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# FORMULATION AND EVALUATION OF CARVEDILOL NASAL MICROSPHERES

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## ABSTRACT

The aim of this research work was the formulation and evaluation of nasal microsphere of loaded with carvedilol. Microsphere was prepared by simple w/o emulsification-cross linking process. The microspheres were formulated using Chitosan in different drug to polymer ratio ie. 1:1,1:1.5, 1:2, 1:2.5 and 1:3, by keeping stabilizer, cross linking, and stirring speed constant. Total five batches were prepared and batches were subjected to characterization study like % yield, particle size analysis, drug entrapment efficiency, drug content and % mucoadhesion. It was found that average percentage yield was greater than 50 % for all the batches. It was found that % yield increases with increase in polymer weight concentration. Drug entrapment efficiency and % muchoadhesion was found to be optimum for all batches. It was noted after study that as the concentration of polymer increases, drug entrapment and percentage muchoadhesion also increases. The in vitro drug release profile of all the formulation of Carvedilol was showed sustained release of drug for extended period of time. The developed formulation (F5) was found to be stable during the stability study period of 3 month indicating good stability of the microsphere.

**KEYWORDS:** Carvedilol, Mucoadhesion, Chitosan, Nasal Microsphere.

## INTRODUCTION

Microspheres are spherical particles that range in diameter from 10 µm to 1000 µm. Microspheres are crucial for enhancing the absorption of traditional medications and reducing their adverse effects. The controlled release of the medicinal content is the primary benefit of using microspheres as a drug delivery mechanism. By delaying the release of the medication from dosage forms, microencapsulation lowers side effects and improves patient compliance. This method uses emulsion solvent diffusion evaporation to coat an aqueous insoluble coat (polymer) over an aqueous insoluble core (drugs) to create a sustained release drug delivery system. There are several methods for creating microspheres, such as phase separation, spray-dry, and emulsification using single or double solvent evaporation systems. Microspheres can be prepared by dissolving the starting materials in volatile solvents and then dispersing them in another solvent which is not miscible with the previous. Later complete evaporation of the last solvent will produce a fine powder called microspheres which is soluble in water. There are two types of microspheres Microcapsules and Micrometrics.[1-2]

Mucoadhesive microspheres which are of 1-1000 mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, *e. g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.[3-4]

Carvedilol is about 25% to 35% bioavailable following oral administration due to extensive first-pass metabolism. Absorption is slowed when administered with food, The compound is metabolized by liver enzymes, CYP2D6 and CYP2C9 via aromatic ring oxidation and glucuronidation, then further conjugated by glucuronidation and sulfation.[5]

## MATERIALS AND METHODS

### Materials

Carvedilol was obtained as gift sample from Cipla Ltd. Mumbai, Chitosan was obtained by Central Institute of Fisheries Technology, Cochin., all other chemicals are analytical grade.

## Methods

### Preformulation Studies

Preformulation studies are the first step in the rationale development of dosage form of a drug substance. It is the study of a drug substance's physical and chemical characteristics both by itself and in combination with an excipient. Preformulation testing's main goal is to produce data that will help the formulator create a dosage form that is safe, effective, and stable. Preformulation research was therefore done on the drug sample in order to identify it and determine compatibility.

### Drug Excipients Compatibility Studies

Compatibility study of drug with the excipients was determined by I.R. Spectroscopy (FTIR) using Shimadzu affinity-one, Japan FT-IR spectrometer model. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of the drug and other ingredients in the formulations were compared with that of the pure drug.

### Formulation of Nasal Microsphere of Carvedilol

Carvedilol nasal microspheres were prepared by using simple w/o emulsification-cross linking process using different ratio of drug to polymer (1:1, 1:1.5, 1:2. 1:2.5 and 1:3). Total five formulations (F1 to F5) was prepared using different concentration of chitosan. The external phase was used as mixture of heavy and light liquid paraffin in 1:1 ratio. Firstly, an accurately weighed quantity of polymer was dissolved in 2% aqueous acetic acid solution by continuously stirring until a homogeneous solution was obtained. Required quantity of drug was then added in polymer solution and then the dispersion was added slowly through syringe to the mixture of heavy and light (1:1) liquid paraffin containing 1 ml span 80 as stabilizer under constant stirring at speed of 1000 rpm for 30 min using a high speed stirrer. To this W/O emulsion, appropriate quantities of glutaraldehyde were added as cross-linking agent slowly and stirring was further continued for 3 h. After complete stirring the prepared microspheres were separated by filtration. The prepared microsphere was then washed several times with hexane to remove oil. Finally, microspheres were washed with distilled water to remove unreacted glutaraldehyde. The washed microspheres were air dried for 24 h and then stored in desiccator. The details for the formulation of drug loaded nasal microspheres was shown in table 1.[6-8]

**Table 1: Formulation of Carvedilol Nasal Microsphere.**

| Batch Code | Drug (mg) | Chitosan (mg) | Aqueous to oil Phase ratio | Glutaraldehyde (ml) | Span 80 (ml) |
|---|---|---|---|---|---|
| F1 | 100 | 100 | 01:10 | 2 | 1 |
| F2 | 100 | 150 | 01:10 | 2 | 1 |
| F3 | 100 | 200 | 01:10 | 2 | 1 |
| F4 | 100 | 250 | 01:10 | 2 | 1 |
| F5 | 100 | 300 | 01:10 | 2 | 1 |

### Characterization of Nasal Microspheres

### Percentage yield (%)

Percentage yield of nasal microspheres was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of nasal microspheres and is represented by following formula.[9]

$$\% \text{ Yield} = \frac{\text{Weight of Nasal Micropsheres}}{\text{Weight of drug and polymer}} \text{X } 100$$

### Particle size analysis

Particle size of the microspheres was determined by optical microscopy. The freshly prepared microspheres were examined on an optical microscope by pre-calibrated ocular micrometre and stage micrometre. The microspheres were suspended in water and a drop of microspheres was taken with a drop of glycerine and covered it with cover slip. Prepared slide of microspheres sample was examined under optical microscope. About 100 particles of each formulation were observed and measured. Mean of particle size is shown in tables.[10]

### Percentage Drug Entrapment Efficiency

To determine the % drug loading efficiency 50 mg of microspheres were taken and crushed using mortar and pestle, and then the crushed powder was transferred into 100 mL volumetric flask. Small quantity of methanol was added to the volumetric flask and the resulting solution was centrifuged for 10 min. Further volume was made up with methanol and filtered. Filtered sample was then further diluted with methanol so that to obtain the solution of desired drug concentration. The absorbance was measured spectrophotometrically at 241 nm. (Shimadzu Model 1601, Japan). The percentage drug loading efficiency of each microspheres formulation batch is shown in Tables.[11-12]

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Practical drug content}}{\text{Theorectical drug content}} \text{X } 100$$

### In vitro mucoadhesion studies

The mucoadhesion of microspheres was evaluated with little modifications to the previously reported method. Freshly isolated goat intestinal mucosa was used to study the in vitro mucoadhesion of microspheres. The intestinal section of a goat that was purchased from the nearby slaughter house had its intestinal mucosal tissues meticulously removed. The tissues were sliced into 1x1

cm pieces and then adhered to the glass slide. Accurately weighed microspheres (10 mg) were sprinkled on the mucosa. This glass slide was kept in desiccator for 1 hr to allow the polymer to interact with the membrane and finally placed in the cell that was attached to the outer assembly at an angle of $45^0$. Phosphate buffer solution pH 6.8, previously warmed to $37^0$C was circulated all over the microspheres and membrane at the rate of 1 ml/min. Washings were collected after 1 hr and microspheres were centrifuged and dryed at $50^0$C. The weight of washed out microspheres was determined and percent mucoadhesion was calculated by standard formula.[13]

**Surface Morphology**

The surface morphology of the drug loaded microsphere was investigated by scanning electron microscopy. Studies using SEM provided a better understanding of the morphological characteristics of the microspheres.[14]

**In Vitro Drug Release Studies**

In- vitro release study was performed using Franz diffusion cell was used for permeation studies. It consists of two compartments, one is donor compartment and another is receptor compartment. A piece of goat nasal mucosa obtained from local slaughter house was mounted in between the donor and receptor compartment of Franz diffusion cell. Receptor compartment was filled with phosphate buffer of pH 6.8 as a dissolution medium. A magnetic bead was placed in the receptor compartment, and the whole assembly was placed on the magnetic stirrer. The microspheres equivalent to 6.25 mg of carvedilol was placed in the donor compartment. At predetermined time interval, 1 ml sample was withdrawn from the acceptor compartment and equal amount of fresh buffer solution was replaced so as to maintained sink condition. The collected sample were suitably diluted and analyzed spectrophotometrically at 241 nm.[15-16]

**Stability Studies**

The accelerated stability studies were carried out according to ICH guidelines optimized formulation was packed in strip of aluminium foil and this packed formulation was stored in stability chamber maintained at $40^o$C and 75% RH (Zone III conditions as per ICH Q1 guidelines) for 3 months. The microsphere was evaluated before and after 1 month for change in appearance, drug content and *In vitro* release.[17-19]

**RESULT AND DISCUSSION**

**Compatibility Studies (FT-IR)**

Both the polymer and pure drug's infrared spectra are examined. It has been found in this investigation that there is no chemical interaction between the polymer and carvedilol. The major peak in the drug and polymer mixture's infrared spectra was found to remain unchanged, indicating that there was no physical interaction due to bond formation between the two substances.

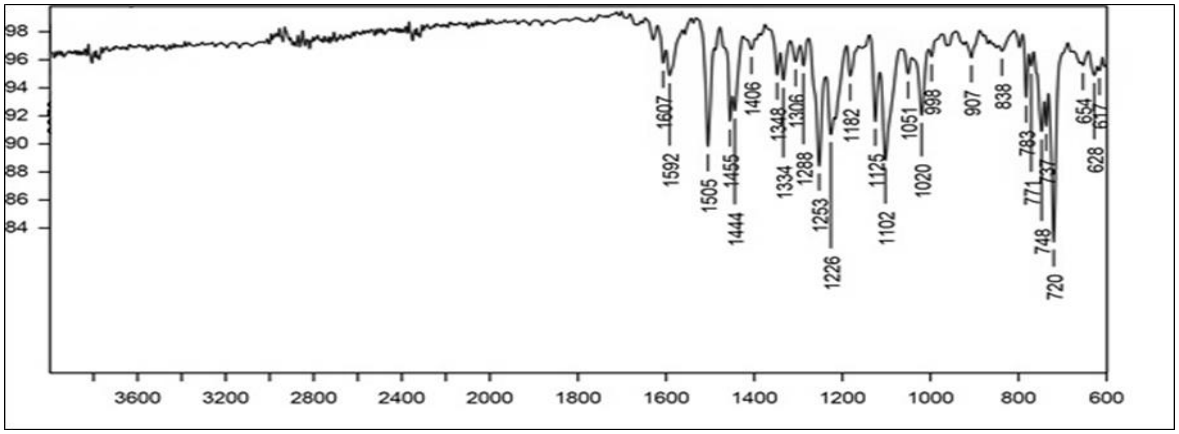


**Figure 1: IR spectra of pure drug Carvedilol.**

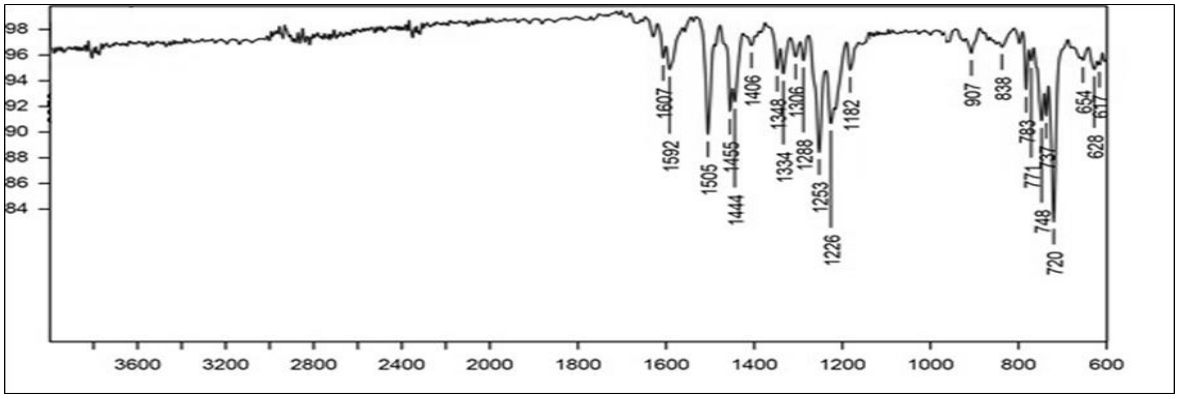


**Figure 2: IR Spectra of Carvedilol Chitosan Microsphere.**

**Characterization of Nasal Microspheres**

**Percentage yield**

The Percentage yields of nasal microspheres were found in the range of 64.23 to 82.70%. Increased in percentage yield of nasal microsphere was found as the polymer concentration increased. Formulation F5 showed highest yield while formulation F1 showed lowest yield. It was found that average percentage yield was greater than 50 % for all the batches which shows the suitability of this method for preparation of microspheres. The results were showed in table 8.2.

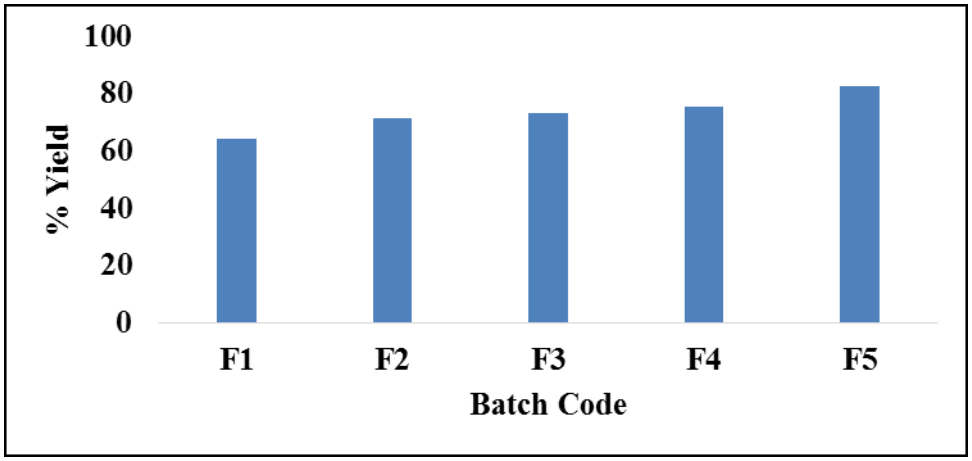


**Figure 3: Percentage yield of formulations F1 to F5.**

**Particle Size Analysis**

Particle size of the microsphere is the crucial parameter during the formulation. The average particle size for formulations found in the range of 51±1.26 to 54±2.62. The results were showed in table 8.2. Microspheres prepared with low chitosan concentration yields lower particle size. Increased chitosan concentration increases the viscosity of solution that will caused decreases in the stirring efficiency, which results in increased particle size. Formulation batch F1 showed lowest particle size, while batch F4 showed highest particle size of microsphere. All batch formulation showed the size of microsphere in micron range, showing effectiveness of method and technique.

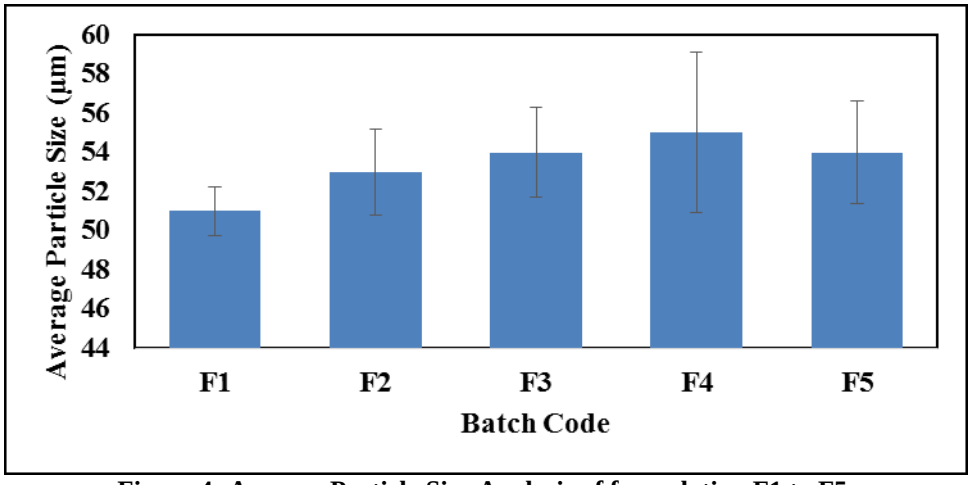


**Figure 4: Average Particle Size Analysis of formulation F1 to F5.**

**Drug Entrapment Efficiency and Drug Content**

The drug entrapment efficiency of all formulations was found to be in the range between 76.52±1.78 to 83.54±1.80 % and the drug content was found to be in the range of 73.45±1.23 to 84.27±0.56 %, the results were showed in table 8.2. It was observed from the results that, as the polymer concentration increases, the entrapment efficiency was also increases, this could be because of more encapsulation efficiency with higher polymer weight. An increase in polymer concentration in the internal phase shows increase in drug loading. This may be due to increase in viscosity of internal phase which reduces the migration of drug in aqueous phase, thus entrapping greater amount of drug.

**In vitro mucoadhesion studies**

All formulations were tested for in vitro mucoadhesion studies and showed excellent muchoadhesive strength. It was noted that with increased in amount of polymer, the mucoadhesive strength of microparticles was increased. Formulation batch F5 prepared with 1:3 drug to chitosan ratio, showed highest muchoadhesive strength

(86.45±2.04) among others. The results cleared that the microparticles remain adhered for a prolonged period. The mucoadhesion of all batch formulation was found in the range of 80.34±1.65 – 86.45±2.04.

**Table 2: Characterization of Nasal Microspheres.**

| Batch | Percentage yield (%) | Average particle size (µm) | Drug content (%) | Drug Entrapment Efficiency (%) | Mucoadhesion (%) |
|---|---|---|---|---|---|
| **F1** | 64.23 | 51±1.26 | 75.10±1.56 | 76.52±1.78 | 80.34±1.65 |
| **F2** | 71.40 | 53±2.18 | 73.45±1.23 | 78.45±2.56 | 83.10±1.24 |
| **F3** | 73.36 | 54±2.30 | 78.32±1.36 | 80.10±2.19 | 84.42±0.78 |
| **F4** | 75.54 | 55±4.10 | 80.17±1.14 | 81.40±1.64 | 85.21±1.20 |
| **F5** | 82.70 | 54±2.62 | 84.27±0.56 | 83.54±1.80 | 86.45±2.04 |

(Values are average SD±, n=3)

**In Vitro Drug Release Study**

In order to study the effect of different polymer concentration and to compare the drug release pattern of all prepared batches of nasal microsphere, it was subjected to in vitro release study. *In-vitro* drug release studies were performed using Franz diffusion cell in 6.8 pH phosphate buffer for the period of 12 hr. The results of cumulative drug release were showed in table 8.3. The graph was plotted between percentage drug release and time and it was showed in figure 8.6. The formulation batches F1 prepared with drug to chitosan ratio (1:1) showed drug release of 95.64% in 6 hrs, unable to hold the drug for longer duration. Batch F2 prepared with drug to chitosan ratio (1:1.5) gives the drug release of 94.16% in 7 hrs. Batch F2 prepared with drug to chitosan ratio (1:2) gives the drug release of 96.40% in 8 hrs. Batch F4 and F5 F2 prepared with drug to chitosan ratio (1:2.5 and 1:3) gives the drug release of 94.28% in 10 hrs and 98.32% in 12 hrs respectively. Batch F1, F2, F3 and F4 are not able to sustained the drug release up to 12 hrs. From the study it was observed that, in formulation F1 to F4, the concentration of chitosan is not optimum to hold the drug for longer time. Other hand the formulation F5, effectively controlled the release of drug for longer duration of 12 hrs and found to be optimum. From the study it was observed that as the concentration of chitosan increases, the drug release decreases. Among the formulations, batch F3 prepared with drug to chitosan in 1:3 ratio showed slow release of drug in sustained manner over a period of 12 hr when compare with other formulations.

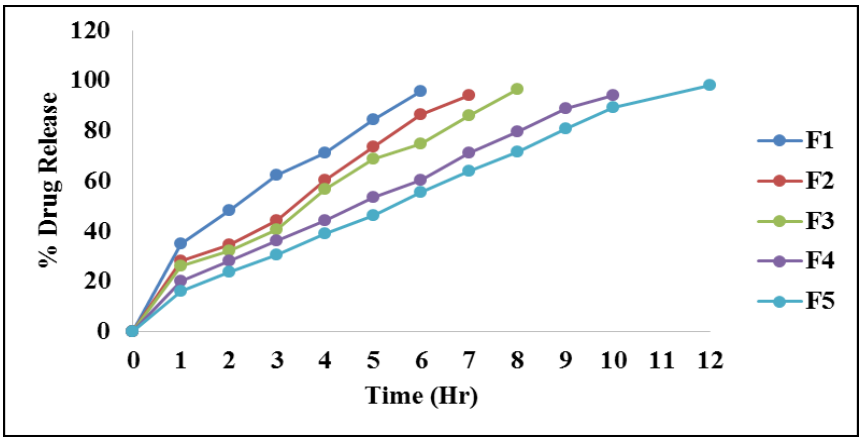


**Figure 5: In Vitro Dissolution Profile of Formulations F1 to F5.**

**Stability Studies**

The accelerated stability studies were carried out according to ICH guidelines optimized formulation F5 was packed in strip of aluminum foil and this packed formulation was stored in stability chamber maintained at 40°C and 75% RH (Zone III conditions as per ICH Q1 guidelines) for 3 months. The microspheres were evaluated before and after specified period of time for change in appearance, drug content, percentage muchoadhesion and *In vitro* release. After a period of 3 months, the sample were observed for any change on appearance. It was observed that microsphere was devoid of any change in color 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. The drug content of formulation F5 after 3 months was found to be 83.20 ±1.12% which shows there was small decrease in drug content but difference is insignificant. *In vitro drug release* of optimized formulation F5 after stability period was found as 97.66±1.80%. The % muchoadhesion of optimized formulation F5 was found to be 87.41±0.83% after stability period. Thus from the stability study data it was confirmed that, the optimized batch F5 showed very negligible changes in results after stability period and hence found to be stable. The data of stability study was given in table 8.5.

**Table 3: Stability studies of formulations F5.**

| Evaluation Parameter | Before Stability | After Stability |
|---|---|---|
| **% Muchoadhesion** | 86.45±2.04 | 87.41±0.83 |
| **Drug Content** | 84.27±0.56 | 83.20 ±1.12 |
| **% Drug release** | 98.32±1.66 | 97.66±1.80 |

## CONCLUSION

The nasal microsphere of Carvedilol can be prepared by simple w/o emulsification-cross linking process by using chitosan as rate controlling and mucoadhesive polymer. All the prepared formulations were showed satisfactory results. IR-spectroscopic studies indicate no drug-excipient interaction in formulation. The in vitro dissolution profile of all the prepared microsphere formulations of Carvedilol were found to extend the drug release over a longer duration. Release of Carvedilol from the formulation F5 follow zero order kinetics and Peppas equation indicates that the drug release was by non- Fickian mechanism. Comparing all the formulation F5 was consider as the ideal formulation which on the basis of cartelization parameters. Future details investigation is required to established in vivo efficiency of Carvedilol nasal microsphere and long term stability study need to be confirm the stability of Carvedilol nasal microsphere.

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