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# FORMULATION DEVELOPMENT OF AMOXICILLIN MICROSPHERE USING NOVEL NATURAL POLYMER

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**Keywords:**

Amoxicillin, Microspheres, Kondagogugum, Polydispersity index, *In-vitro* drug release

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**ABSTRACT:** Amoxicillin is an antibiotic beneficial for the treatment of some bacterial infections. When orally administered it is slowly and scarcely absorbed from the gastrointestinal tract. The objective of the present work was to formulate and evaluate microspheres of Amoxicillin and produce sustained drug delivery. Microspheres can be manufactured from various natural and synthetic materials. In these 14 batches of Amoxicillin, microspheres were prepared using natural polymer Kondagogu gum and other ingredients by solvent evaporation technique. The prepared microspheres were evaluated for different parameters i.e % drug yield, % drug entrapment, shape, surface morphology, particles size, polydispersity index, zeta potential and *in-vitro* drug release for 48 hours in phosphate buffer 7.4. The best batch performed stability studies for 6 months. The research concluded that Amoxicillin microspheres could be an alternative for conventional dosage form and other phytochemical in herbs. The optimized formulation was found with significant loading efficiency.

**INTRODUCTION:** Microspheres are one of the multi particulate drug delivery systems and are prepared to obtain prolonged (or) controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Microspheres can be defined as solid, approximately spherical particles ranging from 1 to 1000µm, containing dispersed drug in either solution (or) microcrystalline form [1, 2]. These microspheres are suitable alternatives for conventional dosage forms [3]. Several methods, including Emulsion solvent evaporation technique [4], phase-separation or coacervation method [5], emulsification diffusion method and spray drying method [6] are commonly used for the preparation of microspheres.

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The solvent evaporation method has gained much attention due to its ease of fabrication without compromising the activity of the drug. This technique offers several advantages and is preferable to other preparation methods such as spray drying, sonication and homogenization because it requires only mild conditions such as ambient temperature and constant stirring. Thus, a stable emulsion can be formed [7] and microspheres are formed by the evaporation of an organic solvent from dispersed oil droplets containing both polymer and drug [8].

Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications

depending on what material they are constructed of and what size they are. Glass microspheres are primarily used as filler for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology. Ceramic microspheres are used primarily as grinding media. Microspheres vary widely in quality, sphericity, uniformity of particle and particle size distribution [9].

Gums are natural polymers, which mainly consists of carbohydrates sometimes with small amounts of proteins and minerals. Increasing demand of natural ingredients over synthetic ones immensely contribute to explore and develop new plant based materials. Gum kondagogu (*Cochlospermum gossypium*) is a tree exudate derived from the Bixaceae family, originating from India. Natural gums are obtained as exudates from different tree species, which exhibit unique and diverse physicochemical properties and have a wide variety of applications [10].

Commercially important tree gums include gum arabic, gum karaya, and gum tragacanth [11]. Karaya polysaccharide (*Sterculia urens*) and gum kondagogu (*C. gossypium*) are used as food additives [12, 13]. The physicochemical properties and toxicological evaluation of gum kondagogu has been established earlier [14, 15]. Morphological and structural characterization and physicochemical aspects of gum kondagogu have been elucidated recently, suggesting that this gum belongs to the group of substituted rhamnogalacturonan [16].

Understanding of the rheological properties of gum is essential for their application and use as food thickeners, stabilizers, and emulsifiers. Amoxicillin is known by its IUPAC name as (2S, 5R, 6R)-6 {[(2R) - 2 - amino - 2 - (4 - hydroxyphenyl) - acetyl] amino}-3, 3-dimethyl - 7 - oxo - 4 - thia-1-azabicyclo [3.2.0] heptane-24 carboxylic acid. This drug acts by means of inhibiting the synthesis of bacterial cell wall. It inhibits move-linkage between the linear peptidoglycan polymer chains that make up a primary thing of the cell walls of each Gram positive and Gram-negative bacteria. It has ionizable groups in the physiological variety (the amino organization in alpha-function to the amide carbonyl institution and the carboxyl organization). The main objective of this work was to investigate the possibility of obtaining a sustained release formulation of Amoxicillin microspheres by the solvent evaporation method using gum kondagogu and Investigation of the effect of drug to polymer ratio.

## MATERIAL AND METHOD:

**Material:** Amoxicillin was procured from Scan Research Laboratories, Bhopal (MP). Kondagogu Gum procured from Scan Research Laboratories. Dialysis membrane (MWCO, 15 KDa), Span 80, Tween 80, Glutaraldehyde, Toluene were purchased from Himedia (Mumbai, India). All other reagents and chemicals used were of analytical grade.

### Method:

**Preparation of Kondagogu Gum Microsphere:** The microspheres of the polysaccharide, Kondagogu Gum were prepared by emulsifying method using liquid paraffin as a dispersing medium and glutaraldehyde used as a cross-linking agent. Kondagogu Gum dispersion (2.5 % w/v) was prepared by mixing of Kondagogu Gum in double distilled water with Tween 80 (0.5% w/w). Drug was previously dissolved in double distilled water. The prepared, 10 mL of Kondagogu Gum solution with drug was added dropwise in a beaker containing 100 mL of liquid paraffin light and heavy in ratio of 50:50. Span 80 (1.0% w/v) was previously added in liquid paraffin. The system was kept under stirring at 3000-4000 rpm using two blade mechanical stirrers. 1.5 mL of toluene saturated glutaraldehyde was added to above solution after 30 min of stirring. Stirring was continued for 4 hour at 400C at 4000 rpm.

The microspheres were separated from dispersion medium by centrifugation after stirring and washed two times with petroleum to remove liquid paraffin and then washed three times with acetone. Dispersion was poured in petri dish to remove acetone. After complete evaporation of acetone, dried drug loaded microsphere were collected and stored in tight container for further evaluation.

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**Optimization of Microsphere:** Optimization of microsphere formulation was carried out by optimizing the different dependent and independent process and formulation variables. Optimization was carried out on the basis of particles size, polydispersity index and % Drug Entrapment and it is done by changing the one variable and kept constant for other variables given in **Table 1.** The temperature was maintained at 400C and the concentration of toluene saturated glutaraldehyde was used 1.5 mL in the preparation of each formulation.

***In-vitro* Characterization of Microspheres:** Particle size, polydispersity index Average particles size, polydispersity index (PDI) of prepared microsphere was determined using zetasizer (DTS Horriba instrument, India). The microsphere formulation was diluted with deionized water (1:9 v/v) and analysed for average size and PDI and it was performed at the department of pharmaceutical science, VNS pharmacy college Bhopal, India.

**Shape and Surface Morphology:** The shape and surface morphology of the microspheres were investigated using scanning electron microscopy (IISER, Bhopal). The microspheres were fixed on supports with carbon-glue, and coated with gold using a gold sputter module in a high-vacuum evaporator. Samples were then observed with the Scanning Electron Microscope at 10 kV.

**Determination of Drug Content:** The amount of drug entrapped in the microspheres was determined using a UV spectrophotometer. The weighed amount of the microspheres was incubated with PBS, pH 7.4, for 48 h. It was centrifuged at 10,000 g for 30 min and the supernatant was diluted 10 times before analysis into the UV spectrophotometer system at $\lambda_{max}$ 233 nm.

***In-vitro* Drug Release from Microspheres:** The drug release was performed in PBS (7.4 pH) for Amoxicillin loaded Kondagogu Gum microsphere. The drug release was performed in PBS (7.4 pH) for preprared microsphere using dialysis bag technique. In this study suspension of microsphere equivalent to 20 mg of drug was taken in dialysis tubing (MWCO, 15KDa, Himedia) and placed in a beaker containing 50ml of PBS pH 7.4.

The dialysis bag retains microsphere and allows passing of free drug into the dissolution media. Temperature was maintained at 37±10C throughout the study. The samples were withdrawn after specified time intervals that is 0.5, 1, 2, 3, 4, 5, 6, 7.8.12, 24 and 48 hours and replaced with the same volume of fresh PBS pH 7.4 and analyzed for drug concentration by using UV spectrophotometer a $\lambda_{max}$ 233 nm.

**RESULT AND DISCUSSION:** The mean diameter of glutaraldehyde cross linked microspheres of Kondagogu gum increased from 56.70±2.15 µm to 88.15±4.25 µm with increasing polymer concentration from 1.0 to 3.0 % w/v. In the present investigation a 2.5% w/v Kondagogu gum concentration was found to be optimized

which give the required size of microspheres. The average particle size of microspheres increased with increasing polymer concentration, since at higher concentrations the polymer solution dispersed into larger droplets due to increasing the viscosity of polymer solution and it was the reason behind the enhancement of average particle size of microsphere.

Mean particle size and size distribution were studied to observe the effect of drug concentration. It was found from previous study that there was no major change observed on particle size and size distribution of microsphere with varying concentration of the crosslinking agent so it was kept constant in every formulation. Percent encapsulation efficiency has increased up to 81.37±3.54 with increasing polymer drug concentration from 15% to 25% w/w. But further increasing the concentration of drug, there was no significant enhancement was found in entrapment efficiency.

The *in-vitro* dissolution profile of Amoxicillin in PBS pH 7.4 was found 89.67±0.98 after 48 hrs for optimized formulation (AMT-16) and follow the matrix diffusion Higuchi release kinetics.

**TABLE 1: FORMULATION OF MICROSPHERE**

| F. code | Kondagogu Gum (%w/v) | Tween-80(%) | Span-80 (%) | Stirring Speed | Drug Conc. (% w/w) | PDI | Particle Size (um) | % Drug Entrapment |
|---|---|---|---|---|---|---|---|---|
| AMS-1 | 1.5 | 1 | 0.5 | 2000 | - | 0.210±0.005 | 56.70±2.15 | - |
| AMS-2 | 2 | 1 | 0.5 | 2000 | - | 0.316±0.025 | 64.34±3.26 | - |
| AMS-3 | 2.5 | 1 | 0.5 | 2000 | - | 0.153±0.023 | 71.62±4.56 | - |
| AMS-4 | 3 | 1 | 0.5 | 2000 | - | 0.331±0.045 | 88.15±4.25 | - |
| AMT-5 | 2.5 | 1 | 0.5 | 2000 | - | 0.263±0.012 | 65.45±0.12 | - |
| AMT-6 | 2.5 | 1.5 | 0.5 | 2000 | - | 0.143±0.045 | 58.56±0.45 | - |
| AMT-7 | 2.5 | 2 | 0.5 | 2000 | - | 0.201±0.036 | 47.36±0.32 | - |
| AMT-8 | 2.5 | 1.5 | 0.75 | 2000 | - | 0.150±0.012 | 38.62±3.26 | - |
| AMT-9 | 2.5 | 1.5 | 1 | 2000 | - | 0.147±0.054 | 32.54±4.56 | -- |
| AMT-10 | 2.5 | 1.5 | 1.25 | 2000 | - | 0.164±0.005 | 28.27±2.66 | - |
| AMT-11 | 2.5 | 1.5 | 1 | 2000 | - | 0.170±0.012 | 31.63±4.53 | - |
| AMT-12 | 2.5 | 1.5 | 1 | 3000 | - | 0.135±0.023 | 22.54±3.12 | - |
| AMT-13 | 2.5 | 1.5 | 1 | 4000 | - | 0.120±0.015 | 18.37±2.12 | - |
| AMT-14 | 2.5 | 1.5 | 1 | 4000 | 15 | 0.175±0.056 | 14.87±0.18 | 75.23±4.56 |
| AMT-15 | 2.5 | 1.5 | 1 | 4000 | 20 | 0.196±0.043 | 17.29±0.15 | 79.49±3.34 |
| AMT-16 | 2.5 | 1.5 | 1 | 4000 | 25 | 0.205±0.047 | 21.42±0.26 | 81.37±3.54 |
| AMT-17 | 2.5 | 1.5 | 1 | 4000 | 30 | 0.430±0.065 | 28.19±0.61 | 81.62±3.78 |

**TABLE 2: *IN-VITRO* DRUG RELEASE**

| S. no. | Time (h) | Cumulative % Amoxicillin Release* | |
|---|---|---|---|
| | | Plain drug | Amoxicillin Loaded Microsphere |
| 1 | 0.5 | 46.35±1.25 | 9.43±0.21 |
| 2 | 1 | 59.65±0.45 | 19.53±0.65 |
| 3 | 2 | 82.86±0.64 | 32.26±0.45 |
| 4 | 3 | 95.29±0.54 | 38.68±0.69 |
| 5 | 4 | - | 49.35±0.45 |
| 6 | 5 | - | 58.76±0.36 |
| 7 | 6 | - | 66.38±0.45 |
| 8 | 8 | - | 72.87±0.32 |
| 9 | 12 | - | 78.29±0.45 |
| 10 | 24 | - | 84.41±0.78 |
| 11 | 48 | - | 89.67±0.98 |

**Effect of Kondagogugum Concentration:** In the formulation microsphere were prepared by taking different concentration of Kondagogu Gum and other parameter such as concentration of Span 80, Tween 80, Glutradehyde, Stirring speed was kept constant.

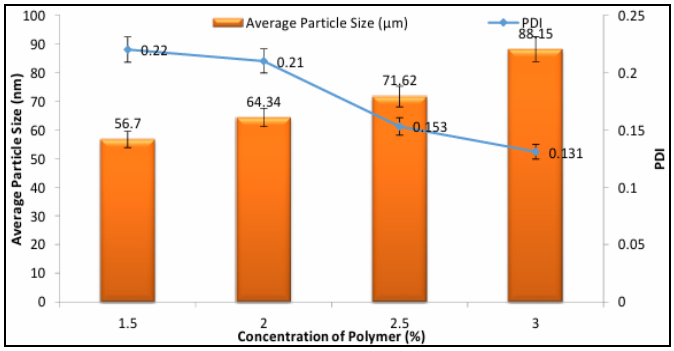


**FIG. 1: EFFECT OF KONDAGOGUGUM CONCENTRATION ON AVERAGE PARTICLE SIZE AND PDI OF MICROSPHERE**

**Effect of Concentration of Tween 80:** In the formulation microspheres were prepared by taking different concentration of Tween 80 and other parameter such as concentration of kondagogu gum, Span 80, Glutradehyde, stirring speed was kept constant.

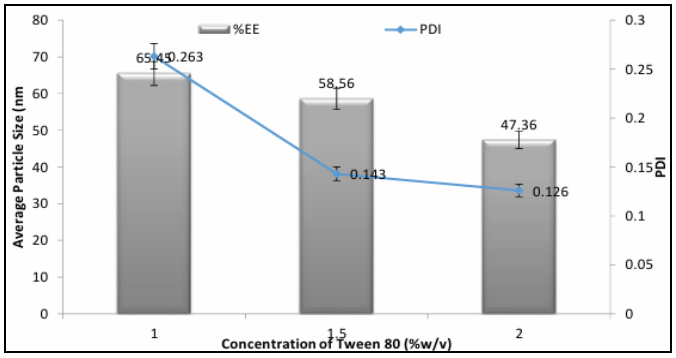


**FIG. 2: EFFECT OF CONCENTRATION OF TWEEN 80 ON AVERAGE PARTICLE SIZE AND PDI OF MICROSPHERE**

**Effect of Span 80 Concentration:** In the formulation microspheres prepared by taking different concentration of span 80 and other parameter such as concentration of kondagogu Gum, Tween 80, Glutradehyde, Strirring speed was kept constant.

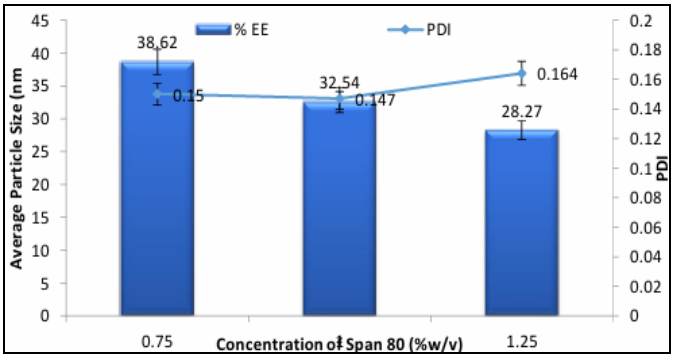


**FIG. 3: EFFECT OF SPAN 80 CONCENTRATION ON AVERAGE PARTICLE SIZE AND PDI OF MICROSPHERE**

**Effect of Stirring Speed:** In the formulation microspheres prepared by varying stirring speed and other parameter such as concentration Of Kondagogu gum, Tween 80, Span 80, Glutradehyde was kept constant.

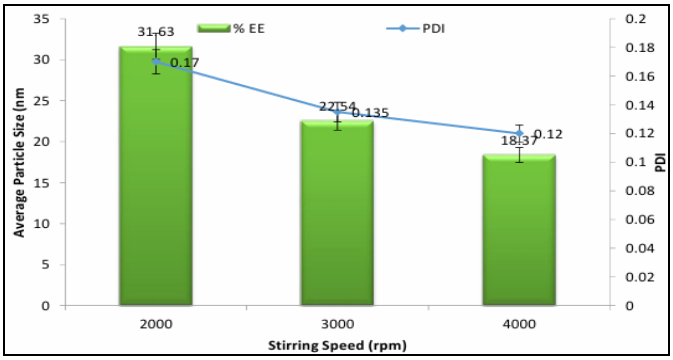


**FIG. 4: EFFECT OF STIRRING SPEED CONCENTRATION ON AVERAGE PARTICLE SIZE AND PDI OF MICROSPHERE**

**Effect of Drug Concentration:** In the formulation microsphere was prepared was prepared by taking different concentration of drug and other parameter such as concentration of Kondagogu Gum, Tween 80, Span 80, Glutradehyde, Stirring speed was kept constant.

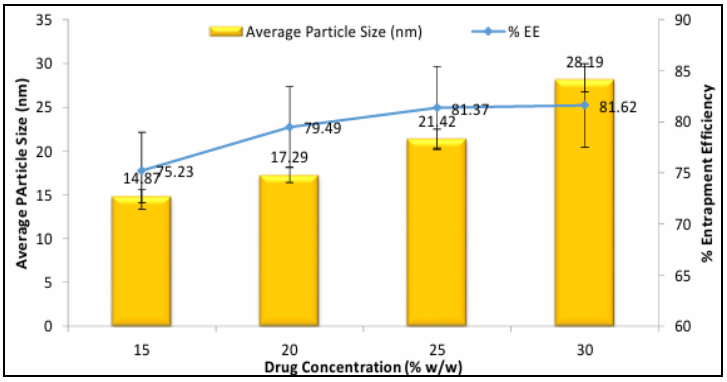


**FIG. 5: EFFECT OF DRUG CONCENTRATION ON AVERAGE PARTICLE SIZE AND % ENTRAPMENT EFFICIENCY OF MICROSPHERE**

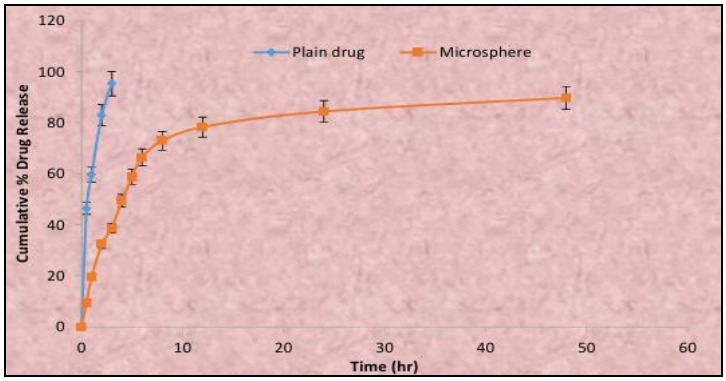


**FIG. 6: CUMULATIVE % AMOXICILLIN RELEASE**

**CONCLUSION:** It was concluded that from this study that the microsphere can be prepared from kondagogu gum by emulsifying solvent evaporation method and can be loaded with drug amoxicillin for it sustained delivery in GIT system. The prepared microspheres were optimized for different formulation and process variables concentration and found that microsphere was uniform and acceptable size range. They were found smooth and spherical in shape. The optimized formulation was found significant loading efficiency of Amoxicillin that can release the Amoxicillin in sustained manner which was followed matrix diffusion Higuchi release kinetic.

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**CONFLICTS OF INTEREST:** Nil

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