

Formulation and characterization of controlled release ketoprofen microsponges

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Abstract

Microsponges are porous, polymeric microspheres drug delivery systems. They bestow a controlled release of drugs, reduce systemic side effects and enhance stability. The aim of the present work was to formulate microsponges loaded with Ketoprofen (KP) by the quasi emulsion solvent evaporation method using Ethyl cellulose (EC) as a polymer and the polyvinyl alcohol (PVA) as an emulsifying agent, to study the influence of drug: polymer ratio (Ra), emulsifier concentration (Emc) and stirring rate (Sr) on the production yield (PY), encapsulation efficiency (EE) using the design of experiment to identify the key factors and establish a relationship between the choosing response and those factors using analyze of variance (ANOVA) and to study the drug release and kinetics evaluation. Results revealed that the production yield and the entrapment efficiency are affected by polymer ratio (Ra), when the ratio change from 1:1 to 1:5 the production yield change from 40.42% to 81.97% and the encapsulation efficiency varies from 36.41% to 56.28% of Ketoprofen. The stirring rate and emulsifier concentration have no effect on production yield values. When we increase Sr and Emc from the min value to the max value, EE decrease from 48.37% to 43.72% and from 60.37% to 32.32% respectively. In vitro drug release studies were carried out up to 8 h in phosphate buffer (pH 6.8) media and the release data showed good correlation with the Higuchi model.

Keywords: Microencapsulation, Ketoprofen, Ethyl Cellulose, Microsponges, Design of experiment;

1. Introduction

Ketoprofen (KP) is a poorly water-soluble non-steroidal anti-inflammatory, antipyretic and analgesic drug, frequently used for the treatment of rheumatoid arthritis, osteoarthritis and mild to moderate pain [1]. Ketoprofen is a potent non-steroidal anti-inflammatory drug. Its oral administration is associated with a high risk of adverse effects such as irritation, ulceration of the gastrointestinal tract, oedema, dizziness, and peptic ulceration when taken orally for a prolonged period. These attributes make KP a good candidate for controlled release dosage forms. Microspheres are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged drug delivery, improve bioavailability or stability and target drug to specific sites. They have played a vital role in the development of controlled/sustained release drug delivery systems [2]. Delivering drug at controlled rate, slow delivery and targeted delivery are very attractive properties to look for any form of medicine and it has been one of the biggest challenges faced.

The main objective of this work was to investigate the possibility of obtaining a sustained release formulation of ketoprofen microspheres by the solvent evaporation method using Ethyl Cellulose (EC). Investigation of the effect of various processing and formulation factors such as drug to polymer ratio, stirring speed, surfactant

concentration on the yield of production and encapsulation efficiency, and in-vitro release rate of drug from the microspheres were performed.

2. Materials And Methods

2.1. Apparatus

The compatibility of the drug with the formulation components was established by Fourier Transform Infrared Spectra (IR Affinity-1S) and thermogravimetric analysis (Mettler TG50). The morphology of the microsponges prepared was investigated using scanning electronic microscopy (JEOL 7200) and optical microscope (Oxion).

2.2. Reagents

ketoprofen (KP) is a gift sample from a national company. Ethyl cellulose (EC), Polyvinyl alcohol (PVA) and Dichloromethane were purchased from SIGMA-ALDRICH.

2.3. Qualitative drug analysis

A validated UV spectroscopy using a SHIMADZU UV-1800 spectrophotometer was adopted to quantify ketoprofen content in the microsponges at a maximum

wavelength of 260 nm. A stock solution (20 mg/mL) of ketoprofen was prepared in water (pH=6.8). A calibration curve was plotted using a series of standard solutions of ketoprofen in the concentration range of 2-20 mg/mL. A linear regression was applied to obtain linear equation ($y = 0.0332x + 0.0041$) with $R^2 = 0.9996$

2.4. Preparation of ketoprofen-loaded microsponges

The ketoprofenloaded Ethyl cellulose microsponges were prepared by the conventional emulsion solvent evaporation method, which was adapted from the process described by [3].

The drug:polymer ratio (Ra): for the low level -1 we chose 1:1 and for the high level +1 we chose 1:5, the concentration of the emulsifier (Emc): 0.1% is chosen for the low level and 1% for the high level and the stirring rate (Sr): is varied from 500 rpm (-1) to 1000 rpm (+1).

The required amount of the polymer was dissolved in 10 ml of dichloromethane. The calculated amount of KP powder was dissolved in the polymeric solution. The prepared dispersion was slowly poured into 100 ml of aqueous solution and was emulsified by vigorous stirring at room temperature using a three-blade mechanical stirrer. The dispersed drug and polymer were immediately transformed into fine droplets, which were subsequently solidified into rigid microspheres due to solvent evaporation. Stirring was continued for 2 hrs until all solvent was evaporated. The formed microspheres were filtered and washed several times with distilled water. The microspheres were dried and stored until further analysis.

The production yield (PY%) and the efficacy encapsulation (EE%) can be determined according to the below equations: (Moin A et al, 2016c)

$$PY (\%) = \frac{\text{practical mass of microsponges}}{\text{theoretical mass (polymer + drug)}} \times 100 \quad (1)$$

$$EE (\%) = \frac{\text{mass of the non encapsulated drug}}{\text{theoretical mass of the drug}} \times 100 \quad (2)$$

2.5. Preparation of ketoprofen-loaded microsponges

In the present study, the two level full factorial design was used to evaluate the effect of Ra, stirring speed (Sr) and emulsifier concentration (Emc) on the responses: production yield PY(%) and entrapment efficiency EE (%).

The measured response function (Y) of the full factorial design was explained by using following equation [4]:

$$Y = a_0 + \sum_{i=1}^p a_i * X_i + \sum_{i=1}^p \sum_{j=1}^p a_{ij} * X_{ij} + \sum_{i=1}^p \sum_{j=1}^p \sum_{k=1}^p a_{ijk} * X_{ijk} + \dots \quad (3)$$

Where, Y is the response, a_0 is the mean response a_i is the main effects, a_{ij} and a_{ijk} are the interactions effects.

3. Microsponges morphology and characterization

The morphology of the microspheres was investigated using an optical microscope (Oxion) and scanning electronic microscopy (SEM). The compatibility of the drug with formulation components was established by Fourier Transform Infrared spectra (Shimadzu).

4. In-vitro dissolution studies of KP-loaded microspheres

In vitro release rate studies were carried out in dissolution apparatus (Distec). Accurately 20 mg of microsponges were used. They were placed in pH 6.8 phosphate buffer solution at 37 °C and rotated at 100 rpm. Five ml aliquots were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min and then hourly intervals up to 8 h. The samples were assayed at 260 nm. Each determination was carried out in triplicate.

5. Results and Discussion

The obtained screening results are in the following table:

Table1: Design matrix and observed values of response

	Factors							
Run	Ra (KP:EC)		Sr (rpm)		Emc (%)		PY (%)	EE (%)
1	-1	(1 : 1)	-1	500	-1	0.1	40,42	55,15
2	+1	(1 : 5)	-1	500	-1	0.1	86,62	75,06
3	-1	(1 : 1)	+1	1000	-1	0.1	50	42,33
4	+1	(1 : 5)	+1	1000	-1	0.1	83,72	68,95
5	-1	(1 : 1)	-1	500	+1	1	41,42	26,4
6	+1	(1 : 5)	-1	500	+1	1	79,19	39,29
7	-1	(1 : 1)	+1	1000	+1	1	34,83	21,79
8	+1	(1 : 5)	+1	1000	+1	1	78,36	41,82



Figure 1. SEM images of microsponge containing ketoprofen

5.1. Microsponges morphology and characterization

Morphology analysis by SEM (Figure 1) and optical microscope (Figure 2) and showed that the microsponges look spherical shape, have smooth surface and shriveled to the size range 17.48-55.83 μm .

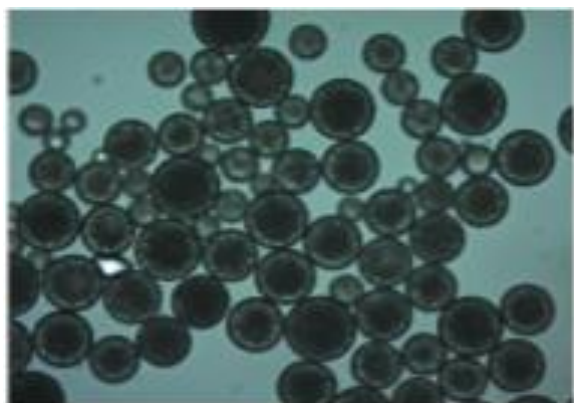


Figure 2. Optical microscop images of microsphere containing ketoprofen.

FTIR spectroscopy study results discovered no any new peak appearance or disappearance of existing peaks, discarding any chemical interaction probability among drug and polymer used as represented on Figure 3. All characteristic peaks of ketoprofen were experiential in the microsphere formulation spectrum. Thus, IR spectroscopy results depicted that drug was compatible with selected polymer in microsphere formulation.

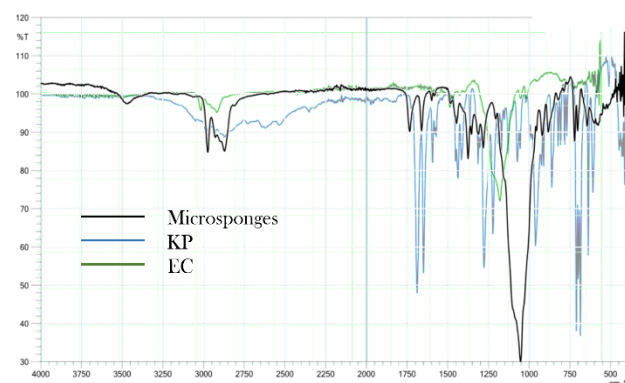


Figure 3. FTIR spectras of ketoprofen, Ethyl Celullose, and microsphere formulation.

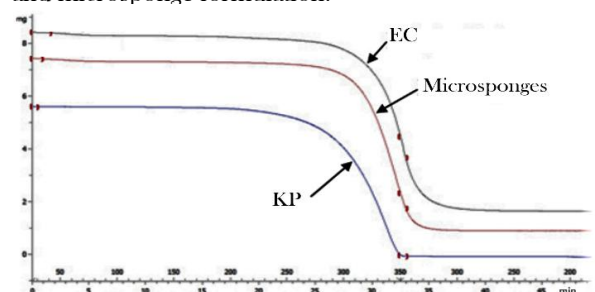


Figure 4. TGA of ketoprofen, Ethyl Celullose, and microsphere formulation.

Stability of KP in EC microsponges was investigated by thermal analysis using TGA (Figure 4) thermograms. Such information is crucial for solid dosage forms as the storage conditions may vary, in term of temperature. It can be seen that all the thermograms have the same pace, which is characterized by a single decomposition zone and only two zones of stability. The instability start temperature for Microsponges is up to 250°C, the same of EC, which means that KP is perfectly encapsulated.

5.2. Main effects of Ra, Sr and Emc on production yield

Figure 5 represents the main effects of Ra, Sr and Emc on production yield and revealed that the production yield is affected by polymer ratio (Ra), when the ratio change from 1:1 to 1:5 the production yield change from 40.42% to 81.97% of Ketoprofen.

The stirring rate and emulsifier concentration have no effect on production yield values.

The linear regression equation for YP is:

$$PY (\%) = 61.82 + 20.152 Ra - 0.093 Sr - 3.37 Ec - 1.762 Emc * Sr \quad (4)$$

With R^2 (adj) = 99.40% and the variance is $S=1.17$

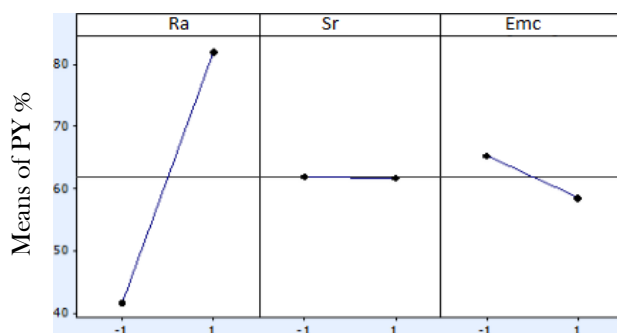


Figure 5. Main effects of Ra, Sr and Emc on production yield of microsphere formulation.

5.3. Main effects of Ra, Sr and Emc on encapsulation efficiency

The graph below shows that the polymer ratio and emulsifier concentration have an important effect on the entrapment efficiency. As the Ra change from 1:1 to 1:5, the EE increase from 36.41% to 56.28% of Ketoprofen. When we increase Emc from the min value to the max value, EE decrease from from 60.37% to 32.32%.

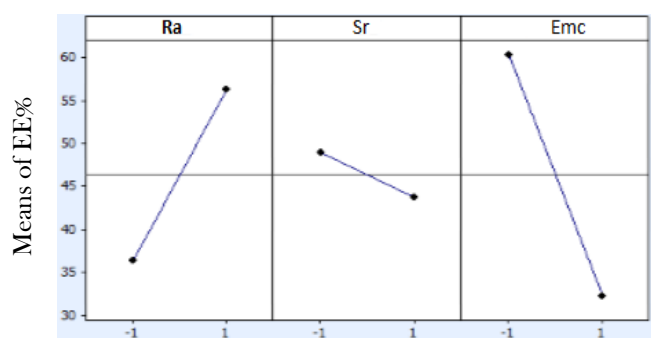


Figure 6. Main effects of Ra, Sr and Emc on encapsulation efficiency of microsphere formulation.

The stirring has no effect on EE values because when we increase Sr from 500rpm to 1000, EE decrease from 48.37% to 43.72%.

The linear regression equation for EE is:

$$EE(\%) = 46.35 + 9.93 Ra - 2.63 Sr - 14.02 Emc + 1.73Ra * Sr - 17.012Ra * Emc + 2.106Sr * Emc \quad (5)$$

With $R^2(\text{adj}) = 99.99\%$ and the variance is $S = 0.152$

5.4. Main effects of Ra, Sr and Emc on production yield

The 1, 2, 3 and 4 formulations of ketoprofen microspheres modified the release of ketoprofen when compared drug itself. From the obtained data, it could be concluded that ketoprofen loaded microspheres exhibited prolonged and controlled release.

Drug release of microspheres can be explained by Higuchi matrix model [5].

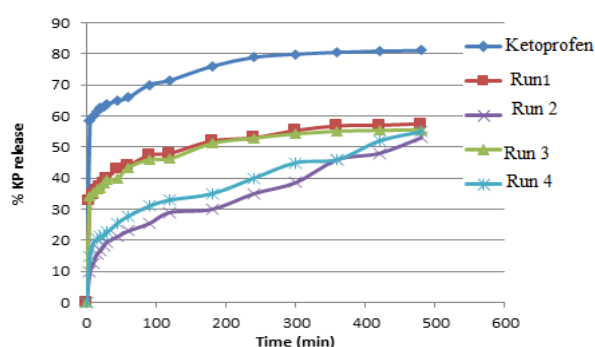


Figure 7. Release profiles of ketoprofen from microspheres in pH 6.8

6. Conclusion

The aim of this work is to formulate microspheres loaded Ketoprofen and evaluate them using the two level

full factorial design for screening and modeling the process. The obtained results showed that the production yield changed from 40.42% to 81.87% when the ratio is varied from 1:1 to 1:5 respectively. Increasing the stirring rate from 500 rpm to 1000 rpm and the variation of the PVA's concentration from 0.1% to 1% has no effect.

The encapsulation efficiency increase from 36.41% to 56.28% when the ratio changed from 1:1 to 1:5 respectively and it is also decrease from 60.37% to 32.32% with the variation of the PVA's concentration from 0.1% to 1% respectively.

For the production yield, the drug:polymer ratio was found to be the key factor that had the biggest influence compared to the two other factors as it increases, the yield increases in the same way, while the stirring rate had a weak negative effect that can be neglected.

Drug release of microspheres can be explained by Higuchi matrix model.

The accepted models can be used for the calculation of the responses for any given value in the chosen ranges of each factor

As a conclusion, the presented work was limited in studying only three factors in specific ranges. Thus, for further works, the studies can be carried out in different ranges for different factors, and other designs are recommended such as: Response surface, Plackett-Burman design.

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