INTRODUCTION

The drug delivery system employed plays a vital role in controlling the pharmacokinetic profile of the drug, as it can influence the pharmacodynamic profile. Conventional drug delivery systems have numerous limitations such as undesirable side effects due to fluctuating plasma drug level, high peak-to-trough variations, inability to maintain plasma drug concentration within the therapeutic range, larger doses in order to obtain adequate therapeutic effect may result in undesirable, toxicological and immunological effects in non-target tissues. An appropriately designed controlled release system can be a major step toward solving the problem associated with conventional drug delivery systems. This review article includes the history and rationale behind controlled drug delivery systems. A variety of approaches have been investigated for controlled release of drugs and targeting to selective sites which include polymeric microspheres, liposomes and solid lipid nanoparticles. Microparticles are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 μm. Microparticles have numerous medical applications such as oral, vaccine, intranasal and ocular delivery of drugs. A detailed focus has been given on preparation techniques of microparticles viz. solvent evaporation method, spray drying method, freeze drying technique, hot pressure homogenization method, thermal cross-linking method and coacervation phase separation method. The range of techniques for preparation of microparticles offers a variety of opportunities to control aspects of drug administration and enhance therapeutic efficacy.

KEY WORDS: Controlled drug delivery system, conventional drug delivery system, microspheres, liposomes, therapeutic efficacy.
Controlled drug delivery has been categorized into four categories i.e. delayed released, sustained released, site-specific targeting and receptor targeting.

**Approaches for CDDS**

New technological advances have brought many innovative drug delivery systems into the commercial circulation. A variety of approaches have been investigated for controlled release of drugs and targeting to selective sites which includes polymeric microspheres, liposome, SLNs and microencapsulation.

- Polymeric microspheres have proved to be more physicochemical stable than liposomes but have some disadvantages i.e. preparation methods require organic solvents and large scale production is rather difficult [11].
- Liposomes are spherical particles composed of one or more concentric phospholipids bilayers alternating with aqueous partition [12].
- SLNs were developed in early 1990s and have been considered as promising drug carrier to obtain sustained release profile of incorporated active ingredient. They are particles of submicron size (50-1000 nm) composed of lipidic polymer matrix [13].
- Microencapsulation is the process in which small droplets of liquid or solid particles are coated by continuous film of polymeric materials. The first microencapsulation procedure was discovered by Bungenburg de Jon and Kan in 1931 for preparation of gelatin microspheres using gelatin coacervation process [11, 14].

**Microparticles as innovative CDDS**

Microparticles are particulate dispersions or solid particles of size range of 1-1000 μm. Depending upon whether drug has been entrapped or dispersed, they have been classified into microcapsules or microspheres as depicted in Figure 1. Microcapsules contains well defined core in which drug is confined surrounded by unique polymer membrane envelope. The core can be solid, liquid or gas and envelope is made of continuous, porous or non-porous polymeric phase. Microspheres are matrix system in which drug is physically and uniformly dispersed [11, 14].

**Applications of microparticles**

**General application** [15, 17]
- Separation of incompatible entities.
- Conversion of liquid to free flowing powder.
- Improvement in dissolution rate and bioavailability of drugs.
- Protection of compounds from atmospheric decomposition.
- Disguising unfavourable odour and taste.
- Sustained and prolonged release of drugs.
- Gastroretentive dosage form, hollow microspheres.
- Bioadhesive microspheres for intestinal and nasal administration.
- Radio opaque hydrogel microspheres for x-ray contrast properties.

**Technical application** [16]

Microspheres have ability to disperse in water to form clear colloidal solutions. This property can be a useful means of producing agricultural fertilizers releasing active ingredients in a controlled manner into large bodies of water. In addition, if polymers are biodegradable, they will not continue to pollute the environment. The microspheres are applicable in veterinary field, in order to administer drug in animals by giving drug loaded microspheres in drinking water.

**Medical application**

**Vaccine delivery**

The prerequisite of vaccine is protection against microorganism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. The aspect of safety and minimization of adverse reaction is complex issue. Lee et al. (2012) carried in-vivo studied of a vaccine delivery system based on thioltated eudragit microsphere for its ability to elicit mucosal immunity against enterotoxigenic escherichia coli (ETEC). The results suggested that thioltated eudragit microsphere may be a promising candidate for an oral
vaccine delivery system to elicit systemic and mucosal immunity [19].

Ocular delivery
The eye and cornea are easily accessible targets. However, the washout effect presents difficulties in retention of microparticulate drug carrier in corneal sac. A novel approach to increase the retention of microparticulate system can be by changing them to gel form in the cul-de-sac of eye. The rapid conversion of particulate suspension to gel form reportedly leads to their longer retention in the eye. Ana Rita et al. (2007) prepared ophthalmic drug delivery systems of acetazolamide using eudragit RS 100 and RL 100 by compressed anti-solvent technology. The prepared microparticles exhibited slower release than single drug. Drug release rate was controlled by diffusion mechanism, however; polymer swelling also contributes to overall transport mechanism [20].

Oral delivery
Oral route is one of the most preferred and convenient route for administration of drug. Thus, a number of controlled release systems have been developed for oral administration. Momoh et al. (2014) formulated and evaluated eudragit RS100/RL100 microspheres by solvent-evaporation technique for improved delivery of diclofenac sodium. Effective clinical utilization of non-steroidal anti-inflammatory drugs such as diclofenac sodium is significantly limited by ulcerogenic potential and poor bioavailability after oral administration. It was found that microsphere formulations based on eudragit polymers would likely offer a reliable and alternative means of delivering diclofenac sodium orally [21].

Intranasal delivery
The intranasal route is exploited for delivery of peptides and proteins. The conventional dosage forms are rapidly cleared from nasal mucosa. Bioadhesive gels have been proposed to increase retention of insulin and calcitonin. The bioadhesive microspheres providing greater control over surface character and release pattern is better alternative to gel dosage formulations. Yadav et al. prepared domperidone microspheres for intranasal administration by emulsification cross-linking technique using starch and epichlorhydrine as cross-linking agent. They showed good mucoadhesive property and swelling behaviour [22].

Buccal and sublingual drug delivery
The buccal mucosa may have potential for delivering peptide drugs low molecular weight, high potency and long biological half-life [23]. Nerkar et al. developed mucoadhesive microspheres of venlafaxine using linseed mucilage as a mucoadhesive agent by spray-drying technique for buccal delivery with an intention to avoid hepatic first-pass metabolism, by enhancing residence time in the buccal cavity. It was found that there was a marked increase in bioavailability after buccal administration as compared to oral route. It was concluded that linseed mucilage can be successfully used in production of mucoadhesive microspheres of venlafaxine [24].

Colon specific drug delivery
The colon specific drug delivery system should be capable of protecting the drug route to colon Drug release and absorption should not take place in stomach and small intestine. The bioactive agent should not be degraded, released or absorbed till the system reaches colon [25]. Deore et al. formulated colon targeted tinidazole microspheres by emulsion solvent evaporation method using eudragit polymer. It was concluded eudragit microspheres are promising as a carrier for colon targeted delivery of tinidazole [26].

Gene delivery
Gene delivery is the process of introducing foreign DNA into host cells. Gene therapy has become a promising approach for treatment of numerous inheritable or acquired diseases that are presently contemplated cureless [27].

Production techniques for microparticles
Numerous techniques for fabrication of microparticles have been represented in Figure 2. Table 1 depicts drug loaded polymeric or lipidic microparticles prepared by appropriate method.

Figure 2. Various production techniques for microparticles

Single emulsion solvent evaporation
Double emulsification technique
Spray drying method
Spray congealing method
Melt dispersion technique
Chemical and thermal cross-linking
High pressure homogenization method
Coacervation phase separation method
Microchannel emulsification

Single emulsion solvent evaporation method
It involves dissolution of polymers in an organic solvent followed by emulsification in an aqueous phase containing emulsifying agent. The resulting o/w emulsion is stirred for several hours under ambient conditions in order to allow solvent evaporation followed by filtration, rinsing and drying in desiccators [28]. Yukel et al. prepared polymeric microspheres containing nicardipine
hydrochloride with eudragit RS and eudragit RL by solvent evaporation method using sucrose stearate as droplet stabilizer [29]. Behera et al. prepared 5-fluorouracil-ethyl cellulose microspheres by solvent evaporation technique using dichloromethane and acetonitrile for preparation of microspheres. Polyvinyl alcohol was used as processing medium to solidify the microspheres. Scanning electron microscopy of microspheres had shown their spherical shape with smooth surface. It was found that prepared microspheres followed higuchi model indicating that drug release form homogenous matrix was through diffusion [30].

Phutane et al. designed and systematically evaluated sustained release microspheres of glipizide for delivering microparticulate system using polymer mixture of ethyl cellulose and eudragit S100 as controlled release polymer by emulsion solvent diffusion-evaporation technique using modified ethanol-dichloromethane co-solvent system. The drug release pattern from microspheres followed korsmeyers-peppas model and zero-order release kinetic model which indicates that drug release was followed by anomalous non-fickian diffusion. It was concluded that microparticulate system can be successfully designed for sustained delivery of glipizide [9].

The schematic representation of o/w single emulsion solvent evaporation method has been represented in Figure 3.

**Figure 3. Schematic representation of o/w single emulsion solvent evaporation method**

![Schematic for Double Emulsification Technique](image)

**Double emulsification technique**

Double emulsification technique involves the formation of double emulsion of either w/o/w or o/w/o. The aqueous drug solution is dispersed in a lipophilic organic continuous phase. The continuous phase that consists of polymer solution eventually encapsulates drug contained in dispersed aqueous phase to form primary emulsion. The pre-formed emulsion is subjected to homogenization or sonication before addition to aqueous solution of polyvinyl alcohol (PVA) to form double emulsion. Das et al. prepared zidovudine-ethylcellulose microspheres by water-in-oil-in-oil double emulsion solvent diffusion method. The drug release pattern from microsphere was best fitted in higuchi model, indicating diffusion-controlled principle [31].

Jelvehgari et al. evaluated microencapsulated controlled release preparations of tolmetin sodium using ethyl cellulose as retardant material, span 80 as droplet stabilizer and n-hexane as hardening agent using water-in-oil-in-oil double-emulsion solvent diffusion method. The prepared microspheres were characterized for micromeritic properties, drug content, loading efficiency and production yield and particle size.

The drug-loaded microspheres extended drug release up to 24 hours and was found to be diffusion and erosion controlled [32]. The solid microspheres are subsequently obtained by filtration and washing as shown in Figure 4.

**Figure 4. Schematic diagram of double emulsion method**

![Diagram of Double Emulsion Method](image)

**Spray drying method**

Drug and polymer coating material are dissolved in suitable solvent to form solution which is subjected to spray through nozzle in a spray drier under different experimental conditions (Figure 5). The size of microparticles are controlled by various factors like rate of spraying, feed rate of drug-polymer solution, nozzle size, temperature of drying and collecting chamber [28].

Pavanetto et al prepared vitamin D3 microspheres using five different polymers of lactide class such as poly-L-lactide 57000 MW, poly-D, L-lactide 209,000 MW, 109,000 MW, 16,000 MW, and polylactide-co-glycolide 22,000 MW by spray drying. It was evaluated with rotating bottle method that different release profiles were obtained from microspheres depending on type of polymer [33].

**Spray congealing**

Drug is dissolved into melt of lipophilic polymer material to form hot mixture and allowed to atomize with pneumatic nozzle into a vessel that is stored in a carbon dioxide ice bath. Fabricated microparticles are vacuum dried at room temperature for several hours [18]. Figure 6 shows schematic diagram of spray congealing microencapsulation method. Gao et al. prepared lipid-polymer composite microspheres (LP-MS) of 10-
hydroxycamptothecin for colon-specific drug delivery using pH-sensitive polymer Eudragit S100 and non-polar lipid Compritol 888 ATO by an ultrasonic spray freeze-drying technique.

Drug release studies indicated that less than 15% of drug was released below pH 6.8, whereas more than 30% was released with a sustained-release model at pH 7.4. It was concluded that LP-MS could be a promising tool for colon drug delivery [34].

Figure 5. Schematic diagram of spray drying method

Figure 6. Schematic diagram of spray congealing method

Melt dispersion technique

Hot mixture of drug in melt of polymer is emulsified into an aqueous surfactant solution that has been heated above polymer melting point to form emulsion which is finally allowed to cool in an ice bath. Ghaly et al. fabricated microspheres by melt dispersion technique to entrap ibuprofen into carnauba wax as carrier with the aid of pluronic L-62. Microsphere prepared by using aqueous vehicle was spherical and smooth. It was concluded that melt dispersion technique was successful method for preparation of sustained release ibuprofen microspheres [35,36]. The Schematic representation for preparation of microspheres by o/w melt dispersion technique has been shown in Figure 7.

Figure 7. Schematic representation of melt dispersion technique

Chemical and thermal cross-linking method

Aqueous solution of natural polymer containing drug to be incorporated is dispersed in organic phase to form w/o emulsion followed by solidification either by thermal crosslinking or addition of chemical crosslinking agent such as glutaraldehyde [37]. Joseph et al. developed diclofenac sodium loaded biocompatible microspheres to reduce dosing frequency, gastrointestinal side effects and improve patient compliance. The microspheres were prepared by emulsion thermal cross-linking process using bovine serum albumin. It was reported that drug release from microspheres was prolonged to provide sustained release pattern [38]. Samad et al. designed oral controlled release microspheres of rifampicin (RIF) by using a biodegradable and biocompatible polymer, gelatin B and natural cross-linker, sucrose by thermal gelation method. Microspheres were prepared to circumvent required regular high dose of conventional dosage forms by controlled release for drug in gastrointestinal tract. The results of dissolution and scintigraphy studies prove the utility of formulation for whole intestine [37]. Figure 8 represents schematic representation of microspheres preparation by thermal cross-linking method.

Figure 8. Schematic representation of thermal cross-linking method
Hot-pressure homogenization method

The homogenization method which can be hot homogenization or cold homogenization can reduce particle size to micrometer or nanometer size depending on composition and process parameters. In hot homogenization method, pre-emulsion is obtained by mixing a hot aqueous surfactant solution with drug loaded melt of polymer using high shear homogenizer which has been preheated at temperature above melting point of polymer. The pre-emulsion is put through homogenizer once or several times followed by cooling at room temperature. The cold homogenization method involves dissolution of drug into melt of polymer followed by solidification in liquid nitrogen or dry ice and homogenization. Grinded particles are dispersed into an aqueous surfactant solution heated at temperature below the polymer melting point [28].

Attama et al. formulated surface-modified solid lipid microspheres containing halofantrine using lipid matrix formed from goat fat and a phospholipid (P90H) by hot homogenization method. The prepared microspheres were evaluated by in-vitro drug release studies for comparing drug release from commercial dosage form (Halfan® 250 mg tablet, Glaxo-Smithkline, Mayenne France) using simulated gastric fluid (SGF pH 1.2), simulated intestinal fluid (SIF pH 7.2) and phosphate buffer (pH 6.8) as biorelevant media. It was concluded that solid lipid microspheres of halofantrine presents a better alternative to conventional tablet formulation as in-vitro dissolution of lipophilic halofantrine was highly improved [39].

Coacervation phase separation method

Coacervation is the separation of macromolecular solution into two immiscible liquid phases out of which one is dense coacervate phase while another is dilute equilibrium phase. This may be simple or complex coacervation depending upon whether one macromolecule is present or more than two macromolecules of opposite charges are present [18]. Simple coacervation may be achieved by addition of salts, by non-solvent addition, by temperature change and by addition of incompatible polymer. Electrostatic interactive forces drive complex coacervation between two or more macromolecules. This system is potentially useful for the delivery of proteins, polypeptide drugs and materials which cannot withstand cross-linking process [40].

Arunachalam et al. prepared gelatin microspheres containing ofloxacin using glutaraldehyde as cross-linker by coacervation phase separation method. The microspheres were analyzed for drug entrapment, bulk density, angle of repose, particle size and in-vitro release pattern. It was found that prepared microspheres could sustain drug release over a period of 8 hrs [41]. The schematic representation for fabrication of microspheres by coacervation phase separation technique has been shown in Figure 9.

Drug release mechanism

Drug release from microparticles occurs either by erosion or diffusion as depicted in Figure 10. Erosion which may surface erosion or bulk erosion is the physical dissolution of polymer as a result of its degradation. In surface erosion, water is confined to the surface of matrix leading to chain scission of surface matrix. In this case, degradation rate is faster than penetration of water into polymer bulk and drug will be released as polymer matrix erodes.

Microchannel emulsification technique

This technique is considered to be novel method used to prepare monodisperse o/w and w/o emulsions without high mechanical stress and at lower energy input compared with conventional emulsification processes. A silicon microchannel plate which has been fabricated by micromachining technology is used to produce monodisperse droplets by forcing dispersed phase into continuous phase through microchannels followed by cooling the emulsion at room temperature. The droplet size is precisely regulated by structure of microchannels [42].

Jihong et al produced super-monodisperse oil-in-water microspheres (O/W-MS) using lecithin and lysophosphatidylcholine (LPC) as surfactant by novel microchannel (MC) emulsification technique. Monodispersed O/W-MS were successfully produced and it was further improved by a special surface oxidation treatment of MC plate [42]. Isao et al. prepared micron-scale monodisperse oil-in-water (O/W) microspheres (MS) using soybean oil and medium-chain triacylglycerol (MCT) as dispersed phase and physiological saline as continuous phase by a novel microchannel (MC) emulsification technique. The size distribution of recovered O/W-MS demonstrated their long-term stability [43].

Fig. 9. Schematic representation of coacervation phase separation technique

![fig9](Image 324x500 to 563x684)
Surface erosion is characterized as zero order release since the rate of degradation is constant. If diffusion of water into polymer matrix is faster than rate of hydrolysis, erosion will occur throughout the entire material leading to bulk erosion.

Bulk erosion rates are difficult to control since it is not zero order. The diffusion-based drug release can be either fickian or non-fickian. In fickian diffusion, the rate of release is independent of drug concentration in microspheres [44].

### Table 1. Drug loaded polymeric or lipidic microparticles prepared by appropriate method

<table>
<thead>
<tr>
<th>Technique</th>
<th>Drug loaded</th>
<th>Polymer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single emulsion solvent evaporation</td>
<td>Nicardipine hydrochloride</td>
<td>Eudragit RS and Eudragit RL</td>
<td>[29]</td>
</tr>
<tr>
<td>Single emulsion solvent evaporation</td>
<td>5-Flourouracil</td>
<td>Ethyl cellulose</td>
<td>[30]</td>
</tr>
<tr>
<td>Single emulsion solvent evaporation</td>
<td>Glipizide</td>
<td>Ethyl cellulose and Eudragit S100</td>
<td>[9]</td>
</tr>
<tr>
<td>Double emulsion solvent diffusion</td>
<td>Zidovudine</td>
<td>Ethylcellulose</td>
<td>[31]</td>
</tr>
<tr>
<td>Double emulsion solvent diffusion</td>
<td>Tolmetin sodium</td>
<td>Ethylcellulose</td>
<td>[32]</td>
</tr>
<tr>
<td>Spray drying</td>
<td>Vitamin D3</td>
<td>Poly-L-lactide, Poly-D,L-lactide and Poly lactide-co-glycolide</td>
<td>[33]</td>
</tr>
<tr>
<td>Ultrasonic spray freeze-drying</td>
<td>10-hydroxycamptothecin</td>
<td>Eudragit S100 and Compritol 888 ATO</td>
<td>[34]</td>
</tr>
<tr>
<td>Melt dispersion</td>
<td>Ibuprofen</td>
<td>Carnauba wax</td>
<td>[35]</td>
</tr>
<tr>
<td>Thermal gelation</td>
<td>Rifampicin</td>
<td>Gelatin B</td>
<td>[37]</td>
</tr>
<tr>
<td>Thermal cross linking</td>
<td>diclofenac sodium</td>
<td>Bovine serum albumin</td>
<td>[38]</td>
</tr>
<tr>
<td>Hot homogenization</td>
<td>Halofantrine</td>
<td>Goat fat and phospholipid (P90H)</td>
<td>[39]</td>
</tr>
<tr>
<td>Coacervation phase separation</td>
<td>Ofloxacin</td>
<td>Gelatin</td>
<td>[41]</td>
</tr>
<tr>
<td>Microchannel emulsification</td>
<td>Soybean oil</td>
<td>Medium-chain triacylglycerol (MCT)</td>
<td>[43]</td>
</tr>
</tbody>
</table>

### CONCLUSION

Several benefits can be derived from controlled drug delivery system which includes reduced dose frequency that can lead to improved patient compliance and reduced side-effect profile especially those related to rapid rise in peak serum concentration and local irritation due to a slow release or targeted nature of delivery. Other advantages offered by CDDS include improved drug tolerance, reduced peak-to-trough variations and maintaining plasma levels within therapeutic ranges. Controlled release formulations also provide increased duration of drug therapeutic effect. For pharmaceutical companies, controlled release formulations are better alternative to conventional drug delivery system to maintain therapeutic level of drug in body for sustained period of time. A variety of approaches have been investigated for controlled release of drugs and targeting to selective sites which includes polymeric microspheres, liposome and SLNs. Microparticles have numerous medical applications such oral, vaccine, intranasal and ocular delivery of drugs. Moreover, the range of techniques available for preparation of microparticles offers a variety of opportunities to control aspects of drug administration and enhance therapeutic efficacy of pharmaceutical entity.

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### CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

### REFERENCES


