Development of polymeric matrix for controlled release device: experimental optimization

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Biocompatible polymers used as matrices for controlled release devices are well established as drug carriers in pharmacy practice. Its development, however, is troublesome due to the broad number of parameters involved in establishing the polymeric matrix and its production process. Therefore, a careful experimental project has to be developed. In this work we studied polymeric matrix composed by poly vinyl pyrrolidone (PVP) and poly ethylene glycol (PEG) crosslinked by gamma radiation. Prostaglandin type E, employed as a pharmaceutical agent model, was used and in vitro release study was carried out in pH 5.4 phosphate buffer solution (PBS). Moreover, formulations were prepared by utilizing 2^3 factorial design. The evaluation of the effect of radiation dose, PEG molar mass and drug concentration in drug release rate was lead through analysis of variance. As a result, increasing drug concentration and decreasing radiation dose improved drug release rate whatever the PEG molar mass.

Introduction

Biocompatible polymers employed as matrices for drug delivery systems are well established drug carriers in pharmacy practice. Due to the large number of parameters involved in establishing the matrix and its production process, its development, however, is quite troublesome. When working with biomaterial development, it is particularly important to understand the variety and range of the following process parameters in order to cope with the expected features: [1, 2]

- The ability to easily form the product to fit a variety of shapes, ideally in situ;
- Erosion resistance or biodegradation rate;
- Environmental durability in a variety of conditions;
- Well-characterized bioactivity;
- Appropriate mechanical properties;
- Potential for use in multiple applications;
- Cost-effectiveness; and
- The ability to deliver the material in a sterile and bioactive state out of the package and directly into the application.

A time line for the development of new materials and drug formulations ranging from the early concept stage to commercial availability is presented by Langer and Tirrel.[2]. Each stage consists of tasks and requirements that must be satisfied as product development proceeds. The amount of time needed to get a product to the market will depend on where it is placed on this time line. Consequently, due to the broad number of parameters involved in establishing the matrix and its production process, a careful experimental project has to be developed. Factorial design, a statistical tool, has been used to minimize the number of assays[3].
In this work, a preliminary study to obtain a polymeric matrix composed by poly vinyl pyrrolidone (PVP) and poly ethylene glycol (PEG) crosslinked by gamma radiation was carried out applying a first order factorial design for three parameters with prostaglandin type E as an active drug model.

Experimental

The polymeric matrix was prepared with PVP (K 90) provided by BASF and PEG (Macrogol) by Oxiteno in 43% and 57% proportion respectively. PVP concentration was kept constant in the experimental design.
The experimental conditions were studied by a simple factorial design class where each parameter was examined in two levels: high and low value, considering three parameters, as follow: i) irradiation dose (D), ii) PEG molar mass (MM) and iii) concentration of drug ([drug]).
Table 1 shows variables and respective values according attributed levels. Total number of tested assays was 16 ($2x2^3$).

Table 1 – Attributed level and values to variables used in the factorial design.

Variable	Low level (-)	High level (+)
MM_{PEG} (g/mol)	300	600
Irradiation dose (kGy)	50	100
Drug Concentration	25	100

Table 2 presents the codified levels of studied variables of the factorial design 2^3.

Table 2 – Factorial design of 2^3 matrix.

Assay	MM_{PEG}	Irradiation Dose	Drug conc.
1	-	-	-
2	+	-	-
3	-	+	-
4	+	+	-
5	-	-	+
6	+	-	+
7	-	+	+
8	+	+	+

The signals + and – represent codified levels of studied variables.

The effect was analyzed by the drug release rate carried out by *in vitro* release assay in phosphate buffer solution (PBS) pH 5.4 in a shaker incubator at 37°C during 4h and prostaglandin quantified by HPLC.

Results and Discussion

Prostaglandin release results are shown in Table 3.

Table 3 – Results of drug release.

Assay	Drug release results (µg)			
	Duplicate		Diference	Medium
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	6.585	0	6.585	3.275
5	56.124	55.224	0.900	55.674
6	61.290	48.543	12.747	54.917
7	28.170	31.791	3.621	29.980
8	38.757	36.363	2.394	37.560

Evaluation of results was lead by *t Student test* with 95% confidence. According to Neto et al *Statistic Table* t value is 2.306 (8 degree liberty). The standard deviation value of one effect (δε) was 1.88.
The estimation effects based on drug release rate were calculated and described in Table 4. To consider a variable with statistical significance the effect has to shown minimum absolute value of $t \times \delta_E = 4.34$.
The results showed in Table 4 indicate that only the parameters radiation dose and drug concentration showed statistical significance, i.e., these variables had direct influence on drug release rate. Increasing drug concentration and decreasing radiation dose improved drug release rate independently of PEG molar mass.
To analyze how these variables modify drug release degree it is necessary other assays utilizing *central point analysis* technique.

Table 4 – Estimation effect from values of drug release degree described in Table 3.

Assay	Variables	Estimation effect ± Standard deviation
1	Medium	-22.25 ± 0.94
2	Molar mass PEG (MM_{PEG})	2.50 ± 1.88
3	Irradiation Dose (D)	-10.00 ± 1.88
4	(MM_{PEG}). (D)	3.00 ± 1.88
5	Drug Concentration ([drug])	43.00 ± 1.88
6	(MM_{PEG}). ([drug])	1.00 ± 1.88
7	(D).([drug])	-11.50 ± 1.88
8	(MM_{PEG}). (D).([drug])	1.50 ± 1.88

Conclusion

To conclude, the study showed that factorial design is an extremely useful tool to minimize the number of assays performed aiming at analyzing different factors in order to obtain a suitable polymeric matrix that composes controlled release device.
This study was, however, a preliminary one. For the purpose of analyzing the influence of variables in the drug release rate, central point analysis technique must be applied.

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