

MECHANISM OF DISSOLUTION OF DELAYED RELEASE FORMULATION OF DICLOFENAC SODIUM

Roli JAIN¹, Archna PANDEY², Sashi S. PANDEYA²

¹Dr. H.S. Gour University, Sagar (M.P.) INDIA

²Veterinary College Mhow (M.P.), INDIA

Abstract. Diclofenac sodium [o-(2,6-dichloranilino) phenyl] acetate is a potent non steroidal drug (NSAID) and used as an anti-inflammatory and analgesic agent; is one of the least soluble compounds even though present as sodium and potassium salt. In present study we are trying to increase the dissolution rate of that poor water soluble drug by the solubilization capacities of micellar solution of diblock copolymer polyethylene glycol 400. The λ_{max} is obtained at 276nm, and the Beer's law is obeyed up to 5 to 50 $\mu\text{g/ml}$. The critical micellar concentration (CMC) of polyethylene glycol 400 was found at $1.25 \cdot 10^{-3} \text{ mol/L}$ by UV method. The different polymeric concentrations of PEG were used to verifying how the different dissolution media would influence the release drug characteristics. The mechanism of drug release was determined using the Korsmeyer-Peppas model.

Keywords: diclofenac sodium, polymeric micelles, polyethylene glycol 400, Korsmeyer-Peppas model, delayed formulation

Introduction

The ever-increasing evolution of the pharmaceutical field, discovery of disease mechanisms and improved understanding of the human body physiology have rendered the need of 'smart' delivery systems more compelling over the last decade [1-5]. The ultimate goal in developing a new drug delivery system is improvement of the efficacy of the active compound administered, attenuation of undesired side effects,

and ultimately increase of the patient compliance. Polymeric net-works and controlled drug delivery systems possess great potential for filling the need for better control of drug administration.

Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate. They have been consequently objects of numerous researches to improve this behavior. Among common NSAID, diclofenac sodium [o-(2,6-dichloranilino) phenyl] acetate has molecular weight is 318.13 . A potent anti-inflammatory drug of this class is one of the least soluble compounds even though present as sodium and potassium salt [6-11]. It is poorly soluble in acidic medium, 0.003 g/L in simulated gastric fluid, and highly soluble in basic medium, 13 g/L in simulated intestinal fluid sodium [12], suggesting that the pH affects the solubility and absorption of diclofenac. So it required a delayed release mechanism, most often accomplished with stable coating that prevent the drug in stomach and there by delayed release. The formulation is in move favorable environment of the small intestine; this technology commonly referred as enteric coating system [13,14]. Low molecular weight surfactant and the many block copolymers have been widely used to enhance the solubility of hydrophobic drugs upon oral administration [15].

Experimental

Diclofenac sodium was obtained from IPCA laboratories Ratlam as a gift sample, PEG-400 (Meark), Hydrochloric acid (SD fine chemical), and potassium dihydrogen phosphate (SD fine chemical) All chemicals are used as analytical grade. In order to determine the standard calibration curve of diclofenac sodium UV-Visible spectrophotometer (Perkins Elmer, Lamda 35) has been used.

The stock solution of diclofenac sodium was prepared as 0.25 g/L in distilled water containing 1ml of methanol, the dilution were made to prepare a series of solution containing diclofenac sodium in different concentration against water as blank. The critical micellar concentration, CMC, was determined by using UV-visible spectroscopy. The comparative dissolution rate studies on conventional diclofenac sodium tablet were carried out according to apparatus 1 (Basket method) USP-29 at Electro lab TDT08L. Enteric coated dissolution properties of tablet were studied using dissolution testing for 2h in 0.1 N HCl (stomach medium) and followed by testing 45min in polymicellar media and without polymicellar media at pH 6.8 phosphate buffer on 6 units. Dissolution medium (900ml) was maintain at 37°C and agitated at a speed of 75rpm under sink condition, withdraw the 10ml of sample at each time interval 120,130,135,140,150,165min, from the dissolution apparatus and withdrawal volume replaced by fresh dissolution media to maintain the sink condition, filter the withdraw volume and prepared appropriate dilution. The sample solution was analyzed at 276nm by UV spectrophotometer and calculate the amount of drug present is in the sample has calculated.

Results and discussion

The calibration curve of diclofenac sodium was plotted between different concentration of diclofenac sodium Vs absorbance (Fig. 1, Table 1).

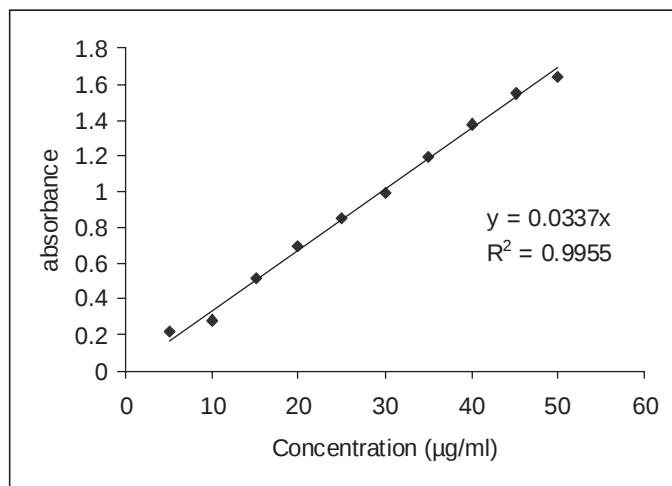


Fig. 1. Verification of the Beer - Lambert law

Table 1. Optical and linear regression data for Beer's law

Parameter	Result
Beer's Range	5- 50 µg/ml
Linear Regression (R^2)	0.9955
Correlation coefficient	0.9978
Slope	0.033
Intercept	0.0136
Molar absorptivity ($\text{lmol}^{-1}\text{cm}^{-1}$)	1.0×10^{-4}
Sandell's sensitivity ($\mu\text{g}/\text{cm}^2/0.001$ absorbance unit)	0.296

The critical micelle concentration (CMC) of PEG with diclofenac sodium was found that $1.25 \times 10^{-3} \text{ mol}$ (Table 2, Fig. 2.). It is based on the fact that some polymer like polyethylene glycol has a tendency to associate with micelles rather than water phase and their absorbance changes depend on the surrounding. The break in curve (between absorbance Vs [PEG 400]) is taken as CMC Fig. 2. The minima occurs at concentration of PEG which is below the reported CMC of PEG .This is attributed

either some micelle aggregates are formed or CMC it self lowered due to solubilization of diclofenac sodium in hydrophobic core

Table 2. Determination of critical micellar concentration of PEG

S. No.	Surfactant concentration (%)	Absorbance at $\lambda_{\max}$ 276nm
1	0.01	0.3514
2	0.02	0.3992
3	0.03	0.3804
4	0.04	0.3779
5	0.05	0.3814
6	0.06	0.3583
7	0.07	0.3853
8	0.08	0.3844
9	0.09	0.3628

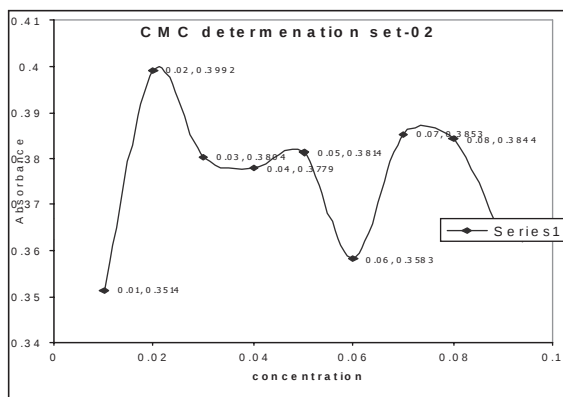


Fig. 2. Determination of critical micellar concentration of PEG

The dissolution profile of the three commercial product of diclofenac sodium was compare in with and without polymicellar media at pH 6.8. (Table 3, Fig. 3). The enteric-coated conventional tablet does not show release in the acidic medium. However, as the drug passes the stomach and enters the small intestine, it is subjected to the intestinal fluids (pH 5.5–6.8). At this pH, the enteric coated tablets show high dissolution and hence higher absorption into the blood stream. Polyethylene glycol 400 enhances the rate of drug release.

Table 3. Comparative average (n=6) dissolution of diclofenac sodium (50mg) different formulation available in Indian market in polymicellar media and without polymicellar media

Time (min)	Dissolution in polymicellar media (in %)			Dissolution without polymicellar media		
	V1	V2	V3	V1	V2	V3
120	2	2	5	2	3	6
130	35	37	18	17	8	12
135	61	60	41	29	22	23
140	85	76	60	51	32	28
150	93	86	93	66	58	42
165	96	93	97	93	88	92

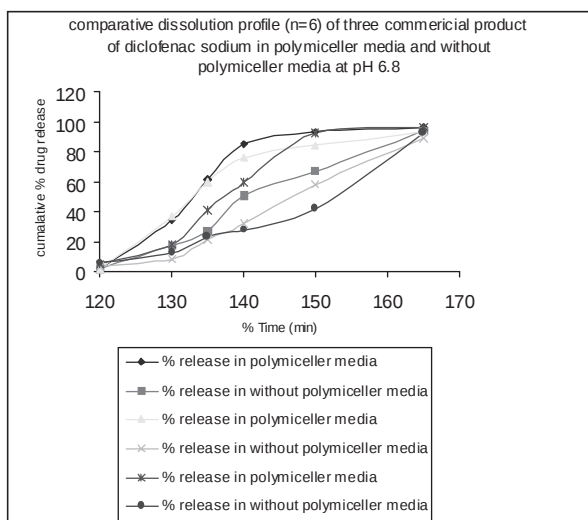


Fig. 3. Comparative dissolution profile (n=6) of three commercial products of diclofenac sodium in polymicellar media and without polymicellar media at pH 6.8

The mechanism of drug release during the dissolution investigation in 0.1n HCL or pH 6.8 was determined using the Korsmyer-Peppas model [16-20]:

$$M_t / M_{\infty} = at^n$$

where M_t corresponds to the amount of drug released at time t , M_{∞} is the total amount of drug released at time $t \rightarrow \infty$, the constant a incorporates structural and geometric characteristics of the drug dosage form and n is released exponent.

The rate of release of drug strictly follows first order kinetics. It is further conformed by plotting a graph between log of % drug release Vs log of time (Table 4, Fig. 4).

Table 4. Kinetic parameter for *in-vitro* drug release

Brand name	Value of k	Graphical k (2.303 X SLOPE)	Valve of "n"	R ²
V1	2.56×10^{-2}	2.50×10^{-2}	0.70	0.9992
V2	2.52×10^{-2}	2.24×10^{-2}	0.69	0.9975
V3	1.79×10^{-2}	1.79×10^{-2}	0.52	0.9935

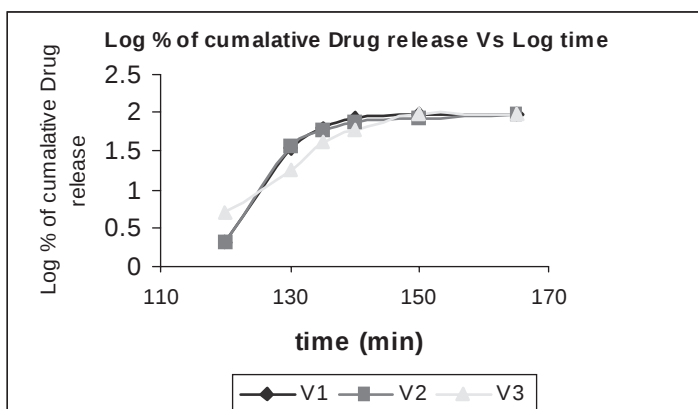


Fig. 4. Plot for first order equation

The mechanism by which the drug is released

Based on various mathematical models, the magnitude of the release exponent “*n*” indicates the release mechanism (Fickian diffusion, case II transport or anomalous transport). In the present study the limits considered were $n = 0.45$ (indicates a classical Fickian diffusion-controlled drug release) and $n = 0.89$ (indicates a case II relaxation release transport; non-Fickian, zero-order release). Values of n between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport. From the release exponent in the Korsmeyer-Peppas model ($n = 0.8733$) it could be suggested that the mechanism that led to the release of diclofenac sodium was an anomalous transport.

Conclusion

The use of polymeric solution of polyethylene glycol 400 appears to be a reliable manner to enhance the in-vitro release of diclofenac sodium delayed release formulation.

REFERENCES

1. **Fini, A., M. Garuti, G. Fazio, J. Alvarez-Fuentes, M.A. Holgado.** Diclofenac Salts. I. Fractal and Thermal Analysis of Sodium and Potassium Diclofenac Salts. *J. Pharm. Sci.* **90**, 2049-2057 (2001).
2. **Leuner, C., J. Dressman.** Improving Drug Solubility for Oral Delivery Using Solid Dispersions. *Eur. J. Pharm. & Biopharm.* **50**, 47-60 (2000).
3. **Menasse, R., P.R. Hedwall, J. Kraetz, C. Pericin, L. Riesterer, A. Sallmann, R. Ziel, R. Jaques.** Pharmacological Properties of Diclofenac Sodium and Its Metabolites. *Scand. J. Rheumatology* **7**, Suppl. 22, 5-16 (1978).
4. **Sood, A., R. Panchagnula.** Design of Controlled Release Delivery Systems Using a Modified Pharmacokinetic Approach: A Case Study for Drugs Having a Short Elimination Half-life and a Narrow Therapeutic Index. *Int. J. Pharmaceutics* **261**, 27-41 (2003).
5. **Friend, D.R.** New Oral Delivery Systems for Treatment of Inflammatory Bowel Disease. *Adv. Drug Delivery Rev.* **57**, 247-255 (2005).
6. **Tomford, W.W.** Chondroprotective Agents in the Treatment of Articular Cartilage Degeneration. *Operative Techniques Sports Medicine* **8**, 120-221 (2000).
7. **Kearney, P.M., C. Baigent, J. Godwin, H. Halls, J.R. Emberson, C. Patrono.** Do Selective Cyclo-oxygenase-2 Inhibitors and Traditional Non-steroidal Anti-inflammatory Drugs Increase the Risk of Atherothrombosis? Meta-Analysis of Randomised Trials. *BMJ* **332**, 1302-1308 (2006).
8. **Lacy, J.E., L.L. Armstrong, M.P. Goldman, L.L. Lance (Eds.).** *Drug Information Handbook with International Trade Names Index.* Lexi-Comp, Hudson, 2009.
9. **Yaginuma, H., T. Nakata, H. Toya, T. Murakami, M. Yamasaki, A. Kamada, H. Shimazu, I. Makita.** Rectal Delivery of Antiinflammatory Drugs. II. The Influence of Basic Amino Acid Salts on Rectal Absorption of Diclofenac. *Chem. Pharm. Bull.* **29**, 3326-3333 (1981).
10. **Solomon, L., G. Abrams.** Voltaren in the Treatment of Rheumatoid Arthritis. *South African Med. J.* **11**, 949-952 (1974).
11. **Oberli, R.L., H. Das, S.L. Wong, K.K.H. Chan, R.J. Sawchuk.** Pharmacokinetics and Metabolism of Diclofenac Sodium in Yucatan Miniature Pigs. *Pharm. Res.* **11**, 698-703 (1994).
12. **Nykanen, P., K. Krogars, M. Sakkinen, J. Heinamaki, H. Jurjenson, H. Veski, M. Marvola.** Organic Acids as Excipients in Matrix Granules for Colon-specific Drug Delivery. *Int. J. Pharm.* **184**, 251-261 (1999).
13. **Nykanen, P., S. Lempaa, M.L. Aaltonen, H. Jurjenson, H. Veski, M. Marvola.** Citric Acid as Excipient in Multiple-unit Euteric-coated Tablets for Targeting Drugs on the Colon. *Int. J. Pharm.* **229**, 155-162 (2001).
14. **Lee, E.-J., S.-W. Lee, H.-G. Choi, C.-K. Kim.** Biavailability of Cyclosporin A Dispersed in Sodium Lauryl Sulfate-Dextrin Based Solid. *Int. J. Pharm.* **218**, 125-131 (2001).
15. **Palma, S., R.H. Manzo, D. Allemandi, L. Fratoni, P. Lo Nostro.** Solubilization of Hydrophobic Drugs in Octanol-6-O-ascorbic Acid Micellar Dispersions. *J. Pharm. Sci.* **91**, 1810-1816 (2002).

- 16. Korsmeyer, R.W., R. Gurny, E.M. Doelker, P. Buri, N.A. Peppas.** Mechanisms of Solute Release from Porous Hydrophilic Polymers. *Int. J. Pharm.* **15**, 25-35 (1983).
- 17. Peppas, N.A.** Analysis of Fickian and Non-Fickian Drug Release from Polymers. *Pharm. Acta Helv.* **60**, 110-111 (1985).
- 18. Siepmann, J., N.A. Peppas.** Modeling of Drug Release from Delivery Systems Based on Hydroxypropyl Methylcellulose (HPMC). *Adv. Drug Delivery Rev.* **48**, 139-157 (2001).
- 19. Peppas, N.A., J.J. Sahlin.** A Simple Equation for the Description of Solute Release. III. Coupling of Diffusion and Relaxation. *Int. H. Pharm.* **57**, 169-172 (1989).
- 20. Moore, J.W., H.H. Flanner.** Mathematical Comparison of Dissolution Profiles. *Pharma Tech.* **20**, 64-74 (1996).

✉ **Roli Jain,**
Department of Chemistry,
Dr. H.S. Gour University, Sagar (M.P.), INDIA,
✉ **Archna Pandey** (corresponding author), **Sashi S. Pandeya,**
Department of Surgery,
Veterinary College Mhow (M.P.), INDIA
E-Mail: archnapandey@indiatimes.com