RESEARCH ARTICLE

Formulation and *in vitro* evaluation of nifedipine-controlled release tablet: Influence of combination of hydrophylic and hydrophobic matrix forms

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The aim of the present work was to develop controlled release matrix formulation of nifedipine and investigate the effects of both hydrophilic and hydrophobic polymers on *in vitro* drug release. Matrix tablets were prepared by wet granulation technique using different concentration of hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC), compressible Eudragits (RSpo and RLpo) and their combination in different ratios to examine their influence on tablet properties and drug release profile. Tablets were evaluated by measurement of hardness, friability, content uniformity, weight variation and drug release pattern. 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 amount of drug released was determined at 238 nm by UV-visible spectrophotometer. *In vitro* dissolution studies indicated that hydrophobic polymers significantly reduced the rate of drug release compared to hydrophilic ones in 12 hrs and combination of both polymers exhibited the best release profile to sustain the drug release for prolong period of time. As a result, the tablet containing HPMC:EC in ratio of 0.75:1 showed better controlled release pattern over a period of 12 hrs. In selected formulation, the calculated regression coefficients for release models fitted best to zero-order models.

Key words: *Controlled release, matrix tablet, nifedipine, release kinetics*

INTRODUCTION

Biopharmaceutics Classification System (BCS) class II drugs exhibit low solubility and high permeability characteristics. Their oral absorption is mostly governed by *in vivo* dissolution; 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.[1]

Nifedipine is a calcium channel blocker of the dihydropyridine type which is mainly used for the treatment of hypertension and angina pectoris. Nifedipine is a suitable candidate for CR administration due to its short elimination half-life of 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.[2,3] The importance of reduced peak plasma levels in order to avoid adverse effects such as reflex tachycardia has also been demonstrated.[4]

Conventional tablets need to be administered three to four times a day and controlled release formulations of nifedipine would be effective in overcoming the dissolution limitation by slowing supplying the drug from the intact matrix base during its sojourn in the gastrointestinal tract and is thus expected to decrease side effects and improve patient compliance.[1]

A controlled release formulation of nifedipine has become available,[5] such as coated granules and matrix tablets,[6] polyacrylate polymethacrylate microspheres,[7] microcapsules and solid dispersions of nifedipine in polyvinyl pyrrolidone (PVP)-microcrystalline cellulose[8] and sustained-release tablets containing hydroxyl propyl methyl cellulose (HPMC) and cross-linked sodium carboxy methyl cellulose (CMC).[9]

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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, thanks to a simple and fast producing technology, low cost and low influence of physiological variables on their release behavior.

Matrix systems are usually classified in to three main groups; hydrophilic, hydrophobic and plastic (inert).

Hydrophilic polymers, based on their solubility in water, could be divided into two types; i) water-insoluble polymers including some carbomers and ii) water-soluble polymers such as HPMC.[10] HPMC is the most important hydrophilic polymer used at levels of 10-80% w/w to retard the release of drugs from the oral delivery systems.[11] This extensive use originates from the non-toxicity, high drug-loading capacity and non-pH dependence of the polymer.[12] When a hydrophilic matrix comes into contact with an aqueous medium, it absorbs water, hydrates and swells to form a gel through which the dissolved drug diffuses out. In terms of water-soluble polymer, dissolution of the polymer results in a gradual erosion of this gel layer. However, at higher concentrations, the polymer chains entangle to a greater degree culminating in virtual cross-linking and therefore formation of a stronger gel layer. These hydrogels do not erode in the same manner to HPMC and therefore, remain intact in the release medium, and the drug continues to diffuse through the gel layer at a uniform rate.[10]

Hydrophobic and inert polymers, which are capable of forming insoluble or skeleton matrices, have been widely used for controlling the release of drugs due to their inertness and drug embedding ability. Liquid penetration into the matrix is the rate controlling step in such systems, unless channeling agent are used.[13] Ethylcellulose (EC) and Eudragit RL or RS are among the well-known polymers in this category. EC is a non-toxic, stable, compressible, inert, hydrophobic polymer that has been widely used to prepare pharmaceutical dosage forms. The properties of EC-sustained release products, including film-coated tablets,[14] microspheres,[15] microcapsules[16] and matrix tablets for both soluble and poorly soluble drugs[17] have been reported. On the other hand, acrylic polymers are widely used as tablet coatings and as retardants of drug release in sustained-released formulations.[14,15] The most interesting acrylic polymers are high-permeable Eudragit RL and low-permeable Eudragit RS, both of which are neutral copolymers of poly(ethylacrylate, methyl methacrylate) and trimethyl aminoethyl methacrylate chloride, and are insoluble in water and digestive juices; but they swell and are permeable, which means that drugs embedded in their matrices can be released by diffusion. Therefore, the permeability of drug through Eudragit RS and/or RL is independent of the pH of the digestive tract. The degree of permeability depends on the relative proportion of quaternary ammonium groups in Eudragit. The proportion of functional quaternary ammonium groups in Eudragit RS and Eudragit RL is 5 and 10%, respectively.[18]

The aim of this study was to design and compare the release characteristics of controlled release oral formulations of nifedipine prepared using hydrophilic polymers such as methocel (HPMC) as well as hydrophobic polymers including Ethocel (EC), Eudragit RL and Eudragit RS either alone or in combination.

Another objective of this work was to evaluate drug release data using various kinetic models in order to determine the mechanism of drug release.

MATERIALS AND METHODS

Material

Nifedipine was obtained from Sigma Chemicals Co., USA. Eudragit RSpo, Eudragit RLpo, EC and HPMC were purchased from Rohm Pharma, Germany.

PVP-K90 was purchased from Mowiol (Germany). Microcrystalline cellulose (Avicel® pH 101), Lactose and magnesium stearate (MgSt) were provided from (Nordland Chemie, Germany). Acetone, methanol, potassium dihydrogen phosphate were obtained from Merck (Darmstadt, Germany). All other chemical reagents used were of pharmaceutical grade. All aqueous solutions were prepared exclusively in distilled water.

Preparation of the matrix table

Matrix tablets were prepared by wet granulation technique. All the components except lubricants were mixed for 15 minutes in the plastic bag. PVP K90 (5%) was dissolved in quantity sufficient of ethyl alcohol, and this solution was added into the above drug mixture to form a coherent mass. The wet mass was passed through a No. 12 sieve and it was dried at room temperature, 20-22°C for 8 hrs. Then, the granules were sized by passing through a "No. 16" mesh screen. Then mixed with 1% MgSt and compressed into 7-mm convex tablets using a single-punch tablet machine (Erweka, Germany). The compressed tablets were evaluated for various parameters. The amount of polymers and other ingredients are given in Table 1.

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.[19,20]

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

Table 1: Composition of controlled release matrix tablets of nifedipine (All the quantities expressed in percent)

Formulations	Nifedipine	Eudargite RLpo	Eudragite RSpo	EC	HPMC	Lactose	Avicel	PVP K90	MgSt
F_1	20	15	-	-	-	40	24	5	1
F_2	20	15	-	-	-	35	24	5	1
F_3	20	20	-	-	-	30	24	5	1
F_4	20	25	-	-	-	25	24	5	1
F_5	20	-	10	-	-	40	24	5	1
F_6	20	-	15	-	-	35	24	5	1
F_7	20	-	20	-	-	30	24	5	1
F_8	20	-	25	-	-	25	24	5	1
F_9	20	-	-	10	-	40	24	5	1
F_{10}	20	-	-	15	-	35	24	5	1
F_{11}	20	-	-	20	-	30	24	5	1
F_{12}	20	-	-	25	-	25	24	5	1
F_{13}	20	-	-	-	10	40	24	5	1
F_{14}	20	-	-	-	15	35	24	5	1
F_{15}	20	-	-	-	25	25	24	5	1
F_{16}	20	-	-	-	35	15	24	5	1
F_{17}	20	5	10	-	-	35	24	5	1
F_{18}	20	7.5	7.5	-	-	35	24	5	1
F_{19}	20	10	5	-	-	35	24	5	1
F_{20}	20	-	-	16	4	30	24	5	1
F_{21}	20	-	-	13.5	6.5	30	24	5	1
F_{22}	20	-	-	10	10	30	24	5	1
F_{23}	20	-	-	6.5	13.5	30	24	5	1
F_{24}	20	-	-	11.42	8.58	30	24	5	1

Bulk density (BD)

An accurately weighed 25 g 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:[19,20]

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

Tapped density (TD)

An accurately weighed 25 g of granules transferred in a 100-ml 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±2 mm 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:[19, 20]

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

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 (19, 20). The formula for Carr's index is as below:

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 (19, 20).

Hausner's ratio = TD / BD

Evaluation of nifedipine matrix 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.[21]

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 25 rpm for 4 min. The tablets were weighed before and after the friability test, and friability was determined as percent weight change.[21]

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.[21]

Drug content (Assay)

Ten tablets were weighed from each formulation, powdered and equivalent to 20 mg of nifedipine were weighed and dissolved in sufficient quantity of methanol and make up to 100 ml with methanol. The solutions were suitably diluted with buffer solution pH 1.2 and the content of nifedipine was estimated spectrophotometrically at 238 nm using pH 1.2 as a blank.[21]

***In vitro* drug release study**

In vitro release rate studies were carried out using dissolution apparatus type 2 (USP XXVIII) in 900 ml 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 12 hrs. After appropriate dilutions, the samples were analyzed by the UV spectrophotometric method at 238 nm. 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 matrix tablets, the release data were fitted to the following equations:

Zero order equation[22]

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

First order equation[23]

$\ln (100\text{-}Q_t) = \ln 100 - k_1.t$ where k_1 is the release rate constant;

Higuchi's equation[24]

$Q.t = k_H.t^{1/2}$ 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[25] 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%.[10]

RESULTS AND DISCUSSION

Evaluation of nifedipine granules

Prepared granules of optimized formulation of nifedipine were evaluated for the flow properties [Table 2]. Results of characterization of prepared granules showed angle of repose 34° 75', Carr's index 10.54 and Hausner's ratio 1.13. These values indicate that the prepared granules exhibited good flow properties.

Physical characterization of the tablets

All the formulations were prepared according to the formula given in Table 1. The prepared matrix tablets were evaluated for various physical properties as indicated in Table 3. 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 3, all formulations showed uniform thickness. The weight variations of the tablet were between 0.38 and 1.67% which complying with pharmacopoeial specification.[21] The drug content of all formulations ranged from 95.41 to 102.31%, indicating the presence of an acceptable amount of drug in the formulations.[15] Different polymers yielded matrix tablets with various hardness values, ranging from 55.89 N (for formulations containing HPMC) to 93.16 N (for those prepared using binary mixture of Eudragit RLpo and RSpo) indicating satisfactory mechanical strength. The tablets also passed the friability test while the friability ranged from 0.1(for formulations containing EC) to 1.8% (for formulations containing Eudragit RSpo). These results showed that except of formulations containing Eudragit RSpo, other formulations are within the prescribed limits.[26]

***In vitro* drug release studies**

In this study, various retarding hydrophilic and hydrophobic polymers were used to control the release of nifedipine from matrix tablets. In order to investigate the effect of polymer type and percentage on drug release profile, different formulations containing various percentages of HPMC, EC, Eudragit RSpo and RLpo and their combinations were prepared. The drug release results are shown in Figures 1 and 2.

Hydrophilic matrix

Figures (1a and 1b) show the effect of different concentrations of Eudragit RLpo or RSpo (10, 15, 20 and 25 w/w) on release rate of nifedipine.

As it can be seen in Figure 1a, formulation F1, which contained 10% of RLpo, about 80% of the drug released in the first 2 hrs and a sustained-released profile was not observed. This might be due to the higher number of quaternary ammonium groups and greater permeability of RLpo. By increasing the amount of RLpo in the formulation, release rate was decreased.

Formulation F2, F3 and F4 containing 15, 20 and 25% RLpo showed 95.93±1.7, 91±4.4 and 88.3±1.47% released drug

Table 2: Evalution of granules of optimized formulation

Optimized formulation	Bulk density (%)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
F^{24}	0.3691±0.01	0.4126±0.02	10.54±0.05	1.13±0.01	34.75±0.11

Table 3: Physical characteristics of designed controlled release matrix tablets of nifedipine

Batch	Hardness (N)	Thickness (mm)	Friability (%)	Weight variation (%)	Drug content (%)
F_1	77.86±0.6	2.27±0.086	0.6	0.54	99.47±0.3
F_2	82.57±0.21	2.25±0.027	0.7	0.5	99.98±0.51
F_3	69.23±1.44	2.25±0.043	0.9	1.38	99.54±0.16
F_4	76.29±1.36	2.22±0.018	0.6	0.61	98.32±0.58
F_5	62.27±0.22	2.25±0.028	1.8	0.38	98.66±0.96
F_6	64.72±0.96	2.22±0.053	1.6	1.32	99.7±0.15
F_7	77.47±0.55	2.36±0.039	1.3	1.25	98.82±0.56
F_8	66.68±0.63	2.28±0.036	1.4	0.68	99.11±0.64
F_9	71.58±0.47	2.16±0.029	0.1	0.64	99.39±0.052
F_{10}	64.72±0.45	2.25±0.042	0.2	1.33	99.76±0.10
F_{11}	67.66±0.78	2.35±0.046	0.5	1.19	98.38±0.46
F_{12}	59.52±0.31	2.41±0.032	0.6	1.48	99.49±0.16
F_{13}	55.89±1.89	2.42±0.01	0.8	0.8	100.02±0.84
F_{14}	62.76±0.68	2.35±0.13	0.9	0.92	101.36±0.98
F_{15}	85.31±0.57	2.21±0.046	1	0.91	99.48±1.21
F_{16}	76.49±0.36	2.4±0.015	1.1	0.99	98.5±0.48
F_{17}	82.37±0.84	2.22±0.075	0.9	1.23	99.2±1.18
F_{18}	93.16±0.28	2.1±0.026	1	0.9	96.8±0.15
F_{19}	88.45±0.6	2.17±0.078	1.1	0.83	102.3±0.89
F_{20}	74.53±0.1	2.33±0.063	0.5	1.36	95.41±1.3
F_{21}	76.49±0.16	2.3±0.046	0.6	1.16	97.83±0.68
F_{22}	84.33±0.77	2.22±0.055	0.9	1.29	98.8±0.19
F_{23}	92.18±0.64	2.23±0.058	1.1	1.63	96.99±0.96
F_{24}	81.37±0.19	2.28±0.042	0.7	1.37	102.4±1.17

in 12 hrs, respectively, indicating a significant effect of RLpo concentration on a reduction in the release rate.

According to Figure 1b, formulations containing RSpo released their drug content in a more sustainable fashion than formulations containing RLpo, because Eudragit RLpo tends to swell and permeable more than RSpo in aqueous medium.[27,28]

Similarly, formulations containing 10-25% of Eudragit RSpo was unable to act as sustained-release matrix tablets, but RSpo (15%) with desired release profile was selected for further studies. However, the results of the present study were in good agreement with the results obtained by other researcher.[28,29]

According to Figure 1c a new series of matrix tablets was then prepared by using combinations of Eudragit RLpo with Eudragit RSpo with the aim of obtaining more regular and reproducible release profiles. To produce the mixed granules, 15% w/w of combined matrix proportion was selected. Each set contained three different ratios of RLpo and RSpo. The release rate of nifedipine in 8 hrs was 78.63, 84.5, and 72.33% from the formulations with different ratios (1:1, 1:2 and 2:1) of RLpo and RSpo. So, according to the results, none of these combinatory formulations provided a suitable sustained-release profile.

It is reported in the literature, that released drug more than 30% in the first hour of dissolution indicates the chance of dose dumping. As indicated in Figures 1-2, tablets containing Eudragit RLpo and RSpo alone and in combination (F1, F5, F17 and F18) showed initial burst release during first hour. This phenomenon may be attributed to surface erosion or initial disaggregating of the matrix tablet prior to gel layer formation around the tablet core.[29]

Hydrophobic matrix

Figure 2a shows the release of nifedipine from hydrophobic matrix tablet containing 10-25% EC (F9-12). Incorporating EC in the matrix tablets considerably decreased the drug release profiles. Formulation F9 and F10 containing 10 and 15% EC were able to sustain the drug release for 8 and 10 hrs, respectively.

In case of formulation F11, F12 containing 20 and 25% EC

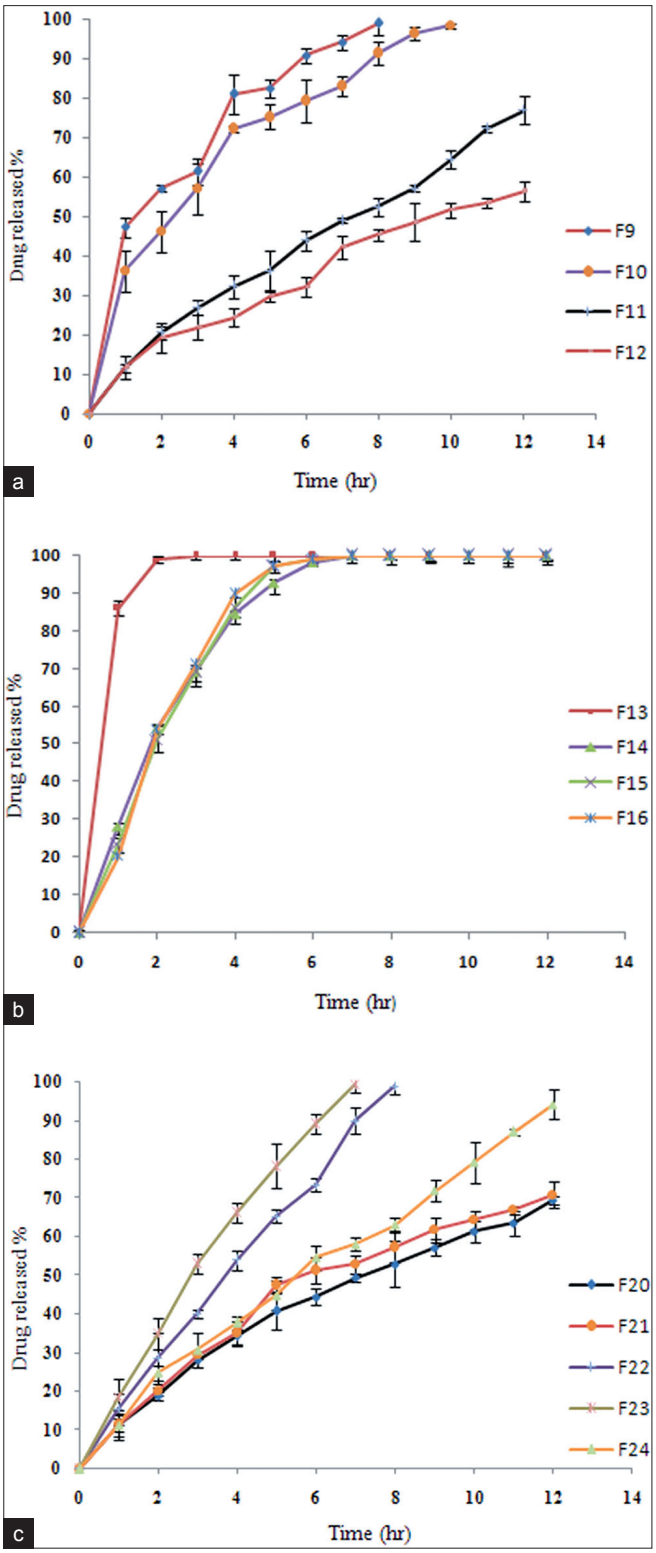

Figure 1: Comparative release (mean±SD) profiles of nifedipine from CR matrix tablets prepared using different proportions of (a) Eudragit RLpo, (b) Eudragit RSpo and (c) combination of both Eudragit RLpo and RSpo

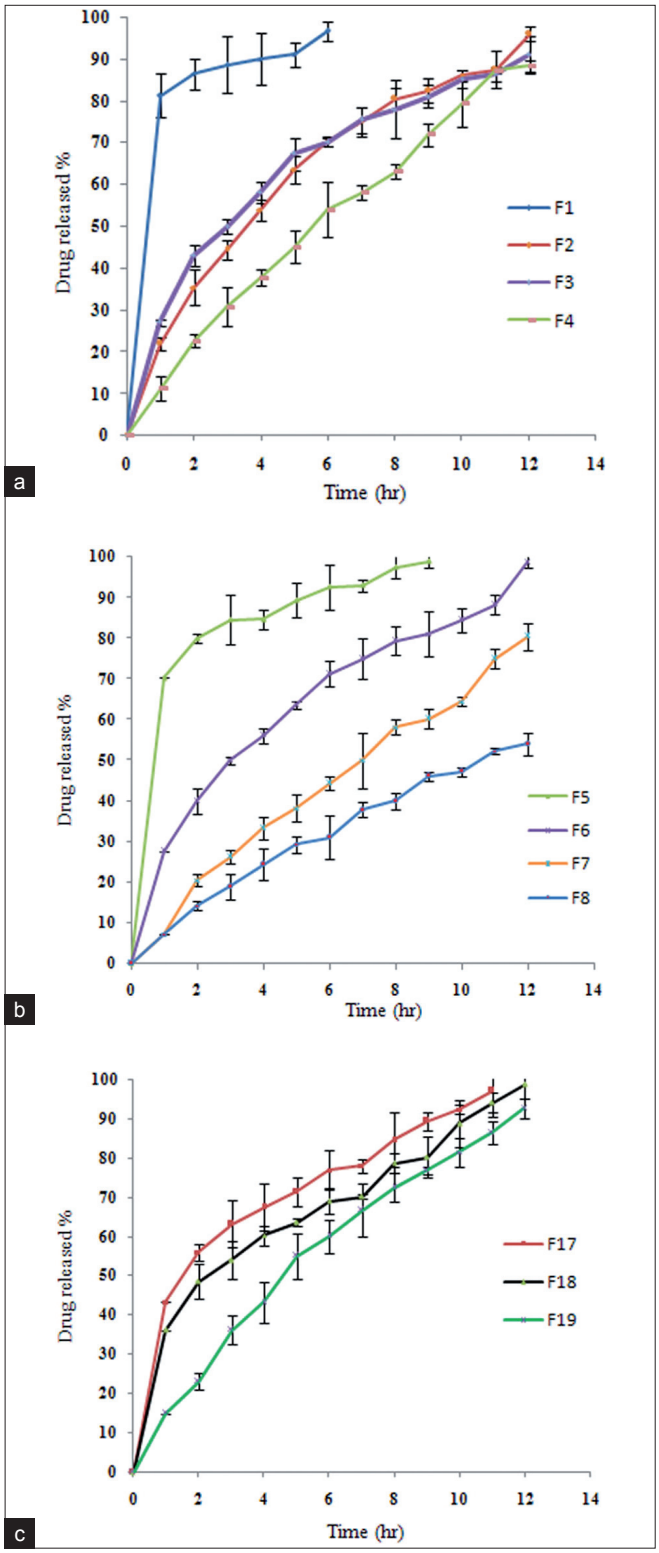

Figure 2: Comparative release (mean±SD) profiles of nifedipine from CR matrix tablets prepared using different proportions of (a) EC (b) HPMC and (c) combination of both EC and HPMC

showed 77±3.73 and 56.45±2.39% drug released in 12 hrs, respectively, and in formulations F11, F12 only 56 to 77% of drug was released. In fact, drug released too slow to be not suitable for a sustained-release system.

EC could reduce the drug release, due to a reduction in the penetration of the solvent molecules into the system because of the hydrophobic nature of polymer on the surface of the tablet.[28] Also, it is concluded that the hydrophobic nature of

EC restricts the formation of gel layer around the matrix.[28] This observation was in agreement with the other reported works, in which the drug release decreased from the matrix tablets of different drugs as the proportion of EC increased.[30,31] HPMC is hydrophilic cellulose ether, which is used as a retarding polymer in swellable matrices. Figure 2a shows the effect of different concentrations of HPMC 10% (F13), 15% (F14), 25% (F15) and 35% (F16) w/w of nifedipine tablet. All the four formulations released almost 100% of the drug in about 6 hrs and the rate of drug release could not be sustained for more than 6 hrs even by incorporating 35% of HPMC in the formulation. This may be due to structural reorganization of hydrophilic HPMC polymer which increased tortuosity or gel strength of the matrices. When HPMC polymer is exposed to aqueous medium, it undergoes rapid hydration and chain relaxation to form viscose gelatinous layer. Failure to generate a uniform and coherent gel may cause rapid drug release.[31]

Hydrophobic and hydrophilic matrixes

Mixed matrix formulations containing both HPMC and EC were also investigated due to undesirable release profiles obtained from HPMC and EC matrix tablets. To produce the mixed granules, 20% w/w of combined matrix proportion was selected. Each set contained 5 different ratios (0.75:1, 1:1, 1:2, 1:4 and 2:1) of HPMC and EC.

Figure 2c shows the release of nifedipine from the mixed matrix tablets. The release rate of nifedipine in 8 hrs was 63.09, 98.99, 57.42, 53.03 and 99.35% in mentioned different ratios of polymers as compared to 52.51% drug release from 20% EC alone [Figure 2a].

Figure 2c shows that formulation F24 that prepared with the blend of HPMC and EC (0.75:1) showed the desired release profile over the test period of 12 hrs. This formulation could release more than 90% of its content within 12 hrs. Therefore, formulation F24 was selected as the optimized formulation. This may occur due to presence of both hydrophilic and hydrophobic polymer which allows little swelling but did not allow rapid diffusion of the drug from the matrix.

By comparing Figures 2a and c, it is apparent that HPMC in the mixed matrix tablets had increased the drug release rate while EC acted as release retardant. A close examination of Figure 2a indicated that incorporation of release rate whereas slightly higher percentages of HPMC had remarkable effect on the drug release rate due to formation of channels which facilitated the entry of dissolution medium at faster rate.[32] Nevertheless, the combination effect of HPMC and EC slows down the diffusion process.

Drug release kinetics

Regression coefficients of different kinetic models presented in Table 4. When the release data were subjected to first-

Table 4: Kinetics of drug release from nifedipine matrix tablets

Formulations	Peppas		Zero order		First order		Higuchi	
	K_0 (%h^{-1})	R^2	K_1 (h^{-1})	R^2	K_H (%$h^{-1/2}$)	R^2	n	R^2
F_1	-	-	-	-	-		-	-
F_2	12.64	0.9504	0.2288	0.9667	59.66		0.648	0.9987
F_3	10.55	0.9358	0.1805	0.9904	50.06		0.564	0.9855
F_4	13.63	0.9913	0.1721	0.9565	62.88	0.9893	0.784	0.9984
F_5	-	-	-	-	-	-	-	-
F_6	10.98	0.9518	0.1994	0.9263	51.62	0.9933	0.485	0.9994
F_7	12.28	0.9941	0.1267	0.9626	56.56	0.9881	0.864	0.987
F_8	8.22	0.9904	0.0619	0.9963	38.00	0.9922	0.78	0.9985
F_9	14.35	0.9210	0.3293	0.9885	57.43	0.9708	0.416	0.9831
F_{10}	13.10	0.9528	0.3548	0.8479	52.81	0.98	0.446	0.999
F_{11}	11.11	0.9937	0.1115	0.9507	50.85	0.976	0.684	0.996
F_{12}	7.97	97.53	0.626	0.9777	36.57	0.9625	0.619	0.9682
F_{13}	-	-	-	-	-	-	-	-
F_{14}	27.80	0.9463	0.7026	0.9351	98.53	0.9885	0.847	0.9846
F_{15}	30.37	0.9488	0.8230	0.9496	109.14	0.9879	0.969	0.9894
F_{16}	31.37	0.9015	0.6715	0.9483	112.69	0.9607	1.118	0.716
F_{17}	10.11	0.9788	0.1771	0.9770	46.65	0.9773	0.823	0.9964
F_{18}	9.42	0.9679	0.2127	0.9520	42.40	0.9903	0.347	0.988
F_{19}	13.3	0.9712	0.2241	0.8065	62.12	0.9965	0.347	0.9865
F_{20}	9.26	0.9682	0.0825	0.9936	43.41	0.9969	0.675	0.9918
F_{21}	8.28	0.9405	0.0796	0.9836	39.18	0.9873	0.526	0.9843
F_{22}	23.58	0.9968	0.3878	0.8686	91.06	0.9777	0.863	0.9997
F_{23}	26.91	0.9902	0.5930	0.8235	99.88	0.9984	0.952	0.9989
F_{24}	13.43	0.9923	0.1821	0.9574	62.76	0.9893	0.786	0.9983

order, Higuchi, Korsmeyer and zero order models, F3, F8, F9 and F12 formulations showed linearity with regression values between 0.9777 and 0.9963 for first order. The first order rate describes the release from systems, where release rate is concentration dependent.

The calculated regression coefficients for the zero order model during the first part of the release process (up to 4 hrs) for formulations F4, F7, F11, F22 and F24 were between 0.9913 and 0.9968, so the drug release kinetics of these formulations fitted best to the zero order model. The zero-order rate describes systems where drug release rate is independent of drug concentration.

The *in vitro* release profile of drug from F2, F10, F23, F14, F16, F18 and F19 formulations could be best expressed by Higuchi's equation, as the plot showed high linearity (r^2= 0.9973) indicating that the release is principally controlled by diffusion. The Higuchi model is usually considered to be applicable up to about 75-80% of the drug released, or 75-80% of the time needed for complete release.[10]

For formulation F17, the r^2 value obtained from examining the zero order, first order and Higuchi models were found to be very close to each other throughout the whole series of investigated formulations. Similarly, in formulations F20 and F2, first order and Higuchi release kinetic models are more probable because r^2 values obtained from examining the first order and Higuchi models were found to be very close to each other.

To explore the release pattern, results of the *in vitro* dissolution data were fitted to the Korsmeyer and Peppas equations,[28] which characterizes the transport mechanism. Formulations F2, F4, F7, F8, F11, F12, F14, F15, F17, F20, F22, F23 and F24 showed good linearity (r^2= 0.9682 to 0.9997), with the slope or exponential value (*n*) ranging from 0.619 to 0.969. These n values confirmed that the formulations followed non-Fickian diffusion kinetics which indicated the release is controlled by more than one process.

The values of release exponent for formulations F6, F9, F10, F18, F19 and F21 were between 0.347 and 0.485, which were less than 0.5, indicating drug release by Fickian diffusion.

The value of n determined for formulation F16 was 1.118. Based on the value of n>1 obtained using the Peppas equation, release mechanism from matrices containing higher amounts of HPMC was found to be super case II. In super case II, in addition to diffusion, other release mechanism including matrix erosion and polymer relaxation might be involved.[10]

CONCLUSIONS

Results of the present study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release matrix tablets of nifedipine.

Hydrophilic matrix of HPMC alone could not control the nifedipine release effectively for 12 hrs. In hydrophobic matrix increasing the amount of polymers resulted in decreasing the release rate of drug.

It seems that a mixed matrix system containing both HPMC and EC showed that major part of the drug was released during 12 hrs compared to hydrophilic matrix in which almost 100% drug was released within 4 hrs. However, the test matrix tablets prepared by modifying the wet granulation method were found to produce desirable release rate.

The investigated controlled release matrix tablet was capable of maintaining constant plasma nifedipine concentration through 12 hrs. This can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional nifedipine tablets.

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