Woerdenbag HJ, Hanff LM, et al. Personalized medicine in pediatrics: the clinical potential of orodispersible films. *AAPS PharmSciTech.* 2017;18(2):267–272.
- [38] Yir-Erong B, Bayor MT, Ayensu I, et al. Oral thin films as a remedy for noncompliance in pediatric and geriatric patients. *Ther Deliv.* 2019;10(7):443–464.
- [39] General Office of the National Health and Health Commission, Office of the State Administration of Traditional Chinese Medicine. Notice on issuing a new coronary virus pneumonia diagnosis and treatment guidelines (trial version 7) [EB/OL]; 2020; [cited 2020 May 29]. Available from: <http://www.nhc.gov.cn/zyygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml>
- [40] Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther.* 2020; 14(1):58–60.
- [41] Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia. The 6th ed.; 2020; [cited 2020 May 29]. Available from: <http://www.nhc.gov.cn/zyygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2/files/b218cfef1b-c54639af227f922bf6b817.pdf>
- [42] Glenmark begins phase III trials of favipiravir for Covid-19 in India; 2020; [cited 2020 May 29]. Available from: <https://www.clinicaltrialsarena.com/news/glenmark-favipiravir-trial-begins/>
- [43] Favipiravir pharmaceutical composition containing different particle size ranges. Chinese patent application no.: CN104288154. 2020.
- [44] [cited 2020 May 31]; 2020. Available from: <http://www.ipharminc.com/brilacidin-1>
- [45] [cited 2020 May 31]; 2020. Available from: <https://www.cytodyn.com/pipeline/covid-19>
- [46] [cited 2020 May 31]; 2020. Available from: <https://www.roche.com/media/releases/med-cor-2020-03-19.htm>
- [47] [cited 2020 May 31]; 2020. Available from: <http://ir.biocryst.com/news-releases/news-release-details/biocryst-begins-clinical-trial-galidesivir-treatment-patients>
- [48] [cited 2020 May 31]; 2020. Available from: <https://roivant.com/roivant-doses-first-patient-in-pivotal-breathe-clinical-trial-evaluating-gimsilumab-in-covid-19-patients.html>
- [49] [cited 2020 May 31]; 2020. Available from: <http://www.imabbiopharma.com/en/article-491.aspx>
- [50] [cited 2020 May 31]; 2020. Available from: <https://www.airwaytherapeutics.com/airway-therapeutics-announces-filing-with-nih-to-evaluate-at-100-as-a-therapy-for-novel-coronavirus/>
- [51] [cited 2020 May 31]; 2020. Available from: <https://www.tizianalifesciences.com/news-item?s=2020-03-11-tiziana-life-sciences-plc-to-expedite-development-of-its-fully-human-anti-interleukin-6-receptor-monoclonal-antibody-a-potential-treatment-of-certain-patients-infected-with-coronavirus-covid-19>
- [52] Anti-CD3 antibody formulations. Tiziana Life Sciences PLC. US patent publication no.: 20180177880. 2020.
- [53] Formulations of milciclib and therapeutic combinations of the same for use in the treatment of cancer. Tiziana Life Sciences PLC. US patent publication no.: 20190134044. 2020.
- [54] [cited 2020 May 31]; 2020. Available from: <https://www.biospace.com/article/releases/oyagen-inc-announces-a-compound-in-development-with-broad-antiviral-activity-against-coronaviruses-including-sars-cov-2/>
- [55] [cited 2020 May 31]; 2020. Available from: <https://www.beyondspringpharma.com/pressreleases/info.aspx?itemid=2212>
- [56] [cited 2020 May 31]; 2020. Available from: <https://algeronpharmaceuticals.com/covid-19-global-treatment-initiatives/>
- [57] [cited 2020 May 31]; 2020. Available from: <http://www.latticebiologics.com/wp-content/uploads/2013/04/News-Release-6.pdf>
- [58] [cited 2020 May 31]; 2020. Available from: <https://www.synairgen.com/wp-content/uploads/2020/05/200526-Synairgen-initiates-home-setting-trial-of-SNG001-in-COVID-19-final-1.pdf>
- [59] [cited 2020 May 31]; 2020. Available from: <https://www.enanta.com/investors/news-releases/press-release/2020/Enanta-Pharmaceuticals-Announces-Efforts-to-Discover-a-Treatment-for-the-Novel-Coronavirus-Disease-COVID-19/default.aspx>
- [60] [cited 2020 Jun 1]; 2020. Available from: <https://www.virbio.com/pipeline/>
- [61] [cited 2020 Jun 1]; 2020. Available from: <https://www.cuimc.columbia.edu/news/columbia-university-researchers-awarded-2-million-identify-antiviral-drugs-new-coronavirus>
- [62] Shen BD, Shen CY, Yuan XD, et al. Development and characterization of an orodispersible film containing drug nanoparticles. *Eur J Pharm Biopharm.* 2013;85(3 Pt B): 1348–1356.
- [63] Shen C, Shen B, Xu H, et al. Formulation and optimization of a novel oral fast dissolving film containing drug nanoparticles by Box–Behnken design–response surface methodology. *Drug Dev Ind Pharm.* 2014;40(5):649–656.
- [64] Varan C, Şen M, Sandler N, et al. Mechanical characterization and ex vivo evaluation of anticancer and antiviral drug printed bioadhesive film for the treatment of cervical cancer. *Eur J Pharm Sci.* 2019;130:114–123.
- [65] Genina N, Fors D, Palo M, et al. Behavior of printable formulations of loperamide and caffeine on different substrates–effect of print density in inkjet printing. *Int J Pharm.* 2013;453(2):488–497.
- [66] Pandey B, Khan AB. Enhancement of solubility and optimization of orally disintegrating films of acyclovir. *Asian J Pharm Clin Res.* 2018;11(9):280–286.
- [67] Orodispersible film formulation containing entecavir. Korea: Sunsystems Co. Ltd. International patent publication number WO2016052781. 2020.
- [68] World Health Organization. Q&A on coronaviruses; [cited 2020 Jun 2]; 2020. Available from: <https://www.who.int/news-room/q-adeail/q-a-coronaviruses>
- [69] Rastogi S, Pandey DN, Singh RH. COVID-19 pandemic: a pragmatic plan for Ayurveda intervention. *J Ayurveda Integr Med.* 2020.

- [70] Patil A, Dindore P, Aziz A, et al. Clinical effect of suvarna bindu prashan. *J Ayurveda Integr Med Sci*. 2017;2:11–18.
- [71] Rastogi S. Building bridges between Ayurveda and Modern Science. *Int J Ayurveda Res*. 2010;1(1):41–4146.
- [72] Rekha PS, Kuttan G, Kuttan R. Antioxidant activity of brahma rasayana. *Indian J Exp Biol*. 2001;39(5):447–452.
- [73] Sharma PV, editor. Caraka Samhita (text with English translation), Vimansthan, chapter 3, verse 13–14. Vol. I. Varanasi: Chaukhambha Orientalia; 2012. p. 316.
- [74] Srikantha Murthy K, editor. Susruta Samhita, Nidansthan, chapter 5, verse 33–34. Vol. I. Varanasi: Chaukhambha Orientalia; 2014. p. 502.
- [75] [cited 2020 Jun 2]; 2020. Available from: <https://www.ayush.gov.in/>
- [76] [cited 2020 Jun 2]; 2020. Available from: <https://health.ncog.gov.in/ayush-covid-dashbaord/#>
- [77] [cited 2020 Jun 2]; 2020. Available from: <https://home.iitd.ac.in/news-covidawagandha.php>
- [78] [cited 8 Jun 2020]; 2020. Available from: <https://urdip.res.in/covid19/vertical3.jsp>
- [79] [cited 8 Jun 2020]; 2020. Available from: <https://theprint.in/health/sun-pharma-gets-approval-to-test-plant-based-dengue-drug-for-covid-treatment/436,187/>
- [80] Yang Y. Use of herbal drugs to treat COVID-19 should be with caution. *Lancet*. 2020;395(10238):1689–1690.
- [81] Luo H, Tang QL, Shang YX, et al. Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. *Chin J Integr Med*. 2020; 26(4):243–250.
- [82] Antiviral composition comprising of fermented *Isatis indigotica* root extract and its thereof. Korean patent application no.: KR20190033129. 2020.
- [83] Prickly ash preparations and uses thereof as antiviral agents. International patent publication no.: WO2006026853. 2020.
- [84] Bicalin and its derivatives as a treatment for SARS corona virus infection or other related infections. International patent publication no.: WO2005044281. 2020.
- [85] Composition comprising extract of *Angelica dahurica* root or furanocoumarins isolated therefrom for preventing or treating avian influenza, swine influenza or corona virus. Korean patent application no.: KR1020160150250. 2020.
- [86] Herbal composition containing sea salt. US patent publication no.: 20040258712. 2020.
- [87] Herbal composition comprising ginger and goldenrod for the treatment of cold and flu. International patent publication no.: WO2011047473. 2020.
- [88] Rege A, Sadashiv Chowdhary A. Evaluation of *Ocimum sanctum* and *Tinospora cordifolia* as probable HIV-protease inhibitors. *Int J Pharm Sci Rev Res*. 2014;25:315–318.
- [89] Rege AA, Chowdhary AS. Evaluation of some medicinal plants as putative HIV protease inhibitors. *Indian Drugs*. 2013;50:24–28.
- [90] Panche AN, Chandra S, Diwan AD. Multi-target b-protease inhibitors from *Andrographis paniculata*: in silico and in vitro studies. *Plants*. 2019;8(7):231.
- [91] Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films. US 2018-0015033 A1. 2020.
- [92] Visser JC, Eugresya G, Hinrichs WLJ, et al. Development of orodispersible films with selected Indonesian medicinal plant extracts. *J Herb Med*. 2017;7:37–46.
- [93] Verma RK, Yadav R, Singh A. Development and evaluation of oral film of herbal extracts of *Piper betel* and *Foeniculum officinalis*. *Asian J Pharm Educ Res*. 2015;6(1): 102–110.
- [94] Pawar DR, Butle SR. Development of formulation and evaluation of garlic orodispersible films. *Int Res J Pharm*. 2018;9(11):145–155.
- [95] Visser JC, Dohmen WMC, Hinrichs WLJ, et al. Quality by design approach for optimizing the formulation and physical properties of extemporaneously prepared orodispersible films. *Int J Pharm*. 2015;485(1–2):70–76.
- [96] Ismaeel MYY, Dyari HRE, Yaacob WA, et al. In vitro antiviral activity of aqueous extract of *Phaleria macrocarpa* fruit against herpes simplex virus type 1; 2018.
- [97] Chang JS, Wang KC, Yeh CF, et al. Fresh ginger (*Zingiber officinale*) has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. *J Ethnopharmacol*. 2013;145(1):146–151.
- [98] Song JH, Park KS, Han Kwon D, et al. *J Med Food*. 2013; 274–279.
- [99] Sri Wahyuni T, Azmi D, Permanasari AA, et al. Anti-viral activity of *Phyllanthus niruri* against hepatitis C virus. *Malay Appl Biol*. 2019;48(3):105–111.
- [100] Dorra N, El-Berrawy M, Sallam S, et al. Evaluation of antiviral and antioxidant activity of selected herbal extracts. *J High Inst Public Health*. 2019;49(1):36–40.
- [101] Bayan L, Koulivand PH, Gorji A. Garlic: a review of potential therapeutic effects. *Avicenna J Phytomed*. 2014;4(1): 1–14.
- [102] Centers for Disease Control and Prevention – vaccines and immunizations; [cited 2020 May 31]; 2020. Available from: <https://www.cdc.gov/vaccines/vac-gen/immunz-basics.htm>
- [103] World Health Organization – vaccines; [cited 2020 May 31]; 2020. Available from: <https://www.who.int/topics/vaccines/en/>
- [104] [cited 2020 May 31]; 2020. Available from: <https://www.migal.org.il/en/node/6943>
- [105] [cited 2020 May 31]; 2020. Available from: <https://www.entospharma.com/news/entos-pharmaceuticals-is-developing-a-dna-vaccine-against-covid-19-using-its-fusogenix-nanomedicine-platform>
- [106] Recombinant polypeptides for membrane fusion and uses thereof. Entos Pharmaceuticals Inc. US patent publication no.: 20190367566. 2020.
- [107] [cited 2020 May 31]; 2020. Available from: <https://investors.vaxart.com/news-releases/news-release-details/vaxart-announces-selection-its-oral-covid-19-vaccine-lead>
- [108] Formulations for small intestinal delivery of RSV and norovirus antigens. Vaxart, Inc. US patent publication no.: 20180161458. 2020.
- [109] Formulations for small intestinal delivery. Vaxart, Inc. US patent publication no.: 20170224805. 2020.
- [110] [cited 2020 May 31]; 2020. Available from: <http://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiii-human-trials>
- [111] [cited 2020 May 31]; 2020. Available from: <https://altimmune.com/adcovid/>
- [112] Rapid and prolonged immunologic-therapeutic. Altimmune, Inc. US patent no.: 10,183,069.

- [113] [cited 2020 May 31]; 2020. Available from: <https://www.medicago.com/en/covid-19-programs/>
- [114] [cited 2020 May 31]; 2020. Available from: <http://ir.inovio.com/news-releases/news-releases-details/2020/INOVIO-Expands-Manufacturing-of-COVID-19-DNA-Vaccine-INO-4800-With-New-Funding-from-CEPI/default.aspx>
- [115] [cited 2020 May 31]; 2020. Available from: <https://www.modernatx.com/modernas-work-potential-vaccine-against-covid-19>
- [116] [cited 2020 May 31]; 2020. Available from: <https://www.tonixpharma.com/pipeline/tnx-1800-coronavirus-vaccine>
- [117] [cited 2020 May 31]; 2020. Available from: <http://www.cloverbiopharma.com/index.php?m=content&c=index&a=show&catid=11&id=41>
- [118] [cited 2020 May 31]; 2020. Available from: <https://ir.novavax.com/news-releases/news-release-details/novavax-produces-mers-cov-vaccine-candidate>
- [119] Liu YV, Massare MJ, Barnard DL, et al. Chimeric severe acute respiratory syndrome coronavirus (SARS-CoV) S glycoprotein and influenza matrix 1 efficiently form virus-like particles (VLPs) that protect mice against challenge with SARS-CoV. *Vaccine*. 2011;29(38):6606–6613.
- [120] Vaccines containing paucilsmellar lipid vesicles as immunological adjuvants. Novavax, Inc. US patent no.: 6,387,373.
- [121] Compositions comprising Iscom particles and live microorganisms. Novavax, Inc. US patent no.: 9,901,634. 2020.
- [122] [cited 2020 Jun 1]; 2020. Available from: <http://investors.predictive-oncology.com/press-releases>
- [123] Portnoy A, Ozawa S, Grewal S, et al. Costs of vaccine programs across 94 low- and middle-income countries. *Vaccine*. 2015;33(1):A99–A108.
- [124] Gandhi G, Lydon P, Cornejo S, et al. Projections of costs, financing, and additional resource requirements for low- and lower middle-income country immunization programs over the decade, 2011–2020. *Vaccine*. 2013;31(Suppl. 2): B137–B148.
- [125] Oral vaccine fast dissolving dosage form using starch. European patent application no.: EP 11779263.0. 2020.
- [126] Quick-dissolving oral thin film for targeted delivery of therapeutic agents. US patent application no.: 2011/0305768. 2020.
- [127] WT1 peptide cancer vaccine composition for mucosal administration. US patent no.: 10,206,985. 2020.
- [128] [cited 2020 Jun 1]; 2020. Available from: <https://www.sci-technol.com/proceedings/oral-dissolving-film-odf-formulation-of-gonorrhoea-microparticulate-vaccine-10898.html>
- [129] Methods and compositions for stabilization of a virus vaccine. US patent publication no.: 20110243988. 2020.
- [130] Formulation for room temperature stabilization of a live attenuated bacterial vaccine. US patent publication no.: 20110064723. 2020.
- [131] [cited 2020 Apr 17]; 2020. Available from: <https://grantsome.com/grant/NIH/R43-AI108083-01A1>
- [132] Uddin MN, Allon A, Roni MA, et al. Overview and future potential of fast dissolving buccal films as drug delivery system for vaccines. *J Pharm Pharm Sci*. 2019;22(1): 388–406.
- [133] Bajrovic I, Schafer SC, Romanovicz DK, et al. Novel technology for storage and distribution of live vaccines and other biological medicines at ambient temperature. *Sci Adv*. 2020;6(10):eaau4819.
- [134] Tian Y, Bhide YC, Woerdenbag HJ, et al. Development of an orodispersible film containing stabilized influenza vaccine. *Pharmaceutics*. 2020;12(3):245.