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ORIGINAL ARTICLE

Urea co-inclusion compounds of glipizide for the improvement of dissolution profile

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Abstract In the present study, urea, a well-known adductor for linear compounds was successfully utilized for inclusion of glipizide—a highly substituted cyclic organic compound through a modified technique. Formation of glipizide co-inclusion compounds in urea was confirmed by FTIR, DSC and XRD. The minimum proportion of rapidly adductible endocyte (RAE) required for adduction of glipizide in urea was estimated by a modified Zimmerschied calorimetric method. Urea–GLP–RAE inclusion compounds containing varying proportions of guests were prepared and their thermal behaviour studied by DSC. The co-inclusion compounds were found to exhibit good content uniformity. Through the formation of co-inclusion compounds of urea, it was possible to achieve steep improvement in the dissolution efficiency of glipizide, which is a BCS class II drug.

Keywords Adduction · Complexation · Content uniformity · Dissolution rate · Glipizide · Urea inclusion compounds

Introduction

Glipizide (N-[2-[4-[[[(cyclohexylamino)carbonyl]amino] sulfonyl]phenyl]ethyl]-5-methyl pyrazinecarboxamide; GLP) is a second generation sulphonylurea that lowers the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat non-insulin dependent diabetes mellitus (NIDDM) [1, 2]. Glipizide (Fig. 1) is a weak acid with pKa at 5.9 [3]. The drug, being insoluble in water, belongs to BCS class II [4] and its dissolution is considered to be a rate-determining step in its absorption from the gastro-intestinal fluids. Recently, attempts have been made to study detailed solubility/dissolution profile of GLP and to improve its dissolution behaviour using cyclodextrin inclusion compounds or as solid dispersion in water-soluble carriers [3, 5–7]. An attempt has been made in the present study for steep enhancement of dissolution rate of GLP through formation of co-inclusion compounds of GLP in urea using a modified technique [8, 9].

Conventional urea inclusion compounds are characterized by urea molecules forming extensively hydrogen-bonded honey-comb network containing parallel helical tunnels, tunnel centers separated by *ca* 8.2 Å [10]. The walls of the tunnel are covered with the smooth faces of the urea molecules joined together via hydrogen bonds into helical ribbons running in the opposite directions (Fig. 2) [12, 13]. A variety of adductees, which include *n*-alkanes, α-alkenes and their derivatives, can be accommodated in the tunnels [14]. The adductees are arranged in a periodic repeat distance that is approximately same as the length of guest molecule in the type of linear confirmation that it must adopt in order to fit within the confined space available inside the channel [15]. Guest molecules interact only weakly with the tunnel walls and undergo substantial translational and vibrational motion along tunnel axis [16, 17].

Because the cross-section of the channels (defined by the van der Waals surface of the tunnel wall) is *ca* 5.5–5.8 Å, only guest molecules based on a sufficiently long

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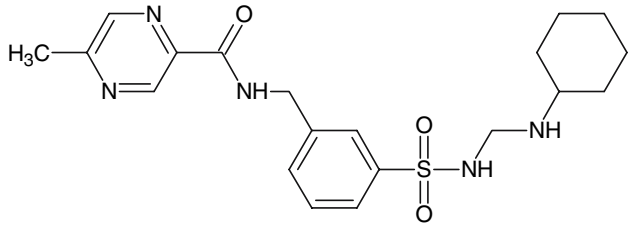

Fig. 1 Chemical Structure of Glipizide

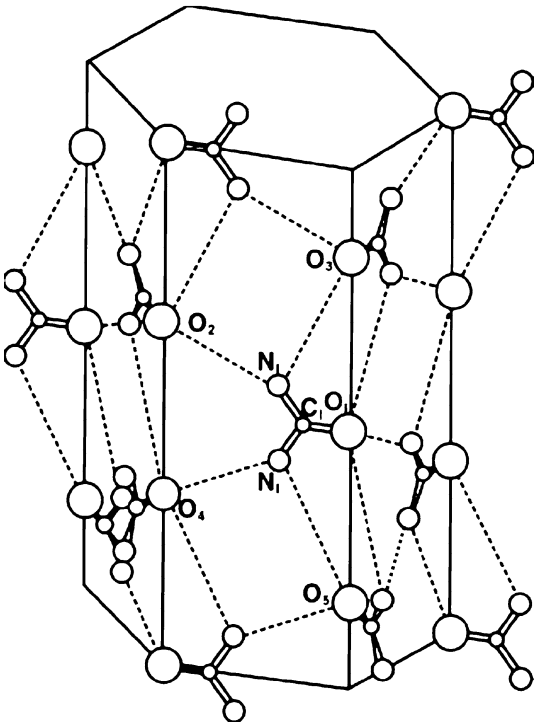

Fig. 2 Arrangement of hydrogen bonding in urea *n*-hydrocarbon complexes. (Reproduced by due permission of International Union of Crystallography [11])

n-alkane chain with a limited degree of substitution can fit within these channels [18]. The minimum chain length required for the inclusion of a given class of guest molecules depends strongly upon the size, polarity and position of the substituents [19]. In general molecules containing benzene or cyclohexane rings do not form inclusion compounds with urea, presumably because these structural components are too wide to fit comfortably inside the tunnel [14]. If however benzene carries a long chain substituent, then an inclusion compound may be formed. The long chain of this compound is readily adducted and apparently the unit cell can easily withstand the distortions caused by an occasional benzene group [20]. Also, 3-methyl heptane, which is normally a non-adductible endocyte (NNAE), forms adduct with urea only when a slenderer hydrocarbon (e.g., n-C_6H_{14})—a Rapidly Adductible Endocyte (RAE) serves as a "pathfinder" [20, 21]. The adductees possessing a sufficiently long *n*-alkane chain and hence easily adductible within urea channels can be considered as Rapidly Adductible Endocytes (RAE) while sufficiently substituted and/or cyclic adductees which are known to be non-adductible in urea may be named normally non-adductible endocytes (NNAE).

Steep enhancement of dissolution profile of amiloride hydrochloride and enalapril maleate—potent NNAE drugs through co-inclusion in urea has been recently reported [22, 23]. In the present study, an attempt has been made for the enhancement of dissolution profile of GLP (another potent NNAE) by including the drug in urea in the presence of a suitable RAE [9]. GLP is significantly substituted (Fig. 1) and is not known to form adduct with urea under any known conditions. However, using the modified technique, it can be readily co-adducted in urea in presence of a RAE.

Materials and methods

Materials

GLP, manufactured by Bal Pharma, Bangalore was supplied as a gift sample by MacLeods Pharmaceutical, Mumbai; the following materials were of analytical grade, urea crystals, extra pure (E. Merck, India), oleic acid (Rankem, India), methanol A.R. grade (Rankem, India). All other reagents were of analytical grade.

Preparation of urea inclusion compounds of GLP with RAE

About 0.5 g of GLP was dissolved in 30 mL methanol containing 5 g urea. Subsequently 0.6 g oleic acid was incorporated as RAE in the above solution leading to immediate precipitation of the crystals of urea co-inclusion compound. The solution was allowed to stand at room temperature for 2–3 h. Crystals were separated from the mother liquor by vacuum filtration, dried and packed in suitable containers [8, 24, 25].

Characterization of urea inclusion compounds

FTIR analysis

The FTIR spectra of the samples was recorded using FTIR spectrophotometer (IR 200 ThermoNicolet, Madison, USA) employing KBr disc technique and all samples were scanned over a range of 400–4000 cm^{-1}.

Differential scanning calorimetry

Thermal analysis of the crystals was performed using a DSC Q10 V 9.0 (275), Waters Ltd., Vienna, Austria. TA system with a differential scanning calorimeter equipped with a computerized data station. All samples (~3 mg) were heated in crimped aluminium pan at a scanning rate of 10 °C/min from 40 to 250 °C in an atmosphere of nitrogen gas by passing at a flow rate of 60 mL/min. An empty aluminium pan was used as the reference pan.

Powder X-ray diffraction

X-ray diffractograms of the crystals were recorded using X-ray Diffractometer (Philips, X'Pert Pro, PW 3050/PW 3071, Lelyweg, The Netherlands). Experimental settings were: Nickel filtered Cu–Kα1 radiations (λ = 1.540598 Å), voltage 40 kV, current 30 mA and scanning rate 2°/min over a 2θ range of 10°–80°.

Determination of minimum ratio of RAE and NNAE for the formation of co-inclusion compounds with urea

The procedure comprised of following two stages.

Stage I

The calorimetric method proposed by Zimmerschied et al. for determination of composition of urea adduct was followed for determination of the stoichiometric ratio between urea, the host and oleic acid, the endocyte [26].

Stage II

Determination of minimum ratio of RAE and drug for formation of co-inclusion compounds with urea The modified Zimmerschied calorimetric method [8, 22, 23] was employed for determination of the minimum amount of RAE required for formation of co-inclusion compounds of GLP and RAE in urea.

Preparation of urea inclusion compounds containing varying proportions of GLP and RAE

A number of urea GLP–RAE co-inclusion compounds containing varying proportions of GLP and RAE were prepared by adding 2 g of endocytes (oleic acid and GLP in varying proportions as per details outlined in Table 1) to 30 mL of methanol containing 10 g urea. The solutions were kept at room temperature for 2–3 h and crystals were isolated from mother liquor by vacuum filtration, dried and packed suitably. All these inclusion compounds were subjected to DSC analysis at temperature range of 40–250 °C.

Table 1 Composition and content uniformity for different GLP–RAE inclusion compounds containing varying proportion of RAE and GLP

Product	RAE:GLP	% drug claimed[a]
GLPIC-1	1:1	97.4 ± 0.5
GLPIC-2	1:0.8	98.6 ± 0.8
GLPIC-3	1:0.6	96.4 + 0.3
GLPIC-4	1:0.4	97.2 + 0.6
GLPIC-5	1:0.2	96.8 + 0.4

[a] Mean + SD for ten randomly drawn samples of inclusion compounds

Assay procedure

Glipizide was estimated by ultraviolet–visible (UV–Vis) spectrophotometric method (Unicam UV–Visible double beam spectrophotometer v1.30). Aqueous solutions of glipizide were prepared in phosphate buffer (pH 7.4) and absorbance was measured on UV–Vis spectrophotometer at 276 nm. The method was found to obey Beer's Law in the concentration range of 5–50 μg/mL (r^2 = 0.999).

Content uniformity analysis

For the purpose of content uniformity determinations, exactly weighed amounts of ten randomly drawn samples of all GLP–RAE–urea co-inclusion compounds containing equivalent of 5 mg of the drug were dissolved in phosphate buffer (pH 7.4) and suitably diluted. The drug contents were determined at 276 nm spectrophotometrically.

Dissolution rate studies

Dissolution study was conducted using USP dissolution apparatus II, in 900 mL phosphate buffer pH 7.4, maintained at 37 ± 0.5 °C at a speed of 100 rpm. The quantity of GLP (5 mg) and of inclusion complexes GLPIC-2 and GLPIC-4 containing amount of drug equivalent to 5 mg was added to the dissolution medium. At predetermined time intervals (2, 5, 10, 20, 30, 45 and 60 min) 5 mL of the samples were withdrawn with volume replacement. The samples were filtered and assayed spectrophotometrically

(276 nm). A cumulative correction was made for the removed samples while determining the total amount of drug dissolved. All experiments were run in triplicate.

Results and discussion

Characterization of urea inclusion compounds

Preparation of co-inclusion compounds of GLP in urea in presence of suitable RAE i.e., oleic acid was attempted. Addition of small amount of oleic acid as RAE to a methanolic solution of urea and GLP led to an immediate precipitation of fine needle shaped white crystals (GLPIC). The formation of inclusion compounds was confirmed by the following instrumental methods.

FTIR spectrophotometry

Figure 3 demonstrates the IR spectra for pure GLP and of GLPIC crystals. IR spectra of GLP shows the bands characteristic of GLP, the important one being bands at 3272, 2943, 1690, 1159 and 1032 cm^{-1} [27]. The IR spectra of GLPIC crystals indicate out-of-phase vibrations at 3413 cm^{-1} and in-phase vibrations at 3245 cm^{-1}, which are characteristic of the hexagonal channel structure of urea [28, 29]. The same vibrations have been reported at 3445 and 3347 cm^{-1} for the tetragonal uncomplexed form of urea [30]. Similarly, the occurrence of four bands between 1675 and 1590 cm^{-1} (due to CO stretching and NH_2 bending vibrations), slight raising of the skeletal out-of-phase bending frequency at 793 cm^{-1} and symmetric C–N frequency increasing from 1000 to 1013.82 cm^{-1} indicate presence of the hexagonal channel structure of urea [28, 29]. These findings suggest the transformation of tetragonal urea to channel-like hexagonal form of urea containing guest moieties.

Differential scanning calorimetry

Thermograms for pure GLP and crystals of inclusion of GLP (GLPIC) are shown in Fig. 4. Pure GLP exhibits single melting endotherm at 210.5 °C [27]. GLPIC thermogram shows that the urea crystals melt in two steps, a characteristic of the complexed form of urea [31]. The first step (114.59 °C) is attributed to the collapse of the hexagonal form of urea inclusion compound to yield the guest moiety and tetragonal solid urea while the second step (135.9 °C) involves melting of tetragonal urea [32]. The disappearance of sharp melting endotherm of GLP at ~210°C clearly indicates the presence of GLP in an amorphous state.

X-ray diffraction

Figure 5 shows the powder X-ray diffraction patterns of tetragonal urea, pure GLP and its urea co-inclusion compound with RAE (GLPIC). The important interplanar spacings indicative of tetragonal form of urea are 4.03, 3.65, 2.84 and 2.54 Å [33]. Pure GLP is crystalline as demonstrated by the sharp and intense diffraction peaks, the important ones at interplanar spacings 5.76, 4.79 and 4.08 Å [34]. However, the diffractogram for GLPIC crystals exhibits the important peaks at interplanar spacings at 4.123, 3.621, 3.889 and 7.217 Å, which are all characteristic of the hexagonal form of urea [35, 36]. Absence of peaks characteristic of tetragonal form of urea further

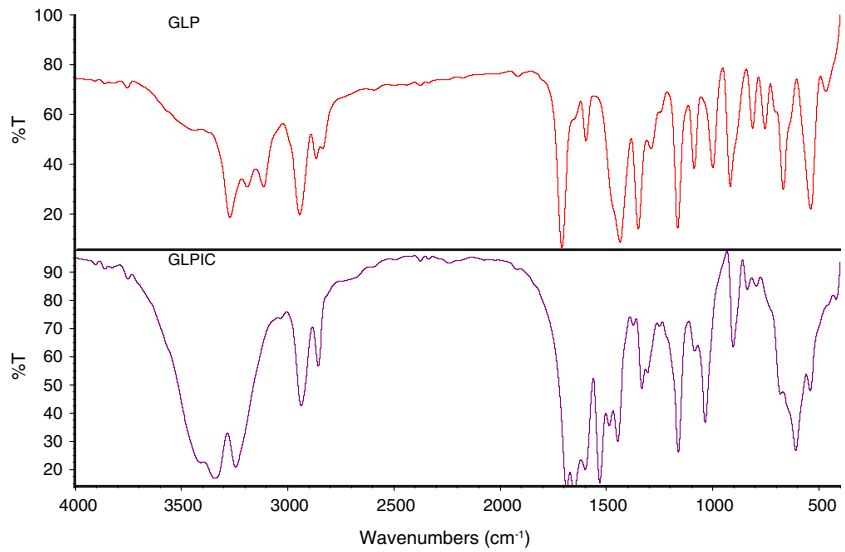

Fig. 3 IR spectra for glipizide (GLP) and GLPIC crystals

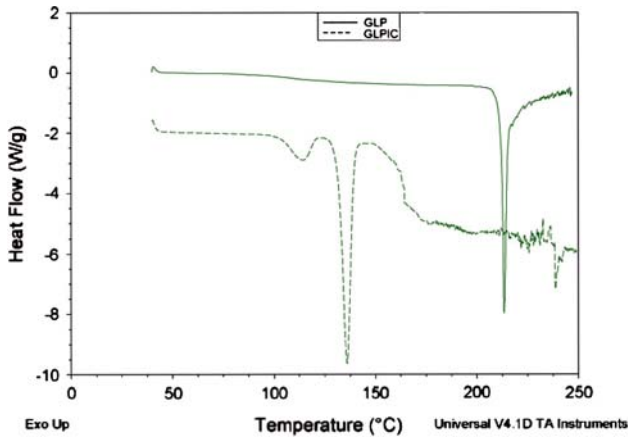

Fig. 4 DCS thermograms of pure glipizide (GLP) and GLPIC

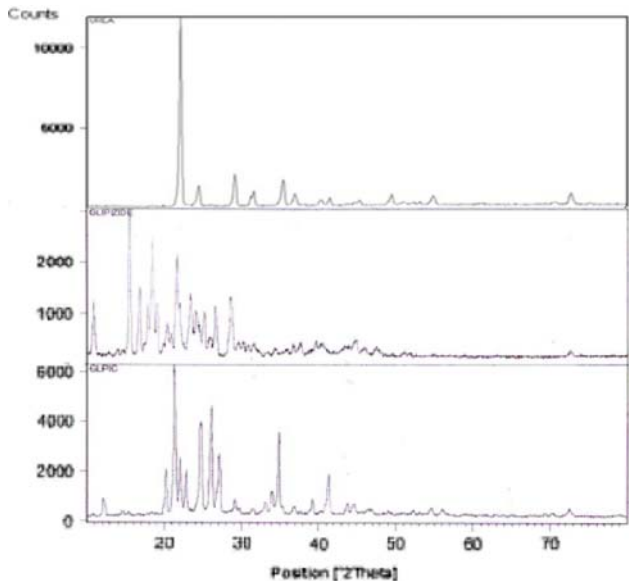

Fig. 5 X-ray diffraction patterns of urea, glipizide (GLP) and GLPIC

indicates the transformation of tetragonal form of urea to hexagonal channels containing endocytes. Complete absence of major peaks of GLP (5.76, 4.79 and 4.08 Å) substantiates the fact that the guest molecules are trapped and isolated from one another in the honey-comb network of urea and do not contribute to the crystal structure except for slight distortions of the hexagonal channels caused by bulky guests [37].

Minimum ratio of RAE and NNAE for inclusion of NNAE in urea

Utilizing the calorimetric method for determination of composition of urea adducts [27], the minimum amount of RAE, which can be adducted in urea, was found to be 2.71 g of oleic acid/10 gm of urea. The minimum ratio of RAE:GLP for adduction of GLP in urea was determined to be 0.954:1 by the modified Zimmerschied method [8, 22, 23].

On the basis of these calculations, urea inclusion compounds containing varying proportions of RAE and drug (Table 1) were prepared and utilized for further studies.

Characterization of inclusion compounds containing varying proportions of RAE and GLP

DSC thermograms of different inclusion compounds containing varying proportions of RAE and GLP are shown in Fig. 6. All these thermograms exhibit a low-temperature endotherm corresponding to collapse of the complexed urea was observed and the absence of a melting endotherm for GLP is also noticeable. Figure 7 shows plot of heat of crystalline transition against proportion of GLP per gram of RAE. The plot clearly indicates that as the proportion of GLP per unit weight of RAE is increased, the stability of co-inclusion compound is reduced ($r^2 = 0.9461$). GLP being an aromatic moiety is presumably too wide to fit inside the hexagonal tunnels formed by the urea host. However, in presence of RAE, GLP is assumed to get co-included with RAE, which, in turn, would lead to distortion of the urea tunnel structure in the vicinity of aromatic ring, the extent of steric strain on the host lattice being proportionate to the amount of NNAE incorporated.

Content uniformity analysis

The contents of GLP were found to vary from 96.1 to 99.2% of the claimed amount of drug (Table 1). Therefore co-inclusion compounds of drug in urea lattice exhibit

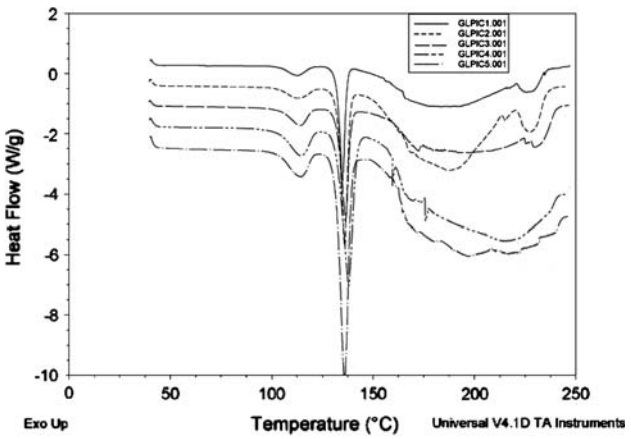

Fig. 6 DSC thermograms of GLP–RAE–Urea co-inclusion compounds containing varying proportions of GLP and RAE

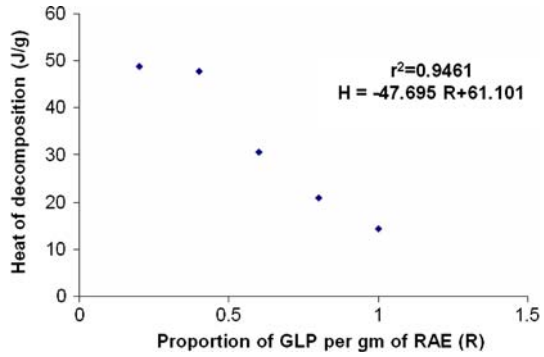

Fig. 7 Plot showing change in heat of decomposition for different GLP–RAE inclusion compounds containing varying proportion of GLP and RAE

good content uniformity and hence can be exploited for the development of a quality formulation.

Dissolution rate studies

Figure 8 exhibits the dissolution profiles plotted from the experimental values of pure GLP and its urea co-inclusion compounds GLPIC-2 released in phosphate buffer pH 7.4. Dissolution of different inclusion compounds containing varying proportions of RAE and GLP i.e., GLPIC-2 and GLPIC-4 were performed and were found to be almost similar. Hence, the profile for one of the samples i.e., GLPIC-2 has been depicted inFig. 7 for the purpose of clarity. The dissolution profiles were evaluated by the dissolution percentage at 5 min. and dissolution efficiency (DE) parameter at 60 min. Dissolution percentage represents percentage drug contents dissolved in dissolution medium. Dissolution efficiency (DE) is a model independent parameter and is employed to compare the dissolution profiles of two different formulations [38]. It is calculated according to the formula

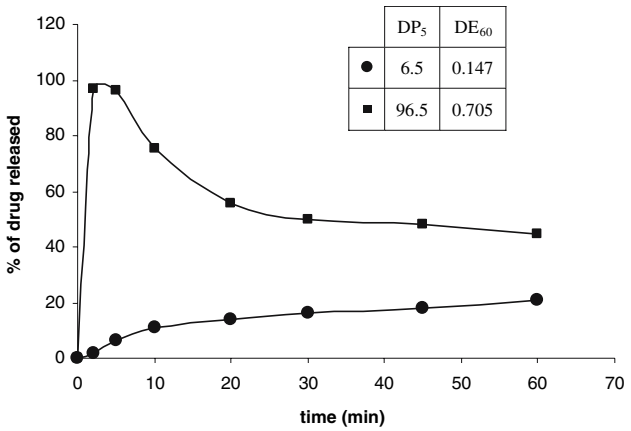

Fig. 8 Dissolution profile of pure GLP (•) and of GLPIC-2 (■)

$$DE_T = \frac{\int_0^T y_t dt}{y_{100} \cdot T},$$

where DE_T is DE at time T, y_t is percent of drug dissolved at any time t, y_{100} denotes 100% dissolution, and the integral represents the area under dissolution curve between time zero and T [38].

Figure 8 reveals that the extent of pure GLP released was found to be quite low exhibiting DE_{60} as low as 0.147. On the other hand, co-inclusion of drug in urea resulted in an immediate and almost complete release of drug as exhibited by release of ~97% of contents within 2 min. However, this immediate release of the drug contents was found to be followed by a subsequent decrease in drug contents in solution and DP_{60} was found to be as low as 44.5. When urea co-inclusion compound system comes in the contact with an aqueous dissolution medium, the urea lattice dissolves almost instantaneously and results in an immediate release of the included drug at the molecular level. Also, the co-inclusion of a NNAE drug along with RAE in urea leads to weakening/distortion of urea host lattice, manifested as an initial increase in the dissolution rate. However, as GLP has limited aqueous solubility under the present dissolution conditions, the initially released drug molecules subsequently tend to crystallize in excess of the solubility. This may be caused by non-sink conditions of the dissolution media. Since GLP is a rapidly permeable drug, therefore, the released drug molecules may rapidly permeate through biological barriers in vivo and a built-up of concentration at the site of dissolution may not actually occur. Thus complete dissolution and subsequent permeation of the drug can be expected in vivo.

Conclusion

Glipizide is a BCS class II drug possessing limited aqueous solubility. In an effort to improve its dissolution profile, co-inclusion compounds of the drug in urea were investigated in the present study. The co-inclusion compounds were found to exhibit improved dissolution profile as exhibited by DE_{60} of 0.75 (compared to DE_{60} of 0.147 for pure GLP). The inclusion compounds were also found to show good content uniformity. Thus, urea co-inclusion compound formation can be exploited as a valuable technique for the development of improved pharmaceutical formulation of GLP.

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References

1. D'Onofrio, F., Pempinello, R., Romis, L.: Clinical and metabolic observations with a new synthetic oral antidiabetic agent, Glipizide. Arzneimittelforschung **2**(11), 1879–1881 (1972).
2. Brogden, R.N., Heel, R.C., Pakes, G.E., Speight, T.M., Avery, G.S.: Glipizide: a review of its pharmacological properties and therapeutic use. Drugs **18**, 329–353 (1979).
3. Jamzad, S., Fassihi, R.: Role of surfactant and pH on dissolution properties of fenofibrate and glipizide—a technical note. AAPS PharmSciTech. **7**, E1–E6 (2006).
4. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER). Chemistry review for metaglip tablets. Available at http://www.fda.gov/cder/foi/nda/2002/21–460_metaglip_Chemr.pdf. Accessed:March 29, 2007.
5. Gidwani, S.K., Singnurkar, P., Tiwari, P.K.: Glipizide-cyclodextrin inclusion compounds and their pharmaceutical compositions. US Patent 6,464,988 B1, 15 Oct 2002.
6. Himasankar, K., Murali, M.B., Krishna, B.P.S.S., Prasad, D.S., Rao, L.N., Raman, K.V.: Studies on solid dispersion systems of glipizide. Indian J. Pharm. Sci. **64**(5), 433–439 (2002).
7. Aly, A.M., Qato, M.K., Ahmad, M.O.: Enhancement of the dissolution rate and bioavalability of glipizide through cyclodextrin inclusion complex. Pharm. Technol. **27**, 54–62 (2003).
8. Madan, A.K.: Microencapsulation of low dose drugs. Ph.D. Thesis, IIT Delhi (1994).
9. Thakral, S., Madan, A.K.: Indian Provisional patent "Urea based inclusion complexes of nicorandil, carvidilol, gliclazide and glipizide and the processes thereof." Indian Patent Application Number 208/DEL/2007 filed on 01/02/2007 (2007).
10. Harris, K.D.M.: Meldola Lecture: understanding properties of urea and thiourea inclusion compounds. Chem. Soc. Rev. **26**, 279–289 (1997).
11. Smith, A.E.: The crystal structure of urea–hydrocarbon complexes. Acta Crystallogr. **5**, 224–235 (1952).
12. Bishop, R., Dance, I.G.: New type of helical inclusion networks. Top.Curr. Chem. **149**, 139–188 (1988).
13. Frank, S.G.: Inclusion compounds. J. Pharm. Sci. **64**, 1585–1604 (1975).
14. Takemoto, K., Sonoda N.: Inclusion compounds of urea, thiourea and selenourea. In: Atwood, J.L., Davis, J.E.D., MacNicol, D.D. (eds.) Inclusion Compounds, vol. 2. pp. 47–67. Academic Press, London (1984).
15. Harris, K.D.M., Thomas, J.M.: Structure aspects of urea inclusion compounds and their investigations by X-ray diffraction: a general discussion. J. Chem. Soc., Faraday Trans. **86**, 2985–2996 (1990).
16. Hollingsworth, M.D., Harris, K.D.M.: Urea inclusion compounds. In: Atwood, J.L., Davis, J.E.D., MacNicol, D.D., Vogtle, F, (eds.) Comprehensive Supramolecular Chemistry. Solid State Supramolecular Chemistry—Crystal Engineering, vol. 6, pp. 177–237. Pergamon Press, Oxford (1996).
17. Smart, S.S., Baghdagi, A.E., Guillaume, F., Harris, K.D.M.: Conformational and vibrational properties of α,ω-dihalogenoalkane/urea inclusion compounds: a Raman scattering investigation. J. Chem. Soc., Faraday Trans. **90**, 1313–1322 (1994).
18. Schiessler, R.W., Flitter, D.: Urea and thiourea adduction of C_5-C_{42}-Hydrocarbons. J. Am. Chem. Soc. **74**, 1720–1723 (1954).
19. Harris, K.D.M.: Urea inclusion compounds. In Atwood, J.L., Steed, J.W. (eds.) Encyclopedia of Supramolecular Chemistry, vol. 2, pp. 1538–1549. Marcel Dekker, New York (2004).
20. Findlay, R.A. Adductive crystallization. In: Schoen, H.M., Mcketta, J.J. (eds.) New Chemical Engineering Separation Techniques, pp. 257–318. Interscience Publishers, New York (1962).
21. Schlenk, W.: Urea addition of aliphatic compounds. Justus Liebigs Ann. Chem. **565**, 204–240 (1949).
22. Thakral, S., Madan, A.K.: Adduction of amiloride hydrochloride in urea through a modified technique for the dissolution enhancement. J. Pharm. Sci. DOI. 10.1002/jps (2007).
23. Thakral, S., Madan, A.K.: Urea inclusion compounds of enalapril maleate for the improvement of pharmaceutical characteristics. J. Pharm. Phamcol. (2007, in press).
24. Madan, A.K., Grover, P.D.: A process for preparation of urea based inclusion compounds of vitamin A esters. Indian Patent 180627, 20 January 1993.
25. Bajaj, V., Madan, A.K.: A process for preparation of urea complexes of vitamin E and its esters. Indian Patent 182620, 24 October 1994.
26. Zimmerschied, W.J., Dinnerstein, R.A., Weitkamp, A.W., Marschner, R.F.: Crystalline adducts of urea with linear aliphatic compounds. Ind. Eng. Chem. **42**, 1300–1306 (1950).
27. Moffat, A.C., Osselton, M.D., Widdop, B., Galichet L.Y.: Clarke's Analysis of Drugs and Poisons, 3rd edn. The Pharmaceutical Press, Glipizide, London 1081–1082 (2003).
28. Fischer, P.H.H., McDowell, C.A.: The infrared absorption spectra of urea-hydrocarbon adduct. Can. J. Chem. **38**, 187–193 (1960).
29. Durie, R.A., Harrisson, R.J.: Effect of urea-adduct formation and physical state on the infrared spectra of *n*-paraffin hydrocarbons. Spectrochem. Acta **18**, 1505–1514 (1962).
30. Keller, W.E.: Evidence of planer structure of urea. J. Chem. Phys. **16**, 1003–1004 (1948).
31. McAdie, M.G.: Thermal decomposition of molecular complexes. Can. J. Chem. **41**, 2144–2153 (1963).
32. White, M.A.: Origins of thermodynamic stability of urea: alkane inclusion compounds. Can. J. Chem. **76**, 1695–1698 (1988).
33. Radell, J., Connolly, J.W.: Urea complexes of partially fluorinated esters. J. Org. Chem. **25**, 1202–1206 (1960).
34. Burley, J.C.: Structure and intermolecular interactions of glipizide from laboratory X-ray powder diffraction. Acta Cryst. B**61**, 710–716 (2005).
35. Brodman, B.W., Radell, J.: X-ray powder diffraction patterns of some *n*-alkanone urea inclusion compounds. Separation Sci. **2**, 139–142 (1967).
36. Radell, J., Brodman, B.W.: Urea inclusion compounds of alkenoic acids and alkyl alkenoates. Can. J. Chem. **43**, 304–305 (1965).
37. Radell, J., Connolly J.W.: Determination of relative stability of urea complexes from X-ray powder diffraction data. In: Muller, W.M. (ed.) Advances in X-ray Analysis, vol. 4, pp. 140–150. Plenum Press, New York (1961).
38. Khan, K.A.: The concept of dissolution efficiency. J. Pharm. Pharmacol. **27**, 48–49 (1975).