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Research Article

Innovative Approach to Sustain the Release of the Drug from Conventional Dosage Form Nifedipine Sustained Release Tablet

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Abstract

Novel drug delivery systems are the best choice for current scenario of Pharmaceutical and medical demands. Novel Drug Delivery Systems (NDDS) and technologies are very effective but at the end the manufacturing cost of finished dosage form goes on top, because of new materials, time consuming process and machinery. In the current research work we were aiming to develop a new excipient from few commonly available materials by mixing together and binding with a binder. Granules of corn starch and pre- gelatinized starch or soluble starch at certain ratio with a binder, works as sustain release agent in conventional dosage form. Formulation with newly prepared material exhibit neither very slow nor very fast rates of drug release. Compressed tablets were prepared by direct compression with SRmixK and wet granulation method using different concentration of Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl Cellulose (EC), Eudragits (RS and RL) to scrutinize their influence on tablet properties and drug release profile. In vitro drug release studies were carried out using USP type II apparatus in 900 mL of sodium phosphate buffer (pH 7.4) with 0.5% (w/v) SDS. The total quantity of drug released was determined at 238nm thru UV-visible spectrophotometer. *In vitro* dissolution studies designated that hydrophobic polymers significantly reduced the rate of drug release compared to hydrophilic ones in 12hrs., while SRmixK exhibited the best release profile to sustain the drug release for prolong period.

Keywords: BCS Classification; Nifedipine; Srmixk; Sustain Release

Introduction

Bio-pharmaceutics Classification System likewise named as BCS, it describes drug molecules in four classes, based on their aqueous solubility and permeability. Classification of system was developed by Amidon, et al. [1].

1. Class I-High Permeability, High Solubility, Class II-High Permeability, Low Solubility
2. Class III-Low Permeability, High Solubility and Class IV-Low Permeability, Low Solubility.

As class II drugs exhibit low solubility and high permeability characteristics. Such drugs have poor oral absorption and are mostly governed by in vivo dissolution rate; the solubility and the dissolution rate are therefore key determinants for the oral bioavailability of these drugs. This implies that a small increase in the dissolution rate will result in a multifold increase in bioavailability [2-5]. Numerous techniques are developed to enhance bioavailability, in-vivo dissolution and manage release pattern of drugs in from the selected dosage form. Scientists are focusing to develop convenient method for such issues. The author aiming to develop a simple approach to manage release pattern of few drug molecules from conventional dosage form. These approaches are related with fine-tuning with formula, process or excipients. In this article au-

thor want to represent that combination of few regular and common excipients can manager drug release profile from the selected dosage form. Selected drug was Nifedipine and dosage form was uncoated tablet and targeted drug release profile was like the USP monograph (12 h) [3,4].

Nifedipine belongs to calcium channel blocker category, which is mainly used for the treatment of hypertension and angina pectoris. Nifedipine is a suitable molecule for controlled release administration due to its short elimination half-life (2-4 hrs.), its rapid and complete drug absorption over the entire gastrointestinal tract, despite its low water solubility and the relationship between drug plasma concentrations and blood pressure reduction. The significance of reduced peak plasma levels to avoid adverse effects such as reflex tachycardia has also been demonstrated [3-5].

Conventional dosage form need to be administered three to four times a day for desired drug in the systems while controlled release formulations are best choice to avoid dosing frequency. On other hand to develop such controlled release formulations are quite expensive because of control release excipients resulting not affordable to the entire poor patient [5].

Every year more than 150 billion U.S. dollars. According to GBI Research, the entire drug delivery market is forecast to grow to $199 billion in 2016 from $101 billion in 2009 while the prediction of controlled and sustained release drug release is expected to reach $92 billion by 2016 from the present value of $49 billion. We are developing few innovative techniques with all common excipients to get a new excipient which will control the drug release pattern from conventional dosage form. We named our new material as SRmixK. Our controlled release formulation of Nifedipine is available with matching all USP monographs such as - dissolution rate as per time. We have avoided any other expensive excipients, process, and equipment and coating technique (Such as coated granules) [6].

On other hand-One of the most commonly used methods of modulating drug release is its inclusion within a matrix system. Matrix systems have achieved extensive importance in controlled drug Delivery. Matrix systems are usually based on hydrophilic, hydrophobic and plastic (inert) polymers. Few common polymers are HPMC, Ethyl cellulose (EC) Eudragit RS and Eudragit RL but these are quite expensive as compared to SRmixK [5,7].

Granulation in Pharmaceuticals

Granulation is a key part for pharmaceutical tablet technology, granules improve product flow ability, increase material density, improve powder compressibility during the tablet compression, eliminate dust and improve drug content uniformity. Alternatively, excipient selection in the entire process can be challenging [4,5,7]. In the current scenario, maximum formulation scientists and leading companies tend to dictate a preference for dry, high-shear or fluid-bed granulation approach. If demand of extended drug-release times is required, concentrations of the polymer must be increased or higher molecular weight polymers must be chosen to achieve the desired release profiles, but here cost of the product will be raised. Since wet granulation can be a labor-intensive operation and high molecular weight polymer like cellulose ethers sometimes impose manufacturing difficulties. For dry granulation technique roller compaction can be an ideal choice but roller compaction also avoids rapid polymer swelling in water. Newly, formulation scientists have shown that hot melt extrusion is a viable option to prepare a solid dispersion of the drug provided the processing temperature is maintained below the polymer glass transition temperature. These all technologies increase cost of the products. Another objective of this work was to evaluate drug release data using various kinetic models to determine the mechanism of drug release [7-9].

Materials and Methods

Materials- we used Diluents-MCC 101, MCC102, Corn Starch, Soluble Starch, Lactose Monohydrate, Glidant -Aerosil, Lubricant-Magnesium stearate, Stearic acid, Binder-PVPK-25 and PVPK-30. All other chemical reagents used were of pharmaceutical grade. All aqueous solutions were prepared exclusively in distilled water and non-aqueous solution in IPA and MDC.

Preparation of SRmixK

We prepared SRmixK as a new excipient to modify the release pattern of the drug. To get granular form of this new excipient we made few small size batches with common excipients, binder and solvent (Table 1).

Sr.	Starch	PG Starch	PVPK-25	PVPK-30	Mannitol	Lactose	MCC 101	MCC 102	Total
S1	19.50	25.60	2.50	-	52.40	-	-	-	100
S2	-	36.50	12.48	3.50	21.78	25.74	-	-	100
S3	-	-	1.50	3.50	65.12	21.50	8.38	-	100
S4	-	54.00	2.20	-	-	-	43.80	-	100
S5	97.20	2.80	-	-	-	-	-	-	100
S6	23.00	18.00	2.50	-	-	-	-	56.50	100
S7	36.00	-	-	2.50	30.00	-	-	31.50	100
S8	25.00	25.00	3.00	-	12.00	9.00	26.00	-	100

S9	-	-	-	7.00	35.00	14.00	-	44.00	100
All above said quantities are in gm Table representing different formulations (S1-S9) with different concentration of excipients. Solvent used to get granular form of SRmixK-Distilled water, IPA, and IPA: MDC (70:30).									

Table 1: Formulation of SRmixK.

We found that granules with soluble starch, Mannitol, Lactose and PVPK-25 were very soft while Corn Starch, PVPK-30, Mannitol and MCC102 were very hard. After numerous trails with excipients we found that corn starch and soluble starch are enough to sustain the release pattern of the Nifedipine from tablet.

Compression of Tablet with SRmixK and other Material

Tablets were compressed by wet granulation method when used materials other than SRmixK and direct compressed method when used SRmixK as main component. After this sustained release material, we have added lubricants, glidant (Flow Promoter) and coating material. B type of tablet tooling used with 6.35mm of diameter. The compressed tablets were evaluated for various parameters

Tablet prepared with SRmixK was performed for film coating as per mentioned coating solution (Table 2).

Film Coating on F5,6,7,8 and F12 Formulation.		
Sr. No.	Material	per tab
1	Film Coating Material	3mg
2	IPA	8mg
3	MDC	8mg
The above table representing film coating of tablets formulated with SRmixK.		

Table 2: Film Coating Parameters.

Evaluation of Granules

Angle of Repose: Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. The angle of repose of the granules was determined by fixed funnel method to assess the flow property of the granules. The diameter of the granules cone (d) and the height (h) of the pile were noted. From the diameter, radius (r) was calculated. The angle of repose (θ) Was calculated using the following formula [8,9].

$$\theta = (\tan)^{-1} * (h/r)$$

Bulk Density (BD): An accurately weighed 25g of granules was transferred in 100-ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent BD in g/ml by the following formula [8,9].

BD = Mass of the granules (W)/Initial volume of the granules (V_0).

Tapped Density (TD): An accurately weighed 25g of granules transferred in a 100mL graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically TD tester that provides a fixed drop of 14±2mm at a nominal rate of 300 drops per min. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tap volume (V_f) to the nearest graduated units. If the difference between the two volumes is less than 2% of final the volume (V_f). Calculate the tapped BD by the following formula [9-11].

TD = Mass of the granules (W)/ Tapped volume of the granules (V_f).

Carr's Index: Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below [9,10].

Carr's index (%) = [(TD-BD) ×100] / TD.

Hausner's Ratio: Hausner's ratio is a number that is correlated to the flowability of a powder.

Hausner's ratio = TD / BD.

Evaluation of Compressed Nifedipine Tablets

Thickness and Diameter: The thickness of the tablets was determined using Vernier caliper and standard deviations were calculated. Five tablets from each batch were used, and average values were calculated.

Uniformity of Weight: Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percent variation of each tablet from the average weight of tablet was calculated [10,11].

Friability: The friability of the tablets was determined using 10 tablets from each formulation, with a friability tester (Erweka TAR-20) at a speed of 25rpm for 4min. The tablets were weighed before and after the friability test, and friability was determined as percent weight change [10,11].

Hardness: Hardness was determined by taking six tablets from each formulation using a digital tablet hardness tester (TBH 210 Erweka) and the average of pressure (N) applied for crushing the tablet was determined

Drug content (Assay): Ten tablets were weighed from each for-

mulation, powdered and equivalent to 20mg of nifedipine were weighed and dissolved in sufficient quantity of methanol and make up to 100ml with methanol. The solutions were suitably diluted with buffer solution pH 1.2 and the content of nifedipine was estimated spectrophotometrically at 238nm using pH 1.2 as a blank.

In Vitro Drug Release Study

In vitro release rate studies were carried out using dissolution apparatus type 2 (USP XXVIII) in 900ml of sodium phosphate buffer (pH 7.4) with 1% w/v sodium lauryl sulfate maintained at 37±0.5°C. The stirring speed was set at 50 rpm. At predetermined time intervals, a 5-ml sample was withdrawn and replaced with fresh dissolution media up to 12hrs. After appropriate dilutions, the samples were analyzed by the UV spectrophotometric method at 238nm. Cumulative percent of drug released was calculated and the mean of three tablets each from three different batches was used in data analysis.

Characterization of Release Kinetics

To study the release kinetics of Nifedipine from the tablets, the release data were fitted to the following equations:

Zero order equation

$Q.t = k_0.t$

Where Q is the percentage of drug released at time t and k_0 is the release rate constant;

First order equation

$\ln (100-Q_t) = \ln 100-k_1.t$

Where k_1 is the release rate constant;

Higuchi's equation

$Q.t = k_H.t^{1/2}$

Where k_H is the Higuchi release rate constant;

Furthermore, in order to better characterize the drug release mechanisms for the polymeric systems studied, Korsmeyer- Peppas semi-empirical model was applied: $Q_t/Q_\infty = k_{KP}.t^n$

Where Q_t/Q_∞ is the fraction of drug released at time t, k_{KP} a constant compromising the structural and geometric characteristics of the device, and n, the release exponent, which is indicative of the mechanism of drug release.

For the case of cylindrical geometries such as tablets, n=0.45 corresponds to a Fickian diffusion release (Case I), 0.45<n<0.89 to a non-Fickian (Anomalous) transport, n = 0.89 to a zero order (Case II) release kinetics and n>0.89 to a super Case II transport. For fitting the release data to the equations, only the points within the interval 10-70% were used. In the case of Higuchi model, the range was 10-60% [11-15].

Results and Discussion

Evaluation of SRmixK and Nifedipine Granules

Prepared granules of optimized formulation of SRmixK and Nifedipine were evaluated for the flow properties, LOD, and Density.

Drug release test were carried out at 1,2,4,6,8,10 and 12 hrs., showed that at 12 hrs. maximum on average 97.5% drug released from F5. Whereas, other batches showed maximum up to 89.9% drug release. Resulting SRmixK is capable to sustain the release patterns of Nifedipine from film coated tablet.

Physical Characterization of the Tablets

All the trial formulations were prepared as per the formula summarized in (Table 1). The prepared matrix tablets were evaluated for various physical properties as indicated in (Table 3).

Sr. No.	Hardness (k/cm)	Thickness (mm)	Friability (%)	Weight variation (%	Disintegration time
F1	4.5	2.62	0.26	0.56	1.1
F2	4.5	2.59	0.3	0.99	1.2
F3	5.3	2.63	0.19	1.25	1.6
F4	5.2	2.67	0.29	1.02	2.1
F5	5	2.66	0.36	1.08	3.3
F6	4.5	2.71	0.21	1.1	4.2
F7	5	2.73	0.26	1.9	3.8
F8	4.5	2.64	0.41	1.21	5.2
F9	5	2.66	0.27	0.48	1.6
F10	5.5	2.75	0.31	0.78	2.6
F11	5.5	2.66	0.36	0.98	6.5
F12	5.5	2.75	0.21	1.98	2.9
F13	6	2.9	0.38	1.24	4.6

Table representing post compression data of Tablets with different formulations.
Disintegration time is in minute.
All formulations had less than 1% of friability.

Table 3: Physical Parameters of compressed tablets.

All the batches were produced under similar conditions to avoid processing variables. Tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, drug content, hardness, friability and *in vitro* dissolution. As summarized in (Table 4).

Sr.	Nife-dipine	Lac-tose	MCC101	MCC102	Starch	Srmixk		Eudrag-ite RS	Eudrag-ite LS	HPMC	Ethyle Cellu-lose	Mg Stearate	Total
F1	20	33	27	-	-	-	3	15	-	-	-	2	100
F2	20	18	21.2	20	-	-	4	-	15	-	-	1.8	100
F3	20	-	32		25	-	2.5	18	-	-	-	2.5	100
F4	20	-	-	45	18.2	-	-	-	-	15	-	1.8	100
F5	20	5	-	66	-	2	-	-	-	-	-	2	95
F6	20	18	-	43.5	-	12	-	-	-	-	-	1.5	95
F7	20	-	61.5	-	-	12	-	-	-	-	-	1.5	95
F8	20	-	32.3	33	-	8	-	-	-	-	-	1.7	95
F9	20	45	-	-	-	-	-	-	-	-	28.5	1.5	95
F10	20	-	29	19.5	5	-	-	-	-	-	20	1.5	95
F11	20	66	-	-	-	-	2	-	15	-	-	2	105
F12	20	-	-	37	28	9	-	-	-	-	10	1	105
F13	20	12	18	-	28	-	2	-	24.5			0.5	105
All above said quantities are in gm/ tablet. Table representing different formulations (F1-F13) of tablets with different concentration of excipients.													

Table 4: Formulation of Sustained Release Tablet of Nifedipine.

All formulations showed uniform thickness. The weight variations of the tablet were between 0.38 and 1.67% which complying with pharmacopoeia specification. The tablets also passed the friability test while the friability ranged <1%. All the results are showing that the sustained release pattern can be achieved by numerous new generation excipients but our aim was to develop an excipient with SR release capacity. We found that SRmixK is having better sustained release capability as compare to Eudragite RS, LS or HPMC.

Stability Studies

Stability Study of a drug, Excipients or finished product has been defined as the ability in a specific packing, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time (Table 5).

Terms of Study	Storage condition		Minimum time period for study
Accelerated	40°C ± 2°C	75% RH ± 5% RH	6months
Long-term*	25°C ± 2°C 30°C ± 2°C	60% RH ± 5% RH 65% RH ± 5% RH	12months
Intermedi-ate**	30°C ± 2°C	65% RH ± 5% RH	6months
Conditions are depending of climatic zones. * It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C±2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH. ** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.			

Table 5: Stability study conditions and duration as per ICH guidelines

Under the influence of a variety of environmental factors such as temperature, humidity a light and enables recommended storage conditions, retest periods and shelf lives to be established. ICH Q1R (2) described all the details of Stability Study [5]. In the present work stability studies were carried out at 400C / 75 % RH for a specific time up to 6 months for the selected formulations and SRmixK.

Drug Release Kinetics

Regression coefficients of selected formulation was analyzed on different kinetic models. When the release data were subjected to first order, Higuchi, Korsmeyer and zero order models, selected formulations showed linearity regression values. The first order rate describes the release from systems, where release rate is concentration dependent.

The in vitro release profile of drug from formulations with SRmixK could be best expressed by Higuchi's equation, as the plot showed high linearity (r2=0.991) indicating that the release is principally controlled by diffusion. The Higuchi model is usually considered to be applicable up to about 75-83% of the drug released (Table 6).

In-vitro drug release from different formulations													
Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	7.2	7.6	6.5	7.2	8.1	6.5	6.9	7.2	7	7.1	6.8	6.5	6.1
2	12.1	11.5	12.8	13.5	14.7	12.6	14.5	12.9	11.8	13.1	12.9	11.98	13.5
4	25.9	26.8	31.2	29.2	35.1	30.5	31.2	29.8	28.9	29.7	29.9	31.8	31.3
6	40.8	39.8	39	39	47.9	42.2	46.8	42.1	39.4	41	43.2	40.8	39.7
8	59.9	53.5	54.1	57.7	67.7	65.2	68.2	60.1	57.8	52.5	58.3	54	64
10	65	60.1	62	72.5	78.1	73.5	75.9	75.2	69.9	68.2	71	70.9	73.3
12	71	69.9	71.2	75.2	97.5	78.2	83.2	85.8	87.6	86.5	84.6	85.2	89.9
Table representing drug releases from compressed SR tablet, with time interval.													

Table 6: In-vitro drug release from different formulations.

In Vitro Drug Release Studies

In the present research study, various retarding hydrophilic and hydrophobic polymers were used to control the release of Nifedipine from matrix tablets. To consider the effect of polymer type and percentage on drug release profile, different formulations containing various percentages of SRmixK HPMC, EC, Eudragit RSpo and RLpo and their combinations were prepared [12-16].

Conclusion

Sustained release formulation is the drug delivery system that is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Sustained release dosage form of Nifedipine using newly prepared material SRmixK and Drug release tested for 12 hours showed maximum for Batch F5 in an average 97.5%. Analysis of parameters for diameter, thickness, average weight, hardness and uniformity of weight under the limit of the Pharmaceutical for its effective formulation purpose. In (Figure 1).

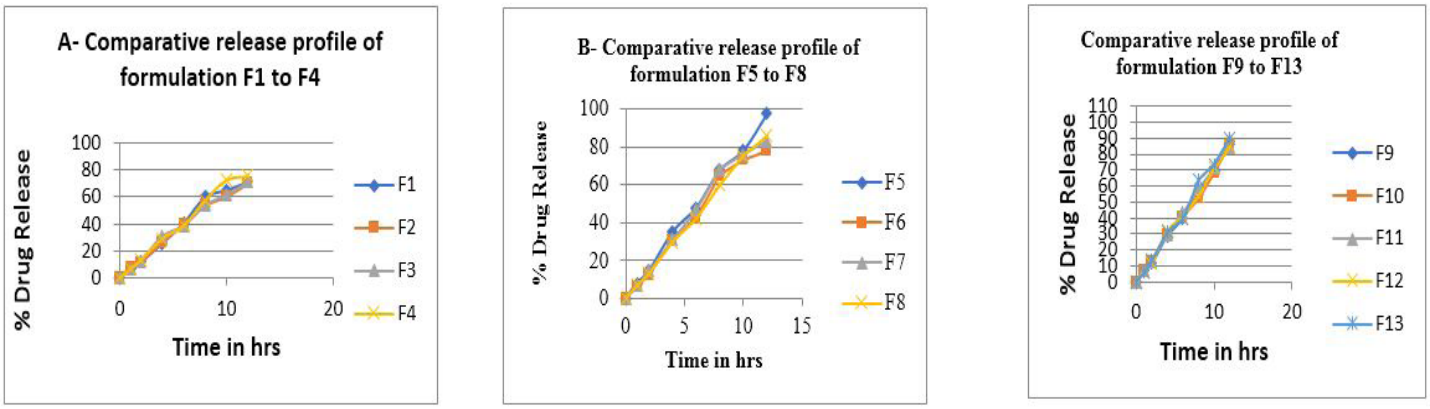

Figure 1: Comparative drug release (mean±SD) profiles from compressed tablet by using different materials and newly prepared SRmixK. clearly representing that prepared mix SRmixK drug release profile better and constant as compare to other materials.

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