



1

Drug Incompatibility and Instability

- **Incompatibility** - a theoretically reversible physicochemical change that may result in precipitation or insolubility, which may not always be visible
 - e.g. midazolam and dexamethasone
- **Instability** - irreversible chemical degradation of the active compound, resulting in loss of potency
 - e.g. glycopyrronium and dexamethasone



2



3



4

Continuous Subcutaneous Infusions

- So what happens when we mix drugs in solution?
- Drugs are often complex organic chemicals
- Potential for chemical reactions
- Unknown events could occur in syringe
- Concentration of active drug may be reduced



5

Continuous Subcutaneous Infusions

- Toxic chemicals could predispose to infusion site reactions or worse.....



6

Periodic Table of the Elements

Standard periodic table of elements with color-coded groups and labels for Lanthanide and Actinide series.

7

nature research

comment

Turning the periodic table upside down

The periodic table is commonly presented for representing some different properties of the chemical elements, but usually it does not take into account other important aspects, such as molecular and pharmacological properties of the elements.

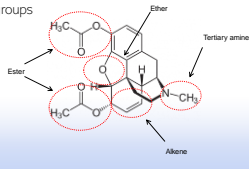
Marino Rubini, Alessandro D. I. M. de Sá, Y. S. S. de Sá, Y. S. S. de Sá, Y. S. S. de Sá

Upside-down periodic table and a portrait of an elderly man with glasses.

8

Drug Incompatibility and Instability

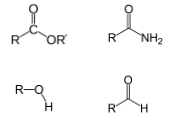
- Physicochemical interactions between drug molecules governed by functional groups
- There are >20
- Each drug has a unique molecular structure consisting of a combination of different chemical or functional groups



9

Drug Incompatibility and Instability

- When drugs are mixed together, the different functional groups may interact
- Risk of physicochemical interactions between drugs used in combination for parenteral administration has long been a recognised problem



10

Drug Incompatibility and Instability

- Rudimentary understanding of acid-base chemistry can predict many drug-drug incompatibilities that result in precipitation
- Most common chemical reactions implicated in parenteral drug degradation involve hydrolysis and/or oxidation
- Parenteral drug degradation affected by exposure to light, pH and temperature



11

Drug Incompatibility and Instability

PRIMER

Drug incompatibility chemistry

DAVID W. NEWSON

Am J Health-Syst Pharm—Vol 66 Feb 15, 2009

12

Drug Incompatibility and Instability

Salt Ion Suffix	Examples
-ium -ate (organic anion)	Dexamethasone sodium phosphate
-ium (base anion)	Diclofenac sodium, phenobarbital sodium
-ate & -ide (acid cations)	Cyclizine lactate, fentanyl citrate, morphine sulphate, octreotide acetate, alfentanil hydrochloride, hyoscine hydrobromide, levomepromazine hydrochloride, metoclopramide hydrochloride, midazolam hydrochloride, oxycodone hydrochloride
-ate -ide -ide -ium -ate -ium ide	} denote quaternary ammonium cations Hyoscine butylbromide Glycopyrronium bromide

13

Drug Incompatibility and Instability

Salt Ion Suffix	Examples
-ium -ate (organic anion)	Dexamethasone sodium phosphate
-ium (base anion)	Diclofenac sodium, phenobarbital sodium
-ate & -ide (acid cations)	Cyclizine lactate, fentanyl citrate, morphine sulphate, octreotide acetate, alfentanil hydrochloride, hyoscine hydrobromide, levomepromazine hydrochloride, metoclopramide hydrochloride, midazolam hydrochloride, oxycodone hydrochloride
-ate -ide -ide -ium -ate -ium ide	} denote quaternary ammonium cations Hyoscine butylbromide Glycopyrronium bromide

14

Drug Incompatibility and Instability

BMC Palliative Care
 RESEARCH ARTICLE
 Identification of drug combinations administered by continuous subcutaneous infusion that require analysis for compatibility and stability
 Andrew Dickson¹, Matthew Bickert¹, Richard Jackson¹, Jovelle Schneider¹, Stephen Mason¹ and John Eldon^{1*}



15

Extended Infusion Time?

- Are a range of significant economic challenges to the NHS's provision of good palliative and end of life care
- Projected 20% increase in deaths per year between 2014 and 2035/36
- Number of qualified UK district nurses have fallen by over 40% in the past decade
- Need new ways of providing and structuring services are required to optimise care for patients and make best use of available resources



16

48 hour CSCI?



17

Drug Incompatibility and Instability

Exploring the potential utility of 48-hour continuous subcutaneous infusions (CSCI): An evaluation of the frequency doses and drugs administered by CSCI are altered across seven NHS acute hospitals.

Baker J et al. [manuscript submitted]

- Seven acute NHS hospitals in the UK participated
- 582 combinations recorded
- Median duration of an unchanged CSCI was 48 hours
 - 55% (320/582) remained unchanged for 2 days or longer
 - 33% (106/320) included a weekend



18

Drug Incompatibility and Instability

Exploring the potential utility of 48-hour continuous subcutaneous infusions (CSCI): An evaluation of the frequency doses and drugs administered by CSCI are altered across seven NHS acute hospitals.

Baker J et al. [manuscript submitted]

- There is potential for the utilisation of 48-hour CSCI infusions in a large proportion of patients requiring CSCI therapy for symptom control
- Robust chemical and microbiological stability data will be required before practice can change



19

Drug Incompatibility and Instability

RESEARCH ARTICLE

The current evidence base for the feasibility of 48-hour continuous subcutaneous infusions (CSCIs): A systematically-structured review

James Baker^{1,2*}, Andrew Dickman^{3*}, Stephen Mason¹, John Ellershaw^{3,4}

1 Pharmacy Department, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, Merseyside, United Kingdom, **2** Palliative Care Institute Liverpool, University of Liverpool, Liverpool, Merseyside, United Kingdom, **3** Academic Palliative and End of Life Care Department, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, Merseyside, United Kingdom

PLOS ONE | <https://doi.org/10.1371/journal.pone.0194236> March 14, 2018

- 21 studies reviewed
- Limited evidence for the stability over 48 hours
- More data are required!



20



21