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Original Research Article

Formulation and Optimization of Oil Entrapped Floating Alginate Beads of Diclofenac Sodium

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Abstract

The objective of present investigation is to prepare and optimize an oral floating alginate gel beads of Diclofenac sodium using sodium alginate and oils was utilized as a dispersed phase to generate a uniform emulsion to create multiple tiny chambers in the alginate matrix for better buoyancy. Diclofenac sodium loaded beads were prepared by emulsion gelatin method. In this method pre gelation liquid of sodium alginate solution (2-4% w/v) was prepared. Oil (Light liquid paraffin, coconut oil, and olive oil) in the concentration (10%, 20% and 30%, was then added to the polymer solution. From the results formulation F3 was chosen as the most optimized formulation as it possessed all the required physicochemical characters and sustained drug release. The *in vitro* release data fitted with higher values in matrix model and the release was found to be Non- Fickian diffusion (anomalous transport) as the n value is in between 0.5 to 1. Entrapment efficiency and drug release of optimized batch FL3 were found to be 78.22% and 92.63% respectively. Drug absorption from the gastrointestinal tract is highly variable process and prolonging gastric retention of the dosage form is a challenging task. Under such circumstances, floating drug delivery system proves to be promising approach for gastric retention. The optimization of floating, drug entrapment efficiency and drug release behavior of Diclofenac beads was done by applying design expert

Keywords: Diclofenac sodium, FL3, Emulsion gelatine method, Sodium alginate.

INTRODUCTION

The objective of controlled release drug delivery includes two important aspects, namely spatial placement and temporal delivery of the drug. Spatial placement relates to targeting a drug to a specific organ or tissue. While temporal delivery refers to controlling the rate of drug delivery to the target tissue [1].

An appropriately designed controlled release drug delivery system can be major advance towards solving these two problems. It is for this reason that the science and technology responsible for development of controlled release pharmaceuticals have been and continue to be the focus of a great deal of attention in both industrial and academic laboratories [2].

In the exploration of oral controlled release drug administration one encounters three areas of potential challenges.

- Development of a drug delivery system-capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for potential treatment.
- Modulation of G.I. transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.
- Minimization of hepatic first pass elimination, If the drug to be delivered is subjected to extensive hepatic first pass elimination, preventive measures should be devised to either by pass or minimize the extent of hepatic metabolic effect[3].

EXPERIMENTAL METHOD

Material

Diclofenac sodium procured from New Era Scientific, Meerut. But Calcium Chloride & Sodium Hydroxide procured from Thermo Fisher Scientific India Pvt. Ltd. Most important drug, Sodium Alginate procured from Loba Cheime Pvt Ltd. All chemicals used for work, were analytical grade.

Method of Preparation of micro beads

Diclofenac sodium loaded beads were prepared by "Emulsion Gelatin Method". In this method pre-gelation liquid of sodium alginate solution (2-4% w/v) was prepared. Oil (Light liquid paraffin, coconut oil, and olive oil) in the concentration 10%, 20% and 30% was then added to the polymer solution. To ensure emulsion stabilization, the mixtures were homogenized at 1000 rpm using a homogenizer (Remi-motors (Mumbai, India) for 20 min with the addition of emulsifier Span 80(Sorbitan monooleate). Diclofenac sodium was then dispersed in the formed emulsion. The bubble free emulsion was extruded, using a 20 gauge syringe needle into 100 ml of gently agitated (4%, w/w) $CaCl_2$ solution at room temperature. The emulsion gel beads were allowed to stand in the solution for 40 min before being separated and washed with distilled H_2O. The beads were dried in the tray dryer oven [4]. Factorial design was used in this study and 2 factors were evaluated, each at 3 levels, experimental trials were performed at all 27 possible combinations. The amount of sodium alginate and oils (X2) were selected as independent variables. All other formulation and processing variables were kept invariant throughout the study. The resulting data were fitted into Design Expert Software (V.8.0.7.1) and analysed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of sodium alginate and oils on dependent variables [5].

Experimental design [6]

Table-1: Experimental design for preparation of oil entrapped beads

S. No.	Batch code	Actual level of factor		Level of factor	
		Sodium Alginate (%, X1)	Oil (%, X2)	Sodium Alginate (%, X1)	Oil (%, X2)
1	F1	2	10	-1	-1
2	F2	2	20	-1	0
3	F3	2	30	-1	+1
4	F4	3	10	0	-1
5	F5	3	20	0	0
6	F6	3	30	0	+1
7	F7	4	10	+1	-1
8	F8	4	20	+1	0
9	F9	4	30	+1	+1

Determination of buoyancy of beads

Floating properties of beads were evaluated using USP dissolution apparatus containing 500 ml SGF pH (7.4). The temperature of medium was maintained at 37 ± 5^0C fifty beads were placed in the media and total floating time was measured by visual observation.

Swelling properties

The swelling properties of prepared micro beads were determined in acidic buffer pH1.2. Thirty dried bead were placed in a beaker to which 200 ml of buffer solution and then stirred with a magnetic stirrer at a speed 50 rpm. After 1hr interval, the equilibrium swollen beads were observed and measured under optical microscope. The magnitude of swelling was presented by the ratio of the mean diameter of swollen beads to the mean diameter of the dried beads before the test [7].

***In-Vitro* Dissolution Studies**

The physic-chemical property of most drugs that has greatest influence on their absorption characteristics from the GIT is dissolution rate. "The drug is expected to release from the solid dosage forms (granules, tablets, capsules etc) and immediately go into molecular solution. This process is called as dissolution" [8, 9].

Statistical analysis of the data and validation of the model

The targeted response parameters were statistically analyzed by applying one way ANOVA (analysis of variance) and significance of the model was estimated using the statistical package Design Expert (8.0.7.1 trial version). The individual parameters were evaluated using "f test" and mathematical relationship was generated between the factors (independent variables) and the responses (dependent variables) using multiple linear regression analysis for determining the level of factors which yield optimum dissolution responses.

RESULTS

Central composite design (face-centered) was used in this study and 2 factors were evaluated, each at 3 levels, experimental trials were performed at all 27 possible combinations. The amount of sodium alginate and oils (X2) were selected as independent variables. All other formulation and processing variables were kept invariant throughout the study. The resulting data were fitted into Design Expert Software (V 8) and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of sodium alginate and oils on dependent variables.

Table-2: Determination of particle sizes of beads

S. No.	Formulation	Olive oil	Coconut oil	Light liquid paraffin oil
1	F1	1.70±0.14	1.72±0.12	1.17±0.17
2	F2	1.82±0.14	1.85±0.13	1.22±0.14
3	F3	1.92±0.15	1.98±0.16	1.38±0.20
4	F4	2.10±0.10	2.21±0.18	2.10±0.14
5	F5	2.25±0.10	2.35±0.20	2.19±0.17
6	F6	2.47±0.16	2.65±0.16	2.32±0.13
7	F7	2.85±0.14	2.72±0.13	2.43±0.11
8	F8	2.90±0.16	2.83±0.12	2.58±0.13
9	F9	2.97±0.18	2.98±0.18	2.63±0.15

Table-3: Determination of buoyancy of beads

S. No.	Formulation	Conc. of oil (%)	Buoyancy(h) Coconut oil	Buoyancy(h) Olive oil	Buoyancy(h) Light liquid paraffin	Shape
1	F1	10	7	8	9	Spherical
2	F2	20	9	9	11	Spherical
3	F3	30	10	10	7	Spherical
4	F4	10	7	7	8	Spherical
5	F5	20	8	9	12	Spherical
6	F6	30	9	10	9	Spherical
7	F7	10	9	8	10	Spherical
8	F8	20	7	9	12	Spherical
9	F9	30	9	10	9	Spherical

Table-4: Table of drug entrapment efficiency of coconut, Light liquid paraffin and olive oil

S. No.	Formulation	Olive oil	Coconut oil	Light liquid paraffin
1	F1	40.14%	52.12%	65.32%
2	F2	56.21%	55.32%	71.12%
3	F3	58.13%	58.12%	78.22%
4	F4	43.15%	50.15%	68.32%
5	F5	46.12%	54.18%	75.43%
6	F6	57.32%	57.13%	80.21%
7	F7	39.15%	53.21%	74.13%
8	F8	44.21%	55.24%	82.23%
9	F9	50.23%	59.23%	84.18%

Table 5: drug release of light liquid paraffin

Batch code	Drug release (%)
FL1	97.99
FL2	94.54
FL3	92.63
FL4	88.92
FL5	80.44
FL6	78.88
FL7	76.83
FL8	73.99
FL9	70.04

DISCUSSION

An attempt was formulate made to oil entrapped floating beads of Diclofenac sodium. The drug and polymers were subject for compatibility studies by FTIR. The beads were prepared by inotropic gelation technique. The prepared beads were evaluated for various physicochemical parameters such as, morphology, swelling studies, floating charactertics, drug entrapment efficiency and *in-vitro* release studies.

Traditionally, pharmaceutical formulators develop formulations by changing one variable at a time and method is time consuming. It is therefore important to understand the influence of formulation variables on the formulation quality with a minimal number of trials and subsequent selection of formulation variables to develop optimized formulation using established statistical tools such as factorial design. For the 3^2 factorial design, a total 27 trial formulations were prepared by Design-Expert 8.0.6.1 software for three two independent variables: sodium alginate and oils, which were varied at three different levels (low, medium and high). The effect of these

independent variables on Drug entrapment efficiency (%), buoyancy (h), Particle size (mm) and drug release (%) were investigated as optimization response parameters in the study. According to this trial proposal, various oil entrapped alginate beads containing Diclofenac sodium were prepared by iontropically emulsion gelation technique. Graphical optimization was performed by superimposing the countour plots (Figs.1 & 2) of all four responses and locating the area of interest (optimal surface) common to all four plots. Since optimal area was small, only one formulation was chosen in centre of the area.

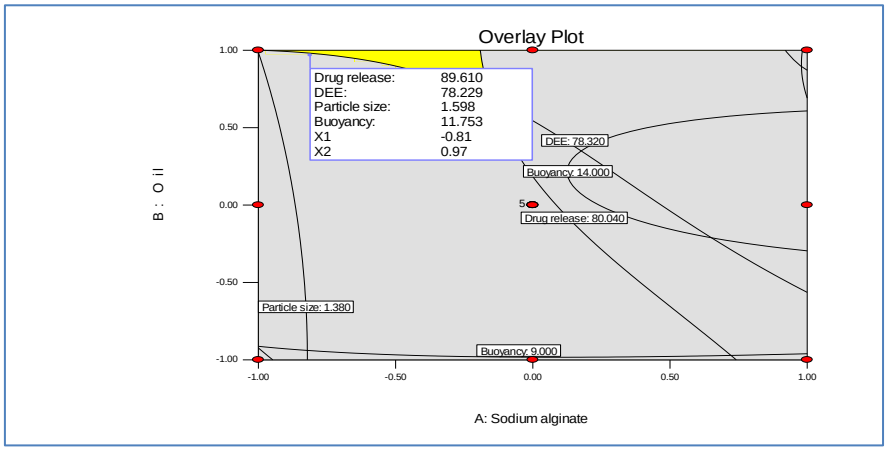

Fig-1: Optimized formulation in area of interest in overlay plot

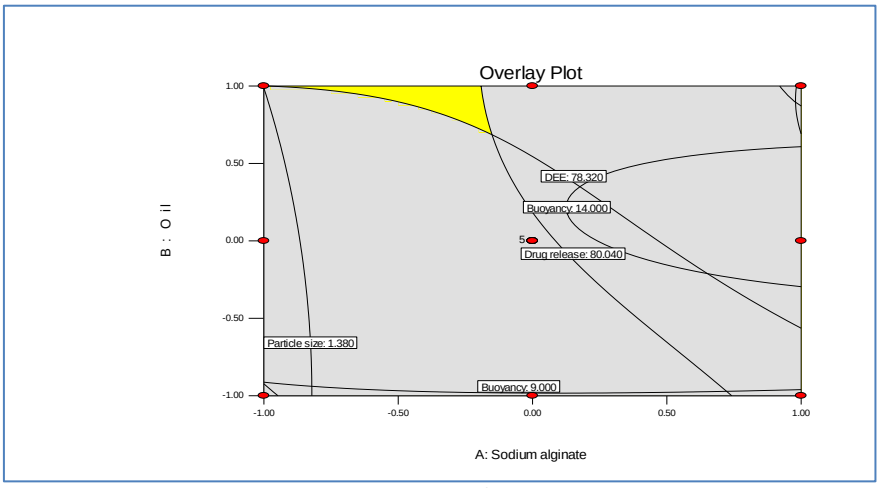

Fig-2: Overlay plot showing area of interest in yellow region

To verify the reproducibility the optimized formulations were prepared according to the predicted independent variables and evaluated for the responses. The results showed a good closeness between experimental and predicted values, which confirms the practicability of the models developed. The results are shown in (Table 6).

It can be observed from (Table 6) that R^2 is high for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R^2 value is in good agreement with the adjusted R^2 value, resulting in reliable models.

Table-6: Model Summary Statistics-Influence of formulation variables on the response factors

Response Factor	St. Dev	R^2	Adjusted R^2	Predicted R^2
Drug release	1.39	0.9835	0.9717	0.8636
Drug entrapment	0.20	0.9994	0.9987	0.9352
Particle size	6.499E-003	0.9999	0.9998	0.9914
Buoyancy	0.93	0.8782	0.8276	-7.3478

Table-7: Check point variables

Batch code	X1 (sodium alginate)	X2 Oil
FL1	-0.81	0.97
FL2	-0.58	0.98
FL3	-0.20	0.97
FL4	-0.17	0.71

Table-8: Result of optimize batch

Check point variables	Drug entrapment	Drug release	Particle size	Buoyancy
FL1	78.229	89.610	1.598	11.753
FL2	78.590	85.758	1.839	11.835
FL3	79.346	80.194	2.171	11.994
FL4	78.214	80.214	2.157	12.917

From the results formulation F3 was chosen as the most optimized formulation as it possessed all the required physicochemical characters and sustained drug release. The *in vitro* release data fitted with higher values in matrix model and the release was found to be Non- Fickian diffusion (anomalous transport) as the n value is in between 0.5 to 1.

CONCLUSION

Entrapment efficiency and drug release of optimized batch FL3 were found to be 78.22% and 92.63% respectively. Mean particle size were found to be 1.38 mm. Buoyancy was found to be 12 h. The optimization of floating, drug entrapment efficiency and drug release behavior of Diclofenac beads was done by applying Design Expert. From kinetic modeling of the dissolution profile of the optimized formulation, it can be concluded that there is controlled release diffusion of Diclofenac sodium from the alginate beads.Stability studies of the optimized formulation were carry out stability testing at 25^0C, 30^0C and 40^0C temperatures for a period of 3 months and show that there was no major effect of temperature on % drug release.

REFERENCES

1. Singh, B., & Kwon, H. (2002). Drug delivery oral route, *Encyclopedia Pharmaceutical Technology*. 1242-1262
2. Charles, S.L., & Joesph, R. (1999). Sustained release drug delivery systems. Remington's Pharmaceutical Sciences, 19th ed., Mac Publishing Company.1660-1663.
3. Chein, W. Yie. (1992). Oral drug delivery and delivery systems, 2nd ed. Marcel Dekker Inc. New York, 139-141.
4. Bakan, J. A. (1987). Microencapsulation. The Theory and Practice of Industrial Pharmacy, 3rded. Varghese Publishing House, Bombay, 42.
5. Subrahmanyam, C.V.S. (2000). Text Book of Physical Pharmaceutics", 2nd ed Vallabh Prakashan, 85.
6. The United States Pharmacopoeia XXIV– NFXIX. (2000). Asian Edition USP Convention Inc, 1739-1742.
7. Cheng, G., AN, F., Zou, M. J., Sun, J., Hao, X. H., & He, Y. X. (2004). Time-and pH-dependent colon-specific drug delivery for orally administered diclofenac sodium and 5-aminosalicylic acid. *World Journal of Gastroenterology: WJG*, *10*(12), 1769.
8. Manna, A., Ghosh, I., Goswami, N., Ghosh, L. K., & Gupta, B. K. (1999). Design and evaluation of an oral controlled release microparticulate drug delivery system of nimesulide by ionotropic gelation technique and statistical optimization by factorial analysis.
9. Mirghani, A., Idkaidek, N. M., Salem, M. T. S., & Najib, N. M. (2000). Formulation and release behavior of diclofenac sodium in Compritol 888 matrix beads encapsulated in alginate. *Drug development and industrial pharmacy*, *26*(7), 791-795.
10. Tønnesen, H. H., & Karlsen, J. (2002). Alginate in drug delivery systems. *Drug development and industrial pharmacy*, *28*(6), 621-630.