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Solubility enhancement using poly(meth)acrylate based solid dispersions

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ABSTRACT

The present study investigated the usage of poly(meth)acrylates for solubility enhancement of nifedipine via spray drying based solid dispersion technology. Solvent casting method was used for selection of suitable poly(meth)acrylates. A 2^3 full factorial design of experiment was undertaken to study the effect of spray drying process parameters like inlet temperature, feed rate and feed concentration on various evaluation parameters like % yield, mean particle size, % LOD and % in-vitro drug release at 20 min. Spray dried solid dispersion was characterized by different thermal methods and in-vitro dissolution.

Based on preliminary screening of different poly(meth)acrylates using solvent casting trials, EUDRAGIT® E PO (cationic polymer) was chosen as an appropriate polymer for solubility enhancement. In-vitro dissolution showed more than 90% of drug releases within 20 min for spray dried solid dispersion while pure drug exhibited about 12% drug release after 20 min. SEM images showed changes in the surface morphology of processed nifedipine from crystalline shape to spherical uniform particles. DSC and XRD confirmed that crystalline drug was converted into amorphous form which was stable even after 3 months of storage. Particle size analysis confirmed uniform particle size distribution. FT-IR revealed no significant interaction between drug and polymer. Outcome of process parameter indicates that feed rate has significant effect on in-vitro dissolution and % LOD while solid content has the major effect on the process yield.

1. Introduction

Solid dispersion is a well-established approach for solubility enhancement wherein one or more active ingredients can be incorporated at molecular level in an inert carrier or matrix [1–10]. In this system, individual API molecules are dissolved and physically entrapped and immobilized in its highest energy (amorphous) form within a polymer matrix which increases the dissolution rate and finally the bioavailability of poorly water-soluble.

Solid dispersion systems can be broadly classified as single phase amorphous system and two phase system. The former, also known as solid glassy solution, contains both drug and carrier molecularly dispersed with each other and exhibits single peak in DSC analysis. The later, also known as amorphous crystalline suspension, has drug partially or completely dissolved in carrier polymer and is more prone to undergo recrystallization during storage. They contain polymer in amorphous phase while drug in crystalline phase which exhibits one glass transition temperature (Tg) peak for polymer and other melting peak for drug. Stabilization of drug's amorphous state during storage is a major challenge in the development of solid dispersion which is only possible if drug remains in a solid glassy state (single Tg peak in DSC) throughout the storage period.

Polymeric properties such as Tg, hygroscopicity, solubility in organic solvents and polymorphic state must be considered to improve stability of solid dispersions. Polymers with higher Tg value are capable of reducing the molecular mobility and nucleation rate of drug in solid dispersion and are comparatively suitable to prevent the conversion of drug from amorphous to crystalline state during storage. In addition, solubility of the polymer in organic solvent is a critical factor in spray drying to attain the complete solubility of polymer at the required concentration. Polymers with less water uptake capacity are considered more suitable to improve stability of solid dispersion as water by itself works as a plasticizer to reduce Tg [11–15].

The objective of the present work was to evaluate various poly(meth)acrylates as carriers for solid dispersion. These polymers are amorphous in nature, have minimum hygroscopicity, are soluble in common organic solvents and have relatively high Tg value. Based

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on the classification of poly(meth)acrylates, three polymers from each class were selected for solid dispersion trials viz. EUDRAGIT® E PO (cationic polymer with pH dependent release), EUDRAGIT® RL PO (cationic polymer with pH independent release) and EUDRAGIT® L 100 (anionic polymer). Tg of EUDRAGIT® E PO, EUDRAGIT® RL PO and EUDRAGIT® L 100 is about 48 °C, 63 °C and 130 °C respectively. All the above polymers are non-hygroscopic in nature, exhibit minimum water vapor permeability and are freely soluble in common organic solvents [16] which could be helpful to generate a stable solid glassy solution system. EUDRAGIT® polymers have been previously reported for solubility enhancement of felodipine [17], itraconazole [18] and celecoxib [19] via solid dispersion process.

In the present work, nifedipine (Fig. 1), a calcium channel blocker, was selected as a model poorly water soluble drug (BCS Class-II). The drug exhibits high first pass metabolism and short elimination half-life (7 h) which leads to low plasma concentration and accounts for its highly variable bioavailability in humans which makes this drug a suitable candidate for the current study [10,11].

2. Material and methods

2.1. Materials

Nifedipine was obtained as a gift sample from Cipla Ltd. (Mumbai, India), EUDRAGIT® E PO, EUDRAGIT® RL PO and EUDRAGIT® L 100 were obtained from Evonik India Pvt. Ltd. (Mumbai, India) and disodium hydrogen phosphate was obtained from Merck Ltd. (Mumbai, India). All other solvents were of analytical grade.

2.2. Drug saturation solubility study in different pH

Excess quantity of nifedipine was added in different medium (purified water, 0.1 N HCl, pH 4.0 buffer, pH 6.8 phosphate buffer and pH 9.0 phosphate buffer) to study the effect of pH on its solubility. The beaker containing drug was kept under stirring using a magnetic stirrer (Remi, India) at 37 ± 5 °C until equilibrium was achieved (24 h). As the drug is sensitive to light, all experiments were performed under subdued light.

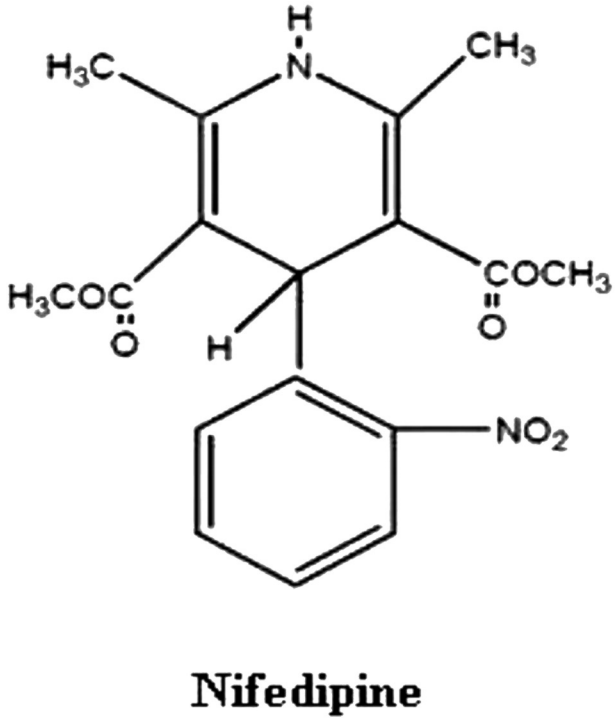

Fig. 1. Chemical structure of nifedipine.

Table 1
Formulation trials for solvent casting method.

Formulation trials	1	2	3	4	5	6	7	8	9	10
Nifedipine [mg]	100	100	100	100	100	100	100	100	100	100
EUDRAGIT® E PO [mg]		300			500			800		
EUDRAGIT® RL PO [mg]			300			500			800	
EUDRAGIT® L 100 [mg]				300			500			800
Total [mg]	100	400	400	400	600	600	600	900	900	900

The aliquots were filtered through 0.45 μm PDA filter. The filtrates were diluted appropriately with a suitable buffer medium and analyzed spectrophotometrically at 236 nm λ_{max}. Samples were analyzed in triplicate and results were reported as average.

2.3. Design of experiment (DoE)

2.3.1. Optimization of type and concentration of polymer by solvent casting method

Solvent casting method is primarily a lab evaluation method which is useful to identify the possible interaction between drug and polymer. Total number of formulation trials for solvent casting methods is highlighted in Table 1.

Accurately weighed quantities of nifedipine and mixture of nifedipine with different EUDRAGIT® polymers in different ratios were dissolved in methanol. The solution was then transferred into petri plate for complete solvent evaporation. The films were dried completely at room temperature for 12 h and then under tray dryer at 40 °C for additional 12 h. Physical appearance of film after solvent evaporation was studied visually. Powder was collected by crushing the film and passing through 40# ASTM sieve and finally dried until LOD was below 2% w/w. The powder was filled in double liner self-sealing polythene bag and covered using aluminum foil to minimize photolytic degradation of drug and stored in desiccators until further use. The main parameters studied were physical appearance of the film and drug's solubility.

2.3.1.1. Solubility study of drug in solvent casted films. Dried powder obtained from solvent casted film containing 20 mg equivalent of drug was dissolved in 100 ml of 0.1 N HCl and 6.8 pH phosphate buffer. Both suspensions were magnetically stirred at room temperature in a dark room at 37 ± 5 °C until equilibrium was achieved (24 h). Samples were withdrawn and filtered through 0.45 μm filters. The filtrates were suitably diluted and analyzed by UV–visible spectrophotometer at 236 nm. Samples were analyzed in triplicate and an average result was reported.

2.3.2. Design of experiment (DoE) for spray drying process optimization

Based on the results obtained from film casting process, the best polymer was selected and its solid dispersion with the drug was prepared by applying a 2^3 full factorial design in order to investigate the joint influence of formulation and process variables using MODDE (version 9.1) software. In this design, 3 factors were evaluated, each at 2 levels, and experimental tests were performed at all possible combinations. The experimental tests were taken for all 8 combinations. The inlet temperature (X1), feed rate (X2) and solid content of feed solution (X3) were selected as independent process variables at 2 levels. The % yields (Y1), % LOD (Y2), mean particle size (Y3) and % in-vitro drug

Table 2
Independent process variables with level.

Sr. no	Independent factors	Units	Low level (−1)	High level (+1)
1	Inlet temperature (X1)	°C	60	80
2	Feed spray rate (X2)	ml/min	5	10
3	Solid content of feed solution (X3)	% w/w	15	30