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Research Article

Studies on the solid dispersions of gliclazide

D. Nagasamy Venkatesh*, Anindita De, K. Vindya Komali, S.N. Meyyanathan, K. Elango

Department of Pharmaceutics, JSS College of Pharmacy, (Off Campus College of JSS University, Mysore), Ooty – 643 001 Tamil Nadu, India

ABSTRACT

Gliclazide and β-cyclodextrin (Gli/β-CD) dispersions were prepared with a view to study the influence of β-CD on the solubility and dissolution rate of this poorly soluble drug. Phase-solubility profile indicated that the solubility of gliclazide was significantly increased in the presence of β-cyclodextrin and was classified as A_L-type, indicating the 1:1 stoichiometric inclusion complexes. Physical characterization of the prepared systems was carried out by differential scanning calorimetry (DSC), X-ray diffraction studies (XRD) and IR studies. Solid state characterization of the drug β-CD binary system using XRD, FTIR and DSC revealed distinct loss of drug crystallinity in the formulation, ostensibly accounting for enhancement of dissolution rate. The drug release from solid dispersion obeyed first order kinetics. Solid dispersions of gliclazide exhibited a 14 times fold increase in dissolution rate over pure drug.

Keywords: Gliclazide; dissolution; β-cyclodextrin; kneading method; release kinetics.

INTRODUCTION

Poor water soluble drugs are generally associated with slow drug absorption leading eventually to inadequate and variable bioavailability (Amidon et al., 1995. Leuner and Dressman J. 2000).

Nearly 40% of new chemical entities currently being discovered are poorly water soluble drugs (Lipinski C 2002. Hu J et al., 2004).

Attempts to enhance drug solubility of these therapeutic agents correlate well with enhancement of their bioavailability (Hye JA et al., 1997. Sekiguchi K et al., 1961).

Among them solid dispersion technology was most widely employed (Law SL et al., 1992.Corrigan OI. 1985. Craig DQM 1990. Ford JL. 1986). Number of insoluble drugs has shown to improve their dissolution character when converted to solid dispersion (Madhusudhan B et al., 2002). Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers (Delahaye N et al., 1997).The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water soluble drug is increasing (Okimoto K et al., 1997. Yamada T et al., 1999). Various hydrophilic carriers such as polyethylene glycol (Margarit MV et al., 1994), polyvinylpyrrolidone (Yagi N et al., 1996) and sugars (Danjo K et al., 1997) have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs.

Cyclodextrins are cyclic (α-1, 4)-linked oligosaccharides of α-D-glucopyranose, containing a relatively hydrophobic central and hydrophilic outer surface. During the past two decades, cyclodextrins and their derivatives have been attracted considerable attention in the pharmaceutical field owing to their potential in forming complexes with a variety of drug molecules. Cyclodextrins are used to increase the solubility of water insoluble drugs, through inclusion complexation (Narang A et al.,1990. Chiou WL et al., 1971. Chiou WL et al., 1969 Millic AJ et al., 1997).

Generally, the small drug molecules, and those compounds with lowest water solubility showed a percent increase in solubility as a function of cyclodextrin concentration. Therefore, cyclodextrins have been used in pharmaceutical preparations in order to increase the stability and bioavailability of poorly water soluble (Moyano JR et al., 1997). Natural cyclodextrins have been used extensively for this purpose. However, they are characterized by a relatively low solubility in water, which limits their application. Hence, a chemically modified cyclodextrins are gaining considerable attention to improve the physicochemical properties of cyclodextrin. Cyclodextrin are known to form an inclusion complex with many drugs of appropriate molecular size and polarity in hydrophobic drug molecules. The resulting complex generally leads to an improvement in some of the properties of drugs in terms of its solubility, bioavailability and tolerability. Gliclazide, is chemically 1-[3-azabicyclo(3.3.0) oct 3-yl] 3-p-toly sulphonyl

* Corresponding Author
Email: nagasamyvenkatesh@rediffmail.com
Contact: +91-423-2443393
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urea, used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). The major drawback of this drug is its poor aqueous solubility, and therefore its oral bioavailability is only 50% (Martindale. 2002).To overcome these difficulties, increase in the aqueous solubility of gliclazide is an important goal. Hence, in this present investigation, inclusion complexation of gliclazide was tried with an aim to improve its pharmaceutical properties such as aqueous solubility and dissolution properties.

In this study, an attempt was made to improve the solubility and dissolution rate of gliclazide by complexing with β-CD thereby increasing its bioavailability and therapeutic efficacy. The characterization of drug, β-CD and complex was done by differential scanning calorimetry (DSC), FTIR and Powder X-ray diffractometry (PXRD). *In vitro* aqueous solubility and dissolution rate profiles of the complex were performed.

MATERIALS AND METHODS

Gliclazide was obtained as a gift sample from Amanath Pharma, Puducherry, India. β-cyclodextrin (β-CD) was obtained from Sigma, USA. All other materials used in the study were of analytical or HPLC grade.

Methods

Preparation of gliclazide and β-cyclodextrin solid dispersion (GSD)

A mixture of gliclazide and β-cyclodextrin (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 and 1:10 w/w) was wetted with a mixture of acetone and water (1:1) and kneaded thoroughly for 30 min in a glass mortor (Aftab Modi et al., 2006). The paste formed was dried under vaccum for 24 h. Dried powder was scrapped, crushed, pulverized and passed through sieve no 100 (ASTM-100, 150 μm) and stored in dessicator for further studies.

Solid state studies

Fourier Transform Infrared (FTIR) spectroscopy

FTIR spectra were recorded on samples prepared by kneading method in different ratios of carrier (w/w) in a KBr pellets (Shimadzu, Japan). The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

Differential scanning calorimetry (DSC)

DSC analysis was performed using Netzsch DSC 204, Tokyo, Japan. The samples were heated in a sealed aluminum pans at a rate of 10° C per min^{-1} in a 30 to 300° C temperature range under nitrogen flow of 40 mL/min.

X-ray powder diffractometry (XRD)

X-ray powder diffraction patterns were recorded on an X-ray diffractometer (Jeol JDX, Japan) using Ni-filtered, Cu Kα radiation, a voltage of 40 kV and a 25-mA current. The scanning rate employed was 1° min^{-1} over the 10 to 30° diffraction angle (2θ) range.

Liquid State Studies

An excess of gliclazide (50 mg) was added to screw capped bottles containing various concentrations of β-cyclodextrin solution (0.2, 0.4, 0.6, 0.8 and 1 mM×10^3). Vials were shaken mechanically at 25±0.5° C for 24 h using rotary flask shaker. After 24 hrs of shaking to achieve equilibrium, 5 mL of aliquots were withdrawn, filtered (0.45 μm pore size) and spectrophotometrically analyzed for drug content at 230 nm by UV spectrophotometer (Shimadzu-UV 160 A, Japan) (figure 1). Each experiment was performed in triplicate. (Coefficient of variation [CV] <3%) (Higuchi T et al.,1965).

Dissolution rate studies

Dissolution rate studies were performed in phosphate buffer (pH 6.8) maintained at 37±0.5° C, using USP XXII apparatus (Electrolab, Mumbai, India) with paddle rotating at 50 rpm. Solid products each containing 100 mg of drug was subjected to dissolution. At fixed time intervals, samples withdrawn were filtered (0.45 μm pore size) and spectrophotometrically assayed for drug content at 230 nm. Each test was performed in triplicate (CV<3%). Dissolution efficiency (DE) was calculated from area under the dissolution curve at time 't' (measured using trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time (Khan KA 1975).

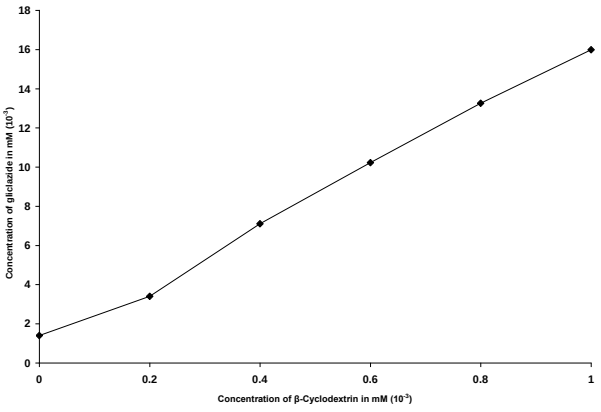

Figure 1: Phase solubility study of gliclazide and β-cyclodextrin at 25° C

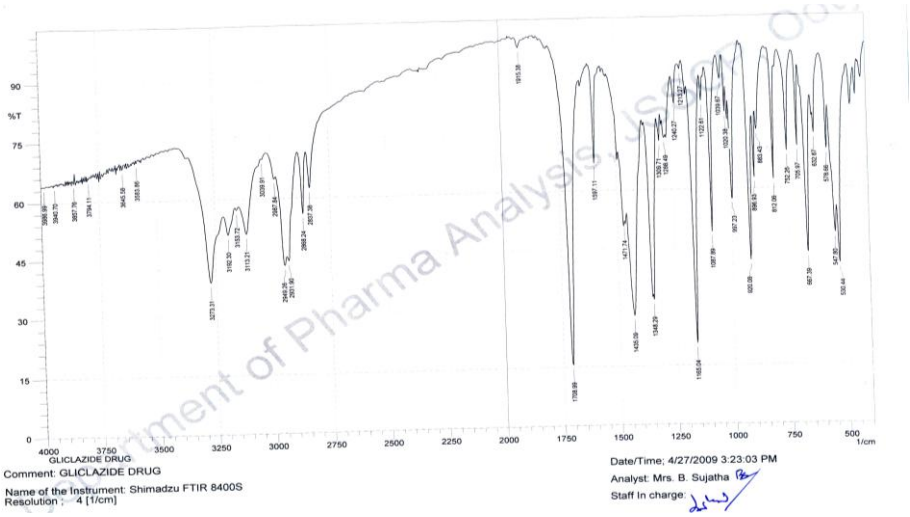

Figure 2:(a) FTIR spectra of gliclazide

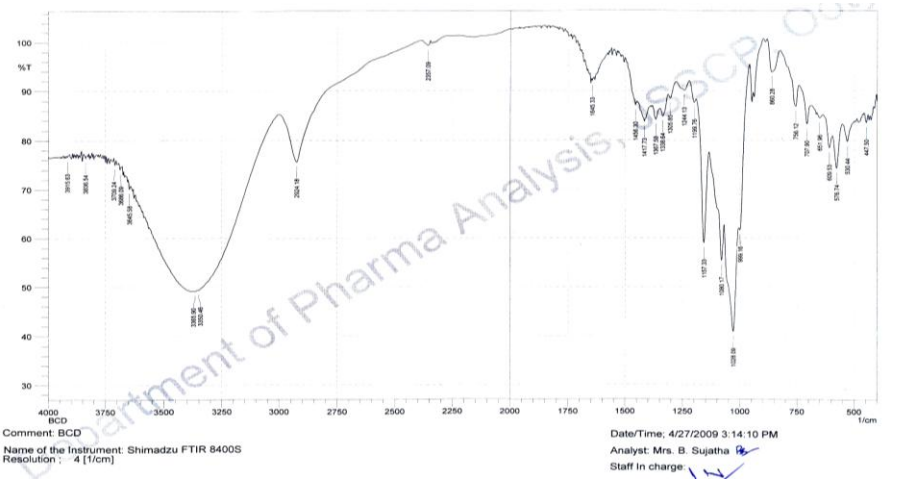

Figure 2:(b) FTIR Spectra of β-cyclodextrin

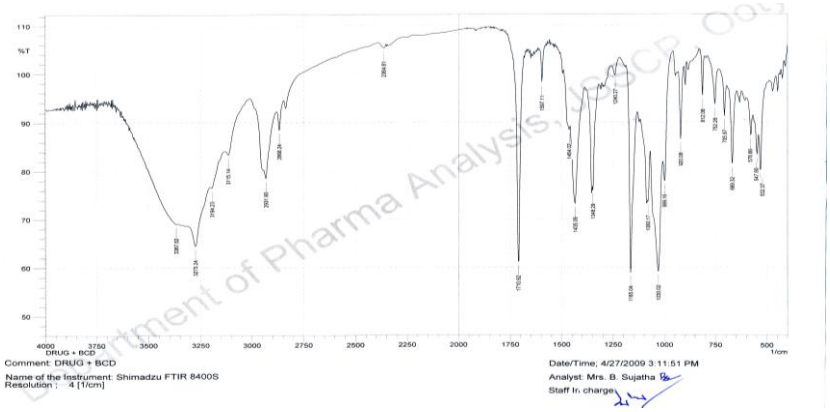

Figure 2:(c) FTIR spectra of gliclazide and β-cyclodextrin

RESULTS AND DISCUSSION

The phase solubility diagram for complex formation between gliclazide and β-cyclodextrin is shown in figure 1.

The aqueous solubility of gliclazide is increased linearly (r = 0.9900) as a function of carrier concentration. The phase solubility diagram showed A_L type, due to a straight line had a slope less than unity; indicates the formation of complex. The apparent stability constant, K_C was calculated from the linear plot of the phase solubility diagram according to the equation.

$K_C = \text{Slope} / S_0 (1\text{-Slope})$

Where, 'S_0' is the solubility of gliclazide in the absence of β-cyclodextrin. The stability constant, 'K_C' of gliclazide and β-cyclodextrin complex was found to be 680.44 mmol, which indicates the formation of stable complex for A_L type solid complexes prepared by kneading method. The FTIR spectra of gliclazide and its

binary systems with β-cyclodextrin are presented in figures 3a, 3b and 3c.

Pure drug showed sharp characteristic peaks at 3278 cm^{-1} (N-H), 1067 cm^{-1} (S=O), and 2949 cm^{-1} (C-H), 1165 cm^{-1} (C-N) and 1708 cm^{-1}(C=O). All the above characteristic peaks appear in the spectra of binary systems at same wave number indicating no modification or interaction between drug and carrier.

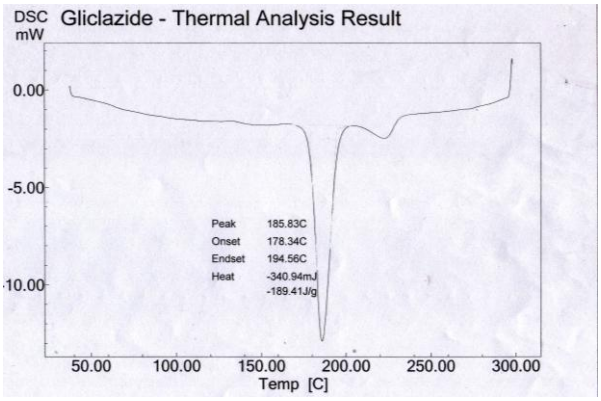

Figure 3:(a) DSC thermogram of gliclazide

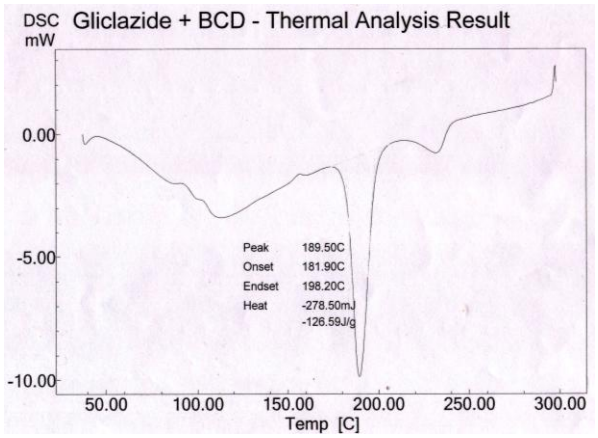

Figure 3:(b) DSC thermogram of gliclazide and β-cyclodextrin

Thermal behavior of pure drug and corresponding drug with carrier system are depicted in figures 4a and 4b. The DSC curve of gliclazide showed a sharp exothermic peak (T peak 185.8°C) corresponding to its melting point. However, the characteristic exothermic peak, corresponding to drug was broadened and shifted towards lower temperature, with reduced intensity in the solid dispersions. This could be due to the higher concentration and uniform distribution of drug in the crust of carrier, resulting in the complete miscibility of drug and carrier. Moreover, the data also indicates there seems to be no interaction between the components of binary systems. No significant difference in DSC pattern of dispersions suggest that even the kneading process could not induce any interaction at molecular level and the solid dispersion formed as highly dispersed drug crystals in carrier.

The XRD studies revealed that an intense peak was observed in pure gliclazide at 18°, which was broadened in the binary mixture. This ensures the overall amorphous form with poor crystalline structure present in the mixture which ensures conversion of crystalline to amorphous form were illustrated in figures 5a, 5b and 5c.

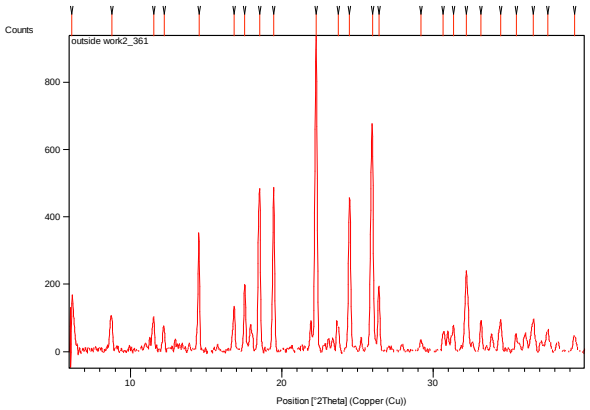

Figure 4: (a) XRD of gliclazide

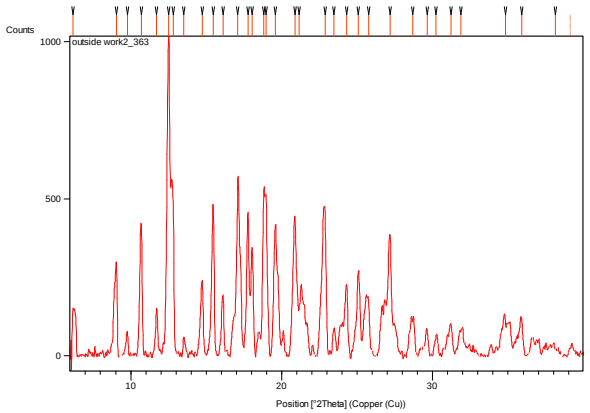

Figure 4:(b) XRD of β-cyclodextrin

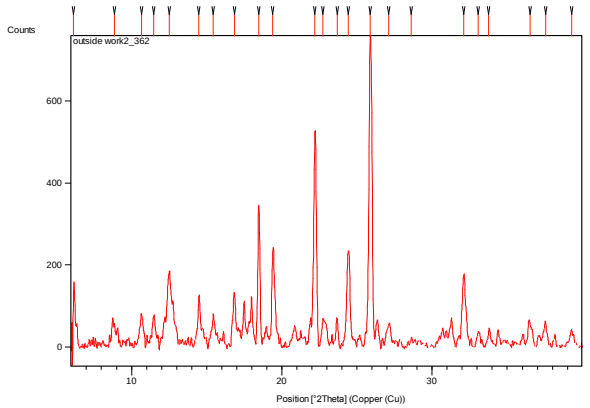

Figure 4:(c) XRD of gliclazide and β-cyclodextrin

Solid dispersions were found to be fine and free flowing in characteristics. The physicochemical evaluations of solid dispersions were shown in table 1.

The release of drug from the solid dispersion prepared by kneading method were 23.11% (1:1), 30.15% (1:2), 38.14% (1:3), 44.56% (1:4), 56.57% (1:5), 63.88% (1:6), 71.47% (1:7), 75.66% (1:8), 79.65% (1:9) and 94.66% (1:10) at the end of 60 min. The t^{50} values of batches

Table 1: Physicochemical evaluation of gliclazide solid dispersions

S.No	Batch code	Drug:carrier ratio	Yield (%)	Angle of re-pose (°)	Bulk density (g/cc)	Compress-bility (%)	Moisture uptake (%)	Drug content (%)	DE_{50} (%)
1	Pure drug	--	--	22±1.4	0.80±0.05	15±0.7	4±0.7	99±1.0	10.23
2	GSD-I	1:1	92.17±1.1	21±1.6	0.81±0.04	16±0.9	6±0.7	95±1.1	22.74
3	GSD-II	1:2	91.76±1.5	22±1.0	0.82±0.05	16±0.7	6±0.9	95±1.4	31.45
4	GSD-III	1:3	94.96±1.8	24±0.8	0.82±0.06	16±1.1	6±0.6	95±1.5	43.33
5	GSD-IV	1:4	95.68±1.9	23±1.3	0.83±0.03	17±1.3	7±0.8	97±1.4	57.96
6	GSD-V	1:5	95.22±1.1	22±1.2	0.86±0.01	17±1.2	7±0.7	98±1.3	74.11
7	GSD-VI	1:6	94.33±1.4	23±1.5	0.81±0.02	17±1.1	7±1.1	98±1.3	79.03
8	GSD-VII	1:7	93.12±1.2	21±1.8	0.80±0.06	18±1.9	7±1.2	97±1.3	83.03
9	GSD-VIII	1:8	93.44±1.8	22±1.4	0.85±0.08	17±1.5	7±1.7	98±1.3	88.11
10	GSD-IX	1:9	94.75±1.2	24±1.2	0.84±0.05	17±1.1	7±0.7	96±1.8	91.22
11	GSD-X	1:10	94.57±1.5	22±1.9	0.83±0.07	17±1.4	7±0.9	98±1.4	94.38

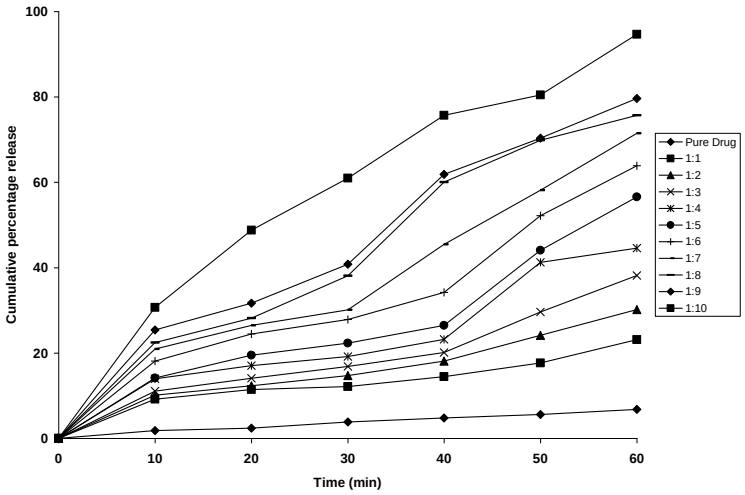

Figure 5: *In vitro* dissolution profiles of solid dispersion containing gliclazide. Samples were withdrawn at different time intervals and drug content was determined by UV spectrophotometer

prepared with 1:9 and 1:10 drug: carrier ratio were 34 and 21 minutes respectively. The batch prepared using the ratio of 1:10 (drug: carrier) showed better *in vitro* release and better t^{50} values, as compared with pure drug. The pure drug showed a release of 6.76% at the end of 60 min.

The solid dispersions prepared using kneading method improved 14 fold increases in the dissolution rate compared to pure drug. The enhancement of dissolution of gliclazide from the drug carrier may be due to several factors such as lack of crystallinity, increased wettability and dispersibility. Incorporation of drug with a hydrophilic carrier system offered an increased wetting and reduction in interfacial tension between hydrophobic drug and dissolution medium (Higuchi T et al., 1965).

It was observed during the dissolution studies that drug release from solid dispersion was found to be faster. As the proportion of β-cyclodextrin in solid dispersion increases, there was an increase in the dissolution rate of the drug was observed. The solid dispersion prepared using 1:10 drug carrier ratios (GLI-X) achieved maximum dissolution rate of drug. The 'k' values of solid dispersion were found to be more than pure drug and followed first order kinetics (Gopal Rao M et al., 2005).

CONCLUSION

The study showed that the dissolution rate of gliclazide can be enhanced to a greater extent by employing solid dispersion technique using an industrially feasible kneading method. The solid dispersion complex of drug

was exhibiting a better dissolution profile as compared to pure drug. This in turn, can reduce the doses of drug; reduction in dose related adverse effects and improved oral bioavailability.

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