*Available online www.jocpr.com*

**Journal of Chemical and Pharmaceutical Research, 2018, 10(2):20-24**

**Research Article**

**ISSN : 0975-7384**
**CODEN(USA) : JCPRC5**

# Formulation and Evaluation of Sustained Release Granules of Nitazoxanide

**Rashmi Dahima***

*School of Pharmacy, Devi Ahilya Vishwavidyalaya, Indore, Madhya Pradesh, India*

---

**ABSTRACT**

*The advantages of controlled release products are well known in the pharmaceutical field and include the ability to maintain a desired blood level of a medicament over a comparatively longer period of time. While many oral controlled and sustained release formulations are already known, certain drugs that are relatively insoluble in water and which further have relatively high dose requirements (based on weight) present formulation difficulties which render them unsuitable for inclusion in sustained release formulations. Nitazoxanide, a high dose, water insoluble antiprotozoal drug, is commercially available as immediate release dosage form. There is still a need in the art of formulation of sustained release dosage forms to formulate insoluble antiprotozoal that have enhanced bioavailability and provide suitable release profiles of the drug. The study was undertaken with the aim to formulate and evaluate Nitazoxanide sustained release granules using HPMC grades of polymer as retarding agent. These granules were coated with beeswax/cetyl alcohol. The in vitro dissolution studies were carried out with granules equal to 500 mg drug, using USP apparatus type I (Basket) at 100 rpm. Using 750 ml of 0.1N hydrochloric acid for the first 2 hours followed by 1000 ml of phosphate buffer pH 6.8 from 3 to 24 hours, medium maintained at 37°C ± 0.5°C. A sustained release profile was shown up to 24 hrs. The slope value of more than 0.7, however, appears to indicate a coupling of diffusion and erosion mechanisms – so called anomalous diffusion.*

**Keywords:** Controlled release; Sustained release; Oral; Nitazoxanide; Antiprotozoal

---

## INTRODUCTION

Two aspects most important to a drug delivery are spatial placement and temporal delivery of a drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue [1]. Conventional (immediate release) pharmaceutical dosage forms now in use are unable to control either the rate or site specific drug delivery. Immediate release from a conventional dosage form employs that absorption of drug across a biological membrane is the rate limiting step in the delivery of the drug to its target area. For non-immediate release dosage forms the release of the drug from the dosage form is the rate limiting step. The effort to develop a non-immediate release delivery system must be directed primarily at altering the release rate [2]. An appropriately designed controlled release drug delivery system can be a major advance toward solving the problems of spatial placement and temporal delivery [1]. Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose [3]. Key advantages to the use of this technology are prolonged activity, fewer doses, control on fluctuations, fewer side effects and reduced toxicity [4]. The principle method of granulation may be classified into three main categories *viz.*, wet process (wet massing, fluid bed granulation, spray drying, pan granulation and extrusion and pelleting), dry process (roller compaction and slugging) and other processes (humidification, prilling and melt pelletization) [5].

Nitazoxanide ($C_{12}H_9N_3O_5S$; mol. wt.=307.283 g/mol) is an antiparasitic drug used in the treatment of amoebiasis, giardiasis, helminthic infestations, anaerobic infestations, cryptosporidiosis in immunocompetent and HIV positive individuals, fasciolasis and to fight *H. pylori* resistant to metronidazole. It has a hydrophobicity of 2.565.

Nitazoxanide is a prodrug forming short lived redox active intermediate. Upon oral administration it is rapidly converted by esterases to an active metabolite, tizoxanide; parent compound is not detected in the plasma. The peak serum concentration is reached within 1-4 hours. In plasma, more than 99% of tizoxanide is bound to proteins. Tizoxanide has an elimination half-life of 1-1.6 hours. Only small amounts of tizoxanide are recovered in urine, bile and faeces [6-13].

## EXPERIMENTAL METHOD

### Preparation of Granules

Granules of Nitazoxanide with the selected excipients were prepared by wet granulation method. All the ingredients were separately passed through sieve of 60 mesh size. According to the formula, the selected excipients and drugs for particular batch formulation were weighed accurately and were poured in a polythene bag in geometric dilution manner. All the ingredients were then blended uniformly for 10 minutes and then sufficient volume of isopropyl alcohol was added drop by drop with continuous mixing. The wet mass was passed manually through sieve of 44 mesh size to form the granules. These wet granules were dried at room temperature for 24 hours and after drying coating was done with bees wax/acetyl alcohol (Table 1).

For coating, granules were placed in molten wax/acetyl alcohol and were uniformly mixed for 5 minutes under elevated temperature. The temperature was then reduced and slow mixing was continued until room temperature was reached. These coated granules were passed through sieve of 22 mesh size to yield uniform granules. The preparations were stored in air tight containers at room temperature for further study.

**Table 1: Concentration of ingredients in different batches for approximation of sustained release formulation**

| S. No. | Ingredient | Quantity [in %] | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | NA | NB | NC | ND | NE | NF | NG | NH | NI | NJ | NK | NL | NM | NN |
| 1 | Drug | 60 | 60 | 60 | 60 | 58 | 58 | 58 | 80 | 70 | 70 | 70 | 70 | 70 | 70 |
| 2 | PVP K30 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 3 | 4 | 4 | 4 | 4 | 4 | 4 |
| 3 | Lactose | 5 | 5 | 5 | 5 | 5 | - | 5 | 3 | 4 | 4 | 4 | 4 | 4 | 4 |
| 4 | Dextrose | - | - | - | - | - | 5 | - | - | - | - | - | - | - | - |
| 5 | HPMC K15 M | 20 | - | 10 | - | - | - | - | - | - | - | - | 6 | - | - |
| 6 | HPMC K100 M | - | 20 | - | 10 | 8.5 | 8.5 | 3 | 4 | 8 | 8 | 4 | - | 6 | 4 |
| 7 | Ethyl Cellulose | - | - | 10 | 10 | 10.5 | 10.5 | 16 | 4 | - | - | 4 | 4 | 4 | 6 |
| 8 | Bees Wax | 10 | 10 | 10 | 10 | 13 | 13 | 13 | 6 | 8 | - | 8 | 8 | 8 | 8 |
| 9 | Cetyl Alcohol | - | - | - | - | - | - | - | - | - | 8 | - | - | - | - |
| 10 | Xanthan Gum | - | - | - | - | - | - | - | - | 5 | 5 | 5 | 3 | 3 | 3 |
| 11 | Aerosil 200 | - | - | - | - | - | - | - | - | 1 | 1 | 1 | 1 | 1 | 1 |
| 12 | IPA | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. |

### Evaluation of Granules

Prepared sustained release granules were evaluated for Angle of Repose, Bulk Density, Compressibility Index, Drug Content and Dissolution Studies.

For Drug Content, an accurately weighed amount of powdered drug granules (100 mg) was extracted with methanol and the solution was filtered through 0.45 µ filter. The absorbance was measured at 414 nm after suitable dilution with phosphate buffer pH 6.8. Further calculations were done with reference to the calibration curves.

### *In vitro* Release Studies

The *in vitro* dissolution studies were carried out with granules equal to 500 mg drug, using USP apparatus type I (Basket) at 100 rpm. Using 750 ml of 0.1 N hydrochloric acid for the first 2 hours followed by 1000 ml of phosphate buffer pH 6.8 from 3 to 24 hours, medium maintained at 37°C ± 0.5°C. A 1 ml sample was withdrawn at appropriate time interval and it was replaced with fresh dissolution medium.

After suitable dilution and filtered through 0.45 µ filter, the drug release at different time intervals was measured by UV-visible spectrophotometer at 346 nm for HCl and at 414 nm for phosphate buffer pH 6.8. The amount of drug present in the samples was calculated with the help of standard calibration curves in same media. The results were presented in table below and graphically plotted in Figure 1.

## RESULT AND DISCUSSION

### Micromeritic Properties

Table 2 displays the micromeritic properties of the granules. Batches NA, NE, NI, NL, NM and NN show angle of repose <30°. Batches NA, NC, NF, NH, NJ and NN show compressibility index >20% showing poor flow properties. The BD ranges from (0.34 ± 0.10) to (0.41 ± 0.06) while the TD ranges from (0.43 ± 0.10) to (0.54 ± 0.05), for free flow property, the bulk density and tapped density should be close in value. The Hausner ratio for batches NA, NC, NF, NH and NN were >1.26 showing poor flow. The drug content ranges from (95.82 ± 0.02) to (98.68 ± 0.08), this shows a high degree of drug content uniformity among different batches.

**Table 2: Evaluation of granules**

| Batch | Angle of Repose | Bulk Density (g/ml) | Tapped Density (g/ml) | Compressibility Index (%) | Hausner Ratio | Drug Content (%) |
|---|---|---|---|---|---|---|
| NA | 29.2 ± 0.03 | 0.35 ± 0.05 | 0.46 ± 0.04 | 23.91 ± 0.06 | 1.31 ± 0.02 | 97.90 ± 0.03 |
| NB | 33.6 ± 0.04 | 0.36 ± 0.02 | 0.43 ± 0.05 | 17.20 ± 0.03 | 1.21 ± 0.02 | 96.54 ± 0.08 |
| NC | 39.3 ± 0.21 | 0.34 ± 0.10 | 0.44 ± 0.06 | 22.73 ± 0.07 | 1.29 ± 0.03 | 95.97 ± 0.13 |
| ND | 33.7 ± 0.10 | 0.38 ± 0.08 | 0.43 ± 0.05 | 11.54 ± 0.06 | 1.13 ± 0.07 | 95.82 ± 0.02 |
| NE | 29.7 ± 0.03 | 0.36 ± 0.12 | 0.44 ± 0.08 | 18.18 ± 0.05 | 1.22 ± 0.05 | 97.46 ± 0.11 |
| NF | 37.2 ± 0.01 | 0.34 ± 0.10 | 0.43 ± 0.07 | 21.80 ± 0.03 | 1.28 ± 0.04 | 96.14 ± 0.06 |
| NG | 35.3 ± 0.09 | 0.38 ± 0.06 | 0.46 + 0.05 | 16.39 ± 0.05 | 1.20 ± 0.06 | 96.42 ± 0.05 |
| NH | 38.6 ± 0.18 | 0.40 ± 0.05 | 0.54 ± 0.05 | 25.93 ± 0.06 | 1.35 ± 0.02 | 98.36 ± 0.16 |
| NI | 29.3 ± 0.04 | 0.35 ± 0.04 | 0.43 ± 0.10 | 19.50 ± 0.05 | 1.24 ± 0.02 | 97.71 ± 0.09 |
| NJ | 31.3 ± 0.09 | 0.34 ± 0.05 | 0.43 ± 0.02 | 20.93 ± 0.04 | 1.26 ± 0.03 | 96.36 ± 0.16 |
| NK | 33.1 ± 0.12 | 0.41 ± 0.06 | 0.48 ± 0.04 | 13.90 ± 0.05 | 1.16 ± 0.04 | 97.93 ± 0.07 |
| NL | 28.4 ± 0.11 | 0.37 ± 0.05 | 0.44 ± 0.05 | 15.82 ± 0.04 | 1.10 ± 0.02 | 96.91 ± 0.05 |
| NM | 29.6 ± 0.04 | 0.38 ± 006 | 0.46 ± 0.05 | 16.39 ± 0.06 | 1.20 ± 0.04 | 98.68 ± 0.08 |
| NN | 28.8 ± 0.03 | 0.37 ± 0.05 | 0.47 ± 0.02 | 21.20 ± 0.05 | 1.27 ± 0.02 | 97.47 ± 0.04 |

All values are expressed as mean ± SD, n=3

### *In-vitro* Drug Release Study

Table 3 displays drug release profile of the granules. Upon comparison of batches NA and NB, NA shows good release profile, it may be due to high viscosity grade of HPMC. Desired effect was found on the drug release from ND batch and it also shows good compressibility index and BD while a drug dump was found from NC batch at the end of 6 hours. So formulation ND was further modified to NE, NF and NG by incorporating less amount of HPMC K100M and increasing the amount of ethyl cellulose and bees wax with lactose/dextrose. Amongst these NE and NF show similar profile but NE, which has lactose, shows good values of angle of repose, BD, TD, compressibility index and drug content than compared to NF which contains dextrose. So, dextrose is dropped out for further studies. NG which has higher amount of ethyl cellulose and only 3% of HPMC K100M gives a release of only 39.8% at the end of 24 hours. Batch NH was formulated with 80% drug and the excipients were 3-6% of total weight of granules. It released 74.46% of drug at the end of 8 hours and a total of 97.62% drug was released at the end of 24 hours. Batches NI, NJ and NK were formulated with 70% drug and xanthan gum, aerosol were used in different concentrations in combination with HPMC K15M, bees wax/cetyl alcohol and ethyl cellulose. On study it was found that at the end of 4 hours batches NL, NM and NN showed drug release of 18.42%, 16.44% and 23.27% respectively which is near about 20% of the final drug concentration in the preparation. At the end of 10 hours the release was 53.76%, 45.84% and 72.77% respectively. The batches NL and NN showed more than 50% which is a requirement of ideal sustained release preparation along with which it should release more than 80% of the drug at the end of 24 hours. These batches, at the end of 24 hours show 88.71%, 72.38% and 97.62% drug release respectively.

**Table 3: Cumulative % drug release of different batches after certain time interval**

| Time (hr) | Cumulative % Drug Release of Batch | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NA | NB | NC | ND | NE | NF | NG | NH | NI | NJ | NK | NL | NM | NN |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 20.13 | 15.19 | 14.43 | 13.67 | 9.68 | 14.24 | 13.1 | 7.41 | 5.13 | 11.39 | 14.05 | 10.06 | 6.46 | 15.57 |
| 4 | 38.42 | 20.4 | 49.9 | 34.06 | 20.59 | 21.88 | 20.2 | 26.24 | 15.15 | 16.53 | 25.35 | 18.42 | 16.44 | 23.27 |
| 6 | 56.14 | 25.74 | 101.88 | 45.64 | 27.52 | 33.56 | 26.24 | 45.35 | 19.5 | 23.17 | 27.23 | 36.04 | 25.64 | 42.48 |
| 8 | 58.32 | 32.67 | 101.98 | 61.68 | 29.9 | 35.35 | 27.33 | 74.46 | 25.74 | 26.34 | 29.6 | 49.11 | 36.44 | 58.71 |
| 10 | 77.33 | 39.5 | 100.99 | 67.43 | 35.25 | 38.22 | 29.31 | 88.12 | 33.86 | 32.87 | 30.89 | 53.76 | 45.84 | 72.77 |
| 17 | 81.78 | 42.18 | 101.39 | 87.72 | 44.16 | 45.94 | 30.1 | 94.85 | 49.41 | 39.8 | 37.62 | 71.78 | 67.52 | 91.29 |
| 20 | 85.25 | 44.95 | 101.49 | 95.25 | 49.31 | 51.29 | 32.57 | 97.13 | 53.96 | 43.37 | 39.11 | 78.81 | 69.5 | 94.95 |
| 24 | 85.35 | 52.08 | 101.49 | 98.22 | 58.51 | 63.86 | 39.8 | 97.62 | 60.59 | 54.06 | 39.7 | 88.71 | 72.38 | 97.62 |

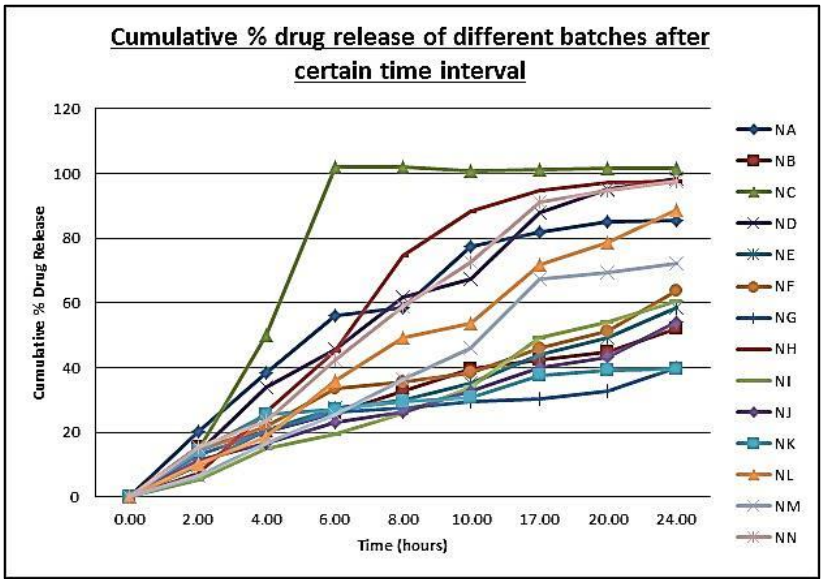


**Figure 1: Cumulative % drug release of different batches after certain time interval**

To know the mechanism of drug release from these formulations, the data were treated according to first order (log cumulative percentage of drug remaining vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time) and Korsmeyer et al. (log cumulative percentage of drug released vs. log time) equations along with zero order (cumulative amount of drug released vs. time) pattern. As clearly indicated all formulations did not follow a zero order release pattern. The release rate kinetics data for all other equations can be seen in Table 4. When the data was plotted according to the first order equation, the formulations showed a fair linearity, with regression values between 0.7086 and 0.9970 with mean 0.9223. Release of the drug from a matrix containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the *in-vitro* study fluid depending on the concentration. As gradient varies, the drug is released and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics or Higuchi's kinetics.

In our experiments, the *in-vitro* release profiles of drug from all the formulations could be best explained by the Higuchi's equation, as the plot showed high linearity ($R^2$ : 0.7836 to 0.9844 with mean 0.9404). To confirm the diffusion mechanism, the data were fit into Korsmeyer et al. equation. The formulations NA to NN showed linearity ($R^2$: 0.2205to 0.9794) with slope (n) values ranging from 0.4447 to 0.8902 except NN (2.0232). Batch NL showed high linearity with a comparatively high slope value of 0.7429 and also good result with first order (0.9828) and Higuchi's (0.9614) equations. The slope value of more than 0.7, however, appears to indicate a coupling of diffusion and erosion mechanisms – so called anomalous diffusion. The relative complexity of this formulation and its components may indicate that the drug release is controlled by more than one process.

**Table 4: Kinetic values obtained from different plots of formulation**

| Batch | First Order Plots * | Higuchi Plots † | Korsmeyer et al. Plots ‡ | |
|---|---|---|---|---|
| | $R^2$ | $R^2$ | n | $R^2$ |
| NA | 0.9144 | 0.9368 | 0.4185 | 0.7644 |
| NB | 0.9169 | 0.9772 | 0.6558 | 0.8473 |
| NC | 0.7086 | 0.7836 | 0.4351 | 0.5077 |
| ND | 0.9697 | 0.9565 | 0.4935 | 0.8775 |
| NE | 0.9739 | 0.9844 | 0.7328 | 0.9347 |
| NF | 0.9431 | 0.9759 | 0.6661 | 0.9002 |
| NG | 0.7947 | 0.9253 | 0.627 | 0.7434 |
| NH | 0.965 | 0.8893 | 0.2205 | 0.7989 |
| NI | 0.997 | 0.9543 | 0.8902 | 0.9794 |
| NJ | 0.9699 | 0.9816 | 0.7512 | 0.9441 |
| NK | 0.8065 | 0.9394 | 0.6031 | 0.7431 |
| NL | 0.9828 | 0.9614 | 0.7429 | 0.9457 |
| NM | 0.9809 | 0.9474 | 0.8591 | 0.9483 |
| NN | 0.9892 | 0.9528 | 2.0232 | 0.9039 |

$R^2$ = Regression Coefficient; * First Order Equation {$\log C = \log C_0 - Kt/2.303$}; †Higuchi's Equation {$Q = Kt^{1/2}$}; ‡ Korsmeyer et al. Equation {$M_t/M_\alpha = Kt^n$}

## CONCLUSION

The study was undertaken with the aim to formulate and evaluate Nitazoxanide sustained release granules using HPMC grade of polymer as retarding agent. From the above results and discussion, it is concluded that sustained release granules of Nitazoxanide can be prepared using HPMC, xanthan gum, ethyl cellulose with lactose as diluents and PVP as binder and bees wax as coating agent by wet granulation method. This can be optimized formulation of sustained release granules for 24 hours release as it fulfills all the requirement of sustained release preparation and study encourages further clinical trials and long term stability study on this formulation.

## REFERENCES

[1] AR Gennaro. Remington's Pharmaceutical Sciences, 18th edition, **1990**, 1677-1678.
[2] NK Jain; RK Khar. Controlled and Novel Drug Delivery, 1st edition, CBS Publishers, Delhi, India, **2002**, 6-53, 55-56.
[3] BE Ballard. An Overview of Prolonged Action Drug Dosage Form in Sustained Release and Controlled Release Drug Delivery Systems, Edited by J.R. Robinson. New York, Marcel Dekker, **1978**.
[4] E Ojoe; EM Miyauchi; TC Viviani; VO Consiglieri; *Braz J Pharm Sci*. **2005**, 41(3), 377-384.
[5] PC Record. *Int J Pharm Technol Prod Manuf.* **1988**, 1, 32-39.
[6] SC Sweetman. In: Martindale, The Complete Drug Reference. 33rd edition, Pharmaceutical Press, London, **2002**, 598-599.
[7] MJ O'Neil. In: The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals. 13th edition, Merck & Co. Inc., Whitehouse Station, NJ, **2001**, 1177.
[8] http://www.fda.gov/cder/foi/nda/2004/21-497_Alinia_Prntlbl.pdf
[9] National PBM Drug Monograph – Nitazoxanide (Alinia®)
[10] http://redpoll.pharmacy.ualberta.ca/drugbank/cgibin/getCard.cgi?CARD=APRD00558.txt
[11] A Stockis; X Deroubaix; R Lins; B Jeanbaptiste; P Calderon; JF Rossignol. *Int J Clin Pharmacol Ther*. **1996**, (34), 349-351.
[12] LM Fox; LD Saravolatz. *Clin Infect Dis*. **2005**, 40, 1173-1180.
[13] A Parashar; R Arya. *Indian Pediatr*. **2005**, 42, 1161-1165.