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EFFECT OF FORMULATION VARIABLES ON THE RELEASE OF ACECLOFENAC FROM HPMC MATRIX TABLETS

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ABSTRACT

The objective of this work was to study the effect of concentration and viscosity grade of HPMC, different diluents and inclusion of solid dispersions on the matrix tablets of aceclofenac. In present study, aceclofenac, a novel NSAID used for symptomatic treatment of pain and inflammation was formulated into matrix tablets with HPMC of two different viscosity grades (E50 LV and K15 M) by direct compression method. Before compression the formulations were evaluated for angle of repose, % compressibility and Hausner's ratio. Tablets were evaluated for hardness, friability, weight variation, uniformity of thickness and diameter, and drug content. All pre-compressional and post-compressional parameters were found within the official limits. In vitro drug release studies were conducted for a period of 8 hrs using USP paddle method (II) at 37±0.5^{o}C and at 75rpm speed in pH 7.2 phosphate buffer. Type of polymer and its concentration has influenced the drug release from matrix tablets. With increasing concentrations and increasing polymer viscosity the release rate decreased. Release rate increased with the addition of PEG and PVP. There was significant increase in drug release by inclusion of solid dispersions in the matrix tablets. It can be concluded that by incorporating water soluble excipients such as PEG and PVP and solid dispersions of drug with PVP into the matrix, drug release can be increased. Dissolution data was analysed by Power law expression, $M_t / M_\infty = kt^n$. Release of drug from the tablets varied on the basis of formulation and was found to be non-Fickian and case II transport with different formulations.

INTRODUCTION: Tablet forms the majority of oral dosage forms. Important reasons for their popularity are their convenience of application (patient compliance) and ease of preparation on an industrial scale [1].

In the last two decades, controlled-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Preparation of drug-embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation.

The matrix system is commonly used for manufacturing controlled release dosage forms because it makes such manufacturing easy. A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept [2].

The use of hydrophilic polymers is actually the most used method in controlling the release of drugs in the formulation of oral pharmaceutical dosage forms. Hydroxypropyl methylcellulose has been extensively used since the early 1960s as a rate-controlling polymer in oral extended-release dosage forms [3], due to its fabrication and its availability in different chemical substitution, and hydration rates and different viscosity grades, and also due to less adverse effects associated. HPMC offers advantages of being nontoxic, relatively inexpensive; it can be compressed directly into matrices, and its capacity to accommodate high levels of drug loading and its non pH-dependence [4].

The process of drug release from the HPMC-drug matrix involves the solvent penetration into the dry matrix, rapid formation of a gel layer at the matrix periphery exposed to aqueous fluids, diffusion of soluble drug through water filled pores. Consequently the release rate is associated to porosity or tortuosity of a swellable matrix is primarily attributed to polymer swellability.

Changing several formulation factors, such as type of excipients and manufacturing processes, and particle size, viscosity and proportion of HPMC modify the characteristics of porosity, tortuosity of the swollen matrix and therefore modify the release rate of drugs. Increasing proportions of HPMC in the matrix system decrease the release rate. An increasing particle size of HPMC produces increasing release rates from the tablets and decreasing release rates occur often with an increasing viscosity grade [5-10].

Aceclofenac, (2-[2-[22, 6-dichlorophenyl) aminophenyl] acetyl] oxyacetic acid) is a non-steroidal anti-inflammatory drug (NSAID) [11] and has been indicated for various conditions like post-traumatic pain, rheumatoid arthritis, ankylosing spondylitis [12]. It is well tolerated with lower indications of gastro intestinal adverse effects and hence resulted in a greater compliance with treatment [13].

Aceclofenac is found to have better safety profile than many drugs like ketoprofen [14], diclofenac [15], indomethacin [16], tenoxicam [17], naproxen [18], piroxicam [19]. Aceclofenac is rapidly and efficiently absorbed after oral administration, with an associated half-life of 4 hours. Non steroidal anti-inflammatory drugs (NSAIDs) have commonly been associated with upper gastrointestinal (GI) tract side effects including a high incidence of gastric and duodenal ulceration. A trend in dosage form development has been to improve therapeutic efficacy and reduce the severity of upper GI side effects through altering dosage forms of NSAIDS by modifying the release. These formulations are designed to increase patient compliance through a prolonged effect and reduced adverse effects through reduced fluctuations in plasma concentrations [20].

The aim of the present work is to develop aceclofenac controlled release matrix tablets based on HPMC and to evaluate the factors/excipients influencing the drug release.

MATERIALS AND METHODS: Aceclofenac was obtained as a gift sample from Rantus Pharma, Hyderabad. Hydroxypropyl methylcellulose E50 LV and K15 M grades were generously supplied by Aurobindo Pharmaceutical Laboratories, Hyderabad. Mannitol, magnesium stearate, aerosil, polyethylene glycol, polyvinyl pyrrolidone all were purchased from SD fine chemicals Pvt. Ltd., Mumbai.

Preparation of Tablets: Aceclofenac, HPMC, filler, magesium stearate and aerosil were blended together by dry mixing in a laboratory mixer for 10 mins. Before compression the formulations were evaluated for preformulation studies like angle of repose, % compressibility, Hausner's ratio. These studies indicated that the powder mixtures were free flowing in character and suitable for direct compression. The powder mixture was then compressed in 10 station rotary punch machine using 12 mm standard concave punch and die set (Rimek mini press 1), at a compression force of 6 ton. The formulations of the tablets with their codes are listed in **tables 1, 2 and 3**.

In all formulations the amount of aceclofenac is 200 mg. Total tablet weight is kept at 600 mg. In E1- E4 and K1- K3 formulations HPMC grades E50LV and K15M are used respectively with increasing concentrations. The formulae for different formulations with two different grades are given in the **table 1**. All given amounts in tables are in mg. formulae to study the effect of fillers for E3, E4 and K3 formulations by replacing mannitol with PEG and PVP were given in the **table 2**.

TABLE 1: FORMULATIONS CONTAINING ACECLOFENAC WITH HPMC GRADES E50 LV AND K15M

INGREDIENTS	E1	E2	E3	E4	K1	K2	K3
Aceclofenac	200	200	200	200	200	200	200
E50 LV HPMC	50	100	200	300	--	--	--
K15 M HPMC	--	--	--	--	50	75	100
Mannitol	342.5	292.5	192.5	92.5	342.5	292.5	317.5
Aerosol-200	5	5	5	5	5	5	5
Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
PEG	-	-	-	-	-	-	-
PVP	-	-	-	-	-	-	-

TABLE 2: FORMULAE TO STUDY THE EFFECT OF DILUENTS ON E3, E4 AND K3 FORMULATIONS

INGREDIENTS	E3-II	E3-III	E3-IV	E3-V	E4-II	E4-III	K3-II	K3-III	K3-IV	K3-V
Aceclofenac	200	200	200	200	200	200	200	200	200	200
E50 LV HPMC	50	100	200	300	--	--	--	--	--	--
K15 M HPMC	--	--	--	--	--	---	100	100	100	100
Mannitol	92.5	--	92.5	--	--	--	92.5	92.5	--	--
Aerosol-200	5	5	5	5	5	5	5	5	5	5
Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
PEG	100	192.5	-	-	92.5	-	200	-	292.5	-
PVP	-	-	100	192.5	-	92.5	-	200	-	292.5

Preparation of solid dispersion: Solid dispersions of aceclofenac are prepared using PEG and PVP by coprecipitate method. The solvents employed for preparing solid dispersions are methanol: dichloromethane (1:2) to get the clear solutions of PVP. To the solutions of PVP, weighed amounts of aceclofenac are added individually. The solvents are evaporated at 50^{o}C and dried in desiccator until the dry mixtures attain constant weights. The solidified masses are crushed, pulverized and passed through mesh no. 80. **Table 3** shows formulae for the preparation of solid dispersions.

TABLE 3: FORMULAE FOR THE PREPARATION OF SOLID DISPERSIONS

INGREDIENTS	E4	IV	E4	IV
Aceclofenac	200	200	200	200
E50 LV HPMC	300	300	--	--
K15 M HPMC	--	--	100	100
Mannitol	42.5	--	92.5	-
Aerosol-200	5	5	5	5
Mg. stearate	-	-	-	-
PEG	-	-	-	-
PVP (Solid Dispersion)	50	92.5	200	292.5

Evaluation of Tablets: The prepared matrix tablets were evaluated for weight variation, hardness, friability, uniformity of diameter and thickness, and drug content.

To study tablet weight variation 10 tablets of each formulation were weighed individually using Shimadzu digital balance and average weight was calculated. The individual weights were compared with average weight. Monsanto hardness tester and Roche friability apparatus used to test the hardness and friability of tablets respectively.

The crown to crown thickness and diameter of the tablets from each batch were determined using Vernier calipers. For determination of drug content at least four tablets from each formulation were weighed individually, pulverized, and dissolved in 5ml of methanol and diluted to 250ml with sufficient amount of pH 7.2 phosphate buffer. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 274 nm.

Dissolution Studies: *In vitro* drug release studies for the prepared matrix tablets were conducted for a period of 8 hours using a 8 station USP TDT-08L (Electro lab) apparatus at 37$\pm$0.5^{o}C and at 75 rpm speed. The dissolution studies were carried out in phosphate buffer of pH 7.2 under sink condition using USP paddle method (II). At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 274 nm for aceclofenac by a UV-Visible spectrophotometer.

The amount of drug present in the samples was calculated. Drug dissolved at specified time periods was plotted as percent release Vs time (min) curve.

RESULTS AND DISCUSSIONS: Post compressional parameters of all formulations were within the official limits, and there was no significant change with change in formulation.

Effect of Polymer Grade and Concentration: The formulations, E1, E2, E3 and E4 were prepared using E50 LV grade of HPMC and K1, K2 and K3 were prepared using K15 M grade of HPMC at different levels (drug: polymer ratio, 1: 0.25, 1:0.5, 1:1, 1:1.5 respectively) (drug: polymer ratio, 1: 0.25, 1: 0.375, 1:0.5 respectively).

Figure 1 shows that release of the drug decreased with increase in the concentration of HPMC in the tablets with both grades of HPMC. In case of formulation E1 or K1, almost total drug released within 3 hrs of dissolution time. However, in case of (E2-E4 or K2 and K3) release prolonged with increase in the concentration of polymer in the matrix. Amount released at any interval decreased with increase in the concentration of polymer in the matrix or decrease in the concentration of filler, because, a hydrophilic matrix release system is a dynamic system composed of polymer wetting, hydration and dissolution.

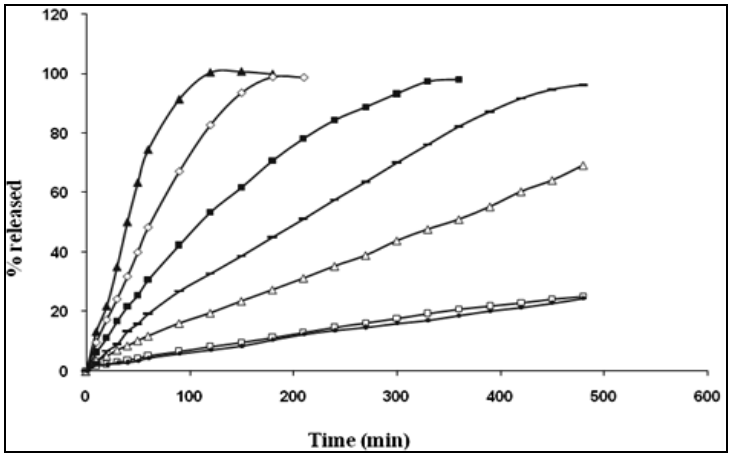

FIG. 1: EFFECT OF GRADES AND CONCENTRATION OF HPMC ON THE RELEASE OF ACECLOFENAC

Key: (▲) - E 1; (■) – E2; (Δ) - E3; (□) - E4; (◊) - K1; (✒) - K2; (•) - K3; Max ± SD = 1.25, n = 4

At the same time, other soluble excipients (or drugs) will also wet, dissolve, and diffuse while the insoluble ingredients will be held in place until the polymer erodes or dissolves [21]. Changing the polymer/filler ratio influences the release by altering the diffusivity of the drug in the gel layer. Water diffusivity depends only on the total concentration of viscosity inducing agents in the system irrespective of their nature of polymerization degree [22]. Replacement of HPMC by mannitol decreases the concentration of polymer in gel layer (E4 to E1 and K3 to K1) and therefore diffusion of water into the tablets is facilitated.

Mannitol also decreases the tortuosity of the path length diffusion. These results confirmed that release of insoluble drug, aceclofenac, may primarily be controlled by gel thickness [21, 22]. These results confirm that, replacing polymer in the tablet matrix by a soluble diluent (mannitol), the tortuosity of the matrix decreases during dissolution and comparatively, a faster dissolution was seen with increasing concentrations of diluent. As the concentration of mannitol increased, the dissolution also increased in the order E1>E2>E3>E4 and K1>K2>K3.

Comparison of release profiles (figure 1) of tablets prepared with same drug: polymer ratio (1:0.5) using two different HPMC grades (formulations E2 and K3) shows a large variation in dissolution behavior. Because at 5th hr almost complete (93.3%) drug released from E2, whereas, only 24.59% of the drug released from K3 even at 8th hr. It indicates that drug release from tablets based on E50 LV HPMC shows the highest release compared to that having higher viscosity grade K15 M. These results obtained are in accordance with the data reported in the literature [23]. Thus the efficiency of viscosity grades in sustaining the release was observed to be in the following order E50 LV < K15 M.

Effect of Diluents: As the release of the aceclofenac from the E3, E4 and K3 formulations was incomplete, the mannitol was replaced partially/ completely with PEG and PVP to study the effect of other soluble excipients on the release.

Figure 2 shows the release profiles of formulations E3-II, E3-III, E3-IV and E3-V having different concentrations of PEG and PVP. As the mannitol was replaced with PEG partially (100mg)/ or completely (192.5mg), the release increased from 55.5% to 64.9/or 69.04% respectively at 8th hr of the dissolution study.

Whereas, replacing mannitol with PVP partially (100mg)/ or completely (192.5 mg), the release increased significantly from 55.5% to 80.58 at 8th hr/ 96.62% at 5th hr respectively. It indicates that, of the three fillers used, PVP is more effective in increasing the release of aceclofenac from the matrix tablets.

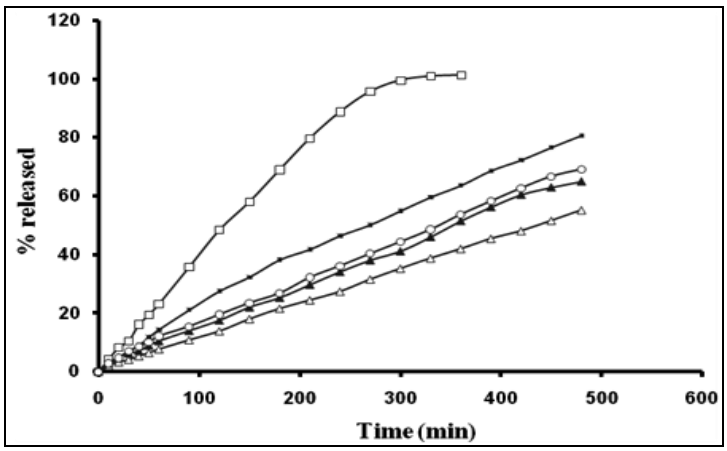

FIG 2: EFFECT OF DILUENTS PEG AND PVP ON E3 FORMULATIONS

Key: (△) - E3; (▲) - E3- II; (○) - E3-III; (■) - E3-IV; (□) - E3-V; Max ± SD = 1.05, n = 4

Similarly, in formulation E4, where the release was incomplete (27.517% up to 8th hr), mannitol was completely replaced with PEG (E4-II) and PVP (E4-III) to check the effect on the release of aceclofenac. **Figure 3** shows the effect of PEG and PVP on the release of aceclofenac from E4 formulations indicates that only upto 27% / 29.5% of the drug was released from these formulations.

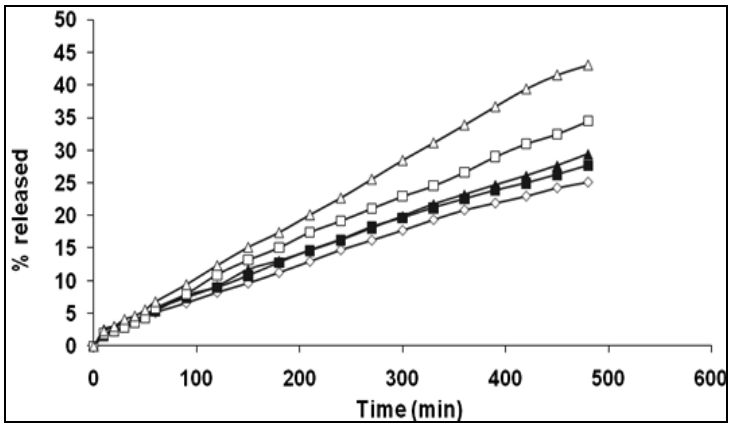

FIG 3: EFFECT OF DILUENTS AND SOLID DISPERSION ON E4 FORMULATION

Key: (◊)- E4; (■)- E4-II; (▲)- E4-III; (□)- E4-IV; (Δ)- E4-V; Max ± SD = 1.25, n = 4

It indicates that release rate was not affected by the type of diluent as the concentration of polymer is very high and formation of thick, viscous and tortuous gel at the surface of wetted tablets did not easily allow the penetration of solvent molecules and thus hindered the release of drug. As the release was not satisfactory with K3 tablets (24.6% up to 8th hr), the mannitol was replaced partially (200mg)/completely (292.5 mg) with both PEG and PVP to check effect on the release of drug.

Figure 4 show that as mannitol was replaced with PEG or PVP, release increased with increase in the amount of diluents. The amount released from different K3 formulations at any time increased with change of diluent type. However, these results indicate that, PVP was more effective in increasing the release of poorly soluble aceclofenac from the tablets.

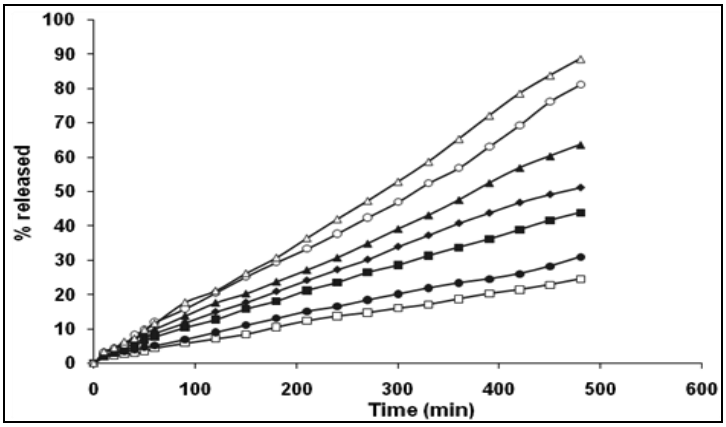

FIG 4: EFFECT OF DILUENTS AND SOLID DISPERSION ON K3 FORMULATIONS

(□)- K3; (●)- K3-II; (■)- K3-III; (◊)- K3-IV; (▲)- K3-V; (○)- K3-VI; (Δ)- K3-VII Max ± SD = 2.15, n = 4

Effect of Solid Dispersions: In the previous experiments, although release increased by replacing the mannitol with PEG or PVP, complete release of the drug was not seen in some formulations (such as E4 and K3). It indicates that polymer concentration and type plays a dominant role in preventing the complete release of insoluble drug.

Hence, further studies were carried out to increase the solubility of drug through the formation of solid dispersion in soluble carrier such as PVP.

In E4 formulations, PVP was replaced in the form of solid dispersion with drug. In E4-IV formulation (50 mg of the PVP was in the form of solid dispersion), up to 8 hr, 34.45% of the drug was released. However, the release increased up to 43.02% with E4-V formulations where total (92.5 mg) amount of PVP was incorporated in the form of solid dispersion (figure 3).

In case of K3 formulations, either 200 mg/or 292.5 mg of the PVP in the formulation was replaced in the form of solid dispersion (K3-VI and K3-VII respectively). Figure 4 depicts the effect of solid dispersion on the release profiles of aceclofenac from K3 formulations. The release of drug from K3 formulations were increased from 24.6% to 81.14/ or 88.64% respectively in K3-VI and K3-VII formulations. These results indicate that release of aceclofenac from the K3 formulations increase with the incorporation of PVP in the form of solid dispersion.

Kinetics and Mechanism of Drug Release: In general, the release data from swellable systems can be analyzed according to the following power law expression (Korsmeyer 1983) [24].

$$M_t / M_\infty = kt^n \quad \text{----------} \quad (1)$$

Where, M_t / M_∞ is the fraction of drug released at time, t, k is the proportionality constant which accounts for the structural and geometrical properties of the matrix, and n is the diffusional exponent indicative of the mechanism of drug release. According to the criteria for release kinetics from swellable systems, a value of release exponent, n = 0.45, 0.45<n<0.89 and 0.89<n<1.0 indicates Fickian (case I) diffusion, non-Fickian (anomalous) diffusion and zero-order (case II) transport, respectively [25].

The initial dissolution profiles (≤ 60%) of the formulations were fitted into equation (1). The values of release parameters n and k, were determined after plotting the % drug released as a function of time according to equation (1) by subjecting the data points to least square linear regression method. The calculated values of n and k, r^2 are shown in **table 4**.

As evident from the table 4, the correlation coefficients (r^2) following regression analysis of the release data, showed an excellent fit in equation 1 and exhibited a linear relationship up to ≤ 60% of the drug release. The values of diffusional coefficient, n, for E1 and E2 tablets were around 1 which indicates that the drug release was inconsistent with the case II transport, while the drug release was of anomalous behavior (n = 0.7499) with E3, indicating that the drug partially diffuses through the swollen polymer matrix and also partially through the gradually expanding hydrated matrix.

The values of n, for K1 tablets was ≈ 1 while for K2 and K3 were 0.84 and 0.72 respectively, indicating that drug release is by case II transport in K1 formulations and of anomalous behavior in K2 and K3 formulations. As the mannitol (from E3) was replaced by PEG (E3-III) and increasing amounts of PVP (E3-IV and E3-V), the n values increased to ≈ 1, indicating that PVP based tablets (E3-V) release the drug by case II transport.

When the drug was incorporated in the form of solid dispersion (K3-VI and K3-VII) in K3 formulations, the 'n' values shifted to higher values ≥ 0.9, indicating that the drug release was leaning towards case II transport.

TABLE 4: KINETIC PARAMETERS OF DISSOLUTION DATA DESCRIBED BY KORSMEYER-PEPPAS EQUATION

FORMULA	r^2	n	k
E1	0.9946	1.2398	.5504
E2	0.9979	0.9593	0.5862
E3-I	0.996	0.7499	0.6154
K1	0.999	1.0905	0.5568
K2-I	0.9982	0.8424	0.5835
K3	0.9872	0.7262	0.6446
E3-III	0.9929	0.8302	0.3693
E3-IV	0.9951	0.8889	.3599
E3-V	0.9971	1.0029	0.3493
K3-VI	0.9969	0.9005	0.2795
K3-VII	0.9973	0.9391	0.2447

CONCLUSIONS: HPMC has been used in the tablets as release retardant. It is well known that, viscosity of HPMC has a profound influence on the release kinetics. In this study, two grades of HPMC (E50 LV and K15 M) have been used. Initially, the tablets containing 200mg of aceclofenac are prepared using both HPMC grades at different levels (drug: polymer ratio of 1:0.25, 1:0.5, 1:1, 1:1.5 with E50 LV and 1:0.25, 1:0.375, 1:0.5 with K15 M grade of HPMC, E1 - E4 and K1- K3).

The preformulation studies (angle of repose, % compressibility and Hausner's ratio) are conducted on the powder mixture before compression. The results of preformulation studies revealed that powder mixtures are free flowing and suitable for direct compression. The powder mixture is compressed in a ten station rotary punching machine (12 mm punch and set). Tablets are evaluated for hardness, friability, weight variation, uniformity of thickness and diameter, drug content.

Results indicate that all the parameters are compliant with the Indian Pharmacopoeia limits and none of the parameters is significantly influenced by the variables. With an intention to study the effect of viscosity of HPMC on release, two grades of HPMC (E50 LV and K15 M) at different levels are used. The results indicated that as the viscosity and concentration of HPMC increased, release of the drug decreased. In formulations, E3, E4 and K3, the release was found to be incomplete before the dissolution test period ended. In these formulations, the mannitol was replaced with PEG and PVP partially/ completely.

Change of diluent(s) although improved the release (E3), the release was incomplete in some formulations (E4 and K3). In the next set of formulations (E4 and K3), drug was incorporated in the form of solid dispersion with PVP. The release of drug from these formulations (except E4) increased significantly. The incomplete release from the formulations (E4) containing E50 LV grade of HPMC may be attributed to the high viscosity of the HPMC.

Thus, it can be concluded that selection of appropriate diluent, HPMC grade and concentration would give required release of the aceclofenac from the HPMC based matrix tablets.

REFERENCES:

1. Chien YW: Controlled and modulated-release drug delivery systems, in: J. Swarbrick and JC Boyland (Ed.), Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker, 1990.
2. Reza MS, Quadir MA and Haider SS: Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J Pharm Pharmaceut Sci 2003; 6:282-91.
3. Ochoa L, Igartua M, Hernandez RM, Gascon AR and Pedraz JL: Preparation of sustained release hydrophilic matrices by melt granulation in a high-shear mixer. J Pharm Pharmaceut Sci 2005; 8:132-40.
4. Takka S, Rajbhandari S and Sakr A: Effect of anionic polymers on the release of propranolol hydrochloride from matrix tablets. Eur J Pharm Biopharm 2001; 52:75-82.
5. Gonzalez IM and Robles LV: Influence of enteric citric acid on the release profile of 4-aminopyridine from HPMC matrix tablets. Int J Pharm 2003; 251:183-93.
6. Espinoza R, Hong E and Villafuerte L: Influence of admixed citric acid on the release profile of pelanserin hydrochloride from HPMC matrix tablets. Int J Pharm 2000; 201:165-73.
7. Vandelli MA, Leo E, Foni F and Bernabei MT: Drug release from perforated matrices containing hydroxypropyl methylcellulose. Int J Pharm 1998; 171:165-75.
8. Huang Y, Khanvilkar KH, Moore AD and Hilliard-Lott M: Effects of manufacturing process variables on in vitro dissolution characteristics of extended release tablets formulated with hydroxypropyl methylcellulose. Drug Dev Ind Pharm 2003; 29:79-88.
9. Thapa P and Ghimire M: Effect of drug solubility and polymer viscosity on in-vitro drug release from HPMC matrix tablet. Indian Drugs 2005; 42:389-91.
10. Kumar MT, Srinivas G, Balasubramaniam J and Pandit JK: HPMC-based matrix tablets of atenolol and cisapride: Effect of viscosity of polymer and drug solubility on in vitro release. Indian J Pharm Sci 2005; 67:414-21.
11. Basak SC, Srinivasa Rao Y, Manavalan R and Rao PR: Controlled release HPMC matrix tablets of propranolol hydrochloride. Indian J Pharm Sci 2004; 42:827-30.
12. Hinz B, Auge D, Rau T, Rietbrock S, Brune K and Werner U. Simultaneous determination of aceclofenac and three of its metabolites in human plasma by high-performance liquid chromatography. Biomed Chromatogr 2003; 17:268-75.
13. Kousy NMEI: Spectophotometric and spectrofluorimetric determination of etodolac and aceclofenac. J Pharm Biomed Anal 1999; 20:185-95.
14. Legrand E: Aceclofenac in the management of inflammatory pain. Expert Opin Pharmacother 2004; 5:1347-57.
15. Martin Mola E, Gijon Banos J and Ansoleaga JJ: Aceclofenac in comparison to ketoprofen in the treatment of rheumatoid arthritis. Rheumatol Int 1995; 15:111-6.
16. Pasero G, Marcolongo R, Serni U, Parnham MJ and Ferrer F: A multi-centre, double-blind comparative study of the efficacy and safety of aceclofenac and diclofenac in the treatment of rheumatoid arthritis. Curr Med Res Opin 1995; 13:305-15.
17. Kornasoff D, Maisenbacher J, Bowdler J and Raber A: The efficacy and tolerability of aceclofenac compared to indomethacin in patients with rheumatoid arthritis. Rheumatol Int 1996; 15:225-30.
18. Perez-Ruiz F, Alonso-Ruiz A and Ansoleaga JJ: Comparative study of the efficacy and safety of aceclofenac and tenoxicam in rheumatoid arthritis. Clin Rheumatol 1996; 15:473-7.
19. Kornasoff D, Frerick H, Bowdler J and Montull E: Aceclofenac is a well-tolerated alternative to naproxen in the treatment of osteoarthritis. Clin Rheumatol 1997; 16:32-8.
20. Busquier MP, Calero E, Rodriguez M, Arce PC, Bermudez A and Linares LF: Comparison of aceclofenac with piroxicam in the treatment of osteoarthritis. Clin Rheumatol 1997; 16:154-9.
21. Amaral MH, Lobo JMS and Ferreira DC: Effect of hydroxypropyl methylcellulose and hydrogenated castor oil on naproxen release from sustained-release tablets. AAPS PharmSciTech 2001; 2: 6-9.
22. Rekhi GS, Nellore RV, Hussain AS, Tillma LG, Malinowski HJ and Augsburger LL: Identification of critical formulation and processing variables for metoprolol tartrate extended-release (ER) matrix tablets. J Contr Rel 1999; 59:327-42.
23. Gao P and Fagerness PE: Diffusion in hydroxypropyl methylcellulose hydrogels. Determination of drug and water diffusivity by pulsed-field-gradient spin-echo NMR. Pharm Res 1995; 12:955-64.
24. Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA: Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm 1983; 15:25-35.
25. Ritger PL and Peppas NA: A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J Contr Rel 1987; 5:37-42.

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