JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A review on preparation and estimation techniques of sustain released Verapamil Hydrochloride microspheres

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Abstract: **The sustain release drug delivery system was developed to obtain prolonged pharmacological action by the continuous release of medicine after the drug administration along with minimum side effects. This can be an advanced approach towards the drugs with short half-life, elimination rate and are absorbed from the absorption window. The microspheres are termed as solid and curved molecules (1-1000 µm), with colloidal properties and a great proportion with respect to surface and volume. The microspheres are made up of wax, polymers (polyglycolic acid (PGA), polylactic acid (PLA) and natural products (starch, gum, protein, fat and wax etc). For the microspheres formulation, the polymer dissolving solvents are selected on the basis of drug-polymer solubility and stability, process safety and financial considerations. The interfacial properties of microspheres play an important role by indicating their activity. Verapamil hydrochloride (VRH) is a drug of choice for microsphere formulation process. It is categorized as calcium channel blocker with a half-life of about 2.8-7.4 hours and approximately 90% absorption rate. It is commonly used in cardiac arrhythmias and hypertension. The goal of this study is to review the formulation and evaluation techniques of Verapamil hydrochloride microspheres (VRHMs) which is meaningful in contrast of highlighted formulation techniques, drug selection parameters and advance novel research for SRDDs by an ionotropic gelation method using different polymers like Guar gum, Xanthan gum, HPMC (K100M) and Sodium alginate (SA) as a cross linking agent.**

KEYWORDS: **Verapamil hydrochloride, Sustain release, Microspheres, Ionotropic gelation, Natural polymers, Sodium Alginate.**

I. INTRODUCTION

Oral drug administration is well known, suitable and preferable method for the systemic delivery for decades because of easy drug administration, patient compliance and dosing flexibility. The drug in intestine will empty along with fluids covering entire surface area available for absorption. The sustained release delivery system with property of being preserved in intestine is known as gastro-retentive transmission system. The polymer microspheres possessing central space are formulated by deacidification when adjoining into an acidic vehicle. Verapamil's buoyant and empty microspheres represent gastro-retentive controlled-release delivery system. Studies have shown that sustained release oral formulations face two main problems, short-term gastric habitation and uncertain gastric clearance. The rate of drug absorption in GIT can be very short [1,2]. The sustain release drug formulations are acquiring higher acceptance as compared to other standard dose formulations provide in different medical situations [3]. Microsphere system or microcapsules have gained much advantages in delivering the medicament attractively because it offers productive taste masking, improved flow property, protection and constant sustain drug release properties[4]. Microspheres formulated by the microencapsulation process, are involved in the implementation of a very thin coat to each and every core material[5,6]. Microspheres appear to be very small spherical particles containing their area in micrometer domain (1-1000 µm) hence referred to as micro particles composed of polymer, wax, biodegradable synthetic protective materials and some natural products (starch, gum, protein). Solvents are selected based on their drug-polymer solubilisation properties, stability, ease of processing and financial arrangements. Microspheres have larger surface-to-volume ratio because of their microscopic size and colloidal property, hence can be used alone

or in a combination with other drug delivery systems suitable for various routes of drug administration. Microspheres are biocompatible molecules, providing high bioavailability and capable of providing prolonged pharmacological action. Microspheres represent a monolithic spherical preparation containing drug molecule distributed all over the matrix as a dispersion of particles[7,8]. The process of microencapsulation by using the solvent evaporation method is relatively a complex process, influenced by the solvent evaporation rate, thermal variations, polymer solubility, excipients and drug molecule presented in emulsion phases, dispersion stirring rate, viscosity, mixing, volume ratio between both the phases, the amount of drug and polymer and physicochemical characteristics[9]. The advantages include uniform dispersion in the GIT, higher drug absorption and minimal local irritation[10]. The microspheres offer a linear and prolonged pharmacological action, by minimized gastrointestinal toxicity and dose frequency improving patient compliance. Sustained release formulations enhance drug's bioavailability, minimising the side effect severity in the patients. Architecture of microspheres permits a controlled variation in deformation and drug release[11]. Solvent evaporation process has acquired a lot of recognition because of ease of fabrication with zero alteration in drug activity [12]. The aim in programming this system is to minimise dosing frequency, minimising final dose and availing constant drug delivery [13]. Oral sustained release formulations are majorly used due to adjustability in dosage form modeling[14]. The microspheres have acquired broad affirmation as a method of achieving oral drug delivery and intravenous control systems. It often requires polymer working as both a carrier and base medium. Methods developed to formulate the microspheres, solvent evaporation process and the process of ionization by ionotropic gelation method have received great recognition because of their manufacturing ease with no drug activity compromise [15,16]. Fabrication is the leading factor for the encapsulation process and release of medicament. Factors with strong impact on rate of drug delivery involve polymer type, molecular weight, co-polymer molecule arrangement, excipient's nature involved in the formulation of microsphere. A number of excipients are added to the formulations for the drug stabilization during fabrication and may impact drug release through several different mechanisms[17]. Nano formulations may be potent and beneficial route of administration.[30]

The natural polymers last attractive because they are the natural products of living organisms, freely available, comparably affordable and capable of any chemical remodeling. Most of the protein-based drug delivery systems have been designed as solid cross linked microspheres dispersing the drug throughout the polymer matrix[18,19]. The use of natural polymers for drug delivery appears to be an interesting research area for drug compatibility due to natural origin, ease of availability and reasonable prices. Mouth dissolving tablets are optimum for the antihypertensive activity.[31]

Chitosan and sodium alginate are majorly employed in microsphere formulation for biomedical applications. The accumulation of Sodium alginate in rigid tumour develops the hypothesis for designing Alginate base drug delivery systems for tumour targeting. This has been practised in micro as well as nanoparticle preparations for the guided bioactive substance delivery for their gelation, bio adhesiveness and pH reactive qualities. Sodium alginate along with H_2-receptor antagonist is used for the treatment of gastroesophageal reflux disease and also as a hemostatic agent in surgical dressings to treat exuding wounds. Sponges prepared with sodium alginate and chitosan, generate a sustained drug release. Micro emulsifying is the novel approach of drug delivery system and it may be very significant for various prospectus.[35] Currently researchers are working on nano and microencapsulation for the improvement of dosage forms.[32] Some antihypertensive like atenolol was developed in the form of mucoadhesive fast melt away wafers which showed the significant effect by using various polymers such as HPMC E15, HPMC E6 and HPMC E5 .[33] Adhesive polymers are used in transdermal delivery system and have an important role in drug delivery system.[36] It may improve the pharmacokinetic property of drugs. Glyceromes may improve the bioavailability and may have impact on drug delivery system. Various matrix are improving the drug delivery system.[37,39] Nano emulsions are an important tool for the drug delivery system.[38]

DRUG PROFILE (VERAPAMIL HYCHLORIDE):

Molecular formula :$C_{27}H_{39}ClN_2O_4$

Molecular weight :491.6 gm/mol

IUPAC name :2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-(propan-2-yl)pentanenitrile;hydrochloride

Melting point: 145°C

pKa value: 9.68

Solubility: Methanol, Ethanol, Benzene, Ethyl alcohol and Acetone

Insolubility: Ether, Hexane and Water

Polar surface area: 63.95 $Å^2$

Refractivity: 132.65 m^3mol^{-1}

Polarizability: 52.66 $Å^3$

Chemical nature: Acute toxic

Synonyms: Verapamil HCl, Veleran, Calaptin, Civicor, Ikapress, Jenapamil.

Verapamil is a L-type calcium channel blocker (CCB) and vasodilator alkaloid found in the opium poppy[20,21]. It is classified as antihypertensive agent and is utilised in the management of heart diseases (angina pain, ischemic heart disease, high blood pressure and hypertrophic cardiomyopathy). The movement of calcium (Ca^{2+}) through the membrane layer is an important key for cardiac and smooth muscles shrinkage as well as the transmitter liberation at the nerve fibers. Verapamil Hydrochloride can be the drug of choice for the microsphere preparation because it obtains 90% GIT absorption rate and undergoes substantial presystemic metabolism that's why its bioavailability is decreased to 20-30% rising in drug administration frequency up to 3–4 times a day[22,23]. Hypertension is a medical condition, including elevated blood pressure levels occurred as a result when the high cardiac output exerts pressure on the arterial walls as the blood flow increases[25]. This can also be seen as comorbid condition among patients with different medical conditions including diabetes, anxiety, ischemic stroke, stress, renal failure, myocardial infarction, etc[24,25].

TYPES OF MICROSPHERES:

a) Floating Microspheres: Such types of microspheres are intended for making the gastro-retentive formulation. They promote a prolonged gastric retention time and minimised plasma drug concentration variation due to less density as compared to gastric fluids.

b) Radioactive Microsphere: They are used for the drug delivery of drugs with higher concentration to the target site. They also do not produce any local tissue injury.

c) Hollow Microsphere: Such types of microspheres are termed as micro-balloons containing drug molecules filled up in their outer polymer shells.

d) Magnetic Microsphere: These are the microspheres in which the drug particles are magnetically targeted to the target organ without circulating the drug particles throughout the body.

e) Mucoadhesive Microspheres: The microspheres stick to mucus layer and release the drug at a controlled rate. With this technique, the bioavailability of even a poorly absorbed drug can be enhanced[26].

USES OF MICROSPHERES:

a) Transformation of the liquid preparations including oils can be solidifying making the preparation easy to handle.
b) Concealing of taste and smell of formulation.
c) Drug stability can be improved against natural conditions (climate change).
d) Volatality of the drug can be delayed.
e) In the segregation of two or more antagonistic materials.
f) Advancement of the powder flow property.
g) Safeguarding of the toxic chemicals.
h) To intensify the imperfectly polar soluble drug particles by aiding in dispersing of the core component in liquid medium.
i) Formulation of the sustain release and targeted drug delivery system.

MICROSPHERES FORMULATION TECHNIQUES

Procedure to be followed for the formulation process depends upon various factors including: desired particle size, drug administration route, pharmacological action time span etc. The particle size should be minimized with respect to parenteral formulations to avoid irritation and allergic response at injection site. To fulfill desired action formulated microparticles must be stable having an appropriate life span. Parameters to be considered during formulation are:

a) Polymer structure
b) Amount of polymer

c) Rate of agitation

d) Amount of Cross linking agent

e) Amount of surfactant

f) Oil used in formulation.

WAX COATING AND HOT MELT METHOD

The molten wax is sprayed onto the core drug molecules for coating by drug encapsulation. Wax solution is distributed at high mixing rate into liquid paraffin cold solution. The mixture is then subjected to ruffle mechanically for an hour. Liquid paraffin is poured over the microspheres resulting them to suspend in a non-miscible solvent, allowing to air dry. The wax coated micro particles liberate the drug faster as compared to polymer microspheres. Carnauba wax and beeswax are the examples of good quality coating materials.

SPRAY COATING AND PAN COATING METHOD

These techniques are utilized by heat-jacketed coating pans containing solid drug core particles, into which the coating material is sprayed. The core particle size ranges from μm to mm. Coating agent is allowed to spray inside the pan at an appropriate angle. Microspheres with different coating thickness can be formulated in order to achieve certain sustain release pattern.

COACERVATION

It is an easy separation technique employed for bimolecular solution to be separated into two non-miscible liquid phases and is termed as simple coacervation when it deals with only one macromolecule and as a complex coacervation when it deals with two or more macromolecules possessing opposite charges. Coacervate phase is induced by temperature variation, non-solvent or micro ions inclusion resulting in dehydration of macromolecules. Dilute phase can be induced by pH value, ion strength, amount, ratio and macromolecular weight of macromolecules. All these factors can be influenced to formulate the microspheres with distinct features.

SPRAY DRYING

It is single step, closed-system technique and can be applied to different type of heat-labile materials. Coating agent is diffused in liquid phase or the drug may be available in suspension form. The biodegradable micro particles are dispersing the drug particles along with polymer. Micro particles size can be assisted by the spray speed, drug-polymer solution feed rate, nozzle size, drying temperature and the size of collecting chambers. Spray dried product's quality is enhanced by adding plasticizers promoting the polymer coalescence and film formation.

SOLVENT EVAPORATION METHOD

It is performed in an aqueous manufacturing solution. The microsphere coating agent is diffused in volatile solvent. The core material is then allowed to agitate with aqueous phase in order to obtain desired microcapsules. The mixture is heat treated to evaporate the volatile solvent. Matrix-type microspheres are formulated dispersing the core material into the coating mixture. This method is employed to formulate a wide variety of microspheres and the core material can be either polar or non-polar in nature.

PRECIPITATION

Emulsions are the liquid dosage form composed of aqueous droplets diffused in the non-aqueous medium. The dissolvent part can be eliminated by addition of a co-solvent part. This result in an elevation in the polymer strength causing the precipitation process take place forming a microsphere suspension.

FREEZE DRYING

Freeze drying process is concerned with the freezing of emulsion. The organic product can be the continuous phase, eliminated by sublimation process at low pressure and temperature. Ultimately diffused solvent's droplets are eliminated by the sublimation process which leaves drug-polymer particles behind.

CHEMICAL AND THERMAL CROSS-LINKING METHOD

The microspheres are formulated by the cross-linking method including albumin, dextran and gelatin as polymer. A water-in-oil emulsion is produced including water as polymer solution which possesses the main drug to be involved. An appropriate vegetable oil is used as emulsifying agent in the formulation. Aqueous soluble polymer is subjected to solidify by heat application when the desired water-in-oil emulsion is formulated. In case of chemical or cross-linking method, the chemical concentration, time and thermal magnitude are the important factors which help to determine the rate of drug delivery and swelling characteristics of microspheres.

IONOTROPIC GELATION METHOD

Ionotropic gelation method involves the polyelectrolytes potential to cross link accompanied by the counter ions to form gelispheres. They are curved, cross-linked, hydrophilic in nature, able to swell in biological fluids. Their release can be authorized by the polymer relaxation. The gelispheres can be formulated by dropping adrug-loaded polymer solution in the polar polyvalent cation solution. The cations are then diffused into the polymeric drops and 3D lattice of ionically cross-linked fraction are produced.

NATURAL POLYMERS USED IN FORMULATION

ALGINATE

It is non-poisonous, water soluble, biodegradable, naturally obtained polysaccharide originated from aquatic brown algae (bacterial genus). Sodium salt of alginic acid is well known as Sodium alginate.

GELLAN GUM

It is a bacterial exopolysaccharide molecule produced for trading by the aerobic fermentation of Sphingomonas Eloda (anionic polysaccharide consisting of glucose and rhamnose).

CHITOSAN

It is a non-poisonous, simply bio-absorbable and natural poly-aminosachharide molecule. It structurally resembles to glycosaminoglycans.

CARBOXYMETHYL CELLULOSE

It is a herbal substance, redesigned as carboxymethylcellulose (CMC) by carboxymethylation process. Its major group shows relationship with metal ions which can be used for the ionotropic gels formulation.

PECTIN

It is low-cost, non-poisonous, polysaccharide molecule extracted from citrus peels, employed as food additives, thickening agent and gelling agent. Primarily, it is a fiber found in fruits, sometimes used to make medicines for high cholesterol, high triglyceride and heartburn conditions. D-galacturonic acid with 1-4 linkages is the major component of pectin.

FACTORS AFFECTING IONOTROPIC GELATION METHOD

a) Amount of polymer-cross-linking electrolyte
b) Heating rate
c) pH value of cross-linking solution
d) Amount of drug
e) Amount of gas producing vehicle[27]

MICROSPHERE SIZE EVALUATION PARAMETERS

1. Microcapsules containing Verapamil Hydrochloride are developed by employing Sodium alginate along with co-polymers like, Methyl Cellulose, Sodium Carboxymethyl Cellulose, Pplyvinylpyrridone and Xanthan gum. Kondo (an emulsification method) followed for the development of Sodium alginate microspheres.
2. **Microsphere size evaluation**

   Sieving process is applied to separate the different size molecules in a batch. Standard sieves range includes 12/16, 16/20, 20/30, 30/40 and amounts left over the different sieves are measured by the scale. Following equation is applied to calculate the average particle size:

   $$\mathbf{Dave = \sum Xifi/fi}$$

   Here, Xi = mean range size,

   fi = % amount left at smallest sieve.

3. **Angle of repose**(Θ) is used to determine the flow ability by using the formula given below:

$$\Theta = \tan^{-1}(h/r)$$

4. **Surface Morphology of Microspheres**

The structural properties of the microspheres are analysed using Scanning Electron Microscope (SEM) to draw morphological characterization of microcapsules.

5. **Calculation of Drug Loading and Encapsulation Efficiency**

$$\textbf{\% Drug loading} = \frac{\textbf{Mass of microspheres}}{\textbf{Estimated drug content}} \times 100$$

$$\textbf{Microencapsulation efficiency} = \frac{\textbf{Theoritical drug content}}{\textbf{\% yield of microspheres}} \times 100$$

$$\textbf{\% yield of microspheres} = \frac{\textbf{Obtained amount}}{\textbf{Theoritical amount}} \times 100$$

6. **Polymer-Drug Relationship**

FTIR study using FTIR Spectrophotometer determines relationship between the drug, polymer and copolymer. Powder sample is blended with hydrous Pot. Bromide and added to diffused reflectance sampler for scanning at 4000-500cm^{-1} wavelength.

7. **Microsphere dimensions**

Microspheres size is determined by a microscope fitted with an ocular micrometer and stage micrometer. Formulated microsphere surface is studied by scanning electron microscopy by mounting directly onto sample stub coated with gold film (~200 nm) under reduced pressure (0.133 Pa).

8. **Isoelectric point**

Micro-electrophoresis apparatus is employed for the evaluation of electrophoresis mobility (relates to surface charge) of microsphere particles to find out the isoelectric point. Mean velocity ranges from 3-10 and is calculated by measuring the particle movement time over a length of 1 mm[28,29].

MICROSPHERE SYSTEM LIMITATIONS

a) Drugs showing less solubility with digestive fluids are not suitable for the microsphere system.

b) The drug should be administered with plenty of water (200 ml).

c) Drugs, absorbing through GIT and following presystemic metabolism are not considered appropriate candidates (nifedipine).

d) A few drugs can produce gastric mucosal irritation.

e) A drug subjected to be formulated in sustained release dosage form should possess:

- Appropriate half life ($t_{1/2}$)
- Elevated therapeutic range
- Compact dose strength
- Advantageous solubility and absorption properties
- Sensible absorption range
- Presystemic metabolism

f) A drug representing slow rate of dissolution is immanently steady and the dissolution rate can be minimised by a relevant salt formation. Such a system is commonly used to formulate the enteric coated medicines which protect the abdomen from harmful effects of aspirin. Coating media dissolved in alkaline phase is employed to retard drug release from apparatus until it obtains maximum intestine pH.

II. CONCLUSION

THIS REVIEW ARTICLE IS INTENDED ABOUT THE DEVELOPMENT AND EVALUATION TECHNIQUES OF SUSTAINED RELEASE VERAPAMIL HCL MICROSPHERES ENCAPSULATED WITHIN SODIUM ALGINATE POLYMER. VERAPAMIL HYDROCHLORIDE DRUG PROFILE, DRUG CHARACTERISTICS, PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS WERE ALSO STUDIED IN ORDER TO MINIMISE THE DOSING FREQUENCY TO AVOID DRUG OVERLOAD.

III. ACKNOWLEDGMENT

The authors would like to express a huge admiration and appreciation to our source of inspiration Dr. J.K Singh, Chairman, J K Institute of Pharmacy & Management. We would also like to share our deepest gratitude to Mr. Lalit Parihar and Ms. Pratiksha Chaudhary, Assistant Professor R V Northland Institute of Pharmacy and Mr. Naveen Sharma, R&D Department Jubilant, for their uninterrupted guidance and encouragement to complete this work in time.

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