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PREPARATION AND CHARACTERIZATION OF ETHYL CELLULOSE MICROSPHERES CONTAINING DICLOFENAC SODIUM

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ABSTRACT

The study is concerned with the preparation of Ethyl cellulose microspheres of Diclofenac sodium using different drug: polymer ratios by an emulsification solvent evaporation method in presence of Tween 80 as an emulsifying agent and the influence of process parameters such as solvent mixture, composition, concentration of an emulsifying agent and stirring speed has been examined. The microspheres have been analyzed for their size, drug loading capacity and drug release study. The percentage yield is found between 75.34±0.94 % to 80.34±0.86 % in all formulations. Use of acetone in the oil phase drastically reduced the particle size. Spherical and smooth surfaced microspheres with desired encapsulation efficiencies were obtained. The drug-loaded microspheres (F-I to F-VI) showed the entrapment efficiency of 58.93±0.35 % to 90.47±0.93 % and shown retarded drug release observed up to 8hrs using phosphate buffer (pH 6.8). All formulated batches indicate compliance with Higuchi's plot and reveals that the drug release followed first order release kinetics. Stability study of best batch showed good results with no-observable physical changes. It could be conclude that the prepared microspheres were shown satisfactory results and suitable for potential therapeutic uses.

KEYWORDS

Diclofenac Sodium, Emulsification solvent evaporation method, Ethyl cellulose and Microspheres.

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INTRODUCTION

Despite tremendous advancements in drug delivery, conventional oral route remains the preferred route for the drug administration, but its cause's greater fluctuations in plasma drug levels. Among them, the development of innovative pharmaceutical dosage forms, can modify the drug bioavailability without altering the structure of the moiety being

transported and such systems incorporate lower amount of a molecule for a therapeutic within a polymeric structure for oral as well as IV administration of the drug, in such a way that it could minimize toxicity and adverse effects[1-4]. Microspheres carrier are multiparticulate drug delivery systems (size range: 1-1000µm), which improve the bioavailability in spite that the drug undergoes extensive first-pass metabolism. Such system provides constant and prolonged therapeutic effect and target drug to specific sites with minimizing side effects[5-9].

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug (NSAIDs) having a potent phenyl acetic acid derivative (Figure No.1) and used for relief pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, spondylitis and acute gout. It has a short biological half-life about 1-2hrs requires multiple dosing to maintain therapeutic effect and leads to fluctuation in drug blood levels[10-12]. And long term administration is reported as gastro-intestinal disturbances, peptic ulceration and gastro-intestinal bleeding[13]. An overcome the limitations of diclofenac sodium, sustained release dosage forms are designed which are able to maintain steady state drug plasma levels for extended periods of time and drug related side effects are minimized[14].

Although in number of polymers, Ethyl cellulose (EC) is selected. It is a polymer of ß-hydro-glucose building blocks joined together by acetal bonding and considered as a non-toxic, bio-compatible, non-biodegradable and water insoluble polymer. EC based microencapsulated drug delivery systems are being extensively studied for achieving extended drug release and protecting the core substance from degradation, also *in-vitro* drug release behavior based on the characteristics of drug-EC linkage[15-16].

DS with low oral bioavailability and short plasma half-life, it's an ideal candidate for microspheres formulation which is useful to reduce the dosage frequency and gastric irritation. So main objective of this study to investigate an obtaining microspheres by an emulsion solvent evaporation method[17] which enables the entrapment and its prepare using different concentration of EC, different composition of solvent mixture, different concentration of emulsifying agent and different stirring rate and determine an *in- vitro* drug release profile.

MATERIAL AND METHODS

Chemicals

Diclofenac Sodium (Yarrow Chem, Mumbai, India), Ethyl cellulose and Tween -80 (Qualigen Fine Chem, Mumbai, India), Ethyl acetate and Acetone (Chemdyes Corporation, Gujarat, India). All other chemicals and solvents were used are of analytical grade.

METHODS

IR Spectral Analysis

The FT-IR Spectrum of Diclofenac sodium and polymer was recorded using KBr mixing method on the FT-IR instrument (JASCO-4600). The drug alone and in combination with polymer (mixed ratio of 1:1) was taken and subjected to FT-IR studies[18].

Preparation of Diclofenac sodium Microspheres

Diclofenac sodium (DS) microspheres were prepared based on emulsification solvent evaporation technique by using ethyl cellulose (EC) as a polymer. Different formulations were prepared with slight modifications[19-21] by dissolving the polymer and drug in ethyl acetate (oil phase) and acetone. This solution was poured slowly into 125 ml distilled water containing tween 80 as an emulsifying agent with continuous stirring using propeller stirrer (Remi, Mumbai, India). The resultant mixtures were emulsified at speed mentioned (Table No.1) for about 4 hrs.

During the emulsification, the dispersed drug and polymer in solvent phase was converting into the fine droplets and subsequently solidified into rigid microspheres due to the solvent evaporation. Finally, an obtained microsphere are filtered and washed by distilled water for removal an excess oil and microspheres are dried in hot air oven at 60˚C and characterized.

CHARACTERIZATION OF MICROSPHERES

Percentage yield

The collected dried microspheres were weighed and percentage yield was calculated by following formula:

Percentage yield = The amount of microspheres obtained / Theoretical amount X 100.

Determination of Particle size

The sample of prepared microspheres was randomly selected and particle size was determined by an optical microscope (Olympus, India).

Micromeritic Properties

Bulk Density, Taped Density, Carr's index and Angle of repose of each formulation are carried out and the results are analyzed[22-23].

Morphological studies

Scanning electron microscopy (JOEL JSM 6701F, Japan) of best formulation was carried out to study their morphological characteristics of DS microspheres[24].

Entrapment efficiency

The amount of drug was estimated by crushing the microspheres using a glass mortar by pestle and equivalent to 5 mg are weighed. These microspheres were suspended in 25 ml phosphate buffer pH 6.8. After 24 hrs, the solution was filtered and 1ml filtrate was pipetted out and diluted to 10 ml and analyzed for their drug content using UV visible spectrophotometer at 276 nm[25-26].

In-vitro drug release study

The *in-vitro* drug release studies were conducted in gastric pH using paddle type dissolution apparatus. Accurately weighed quantity of microspheres was taken into 900 ml of dissolution medium (pH 6.8) which was maintained at 37 ± 0.5^0 C with paddle rotating at 100 rpm. Aliquot of sample was withdrawn at various intervals like 30, 60, 120, 180, 240, 300, 360, 420 and 480 min are filtered. Aliquots were withdrawn and same portion of fresh medium was refilled immediately. Finally, the collected samples are diluted and analyzed spectrophotometrically at 276 nm. The dissolution studies were carried in triplicate manner and the percentage drug release was calculated[27]. The results obtained from *in-vitro* drug release studies were plotted in four different kinetic models such as Zero order rate kinetics, First order rate kinetics, Higuchi's diffusion model and Korsmeyer-Peppa's exponential[28].

Stability Studies

Best formulation were placed in borosilicate screw capped glass containers and stored in 27 ± 2^0C, 60 ± 5% RH and 45 ± 2^0C, 70 ±5% RH and at the end of 30, 60, 90 days period, aliquots samples were withdrawn and analyzed for their drug content[29].

RESULTS AND DISCUSSION

IR Spectral Analysis

FT-IR spectra of prepared sample were taken in the wavelength region was 600-3800 cm^{-1}at ambient temperature and the resolution was $4cm^{-1}$ and compared the position and relative intensity of absorption band of physical admixtures and pure drug. From results (Figure No.2), IR Spectrum of pure drug was found to be similar to the standard IR spectrum which indicates that the obtained sample was Diclofenac Sodium. The IR Spectra of all pure samples and DS physical admixtures of suitable proportion of polymer were subjected to the study. From the results, it was observed that the drug were compatible with the polymer and were expected to stable during the encapsulation process because there was no significant interactions between the drug and polymer in the physical admixtures[30].

Micromeritic Properties

From the results of physical characterization (Table No.2), bulk density and tapped density values of formulated microspheres (F-I to F-VI) were lies in between 0.640 to 0.695 and 0.753 to 0.803 g/cm^3 and Carr's index values were 13.06% to 16.67% and it was observed that, the bulk density and tapped density indicating good packing and Carr's index values indicating good flow characteristics of microspheres. The angle of repose for various ratios is found to be less than 40^0 indicate good flow properties of microspheres.

Percentage yield

The result of percentage yield of microspheres is found between 75.47% to 80.34% (Table No.3). And there was no significant difference observed by solvent mixture and concentration of emulsifying agent but concentration of polymer and stirring rate

affecting the percentage yield of prepared microspheres.

Determination of Particle size

The result of average particle size is found between 382.45±0.65 to 998.15±0.79µm (Table No.3). And it was observed that the particle size of microspheres is increased as the drug: polymer ratio was increased and shown in uniform size distribution. The increase in size may be attributed to an increase in viscosity of polymer solution with increasing concentration, which resulted in the formation of larger emulsion droplets and finally greater size of microspheres. As the concentration of the emulsifying agent (Tween 80) was increased, the particle size of the microspheres was decreased from. This may be due to the decrease of interfacial energy between two droplets and the presence of emulsifying agent in the cross linking medium, allowing the stabilization of the microspheres to maintain their size until completion of the cross linking reaction. As the stirring rate was increased, the particle size of microspheres was decreased from. This may be due to formation of small size droplets on higher stirring rate. Also the concentration of acetone was significantly affected the size of microspheres and indicated that as the concentration of acetone in comparison to ethyl acetate was increased, the size of microspheres was decreased[31-32].

Entrapment efficiency (EE)

From the results (Table No.3), a maximum of 93.48% of drug entrapped in microspheres (F-V) and suggesting that the stirring rate was decreased, the entrapment efficiency was increased and it may be due to formation of large size microspheres with decreased surface area and lower stirring rate was diminish the diffusion of drug from such microspheres to aqueous solvent. However the results were indicated that the change in the concentration of the emulsifying agent and concentration of acetone was no significant effect in entrapment efficiency of the microspheres[33].

***In-vitro* drug release study**

An *in-vitro* drug release of prepared microspheres (F-I to F-VI) was studied by using phosphate buffer (pH 6.8) and the results were shown in Figure No.3 to Figure No.6. Formulation FI and FII were designed to check the effect of the concentration of EC on the characteristics of microspheres. Similarly, FI, FIII and FIV were designed to check the effect of solvent mixtures, FI and FV were designed to study the effect of stirring rate, FI and FVI were designed to study the effect of concentration of emulsifying agent.

The *in-vitro* results indicate that, when drug: polymer ratio was increased (F-II), the drug release from microspheres was decreased (57.28 %) which may be due to increased path length for diffusion of drug molecule from microspheres than F-I formulation (Figure No.3). *In-vitro* drug release from F-I microspheres was higher (86.16 %) prepared at higher stirring rate, but only 55.15% of drug released from F-V microspheres prepared at 500 rpm and hence effective surface area was less than those prepared at 1000 rpm (Figure No.4). The *in-vitro* results (Figure No.5 and Figure No.6) revealed that, the concentration of acetone in solvent mixture (F-III and F-IV) and concentration of emulsifying agent (F-VI) was not significantly affect the drug release from the microspheres.

In order to study the exact mechanism, *in-vitro* release data was analyzed using different kinetics models and mechanism of drug release was determined. From the kinetics data's (Table No.4), the correlation coefficient (r) values of all formulations followed first order kinetics and it was found to be 0.9992, 0.9903, 0.9942, 0.9973, 0.9916, and 0.9981 respectively. When the drug release data were put into Higuchi's equation, good correlation coefficient (r) values 0.9917 to 0.9979 were obtained, indicating that the drug release was diffusion mechanism. The drug release data were also put in Korsmeyer-Peppas model in order to find n values, which describe the drug release mechanism. From the results, n values were found to be 0.853 to 0.984 with correlation coefficient values ranging from 0.9552 to 0.9815 indicating non-fickian diffusion mechanism and the corresponding plot for Korsmeyer–Peppas equation indicated a good linearity. Hence the above observations, the release of drug from microspheres provides sustained manner and kinetics study shows

that 'r' values of all formulated batches indicates compliance with Higuchi's plot which reveals that drug release follows non-fickian diffusion mechanism[34].

Stability studies

Best formulation was taken for stability analysis based upon *in-vitro* drug release studies. The data results is indicated that there is about 88.14% to 89.67% of drug found in microspheres (F-V)with no-observable physical changes up to three months during different storage condition which indicates a good stability (Table No.5).

Morphological studies

The surface morphology of F-V microspheres was determined by SEM for characterization of shape and size of microspheres. SEM scanned images (Photomicrograph No.1 and 2) showed that the microspheres showed good specificity, spherical and uniform shape with smooth surface and particles are distributed without any lumps.

Table No.1: Composition of Diclofenac Sodium Microspheres

S.No	Ingredients	FI	FII	FIII	FIV	FV	FVI
1	Diclofenac Sodium (mg)	100	100	100	100	100	100
2	Ethyl Cellulose (mg)	100	200	100	100	100	100
3	Ethyl Acetate (ml)	40	40	30	20	40	40
4	Acetone (ml)	--	--	10	20	--	--
5	Tween 80 (g)	0.4	0.4	0.4	0.4	0.4	0.8
6	Distilled Water (ml)	125	125	125	125	125	125
7	Stirring Rate (Rpm)	1000	1000	1000	1000	500	1000

Table No.2: Micromeritic Properties of different batches of Microspheres

S.No	Formulations code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Angle of repose (θ)
1	F-I	0.651±0.025	0.760±0.015	14.34±0.87	$27^0.10'$±0.48
2	F-II	0.695±0.033	0.803±0.017	13.45±0.63	$29^0.77'$±0.55
3	F-III	0.652±0.027	0.771±0.021	15.51±0.73	$28^0.87'$±0.61
4	F-IV	0.640±0.021	0.768±0.013	16.67±0.93	$27^0.80'$±0.28
5	F-V	0.655±0.043	0.753±0.011	13.06±0.68	$27^0.21'$±0.44
6	F-VI	0.670±0.037	0.793±0.025	15.56±0.96	$26^0.35'$±0..41

Results are mean ± S.D of three trials (n=3)

Table No.3: Percentage yield, Average Particle size and Drug entrapment of microspheres

S.No	Formulations code	Percentage Yield (%)	Average particle size (µm)	Entrapment efficiency (%)
1	F-I	75.47± 0.72	661.72±0.71	58.93±0.35
2	F-II	80.34± 0.86	703.90±0.56	86.87±0.93
3	F-III	77.56± 0.76	659.93±0.63	77.24±0.51
4	F-IV	78.54± 0.94	382.45±0.65	73.02±0.68
5	F-V	76.83±0.57	998.15±0.79	93.48±0.74
6	F-VI	79.33±0.63	565.69±0.83	71.42±0.63

Results are mean ± S.D of three trials (n=3)

Table No.4: Kinetic Analysis Data of Diclofenac Sodium Microspheres

S.No	Formulations Code	Release model							
		Zero order		First order		Higuchi's		Korsmeyer and peppa's	
		R	S	R	S	R	S	R	S
1	F-I	0.9470	10.966	0.9992	-0.11	0.9935	40.43	0.9572	0.653
2	F-II	0.9603	6.813	0.9903	-0.04	0.9954	24.97	0.9586	0.853
3	F-III	0.9833	9.687	0.9942	-0.08	0.9917	35.02	0.9815	0.984
4	F-IV	0.9695	9.774	0.9973	-0.08	0.9979	35.70	0.9626	0.989
5	F-V	0.9653	6.512	0.9916	-0.04	0.9960	23.81	0.9552	0.841
6	F-VI	0.9591	10.954	0.9981	-0.11	0.9957	40.18	0.9638	0.863

Table No.5: Stability studies data of Diclofenac Sodium Microspheres (F-V)

S.No	At the end (in days)	Physical appearance	Percentage drug content	
			27 ± 2^0C, 60±5% RH	40 ± 2^0C, 70± 5% RH
1	30	No change	89.67±1.36	89.34±1.32
2	60	No change	88.85±1.55	88.52±1.46
3	90	No change	88.81±1.63	88.14±1.61

Results are mean ± S.D of three trials (n=3)

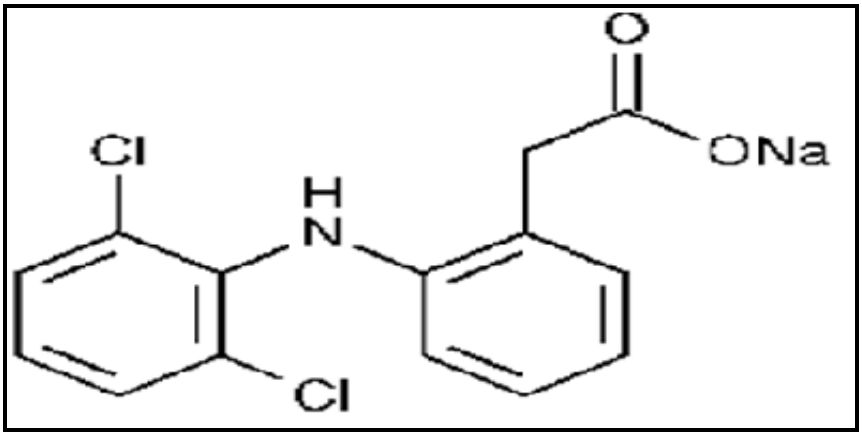


Figure No.1: Structure of Diclofenac sodium

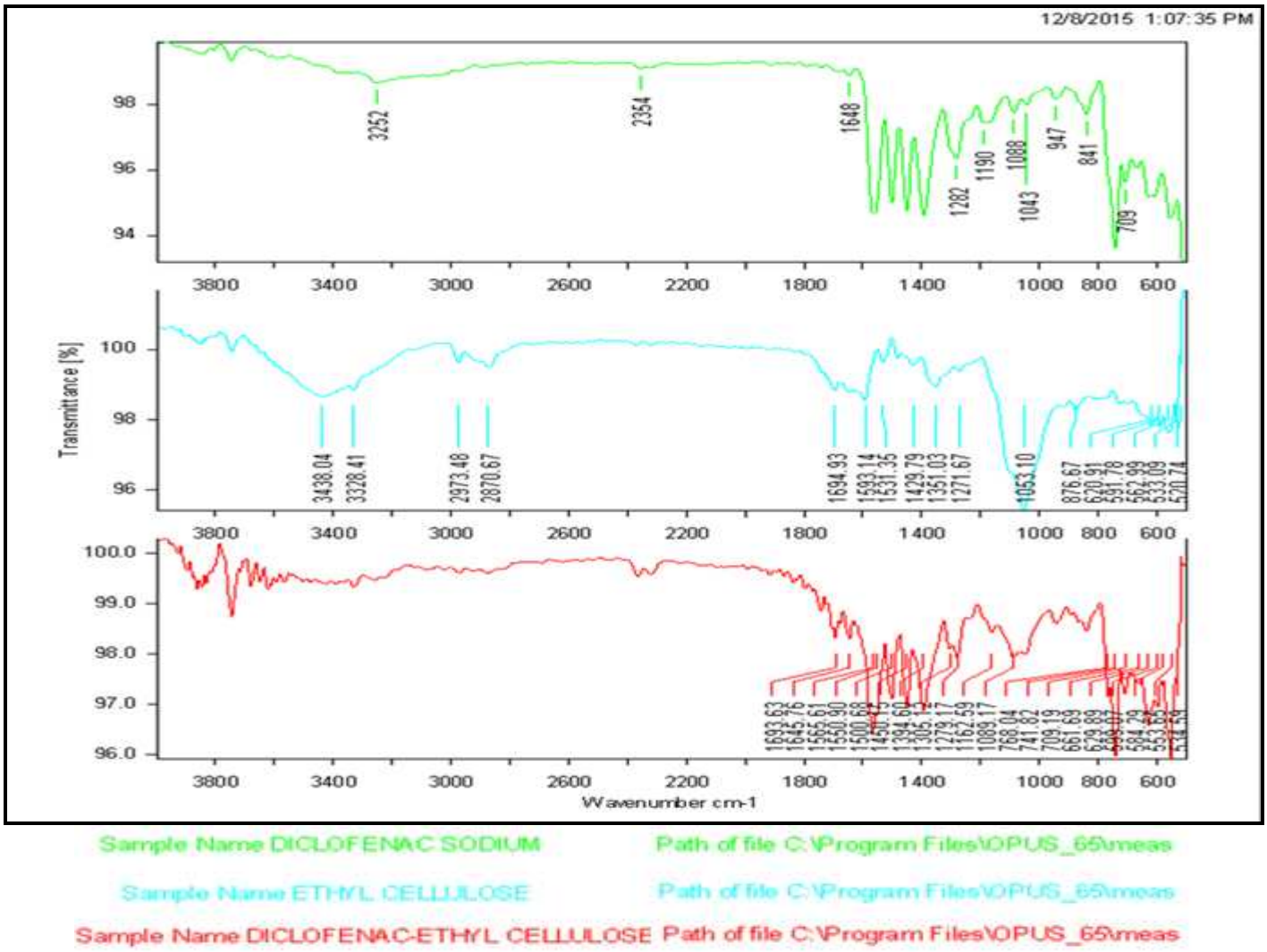


Figure No.2: IR spectra studies of pure Diclofenac Sodium, pure Ethyl Cellulose and Physical admixtures

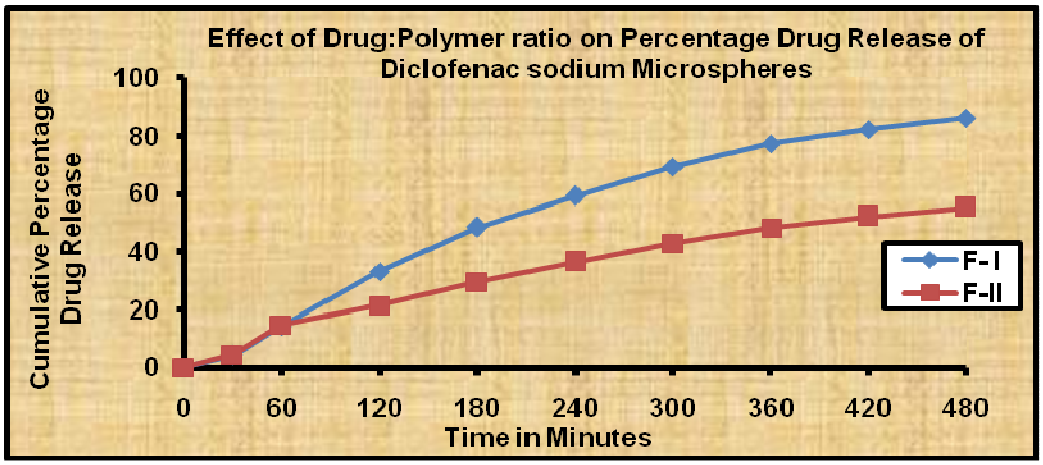


Figure No.3: Effect of Drug: Polymer ratio on Percentage Drug Release of Diclofenac sodium Microspheres (F-I and F-II)

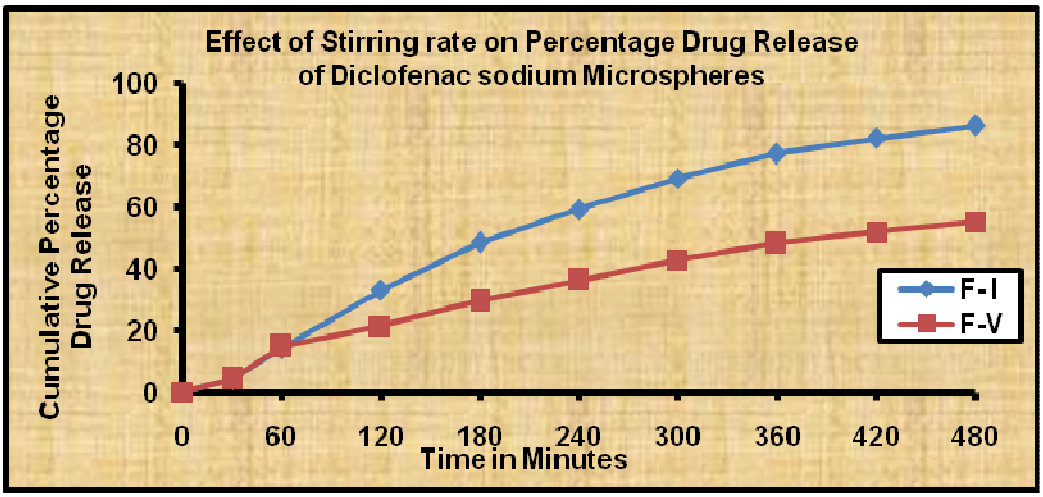


Figure No.4: Effect of Stirring rate on Percentage Drug Release of Diclofenac sodium Microspheres (F-I and F-V)

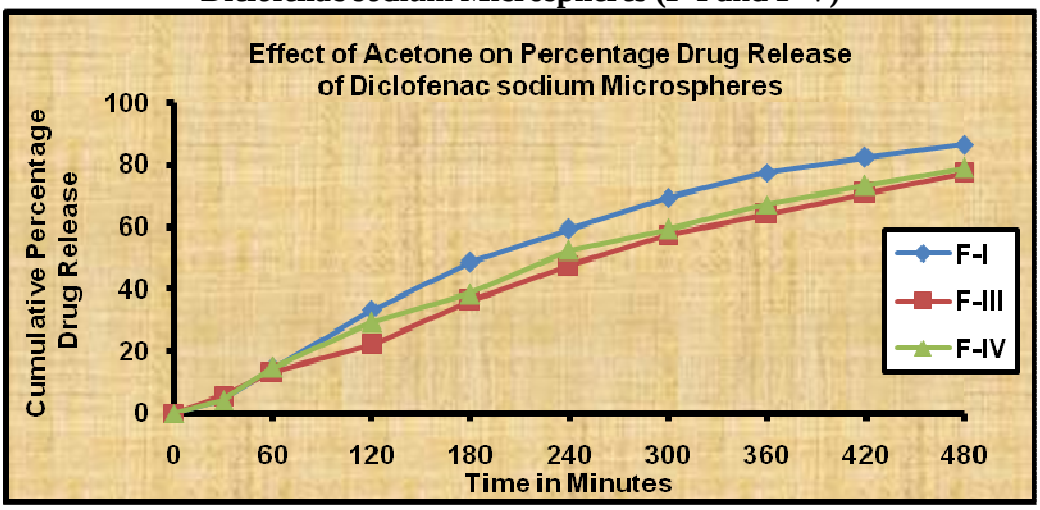


Figure No.5: Effect of Acetone on Percentage Drug Release of Diclofenac sodium Microspheres (F-I, F-III and F-IV)

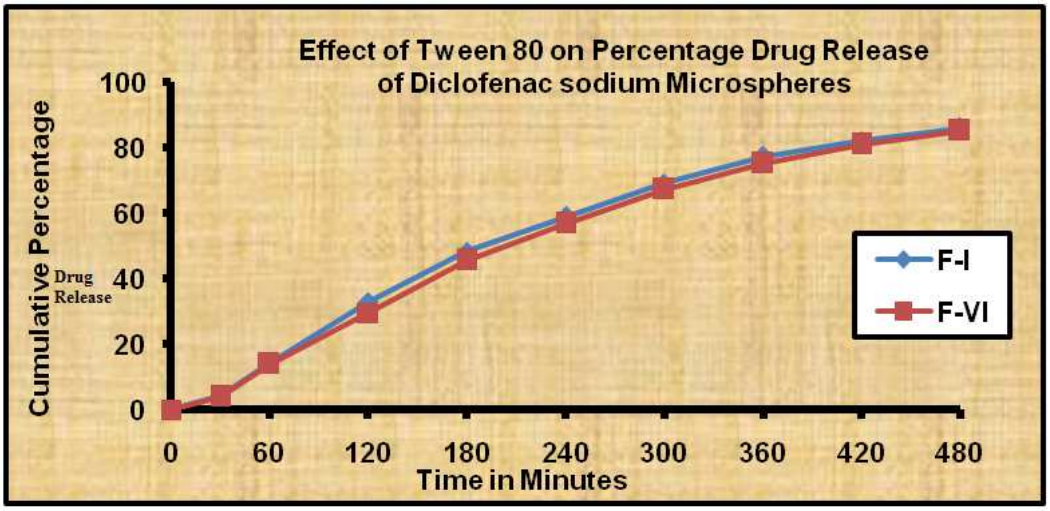
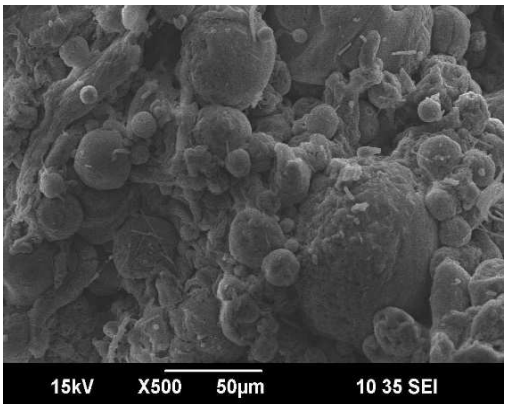
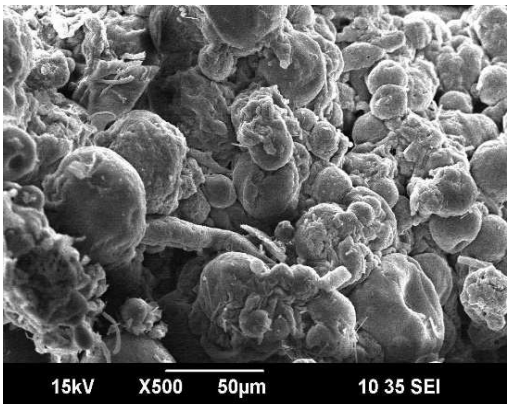


Figure No.6: Effect of Tween 80 on Percentage Drug Release of Diclofenac sodium Microspheres (F-I and F-VI)





(1) **(2)**

Photomicrograph No.1 and 2: SEM images of Diclofenac Sodium Microspheres (F-V)

CONCLUSION

Ethyl cellulose microspheres of Diclofenac Sodium were successfully prepared by emulsification solvent evaporation method and confirmed that it is a best method for preparing microspheres from its size uniformity and spherical shape. Higher percentage of drug loading was obtained by increasing the concentration of polymer. The particle size of microspheres is shown in uniform size distribution and found to be 382 µm to 998µm. The various parameters such as different composition of solvent mixture, different concentration of EC, different concentration of emulsifying agent and speed of stirring have found significant effect on microspheres size and drug loading capacity. The *in-vitro* dissolution of microspheres showed better sustained effect in sufficient hours. Overall the drug release rate will be retarded leading to prolonged effect, improved patient compliance, decreased side effect and prepared microspheres can be administered in less frequency period.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Ashford M. "Avaliacao de proprieties biopharmaceuticals", in: "Delineamento de form as pharmaceuticals" (M. E. Aulton, ed.), *Artmed, Porto Alegre*, 2nd edition, 2005, 265-284.
2. Alagusundaram M, Madhu Sudana chetty and Umashankar C. Microspheres as a Novel drug delivery system, *International Journal of chem, Tech Research,* 1(3), 2009, 526-534.
3. Collet J and Moreton C. "Formas farmacêuticas perorais de liberação modificada", In: "Delineamento de formas farmacêuticas" (M.E. Aulton, ed.), *Artmed, Porto Alegre*, 2nd edition, 2005, 298-313.
4. Vidyavathi Maravajhala, Nirmala Dasari, Asha Sepuri and Joginapalli S. Design and evaluation of Niacin Microspheres, *IJPS,* 79(6), 2009, 34-43.
5. Tasnem Ahmed, Farid Hasan S M, Nasira Talib and Fouzia Hasan. Pharmacokinetics of Diclofenac sodium in normal man, *Pak. J. Pharm. Sci*, 18(1), 2005, 18-24.
6. Hindustan Abdul Ahad, Chitta Suresh Kumar, Kishore Kumar Reddy B, Ravindra B V, Sasidhar C G S, Abhilash C and Sagar N R V. Designing and Evaluation of Diclofenac sodium sustained release matrix tablets using *Hibiscusrosa-Sinensis* leaves mucilage, *IJPSR*, 1(2), 2010, 45-52.

7. Jain N K. Controlled and Novel Drug Delivery, *CBS Publishers, New Delhi*, 4th edition, 21(3), 2004, 236-237.
8. Vyas S P and Khar R K. Targeted and Controlled Drug Delivery-Novel Carrier Systems, *CBS Publishers, New Delhi*, 1st edition, 2006, 414-458.
9. Mahmood Ahmad, Asadullah Madni, Muhammad Usman, Abubakar Munir, Naveed Akhtar, Haji M, Shoaib Khan. Pharmaceutical Microencapsulation Technology for Development of Controlled Release Drug Delivery systems, *WASET*, 51(3), 2011, 384-387.
10. Robert Jackson, Land Marrow D, Jason in Goodman S and Gilman A. The Pharmacological Basis of Therapeutics, McGraw *Hill Publishers, New York*, 10th edition, 2001, 1445.
11. Ackgoz, M, Kas H S and Hncal A A. Diclofenac Sodium, Bioavailability File, FABAD, *Far.Bil.Der*, 19(1), 1994, 37-47.
12. Gang Cheng, Feng An, Mei-Juan Zou. Time and pH dependent colon specific drug delivery for orally administered diclofenac sodium and 5-amino salicylic acid, *World J Gastroenterol*, 10(12), 2004, 1769-1774.
13. Chourasia M.K and Jain S K. Polysaccharides for Colon Targeted Drug Delivery, *Drug Delivery*, 11(2), 2004, 129-148.
14. Gibaud S, Bonneville A, Astier A. Preparation of 3, 4-diaminopyridine microparticles by solvent-evaporation methods, *International Journal of Pharmaceutics*, 242(1-2), 2002, 197-201.
15. Hitesh K, Koshy M K, Shubhini A S. Gastro retentive Ethyl Cellulose Floating Microspheres containing Ranitidine Hydrochloride, *IJDDR*, 4(2), 2009, 315-321.
16. Shiva Kumar H N, Desai B G and Deshmukh G. Design and Optimization of Diclofenac Sodium Controlled Release Solid Dispersions by Response Surface Methodology, *IJPS*, 70(1), 2008, 22-30.
17. Ghaly E S. Sepulveda S. *In-vitro* evaluation of sustained release ibuprofen microspheres, *PRHSJ*, 15(2), 1996, 97-100.
18. Rajamanickam D, Rajappan M, Varadharaan M, Srinivasan B. Formulation and Evaluation of Albumin Microspheres Containing Aceclofenac, *IJPSR*, 4(1), 2010, 112-117.
19. Kilicarslan M., Baykara T. The effect of the drug/polymer ratio on the properties of the verapamil HCl loaded microspheres, *IJIPS*, 252(1-2), 2003, 99-109.
20. Naveen Chella, Kiran Kumar Yada, Rashmi Vempati. Preparation and Evaluation of Ethyl Cellulose Microspheres containing Diclofenac Sodium by Novel W/O/O Emulsion Method, *JPSR*, 2(12), 2010, 884-888.
21. Remington S. The Science and Practice of Pharmacy, Lippincott, Williams and Wilkins, *Philadelphia*, 21st edition, 1, 2006, 316.
22. Gupta G D, Garg R. Gastro retentive floating microspheres of Silymarin: Preparation and *in-vitro* evaluation, *Trop J Pharm Res*, 9(1), 2010, 59-66.
23. Trivedi P, Verma M L, Garud N. Preparation and Characterization of Aceclofenac microspheres, *Asian Journal of Pharmaceutics*, 2(2), 2008, 110-115.
24. Giovanni F. Plamier preparation microencapsulation of semisolid Ketoprofen/ polymer microspheres, *International Journal of Pharmaceutics*, 242(1-2), 2002, 175-178.
25. Saravanan M, Dhanaraju D, Sridhar S K, Ramachandran S, Kishore G S, Anand P, Bhaskar G, Srinivasarao. The Preparation, Characterization and *in-vitro* release kinetics of ibuprofen polystyrene microspheres, *IJPS*, 66(3), 2004, 287-292.
26. Sunitha S, Amareshwar P, Santhosh Kumar M. A study on the effect of different cellulose polymers on release rate from Tramadol loaded microspheres prepared by

emulsion solvent evaporation, *Asian J Pharm and Clin Res*, 3(4), 2010, 35-39.
27. Sudhamani T, Naveenkumar R K, Ravikumar V R, Revathi R, Ganesan. Preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery, *IJPRD*, 2(8), 2010, 119-125.
28. Higuchi T. Mechanism of rate of Sustained-action medication, *JPharm Sci*, 52(11), 1963, 1145-1149.
29. Kumar Ravi, Patil Swati, Patil B M, Patil Sachin R, Mahesh S, Paschapur. Design and *in-vitro* evaluation of oral floating matrix tablets of Aceclofenac, *International Journal of Chem. Tech Research,* 1(4), 2009, 815-825.
30. Uma Mahesh B, Lavanya N, Kusuma P. Kumar, Guggilla. Design and Evaluation of gelatin microspheres containing Diclofenac sodium, *IJPDT*, 2(1), 2012, 11-14.
31. Venkatesan P, Manavalan R, Valliappan K. Preparation and evaluation of sustained release loxoprofen, *JBCP*, 2(3), 2011, 159-162.
32. Zinutti C, Kedzierewicz F, Hoffman M, Maincent P. Preparation and Characterization of ethyl cellulose microspheres containing 5- fluorouracil, *J Microencapsul,* 11(5), 1994, 555-563.
33. Sen G M, Srinivas R S. Formulation and evaluation of ethyl cellulose microsphere, *IJPRBS*, 1(3), 2004, 391-395.
34. Yang Z, Song B, Li Q, Fan H and Ouyang F. Preparation of Microspheres with micro balloons inside for floating drug delivery systems, *Journal of Applied Polymer Science*, 94(1), 2004, 197-202.

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