DDELEB 11(2) 2004 ISSN 1071-7544

THE JOURNAL OF DELIVERY AND TARGETING OF THERAPEUTIC AGENTS

DRUG DELIVERY

Volume 11 • Number 2 • March–April 2004

Taylor & Francis
healthsciences

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Abstracted/indexed in: Biochemistry & Biophysics Citation Index, Chemical Abstracts, EMBASE, Index Medicus, and MEDLINE, Research Alert, and SciSearch.
Drug Delivery (USPS permit number 014-497) is published bimonthly by Taylor & Francis Inc., 325 Chestnut Street, Philadelphia, PA 19106. Periodicals postage paid at Philadelphia, PA and additional mailing offices.
US Postmaster: Please send address changes to UDRD c/o IMS, PO Box 1518, Champlain, NY 12919, USA.
Annual Subscription, Volume 11, 2004
Print ISSN - 1071-7544, Online ISSN - 1521-0464
Institutional subscribers: $787 (US), £477 (UK)
Personal subscribers: $380 (US), £230 (UK)
An institutional subscription to the print edition includes free access to the online edition for any number of concurrent users across a local area network.
Production and Advertising Office: 325 Chestnut Street, Philadelphia, PA 19106. Tel - 215-625-8900, Fax - 215-625-8563.
Production Editor: Jeannine Kienzle.
Subscription Offices
USA/North America: Taylor & Francis Inc., 325 Chestnut Street, Philadelphia, PA 19106. Tel: 215-625-8900, Fax: 215-625-2940.
UK/Europe: Taylor & Francis Ltd., Rankine Road, Basingstoke, Hampshire RG24 8PR, UK. Tel: +44 (0) 1256 813 000, Fax: +44 (0) 1256 330 245.
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10717544(2004)11(2)

Taylor & Francis
healthsciences

Drug Delivery, 11:89–95, 2004

ISSN: 1071-7544 print / 1521-0464 online
DOI: 10.1080/10717540490280688

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Development of Mucoadhesive Dosage Forms of Buprenorphine for Sublingual Drug Delivery

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The development of mucoadhesive formulations of buprenorphine for intended sublingual usage in the treatment of drug addiction is described. The formulations include mucoadhesive polymer films, with or without plasticizers, and mucoadhesive polymer tablets, with or without excipients that enhance drug release and/or improve tablet compaction properties. The mucoadhesive polymers studied include carbomers such as Carbopol 934P, Carbopol 974P, and the polycarbophil Noveon AA-1, with excipients chosen from pregelatinized starch, lactose, glycerol, propylene glycol, and various molecular weights of polyethylene glycol. The development of plasticizer-containing mucoadhesive polymer films was feasible; however, these films failed to release their entire drug content within a reasonable period. Thus, they were not determined suitable for sublingual usage because of possible loss by ingestion during routine meal intakes. The mucoadhesive strength of tablet formulations containing Noveon AA-1 appears to be slightly superior to the Carbopol-containing tablets. However, the Carbopol 974P formulations exhibited superior drug dissolution profiles while providing adequate mucoadhesive strength. The tablet formulations containing Carbopol 974P as mucoadhesive polymer, lactose as drug release enhancer, and PEG 3350 as compaction enhancer exhibited the best results. Overall, the mucoadhesive tablet formulations exhibited superior results compared with the mucoadhesive film formulations.

Keywords Buprenorphine, Compressed Tablet, Drug Abuse, Film, Mucoadhesion, Sublingual

Therapies to prevent and/or treat drug abuse need careful consideration of the biopharmaceutical aspects of the treatment drugs and suitable delivery systems that can provide an ideal therapeutic profile and improve patient compliance. Ideally, drugs for the treatment of abuse must possess sufficiently long half-lives that allow reduction in frequency of administration, slow metabolism to inactive metabolites, thus requiring less drug to be administered, and lack of addiction potential of their own. Buprenorphine has gained much interest in recent years in the treatment of opioid-type drug addiction. It has strong analgesic and narcotic antagonist activity and is 25–50 times more potent than morphine (Gutstein and Akil 2001). Pharmacologically, buprenorphine, a highly lipophilic semisynthetic derivative of the opioid alkaloid thebaine, is a partial opiate agonist. It has agonistic effect on the mu and antagonistic effect on the kappa receptors, with the agonist properties predominating at low doses and antagonist properties predominating at higher doses (Cowan, Lewis, and Macfarlane 1977). A partial agonist is less likely to cause respiratory depression, which is the major toxic effect of opiate drugs, compared with full agonists such as heroin and methadone. Buprenorphine hydrochloride, the water-soluble salt form of buprenorphine, has a mean plasma half-life of 3.21 hr (Kuhlman et al. 1996) and is highly metabolized in the intestinal wall and liver to norbuprenorphine, which is a weakly active metabolite with half-life of 57 hr (Kuhlman et al. 1998). Both buprenorphine and norbuprenorphine form inactive glucuronides (Iribarne et al. 1997).

Compared with the potential of buprenorphine as a first- or second-line agent in the treatment of opiate addiction, studies on buprenorphine drug delivery systems are relatively few. A subcutaneously implanted system utilizing a cholesterol-glyceryl tristearate matrix produced sustained analgesic effect in rats for 12 weeks or more (Pontani and Misra 1983). In an early study on noncrystalline prodrugs of buprenorphine, synthesized for transdermal delivery, success was limited because the lipophilic form was sequestered in the lipid-rich skin layers (Stinchcomb et al. 1996). A matrix-type transdermal patch of buprenorphine (Transtec®, Napp Pharmaceuticals) was recently introduced in the European market for the management of stable cancer and noncancer pain, and early clinical efficacy reports are fairly promising (Radbruch 2003). Eriksen et al. (1989) reported that the systemic bioavailability of buprenorphine administered by nasal spray is greater than 40%, which is comparable to the

Received 2 July 2003; accepted 12 August 2003.
The authors acknowledge Peter Willeitner for his technical assistance during the preliminary formulation phase of the dosage forms.
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30–40% bioavailability via the intramuscular and subcutaneous routes. Addition of 30% polyethylene glycol (PEG) 300 as a co-solvent to a nasal formulation of buprenorphine does not enhance bioavailability of the drug any further (Lindhardt et al. 2001). Buprenorphine has been studied in a microcapsule system intended for parenteral use and produced a steady in vitro release for 45 days (Mandal 1999). Concerns over residual organic solvents used in most microparticle preparations have restricted FDA approval of parenteral microparticulate systems, in general, and further studies are needed to evaluate their efficacy and safety in vivo.

Intravenous buprenorphine has been used in pain management for many years. The oral route of administration produces poor bioavailability of approximately 15% (McQuay, Moore, and Bullingham 1986) and lacks commercial potential. Systemic bioavailability following sublingual administration, which bypasses first pass metabolism, is much superior and has been reported to be up to 58% (Bullingham et al. 1982). The sublingual region offers a nonkeratinized epithelium with high permeability and a smooth and relatively immobile surface with easy accessibility. For the treatment of drug abuse, an immediate release sublingual tablet of buprenorphine, Subutex™ (manufactured by Reckitt Benckiser), was recently introduced in the U.S. market. This delivery system for buprenorphine has been available in Europe for nearly a decade and is widely used as an alternative to methadone in the treatment of opiate addiction (Gasquet, Lancon, and Parquet 1999). Literature on bioavailability of sublingual buprenorphine presents variable numbers ranging from 19–58% of the administered dose. Although sublingual delivery of buprenorphine has been proven effective, bioavailability by this route can be erratic because of salivary washout and involuntary swallowing.

We hypothesize that increasing the contact time with the sublingual mucosa with a mucoadhesive delivery system could improve sublingual bioavailability and result in more predictable plasma levels of the drug, leading to better therapeutic efficacy and reproducibility. No study has been published to date on mucoadhesive sublingual delivery of buprenorphine aimed at the treatment of drug addiction. These dosage forms would adhere to the sublingual mucosa and withstand tongue movement for a significant period, potentially decreasing the chances of involuntary swallowing of the dosage form. A sustained release effect also may be expected from the dosage form, which would make delivery of higher doses of buprenorphine for the preferred 3-times/week dosing regimen feasible with minimal side effects. With easy accessibility to the sublingual area, the delivery systems can be self-administered by the patient with minimal or no supervision that in turn can reduce health care costs involved in the treatment of drug addiction.

In this article, we discuss the development of mucoadhesive polymer films and tablets of buprenorphine and evaluation of their physical properties and drug release characteristics. The effect of plasticizers on the film properties was studied, as well as the effect of excipients on "tabletability" and drug release properties from the compressed tablets. The polymeric dosage forms described are hydrogels that swell on coming in contact with water and do not allow prompt dissolution like an immediate release tablet; therefore, we anticipate that potential for diversion of these dosage forms as a street drug for intravenous use would be limited if applied in the clinical arena in the future.

MATERIALS AND METHODS

The carbomers Carbopol 934P, 974P and Noveon AA-1 were obtained by the courtesy of Noveon Inc. (OH, USA). Starch 1500 (pregelatinized maize starch) was obtained by the courtesy of Colorcon Inc. (PA, USA). Lactose monohydrate, glycerol, propylene glycol, PEG (MW 400, 1000, 3350, and 8000), mucin, and buprenorphine were obtained from Sigma Chemical Co. (MO, USA).

Preparation of Mucoadhesive Polymer Films

Considering the comfort issue involved with a drug delivery system designed to adhere to a sensitive and mobile area, we adjudged that a thin, flexible polymer film would be ideal for sublingual use. A general protocol used in several literature references describing polymer films was adopted. Double-filtered deionized water was degassed under vacuum before adding the polymers to minimize the formation of air bubbles within the gel. Each of the following polymers in 200–500 mg quantities, Carbopol 934P, Carbopol 974P, and Noveon AA-1, were solubilized in water or 95% ethanol using a paddle stirrer at 1000 rpm for 10 min to result in 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0% w/w gels. Homogeneous gel formation for the higher concentrations (4.5 and 5% w/w) proved difficult by stirring and was achieved by placing the mixtures in plastic bags and kneading by hand to prevent formation of poorly wetted polymer agglomerates. Amounts higher than 5.0% w/w could not be homogeneously solubilized. All gels were kept overnight at 4°C to allow complete hydration, following which they were centrifuged at 5000 rpm for 30 min to remove air bubbles before film casting. Two techniques were used to cast the polymer films: (a) gels poured on Teflon® plates and placed in the oven at 40°C for 24 hr or until dry to the touch; and (b) gels placed between two Teflon® plates separated with 1 mm thick spacers at the edges and dried in a desiccator under vacuum for 48–72 hr.

Preparation of Plasticizer Containing Mucoadhesive Polymer Films

Plasticizers were added to the aqueous gel systems described above to reduce brittleness, improve flexibility, and improve surface texture and smoothness of the films. PEG has been described in the literature to also improve mucoadhesion properties of certain polymers. Glycerol, propylene glycol, or PEG 400, 1000, 3350, or 8000 were each added to the aqueous gel systems to result in final concentrations of 0.5, 1.0, 5.0, or 10.0% w/w plasticizer in the system and stored overnight under refrigeration

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