P-117	**Optimization of pH-responsive gelatin /HPMCP microparticles containing peppermint oil using central composite design**	

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INTRODUCTION AND OBJECTIVES

As different techniques of drug encapsulation involve many interacting variables and operating conditions, experimental design methods are extensively being used in the encapsulation studies (1-2). These statistical techniques enable understanding the effect of the input variables and provide a powerful tool for simultaneous evaluation of the effect of each individual variable and also their interactions on the system.

In recent years, there has been a shift toward the use of natural products for IBS therapy. Peppermint oil (PO) is a useful therapy in IBS through its relaxation of smooth muscles; carminative and antibacterial actions. To deliver the required dose of PO to the site of action and prevent the side effects, delayed release dosage forms have been extensively designed and marketed. The present study was carried out to use statistical techniques of central composite design (CCD) to develop and optimize spherical macroparticles for site-specific release of PO.

MATERIALS AND METHODS

Peppermint oil (PO, grade BP) was purchased from Zardband Co., (Tehran, Iran). HPMCP (HP-55) manufactured by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Gelatin, sodium hydrogen carbonate and citric acid were purchased from Sigma Chemical Co., (Poole, UK). Also, menthol standard, di-sodium hydrogen phosphate and hydrochloric acid were supplied from Merck (Darmstadt, Germany).

Preparation and characterization of microcapsules

An oil in water/precipitation technique was developed for encapsulation of PO in a mixture of gelatin and pH sensitive polymer (i.e. HPMCP), as described before. The resulting macrocapsules were then filtered and dried at room temperature and characterized in terms of drug release, PO loading and efficiency (also described previously).

Experimental design

The design of the statistical experiments and their evaluation were performed using the Design-Expert 6.0.10 trial software.

RESULTS AND DISCUSSION

Typical chromatograms of a standard and a sample solution of menthol, containing linalool as the internal standard are shown in Figures 1a-b. The results of the method validation showed a very good linearity (r^2= 0.995) within the specified menthol concentration range (i.e. 200-2000ppm).

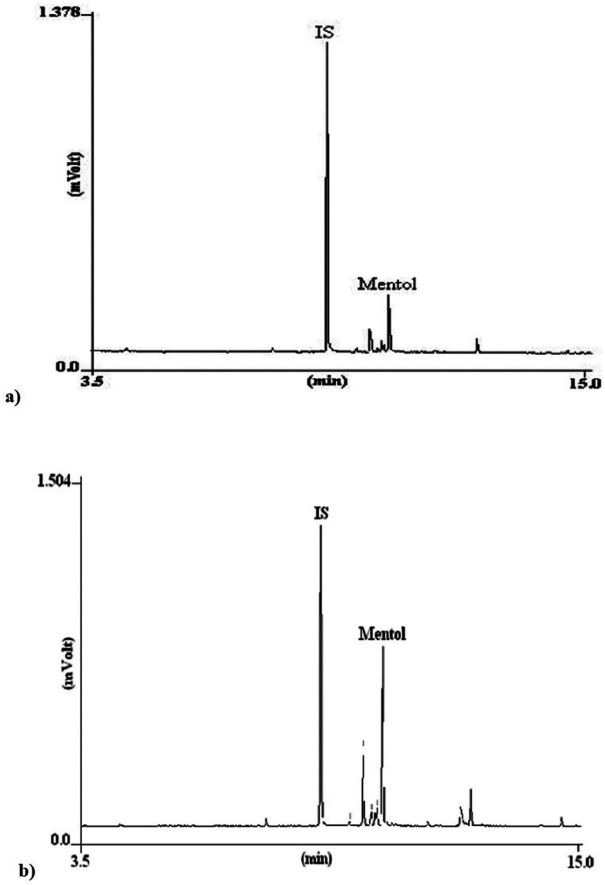

Fig 1: GC-FID chromatogram of a standard solution (a) and the sample extracted from macrocapsule (b)

Different formulations prepared using a central composite design. The characteristics of the resulting microcapsules are summarized in Table 1.

Table 1: Formulations and responses based on CCD

Run	A:%polymer	B:G/H	C: O/W%	Load-ing	Efficiency
1	12.00	55.00	15.00	39.00	63.50
2	8.00	55.00	15.00	42.90	60.40
3	8.00	55.00	25.00	45.40	43.00
4	10.00	50.00	20.00	43.80	55.10
5	10.00	50.00	20.00	47.60	61.20
6	6.64	50.00	20.00	37.60	36.30
7	10.00	50.00	28.41	53.30	57.80
8	8.00	45.00	15.00	35.40	40.00
9	10.00	50.00	20.00	40.60	52.00
10	8.00	45.00	25.00	51.50	46.30
11	12.00	45.00	15.00	37.00	62.70
12	10.00	50.00	20.00	44.50	60.60
13	10.00	50.00	11.59	36.10	59.30
14	12.00	45.00	25.00	48.00	65.40
15	10.00	58.41	20.00	41.70	61.20
16	10.00	41.59	20.00	47.60	67.00
17	10.00	50.00	20.00	46.00	62.90
18	10.00	50.00	20.00	47.16	69.00
19	13.36	50.00	20.00	48.30	76.80
20	12.00	55.00	25.00	52.30	75.30

Encapsulation efficiency is even more important parameter than loading, due to the high value of the essential oil in the encapsulation process. Therefore, the optimization of the encapsulation conditions, where the loss of the essential oil is minimized would be highly desirable. The results show that the model F-value of 19.95 is proposing a significant relationship between the selected variables and the encapsulation efficiency ($P<0.0001$).

Efficiency = - 12.02055 + 5.40800 A + 0.30301 B + 0.047995 C

Also, ANOVA analysis showed that the polymer concentration is the most important parameter in increasing the efficiency of encapsulation.

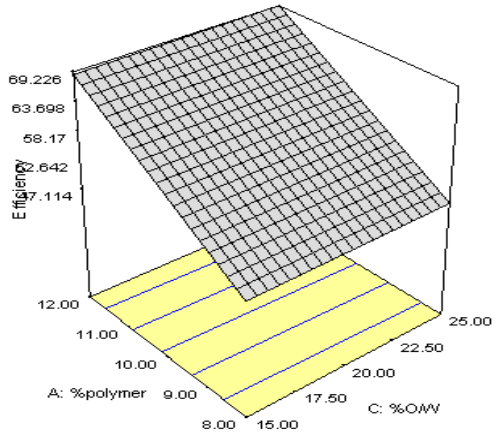

Fig 2: Surface response analysis for efficiency of PO encapsulation efficiency

The results show that the model F-values 19.78 is proposing a valid relationship between the selected variables and PO loading within the specified variable ranges. In another word, there is only a 0.01% chance that a model with F-value this large could occur by experimental errors. In this model, the o/w ratio ($F<0.0001$) is a significant factor, wherein, as the volume fraction of PO increases, the PO loading also increases.

Loading = 18.61987 + 0.74371 A – 0.075018 B + 1.09435 C

To optimize the formulation conditions based on the desired properties, the software proposed the following conditions (Table 2). The experimental data were very closed to the proposed conditions, showing the applicability of CCD for microencapsulation using the present study.

Table 2: Optimum formulation conditions proposed by software and experimental data

Loading		Efficiency		C	B	A	Factors
Experim*	Predict	Experim*	Predict				
47.1	53.3	71.2	77.3	25	40	14	Optimum Level

CONCLUSION

Experimental design can be successfully used to prepare pH responsive gelatin/HPMCP microparticles.

REFERENCES

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