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# Formulation, Development and Characterization of Besylate Amlodipine Loaded Microsphere

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**ABSTRACT:** Hypertension is one of the well known risk factor related to cardiovascular diseases and calcium channel blockers are the oldest class of anti-hypertensive drugs. Amlodipine besylate belongs to dihydropyridine family and known for effective treatment of hypertension. The aim of the present study is to design a microsphere such that it can be used in the treatment of hypertension in order to decrease dosing frequency, to improve bioavailability and to reduce incidence of adverse effect. The microsphere was prepared by solvent evaporation techniques and were analysed for pre-formulation and post-formulation studies. . Both pre-formulation studies and post-formulation studies showed the satisfactory results. In post-formulation studies, among all the formulation F8 showed the best and satisfactory results in particle size determination, drug entrapment study, swelling index and percentage yield. The drug content in formulation F8 was 92% which is acceptable and stability study also showed good results. Hence, the microsphere formulation formed is stable and optimized.

**Keywords**: Hypertension, Bioavailaibility, Microsphere, Optimization.

## I. INTRODUCTION

Hypertension is a very common and serious medical condition which can complicate many health problems. This is a disease which is increasing abruptly worldwide. According to the study it states that around 1.13 billion of people worldwide have hypertension, most two – thirds) living in low and middle income countries. It is the major cause of premature death worldwide. The risk of cardiovascular mobility and mortality is directly correlated with BP (R A Siyad). Hypertension is a "silent killer" as it initially does not have any symptoms. Idiopathic (Essential) hypertension is the most common type of hypertension, which affects 95% of hypertensive patients; it tends to be familiel or an interaction between genetic and environmental factors. It increases the risk of cerebral, cardiac and renal events. Causes of hypertension are Excess salt ,Abnormal arteries, Increased blood volume ,Genetic disorders, Stressful life, Recreational drugs, Health conditions, Pregnancy, Hormonal therapy etc.. Treatment of Hypertension are given as follows Antihypertensive drugs , Non pharmacological management of hypertension ,Reduction of body weight , Sodium restriction , Alcohol restriction , Physical exercise (Midha Kanav et al.).

Anti- hypertensive drugs are a class of that is used to treat high blood pressure. There are several drugs which are classified under this category. Among the most widely used medication some are: Thiazide diuretics, Calcium channel blockers, Beta blocker and ACE inhibitors. Among these classifications of drugs amlodipine is a dihydropyridine calcium channel blocker which has many qualities that set it apart from any other antihypertensive agents of this class. CCBs (Calcium Channel Blockers) were the first over 35 years who were introduced initially for the coronary heart disease, but they soon proved there efficacy in hypertension. Amlodipine is a long acting, lipophilic, 3rd generation dihydropyridine calcium channel blockers that exerts its action through blocking the calcium influx into vascular smooth muscles cells and myocardial cells , which leads to decrease in peripheral vascular resistance. Amlodipine is indicated for the treatment of hypertension and angina. The usual dose of amlodipine is only once in daily basis because of its long half-life which is favourable for patient compliance. Other than this amlodipine has high bioavailability of about 60-80% (Fares Hassan et al.).

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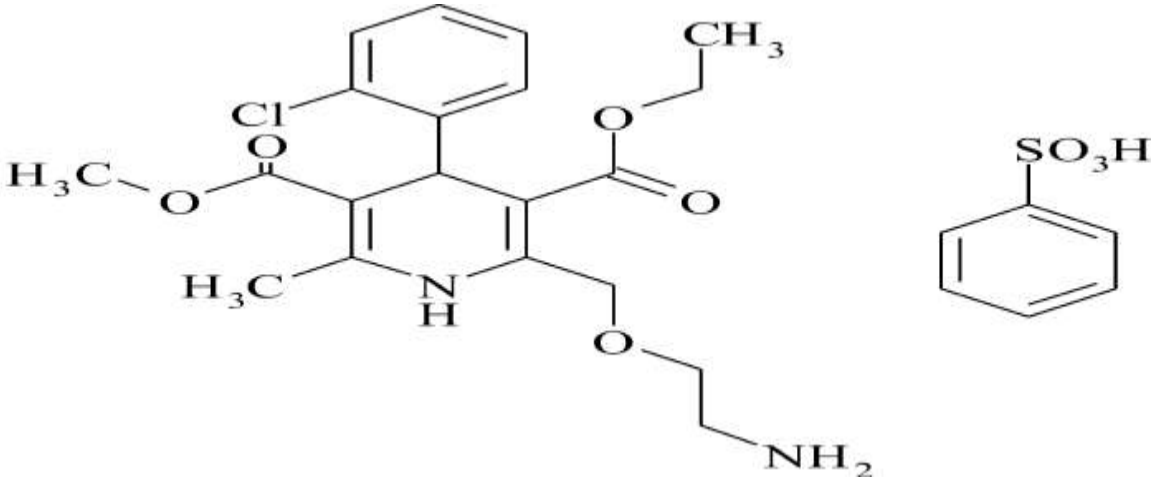


**Figure1. Structure of Amlodipine besylate**

In country like India in which there is ever increase in population, the demand for health care services is also increasing with increase in population. With the change in the lifestyle and so called "fast culture" good health is almost deprived part. With the upgradation in lifestyles of people, the concept and severity of illness, disease and disorders have been also changed. The major problem faced by health care professionals in this view is the gradation of the available drug delivery system. Development of new drug molecules is expensive and time consuming process (Jawed saniya et al.). Drug therapy, dose titration and therapeutic drug monitoring are the methods attempted for improving the safety efficacy ratio of "old" drugs. Delivering drugs in controlled rate, slow delivery, and targeted delivery are the other attractive methods that have been pursued vigorously. Microspheres are novel drug delivery system used for sustained release of drug for a prolonged period of time. Microspheres have the potential to deliver the drug in a controlled manner. They are spherical free flowing particles consist of proteins and synthetic polymers, which are biodegradable in nature. Microsphere can be formed as microcapsules or micromatrices (Midha kanav et al.).In other words, microsphere are the formulation with size varying from 50nm to 2 micrometre consist of core substance which shows slow action of drug at a predetermined rate by maintaining a relatively constant, effective drug level in the body with expected reduction of undesirable adverse and side effects and hence this is the main goal of sustained drug delivery system. Novel Drug Delivery Systems are developed to address the challenges of drug development such as Bioavailability, Permeability and Poor solubility. The bioavailability of any drug describes the efficiency of the drug therapy which must be therapeutically effective and non toxic. Especially in this type of formulation drug must be therapeutically effective and stable for a prolonged period of time (M,Alagusundaram et al.).

## II. MATERIALS AND METHOD

### 2.1 Materials:

Amlodipine besylate was a gift sample from Cadila Pharmaceuticals, Ahmedabad (Gujarat). HPMC and chitosan were the polymers purchased by Hi –media (Mumbai, India). All the solvents used were of analytical grades and were used as obtained.

### 2.2 Preparation of amlodipine besylate microsphere:

Microsphere was prepared by solvent evaporation (oil in water emulsion) technique. Amlodipine besylate (Drug) microsphere were made in different batches named F1 to F8, chitosan and HPMC are the polymers whose concentration is varied respectively. Then the weighed quantity of drug and polymers were dissolved in a mixture of DMF and DCM (1:1 solvent ratio) at room temperature. The mixture was poured into 250ml water containing 0.02% Tween 80 maintained at a temperature of 30-40 C and subsequently stirred at ranging agitation speed for 20min to allow the volatile solvent to evaporate. The microsphere formed were filtered, washed and dried overnight at room temperature. Concentration of polymer was optimized based on %drug release and %drug entrapment efficiency.

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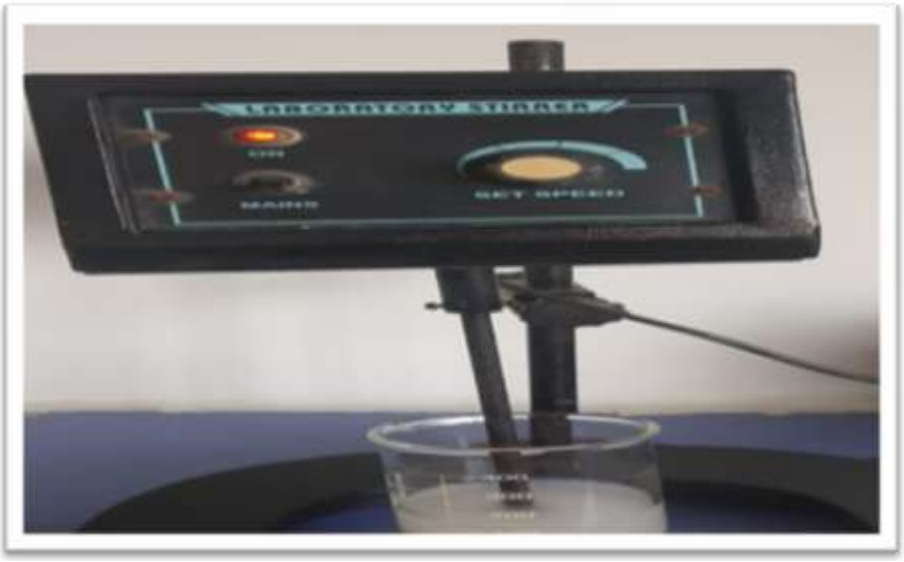

**Figure 2. Preparation of microsphere**

**2.3 PREFORMULATION STUDIES**

Preformulation is the branch of pharmaceutical science that utilizes biopharmaceutical principles in the investigation of physicochemical properties of the new drug compound that could affect drug performance and development of an efficacious dosage forms. There physical, chemical and mechanical properties of a new drug molecule are characterized with a goal to formulate elegant, safe, efficacious dosage form with good bioavailability.

**2.3.1. Organoleptic characteristics:**

The drug sample was observe for physical appearance and compared with the standard mentioned in Indian Pharmacopoeia. It basically consists of three parameters and they are colour, odour and taste.

**2.2.2 .Particle size characterization**: -

Optical microscope is used for the determination of particle diameter of the microsphere. The sample was suspended in dispersion and individual diameter of microsphere was measured using micrometer.

**2.2.3. Solubility analysis:**

A semi-quantitative determination of the solubility was performed by addition of solvent in minute quantity to a test tube containing fixed amount of solute or vice-versa.

**2.2.4. pH:**

The pH is the measure of negative logarithm of hydrogen ion concentration of an aqueous solution. It is determined through litmus paper.

**2.2.5. Partition coefficient:**

The partition coefficient is defined as the ratio of unionized drug distributed between organic phase and aqueous phase at equilibrium.

$$\text{Partition coefficient (p)} = \frac{\text{Conc.of Drug in org.phase.}}{\text{Conc.of Drug in aq.Phase}}$$

**Shake flask method:** The drug (Amlodipine besylate) was accurately weighed and dissolved in distilled water. The resulting solution was shaken with equal volume of HPMC for 30 minutes in a separating funnel and allowed to stand for 24 hours. The majority of lower aqueous phase was run off and the drug content was determined in both solutions by measuring the absorbance by UV spectrophotometer.

**2.2.6. Melting point: -**

It is used in the determination of the drug sample and to analyse the purity of the drug. It is performed by open capillary method in which drug was taken in glass capillary tube whose one end was sealed by means of flame. The capillary tube

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was placed in a melting point apparatus attached to a thermometer to measure the melting point. The sample holder was heated gradually and the temperature at which drugs melts was recorded.

**2.3 POST FORMULATION STUDIES:**

**2.3.1. Particle size analysis: -**

The sample of around 100 prepared microspheres was randomly selected and their size was determined through optical microsphere (Sahu S.et al.).

**2.3.2. Compatibility studies: -**

The pure drug (amlodipine besylate) and the mixture of drug-chitosan and drug-HPMC in 1:1 ratio were kept at the room temperature for 1 month. The samples were subjected to FT-IR studies to compare the interaction between the drug and excipients used for formulating microsphere (Mishra A.et al.).

**2.3.3. Shape and Surface morphology: -**

The shape and surface morphology is studied by using scanning electron microscope (SEM) (Pandey Noopur et al.).

**2.3.4. Determination of Drug content:**

The microsphere equivalent to 50mg of amlodipine besylate was accurately weighed and crushed. The powdered microsphere was kept in 100ml volumetric flask and the volume were made up with phosphate buffer of pH 6.8 and kept for 24hrs. The solution was filtered through whatmann filter paper. The solution was diluted through fresh solvent and absorbances were measured at 360nm using UV spectrophotometer and the percentage drug content was calculated (Pandey Noopur et al.).

**2.3.5. Percentage yield:**

The percentage yield of different formulations was determined by weighing the prepared microsphere after drying. The percentage yield was calculated as follows: (Mannan Abdul et al.).

$$\% \text{ Yield} = \frac{\text{Total weight of prepared microsphere}}{\text{Total weight of drug and and polymer}} \times 100$$

Efficiency of drug loading of each formulation was calculated in terms of % drug loading as per the formula: (Kathle, Pankaj kumar et al.)

**2.3.6. Drug loading efficiency and drug loading efficiency: -**

$$\%\text{Drug Loading} = \frac{\text{Total drug} - \text{free drug}}{\text{Total drug}} \times 100$$

Efficiency of drug entrapment of each formulation was calculated in terms of % drug entrapment as per the following formula: (Kathle, Pankaj kumar et al.)

$$\% \text{ Drug Entrapment} = \frac{\text{Practical drug content}}{\text{Theoritical drug content}} \times 100$$

**2.3.7. Swelling Index:**

This is also a vital factor to ensure buoyancy and drug dissolution of microsphere. The microsphere composed of polymeric matrices build a gel layer around the microsphere core when they come in contact with water. This gel layers governs the release of drug from the microsphere. Swelling ratio describe the water content in hydrogel at equilibrium (Mishra A. et al.).

**2.3.8. In-Vitro Drug Release Studies:**

Drug release from the developed formulation was studied in PBS pH 7.4 using dialysis bag (12,000 MW) diffusion. The developed formulations were placed in the dialysis bag which was pre-soaked in the PBS overnight and immersed into 200 ml of PBS. The entire system was kept at 37 ± 1 C at a stirring rate of 300 rpm. At the predetermined time intervals (30 min, 1, 2, 3, 4, 6, and 8 h) 5 ml samples were withdrawn and replaced by fresh buffer. The samples were diluted with PBS and determined by ultraviolet spectrophotometer at 238 nm (Kathle, Pankaj kumar et al.).

**2.3.9. Stability studies:**

The success of an efficient formulation was evaluated only through the stability studies. The purpose of the stability studies was to obtain a stable product which assures its safety and efficacy

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up to the end of shelf life. In this study, the prepared microsphere was kept under different temperature conditions like –room temperature, 30ºCand 60%RH, 40ºC and 75% RH. The samples were assayed for drug content at regular intervals for 2 weeks (Sahu S. et al.).

## III. RESULT AND DISCUSSION

### 3.1 PREFORMULATION STUDIES:

**Table 1: Organoleptic Characteristics**

| S.NO. | CHARACTERISTICS | RESULTS |
|---|---|---|
| 1 | Colour | White crystalline powder |
| 2 | Odour | Odourless |
| 3 | Taste | Tasteless |

**Figure 3. Amlodipine besylate powder**

Inference: The amlodipine besylate powder was white crystalline in colour, odourless and tasteless.

**Table 2: Particle size**

| RAW MATERIALS (API) | NATURE OF SAMPLE |
|---|---|
| Amlodipine besylate | Fine powder |

Inference: The crystalline particles of powder were very fine and small.

**Table 3: Solubility**

| RAW MATERIALS (API) | RESULT |
|---|---|
| Amlodipine besylate | Water- Slightly Soluble<br>Methanol – Freely Soluble<br>Ethanol- Sparingly Soluble<br>2-Propanol- Slightly Soluble |

This was slightly soluble in water and 2-propanol, freely soluble in methanol and sparingly soluble in ethanol.

**Table 4: pH analysis**

| RAW MATERIALS (API) | RESULTS |
|---|---|
| Amlodipine besylate | 1-6 at 37ºC (Approx..body temperature) |

The pH was determined as 1-6 at approx. body temperature.

International Journal of Pharmaceutical Research and Applications
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**Table 5: Partition coefficient (pka)**

| S.NO. | SAMPLE RESULT | AVERAGE |
|---|---|---|
| 1 | 8.7 | 8.6 |
| 2 | 8.6 | |
| 3 | 8.6 | |

The average of pka was determined as 8.6.

**Table 6: Melting point**

| RAW MATERIALS (API) | RESULTS |
|---|---|
| Amlodipine besylate | 178-179ºC |

The melting point was determined as 178-179ºC.

**3.2 POST FORMULATION STUDIES:**

**3.2.1 Particle size analysis**: The mean particle size of the microsphere was found to be increased with increasing chitosan concentration and was in the range 187µm to 482µm shown in Table no.8. The viscosity of the medium increases at higher concentration of chitosan resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities.

**3.2.2Compatibility studies**: The IR spectrums of the drug, drug-chitosan mixture, drug-HPMC mixture and microsphere formulation F8 were compared to find any change in frequency of functional group in microspheres with respective functional group of the drug. The observations noted by spectra indicate that the principal IR absorption peaks observed in the spectra of drug were very close to those in the spectra of the microspheres containing drug. IR spectrums indicate that there is no strong interaction between the drug and the polymers.

**3.2.3 Shape and Surface morphology**: Morphology of microsphere was examined by SEM .The SEM images of prepared microsphere were showed in figure 3. SEM analysis showed that the prepared formulation was having size in micrometers and particles were nearly spherical.

**3.2.4 Drug content**: The drug content of formulation was found to be 92% which shows there was small decrease in drug content but difference is insignificant and manageable.

**3.2.5 Percentage yield**: The percentage yield was found in the range of 51-89%. It was observed that average percentage yield was greater than 50% for all batches of formulation hence this indicates that method of preparation used is suitable.

**3.2.6 Drug loading efficiency and drug entrapment efficiency**: The drug loading efficiency of microsphere varied from 50-96% and drug entrapment efficiency varied from 20-28%. Results states that increase in chitosan concentration increase the loading and entrapment of the drug (Table 8).

**3.2.7 Swelling index**: From this result it was concluded that the swelling index increase with time because the polymer gradually absorbs water due to its hydrophilicity. The outer most layers of the polymer hydrates, swells and a gel barrier is formed at the outer most surface. As the gelatinous layer progressively dissolved or is dispersed, the hydration, swelling and release process is repeated towards new exposed surface, thus it maintains the integrity of dosage forms. In the present study, the higher swelling index was found for formulation F8 (Table 8) on immersion in 0.1N HCl, pH 1.2 solution at 37±0.5ºC.

**3.2.8 In-vitro drug release:** In-Vitro dissolution study was carried out using dialysis bag phosphate buffer pH 7.4. The release rate for the formulations was found to be slow. Formulation showed best drug release rate. In vitro dissolution data of optimized formulations F8 during stability showed is tabulated in table 8.

**3.2.9 Stability studies**: The accelerated stability studies were carried out according to ICH guidelines optimized formulation F8 was packed in strip of aluminum foil and this packed formulation was stored in stability chamber maintained at room temperature, 30ºC and 60%RH ,40$^{o}$C and 75% RH (Zone III conditions as per ICH Q1 guidelines) for 1 month. The microspheres were evaluated before and after 1 month for change in appearance and In vitro release. After a period of one month, the samples were observed for any change on appearance. It was observed that microsphere that microsphere was devoid of any change in colour or appearance of any kind of spot on it. It was also noted that microsphere was free of any kind of microbial or fungal growth or bad odour.

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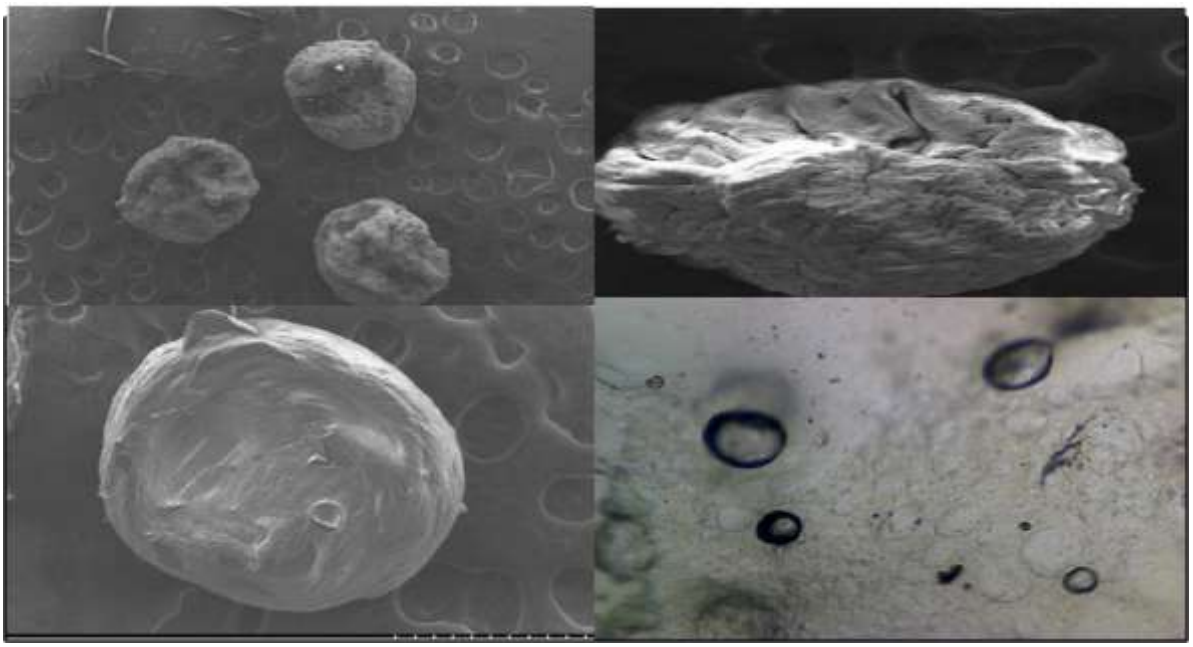

**Figure 4. Surface morphology of microsphere**

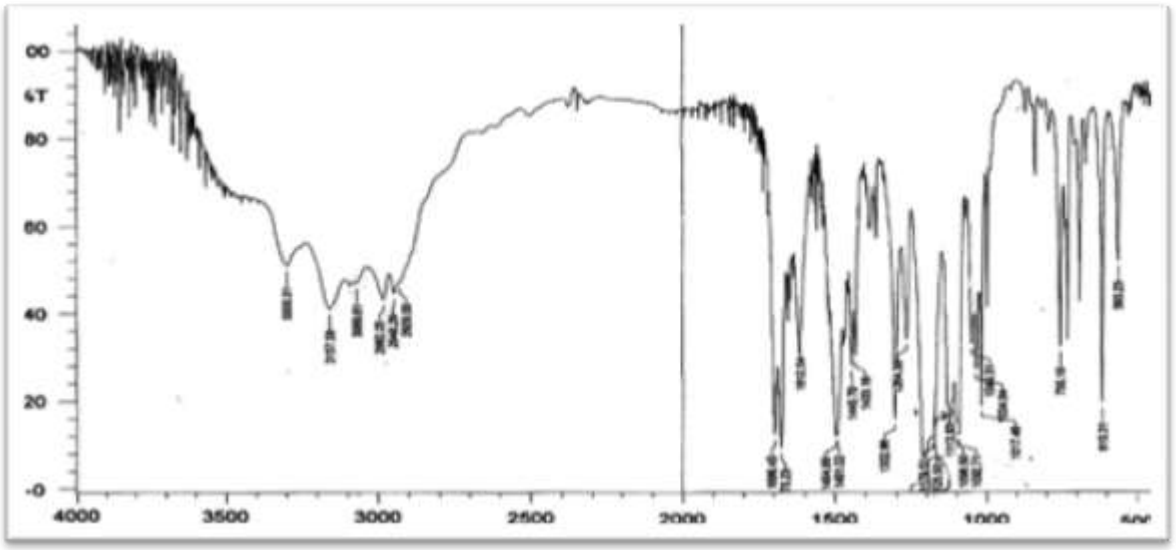


**Figure 5. FT-IR of Amlodipine Besylate**

International Journal of Pharmaceutical Research and Applications
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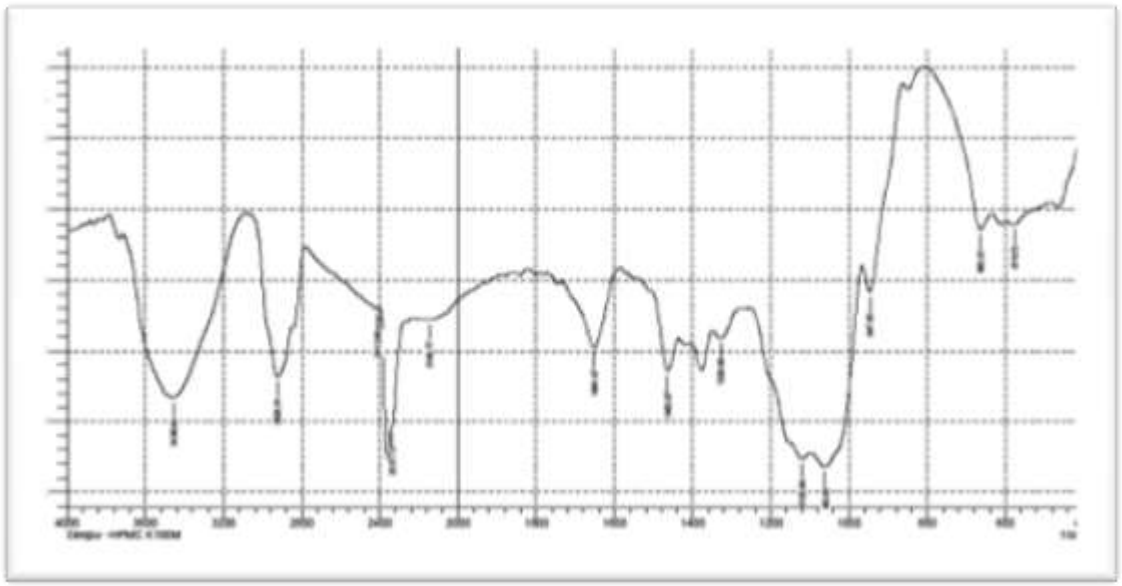

**Figure 6. FT -IR of HPMC**

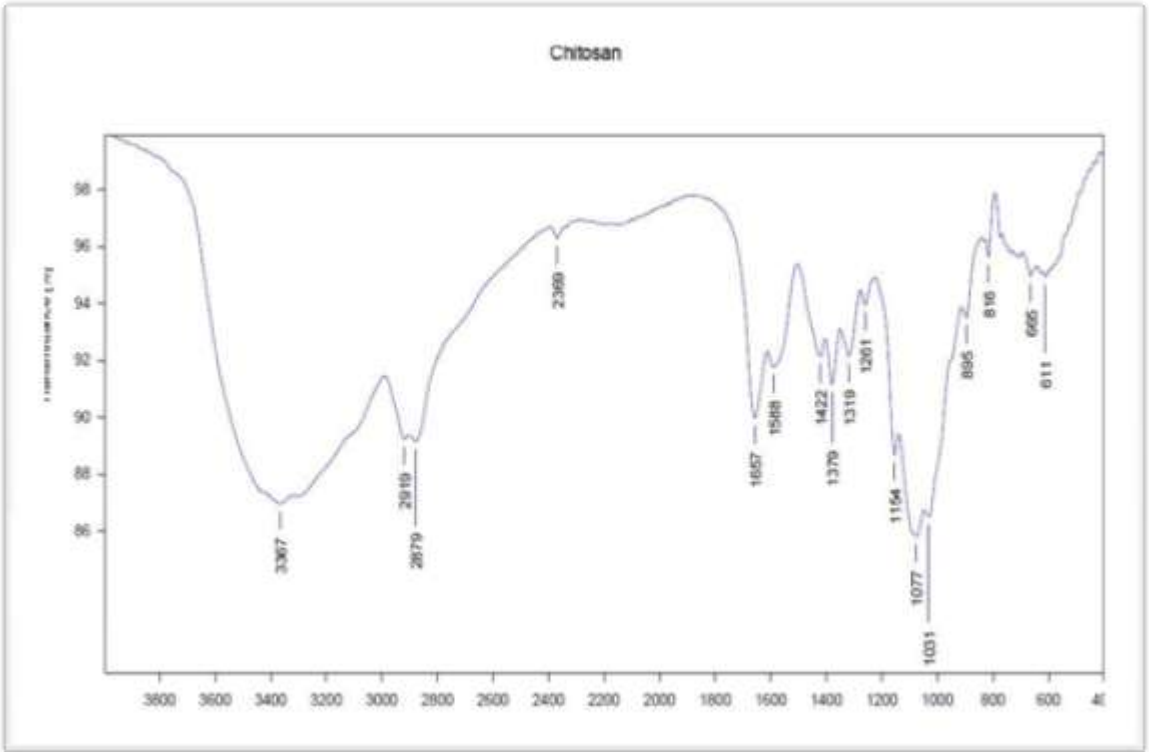


**Figure 7. FT-IR of Chitosan**

**Table 7: Formulation of Amlodipine besylate Microsphere**

| **Ingredients** | **FORMULATIONS** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| Amlodipine besylate(g) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Chitosan(g) | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 |
| HPMC(g) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 274-284 www.ijprajournal.com ISSN: 2249-7781

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| DMF(ml) | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| DCM(ml) | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| (1%w/v)SLS (ml) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 8: Particle Size, %Yield of Microsphere, Drug Entrapment Efficiency, Drug loading, Swelling Index**

| Formulation Code | Mean Particle Size (µm) | % Yield | Drug Entrapment Efficiency (%) | Drug loading efficiency | Swelling index (%) |
|---|---|---|---|---|---|
| **F1** | 187 | 51 | 28 | 50 | 83 |
| **F2** | 199 | 57 | 26 | 66 | 93 |
| **F3** | 257 | 68 | 22 | 67 | 159 |
| **F4** | 280 | 73 | 27 | 73 | 162 |
| **F5** | 327 | 80 | 25 | 78 | 176 |
| **F6** | 374 | 80 | 21 | 80 | 179 |
| **F7** | 418 | 79 | 22 | 82 | 183 |
| **F8** | 482 | 89 | 20 | 96 | 196 |

**Table 9: Initial %CDR and after 1 month %CDR (In-vitro drug release)**

| Time ( in hours) | Initial % CDR | After 1 Month % CDR |
|---|---|---|
| 1 | 14 | 12 |
| 2 | 32 | 28 |
| 3 | 44 | 40 |
| 4 | 60 | 58 |
| 5 | 70 | 66 |
| 6 | 80 | 79 |
| 7 | 90 | 86 |
| 8 | 98 | 95 |

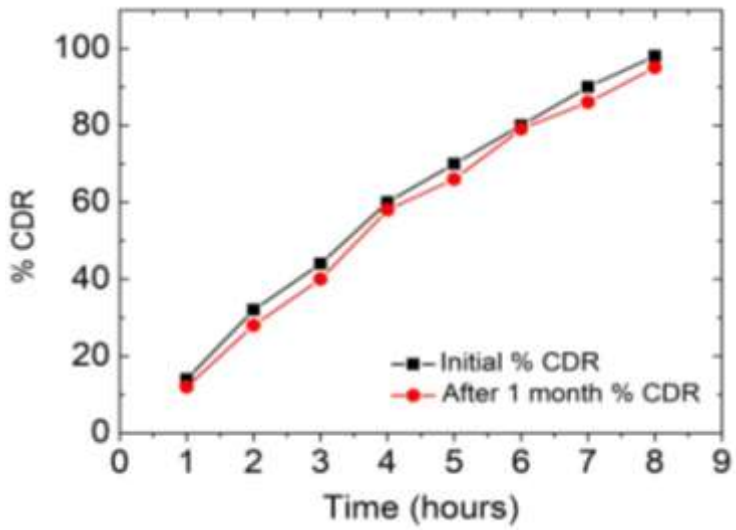


**Figure 8: In-vitro drug release**

## IV. CONCLUSION

The amlodipine besylate microsphere were successfully prepared by solvent evaporation technique (oil in water type emulsion) and concluded that it is one of the best techniques for the preparation of microsphere in laboratory. Both

preformulation studies and post formulation studies showed the satisfactory results. In post formulation studies, among all the formulation F8 showed the best and satisfactory results in particle size determination, drug loading efficiency, drug entrapment study, swelling index, invitro drug release and percentage yield. The drug content in formulation F8 was 92% which is acceptable and stability study also showed good results. Hence, the microsphere formulation formed is stable and optimized.

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