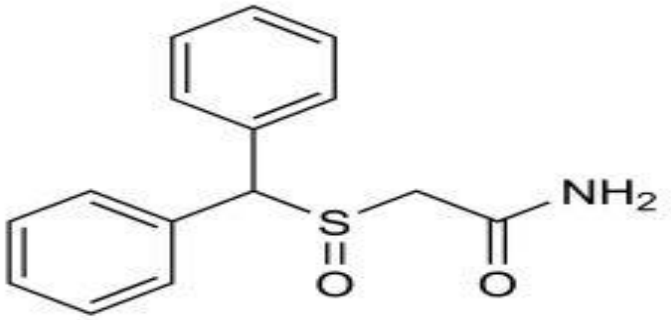
Chapter 3
Drug and Excipients Profile

Management of Dyslexia and ADHD

3.1 Drug Profile

3.1.1 Physico-Chemical Property of The Drug: Modafinil (1, 2)

Table 3.1 Physico-Chemical Property of Modafinil

Name	Modafinil
IUPAC Name	2-benzhydrylsulfinylacetamide
Chemical Formula	$C_{15}H_{15}NO_2S$
Molecular weight	273.3501 gm/mol
Chemical Class	Diphenyl methanes
Category	Central nervous system stimulant (vigilance promoting), Neuroprotective Agent.
Indication	For the treatment of Narcolepsy, Shift-work sheep disorder, Obstructive sleep apnea, ADHD etc.
Structure	
State	White to off-white crystalline powder
Melting Point	164-166 °C
Solubility	Insoluble in water but slightly soluble in ethanol, sparingly soluble in methanol, acetonitrile and acetone.
Log P value	1.75
Elimination Half life	8-18 hrs
Metabolism	Hepatic, including CYP3A4 and other pathways
pKa	8.1 (Strongest acidic)
Brand names	Provigil, Modalert, Modvigil, Sparlon,etc.
Administration route	Oral
Dose	100, 200 mg once a day on the basis of severity of disorder

3.1.2 Pharmacology

3.1.2.1 Indication

Modafinil is a stimulant drug marketed as a 'wakefulness promoting agent' and is one of the stimulants used in the treatment of attention-deficit/hyper activity disorder (ADHD) and narcolepsy.

3.1.2.2 Mechanism of Action

Modafinil may enhance cognition and is used off-label for the treatment of cognitive dysfunction in some psychiatric disorders (ie, schizophrenia, ADHD).(3) The mechanisms of action of modafinil are not well understood but are believed to differ from those of stimulant medications (methylphenidate and amphetamine), which increase dopamine in brain by targeting the dopamine transporters.(3) The pattern of neuronal activation in the brain differs between modafinil and CNS stimulants such as methylphenidate and amphetamine. It is theorized that it's effects in the brain include γ-aminobutyric acid, epinephrine, hypocretin, glutamate and histamine.(3)

Modafinil has weak to negligible interactions with receptors for dopamine, norepinephrine, serotonin, GABA, adenosine, histamine-3, melatonin, and benzodiazepines. In vitro studies have shown it to inhibit the reuptake of dopamine by binding to the dopamine reuptake pump, and lead to an increase in extracellular dopamine. Modafinil is thought to have less potential for abuse than other stimulants due to the absence of any significant euphoric or pleasurable effects. It is possible that modafinil acts by a synergistic combination of mechanisms including direct inhibition of dopamine reuptake, indirect inhibition of noradrenalin reuptake in the hypothalamus and orexin activation. Modafinil has partial alpha1B-adrenergic agonist effects by directly stimulating the receptors. A drug known for increasing attention and arousal would increase memory. It may be that at low doses, modafinil selectively enhances associative ability while at high doses, it may benefit tasks that require increased attention and arousal or working memory.

3.1.2.3 Pharmacokinetic Profile

Table 3.2 Pharmacokinetic Profile of Modafinil (2)

Parameters	Inference
Bioavailability	The bioavailability of Provigil tablets is approximately equal to that of an aqueous suspension. The absolute oral bioavailability was not determined due to the aqueous insolubility (<1 mg/mL) of modafinil, which precluded intravenous administration.
Plasma Protein Binding	Approximately 60%, mainly to albumin, modafinil exhibits no displacement of protein binding of warfarin, diazepam or propranolol.
Volume of Distribution	0.9 L/kg
Metabolite	In preclinical models, modafinil acid, modafinil sulfone, 2-((diphenylmethyl)sulfonyl) acetic acid and 4-hydroxy modafinil, were inactive or did not appear to mediate the arousal effects of modafinil
Route of Elimination	The major route of elimination is metabolism (~90%), primarily by the liver, with subsequent renal elimination of the metabolites.
Elimination Rate	Effectively, elimination half-life is about 15 hours after multiple dosing; the elimination half-life of the levo-isomer is about three times that of the dextro-isomer.

3.1.2.4 Pharmacodynamic Profile

Modafinil is a stimulant drug marketed as a 'wakefulness promoting agent' and is one of the stimulants used in the treatment of narcolepsy as approved drug while use for ADHD as off label drug.

3.1.2.5 Adverse Drug Reaction

Most common side effects are headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia. High dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. Rare cases of serious or life-threatening rash, including Stevens - Johnson syndrome.

3.1.2.6 Drug Interaction

Modafinil studied in human drug drug interaction is discussed in Table 3.3.

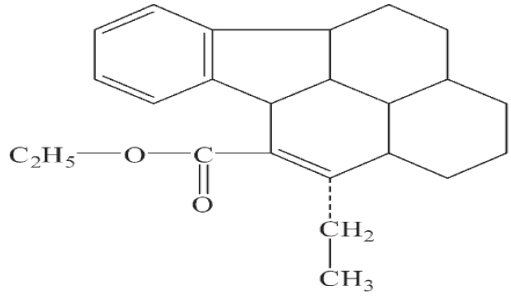
Table 3.3 Drug-Drug Interaction for Modafinil (4)

Drug	Use	Interaction
Carisoprodol	Centrally acting muscle relaxant	Modafinil may decrease the metabolism of CYP2C19 substrates such as carisoprodol.
Clozapine	Antipsychotic	Increases the effect and toxicity of Clozapine
Ethinyl Estradiol	Oral contraceptive, Hormone Replacement Therapy	Modafinil may decrease the contraceptive effect of Ethinyl estradiol. Hormonal contraception should not be solely relied on during concomitant therapy with Modafinil.
Mestranol	Oral contraceptive	Modafinil decreases effect of contraceptive.
Voriconazole	Broad Spectrum Anti-Fungal	It is a strong CYP3A4 inhibitor, may increase serum concentration of modafinil by decreasing its metabolism. Monitor for changes in therapeutic and adverse effects of modafinil if voriconazole is initiated, discontinued or dose changed.
Triazolam	To treat Insomnia	Modafinil decreases the effect of Triazolam

3.1.3 Physico-Chemical Property of The Drug: Vinpocetine

Table 3.4 Physico-Chemical Property of Vinpocetine (5-9)

Name	Vinpocetine
IUPAC Name	(3α,16α)-Eburnamenine-14-carboxylic acid ethyl ester
Chemical Formula	$C_{22}H_{26}N_2O_2$
Molecular weight	350.454 gm/mol
Category	Nootropics (substance that enhances cognition and memory and facilitates learning) and neuroprotective
Classification	Nootropic, Neuroprotective agent, CNS agent, Protective agents, Cardiovascular agent, Phosphodiesterase Inhibitor, Vasodilator agent.

Structure	
State	White crystalline powder
Melting Point	147- 153 ^{o}C
Solubility	Practically insoluble, Soluble in chloroform, slightly soluble in anhydrous ethanol
Metabolism	Hepatic
Bioavailability	7 %
Log P value	4.35
Biological Half life	2.54 hrs ± 0.48 hrs
pKa	6.94 (Strongest basic)
Brand names	Cognitol, Cavinton
Administration route	Oral
Dose	5,10,40 mg vinpocetine 2 times daily

3.1.4 Pharmacology

3.1.4.1 Indication

Vinpocetine, nootropic drug is an alkaloid extracted from the periwinkle plant and has been tested as a neuronal plasticity enhancer and marketed as a "memory booster." Vinpocetine treatment has been shown to facilitate long-term potentiation, improve spatial memory in animal models, and enhance performance on cognitive tests in humans. A nootropic drug is characterized by a direct functional activation of the higher integrative brain mechanisms that enhances cortical vigilance, a telencephalic functional selectivity, and a particular efficiency in restoring deficient higher nervous activity. (10)

3.1.4.2 Mechanism of Action (11-15)

Vinpocetine is is an alkaloid of the common periwinkle plant and it is a Vincamine derivative. It selectively dilates the arteries and capillaries in the head area, which improves circulation to the brain, thus alleviating cerebral insufficiency. Antioxidant and hydroxyl radical scavenging properties of Vinpocetine has been shown *in vitro*. The cognitive

enhancement function of vinpocetine comes from its inhibition of phosphodiesterase 1 (PDE type 1), which leads to an increase in cAMP and cGMP levels, thus improves cerebral blood flow in the brain. These cyclic nucleotides can in turn activate a series of kinases that phosphorylate the transcription factors cAMP response element binding protein (CREB) and serum response factor (SRF), leading to the expression of plasticity-related genes. It is reported that in rats, Vinpocetine prevent damage of neuron and modulate cholinergic function thus helps to improve memory. Fig.3.1 shows a mechanism of action of Vinpocetine. At the neuronal level, it blocks the sodium channel (Na+) by preventing intracellularly high concentrations of Ca2+. Neurotransmitter adenosine uptake inhibits by it and thus reduces action of Ca2+. In addition, relaxing muscles of blood vessel, cGMP reduces whereas cAMP increasing by impede phosphodiesterase type I (PDE1) enzyme.

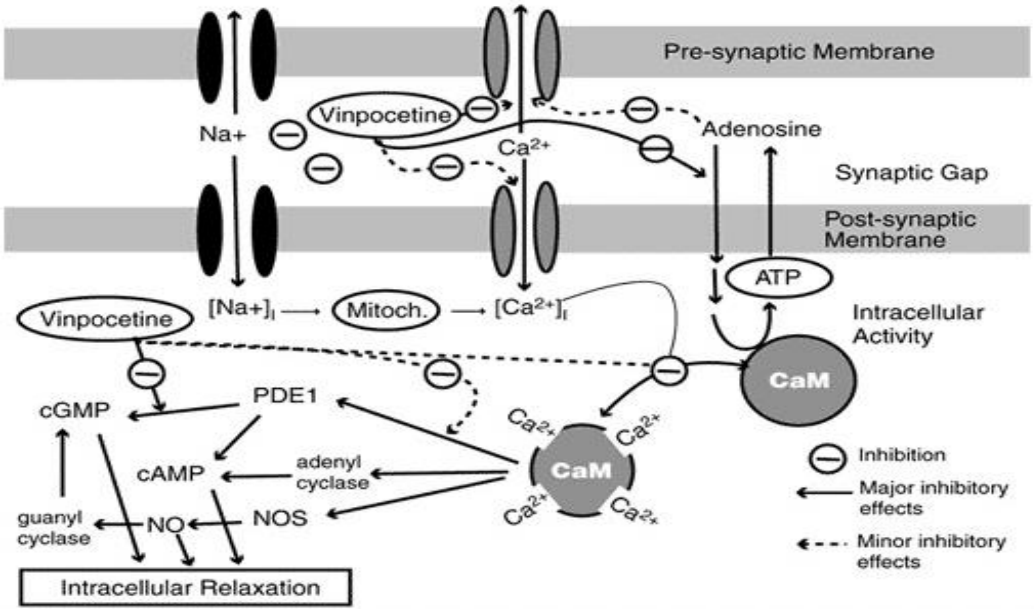


Fig. 3.1 Presumable Mechanisms of Action of Vinpcetine (16)

Ongoing research around the world indicates that it help in improve learning ability, insomnia, hearing, eyesight, and effects of menopause, and increase tolerance to damage caused by hypoxia (lack of oxygen, such as occurs with a stroke or heart attack). For the treatment of cerebral circulatory disorders such as acute stroke, memory, apraxia, tinnitus, motor disorders, aphasia, dizziness, headache and ear it is used. Vinpocetine improved speed of reaction in short term memory, this improvement is possibly linked to an improvement in

cerebral circulation and enhanced neurotransmitter turn over. (14) Vinpocetine boosts circulation to the brain by increasing the amount of blood traveling through blood vessels in and around the brain. In addition, it is thought that Vinpocetine accelerates the cells' activities in at least four other ways: (i) It speeds up the rate of production of the energy within nerve cells. (ii) It increases the amount of glucose used by the nerve cells. (iii) It increases the rate at which brain cells use the oxygen molecules taken from the blood. (iv) It increases a number of different neurotransmitters in the brain, including norepinephrine, dopamine, acetylcholine and serotonin. Vinpocetine boosts the concentration of these critical neurotransmitters and may promote memory processing.

3.1.4.3 Pharmacokinetic Profile

Table 3.5 Pharmacokinetic Profile of Vinpocetine (17, 18)

Parameters	Inference
Bioavailability	7% in humans, 50% in rats and 20% in dogs (20%)
Plasma protein binding	90%
Metabolite	Apovincaminic acid
Route of Elimination	The major route of elimination is metabolism, primarily by the liver

Vinpocetine is clear through hepatic metabolism in all species. As shown in table bioavailability is different in each species because magnitude of metabolism is different. It metabolized in the liver in a humans as well in dog but not in rat. (18, 19)

3.1.4.4 Pharmacodynamic Profile

It has been reported that Vincamine, precursor of Vinpocetine, help to improve in function of brain. It has been reported that learning and recall enhancement, better concentration and enhancement in short-term memory can be achieved by vinpocetine. Therefore it is has been proposed as a supplement, like ginkgo biloba a brain-booster, for protecting against aging related problems. (20, 21)

3.1.4.5 Adverse Drug Reaction

Vinpocetine is generally well tolerated, and no significant adverse effects have been seen in clinical trials. There is one case report of vinpocetine apparently causing reversible agranulocytosis. In addition, vinpocetine reportedly impairs platelet aggregation. (22)

3.1.4.6 Drug interaction

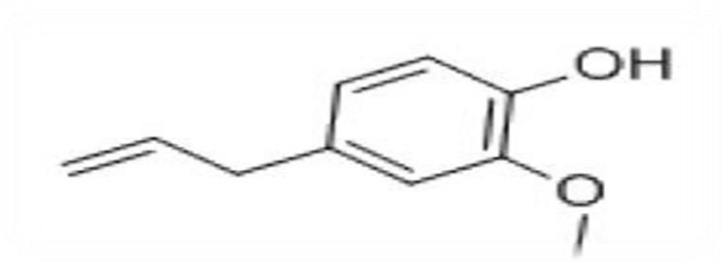
Table 3.6 Drug-Drug interaction for Vinpocetine

Drug	Mechanism of Action	Interaction
Warfarin (23)	Warfarin inhibits the vitamin K-dependent synthesis of biologically active forms of the calcium-dependent clotting factors II, VII, IX and X, as well as the regulatory factors protein C, protein S and protein Z	slightly influence prothrombin time, a measure of the clotting time of blood plasma

3.2 Excipients Profile

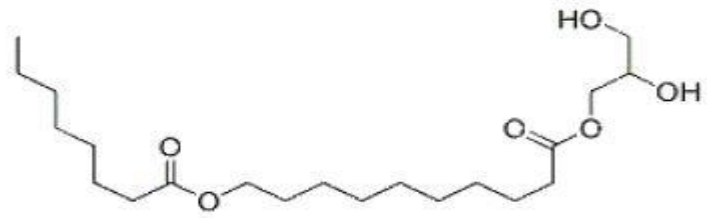
3.2.1 Clove oil

Table 3.7 Pharmaceutical Specification for Clove Oil (24-26)

Parameters	Property
Synonyms	Oleum caryophyli, Eugenol, 4-Allylguaiacol, 4-Allyl-2-methoxyphenol, Eugenic acid, Caryophyllic acid, Allylguaiacol, p-Allylguaiacol, Eugenol.
Chemical Name	2-methoxy-4-prop-2-enylphenol
Empirical Formula	$C_{10}H_{12}O_2$
Molecular Weight	164.20
Structural Formula	
Functional Category	Antibacterial, Carminative, antispasmodic
Physical Description	Clove oil is clear, light yellow to yellow-green to brown colored liquid. It has characteristic aroma and burning taste.
Viscosity	12.8 cps
HLB value	6-7
Solubility	Oil is insoluble in water and soluble in ethanol and diethyl ether. It is miscible with methylene chloride, toluene and fatty acids.
Incompatibility	Clove oil is incompatible with strong acid, strong base and strong oxidizing agents.
Safety	Clove oil is generally regarded as a relatively nontoxic and nonchronic material when used as an excipient. Oral LD50 (rat): 1,370 mg/kg Dermal LD50 (rabbit): 1,200 mg/kg
Application	Clove oil is widely used in cosmetics, food products, and pharmaceutical formulations. In pharmaceutical formulations, Clove oil is most commonly used in topical creams and ointments at concentrations of 5–12.5%. Due to its antibacterial, analgesic and anti-oxidant effects. Clove oil is the active ingredient in several mouthwashes and toothache pain-relief preparations.

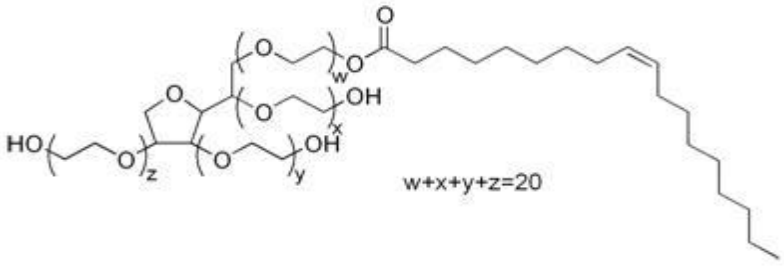
3.2.2 Capmul MCM C8 (26)

Table 3.8 Pharmaceutical Specification for Capmul MCM C8

Parameters	Property
Synonyms	Glycerol monocaprylocaprate, Glyceryl mono- and dicaprylo/caprate, Mono-diglyycerides of Caprylic/Capric acid
Chemical Name	Glyceryl Caprylate/Caprate
Empirical Formula	C21H40O26
Molecular Weight	388.53
Structural Formula	
Functional Category	Bioavailability Enhancer, Emulsifier/Co- Emulsifier, Solubilizer, Carrier (vehicle), Penetration enhancer (dermatological applications.
Physical Description	Capmul MCM is clear, almost colorless or off- white colored viscous oil. It has a Mild, fatty, or grease smell.
Viscosity	43-48 millipascal-second (mPa.s)
HLB value	5-6
Solubility	It is miscible with chloroform, diethyl ether, ethanol, glacial acetic acid and methanol; freely soluble in ethanol (95%) and petroleum ether; practically insoluble in water; practically insoluble in mineral oil unless mixed with another vegetable oil.
Safety	Capmul MCM is generally used in oral and topical pharmaceutical formulations and regarded as a relatively non-irritant and nontoxic material.Oral (rat) LD50: 5 gm/kg
Incompatibility	It is incompatible with strong oxidizing agents.
Regulatory Status	Capmul MCM is generally recognized as safe (GRAS) by USFDA.
Application	Capmul MCM is most preferably used in preparation of emulsion because it acts as a solubilizer for poorly soluble compounds or as a suspension medium to facilitate absorption and improve bioavailability. Capmul MCM is an emulsifier or co-emulsifier in preparation of stable self-emulsifying lipid-based microemulsions.

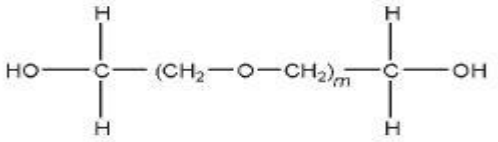
3.2.3 Polysorbate 80 (Tween 80)

Table 3.9 Pharmaceutical Specification of Tween 80 (26, 27)

Parameters	Property
Synonyms	Capmul POE-O, Armotan PMO 20, Cremophor PS 80, Eumulgin SMO, Durfax 80K, Crillet 50, Drewpone 80K, E433, Emrite 6120,.
Chemical Name	Polyoxyethylene 20 sorbitan monooleate
Empirical Formula	$C_{64}H_{124}O_{26}$
Molecular Weight	1310 g/mol
Structural Formula	
Functional Category	Non-ionic surfactant, emulsifying agent, wetting agent, solubilizing agent, dispersing and suspending agent.
Physical Description	It has a characteristic odour and bitter taste. Their colour and physical form at 25°C are Yellow oily liquid.
Viscosity	425 mPa.s at 25°C
HLB value	15
Surface Tension	42.5 dyne/cm at 20°C
Solubility	It is miscible with vegetable oil, ethanol and water. Immiscible with mineral oil.
Safety	It is mildly toxic by ingestion but moderately toxic by IV route.
Incompatibility	Precipitation and discoloration occur with substances specially tannins, phenols, tarlike materials and tars. In the presence of it, antimicrobial activity of paraben preservatives is reduced.
Application	Used as emulsifying agents in O/W emulsions preparation. It has a wetting property and widely used as solubilizer in formulation of parenteral and oral suspensions. It is also used in food products and cosmetics.

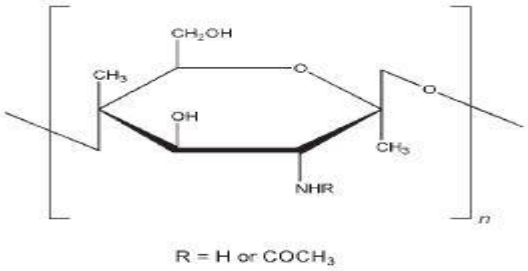
3.2.4 Polyethylene Glycol 400

Table 3.10 Pharmaceutical Specification for PEG 400 (26, 27)

Parameters	Property
Synonyms	Macrogol 400, Carbowax Sentry, Lipoxol, Lutrol E, Macrogola, PEG, Pluriol E, polyoxyethylene glycol-400.
Chemical Name	a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)
Empirical Formula	$C_{2n}H_{4n+2}O_{n+1}$
Molecular Weight	380-420
Structural Formula	
Functional Category	Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant, Solubility enhancer
Physical Description	It is a clear, colourless, viscous liquid of low volatility, which is odourless and sweet in taste.
Viscosity	105–130 mPa.s at 25°C
Surface Tension	44 dynes/cm
Solubility	Miscible with water, ethanol, acetone, chloroform and in some essential oils. Better solvent for oils and organic chemicals.
Safety	Propylene glycol 400 is estimated to be one-third as intoxicating as ethanol. Laxative if taken orally, ototoxicity; cardiovascular effects; seizures; hyper osmolarity, lactic acidosis, both occur most frequently in patients with renal impairment. LD50 (Rabbit, PO): 26.8 g/kg LD50 (Rat, PO): 28.9 g/kg
Incompatibility	The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.
Regulatory Status	Included in the FDA Inactive Ingredients Database (dental and ophthalmic preparations; IM and IV injections; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations).
Application	Use as a Solvent in many pharmaceuticals, including oral, injectable or topical formulations. Use as emulsifying agent in o/w emulsions. It is germicide of equally strength to Ethanol. In solutions it suppresses the growth of microorganisms.

3.2.5 Chitosan

Table 3.11 Pharmaceutical Specification for Chitosan (26, 28)

Parameters	Property
Synonyms	2-Amino-2-deoxy-(1,4)-b-D-glucopyranan, chitosanihydrochloridum, deacetylated chitin, deacetylchitin; b-1,4-poly-D-glucosamine.
Chemical Name	Poly-b-(1,4)-2-Amino-2-deoxy-D-glucose
Structural Formula	
Functional Category	Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity and permeation increasing agent.
Physical Description	Chitosan occurs as odorless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look 'cotton like.
Viscosity	1% acetic acid at pH 4.1 shows viscosity 260mPa-s and same for 5% acetic acid at pH 3.3.
Solubility	Sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents. Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids (except phosphoric and sulfuric acids).
Safety	Chitosan is nontoxic and nonirritant material, biocompatible and biodegradable. LD50 (mouse, oral): >16 g/kg
Incompatibility	It is incompatible with strong oxidizing agents.
Regulatory Status	Chitosan is registered as a food supplement in some countries.
Application	Use as an excipient in oral and other pharmaceutical formulations and in cosmetics.

3.3 References

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