Drug Development and Industrial Pharmacy, 2010; 36(4): 428–430

informa
healthcare

ORIGINAL ARTICLE

Influence of fulvic acid and hydroxy propyl-β-cyclodextrin on aspirin degradation

Mohammad Khalid Anwer[1,2], Suraj Prakash Agarwal[1], Asgar Ali[1] and Yasmin Sultana[1]

[1]*Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India and* [2]*Department of Pharmaceutics, College of Pharmacy, King Saud University, Al-kharj, Riyadh, Kingdom of Saudi Arabia*

Abstract

Objective: The degradation of aspirin (ASA) was investigated to reveal information about the influence of complexation with fulvic acid (FA), as a new complexing agent and compared with hydroxy propyl-β-cyclodextrin complex. *Materials and methods*: ASA was complexed with FA in the molar ratio 1:0.5, 1:1, and 1:2 by different methods through lyophilization, solvent evaporation, and spray drying. Spray-dried (1:1) ASA–hydroxy propyl-β-cyclodextrin complex was prepared and compared with optimized complex of FA. All the complexes and ASA alone were packaged in well-labeled sealed polythene-lined aluminum pouches and stored in stability chamber at 40 ± 2°C and 75 ± 5% relative humidity for 120 days. Samples were analyzed for salicylic acid content at 0, 30, 60, 90, and 120 days. *Results*: Overall 4.31% salicylic acid was formed in 1:1 ASA–FA spray-dried complex, which was optimized stable complex among other complexes of FA prepared by different methods in different molar ratios. However, 2.35% salicylic acid was measured with 1:1 spray-dried ASA–hydroxy propyl-β-cyclodextrin complex. Stability of ASA increased more when complexed with hydroxy propyl-β-cyclodextrin as compared to FA. *Conclusions*: A novel complexing agent in the form of FA was investigated to increase the stability of ASA. A marked improvement in stability of ASA was observed when complexed with hydroxy propyl-β-cyclodextrin (1:1) by spray drying as compared to 1:1 spray-dried ASA–FA complex.

Key words: *Aspirin; complexation; fulvic acid; hydroxy propyl-β-cyclodextrin; shilajit; stability*

Introduction

Aspirin (ASA) is a very old drug that still has excellent medicinal value, and its health protection function, such as analgesic, anti-inflammatory, antithrombotic, and antipyretic, has received more and more attention[1,2]. The ASA molecule has a carboxyl group and an ester group. The ester group can be easily hydrolyzed, which reduces the medicinal usefulness and has gastrointestinal side effects on humans[3]. A need exists to learn how to inhibit the hydrolysis of ASA. A number of literatures are available describing decomposition of ASA[4–6]. ASA is degraded into salicylic acid and acetic acid by influence of moisture[3]. The decomposition of ASA complexes with cyclodextrin has been studied and significant degradation has been found during 6 months of storage as compared to ASA[4]. In another study, influence of cellulose powder with lower crystallinity index exhibited lower degradation rate of ASA than the sample with the higher crystallinity index[5]. The degradation of ASA increased by increasing the specific surface area of excipient (dicalcium phosphate dehydrate powders)[6].

Shilajit is a pale-brown to blackish-brown exudate obtained from layer of rocks in many mountain ranges (especially the Himalayan ranges of the Indian subcontinent) of the world. Its curative potentials were found documented in ancient books and were used to treat many ailments since antiquity days[7,8]. Major portion of Shilajit was found to consist of humic substances [humic and fulvic acids (FAs)]. FAs are the major constituent of shilajit, having relatively open, flexible structure punctured by voids (micropores) of different diameters[9,10]. These compounds were, presumably, loosely held in the core

Address for correspondence: Dr. Mohammad Khalid Anwer, Ph.D., Department of Pharmaceutics, College of Pharmacy, King Saud University, Al-kharj, Riyadh, Kingdom of Saudi Arabia. Tel: +966 535887375. E-mail: mkanwer2002@yahoo.co.in; manwer@ksu.edu.sa

(Received 14 Apr 2009; accepted 31 Jul 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.3109/03639040903225091

structure of Shilajit[11]. The plant's secondary metabolites that are trapped in the internal voids of FAs are spared from and become resistant to common chemical and biological decomposition[12]. Taking a clue on this point we started to investigate the potential of FA as a new complexing agent to increase the stability of ASA. These FAs provide the protective layer around ASA in which water is excluded as much as possible and reduce the decomposition.

Materials and methods

Acetylsalicylic acid was procured from Sigma Aldrich (New Delhi, India). Rock shilajit was kindly provided as a gift sample from Dabur Research Foundation (Ghaziabad, India). Hydroxypropyl-β-cyclodextrin was purchased from Sigma Aldrich. A slightly modified reported method[13] was used to extract FA. Finely powdered shilajit was extracted with hot organic solvents of increasing polarity (chloroform, ethyl acetate, and methanol) to remove the bioactive components. The residue was dissolved in 0.1 N NaOH with intermittent shaking in presence of nitrogen. The suspension was filtered and the filtrate was acidified to a pH of less than 3 to precipitate the humic acid. The filtrate thus obtained was shaken with macroporous ion-exchange resin to adsorb the FA, which was then eluted using 0.1 N aqueous sodium hydroxide solution. The FA obtained in 0.1 N NaOH was passed through hydrogen-saturated cation exchange resin to exchange the sodium ions with hydrogen ions. The final FA solution was concentrated and freeze dried to obtain amorphous FA[11,14]. Complexes of ASA with FA and hydroxypropyl-β-cyclodextrin were prepared using different techniques such as solvent evaporation, freeze drying, and spray drying in the molar ratios 1:0.5, 1:1, and 1:2 (ASA:FA/HP-β-CD).

ASA and FA were dissolved in double-distilled water and the solution was sonicated for 2 hours to get a clear solution. The solution was frozen in ultrafreezer by keeping for 24 hours and freeze dried over 12 hours in Lyph-lock apparatus (Drywinner, DW-8-85 Heto Holten, Allerød, Denmark). The resulting amorphous powder is powdered in glass mortar and pestle and passed through 100-mesh sieve to obtain a uniform size fine powder. Complexes of ASA–FA were also prepared by dissolving the required quantity of ASA in 50 mL of chloroform and FA in 100 mL of water. The FA solution was then added to ASA solution with stirring and the solution was sonicated in the ultrasonicator bath for 2 hours. The solution thus obtained was dried in a rotary evaporator (Scientific System, Bangalore, India) under reduced pressure on boiling water bath. The complex was then dried in oven, collected, and passed through sieve no. 60. It was stored in vacuum desiccator till use.

Spray-dried complex of ASA and FA was prepared by dissolving the required quantity (in the molar ratios 1:0.5, 1:1, and 1:2 of ASA:FA) in 100 mL of double-distilled water. Solution was sonicated in the ultrasonicator bath for 2 hours. The solution thus obtained was then spray dried (S. M. Scientech, Calcutta, India) using the following optimized condition flow rate, 1.6 mL/min; outlet temperature, 135°C; atomizing air pressure, 3 kg/cm^2. Same method was followed to prepare ASA and HP-β-CD in the molar ratio of 1:1.

All the complexes and ASA alone were packaged in well-labeled sealed polythene-lined aluminum pouches and stored in stability chamber at 40 ± 2°C and 75 ± 5% relative humidity for 120 days. Accurately weighed powder equivalent to 18 mg of the ASA present in complex was dissolved in 100 mL of ethyl alcohol (180 µg/mL). The solution is vigorously shaken putting the conical flask in sonicator bath for 15 minutes. Samples were analyzed by high-performance liquid chromatography[15] for salicylic acid content at 0, 30, 60, 90, and 120 days. A mixture of water:methanol:acetic acid (65:30:5, v/v) used as the mobile phase and detection were done at 280 nm for high-performance liquid chromatography analysis.

Results and discussion

The overall profile of ASA degradation in the two complexes like FA and HP-β-CD was studied at 40 ± 2°C and 75 ± 5% relative humidity for 120 days indicated by the rate of appearance of salicylic acid. Degradation of ASA was more in lyophilized complex of FA as compared to solvent-evaporated and spray-dried complexes. However, very less content of salicylic acid (4.31%) was determined in 1:1 spray-dried complex among other FA complexes and optimized. This same optimized technique was followed for the preparation of complex of ASA with HP-β-CD and compared with optimized complex of FA. However, maximum stability was observed with 1:1 spray-dried optimized complex of HP-β-CD (2.35% salicylic acid content after 120 days). It was concluded that a significant improvement in ASA stability was observed with both HP-β-CD and FA when compared to ASA alone (Figure 1).

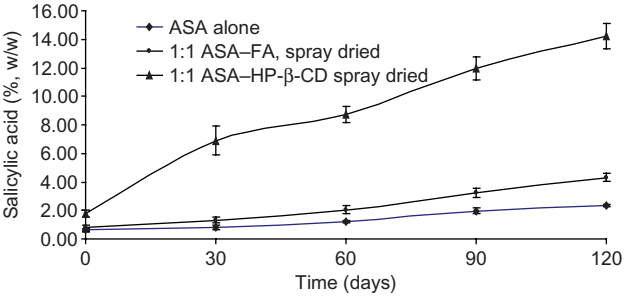

Figure 1. Degradation pattern of ASA in HP-β-CD and FA complexes.

Conclusion

A novel complexing agent in the form of FA was extracted from shilajit to increase the stability of ASA. It was observed that the degradation of ASA was more in lyophilized complex of FA. This was ascribed to partial entrapment of ASA inside the void of FA[16]. A significant amount of salicylic acid was formed when ASA alone was stored at 40 ± 2°C and 75 ± 5% relative humidity for 120 days, whereas a marked improvement in stability of ASA was observed when complexed with HP-β-CD (1:1) by spray drying as compared to 1:1 spray-dried ASA–FA complex.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Choi HS. (1992). Molecular recognition: α-Cyclodextrin and ASA inclusion complexation. Bull Korean Chem Soc, 13:474–9.
2. Kapetanovic IM, Bauer KS, Tessier DM, Lindeblad MO, Zakharov AD, Lubet R, et al. (2009). Comparison of pharmacokinetic and pharmacodynamic profiles of aspirin following oral gavage and diet dosing in rats. Chem Biol Interact, 179:233–9.
3. Connors KA, Amido GL, Stella VJ. (1986). Chemical stability of pharmaceuticals. 2nd ed. New York: Wiley, 18–26.
4. Williams RO, III, Liu J. (1999). Influence of formulation technique for hydroxypropyl-β-cyclodextrin on the stability of aspirin in HFA 134a. Eur J Pharm Biopharm, 47:145–52.
5. Mihranyan A, Strømme M, Ek R. (2005). Influence of cellulose powder structure on moisture induced degradation of acetylsalicylic acid. Eur J Pharm Sci, 27:220–5.
6. Landin M, Perezmarcos B, Casalderry M, Martinez-Pacheco R, Gomez-Amoza JL, Souto C, et al. (1994). Chemical stability of acetylsalicylic acid in tablets prepared with different commercial brands of dicalcium phosphate dehydrate. Int J Pharm, 107:247–9.
7. Chopra RA, Chopra IC, Handa KL. (1958). Indigenous drugs of India. Calcutta: U.N. Dhar & Sons, 457–61.
8. Ghosal S. (1992). Shilalit: Its origin and significance. Indian J Indign Med, 9:1–4.
9. Agarwal SP, Aqil M, Anwer MK. (2007). Enhancement of the dissolution and diuretic effect of furosemide through a novel complexation with humic acid extracted from shilajit. Asian J Chem, 19:4711–8.
10. Agarwal SP, Khanna R, Karmarkar R, Anwer MK, Khar RK. (2007). Shilajit: A review. Phytother Res, 21:401–5.
11. Agarwal SP, Aqil M, Anwer MK. (2008). Complexation of furosemide with fulvic acid extracted from shilajit: A novel approach. Drug Dev Ind Pharm, 34:506–11.
12. Agarwal SP, Khanna R, Karmarkar R, Anwer MK, Khar RK. (2007). Physico-chemical, spectral and thermal characterization of shilajit, a humic substance with medicinal properties. Asian J Chem, 20:209–17.
13. Ghosal S. (1989). The facets and facts of shilajit. In: Vohara SB, Dandiya PC, eds. Research and development of indigeneous drugs. New Delhi: Institute of History of Medicine and Medical Research, 72–80.
14. Khanna R, Witt M, Anwer MK, Agarwal SP, Koch BP. (2008). Spectroscopic characterization of fulvic acids extracted from the rock exudate shilajit. Org Geochem, 39:1719–24.
15. Sethi PD. (1997). Quantitative analysis of drugs in pharmaceutical formulations. New Delhi: CBS Publishers and Distributors, 423.
16. Anwer MK. (2005). Novel formulation of furosemide using humic and fulvic acid. M.Pharm thesis, Jamia Hamdard, New Delhi.