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Research Article

Development of Sustained Release Pellets of Nifedipine by Extrusion-Spheronization Method

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ABSTRACT

Nifedipine is an antihypertensive drug used for the treatment of hypertension. Nifedipine is Biopharmaceutical Classification system (BCS) class-II drug having low solubility and high permeability. The sustained release pellets were formulated to reduce the side effects, decrease the administration frequency, and maintain plasma concentration within a therapeutic range to provide a consistent drug concentration at absorption site. These pellets in the size range of 650 to 900 µm that they tend to disperse more effectively in the gastrointestinal tract, enhancing drug absorption and minimizing local irritation. The sustained release pellets were prepared by extrusion-spheronization method using microcrystalline cellulose as filler, hydroxypropyl methyl cellulose as the release polymer and isopropyl alcohol as binder. The sustained release pellets of Nifedipine were characterized for Pellet size analysis, Drug content, micrometric properties. The best formulation was characterized for the In-vitro release studies and stability studies. The F2 batch had the particle size of 750µm, drug release of 82.12±0.05% after 8 hours. Accelerated stability studies and long term stability studies was performed and found to be satisfactory. Thus, it can be concluded that the developed formulation would be a promising delivery system with potential dissolution, patient compliance and sustained release of the drug.

INTRODUCTION

Oral drug delivery is the common route of drug administration. It provides high degree of patient satisfaction, flexibility in formulation and stability. This also has an advantage of cost effectiveness in its manufacturing process [1]. Some factors that affect the absorption of these orally administered drugs include frequent dosing, that leads to fluctuation in plasma concentration

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and can also leads to toxicity. The drug delivery system was modified to extended release dosage forms to overcome these demerits [2]. The goal of developing a sustained release (SR) dosage form is to keep the drug at blood or tissue levels for a longer duration of time. Drug delivery systems with sustained release minimize side effects, decrease administration frequency, maintain plasma concentration within a therapeutic range, and provide a consistent concentration at the absorption site. The SR dosage forms are two type; single unit dosage forms and multiunit dosage forms (MUDF) where the MUDF present some biopharmaceutical advantages, in the duration of action, gastric emptying when compared to single unit dosage forms. Recently, there has been an increase in the use of MUDF, like pellets and granules.[3]. As a dosage form, pellets have been gaining more and more attention recently. Therapeutic benefits of using pellets as a drug delivery system include decreased gastrointestinal tract irritation and a decreased chance of adverse effects from dose dumping.

Pellets

Pellets has been used to characterize a range of geometrically defined, systematically produced agglomerates that were obtained from various starting materials under various processing conditions. Their typical size falls between 0.5 and 1.5 mm, and they are primarily meant to be taken orally. In addition to their technological benefits, pellets as a drug delivery system have better flow characteristics, a less friable dosage form, a narrow particle size distribution, ease of coating, and uniform packing. Some desired benefits of pellets include their ability to design and develop flexible dosage forms, reduce variability in drug dissolution and plasma profiles, and uniform packing characteristics, improve drug safety and efficacy, and allow the drug to freely spread throughout the GIT[4-6]. Main two methods of formation of pellets are by melt pelletization and extrusion spheronization method (ESM). The extrusion–spheronization technique is most popular among the method of producing pellets. This includes mainly four steps: [7]

- Preparation of wet mass (Granulation)
- Shaping the wet mass into cylinders
- Breaking the extrudate and rounding the particles into spheres (spheronization)
- Drying the pellets

The process of ESM is the most commonly used technique for producing pellets. Extrusion/spheronization is a cost-effective technique for creating pellets with high drug loading and strength. When processing pellets using the ESM, a number of formulation and processing parameters must be determined and managed [8-9]. ESM is used in the pharmaceutical industry for the formulation of spherical particles of even size. This method is useful for the preparation of pellets with potential of high drug loading capacity. The formulated pellets can be used for the development of SR oral dosage forms. This technique provides the benefit of minimum possible use of excipients, simple, easy and fast processing and high efficiency [10-13].

Nifedipine

Hypertension is the most common preventable risk factor for cardiovascular disease (CVD); including coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation and peripheral artery disease, chronic kidney disease and cognitive impairment, and is the leading single contributor to all-cause death and disability worldwide. The relationship between BP and the increased risk of CVD is graded and continuous, starting at BPs as low as 115/75 mm Hg, well within what is considered to be the normotensive

range.[14,15]. Nifedipine is a calcium channel blocking agent used in the treatment of various cardiovascular diseases, long term treatment of hypertension and angina pectoris. During the depolarization phase of smooth muscle cells, there is an influx of calcium ions through voltage-gated channels. Nifedipine inhibits the entry of calcium ions by blocking these voltage-dependent L-type calcium channels in vascular smooth muscle and myocardial cells. Reduced intracellular calcium reduces peripheral arterial vascular resistance and dilatation of coronary arteries, leading to a reduction in systemic blood pressure and increased myocardial oxygen delivery. Nifedipine thus has hypotensive and antianginal properties [16].

MATERIALS AND METHODS

Materials

Nifedipine (Yarrow chem products, Mumbai) was used as drug of choice, Microcrystalline Cellulose (Yarrow chem products, Mumbai) used as pelletizing agent for formulation of pellets. Hydroxypropyl methyl cellulose (Yarrow chem products, Mumbai) used as the polymer for the sustained release.Dicalcium phosphate (HiMedia) was used as filler and spheronising agent. Isopropyl alcohol (Loba Chemie) was used as solvent for the preparation of sustained release pellets. All other chemicals and reagents were of analytical grades.

Pre-formulation studies

The color, nature and odor of the drug was determined by visual examination.

Determination of solubility:

Nifedipine solubility was determined by dissolving an excess amount of the drug in 10 ml of various solvents. The mixtures were shaken for 24 hours at 37±0.5°C. Samples from each solvent system were filtered and diluted accordingly. A UV spectrophotometer was used to measure the concentration of Nifedipine in each solution. Measurements were made in triplicate.

Method of preparation of Nifedipine Pellets

Extrusion/spheronization technique was applied to prepare SR pellets of Nifedipine. The compositions of SR pellets are tabulated in Table 01. All the dry ingredients were added and mixed together in the mortar. Sufficient amount of Iso-propyl alcohol was added to dissolve the drug completely. Required amount of water was added to prepare the wet mass. The prepared wet mass was loaded into the extruder of pore size 1mm. The extrusion process was done at speed of 50 rpm. The formed extrudates were added to the spheronizer and made to rotate at speed of 1200 rpm. The prepared pellets were dried in hot air oven for 8 hours[17].

Table 01: Composition of sustained release pellets of Nifedipine

Ingredients (in mg)	F1	F2	F3	F4	F5
Nifedipine	30	30	30	30	30
MCC	55	54	52.8	52.4	51
HPMC K100 M	5	6	7.2	7.6	9
Dicalcium phosphate	10	10	10	10	10
Magnesium stearate	0.9	0.9	0.9	0.9	0.9
Isopropyl alcohol	qs	qs	qs	qs	qs

Characterization of Nifedipine Pellets:

Pellet size analysis

The particle size of the pellet formulation was done through sieve analysis. All the formulation were passed through 3 different meshes (# 16, # 20, # 22). The percentage retained were calculated and the mean particle size was determined [19].

Drug content

The drug content of prepared pellets was measured using UV spectrophotometry. 10 mg equivalent pellets were weighed and crushed. The powdered pellets were dispersed in methanol and filtered. 1 ml of the filterate was made up to 10ml using HCl buffer pH 1.2. The absorbance was determined by UV spectrometry [18].

Micromeritics properties: [20]

Angle of Repose: The angle of repose of prepared pellets was determined by fixed funnel method. Each formulation of pellets was allowed to flow through the funnel freely onto the surface. The radius of the pellet cone was measured and angle of repose was calculated using the formula,

$$\text{Angle of Repose } (\theta) = \tan^{-1} \left(h/r \right)$$

Where h and r are the height and radius respectively

Determination of Bulk density (BD) and tapped density (TD): Each formulation was poured into measuring cylinder and the volume was measured. The cylinder was set for 100 taps and after that volume was measured. The bulk density and tapped density were calculated using the formula,

$$\text{Bulk density} = \text{Mass of pellets} / \text{Bulk volume}$$

$$\text{Tapped density} = \text{Mass of pellets} / \text{Tapped volume}$$

Compressibility index (Carr's index): The Carr's index was calculated by the formula,

$$\text{Carr's index (\%)} = [(TD - BD) / TD] \times 100$$

Where TD is the tapped density and BD is bulk density

Hausner's Ratio: It was measured by the ratio of tapped density to bulk density

$$\text{Hausner's Ratio} = \text{Tapped density} / \text{Bulk density}$$

***In-vitro* drug release studies:**

The USP dissolution basket method was used for the in-vitro release of the prepared sustained release pellets. 30 mg equivalent weight of pellets were weighed and added to 900 ml dissolution medium (HCl buffer pH 1.2). The temperature was maintained at 37±0.5°C. The samples were withdrawn for a time period of 8 hours and absorbance was measured by UV spectrometry.

Stability studies as per ICH guidelines:

Stability studies was carried out for one of the best sustained release pellet formulation as per the ICH guidelines. Stability studies were conducted under accelerated (40 ± 2°C, 75% ± 5% relative humidity (RH)) condition for over a period of 3 months. The samples were taken at different intervals (0, 1, and 3 months) and evaluated for physical appearance, drug content and drug release studies [21].

RESULTS AND DISCUSSION

Pre-formulation studies

The observed results showed that the organoleptic properties were within the reported literature limits and indicated the drug was pure. The solubility was determined in various solvents and the values indicated the high solubility of Nifedipine in Iso propyl alcohol and methanol.

Pellet size analysis

From the observed values of pellet size, the mean size of the pellets of 5 batches are given in the table. The pellet produced have a size range from 657.5 to 888 µm. It was observed that the mean pellet size increased with the increase in the polymer concentration of HPMC K 100M.

The values of angle of repose for all 5 formulations are less than 25° indicating excellent flow properties. The Carr's index values were less than 10% and Hausner's ratio were within 1 to 1.11. Both values shows that the prepared pellets had an excellent flow properties.(Table 02)

Micromeritic parameters

Table 02: Micromeritic parameters of sustained release pellets of Nifedipine (F1 to F5)

Formulation code	Angle of repose (°)	Bulk density (g/cc)	Tapped density	Carr's Index	Hausner's Ratio
F1	25.82±0.21	0.649±0.01	0.653±0.03	0.612±0.015	1.0061±0.01
F2	25.46±0.15	0.671±0.03	0.674±0.02	0.445±0.011	1.0044±0.04
F3	27.43±0.25	0.633±0.02	0.636±0.01	0.471±0.020	1.0047±0.02
F4	29.05±0.18	0.619±0.04	0.623±0.03	0.642±0.014	1.0048±0.02
F5	29.51±0.20	0.617±0.03	0.625±0.01	0.483±0.014	1.0064±0.03

Drug content

The results obtained showed the Nifedipine content ranged from 82 to 88% of the theoretical content that revealed a homogeneous drug distribution in the prepared pellets.

***In-vitro* release study**

The dissolution test was carried out for all the formulations. F1 release was found to be 85.5% at 8 hours which is due to the less concentration of release polymer HPMC K100M. The release profiles of all 5 formulations are shown in the table 03. The release of formulation F2 to F5 was found to be decreasing from the release value of F1 as the concentration of polymer increases. The dissolution profile is given in the. Fig. 1

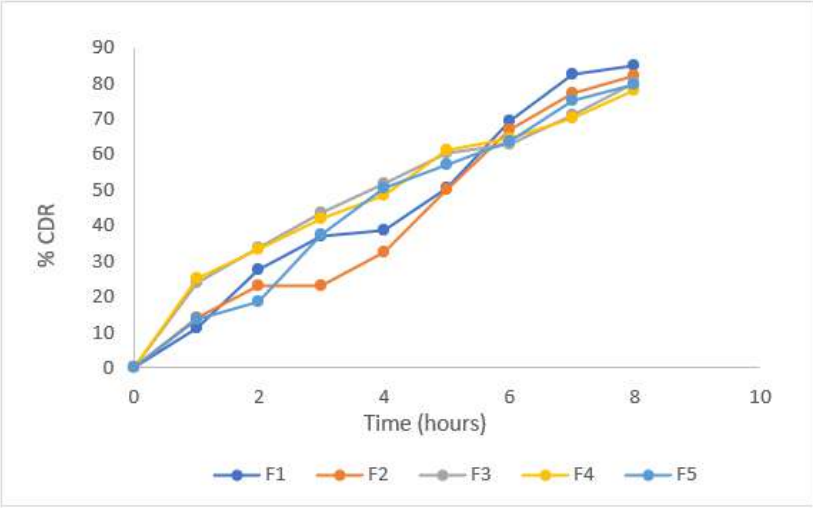

Figure 1: *In-vitro* Drug release profile of Nifedipine (F1-F5)

Table 03: *In-vitro* drug release profile

Time (hours)	% Cumulative drug release				
	F1	F2	F3	F4	F5
0	0 ± 0.00	0± 0.00	0± 0.00	0± 0.00	0± 0.00
1	11.33±0.51	14.18±0.73	23.91±0.53	25.27±0.13	13.87±0.46
2	27.74±0.60	22.97±0.38	33.95±0.26	33.44±0.33	18.66±0.29
3	37.18±0.16	23.10±0.16	43.70±0.24	41.83±0.24	37.52±0.33
4	38.50±0.50	32.43±0.33	51.77±0.72	48.65±0.49	50.51±0.21
5	50.69±0.49	50.12±0.38	60.57±0.24	61.26±0.33	57.10±0.16
6	69.18±0.16	67.07±0.30	62.73±0.58	64.47±0.21	63.63±0.13
7	82.56±0.73	77.06±0.29	69.24±0.16	70.23±0.73	75.25±0.49
8	85.05±0.21	82.12±0.53	80.05±0.38	79.94±0.29	79.44±0.33

Stability studies

The accelerated stability studies of F2 formulation showed satisfactory results for the physical appearance, drug content and % cumulative drug release for 8 hours at different intervals 0, 30, 60 and 90 days.

CONCLUSION

The sustained release pellets were prepared by extrusion spheronization method. The prepared pellets were evaluated for characterization of the pellets for different parameters and *in-vitro* drug release studies. The FTIR spectra revealed that, there was no significant interaction between the drug and the excipients, thus indicating the compatibility of Nifedipine and excipients used. The particle size of the prepared batch of pellets were between 600 to 900 µm indicating more dispersibility in the GIT. The micromeritics characterization for the pellets were found to be within the literature limits. The values of angle of repose and other micromeritic values revealed that the pellets had an excellent flow property. The *in-vitro* drug release showed that 85.05±0.021% of drug was released in 8 hours and the release rate decreases as the concentration of the release polymer, HPMC K100M increases. Hence it was proved that the prepared formulation was found to be stable.

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