Novel polyurethane microcapsules containing variety of bioactive agents

P.G. Shukla
PSE Division, National Chemical Laboratory, Pune 411 008, India
(pg.shukla@ncl.res.in)

Introduction

Microencapsulation by in-situ polycondensation is an important process to encapsulate variety of active agents as the process is industrially viable and can produce microcapsules with high active agent loading (Arshady, 1989 and Shukla, 2006). In the case of polyurethane though polymerization proceeds via polyaddition it is generally categorized as polycondensation. Preparation of polyurethane (PU) microcapsules is known in the literature (Choi et al. 1990). Most of the methods used to prepare PU microcapsules involve preparation of capsules in aqueous medium and thus are useful only to encapsulate water-insoluble active agents. Also the encapsulating wall material formed due to presence of water may contain polyurea moieties along with polyurethane. There are very few reports which describe preparation of capsules in non-aqueous medium (Yabuuchi, N. et al.,1997). We have developed a novel method to prepare PU microspheres with desired particle size, in non-aqueous medium (Shukla and Sivaram, 1998, 1999a). This method is then extended to prepare PU microcapsules in non-aqueous medium (Shukla et al. 1999b 1999c 2002). In the present paper formation and characterization of PU microcapsules containing variety of water soluble and insoluble bioactive agents viz. pesticide, fungicide and drug for agriculture, paints and pharmaceutical applications respectively, have been described and compared.

Materials and methods

PU microcapsules (Table 1) containing monocrotophos (MCR), Ibuprofen-Na (IBS) and Zinc Pyrithione (ZnP) were prepared as per the procedures described earlier. (Shukla et al 1999b 1999c, 2002, 2006, Shinde et al. 2006) Isocyanates used were toluene diisocyanate (TDI) and isophorone diisocyanate (IPDI). Different diols namely ethylene glycol (EG), 1,3 propane diol (PD) and 1,4 butane diol (BD) which are insoluble in paraffin oil and 2-ethyl 1,3 hexane diol (EHG) which is soluble in continuous phase (paraffin oil) were used. Steric stabilizers used were poly (butadiene-b-ethylene oxide), Polylauryl methacrylate-g-polyethylene oxide (PLMA-g-PEO) graft copolymer and Hypermer-2296. All above microcapsules were examined by scanning electron microscopy (SEM).

Bioactive agent	Diol (solubility in paraffin oil)	Isocyanate (solubility in paraffin oil)	Stabilizer	Type of polymerization	Capsule morphology
MCR	EG (insoluble)	TDI (~ 10% soluble)	poly (butadiene-b-ethylene oxide)	Interfacial	Reservoir
MCR	EHG (soluble)	IPDI (soluble)	PLMA-g-PEO	Normal	Monolith
IBS	EG/ PD/ BD (insoluble)	IPDI (soluble)	PLMA-g-PEO	Interfacial	Reservoir*
ZnP	EG (insoluble)	TDI (~10% soluble)	Hypermer 2296	Normal	Monolith*

*Expected morphology

Table 1: Description of PU microcapsules – Monomers, bioactive agent and stabilizer used which result in specific capsule morphology by specific polymerization route.

Release of MCR and Ibuprofen-Na in distilled water were carried out under perfect sink conditions using HPLC and UV spectrophotometry respectively (Shukla et al 2002, Shinde et al. 2006). Biocidal activity of microcapsules of ZnP and unencapsulated ZnP dispersed in paint formulation was evaluated by filter paper bioassay by measuring zone of inhibition as per the detail procedure described elsewhere (Shukla et al. 2007, 2008)

Results and Discussion

PU microcapsules containing MCR

Monocrotophos is a systemic as well as contact pesticide. Physical and Chemical properties of MCR demand that any technique of encapsulation should be such that it does not involve water, any reactive substance like amine and temperature above 50^{o}C. This severely limits the choice of polymer and the methods available for encapsulation. Keeping these constraints in mind, a novel method to produce MCR microcapsules was developed without any deleterious effect on MCR.

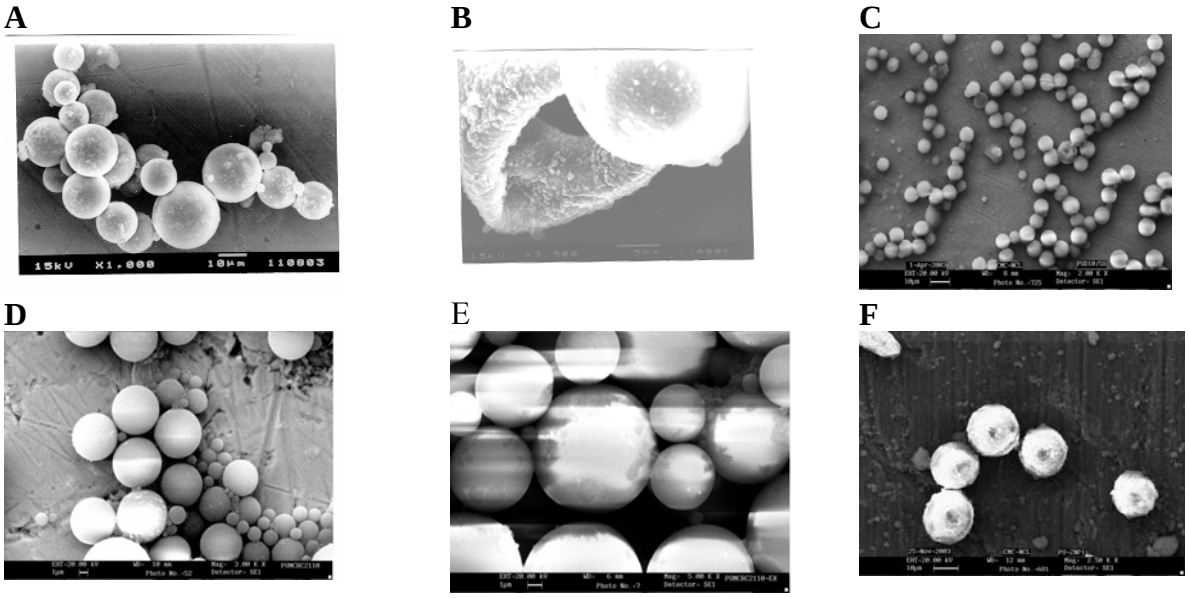

Fig 1 : SEM photographs of PU microcapsules (A) MCR microcapsules with EG (B) MCR microcapsules with EG from which MCR is extracted out (C) Ibuprofen-Na microcapsules (D) MCR microcapsules with EHG (E) MCR microcapsules with EHG from which MCR is extracted out (F) Zinc Pyrithione microcapsules

Microcapsules when prepared with EG (Fig 1A) MCR is soluble in one of the monomer (EG). Another monomer (TDI) is considered as soluble in continuous medium as TDI has some solubility (~10 % w/w) in paraffin oil and is added slowly drop-wise Here polymerization takes place at the interface of droplets of (diol + MCR) and paraffin oil and thus follows typical interfacial type polycondensation resulting in reservoir type microcapsules. However when EHG is taken as diol , EHG and TDI are soluble in continuous phase and thus both monomers are formally present in one phase. MCR is not soluble in paraffin oil, but is emulsified in the continuous phase. As the polymerization starts initially low molecular weight PU prepolymer is formed and subsequently grows in size and MCR gets entrapped in this polymer, forming PU microcapsule (or we can say microsphere) (Fig 1D). When MCR is extracted out from PU microcapsules by refluxing capsules in suitable solvent, extracted (or broken) capsules prepared with paraffin oil-insoluble EG show typical reservoir type structure (Fig 1B). However extracted capsules prepared with EHG show

porous or loose microsphere structure indicating capsules formed are monolith type (Fig 1E). Also when release of MCR is studied in water as a function of loading (Shukla et al. 2002), increase in release rate with decrease in MCR loading is obsserved. This is characteristics of non-porous monolith system (Roseman and Cardarelli 1980)

PU microcapsules containing Ibuprofen-Na

PU microcapsules containing model drug- Ibuprofen-Na (Fig 1C) were prepared with different diols namely EG, PD and BD and also with different level of crosslinking achieved through incorporation of crosslinker Trimethylol propane (TMP) along with diol. In the preparation of these microcapsules, Ibuprofen-Na is soluble in one of the monomer (diol) and the second monomer (IPDI) is soluble in continuous phase (paraffin oil). Thus PU wall is formed by typical interfacial polycondensation process (Table 1).

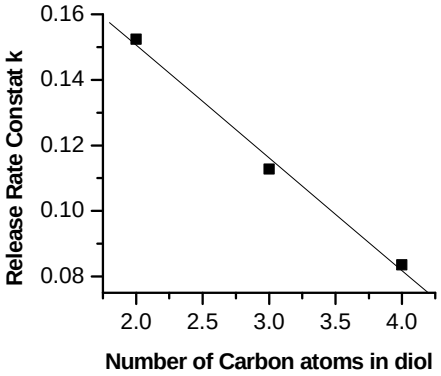

Fig 2: Release of Ibuprofen from PU microcapsules. Effect of number of carbons in diol on release rate constant

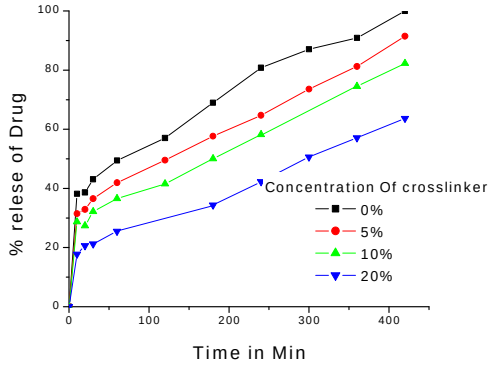

Fig 3 : Release of Ibuprofen from PU microcapsules. Effect of level of crosslinker (w/w % based on diol)

Release of drug was analyzed by general Peppas equation $M_t / M_\infty = kt^n$ where M_t / M_∞ is fraction of drug release, k is release rate constant and n describes type of release mechanism. It has been observed that release of drug increases with decrease in number of carbons in the diol (BD – 4, PD-3 and EG- 2 carbons) (Fig 2). This faster release of hydrophilic drug can be attributed to increase in hydrophilicity with decrease in number of carbons in the diol (Shinde et al. 2006). Release of drug can be also controlled by incorporation of crosslinker. Increase in amount of crosslinker (TMP) decreases the release rate (Fig 3)

PU microcapsules containing fungicide Zinc Pyrithione (ZnP)

Biocides (fungicide, algaecide) play an important role in paint composition. However their chemical degradation and fast dissipation due to washing out from paint film result in reduction in biocidal activity and thus in life period of paint. It has been shown that PU microcapsules containing ZnP can overcome these problems (Shukla et al. 2007, 2008). Fig 1F shows SEM pictures of PU microcapsules containing ZnP. Biocidal activity of these microcapsules was evaluated as indicated by zone of inhibition. If fungus growth is controlled very well then reduction in inhibition zone is negligible or very less. Table 1 shows biocidal activity of encapsulated ZnP. Microcapsules of Zinc Pyrithione and unencpasulated Zinc Pyrithione are dispersed in paint such that the concentration of Zinc Pyrithione is around 5 wt % based on weight of paint. Microencapsulated Zinc Pyrithione sample shows very less % reduction in inhibition zone as compared to unencapsulated Zinc Pyrithione demonstrating that extended duration of activity of biocide is achieved through microencapsulation.

Description of Sample	Zone of inhibition (mm) A (after2days)	Zone of inhibition (mm) B (after100days)	% Reduction in inhibition zone C=[(A-B)x100/A
Unencapsulated ZnP (100% a.i.)	41	32	21.9
PU–ZnP microcapsules (60% a.i.)	40	40	0.0

Table 1: Inhibition zone after 2 days, 100 days, obtained for various samples taken for analysis after 0 days (the day on which microcapsule dispersed in paint)

Conclusion

A novel technique developed to prepare polyurethane microcapsules in non-aqueous medium can be employed to encapsulate variety of water-soluble and water-insoluble bioactive agent used in different applications such as agriculture, pharmaceuticals and paints. Depending on choice of monomers (diol and diisocyanate) and solubility of active agent in diol, reservoir or monolith type microcapsules are obtained. Release of active agent from PU microcapsules can be controlled by proper choice of monomers and /or incorporation of crosslinker in PU architecture.

References

Arshady, R., (1989) *Preparation of microspheres and microcapsules by interfacial polycondensation techniques*, Journal of Microencapsulation. 5 13-28

Shukla, P. G. (2006) *Microencapsulation of liquid active agents Chapter* 5, In: Functional Coatings, Ed. Swapan Kumar Ghosh, WILEY-VCH Weinheim, Germany

Choi, K.Y. et al. (1990) *Microencapsulation of pesticides by interfacial polymerization 1. Polyurethane microcapsules containing oil-soluble drug,* Polymer (Korea). 14 392-400

Yabuuchi, N. et al. (1997) *Method of preparing microcapsules* US Patent No. 5,603,986

Shukla, P.G. and Sivaram, S. (1998) *Process for the preparation of polyurethane microspheres* US Patent No. 5,814,675

Shukla, P.G. and Sivaram, S. (1999a) *Polyurethane microspheres* US Patent No. 5,859,075

Shukla P.G. et al. (1999b) *Process for the preparation of polyurethane microcapsules of Monocrotophos* US Patent No. 5,962,003

Shukla P.G. et al. (1999c) *Microencapsulation of water-soluble pesticide Monocrotophos by oil in oil interfacial Polyaddition method* J. Microencapsulation. 16(4) 517-521

Shukla P.G. et al. (2002) *Preparation and characterization of Mcirocapsules of water-soluble pesticide Monocrotophos using polyurethane as carrier material* J. Microencapsulation. 19(3) 293-304

Shinde, S. A. et al. (2006) *Release of Ibuprofen-Na from Polyurethane microcapsules prepared with different diols* 33rd International Symposium on Controlled Release of Bioactive Materials, held at Vienna, Austria p1559

Shukla P.G. and Sivaram S. (2006) *Polyurethane microcapsules containing biocide and process for preparation thereof* US Patent Application No. 2006/ 0251688 A1

Shukla P.G. et al. (2007) *Composition of polymer microcapsules of biocide for coating material* US Patent Application No. 2007/ 0053950A1

Shukla P.G. et al (2008) *Microcapsules containing biocide useful in coating application* (In preparation)

Roseman, T. J. and Cardarelli N.F. (1980) *Monolithic polymer devices* Chapter 2 In : Controlled Release Technologies: Methods, Theory and Applications, Ed A.F. Kydonieus CRC Press, USA