Microparticle Formulation of Doxycycline - A Review

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ABSTRACT

Microspheres drug delivery system has gained enormous attention due to its wide range of application as it covers targeting the drug to particular site to imaging and helping the diagnostic features. It also has advantage over various other dosage forms like we know for lungs disease now a days aerolite drugs are used for local delivery of drugs but it has disadvantage of shorter duration of action so for sustained release and reducing side effects and hence to achieve better patient compliance microspheres can be used. It also has advantage over liposomes as it is physico-chemically more stable. Moreover the microspheres are of micron size so they can easily fit into various capillary beds which are also having micron size. Doxycycline HCl is a broad spectrum tetracycline antibiotic. Doxycycline HCl is highly water soluble drug. It is bitter solid, irritative to mucous membrane, unstable in aqueous solution. The plasma concentration–time profile depicts that the drug release is not immediate but modified drug release. Thus formulation of conventional oral liquid dosage forms is not possible. There is a need to formulate an oral liquid modified release drug delivery system. The purpose of the review is to compile various methods to formulate lipid microspheres for oral suspension as modified release oral liquid preparation. Lipid microparticles can be prepared using lipid materials such as compritol 888 ATO, glyceryl monostearate, carnauba wax. Widely used and the most convenient technique for formation of free-flowing particulates of controlled particle size is spray congealing method as reported in the literature. High encapsulation efficiency, high drug loading, required particle size for sustain release, mass production can be obtained without use of any solvent using this technique. Apart from easy swallowability, flexible dosing and improved bioavailability, it has capability of controlling the release of the active ingredients which improves patient compliance and also reduces the gastrointestinal side effects significantly by reducing the concentration of the drug exposed to the gastrointestinal mucosa.

Key words: Microspheres drug delivery system, aerolite drugs, Doxycycline HCl.

INTRODUCTION: [1, 13]

In contrast to drug delivery system, the word novel is searching something out of necessity. The drug has to be delivered for a prolonged period of time and many medicines have to be taken simultaneously in case of chronic patients. Frequent administration of drug is necessary when those have shorter half-life and all these leads to decrease in patient’s compliance. In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect, adverse effect decreases by lowering peak plasma concentration. The controlled release dosage form maintaining relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time. One such in Microspheres as carriers of drug become an approach of controlled release dosage form in novel drug delivery system. Microspheres are defined as “Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles” (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size of (1-1000nm). Further, currently available slow release oral dosage forms, such as enteric coated/ double-layer tablets which release the drug for 12-24 hours still result in inefficient systemic
delivery of the drug and potential gastrointestinal irritation.

Microspheres are discrete spherical particles ranging in average particle size from 1 to 50 microns. Because of their size and shape, Microspheres offer a ball-bearing effect which will impart finished products with an elegant silky texture, increased payoff, and enhanced slip. This ball-bearing effect promotes better bendability on the skin and a more natural finish. Microspheres are also able to scatter light to diminish the look of fine lines on the skin, while letting enough light through so the look of the skin is natural. This phenomenon is known as “Soft Focus Effect” or “Optical Blurring.” Some Microspheres are porous and have a high oil absorption capacity; they can act as carriers to absorb and deliver materials, and can be used for sebum control. A special use of Microspheres is in mascaras. The non-absorbent grades of silica of different diameters have a volumizing effect, with minimum absorbency. Cellulose Beads are hydrophilic Microspheres made of cellulose which have a high capacity to absorb moisture. They are also available coloured with inorganic colorants. Since they can be used in all product forms (powders, anhydrous hot pours, emulsions, etc.), Microspheres, whether used individually or in combination, have become indispensable to formulation of state-of-the-art cosmetic products.

Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multi-particulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided. Microencapsulation is used to modify and retard drug release. Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa. Drug release and absorption is achieved by degradation of lipid matrices by lipase enzyme in the small intestine. Apart from easy swallowability, flexible dosing and improved bioavailability, it has capability of controlling the release of the active ingredients which improves patient compliance and also reduces the gastrointestinal side effects significantly by reducing the concentration of the drug exposed to the gastrointestinal mucosa. Doxycycline HCl is a broad spectrum tetracycline antibiotic. Doxycycline HCl is highly water soluble drug. It is bitter solid, irritative to mucous membrane, unstable in aqueous solution. The plasma concentration–time profile depicts that the drug release is not immediate but modified drug release. Thus formulation of conventional oral liquid dosage forms is not possible.

**DRUG DESCRIPTION: (doxycycline monohydrate/Vibramycin Monohydrate)**

Vibramycin is a broad-spectrum antibiotic synthetically derived from oxytetracycline, and is available as Vibramycin Monohydrate (doxycycline monohydrate); Vibramycin Hyclate and Vibra-Tabs (doxycycline hydrochloride hemihemololate hemihydrate); and Vibramycin Calcium (doxycycline calcium) for oral administration.

The structural formula of doxycycline monohydrate is:
With a molecular formula of C22H24N2O8•H2O and a molecular weight of 462.46. The chemical designation for doxycycline is 4-(Dimethylamino)-1,4,4a,5,5a,6,Il,12a-octahydro-3,5,10,12,12a-pentahydroroxy-6-methyl-Il,II-dioxo-2-naphthacenecarboxamide monohydrate. The molecular formula for doxycycline hydrochloride hemihydrate is (C22H24N2O8•HCl)2-C2H6O•H2O and the molecular weight is 1025.89. Doxycycline is a light-yellow crystalline powder. Doxycycline hyclate is soluble in water, while doxycycline monohydrate is very slightly soluble in water.

**Properties:**

- **Physical:**
  1. Melting point: -201°C
  2. Stability: -10 – 15% degraded at 70°C
  3. Colour: Yellow

- **Pharmacokinetics:**
  1. Bioavailability- 95-100%
  3. Half-life – 18-22Hrs
  4. Excretion – urine & faeces. (40%/72 hours)

- **Clinical Treatment:**
  1. Respiratory tract infections caused by Mycoplasma pneumoniae.
  2. Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by Rickettsia.

**Various Formulations of Doxycycline monohydrate:**

Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Inert ingredients in the capsule formulations are: hard gelatin capsules (which may contain Blue 1 and other inert ingredients); magnesium stearate; microcrystalline cellulose; sodium lauryl sulfate. Inert ingredients for the oral suspension formulation are: carboxymethylcellulose sodium; Blue 1; methylparaben; microcrystalline cellulose; propylparaben; raspberry flavor; Red 28; simethicone emulsion; sucrose.

Inert ingredients for the tablet formulation are: ethylcellulose; hypromellose; magnesium stearate; microcrystalline cellulose; propylene glycol; sodium lauryl sulfate; t alc; titanium dioxide; Yellow 6 Lake.

**TYPES OF ORAL LIQUID FORMULATION:**

- **Mono-Phasic**
  4) Solution
    - Aqueous solutions
    - Non-aqueous solutions

- **Polyphasic**
  5) Colloidal dispersions
    - Liposomes
    - Niosomes
    - Polymeric/mixed micelles
    - Nanoparticle
      - Nano suspensions
      - Nano emulsion/Micro emulsion
      - Solid Lipid Nanoparticles(SLN)
      - Nanostructure lipide carriers(NLC)
      - Lipid drugs conjugated (LDC) nanoparticles

- **Microparticles**
  6) Microspheres
  7) Microcapsules
  8) Micro-emulsion

**Dry Powders for reconstitution**

**TYPES OF MICROSPHERES**

**Bio adhesive microspheres:**

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.
Magnetic microspheres: [12,13]
This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. 5 different types are

Therapeutic magnetic microspheres: Are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system. Diagnostic microspheres: Can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming Nano size particles supramagnetic iron oxides.

Floating microspheres: [17,18]
In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) given through this form.

Radioactive microspheres: [19]
Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So all these conditions; radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

Polymeric microspheres
The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

• Biodegradable polymeric microspheres: Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment.

Synthetic polymeric microspheres: The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible. But the main disadvantage of these kinds of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

Table: Various types of polymers and their application [18,23,26,27]

<table>
<thead>
<tr>
<th>POLYMER</th>
<th>MECHANISM</th>
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<tbody>
<tr>
<td>Modified starch, HPMC, Carbopol 974P</td>
<td>Slower release of drug.</td>
</tr>
<tr>
<td>Ethyl Cellulose</td>
<td>Controlled release for longer period of time.</td>
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<tr>
<td>PLGA, Chitosan</td>
<td>Vaccine delivery.</td>
</tr>
<tr>
<td>PLA, PLGA, Starchycanoacrylate(PEG) liposomes.</td>
<td>Drug delivery without toxic side effects.</td>
</tr>
<tr>
<td>Magnetic polystyrene microspheres</td>
<td>Specific cell labelling.</td>
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<tr>
<td>Polymer resins such as Agarosepolyacroline, sephadex</td>
<td>Affinity chromatography.</td>
</tr>
<tr>
<td>Chitosan coated PIGA microspheres</td>
<td>Targeted drug delivery</td>
</tr>
<tr>
<td>Polyvinyl alcohol, polyacrylamide</td>
<td>Adsorption of harmful substances in blood.</td>
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</tbody>
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METHOD OF PREPARATION: [1,14]
Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking,
drug of cross linking, evaporation time, co-precipitation etc. The various methods of preparations are

**Emulsion solvent evaporation technique:**
In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of pvp as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs. Aceclofenac microspheres are prepared by this technique.

**Emulsion cross linking method:**
In this method drug was dissolved in aqueous gelatine solution which was previously heated for 1 hr at 40°C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35°C, results in w/o emulsion then further stirring is done for 10 min at 15°C. Thus the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glycine solution containing 0.1% Tween 80 at 37°C for 10 min to block un-reacted glutaraldehyde Examples for this technique is Gelatin A microspheres.

**Co-acervation method:**
Co-acervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80°C by heating. Then the drug was finely pulverised and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twice with cyclohexaneand air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule. Co-acervation non solvent addition: Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propylisobutylenein closed beaker with magnetic stirring for 6hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15mins. Then phase separation is done by petroleum benzoin 5 times with continuous stirring. After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50oc for 4 hr.

**Spray drying technique:**
This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent. Organic solution of poly (epsilon-caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may lose crystalinity due to fast drying process.

**Emulsion-solvent diffusion technique:**
In order to improve the residence time in colon floating micro particles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a desiccator at room temperature. The following micro particles were sieved and collected.

**Multiple emulsion method:**
Oral controlled release drug delivery of indomethacin was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acetate. The the primary emulsion was then re emulsified in aqueous medium. Under optimised condition discrete microspheres were formed during this phase.

**Ionic gelation:**
Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25 % (w/v) of diclofenac sodium was added to 1.2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca²⁺/Al³⁺ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gelification followed by filtration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.
Hydroxyl appetite (HAP) microspheres in sphere morphology: [7]
This was used to prepare microspheres with peculiar spheres in sphere morphology microspheres were prepared by o/w emulsion followed by solvent evaporation. At first o/w emulsion was prepared by dispersing the organic phase (Diofenac sodium containing 5% w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co solvencing and helped them to stay individual droplets .While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres.

CHARACTERIZATION/ EVALUATION OF MICROSPHERES: [26,27,29]
Particle size analyser: [26]
Microsphere (50 mg) was suspended in distilled water (5mL) containing 2%w/v of tween 80, Toprevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size was expressed as volume mean diameter in micrometre.

Optical microscopy: [27]
This method was used to determine particle size by using optical microscope (Meizer OPTIK) The measurement was done under 450x (10x eye piece and 45x objective) and 100 particles were calculated.

Scanning electron microscopy (SEM): [28]
Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure.

Swelling index: [29]
This technique was used for Characterization of sodium alginate microspheres were performed with swelling index technique Different solution (100mL) were taken such as (distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and alginate microspheres (100mg) were placed in a wire basket and the above solution and swelling was allowed at 37°C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.

Entrapment efficiency:
Microspheres containing of drug (5mg) were crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, and was filtered then assayed by uv-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.

X-ray diffraction:
Change in crystalinity of drug can be determined by this technique. Microparticles and its individual components were analysed by the help of D & discover (Bruker, Germony). Scanning range angle between 8 0C - 70 0C.

Scan speed - 4o/min
Scintillation detector
Primary silt=1mm
Secondary silt=0.6 mm

Thermal analysis of microcapsule and its component can be done by using-
Differential scanning calorimetry (DSC)
Thermo gravimetric analysis (TGA)
Differential thermometric analysis (DTA)

Accurately the sample was weighed and heated on alumina pan at constant rate of 10oc/min under nitrogen flow of 40 ml/min

UV-FTTR (Fourier transform infra red): [30]
The drug polymer interaction and also degredation of drug while processing for microencapsulation can be determined by FTIR.

Stability studies: [19]
By placing the microspheres in screw capped glass container and stored them at following conditions:
1. Ambient humid condition
2. Room temperature (27+/=2 0C)
3. Oven temperature (40+/=2 0C)
4. Refrigerator (5 0C -80C).
It was carried out of a 60 days and the drug content of the microsphere was analysed.

Zeta potential:
The polyelectrolyte shell was prepared by incorporating chitosan of different molecular weight into the W2 phase and the resulting particles were determined by zeta potential measurement.

FORMULATION STRATERGY FOR DOXYCYXLINE MONOHYDRATE:
Multiparticulate system as oral liquid suspension: [4,5]

Microspheres are defined as “Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles” (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size of (1-1000nm). Microencapsulation is used to modify and retard drug release. Due to its
small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa.

A novel oral controlled-release drug delivery system which consists of microspheres of 75–500 μm in diameter has been designed and developed. A drug is dispersed in a spherical micro matrix. Drug is release affected by the size of the microspheres and the drug content in the microspheres. However, release of the drug could be regulated by selecting an appropriate hydrophilic-lipophilic balance value for polymers.

Potential use of microspheres in the Pharmaceutical industry: [6,7]
1) Taste & odour masking.
2) Conversion of oils & other liquids to solids for ease of handling.
3) Protection of drugs against the environment (moisture, light, heat).
4) Separation of incompatible materials (other drugs or excipients).
5) Improvement of flow of powders.
6) Aid in dispersion of water-insoluble substance in aqueous media, & production of sustained release, controlled release, & targeted medications.

Types of Microspheres: [6,7,9]
1) Microcapsule: consisting of an encapsulated core particle. Entrapped substance completely surrounded by a distinct capsule wall.
2) Micro matrix: consisting of homogenous dispersion of active ingredient in particle.

Types of Polymer Used: [18,23,26,27]

Biodegradable:
Biodegradable polymers have the advantages that they do not require surgical procedures for implantation & removal. They are degraded in the body to biocompatible materials. Eg’s:- Poly lacti-co – glycolic acid (PLGA), Polyalkyl cyanoacrylates, Polyanhydrides.

Applications:
1) Control drug release rates.
2) Conserve the stability of some drug as proteins & peptides.
3) Also to target drug to specific sites in the body, thereby optimizing their therapeutic response, decreasing toxic side effects, & eliminating the inconveniences of repeated injections.

4) They are also used in gene delivery & diagnostic material.

Non-Biodegradable:
Eg’s:- Poly-methyl methacrylate, Acrolein, Epoxy polymers.

Natural Materials
- Proteins.
  - Albumins.
  - Gelatin.
  - Collagen.
- Carbohydrates.
  - Starch agarose.
  - Carrageena.
  - Chitosan.
- Chemically modified carbohydrates.
  - Poly (acryl) dextran.
  - Poly(acryl) starch.
- Vegetable lipids.

Techniques for preparation of microspheres: [7]
1) Single Emulsion technique.
2) Double emulsion technique.
3) Polymerization techniques
   a) Normal polymerization.
   b) Interfacial polymerization.
4) Coacervation phase separation techniques.
5) Spray drying & spray congealing.
6) Solvent extraction.

Spray congealing: [33,34]
To prepare controlled-release microspheres, a coacervation/phase separation technique, interfacial polymerization technique, solvent evaporation method, spray-drying method, fluidized bed coating method, centrifugal fluidization method and so on can be used. These methods, however, are complicated and multiple-process operations which do not use water or organic solvents.

A spray-congealing method can be attempted to prepare microspheres, because it is a single stage, rapid and continuous particle processing operation. Microspheres prepared by the spray-chilling method had a spherical form and a smooth surface as reflected in their good flowability. In addition, the microspheres had a narrow particle size distribution.
Method for preparation of Microparticles:

Microparticles with a theoretical drug loading of 20% and 30% (w/w) were produced by the spray-congealing process using the wide pneumatic nozzle (WPN). WPN is a two fluid atomizer equipped with a thermostated reservoir with a wide orifice opening. This nozzle configuration implies an external mixing of the fluid and of the gas outside the nozzle orifice. As a consequence, atomization can be varied by changing the gas pressure without affecting the liquid flow rate and high concentration and viscous products are better atomized. The WPN requires modest air consumption (1–3 bar, depending on the desired particle size) and it generates a uniform spray pattern. The microparticles solidify along the congealing chamber and are collected at the bottom.

The carrier was heated at a temperature of 10°C above its melting point. First the drug were added to the molten Lipide and stirred to obtain a suspension, which was then loaded into the feeding chamber of the WPN, kept at 65°C to avoid the solidification of the suspension in the nozzle orifice. The inlet air pressure was set at 1.5 bars.

Spray congealing Technique The transition of a melt from a soft or fluid state to a rigid or solid state by cooling is called congealing. The various droplet formation techniques and the efficient droplet / air contact make the spray drying concept ideal for making spherical particle powder by congealing of melts.

Advantages of Formulating Doxycycline monohydrate into microsphere:
1) Sustained release of drug.
2) Prevents GI Irritation.
3) Stable for long time.
4) Protection from light, moisture etc.
5) Mask the bitter taste.
6) No use of organic solvent
7) High drug loading and encapsulation capacity compare to other carriers
8) Feasibility of scale up

APPLICATION OF MICROSPHERES: [7,18]
Medical application:
1) Release of proteins, hormones and peptides over extended period of time.
2) Gene therapy with DNA plasmids and also delivery of insulin.
3) Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control.
4) Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intraarterial/ intravenous application.
5) Tumour targeting with doxorubicin and also treatments of leishmaniasis.
6) Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
7) Used in isolation of antibodies, cell separation and toxin extraction by affinity chromatography.
8) Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.

Radioactive microsphere’s application: \(^{[7,18]}\)
1) Can be used for radio-embolisation of liver and spleen tumours.
2) Used for radio-synvectomy of arthritis joint, local radiotherapy, interactivity treatment.
3) Imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep vein thrombosis can be done.

Other applications:
1) Fluorescent microspheres can be used for membrane based technologies for flow cytometry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbent Assay.
2) Yttrium 90 can be used for primary treatment of hepatocellular carcinoma and also used for pretransplant management of HCC with promising results.

FUTURE CHALLENGES:
Future challenges of microspheres look bright particularly in the area of medicinal field because of its wide spectrum of application in molecular biology, eg: microsphere based genotyping platform is used to detect six single nucleotide polymorphism, yttrium-90 microspheres is used to prevent tumour after liver transplantation and it’s advanced way in delivery of vaccines and proteins.

CONCLUSION
It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of target specificity and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumours, detecting bio-molecular interaction etc. So, in future microspheres will have an important role to play in the advancement of medicinal field.

Thus we conclude that, lipids should find increased use in applications as diverse as enhanced bioavailability, extended release in oral drug delivery and taste masking. Multi-particle system for oral suspension was chosen as a liquid drug delivery system because of several advantages offered by this system over other conventional systems. Apart from easy swallowability, flexible dosing and improved bioavailability, it has capability of controlling the release of the active ingredients which improves patient compliance and also reduces the gastrointestinal side effects significantly by reducing the concentration of the drug exposed to the gastrointestinal mucosa. Spray congealing technique is a most convenient method of transforming melted feed stocks into free-flowing particulates of controlled particle size. Packaging can be done in sachets. Thus, lipid microparticles as oral suspension prepared by spray congealing method packed in sachet is the simplest, economical and easy to scale-up method as compared to other formulation and techniques.

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