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Review Article

Microspheres for the Drug Delivery Applications

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Abstract

Conventional dosage forms provide a sharp increase in plasma drug levels that falls below the therapeutic range after short interval of time until the re-administration of drug. There is a need of such dosage forms which provide not only sustained drug delivery but also reduce the plasma drug levels fluctuations. Microspheres used in drug delivery systems due to their ability to sustain the drug release, their biodegradability and compatibility and targeted drug delivery. In this review different types of microspheres their methods for the preparation with different hydrophilic and hydrophobic polymers, drug loading capacities will be discussed. Different characterizations like SEM, FTIR, XRD, DSC, rheological properties and invitro drug release are successfully described.

Keywords: Biodegradable, Dosage forms, Microspheres, SEM, FTIR, XRD

Introduction

Conventional dosage form provide a sharp increase in drug concentrations and drug concentration falls below the therapeutic range after a short interval of time until the re-administration of drug. So there is need of such dosage forms which provide not only the sustained delivery of drug but also reduce the fluctuations in the plasma drug levels and frequency of administration (Freiberg and Zhu, 2004).

Recently a lot of work has been done to develop and formulate oral control release multiple unit dosage forms using natural and synthetic polymers, which are becoming more popular than the conventional single unit dosage forms due to its inherent advantages of providing uniform drug delivery; avoiding the vagaries of gastric emptying and different transit rates throughout the gastro-intestinal tract. This fact coupled with their ability to prolong the release of drug has increased the interest in developing the controlled drug delivery (Banerjee et al., 2012).

One of the methods to achieve controlled drug delivery is developing the microspheres. These systems act as a reservoir of therapeutic agents, with spatial and temporal release of drugs for the desired therapeutic outcomes. The microspheres should have ability to incorporate drugs without loss of activity, tunable release kinetics, sufficient in vivo stability, biocompatibility, lack of toxicity, biodegradability and ability to target specific organs or tissue (Isıklan et al., 2011). Desired drug release rates by using microspheres can be achieved by rate controlling membrane or by the matrix of polymer containing the suspended drug.

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The idea of controlled release dates back to 1960 through the implementation of silicone rubber and polyethylene in the controlled drug delivery systems (Folkman and Long, 1964). However biodegradability of this system was a big issue and required the surgical removal of the system. Recently, the biodegradable and biocompatible polymers have attracted much attention for use in the drug delivery systems by using natural polymers like chitosan, carboxymethylcellulose (CMC), polylactic acid (PLA), polyvinyl alcohol (PVA) and Sodium alginate etc. The microspheres made from these polymers provide an excellent way to deliver drug in controlled release manner with biodegradability.

There are various methods that are used to develop the microspheres with each method having its own advantages and disadvantages and suitability for different types of polymers and drugs. Different methods also affect the morphology and characteristics of microspheres which in turn affect the drug release behavior of the system. In this review, different types of microspheres, their methods of preparation with different hydrophilic and hydrophobic polymers will be discussed. Different characterizations like SEM, FTIR, XRD, DSC, rheological properties and invitro drug release are successfully described.

Bioadhesive microspheres

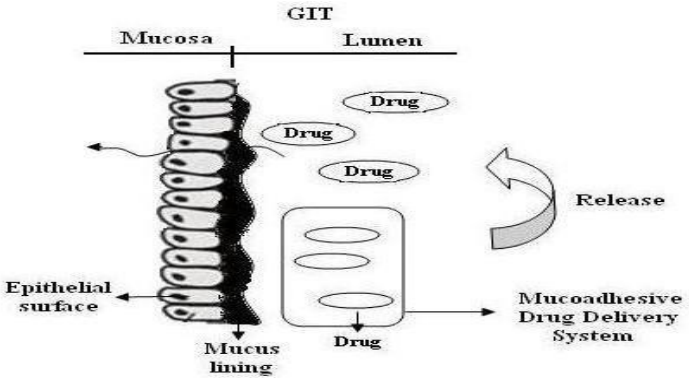
Biological substrates may be ocular, nasal, buccal or rectal mucosal membranes. Due to sustained release property, frequency of dosing is low and increased patient compliance. The exact mechanism of mucoadhesion is still unknown but general mechanism is shown in the figure (Ketul et al., 2012).

Main advantages of mucoadhesive drug delivery system are localization in the region where they applied, increase the intimate contact time and long residence time of the system which reduces the dosing frequency. In previous literature, polyvinyl alcohal (PVA) and gum ghatti has also been reported (Jain and Banik, 2013).

Floating Microspheres

Bulk density is the real cause of buoyancy or sinking of microspheres. These microspheres are specially designed to remain buyout at the surface of gastric fluids. The drug release from the microspheres is not affected by gastric emptying because they remain floating in the fundus region of stomach. The drug is released in sustained pattern. Gastric retention time is prolonged and frequency of dosing is decreased (Ketul et al., 2012). Vandana Singh and his friend developed floating microspheres of eudragit by solvent evaporation method containing ranitidine (Singh and Chaudhary, 2011).

Figure 1 Mechanism of mucoadhesion



Magnetic microspheres

Magnetic targeting drug delivery system is important in site specific drug delivery system resulting in the formation of magnetic microspheres. Methods used for the preparation of magnetic microspheres are Phase separation emulsion polymerization (PSEP) and continuous solvent evaporation (CSE). Magnetic microspheres are supra-molecular moieties with diameter less than 4µm. The drug is bound to the magnetic compound and administered into the circulation of patient which is controlled with powerful magnetic field at target area, to release drug slowly. Chitosan and dextran are mostly used to deliver chemotherapeutic agents, proteins

and peptides (Ketul et al., 2012,). Chitosan and Poly (acrylic acid) magnetic microspheres has also been reported for their potentials in drug delivery (Guo et al., 2010).

Radio Active Microspheres

These are of two types; Therapeutic Radioactive microspheres and diagnostic radioactive microspheres. Many radio labeled isotopes are best for the treatment of certain type of disorders. The use of radioactive microspheres is still in experimental stages, because of unwanted toxicity and suboptimal therapeutic results. These were used for the treatment of rheumatoid arthritis, cystic brain tumor and liver tumor. Certain types of polymers like PLA, polylactide-co-glycolide (PLGA), chitosan, Polyanhydride, Polycyanoacrylate, Agarose, Polyacrolein used for radiolabelling (Häfeli, 2006). First diagnostic radioactive microspheres used were white and red blood cell. These were labeled with certain radio isotopes and injected. Red blood cells labeled with chromium used to detect the mass of RBCs as well as function of spleen. Radioactive microspheres are injected into the arteries, reach to the tumor, and release high dose of radiation without damaging the surrounding tissues (Ketul et al., 2012).

Biodegradable Polymeric microspheres

Biodegradable polymeric microspheres can easily be synthesized with natural or synthetic polymers. The selection of polymer should be so wise that the end product should be nontoxic because sometimes it enter into the general circulation and might be dangerous. Drug can be incorporated for few days or few years. Enzymatic system and hydrolysis process in the body degrade the natural polymers like protein or polysaccharides (Singh et al., 2011). Natural polymers have more sustained release property because have prolong residence time when come in contact with water.

Synthetic polymeric microspheres

Synthetic polymeric microspheres have a lot of clinical uses. They are used as fillers and bulking agents for soft tissues also have a role in embolotherapy. Depot formulation has also been made with such microspheres. The alarming drawback of this system is the transmigration to adjacent site of injection causing embolism and further organ damage. The examples of such polymers are PLA, Poly (Glycolic acid), Polycaprolactone (PCL) (Saralidze et al., 2010).

Methods of preparation of microspheres

Solvent Diffusion method

Hollow microspheres can be prepared by solvent-diffusion-evaporation method. In this method EC and Polyvinyl pyrollidone (PVP) were dissolved or dispersed in ethanol, followed by the addition of drug and ether. This polymer blend containing drug was added to the liquid paraffin premixed with span-80, which was in water bath at 30^{o}C with continuous stirring at 300 rpm. Prepared microspheres were collected by filtration, washed and dried (Zhao et al., 2010). Similar method had also been used to prepare eudragit SR-100 microspheres (Yang et al., 2003). Poly acrylic acid (PAA) and PVP microsphers have also been reported (Chun et al., 2005). Kawashima et al prepared hollow microspheres by emulsion solvent diffusion method (Sato et al., 2004).

Coacervation Method

Polymer is first dissolved in organic solvent containing active pharmaceutical ingredient, which may be solid or liquid. Desolvation of polymer is done by the addition of nonsolvent or polymer coacervating agent. Solubility of the polymer will be decreased in the organic phase, two phases will be formed and the coacervates will be settled at the surface of active principle. Curing agent will be added for the formation of polymer lining on the surface of active principle (Weinbreck et al., 2004). In another study Liu and his coworkers prepared double walled microspheres by this method using Chitosan as polymer (Liu et al., 2007a). Chitosan

microspheres were prepared by modifying this technique in which the solution of drug and crosslinker was sprayed on the polymeric solution (El-Leithy et al., 2010). Salbutamol loaded Gelatin microspheres by coacervation phase separation were prepared (Jayan et al., 2009).

Table 1 Different methods of preparation of microspheres with different Polymers and their characteristics

Method Of Preparation	Polymer Used	Drug Loaded	Characterization & Results				Year	References
			Mean Diameter (um)	Drug Loading (%)	%age Yield (%)	EE (%)		
Solvent Diffusion Method	EthylCellulose & PVP	Nifedipine	668 um	15.9	80	63	2010	(Zhao et al., 2010)
	Eudragit RS	Nitrendipine	762um	13.1	67.83	93.6	2003	(Yang et al., 2003)
	PVP & PAA	Claithromycin	67.1um	37.8	87.6	75.5	2005	(Chun et al., 2005)
Coacervation Method	Chitosan	Diclofenac Sodium	19um	55	80	72.5	2010	(El-Leithy et al., 2010)
	Gelatin	Salbutamol	12.34um		78	77.5	2009	(Jayan et al., 2009)
	Gelatin	Vitamin A	132.5%		55.6	44	2011	(Wakode and Bajaj)
Solvent Evaporation Method	Ethyl Cellulose	Nimodipine	316um	45	83		2005	(Atyabi et al., 2005)
	Ethyl Cellulose	Diclofenac Sodium	5um	-	-	-	2007	(Baccarin et al., 2007)
	Eudragit RS Eudragit Rl	Glipizide	511um	-	87	68	2008	(Behera et al., 2008)
	PLGA	Cephalexin	3.94um	-	-	18.7	2009	(Chaisri et al., 2009)
Ionotropic Gelation Method	Sodium-Alginate and Pectin	Acelofenac	0.72um	-	92.6%	85%	2010	(CHAKRABORTY et al., 2010)
Emulsion crosslinking	CMC+PVA	diclofenac	461.83	-	84.53	58.28	2012	(Banerjee et al., 2012)
	o-carboxy-methylchitosan	Pazufloxacin mesilate	7.56	32.38		72.9	2007	(Liu et al., 2007b)

	Starch	Rofecoxib	98.23	-	73.5		2009	(Thombre et al., 2009)
	Chitosan	resveratral	53-311	-	-	93.6	2010	(Peng et al., 2010)
	PVA+NA Alg	diclofenac	281.61	-	78.03	55.8	2010	(Banerjee et al., 2010)
Spray Drying	Hayalouronic acid	fexofenadine	23.86	16.3		94.1	2010	(Bindu and Sriram, 2012)
	Chitosan+tripolyposphate	acetaminophin	6.74	-	-	88.7	2005	(Desai and Park, 2005)

Solvent Evaporation Method

Solvent evaporation is a well known method having two types, Single emulsion technique and double emulsion technique (Singh et al., 2011). Microspheres of natural polymers can easily be prepared by this method. Polymers and drugs are dissolved in aqueous medium and this mixture is dispersed into the non aqueous medium. The cross linking of polymer can be done either with heat or chemical crosslinkers like glutaraldehyde (GA). Double emulsion technique involves the formation of multiple emulsions e.g. w/o/w (Khan et al., 2012). Successful encapsulation of certain hydrophilic drugs, vaccines, proteins and peptides was reported in previous literature. Protein aqueous solution was made and added to lipophilic organic solvent act as continuous phase, which contain the polymers to encapsulate the protein in aqueous phase. Primary emulsion was formed, added into aqueous solution of PVA then subjected to solvent evaporation (Yang et al., 2001). Ethylcellulose (EC) and eudragit microspheres by solvent evaporation method have been reported in literature. (Atyabi et al., 2005, Baccarin et al., 2007).

Ionotropic Gelation method

Polymer solution is made and added dropwise into the crosslinker solution. Mostly used crosslinkers are divalent cation, like Calcium chloride ($CaCl_2$), Zinc chloride. The size of microspheres depends upon the gauge of needle. Large size microspheres are formed, termed as pellets or beads. Microsphers by using Chitosan coated with alginate-gelatin have been studied and evaluated by this method (Khan et al., 2012).

Emulsion Crosslinking

Mixture of hydrophilic polymers and drug (dissolved or dispersed) is poured into oil phase with constant magnetic stirring, forming w/o emulsion using suitable surfactant and then adding specified amount of crosslinker to form the microspheres, hardened them by continous stirring for 2 to 3 hours. Microspheres collected by filtration washed with acetone and distilled water, dried at 40^{o} C in oven and stored (Banerjee et al., 2010).

Chitosan microspheres crosslinked with epicholorohydrin has been prepared by dissolving chitosan in acetic acid solution. Oil phase used was liquid paraffin contain a mixture of span 80 and tween 80 (1:1v/v) emulsifiers and vanillin as crosslinker (Peng et al., 2010). Other polymers like starch (Thombre et al., 2009); carboxymethylchitosan (Liu et al., 2007b); and protein like albumin (Mathew et al., 2009); has also been used.

Spray Drying

It involves the drying of mist of polymer and drug in the presence of hot air. The polymers are first dissolved in a suitable organic solvent and the drug is then dispersed in the polymer solution under high speed homogenization.

Table 2 : Types of microspheres with different polymers and drug loaded

Type of Microsphere	Polymer used	Drug loaded	Method of Preparation	Year	Reference
Bioadhesive Microspheres	Na-Alg	Glipizide	Ionotropic Gelation	2012	(Kumar and Kalekar)
Floating Microspheres	Eudragit	Ranitidine	Solvent Evaporation method	2011	(SINGH and CHAUDHARY, 2011)
Magnetic Microspheres	Chitosan & PAA	Starch Fe_3O_4		2012	(Guo et al., 2010)
Radio Active Microspheres.	PLA, PLGA, Chitosan	Radio Isotope		2006	(Häfeli, 2006)

is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in the stream of hot air which leads to the formation of microspheres (1-10um). Microparticles are then separated by cyclone separator from the hot air while the traces of solvent are removed by vacuum drying (Bindu and Sriram, 2012). Nifedipine loaded PVA microspheres (Saigal et al., 2013); hollow microspheres of hydroxyappatite (Sun et al., 2009); PLA and PLGA microspheres (Blanco et al., 2006); and bupivacaine loaded PCL microspheres (Blanco et al., 2003); have been reported by spray drying method.

Characterization

Measurement of microsphere hydration (%)

Microspheres are weighed immediately after filtration (M_1) and weighed again after drying to constant weight (M_2)

$$\text{Microspheres hydration (\%)} = \frac{M_1}{M_2} \times 100 \qquad (1)$$

Recovery of microspseres (%)

Recovery of formed microspheres is calculated by dividing the weight of obtained microspheres to the total weight of all ingredients charged during the preparation of drug polymer mixture.

$$\text{Percent yield (\%)} = \frac{W_1}{W_0} \times 100 \qquad (2)$$

Where W_1 is the weight of obtained microspheres and W_0 is the weight of all the ingredients charged in grams.

Rheological studies

Bulk and tapped density

Bulk density and tapped density will be calculated by following formula

$$\text{Bulk Density} = \frac{m}{V} \qquad (3)$$

m represents the weight of microspheres and V is the volume.

Tapped density can be calculated by using following formula (Ranjha et al., 2010)

$$\text{Tapped density} = \frac{m}{V_{100}} \qquad (4)$$

Where m is weight and V_{100} is volume of microspheres after 100 tapings.

Compressibility index and Huasner's ratio

Hausner's ratio is calculated by using following formula

$$\text{Hausner's ratio} = \frac{V1}{V2} \quad (5)$$

Where vi is volume before tapings and V2 is volume after tapings. A value closer to 1 indicates good flow properties (Shariff et al., 2007). Compressibility index also called Car's index is a indirect method of measurement for bulk density as the factors like size, shape, surface area and moisture content influence its value (Shariff et al., 2007)

$$\text{Compressibility index (\%)} = \frac{V_i - V_f}{V_i} \times 100 \quad (6)$$

Vi is initial volume, Vf is the final volume.

Angle of Repose

Angle of repose is measured by passing the microspheres through funnel to a petri dish then measuring the height (h) of heap formed and the radius (r) of the petri dish angle of repose is calculated as

$$\text{Tan}^{\theta} = \frac{h}{r} \quad (7)$$

Encapsulation Efficiency

Encapsulation efficacy is expressed as percentage of actual drug loading to the total amount of drug initially used. A specified amount of microspheres were extracted for drug at 50^0C for 24 hours. The solution is then filtered and the amount of drug is calculated by UV-Spectrophotometer at specified wavelength (Banerjee et al., 2010).

$$\text{Encapsulation Efficiency} = \frac{\text{experimental drug content}}{\text{theoretical drug content}} \times 100 \quad (8)$$

Scanning Electron Microscopy

SEM uses electrons instead of light to form image. SEM images have characteristic three dimensional appearances and used to investigate the size, surface structure, morphology and texture of the prepared microspheres.

Fourier Transform Infrared Spectroscopy

FTIR is carried out to study the polymer-polymer interaction and polymer drug interaction provides information about the interaction of different functional groups in grafting and crosslinking. The spectra were recorded for pure drug and drug loaded microspheres and samples are prepared in KBR disc. Also provides the information about the presence of free and chemically bound drug in the microspheres.

X-Ray Powder Diffractrometery

To study the effect of microencapsulation on the crystallinity of the drug in the microspheres, carried out on pure drug, blank microspheres and drug loaded microspheres.

Differential Scanning Calorimetery

Pure drug, polymer and drug loaded microspheres are evaluated by DSC for possible drug polymer interaction, by triturating separately and then heating at aluminium pan at a rate of 10^0 C/min from 0 to 120^0 C under constant nitrogen flow. Samples are run in triplicate for reproducibility.

In vitro drug release

In vitro drug release, from different formulations of microspheres was studied by using dissolution apparatus I or II in previous literature (Baccarin et al., 2007). Composition of microspheres plays an important role in the drug release behavior and the release pattern is studied by different in vitro kinetic models as follows

Zero order release equation (Kaushal et al., 2004)

$$F_t = K_o t \quad (9)$$

Where Ft is the release of drug at a specific time and K_0 is the zero order rate constant

First order release (Mehrgan and Mortazavi, 2010)

$$\text{Ln}\,(1 - F) = K_1 t \quad (10)$$

F is the fraction of drug released and K1 is the first order rate constant

Higuchi equation

$$F = k_2 t^{½} \quad (11)$$

Where k_2 is Higuchi constant

Hixon-crowell equation

$$Qo^{1/3} - Qt^{1/3} = K_{HC} \quad (12)$$

Korsmeyer-peppas equation

$$\frac{M_1}{M_\infty} = k_3 t^n \quad (13)$$

M_1 and M_∞ are the released drug at time 0 and ∞ and n is the diffusion constant.

Conclusion

It is generally observed that as compared to other conventional dosage form, microspheres are useful option for controlled and sustained drug delivery, targeted drug delivery (Active and passive targeting), radioactive and diagnostic purposes, localized drug delivery system. They show better patient compliance. Microspheres are also good candidate for oral, nasal and pulmonary delivery. So they play a very important role in the advancement of medical field. Various methods are used to prepare microspheres of required size, shape and surface morphology. Different properties like size, surface charge, hydrophilic and hydrophobic nature of the microspheres are responsible for determining the fate of microspheres in the body. As compared to existing technologies microspheres offers several advantages. They have shown new ways to biologist, biotechnologist and researcher as well to bring revolution in the area of drug delivery. In the recent years a lot of studies have been done on microspheres which shows that they are good alternatives for conventional as well as some novel drug delivery system. In future microsphere will attain central position in novel drug delivery system by combining them with various other systems

List of abbreviations

CMC Carboxymethycellulose

DSC Differential scanning calorimetery

FTIR Fourier transform infrared spctroscopy

GA Glutaraldehyde

HA Hayalouronic acid

PLA Polylacctic acid

PLGA Polylactide-co-glycolide

PVA Polyvinyl alcohol

SEM Scanning electron microscopy

XRD X-ray powder diffractometery

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