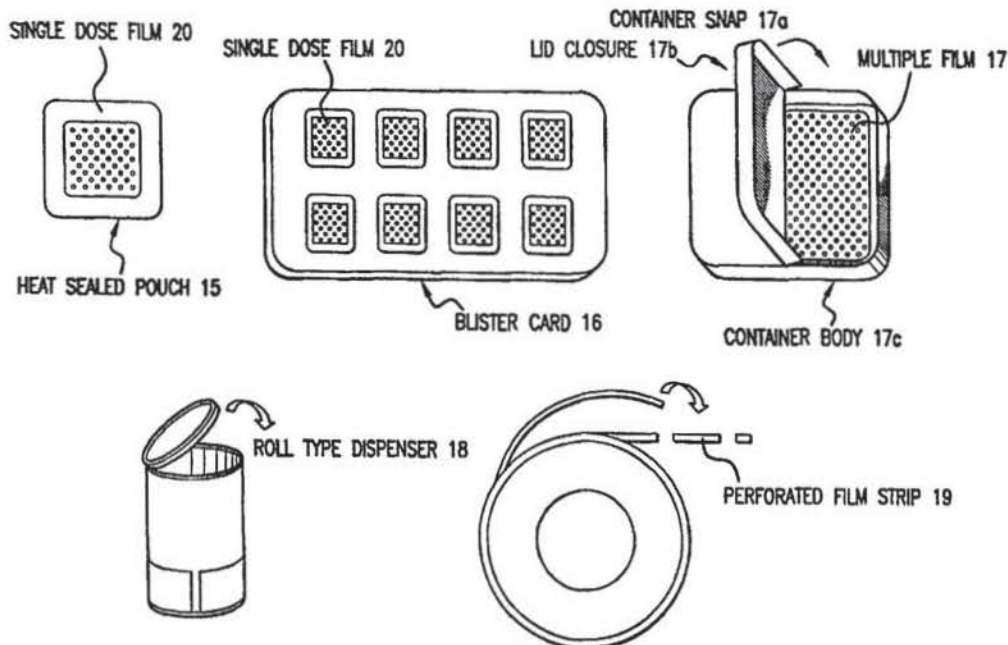




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>A61K 9/70</b>	<b>A2</b>	(11) International Publication Number: <b>WO 00/42992</b> (43) International Publication Date: 27 July 2000 (27.07.00)
<p>(21) International Application Number: PCT/US99/31327</p> <p>(22) International Filing Date: 30 December 1999 (30.12.99)</p> <p>(30) Priority Data: 60/116,823 21 January 1999 (21.01.99) US 09/434,878 5 November 1999 (05.11.99) US</p> <p>(71) Applicant: LAVIPHARM LABORATORIES, INC. [US/US]; Suite 6, 131 Ethel Road West, Piscataway, NJ 08854 (US).</p> <p>(72) Inventors: CHEN, Li-Lan, H.; 3906 Victory Court, Edison, NJ 08817 (US). PFISTER, William, R.; 16 Saxony Lane, Robbinsville, NJ 08691 (US). RENN, Donald, W.; 4 Brewster Point, Glen Cove, ME 04846-0088 (US). BURANA-CHOKPAISAN, Thitiwan; 4 Stout Court, Lawrenceville, NJ 08648 (US). OSBORNE, James; Lavipharm Laboratories, Inc., Suite 6, 131 Ethel Road West, Piscataway, NJ 08854 (US). TAN, Hock, Seng; 25 Jaime Court, Old Bridge, NJ 08857 (US). TAO, Li; Lavipharm Laboratories, Inc., Suite 6, 131 Ethel Road West, Piscataway, NJ 08854 (US).</p> <p>(74) Agent: STRIMPEL, Harriet, M.; Bromberg &amp; Sunstein LLP, 125 Summer Street, Boston, MA 02110-1618 (US).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i></p>	

(54) Title: COMPOSITIONS AND METHODS FOR MUCOSAL DELIVERY



(57) Abstract

A dosage unit comprising a water-soluble hydrocolloid and a mucosal surface-coat-forming film, such film including an effective dose of active agent. In the dosage unit sildenafil citrate, nicotine, hydromorphone, oxybutynine or estradiol are used as active agents.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## COMPOSITIONS AND METHODS FOR MUCOSAL DELIVERY

Technical Description

5           The present invention is directed to a device and method for administering agents in a dissolving film configuration.

Background to the Invention

Many pharmaceutical dosage forms are administered orally in the form of solid shaped articles such as tablets, pills, caplets and capsules that retain their shape under  
10 moderate pressure. Generally these dosage forms are designed to be swallowed whole or chewed to deliver the medication with adequate amounts of liquid. Some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Certain patients such as children or animals resist taking medication, and may try to hide a solid pill in order to spit it out later. In addition, many pediatric and  
15 geriatric patients are unwilling to take a solid dosage form because the active agent is difficult to swallow or is retained in the pharynx or gullet even when liquids are consumed with the dosage unit. Furthermore, the availability of liquids at the time of administering medications may be limited for certain patients and may be restricted for certain diseases and/or treatments. Chewable tablets provide some advantages over the  
20 conventional tablets. However, they are not suitable for children wearing braces and the taste of the medication may be unpleasant and difficult to mask in a chewable tablet. At the same time, water may be still required for the administration of chewable tablets.

In addition, the standard oral dosage forms, such as tablets, pills, caplets, and capsules, are designed for short residence time in the mouth. Absorption of the agent  
25 from these dosage forms occurs in the gastrointestinal (GI) tract, after the agent has separated from the dosage form and dissolved in the gastric fluids. For some active agents, it is desirable to achieve absorption through the oral mucosal tissues in order to accelerate onset of the therapeutic effect.

Many active agents are poorly absorbed, even after they are dispersed in the  
30 stomach, because of low solubility or slow dissolution rate in the gastric fluids. Tablets may be formulated so as to be quick dissolving. These tablets are commonly placed on the tongue and disintegrate rapidly in the oral cavity. However, these dosage units are

not fixed to a mucosal surface and may move around in the mouth. Consequently, they do not overcome a risk associated with choking or gagging that occurs with subjects having limited control of their swallowing reflexes. However, once placed in the mouth, these tablets dissolve rapidly in the saliva to provide a liquid formulation which is then  
5 swallowed. Quick dissolving tablets may be formed from a particulate support matrix containing the therapeutic agent, where the particulate support matrix is a protein (US 5,807,576, US 5,635,210, US 5,595,761). Alternatively, the tablet may be formed from a laminate with several layers and an outer coating (JP 100535518). Tablets have also been manufactured from shearform matrices which are substantially amorphous sugar  
10 formed when crystalline sugar is subjected to heat and shear (WO 95/07194; WO 95/35293). Other methods of forming quick dissolving tablets include wet granulation methods (EP 0627 218) and dry granulation methods (EP 0124027A1) and by freeze-drying techniques (EP 0084705A2). Generally, quick dissolving tablets are formed using complex multi-step manufacturing processes. In addition, these tablets may have  
15 poor mechanical strength, are fragile and friable and have insufficient holding capacity for active ingredients (US 5,720,974) and may be difficult to store and handle.

Therapeutic compounds are sometimes provided as powders or granules which may be difficult to swallow and cause unpleasant sensations in the mouth. Furthermore, many quick dissolving tablets contain particulates (>25 microns) which leave a "gritty"  
20 and unpleasant taste in the mouth. In the elderly, powders may cause choking and discomfort associated with trapping of granules in dentures. Powders and granules are generally packaged in a sealed pouch which requires tearing before use. This causes problems for geriatric patients and those suffering from arthritis in the fingers as well as for children. Consequently, problems of spillage of the contents arise in this group of  
25 patients. Furthermore, these oral preparations should be taken with water which for certain patients are inconvenient and may cause reduced patient compliance.

Liquid, syrups or suspensions are an alternative to solid dosage forms and are considered desirable for pediatric and geriatric patients who have problems in swallowing tablets. However, these dosage forms are often difficult to measure  
30 accurately and administer easily. Liquid formulations deteriorate rapidly upon exposure to heat or atmosphere and consequently have a relatively short shelf life. Furthermore, liquid formulations require a relatively large volume and are bulky to store.

In addition to solid and liquid dosage forms, rapidly dissolving buccal/oral delivery systems have been developed. These systems are commonly freeze dried preparations which are more expensive to manufacture as compared to tablets (US 5,648,093). Furthermore, freeze dried preparations are brittle and fragile when handled and must be kept in dry conditions to avoid disintegration. The instability of freeze-dried preparations has been reduced somewhat by the addition of mannitol (US 4,946,684). WO 9820862 reports a film that is formed according to a method that does not utilize freeze drying and avoids problems described in the art such as rigidity of the films, delayed softening and poor solubility in the mouth (US 4,876,092; EP 0200508; EPO 381194; CA-PS 1-26331; DE 2449865.5; DE 3630603; EP 0452446 and EP 0219762). However, the film described in WO 9820862 relies on the use of at least two different non-ionic surfactants to achieve immediate wettability.

It is desirable that a dosage unit should provide a non-invasive, effective and economic means to deliver an active agent to the target site. Where the target site is the plasma, additional issues arise concerning the rate of delivery of the active agent to that site as measured by bioavailability. For many types of active agent, fast onset of the therapeutic effect is desirable. Traditional oral dosages, such as tablets, are limited in onset time by the rate of absorption in the gastro-intestinal tract. Formulations have been developed which, when applied in the mouth, lead to faster onset than the traditional oral dosages because they target the oral mucosa. These formulations include dosage units containing 75%-90% polyethylene glycol that melt at body temperature, in the mouth. (US 5,004,601 and 5,135,752) Other formulations include liquid forms, lozenges or tablets that are administered sublingually or by a sweetened matrix on a stick. (US 5,770,606, Streisand et al. and Zhang et al., Christie et al., Sasaki et al.). Whereas the above references address the delivery route, they do not address the problems of bioavailability that arise from poor solubility or low dissolution rate.

A delivery device that addresses the above limitations would represent a desirable improvement on existing delivery systems.

#### Summary of the Invention

A novel dosage unit and its method of manufacture and use is provided. In an embodiment, the dosage unit includes a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an active agent.

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.