Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2015, Volume 3, Issue 6
ISSN: 2321–3647(online)

Design and Characterization of Sustained Release Nevirapine Matrix Tablets Containing Tamarind Seed Polysaccharide

Lalita Naiknaware[1*], Pooja Pawar[1], Sonali kale[1]
1. D.S.T.S.M's college of pharmacy, Solapur-413004.

ABSTRACT

The present study was aimed to develop generic formulation of sustained release matrix tablets of Nevirapine using TSP as a hydrophilic polymer. The tamarind seed polysaccharide was extracted from tamarind kernel powder and this polysaccharide was utilized in the formulation of matrix tablets containing Nevirapine by wet granulation technique and evaluated for its drug release characteristics. TSP is a hydrophilic and rate controlling polymer. Granules were prepared and evaluated for loose bulk density, tapped density, compressibility index and angle of repose, shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations.), *in vitro* drug release and stability studies. All the formulations showed compliance with pharmacopoeial standards. The *in vitro* release study of matrix tablets were carried out in phosphate buffer pH 7.4 for 12hr. Among all the formulations, F5 shows 99.062% better controlled release at the end of 12 hr. The results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. The release data was fitted to various mathematical models such as, Higuchi, Krosmeyer-Peppas, first-order, and zero order to evaluate the kinetics and mechanism of the drug release. The drug release of optimized formulations F5 follows Krosmeyer-Peppas kinetics and the mechanism was found to be diffusion coupled with erosion (non-Fickian diffusion). The stability studies were carried out according to ICH guideline which indicates that the selected formulation were stable.

Keywords: Nevirapine, Extracted tamarind seed polysaccharide, matrix tablet, sustained release, Non-nucleoside reverse transcriptase inhibitors (NNRTI's)

*Corresponding Author Email: pinkynaik007@gmail.com
Received 23 May 2015, Accepted 04 June 2015

Please cite this article as: Naiknaware L *et al*., Design and Characterization of Sustained Release Nevirapine Matrix Tablets Containing Tamarind Seed Polysaccharide. American Journal of Pharmacy & Health Research 2015.

INTRODUCTION

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulation available in the market and preferred by the patients and physician alike. In long-term therapy for the treatment of chronic disease conditions conventional formulations are required to be administered multiple doses and therefore have several disadvantages[1]. The primary benefit of a sustained release dosage form, compared to a conventional dosage form, is the uniform drug plasma concentration and therefore uniform therapeutic effect. Over the past two decades, sustained release dosage forms have significant progress in terms of clinical efficacy and patient compliance. Matrix devices, due to their chemical inertness, drug embedding ability and drug release character, have gained steady popularity for sustaining the release of a drug[2]. Hydrophilic matrices are an interesting option when developing an oral sustained release formulation. The drug release from such matrices can be controlled through their physical properties. Polysaccharides are the choice of materials among the hydrophilic polymers used, because they are nontoxic and acceptable by the regulating authorities. The various polysaccharides used in drug delivery application are cellulose ethers, Xanthan gum, locust bean and guar gum. Another natural polysaccharide, tamarind seed polysaccharide (TSP) obtained from the seed kernel of *Tamarindus indica*, possesses properties like high viscosity, broad pH tolerance, noncarcinogenicity, mucoadhesive nature, and biocompatibility. It is used as stabilizer, thickner, gelling agent and binder in food and pharmaceutical industries. The TSP constitutes about 65% of the tamarind seed components[3]. Nevirapine [NVP], a non- nucleoside reverse transcriptase inhibitor [NNRTI] of human immune-deficiency virus type 1 [HIV-1], block polymerase activity after binding directly to the HIV-1 reverse transcriptase leading to disruption of the enzymes catalytic site. NVP is a 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%. A study conducted on comparison of Nevirapine SR formulation versus Nevirapine immediate release in treatment of native patients, it was found that Nevirapine sustained release formulations dosed once daily has more clinical efficacy[4] than Nevirapine immediate release formulation dosed twice daily. Hence Nevirapine can be suitably formulated as a sustained release matrix tablets owing to its high clinical efficacy when compared to Nevirapine immediate release formulation.

MATERIALS AND METHOD

Tamarind kernel powder, obtained from Gote Ayurvedic shop Solapur, Nevirapine was obtained

as gift sample from Cipla Ltd. (Mumbai), microcrystalline cellulose, magnesium stearate, talc were purchased from SD fine chemicals Mumbai. All other chemicals were of laboratory grade.

Extraction of Tamarind seed powder

To 20 gm of tamarind kernel powder, 200ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800ml of boiling distilled water. The solution was boiled for 20 minutes under stirring condition in a water bath. The resulting thin clear solution was then centrifuged at 5000 rpm for 20 mints. The supernatant was separated and poured into twice the volume of absolute ethanol by continuous stirring. The precipitate was washed with absolute ethanol, diethyl ether, and then dried at 50-60^{o} C under vacuum. The dried material was ground and sieved to obtain granules of different particle size range of 150-75 microns was used for preparation of tablets[5].

Preparation of matrix tablets:

Tablet formulations were prepared by wet granulation method. A non-aqueous granulation process was adopted to prepare Nevirapine tablets. Granules were prepared as follows. Proportion of excipients with drug was as given in Table 1. All ingredients were sifted through sieveno.60 and microcrystalline cellulose was mixed with Nevirapine manually and the obtained blend was mixed with TSP (F1 to F6) to form final blend. PVPK 30 was dissolved in PVA (5% w/v) and used for wet granulation of the final blend. The wet mass was passed through sieve no. 12 and wet granules were dried at 50°C in an oven for 30 mints. Dried granules were sized by passing it through sieve no.16 and lubricated with magnesium stearate and talc for 1 mint. Tablets were compressed using Rotary tablet machine with12.08 mm standard concave punch. Tablet weight was (500 mg) kept constant as shown in table 1.

Table 1: Tablet composition of different formulations of Nevirapine matrix tablet

Formulation no.	Drug (mg/tablet)	Tamarind seed polysaccharide(mg/tablets)	MCC (mg/tablet)	PVP K30 (5%) (mg/tablet)	Talc (mg/tablet)	Magnesium stearate (mg/tablet)
F1	200	50	222	25	01	02
F2	200	75	197	25	01	02
F3	200	100	172	25	01	02
F4	200	125	147	25	01	02
F5	200	150	122	25	01	02
F6	200	175	97	25	01	02

Evaluation of granules

The angle of repose was measured by using funnel method which indicates the flow ability of the granules[6]. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the

formula: LBD= weight of the powder / volume of the packing.[7] TBD= weight of the powder / tapped volume of the packing[7]. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100[8]. The physical properties of granules were shown in Table 2.

Table 2: Granular properties of F1 to F6 of Nevirapine sustained release matrix tablet.

Formulation no.	Angle of repose	Loose bulk density(g/ml)	Tapped bulk density(g/ml)	Compressibility index (%)
F1	27.22±1.6	0.495±0.004	0.547±0.019	13.29±0.75
F2	27.15±1.31	0.494±0.003	0.555±0.016	12.10±1.63
F3	26.22±1.58	0.470±0.003	0.526±0.012	10.64±1.33
F4	29.45±1.42	0.470±0.009	0.520±0.013	13.40±1.48
F5	28.12±1.57	0.465±0.006	0.536±0.014	16.21±0.78
F6	25.90±1.22	0.465±0.005	0.512±0.011	15.61±1.35

Evaluation of tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods.[9] shown in Table 3

Table 3: Tablet properties of formulations F1 to F6 of Nevirapine sustained release matrix tablets with TSP

Sr. No.	Hardness (kg/cm^2)	Thickness (mm)	% friability	weight variation (mg)	%Drug content
F1	5.8±0.10	3.88±0.16	0.16±0.13	501.0	99.45
F2	6.0±0.24	3.89±0.18	0.22±0.41	500.0	99.89
F3	5.7±0.14	3.85±0.32	0.32±0.21	500.4	100.04
F4	5.9±0.12	3.90±0.03	0.26±0.12	500.1	99.65
F5	6.3±0.35	3.93±0.16	0.42±0.35	500.1	99.36
F6	6.2±0.13	3.96±0.14	0.49±0.21	500.5	99.51

Uniformity of drug content

Accurately weighed quantity of the powder tablet equivalent to 100 mg of the drug was transferred to 100 ml volumetric flask. 50 ml of buffer solution of pH-7.4 was added. Mix with the aid of ultrasound for 10 min, and then the volume was made up to 100 ml with the same buffer solution, mixed solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.45µm. 5 ml of the filtrate was diluted to 100 ml with same buffer solution and examined under U.V Spectrophotometer at 284 nm.

***In vitro* drug release studies**

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type 2 (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of pH 7.4-

phosphate buffer, maintained at 37 + 0.50 c. The drug release at different T intervals was measured using an UV spectrophotometer (Lab India, Mumbai, India) at 284 nm. The study was performed in triplicate.

Characterization of drug release kinetics[10, 11]

The Korsmeyer and Peppas equation was used to analyze the data obtained from the in vitro release studies to evaluate the kinetic models and release mechanism of Nevirapine from the matrices. The Korsmeyer and Peppas equation is: Mt/M = k tn. Where Mt/M is the fraction of drug released at time t, k is a constant incorporating the properties of the macromolecular polymeric system and the drug and n is an exponent used to characterize the transport mechanism. For example, n = 0.45 for Case I or Fickian diffusion, 0.45 < n < 0.89 for anomalous behaviour or non- Fickian transport, n = 0.89 for Case II transport, and n > 0.89 for Super Case II transport. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion

Stability Study

The optimized formulation was subjected to stability at 40 ± 2 ^{0} C and 75 ± 5 % RH for period of six months. After each month tablet sample was analyzed for physical characteristics and drug release profile.[12]

RESULTS AND DISCUSSION

Characterization of granular properties

Granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Table 2. Angle of repose was in the range 24.10 ± 1.60 to 29.82 ± 1.420, which indicates excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.465 ±0.006 to 0.495 ±0.004 gm/cc; the tapped density was in the range of 0.555 ± 0.016 to 0.512 ± 0.011 gm/cc, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 16.21 ± 0.78 to 10.64 ± 1.33; indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Physicochemical properties of matrix tablets

When Weight variation test is performed it was found that the weight of tablets in the range of 500.1 to 501 mg. Tablets with a weight of 500 mg, a diameter of 12.08 mm were obtained and

subjected to quality control tests such as hardness, friability and drug content (Table 3). The Drug contents of the formulations were found to be uniform, since the amount of the active ingredient in each of the10 units tested was within the range of 100.04% – 99.36% and the relative standard deviations were less than 2.0%, indicating uniform mixing of tamarind gum, microcrystalline cellulose and drug. The mean values for hardness were over 5.6kg/cm2 and all formulations exhibited a friability of not more than 0.6% during the friability determination. The punches used to compress the tablets were 12.08mm, spherical shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 5.6 ± 0.13 to 6.4 ± 0.34 Kg/ cm^2. It was within the range of monograph specification. Thickness of the tablets was found to be in the range of 3.74 ± 0.03 to 3.96 ± 1.6 mm. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.

Determination of the release kinetics

To know the drug release kinetics for the optimized formulation, the dissolution data was subjected to different kinetic model such as Zero order, First order and Higuchi's square root and Korsmeyer Peppa's. The Kinetic studies for all formulations are shown in Table 5. The regression coefficient was considered as main parameter to interpret release kinetics. The regression coefficient (R^2) value of Zero order, First order, Higuchi's order, Hixon Crowell and Peppas plots for formulation F5 were found to be 0.9907, 0.9883, 0.8880, 0.9891 and 0.9979. On comparing equation of line and regression coefficient (R^2) for different models it was found that the optimized formulation F5 follows Korsmeyer Peppas drug release (value of $R^2$is 0.9979) is found to be linear, this confirms that drug release through the matrix was diffusion and slope (n) value of optimized formulations F5 was found to be 1.3284. Formulation F5 releases 5.9 % of drug in the first one hour and prolongs the release of remaining drug upto 12 hours. Hence considering the dissolution studies and all other evaluation parameters formulation F5 was considered as an optimized formulation.

Table 4: *In-vitro* release study for the Batches from F1 - F6

Sr.No.	Time	F1	F2	F3	F4	F5	F6
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	1	5.934	4.534	5.672	3.939	5.917	4.289
3	2	10.775	7.990	8.00	10.253	10.200	7.868
4	3	20.321	15.47	19.97	26.919	18.590	14.436
5	4	28.124	24.681	27.263	36.522	28.640	21.928
6	5	33.270	32.207	33.270	40.738	37.548	28.649
7	6	40.908	39.207	43.631	48.965	46.184	36.649

8	7	52.518	49.134	58.935	53.899	58.102	41.182
9	8	58.945	57.936	64.124	58.437	61.973	48.852
10	9	66.465	72.564	71.067	64.084	72.821	63.751
11	10	75.611	80.900	76.107	77.302	89.827	77.594
12	11	85.519	88.148	82.561	87.626	92.037	81.246
13	12	95.794	96.611	91.874	93.052	99.062	90.567

Table 5: Release Kinetics parameters of designed sustained release matrix tablets of Nevirapine

Batches	Zero order plots	First order Plots	Higuchi's plots	Hixson Crowell	Peppas plots		
	R^2	R^2	R^2	R^2	R^2	slope	K
F1	0.9938	0.9913	0.8934	0.9922	0.9983	1.2077	0.6104
F2	0.9843	0.9810	0.8683	0.9821	0.9977	1.4004	0.4058
F3	0.9931	0.9926	0.9070	0.9928	0.9860	1.2796	0.5474
F4	0.9932	0.9930	0.9186	0.9931	0.9763	1.3225	0.5223
F5	0.9907	0.9883	0.8880	0.9891	0.9979	1.3284	0.5190
F6	0.9700	0.9665	0.8435	0.9677	0.9652	1.4769	0.2973

CONCLUSION

The matrix tablets were found to be effective in sustaining the drug release up to 12 hr. This is mainly due to formation of a thick gel structure that delays drug release from tablet matrix, Drug release was found to be diffusion coupled with erosion. Stability studies revealed that there was no significant change in drug content and dissolution profile of matrix tablets. It can be concluded that stable formulation could be developed by incorporating hydrophilic polymer (TSP) in a definite proportion, so that the controlled released profile is maintained for an extended period.

ACKNOWLEDGEMENT

The authors are thankful to Prof. Dr. Y.S. Thorat sir, Mr. Ajit Gaikwad and Santosh Pomaji, College of Pharmacy, Solapur for providing grateful help and for providing required facilities to carry out this work.

REFERENCES

1. Ravi PR, Ganga S and Saha RN. Design and study of lamivudine oral controlled release tablets. American Association of Pharmaceutical Scientists Pharm Sci Tech 2007; 8: 1-9.
2. Basak SC, Kumar KS and Ramalingam M. Design and release characteristics of sustained release tablet containing metformin Hcl. Brazilian J Pharma Sci 2008 ;44 : 477-482.
3. Deveswaran R, Abraham S, Bharath S, Basavaraj BV, Furtado S, Madhavan V. Design and characterization of diclofenac sodium tablets containing tamarind seed polysaccharide as

release retardant. International Journal of PharmTech Research. 2009; 1: 191-195.

4. Joseph Gathe, Jaime Andrade Villanuava. Efficacy and safety of Nevirapine sustained release daily versus Nevirapine immediate release twice daily in treatment naïve HIV-1 patients. Int Med press. 2011; 3: 759-769.
5. Sumathi S, Ray AR. Release behaviour of drugs from tamarind seed polysaccharide tablets. Journal of Pharmacy and Pharmaceutical Science. 2002; 5: 12-18.
6. Cooper J, Gunn G. Powder flow and compaction, In; Tutorial pharmacy, CBS Publishers and distributors, New Dehli; 1986.
7. Shah DY, Rampadhan M. Development and evaluation of controlled release dilitiazem hydrochloride microparticles using cross-linked polymer. Drug Develop Industrial Pharm 1997; 23: 567-574.
8. Aulton ME, well TI. Pharmaceutics: The Sciences of Dosage form Design, Churchill Livingstone, London, and England;1998.
9. Lachman L and Lieberman HA. Pharmaceutical Dosage Forms: Tablets. In: The Theory and Practice of Industrial Pharmacy. 3rd ed., U.S.A.: Lea and Febiger; 1991:293-345.
10. Ritger PL, Peppas NA. A simple equation for description of solute release II Fickian and anomalous from swellable devices. Journal of Controlled Release.1987; 5: 37-42.
11. Peppas NA, Sahlin JJ. A simple equation for the description of sustained release III Coupling of diffusion and relaxation. Int J Pharma 1989; 57: 169-172.
12. Cartensen JT. Drug Stability: Principle and Practices.2nd ed., New York: Marcel Dekker; 1995: 538-550.