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EFFECT OF HYDROPHILIC POLYMERS ON DISSOLUTION OF NIMODIPINE

Esmat E. Zein El Dien[1], Nageh A. El Mahdy[2] and Wesam Samy[3]*

[1]Professor of Pharmaceutical Technology, Pharmaceutical Technology Dept., Faculty of Pharmacy, Tanta University, Egypt.

[2]Professor of Pharmacology, Pharmacology Dept., Faculty of Pharmacy, Tanta University, Egypt.

[3]Pharmacist at General Mahalla Hospital, El-Mahalla El-Koubra, Egypt.

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***Corresponding Author**
Dr. Wesam Samy
Pharmacist at General Mahalla Hospital, El-Mahalla El-Koubra, Egypt.

ABSTRACT

Nimodipine (NMD), a calcium channel blocker, has a low oral bioavailability due to poor solubility and insufficient dissolution rate. In order to improve drug´s solubility, various techniques were employed, solid dispersion(SDs) for drug and its formulation by solvent evaporation technique were used . Formulations so prepared were estimated by differential scanning calorimetry (DSC), IR and were investigated for, solubility studies. The dissolution of the prepared formulations prepared with polymers PloxamerF68, Eudragit Epo, HP-beta- CD were tested, All polymers in tested formulations showed improvement in the dissolution rate ofthe drug.

KEYWORDS Nimodipine, solvent evaporation, polymers, solid dispersion, dissolution.

INTRODUCTION: Nimodipine is chemically described as 3-(2-methoxyethyl) 5-propane-2-yl 2, 6-dimethyl-4-(3 nitrophenyl)-1,4- dihydropyridine- 3,5-dicarboxylate, it is used in the treatment of various cardiovascular disorders such as angina pectoris, cardiac arrhythmia and hypertension.[1]

Nimodipine is rapidly absorbed from GIT following oral administration, but undergoes extensive first-pass metabolism in the liver. The oral bioavailability is reported to be about 9 hrs, Nimodipine is practically insoluble in water but highly permeable drug class ll. The rate-limiting step in its absorption is its dissolution rate in gastrointestinal fluids (GIT).[2] The rate

of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion).[3]

Poor aqueous solubility of drugs is a major limiting factor with many new drugs in their successful launch in market in spite of their potential pharmacokinetic activity. Poor solubility (less than 10 %) of a drug, leads to poor dissolution in the (GIT) hence, incomplete and erratic absorption ultimately limits its clinical utility.

Further, poorly soluble drugs are generally administered at much higher doses than the actual dose in order to achieve necessary drug plasma levels leading to increased adverse reactions & cost of therapy and often yields erratic pharmacological response and hence poor patient compliance.

About 40% of drugs being in the pipeline of pharmaceutical companies are poorly soluble, which emphasizes the need of a technique to overcome such problems.[4]

Poorly water-soluble drugs are associated with slow drug dissolution followed by slow absorption leading eventually to inadequate and variable bioavailability. Solubilty, as the dissolution rate is the most essential factor controlling the rate and extent of drug absorption, A poorly water soluble drug, more recently, has been defined in general terms which requires more time to dissolve in the GIT fluid than it take to be absorbed in the GIT.

A greater understanding of dissolution and absorption behaviors of drugs with low aqueous solubility is required to be successfully formulated into bioavailable drug products.[5] Nimodipine (NMD), a calcium channel blocker, was selected as a model drug for this work as the drug has low aqueous solubility where its GIT absorption is limited by its dissolution in the gastrointestinal fluids exhibiting a low bioavailability after oral administration.[6] A number of approaches are practiced to improve the aqueous solubility of poorly solubledrugsviz., soliddispersion (solventevaporationmethod), Sphericalagglomeration[7], microcrystallizationand supersaturation. These techniques result into polymorphic changes or changes in crystal structure or hydrophilicity changes due to formation of a molecular dispersion. The formulations were evaluated by studying these changes in drugs along with their dissolution and other properties. The solubility and in vitro study were evaluated by the detection of concentration in the dissolution media. The polymorphic form of the formulation is evaluated by the differential scanning calorimetry (DSC). In the present investigation the

technique utilized was solid dispersion of the drug with different polymers (Ploxamer F68, HP-betaCD, Eudragit EPO).

MATERIALS AND METHODS

Nimodipine (Hangzho Uniwise InternationalCo., Ltd. China) -
Ploxamer F68, Eudragit Epo and HP-Beta cyclodxtrine(Sigma- Chem. co. USA,),
All other chemicals were of extra pure reagent grade and were used as received.

Methods preparation of solid dispersion by solvent evaporation technique 0.25 gm of NMD were mixed with different ratios of Ploxamer F68,Eudragit Epo and HP-betaCD (1:1,1:2,1:3) drug:polymer respectively(0.25,0.5,0.75)of each polymer in binary system i.e F1 -F9(Drug:Ploxamer1:1,
Drug:Ploxamer1:2,Drug:Ploxamer1:3),(Drug:HPBCD1:1,Drug:HPBCD,1:2,Drug:HPCD1:3), (Drug:EudragitEPO1:1, Drug: Eudragit Epo1:2, Drug:Eudragit Epo1:3) and were mixed with ethanol and dichloromethane mixture in a ratio of (50:50%) and the solvents were then evaporated in open air until dried and the pericptate was scrapped and ground.

Evaluation and characterization

- **-Diffrential scanning calorimetry (DSC):** DSC thermograms were obtained using DSC-50 differential scanning calorimeter (shimadzu, seisakusho ltd, Kyoto, japan). Samples (3-4gm) were weighed in aluminium pans and heated at a scanning rate of 10c /min from 20 to 400 oc in the prescence of nitrogen at a flow rate of 20ml /min, H, joule/g).

Fourier transform infrared spectroscopy (FT-IR): FT-IR spectra of the drug alone as well as the selected solid dispersion using FT-IR Tensor 27 Boker, Germany, was at the range of 400-4000cm^{-1}. Potassium bromide (KBr) disc method was used, the samples were ground, mixed thoroughly with KBr and compressed.

Drug content studies: Weights equal to 30mg of nimodipine and equal weights from polymers were taken but with different ratios from solid dispersion (1:1,1:2,1:3) ratios and mixed with solvent mixture(ethanol and dichloromethane50:50%) up to 50ml, one ml was taken by micropipette and completed up to 50 ml with ethanol only and the absorbance was detected spectrometrically.

In vitro dissolution study: Dissolution of the drug as well as solid dispersion were studied using USP, dissolution apparatusII (Paddle type)Accurately weighted amounts of each

formulation equivalent to 60mg of NMD were dispersed over 900ml of the dissolution medium [Distilledwater+0.5%SLS(sodium lauryl sulfate)][14] and for Eudragit Epo the media was PH 4.5 at 37°c stirred at 50 rpm(8) at appropriate intervals, samples were withdrawn (5ml aliquots) over a period of 1hour and were replaced by equal volumes of pre warmed media, the samples were filtered throught filter paper0.24µm and NMD content was determined spectrophotmetrically at 237 nm.

All experiments were carried out in triplicate(n=3) and the average was determined±SD.

RESULTS AND DISCUSSION

Differential scanning calorimetric (DSC): Figure (4) show DSC thermograms of pure drug and corresponding drug polymers systems. The DSC curve of Nimodipine (NMD) shows a sharp endothermic peak (Tpeak = 127.03°C) corresponding to its melting, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug melting point was broadened and shifted toward lower temperature, with reduced intensity, in all the formulations. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Moreover, the data also indicate no interaction between the components. also suggests that in the process of SD did not induce interaction at the molecular level and solid dispersion formed is a physical mixture with highly dispersed drug crystals in polymer.

FTIR Study: Figure(5) indicates the IR Spectrum of NMD, There is a characteristic band at 3296cm^{-1}, related to N-H stretching, at 1694cm^{-1}, associated with the carbonyl bond C=O and at 1496cm^{-1}representing the No2group.[9]

- FTIR of PLoxamer(Pluronic F68)

FTIR displayed broad band at 3355-3610cm-1 due to (o—H) group[10]

-F 2 shows FTIR Of ploxamer pf68and NMD in ratio1:1and this height peak did not prevent peaks of drug to appear and show possibility of hydrogen bond between oH and N-H make the drug in amorphous shape.

- FTIR OF Eudragit Epo

FTIR shows bands of the ester group at 1150cm^{-1},1243 cm $^{-1}$,1273cm $^{-1}$ as well as the C=O ester vibration at 1730cm^{-1} in addition (CHn) vibrations can be discerned at

1391cm^{-1},1458cm^{-1},1637cm^{-1}, 2957cm^{-1} the absorbtion at 2775cm^{-1} and (7), 2825 cm^{-1}can be assigned to the dimethyl amino groups and due to oH bond at 3438cm^{-1}

- F5 shows FTIR OF NMD and Eudragit Epo in ratio (1:1)all characteristic bands of drug and polymer appeared and indicating no interaction between drug and polymer and show propability of forming Hydrogen bond between C=O and NH of Nimodipine.

- HP-beta CD shows FTIR of Hydroxy propyl beta cyclodextrine(HP-beta CD)
FTIR show(0H)n characteristic band of oH Vibrational stretch at 3416cm-1,2931cm-1 for(c-H2)stretching vibration ,(S=o)and(c-H)n 1156cm-1,1084cm-1stretching vibration (11).

- F8 Shows FTIR of NMD and in ratio 1:1 HP-beta CD
In it broadening of the peak was observedat 2939cm^{-}1 due to C-H2 stretching vibration and all peaks of drug and polymer appeared indicate no chemical interaction and show propability of forming hydrogen bond between N---H and oH.

All figures, in it all characteristic peaks of parent drug Nimodipine and other three polymers were appeared, visible and indicate no chemical interaction.

Drug content study; The drug content of the prepared formulations of Nimodipine was observed to be varying from 98-100% showed in table 1.\

Table1: Drug content of various formulations batches.

Sr.NO	Drug content (n=3±SD)
F1	100±0.28
F 2	100±0.34
F 3	99±0.25
F 4	98.9±0.8
F 5	98.8±1.00
F6	100±0.2
F7	100±0.5
F8	99±0.5
F9	100±0.41

In vitro dissolution studies: Table(2) and figures (1-3) shows the amount released of NMD from different formulations in comparison with original drug, it was observed all formulation show the increase in the %release of the drug with increase in polymer ratio up to 1:3, It was observed that the formulations F-3,F-6and F-9 show the most increase in the %release of the

drug formulations, F-4 and F-7 which show the lesser % release of the drug in the dissolution medium, This is indicate that the more increase in the tratio of polymer to drug increase in drug dissolution rate until it reach 1:3 give the most increase dissolution rate

EFFECT of different polymers on the dissolution of nimodipine

SDs were performed include. Incorporation of polymer(Ploxamer F68,Eudragit Epo and HP-betaCD) enhanced the dissolution rate of nimodipine. In addition, the dissolution of the drug is improved. The enhancement of dissolution of drug from drug polymer systems can be ascribed to several factors. The mechanism of dissolution rate improvement from solid dispersion is lack of crystallinity and particle size reduction considered to be important factors for dissolution rate enhancement. mixing of drug with a hydrophilic polymer results in greater wetting and increase surface available for dissolution by reducing interfacial tension between the hydrophilic drug and dissolution media. It was noted that drug polymer system sink immediately, while pure drug keeps floating on the surface for a longer time interval.(12) The dissolution parameters of drug (nimodipine) solid dispersion with various polymers Ploxamerf68,Eudragitepo and HPbetaCD in same concentration of each polymer. The dissolution rate of pure drug is low as 22% of the drug gets dissolved 60min respectively. Solid dispersions formulated with all the polymers exhibited significant improvement in the dissolution parameters of drug. The order of dissolution enhancement with various binary systems was found to be (F-9,6>F-3,1,2>F-4,5,8,7) for nimodipine. The increase in the dissolution rate of the solid mixtures might be due to size reduction and increase in the wettability of the drug molecules in presence of the polymers. Polymers also lowering the surface tension, hence increasing the solubilizing effect.

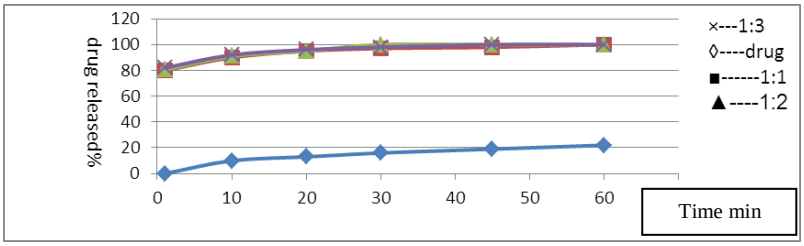
This technique can be extended for improvement of dissolution rate of drug showing poor dissolution profiles and causing erratic bioavailability.[11] The present invention often produces particles having reduced crystallinity as compared to the bulk drug, which enhances dissolution of the drug.[13]

CONCLUSION

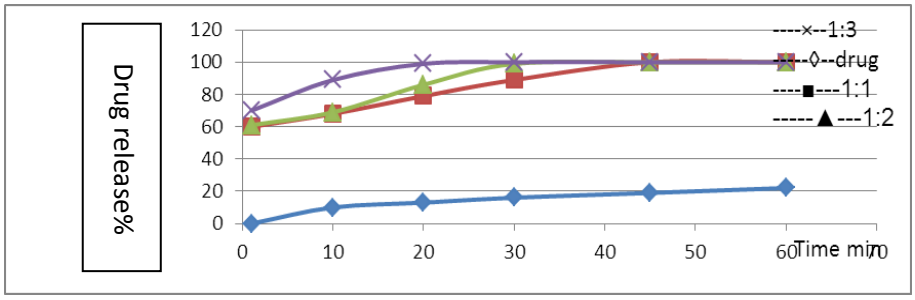
The addition of polymers to NMD by SD technique give increase in its dissolution rate and the ternary system give apronounced increase in drug release and so increase in its dissolutinn rate and bioavailability.

Table 2: Percent drug release in (%) from different formulations.

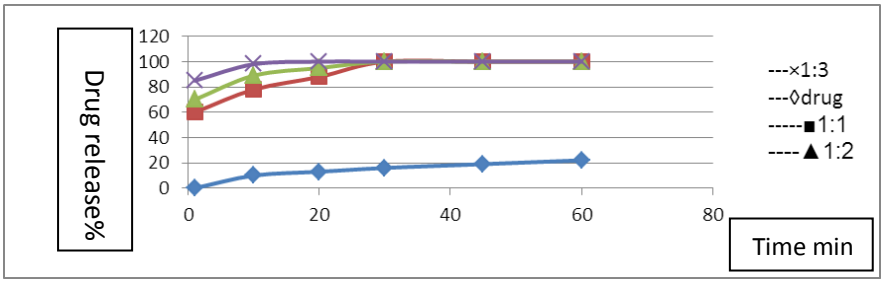
Sr .no	Amount releasedof NMD in(%)				
Time	10	20	30	45	60
Drug	10±0.27	13±0.35	16±0.3	19±0.4	22±0.21
F1	90±0.23	95±0.54	97±0.5	98±0.31	100±0.25
F2	91±0.31	95±0.22	98.±0.4	100.±0.21	100±0.41
F3	92±0.25	96±0.4	100±0.27	100±0.29	100±0.34
F4	68±0.41	79±0.5	89±1	100±0.2	100±0.39
F5	69±0.5	86±1	99±0.3	100±0.7	100±0.9
F6	89.±0.6	99±0.3	100.±0.34	100.±0.51	100±0.7
F7	78±0.34	89±0.61	100±0.2	100±32	100±0.45
F8	88±0.21	95±0.7	100±0.3	100±0.5	100±0.8
F9	98±0.3	100±0.2	100±0.4	100±0.7	100±0.9



Figure(1)Dissolution of NMD and Ploxamer F68 in different ratios (1:1,1:2,1:3)in relation to pure drug.



Figure(2)Dissolution of NMD and Eudragit Epo in different ratios (1:1,1:2,1:3)in relation to pure drug



Figure(3)Dissolution of NMD an HP-BCDin different ratios (1:1,1:2,1:3)in relation to pure drug.

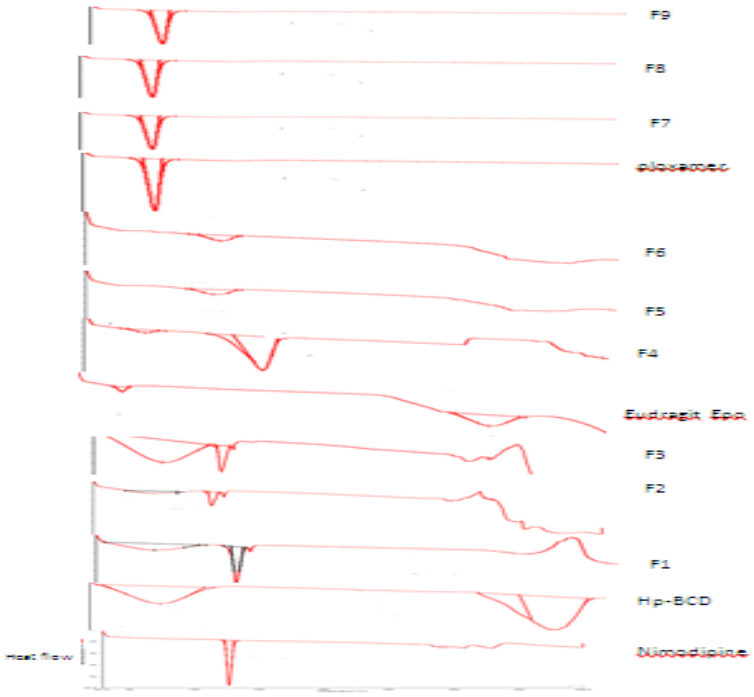


Figure 4: DSC of pure Nimodipine and its formulations prepared by Solid dispersion (SD)

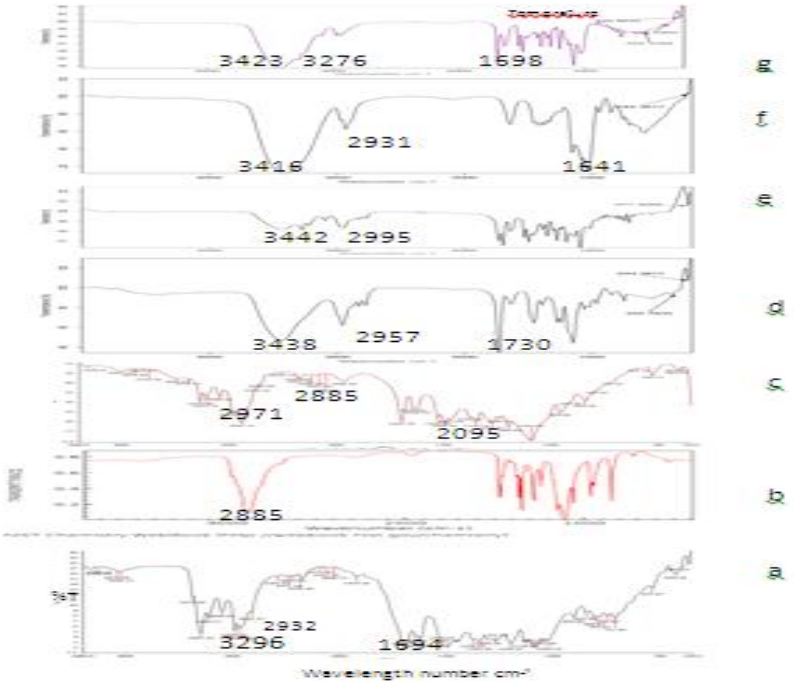


Figure (5): FT-IR of Nimodipine and its formulations with polymers with (a)Nimodipine,(b)Ploxamer(c)Ploxamr(1:1) (d) Eudragit Epo(e) Eudragit Epo1:1 (f) HP-BCD(g) HP-BCD1:1

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