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ORIGINAL ARTICLE

Development of novel spray coated soft elastic gelatin capsule sustained release formulations of nifedipine

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Abstract
Nifedipine release from coated commercially available immediate release soft elastic gelatin capsules was investigated. Capsules were spray coated using two different polymeric combinations, ethylcellulose and hydroxypropylmethylcellulose or pectin, at different coating loads. In vitro drug release studies were conducted in three different dissolution media: with gastric pretreatment, without gastric pretreatment, and in water to investigate the pH effect on nifedipine release. Convolution of in vitro dissolution data for selected formulations and commercially available sustained release nifedipine formulations showed that the tested formulations provided release profiles of nifedipine that are very promising in terms of desirable sustained release formulations.

Key words: *Film coating; HPMC; nifedipine; simulation; soft elastic gelatin capsules; surelease®; Sustained release*

Introduction

Sustained release delivery systems have been extensively investigated over the past years. These systems provide numerous benefits over immediate release (IR) dosage forms that do not control rate of drug input. Frequent administration of IR dosage forms of short half-life drugs is required to maintain drug concentrations in the therapeutic range. As a result, drug concentrations fluctuate considerably in blood or tissues over time. Sustained release dosage systems are designed to release drug over an extended period of time to achieve a desirable pharmacodynamic response. Sustained release systems can maintain therapeutic concentrations of drug within narrow fluctuation, reduce frequency of dose administration, increase patient compliance, and minimize adverse side effects while reducing health care costs[1].

Formulation of drug into soft elastic gelatin (SEG) capsules has been used for many years as an IR oral dosage form. SEG capsules have several advantages: it can increase bioavailability of hydrophobic drugs as the drug can be incorporated in a liquid form, improve stability of drugs that are susceptible to oxidation or hydrolysis, eliminate many problems associated with tablet manufacturing including lack of content or weight uniformity and poor compaction[2].

Coating of SEG capsules has been reported to mask unpleasant taste, to improve appearance, and to control site of action. Recently, research has been published involving conversion of liquid-filled SEG capsules into controlled release dosage forms by application of a composite wall on the surface of IR SEG capsules. This wall is composed of a barrier layer formed over the surface of the gelatin capsules and then an expandable layer formed over the barrier layer, and a final coating layer that is a semi-permeable layer formed over the expandable layer. Drug release occurred through an orifice in the external layer formed by mechanical or laser drilling[3]. Production of such systems is complicated and costly. Therefore, conversion of IR SEG capsules to a sustained release formulation by applying a diffusional barrier membrane in only one extra step starting with commercially available, marketed SEG

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capsules and commonly used polymeric materials is reported herein, and represents a significant advance on the industrial scale.

Controlled release of drug from oral dosage forms can be influenced by film coating, which also depends upon the type of polymeric materials used in the coat. Controlled release of drug is influenced by application of permeable or semi-permeable coating. In permeable coating, water can diffuse into the drug-loaded core. If the drug is water soluble, it can permeate through the coat and drug release is controlled by permeability of the film membrane. However, if the film coat is permeable to water but not to the drug, drug release occurs through pores in the film coat under the influence of the osmotic pressure developed in the core. Controlled release by applying semi-permeable membrane can be achieved by formulation of an osmotically active system in which the tablet core is coated with a semi-permeable membrane, and drug release occurs through a laser drilled orifice by internally generated pressure.

Nifedipine was chosen as a model drug. Nifedipine is a calcium channel blocker known to be effective in treatment of stable, variant, and unstable angina, mild to severe hypertension, and Raynaud's phenomenon[4]. Conventional dosage forms of nifedipine must be dosed either twice daily (tablet) or three times a day (SEG capsules). Subsequent drug absorption is rapid and this coupled with a short elimination half life (2–5 hours)[4–6] results in significant fluctuation of peak and trough concentrations. Because of this pharmacokinetic profile, nifedipine conventional dosage forms may produce side effects such as tachycardia and flushing in some patients[4].

Controlling nifedipine delivery can alter this pharmacokinetic profile and provide constant plasma concentrations with minimal fluctuation. Nifedipine is a water-insoluble drug, solubility = 10 μg/mL, so it represents a challenge for the development of sustained release formulations of nifedipine[7].

Nifedipine sustained release formulations are available in the market as either a matrix tablet in which drug is dispersed in a polymeric matrix and release occurs by erosion (Adalat CC®, Bayer Pharmaceuticals Inc., West Haven, CT, USA)[8], or an osmotic pump tablet in which drug is released in a zero-order manner (Procardia XL®, Pfizer Laks, Division of Pfizer Inc., New Jersey, NJ, USA). However, there is no sustained release dosage form of nifedipine in a capsule form[9].

Goals of this research were: (a) to produce a sustained release action dosage form from a marketed IR dosage formulation in a process which is easy to manufacture, by applying a coating layer around an IR SEG capsule using a combination of polymeric materials. Two polymeric combinations were studied, ethylcellulose (Surelease®) as a water-insoluble polymer with hydroxypropylmethylcellulose (HPMC) (Opadry®), or pectin, as a water-soluble polymer with different ratios and (b) to study the effect of gastric pretreatment on drug release from this new delivery system on both polymeric combinations.

Materials and methods

Materials

All chemicals used in this study were purchased from standard sources. Nifedipine, poly-oxyethylene sorbitan monooleate (Tween 80, Sigma Chemicals Co., St. Louis, MO, USA), nifedipine SEG capsules, USP, 10 mg dose (Purpac Pharmaceutical Co., Piscataway, NJ, USA), ethylcellulose aqueous dispersion—Surelease®, and HPMC-based coating formula—Opadry® (Colorcon, West Point, PA, USA), Pectin PE 100 (Spectrum Quality Products INC, Gardena, CA, USA, New Brunswick, NJ, USA), acetonitrile, methanol (high-performance liquid chromatography [HPLC] grade), sodium hydroxide, sodium phosphate monobasic monohydrate, tribasic sodium phosphate, sodium chloride, hydrochloric acid (Fisher Scientific, Fair Lawn, NY, USA), Pectinex Ultra SP-L (gift supplied by Novo Nordisk Biochem., North America Inc., Franklinton, NC, USA) was used to mimic pectinolytic enzymes in the colon. Water was distilled deionized water using Milli-Q reagent water system (Millipore, Bedford, MA, USA).

Methods

Coat preparation

Two different polymeric combinations were studied, Surelease® (ethylcellulose) with Opadry® or pectin. Four different coating combinations were studied for Surelease® with Opadry® and two coating combinations were studied for Surelease® pectin combination as shown in Tables 1 and 2, respectively.

Table 1. Compositions of Surelease®–Opadry® coat formulations.

Formula	Component	Volume (mL)	Amount of solid (g)
O1	Surelease®	60	14.9
	Opadry®	75	15
	Water	60	Solids ratio 1:1
O2	Surelease®	55	13.64
	Opadry®	45	8.75
	Water	55	Solids ratio 3:2
O3	Surelease®	50	12.4
	Opadry®	32.5	6.5
	Water	50	Solids ratio 2:1
O4	Surelease®	62.5	15.5
	Opadry®	31.25	6.25
	Water	62.5	Solids ratio 3.5:1.5

Table 2. Compositions of Surelease® pectin coat formulations.

Formula	Component	Volume (mL)	Amount of solid (g)
P1	Surelease®	50	12.4
	5% Pectin	130	6.43
	Water	50	Solids ratio 2:1
P2	Surelease®	100	24.8
	5% Pectin	100	5
	Water	100	Solids ratio 5:1

Film coat suspension preparation

The film coat suspension was prepared by mixing the exact amount of Opadry® or pectin into a 400 mL beaker. Then, measuring the exact volume of distilled water and transferring it into the beaker with stirring to form a homogenous solution of 20% (wt/vol) Opadry® solution or 5% (wt/vol) pectin solution. Based on manufacturer's recommendations, Surelease® was diluted with distilled water to give (1:1) ratio with stirring gently for at least 30 minutes to ensure homogeneity of the coating solution.

Coating process

A number of 9–27 commercially available SEG nifedipine capsules and placebo sugar-filled hard gelatin capsules as 'filler' for the chamber to give a total capsule weight of 50 g were placed into a Fluid-bed spray coater chamber (Strea-1, Nitro-Aeromatic, Columbia, MD, USA) with a modified Wurster column insert and prewarmed for 5 minutes to equilibrate with the coating temperature (60°C). The coating solution was delivered using peristaltic pump (Rabbit® peristaltic pump, Gilson Medical Electronics, Middleton, WI, USA) with a flow rate of 1.75 mL/min and was applied through a 1.0 mm spray nozzle. Coating was performed at 60°C inlet air temperature and 50°C outlet air temperature. Air pressure was maintained at 10–15 psi to ensure continuous cyclic flow of capsules inside the chamber. During the coating process, coating solution was continuously stirred gently to ensure homogeneity of the solution.

Coating solution was applied onto the capsules to provide different percent weight gains. Percent weight gain is the actual weight gained relative to the weight of uncoated nifedipine SEG capsules.

Dissolution studies

Dissolution of coated SEG nifedipine capsules was conducted using the dissolution tester (Dissolution Apparatus VK 7000®, Vankel Industries, Inc., Cary, NC, USA). All tests were conducted in 1 L dissolution medium maintained at 37 ± 0.5°C (Heater VK 750 D®, Vankel Industries, Inc., Cary, NC, USA) with a paddle speed of 75 rpm. Dissolution studies of coated SEG nifedipine capsules were performed in triplicate and carried out in three different dissolution media: simulated gastric fluid (SGF) containing 1% Tween 80 for 2 hours, then pH was adjusted to 7.4 using 0.2 M tribasic sodium phosphate for 22 hours, simulated intestinal fluid (SIF) containing 1% Tween 80 for 24 hours (pH 7.4), and distilled water containing 1% Tween 80 for 24 hours.

Three mL samples of dissolution medium were collected without replacement at 5, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 20, and 24 hours using a computerized auto-sampler (VK 8000®, Vankel industries, Inc., Cary, NC, USA) with peristaltic pump (VK 810®, Vankel industries, Inc., Cary, NC, USA) with tube filter tips of 70 μm.

Because nifedipine is a light-sensitive drug, all dissolution studies were shielded from light. Dissolution vessels were amber colored wrapped with aluminum foil. In addition, efforts were made with the sample handling to keep away from direct light as much as possible. Nifedipine analysis was conducted using HPLC. HPLC results show minimal nifedipine degradation during these studies.

Chromatographic conditions

The HPLC column was a reverse phase micro particulate C_{18} (Prosphere C_{18}, particle size 5 μm, 250 × 4.6 mm, Alltech Associates, Inc., Deerfield, IL, USA) preceded by a C_{18} guard cartridge (ODS, 4 × 3 mm, Phenomenex, CA, USA).

The HPLC analytical method for nifedipine is similar to that in USP 25[10] with some modification. Eluent was acetonitile:methanol:water in the ratio of 35:17:48. Mobile phase was prepared by mixing exact volumes of acetonitile, methanol, and water. Water used in the preparation of mobile phase was filtered under vacuum through a 0.2 μm filter. Mobile phase was degassed before use. The flow rate was 0.8 mL/min in a HPLC integrated system composed of a delivery pump, UV detector, and automatic sampler injector (LC Module I integrated system, Waters Associates, Milford, MA, USA) connected to an integrator (CR 501 Chromatopac, Schimadzu Corp., Kyoto, Japan). The UV detector was set at 240 nm wavelength.

Sample preparation

Samples were filtered through 0.45μm filters, diluted with mobile phase in a ratio of 1:4, then vortex mixed for 30 seconds. Then 100 μL of this mixture was transferred into an HPLC vial containing 100 μL mobile phase and vortex mixed for 30 seconds. A volume of 100 μL was injected into the HPLC column.

Standard solution preparation

Nifedipine standard stock solution was prepared to contain 100 μg/mL of nifedipine by dissolving 10 mg nifedipine in 100 mL methanol in 100 mL amber colored volumetric flasks. This stock solution was diluted to prepare a second stock solution of 10 μg/mL with

mobile phase. The second stock solution was serially diluted with mobile phase to contain 100, 200, 400, 500, 1000, 1500, and 2000 ng/mL of nifedipine. All solutions were prepared in amber colored volumetric flasks and refrigerated unless in use. Freshly prepared standard solutions were prepared from time to time. It is reported that nifedipine standard solution if prepared under light protection conditions and stored in a refrigerator will be stable for at least 3 months[11]. Standard solutions of nifedipine were injected into HPLC with each run of samples. A standard curve was constructed by plotting peak area against nifedipine concentration.

Convolution analysis

Convolution of in vitro dissolution profiles for certain nifedipine coated SEG capsule formulations and commercially available nifedipine formulations were conducted to predict plasma concentration versus time profiles, assuming these formulations are administered in vivo. The dissolution–time profile from nifedipine SEG capsules coated with the O3 (13% weight gain) coat formulation, P1 (14% weight gain) coat formulation, Procardia XL® 30 mg dose, and Adalat CC® 30 mg dose were convolved to produce simulated plasma concentration–time profiles using a spread sheet. Simulated plasma concentration–time profiles were compared with published data of plasma concentration–time profiles for commercially available sustained release formulations of nifedipine[4].

Results and discussion

Difficulties often arise during coating of SEG capsules. It has been reported that problems associated with coating of SEG capsules were generally related to the physical properties of gelatin: capsules smooth surfaces, and their flexibility or elasticity. Application of aqueous solution as a coating solution caused solubilization of gelatin that composed the capsule shell which leads to softness and stickiness of capsules in the coating chamber[12]. To overcome these difficulties, several trials have been made in search of optimum conditions for coating SEG capsules. Pre-warming of capsules before coating is an important step which increases the temperature of the filled liquid to that of the bed temperature and allows coating to dry more uniformly which resulted in a homogenous film around the surface of the capsules. If the capsules were not pre-warmed, the capsule is cold and after completion of the coating process, the outer layers dry faster than the inner layers causing bubble formation in the film[12].

An excellent drying temperature was 60°C, which allows fast drying of the film coat formed around the surface of the gelatin capsules. At lower temperatures, the drying process was not fast enough to prevent solubilization of the gelatin shell. At higher temperatures, the distortion temperature of the gelatin shell can be reached (which is reported to be 80°C) causing deformation of the gelatin shell[13]. A good flow rate for the equipment used was 1.75 mL/min. Higher flow rates produced stickiness of capsules because of incomplete drying of the film coat applied.

Plasticizers are an especially necessary component in the coating solutions, which were already included in the commercially available aqueous dispersion of ethylcellulose (Surelease®) and in Opadry®. Plasticizer helps produce a smooth film, reduce brittleness, increase strength, and reduce tear resistance of the film coat[14]. It was observed that coating solutions with higher pectin ratios produce flakes in the coating chamber, thought to be mainly because of low amount of plasticizers in these solutions.

Coating applied to the SEG capsules was stable, and adhered to the surface without cracking during the coating process. However, the shape of the capsules appeared expanded after the coating process.

In vitro evaluation of coat performance

Dissolution studies of coated nifedipine SEG capsules and commercially available nifedipine formulations were conducted in three different dissolution media: SGF for 2 hours followed by pH adjustment to simulate intestinal fluid for 22 hours; SIF; and water containing 1% Tween 80 to study pH effect on drug release from these formulations. Dissolution profiles of some commercially available nifedipine formulations are shown in Figures 1–3. Hundred percent drug release occurred

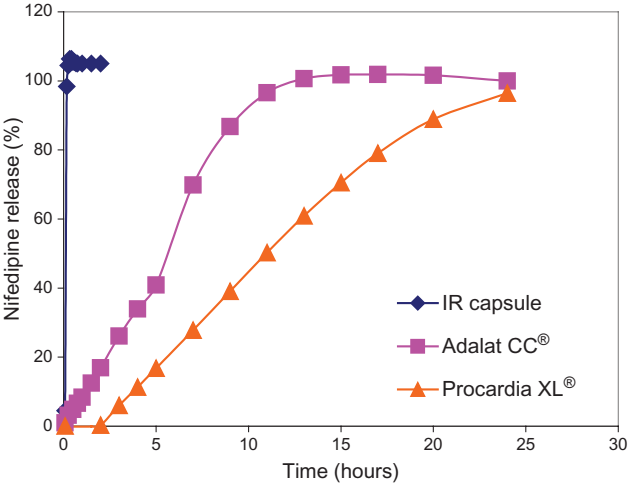

Figure 1. Mean dissolution profiles of immediate release (IR) and sustained release nifedipine from commercially available formulations in simulated gastric fluid for 2 hours followed by pH adjustment to simulate intestinal fluid for 22 hours containing 1% Tween 80 (error bar represents SD, $n = 3$).

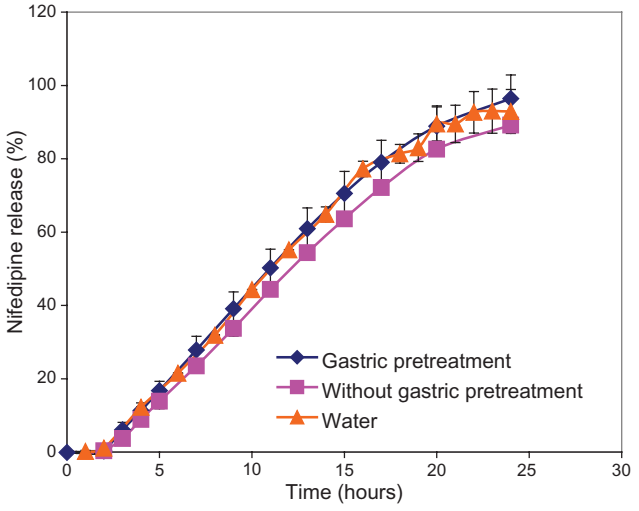

Figure 2. Mean dissolution profiles of nifedipine from osmotic pump tablet (Procardia XL®) over 24 hours wherein dissolution occurred in simulated gastric fluid for 2 hours followed by intestinal fluid for 22 hours (—♦—); simulated intestinal fluid (—■—); and in water (—▲—) containing 1% Tween 80 (error bar represents SD, $n = 3$).

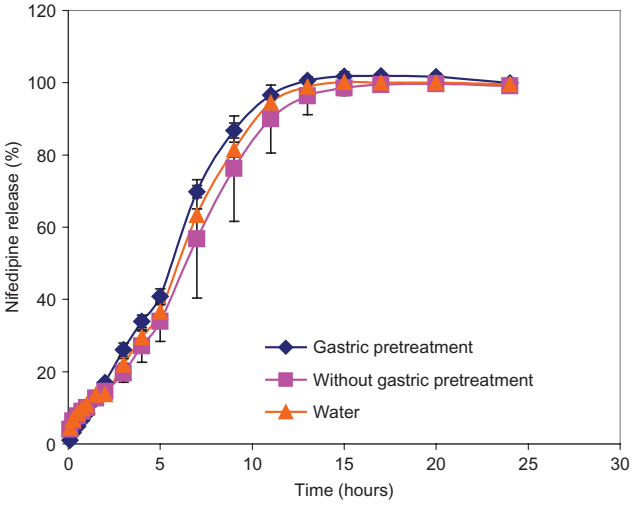

Figure 3. Mean dissolution profiles of nifedipine from matrix tablet (Adalat CC®) over 24 hours wherein dissolution occurred in simulated gastric fluid for 2 hours followed by intestinal fluid for 22 hours (—♦—); simulated intestinal fluid (—■—); and in water (—▲—) containing 1% Tween 80 (error bar represents SD, $n = 3$).

from uncoated nifedipine SEG capsules in gastric fluid within 15 minutes. Nifedipine release from matrix tablet (Adalat CC®, Bayer) occurred by erosion and continues until 100% drug release after 11 hours with no lag time, and drug release was independent of pH of dissolution media used in the dissolution studies. Nifedipine release from osmotic pump tablets (Procardia XL®, Pfizer) has 2hours lag time followed by zero-order drug release that continues until 24 hours, and is also independent of pH.

Surelease®–Opadry® combination

Nifedipine release from SEG capsules coated with four different coat formulations O1 (1:1 solid ratio), O2 (3:2 solid ratio), O3 (2:1 solid ratio), and O4 (3.5:1.5 solid ratio) with different actual weight gains was performed in three different dissolution media in triplicate, in SGF for 2 hours followed by pH adjustment to simulate intestinal fluid for 22 hours, in SIF, and in water containing 1% Tween 80. A summary of dissolution profiles obtained from all Surelease®–Opadry® coated SEG capsules in three different dissolution media are shown in Figures 4–6, respectively.

Percentage of drug released from nifedipine SEG capsules showed no pH-dependent effect with formulation coated with 16% actual weight gain for O1 formulation, 14% O2 coat formulation but there was a pH-dependent effect for 17% O2, 21% O2, 13% O3, 18% O3, 21% O3, and 15% O4 coat formulations. This pH effect for Surelease® HPMC containing films on dosage forms is surprising because the solubility of ethylcellulose (Surelease®) has been reported to be pH independent[15]. However, it was reported that release rates of theophylline, phenylpropanolamine HCl, propranolol HCl[15], ketoprofen, and nicardipine HCl[16] from Surelease® coated beads were pH dependent. Release rate from Surelease® coated beads (with high percent coating) was controlled by diffusion through the coating film and therefore based on the concentration of non-ionized form of drugs. Nifedipine, with unknown pK_a, has a faster rate of drug release from O2 coat formulation with 21% actual weight gain in a basic medium than in an acidic medium, thus suggesting that nifedipine is expected to be in the ionized form in an acidic medium with less diffusion through the film coat while nifedipine will be in the nonionized form in a basic medium.

Percentage of drug released from nifedipine SEG capsules coated with 16% O1 formulation showed ineffective polymer coating. Higher HPMC ratios in the coat provide a point of entry for dissolution media to enter the capsules which increases the dissolution rate of drug. For O2 coat formulations, drug dissolution curves are quite different from commercially available products but it can be noted that drug release from the 21% O2 formulation is promising in terms of relatively rapid release over the first 5 hours followed by sustained release which is desirable in many cases. With O3 coat formulations, higher Surelease® results in delaying nifedipine release with gastric pretreatment and only 90% of nifedipine was released during 24 hours, compared to 100% drug release in either intestinal fluid or water dissolution media without pretreatment in gastric fluid. With higher percent weight gain of coating, it is expected that this effect will be

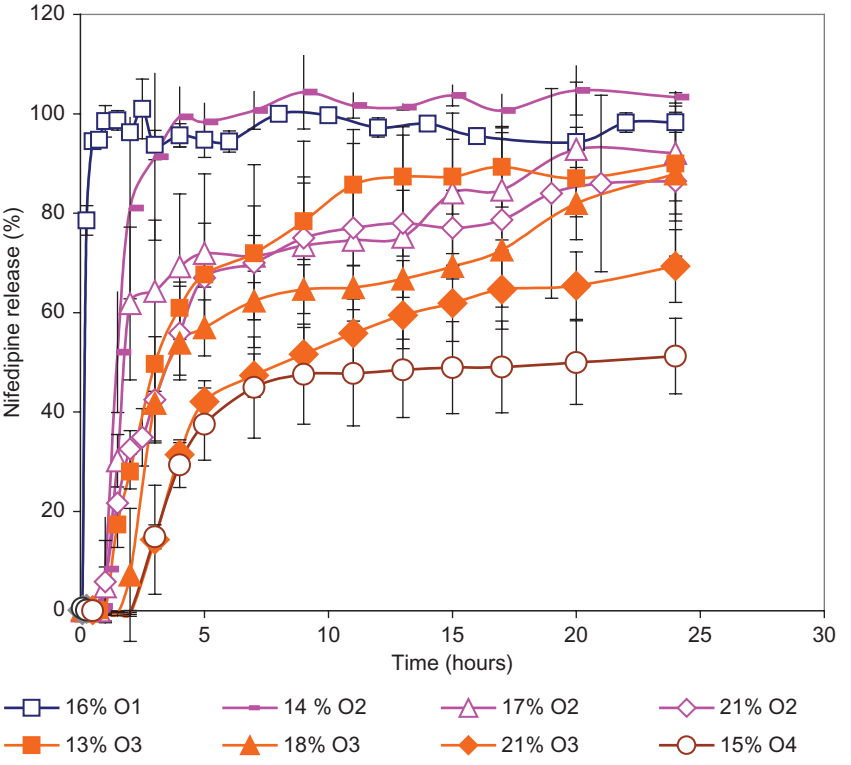

Figure 4. Mean nifedipine release from SEG capsules coated with O1, O2, O3, and O4 coat formulations in simulated gastric fluid for 2 hours followed by pH adjustment to simulate intestinal fluid for 22 hours containing 1% Tween 80 (error bar represents SD, $n = 3$).

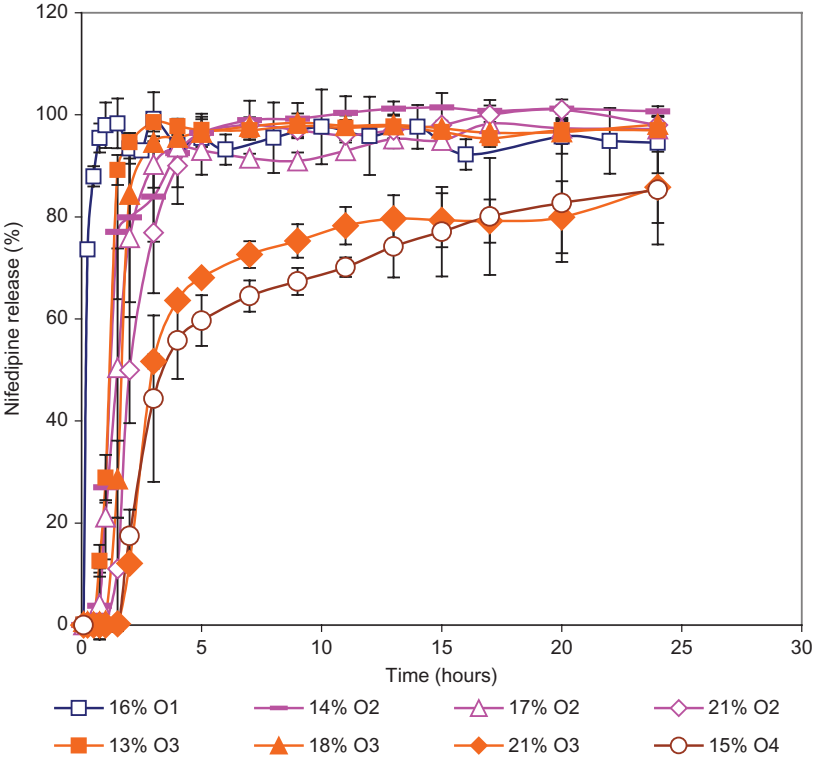

Figure 5. Mean nifedipine release from SEG capsules coated with O1, O2, O3, and O4 coat formulations in simulated intestinal fluid containing 1% Tween 80 (error bar represents SD, $n = 3$).

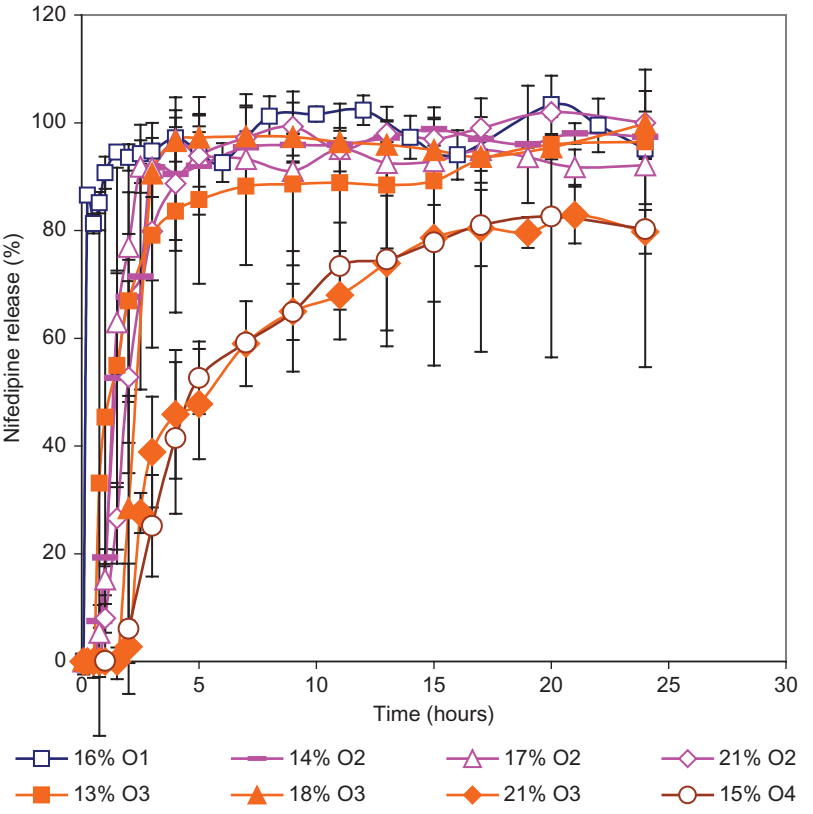

Figure 6. Mean nifedipine release from SEG capsules coated with O1, O2, O3, and O4 coat formulations in water containing 1% Tween 80 (error bar represents SD, $n = 3$).

more pronounced. Nifedipine capsules coated with 21% O3 coat formulation after 24 hours dissolution showed nifedipine precipitation into yellow crystals inside the capsule shell. The precipitation of nifedipine was an unexpected and surprising finding and will be discussed in more detail later on.

A comparison between mean nifedipine release from O2 and O3 coat formulations with commercially available formulae (IR and sustained release) with gastric pretreatment are shown in Figures 7 and 8, respectively.

Increasing Surelease® ratio (3.5:1.5) in O4 coat formulation decreased the percentage of drug released. With low HPMC ratio there are fewer holes or 'pores' developed in the coat around the surface of the capsules which allow a small volume of dissolution media to enter into the core. Because nifedipine is a water-insoluble drug, nifedipine precipitated inside the capsules when the water entered thereby trapping the drug inside the SEG capsule such that nifedipine could not diffuse out of the SEG capsule.

Opadry®, a water-soluble polymer used in these coating formulations, forms holes in the nonporous film formed by the water-insoluble polymer Surelease®. Pores act as a point of entry for dissolution fluid into the capsule core and as points of exit for dissolved drug into dissolution media. Drug release occurs through the hydrated polymeric gel. An increase in coat thickness was accompanied by a decrease in drug release rate. The decreased drug release rate was complicated by the drug precipitation effects that occurred inside the SEG capsule when the water flows too slowly into and back out of the coated SEG capsule. During the coating process, the application of multiple coats increased the weight gain and thickness of the film formed around the surface of the capsules. Holes in thin films are gradually blocked. Therefore, the greater the coating thickness the slower the drug dissolution rate. It was also discovered that the formulations investigated could be modified to produce lag time in drug release. Lag time is correlated with film thickness.

By increasing the percent coat weight gain, there are increases in the diffusion path length and diffusional resistance for dissolution media to enter the core and for dissolved drug to come out from the core. This partially accounts for the much lower release rates for capsules with higher coating levels along with drug precipitation inside the SEG in some cases. As small volumes of dissolution media entered the core, nifedipine will precipitate inside the coated SEG for some formulations and make it difficult for the drug to be released, especially with coat formulations containing higher ratios of Surelease®.

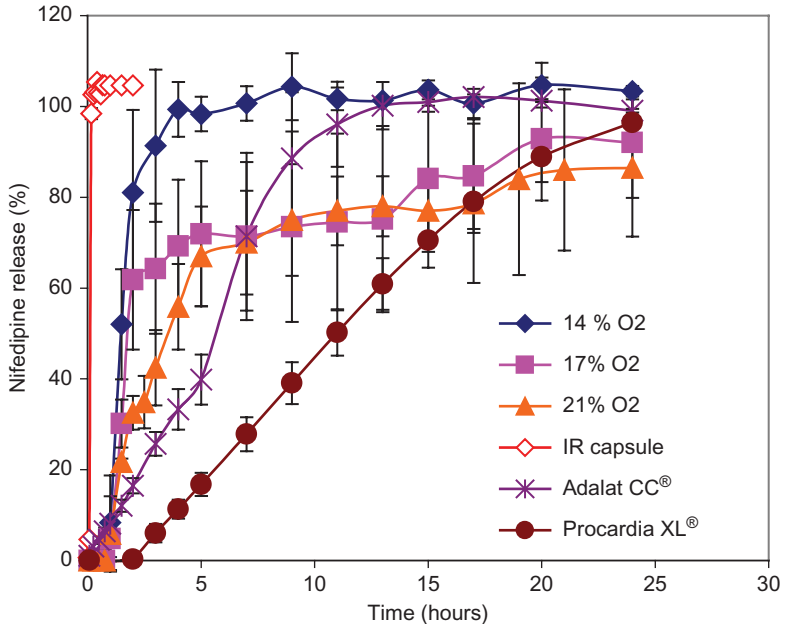

Figure 7. Nifedipine release from commercially available formulae (immediate release, IR, and sustained release) and O2 SEG coat formulations in simulated gastric fluid for 2 hours followed by pH adjustment to simulate intestinal fluid for 22 hours (error bar represents SD, $n = 3$).

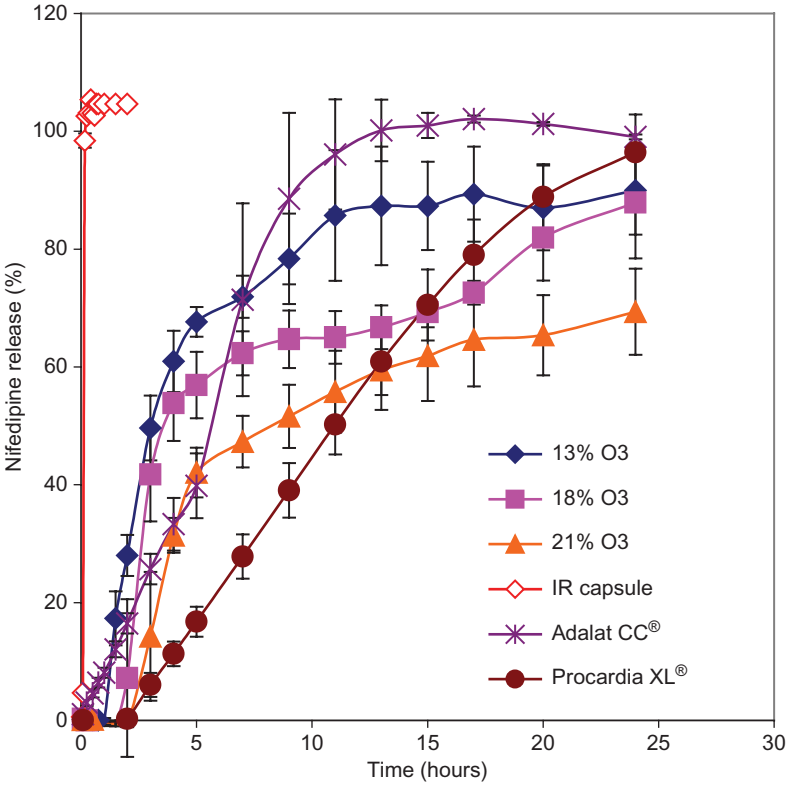

Figure 8. Mean nifedipine release from commercially available formulae (immediate release, IR, and sustained release) and O3 SEG coat formulations in simulated gastric fluid for 2 hours followed by pH adjustment to simulate intestinal fluid for 22 hours (error bar represents SD, $n = 3$).

Surelease® pectin coat formulations

Two coat formulations containing pectin (P1 and P2) have been studied with different coating weight gains. Pectin is an anionic polysaccharide water-soluble polymer. It is non-ionized and less soluble in gastric fluid (at lower pH). Gastric pretreatment of pectin-containing films results in low pectin solubility and prevents drug release in gastric fluid[17]. With higher percent weight gains of Surelease® pectin, more film coat was applied which may have blocked holes or pores in the thinner film coats, which may have apparently caused a gradual reduction in the dissolution rate of nifedipine.

Percentages of drug released from capsules coated with Surelease® pectin P1 and P2 coat formulations in different dissolution media are shown in Figures 9–11 with different actual coat weight gains. Fourteen percent P1 coat formulation showed 100% drug release within 2–4 hours with 15 minutes lag time in intestinal fluid and in water. Gastric fluid pretreatment for 2 hours prolonged the lag time to 2 hours and 100% drug release occurred during 15 hours period. With the P1 formulation, the release rate of nifedipine continued to be slowed after adjusting pH to intestinal fluid even though pH was neutral. This suggests that pH effected nifedipine release from SEG capsule. With P1 coat formulation containing pectin, increasing the percent weight gain did not produce a difference in drug release when comparing 14% and 17% weight gains.

Nifedipine release from SEG capsules coated with P2 coat formulation with 12% actual coating weight gain did not release 100% drug over a 24 hours period. Dissolution with gastric fluid pretreatment showed 3 hours lag time and 61% drug release over a 24 hours period compared to 1.5 hours lag time and 95% and 89% drug release in intestinal fluid and in water, respectively. With 17% weight gain, dissolution with gastric fluid pretreatment for 2 hours showed 4 hours lag time with 38% drug release over a 24 hours compared to 2 hours lag time and 68% and 73% drug release after 24 hours dissolution in intestinal fluid and in water, respectively. Hundred percent drug release was not obtained for any P2 coat formulation for the weight gains studied over the 24 h period. Nifedipine precipitation occurred inside the SEG capsule shell coated with P2 coat formulation in all dissolution media. Nifedipine precipitation may be explained by assuming that a lower pectin ratio in this coat formulation produced fewer holes in the film coat, which allowed a small volume of dissolution fluid to enter the SEG capsule. With the high nifedipine concentration inside the capsules, some nifedipine precipitated and were unable to diffuse through the film coated SEG capsule. In addition, a gel formed inside the SEG capsule retaining nifedipine inside but not in the form of yellow crystals as seen with Surelease®–Opadry® coat formulations. Gelation of pectin has been reported to occur by two different mechanisms: (a) high methoxyl pectins gel in the presence of high concentration of soluble solids and low pH; and (b) low methoxyl pectins gel in the presence of divalent cations[18]. The pectin used in the P1 and P2 coatings is low methoxyl pectin,

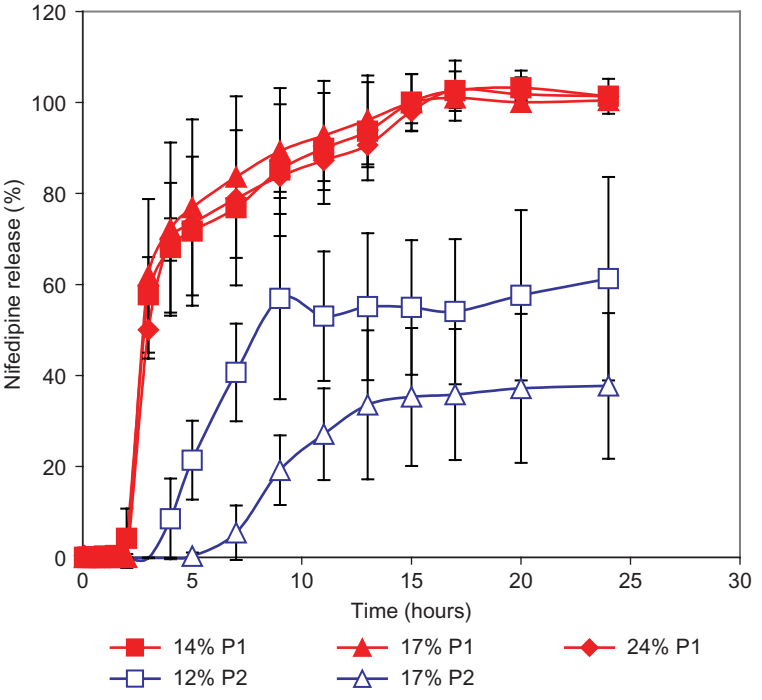

Figure 9. Nifedipine release from SEG capsules coated with P1 and P2 coated formulations in gastric fluid for 2 hours followed by intestinal fluid for 22 hours (error bar represents SD, $n = 3$).

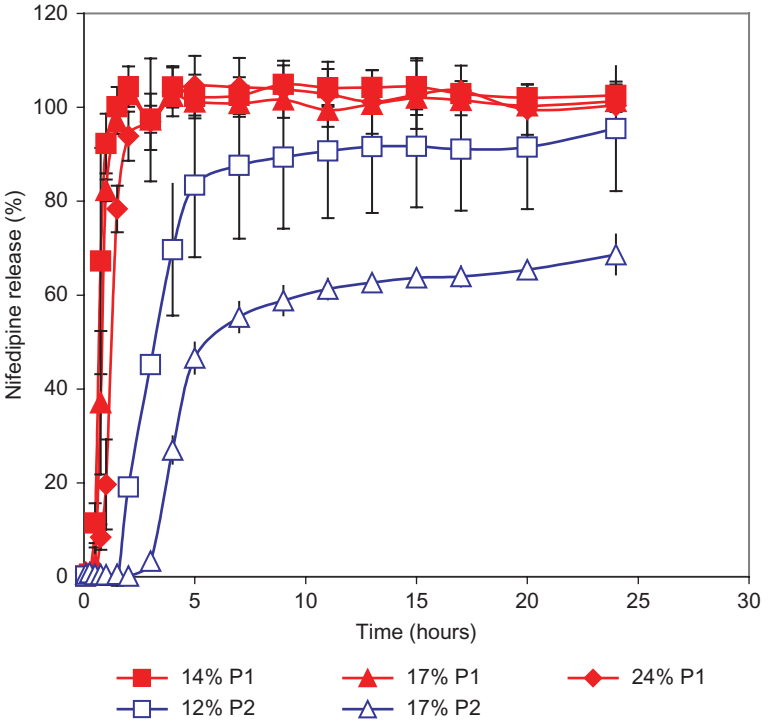

Figure 10. Mean nifedipine release from SEG capsules coated with P1 and P2 coated formulations in intestinal fluid (error bar represents SD, $n = 3$).

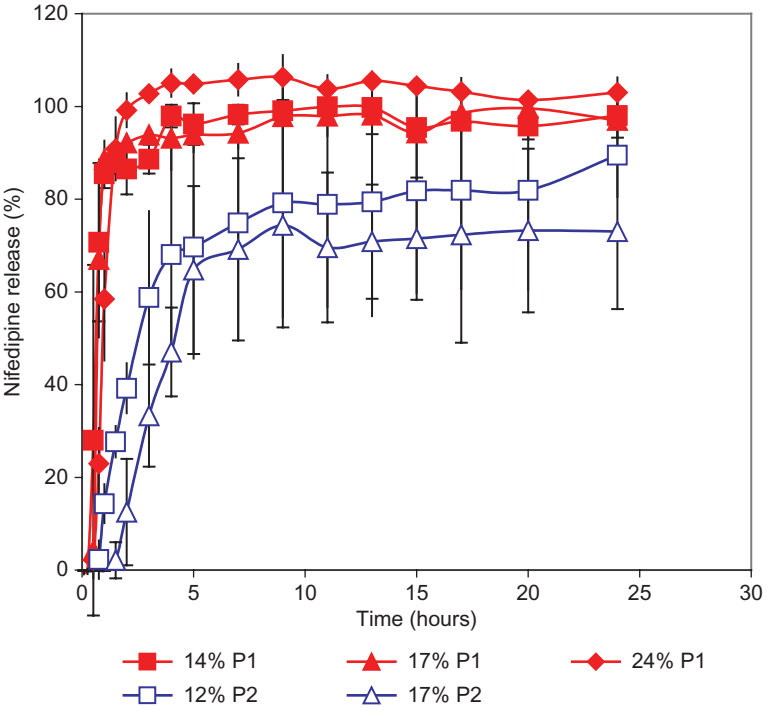

Figure 11. Mean nifedipine release from SEG capsules coated with P1 and P2 coated formulations in water (error bar represents SD, $n = 3$).

which may have gelled in the presence of the polyvalent cations such as Ca^{2+}, Ba^{2+}, Sr^{2+}, Cd^{2+}, Ni^{2+}, or Pb^{2+} [19]. The effect of divalent cation on the gelation of pectin may explain the gelation inside the SEG capsule shell. This gelation may be because of the effect of ferric (trivalent) cation or titanium (tetravalent) cation on the carboxylic acids of pectin which are present as an excipient in the commercially available SEG capsule. Gel formation inside SEG capsules coated with Surelease® pectin may be because of some pectin leaching from the coat and driven into the capsule core with the dissolution media resulting in gel formation inside the capsule core, which can eventually retard nifedipine diffusion from inside the capsule. A comparison of dissolution profiles for P1 and P2 coat formulations with those of commercially available nifedipine formulations are shown in Figures 12 and 13.

Convolution analysis

Developing once-daily formulations of antihypertensive drugs represents a challenge and should provide antihypertensive effect until the end of the dosing interval, as well as prolong duration of action through the daily time of peak hypertension. Blood pressure (BP) is subjected to circadian rhythm. Its lowest level occurs during the sleep cycle and rises steeply during the early morning around 6 am. One importance of giving a sustained release formula for hypertensive patients is to deliver the drug in a higher concentration during the time of greatest need (the early morning period). Coca et al.[20] mentioned that most studies performed on the effect of antihypertensive drugs on circadian rhythm showed that most antihypertensive agents have relatively little effect on circadian rhythm of BP. However, there is a tendency for antihypertensive agents to decrease BP a little more during the day[20]. They also observed that all calcium channel blockers investigated, such as verapamil and nifedipine, have been found to decrease BP without altering the circadian BP profile.

Simulation of expected nifedipine plasma concentration versus time profiles was calculated from dissolution data with gastric pretreatment (convolution) for two commercially available sustained release dosage forms and some new SEG formulations reported herein. This helps guide formulation modification and in recommending dosage regimens for hypertensive patients, especially for dosing in the morning versus night (Figure 14). Simulation results obtained from the dissolution data of Procardia XL® were consistent with reported data[4]. Procardia XL® is an osmotic pump tablet that has a 2 hours lag time which is primarily the hydration time of the tablet before the plasma nifedipine concentration starts to rise. A plateau concentration is obtained after 6–8 hours, ~22–24 ng/mL,

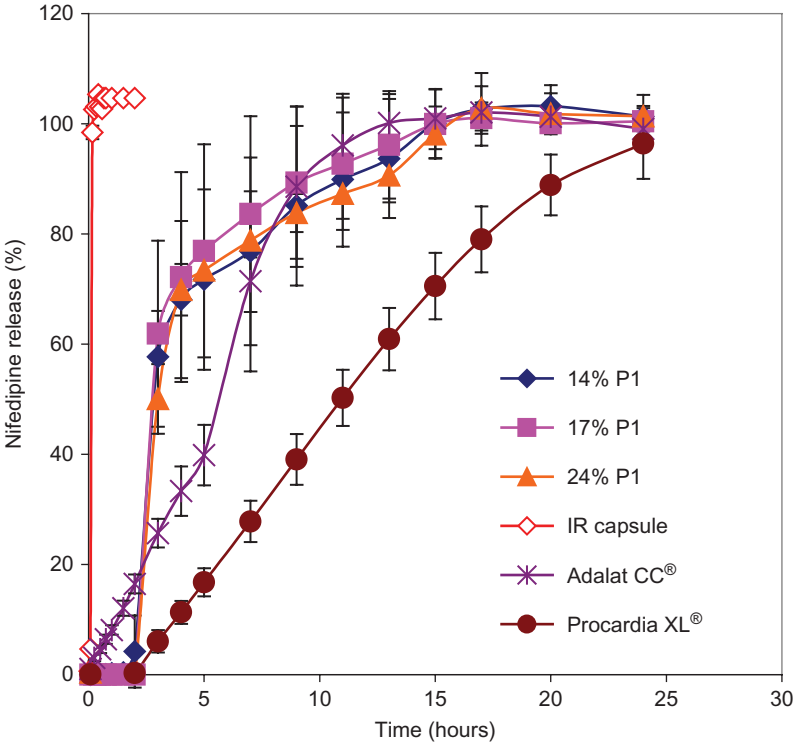

Figure 12. Mean nifedipine release from commercially available formulae (immediate release, IR, and sustained release) and P1 SEG coat formulations in simulated gastric fluid for 2 hours followed by pH adjustment to simulate intestinal fluid for 22 hours (error bar represents SD, $n = 3$).

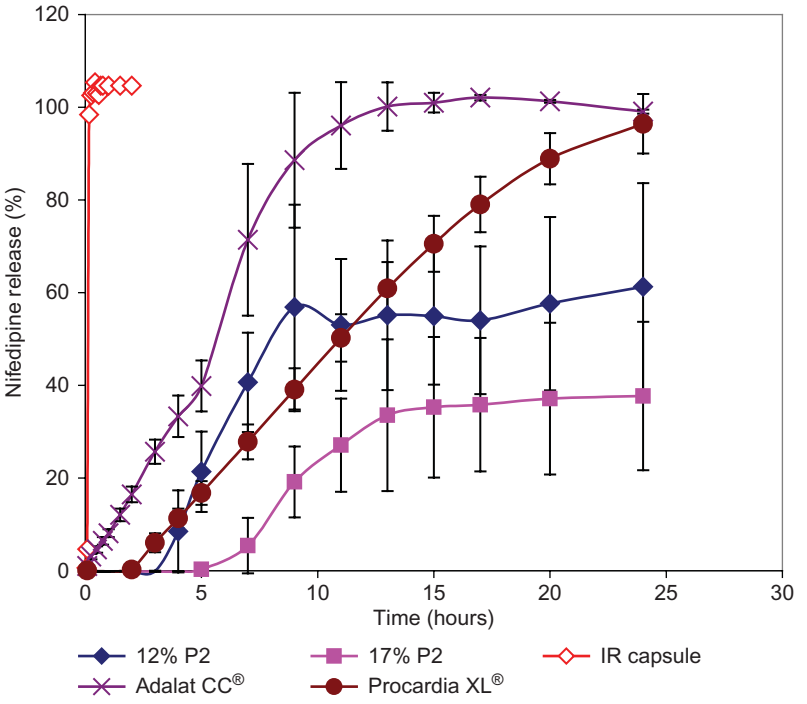

Figure 13. Mean nifedipine release from commercially available formulae (immediate release and sustained release) and P2 SEG coated formulations in gastric fluid for 2 hours followed by pH adjustment to simulate intestinal fluid for 22 hours (error bar represents SD, $n = 3$).

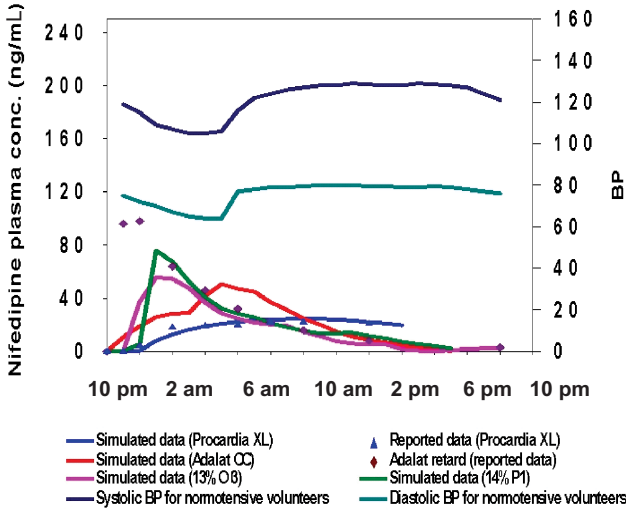

Figure 14. Simulated nifedipine plasma concentration after administration of commercially available and selected SEG formulations compared with reported data along with systolic and diastolic blood pressure (BP) from healthy volunteers*. (*Blood pressure (BP) pattern showing circadian rhythm obtained from 12 normotensive volunteers[21].)

over the 24 hours dosing interval of a 30 mg tablet. Nifedipine matrix tablet Adalat CC® did not have a lag time and a small peak was seen after 3 hours. The predicted nifedipine concentration increased until nifedipine plasma concentration reaches a maximum (50 ng/mL) after 7 hours following an oral dose of a 30 mg tablet.

Nifedipine SEG capsules coated with O3 (13% weight gain) coat formulation showed 1 hour lag time and drug release occurred with a maximum concentration of 55 ng/mL after 3 hours. Note that simulated curves are acceptably close to published data points. Nifedipine SEG capsules coated with P1 (14% weight gain) coat formulation showed 1 hour lag time and drug release occurred with a maximum concentration of 67 ng/mL after 4 hours. From these results, it was concluded that none of the tested dosage forms of coated nifedipine SEG capsules provided dissolution profiles that matched dissolution profiles from the commercially available tablets of nifedipine.

However, simulation for the new formulations provided a drug concentration above the minimum effective concentration around 6 am, which is the time of greatest need for antihypertensive effect in hypertensive patients and remained above the minimum effective concentration for more than 12 hours. These results suggest the new formulation is expected to be a successful sustained release product. These formulations did not duplicate Adalat CC® but they did prolong nifedipine release for up to 12 hours which was similar to Adalat CC®.

Conclusions

SEG capsules were successfully coated using a laboratory spray coater with a modified Wurster column

insert. The coat was uniform and was applied onto the surface of the capsule without any cracking or flaking during the coating process. Sustained release action of nifedipine was obtained by coating IR SEG capsules with a combination of polymers, Surelease® as a water-insoluble polymer and Opadry® or pectin as a water-soluble polymer.

Unexpectedly, there was also a pH effect on drug release from nifedipine capsules coated with Surelease®–Opadry® combination with O2, O3, and O4 coat formulations. This effect was not detected with O1 coat formulation because of the rapid release of nifedipine. Surelease® pectin combination also showed a very surprising pH-dependent effect with no drug release in gastric fluid. This effect was more pronounced than that of Surelease®–Opadry® coat combinations. The release patterns of nifedipine were generally sigmoidal with a high curvature; thus, clearly indicating nonlinear release. The expected plasma concentrations obtained by convolution simulation of tested formulations and commercially available sustained release formulations showed that the tested formulations provided release profiles of nifedipine that are very promising in terms of desirable sustained release formulations. Formulation of sustained release dosage forms with water-insoluble drugs in a SEG capsule represents a challenge. The problem of the precipitation of nifedipine inside the SEG capsule must be solved to obtain desired drug release patterns. Further investigation is required to elucidate the process of drug precipitation inside the SEG capsule.

Declaration of interest: The authors report no conflicts of interest.

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