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# Formulation and Evaluation of Sustained Release Solid Dispersed Nifedipine Microcapsules

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Abstract

Conventional drug delivery system for treating the angina and hypertension are not much effective as the drug do not reach the site of action in appropriate amounts. Thus potent and guarded therapy of this angina and hypertension disorder using specific drug delivery system is a challenging task to the pharmaceutical professionals. The study was aimed at increase the solubility of poorly soluble drug nifedipine and formulating it in sustained release dosage form. Solid dispersion of drug was prepared using Poly vinyl pyrrolidone (PVP) as inert hydrophilic carriers by solvent evaporation technique. A 17-fold increase in dissolution rate of nifedipine was observed with solid dispersion prepared with PVP (K30). Sustained release microcapsules of nifedipine were formulated using Eudragit RS 100 as a polymer, acetone as polymer solvent for Eudragit RS100, N-hexane as a non-solvent, liquid paraffin vehicle, with solid dispersion of nifedipine as core by emulsion solvent evaporation method and modified emulsion solvent evaporation method. Microcapsules from all the batches were found to discrete, spherical and free flowing and % entrapment efficiency was found to be in range of 96.01% to 97.87%. All the batches of microcapsules showed sustained release curve in pH 7.4 phosphate buffer up to 12hours with maximum release up to 97.22% after 12hrs was found to be in B2. SEM studies of the microcapsules showed the surface topography states that prepared microspheres were spherical in shape. Shiny and uniform covered surface with polymer.

**Keywords:** Nifedipine, Poly vinyl pyrrolidone, Solid dispersion, Microcapsules, Emulsion solvent evaporation method

## Introduction

Hypertension is one of the most common cardiovascular diseases, which have become the leading cause of death for human[1], [2]. Successful treatment of hypertension in clinical practice means maintenance of blood pressure at a normal physiological level. In long-term therapy for the treatment of hypertension, the antihypertensive drugs have to be taken for life. In general, conventional formulations of the antihypertensive drugs need to be administered twice or three times a day to achieve effective therapeutic concentration, which results in marked blood pressure fluctuations and poor patient compliance. However, the formulations of drug sustained (controlled) release delivery systems have many advantages including reduced frequency of administration and fluctuation in plasma drug concentration, maintained stable blood pressure and improved patient compliance[3,4]. Therefore, the oral drug sustained (controlled) release delivery systems for the treatment of hypertension are an ideal solution. Nifedipine is a calcium channel blocker of the dihydropyridine type which is mainly used for the treatment of hypertension and angina pectoris. Nifedipine is a suitable candidate for CR administration due to its short elimination half-life of 2-4 hrs, its rapid and complete drug absorption over the entire gastrointestinal tract, despite its low water solubility and the relationship between drug plasma concentrations and blood pressure reduction. The importance of reduced peak plasma levels in order to avoid adverse effects such as reflex tachycardia has also been demonstrated[5]. Numerous attempts have been made to modify the dissolution characteristic of drug to attain more rapid and complete absorption[6-8]. Solid dispersion is one of the techniques which are originally used to enhance the dissolution rate of poorly water-soluble drugs using inert hydrophilic carriers[9]. The enhancement in the dissolution rate is obtained by one or a combination of the following mechanism: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wettability due to close contact with a hydrophilic carrier, precipitation as a metastable crystalline form or a decrease in substance crystallinity. The type of solid dispersion formed depends on both the carrier-drug combination and the method of manufacture[10]. Hydrophilic polymers like polyethylene glycols (PEG) [11-13]. Polyvinyl pyrrolidone (PVP) [14,15] and hydroxyl propyl methyl cellulose (HPMC) [16] are among the popular carriers commonly used to prepare solid dispersions. Being freely soluble in water, these polymers are mainly used as excipients, to enhance the dissolution rate of drugs[17, 18]. Pluronic F-68 is being used as a newer material for preparation of solid dispersion to enhance the dissolution rate of poorly water soluble nifedipine[19]. The aim of this study is to improve the solubility of the poorly water soluble drug nifedipine by preparing solid dispersions using various hydrophilic carriers and using optimized solid dispersion to

fabricate microcapsules for sustained release delivery of the drug with better bioavailability.

## Materials and methods

### Materials

Nifedipine was obtained from Cipla Ltd. Mumbai, India. Polyvinyl pyrrolidone K30 was obtained as a gift from Blessings Pharmaceuticals Nagpur, India. Eudragit RS 100 was obtained as a gift from Rohm Pharma GMBH, Germany. Liquid paraffin was obtained from Shaw Wallace, India. Methanol, acetone was purchased from Loba Chemicals, India. Other reagents/chemicals were of AR/GR grade and purchased locally.

### Method

### Preformulation study[20-22]

#### *Solubility*

Solubility study was conducted to determine the effect of different buffers on the drug. An excess amount of drug was dispersed in 5 ml of distilled water, methanol, acetone, phosphate buffer solution (pH 6.8 and 7.4), 0.1N HCl, in glass stoppered tubes respectively, all the glass tubes were closed with stopper and covered with cellophane membrane to avoid solvent loss. Tubes were kept in water bath shaker at 37°C for 24 hrs. As the samples attain equilibrium, they were subjected for centrifugation at 3000 RPM for about 5 minutes. After completion of centrifugation the samples get separated, then supernatant liquid is filtered through membrane filter and then analyzed by UV spectrophotometer at 238nm respectively.

#### *Melting point determination*

Melting point of nifedipine was determined by open capillary method.

#### *Determination of partition coefficient*

25 mg of nifedipine with aqueous phase and n-octanol was taken in three separating funnels. The separating funnels were shaken for 2 hrs in a wrist action shaker for equilibration. Two phases were separated and the amount of the drug in aqueous phase was analyzed spectrophotometrically. The partition coefficient of the drug in phases was calculated.

#### *Determination of λmax*

A solution of nifedipine containing the concentration 10µg/ml was prepared in phosphate buffer 7.4 pH and UV spectrum was taken using Shimadzu (UV-1800) double beam spectrophotometer. The solution was scanned in the range of 200- 400 nm.

#### *Preparation of standard calibration curve of nifedipine*

100mg of drug was accurately weighed and dissolved in 100ml phosphate buffer 7.4 pH in 100 ml volumetric flask, to make (1000µg/ml) standard stock solution (1). Then 10 ml stock solution (1) was taken in another 100 ml volumetric flask to make (100µg/ml) standard stock solution (2), then again 0.5, 1, 1.5, 2, 2.5 and 3.0 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 5, 10, 15, 20, 25 and 30µg/ml with distilled water. The absorbance of standard solution was determined using UV/VIS spectrophotometer (Shimadzu UV-1800) at 238nm. Linearity of standard curve was assessed from the square of correlation coefficient ($r^2$) which determined by least-square linear regression analysis.

#### *FTIR spectroscopy*

The concentration of the sample in KBr should be in the range of 0.2% to 1 %. The pellet is a lot thicker than a liquid film, consequently a decrease concentration in the sample is required (Beer's Law). For the die set that you'll be the usage of, about 80 mg of the mixture is wanted. Too excessive of an attention causes typically difficulties to obtain clean pellets. FTIR spectra of the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolution.

### Preparation of solid dispersions

All procedures of experiments were performed in darken conditions for avoidance nifedipine light deprivation

#### *Physical mixtures procedure*

Nifedipine and polymer PVP-K30 taken in various concentrations like (1:2, 1:4, 1:6, and 1:8) [23].

#### *Solid dispersions procedure*

Using solvent evaporation technique, nifedipine as well as PVP K-30 uniformly dissolved in methanol taking various concentrations like (1:2, 1:4, 1:6, 1:8 and 1:10) after wards at $40^0$C the solvent evaporated. Resultant solid dispersed material passed through 100 meshes sieve.

### Solid dispersion evaluation

#### *Estimation solubility procedure*

The solubility study carried out for pure nifedipine, prepared physical mixtures and solid dispersions using thermostatic shaker water bath. Concentrated saturated solutions in 0.1 N HCl shake for 96 hrs at $37^0$C. At end solutions were removed filtered diluted drug concentration was found by spectrophotometrically at 238 nm[23, 24].

#### *Estimation of nifedipine*

Precisely weighted nifedipine samples were hauling out into methanol then extracts diluted using buffer solution (pH–7.4). Resultant extract analysed for nifedipine spectrophotometrically at 238 nm against buffer solution (pH 7.4) used blank solution. The method followed beers lamberts law in concentration range of 1-10µg/ml[23, 24].

#### *Solid dispersions in vitro dissolution*

Studies performed using (type II) USP XXIV dissolution test apparatus using the media 0.1 N HCl 900ml Dissolution medium for 1 hr, at 50 rpm and 370C- 10C temperatures. 5ml of samples taken at different time intervals and 5ml of same dissolution medium added to maintain sink condition. Withdrawn aliquots suitably diluted and analysed at 238 nm using U.V. Spectrophotometer. The percent release of nifedipine calculated and graph plotted against time[23, 24].

### Formulation of microcapsules

Two techniques used to prepare microcapsules. Emulsion solvent evaporation (ESE) and modified emulsion solvent evaporation (MESE). In each case of this techniques, Eudragit RS 100 as a polymer, acetone as polymer solvent for Eudragit RS100, N-hexane as a non- solvent, liquid paraffin vehicle, in following A1, A2 and B1, B2 batches using 1:2 and 1:4 Core to coat ratios for each[25].

#### *Emulsion solvent evaporation method (ESE)*

Polymer dissolved in 15ml acetone. Solid dispersed nifedipine added into polymeric solution with agitation. Then obtained mixture transpired drop wise by syringe having needle size (15guage,2.5 inch) to the dispersion media containing liquid paraffin 100ml, containing Polysorbate ( Tween 80) (1%) w/w contained beaker study stirring at 600 rpm. at $25^0$C- $20^0$C

(room temperature) until solvent acetone completely evaporated. Lastly liquid paraffin separated by decantation and filtration procedure. Collected microcapsules washed using N-hexane for removal of traces of vehicle. The prepared microcapsules then dried at room temperature[25, 26].

***Modified emulsion solvent evaporation method (MESE)***

This technique was same as ESE method. Difference is that when addition of polymeric solution in over after 10-15min n-hexane was poured to vehicle phase. Acetone to hexane ratio 3:2. Produced microcapsules processed like a process given for ESE method[25,26].

**Evaluation of microcapsules**[27-30]

***Drug content determination***

From precisely weighted sample nifedipine haul out inside methanol, and then aliquots marked up using buffer solution (pH-7.4). Resultant extract analysed for nifedipine spectrophotometrically at 238nm against buffer solution (pH 7.4) used blank solution. Technique pursued beers lamberts law within 1-10µg/ml concentration range.

***Encapsulation efficiency***

Sieved microcapsules (50 mg) were grounded in a mortar and the drug content was extracted in pH 7.4 phosphates buffer. After suitable dilution of the sample, the drug content was analyzed spectrophotometrically at a wavelength of 238nm. Every batch of microcapsule was analyzed in a triplicate.

***Particle size***

Particle size determined using Sieve shaker, using different range of standard sieve and the quantity failed on different sieves were noted measured and standard (Avg) diameter of the particle was calculated.

***Invitro dissolution***

The dissolution studies performed using (type II) USP XXIV dissolution rate test apparatus in 0.1 N HCl for 2 hrs followed by pH 7.4 900ml dissolution medium containing 20% methanol at 50 rpm and 37$^0$C, temperature up to 12 hrs. 5ml of samples taken at different time intervals and 5ml of same dissolution medium added to maintain sink condition. Withdrawn aliquots diluted and analysed spectrophotometrically on 238 nm using U.V. Spectrophotometer. Nifedipine percent release calculated and graph plotted against time.

***Accelerated stability study***

The microcapsules from the selected and optimized batch were studied for stability and kept under the accelerated conditions of temperature and moisture (humidity) for the period of six months. These microspheres stability was studied at temperature 40°C and Humidity 75% RH conditions. Every sample separately weighed and enclosed by aluminium foils and sealed in black PVC bottle and kept in specified conditions at humidity chamber for six months. The formulations were checked for physical changes also analysed for dissolution study.

***Scanning electron microscopy (SEM) study***

Microcapsules mounted directly on scotch double adhesive tape analysed under scanning electron microscope SEM model, S-410 operated at 15K SEM thickness of 100% using Hitachi vacuum at 15 kv.

## Results and Discussion

The nifedipine is found to be soluble in methanol, chloroform, freely soluble in phosphate buffer (pH 7.4) and practically insoluble in ethanol and distilled water. The melting point of nifedipine was 170 ºC -174ºC and $\lambda_{max}$ of nifedipine was found to be 238nm by using U.V. spectrophotometer (Shimadzu UV-1800). The calibration curve of nifedipine was found to be linear in the concentration range of 5-30µg/ml at 238nm Figure 1. The partition coefficient of nifedipine was found to 0.562 in octanol: water. Identification of nifedipine was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification Figure 2. As concerned with solubility of the solid dispersions, it was found that drug, polymer ratios (1:8) shown enhanced solubility than other batches. Prepared whole batches of physical-mixture represented reduced solubility of drug and discharge than solid dispersions. Batch of solid dispersions composed 1:8 shown more discharge of drug. The pure nifedipine was shown 9.2% released within one hr. The enhanced drug dissolution is because of wetting ability enhanced also solubilization effect of polymer near diffusion level, another parameter is expansion of nifedipine solubilization through solid dispersion is due to the amorphous structure of nifedipine, no aggregation, particle size reduction in solid dispersions. Nifedipine solubility from dispersion was enhanced as extent of PVP K-30 increased up to 1:8, after increase in concentration of PVP decreased the dissolution. Reason might be that high polymer proportions cause's difficulty in leaching to drug during dissolution Table 1 & 2. The drug content of all physical mixture lies between 8.50 to 32.49 % and for solid dispersions it was 8.20 to 31.69 % Table 3 & 4. Dissolution profile of physical mixture and solid dispersions was given in Table 5 & 6. The microencapsulating efficiency determined by using drug content of microcapsules and formula. Nifedipine amount for total batches perceived in uniform quantity. The higher percentage of 97.87% entrapment efficiency was found in batch B2 when compare to other formulation Table 7. An *in vitro* dissolution rate study was done for whole batches of microcapsules. Batch A1 shown 78% drug release up to 12 hrs, Batch A2 (94.012%) and batch B1 shown 82.32 % drug release and batch B2 (98.22%) showed highest percentage of drug release up to 12 hrs. This study reveals as the polymer amount raised the drug release retarded. The drug released by erosion of coating material. In MESE methodology, hexane added which is miscible in acetone as well as liquid paraffin. Little bit amount of Hexane get miscible with liquid paraffin increases attraction of liquid paraffin to acetone leads in an enhanced extent of solvent evaporation Figure 3. The microcapsules from the selected and optimized batch (B2) were studied for stability and kept under the accelerated conditions like raised temperature and moisture up to period of six months. The results revealed no marked alterations in physical appearance and drug releasing properties Figure 4. The surface topography states that prepared microspheres were spherical in shape. Shiny and uniform covered surface with polymer Figure 5.

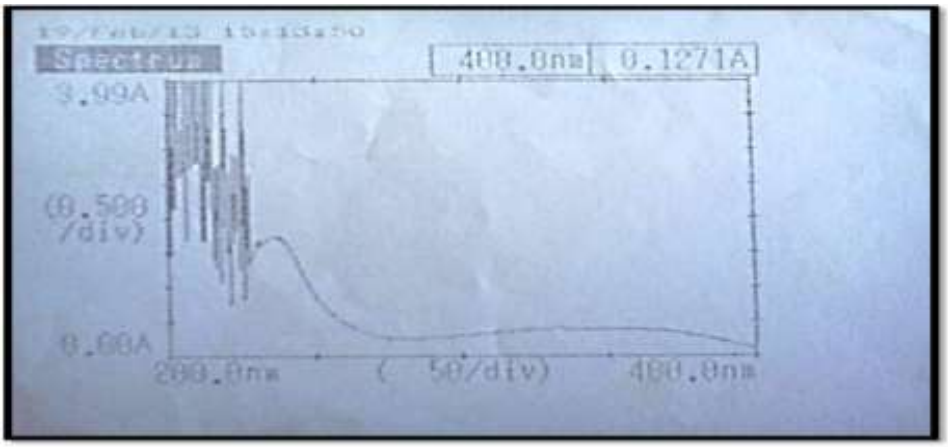


**Figure 1: Wavelength maxima of nifedipine**

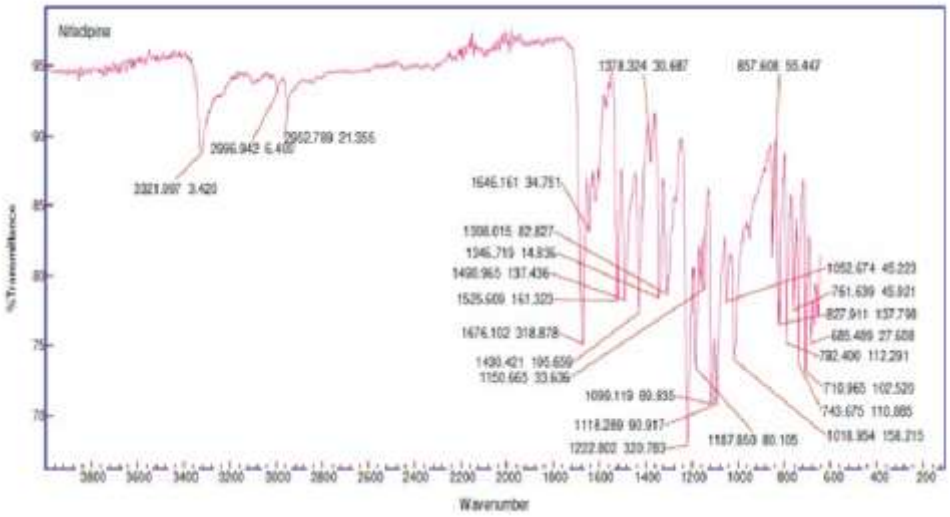


**Figure 2: FT-IR spectrum of pure drug (nifedipine)**

**Table 1: Solubility study of physical mixture**

| Carrier | Concentration of nifedipine in physical mixture (µg/ml) | | | | |
|---|---|---|---|---|---|
| | 1:2 | 1:4 | 1:6 | 1:8 | 1:10 |
| PVP(K30) | 7.483 | 7.882 | 9.905 | 9.563 | 8.963 |

**Table 2: Solubility study of solid dispersion**

| Polymer | Concentration of nifedipine in solid dispersion (µg/ml) | | | | |
|---|---|---|---|---|---|
| | 1:2 | 1:4 | 1:6 | 1:8 | 1:10 |
| PVP (K30) | 12.321 | 14.516 | 15.65 | 17.898 | 15.762 |

Pure nifedipine: Solubility found to be 8.94 µg per ml

**Table 3: Nifedipine %yield physical mixture**

| Sr. No. | Nifedipine: povidone | Theoretical yieldmg % | Physical mixture practical yield % |
|---|---|---|---|
| 1. | 1:2 | 33.33 | 32.49 |
| 2. | 1:4 | 20 | 19.53 |
| 3. | 1:6 | 14.28 | 13.03 |
| 4. | 1:8 | 11.11 | 10.24 |
| 5. | 1:10 | 9.09 | 8.50 |

**Table 4: Nifedipine %yield solid dispersions**

| Sr. No. | Nifedipine: povidone | Theoretical | Solid dispersions practical |
|---|---|---|---|
| 1. | 1:2 | 33.33 | 31.69 |
| 2. | 1:4 | 20 | 19.23 |
| 3. | 1:6 | 14.28 | 12.56 |
| 4. | 1:8 | 11.11 | 10.04 |
| 5. | 1:10 | 9.09 | 8.20 |

**Table 5: Dissolution profile of physical mixture**

| TimeMin | Nifedipine | Povidone(1:2) | Povidone(1:4) | Povidone(1:6) | Povidone(1:8) | Povidone(1:10) |
|---|---|---|---|---|---|---|
| **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| 10 | 0.89 | 1.53 | 2.62 | 3.92 | 5.03 | 5.5 |
| 20 | 1.92 | 3.89 | 5.01 | 6.03 | 7.12 | 8.12 |
| 30 | 2.85 | 4.56 | 8.05 | 8.12 | 10.9 | 9.98 |
| 40 | 5.06 | 8.21 | 11.12 | 12.52 | 15.56 | 15.78 |
| 50 | 7.36 | 10.72 | 14.31 | 15.62 | 18.52 | 18.21 |
| 60 | 9.29 | 13.91 | 17.17 | 19.06 | 22.06 | 22.56 |

**Table 6: Solid dispersions dissolution profiles**

| Time Min | Nifedipine | Povidone(1:2) | Povidone(1:4) | Povidone(1:6) | Povidone(1:8) | Povidone(1:10) |
|---|---|---|---|---|---|---|
| **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| 10 | 0.65 | 7.53 | 9.52 | 13.87 | 15.72 | 12.56 |
| 20 | 1.82 | 13.9 | 19.25 | 26.52 | 32.52 | 28.57 |
| 30 | 2.2 | 19.8 | 28.82 | 35.21 | 48.25 | 43.56 |
| 40 | 5.06 | 28.06 | 39.56 | 49.72 | 63.21 | 59.15 |
| 50 | 7.3 | 35.72 | 49.25 | 61.82 | 78.92 | 72.76 |
| 60 | 9.2 | 43.57 | 59.52 | 75.21 | 96.31 | 87.65 |

**Table 7: Drug content and entrapment efficiency**

| Sample | % Drug content | % of Entrapped |
|---|---|---|
| Pure drug | 99.97 | ------- |
| A1 | 10.89 | 96.01 |
| A2 | 8.79 | 96.69 |
| B1 | 10.76 | 96.84 |
| B2 | 8.89 | 97.87 |

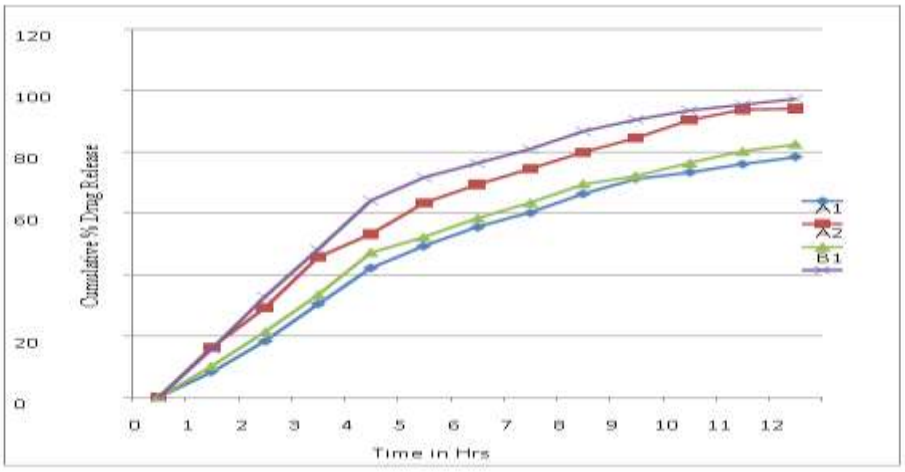


**Figure 3: Cumulative % drug release of all batches**

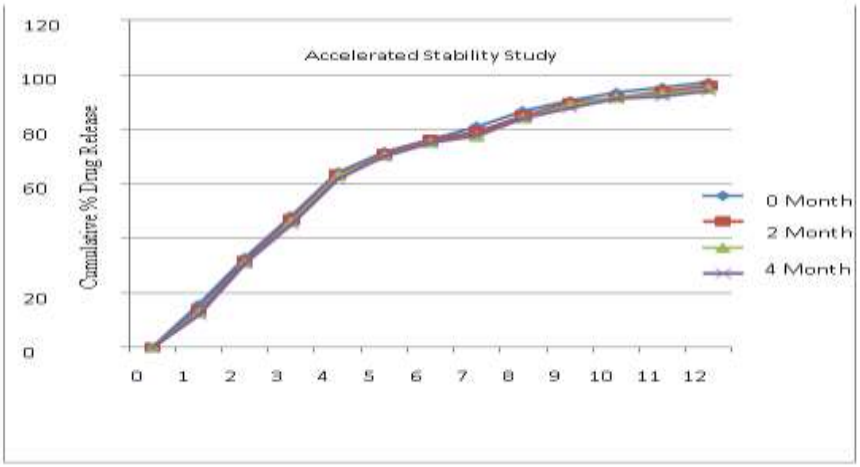


**Figure 4: Cumulative % Drug release study of optimized formulation at accelerated conditions**

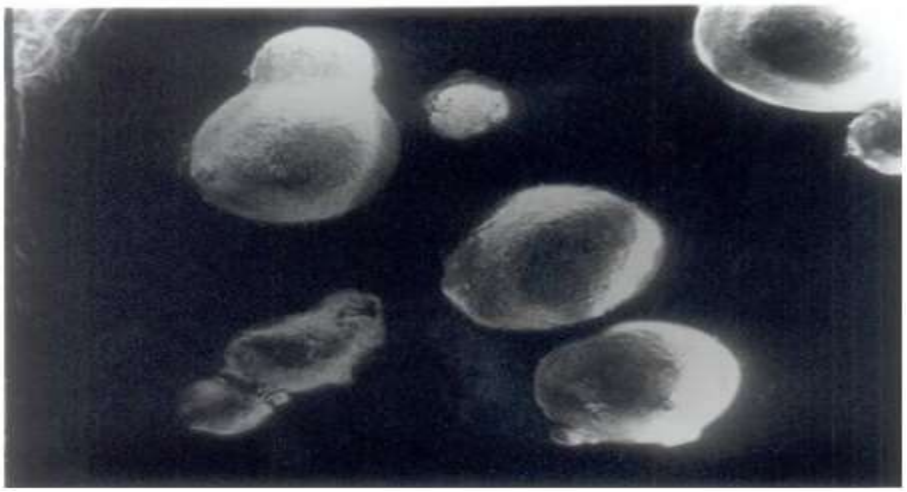

**Figure 5: Microcapsulesbatch B2 at 15kV 50x**

## Conclusion

Extended release dosage forms of nifedipine are difficult to formulate due to its poor solubility. Approach of solid dispersion was employed in which hydrophilic carriers like PVP were used. PVP markedly enhanced the dissolution rate of nifedipine. IR studies also indicated no chemical interaction between nifedipine and excipient. Thus, solid dispersion was then microencapsulated using different material using emulsion solvent evaporation method and modified emulsion solvent evaporation method. Microcapsules formulated were found to be spherical and discrete as seen in SEM photomicrographs and were also having good encapsulating efficiency. Nifedipine release up to 97.22% after 12hrs was observed.

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