National Addiction Centre

Institute of Psychiatry at The Maudsley

KING'S College LONDON

Buccal naloxone

Professor Sir John Strang & Rebecca McDonald
National Addiction Centre,
King's College London & SLaM NHS FT

KING'S HEALTH PARTNERS

Pioneering better health for all

Declarations RM

- RM has undertaken an unpaid student industry placement with Mundipharma Research Ltd., with focus on the analysis of naloxone nasal spray formulations.

- King's College London has separately applied to register intellectual property on a novel buccal naloxone formulation with which JS and RM are involved.

- RM is a consultant for the United Nations (UNODC), supporting a naloxone study in Central Asia.

Declarations JS (personal & institutional)

- NHS provider (community & in-patient); also Phoenix House, Lifeline, Clouds House, KCA (Kent Council on Addictions).
- Dept of Health, NTA, Home Office, NACD, EMCDDA, WHO, UNODC, NIDA.
- Dialogue and work with pharmaceutical companies re actual or potential development of new medicines for use in the addiction treatment field (incl re naloxone products), including (past 3 years) Martindale, Indivior, MundiPharma, Braeburn and trial product supply from iGen.
- SSA (Society for the Study of Addiction); UKDPC (UK Drug Policy Commission), and two Masters degrees (taught MSc and IPAS) and an Addictions MOOC.
- Work also with several charities (and received support) including Action on Addiction, and also with J Paul Getty Charitable Trust (JPGT) and Pilgrim Trust.
- The university (King's College London) has registered intellectual property on a buccal naloxone formulation, and JS has been named in a patent registration by a Pharma company as inventor of a novel concentrated naloxone nasal spray.

1 | Nasal naloxone: What have we solved?

The formulation:

- Nasal spray volume
- Max injectable concentration – 1mg/ml
- Best guess PK – 30-50% ??
- Vertical/horizontal

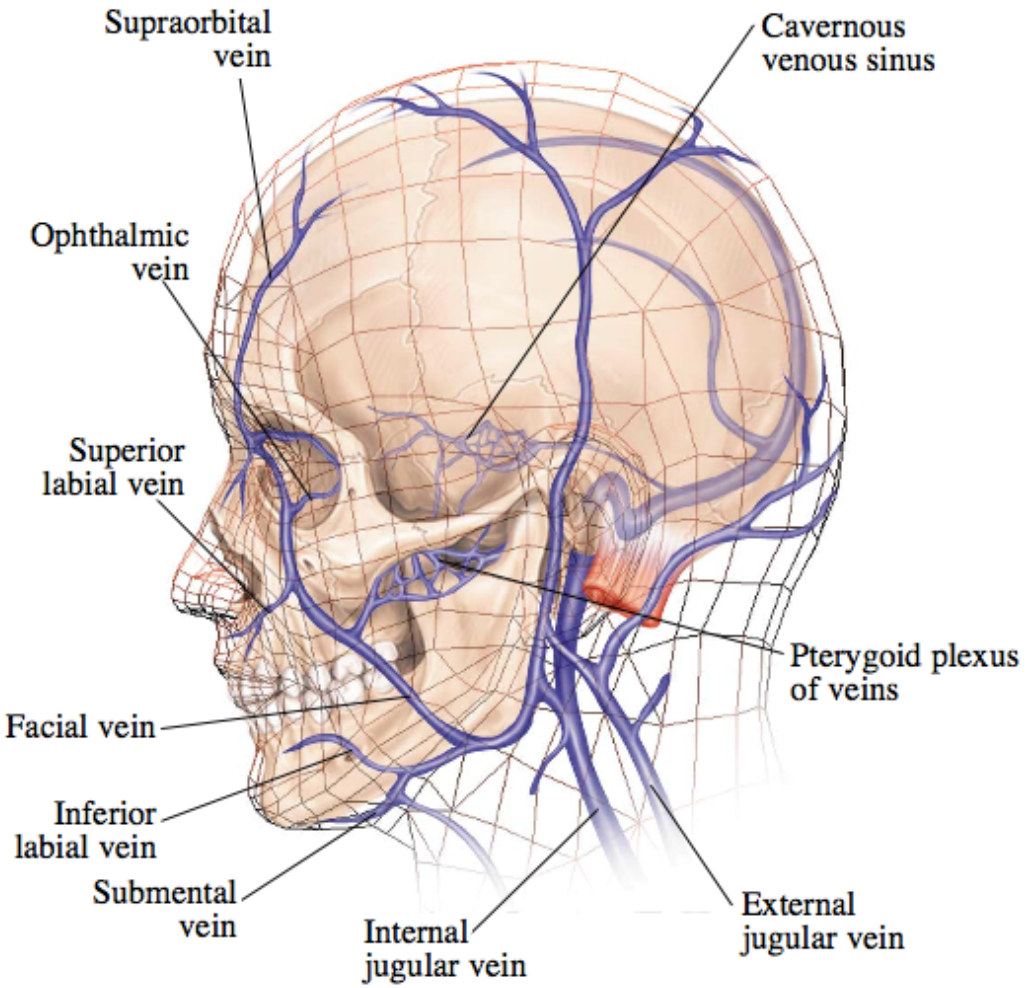
Max. dose through 2 nostrils – 0.2mg naloxone (old school)

1 | Nasal naloxone: What's still a worry?

The route in practice:

- Nasal membrane abuse and damage
- Vomitus and secretions
- Bar set high – highly effective and easy IM (and low-cost)

2 | Injection-free alternatives: Buccal



International Journal of Pharmaceutics, 36 (1987) 127–130
Elsevier

IJP 01217

Buccal and oral bioavailability of naloxone and naltrexone in rats

Munir A. Hussain, Bruce J. Aungst, Albert Kearney and Eli Shefter

Du Pont, Medical Products Department, Experimental Station, Wilmington, DE 19898 (U.S.A.)

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(Accepted 18 November 1986)

Key words: Buccal administration; Naloxone; Naltrexone; opioid antagonist; Pharmacokinetics; First-pass metabolism

Summary

The opioid antagonists naloxone and naltrexone are both known to undergo extensive first-pass metabolism after oral dosing. The buccal route was investigated as a potential alternative to oral administration. Oral and buccal bioavailabilities of naloxone and naltrexone were determined in rats. Less than 1% of oral naloxone or naltrexone was bioavailable, but buccal administration resulted in approximately 70% bioavailability for each drug.

2 | Other buccal products: Emergency midazolam

- Recent development for interim treatment of status epilepticus
- Similarly for emergency administration while awaiting ambulance
- Buccal route deemed suitable for family administration

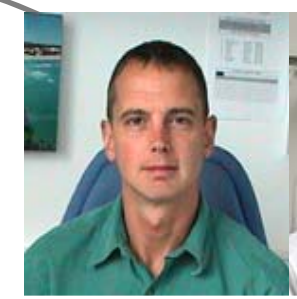
2 | The possibility of buccal naloxone

The specification:

- Speed and reliability of effect
- Stable over time and extremes of temperature
- Easy to carry
- Good acceptability
- Low price for mass pre-provision

3 | Collaboration partners

Prof David Taylor
Psychopharmacology CAG; and Pharmacy, SLaM



Drs Ben Forbes & Paul Royall
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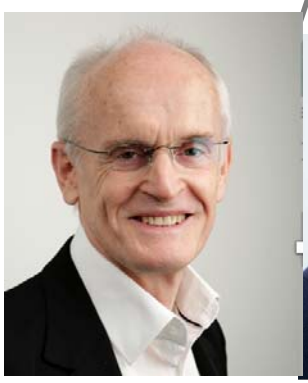

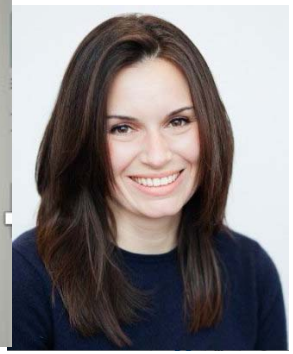

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Addictions Department, IoPPN
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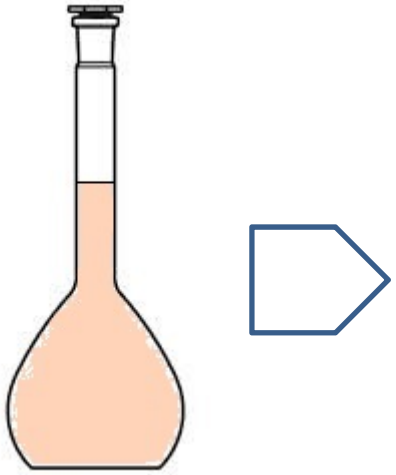
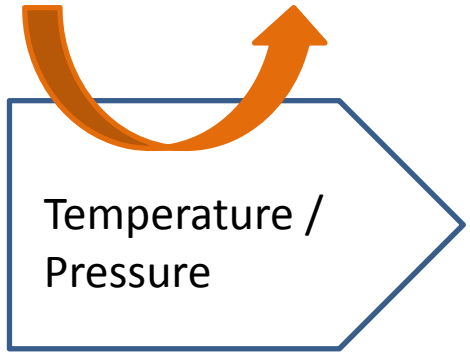
Prof Peter Goadsby and colleagues
Clinical Research Facility (CRF)
King's College Hospital | Denmark Hill

Prof Bob Flanagan
Toxicology Unit
King's College Hospital

3 | Instant-dissolving tablet: Development

SOLUTION → FREEZE → DRY → TABLET





Stock solution
Naloxone and pharmaceutical grade excipients in water for injection

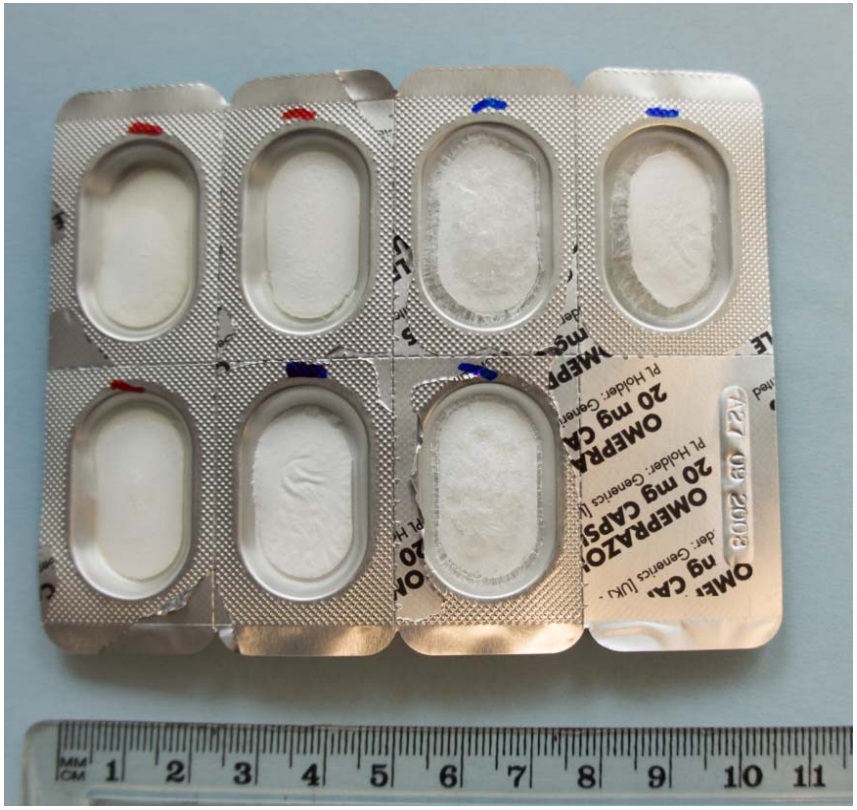
Solution pipetted into blister wells (top) and frozen (bottom) ready for lyophilisation

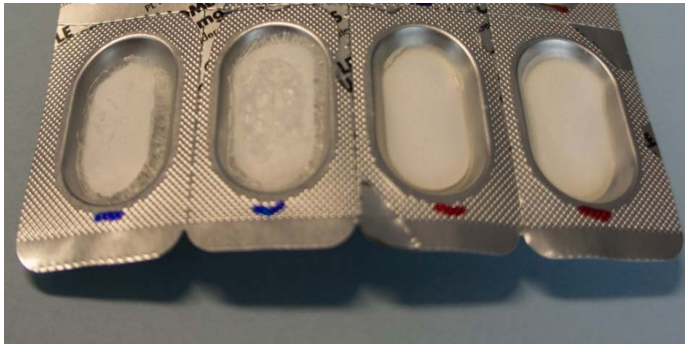
Frozen tablets lyophilised using tailored temperature and pressure cycle

Instant-dissolving tablet

3 | Instant-dissolving tablet: Prototype

Naloxone 0.8 mg instant dissolving tablet
White porous tablet (17 mg, 10 x 20 mm)





4 | In vitro testing: Stability

Table 1 | Instant-dissolving tablet specification and stability (n=6; 2 tablets per 3 batches)

		Stability		
Parameter	Specification	0 months	9 months 4°C	9 months 25°C
Tablet weight (mg)	16.9 - 20.7	17.8 ± 0.5	17.8 ± 0.5	17.6 ± 0.5
Dimension - length (mm)	20.0 - 30.0	29.4 ± 0.2	29.1 ± 0.3	29.1 ± 0.7
Dimension - width (mm)	14.0 - 18.0	16.1 ± 0.5	16.1 ± 0.3	16.0 ± 0.3
Disintegration test (s)	≤180	14.0 ± 5.9	9.0 ± 5.0	10.0 ± 5.0
Naloxone HCL assay (mg)	0.76 - 0.84	0.80 ± 0.01	0.81 ± 0.02	0.80 ± 0.03

- The tablets conformed reproducibly to quality specifications
- Chemical and physical stability over 9-months' storage (25°C), with target drug content of 0.8 mg of naloxone HCl/tablet (HPLC assay)

Alqurshi, A., Kumar, Z., McDonald, R., Strang, J., Buanz, A., Ahmed, S., ... & Holt, C. (2016). Amorphous formulation and in vitro performance testing of instantly disintegrating buccal tablets for the emergency delivery of naloxone. *Molecular Pharmaceutics*, *13*(5), 1688-1698.

4 | In vitro testing: Digital imaging dissolution assay

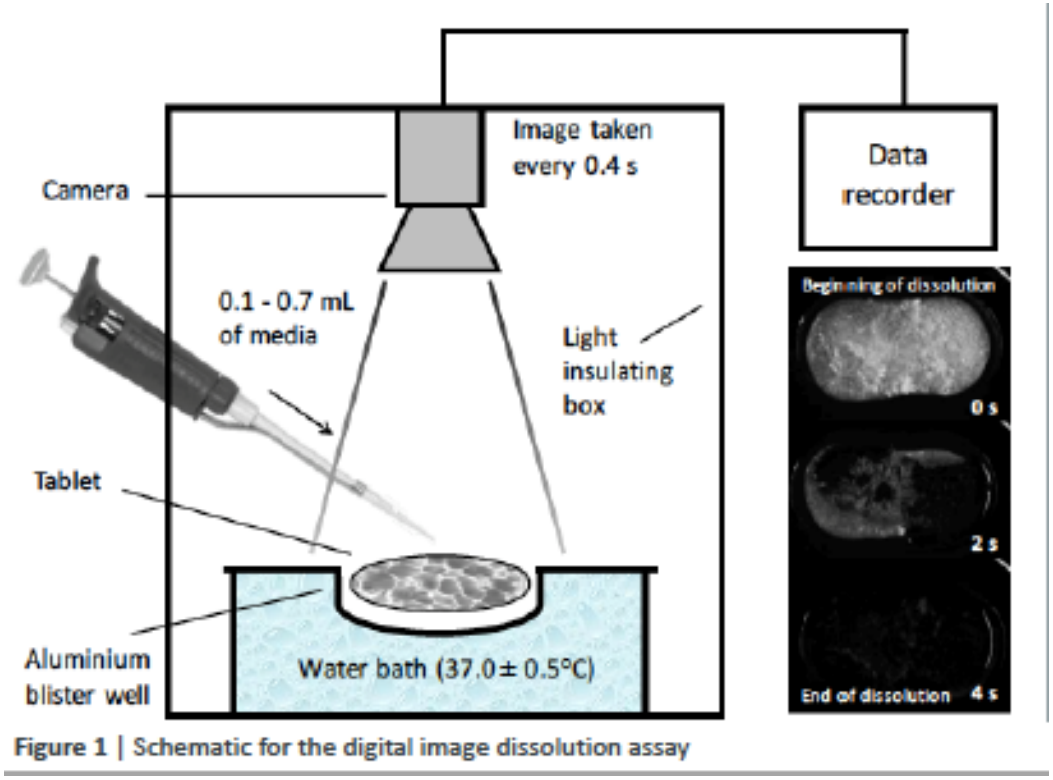


Figure 1 | Schematic for the digital image dissolution assay

- Under all conditions, tablets dissolved fully (>90%) within 30 seconds (variation of: temperature, volume of fluid, dissolution medium)

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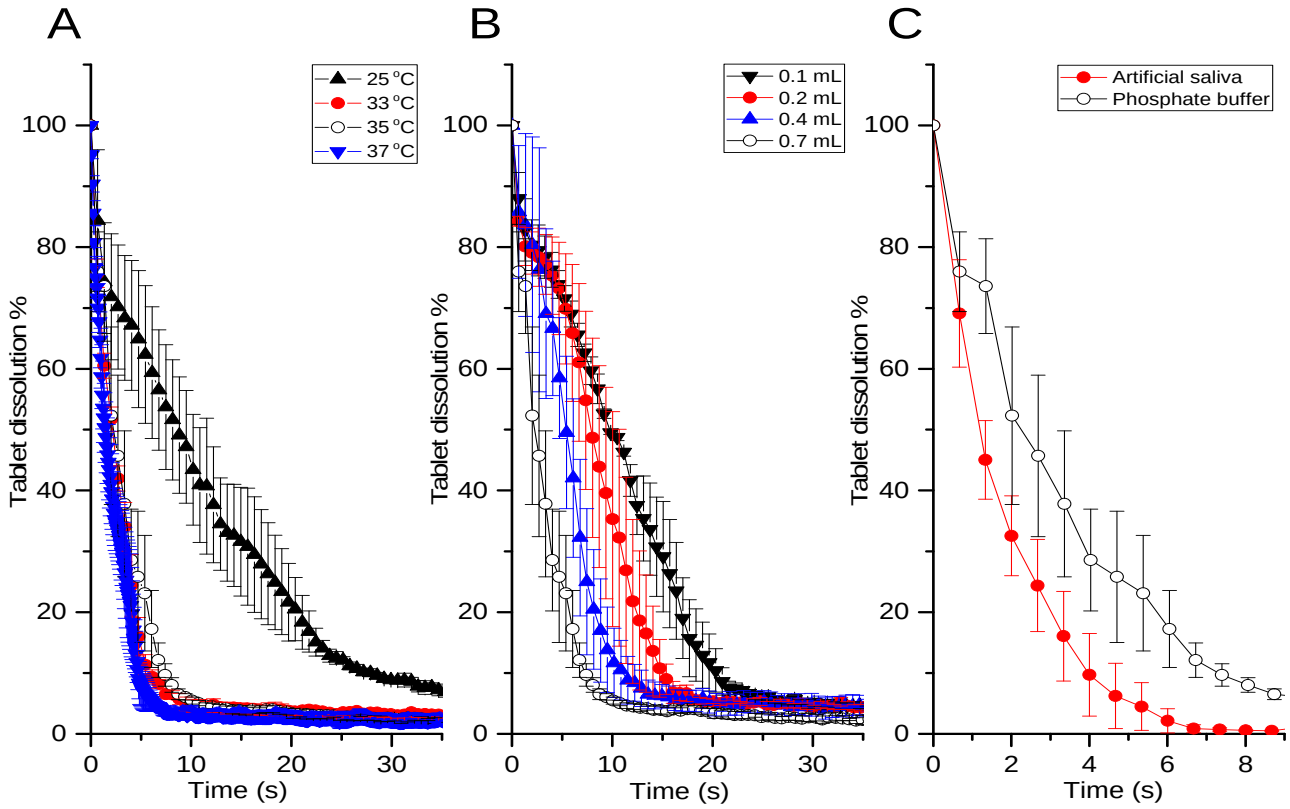

Figure 5. Effect of (A) temperature [volume 0.7 mL; medium – phosphate buffered saline], (B) fluid volume [temperature 35°C; medium – phosphate buffered saline], (C) dissolution medium [temperature 35°C; volume 0.7 mL] on the dissolution of the instant dissolving tablet using a digital image dissolution assay. Data represent mean ± SE, n=3.

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5 | Buccal naloxone: Summary

- Advantage over solution: tablets greater stability?
- Ease of transport
- Addition of absorption enhancers possible
- Next steps: in vivo testing – human volunteer PK study

Thank you