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Cyclodextrin based ternary system of modafinil: Effect of trimethyl chitosan and polyvinylpyrrolidone as complexing agents

Parth Patel, Y.K. Agrawal, Jayrajsinh Sarvaiya*

Institute of Research & Development, Gujarat Forensic Sciences University, DFS Headquarter Campus, Gandhinagar, India

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ABSTRACT

Modafinil is an approved drug for the treatment of narcolepsy and have a strong market presence in many countries. The drug is widely consumed for off-label uses and currently listed as a restricted drug. Modafinil has very low water solubility. To enhance the aqueous solubility of modafinil by the formation of a ternary complex with Hydroxypropyl-β-cyclodextrin and two hydrophilic polymers was the main objective of the present study. Pyrrolidone (PVP K30) and a water soluble chitosan derivative, trimethyl chitosan (TMC) were studied by solution state and solid state characterization methods for their discriminatory efficiency in solubility enhancement of modafinil. Phase solubility study depicted the highest complexation efficiency (2.22) of cyclodextrin derivative in the presence of TMC compared to the same in the presence of PVP K30 (0.08) and in the absence of any polymer (0.92). FT-IR analysis of binary and ternary complex expressed comparable contribution of both polymers in formation of inclusion complex. The thermal behaviour of binary and ternary complex, involving individual polymers disclosed the influence of TMC on polymorphism of the drug. DSC study revealed efficiency of TMC to prevent conversion of metastable polymorphic form to stable polymorphic form. Ternary complex, involving TMC enhanced water solubility of the drug 1.5 times more compared to the binary complex of the drug whereas PVP K30 reduced the Solubility.

1. Introduction

Modafinil, 2-benzhydrylsulfinylethanamide (Fig. 1) is an approved drug for the treatment of narcolepsy in many countries. The drug has posted global market share worth of $700 million and $1.2 billion in the year 2008 and 2012, respectively, according to IMS data. Apart from approved uses like shift work sleep disorder and hyper sleepiness associated with obstructive sleep apnea, modafinil is used off label for cognition enhancement in patients with attention deficit hyper activity disorder and in healthy individuals [1]. Actually off label use of modafinil is far more than the prescribed use of modafinil [2]. Currently, World Anti Doping Agency (WADA) has listed this drug in prohibited substance for the consumption by the athletes. These facts necessitates a safe dosage form and enhanced safety profile of the drug. One of the main concerns of modafinil is its poor aqueous solubility [3] which can be improved by the use of suitable excipients to make low dose strength products in order to enhance the safety profile of the drug.

The complexation of modafinil with cyclodextrin [4] and PEG 6000 [5] has been reported to improve water solubility by formation of binary complex formation. Prior to these efforts, Jacob and Patel claimed in their patent that the enhanced water solubility and bioavailability of modafinil by cyclodextrin based binary complex formation is possible [6]. Though their claims are based on the use of very high quantity of the cyclodextrin compared to pure drug apart from the claim of 1:1 inclusion complex formation. Loftsson et al. [7] have reported limitations of the use of cyclodextrin a very high concentration in pharmaceutical dosage forms specifically related to cost, toxicology and processing points of view. Moreover, seven polymorphic forms have been identified so far for this drug which also offers a challenge in processing of this drug for the purpose of solubility enhancement by any of the advanced techniques including nanonization.

The use of auxiliary agents along with cyclodextrin and its derivative are reported to enhance water solubility of poorly soluble drug up to a certain extent in most of the cases. A large number of hydrophilic polymers have been tested at a very low concentration (0.1 to 1.5% w/w) (Table 1) as an auxiliary agent along with cyclodextrin based inclusion complex of the drug. The influence of addition of polymers does not necessarily enhances the solubility of the drug in comparison of the binary complex every time, but it

* Corresponding author. Tel.: +91 9638344845.
E-mail address: jayrajsinh.sarvaiya@gmail.com (J. Sarvaiya).

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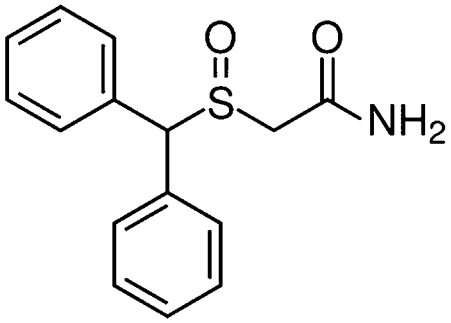

Fig. 1. *Structure of Modafinil.* Sample 1: Ternary complex (TMC) in buffer.

depends on the nature of the drug and polymers, reactivity between polymeric molecule and cyclodextrin. Hydrophilic polymers makes co-complex among the cyclodextrin based inclusion complex of the drug and polymeric chain [32]. The aim of the present work was focused to find the influence of two selected hydrophilic polymeric substances on solubility enhancement of modafinil by formation of ternary complex. PVP K30, a widely utilized hydrophilic polymer and trimethyl chitosan, a water soluble derivative of chitosan were selected to study HP-beta-Cyclodextrin based ternary complex with modafinil. Chitosan has been extensively reported for its ability to enhance permeability of the drugs [33] and for its suitability as a carrier system for drug targeting [34]. Trimethyl chitosan (Trimethyl Chitosan) is a well studied derivative of chitosan specially for its efficiency to enhance drug permeation and bioavailability through the intestinal mucosa [35], bioadhesiveness and biocompatibility [36], but the macromolecule has not been used previously for its application information of a ternary complex with cyclodextrin or cyclodextrin derivative and poorly water soluble drug to our knowledge. Solution state characterization of a ternary complex of both the polymers was performed, followed by solid state characterization of binary and ternary complex to identify the influence of both PVP K30 and TMC in solubility enhancement of modafinil.

2. Materials and methods

2.1. Materials

Modafinil was procured from Alembic Pharmaceutical (Vadodara, India). HP-beta-Cyclodextrin, PVP K 30 was purchased from Otto chemicals (India). Chitosan extrapure (DD 95%), N-methyl pyrrolidone, methyl iodide, sodium iodide, sodium hydroxide and methanol were purchased from Sisco research laboratories pvt. ltd (India). Phosphate buffer pH 6.8 was prepared according to the procedure mentioned in USP 29. Monobasic potassium phosphate was purchased from Finar chemicals (India). All other chemicals and solvents used in this work were of analytical reagent grade.

2.2. Preparation of trimethyl chitosan

Trimethyl chitosan was synthesized from extra pure chitosan with high degree of deacetylation (95%) by the method reported by Snyman et al. [37] with slight modification. Briefly, 1 g chitosan was mixed with 2.4 g sodium iodide in 5.5 ml 15% w/v sodium hydroxide solution. 5.5 ml methyl iodide and previously prepared sodium hydroxide containing solution was added to 40 ml *N*-methyl pyrrolidone (NMP) followed by refluxation at 60 C for at least 1 h. Isopropyl alcohol (IPA) was added in refluxed mixture to get the precipitates which were collected by centrifugation (Beckman, USA). The chitosan derivative containing iodine was collected as precipitates and washed with petroleum ether to remove IPA and then dissolved in 40 ml NMP at 60 C after removing ether. 2.4 g NaI, 5.5 ml of 15% NaOH solution and 3.5 ml methyl iodide were added with rapid stirring while heating in a water bath at 60 C for 30 min.

Table 1
Reported ternary complex of various drugs involving hydrophilic polymers.

Sr.no	Drug	Studied cyclodextrin derivative	Polymer used in ternary complex	Reference
1	Famotidine	β-Cyclodextrin	Hydroxyl propyl methyl cellulose (HPMC) (5 cps)	[8]
2	Fenofibrate	β-Cyclodextrin	Polyvinyl pyrollidone	[9]
3	Glimepiride	HPCD sulfobutylether-β-cyclodextrin (SBE-β-CyD)	PEG 4000	[10]
4	Itraconazole	HPCD hydroxybutenyl-β-cyclodextrin	Soluplus®	[11]
5	Naproxane	β, methyl β, hydroxyl propyl-β-cyclodextrins	CMC, HPMC,PVPK 60, PEG 6000	[12]
6	Daidzein	β-Cyclodextrin, methyl-β-cyclodextrin and HPCD	CMC,HPMC, PEG, PVP	[13]
7	Vinpocetine	SBE-β-CyD	PVP, Hydroxy methyl cellulose	[14]
8	Naproxen	HPCD	PVP	[15]
9	Vinpocetine	β-Cyclodextrin, HPCD	PVP, HPMC	[16]
10	Naproxane	β-Cyclodextrin	PEG (Mw 35000)	[17]
11	Triclosan	β-Cyclodextrin	Water-soluble epichlorohydrin polymer	[18]
12	Econazole nitrate	Sulfobutyl-βCD (SBEβCD) HPCD	l-amino acids, citric acid, hydrophilic polymers	[19]
13	Lansoprazole	HPCD	PVP K30 and PEG 6000	[20]
14	Dihydro artemisinin	HPCD	Lecithin	[21]
15	Diosmin	β-Cyclodextrin	HPMC, PEG 6000	[22]
16	Zaleplone	β-Cyclodextrin and randomly methylated-β-cyclodextrin (RMβCD)	Hypromellose, PVP, HPMC	[23]
17	Dapsone	HPCD and β-cyclodextrin	PVP K30, HPMC	[24]
18	Cefixime	β-Cyclodextrin and HPCD	L-Arginine	[25]
19	Carbamazepine	HPCD	Soluplus® and two types of hydroxypropyl methylcellulose-Metolose® 90SH-100 and Metolose® 65SH-1500	[26]
20	Benznidazole	RMβCD	HPMC	[27]
21	Glyburide	HPCD	Sodium lauryl sulphate, Poloxamer-188, Polyvinylpyrrolidone K-30, lactose and l-arginine	[28]
22	Ezetimibe	HPCD	D-α-Tocopheryl polyethylene glycol 1000 succinate and L-ascorbic acid-2-glucoside	[29]
23	Cefuroxime axetil	HPCD	PVP K30, HPMC, poloxamer 188, PEG 4000 along with Aerosil®200	[30]
24	Carvedilol	β-cyclodextrin, HPCD	Tartaric acid, PVPK 30 and Poloxamer-407	[31]