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A REVIEW ON "SUSTAIN RELEASE MATRIX TABLET BY USING NATURAL POLYMER

***[1]Satish R. Payghan and [2]S. C. Atram**

[1]Department of Pharmaceutics, Vidyabharati College of Pharmacy, Amravati, MH, india.
[2]Assistant Professer, Vidyabharati College of Pharmacy, Amravati. MH, India.

***Corresponding Author: Satish R. Payghan**
Department of Pharmaceutics, Vidyabharati College of Pharmacy, Amravati, MH, india.

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ABSTRACT
The oral route of drug delivery is the most preferred route for administration of drugs. The rationale for the development of a sustained release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effect while improving the management of the diseased condition. Sustained drug delivery systems significantly improve the therapeutic efficacy of drugs. Drug-release-retarding polymers are the key performers in such systems. Nifedipine is a 1,4-dihydropyridine calcium channel blocker. It is used for the treatment of angina pectoris, hypertension, and Raynaud's phenomenon. Nifedipine has a half-life of 2 hrs. Organoleptic properties, melting point determination, solubility studies, FT-IR frequencies showed that the Nifedipine used was similar to the reported values. After the comparison of FTIR results, it was concluded that there was no incompatibility between drug and polymers. Natural gums like Guar gum and Xanthan gum were chosen as polymers for the formation of sustained release matrix tablets. In this study, 12 formulations were prepared by direct compression method using differentpolymers at varying ratios, Microcrystalline cellulose and HPMC E5 were used which helps in the slow erosion of matrix from the tablet and Talc and Magnesium stearate as lubricants

KEYWORDS: Sustained release, Nifedipine, Guar gum, Xanthan gum, Matrix tablet.

INTRODUCTION
The oral route of drug delivery 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. The rationale for the development of a sustained release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effect while improving the management of the diseased condition.[1]

Sustained drug delivery systems significantly improve the therapeutic efficacy of drugs. Drug-release-retarding polymers are the key performers in such systems. Sustained release delivery systems can achieve an extended duration of activity for drugs with half-life 2-4 hrs. Decreased toxicity, reduction of required dose, optimized therapy, and better patient compliance. With the aim of maximizing the bioavailability of conventional drugs withminimum side effects, new drug delivery systems continue to attract much attention. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness and broad regulatory acceptance.[2] Among the hydrophilic polymers, cellulose derivatives such as methylcellulose, hydroxypropyl, and sodium carboxymethylcellulose are generally considered to be stable and safe as release retardant excipients in the development of oral controlled release dosage forms. These semi-synthetic polymers are quite expensive when compared with natural polymers such as guar gum, xanthan gum and so forth. The natural polymers are nontoxic and easily available.[3]

Sustained release formulations can offer many pharmacokinetic and pharmacodynamics advantages over conventional dosage forms, including maintenance of constant therapeutic levels for a longer period of time and reduction of fluctuations in plasma drug concentrations. Sustained release formulations can reduce the risk of treatment failure due to inadequate dosing of antibiotics.[4]

Preparation of sustained release formulation by matrix technique is a commonly employed method because of the ease of preparation, flexibility and cost efficiency.

Matrix tablets are widely accepted for oral sustained release (SR) as they are simple and easy to formulate. Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed.[5]

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastro intestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal tract. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation.[6]

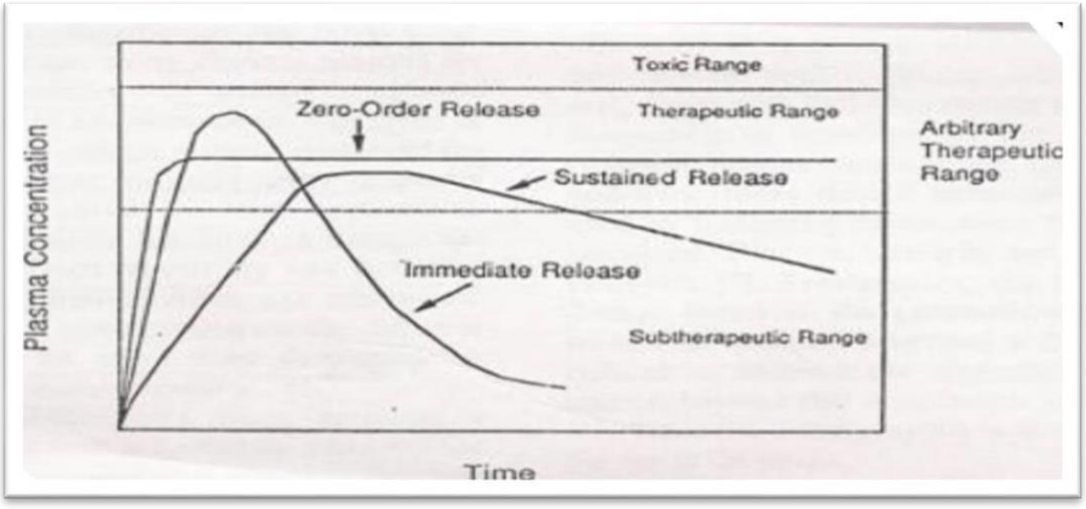


Fig. 1: Plasma Concentration-profiles Vs Time.

Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is ofa temporal nature, spatial nature or both. Sustained release system generally do not attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval.

Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example. Enteric coated tablet. A sustained release dosage form will provide a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in apeak concentration ratio.[7]

Advantages Of Sustain Release Dosage Forms

- Reduction in frequency of intakes.
- Reduce side effects.
- Uniform release of drug over time.
- Better patient compliance.

Disadvantages Of Sustained Release Drug Delivery

- Increased cost.
- Toxicity due to dose dumping.
- Unpredictable and often poor *in vitro-in vivo* correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Increased potential for first- pass clearance.
- Need for additional patient education and counseling.

Selection of drug

Nifedipine is a 1 4-dihydropyridine calcium channel blocker. It is used for the treatment of angina pectoris, hypertension, and Raynaud's phenomenon. Nifedipine has a half-life of 2Hrs. The aim of proposed work was intended to formulate and evaluate sustained release matrix tablet of Nifedipine, with a view to reducing the dosing frequency and the side effects.The main objective of the present work was to prepare and evaluate sustained release matrix tablet of Nifedipine using natural polymers.

Absorption

Sublingual dosing leads to a Cmax of 10ng/mL, with a Tmax of 50min, and an AUC of 25ng*h/mL. Oral dosing leads to a Cmax of 82ng/mL, with a Tmax of 28min, and

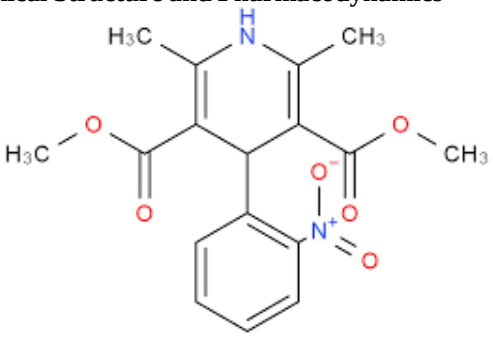
an AUC of 152ng*h/mL.[7]

Volume of distribution
The steady state volume of distribution of nifedipine is 0.62-0.77L/kg and the volume of distribution of the central compartment is 0.25-0.29L/kg.

Protein binding: Nifedipine is 92-98% protein bound in serum. Nifedipine is 97±12% bound in a 40g/L solution of pure albumin. Nifedipine is 51.4±5.9% protein bound in a 50mg/100mL solution of alpha-1-acid glycoprotein, and 75.5±3.5% protein bound in a 150mg/mL solution.[8]

Metabolism
Nifedipine is a Biopharmaceutics Classification System Class II drug, meaning it has low solubility and high intestinal permeability. It is almost completely absorbed in the gastrointestinal tract but has a bioavilability of 45-68%, partly due to first pass metabolism.[9]

Chemical Structure and Pharmacodynamics



Nifedipine is an inhibitor of L-type voltage gated calcium channels that reduces blood pressure and increases oxygen supply to the heart. Immediate release nifedipine duration of action requires dosing 3 times daily. Nifedipine dosing is generally 10-120mg daily. Patients should be counselled regarding the risk of excessive hypotension, angina, and myocardial infarction.[10]

Mechanism of action
Nifedipine blocks voltage gated L-type calcium channels in vascular smooth muscle and myocardial cells. This blockage prevents the entry of calcium ions into cells during depolarization, reducing peripheral arterial vascular resistance and dilating coronary arteries. These actions reduce blood pressure and increase the supply of oxygen to the heart, alleviatingangina.[11]

Route of elimination
Nifedipine is 60-80% recovered in the urine as inactive water soluble metabolites, andthe rest is eliminated in the faeces as metabolites.

Half-life
The terminal elimination half-life of nifedipine is approximately 2 hours.

Clearance
The total body clearance of nifedipine is 450-700mL/min.

Selection of natural polymer
Xanthan gum is a polysaccharide gum derived from Xanthomonas campestris by a pure-culture fermentation process and purified by recovery with isopropyl alcohol. The major constituents include D-glucose, D-mannose, and D-glucuronic acid. Xanthan gum is a direct food additive permitted for direct addition to food for human consumption by the FDA. It is used as a thickening agent and stabilizer in tablet.

Guar gum also called guaran, is a galactomannam polysaccharide extracted from guar beans that has thickening and stabilizing properties useful in the food, feed and industrial application.

LITERATURE SURVEY

- Literature survey was carried out on the proposed topic by referring various scientific journals, online and offline also referred various text books available in college library. This survey reveals that no such articles were reported on the proposed work and somerelated articles are mentioned below
- ***Deepa C et al.***[12] Studied on the slow release form of the drug nimesulide by using different polysaccharide bases like HPMC, Chitosan, chitin CMC, etc all the polymers shows release behavior over 9 hours except chitin.
- **Haung *et al.***[13] Have optimized formulations of extended release tablets of propranolol containing hydroxy propyl methyl cellulose, microcrystalline cellulose and lactose by using response surface methodology.
- **Hayashi *et al.***[14] Have prepared sustained release matrix tablets of a theophylline and compared drug release mechanism of each preparation by using release kineticstheories.
- **Hu *et al.***[15] Have prepared sustained release pellets of metformin hydrochloride by centrifugal granulation method by using methacrylic acid copolymers (eudragit L30D- 55, NE30D), hydroxy propyl methyl cellulose and microcrystalline cellulose which were subjected to surface modification by talc before coating and resulted that it controls drug release and avoids drug dumping.
- **Mandal *et al.***[16] Have optimized *in vitro* release profile of metformin hydrochloride 500 mg sustained release matrix tablets using artificial neural network (ANN) based on multilayer perceptrons (MLP) model by using hydroxy propyl methyl cellulose K15M, microcrystalline cellulose Avicel PH 101 and polyvinyl pyrrolidone K30.

NEED OF STUDY
The main aim of the present work was to formulate sustain release matrix tablets of Nifedipine using various concentration of polymer like guar gum and xantham gum and release retardant polymers. Tablets are considered as safe, cheap and stable dosage form with

better patient compliance and convenience. Due to its shorter half-life, this drug is best candidate for formulation of sustain released dosage form tablets.

OBJECTIVES

The objective of this research work was to prepare and evaluate sustain release matrix tablets of Nifedipine by direct compression method using various polymers and excipients.

- To Enhance The Bioavailability.
- To Formulate SR tablet of Nifedipine.
- To Reduce Dose.
- To Reduce Dosing Frequency.
- Patient compliance can be improved, and drug administration can be made more convenient as well.
- To achieve the greater therapeutic efficacy.

Preformulation studies

Determination of organoleptic properties

The physical appearance of the drug was observed and compared with the pharmacopoeialspecifications.

Determination of melting point

The melting point of Nifedipine was determined by the capillary method.

Solubility Small increments of Nifedipine was added to 10ml of solvent (distilled water, acetone, ethanol, diethyl ether, acetic acid) in a 25ml stoppered standard flask with vigorous shaking. Visually observed the solution, if the solution was clear and no undissolved particles were observed if it was insoluble again another increment of particular solvent was added and the procedure was continued until undissolved Nifedipine was found.

Precompression parameter studies

Bulk density

The bulk density of a powder is the ratio of the mass of the powder sample to its volume includingthe contribution of the inter-particulate void volume. The bulk density is expressed in grams permilliliter (g/ml) or grams per cubic centimeter (g/cm3). The bulk volume (Vb) and weight of thepowder (M) were calculated using the formula.

ρb = M/Vb

Tapped density

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was taken. The tapped density (ρt) was calculated by using formula. ρt = M/Vt Angle of repose. The angle of repose or critical angle of repose of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. The angle of repose (Θ) was calculated using the formula

ρt = M/Vt

Angle of repose

The angle of repose or critical angle of repose of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. The angle of repose (Θ) was calculated using the formula

Θ = tan-1 (h/r)where, h = height of the heap r = radius of the heap

Table Angle of Repose As An Indication of Powder Flowability.

Sr. No.	Angle ofrepose (degrees)	Type offlow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>40	Very poor

Compressibility Index (CI)

Compressibility Index is an indication of the compressibility of a powder. The Carr index is calculated by the formula

CI = 100[(Vb - Vt)/Vb]

Where Vb is the volume that a given mass of powder would occupy if let settled freelyVt is the volume of the same mass of powder would occupy after "tapping down".

Table: Compressibility Index As An Indication of Powder Flowability

Sr. No.	Carr's index (%)	Type of flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Hausner ratio (HR)

The Hausner ratio is a number that is correlated to the flowability of a powder or granularmaterial. The Hausner ratio is calculated by the formula.

HR = ρt/ρb
where ρb is the freely settled bulk density of the powder
ρt is the tapped density of the powder.

Table: Hausner's ratios An Indication of Powder Flowability.

Sr. No.	Hausner's ratio	Type of flow
1	1.00-1.11	Excellent
2	1.12-1.18	Good
3	1.19-1.25	Fair to passable
4	1.26-1.34	Passable
5	1.35-1.45	Poor
6	1.46-1.59	Very poor
7	>1.60	Extremely poor

Formulation Process

Sr. No.	Materials	Category
1	Nifedipine	API
2	Guar gum	Polymer
3	Xanthan gum	Polymer
4	HPMC E5	Syn. Polymer
5	Microcrystalline cellulose	Diluent/Binder
6	Talc	Glidant
7	Magnesium stearate	Lubricant

Evaluation Of Sustained Release Matrix Tablet of NifedipinePost-Compression Parameters

Physical appearance
The shape of the tablet can be dimensionally described, monitored and controlled.

Weight variation
Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

Table: weight variation limit.

Sr. No.	Average weight ofTablets	Max. percentagedeviation
1	80 mg or less	±10
2	More than 80 mgbut less than 250 mg	±7.5
3	300 mg or more	±5

Hardness test
The hardness of the tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage, transportation, and handling before usage depends on its hardness. The hardness of the tablet is found using Pfizer tester.

Thickness
Tablet thickness is an important characteristic in reproducing appearance and also in counting byusing the filling equipment. The thickness of the tablets was measured using Vernier calipers. It is expressed in mm.

Friability
It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets has determined by using Roche friabilator. The percentage friability is calculated by, F = [(Wi -Wf)/Wi] 100

Where; F = friability, Wi = initial weight, Wf = final weight

Content uniformity
Ten tablets were weighed and powdered. The powder equivalent to 100 mg Nifedipine content was determined by measuring the absorbance at 235 nm after appropriate dilution.

Swelling index
The extent of swelling was measured in terms of % weight gain by the tablet. One tablet from each formulation was kept in a Petri dish containing a pH 6.8 phosphate buffer. At the end of 1 hr tablet was withdrawn, wiped with tissue paper and weighed. Then for every 1 hr, weights of the tablets were noted and the process was continued for 12 hr. Percentage weight gain by the tablet was calculated using the formula.

SI = (Mt – M0) / M0 ×100
where, SI = Swelling index
Mt = weight of tablet at time 't' M0 = weight of tablet at time t = 0

In vitro dissolution studies

The release rate of Nifedipine from sustained release matrix tablet was determined using the United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of dissolution medium at 37± 0.500C and 50 rpm. 0.1N HCl was used as dissolution medium for the first 3 hr, followed by pH 6.8 phosphate bufferfor 1 hr and stimulated colonic fluid (pH 7) for further 8 hr. A sample (5ml) of the solution was withdrawn from the dissolution medium after every hour and was replaced with an equal volume of fresh dissolution medium. Collected samples were diluted with the dissolution medium and the absorbance of these solutions was measured at 235 nm using a Shimadzu UV/Visible double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equationobtained from a standard curve.

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