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In-vitro studies of diclofenac sodium controlled-release dosage from biopolymeric hydrophilic matrices

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ABSTRACT

The objective of the present study was to develop diclofenac sodium tablets from polymeric matrices [HPMC K-15 and Eudragit NE 30D] and characterization of its physicochemical properties, invitro release studies by using different disintegrants like sodium starch glycollate and polyplasdone in different ratios to optimize its release profile with the standard market product. Matrix tablets were prepared by wet granulation method using PVP K30 as binding agent. The method of preparation of matrix system and its concentration were found to have pronounced effect on the release of diclofenac sodium The matrix tablets were evaluated for its thickness, hardness, friability, weight variation, drug content and invitro release studies. The drug delivery was analyzed using the paddle method according to USP XXIII, all the studies were done in phosphate buffer pH 6.8. The dissolution release profile of formulation made with Eudragit NE 30 D (10%w/w) with polyplasdone (2%w/w) was comparable with the market formulation and the f1 and f2 value were found to be 6.28 and 67.17. Stability studies were carried out as per ICH guidelines and tested for its physicochemical properties and invitro studies. The stability study results revealed that the prepared formulation was stable in the stress condition.

KEYWORDS: Diclofenac sodium. HPMC. Eudragit NE 30D. Sustained release matrix. Tablet disintegrant.

RESUMEN

El objetivo del presente estudio fue desarrollar comprimidos de diclofenaco sódico en matrices poliméricas (HPMC K-15 y Eudragit NE 30D) y la caracterización de sus propiedades fisicoquímicas, así como estudiar la liberación in vitro mediante diferentes disgregantes, como glicolato sódico de almidón y poliplasdona en varias concentraciones, para optimizar su perfil de liberación con el producto estándar del mercado. Los comprimidos de la matriz se prepararon mediante el método de granulación húmeda usando como aglutinante PVP K30. El método de preparación del sistema de la matriz y su concentración resultó tener un efecto pronunciado en la liberación de diclofenaco sódico. Los comprimidos se evaluaron según su espesor, dureza, friabilidad, variación de peso, contenido farmacológico y estudios de liberación in vitro. La liberación del fármaco se analizó a través del método Paddle. Conforme a la normativa USP XXIII, todos los estudios se realizaron en buffer fosfato con un pH de 6,8. El perfil de liberación de la disolución de la formulación hecha con Eudragit NE 30D (10%w/w) y poliplasdona (2%w/w) fue comparable a la formulación comercial y los valores f1 y f2 fueron de 6,28 y 67,17 respectivamente. Se llevaron a cabo estudios de estabilidad según las normas ICH para evaluar las propiedades fisicoquímicas y los estudios in vitro. Los resultados de los estudios de estabilidad revelaron que la formulación preparada era estable en la condición de estrés.

PALABRAS CLAVE: Diclofenaco sódico. HPMC. Eudragit NE 30D. Matriz de liberación sostenida. Comprimido de desintegración.

INTRODUCTION

Treatment of a disease in most cases requires maintaining a desired drug plasma concentration level over a prolonged period of time. Such clinical needs often are satisfied by a multiple dose therapy, which can involve frequently dosing of two to four doses per day. The most common approach to minimizing patient non-compliance is by using extended release drug delivery systems to decrease the number of doses.

NSAID's are amongst the most commonly prescribed medications in the world attesting to their efficiency as anti-inflammatory, anti-thrombotic, anti-pyretic and analgesic agents.[1] Number of processes has been developed in modified release oral forms to avoid frequent dosage. Oral controlled release dosage forms have been developed and studied to restrict systems to specific regions as well as to improve the pharmacological activity and to reduce toxic effects.[2] Incorporation of the drug in a matrix containing a hydrophilic or rate controlling polymer is a method of fabricating controlled release formulations.[3,4] The matrix system is commonly used for manufacturing sustained release dosage forms because of its easy manufacturing process. Hydrophilic matrix systems are among the most widely used for controlling drug release from solid dosage forms.[5] The adjustment of the polymer concentration, viscosity grade and the addition of different types and levels of excipients can modify the drug release rate.[6-8]

Diclofenac sodium, a potential non-steroidal anti-inflammatory drug with pronounced analgesic properties, is used in the long-term treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitts. Its biological half-life has been reported as 1 –2 h.[9-10]

The objective of the present study was to develop diclofenac sodium tablets from polymeric matrices and characterization of its invitro release profile by using different disintegrants like sodium starch glycollate and polyplasdone in different ratios and to optimize its release profile with the standard market product.

MATERIALS AND METHODS

Materials

Diclofenac sodium, Eudragit NE 30D, HPMC K-15M, lactose, talc, magnesium stearate, PVP K-30, sodium starch glycollate and polyplasdone were procured from Inventis Drug Delivery systems Pvt Ltd. Potassium dihydrogen phosphate, sodium chloride and sodium hydroxide were procured from Nice Chemicals, India.

Diclofenac sodium calibration curve

Calibration curve of Diclofenac sodium was prepared using buffer pH 6.8 in the concentration range from 5 to 30µg/ml. The drug was analyzed spectrophotometrically (UV 1601 Shimadzu, Japan) at 285 nm.

Formulation and preparation of matrix tablets

Eighteen batches of diclofenac sodium tablets were prepared by utilizing Eudragit NE 30 D and HPMC K-15 M as polymeric matrix forming material. Formulations were made by wet granulation technique using PVP K30 (5%). Diclofenac sodium was blended with lactose and matrix forming polymer in a planetary mixer for 5 min and granulated with PVP K-30 (5%) and dried in hot air oven at 50°C for 3 hrs. Tablets were prepared from these granules after addition of talc, magnesium stearate and the particular level of the disintegrant chosen for the formulation and compressed in a 16-station rotary tabletting machine. The composition of the formulation is shown in table 1 and 2.

Drug-excipient interaction studies

Preformulation studies are very important for the successful formulation of any dosage form. Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared spectroscopy (FTIR) were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers, diluents and lubricants used in the tablet formulations. The earlier investigations recommended that 1:1 ratio of drug excipients maximizes the possibility of interaction and helps in easier detection of incompatibilities.[11,12]. Therefore, in the present study 1:1 ratio was used for preparation of physical mixtures and analyzed for compatibility studies.

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry (DSC) study was carried out using DSC 60, having TA60 software, Shimadzu, Japan. The instrument is very versatile as far as interaction and compatibility studies at pre-formulation stage was concerned and used to evaluate melting point, enthalpy changes and glass transition temperatures of drug with excipients and polymers. Diclofenac Sodium was mixed with the excipients and the DSC analysis of each sample under the analogous conditions of temperature range 40–300° C, heating rate at 10°C/min, in nitrogen atmosphere (20ml/min) and alumina as reference. Differential Scanning Calorimetry (DSC) was performed on pure drug, excipients and composition of final formulation.

Fourier transform infrared (FTIR)

FTIR studies are very helpful in the evaluation of drug–polymer interaction studies. If there is any incompatibility between the drugs and excipients, these can be predicted by changes in the functional peaks (characteristic wave numbers). Diffuse reflectance technique was used (400 to 4000 cm^{-1}), drug and various polymers were thoroughly mixed with 300mg of potassium bromide, compressed and the spectrum was obtained by placing the thin pellet in light path.

Table 1. Composition of diclofenac sodium matrix tablet

Material	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diclofenac sodium (mg)	100	100	100	100	100	100	100	100	100
Lactose	20%	20%	20%	20%	20%	20%	20%	20%	20%
HPMC K-15M	20%	20%	20%	20%	20%	20%	20%	20%	20%
Sodium starch glycollate	5%	10%	20%	---	---	---	---	---	---
Polyplasdone	---	---	---	1%	2%	5%	7.5%	10%	20%
Talc	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%
Magnesium stearate	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
PVP K-30 (5%)	10%	10%	10%	10%	10%	10%	10%	10%	10%

Table 2. Composition of diclofenac sodium matrix tablet

Material	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diclofenac sodium (mg)	100	100	100	100	100	100	100	100	100
Lactose	20%	20%	20%	20%	20%	20%	20%	20%	20%
Eudragit NE 30D	10%	10%	10%	10%	10%	10%	10%	10%	10%
Sodium starch glycollate	5%	10%	20%	---	---	---	---	---	---
Polyplasdone	---	---	---	1%	2%	5%	7.5%	10%	20%
Talc	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%
Magnesium stearate	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
PVP K-30 (5%)	10%	10%	10%	10%	10%	10%	10%	10%	10%

Figure 1. In vitro release profile of Diclofenac sodium from matrix tablets

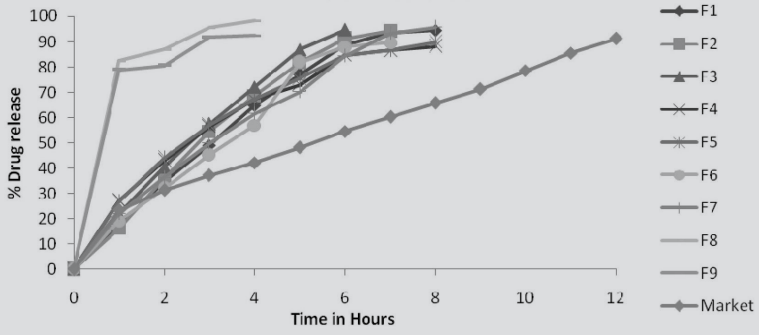
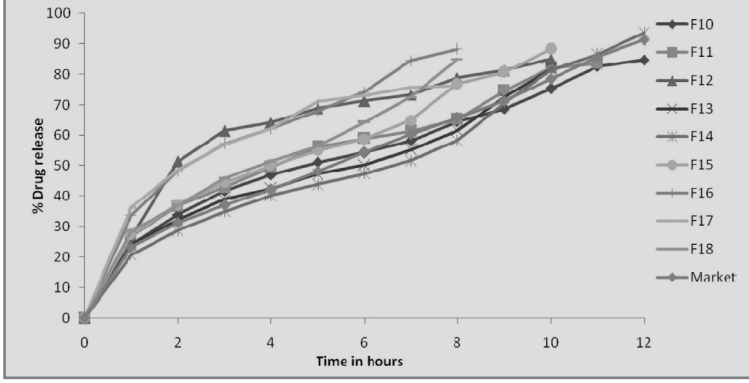


Figure 2. In vitro release profile of Diclofenac sodium from matrix tablets



Evaluation of tablet formulations[13,14]

Evaluation of characteristics of powder blend and tablets

The various characteristics of powder blend like angle of repose, bulk density, tapped density, compressibility index, flowability and drug content were studied. The formulated tablets were evaluated for hardness, friability, uniformity of weight and drug content.

Drug content of formulated tablets

Five tablets from each formulation were randomly chosen, pulverized and weighed equivalent to 100mg of diclofenac sodium was extracted with 100ml phosphate buffer (pH 6.8). Aliquot from subsequent filtered solution was further diluted in phosphate buffer (pH 6.8) in such a way that theoretical concentration was same as that of standard concentration. Resultant solutions were analyzed by using a UV spectrophotometer (in triplicate) and the average results were taken.

In vitro dissolution studies

The dissolution studies were performed in triplicate for all the batches in a USP XXIII dissolution rate test apparatus (type II). The

Table 3. Pre-compression parameters for diclofenac powder blend

Parameters	Values
Angle of repose (0)	Between 26.21 and 31.75
Bulk Density (g/cc)	Between 0.477 and 0.573
Tapped density (g/cc)	Between 0.549 and 0.653
Percentage compressibility	Between 10.12 and 14.98
Flowability	Good

release studies were performed at 100 rpm in 1000ml of phosphate buffer pH 6.8 at 37 ± 0.2ºC. Five milliliters aliquots were withdrawn at predefined intervals, and the volume of the dissolution medium was maintained by adding the same volume of fresh prewarmed dissolution medium. The absorbance of the withdrawn samples was measured spectrophotometrically at 285 nm.

Stability studies

The formulation which showed best in vitro release was selected for stability studies. The accelerated stability studies were conducted according to the ICH guidelines for a period of 6 months.

RESULTS AND DISCUSSION

Extended release pharmaceutical dosage forms have received much attention in recent years and highly desirable for providing a constant level of pharmaceutical agent to a patient. The nature of the delivery system is dictated by the properties and dose of the drug, desired release profile and physiological factors. Such dosage form not only increase patient compliance due to reduction in frequency of dosing, but they also reduce the severity and frequency of side effects as they maintain substantially constant blood levels and avoid fluctuations associated with the conventional immediate release formulations.

Calibration curve of diclofenac sodium was found to be linear in phosphate buffer pH 6.8 at wavelength 285nm between the concentration range of 5 and 30µg/ml, the correlation coefficient was found to be 0.9988.

Compatibility studies were carried out between the drug and the common excipients by DSC and, FTIR techniques. There was no considerable change observed in melting endotherm by DSC and no new bands or shift in characteristic peaks appeared by FTIR. The results revealed that there was no interaction between the drug and the excipients used in the formulation.

Tablets were made by wet granulation technique in order to prevent segregation of the constituents of the powder mix, to improve flow properties of the mix and to improve the compaction characteristics of the mix.

The dried powder mixtures were tested for powder properties like angle of repose, bulk density, tapped density, percentage compressibility and flowability. The results are shown in table 3. The evaluation results revealed that all the powder mixture had good flow properties.

The formulated tablets were evaluated for its physical properties like weight variation, hardness, friability and content uniformity. The results are shown in table 4. All the tablets were found to pass the uniformity of weight. Drug content of diclofenac sodium from all formulations was found in the range of 98.40 to 99.65%. The hardness of tablets from all formulations was between 4 and 6 kg/cm2. All the formulations showed friability between 0.55 and 0.85% indicating that the tablets could withstand the mechanical shock.

The performance of sustained release formulation has been reported to be greatly affected by physicochemical properties of polymer. Eighteen different combination of polymers with disintegrant was used to prepare the sustained release matrix tablets. Invitro release study results revealed that the release of drug was retarded with the proportional increase of the disintegrant concentration. The cumulative percentage release of formulation made with Eudragit NE 30D with polyplasdone 2% after 12h was found to be 93.45% whereas the standard market product showed 91.25%, which was comparable with the market formulation. The release results are shown in figure 1 and 2. Comparative dissolution profile between the optimized formulation and market formulation is shown in figure 3. The similarity factor f2 was found to be 67.17; which indicate that the invitro release profile is comparable. Stability studies were carried out at 40°C and 25°C and tested for its physical properties and invitro release studies.

Table 4. Post compression parameters of the formulated tablets

Parameters	Values	Permissible limits
Thickness (mm)	Between 3.20 and 3.25	---
Weight variation (as per USP)	Between 4.8 % and 5.20%	< 7.5%
Hardness (kg/m2)	Between 4 and 6	---
Friability	Between 0.55 and 0.85	0.5 – 1.0 %
Drug content	Between 98.40 % and 99.65%	95.0 – 105.0 % w/w

Figure 3. Comparison of in vitro release of optimized formulation and market formulation

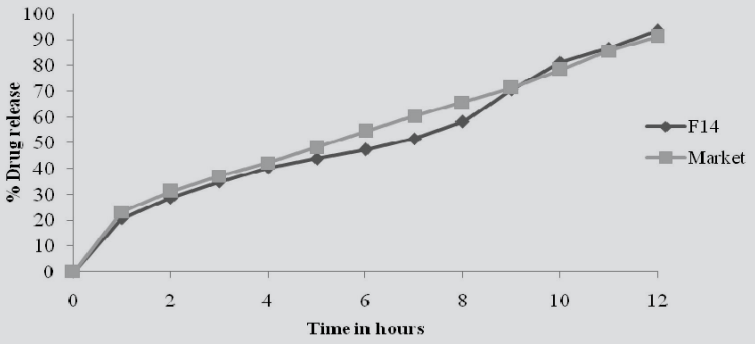
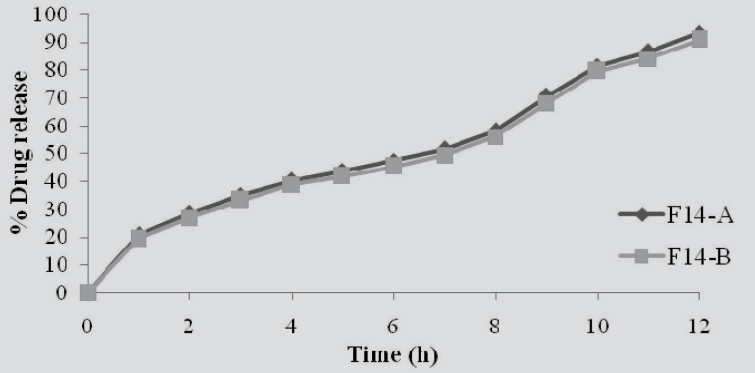


Figure 4. Comparison of in vitro release of optimized formulation before (F14-A) and after (F14-B) studies



Statistical analysis of the mean cumulative drug release in phosphate buffer (pH 6.8) have shown that the differences are non significant ($P \geq 0.05$). A comparative in vitro release of the optimized formulation before and after stability studies indicated that there was no significant difference in the release rate of the formulation. Comparative in vitro release study result is shown in Figure 4. F14-A represents the cumulative percentage drug release of the formulation F14 before the stability studies and F14-B represents the cumulative percentage drug release of the formulation F14 after the stability studies.

REFERENCE

1. Davies NM. Sustained release and enteric coated NSAIDs: Are they really GI safe?. J Pharm Pharmaceu Sci. 1999; 2: 5-14.

2. Roseman TJ, Cardinelli NF. In Kydonieus AF. Controlled release technologies Vol 1, CRC Press, Boca Raton, FL, 1980.

3. Ranga Rao KV, Padmalatha Devi K. Swelling controlled release systems: Recent development and applications. Int J Pharma. 1988; 48: 1-13.

4. Salsa T, Veiga F, Pina ME. Oral controlled release dosage forms: I. Cellulose ether polymers in hydrophilic matrices. Drug Dev Ind Pharm. 1997; 239: 929-938.

5. Lakshmana Prabu S, Shirwaikar A, Shirwaikar AA, Ravikumar, Aravind Kumar G, Abraham Jacob. Formulation and evaluation of oral sustained release of Diltiazem Hydrochloride using rosin as matrix forming material. ARS Pharma. 2009: 50(1): 32-42.

6. Sung KC, Nixon PR, Skoug JW, Ju TR, Gao P, Patel MV. Effect of formulation variables on drug and polymer release from HPMC based matrix tablets. Int J Pharm. 1996; 142: 53-60.

7. Siepmann J, Kranz H, Bodmeier R. HPMC matrices for controlled drug delivery: A new model combining diffusion, swelling and dissolution mechanism and predicting the release kinetics. Pharm Res. 1999; 16: 1748-1756.

8. Ford JL, Mitchell K, Rowe P, Armstrong DJ Elliot PNC, Rostron C. Mathematical modeling of drug release from hydroxyl propylmethyl cellulose matrices: Effectof the temperature. Int J Pharm 1991; 71: 95-104.

9. Arica B, Arica MY, Kas HS, Hincal AA, Hasirci V. In vitro studies of enteric coated Diclofenac sodium carboxymethylcellulose microspheres. J Microencaps 1996; 13: 689-699.

10. Todd PA, Sorkin EM. Diclofenac sodium, a reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. Drugs 1988; 35: 244-285.

11. Loganathan V, Senthil Kumar K, Siva Prasada Reddy MV, Sreekanth N, Senthil Kumar B. Studies on preformulation compatibility between lomefloxacin and tablet excipients through DSC and X-ray diffraction analysis. Int Journal of Pharmaceutical Excipients April-June, 2003; 38-49.

12. Giordano, F., Rossi, A., Pasquali, I., Bettini, R., Frigo, E., Gazzaniga, A., Sangalli, M.E., Mileo, V., Catinella, S., 2003. Thermal degradation and melting point determination of diclofenac. J. Thermal Anal. Calorim. 73, 509–518.

13. Banker GS, Anderson. In: Lachman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy, 3rd ed. Varghese publishing house, Mumbai, 1987; p. 383.

14. Arora P, Mukherjee B., 2002. Design, development, physicochemical and in vitro and in vivo evaluation of transdermal patches containing diclofenac diehtylammonium salt. J. Pharma. Sci. 91(9), 2076-89.