Investigation in to the functionality of controlled drug denaturing/ destruction kits

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Abstract

Context

Throughout the UK a large amount of unwanted, expired or patient returned controlled drugs are disposed of every day, in community and hospital pharmacies, veterinary surgeries, hospices, private hospitals, and industrial settings. This is mostly achieved through the use of commercially available controlled drug destruction/ denaturing kits, but what do these kits actually do to the drug within them?

Objective

The primary aim of this study was to investigate the effect of 6 commercially available kits on morphine, a chosen model controlled drug. The secondary aim was to establish if the kits could be adapted to chemically destroy any drug disposed within it.

Materials and methods

Morphine was dispensed in to 6 commercially available controlled drug destruction kits at a known concentration, The instructions on the kits were followed and after 48 h the amount of drug remaining was determined by HPLC. In addition a new kit containing sodium perborate was tested in the same way.

Results

Between 78-111% of the parent drug was found to still be present in the commercial kits tested after 48 h. In the sodium perborate 5% kit this level fell to 22%.

Discussion and conclusions

In conclusion all the commercially available CD denaturing kits tested do not destroy the controlled drug (morphine) tested but simply encapsulated it in gel. This means the parent form of the drug is still present and could potentially be recovered and abused.

The new kit containing sodium perborate was much more effective in chemically destroying the parent drug but care must be taken in its use.

Introduction

Throughout the UK a large amount of unwanted, expired or patient returned controlled drugs are disposed of every day, in community and hospital pharmacies, veterinary surgeries, hospices, private hospitals, and industrial settings. The Controlled Drugs (Supervision of Management and Use) Regulations 2006[i] specified that Controlled Drug Accountable Officers (CDAO) must have procedures in place concerning the destruction of controlled drugs (CD). This is no longer a separate mandatory requirement but it is expected that organisations whose use of CD involves their disposal will wish to ensure they have in place adequate procedures covering this activity and that relevant staff receive the appropriate information and training[ii]

Where CD are destroyed regulation 27 of the Misuse of Drugs regulations 2001 [iii] requires CDAO's to ensure this is witnessed by an appropriate person and that other legislation such as the Environment Agency's Waste Management Licensing regulations 1994[iv] and the Hazardous Waste Regulations 2005[v] are taken in to account. However none of these regulations define what constitutes "destruction" of CD. The environment agency simply state that "*A pharmacy or veterinary surgery is required to denature controlled drugs prior to their disposal*"[vi] again there is no clear definition of the terminology used. The Royal Pharmaceutical Society (RPS) guidance for pharmacists on the safe destruction of controlled drugs[vii] recommends that "*Pharmacists are strongly advised to denature CD and render them irretrievable as a soon as possible*". The document goes on to recommend that pharmacists are advised to use CD denaturing kits in order to denature CD, and indeed this is what the majority of pharmacists routinely do. Alternatively the document mentions some other methods that in the past have been used to denature CD including grinding together with other waste medicines and/or dissolving in soapy water or absorbing on to cat litter[vii].

In essence the regulations require the waste CD to be destroyed or denatured to the extent that they can no longer be recovered. The problem is the majority of the commercially available CD destruction/ denaturing kits work by adding an inert substance to adulterate (denature) the original substance to render it unfit for use; this is not synonymous with destruction.

The primary aim of this study was to determine if commercially available controlled drug denaturing kits actually chemically destroy or denature the drugs within them or simply dissolve the tablets and encapsulate the active drug within a gel matrix.

The secondary aim was to develop a controlled drug denaturing kit that will render chemically destroyed any controlled drugs disposed within it.

Materials and methods

Acetonitrile (HPLC grade), potassium dihydrogen orthophosphate and nylon membrane filters (0.45µM) were purchased from Fisher Scientific (Loughborough, UK). Morphine Sulphate Salt Pentahydrate (100% purity) and sodium perborate were purchased from Sigma-Aldrich (Dorset, UK). The following drug destruction/ denaturing kits were obtained from local suppliers, DenKit® (Denward Manufacturing, Chelmsford, UK), Controlled drugs destruction kit (PHS waste management, Stevenage, UK), Controlled drugs destruction kit (Safer Options, Worcestershire, UK), Controlled drugs destruction kit (National Pharmacy Association, St Albans, UK), CD denaturing kit (Bros Pharma Support, Essex, UK).

Mobile phase preparation

20mM potassium dihydrogen orthophosphate was freshly prepared when required on a 2L scale by accurately weighing 5.436g into a 2L volumetric that was made up to volume using deionised water. A magnetic stirrer was then added and the solution stirred until all powder was completely dissolved. The mobile phase was then filtered using a 0.45µM nylon membrane filter under vacuum.

HPLC assay

A 'fit for purpose' HPLC analytical method with UV detection was developed to analyse morphine. Separation was achieved using a Agilent Technologies 1260 Infinity Quaternary LC system with a Synergi 4µ Hydro – RP 80A column (Phenomenex, UK) fitted with a Security Guard Cartridge AQ C18 4 x 3.0mm. The mobile phase consisted of 95% aqueous solution (as prepared above) and 5% Acetonitrile. Analysis was performed at 20±2°C, detection was by UV at 210nm with an injection volume of 10µL and a 10 min run time. The retention time of morphine was 4.4 min. The method was deemed to be 'fit for purpose' such that the morphine concentration was able to be determined in the presence of any matrices (e.g. excipients) used in the denaturing kits.

The system suitability of the assay was performed by injection of 1, 10 and 100 μg/ml standards in triplicate, injection repeatability, range, linearity, accuracy and precision of the assay were all determined. To determine the accuracy of the HPLC assay quality control (QC, accepted reference) samples were freshly prepared each time the standards samples were analysed. The accuracy of the standards (represented as % accuracy) was assessed by calculating the concentration (MC) of a freshly prepared QC sample using the relevant section of the standard curve and comparing it to the theoretical concentration (TC) according the following equation

$$\% \, accuracy = \left(\frac{MC}{TC} \right) x100$$

The precision of the assay expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the same analytical conditions and is expressed as the % relative standard deviation (% RSD). To determine repeatability six replicate injections of 1, 10 and 100 μg/ml morphine samples prepared in water were analysed on the same day and the % RSD of peak area was determined. Intermediate precision of the assay was determined to ensure that the method would provide the same results within the same laboratory when similar samples are analysed on different days. To test the intermediate precision two standard curves were prepared on separate occasions.

The limit of detection (LOD) and the quantitation limit (LOQ), were identified from the lower concentration range of the standard curve using the equations below:

$$LOD = \left(\frac{STEYX}{Slope} \right) x3.3$$

$$LOQ = \left(\frac{STEYX}{Slope} \right) x10$$

Standard Preparation

Morphine standards were prepared between the range of 10 - 1000μg/ml in water. This was achieved by weighing morphine sulphate (10mg) directly in to a 10mL volumetric flask which was made up to volume with deionised water to create a stock solution of 1000μg/mL. This stock solution was

sequentially diluted to obtain a calibration curve between 1 to 100 μg/mL, all dilutions were carried out in volumetric flasks using deionised water.

Short term stability of standard solutions

A freshly prepared set of morphine standards were immediately analysed by HPLC using the validated method detailed above. The 1 μg/mL and 100 μg/mL samples were then aliquoted in to a series of HPLC vials which were crimped and stored in the fridge at 4ºC. One sample of each was removed from the fridge and analysed by HPLC after 2 days and a further sample analysed after 3 days. All samples were analysed in triplicate.

Compatibility of denaturing kits with HPLC method

In order to confirm non-interference between the excipients of the denaturing kits and the HPLC assay a sample of each type of kit was prepared. Each kit was vigorously mixed by shaking for 2 min with the lid on, a sample of each kit (1g) was accurately weighed in to a glass vial to which an appropriate amount of water was added by weight. The amount of water added was calculated based on the instructions for use of the kit and the total weight of powder within the kit. The actual amounts of water used for each kit are shown in table 1. The samples were diluted 1:100 prior to injection on the HPLC.

Destruction of Morphine using commercial kits

In order to assess the ability of the kits to destroy a controlled drug placed within them, morphine was used as a model drug, it was selected on the basis that it is a commonly used drug and is not prone to hydrolysis. A sample of each kit was prepared in separate glass vials which also contained morphine (8-9mg). Water was then added (w/w) in the proportion indicated on the kit instructions. The kits were immediately mixed using a spatula for 2 min and then left to stand for 2h. All kits were prepared in triplicate. After 2h a 1g sample was taken from the kit by weighing directly in to a 100mL volumetric flask which was then made up to volume using deionised water. A magnetic flea was then added and the volumetric placed on a magnetic stirrer and left for approximately 2h until all gel had visibly dissolved. A sample was then taken from the volumetric flask for analysis by HPLC and use as a T=0

sample. The kit samples were then stored at room temperature for 48h at which point each kit was re-sampled and diluted 1:100 as described above before analysis by HPLC. The concentrations of the 48h samples were then calculated as a percentage of the drug content measured in the T=0 samples.

Forced degradation of morphine

Sodium perborate was used to try and force the degradation of morphine. A 1% sodium perborate solution was made up by dissolving 0.5g in 50mL of water. 5mL of 1000µg/mL morphine stock solution was aliquoted in to a 50mL volumetric and made up to volume using the 1% sodium perborate solution. The resulting mixture was aliquoted into a series of HPLC vials and sealed. 3 vials were analysed by HPLC immediately as T=0 samples, the rest were stored at either room temperature or 40ºC and analysed at 24h and 48h in triplicate.

Results

Analytical method development and validation

All morphine samples and standards were analysed according to the HPLC method described above. Figure 1 shows a typical chromatogram for morphine with a retention time of approximately 4.4 min. Figure 2 shows a typical calibration curve for morphine standards between the range of 10 to 100 µg/mL. Validation of the HPLC method was established to ensure the reliability and accuracy of data generated in the study. The data detailed in Table 2 indicates that all the validation specifications for the analysis of morphine have been met.

Short term stability of standard solutions

Morphine standards were prepared, aliquoted in to HPLC vials and stored in the fridge at 4ºC. Samples were tested at T=0, T=2 and T = 3 days, the results are summarised in Table 3. At both concentrations more than 99% of the parent drug was recovered after 3 days indicating that morphine was stable in the standard solutions over a 3 day period.

Compatibility of denaturing kits with HPLC method

In order to confirm compatibility with the HPLC method a sample of each drug destruction kit was prepared as detailed above. No peaks were seen for any kit that would interfere with the detection of morphine (Figure 3 and figure 4 (top panel)).

Destruction of Morphine using commercial kits

In order to test the ability of the kits to destroy/ denature controlled drugs morphine was used as a model drug. The kits were set up with morphine in them as detailed above. Samples were analysed at 0h and 48h and the amount of drug present at 48h calculated as a percentage of the drug present a 0h (Table 4). A sample chromatogram showing the controlled drug destruction kit (Safer Options) containing drug a T=0 is shown in Figure 4 (lower panel).

In all cases where kits did not contain an oxidising agent, between 78-111% of the original concentration of morphine was recovered after 48 h. There is a degree of experimental error within these results due to the difficulty in accurately measuring and mixing the kits due to their viscous nature, however with the exception of the NPA kit, where the standard deviation was 26%, the error in the other kits was limited to ± 10%. Even allowing for this experimental error it is still apparent that the majority of the drug is still present in an unchanged form in the kits after 3 days. The exception to this was the COMBIKIT (1% and 5%) where the morphine content assayed at T=0, 3 and 48h after hydration were found to be significantly lower (as shown in table 4) than those kits that did not contain an oxidising agent.

Forced degradation of morphine

A solution containing 100 µg/mL morphine and 1% sodium perborate A was prepared as detailed in above. The morphine content of the solution was measured by HPLC at T=0h and T=24h and 48h. The morphine content at T=24 and 48h was calculated as a percentage of the content at T=0h and is shown in Table 4. The morphine stored at 40ºC was completely destroyed by 48 h, while only 5.61 ± 1.23% of the room temperature sample remained at 48h.

Discussion and Conclusions

This brief study describes an investigation of the functionality of 6, commonly used commercially available controlled drug destruction / denaturing kits. In order to achieve this morphine was selected as an example controlled drug to be investigated in this study.

A HPLC method for the detection and quantification of morphine was developed and shown to be fit for purpose for use in this current study. The stability of morphine in aqueous solution was determined to ensure that any degradation of morphine observed in the study was due to the action of the kits and not simply natural degradation of the drug by, for example, hydrolysis. Morphine was found to be stable in solution for at least 3 days (99.60±1.22% at 1 µg/mL and 99.98 ± 0.48% at 100 µg/mL) confirming that any degradation observed in the study was as a result of the action of the kits tested.

Morphine was then added to the CD destruction kits at a known concentration which was confirmed by HPLC analysis at T=0. The kits were handled as described in their instructions for use and the morphine content re-assayed by HPLC after 48 h. It was found that the commercially available drug denaturing/ destruction kits tested did not cause significant chemical degradation of morphine, with between 78-111% of the initial drug concentration still present after 48 h.

In order to chemically degrade morphine a solution of 1% sodium perborate was prepared and this was shown to degrade 94.39% of a 100 µg/mL solution of morphine at room temperature within 48 h and 100% degradation occurred in less than 24 h at 40ºC. Based on these findings, a new controlled drug destruction kit (COMBI) containing either 1% sodium perborate or 5% sodium perborate were

tested to determine their ability to degrade morphine. The 1% COMBI kit resulted in 59.12% degradation of morphine within 48 h while the 5% COMBI kit degraded 78.38% of the morphine in the same time scale.

The primary aim of this study was to confirm if the commercially available CD kits do actually destroy the active drugs or simply denature the dosage form (tablet/ capsule) and encapsulate the active drug in a gel matrix. The results show that with all the kits tested the majority of the drug was still present in its parent form after 48 h in the kit. The danger of this is that current guidelines require CD destruction kits to be securely stored for only 48 h, after which they can be disposed of as pharmaceutical waste. If the drug is still in its active form this leaves the drugs open to potential abuse.

The secondary aim was to determine if a proposed new kit containing an oxidising agent could successfully chemically denature the controlled drug. The 1% COMBI kit resulted in loss of 59% of the parent drug while the 5% COMBI kit destroyed 78% of the parent drug. This is clearly a much higher level of chemical destruction than observed with any of the previously available CD destruction/ denaturing kits. The kits were not tested beyond 48 h in order to be directly comparable with the directions for use on the commercially available kits, but it is expected that had the COMBI kit been left for longer, complete destruction of the morphine would have been observed. Clearly the oxidation agent used in COMBI kit results in the release of a small amount of oxygen during the degradation process and so care must be taken in handling these kits and precautions taken to prevent the build up of the oxygen released.

In conclusion the commercially available CD denaturing kits tested, which did not contain an oxidising agent, did not destroy the controlled drug (morphine) tested but simply encapsulated it in gel. This means the parent form of the drug is still present and could potentially be recovered and abused. It is therefore our conclusion that the commercially available CD denaturing kits recommended by the RPS and routinely used by thousands of Pharmacists are not fit for purpose. Clearly in this simple study using one example schedule 2 CD the drug was not rendered irretrievable, the solid dosage formulation might well be denatured i.e. tablets, capsules or powders lose their physical form and are dissolved, but the parent drug is still present, still active and most importantly still prone to abuse.

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