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FABRICATION OF MATRIX CORE TABLET AS A BI PHASIC DUAL-COMPONENT DELIVERY SYSTEM CONTAINING ACECLOFENAC

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ABSTRACT

The purpose of the present research was to produce a quick/slow biphasic delivery system for aceclofenac. A dual component tablet made of a sustained release tabletted core and an immediate release tabletted coat was prepared by direct compression. Both the core and the coat contained a model drug aceclofenac. The sustained release effect was achieved with polymers hydroxypropyl methylcellulose, ethylcellulose and Xanthan gum to sustain the release of drug. The in-vitro drug release profile from these tablets showed the desired biphasic release behavior of aceclofenac, where the fast releasing component was dissolved within 30 minutes and the drug in the core tablet was released over a period of 12 hours from the matrix tablets. It was observed that Xanthan gum is a better release retarding agent than HPMC and ethyl cellulose as it delayed the release of the drug for more than 15hrs. The results obtained with the dissolution test shows that the release profile is dependent on the type and amount of polymer in the core tablet.

KEYWORDS: *Aceclofenac, Xanthan gum, matrix tablets, dual component system.*

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to its convenience and ease of ingestion but it is problematic if the drug is poorly water soluble or having poor membrane permeability[1]. Immediate release tablets gives fast release of drugs to provide rapid onset of action following zero order kinetics but fails to provide long duration of action. While conventional control release dosage forms delay the release of therapeutic drug by following zero order kinetics and do not provide rapid onset of action[3]. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However it is difficult to achieve because the environment for drug diffusion and or absorption varies along the gastrointestinal (GI) tract[4]. Based on these considerations, biphasic delivery systems are designed to release a drug at 2 different rates or in 2 different periods of time: they are either quick/slow or slow/quick. A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time. This system was designed in the form of a double-component tablet, in which the one portion is formulated to obtain a prompt release of the drug with the aim of reaching a high serum concentration in a short period of time. The second portion is a prolonged-release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time. This type of system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include nonsteroidal anti-inflammatory drugs, antihypertensives, antihistaminics and anti-allergic agents[5].

Non-steroidal anti-inflammatory drugs (NSAIDs) are highly effective in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. But their long term use has lead to gastrointestinal (GI) complications like ulceration, perforation and obstruction. Aceclofenac is chemically 2-[[2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetyl] oxy]-acetic acid. A highly potent member of a new class of compounds of NSAID's available in oral formulations for the management of rheumatoid arthritis, osteoarthritis and

ankylosing spondylitis. It directly blocks the prostaglandin synthesis. It is considered to be the first-line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Due to its short biological half life of 4 hours and dosing frequency of 200 mg daily in 2 divided doses, aceclofenac is an ideal candidate for sustained release formulation[6]. Also because of the rapid metabolization and excretion of aceclofenac, typical immediate release dosage tablets of aceclofenac provide only short window of therapeutic effectiveness for patients and require multiple dosing for maintaining therapeutic effect throughout day. Hence there is a potential need for sustained dosage form of aceclofenac.

A double layer tablet containing one immediate release compartment and one sustain release layer offers advantages such as the drug release from fast releasing layer leads to a rise in the blood concentration initiating the onset of action. Blood level is maintained at steady state as the drug is released from the sustaining layer. Thus the developed single tablet will be sufficient instead of two to three tablets per day, and it will also increase patient compliance and therapeutic efficacy. So this makes aceclofenac an ideal candidate for biphasic drug delivery also[7].

The present study was aimed to formulate and evaluate a quick/ slow delivery dosage form as a as bilayer tablet in which the outer coat released the drug quickly and the central core tablet provided a delayed and control release of aceclofenac to study the influence of the type of matrix core on the *in-vitro* performance.

MATERIALS AND METHODS:

Aceclofenac, microcrystalline cellulose and Xanthan gum was purchased from Yarrow Chem Products, Mumbai. Hydroxy propyl methyl cellulose (HPMC) and Ethyl cellulose (EC) was purchased from Central Drug House Pvt. Ltd, New Delhi. Crosscarmellose Sodium was obtained from Anglo-French Drugs & Industries Ltd. Ethanol was purchased from S.D. Fine chemicals, Mumbai. All other solvents and reagents were analytical grade.

Experimental Method:

1. Formulation of slow release component

Core tablets were prepared from mixtures of aceclofenac and matrix controlling agent like HPMC, ethyl cellulose and Xanthan gum by direct compression. All the materials were sieved through 120 mesh and tablets were prepared by direct compression method using 6mm flat punches in a rotary tablet punching machine (Rimek RSB-4 mini press, Cadmach, Ahmedabad).

2. Formulation of fast release component

The fast release component contained model drug aceclofenac. Microcrystalline cellulose (Avicel PH 102) was used because of its good compaction and disintegration properties. Crosscarmellose sodium was used as a super disintegrant to obtain an immediate release of the drug.

3.Preparation of dual component delivery system

The dual-component delivery system was prepared by compressing a smaller matrix tablet, forming a central core, with a powder mixture containing the fast releasing component to produce a bigger tablet. For the preparation of the quick/slow delivery system, the die of the tableting machine was filled manually with the weighed amounts of the fast release component and the core tablet (**Table 1**) prior to compression. Half of the fast releasing powder was put into the die to make a powder bed, on the centre of which a core tablet was placed. Then the other half of the powder was added to cover the core tablet. The formulations differed in the type and concentration of polymer used in the preparation of the core tablet. Compressed core tablet systems were prepared by direct compression, with flat-tip punches and dies of 13-mm diameter using rotary tablet punching machine (Rimek RSB-4 mini press, Cadmach, Ahmedabad).

Table 1: Composition of dual component system

S.No	INGREDIENTS	FORMULATION (mg)					
		F1	F2	F3	F4	F5	F6
	Fast releasing component						
1	Aceclofenac	100	100	100	100	100	100
2	Micro crystalline cellulose	280	280	280	280	280	280
3	Cross carmellose sodium	20	20	20	20	20	20
	Slow releasing component						
4	Aceclofenac	100	100	100	100	100	100
5	HPMC K 100 M	100	150	X	X	X	X
6	Ethyl cellulose	X	X	100	150	X	X
7	Xanthan gum	X	X	X	X	100	150

EVALUATION OF TABLETS:

i) Fourier Transform Infra-Red spectroscopy: Compatibility studies of pure drug, polymers and the physical mixture of drug and polymers were carried out using FTIR Spectrophotometer (Shimadzu FT-IR 8400-S) in the scanning range of 400-4000cm^{-1} by KBr disc method.

ii) Physical characterization of core tablets and compressed core tablet system.

Core tablets and compressed core tablet systems were characterized for weight variation, thickness, hardness and friability.

iii) In-vitro drug release profile studies.

The *in-vitro* drug release test were performed by USP paddle type II apparatus at 100 rpm using 900 ml of phosphate buffer pH 7.4 as dissolution medium maintained at a temperature of 37^{0}C ± 0.5^{0}C. At designated time intervals 1 ml samples were withdrawn and replaced with 1ml of fresh dissolution medium to maintain sink condition. The samples were diluted suitably and analyzed spectrophotometrically (UV- 1601, Shimadzu, Japan) at 242 nm using pH 7.4 phosphate buffer as blank.

RESULTS:

Tables 2 and 3 list the physical properties (weight, thickness, hardness and friability) of the core tablets and compressed core tablet systems, respectively.

Table 2: Physical properties of the non-compressed core tablet

S. No	Formulation code	Weight variation (mg)*	Hardness (kg/cm^2)*	Friability (%)*	Thickness(mm)*
1	F1	199.5±14.68	4.97±0.02	0.099±0.0	3.376±0.05
2	F2	195.0±8.27	4.99±0.01	0.515±0.02	3.426±0.05
3	F3	203.0 ±11.27	4.05±0.08	0.099±0.01	3.483±0.05
4	F4	204.0±9.94	3.99±0.01	0.500±0.0	3.516±0.05
5	F5	196.25±8.06	5.98±0.02	1.300±0.10	3.630±0.01
6	F6	196.11±9.16	6.01±0.02	1.440±.04	3.586±0.05

***Average of 3 determinations**

Table 3: Physical Properties of the Compressed Core Tablet Systems

S. No	Formulation code	Weight variation (mg)*	Hardness (kg/cm^2)*	Friability (%)*	Thickness(mm)*	% Drug Content*
1	F1	610.00±15.49	5.90±0.10	0.9966±0.05	4.960±0.05	85.00±1.00
2	F2	598.82±16.91	4.93±0.05	0.8233±0.05	5.100±0.10	95.00±1.00
3	F3	595.71±19.01	5.10±0.10	0.3400±0.010	5.233±0.05	102.00±1.00
4	F4	602.85±19.10	5.16±0.15	0.1566±0.005	5.200±0.10	101.33±0.57
5	F5	606.875±15.79	4.90±0.11	0.3333±0.015	5.336±0.05	105.66±0.57
6	F6	607.14±16.37	5.10±0.10	0.1700±0.010	5.836±0.05	99.00±1.00

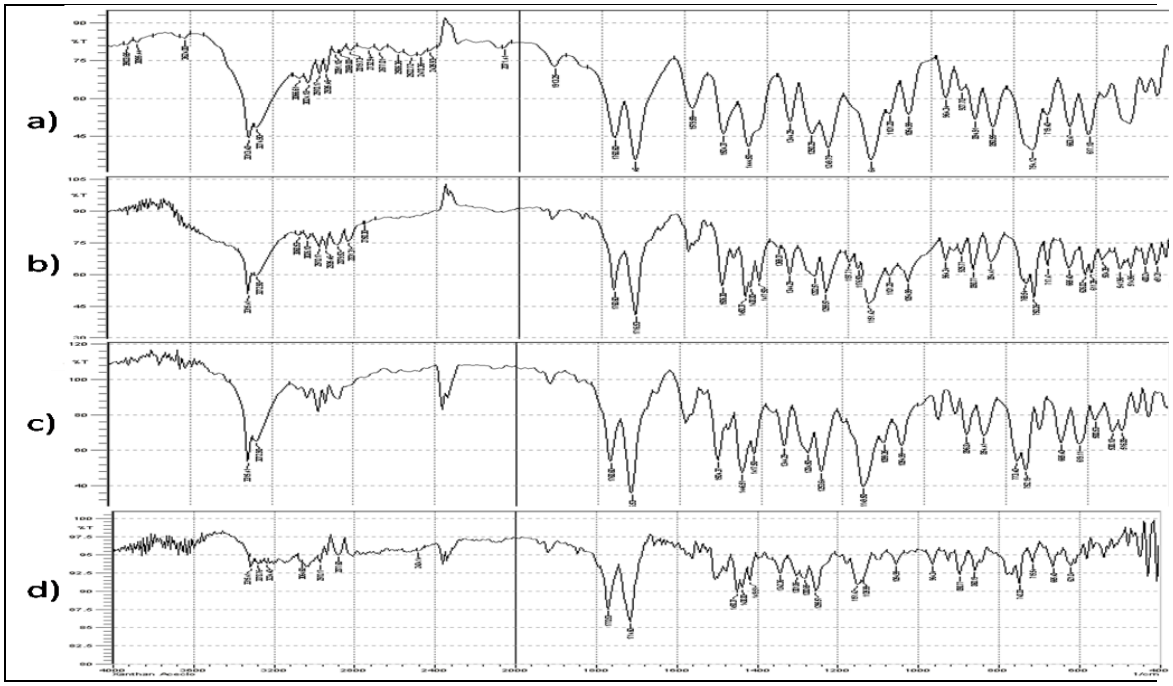
***Average of 3 determinations.**

FT-IR studies:

FT-IR was done to evaluate interactions between the drug and polymer. IR spectra for pure drug, polymers HPMC, ethyl cellulose, Xanthan gum and physical mixture of drug and polymers individually were shown in the figures 1a, 1b, 1c and 1d. The IR spectra of aceclofenac had shown characteristic peaks at 754.12cm^{-1}, 617.18cm^{-1} (C-Cl stretch), 1718.46cm^{-1} (C=O stretch), 1249.79cm^{-1}, 1145.64cm^{-1}(C-0 stretch), 1054.99cm^{-1}(C-N stretch) and 1448.58cm^{-1}(C-C stretch in ring) respectively. The IR spectra of physical mixture of aceclofenac and polymers had exhibited similar characteristic peaks of pure drug which confirmed that there was no interaction between the drug and the polymers.

Figure 1: FT-IR Spectra

a) Infra-red spectra of aceclofenac b) Infra-red spectra of physical mixture of aceclofenac with HPMC c) Infra-red spectra of physical mixture of aceclofenac with ethyl cellulose d) Infra-red spectra of aceclofenac with Xanthan gum.



IN-VITRO DISSOLUTION STUDY AND CURVE FIT DATA:

The *in-vitro* dissolution profile of aceclofenac from compressed core tablets were analysed in phosphate buffer pH 7.4 at 242 nm. The release profile of the compressed core tablets of aceclofenac prepared using HPMC, ethyl cellulose and Xanthan gum were shown in figure 2 and the curve fit data is shown in **table 4**.

Figure 2: *In-vitro* dissolution of dual component delivery system of various formulations

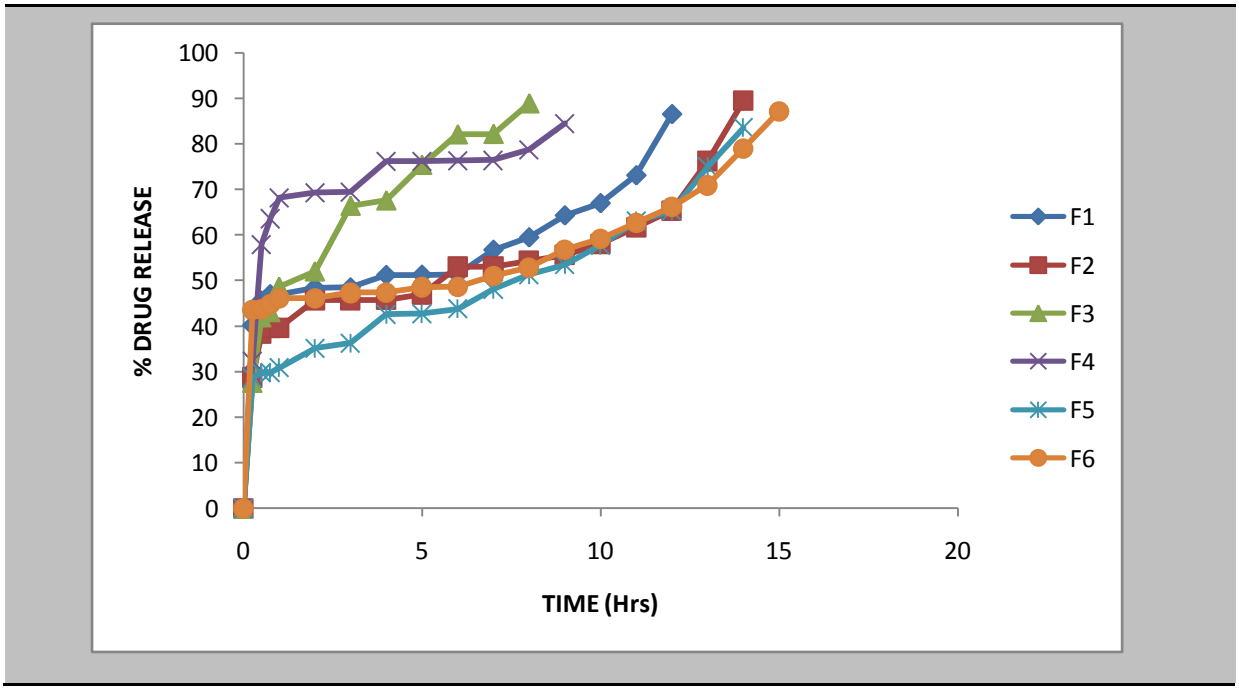


Table 4: Curve fit data for the prepared formulation

S. No	Formulation code	R^2	K	Best fit model
1	F1	0.9999	452.0026	Peppas
2	F2	0.6638	66.7531	Peppas
3	F3	1.0000	364.9744	Peppas
4	F4	1.0000	370.4519	Peppas
5	F5	0.7263	60.7891	Peppas
6	F6	0.7613	63.8204	Peppas

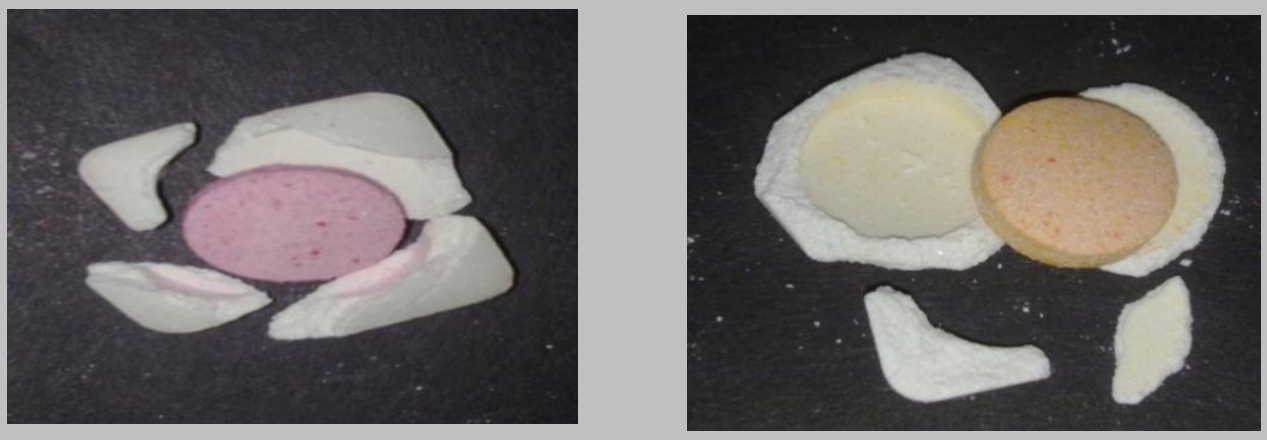
DISCUSSION

Aceclofenac as immediate release layer were prepared by using cross carmellose sodium as super disintegrant. To control the drug release, in the prolonged release component of the biphasic system, ethyl cellulose Xanthan gum and HPMC were used as sustained release agents in the core tablet. In matrix drug delivery systems, the characteristics of the matrix-forming agent play an important role in the release mechanisms of the drug. Among the hydrophilic polymers, HPMC is one of the carriers most commonly used for the preparation of oral controlled drug delivery systems because of its ability to swell upon gellification once in contact with water. The gel becomes a viscous layer, acting as a protective barrier to both the influx of water and the efflux of the drug in solution[8-9]. On the other hand, inert polymers such as ethyl cellulose can serve as alternatives to the swelling polymers by forming inert matrices, with no physiological action, stable at different pH values and moisture levels that control the diffusion of the drug toward the surface of the matrix prior to release.

Both the non-compressed and the compressed core tablets were produced with small weight variations and uniform thickness. Conventional compressed tablets that lose less than 1% of their weight are considered acceptable as per the pharmacopoeial standards. In the present study, the friability was 0.82%, 0.33% and 0.82% for compressed HPMC, ethyl cellulose and Xanthan gum core tablet systems respectively.

The composition of the immediate release component should provide a hard and rapidly disintegrating tablet at low compression forces and the compaction of the core tablet should not affect the integrity or release behaviour of the slow release component. It should be noted that the compaction should not cause the core tablet into a non disintegrating matrix. Upon visual inspection of fractured surfaces after crushing revealed that the core tablet in the compressed system was similar to the original non compressed core tablet. This lack of fragmentation or damage demonstrated that tablet cores were prone to keeping their integrity when compacted and remained as coherent individual units after the process of tableting (**Figure 3a and 3b**). Thus, during the axial compression in the die, although the core tablet was stressed from several directions simultaneously, it resisted the strong compression force applied.

Figure 3: a) Equatorial fracture showing the surfaces of the compressed HPMC core tablet system. b) Equatorial fracture showing the surfaces of the compressed ethyl cellulose core tablet system.



Ideally, the release of the drug should not be affected by the compaction. The main purpose of the compaction of the core tablet is to ensure it has the same properties as the original core. Structural changes like deformation of the core tablet should be minimized, particularly by the application of the compaction force, to avoid modification of the drug release. The percentage drug release from formulations F1 and F2 was 86.5% and 89.45% at the end of 12hr. The percentage drug release from F3 and F4 was 88.88% and 84.45% at the end of 9hr and percentage drug release from F5 and F6 was 83.58% and 87.15% at the end of 14hr. From the above observation it can be noted that as the concentration of polymer was increased the rate of drug release was prolonged. It can be noted that Xanthan gum is a better release retarding agent than HPMC and ethyl cellulose, as it delayed the release of the drug for more than 12hrs. All the prepared formulations showed the R^2 values between 0.6638 to 1.0000 and the drug release mechanism was found to be peppas model that confirmed that the possible drug release would be by diffusion process.

CONCLUSION

The bi phasic dual component delivery system was characterized by a initial immediate release phase corresponding to the drug present in the external layer followed by a period of slow release corresponding to the drug present in the central core tablet. The results obtained with the dissolution test showed that the release profile is dependent on both the type and amount of polymer in the core tablet. After disintegration of the bi-phasic system, Xanthan gum was able to modulate the release of aceclofenac for more than 12hrs with a dissolution profile similar to that of a matrix tablet. Thus a bi-phasic quick/slow delivery system was developed that retarded the release profile thereby reducing the dosing frequency and improving patient compliance.

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