Research Article

Fabrication and *Invitro* Evaluation of Matrix Core Tablet of Navirapine as A Bi Phasic Dual- Component Delivery System

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ABSTRACT

The main motto of present research was to develop a dual phasic tablet of Navirapine using super disintegratant micro crystalline cellulose for the fast release layer and water immiscible polymers such as Ethylcellulose, Xanthum gum for the sustaining layer. A dual component tablet made of a sustained release tabulated core and an immediate release tabulated coat was prepared by direct compression. Both the core and the coat contained a model drug Navirapine.. The sustained release effect was achieved with polymers like (HPMC) hydroxypropyl methylcellulose, (EC) Ethyl cellulose and Xanthan gum (XG) to sustain the release of Navirapine drug. The in-vitro drug release profile from these tablets showed the desired biphasic release behavior of Navirapine, 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: Dual component system ethylcellulose, immediate release, navirapine, xanthan gum.

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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 [2]. In a bi-layer configuration, the immediate release layer of the bi-layer tablet has worked as the loading dose and the sustained release layer has maintained the therapeutic plasma drug concentration for prolonged time. 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. 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 [3]. Nevirapine, a dipyridodiazepinone, is the prototypic member of a class of antiretroviral

compounds referred to as nonnucleoside reverse transcriptase inhibitors. Nevirapine is a potent and selective noncompetitive inhibitor of the reverse transcriptase enzyme, an important therapeutic target for the treatment of HIV-1 infection. The activity of nevirapine does not compete with template or nucleoside triphosphates, nor does it inhibit HIV-2 reverse transcriptase or any of the human DNA polymerases. In completed clinical studies, nevirapine has demonstrated antiretroviral activity both as monotherapy and in combination with nucleoside analogues... Nevirapine has a favourable pharmacokinetic profile, becomes widely distributed throughout body tissues including the central nervous system, and is active in the adult at an oral dose of 200 mg administered twice daily after a two week lead-in dose of 200 mg per day. There are no significant drug-drug interactions noted with the nucleoside reverse transcriptase inhibitors; however, because nevirapine induces cytochrome P450 isoenzymes, the currently used protease inhibitors may undergo more rapid rates of metabolism.. Resistance to nevirapine is rapid when administered as a monotherapy but this is altered and made less clinically relevant when nevirapine is given in combination with one or more of the nucleosides. Nevirapine has a safety profile that does not overlap with other antiretroviral therapies, the most common treatment-limiting reaction being rash. Nevirapine is an active antiretroviral agent with excellent biodistribution and good potential for use in combination with other antiretrovirals across the spectrum of HIV disease as well as in selected populations. [4].

Nevirapine falls in the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of antiretroviral—Both nucleoside and non-nucleoside RTIs inhibit the same target, the reverse transcriptase enzyme, an essential viral enzyme which transcribes viral RNA into DNA. Unlike nucleoside RTIs, which bind at the enzyme's active site, NNRTIs bind allosterically at a distinct site away from the active site termed the NNRTI pocket. [5].

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 NAVIRAPINE an ideal candidate for biphasic drug delivery [5].

MATERIALS & METHODS

NAVIRAPINE, a gifted sample obtained from **HETERO DRUGS**, HYDERABAD, INDIA. Micro crystalline cellulose, Cross carmellose sodium, HPMC K 400 M, Ethyl cellulose, Xanthan gum. All the materials used were of analytical grade and procured from commercial sources.

Experimental Method:

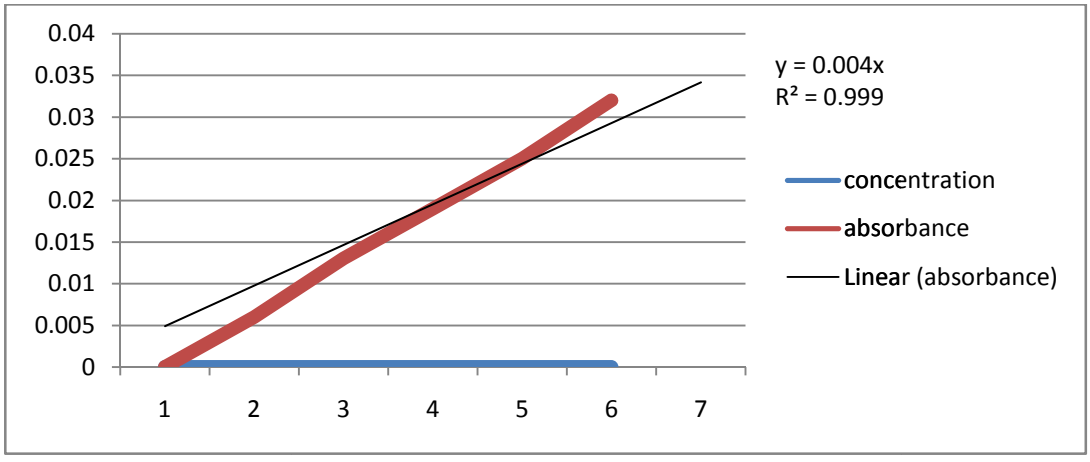
1. **Formulation of slow release component** Core tablets were prepared from mixtures of Navirapine and matrix controlling agent like HPMC, ethyl cellulose and Xanthan gum by direct compression. All the materials were sieved through 120 mesh and tablets were prepared by direct compression method using 6 mm flat punches in a rotary tablet punching machine.
2. **Formulation of fast release component** The fast release component contained model drug Navirapine. 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 [5].

Table 1: Composition of dual component system (mg)

S. NO	F1	F2	F3	F4	F5	F6
			Immediate release components			
Navirapine	100	100	100	100	100	100
Cross carmellose sodium	50	50	50	50	50	50
Micro crystalline cellulose	250	250	250	250	250	250
			Sustained release components			
Navirapine	100	100	100	100	100	100
HPMC 400K	50	x	x	100	x	x
Ethylcellulose LR	x	50	x	x	100	x
Xanthum gum LR	x	x	50	x	x	100

Standard graph of Navirapine :



concentration	absorbance
0ppm	0
2ppm	0.006
4ppm	0.013
6ppm	0.019
8ppm	0.025
10ppm	0.032

Evaluation of Tablets: (listed in Table: 2)

Weight Variation

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight, standard deviation and relative standard deviation were reported. The tablet compression machine was suitably adjusted to produce tablets of uniform weight [6].

Tablet thickness

The thickness in millimetres (mm) was measured individually for 10 preweighed tablets by using a starrett portable dial hand micrometer. The average thickness, standard deviation and relative standard deviation were reported [6].

Tablet hardness

Tablet hardness was measured using a Key hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kilopond (KP) and the average hardness, standard deviations, and relative standard deviations were reported. Tablets hardness was checked at the start and during the compression process to control an acceptable range of tablet hardness [6].

Uniformity of dosage units

This was assessed according to the USP requirements for content uniformity. The batch meets the USP requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85 % to115 % of the label claim and the RSD is less than or equal to 6 %. According to the USP criteria, if one of these conditions is not met, an additional 20 tablets need to be tested. Not more that 1 unit of the 30 tested should be outside the range of 85 % and 115 % of the label claim and no unit outside the range of 75 % to 125 % of label claim. For all RSD should not exceed 7.8 % [7].

Friability

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets were rotated at 25 rpm for 4 minutes (100 rotations) in the tablet friabilator. The tablets were then will dust and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss shown in from the original tablets [6].

In-vitro Disintegration time:

A tablet was placed in each of the six tubes of the basket. Suspend the assembly in water maintained at a temperature of 370c ± 20c and operate the apparatus, simultaneously note the time taken taken to disintegrate completely by using stop watch [7].

In-vitro Drug release profile:

The *in-vitro* drug release test were performed by USP paddle type II apparatus at 150 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 at 230 nm.

FTIR studies:

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.

RESULTS AND DISCUSSION: Tables 2 listing out the physical properties (weight, thickness, hardness and friability) of biphasic system.

Table 2: Physical properties of the biphasic drug of navirapine

s.no	Formulation code*	Weight variation(mg)*	Hardness(kg/cm²)*	Friability* (%)	Thickness* (mm)	Drug content (%)
1	**F1**	540.00±15.49	4.80±0.10	0.9776±0.05	4.960±0.05	85
2	F2	528.82±18.91	4.73±0.05	0.8833±0.05	5.100±0.10	95
3	F3	5305.71±17.01	4.8±0.10	0.8400±0.010	5.233±0.05	102.
4	F4	602.85±19.10	5.16±0.15	0.1566±0.005	5.200±0.10	101.
5	F5	590.875±15.79	4.90±0.11	0.3733±0.015	5.336±0.05	105
6	F6	587.14±13.37	5.10±0.10	0.1600±0.010	5.836±0.05	99

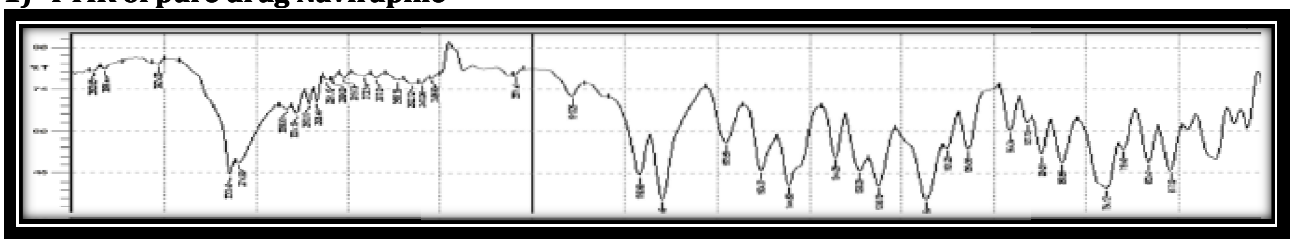
(*= Avg of 3 mean)

FTIR analysis:

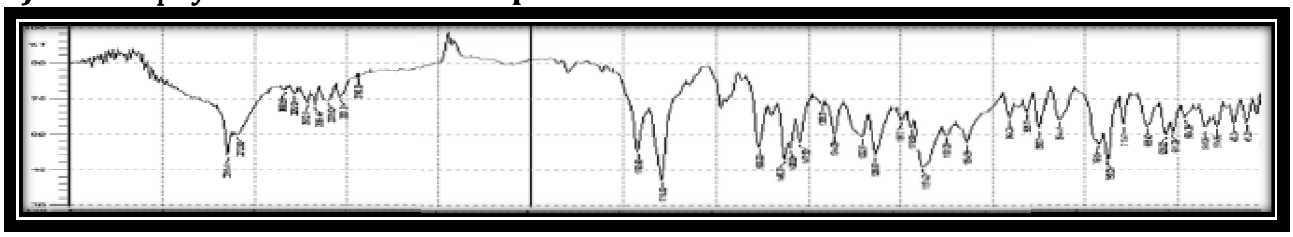
FT-IR was done to evaluate interactions between the drug and polymer. IR spectra for pure drug, polymers HPMC, ethyl cellulose, Xanthan gum and physical mixture of drug and polymers individually were shown in the figures.1

Figure 1:

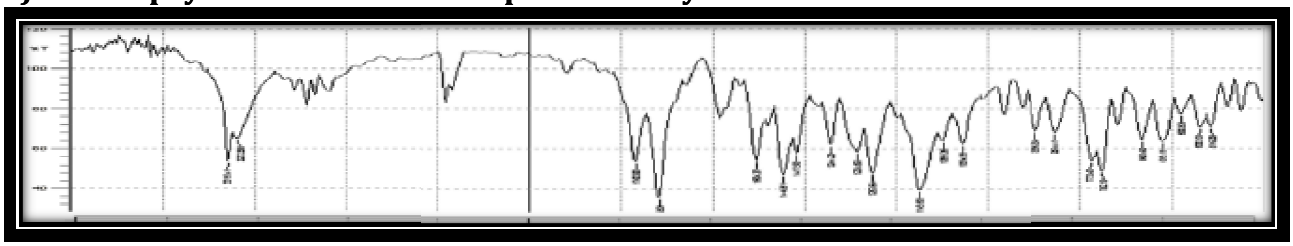
1) FTIR of pure drug Navirapine



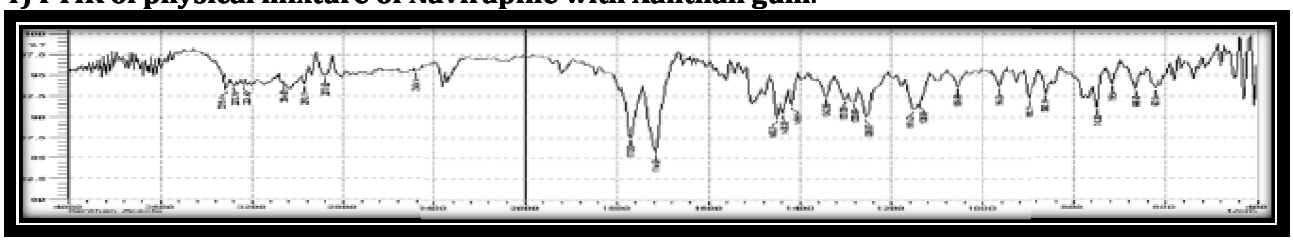
2) FTIR of physical **mixture of Navirapine with HPMC**



3) FTIR of physical mixture of Navirapine with ethyl cellulose



4) FTIR of physical mixture of Navirapine with Xanthan gum.



***IN-VITRO* DISSOLUTION STUDY:**

The *in-vitro* dissolution profile of navirapine from compressed core tablets were analysed in phosphate buffer pH 7.4 at 230 nm. The release profile of the compressed core tablets of navirapine prepared using HPMC, ethyl cellulose and Xanthan gum were shown in (**figure 2, figure 3, figure 4**)

Fig. 2: Comparative dissolution profile of F1 to F6 batches of Only immediate release pattern

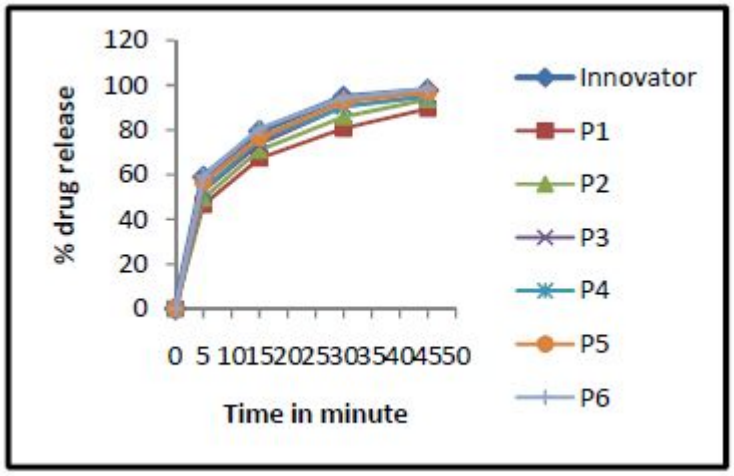


Fig. 3: Comparative dissolution profile of F1 to F6 batches of only sustained release pattern

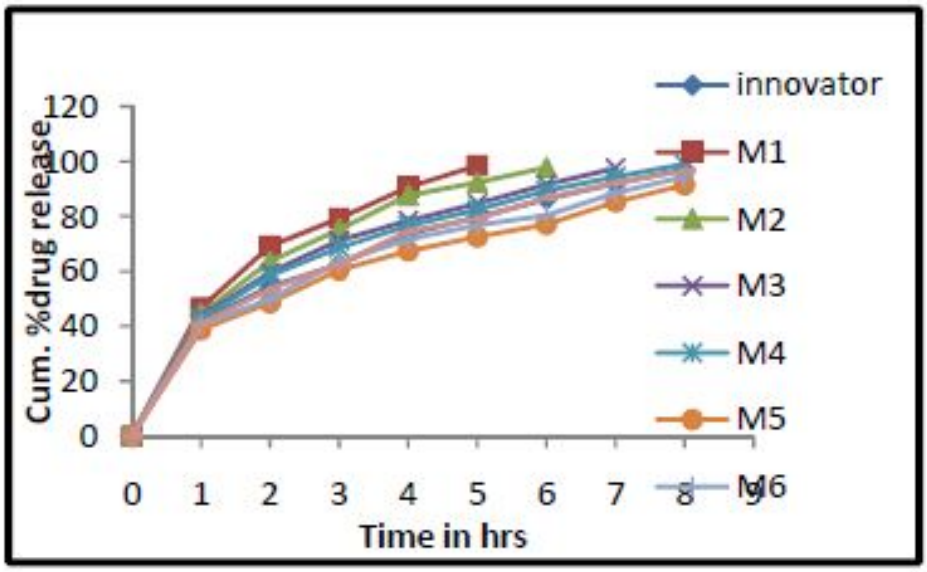
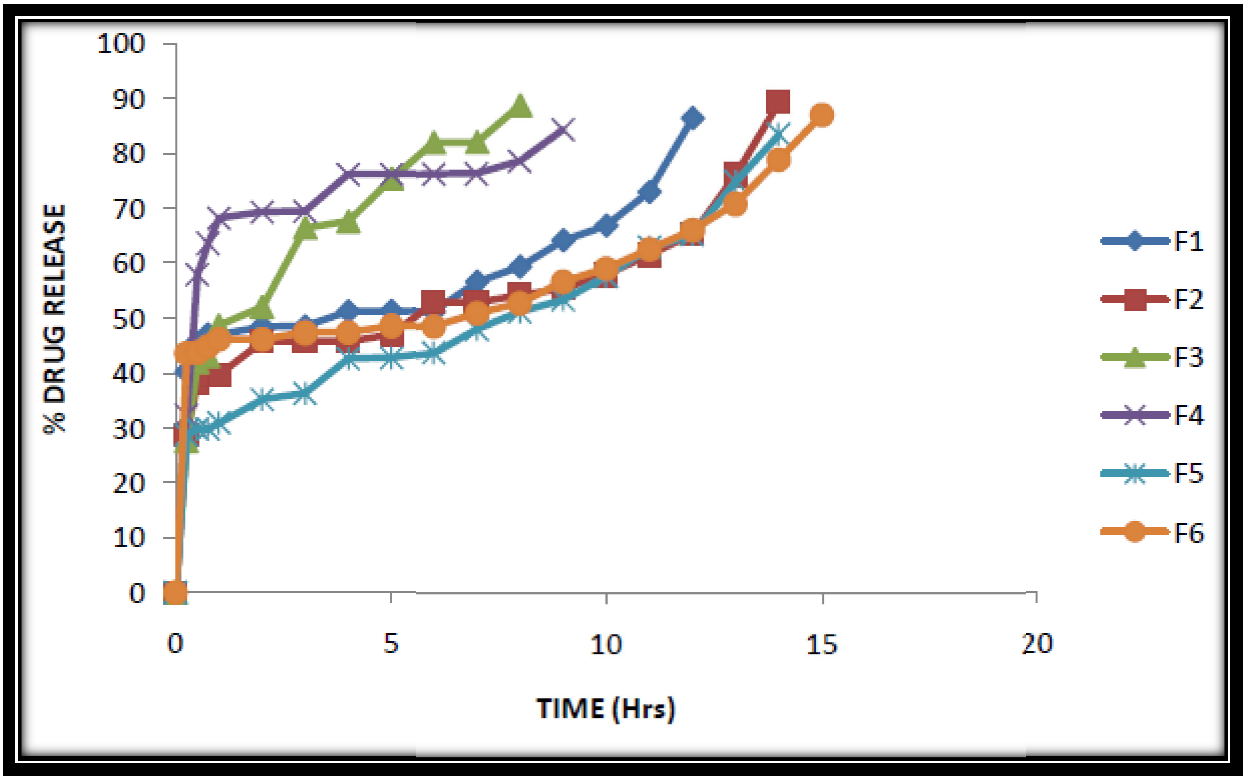


Fig 4: *In-vitro* dissolution of dual component delivery system of various formulations (F1- F6)



DISCUSSION

Both immediate release and sustained release formulation are prepared and their drug release pattern has been shown in fig 2, fig 3, (**Fig 4**) and contain in a single dosage form. The study describes the formulation of both immediate and extended release drug for increased therapeutic efficacy and patient convenience.

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.

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 behavior of the slow release component. The percentage drug release from formulations F1 and F2 was 86.5 % and 89.45 % at the end of 12 hr. 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 12 hrs.

CONCLUSION

The present research was carried out to develop a bilayer tablet of Navirapine using superdisintegrant micro crystalline cellulose and cross carmellose sodium for the fast release layer and ethyl cellulose, HPMC and xanthum gum for the sustaining layer. Dual phasic component delivery system showed an initial burst effect to provide the loading dose of the drug, followed by sustained release for 12 h, indicating a promising potential of the navirapine biphasic delivery system as an alternative to the conventional dosage form.

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