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Minireview

Hydrophilic polymeric nanoparticles as drug carriers

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Polymeric hydrophilic nanoparticles have attracted attention because of their potential usefulness as drug-carriers in target specific cells, tissues or nucleus. Applications are expected through injectable, oral, nasal or ocular routes. Hydrophilic nanoparticles have been prepared that are hydrophilic on the surface as well as inside the core; particles have also been made that are hydrophilic on the outer surface but are hydrophobic within the core. External stimuli responsive hydrophilic nanoparticles are yet another new addition to the spectra of new materials in drug delivery. Water soluble as well as insoluble drugs can be entrapped into these polymers by adjusting the hydrophilicity/hydrophobicity of the core of the nanoparticles. The review discusses the requirements that these hydrogel nanoparticles must meet to be effective in drug delivery, and the importance of the preparative methods for controlling their sizes below 100 nm, with narrow size distribution.

Nanometre size particles popularly known, as nanoparticles are understood to mean different ranges of dimension of particles to different people. Some investigators have considered the solid colloidal particles of diameter between 10 and 1000 nm[1,2] as the nanoparticles, while others have used terms like nanophase and nanostructures to mean particles having diameters[3] below 100 nm. More recently the term was used to mean particles with diameters of 50 nm or below[4]. In this article, the term has been used to mean particles of size between 10 to 100 nm. Polymeric particles within this size range, loaded with drugs, are expected to be extensively investigated during the coming years for targeting tissues, cells and sub-cellular organs such as nucleus. Applications are expected through injectable, oral, ocular or nasal routes.

Polymeric nanoparticles have been extensively investigated over the last two decades after the first report was published[5] in 1976. These particles as drug carriers or carriers of tracer molecules have been presented as solid nanospheres where the active substances have been incorporated either inside the spheres or have been adsorbed on their surfaces or both. They have also been presented as nano capsules where the active substances have either been incorporated within the core or have been loaded on the surface by physical adsorption or by chemical bonding[2] (Fig. 1).

Site-specific drug delivery is yet largely empirical and the methods available are presently imperfect. Non-toxic, nanosize polymers in controlled drug delivery are nevertheless thought to be playing important role, and it has been hypothesised that while the drug should be delivered at rates that maintain its optimum therapeutic activity at the active sites, concurrently the side effects should be brought down to the lowest level[6]. Delivering drugs through polymeric nanocarriers is considered to assist in reducing the adverse reactions and side effects. The polymeric carriers have to be so chosen as to have several characteristics that have been identified and summarised by some investigators[6-11] as under:

(a) the polymers should be compatible with the body in terms of adaptability (non-toxicity and non-antigenicity) and should be biodegradable and bio-compatible.

(b) the particles should preserve and protect the drugs and should not release them till they reach the sites of action.

(c) the nanoparticles should not interact or should not have any harmful effects on the body cells or tissues.

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†Views expressed in this paper are those of the author and they have nothing to do with the organisation to which he belongs.

This work is dedicated to the fond memory of late Prof Bimal K Bachhawat, who inspired me for pursuing science with dedication.

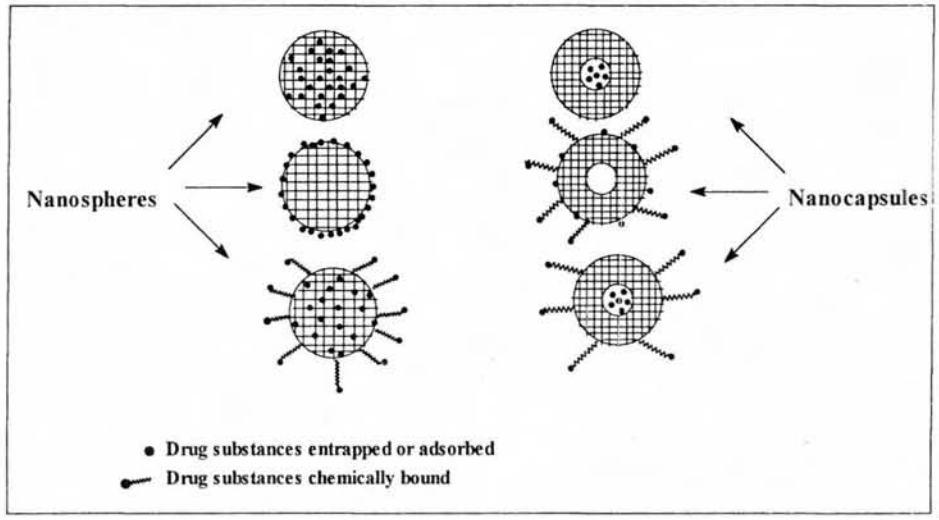

Fig. 1—Drugs or tracer molecules loaded with polymeric hydrophilic nanoparticles in different forms (adopted with modifications from ref. 2)

(d) the particles should be able to traverse the intervening membranes.
(e) the particles should recognise the sites of action and should get bound or associated with the sites of action.
(f) the drugs should be released at rates so as to achieve the desired therapeutic effects on a continuous basis.
(g) after the release of the drugs, the nanoparticles should be degraded or eliminated from the body.

All the polymeric nanoparticle drug carriers that have been designed and investigated so far are to produce the targeting system to achieve the above characteristics.

Mechanisms of drug delivery

The polymeric drug carriers that have been designed would deliver the drug at the tissue site by any one or more of the three general physico-chemical mechanisms[12,13] namely (a) by the swelling of the polymer nanoparticles by hydration followed by release through diffusion (b) by an enzymatic reaction leading to rupture or cleavage, leading to the degradation of the polymer at sites, thereby releasing the drug from the entrapped inner core or (c) by cleavage of the drug from the polymer and its de-adsorption/release from the swelled nanoparticles. Upon injection of a polymeric targeting nano system, the fate of the particle within the body would be governed by their particle size, shape, surface charge and the surface hydrophobic or hydrophilic characteristics. Further, the *in vivo* distribution and accumulation would be affected by the physico-chemical properties of the targeting nanoparticles.

Characteristics of particles for targeting specific sites in the body

The major challenge in the development of polymeric particulate drug carriers has been to create conditions so that the particles can evade the systemic scavenging machinery such as the reticuloendothelial system (RES)[14,15] while in circulation in the body. Phospholipid vesicles (liposomes), which are self-assembled colloidal particles, have been widely explored as drug carriers[16,17]. They were not found suitable for site specific drug targeting as they were cleared fast by the RES of the body. However, such vesicles coated with poloxamers (methyl oxyrane polymers) of different molecular weights were found to be useful in evading the RES uptake and consequently the circulation time of the lipid vesicles could be prolonged in blood[2,18-24]. Coating the lipid vesicles with poloxamers and poloxamines render the surface of the lipid vesicles hydrophilic. This observation led investigators to initiate efforts to modulate the surface hydrophilicity of drug carrier particles to enable the evasion of the systemic scavengers.

It is known that ingested micro-particles of diameter, 7 μm or above are filtered out by the capillary bed of the lung. Such large particles cannot enter the circulatory system of the body[25-27]. Smaller

particles get into circulation, but they are scavenged by the macrophages in blood, spleen and bone marrow. The kinetics and extent of scavenging are fast and critical below certain sizes and depend on the degree of their surface hydrophilicity[28-32].

Importance of preparative methods in controlling the polymeric particle size

Presently, vast literature is available for the preparation of polymeric nanoparticles of all ranges. The polymeric materials used have been diverse as polylactyl lactate[33], polyalkylcyanoacrylates[34,35], polymethylmethacrylates[36], different polymerised vinyl derivatives bearing allyl, acryloyl, acrylamido and methacrylamido groups[37], acrylate or alkyl acrylate terminated polyethylene oxide or polyethylene glycol, or para vinylbenzyl terminated polyethylene glycol or polyethylene oxide or mixtures there of[38], dextran[39], gelatin[40] etc. Known methods are employed for the polymerization of the monomers, dispersed in a suitable manner. Usually, an oil in water (for an oil soluble monomer) or water in oil (for water soluble monomer) type dispersion is made, using suitable surfactants like sodium bis-2-ethylhexylsulfosuccinate (AOT), to enable the formation of desired microemulsion droplets. For water soluble monomers i.e. water in oil type microemulsion polymerization, water soluble initiators like ammonium, sodium or potassium persulfates with activators like tetramethylethylene diamine (TEMED) are used. In order to impart some rigidity to the nanoparticles, cross-liking agents like N, N′ methylenebisacrylamide (MBA) are also used with the monomer. The loci of polymerization are the droplets of the microemulsion phase.

Polymer particles prepared by the conventional emulsion polymerization methods produce highly polydisperse particles with diameters in the range of hundreds to thousands of nanometres. It was shown that the problems of wide size range could be overcome if polymerization was carried out in microemulsion instead of in emulsion[41] as microemulsions are thermodynamically stable and are in monodispersed phase. The polymerisation of methacrylic acid was carried out in reverse microemulsion to produce highly monodispersed particle[42]. The quantity of water that could be solubilised into the non-polar solvent in a reverse microemulsion is also largely dependant upon the type of the surfactant molecule used and it was shown[43] that in water-AOT-isooctane system, the reverse micellar droplets could be made comparatively larger by increasing water to AOT ratio. This is primarily due to a favourable interface-packing factor emanating from the property of free internal rotation of AOT, thereby causing more water to be accommodated inside the droplet. More water inside is tantamount to more free water that can accommodate larger quantities of water soluble extraneous materials inside the core water droplet nano reactors, and the system would therefore be suitable for the preparations of larger quantities of precise nanoparticles.

The water droplet size in reverse micelles is controlled mainly by three factors, namely, the choice and the concentration of surfactants and the content of water that can be associated with the concentration of the surface active agents. Although several investigations had been carried out on the preparation of polymeric nanoparticles in reverse microemulsions[44-52], the influence of water to surfactant ratio on the size of nanoparticles was long overlooked. Another important factor is the use of the right quantity of initiators to optimise the receipt of one-initiator molecule at the most per microemulsion droplet. This was revealed from our recent work where we could consistently prepare polymeric hydrophilic nanoparticles[53,54] of precise size range of 10 to 100 nm. The polymerization was initiated entirely into the individual aqueous core of reverse micellar droplets of the microemulsion phase, but there had also been inter droplet interaction in the process. Our observation had been that about 10-15 droplets take part in such inter-droplet interactions, which lead to the formation of nanoparticle compounds/composites at the end of the polymerization process[53,54].

Process of making polymeric hydrophilic nanoparticles of narrow-size distribution

The surfactant, sodium bis-2-ethylhexylsulphosuccinate, or Aerosol OT (i.e. AOT) was dissolved in n-hexane (usually 0.03 *M* to 0.1 *M* of AOT solution). Water-soluble monomer, N-vinylpyrrolidone, was used and the polymer was cross-linked with MBA for nanoparticle preparation. Aqueous solutions of monomer, cross-linking agent, initiator and FITC-Dextran (FITC-Dx) were added to AOT solution in hexane and the polymerization was carried out following the standard procedure. Additional amount of buffer may be required to be added in

reverse micelles in order to get the host micellar droplets of desired size. In a typical experiment for the preparation of nanoparticles of vinylpyrrolidone containing FITC-Dx as an encapsulated marker material (mol. mass 19.3 kDa), we had taken 40 ml of 0.03 *M* AOT solution in hexane in which 316 µl of freshly distilled N-vinylpyrrolidone, 100 µl of MBA (0.049 g/ml) as cross-linking agent, 20 µl of 1% ferrous ammonium sulphate (FAS), 20 µl of 11.2% aqueous solution of TMED, 30 µl of 20% ammonium persulphate as initiator and 50 µl of marker compound, FITC-Dx (160 mg/ml) were added. The solution was homogeneous and optically transparent. Polymerization was done in N_2 atmosphere at 35°C for 8 hr in a thermostatic bath with continuous stirring. The above method produced PVP nanoparticles cross-linked with MBA and containing FITC-Dx as encapsulated material. The organic solvent was evaporated off in a rotary evaporator and the dry mass was resuspended in 5 ml of water by sonication. Calculated amount of 30% $CaCl_2$ solution was added drop by drop with continuous stirring to precipitate the surfactant as calcium salt of bis (2-ethylhexyl) sulphosuccinate, [$Ca(DEHSS)_2$]. The centrifuged (10,000 rpm for 10 min) aqueous solution contains nanoparticles, which was homogeneous and transparent. The cake of $Ca(DEHSS)_2$ after centrifugation contains some nanoparticles adsorbed on it. It was dissolved in 10 ml of n-hexane and the hexane solution was washed 2-3 times with 1 ml of water. The phase separated aqueous layer was drained out and added to the original centrifugate. The total aqueous dispersion of nanoparticles was lyophilised immediately to dry powder for subsequent use. Lyophilised nanoparticles are easily redispersible in aqueous buffer, which was subjected to gel filtration using Sephacryl S-200 (1 cm×34 cm) column pre-equilibrated with 50 m*M* phosphate buffer saline at a flow rate of 12 ml/hr at 25°C, and the separated nanoparticles free from un-encapsulated FITC-Dx and other unreacted compounds were directly used for bio-distribution and other studies. The size of these particles in buffer was found to be same before and after lyophilisation.

The number of droplets taking part in the interaction depends upon the initial density and size of droplets, temperature of polymerization and the quantity of initiator used to trigger polymerization; the smaller the droplet size, the lower the temperature and lesser the concentration of the initiator (ideally one initiator particle per water droplet), the lesser is the inter-droplet interaction[55].

Fig. 2 shows the relationship between the initial water droplet size (diameter) and the diameter of the nanoparticles produced in our laboratory in hexane-AOT- water system using N-vinylpyrrolidone (VP) as the monomer and N, N′-methylenebis acrylamide (MBA) as the cross linking agent (3.2% w/w of VP) and entrapping within the polymer, FITC-dextran complex (mol. mass 19.3 kDa) upto 3.2% w/w of the polymeric material[56]. This study was carried out to assess the entrapment efficiency of the nano-polymeric particles for the marker water soluble FITC-dextran complex. This relationship shows consistent particle diameter and therefore similar and reproducible degree of polymerization of the nanoparticles, which is explained from the hypothesis that the polymerisable monomers are packed together in micellar droplets by the action of the surfactant AOT in hexane. Inter droplet interaction is also limited within a few water droplet nanoreactors. These results are consistent with the earlier observations on polymerisation of dimethylaminoethyl methacrylate in benzene[57,58] as well as the microemulsion particles produced from the polymerisation of acrylamide in toluene using AOT as the surfactant[48,49]. The molecular mass of the resulting polymers was 10^6 to 10^7 Da. As an example, polyacrylamide nanoparticles

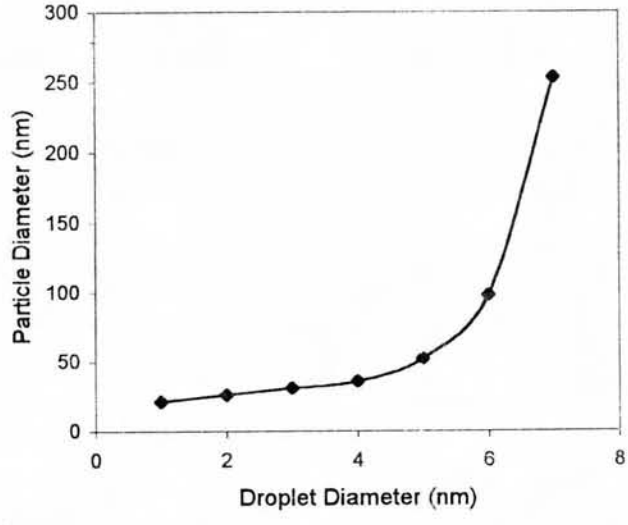

Fig. 2—Inter-relationship between the formation of the size of FITC-Dextran (19.3 kilodalton) loaded nanoparticles and the size of the starting reverse micellar water droplets in which these nanoparticles were prepared. [Loading of FITC-Dextran=3.2% w/w of polymeric material, MBA=1.2% w/w of the polymeric material]

prepared in AOT reverse microemulsion[41] have been reported to have size of 19 nm and molecular mass of 3.2×10^6 Da which can vary depending upon the change in the composition and the size of reverse micellar droplets. Probably the phenomenon of continuous nucleation takes place within the micro-emulsion aqueous core and the polymer chain builds up gradually, till most of the monomers and cross-linking agents are used up. Further, from the correlation of the measurement of the molecular weight and particle diameter of polyacrylamide produced by microemulsion polymerization of acryl-amide in water-AOT-toluene system, it was concluded that the number of polymer chain per particle was only one or two[50] which is also indicative of the building up of the polymer chain within a few water droplet nanoreactors.

Polyvinylpyrrolidone cross-linked with MBA was found to entrap effectively, comparatively larger water-soluble molecules like bovine immuno-globulins and antigenic molecules of *Aspergillus fumigatus* or marker molecules like FITC-Dx (mol. mass 19.3 kDa). These entrapped nanoparticles produced and processed by our methods were found to be non-toxic in mice and had elicited satisfactory antigenic response[53]. Our system of hydrophilic polymeric nanoparticles of polyvinylpyrrolidone with controlled cross-linking by MBA holds potential for entrapping different kinds of bio-active water soluble molecules of molecular mass of 5 kDa and above; these entrapped particles have possibilities of targeting body tissues specially the tumour tissues. Smaller molecules could be converted into prodrugs by conjugating with appropriate water-soluble non-toxic haptens or non-antigenic substances to increase their molecular weights for easing entrapment. These nanoparticles are not easily scavenged by the RES[32] in contrast with most of the presently available nanoparticles that are largely hydrophobic in surface characteristics. However, these polymeric hydrophilic nanoparticles are not suitable for entrapping water insoluble bioactive substances.

Entrapment of water insoluble drug or tracer molecules into nanoparticles of hydrophilic polymeric micelles

In order to entrap water-insoluble bioactive substances, investigation and advancements have been made using outer surface hydrophilic nano-particles of polymeric micelles during the recent time. There are several reports where water-soluble, bio-compatible polymeric micelles have been used as the drug delivery vehicles[59-61]. Polymeric micelles are dynamic aggregates of several hundred molecules of diblock copolymers. They have diameters of 20-50 nm. They are formed as two co-centric polymeric regions where the outer shell is made up of hydrophilic materials and the inner core is of hydrophobic substances. The inner hydrophobic core is responsible for holding or "solubilising" the hydrophobic substances including drugs or marker molecules. The outer hydrophilic periphery empowers the composite to evade the RES of the body when used *in vivo*. Such nano composites of polymeric micelles are made up of self-assemblage of amphiphilic block or graft-copolymers where one part of the polymer is highly soluble in the solvent used (say water solubilising hydrophilic parts of the diblock co-polymer) while the other part is insoluble in the same solvent. Fig 3 illustrates schematically the micellisation of amphiphilic polymers in water.

The hydrophilic non-toxic vehicles extensively used are poly (ethylene oxide), and poly (ethylene glycol); the hydrophobic vehicles often used as the copolymer conjugates with the hydrophilic vehicles are poly (propylene oxide), polystyrene, poly (methylmethacrylate), poly (L-aspartic acid), poly (L-lysine) and poly (L-glutamic acid). Active drugs insoluble in water have also been covalently linked on to the hydrophobic part in such systems. The concept[62] first introduced in 1985 has been extensively studied and reviewed[63-74]. The water insoluble drugs have also been physically entrapped in such hydrophobic core polymeric micelles. Drugs such as indomethacin, amphotericin-B and doxo-rubicin have been used in such entrapment composites[75-78]. Unimolecular dendritic micelles with a hydrophobic core surrounding a hydrophilic shell was prepared on the above concept and the "container" property of the micelles was demons-trated by "solubilising" pyrene in aqueous solution of such micelles[79]. From these studies it can be argued that by proper choice of two or more monomers containing lipophilic and hydrophilic groups, and by maintenance of appropriate ratios of them, it should be possible to produce copolymers of different chain length containing hydrophilic and lipophilic pockets. Such amphiphilic polymers should be useful for solubilising almost all kinds of water insoluble substances of lower molecular weight of say upto

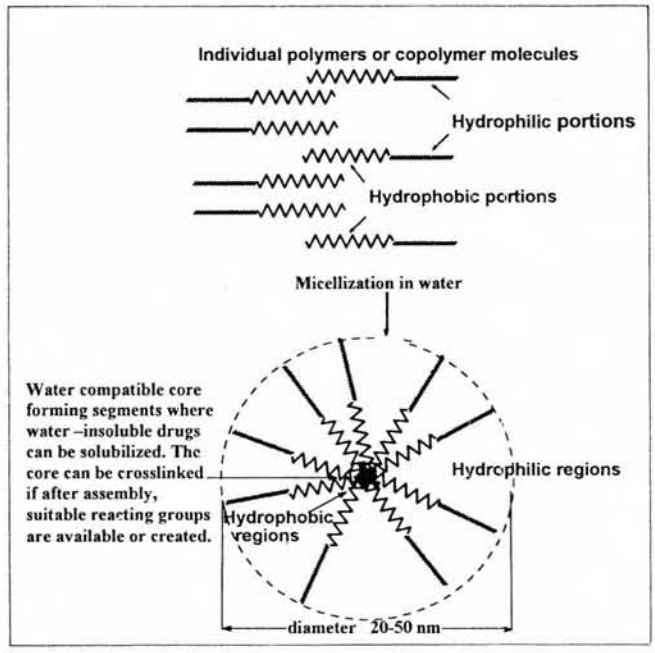

Fig. 3—Schematic illustration of micellization of di-block hydrophilic-hydrophobic copolymer conjugation

5 kDa. The amphiphilic polymers preformed by applying standard procedures of polymerization and thereafter dissolved in water could be contacted with the target compounds solubilised in a suitable solvent to enable their entrapment into the hydrophobic core. Such non-toxic, hydrophilic nanoparticles of polymeric micelles containing target drugs entrapped into the hydrophobic core would find applications in an array of situations for targeting specific tissues and these composite particles would largely be able to evade the RES due to their smaller particle size (below 100 nm) and their peripheral hydrophilic surface characteristics.

Smart hydrophilic nanoparticles

Functional polymers either found in nature or synthesised in the lab which are highly non-linear to external stimuli can be converted into nanosize particles. Small changes in external stimuli such as change in temperature, *p*H, magnetic or electric field or some such parameters in the micro-environment brings about fast reversible changes in the micro-structures of such polymers from a hydrophilic state to the hydrophobic state or *vice versa*. These changes can be perceived at the macroscopic level such as in the manifestation of order-of-magnitude changes in particle size or water-content or formation of precipitate at the site of change of the external stimuli. Such changes are however, reversible and the polymers return to their initial state, when the trigger is removed[80,81]. These polymers wherever biocompatible, when converted into nanosize particles and loaded with drugs are expected to become useful as vehicles for systemic drug delivery. We produced *p*H and thermo-sensitive hydrogel nanoparticles[54] of co-polymers of N-vinylpyrrolidone (VP) and acrylic acid (AA); the co-polymers of different molar ratios between VP and AA were prepared. We showed that the co-polymer of VP and AA containing 20% AA (in moles) per 100 moles of total monomers of VP and AA, that entrapped FITC-Dx (mol. mass 19.3 kDa) up to 1% w/w of the co-polymer had shown different release rates of the marker compound, both at different *p*H as well as at different temperatures. The average particle size of the co-polymer was about 50 nm. The percent hydration (swelling) of the co-polymer with time at different *p*H was also very different, being highest at higher *p*H (*p*H 10) and significantly lower at lower *p*H (*p*H 3). As these co-polymers are biocompatible and as their sizes can be modulated, these are expected to be useful in various drug delivery systems. A *p*H responsive insulin loaded polymer matrix was produced by compressing a *p*H responsive polymer, glucose oxidase and bovine serum albumin[82]. When the matrix was exposed to glucose solution, glucose oxidase oxidised glucose to gluconic acid, which resulted in a decrease in *p*H across the microenvironment. This resulted in

protonation of the polymer and swelling; swelling resulted in the release of insulin. The release of insulin stopped in 10 min of glucose removal and the process could be restimulated by the addition of glucose. Other designs for the delivery of insulin that responds to glucose were also developed earlier[83,74]. Temperature sensitive polymers entrapping active substances and made up of poly N-isopropyl-acrylamide[85,86] or polyethyleneoxide derivative of polymethylacrylic acid[87] from which release of the entrapped active substances can be altered by altering the temperature have also been synthesised. The value of these smart polymers can be increased considerably by converting these into nanoparticles or nanocomposites, as these small composites can be transported to inaccessible body tissues The preparation and properties of micro-capsules and micro-spheres of chitosan, a natural, non-toxic, bio-degradable/bio-absorbable hydrogel polymer has also been described[88,89]. Cross-linked chitosan micro-spheres loaded with 5-fluorouracil and its amino acid derivatives have been prepared; these microspheres were loaded either with anionic polysaccharides or with lipids in multilayers, and the resulting composites had diameters of 250-300 nm with a narrow size distribution. These products showed effective barriers to the release of 5-fluorouracil; the lipid multi-layer coated micro-spheres showed non-linear release of 5-fluorouracil in physiological saline, increasing significantly above the phase transition temperature of 41.4°C and decreasing to lower release rate[90] at 37°C. Such on-off control hydrogel polymer composites for the release of effective drugs via a change in temperature at the site of infliction can be made more effective, if the diameter of the composites can be reduced further, below 100 nm.

Smart amphiphilic nanoparticles were prepared in our laboratory from vinylpyrrolidone and N-isopro-pylacrylamide that were sensitive to temperature[56]. These particles were loaded with paclitaxol with a view to use them as vehicles for drug delivery. Animal experiments on the utility of these nano-particles are in progress and applications for patenting the process have been filed. The preparative method is outlined below.

Smart hydrophilic polymeric nanoparticles of copolymers of vinylpyrrolidone and N-isopro-pylacrylamide

Freshly distilled vinylpyrrolidone (10 mg) and freshly crystallised N-isopropylacrylamide were dissolved in double distilled water (10 ml). To this solution was added 28 µl of MBA (49 mg/ml) and nitrogen gas was passed into the solution for half an hour. To this solution was added 20 µl of TEMED (11.2% w/w in water) and 30 µl of ammonium persulphate (20% w/w) and nitrogen was bubbled for 24 hr. The polymerization was carried out at 35°C. After polymerization, the solution was dialysed for 2 hr. To the dialysed solution was added a saturated alcoholic solution of taxol (40 mg/ml). The entrapped paclitaxol within the polymeric nanoparticles was lyophilised for further experiments.

The Fig. 4 shows the spectra of the particles taken in our Brookhaven 9000 instrument with a BI200SM goniometer. The quasi-elastic light scattering spectra (QELS) were taken in an air-cool argon ion laser operated at 488 nm as the light source. The time dependence of the intensity autocorrelation function of the scattered intensity was derived by using a 128-channel digital correlator. The size of the nanoparticles was determined by the diffusion of the particles using the Stokes-Einstein equation and the representative size distribution spectra was as in Fig. 4. Fig. 5 shows the response of the void and taxol loaded nanoparticles with variation in temperature. The sizes of the nanoparticles increased sharply with a small change in temperature above a critical solution temperature, which was around 40°C.

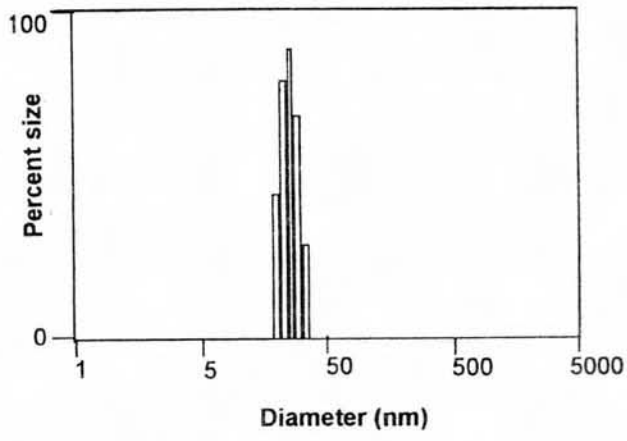

Fig. 4—Quasi-elastic-light-scattering spectra of paclitaxol loaded polymeric nanoparticles

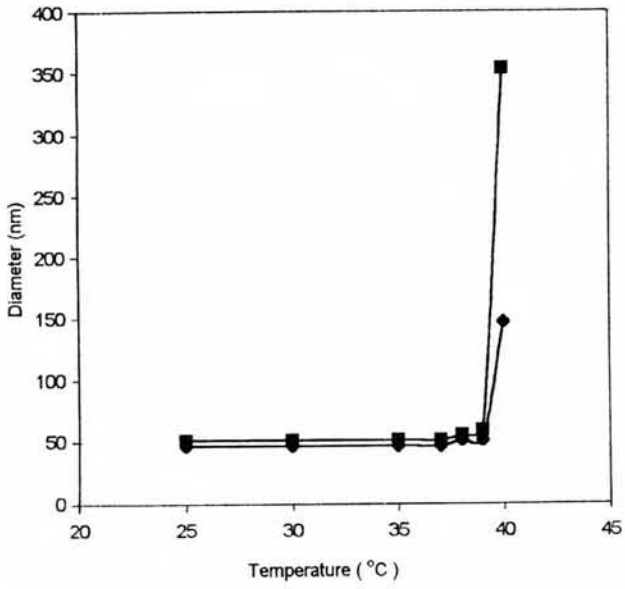

Fig. 5—Size of void (—♦—) and taxol-loaded polymeric nanoparticles (—■—).

Concluding Remarks

Targeting of the drugs using hydrophilic nanoparticles or nanoparticles of polymeric micelles as carriers, couriering water-soluble or water insoluble drug substances respectively has not yet been precisely achieved. But the understanding in this complex area has increased to a considerable extent. The reasons why these drug carrier particles are taken up and cleared from circulation *in vivo* in animal experiments have been considerably understood. The outer surface hydrophobicity of the particles as well as their size above say 100 nm has been attributed to, as the main signals for clearing them from circulation in blood in *in vivo* experiments and consequently the peripheral surface of these carriers has been made highly hydrophilic by the choice of non toxic hydrophilic polymers. Simultaneously preparative methods for the production of highly monodispersed nanoparticles of sizes below 100 nm have evolved. Satisfactory purification methods for removing the toxic monomers and other chemicals used during polymerization have also been found. All these hydrophilic nanoparticles entrapping drugs can be effectively sterilised by simple membrane filtration process due to their smaller size, and can be presented as freeze dried products. Hydrophilic nanoparticles of polymeric micelles have been produced with high drug entrapment efficiency and the freeze-dried products upon reconstitution, have retained the loaded drugs that are released slowly. The present day administration of these particles has remained largely by the injectable route and the administration through oral, ocular or nasal route is yet at the developmental stage.

The future years are expected to witness better understanding of the interaction between the nanoparticles and the phagocytic cells. Improved understanding of delivering the particles at target sites will also evolve to provide a convenient method of site specific drug delivery. The three systems of hydrophilic polymeric nanoparticles reviewed hold great promise of maximising drug effectiveness while minimising drug toxicity.

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