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(54) **DISSOLUTION TESTING OF SOLID DOSAGE FORMS INTENDED TO BE ADMINISTERED IN THE ORAL CAVITY**

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G01N 33/15 (2006.01)

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(58) **Field of Classification Search** 73/866, 73/865.6, 866.4
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,791,222	A *	2/1974	Goodhart et al.	73/866
3,802,272	A *	4/1974	Bischoff et al.	73/866
4,247,298	A *	1/1981	Rippie	73/866 X
4,279,860	A *	7/1981	Smolen	73/866 X
5,127,278	A *	7/1992	Benz	73/866
5,142,920	A *	9/1992	Bart et al.	73/866
5,412,979	A *	5/1995	Fassihi	73/866 X
5,639,974	A	6/1997	Hanson et al.	
5,807,115	A	9/1998	Hu	
6,004,822	A	12/1999	Li et al.	
6,060,024	A	5/2000	Hutchins et al.	
6,163,149	A *	12/2000	Loffler	73/866 X
6,170,980	B1 *	1/2001	Martin	73/866 X
6,799,123	B2	9/2004	Hughes	
6,948,389	B2	9/2005	Brinker et al.	
7,024,955	B2 *	4/2006	Carlson et al.	73/866
2002/0061540	A1 *	5/2002	Grass et al.	435/7.1
2003/0087457	A1	5/2003	Hughes	
2003/0235110	A1	12/2003	Qureshi	
2005/0123601	A1 *	6/2005	Mane et al.	424/451
2006/0134195	A1 *	6/2006	Fu et al.	424/464

FOREIGN PATENT DOCUMENTS

DE	2942129	A *	4/1981	
JP	63230077	*	9/1988	435/283.1

OTHER PUBLICATIONS

Das et al. (2004) "Development of Mucoadhesive Dosage Forms of Buprenorphine for Sublingual Drug Delivery," *Drug Deliv.* 11:89-95.

(Continued)

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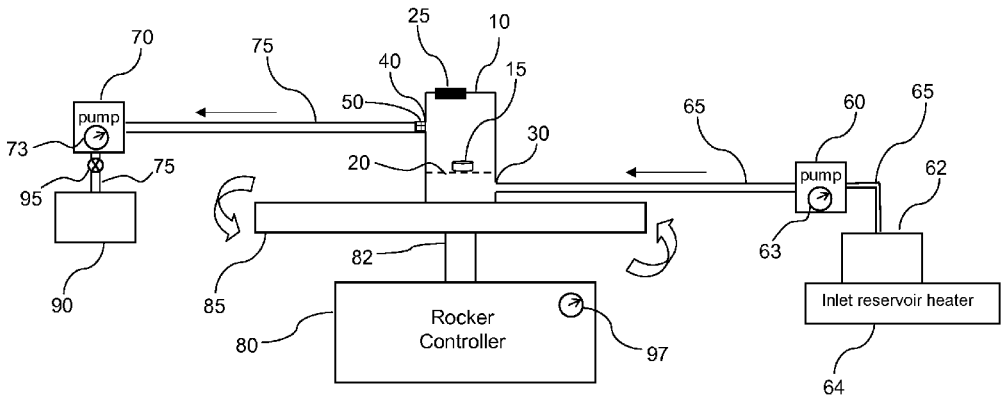
(57) **ABSTRACT**

The invention is a method and device for determining dissolution of a solid compound within the oral cavity. The device models dissolution within the oral cavity with a flow-through cell containing a solid compound and physiological amounts of simulated saliva. The device supplies and removes the simulated saliva at rates similar to production and loss of saliva within the oral cavity. The simulated saliva interaction with the solid compound mimics saliva interaction with a solid compound within the oral cavity. Dissolution of solid compound is determined from simulated saliva collected from the flow-through cell outflow.

19 Claims, 2 Drawing Sheets



OTHER PUBLICATIONS

Tan et al. (2000) "Effect of Carbopol and Polyvinylpyrrolidone on the Mechanical, Rheological, and Release Properties of Bioadhesive Polythylene Glycol Gels," *AAPS PharmSciTech* 1(3):article 24 10 pages.

Varian, Inc. (2004) "Direct Vessel Heating System (DVH)," *Dissolution Systems Application Note PN* 74-2000 1-3 May 2004.

Varian Inc. "VK 7030 Dissolution Tester," 74-1074, Rev. A, 1-2 by Oct. 2005.

* cited by examiner

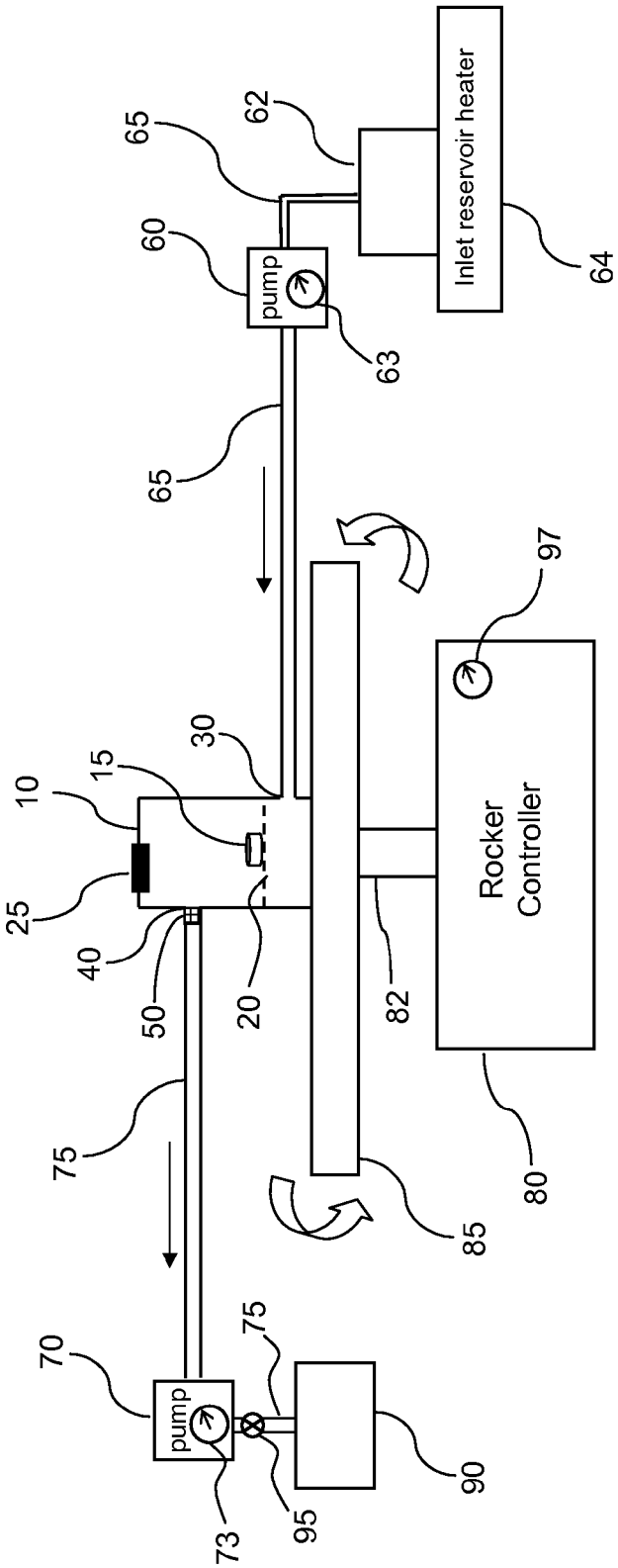


FIG. 1

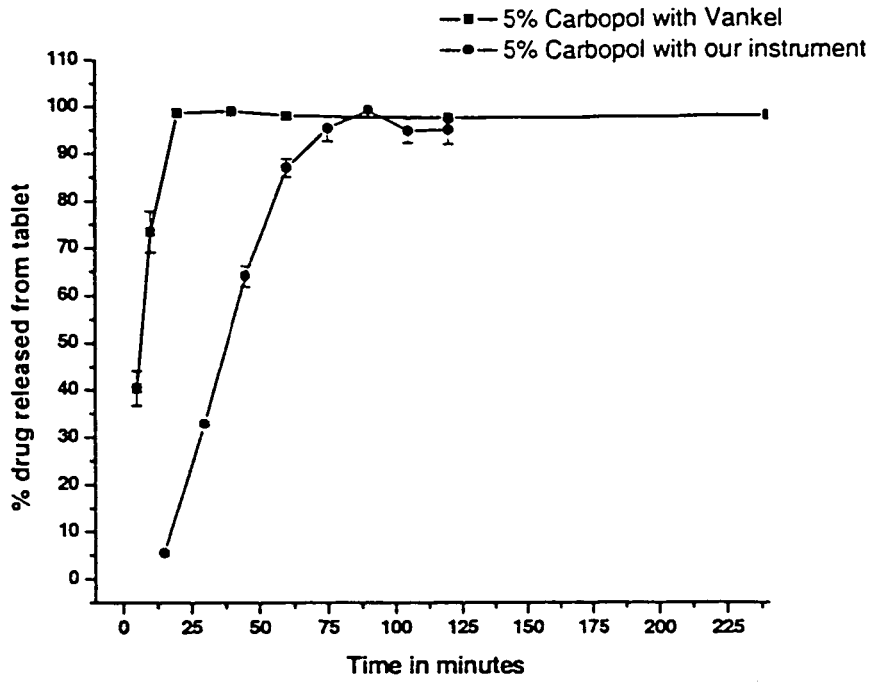


FIG. 2A

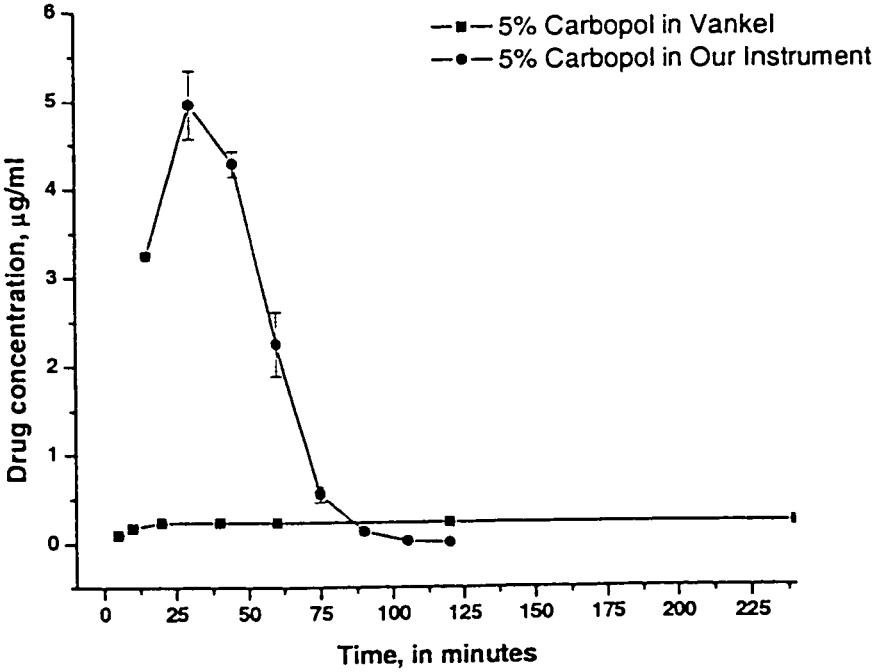


FIG. 2B

DISSOLUTION TESTING OF SOLID DOSAGE FORMS INTENDED TO BE ADMINISTERED IN THE ORAL CAVITY

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made, at least in part, with government support under 1R15DA015358-01 awarded by the National Institute on Drug Abuse. The government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

Not Applicable.

FIELD OF INVENTION

This invention generally relates to a method and apparatus for in vitro evaluation of dissolution of solid dosage forms in the oral cavity, including the buccal and sublingual environments.

BACKGROUND OF THE INVENTION

Administration of pharmaceuticals and other solid formulations via absorption in the oral cavity provide several advantages over administration via absorption from the gastrointestinal (GI) tract. Buccal (against the cheek) and sublingual (under the tongue) dosage forms of drugs can bypass first-pass metabolism that occurs in the intestine during absorption and in the liver immediately following absorption from the GI tract. Such first-pass metabolism results in reduction of available drug material. In addition, drug absorption in the oral cavity can result in a rapid onset of drug action because the oral cavity has a rich supply of blood vessels to transport the drug throughout the systemic circulatory system. Therefore, buccal/sublingual dosage forms can provide more biologically available drug and adequate plasma levels of a drug at lower initial administration dosage compared to drugs delivered via administration from the GI tract. Drugs absorbed within the oral cavity also are delivered systemically faster than drugs absorbed from the GI tract. In order to determine appropriate dosing for drug delivery via the oral cavity, it is important to quantify the time course of a drug's dissolution within the oral cavity. There is need in the art for devices that simulate the flow of saliva in the human mouth and the subsequent dissolution of drugs in the oral cavity. The present invention provides improved methods and apparatus for determining, in vitro, the dissolution of a solid compound placed within the oral cavity.

A number of sublingual dosage forms are available for pain control, heart conditions, asthma, antiemesis and treatment of drug abuse including, for example, nitroglycerine, subutex, suboxone and isoproterenol. Because of the advantages outlined above, further increase in formulations utilizing sublingual dosage forms is expected. An oral delivery route is a non-invasive means to deliver a wide variety of biotechnological or pharmaceutical products including, for example, proteins, peptides, oligonucleotides, siRNA and gene therapy compositions.

There are numerous in vitro apparatuses for testing dissolution of formulations in the gastro-intestinal (GI) tract.

macopeial Convention, USP 25. However, these systems are not suitable for assessing dissolution of solid formulations in the oral cavity. First, the GI apparatuses typically contain up to 900 mL of solution, agitated using either a paddle stirrer or a rotating basket assembly. For stirrer assemblies, the stirrer must be completely submerged in the dissolution fluid. Therefore, the minimum amount of fluid with which the dissolution vessel can be operable is about 450 mL. USP 25 recommends using 900 mL fluid for most studies. The fluid capacity and/or content of the human mouth is much less than 900 mL or even the minimum volume of 450 mL. In addition, the paddle and rotating basket-type assemblies produce considerable agitation of the dissolution medium. Such agitation suitably models peristaltic movement in the GI tract. However, because the oral cavity lacks peristaltic movement, such agitation is inappropriate for simulating dissolution within the oral cavity.

The fluid dynamics of the apparatuses that model GI-tract dissolution are also inappropriate for modeling dissolution within the oral cavity. Such GI apparatuses are closed systems in that the dissolution medium does not continuously enter and leave the vessel. Generally, samples are withdrawn from the vessel at different time intervals and the vessel contents may or may not be replenished by fresh medium. The samples are then analyzed for drug content to determine the rate and extent of dissolution. Such systems may be adequate for modeling dissolution within the GI tract, and especially the stomach cavity, where fluid turnover is minimal. Saliva, in contrast, is produced and swallowed continuously so that a closed vessel design does not accurately simulate the oral cavity.

Hughes (U.S. Pat. Pub. No. 2003/0087457) addresses dissolution of compounds in the buccal cavity prior to passage to the GI. The apparatus in Hughes suffers a drawback in that the interaction of dissolution medium with the solid compound does not realistically model dissolution of the solid in the oral cavity where all surfaces of the solid compound are exposed to dissolution fluid flow. In addition, the apparatus in Hughes is a relatively complex and expensive means for assessing dissolution comprising two outlet ports and an in-line dissolution analyzer. In addition, the dissolution medium is stirred, which inappropriately simulates the relatively gentle fluid movements in the oral cavity and requires larger dissolution fluid volumes to ensure immersion of the stirrer.

Li et al. (U.S. Pat. No. 6,004,822) describe a device to measure dissolution of solids in submilliliter quantities (10 to 400 microliters) of a solvent and correspondingly small amount of the solid. The device in Li unsatisfactorily models dissolution in the oral cavity because, in part, there is no flow-through cell, but rather it is a closed system. The solvent remains within the cell and is pumped between two chambers in fluid communication with one another. The oral cavity, in contrast, contains approximately 50 mL of saliva that is continuously replenished as saliva exits the oral cavity or is absorbed and/or broken down during solid dissolution.

BRIEF SUMMARY OF THE INVENTION

The invention provides devices and methods for assessing dissolution of solid compounds within the oral cavity. In one embodiment, the invention is a device comprising an influx source and efflux sink, each connected to a flow-through cell that holds a volume of dissolution medium and in which a

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