RESEARCH ARTICLE

FORMULATION AND EVALUATION OF ETORICOXIB MICROBEADS FOR SUSTAINED DRUG DELIVERY

Gurleen Kaur* (ID), Sonia Paliwal (ID)

Department of pharmaceutics, Global Institute of pharmaceutical education and research, Kashipur, Uttarakhand, India.

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*Address for Correspondence:
Gurleen Kaur, Department of pharmaceutics, Global Institute of Pharmaceutical education and research, Kashipur, Uttarakhand, India. Tel: +91-8923693553;
E-mail: *gurleensandhu1991@gmail.com*

Abstract

Objective: The aim of the study was to develop novel drug design of etoricoxib microbeads for sustained drug delivery by oral route which reduces the dosing frequency. Etoricoxib is a NSAIDs commonly used by patients so to reduce the dosing frequency of drug administration the etoricoxib loaded microbeads were prepared.

Methods: Formulations were prepared with sodium alginate and calcium chloride in different ratios by inotropic gelation technique and characterized by FTIR, drug entrapment efficiency, particle size, swelling Index and release profile.

Results: The microbeads show that 3.86±0.28% of surface entrapment, drug content 87±0.35%, swelling Index was found to be 80.76. The IR spectrum shows stable character of etoricoxib in the microbeads and revealed an absence of drug polymer interaction. The prepared microbeads were spherical in shape and had a size range of 125±0.02 to 165±0.18 μm, the release of the drug was found to be 64.092±0.24 in F4 formulation among all formulation in 240 minutes which shows that the drug released by sustained effect and shows kinetic release mechanism the formulation F1 shows fickian diffusion and F2, F3 and F4 shows the super-case, transport which depends upon the loss of polymeric chain and the release of drug takes place.

Conclusion: The formulation F4 was found to be the best among all the other formulation because the percentage yield was found to be 80.6% among all formulation.

Keywords: Gelling agent, etoricoxib, ionotropic gelation, microbead, NSAIDS.

INTRODUCTION

A novel sustained drug delivery system releases the drug in the particular body compartment at the controlled rate required for a specific treatment[1]. Now a day's drug delivery system uses bio-degradable, biocompatible and natural bio-polymers and are capable of rate-controlling drug release. This system being solid dosage form entrapped by the drug in natural polymer and forming a bead and named as microbeads[2]. Micro-beads are defined as the monolithic sphere distributed the whole matrix as a molecular dispersion of particle and molecular dispersion defined as the drug particle are dispersed in to the continuous phase of one or more than one miscible polymer[3]. The controlled systemic absorption specifically in the intestinal region offers interesting possibilities for the treatment of diseases such as asthma, arthritis or inflammation[4]. It is a small spherical particle with diameters in the micro-meter range (greater than 0.1μm and less than equal to 5mm) which can vary in chemical composition, size, shape, density, and

function. Microbeads are manufactured for specific purposes, including for use in personal care products also such as scrubs, bath products, facial cleaners, toothpastes. They may also be used in industry (e.g., oil and gas exploration, textile printing), other plastic products (anti-slip, anti-blocking applications) and medical applications[3]. Microbeads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles of treatment with various active agents without major side effects.

Etoricoxib is a sulfone and pyridine derivative a non-steroidal anti-inflammatory drug (NSAID)[5]. Its pharmacological effects are believed to be due to inhibition of cyclooxygenase-2 (COX-2) which decreases the synthesis of prostaglandins involved in mediatinganti pyretic, analgesic, and potential antineoplastic properties[6]. It is used for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, chronic low back pain, acute pain and gout

used to ease mild to moderate pain and widely considered to be the best tolerated drug[7].

The objective of present study was to develop a most effective etoricoxib microbeads encapsulated with sodium alginate a gelling agent it promotes better stability with enhanced pharmacological action, improved and better drug release profile of the drug by preparing a suitable etoricoxib microbeads for the treatment of pain and inflammation.
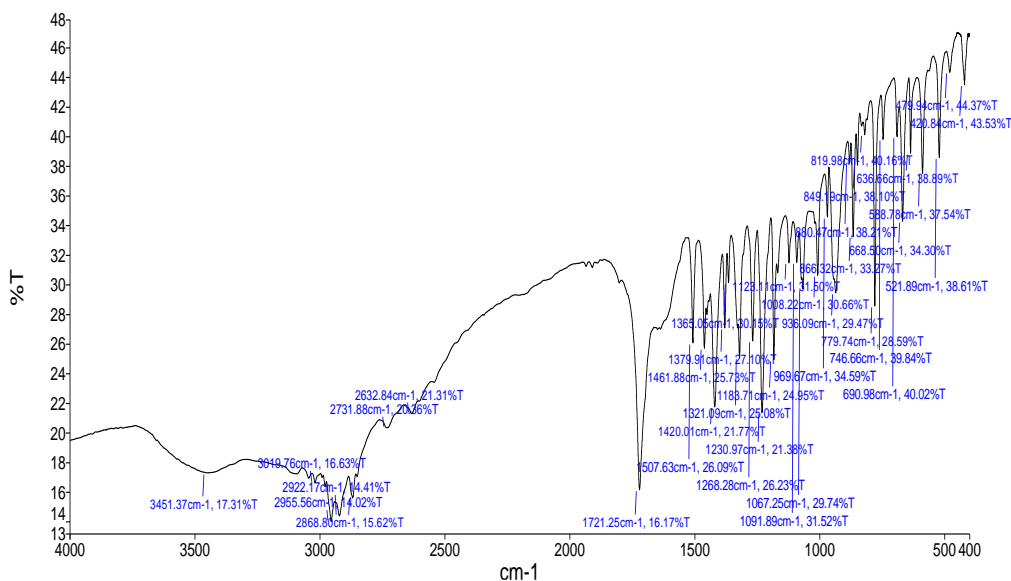

Figure 1: FTIR of mixture of etoricoxib, chitosan and sodium alginate.

MATERIALS AND METHODS

Etoricoxib was obtained from Balaji drugs, India and sodium alginate was obtained from Central drug house, India. Compatibility of etoricoxib with sodium alginate used to formulate microbeads was established by FTIR. Spectral analysis etoricoxib, chitosan and sodium alginate was carried out to investigate any changes in chemical composition of the drug after combining it with the excipients[10].

Table 1: Composition of etoricoxib microbeads formulations.

Ingredients	Formulation code			
	F1	**F2**	**F3**	**F4**
Etoricoxib (mg)	60	60	60	60
Chitosan (%)	0.5	1	-	-
Sodium alginate (gm)	0.5	1	1.5	2
Calcium chloride (w/v)	10%	10%	10%	10%

Method of microbeads preparation:
Microbeads are prepared by ionotropic gelation technique by accurately weighing the materials including the drug (Etoricoxib) used, sodium alginate and calcium chloride. To the weighed quantity of sodium alginate distilled water is added to make mucilage paste and allowed to heat for 5-10 minutes in a hot plate on other side, calcium chloride solution is been prepared. The mucilage paste of sodium alginate is stirred in a magnetic stirrer at a suitable speed for several minutes.

The drug is dispersed in the mucilage paste of sodium alginate and stirred at suitable speed in the magnetic stirrer, micro-beads are formed by dropping the sodium alginate and dispersed drug through syringe needle to the calcium chloride solution air dried for some time and finally, micro-beads were filtered and washed thoroughly with distilled water, dried at room temperature subsequently for few hours[7,9,10].

Evaluation of microbeads

Bulk density and Tapped density
Both bulk density (BD) and tapped density (TD) were determined. A suitable amount of beads was introduced into a 100ml measuring cylinder. After observing its initial volume, the cylinder in the density tapper instrument and density is measured according to USP method II (up to 1250 taps). The tapping was continued until no further change in volume was noted[11].

Hausner's ratio
It is the ratio of tapped to bulk density and was calculated[12].

The Angle of Repose
The value of angle of repose was calculated by using the following formula,

Angle of repose (θ)= $\tan^{-1} h/r$

Where, h= cone height, r= radius of circular base formed by the microbeads on the ground.

Particle size
Determination of average particle size of etoricoxib microbeads was carried out by optical microscopy in which stage micrometre was employed. A minute quantity of microbeads was spread on a clean glass slide and average size was determined in each batch[13].

Percentage Yield
A positive co-relation between the solid content and percentage yield was observed. This may be explained by the fact that, though a constant material is always lost in processing, this loss is proportionately less significant when the solid content is more. The Percentage and theoretical value are determined by which we can calculate the percentage yield[14].

Table 2: Characterisation of etoricoxib microbeads formulations.

Batch	Particle size(µm)	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Angle of repose
F1	125±0.02	0.13	0.20	1.53	30°.20' ±0.11
F2	132±0.12	0.25	0.29	1.16	26°.20'±0.17
F3	140±0.08	0.30	0.33	0.82	23 °.10'±0.22
F4	165±0.18	0.41	0.34	1.1	24 °.30'±0.25

Values are mean± SD, n=3

Table 3: Evaluation parameters of etoricoxib microbeads formulations.

Batch	% Drug content	% yield	Swelling Index	% Drug entrapment	Loose surface crystal %
F1	78±0.12	70.64±0.08	69.69±0.06	78.21±0.59	15.41±0.11
F2	81±0.58	57.21±0.12	75.00±0.16	80.31±0.82	10.21±0.21
F3	85±0.28	72.47±0.09	77.27±0.21	84.04±0.09	7.98±0.25
F4	87±0.35	80.63±0.04	80.76±0.09	88.72±0.07	7.55±0.17

Values are mean± SD, n=3

Drug content

Microbeads were kept in the phosphate buffer 7.4 solution for 24 hours, then filter it. The absorbance of filtrate was taken at λ_{max} 284 nm and concentration was determined[15].

Drug entrapment efficiency

The capture efficiency of microbeads or the percent drug entrapment can be determined by allowing washed microcapsule to lyse. The lysate is then subjected to determination of active constituents as per monograph. The percent encapsulation efficiency (%EE) was calculated using following equation[16].

$$\% \ EE = \frac{Actual \ content}{Theoretical \ content} X100$$

In-vitro dissolution study

The *in-vitro* release studies were carried out for the formulation in dissolution vessel (USP apparatus type-II paddle method) in 900 ml of phosphate buffer 6.8 was placed. The sample was then placed in the vessel and the apparatus was operated for 4 hrs at 50 rpm. At definite time interval 5 ml was withdrawn from the vessel and another 5 ml of the blank was added to the vessel. The withdrawn fluid is then filtered and suitable dilution was made. Samples are then analysed under UV Spectrophotometer at 284 nm[16].

Swelling Index

The weight of the microbeads was taken first and then dissolved in phosphate buffer pH 6.8 for 24 hrs. The excess liquid is removed using blotting paper and the weight of the swollen microspheres is taken[17]. Swelling index is thus calculated using following formula-

$$SI = \frac{weight \ of \ swollen \ microbeads - \ weight \ of \ dried \ microbeads}{weight \ of \ swollen \ microspheres}$$

Loose surface crystal study (LSC)

This study was conducted to estimate the amount of drug present on the surface of the micro beads which showed immediate release in dissolution media. 100 mg of micro beads were suspended in 100 ml of phosphate buffer (pH 6.8), simulating the dissolution media. The samples were shaken vigorously for 15min in a mechanical shaker. The amount of drug leached out from the surface was analysed spectrophotometrically at 284 nm. Percentage of drug released with respect to entrapped drug in the sample was recorded[18].

Statistical analysis

Experimental results were expressed as mean±SD. Student's *t*-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

The result of FTIR spectrum studies showed that there was no significant interaction between the drug and polymer. In present study four formulations of microbeads were prepared by the means of chitosan and sodium alginate. The prepared formulations were evaluated on different parameters.

From the formulations we observed that BD and TD for all the formulations were found in the range between 0.13 to 0.41 g/ml, 0.20 to 0.34 g/ml respectively and formulation F4 was found to be excellent flow character. Results indicate that, as the amount of polymer in the formulation increases, the surface entrapment decreases 3.86±0.28% as a result of increase in drug entrapment 88.72±0.15%. Angle of repose was found in the range of 23.10±0.22° to 30.20±0.11° indicating the good flow properties of the microbeads. As the percentage of Etoricoxib increases the percentage of drug content also increases as in F4 formulation 87±0.35%.
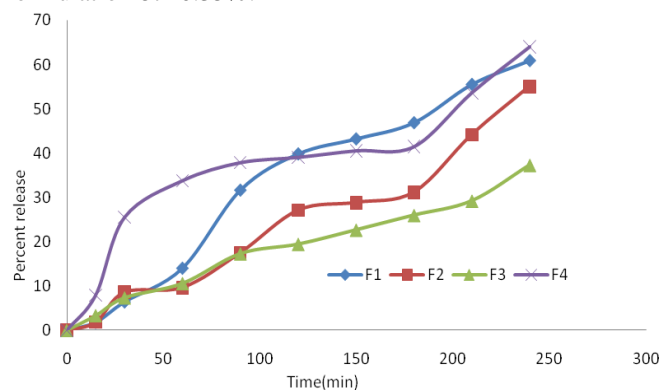
Figure 2: *In-vitro* dissolution study of etoricoxib microbeads formulations.

The particle size varies from 125±0.02 to 165±0.18 μm in all formulation. Loose surface crystal (LSC) study was an important parameter giving an indication of the amount of drug on the surface of the microbeads without proper entrapment. Less dense matrix formation shows the more percent of drug release as F1 formulation. The *in-vitro* drug release of formulation F1 to F4 was studied. All formulation shows different level of drug release ranging from 37.26±0.51% to 64.092±0.24%. It has been evaluated that as the different concentration of gelling agent shows the

significant drug release F1 and F4 (60.94±0.18% and 64.09±0.24%).

Drug release kinetic model are used to illustrate the drug release mechanism. For this various model are used like zero order, Higuchi, first order, Korsmeyer Peppas to obtain the value of R^2 value and n-value for the determination of best fit model. R^2 value was compared for all the formulation which shows the best fit model and by noticing n-value which is obtained from Korsmeyer Peppas model.

Table 4: Data of kinetics of drug release.

Code	R^2			n value	Mechanism of release
	Zero order	First order	Higuchi matrix		
F1	0.9706	0.9627	0.9725	0.5009	Fickian
F2	0.9192	0.9545	0.9267	1.1787	Supercase transport
F3	0.9514	0.9351	0.9456	1.6185	Supercase transport
F4	0.9657	0.9739	0.9616	1.1814	Supercase transport

The observed data of kinetic model shows the best fit model for prepared etoricoxib microbeads was determined by regression coefficient (r^2) in all formulation. The highest r^2 value determine the best fit model, the observed data shows the zero- order release, first order release and Higuchi in all formulation. Formulation F1 shows Fickian diffusion and F2, F3 and F4 show the super-case transport which depends upon the loss of polymeric chain and the release of drug takes place.

CONCLUSIONS

Microbeads are one of the micro particulate systems and are prepared to obtain prolonged or sustained drug delivery, to improve bioavailability or stability and to target drug to specific sites. Microbeads can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance. Microbeads of etoricoxib were prepared according to the using modified ion gelation method by selecting concentration of sodium alginate and calcium chloride as independent variables with chitosan. Increasing polymer concentration led to more sustained release effect whereas, presence of sodium alginate improves the encapsulation efficiency. Calcium chloride can be increased up to certain limit above which encapsulation was decreased. The formulation F4 was found to be optimum formulation among the four formulations, as the amount of polymer in the formulation increases, the surface entrapment decreases 3.86±0.28% as a result of increase in drug entrapment 88.72±0.15%. As the percentage of etoricoxib drug increases the percentage of drug content also increases to 87±0.35%. The particle size varies from 125±0.02 to 165±0.18μm, the formulation F4 containing highest amount of sodium alginate which gives the highest swelling index. Loose surface crystal (LSC) study was an important parameter giving an indication of the amount of drug on the surface of the microbeads without proper entrapment. The formulation F4 was found to be the

best among all the other formulation because the percentage yield was found to be 80.6% among all formulation. Moreover, the effect of each variable on release characteristic was found to be significant in formulation F4 in 240 min the release was found to be 64.092±0.24% as confirmed by data analysis as it shows the super-case transport which depends upon the loss of polymeric chain and the release of drug takes place. Respectively, the present study can be used to design microbeads of desired release characteristic.

AUTHOR'S CONTRIBUTION

Kaur G: writing original draft, methodology, investigation. **Paliwal S:** formal analysis, data curation, conceptualization. All the authors approved the finished version of the manuscript.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Durga DN, Chandana M, Sindhura A. Comparative evaluation of alginate beads prepared by ionotropic gelation technique. Pharmacophore 2010; 1(3): 196-213.
2. Mathew Sam T, Devi Gayathri S, Prasanth V, Vinod B. 'NSAIDS as Microspheres'. The Int J Pharmacol 2008; 6(1): 332-338.

3. Anal A, Stevens W. Chitosan–Alginate multilayer beads for controlled release of ampicillin. Int J Pharm 2005; 290: 45–54. *https://doi.org/10.1016/j.ijpharm.2004.11.015*

4. Badarinath A, Reddy J, Rao M, Sundaram A, Gnanaprakash K, Madhu C, Chetty S. Formulation and characterization of alginate microbeads of flurbiprofen by ionotropic gelation technique. Int J Chem Tech Res 2010; 2(1):361-367.

5. Clarke R, Derry S, Moore RA; Derry; Moore. Single dose oral etoricoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2014; 5 (5): CD004309. *https://doi.org/10.1002/14651858.CD004309.pub4*

6. Augustine M, Sharma P, Stephen J, Jayaseelan E. Fixed drug eruption and generalised erythema following etoricoxib. Indian J Dermatol Venereol Leprol. 2006; 72:307–9. *https://doi.org/10.4103/0378-6323.26732*

7. Thirion, L; Nikkels, AF; Piérard, GE (2008). "Etoricoxib-induced erythema-multiforme-like eruption". Dermatology. 216 (3): 227–8. *https://doi.org/10.4103/2229-5178.171046*

8. Kumaraswamy S, Dhanaraj SA, Ali AN, Sherina M Formulation and evaluation of nifedipine microbeads using guar gum as a release modifier. Int J Pharm Sci Rev Res 2013; 21(1), 270-275.

9. Chakraverty R. Preparation and evaluation of sustained release microsphere of norfloxacin using sodium Alginate. Int J Pharm Sci Rev Res 2012; 3(1): 293-299.

10. Giri TK, Manjusha. Comparative *in-vitro* evaluation of conventional ibuprofen marketed formulation. J Pharm Sci Tech 2013; 2(2):75-80

11. Maejima A. Preparation of spherical beads without any use of solvents by a Novel Tumbling Melt (TMG) method. Chem Pharm Bull 1997; 45:518-24. *https://doi.org/10.1248/cpb.45.518*

12. Shaikh SC, Dnyaneshwar S, Bhusari DV, *et al*. Formulation and evaluation of Ibuprofen gastro-retentive floating tablets**. Univ J Pharm Res. 2018; 3(4): 20-25. *https://doi.org/10.22270/ujpr.v3i4.178*

13. Thulasi V Menon, CI Sajeeth. Formulation and evaluation of sustained release sodium alginate microbeads of carvedilol. Int J Pharm Tech Res 2013; 5(2):746-753.

14. Nayak AK, Khatua S, Hasnain MS, Sen KK. Development of Diclofenac sodium loaded alginate-PVK K 30 microbeads using central composite design. DARU J Pharm Sci 2011; 19(5): 356–366. PMID: 22615682

15. Nagpal M, Maheshwari DK, Rakha P, Dureja H, Goyal S,Dhingra G. Formulation and of development and evaluation of alginate microspheres of ibuprofen. J Young pharm 2012; 3(3): 595-602. *https://doi.org/10.4103/0975-1483.93573*

16. Varma MM, Rao HLN. Evaluation of aceclofenac loaded alginate mucoadhesive spheres prepared by ionic gelation. Int J Pharm Sci Nanotech 2013; 5:1847-1857.

17. Ahmad MF, Mani Babu DJ, Pradhan A. Evaluation of antidiabetic drug Alogliptin for the treatment of inflammation in rats. Univ J Pharm Res. 2018; 3(3): 45-49. *https://doi.org/10.1080/14656566.2019.1645124*

18. Dash S. Kinetic modeling on drug release from controlled drug delivery system. Acta Polonia Pharmaceutical-drug research 2010; 67: 217-223.