INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

FORMULATION OF SUSTAINED RELEASE MATRIX SUPPOSITORIES

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ARTICLE INFO

Article history
Received 02/11/2014
Available online
30/11/2014

Keywords
Suppositories,
Base,
Matrix,
Formulation.

ABSTRACT

Timed release matrix suppositories as reliable rectal drug delivery by passing hepatic metabolism. Various bases like agar, sodium carboxy methyl cellulose (SCMC), polyethylene glycol used to formulate this. In addition, these bases if used in the formulation will have flexibility in storage conditions unlike suppositories formulated with conventional bases that necessitate exacting storage conditions in tropical climate. Unconventional, non-melting, non-disintegrating suppositories prepared and examined for physicochemical characteristics and in vitro release kinetics. Timed release matrix suppository adapting unconventional combinations of bases such as agar, polyethylene glycol for better prolonged release and mainly to reduce severe gastric ulceration, bleeding and hepatotoxicity.

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*Please cite this article in press as **Joymalya Bhattacharya** et al. Formulation of Sustained Release Matrix Suppositories. Indo American Journal of Pharm Research.2014:4(11).*

INTRODUCTION

AIM OF THE STUDY:

To design and evaluate the sustained release matrix suppositories of nimesulide.

REQUIREMENT:

Nimesulide, agar, sodium carboxy methyl cellulose (SCMC), polyethylene glycol (PEG), mold

THEORY:

Timed release matrix suppositories as a reliable rectal drug delivery by passing hepatic metabolism. Various bases like agar, sodium carboxy methyl cellulose (SCMC), and polyethylene glycol were used to formulate this. In addition, these bases if used in the formulation will have flexibility in storage conditions unlike suppositories formulated with conventional bases that necessitate exacting storage conditions in tropical climate. The unconventional, non-melting, non-disintegrating suppositories were prepared and examined for physicochemical characteristics and in vitro release kinetics. Timed release matrix suppository adapting unconventional combinations of bases such as agar, polyethylene glycol and sodium carboxy methyl cellulose for better prolonged release and mainly to reduce severe gastric ulceration, bleeding and hepatotoxicity[1, 2, 3, 4]

EXPERIMENTAL PROCEDURE:

Preparation of Suppositories

Suppositories were prepared by using fusion method (pour molding) after dissolving the polymeric base materials such as agar, SCMC& PEG in a mixture of 0.9 ml of water, 0.3ml glycerin and 0.2 ml of 0.01M sodium hydroxide. Though sodium hydroxide was mainly incorporated to improve the solubility of agar, it also aided the solubilization of nimesulide and there by gave uniform drug dispersion and drug content uniformity. Polymeric bases added to accurately weighed amount of drug to prepare suppositories where dispersed in the aforementioned solvent system and heated using water bath at 70-80oc for 3 minutes and extended. This treatment was found to be efficient enough to yield homogeneous solution of drug molten base. The amount of drug loaded in each batch was constant (600mg). [1, 3, 5]

Evaluation

Preparation of Nimesulide Standard Curve

i. A weight of accurately 100 mg of nimesulide powder was taken & dissolved in 100 ml of 0.1 N NaOH solution < solution A >
ii. From the solution A, 10 ml was pipette out & diluted to 100 ml in a volumetric flask with 0.1 N NaOH solution < solution B >
iii. From solution B different volumes of 0.1 ml,0.2 ml , 0.3 ml, 0.4 ml,0.5ml, 0.6 ml,0.7ml,& 0.8 ml were taken & diluted up to 10 ml with 0.1 NaOH solution
iv. The absorbance was measured at 436 nm in U V spectrophotometer against 0.1 N NaOH solutions as blank[3]
v. A graph was plotted by taking concentration V_S absorbance

In Vitro Drug Release Studies[1, 5]

The dissolution of nimesulide was studied the using USPXXI dissolution apparatus employing basket stirrer. Nimesulide suppositories were placed dissolution medium contain 0.1N NaOH solution. The rpm was adjusted to 50 and a temperature of 37°c was maintained throughout the experiment. A 5 ml of sample was withdrawn at various time intervals and diluted with 0.1N NaOH and analyzed at 436nm using UV spectrometer.

Physical Dimension[1, 2, 5]

The width and length of randomly selected suppositories were measured.

Homogeneity[1, 5]

Randomly selected suppositories were cut longitudinally and the surfaces were examined with the naked eye (subjective evaluation)

Weight Uniformity[1, 3, 5]

About 20 suppositories were taken and the average weight was determined. Not more than two individual suppositories should deviated by 10%.

Crushing Strength[1, 5]

The crushing strength was determined for measuring fragility or brittleness of suppositories, which assessed the suppositories whether they would be able to withstand the hazards of packing, transporting and normal handling are not.

Drug Content Uniformity[1, 3, 5]

Uniformity of drug content was confirmed by analyzing the drug content in equal batch after dissolving the suppositories in 0.1N NaOH and the drug content was determined at 436nm.

TABLE-1: FORMULATION TABLE.

Ingredient/formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Agar	4%	6%	4%	6%	4%	6%	4%	6%
PEG6000	2%	2%	4%	4%	2%	2%	4%	4%
SCMC	1.5%	1.5%	1.5%	1.5%	3%	3%	3%	3%
Water(ml)	1.25	1.21	1.21	1.17	1.22	1.18	1.18	1.14
Glycerin(Ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
NaoH(0.01N)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Drug (Mg)	100	100	100	100	100	100	100	100
TOTAL(GRAM)	2	2	2	2	2	2	2	2

TABLE-2: FOR STANDARD CURVE OF NIMESULIDE.

Concentration	Absorbance
1	0.027
2	0.033
4	0.096
6	0.147
8	0.198
10	0.265

TABLE-3: DRUG RELEASE PROFILE OF F1 NIMESULIDE SUPPOSITORY.

Time (Hr)	Absorbance	Concentration µg/ml	Concentration mg/900 ml	% Drug release
1	0.018	1.08	48.84	48.84
2	0.028	1.45	65.57	65.57
3	0.029	1.49	67.24	67.24
4	0.030	1.53	68.92	68.92
5	0.032	1.60	72.26	72.26
6	0.039	1.86	83.97	83.97
7	0.039	1.86	83.97	83.97
8	0.040	1.86	83.97	83.97

TABLE-4: DRUG RELEASE PROFILE OF F2 NIMESULIDE SUPPOSITORY.

Time (Hr)	Absorbance	Concentration µg/ml	Concentration mg/900 ml	% Drug release
1	0.016	1.01	45.5	45.5
2	0.021	1.197	53.86	53.86
3	0.028	1.440	65.57	65.57
4	0.031	1.560	70.50	70.50
5	0.034	1.680	75.61	75.61
6	0.035	1.717	77.28	77.28
7	0.037	1.791	80.63	80.63
8	0.037	1.791	80.63	80.63

TABLE-5: DRUG RELEASE PROFILE OF F3 NIMESULIDE SUPPOSITORY.

Time (Hr)	Absorbance	Concentration µg/ml	Concentration mg/900 ml	% Drug release
1	0.019	1.09	49.05	49.05
2	0.022	1.234	55.53	55.53
3	0.023	1.271	57.21	57.21
4	0.024	1.308	58.88	58.88
5	0.030	1.53	68.92	68.92
6	0.031	1.56	70.59	70.59
7	0.040	1.903	85.65	85.65
8	0.040	1.903	85.65	85.65

TABLE-6: DRUG RELEASE PROFILE OF F4 NIMESULIDE SUPPOSITORY.

Time (Hr)	Absorbance	Concentration µg/ml	Concentration mg/900 ml	% Drug release
1	0.014	0.936	42.156	42.156
2	0.024	1.308	58.88	58.88
3	0.028	1.457	65.58	65.58
4	0.029	1.494	67.24	67.24
5	0.030	1.531	68.92	68.92
6	0.034	1.680	75.61	75.61
7	0.038	1.82	82.30	82.30
8	0.038	1.82	82.30	82.30

TABLE-7: DRUG RELEASE PROFILE OF F5 NIMESULIDE SUPPOSITORY.

Time (Hr)	Absorbance	Concentration µg/ml	Concentration mg/900 ml	% Drug release
1	0.013	0.899	40.48	40.48
2	0.019	1.122	50.52	50.52
3	0.028	1.45	65.57	65.57
4	0.029	1.49	67.24	67.24
5	0.031	1.56	70.50	70.50
6	0.032	1.60	72.26	72.26
7	0.032	1.60	72.26	72.26
8	0.032	1.64	73.94	73.94

TABLE-8: DRUG RELEASE PROFILE OF F6 NIMESULIDE SUPPOSITORY.

Time (Hr)	Absorbance	Concentration µg/ml	Concentration mg/900 ml	% Drug release
1	0.016	1.01	45.50	45.50
2	0.021	1.197	53.86	53.86
3	0.025	1.34	60.55	60.55
4	0.029	1.49	67.24	67.24
5	0.029	1.49	67.24	67.24
6	0.030	1.53	68.92	68.92
7	0.033	1.64	73.94	73.94
8	0.033	1.64	73.94	73.94

TABLE-9: DRUG RELEASE PROFILE OF F7 NIMESULIDE SUPPOSITORY.

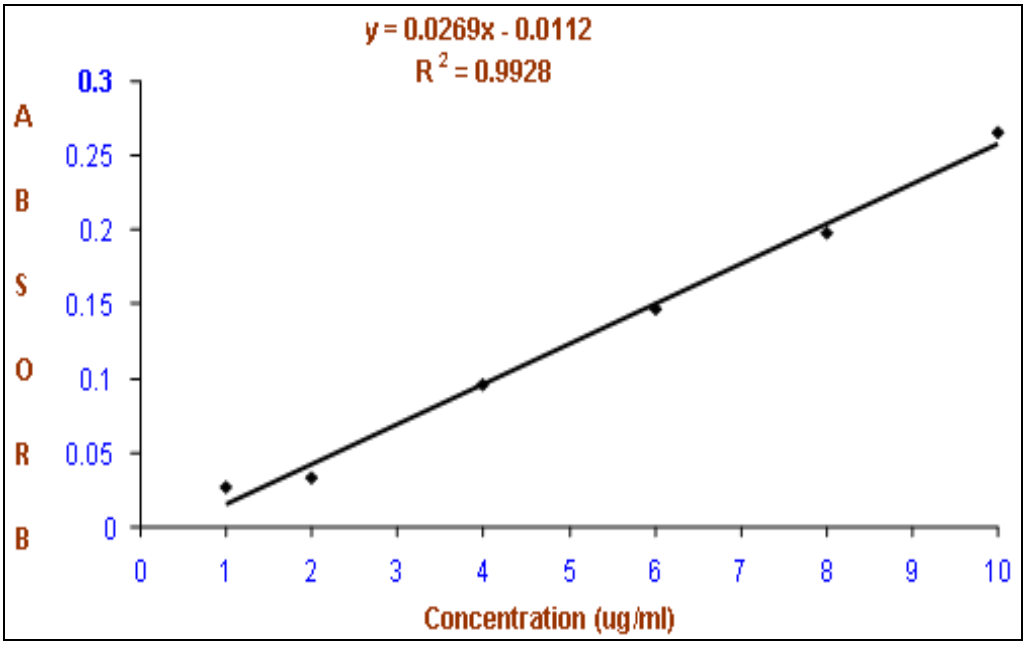
Time (Hr)	Absorbance	Concentration µg/ml	Concentration mg/900 ml	% Drug release
1	0.018	1.08	48.84	48.84
2	0.020	1.18	52.19	52.19
3	0.022	1.234	55.53	55.53
4	0.023	1.271	57.21	57.21
5	0.024	1.308	58.88	58.88
6	0.026	1.382	62.23	62.23
7	0.026	1.382	62.23	62.23
8	0.026	1.382	62.23	62.23

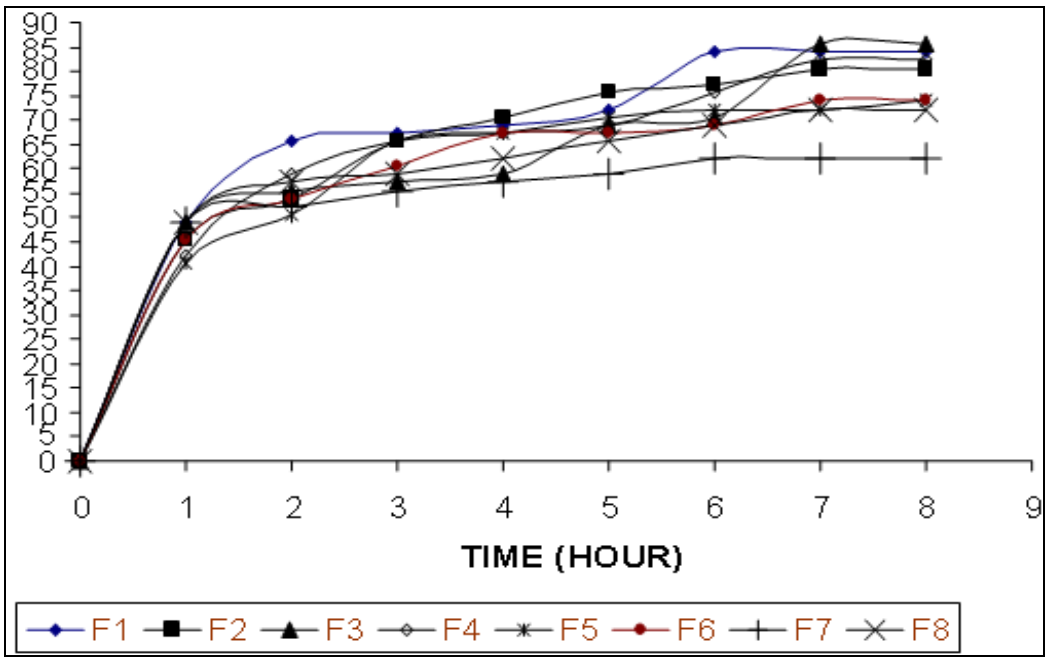
TABLE-10: DRUG RELEASE PROFILE OF F8 NIMESULIDE SUPPOSITORY.

Time (Hr)	Absorbance	Concentration µg/ml	Concentration mg/900 ml	% Drug release
1	0.019	1.09	49.05	49.05
2	0.023	1.271	57.21	57.21
3	0.024	1.308	58.88	58.88
4	0.026	1.382	62.23	62.23
5	0.028	1.45	65.57	65.57
6	0.030	1.53	68.92	68.92
7	0.032	1.60	72.26	72.26
8	0.032	1.60	72.26	72.26

TABLE-11: PHYSICO-CHEMICAL EVALUATION OF FORMULATIONS.

Formulation	Crushing strength (gm)	Drug content (mg)	homogenizing	Weight uniformity(gm)	Physical dimension	
					Length (cm)	Width (cm)
F1	50	62.52	good	1.129	2	0.8
F2	52	100.44	good	1.108	2	0.8
F3	40	103.04	Not proper	1.19	2	0.7
F4	47	70.70	good	1.29	2	0.73
F5	45	86.31	good	1.27	2	0.8
F6	57	75.53	good	1.30	2	0.7
F7	52	78.68	good	1.08	2	0.7
F8	48	74.42	good	1.30	2	0.8





FigFigure-1: Drug release profile of nimesulide suppositories.

RESULT AND DISCUSSION

All formulations were found to have homogeneous drug distribution (except F3 formulation) with excellent drug content uniformly, weight uniformly and sufficient mechanical strength to withstand abrasive forces causing disintegration of drug loaded formulation shown in table 11.Except for few formulation containing high proportion of agar , burst effect was observed in all the formulation .this may be due to the addition of sodium hydroxide ,which solubilise the drug in the matrix. Since the diffusivity of the solubilised molecule is higher than that of un-solubilise one, burst effect was evident in almost all the formulations. in addition to the presence of solubilized drug molecule, resulted in faster drug release shown in table- 3 to table -10 order to elucidate mode and mechanism of drug release, in vitro data were transformed and interpreted at graphical inter face constructed using zero order represented in figure 2.all most all the formulations released the drug in idealist sustained release concentration in independent mode and following diffusion mechanism. With a comparison between all the formulations F7 was found to have better sustained release action.

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