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Research Article

FORMULATION AND EVALUATION OF NEVIRAPINE SUSTAINED RELEASETABLETS WITH DIFFERENT HYDROPHILIC POLYMERS

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Abstract: The present study was aimed to develop generic formulation of sustained release (SR) tablets of Nevirapine anhydrous (NVP) using different hydrophilic polymers in order to increase the gastric residence time (GRT) and comparison of natural and synthetic polymer for better sustained effect. The drug: polymer interaction was determined by IR spectroscopic method. Nevirapine NVP (SR) tablets were prepared by wet granulation method by employing various hydrophilic polymers like HPMC K4M, K100M, xanthan gum and tragacanth. They are prepared by using water as a granulating fluid. The prepared granules were evaluated for various physicochemical parameters as per Indian pharmacopoeia (I.P) and compressed into tablets. In-vitro release profiles of NVP from SR tablets were determined using USP apparatus type I (Basket), at 50 rpm and bath temperature of 37ºC. Tablets dissolution was carried out in 900ml of media (0.04M sodium phosphate buffer pH 6.8 containing 2% SLS). Samples were withdrawn at predetermined time intervals up to 12 Hrs and analyzed using UV detector at a wavelength of 282nm. Among these all formulations (F1 to F5), batch F2 was best formulation and showed very slow release i.e. 76.02% in 12 h and it is nearly similar with innovator product (i2=82.00). The drug release of the other formulation was higher from the innovator product. So the formulation with HPMC K4M shows better sustained release effect than the other polymers. The developed SR tablets of NVP may be used for sustained drug release for at least 12hrs, thereby improving the bioavailability and patient compliance.

Key words: Nevirapine, sustained release tablet, HPMC, hydrophilic polymer.

INTRODUCTION

Despite tremendous advancements in drug delivery the oral route remains the preferred route of administration of therapeutic agents because of low cost of therapy and ease of administration lead to high levels of patient compliance. But the issue of poor bioavailability (BA) of orally administered drugs is still a challenging one; though extensive advancements in drug discovery process are made [3] Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 hours. The sustained release drug delivery systems are useful in such application [1, 2]. Advantages of sustained release tablets are that they can often be taken less frequently than instant release formulations of the same drug, and that they keep steady levels of the drug in the blood stream [4].

Nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immuno-deficiency virus type1 (HIV-1), block polymerase activity after binding directly to the HIV-1 reverse transcriptase leading to disruption of the enzyme' s catalytic site[5]. Anti retroviral therapy with NVP has demonstrated significant activity in HIV infected patients in combination drug with highly active anti retroviral therapy. Nevirapine is weak base with low water solubility, and belongs to BCS class II drug. In human, NVP is well absorbed orally with an estimated absolute bioavailability of about 90%. Generally NVP immediate release 200mg tablets are taken twice a day. A Nevirapine sustained release (NVP SR) once daily tablet formulation could be used to maintain optimum peak plasma concentration for effective viral suppression. US-FDA approved Nevirapine sustained release tablet (Innovator: Boehringer Ingelheim). The present study was aimed to developed generic formulation of sustained release tablets of Nevirapine (NVP) using controlled release polymer [6]. The selection of release retarding excipients is necessary to achieve a constant in-vivo input rate of the drug. The matrix tablets composed of drug and the release retarding materials offer simplest approach in designing a sustained release system. Number of studies showed the use of hydrophilic matrices to formulate the sustained release dosage forms of

different drugs. Various types of polymers are used in the present study like HPMC, xanthan gum, traganth. Among them HPMC is pH independent polymer, widely used for sustained release dosage form and also found in Innovator's tablets [7].

MATERIALSANDMETHODS

Nevirapine Anhydrous was procured from (Cipla Ltd, Mumbai), Lactose monohydrate (DMV, Germany), HPMC K4M and K100M (DOW chemical), Magnesium Stearate (Mallinckrodt), Innovator tablet i.e Viramune XR (boeringer Ingelheim) and all other chemicals and ingredients for analysis were procured as analytical grade.

Preparation of Nevirapine Anhydrous ER Tablet

Tablet formulations were prepared by wet granulation method because of poor flow and high dose of nevirapine anhydrous. An aqueous granulation process was adopted over non aqueous granulation because of its compatibility with API and excipients and also due to its cost effectiveness to prepare sustained release tablet. Proportion of API and polymer of different formulations are given in Table1. Nevirapine anhydrous, lactose mono hydrate and HPMC was co-sifted through sieve no.30 and this sifted material was granulated with water in rapid mixture granulator (RMG). The wet mass was dried at 50ºC in Fluid Bed Equipment (FBE). Dried granules were sized through sieve No.20, and mixed with magnesium stearate in bin blender. Tablets were compressed using rotator tablet machine with 19mm×9.3mm oval, biconvex tablets [11].

Table1. Formulation of Nevirapine SR tablets

Ingradients mg/tab	FI HPMC (4K)	F2 HPMC (4K)	F3 HPMC (K100M)	F4 XANTHANGUM	F5 TRAGACANTH
NVP	200	200	200	200	200
Lactose monohydrate	90	85	90	90	90
Polymer conc'	105	110	105	105	105
Magnesium sterate	5	5	5	5	5
Purified water	q.s	q.s	q.s	q.s	q.s
Tablet weight	400	400	400	400	400

F1, F2 with different concentration of HPMC (4k)
F3 with HPMC k100m
F4 with xanthan gum
F5 with tragacanth gum

Drug-Polymer Interaction Study

The pure drug and prepared floating tablet were subjected to IR spectroscopic study using FT-IR spectrophotometer (IRAffinity-1, Shimadzu). The spectra were scanned over the wave number range from 4000 – 400cm-1. The pellet press techniques were used for sample testing's.

EVALUATION OF GRANULES [18]

Low Bulk Density:

LBD is determined by measuring the volume of powder that has been passed through a screen, into a graduated cylinder. A quantity of 100gr of sample from each formula was introduced into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to tap 500, 750 and 1250 taps and read corresponding values V500, V750 and V1250, to the nearest milliliter. LBD was calculated using in the following formula.

LBD= weight of powder (gm)/volume of packing

Tapped Bulk Density:

TBD is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped, and volume readings are taken little further volume change is observed. The tapped density was calculated using in the following formula.

TBD= weight of powder (gm)/volume of packing

Compressibility Index:

The compressibility index of the granules was determined by measuring both the bulk volume and tapped volume of a powder. Compressibility index was calculated using in the following formula.

CI (%)= (TBD -LBD/TBD) ×100

Hausner Ratio:

Hausner Ratio was calculated using in the following formula.

Hausner ratio= TBD/LBD

The physical properties of granules are shown in Table.2

Table 2: Physical Evaluation Granules

Batch no	Low bulk density gm/ml	Tapped bulk density gm/ml	Compressibility index (%)	Hausner's ratio
F1	0.401	0.528	13.12	1.01
F2	0.486	0.564	13.82	1.16
F3	0.490	0.570	14.04	1.16
F4	0.494	0.576	14.23	1.17
F5	0.497	0.562	11.57	1.13

EVALUATION OF TABLETS

All prepared tablets were evaluated for weight variation, hardness, friability and thickness. Results are shown in Table 3.

Weight Variation Test

Twenty tablets were selected at random and their average weight was determined using electronic balance (type sartorius). The tablets were weighed individually and compared with average weight [14].

Hardness and Friability Test

Friability of tablets was checked by using Roche Friabilator. The device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets at distance of 6 inches with each revolution. Pre weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Tablet requires certain amount of hardness to withstand mechanical shock. Tablet hardness has been defined as "the force required to break a tablet in a diametric compression test. The Pfizer tester and Monsanto tester are mainly used to measure tablet hardness [14].

Thickness

Thickness is measured by sliding caliper scale (Vernier callipers). Tablet thickness should be controlled within 5% variation of a standard value [20].

***In-Vitro* Drug Release Study**

Due to the limited solubility of NVP in conventional buffers, pH 6.8 phosphate media, 2% sodium lauryl sulphate is used as dissolution media to achieve greater bio relevance but without sink conditions as per USFDA guideline. Finally, in-vitro release profiles of NVP from SR tablets were determined using USP apparatus type I with 40 mesh basket. The basket's rotational speed was kept at 50 rpm and bath temperature was maintained at 37ºC. Tablet dissolution was carried out in 900ml of media (0.04M sodium phosphate buffer pH 6.8 containing 2% SLS). Samples were withdrawn at predetermined time intervals up to 12Hrs and analyzed using UV detection at a wavelength of 282nm. Dissolution profile was compared with innovator tablets with the help of similarity factor (i2) calculation [19].

Stability Studies

Final formulation i.e. F2 was kept for stability studies at 40ºC/75% RH for 3 months and dissolution studies, hardness friability were carried out. Results for dissolution studies of stability batches are shown as Figure 2 and results for hardness and friability studies are tabulated in Table 4.

Table 3: Evaluation of tablets

Batch No	Weight (mg)	Hardness(N)	Thickness(mm)	Friability (%)
F1	1060±3%	162-177	6.97±4	0.135
F2	1060±2%	168-179	7.01±5	0.126
F3	1060±2%	160-171	6.95±4	0.144
F4	1060±3%	163-175	6.97±5	0.124
F5	1060±4%	160-178	6.98±4	0.121

All values represent mean ±SD

Table 4: Evaluation of formulation F2

Condition	Hardness (N)*	Frability(%)
Initial F2	162-177	0.135
1Month 40ºC/75%RH	160-178	0.144
2Month 40ºC/75%RH	161-175	0.141
3Month 40º/75%RH	160-179	0.176

*Hardness of 20 tablets given in range

RESULT AND DISCUSSION

Drug polymer interaction study:

Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between NVP and the polymers used. Drug has given peaks due to furan ring, secondary diamine, alkene and two peaks due to nitro functional groups. Form the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. (Figure no 2 and 3)

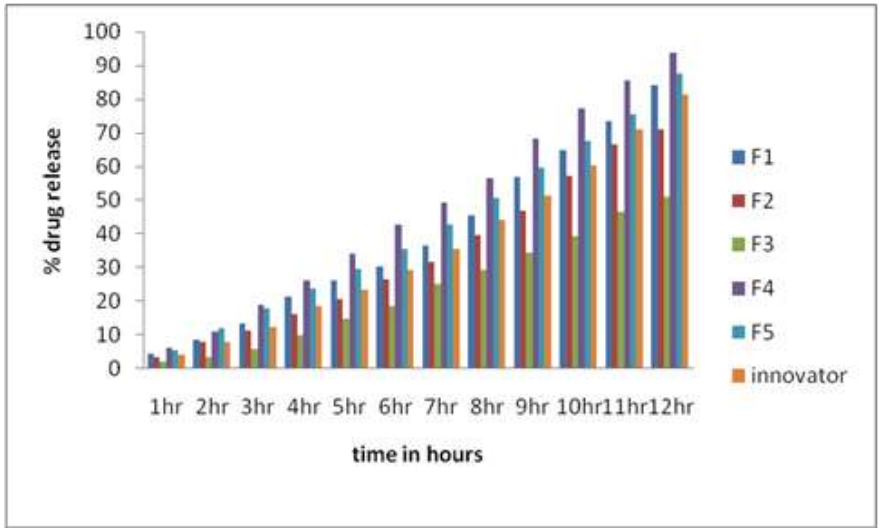

Fig -1: comparative study of in-vitro drug release of different formulations

Nevirapine sustained release tablet's use for anti retroviral therapy in combination with other antiretroviral drugs. Immediate release nevirapine tablets require a frequent administration of twice tablets of 200mg daily dose for best possible effect. Hence, it can be considered as better candidate for development of generic NVP SR tablets. Five formulations of NVP SR tablets were prepared by wet granulation. The formulations differed mainly in the hydrophilic polymer and grade of the release controlling polymer 20 % of all formulations except F2 (25%). Here F1, F2 is made up with K4 HPMC, F3 with K100M HPMC, and F4 with xanthine gum and F5 with traganth respectively. All formulations contained 200mg nevirapine anhydrous and total weight was similar (400mg). Lactose monohydrate used as the diluents and magnesium stearate used as lubricants, the selection of excipients was done on the excipient compatibility study.

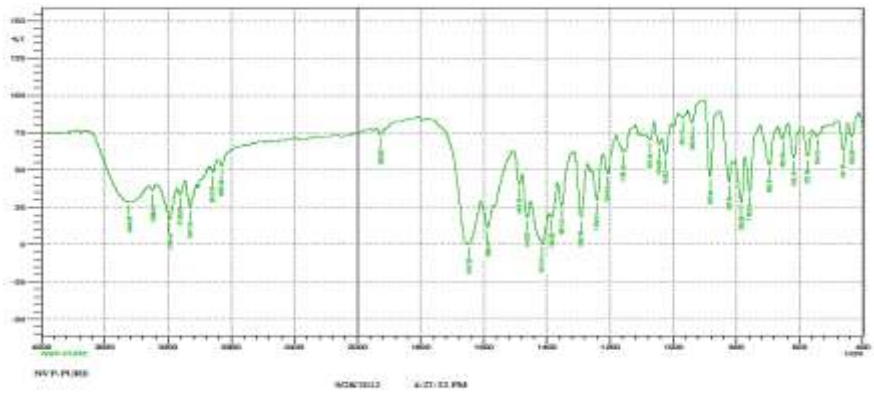

Figure no-2: FT-IR Graph of Nevirapine pure drug

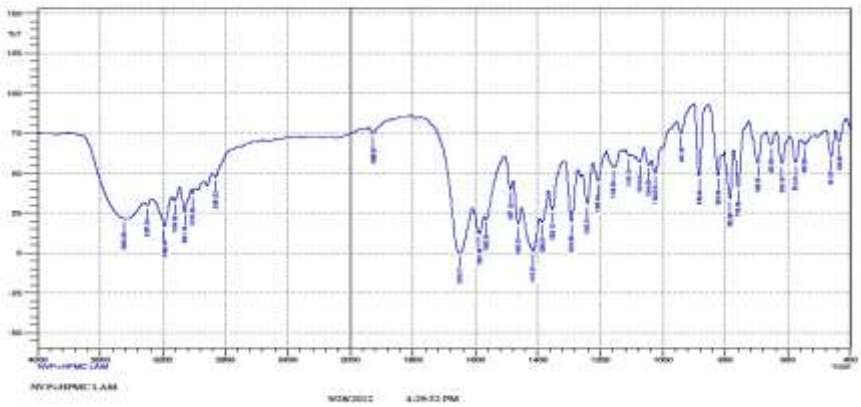

Figure no-3: FT-IR Graph of Drug with HPMC K4M

The granules of different formulation were evaluated for LBD, TBD, and compressibility index and hausner ratio. The LBD and TBD of granules ranged from 0.471-0.497 gm/ml and 0.528-0.576 gm/ml respectively and compressibility index of formulation F1 to F5 were below 25% indicating good flow property (Table 2). All these results indicate that formulation granules possessed satisfactory flow properties and compressibility. The physical properties of compressed tablets, such as hardness, thickness, friability and weight variation were determined as per Indian pharmacopoeia (I.P). The results obtained are shown in Table.3. It is observed that all physical parameters of sustained release tablet were within acceptable limit and friability of all formulation was less than 1%. It can be observed that weight variation of all formulations were well in the range of official limit.

In-vitro drug release profile of all formulations of nevirapine sustained release tablet is compared with marketed formulation (Innovator) as shown in figure1.

It was observed that drug release was fast

in case of formulation F1 as compared with innovator (85.32%). In case of formulation F4 and F5 release rate of drug from matrix tablets was found to be very fast as compared to innovator product (94.79%, 88.73%). In case of formulation F3, release rate of drug from matrix tablets was found to be retained because of higher viscosity grade of polymer (HPMC K100M) and very slow as compared to innovator (51.96%). The drug release profile of formulation F2 and innovator product (marketed formulation) was nearly similar (76.02%, 82%). Further, the formulation F2 was subjected to stress stability study at 40ºC/75% RH for 3 months no much difference was found in dissolution pattern, and hardness and friability as shown Table 4.

CONCLUSION

The present study was attempted to make a generic formulation of nevirapine sustained release 400mg tablet. In-vitro study showed formulation F2 was better than other formulation and it is similar with innovator product. Stability studies carried out at accelerated condition did not show much difference in dissolution, hardness, friability indicating developed formulation is stable. The release kinetics of the formulation F2 shows better sustained release properties as compare to other polymers.

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