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DEVELOPMENT AND EVALUATION OF FAST DISSOLVING DRUG DELIVERY SYSTEM OF CILNIDIPINE

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ABSTRACT

Cilnidipine is poorly water soluble antihypertensive drug (BCS class II). This study was conducted to increase solubility of drug. An attempt was made to formulate fast dissolving tablet of Cilnidipine by solid dispersion using melting method with Pluronic F-68. The API: carrier was taken as 1:1, 1:2 and 1:3. Effect of several variables such as concentration of superdisintegrant, drug: carrier ratios were studied. Formulations were analyzed using Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD) analysis, Fourier Transform-Infrared spectroscopy (FT-IR) and *in-vitro* release studies followed by various release kinetics. Drug release profile of pure drug was found 8% within 15 minutes whereas tablet of Cilnidipine: Pluronic F-68(1:3) prepared by melting method showed NLT 85% drug release in 15 minutes. Accelerated stability study was carried out for period of 3 months, which indicated that tablets were unaffected at all the exposed conditions.

KEYWORDS: Fast Dissolving Tablet**,** Cilnidipine, Pluronic F-68, Melting method, Solid dispersion.

INTRODUCTION

Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The solid dispersion is based on the concept that the drug is dispersed in an inert water-soluble carrier at solid state. Several water soluble carriers such as Pluronic,

methyl cellulose, polyvinyl pyrrolidone and polyethylene glycols 4000 and 6000 are used as carriers for solid dispersion. Thus the solid dispersion technique can be successfully used for the improvement of dissolution of cilnidipine. Poorly water soluble compounds have solubility and dissolution related bioavailability problems. pluronic F-68 is used for solubility enhancement of cilnidipine. The dissolution rate is directly proportional to solubility of drug. The solid dispersion is defined as dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent evaporation or melting-solvent method. The release mechanism of drugs from variety of solid dispersion depends on the physical properties of carriers as well as drug substances and preparation methods.[1,2]

Pluronic F 68 is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene copolymers in a concentration ranging from 20- 30%. In general, pluronic F 68 are composed of white, waxy, free-flowing granules that are practically odorless and tasteless. The aim of the present study was to improve the solubility and dissolution rate of cilnidipine by solid dispersion technique using different ratio of pluronic F- 68.[3,4]

MATERIALS AND METHODS

Materials

Cilnidipine and Neusilin was a gift sample from Emcure Pharmaceuticals Pvt. Ltd. Pune, Pluronic F-68 from Merck Mumbai. All other ingredients used were of analytical grade and purchased from Research Lab Fine Chem. (Mumbai).

Methods

A) Preparation of solid dispersion

Fast dissolving tablets were prepared by using Cilnidipine with variable concentrations of superdisintegrant and drug: carrier ratio. Measured quantity of Pluronic F 68 was taken separately and heated until they get melted. Then measured quantity of Cilnidipine was added in the molten mass of Pluronic F-68 at the same temperature with stirring until both formed homogeneous mass. Melted mixture was then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass was crushed, pulverized and sieved and stored in desiccators for 24 hours. The solid dipersion is prepared in the ratio of 1:1, 1:2, 1:3. The powder X-ray diffraction (PXRD) patterns were recorded using X-ray diffractometer (Bruker D8 Advance analyser) for pure drug, solid dispersions (Fig. 1 and 2).

B) Preparation of tablet

Solid dispersion mass was mixed with excipients thoroughly for 15 min. The resulting powder blends were evaluated for flow parameters. The powder blends equivalent to the 100 mg of drug were directly compressed using 8 mm concave faced round punches. Tablets were evaluated for various tablet parameters.[5,6] (Table No. 1).

Factorial design

Optimization of fast dissolving tablets prepared by using Pluronic F-68 i**s** as shown in Table No.1.

A 3^2 full factorial design was selected and two factors were evaluated at three levels. The percentage of PluronicF-68 (A) and Crospovidone(B) were selected as independent variables and the dependent variables were cumulative % drug release in 15 min (% DR_{15}), and disintegration time. The data obtained were treated using Design Expert 8.0.7.1 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3D response surface methodology to study the interaction of Pluronic F-68 (A) and crospovidone (B) on dependent variables.

Evaluation of tablets

Drug content uniformity of tablets: Five tablets were weighed individually and crushed in a mortar. Quantity of powder equivalent to 100 mg of Cilnidipne was weighed accurately and dissolved in distilled water. The volume was made to 100 ml with Distilled water. Appropriate dilutions of the resulting solutions were done. The drug contents of the resulting solutions were calculated from UV absorbance at 253 nm.

Disintegration time of tablets

The in vitro disintegration studies were carried out using Digital Tablet Disintegration Test Apparatus (Veego Scientific Pvt Ltd, India). One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube. This assembly was then suspended in beaker containing distilled water maintained at 37±2 C. The basket was then moved up and down through a distance of 5 to 6 cm. at a frequency of 28 to 32 cycles per minutes. The time required for complete disintegration of tablets were recorded. The test was performed for tablets of all type of formulation.[7]

Drug release/ dissolution studies

The dissolution study was carried out in 900 ml 0.1% SLS in distilled water at 50 rpm at temperature 37±0.5^{0}C for 15 minutes using USP apparatus type-II (Veego Scientific Pvt. Ltd, India). Appropriate aliquots (10ml sample volume) were withdrawn from the dissolution medium at predetermined intervals (2, 4, 6, 8, 10, 15 min). The samples were filtered through whatman filter paper. Samples were then analyzed at λ max of 253 nm using UV/VIS double beam Spectrophotometer.[8,9]

Stability studies

Stability studies on the optimized formulation of fast dissolving tablet were carried out to determine the effect of temperature and humidity on the stability of the drug. The tablet (optimized batch F9) was stored in stability chamber at a 40°C±2°C/ 75%RH. The sample was withdrawn at 30 days, 90 days and subjected for visual inspection, disintegration test, drug contents and in vitro dissolution.[10,11,12] (Table 2).

RESULTS

Powder Xray Diffraction-

XRD pattern of the solid dispersion prepared with Pluronic F-68 was characterized by less intensity of diffraction peaks as compare to pure drug, suggesting conversion of microcrystalline form of the drug to an amorphous state, which may helps to improve solubility and dissolution of drug (Fig. 1 and 2).

Factorial Design

Response surface plot for cumulative % drug release in 15 min and for disintegration time is as shown in Figure No.3,4.

Final equation in terms of coded factors for % drug release

Drug release=+52.77+24.57A+4.35B

Response surface plots were generated for each response. Coefficient of A was found to be more as compare to B which indicates concentration of pluronic was more significant than concentration of crospovidone. Pluronic helps to increase solubility and dissolution of drug.

Final equation in terms of coded factors for disintegration time

Disintegration time = +58.67 -6.67A -5.67B

Response surface plots were generated for each response. Negative sign indicates increase in in concentration of pluronic and crospovidone decreases disintegration time.

Drug –Pluronic F-68 Solid Dispersion

From drug release profile, it was observed that as the drug:pluronic ratio increases the drug release also increases. Fig. 5 showed 1:3 ratio showed 90% drug release in 15 mins and 1:1 ratio showed 84% in 60 mins. The significant increase in drug release was due to hydrophilic carrier pluronic having HLB value 29 which may have helped to increase the solubility of cilnidipine in the dissolution media. Pluronic is block copolymer and having self emulsifying property that spontaneously form a fine dispersion or emulsion upon contact with water. It forms complex with cilnidipine during melt method. A super-saturation of drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process.

Comparative Dissolution Profile of optimized formulations with Marketed tablet M1

From the dissolution graph it was observed that the marketed formulation (Cilnidipine) showed 60% drug release within 60 min. Our all selected ratios showed much faster drug release.[13,14] (Fig. 6).

Stability studies

Stability studies carried out at 40 ± 2 C/ 75± 5% RH and at room temperature for 90 days shown no significant change in colour, disintegration time, cumulative % drug release and drug content of optimized formulation (F9). It indicated that formulation is stable.[15] (Table 2).

Table No. 1: Formulation of drug: Pluronic F-68 solid dispersion

Formulation Batch	Solid dispersion ratios	Drug (mg)	Pluronic F-68 (mg)	Crospovidone (mg)	Neusilin(mg)	Total weight (mg)
B1	1:1	10	10	-	80	100
F1	1:1	10	10	4	72	100
F2	1:1	10	10	6	72	100
F3	1:1	10	10	8	72	100
F4	1:2	10	20	4	62	100
F5	1:2	10	20	6	62	100
F6	1:2	10	20	8	62	100
F7	1:3	10	30	4	56	100
F8	1:3	10	30	6	54	100
F9	1:3	10	30	8	52	100

Table No. 2: Stability studies

Formulation Batch	Time	Appearance	Disintegration time (seconds)	%Drug Release after 15 min
	Initial	White	45±1	90.669±1.09
F9	**30days**	White	43±2	90.132±1.79
	90days	White	41±1	90.120±1.36

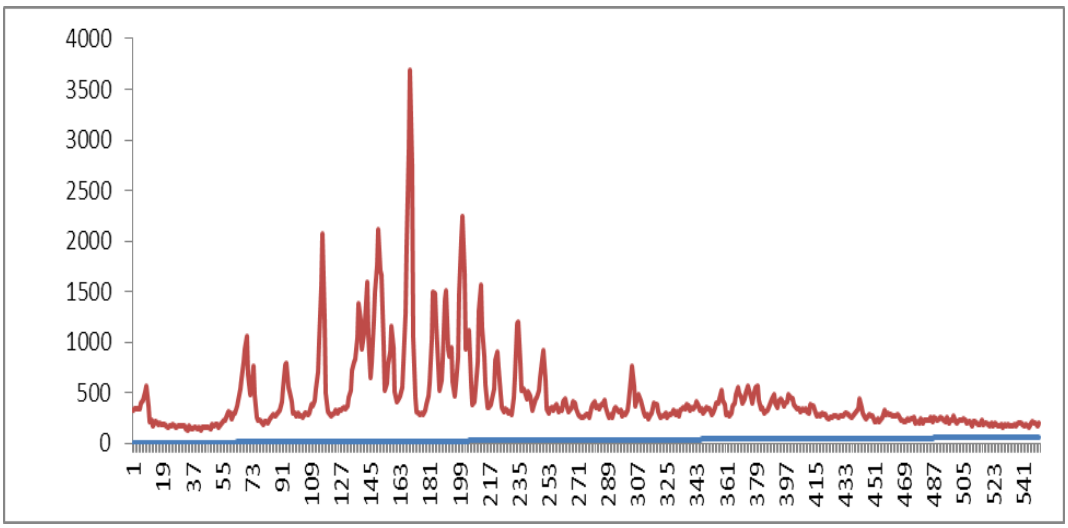

Figure No. 1: Powder X-Ray Diffraction of Cilnidipine

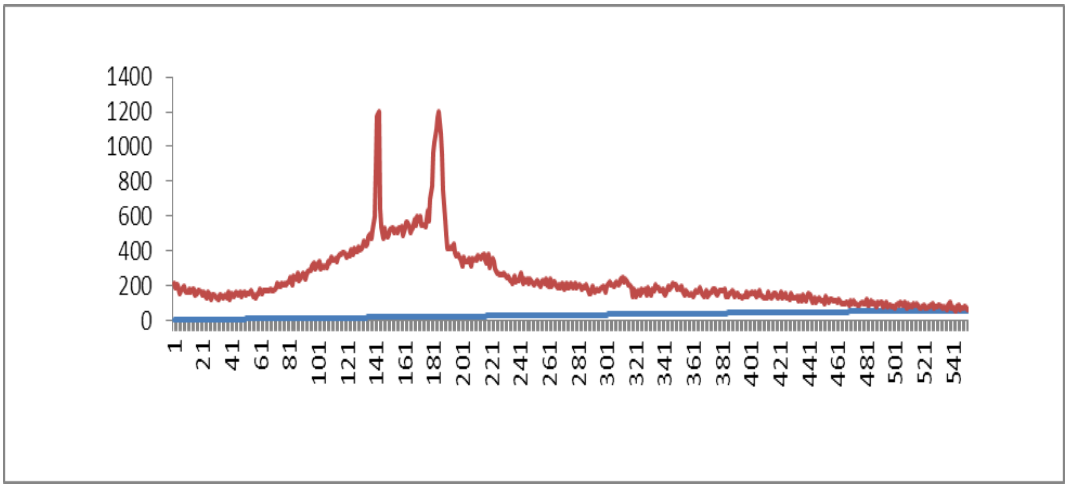

Figure No. 2: Powder X-Ray Diffraction pattern for Cilnidipine –Pluronic F-68 solid dispersion

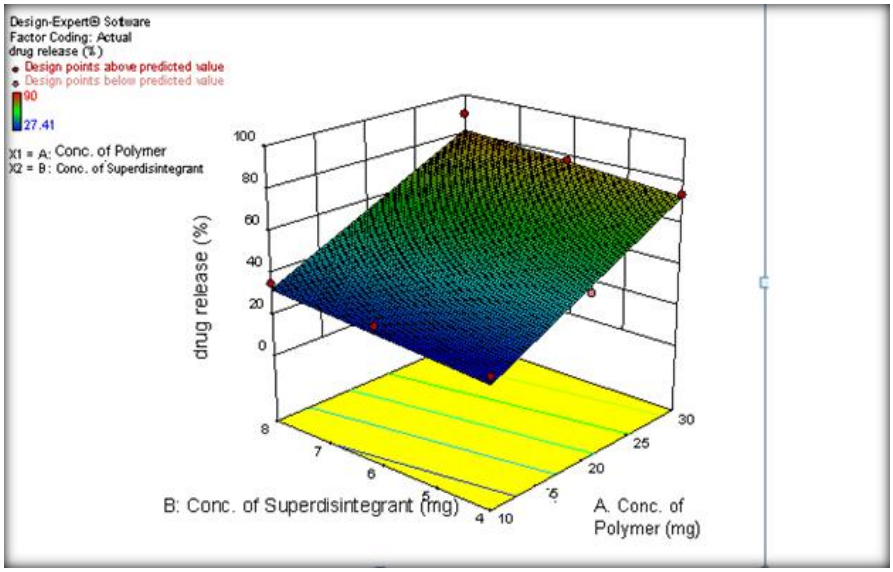

Figure No. 3: Response surface plot for cumulative % drug release in 15 min

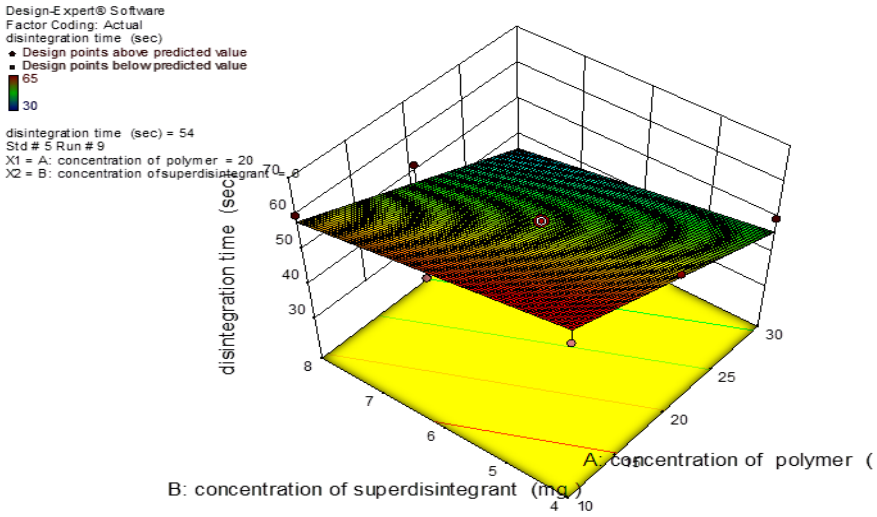

Figure No. 4: Response surface plot for disintegration time

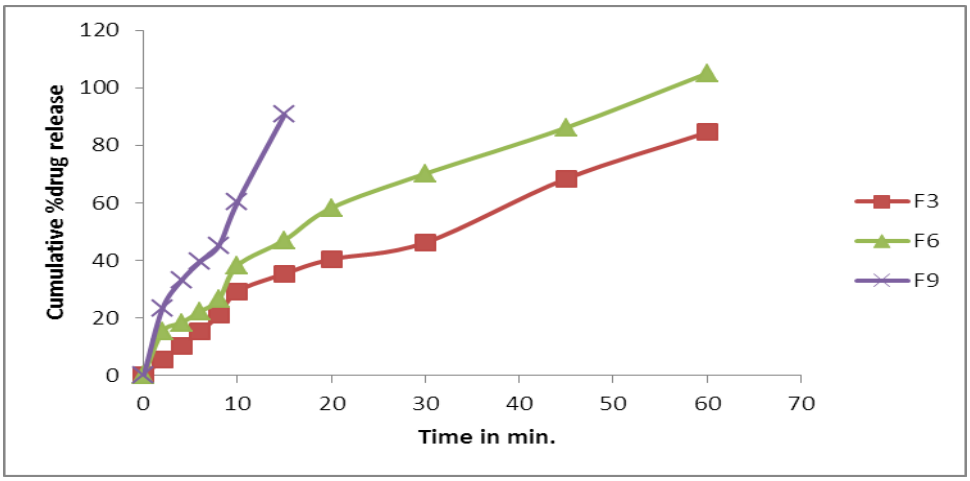

Figure No. 5: Effect of Drug Pluronic F-68 ratio on release of drug

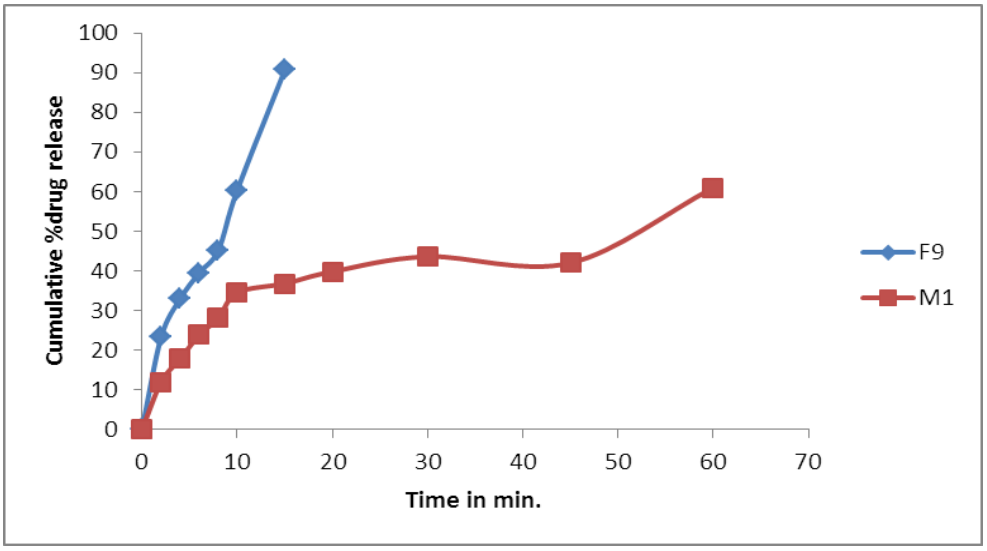

Figure No. 6: Comparative release profile of Marketed tablet M1 with F9 formulation

CONCLUSION

The solid dispersion prepared using pluronic showed increase in release rate of drug. Increase in concentration of pluronic showed increase in dissolution of drug. The superdisintegrant used shown decrease in disintegration time and increase in release rate of drug. The drug: pluronic ratio 1:3 and 8% crospovidone was found to be good in terms of drug release and disintegration time.

From such trials, it was observed that, F9 formulation was found better in terms of disintegration time and drug release profile(DT<3 minutes and drug release NLT 85% in 15 min.).

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