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Compritol and Precirol: Innovative Pharmaceutical Excipients

A.R. MADGULKAR *, M. BHALEKAR, M.R. SHIRADKAR,
M. DAMLE AND R. RODE
A.I.S.S.M.S. College of Pharmacy
Kennedy Road, Near R.T.O. Office, Pune-411 001, India
Fax: (91)(20)26132208, Tel : (91)(20)26132204 (O),(91) (20)25394021 (R)
E-mail: madgulkar@rediffmail.com

To administer active pharmaceutical ingredients in suitable dosage form they need to be combined with non-medical agents (excipients), which impart the desired properties to the formulation. Since excipients form an integral part of formulation, search for new excipients which can be used in low concentrations and serve multiple functions is always a subject of research. Compritol and precirol are semi-synthetic waxes from the Gelucier wax family. In this review various pharmaceutical applications of compritol and precirol as excipients are highlighted.

Keywords : Compritol, Precirol, Pharmaceutical excipients.

INTRODUCTION

The drug substances need to be co-administered with various therapeutically inactive substances called excipients in order to form a suitable dosage form. Various categories of substances such as starches, gums, polymers, sugars and waxes are used for this purpose. Waxes are an important class of pharmaceutical excipients used for varied applications. The term 'wax' generally refers to plastic that is solid at room temperature and liquid of low viscosity above its melting point. Waxes are esters of monohydric long chain fatty alcohols and long chain fatty acid. They usually contain a wide variety of materials including glycerides, fatty alcohols, fatty acids and their esters. Waxes differ from fats in that fats are saponified by aqueous or alcoholic alkali, but waxes can be saponified only by alcoholic alkali[1].

Compritol and precirol belong to the Gelucier family, which represents a wide range of meltable excipients with varying amphiphilic properties. Gelucier is a family of waxes derived from the mixtures of mono-, di- and triglycerides with PEG esters of fatty acids. They are characterized by their melting point range and HLB. They have a wide variety of applications in pharmaceutical preparations of fast release and sustained release formulations. Geluciers containing only PEG esters (*e.g.*, Gelucier 55/18) are used in the preparation of fast release formulations and Geluciers which contain only glycerides or a mixture of glycerides and PEG

esters (*e.g.* Gelucier 54/02, 50/13) are used in the preparation of sustained release formulations [2, 3].

The first number in the prefix of Gelucier products refers to its melting point and the second number refers to the hydrophilic-lipophilic balance (HLB) on a scale ranging from 1 (highly fat soluble) to 18 (water dispersible)[4].

Compritol: Chemically, compritol is glyceryl behenate[5]. Glyceryl behenate is a mixture of glycerides of fatty acids, mainly behenic acid. Compritol is available in three different grades: (a) Compritol 888 is a mixture of approximately 25% monobehenin, 50% dibehenin and 25% tribehenin: CAS 18641-57-1[6]. (b) Compritol® 888 ATO is a mixture of approximately 15% mono-, 50% di- and 35% triglycerides of behenic acid (C22) while fatty acids other than behenic acid account for less than 20%: CAS 18641-57-1[5]. (c) Compritol HD5 ATO PEG-8 behenate and tribehenin[7]. Glyceryl behenate is generally recognized as safe (GRAS) by US FDA[8].

Precirol (synonyms glycerin palmitostearate; glycerol palmitostearate: precirol ATO-5) is chemically glyceryl palmitosterate: CAS 8067–32–1.

Glyceryl palmitostearate is a mixture of mono-, di- and triglycerides of C_{16} and C_{18} fatty acids[9]. Glyceryl palmitostearate is generally recognized as a safe category by US FDA[10]. Glyceryl palmitostearate is manufactured, without catalyst, by the direct esterification of palmitic and stearic acids with glycerin[9].

Waxes are characterized by various properties such as iodine value, saponification value, hydroxyl and peroxide value, melting point, viscosity, colour, specific gravity and refractive index[1, 11].

TABLE-1
CHARACTERISTIC VALUES FOR COMPRITOL AND PRECIROL

Excipients	m.p (°C).	Iodine value	Sponification value	Hydroxyl value	Acid value
Compritol (70/-2)	69–74	< 3	145–165	–	< 4.0
Precirol (54/02)	53–57	< 3	175–195	60–115	< 6.0

Pharmaceutical applications of compritol and precirol

(1) Solid lipid nanoparticles (SLN) and microparticles (SLM): Colloidal drug delivery systems offer a number of potential advantages, such as controlled release, drug targeting, drug stabilization and improved bioavailability for poorly water-soluble drugs[12]. In recent years, biocompatible lipid nanoparticles and microparticles have been reported as potential drug carrier systems as alternative materials to polymers. Melt-emulsified microparticles based on lipids such as compritol, which are solid at room temperature, have been developed as pulmonary drug delivery systems. Compritol and poloxamer (emulsifying agent) were used to prepare solid lipid microparticles for pulmonary administration by emulsification and lyophilization. The particles were characterized and *in vivo* studies showed the microparticles to be suitable for pulmonary administration[13].

In another study[14] lipid microparticles (LMs) based on compritol E ATO were prepared by co-melting procedure and evaluated as a sustained release system for a gonadotropin release hormone (GnRH) antagonist (antide). *In vitro* release of antide from LMs correlated well with the *in vivo* release. It was concluded that LMs could sustain the release of antide for at least 1 month.

Precirol was used as lipid phase for the preparation of lipid nanoparticles containing substances having antiandrogenic properties for local treatment of androgenic alopecia[15].

(2) Lubricant: Solid phase lubricants represent a very important class of excipients. They decrease interparticulate friction during the densification phase and between material and compression die walls during the ejection phase of the compact. These products are often hydrophobic materials in which London interactions dominate. Unfortunately, the hydrophobic nature of lubricants induces two well-known negative effects: the decrease of tablet tensile strength and the slowing of drug release. These effects are particularly prominent for magnesium stearate, the most commonly used lubricant. For this reason, several new lubricants that are less hydrophobic such as Compritol-888 are evaluated. Paracetamol tablets made with Lubritab and Compritol-888, as lubricant were found to be harder than those made with magnesium stearate[7]. The tablet lubricating properties of Compritol-888 were compared with those of magnesium stearate. Prolongation of disintegration time seen with magnesium stearate was not evident with use[16] of Compritol-888. Compritol-888 is chemically inert, has a good lubricating power and can be employed in any concentration without affecting the physical properties of tablets[17]. In the study, the lubricant performance of Compritol-888 ATO has been compared by using classical blending and by hot melt coating on to lactopress by compression tests. Compritol used by hot melt coating allows for a concentration of 0.5% to directly obtain the lubricant performance of 3% of compritol used by blending[18].

Use of compritol as lubricating agent is described in US Patent describing immediate release eplerenone compositions[19].

(3) Coating agent: Solid dosage forms are often coated to sustain drug release, improve the stability or mask the taste of poorly tasting drugs. The use of solvents is under constraint in the production of coated solid dosage forms due to the problems of trace levels and expensive solvent recovery process. Water based coating compositions pose problems due to long evaporation time. Hence it is appealing to use a meltable product like wax or its derivative as coating material[20].

Modification of the drug release of ibuprofen was reported by hot-melt coating with mixes of compritol 888 ATO and non-ionic surfactants[21]. Slow release granules of chloroquin using compritol 888 were prepared which followed dissolution kinetics as per Higuchi model[22].

Faham[23] used hot melt coating on granules using a top-spray technique with Compritol-888 ATO to prolong the theophylline drug release. There was a relationship between the percentage of Compritol-888 ATO and theophylline release rate.

(4) Hard gelatin capsules filled with waxes: At high concentration, waxes are difficult to compress because of melting, resulting in sticking and picking of the formulation. High dose drugs need large amounts of wax to acquire sustain-release properties and are therefore difficult to formulate into the tablets. Such drugs can be filled in hard gelatin capsules as solutions or dispersions in molten waxes. The advantages of such methods are that the drug could be protected against moisture or oxygen, release could be sustained and no other excipients are needed[1].

(5) Wax matrix tablet: Melt granulation or thermoplastic granulation is a process in which powder agglomeration is obtained through the addition of binder that melts or softens at a relatively low temperature. As a one step operation, melt granulation offers several advantages compared to conventional wet granulation since liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvents, in terms of cost and safety, when granulating water-sensitive materials. Lipophilic matrix materials work through a combination of erosion and diffusion. Waxy materials have major applications in sustained release systems, especially for highly water-soluble drugs. Matrix delivery systems utilizing waxy materials usually employ a core of physical blend of the drug and matrix-forming agent. Since they are water-insoluble and non-swellable, drug release takes place by diffusion of drug through the channels created by water-soluble additives.

Glyceryl behenate (compritol) has been evaluated for application as a sustained release agent in concentration of 10%. Theophylline and phenylpropanolamine hydrochloride tablets prepared by using compritol and precirol showed slow release in melt granulation and heat treatment as compared with physical mixing[4].

Precirol (glycerol palmitostearate) was used to prepare a matrix base for sustained release tablets of theophylline and quinidine gluconate[24]. Galal *et al.*[25] blended Precirol with various gelucier waxes to obtain zero order drug release matrix composition for carbamazepine.

(6) Semisolid: In a patent claiming anhydrous semisolid composition to overcome limitations of conventional preparations such as unsuitability of o/w creams for insoluble drugs and staining and lack of water washability of ointments Compritol-888 was used as oil phase miscible with hydrophilic anhydrous vehicle[26]. Use of compritol and precirol as stiffening agents is described in patent applications describing pharmaceutical compositions and dosage forms for administration of hydrophobic drugs[27].

Conclusion

Thus compritol and precirol offer a good choice of excipients to the formulator because of their multifunctional character. There is more need to explore the utility of these in various formulation applications such as semisolid bases, taste masking and stability enhancement. Besides, these agents can be useful in cosmetic products for various applications.

REFERENCES

1. R. Bodmeier and J. Hermann, Encyclopedia of Pharmaceutical Technology, Vol.16, p. 335 (1997).
2. J. Hamdani and J. Andre, *Int. J. Pharm.*, **260**, 47 (2003).
3. S. Shimpi, B. Chauhan, K.R. Mahadik and A. Paradkar, *AAPS Pharm. Scitech.*, **5**, 43 (2004).
4. Yu-E. Zang and J.B. Schwartz, *Drug Dev. Ind. Pharm.*, **29**, 131 (2003).
5. United States Pharmacopoeia, USP23 NF 18, The United States Pharmacopoeial Convention, Roockville, MD, 2249 (1995).
6. Seiden and Paul, United Sates Patent, 5, 288 (1994).
7. A. N'diaye, *Int. J. Pharm.*, **254**, 263 (2003).
8. US FDA, 21-CFR B184.1328.
9. Handbook of Pharmaceutical Excipients, The Pharmaceutical Press, London, 2nd Edn., p. 211 (1994).
10. US FDA, 21-CFR 184.1329.
11. B. Evard, *Drug Dev. Ind. Pharm.*, **25**, 1177 (1999).
12. A. Lippacher, R.H. Muller and K. Mader, *Int. J. Pharm.*, **214**, 9 (2001).
13. V. Sanna, N. Kirschvink, P. Gustin, E. Gavini, I. Roland, L. Delattre and B. Evrard, *AAPS Pharm. Scitech.*; **5** (2004).
14. J. Katja, M. Wolfgang and D. Markus, *J. Controlled Release*, 89 (2003).
15. K. Kraemer and K. Nietsch, US Patent., 6, 875 (2005).
16. B. Glombitza, D. Sorgenfrey and A. Sakr, *Pharmazie*, **47**, 871 (1992).
17. Abramovici and J. Claude, *Bull. Technique Gattefosse*, **78**, 75 (1985).
18. V. Jannin, V. Berard, A. N'Diaye and Y. Pourcelot, *Int. J. Pharm.*, **262**, 39 (2003).
19. S. Thosar, R. Gokhale and D. Tolbert, United States Patent., 6, 863, (2005).
20. P. Barthelemy and J. Laforet, *Eur. J. Pharm. Biopharm.*, 4787 (1999).
21. J.V. Bérard and C. Andrès, International. Microencapsulation Soc., 15th Int. Symposium on Microencapsulation (Sep. 18–21, 2005).
22. A. Faham, P. Prindderre and N. Farah, *Pharmazie*, **55**, 444 (2000).
23. A. Faham, *Drug Dev. Ind. Pharm.*, **26**, 167 (2000).
24. D. Saraiyya and S. Bolton, *Drug Dev. Ind. Pharm.*, **16**, 1963 (1990).
25. S. Galal, M.A. El-Massik and O.Y. Abdallah, *Drug Dev. Ind. Pharm.*, **30**, 817 (2004).
26. P. Tyle and K. Freeburn, United States Patent 5, 314, (1994).
27. Chen and Feng-Jing, US Patent Appl. 20030236236 (2003).

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