International Journal Of Engineering Research And Development
e- ISSN: 2278-067X, p-ISSN: 2278-800X, www.ijerd.com
Volume 20, Issue 4 (April. 2024), PP. 59-64

Stabilization of Diclofenac Sodium

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ABSTRACT
Chemical entities known as drugs should pass the physicochemical properties to satisfy the category of drug. It should be stable and should exhibit its activities devoid of undue adverse effects. It was observed that very common drug diclofenac sodium degrades in aqueous media at a drastic rate. In the present study, we evaluated the ways to shield the diclofenac sodium which can delay the degradation or release and thereby increasing its efficacy.In the present work diclofenac sodium microspheres were prepared using various polymers like gelatin, ethyl cellulose by using solvent evaporation and ionic gelation methods. The prepared formulations were subjected to various evaluation tests like drug content evaluation, invitro drug release studies, characterization of microspheres using microscopic methods.Effect of presence of electrolytes on drug degradation also determined. The results showed that drug release from conventional tablet formulation, pure diclofenac sodium, diclofenac gelatin microspheres was observed upto 4hrs later a steep decline in the drug concentration in dissolution media was observed where as the microspheres prepared by ethyl cellulose and gelatin microspheres coated with ethyl cellulose were released drug upto 24hrs. And presence of electrolytes in the dissolution media protected the dicofenac sodium from degradation of drug by hydroxyl ions. From the study it was concluded that the diclofenac sodium can be stabilized and protected by converting it into ethylcellulose microspheres or by providing electrolytes in the dissolution media .
Key words: *Diclofebac sodium, microspheres, shielding effect, gelatin, ethyl cellulose*

Date of Submission: 04-04-2024 Date of Acceptance: 15-04-2024

I. INTRODUCTION

Chemical entities known as drugs should pass the physicochemical properties to satisfy the category of drug. It should be stable and should exhibit its activities devoid of undue adverse effects. It was observed that very common drug diclofenac sodium (DFS) degrades in aqueous media at a drastic rate. Gaudiano MC et. al., reported that the hydroxyl ions in aqueous media are the cause of degradation of diclofenac sodium. As we are aware that hydroxyl ions are strong oxidants (ref), in our body even many strong oxidants are prevailing which can cause the drug to degrade faster. Moreover, as per literature report(1,2) of the biological half life of DFS, it is approximately 2 hrs.

Chadha R. et. al., also reported the degradation kinetics of DFS in aqueous solution. This substantiates that the diclofenac molecule is degraded by oxidants. In the present study, we evaluated the ways to shield the diclofenac sodium which can delay the degradation or release and thereby increasing its efficacy. If we consider diclofenac as model drug we may be able to apply the knowledge to other drugs even. Here we demonstrate that excipients comparable to gelatin, ethylcellulose could sustain the degradation of the drug molecule for a long period of time. Even the equimolar concentrations of salts exhibited shielding effect. The drug was more stable with ethylcellulose than with gelatin maybe because gelatin retained some moisture in its structure during its preparation.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic reducing pain in conditions such as arthritis or acute injury.

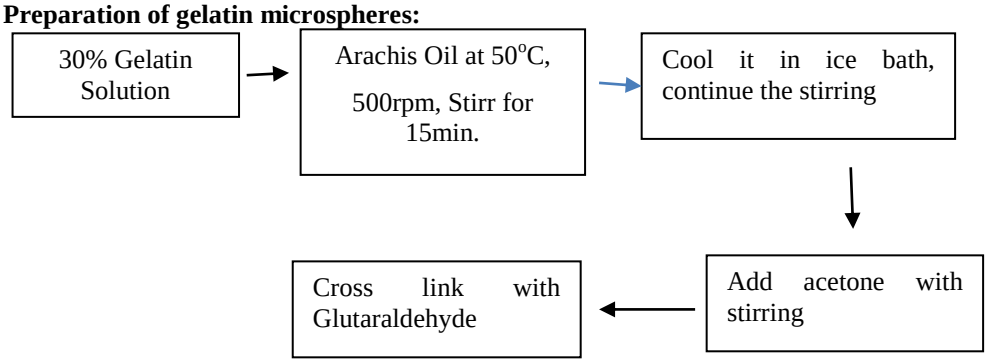
II. DESIGN/METHODS/MODELLING

Materials:
Materials used in the present work include Diclofenac sodium, gelatin, ethyl cellulose (EC), acetone, petroleum ether, arachis oil,

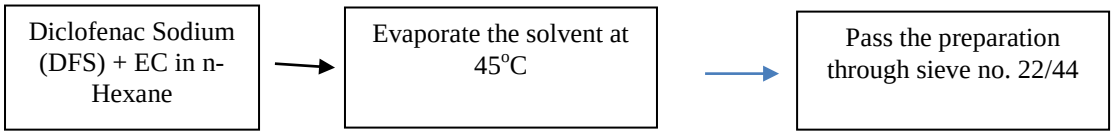
Effect of ions on drug release of Diclofenac Sodium:
Effect of different concentrations of different ions on drug release of diclofenac sodium was tested.

Formulation of dosage forms :
To stabilize the diclofenac sodium different dosage forms like gelatin microspheres, ethyl cellulose coated, matrix preparation, ethyl cellulose coated gelatin microspheres were developed

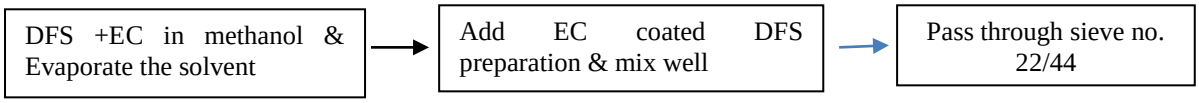
Preparation of gelatin microspheres:



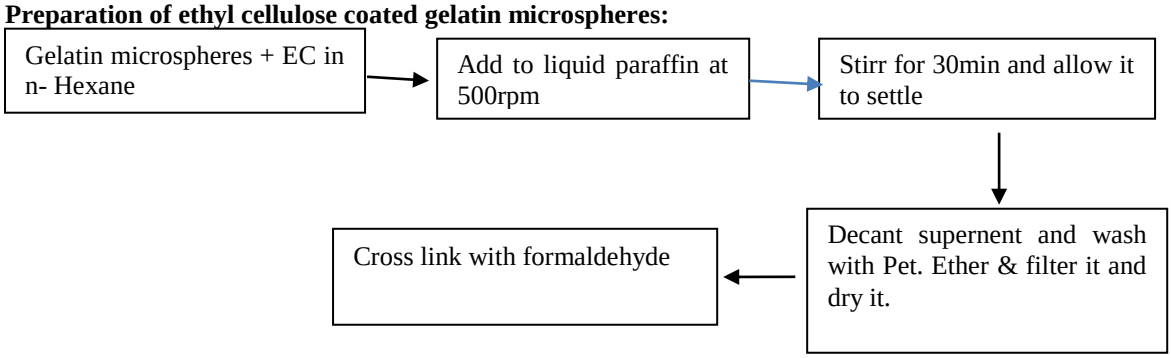
Preparation of ethyl cellulose coated diclofenac sodium microspheres by solvent evaporation:



Preparation of Matrix preparation:



Preparation of ethyl cellulose coated gelatin microspheres:



III. EVALUATION:

Dissolution of Pure diclofenac sodium: The pure diclofenac sodium was subjectd to dissolution by using USP Dissolution Apparatus Model I (Basket) at 50rpm by using 0.1 N HCl for 2hrs and followed by pH7.4 phosphate buffer as dissolution medium.

Particle size analysis: particle size of the microspheres was determined by optical microscopy.

Effect of Ions on drug release of diclofenac sodium:

Effect of Na, K, Ca ions on drug release of diclofenac sodium was tested in 0.1N HCl and pH 7.4 Phosphate buffer.

Drug content evaluation:10mg of Preparation was extracted with acetone and 1ml of solution was diluted with pH 7.4 phosphate buffer and measured at 276nm.

In vitro drug release studies: The preparations were subjected for 24hr dissolution by using USP dissolution apparatus basket model by using 0.1N HCl for 2hrs and followed by pH 7.4 phosphate buffer. 5ml of samples were withdrawn and sink conditions are maintained by replacing fresh medium.

IV. RESULTS AND DISCUSSION

Drug content evaluation: The formulations were subjected for drug content evaluation and the amount of drug present in each formulation was shown in table 1.

Table 1: Drug Content Present in the 10mg of the formulation.

S.No.	Formulation	Amount of drug present (mg)
1	Gelatin Microspheres	4.22 ± 0.325
2	Ethyl Cellulose coated Gelatin microspheres	3.785 ± 0.254
3	Ethyl Cellulose Coated Diclofenac Sodium	3.96 ± 0.27
4	Matrix	3.95 ± 0.372

* No. of trials taken n=3

Particle size analysis: Microspheres were subjected for particle size analysis by microscopic method and the particle size of the microspheres was found to be 3-75microns. The particle size analysis of microspheres was shown in figure 1.

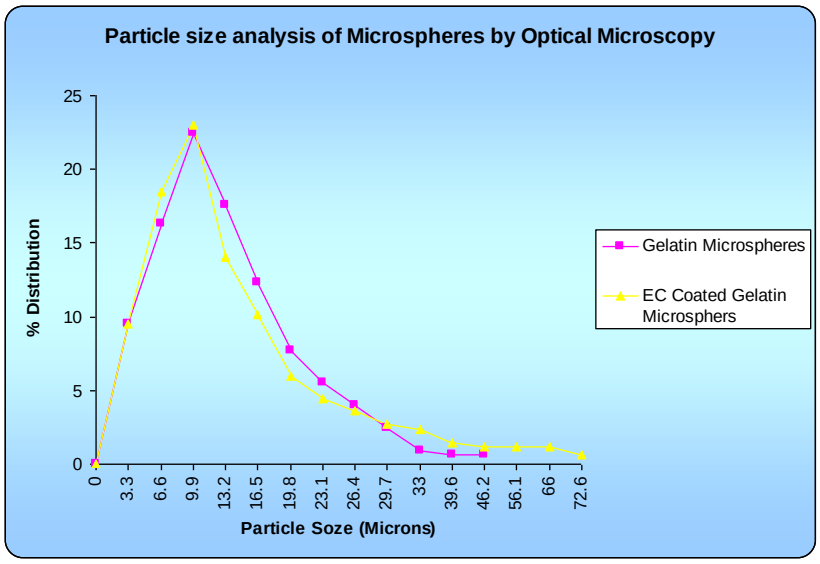


Figure 1: Particle size analysis of microspheres by optical microscopy

The particle size range of gelatin microsphres is from less than 3.3µm to 46.2µm. The particle size range of Ethyl cellulose coated gelatin microspheres is from 3.3µm to 72.6µm.

When gelatin microspheres are coated with ethyl cellulose the particle size of the microsphere will be increased. Because of that there is an increase in the particle size of the microsphere in EC coated gelatin microspheres.

In-vitro Drug release studies:

Gelatin microspheres, gelatin microspheres coated with ethyl cellulose, ethyl cellulose microsphere, ethylcellulose matrix formulations equivalent to 10mg diclofenac sodium and pure diclofenac sodium 10mg were subjected for in-vitro drug release study in 0.1N HCl for 2 hrs and after 2hrs 6.8 pH phosphate buffer for 24 hrs using dissolution apparatus. Dissolution profiles of various formulations were shown in figure 2.

Dissolution of diclofenac sodium:

Dissolution of Pure diclofenac sodium was carried out in 0.1N HCl for 2 hours and followed by pH 7.4 phosphate buffer. It was observed that the drug release of diclofenac was extended upto 4.5 hrs. after 4.5 hrs there is a sharp decline in the drug concentration in dissolution medium. Fairly constant release was observed for diclofenac sodium till 4.5hrs, which declined sharply thereafter, which maybe due to oxidation by hydroxyl ions (1) in dissolution media. In this study, we intend to prevent the degradation of diclofenac sodium, by formulating it with polymer and ions.

Dissolution profile of Different Formulations of Diclofenac Sodium:

The fate of diclofenac sodium was similar even in gelatin microspheres exhibiting rapid decline after 4.5 hrs in dissolution media. The drug release profile of the different formulation of diclofenac sodium shown the release of drug from formulation was extended upto 24 hrs. From the drug release profiles the order of drug release from formulations is,

EC coated DFS > Matrix > EC coated gelatin microspheres.

EC coated gelatin microspheres initially shown a rapid release of the drug then follwed by decline in concentration and the concentration was matained at constant level. But in the case of EC coated DFS and Matrix preparations the drug release was gradually increased. It was observed that diclofenac drug is very susceptible to dissolution conditions. According to Chadha. R et al, hydroxyl ions in dissolution media are responsible for the degradation of the drug molecule. Obviously in *in-vivo* conditions many oxidants are present and thus drug may degrade much faster in those environmental conditions. Moreover the $t_{1/2}$ is reported to be

only 2hrs. Chadha. R et al reported pH profile kinetics, The values of rate constants, k's at 338.15 K, (calculated from the variation of heat evolution with the time) for the degradation of diclofenac sodium at pH 5, 6, 7, 8 and its inclusion complex with β-cyclodextrin at pH 7 are found to be 4.71 x 10^{-4}, 5.69 x 10^{-4}, 6.12 x 10^{-4}, 6.57 x 10^{-4} and 4.26 x 10^{-4} h^{-1} respectively, indicating the drug is stable in low pH.

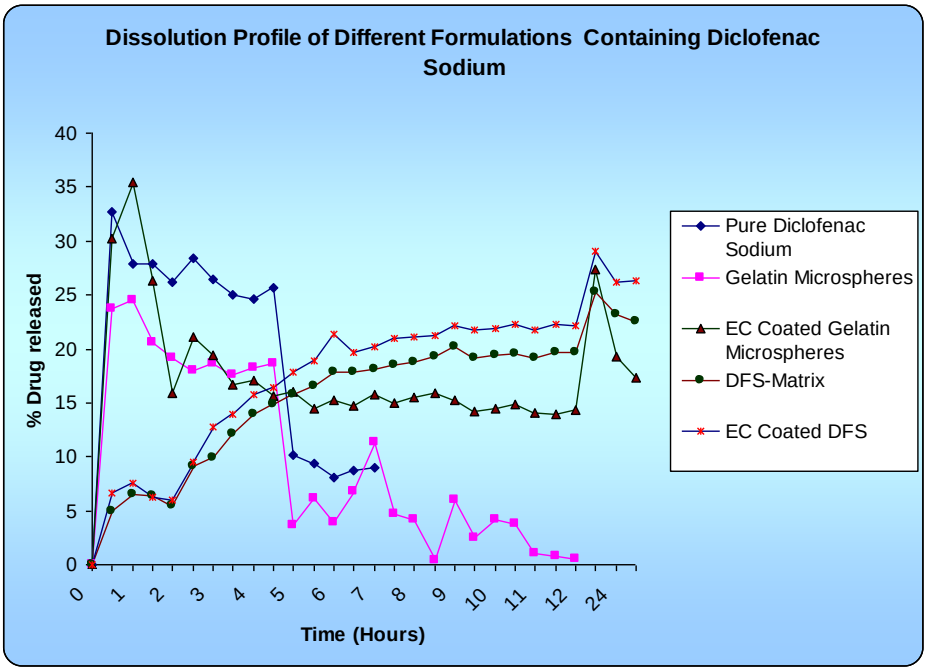


Figure 2: Dissolution profile of Different Formulations of Diclofenac Sodium

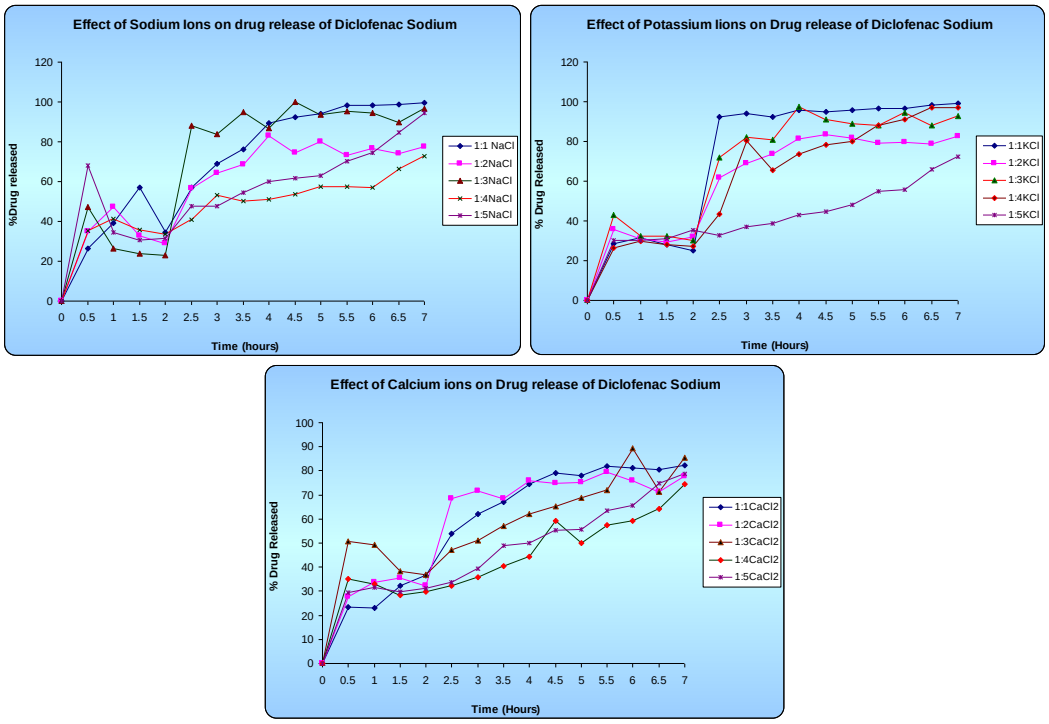


Figure 3: Effect of Sodium, Potassium and Calcium Ions on Drug release of Diclofenac Sodium

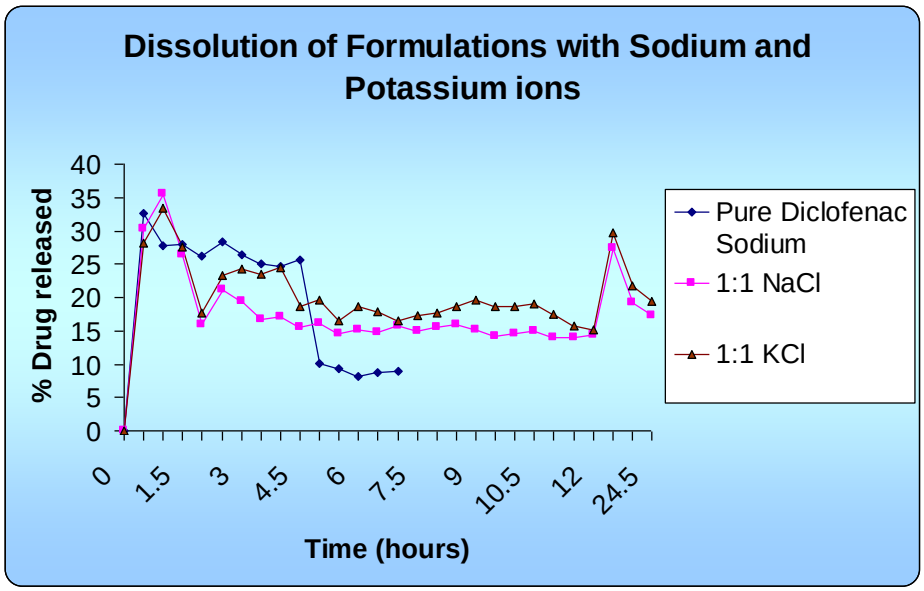


Figure 4: Dissolution of Diclofenac Sodium EC Formulation with 1:1 NaCl and 1:1 KCl

Figure 3 and 4 explains the effect of presence of electrolytes on drug degradation in presence of hydroxyl ions. Presence of electrolytes prevented the drug from degradation.

Microscopic evaluation :

Developed formulations of diclofenc were subjected for observation under microscope before and after dissolution studies. The micrographs of gelatin microspheres, EC coated gelatin microsphere, EC matrix, and EC coated DFS formulations before and after dissolution were showed in figure 5,6,7,8 respectively. the drug release from the formulations was continued upto 24hrs by leaving residue of polymeric coating. After 24hrs of dissolution it was observed that the polymeric coating has undergone some increase in their size.

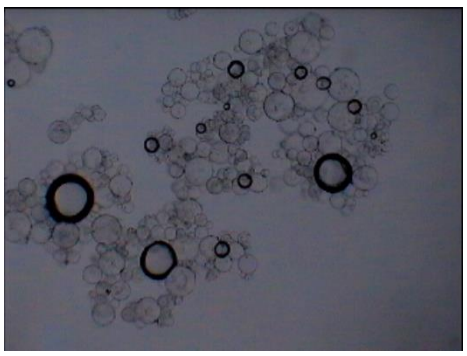
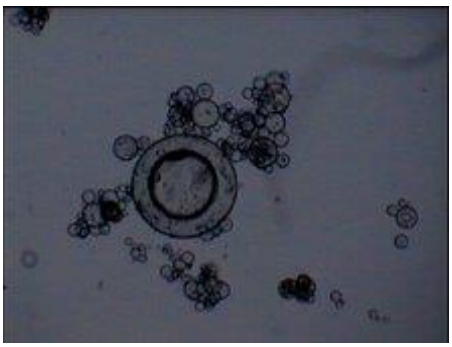
(a)  **(b)** 

Figure 5: (a) Gelatin microspheres before dissolution , (b) Gelatin Microspheres after 24hrs dissolution

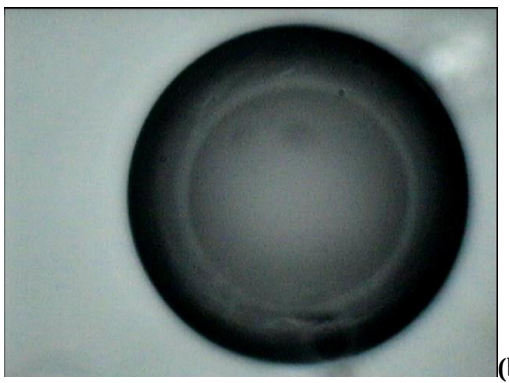
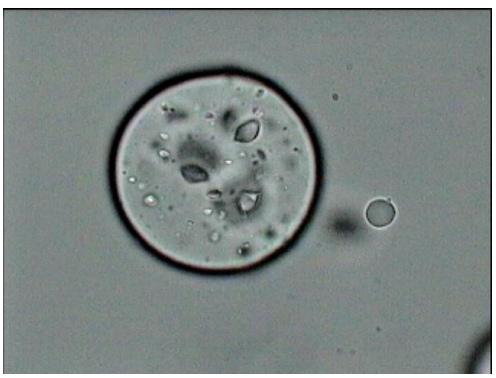
(a)  **(b)** 

Figure 6: (a) EC Coated Gelatin Microspheres before dissolution, (b) EC Coated Gelatin Microspheres After 24 hrs Dissolution

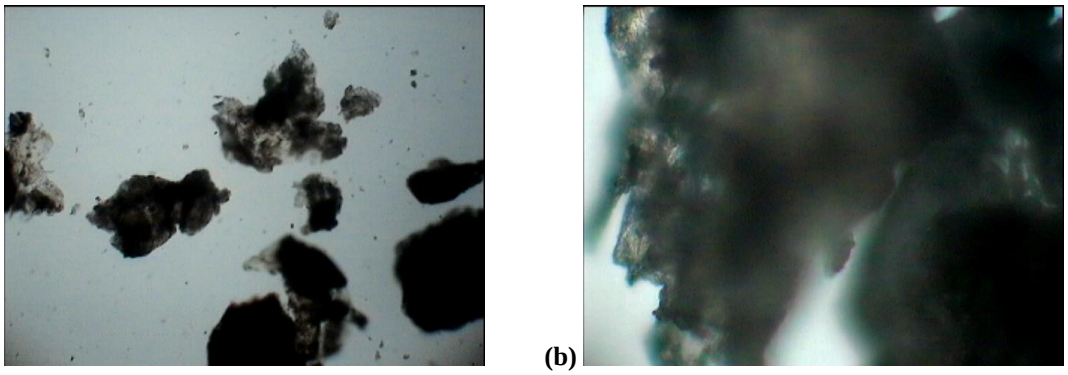


Figure 7: (a) EC Matrix Before Dissolution, (b) EC Matrix After 24 hrs diddolution

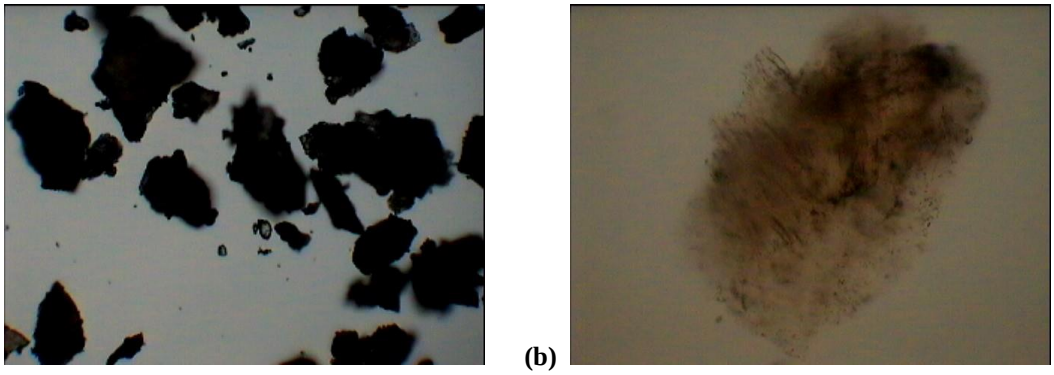


Figure 8: (a) EC coated DFS before dissolution, (b) EC coated DFS After 24 hrs dissolution

V. CONCLUSIONS

The degradation of diclofenac sodium in dissolution conditions can be prevented by introducing ions like sodium, potassium, calcium or by formulating it into controlled release dosage forms like microspheres, coating with ethyl cellulose, matrix preparation etc. from the results of this study it is concluded that development of controlled release systems with ethylcellulose is a valuable polymer for the stabilization of the diclofenac sodium in dissolution conditions.

The consistent release of the drug indicates fairly stable and controlled formulation. The % release graph indicates the release of drug from Gel EC, EC and EC matrix was maintained till the end of 24.5hr experiment. It is obvious that the formulations hardly retain in GI tract for such a long period of time. But if the formulation is made with bio-adhesive polymer maybe it would be expected that the drug dosage form will retain in GI tract for such long periods

ACKNOWLEDGEMENTS

The authors are highly grateful to Koneru Lakshmaiah Education Foundation, Vaddeswaram, GUntur dist., AP, India for providing the essential infrastructure for the preparation of this manuscript.

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Drug information online http://www.drugs.com/pro/diclofenac-potassium.html