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Research paper

Activated carbon as a carrier for amorphous drug delivery: Effect of drug characteristics and carrier wettability

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ABSTRACT

Recent research on porous silica materials as drug carriers for amorphous and controlled drug delivery has shown promising results. However, due to contradictory literature reports on toxicity and high costs of production, it is important to explore alternative safe and inexpensive porous carriers. In this study, the potential of activated carbon (AC) as an amorphous drug carrier was investigated using paracetamol (PA) and ibuprofen (IBU) as model drugs. The solution impregnation method was used for drug loading, with loading efficiency determined by UV spectroscopy and drug release kinetics studied using USP II dissolution apparatus. The physical state of the drug in the complex was characterised using differential scanning calorimetry and X-ray diffractions techniques, whilst sites of drug adsorption were studied using Fourier transform infrared spectroscopy and N_2 adsorption techniques. In addition, the cytotoxicity of AC on human colon carcinoma (Caco-2) cells was assessed using the MTT assay. Results presented here reveal that, for PA/AC and IBU/AC complexes, the saturation solubility of the drug in the loading solvent appears to have an effect on the drug loading efficiency and the physical state of the drug loaded, whilst drug release kinetics were affected by the wettability of the activated carbon particles. Furthermore, activated carbon microparticles exhibited very low cytotoxicity on Caco-2 cells at the concentrations tested (10–800 μg/mL). This study, therefore, supports the potential of activated carbon as a carrier for amorphous drug delivery.

1. Introduction

The effectiveness of an oral dosage form depends on the bioavailability of the drug, which in turn depends on its solubility and dissolution rate. However, more than 90% of active pharmaceutical ingredients have oral bioavailability issues [1] and about 40% have solubility and dissolution limitations [2]. With a limited number of compounds possessing drug like properties, it is important to develop effective techniques to improve the solubility and dissolution behaviour of poorly water-soluble drugs [3].

One of the many solubility enhancing techniques includes conversion of a crystalline drug to an amorphous form; the dissolution rate of amorphous forms of drugs is markedly better than the crystalline form, especially in drugs with high crystal energy [4,5]. The absence of molecular order in amorphous forms of drugs allows greater motion of molecules, resulting in higher solubility, which plays a crucial role in achieving optimum bioavailability. However, amorphous forms have poor stability and often tend to convert back to crystalline forms [6].

Several studies have been performed to develop stabilising strategies for the amorphous form of drugs [7,8], with loading of drugs into porous materials showing great potential [9]; the interactions between the carrier and the adsorbed drug, as well as the small pore size of the carriers, restricts the crystallisation of the drug. Various types of porous materials have been studied as drug carriers for amorphous drug delivery, although there are still many limitations hindering the technique, such as complexity of produc-

Abbreviations: AC, activated carbon; PA, paracetamol; IBU, ibuprofen; PA/AC phy mix, physical mixture of paracetamol and activated carbon; PA/AC complex, paracetamol loaded activated carbon; IBU/AC phy mix, physical mixture of ibuprofen and activated carbon; IBU/AC complex, ibuprofen loaded activated carbon.

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tion, low drug loading efficiency, high production costs and safety concerns, as highlighted in Table 1. Hence, it is important to explore porous materials that can address the aforementioned issues.

This current study investigates the application of activated carbon (AC) as a drug carrier for amorphous drug delivery. AC is inexpensive, commercially available, non-toxic and has a high surface area to volume ratio, which can favour development of an effective, inexpensive and safe carrier for oral drug delivery. AC is produced from a variety of materials rich in carbon (e.g. coal, wood, peat etc.), by either steam activation or chemical activation. Activation develops porosity in the carbon and the pore size is affected by the process of activation [28]. AC consists of a three-dimensional interconnected pore structure, with micropores (pore width <2 nm), mesopores (pore width 2–50 nm) and macropores (pore width >50 nm) [29].

AC is extensively used in drinking water treatment and is also clinically used as an antidote to remove poisonings [30–32], whilst several studies have explored its use for various clinical applications, as noted in Table 2.

In this study, the solution adsorption method was used for drug loading into AC, using paracetamol (PA) and ibuprofen (IBU) as model drugs with different saturation solubilities in ethanol, in order to determine the effect of solubility on drug loading.

2. Experimental section

2.1. Materials

Activated carbon DARCO® G-60 was purchased from Sigma Aldrich, UK. Crystalline paracetamol powder was obtained from GlaxoSmithKline, UK. Crystalline ibuprofen powder was purchased from SLS, UK. Ethanol, dimethyl sulfoxide, sodium dodecyl sulphate, sodium dihydrogen phosphate and disodium hydrogen phosphate were purchased from Fisher, UK. Caco-2 cells were purchased from ATCC. Dulbecco's Modified Eagle's Medium, foetal bovine serum, trypsin-EDTA solution, antimycotic solution, Hank's balanced salt solution, MTT dye, phosphate buffered saline and trypan blue were purchased from Sigma Aldrich, UK.

Table 2
Potential clinical applications of activated carbon.

Potential applications	Result	Reference
Chemotherapy	Drugs adsorbed on to AC nano particles were selectively delivered to regional lymph nodes and retained at the site of injection for a longer duration in rats and cancer patients	[33]
Antacid	Calcium carbonate or sodium carbonate adsorbed on the activated carbon was able to maintain ideal pH and neutralize gastric acidity without any rebound effect *in vitro*	[34,35]
Photo thermal cancer therapy	When exposed to laser radiation, PVP dispersed AC nano particles were able to convert light into heat energy and resulted in tumour growth suppression at the site of injection in mice	[36]
Lymph node staining	AC of particle size <200 nm injected was readily absorbed into regional lymphatics and blackened lymph nodes	[37]
Controlled release	AC containing temperature responsive hydrogel was used to increase the drug loading capacity and mechanical strength of the hydrogel for controlled release	[38]

2.2. Characterisation of activated carbon

2.2.1. Particle size distribution

Particle size analysis of activated carbon was performed using laser diffraction (HELOS, Sympatec GmbH, Germany). 25 mg of carrier was dispersed in 200 mL of ethanol and was analysed for particle size in the measuring range of 0.1–500 μm.

2.2.2. Cell culture and cytotoxicity assay

Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM, with 4500 mg/L glucose, L-glutamine, sodium pyruvate, sodium bicarbonate, amino acids and vitamins) with 10% FBS in culture flasks and incubated at 37 °C in an atmosphere of 5% CO_2, and the medium was changed every 2 days. Cells were subcultured when they reached about 60% confluency. Studies were performed on cells between passages 100 and 120.

Table 1
Porous materials studied as carriers for amorphous drug delivery.

Porous material	Surface area	Synthesis	Advantages	Limitations	Reference
Porous silicon	Up to 1000 m^2/g	Electrochemical etching	Biodegradable Ease of synthesis Ease of fabrication	Undergoes atmospheric oxidation Requires surface modification for stability Possible chemical interactions with drugs	[10–13]
Non ordered porous silica	Up to 800 m^2/g	Sol-gel process	Ease of synthesis	Surface silanol groups can chemically interact with carboxyl groups of drugs via hydrogen bonding or esterification and can pose risk of irreversible drug adsorption or slower drug release, which can be disadvantageous if immediate release is preferred Siloxane bridges might undergo hydrolysis	[12,14–19]
Ordered mesoporous silica (OMS)	Up to 1200 m^2/g	Surfactant templating	Uniform porosity Large surface area	Complicated and expensive synthesis Variable toxicity results Chemical interactions between surface silanol groups and drugs, as with non ordered porous silica Siloxane bridges might undergo hydrolysis	[12,20–23]
Ordered mesoporous carbon	Up to 1400 m^2/g	Hard templating method	Uniform porosity Large surface area Chemically inert Insoluble in biological fluids	Synthesis involves use of OMS as template Poor wettability	[24–27]