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ScienceDirect
International Journal of Pharmaceutics 349 (2008) 30–37
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Imprinted polymers as drug delivery vehicles for metal-based anti-inflammatory drug

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Received 13 May 2007; received in revised form 11 July 2007; accepted 15 July 2007
Available online 20 July 2007

Abstract

A drug delivery system based on metal-chelate imprinting is described for the first time for a metal-based drug, copper salicylate. Metal-chelate embedded polymer (MCEP) material was prepared by adding 2 equiv. of 4-vinyl pyridine, 8 equiv. of 2-hydroxyethyl methacrylate, 32 equiv. of ethyleneglycoldimethacrylate to 1 equiv. of copper salicylate in 10 ml of 2-methoxyethanol and then polymerizing thermally in the presence of 2,2′-azobisisobutyronitrile as initiator. The removal of the embedded copper salicylate from MCEP to prepare metal-chelate imprinted polymer (MCIP) was assessed by X-ray photoelectron spectroscopy (XPS), flame atomic absorption spectroscopy (FAAS) and high performance liquid chromatography (HPLC) techniques. Conventional or non-imprinted polymer material was prepared in a similar manner to MCEP, but without the addition of copper salicylate to the synthesis recipe. The drug release behaviour was examined in vitro with polymer materials having different template to monomer ratio, different crosslinker density and with polymer material loaded with copper salicylate to different extent. Detailed drug release studies with the drug loaded to MCIP and NIP materials unequivocally establish the higher and sustained release of the therapeutic agent over several days in addition to higher drug loading capacity with the former material.

Keywords: Controlled release; Copper salicylate; Drug delivery system; Metal-based drug; Molecular imprinting

1. Introduction

Metal-based drugs are well known since ancient times and various preparations are described in ayurvedic texts of India, the oldest being Charaka's text. These ayurvedic metal-based drugs exported from India, in particular, have acquired dubious proportion in recent times in view of the improper Sodhan (detoxification), Maran (grinding) and Jaran (heating) steps adopted by a few manufacturers with eye on commercialization. Inspite of this, metal-based drugs have received much attention in chemotherapy, photodynamic therapy, chelation therapy and as sensitizers in radiation therapy. These metal-based drugs exhibit powerful anti-cancer, anti-tumour, anti-diabetic, anti-inflammatory, anti-bacterial, anti-viral and anti-parasitic properties (Gielen and Tiekink, 2005). It is pertinent to mention here that the metal-based drugs often have specific requirements for effective delivery systems due to higher chemical reactivities than most organic drugs and possibility of toxicity when they exceed the therapeutic index. Special care needs to be taken in developing appropriate drug delivery systems since many of these therapeutic agents can undergo substitution and/or redox processes in formulations or before they reach their target.

Drug delivery systems (DDS) must be capable of providing either delayed or extended drug release in order to maximize the efficacy and safety of medicines. Efficient DDS should provide a desired rate of delivery of the therapeutic dose, at the most appropriate place in the body, in order to prolong the duration of pharmacological action and reduce the adverse effects, minimize the dosing frequency and enhance patient compliance. Above all, it should be biocompatible and biodegradable such that the delivery system is transformed into non-toxic fragments that are eliminated harmlessly from the body. Eventhough imprinted polymer materials are increasingly used as molecularly selective components in applications such as combinatorial screening, pseudo-immunoassays, heterogeneous catalysis, solid phase extraction, sensors, etc., the applicability

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doi:10.1016/j.ijpharm.2007.07.017

of these materials in controlled DDS has been addressed only in mid-1990s (Alwarez-Lorenzo and Concheiro, 2004; Hilt and Byrne, 2004). The release of the drug in a controlled fashion using molecularly imprinted polymer (MIP) based DDS has been studied for timolol, an ophthalmic drug (Hiratani and Lorenzo, 2004) and norfloxacin, an anti-bacterial agent (Alvarez-Lorenzo et al., 2006). Imprinted polymer concept thus emerged as one of the promising one for achieving this goal (Alexander et al., 2006; Alwarez-Lorenzo and Concheiro, 2004) in view of the improved loading and sustained release behaviour compared to non-imprinted polymers for organic drugs. In spite of the usage of MIP based DDS for a few organic drugs, there exist to date, no example where imprinted polymer is used as the delivery vehicle for metal-based drug (Alexander et al., 2006; Prasada Rao et al., 2006).

In contrast, there are only 3 reports in the last 2 years on the delivery of cisplatin (Yan and Gemeinhart, 2005) dichloro(1,2-diaminocyclohexane)platinum(II) (Nishiyama and Kataoka, 2001) and tripodal $[MgL]^{2+}$ chelates (He et al., 2004) using conventional or non-imprinted polymers. Herein, we report the sustained delivery of copper salicylate, a non-steroidal anti-inflammatory drug using metal-chelate imprinted polymer, which has not been attempted so far. The only example for metal-chelate imprinted polymer is in the area of catalysis–cobalt complex has been used to selectively catalyze the reaction of acetophenone and benzaldehyde to produce chalcone (Matsui et al., 1996).

Eventhough the drug market for inflammatory diseases is well over $10 B, the ulcer causing steroidal drugs and the new generation of ulcer free Cox II inhibitors can have serious side effects and the costs of treating these side effects are even greater than the costs of the drugs themselves. Copper salicylate has a better anti-inflammatory effect than the parent organic drug commonly in use, but without the side effects. In addition, it has also good anti-cancer, anti-tremor and anti-convulsive properties, suitable for treatment of epilepsy and possibly Parkinson's disease. In this report, we present the results obtained during the controlled release study of copper salicylate using metal-chelate imprinted polymer, wherein 4-vinyl pyridine (VP) and 2-hydroxyethyl methacrylate (HEMA) (functional monomers) and ethyleneglycoldimethacrylate (EGDMA) (crosslinking monomer) are used as the building blocks for the platform of the DDS.

2. Materials and methods

2.1. Materials

Copper chloride ($CuCl_2 \cdot 2H_2O$), sodium chloride, 4-vinyl pyridine (VP), 2-hydroxyethyl methacrylate (HEMA), ethyleneglycoldimethacrylate (EGDMA) and 2,2′-azobisisobutyronitrile (AIBN) were purchased from Aldrich, Milwaukee, WI, USA.

2.2. Preparation of metal-chelate imprinted polymers

The synthesis of imprinted polymer based DDS involves four steps: (1) isolation of copper salicylate metal-chelate complex, (2) preparation of metal-chelate embedded polymer (MCEP) material by thermal polymerization, (3) leaching of metal-chelate to form the metal-chelate imprinted polymer (MCIP) material and finally (4) loading of MCIP with the therapeutic agent.

Copper salicylate was prepared by adopting the procedure as described elsewhere (Lemoine et al., 2002). Metal-chelate embedded polymer (MCEP) was prepared by first mixing 2 equiv. of VP, 8 equiv. of HEMA, 32 equiv. of EGDMA and 1 equiv. of copper salicylate in 10 ml of 2-methoxyethanol and then polymerizing at 80 °C in inert atmosphere (by purging with N_2) in the presence of 2,2′-azobisisobutyronitrile (AIBN) as initiator. The polymer material obtained was subjected to leaching for 3 times with 50 ml of 1 M HNO_3 each, in order to remove copper salicylate. The resulting metal-chelate imprinted polymer (MCIP) material will have cavities corresponding to copper salicylate. Non-imprinted polymer (NIP) material was prepared in a similar manner as that of MCEP, but in the absence of copper salicylate and subjected to nitric acid treatment analogous to MCIP. These materials were then loaded with copper salicylate drug by treating MCIP and NIP materials under identical loading conditions. Fig. 1(a) shows the schematic illustration of the preparation of copper salicylate (drug) loaded metal-chelate imprinted polymer material and Fig. 1(b) shows the schematic representation of drug delivery.

MCIP and NIP materials were prepared with different template to monomer ratios such as 1:8, 1:4 and 1:2 (M1 and N1, M2 and N2 and M3 and N3, respectively). In addition to M1 and N1 with the crosslinker, EGDMA at 80% of the total molar amount of monomer and crosslinker in the polymer recipe, M4 and N4 and M5 and N5 with the crosslinker proportion at 66.7 and 50%, respectively were also synthesized. These polymer materials were also leached and reloaded with copper salicylate in a similar manner as mentioned above.

2.3. Characterization studies

The formation of copper salicylate was studied by UV–vis spectral studies. The spectra of $CuCl_2$, salicylic acid and copper salicylate were recorded using Shimadzu-UV-2401 PC controlled double beam spectrophotometer (Shimadzu, Japan). This was confirmed by IR spectral studies. FT-IR spectra of salicylic acid and copper salicylate were recorded in the frequency range 4000–400 cm^{-1} by KBr pellet method using Nicolet MAGNA FT-IR-560 spectrometer (Madison, WI, USA).

The removal of copper salicylate from MCEP was confirmed by X-ray photoelectron spectroscopic analysis (XPS). XPS were recorded using VG scientific ESCA—LAB Mark-II. XPS unit (U.K.) by irradiating the samples with a mean binding energy of 1486.6 eV at a vacuum of 10^{-10} mbar.

The release of copper salicylate from the polymer material was monitored through copper content estimation by flame atomic absorption spectrometric analyses using Perkin-Elmer A Analyst 100 (Perkin-Elmer, Shelton, CT, USA).

The release of copper salicylate during the release study was confirmed by HPLC analysis. The polymer particles remaining in the solution after the drug release was filtered off and the solution was equilibrated with ethyl acetate, the organic layer

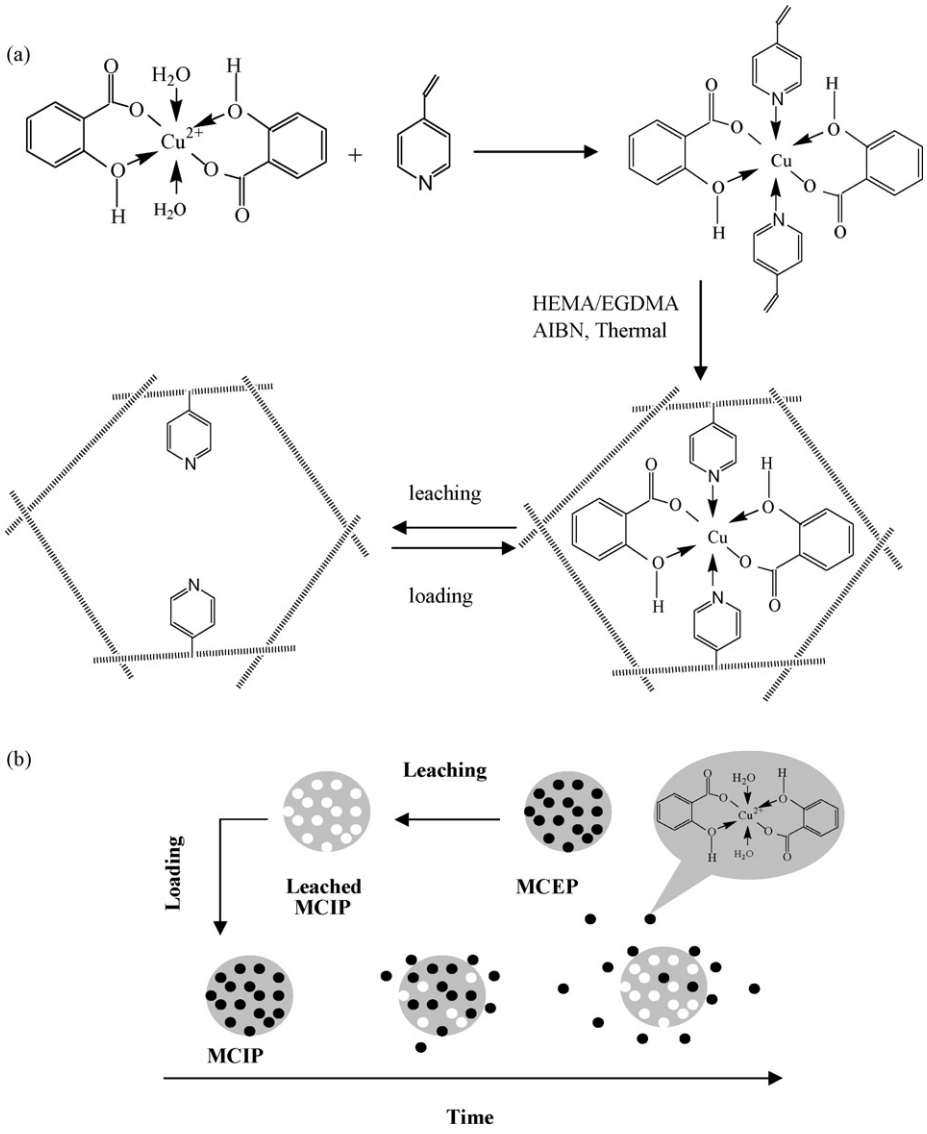

Fig. 1. (a) Schematic representation of the preparation of copper salicylate (drug) loaded metal-chelate imprinted polymer material. (b) Schematic illustration of drug release.

is then evaporated and taken in minimum amount of methanol. LC-8A Shimadzu preparative liquid chromatograph (Shimadzu) with UV–vis detector (SPD-IDA Shimadzu UV–vis detector) was used. Analysis were carried out on R-OD-5-A column (250 mm × 4.6 mm i.d., S-5 μm, 12 nm) (YMC Co. Ltd., Japan). Mobile phase consisted of methanol/water system taken in the ratio 1:1 at a flow rate of 0.5 ml/min.

The rigidity of the polymer material is an important factor as it can decide the drug release behaviour of the material. Swelling ratio, which is a measure of the rigidity of the polymer materials prepared with different crosslinker proportion (M1, M4 and M5 having the crosslinker proportion as 80, 66.67 and 50%, respectively) was measured by volumetric measurement as described elsewhere (Araki and Yoshida, 2000; Kala et al., 2005). 1.0 g sample of the polymer material was taken in a graduated test tube and centrifuged for 30 min at 5000 rpm. The volume of the polymer material was measured as V_1. Excess water was added, vigorously shaken to ensure complete mixing and kept overnight. After the mixture was centrifuged for 30 min at 5000 rpm again, the volume of the swelled polymer material was measured as V_2. The volumetric swelling, S was defined as follows:

$$S = \frac{V_2 - V_1}{V_2} \times 100$$

The influence of pH on the extent of swelling of the polymer materials (M1, M4 and M5) has been checked by conducting the experiment at different pHs, since the physiological pH plays an important role in determining the drug release behaviour of the polymer material. These studies were conducted in PBS buffer solution adjusted to different pHs such as 3, 5, 7 and 9.

2.4. Drug loading

The percentage drug loaded onto the polymer material was determined by stirring definite amount of the polymer material

with 100 μg of copper salicylate present in 50 ml of aqueous phase. The drug loaded on the polymer material was eluted with 10 ml of 1N HNO_3 by stirring for 30 min and determined by FAAS analysis, monitored as copper content. Three identical sets of experiments were conducted.

The percent drug loaded is defined as

$$\%E = \frac{C_D^i - C_D^f}{C_D^i} \times 100$$

where C_D^i and C_D^f are the concentrations of copper salicylate before and after loading.

The experiment was carried out with the polymer materials having different template to monomer ratio. The change in the drug loading by varying the initial concentration of copper salicylate was also checked.

2.5. Drug release

The metal-chelate imprinted and corresponding non-imprinted polymer materials (M1 and N1) were loaded with copper salicylate by immersing 1 g of the material in 50 ml of 40 mM copper salicylate solution for 12 h to get loaded MCIP and NIP materials. These were filtered, washed with 250 ml of water and dried in an oven at 50 °C.

In order to investigate the release behaviour, 0.1 g of the loaded MCIP and NIP materials were suspended in 50 ml of 0.9% NaCl solution without PBS buffer since phosphate ions can disturb the copper salicylate complex. Sample aliquots were withdrawn at regular intervals from the solution and the drug concentration was measured FAAS through copper content profile. The medium was replaced with the same volume of fresh 0.9% NaCl. This experiment was extended to loaded MCIP and NIP materials as well obtained from M2 and N2, M3 and N3, M4 and N4 and M5 and N5 to analyze the influence of the template to monomer ratio and also the crosslinker proportion on the extent of drug release. The release of copper salicylate from the polymer materials, M1 and N1, which had been loaded with different initial concentration of the drug, viz. 20, 40 and 80 mM (M6 and N6, M7 and N7 and M8 and N8, respectively) were also examined. All these studies were conducted in triplicate.

3. Results and discussion

3.1. Characterization studies

The UV–vis spectra obtained for $CuCl_2$, salicylic acid and copper salicylate are shown in Fig. 2. The absorption maximum at 864 nm in the spectrum of $CuCl_2$ solution (see inset of Fig. 2) showed a significant hypsochromic (blue) shift to 761 nm in the case of copper salicylate, while a new absorption peak appeared as a shoulder at 405 nm. Salicylic acid showed no absorption maximum in the region 400–900 nm (see inset of Fig. 2). Also, the addition of increasing molar proportions of salicylic acid to the fixed concentration of $CuCl_2$ results in hyperchromic shift at 761 nm (see Fig. 2). The formation of the copper salicylate complex was again confirmed by the IR analysis, wherein the

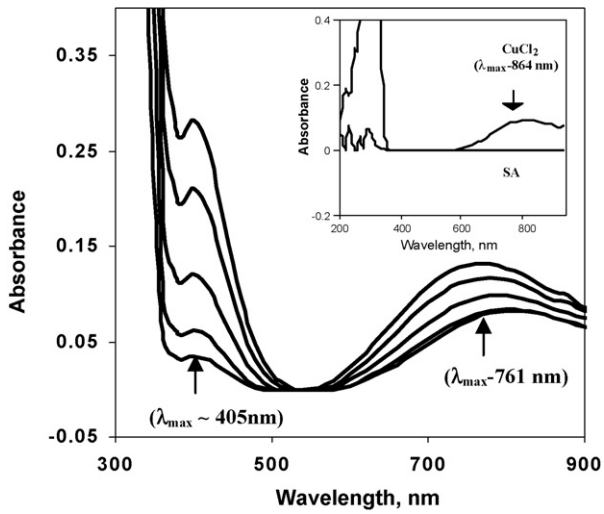

Fig. 2. UV–vis spectra of the solutions with constant concentration of copper chloride and increasing concentration of salicylic acid (spectra of copper chloride and salicylic acid take separately are given in the inset).

carbonyl peak at 1610 cm^{-1} in the spectrum of salicylic acid shifted to 1602 cm^{-1} in the complex.

The XPS analysis conclusively proves the removal of copper salicylate from MCEP during leaching and its uptake during loading. The XPS spectra obtained for copper salicylate, MCEP, MCIP and loaded MCIP are shown in Fig. 3. The peak corresponding to Cu at 932.7 eV in the spectrum of MCEP was absent in the case of the leached particles. This peak reappeared in the spectrum of the loaded MCIP particles. This indicates the removal of copper salicylate from MCEP during leaching and the uptake of copper salicylate while loading the polymer material. The XPS findings were supported by FAAS and energy dispersive spectrometry by looking at the copper content.

Earlier reports have shown that the rigidity or swelling capacity of the polymer can be altered by varying the crosslinker ratio while synthesizing the polymer (Yilmaz et al., 1999). In the case of imprinted polymers, a sufficient rigidity of the polymer is required to preserve the imprinted memory. Also, the swelling capacity of the polymer can determine the amount of drug released, while using the polymer material as a drug carrier. Hence, there should be a compromise in choosing a particular crosslinker proportion so that the imprinted memory is preserved, at the same time retaining a suitable drug release behaviour. As reported by Vinogradov et al. (2005), another factor which determines the swelling capacity of the polymer, is the pH. This plays a decisive role in the events taking place in the physiological system following the administration of the drug imprinted polymer material. Therefore, swelling ratio studies of the imprinted polymer material with different crosslinker proportion (M1, M4 and M5 with the crosslinker proportion as 80, 66.7 and 50%) were conducted in PBS buffer solution at different pHs spanning the range 3–9 at intervals of 2 units. The results obtained are shown in Table 1. The polymer material with 80% crosslinking density was found to have lower swelling ratio than that with 66.7 or 50% crosslinking density.

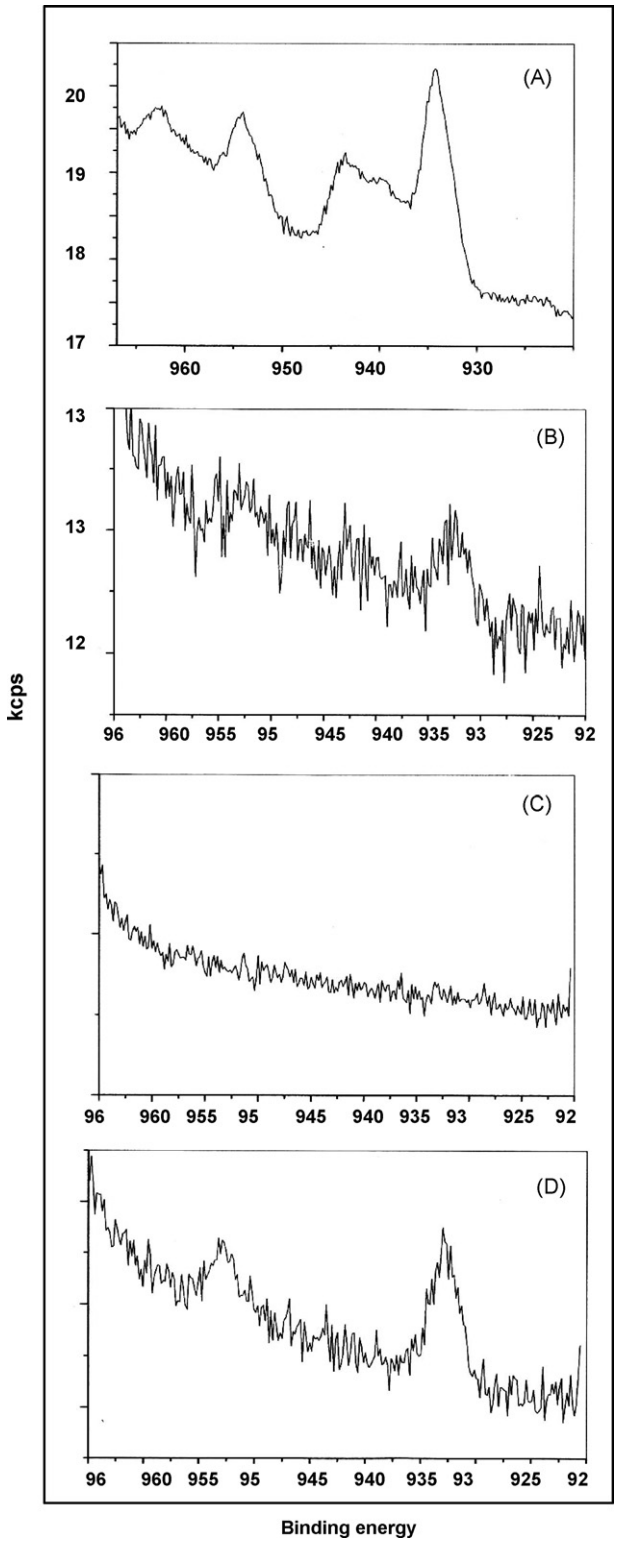

Fig. 3. XPS spectra of copper salicylate (A), MCEP (B), MCIP (C) and loaded MCIP (D) polymer materials.

Also, the swelling degree increased as pH decreased. The polymer material swelled considerably at pH 3 compared to that at pH 9. This observation is analogous to the results obtained by Vinogradov et al. in the case of polyethylenimine based drug carriers for nucleoside analogs (Vinogradov et al., 2005). Again,

Table 1
Swelling ratio of MCIP (M1, M4 and M5) materials with various crosslinking density at different pHs

Crosslinking density (%)	Swelling ratio (%)			
	pH 3	pH 5	pH 7	pH 9
80	30	23.8	22.2	20.6
66.7	61.7	55.5	47.4	44.4
50	83.4	80.5	78.9	75.2

Vinogradov et al. (2005) have shown that the amino groups in the polyethylenimine backbone become protonated in acidic conditions. Similarly, the carbonyl groups present in the backbone of the imprinted polymer prepared in the present work can get protonated at lower pH condition. The presence of charge in the polymer chain causes repulsion which can lead to the swelling of the polymer. The polymer is compacted at pH 9 because no repulsion exists between uncharged polymer chains. As the pH of the intestinal fluid is ~7.0, this pH was selected for subsequent drug loading and release studies.

3.2. Drug loading studies

The drug release from a particular system will definitely depend upon the amount of the drug loaded onto the system. The solubility of copper salicylate was tested in different solvents which showed that water is having a lower solubility of 0.34 g/100 ml compared to 0.66 and 0.69 g/100 ml for methanol and DMF, respectively. Water was chosen as the medium for loading as the solvents with higher solubility can diminish/hamper the extent of loading. The drug loaded onto the MCIP and NIP materials (M1 and N1) synthesized as per the procedures described in Section 2.4 are shown in Table 2. The results indicate that the MCIP is having a notably higher loading capacity than the corresponding NIP material, which is analogous to the results obtained during solid phase extraction using molecularly imprinted polymer (Chapuis et al., 2006) and metal ion imprinted polymers (Prasada Rao et al., 2006) for organic molecules and metal ions, respectively. The excess of loading of the drug in the case of imprinted polymer compared to the non-imprinted polymer is due to the formation of adequate binding cavities in the former one upon synthesis. As reported by Hiratani and Lorenzo (2004), the concentration of the binding sites and the overall affinity for the drug molecule will be higher in the imprinted polymer than the non-imprinted

Table 2
Percent drug loaded using metal-chelate imprinted and non-imprinted polymer materials with different template to monomer ratio such as 1:8, 1:4 and 1:2 (100 μg of copper salicylate, 0.1 g of polymer material, loading time = 30 min, elution time = 30 min, eluent = 10 ml of 1N HNO_3)

Template to monomer ratio	Percent drug loaded	
	NIP	MCIP
1:8	20.9 ± 0.1	24.4 ± 0.1
1:4	25.2 ± 0.1	53.2 ± 0.2
1:2	26.3 ± 0.1	54.5 ± 0.2

one. The results obtained show that the extent of loading can be promoted by the imprinting technique. This facilitates the usage of lesser amount of the loaded MCIP material to administer the required dosage of the drug. As in the case of molecular and ion imprinting, the metal-chelate imprinting employed in this paper also shows a significant imprinting effect.

The loading capacity of the imprinted polymer mainly depends upon the number of binding sites available in the polymer material. The number of binding sites, in turn can be tuned by regulating the ratio between the template and monomer. The change in drug loading capacity of the polymer by altering the template to monomer ratio in the polymer material (M1 and N1, M2 and N2 and M3 and N3 with the ratio as 1:8, 1:4 and 1:2, respectively for imprinted and non-imprinted polymer material) were also examined. The results as shown in Table 2 indicates that the percent drug loaded increases with increasing proportion of template, which can be due to the increase in the number of binding sites. Eventhough the percent drug loaded increased considerably in the case of MCIP material with increase in template proportion, this increase was observed only marginally in the case of NIP material. This observation is due to the increase in the number of binding sites only in the case of MCIP particles, whereas such a possibility does not arise in the NIP particles eventhough these two types of polymers consisted of exactly the same monomer composition. Also, it has to be noted that the MCIP material did not show much increase in percent drug loaded by changing the template to monomer ratio from 1:4 to 1:2.

In order to obtain polymer material with highly loaded drug, the materials were suspended in higher amount of copper salicylate and the extent of loading was checked, the results of which are shown in Table 3. At an initial concentration of 20 mM copper salicylate, the difference in the amount of copper salicylate loaded on to the imprinted and non-imprinted polymer was found to be ~46 μmol/g. On increasing the initial concentration of copper salicylate to 40 mM, the difference increased to 70 μmol/g and remained almost unaltered on further increase to 80 mM. Alvarez-Lorenzo et al. (2006) have noticed that the difference in the amount of norfloxacin loaded by imprinted and non-imprinted hydrogels decreases with increase in initial concentration of the drug and the difference is hardly seen near the maximum loading capacity. In case of the metal-chelate imprinted DDS described in the present report, unlike the non-covalently imprinted hydrogel for norfloxacin, we have not noticed such leveling effect which is presumably due to the absence of low affinity (non-specific) binding sites.

Table 3
Amount of drug loaded on to the NIP and MCIP material with different initial concentrations of copper salicylate (0.1 g of polymer material, loading time = 12 h, elution time = 30 min, eluent = 10 ml of 1N HNO_3)

Conc. of copper salicylate taken for loading (mM)	Polymer material (after loading)	Drug loaded (μmol/g)
20	N6	80.2 ± 0.4
	M6	126.6 ± 0.6
40	N7	150.4 ± 0.7
	M7	220.5 ± 1.0
80	N8	200.8 ± 0.9
	M8	267.1 ± 1.1

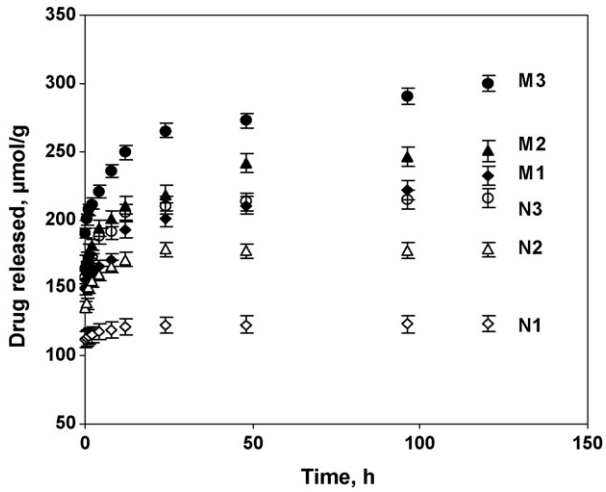

Fig. 4. Release profile of loaded MCIP and NIP materials with different template to monomer ratio (M1 and N1 (1:8), M2 and N2 (1:4) and M3 and N3 (1:2)) (conditions: [Cu-Sal] for loading = 40 mM, loading time = 12 h, weight of polymer taken for release study = 0.1 g).

3.3. In vitro drug release studies

The release profile of copper salicylate with M1 and N1, M2 and N2 and M3 and N3 are shown in Fig. 4. The cumulative release of copper salicylate is almost constant in the case of loaded NIP, while there is a higher and sustained release with loaded MCIP even upto 120 h. The results obtained implies that the drug molecule is preferentially bound in the cavities of the MCIP particles by covalent bonding compared to NIP particles where they are simply sorbed on the surface. This resulted in slower kinetics of release in case of MCIP compared to the corresponding NIP particles. Therefore, the loaded MCIP material makes it possible to yield the therapeutic systemic concentration of the drug over a longer period of time, avoiding the large fluctuations in drug concentration and reducing the need for frequent administration. This observation is on similar lines to the delivery profiles of the organic drugs namely, timolol (Hiratani et al., 2005). As the amount of template is increased during the synthesis of the polymer material, the number of binding sites increases, which results in the higher loading of the drug. As it is clear from the figure, the polymer material with higher loading capacity (M3), showed an enhanced release of the drug, so that lesser amount of the polymer material is sufficient to release the same amount of drug using higher amount of M1 or M2. The amount of the drug released from the polymer particle increases with increasing drug/polymer ratio, indicating the influence of drug loading on to the polymer material. These results are in accordance with those obtained for the organic drug, norfloxacin (Alvarez-Lorenzo et al., 2006). However, as it is evident from Fig. 4, the imprinting effect is more pronounced in the case of the polymer material with a ratio of 1:8 between the template and monomer (M1). The imprinted polymer, M1 showed 1.8

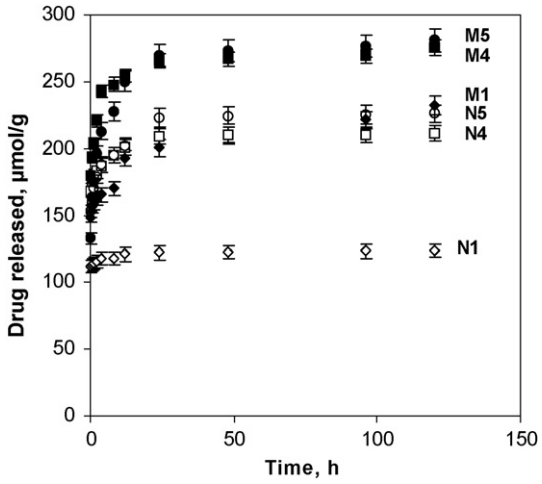

Fig. 5. Release profile of loaded MCIP and NIP materials with varying crosslinker amounts w.r.t. fixed functional monomer (M1 and N1 (80%), M4 and N4 (66.7%) and M5 and N5 (50%)) [conditions: [Cu-Sal] for loading = 40 mM, loading time = 12 h, weight of polymer taken for release study = 0.1 g].

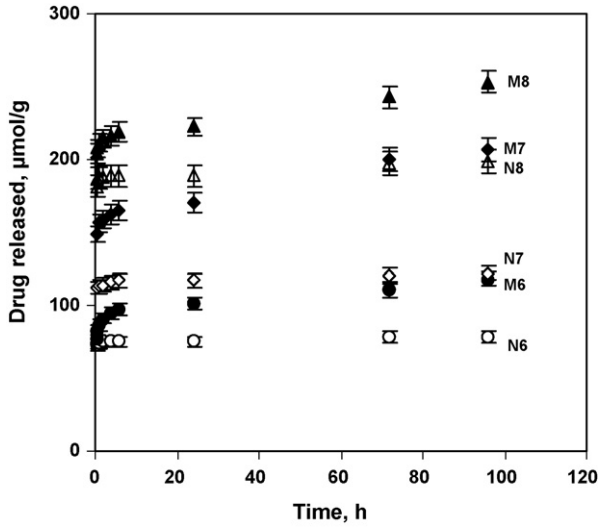

Fig. 6. Release profile of MCIP and NIP materials loaded with 20 mM (▲ [M6] and △ [N6]), 40 mM (● [M7] and ○ [N7]) and 80 mM (■ [M8] and □ [N8]) of copper salicylate [conditions: loading time = 12 h, weight of polymer taken for release study = 0.1 g].

times enhanced drug release after 5 days over the corresponding non-imprinted polymer, N1 compared to an enhancement of 1.2 times for M3 over N3. Hence, a ratio of 1:8 between the template and monomer was preferred for the preparation of imprinted polymer material for drug delivery purpose in further studies.

The release of copper salicylate during the release study was confirmed by HPLC analysis. The NaCl solution remaining after a particular time of drug release from MCIP and NIP materials was extracted into ethyl acetate. The HPLC analysis of the organic solutions gave a characteristic peak with a retention time coinciding with that of standard copper salicylate solution, which confirms the release of copper salicylate from the MCIP/NIP materials in to 0.9% NaCl solution.

Fig. 5 shows the cumulative release of copper salicylate from the polymer materials with different crosslinking density (M1 and N1, M4 and N4 and M5 and N5). The loaded MCIP material, when dispersed in aqueous medium swelled considerably which alters the conformation of the imprinted cavities, decreasing the affinity for the imprinted molecule. This leads to the breaking of the bond between the nitrogen of pyridine ring of the polymeric backbone and copper present in the drug, copper salicylate. A high crosslinker proportion considerably increases the stiffness of the polymer, which leads to the slow release of the drug. As shown in Fig. 5, the polymeric material with a crosslinker density of 80% was found to have slower release of the drug, compared to that with a crosslinker density of 50%, since the former one swelled to a lesser extent compared to the latter one, as explained in the swelling ratio results. Hiratani et al. (2004) have suggested that the release of timolol from imprinted polymer based contact lenses involves the simultaneous adsorption of water and desorption of drug via a swelling-controlled diffusion mechanism. A similar mechanism can be extended in our case also, wherein the swelling leads to the breaking of the bond between the drug and the polymer backbone and ends up with the release of drug. Since the crosslinking proportion influences the swelling of the polymer, it is an important factor in determining the release behaviour of the polymer.

The release profile of copper salicylate with MCIP and NIP materials (M1 and N1, respectively), which have been loaded with different initial concentration of the drug (20 (M6 and N6), 40 (M7 and N7) and 80 mM (M8 and N8)) is shown in Fig. 6. The cumulative release of copper salicylate was found to be increasing correspondingly with higher and higher loading of the drug. This observation is in tune with the findings of Alvarez-Lorenzo et al. in case of norfloxacin. It is interesting to note that the imprinting effect was maintained in all the cases.

4. Conclusions

In summary, a new metal-chelate imprinted polymer based DDS was synthesized by taking copper salicylate (anti-inflammatory drug) as an example, which is extensively used in chelation therapy. Imprinted polymer material allows the release of therapeutic systemic concentration of the drug over a longer period of time, which indicates that the specific binding characteristics of these systems can provide a useful means of sustaining the delivery profile of metal-based drug. This avoids the large fluctuations in drug concentration and eliminates the need for frequent administration. In addition, the imprinted polymer material resulted in enhanced drug loading capacity of the drug delivery vehicle for the higher and sustained release of therapeutic agent over several days compared to conventional or non-imprinted polymer material. The tuning of the release of drug is demonstrated by preparing imprinted polymer materials with varying template to monomer proportion or the crosslinking density. The metal-chelate imprinted materials are easy to prepare and scale up and has great potential in possible design and development of efficient DDS for other metal-based drugs having anti-cancer, anti-tumour, anti-

diabetic, anti-bacterial, anti-viral and anti-parasitic effects in coming years.

Acknowledgements

Authors, Sumi, V.S., Kala, R. and Praveen, R.S. wish to acknowledge CSIR, New Delhi for the award of research fellowships. The financial support received from Department of Science and Technology, New Delhi is also greatly appreciated.

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