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Modifying Drug Release for Intramuscular and Oral Delivery Using Drug-eluting Embolisation Beads

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In recent years, polymer-based embolisation beads have been used to deliver drugs for the treatment of cancer directly to the site of action. Known to be biocompatible implants, these beads have become an ideal drug delivery vehicle for parenteral administration yet have not been considered for the more commonly used drug delivery routes such as oral and intramuscular drug delivery. This work describes the application of a type of polymer beads, formerly used for embolisation, as a formulation option for oral and intramuscular delivery of a model drug, namely imipramine. Following successful incorporation within the beads, dissolution analysis confirmed the potential to provide a modified drug release profile. Thermogravimetric analysis (TGA) permitted determination of the total water content within the beads (96.8%) and differential scanning calorimetry (DSC) indicated that not all of the water within the beads was able to freeze, apportioned as 15.8% non-freezing, 25.1% loosely bound and the remaining 55.9% unbound. In the presence of drug, the size of the beads decreased with a reduced water content (95.4%) comprised of 16.7% non-freezing, 20.5% freezing bound and the remaining 58.2% % unbound.In conclusion,

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the results presented in this study confirm the ability of TGA and DSC to separate the differing types of water within the beads and furthermore, the potential of such beads for a far wider variety of formulation options than those previously adopted.

Keywords: Beads; drug-eluting; DSC; intramuscular; modified; polymer.

1. INTRODUCTION

Although oral delivery of drugs is by far the simplest, cheapest and most desirable route of administration, it is sometimes not possible to formulate in a manner that would ensure a suitable level of bioavailability can be attained. In such cases it is sometimes necessary to create a modified-release formulation that exhibits a drug release profile that facilitates a suitable rate and extent of drug release for patient optimisation. Several strategies to modify drug release have been developed over the years includinggelatin/ non-gelatincapsules [1], mesoporous silica materials [2,3], liposomes/ niosomes [4], inclusion complexes (such as cyclodextrins [5], polymers [6] and many others such as nanocarriers [7,8]. Such formulations have successfully created a wide variety of drug release profiles with a range of positive impacts such as reducing dosing intervals or side effects, in some cases increasing bioavailability and generally increasing patient compliance. However, even with the strategies previously considered, some drugs continue to present a formulation issue and still require the development of a suitable modified release formulation to enhance their drug release profiles [9]. One such drug is imipramine hydrochloride, a tricyclic antidepressant, with a wide bioavailability range from 22 to 77% [10] (Oliver et al., 2022), time to peak drug level of three hours [11] and known age-dependent rate of clearance [12]. The drug is used in the treatment of depression and anxiety, administered either through intramuscular or oral delivery, the former usually for short term dosing and the latter for the longer term. With variable bioavailability both options exhibit far from ideal drug release profiles and ideally an alternative formulation option could be developed that delivers a constant and stable plasma concentration to avoid highly variable pharmacokinetic characteristics [13] also, one which is more suited to the rapidly increasing elderly population [14]. One group of potential formulation enhancers that have not previously been considered for such a purpose are the well-characterised, drug-eluting embolisation beads, currently used in the treatment of liver cancer whereby a drug/device combination is created based on a microspherical polymer bead, such as DC Bead LUMI™ [15,16] or DC Bead *M1*™ [17]. Drugs including doxorubicin are bound to the structure of the bead prior to administration with intended release at the site of action [18]. Previous work from our group has utilised isothermal titration calorimetry to measurethe binding interaction of suchdrug based systems and determined the drug to binding sites on the bead ratio where the intended application is transarterial chemoembolisation [19,20]. However, these drug-eluting beads (DEBs) have only been considered for this specific purpose yet could hold great promise as a simple yet effective method of modified drug release for use in intramuscular and oral delivery for a wide range of drugs, in this case, for imipramine hydrochloride as a model compound.

2. MATERIALS AND METHODS

2.1 Materials

Polymer beads (70-150 µm (DC Bead*M1*™) were kindly donated by Biocompatibles UK Ltd., a BTG International group company (Camberley, UK).Imipramine hydrochloride (>99%)was purchased from Tokyo Chemical Industry Ltd. (Oxford, UK). Potassium phosphate dibasic and potassium phosphate monobasic (both ≥ 99%) were purchased from Sigma Aldrich (Dorset, UK) and used as received. De-ionised water was used throughout the experiments.

2.2 Methods

2.2.1 Imipramine loading into beads

1 mL of DC Bead*M1*™ was transferred into a vial using a measuring cylinder and the majority of the packing salt solution removed with a pipette to leave a slurry of beads. Imipramine hydrochloride solution (10 mg/mL) was added with a volume of 1 mL, 2.5 mL, and 5 mL to target 10, 25, and 50 mg loadings, respectively, followed by occasional gentle agitation and left overnight. The residual solution was diluted and the UV absorbance was measured using UV-Vis spectrophotometry at 250 nm and compared with a standard plot to determine the amount of drug

remaining in solution (and hence by subtraction that loaded into the beads).

2.2.2 Optical microscopy, bead sizing and water content estimation

Optical microscopy and measurement of bead sizes were carried out using a BX50 microscope and a 10x dry objective. (Olympus UK Ltd, Essex, England). The eyepiece graticule used to measure the beads was verified using a calibrated graticule placed on the microscope stage (Graticules Ltd, Kent, England). A monolayer of bead sample was placed in a Petri dish on the microscope stage and using the 10x objective and eyepiece graticule, the diameter of 200 individual beads was measured. The bead sizing data was entered into a spreadsheet and the size histograms generated using Prism 6 (GraphPad Software, Inc., La Jolla, CA). Based on the size change of beads and the assumption that size decrease is a consequence of water displaced from beads by the drug, the water content in drug loaded beads was calculated as follows:

$$\text{Water content} = \frac{\text{Volume of water in bland beads} - \text{Volume of water loss after drug loading}}{\text{Volume of drug loaded beads}} \times 100\%$$

In the calculation, Volume of water loss after drug loading = Volume of bland beads – Volume of drug loaded beads.

2.2.3 Dissolution studies

Drug release testing was carried out by using the USP Type II Method. The drug loaded beads were first washed with 5 mL of deionised water, then were added into 200 mL of pH 7.0 PBS at 37 ^{o}C under constant magnetic stirring. At predetermined time points, 5 mL of solution was withdrawn through a 5 □m filter needle, and 5 mL of fresh PBS was added. The solution was measured by UV spectrophotometry at 250 nm to calculate the drug concentration released. Samples were analysed in triplicate to determine mean drug release percentages and associated error limits. Dissolution profiles were compared with those already published for other drugs alongside imipramine, to allow comparisons with other controlled release formulations.

2.2.4 Thermogravimetric analysis(TGA)

A Mettler Toledo (TGA) was used to investigate the total water content of the beads. Samples were filtered to remove excess water, ranging from 4 – 16 mg, were placed on an aluminium holder and heated from 25 to 120°C with a nitrogen carrier gas flow of 80 mL/min and heating rate of 1°C/min. Weight loss as a function of temperature change was recorded with the total loss equated to the water content within the beads (n=3 per heating rate) both with and without the presence of drug.

2.2.5 Differential scanning calorimetry (DSC)

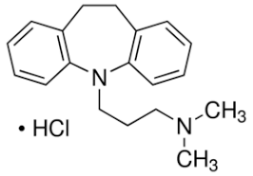
Differential scanning calorimetry (DSC) was performed using a Mettler Toledo DSC 1 equipped with chiller cooling apparatus. Samples (filtered to remove excess water)of water, beads and drug with beads ranging from 4 to 10 mg in sealed aluminium pans were heated at a rate of 1°C/minunder a nitrogen flow of 80 mL/min from -20 to 20°C (n=3 per heating rate). Using this data it was possible to quantify the amount of water within the beads that was able to undergo the freezing process, i.e. was not tightly bound to the polymer structure. This was based on the assumption that 'bound' water would not contribute to the peak observed within the DSC profile thus subtracting the water associated with the peak observed with DSC from the total water content observed from TGA allowed calculation of the amount of 'unbound' water within the beads.

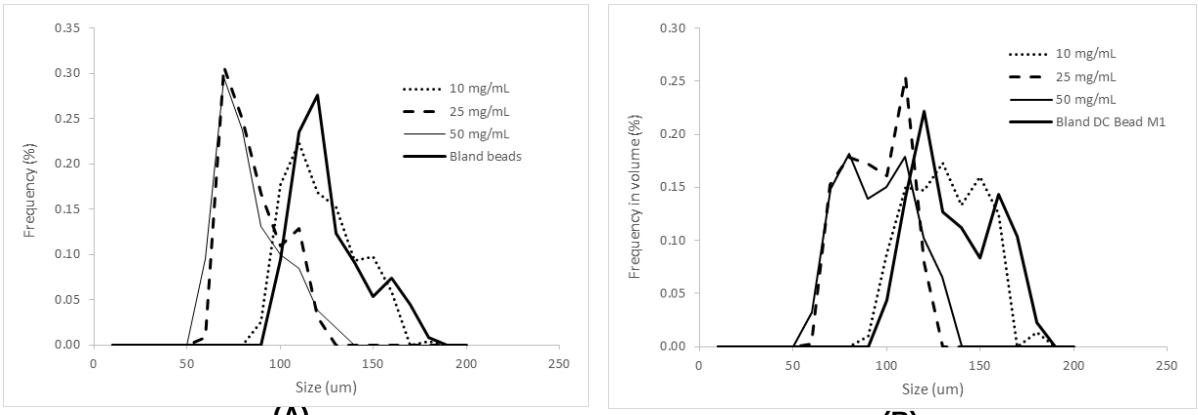
3. RESULTS AND DISCUSSION

3.1 Drug Loading Evaluations

Beads containing the model drug were formulated and then analysed as described in the Methods section. Drug loading studies permitted calculation of the amount of imipramine hydrochloride loaded per mL of hydrated beads from the three different drug concentration solutions (Table 1). For the 10 mgmL^{-1}, 25 mgmL^{-1} and 50 mgmL^{-1}drug concentrations, beads were found to load95.2%, 92.5% and 61.5% of the drug respectively. Drug interaction is presumed to be *via*an ion exchange process as for other reported hydrochloride salts [21] through the tertiary amine group pendent to the ring structure. At lower concentrations (10 & 25 mg), loading efficiency was relatively high (>90%) as the number of cationically-charged binding groups on the drug was less than the number of anionic sulfonate groups in the bead structure. For the 50 mgmL^{-1}loading, the number of drug binding groups is in excess and loading is saturated at 62% loading, where all binding sites are occupied by drug molecules. This equates to around 30 mgmL^{-1}maximum loading potential for imipramine hydrochloride.

Table 1. Drug structure and loading amount and efficiency in 1 mL of DC Bead *M1* (n=3)

	Target loading ($mgmL^{-1}$)	Loading ($mgmL^{-1}$)	Loading yield (%)
	10	9.52 ± 0.01	95.19 ± 0.09
	25	23.13 ± 0.27	92.54 ± 1.09
	50	30.76 ± 2.65	61.53 ± 5.29



(A) **(B)**

Fig. 1. Size (A) and volume (B) distribution of bland DC Bead *M1*, 10 $mgmL^{-1}$, 25 $mgmL^{-1}$, and $mgmL^{-1}$drug loaded beads

Table 2. Data for bead sizes and estimated water fraction in beads

	Bland	10 $mgmL^{-1}$	25 $mgmL^{-1}$	50 $mgmL^{-1}$
Bead size range (μm)	91.1-175.5	84.4-178.9	57.4-118.2	52.3-124.9
Average diameter of beads ± SD (μm)	121.4 ± 19.4	117.4 ± 18.9	80.9 ± 14.9	78.5 ± 16.8
Estimated water content in beads (v/v)	96.30% *	95.90%	87.48%	86.30%

** Data based on a weight measurement previously published [24]*

Optical microscopy analysis of the beads indicated that their average size decreased when drug loading was greater than 10 $mgmL^{-1}$ (Figs. 1 and 2), with the greatest change seen from 121 ± 19 μm to 79 ± 17 μmfollowing loading with the highest concentration of drug (see Table 1). This is consistent with what has been observed previously with other cationically-charged drugs, where bulky drugs with hydrophobic components enter the hydrogel matrix and bind to the anionic sulfonate moieties, resulting in water being displaced from the interstitial spaces between polymer chains, decreasing the water content and causing the beads to shrink in diameter [22,23].

Fig. 2 shows optical micrographs of DC Bead *M1* before and after drug loading at different concentrations. The drug loaded beads remaina spherical shape with no signs of deformation or fragmentation. The blue colour is due to the presence of the Reactive Blue 4 tint on the bead structure and the beads loaded with >25 $mgmL^{-1}$drug appear more intense in colour as the bead shrinkage intensifies the appearance of the dye.

3.2 Dissolution Studies

Three imipramine-based formulations (all containing an equivalent drug content based on drug loading calculations), were analysed to determine the rate and extent of dissolution over a period of 360 minutes, as shown in Fig. 3.

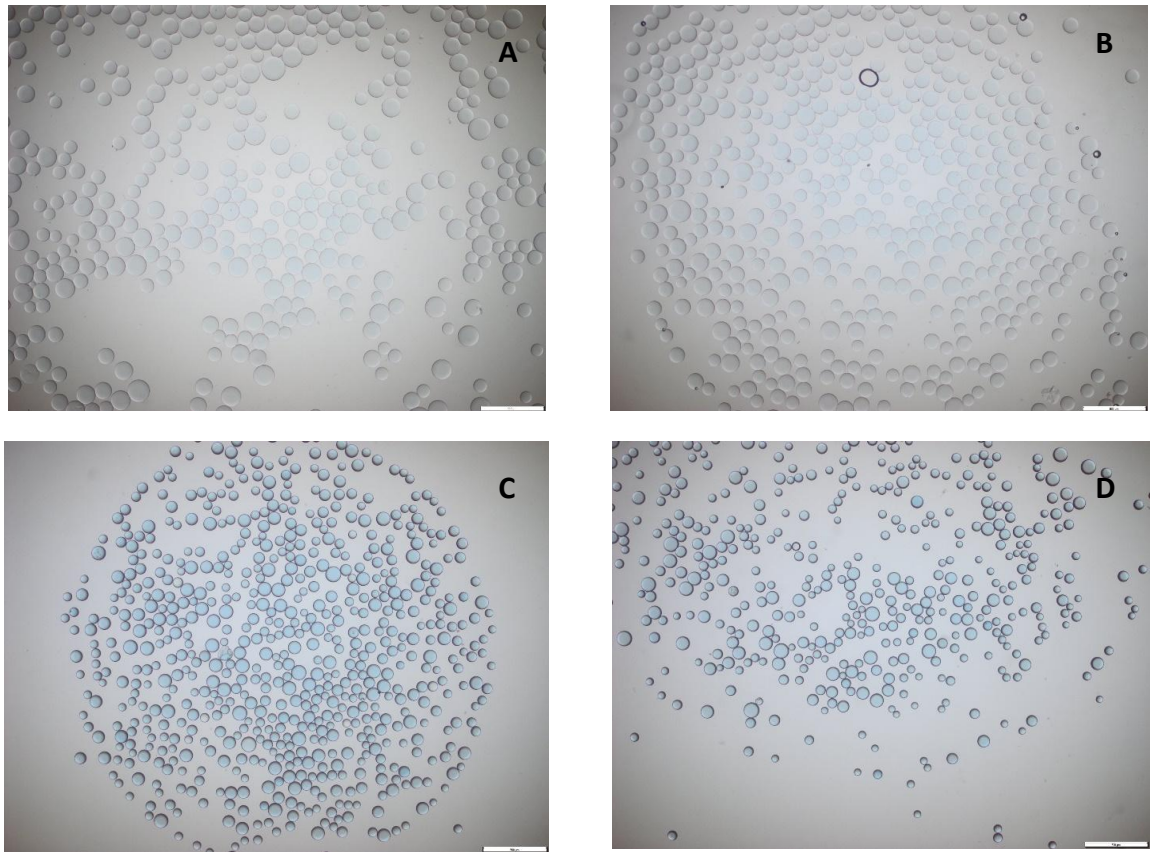
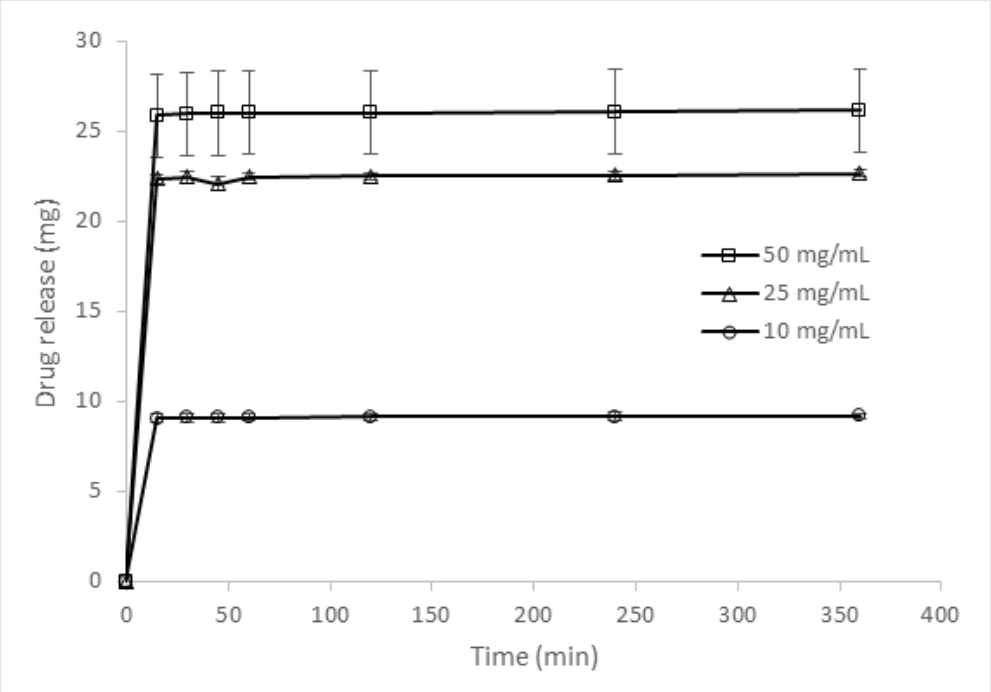
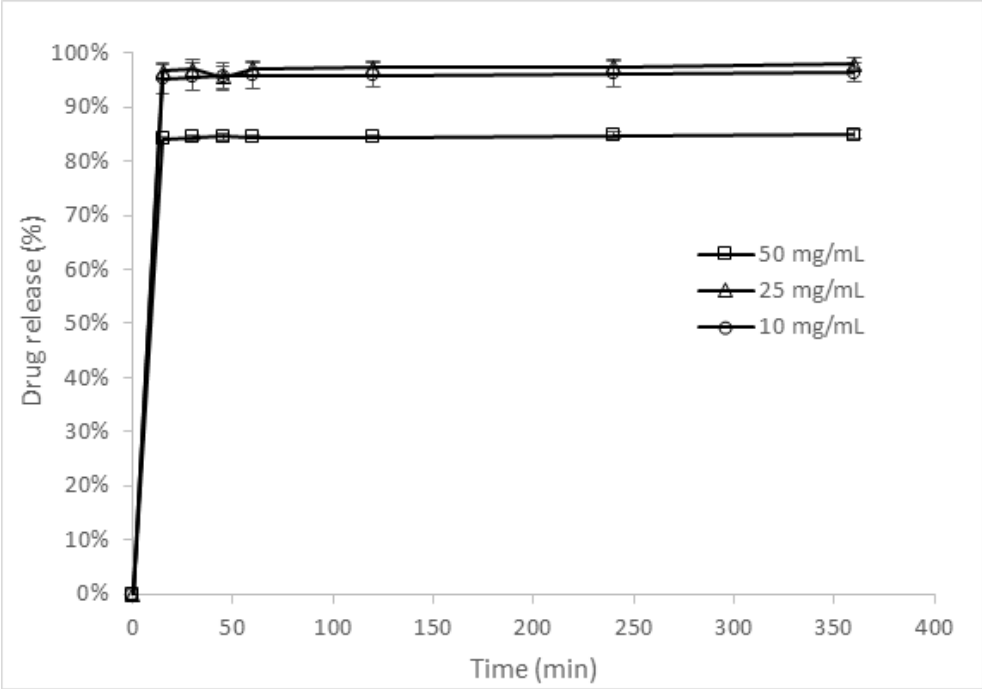


Fig. 2. Microscope images of DC Bead *M1*after loading overnight. A) Bland beads. B) 10 mgmL^{-1}loading. C) 25 mgmL^{-1}loading. D) 50 mgmL^{-1}loading. The scale bar is 500 µm



(A)



(B)

Fig. 3. Release profiles (amount (A) andpercentage release (B)) for beads loaded with 10, 25 and 50 mgmL^{-1}imipramine. Each data point represents the mean of triplicate results (n = 3, ±SD)

Firstly, drug alone was analysed in this studyand it was seen to rapidly undergo dissolution to reach almost 100% of drug in solution within five minutes (data not shown), this rapid process is partially responsible for the undesirable frequent dosing intervals required for patients with this drug. For the three bead-based formulations analysed it can be clearly seen that the presence of the beads modified the release profiles. Three theoretical drug loadings were considered from 10 to 50 mg/mL with confirmed loading values of65-99%, meaning actual loadings of 10, 23 and 31 mgmL^{-1}. Although release is relatively rapid for all formulations, this is not an unusual observation given a USP Type II method was employed that is very efficient at eluting the drug rapidly from the beads. At lower loadings, almost all drug is released within 15 minutes in this test. For the 50mgmL^{-1} formulation, around 85% of drug is released and with a much slower phase for the remaining 15%. It may be this drug is more tightly bound in the bead structure when loaded at high concentration, suggesting potential drug-drug hydrophobic interactions could be at play [25,26] which would account for a much slower second phase of release.

3.3 Thermogravimetric Analysis(TGA)

TGA was undertaken for three samples of beads with a mass loss of 97.2, 95.6and 97.5% indicating the beads to contain an average of3.2% solid content and 96.8% water. Previous research has indicated a percentage of water content of 96.3% using centrifuged mass loss analysis [24]. This is the first published result using TGA to analyse these type of beads and it is reassuring to see that the values from this work and that published previously are very similar, thus confirming the suitability of TGA as a technique to determine total water content within such beads. Following drug loading, three samples of beads were analysed with a mass loss of 94.6, 95.6 and 96.1% indicating the beads contained an average of 95.4% water, i.e. a 1.4% reduction in water content. This finding correlates well with the results observed regarding bead size in that water content decreased as the beads reduced in size.An example of TGA data obtained for the beads in the absence and presence of drug is shown in Fig. 4.

3.4 Differential Scanning Calorimetry (DSC)

DSC analysis was completed for the bead samples, both with and without drug present, along with water to quantify the extent of the water within the beads that could undergo the freezing process. Examples of the data obtained for water alone and a sample of beads are presented in Fig. 5.

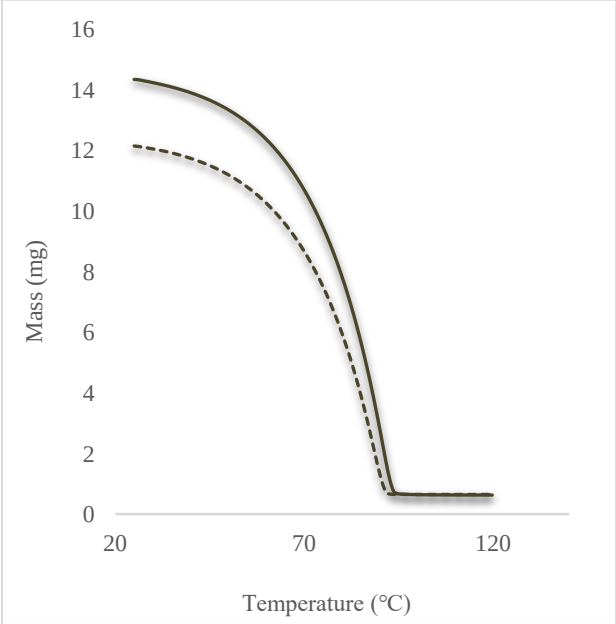


Fig. 4. A TGAsample profilefor beads alone (solid line) and imipramine withbeads (dashed line) indicating the associated mass loss from water

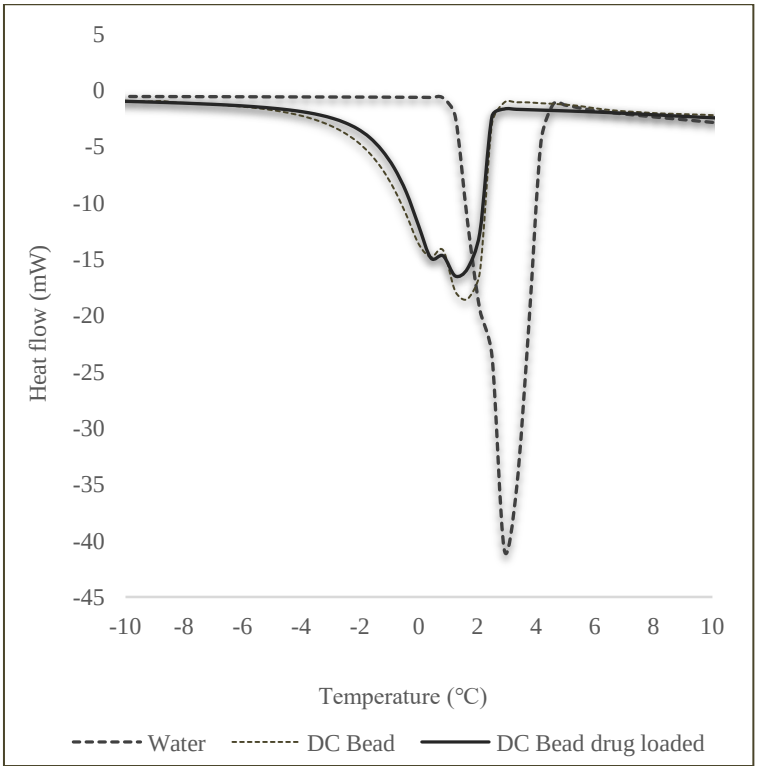


Fig. 5. DSC profiles for water, DC Bead *M1*and DC Bead *M1*drug loaded

Analysis of the data acquired resulted in an average total area for water of 376.8 ±9.2 Jg^{-1} per mg, 317.3±0.6.2Jg^{-1} per mg for beads without drug (assuming an average water content of 96.8%) and 314.1 ±9.3 Jg^{-1} per mg for the beads with drug (assuming an average water content of 95.4%). As the error associated with the two bead profiles is greater than the difference between the values it can be concluded that there was no significant difference in the data, thus implying a similar percentage of water within the beads was available to undergo the freezing process. However, these values are lower than that recorded for water alone, thus a proportion of the water within the beads was so tightly bound that it was unable to freeze (known as non-freezing), as seen in other similar systems [27,28,29]. Through subtracting the normalised integral for the beads from that of pure water it was possible to calculate the percentage of non-freezing water present within the beads, with a value for beads alone of 15.8% (± 3.2%) and beads with drug of 16.7% (±2.9%).These findings indicate that the presence of drug did not affect the non-freezing water content of the beads with both values being similar within experimental error. Interestingly, the peaks observed for the beads alone, and with drug, were not symmetrical, implying that DSC was able to differentiate between the two remaining types of water within the beads, i.e. that which is loosely bound (known as freezing bound) and the remainder which is unbound (known as free water). Through deconvolution of the peaks and subsequent integration of the areas it was possible to determine the percentages of the two within the bead. For beads without drug present the 81.0% water content that was not non-freezing can be further subdivided into 25.1% loosely bound with the remaining 55.9% unbound. For beads with drug present the 78.7% water content that was not non-freezing can be further subdivided into 20.5% loosely bound with the remaining 58.2% unbound, indicating that the presence of drug more significantly decreased the freezing bound water within the bead rather than the unbound water. This inference is plausible as the unbound water, by its very nature, would be free to be displaced in preference to the partially bound water present [30].

4. CONCLUSIONS

In summary, previous studies had focussed on the application of such beads purely for embolisation purposes, in conjunction with drug delivery. This work presents the first successful incorporation of a drug within the beads, intended for intramuscular or oral drug delivery. Dissolution analysis confirmed the potential of such a system to provide a modified drug release profile, with TGA, DSC and optical microscopy providing an insight into the binding behaviour of water within the beads and how this is affected by the presence of the drug. In conclusion, the results presented in this study confirm the suitability of such beads for a far wider variety of formulation options than those previously adopted and could dramatically expand the usage of such a system for pharmaceutical applications.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Gullapalli RP, Mazzitelli CL. Gelatin and non-gelatin capsule dosage forms. Journal of Pharmaceutical Sciences. 2017; 106:1453-1465.
2. Maleki A, Kettiger H, Schoubben A, Rosenholm JM, Ambrogi V, Hamidi M. Mesoporous silica materials: From physico-chemical properties to enhanced dissolution of poorly water-soluble drugs. J Control Release. 2017;262:329-47.
DOI: 10.1016/j.jconrel.2017.07.047, PMID 28778479.
3. Waters LJ, Hanrahan JP, Tobin JM, Finch CV, Parkes GMB, Ahmad SA, et al. Enhancing the dissolution of phenylbutazone using Syloid® based mesoporous silicas for oral equine applications. J Pharm Anal. 2018;8(3): 181-6.
DOI: 10.1016/j.jpha.2018.01.004, PMID 29922487.
4. Manna S, Wu Y, Wang Y, Koo B, Chen L, Petrochenko P, et al. Probing the mechanism of bupivacaine drug release from multivesicular liposomes. J Control Release. 2019;294:279-87.
DOI: 10.1016/j.jconrel.2018.12.029, PMID 30576748.
5. Budai-Szűcs M, Kiss EL, Szilágyi BÁ, Szilágyi A, Gyarmati B, Berkó S, et al. Mucoadhesive cyclodextrin-modified thiolated poly (aspartic acid) as a potential ophthalmic drug delivery system. Polymers. 2018;10(2).

DOI: 10.3390/polym10020199, PMID 30966235.

6. Wersig T, Krombholz R, Janich C, Meister A, Kressler J, Mäder K. Indomethacin functionalised poly (*Glycerol adipate*) nanospheres as promising candidates for modified drug release. Eur J Pharm Sci. 2018;123:350-61.
DOI: 10.1016/j.ejps.2018.07.053, PMID 30063978.
7. Dey M, Das M, Chowhan A, Giri TK. Breaking the barricade of oral chemotherapy through polysaccharide nanocarrier. Int J Biol Macromol. 2019;130:34-49.
DOI: 10.1016/j.ijbiomac.2019.02.094, PMID 30779985.
8. Cai S, Li J, Sun P, Tao J, Fu Y, Yang R et al. Red emissive carbon dots-based polymer beads for recyclable and ultra-sensitive detection of malachite green in fish tissue. Sens Actuators B. 2023;380:133311.
DOI: 10.1016/j.snb.2023.133311
9. Boon-in S, Theerasilp M, Crespy D. Temperature-responsive double-network cooling hydrogels. ACS Appl Polym Mater. 2023;5(4):2562-74.
DOI: 10.1021/acsapm.2c02189
10. Ramey K, Ma JD, Best BM, Atayee RS, Morello CM. Variability in metabolism of imipramine and desipramine using urinary excretion data. J Anal Toxicol. 2014;38(6):368-74.
DOI: 10.1093/jat/bku034, PMID 24782142.
11. Abernethy DR, Divoll M, Greenblatt DJ, Harmatz JS, Shader RI. Absolute bioavailability of imipramine: influence of food. Psychopharmacology. 1984;84(1):146.
DOI: 10.1007/BF00432048
12. Abernethy DR, Greenblatt DJ, Shader RI. Imipramine and desipramine disposition in the elderly. J Pharmacol Exp Ther. 1985;232(1):183-8. PMID 3965690.
13. Ullmann U, Lehnfeld R, Bliesath H, Birkel M, Gebbing H, Gräve M, et al. Relative bioavailability of imipramine (Tofranil) coated tablets in healthy volunteers. Int J Clin Pharmacol Ther. 2001;39(6):271-6.
DOI: 10.5414/CPP39271,
PMID 11430636.
14. Khan MS, Roberts MS. Challenges and innovations of drug delivery in older age. Adv Drug Deliv Rev. 2018;135:3-38.
DOI: 10.1016/j.addr.2018.09.003, PMID 30217519.
15. Caine M, Zhang X, Hill M, Guo W, Ashrafi K, Bascal Z, et al. Comparison of microsphere penetration with LC Bead LUMI™ versus other commercial microspheres. J Mech Behav Biomed Mater. 2018;78:46-55.
DOI: 10.1016/j.jmbbm.2017.10.034, PMID 29132100.
16. Lewis AL, Willis SL, Dreher MR, Tang Y, Ashrafi K, Wood BJ, et al. Bench-to-clinic development of imageable drug-eluting embolization beads: finding the balance. Future Oncol. 2018;14(26):2741-60.
DOI: 10.2217/fon-2018-0196, PMID 29944007.
17. Lewis AL, Dreher MR, O'Byrne V, Grey D, Caine M, Dunn A, et al. Bead DC. M1™: Towards an optimal transcatheter hepatic tumour therapy. J Mater Sci Mater Med. 2016;27:1.
18. Xie H, Zong Y, Chen Y, Hu D, Xu Z, Zhao L. Numerical investigation on preparation of expanded polymer beads using supercritical CO2 in a spouted bed. Chem Eng Sci. 2023;267:118331.
DOI: 10.1016/j.ces.2022.118331
19. Swaine TS, Garcia P, Tang Y, Lewis AL, Parkes G, Waters LJ. Characterizing drug-polymer bead interactions using isothermal titration calorimetry. J Pharm Sci. 2019;108(5):1772-8.
DOI: 10.1016/j.xphs.2018.12.009, PMID 30578801.
20. Waters LJ, Swaine TS, Lewis AL. A calorimetric investigation of doxorubicin-polymer bead interactions. Int J Pharm. 2015;493(1-2):129-33.
DOI: 10.1016/j.ijpharm.2015.07.039, PMID 26209073.
21. Lewis AL. DC Bead™: A major development in the toolbox for the interventional oncologist. Expert Rev Med Devices. 2009;6(4):389-400.
DOI: 10.1586/erd.09.20, PMID 19572794.
22. Lewis AL, Gonzalez MV, Lloyd AW, Hall B, Tang Y, Willis SL, et al. DC Bead: *In vitro* characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol. 2006;17(2 Pt 1):335-42.
DOI:
10.1097/01.RVI.0000195323.46152.B3,
PMID 16517780.
23. Taylor RR, Tang Y, Gonzalez MV, Stratford PW, Lewis AL. Irinotecan drug eluting beads for use in chemoembolization: *In vitro* and *In vivo*

evaluation of drug release properties. Eur J Pharm Sci. 2007;30(1):7-14.
DOI: 10.1016/j.ejps.2006.09.002, PMID 17030118.

24. Ashrafi K, Tang Y, Britton H, Domenge O, Blino D, Bushby AJ, et al. Characterization of a novel intrinsically radiopaque Drug-eluting Bead for image-guided therapy: DC Bead LUMI™. J Control Release. 2017;250:36-47.
DOI: 10.1016/j.jconrel.2017.02.001, PMID 28188808.

25. Gonzalez MV, Tang Y, Phillips GJ, Lloyd AW, Hall B, Stratford PW, et al. Doxorubicin eluting beads - 2: Methods for evaluating drug elution and in-vitro:in-vivo correlation. J Mater Sci Mater Med. 2008;19(2):767-75.
DOI: 10.1007/s10856-006-0040-y, PMID 17653626.

26. Lewis AL, Gonzalez MV, Leppard SW, Brown JE, Stratford PW, Phillips GJ, et al. Doxorubicin eluting beads - 1: Effects of drug loading on bead characteristics and drug distribution. J Mater Sci Mater Med. 2007;18(9):1691-9.
DOI: 10.1007/s10856-007-3068-8, PMID 17483878.

27. Hatakeyama H, Hatakeyama T. Thermal properties of freezing bound water restrained by sodium lignosulfonate-based polyurethane hydrogels. J Therm Anal Calorim. 2019;135(4):2039-48.
DOI: 10.1007/s10973-018-7337-1

28. Mlčoch T, Kučerík J. Hydration and drying of various polysaccharides studied using DSC. J Therm Anal Calorim. 2013; 113(3):1177-85.
DOI: 10.1007/s10973-013-2946-1

29. Talik P, Hubicka U. The DSC approach to study non-freezing water contents of hydrated hydroxypropylcellulose (HPC): A study over effects of viscosity and drug addition. J Therm Anal Calorim. 2018; 132(1):445-51.
DOI: 10.1007/s10973-017-6889-9

30. Smith OEP, Waters LJ, Small W, Mellor S. CMC determination using isothermal titration calorimetry for five industrially significant non-ionic surfactants. Colloids Surf B Biointerfaces. 2022;211:112320.
DOI: 10.1016/j.colsurfb.2022.112320, PMID 35042120.

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