

FILM COATED RANITIDINE HYDROCHLORIDE TABLET

This invention relates to an improved coated ranitidine hydrochloride (HCl) tablet and its preparation. In particular, the invention relates to the incorporation of a certain plasticizer into a film coating composition which increases the stability of the ranitidine HCl tablet and also prevents the film coating from subsequently obscuring distinctive engravings and embossments which may be present in and on the tablet's surface.

Ranitidine, chemically identified as N-[2-[[[5-(dimethylamino)-methyl-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine (see US Patent 4,128,658), is a known antagonist to histamine H₂ receptors. This drug is widely used in the treatment of duodenal ulcers especially as the hydrochloride salt and in the form of tablets.

Film coating of tableted drug products is a process widely practiced in the pharmaceutical field. Typically this process involves spraying a solution or suspension of a polymeric material conventionally utilized for film coating purposes onto a tablet which is being tumbled in a stream of warm air. As the solvent evaporates the polymeric film coating is uniformly deposited on the tablet's surface. Film coating can be done in either aqueous or organic solvent systems, but aqueous systems are often preferred because they avoid the safety and environmental problems associated with many organic solvents. Film coating of ranitidine HCl tablets is utilized to mask the drug's bitter taste, to provide protection from destructive environmental elements, and for esthetic purposes. It is known that ranitidine HCl is subject to degradation upon ageing and that such degradation is accelerated by heat, moisture and light; for example, see Physicians' Desk Reference, 41st ed., page 993 (1987). Further, the drug is not only extremely soluble in water (greater than 900 mg/ml at 25°C) but is also very soluble in many commonly used organic solvents. Such high solubility and propensity to degrade in the presence of heat, moisture and light have therefore made it difficult to maintain the pharmaceutical integrity of polymeric film coated ranitidine HCl tablets.

In the art of tablet film coating, conventional plasticizing agents are frequently added to the polymeric solution or suspension to improve the flexibility of the film coating and thus minimize the filling in or covering over of engraved (cut in to the surface of the tablet) or embossed (raised above the surface) indicia and designs in the tablet face. In order to significantly retard the degradation of ranitidine HCl induced by the natural heat, moisture or light factors of the environment and to successfully mask its taste, the film coating must exceed a minimum thickness. Without a plasticizer this thickness cannot be achieved for a tablet containing ranitidine HCl without considerable loss of the definition of the indicia and designs in or on the tablets. Preservation of such engraved or embossed indicia and designs is important not only for general appearance and trade dress purposes, but more important, to meet government requirements regarding identification of drug products.

Many of the plasticizers in common use in polymeric film coatings of pharmaceutical products, for example, polyethylene glycol, propylene glycol, dibutyl sebecate, mineral oil, sesame oil and diethyl phthalate, are unacceptable for use with ranitidine HCl tablets. Such commonly used plasticizers either tend to react with ranitidine HCl or promote degradation at the tablets' surfaces, resulting in pronounced discoloration which renders the tablets unmarketable. In addition, some conventional film coating polymers are also incompatible with ranitidine HCl and thus accelerate its degradation.

US Patent No. 4,302,440 provides a review of the art of tablet film coating, and discloses a process and formulations for film coatings of aspirin using an aqueous medium of hydroxypropyl methylcellulose (HPMC). More particularly, the patent teaches an HPMC film coating for aspirin which incorporates as the plasticizer of choice, triacetin, but it does not teach an HPMC film coating which would be acceptable for a tablet of ranitidine HCl. The inherent problems associated with ranitidine HCl because, for example, of its high solubility in many commonly used plasticizers, are quite different from those described for aspirin.

It has now been found that the discoloration of HPMC film coated ranitidine HCl tablets can be minimized by including triacetin (also known as triacetyl glycerol, glyceryl triacetate and 1,2,3-propanetriol triacetate) in the film. Surprisingly, a ranitidine HCl tablet coated with an HPMC film coating containing triacetin, shows a significant improvement in protection against drug migration into the film compared with a like tablet coated with similar but unplasticized HPMC films and with one coated by HPMC film coatings containing other commonly used plasticizers.

Accordingly the present invention provides a ranitidine hydrochloride tablet coated with a polymeric film comprising HPMC and triacetin.

The present invention allows an engraved or embossed ranitidine HCl tablet core to be coated to an acceptable thickness for protection from detrimental environmental elements and for taste masking while preserving the engravings or embossments. Further, the triacetin containing film coating of this invention is essentially unreactive with the active drug, i.e., ranitidine HCl. The plasticized film coating of this invention minimizes the migration of ranitidine HCl into the coating and subsequent discoloration of the tablet. The inherent advantages of polymeric film coating including improvement of the appearance of the tablets and enhancement in the ease of swallowing of the tablets are in no way diminished by the present invention. The dissolution profile, and hence, bioavailability, of ranitidine HCl tablets bearing the triacetin containing HPMC coating of this invention remains essentially unaltered, and is comparable in this respect to similar HPMC film coated tablets without a plasticizer.

The plasticizer of the present invention, i.e., triacetin, has the following characteristics :

1. It has a high degree of compatibility with the HPMC coating polymer;
2. It significantly reduces the polymer's glass transition temperature, thus improving film flexibility and definition of the tablet's engravings or embossments;

3. It is a poor solvent for ranitidine HCl (that is, a solubility of less than 0.05mg/ml), thus minimizing drug dissolution and subsequent migration into the film coating during the coating process and thereafter, and also minimizes the concentration gradient driven drug diffusion during ageing;
4. It has a relatively high boiling point (i.e., low vapour pressure) to ensure the permanence of the plasticizer upon the application of heat during the coating operation;
5. It is essentially unreactive with ranitidine HCl;

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An important embodiment of the present invention is an engraved or embossed ranitidine HCl tablet core uniformly coated with about 2.0 to 4.5 parts by weight of hydroxypropyl methylcellulose (HPMC) per 100 parts by weight of the ranitidine HCl tablet core, 5% to 25% w/w (preferably 10% to 15% w/w) of triacetin as a plasticizer based on the dry weight of the HPMC, and optionally 5% to 65% w/w (preferably 25% to 50% w/w) of a colorant or opacifying agent or agents, based on the dry weight of the HPMC. Conventional tableting ingredients such as, for example, flavouring, stabilizing, antioxidant, preserving agents and the like may be included in accordance with standard tableting practice. Furthermore, total film coating solids application to the ranitidine HCl tablet core should be between 2.1 and 5.0 (preferably 3.0 and 4.0) parts by weight of film coating solids per 100 parts by weight of the ranitidine tablet.

25 The preferred HPMC used in the coating composition of the invention produces a viscosity of between 4.0 and 7.2 milli Pascal seconds (mPas) when measured as a 2% by weight aqueous solution at 20°C. Other HPMC's which yield viscosities as low as 2.4 and high as 18.0 mPas when similarly measured may be satisfactorily applied. The most preferred HPMC composition is hydroxypropyl methylcellulose 2910, which is a propylene glycol ether of methylcellulose containing not less than 7.0% and not more than 12.0% hydroxypropoxy, and not less than 28.0% and not more than 30.0% methoxy, calculated on a dry basis. Acceptable coating solutions range from 1% to 20% by weight of HPMC in a solvent system, with the preferred range between 5% and 10% by weight.

5 The polymeric dry film coating is preferably applied to the tablet core in the range of from 2.1 to 5 parts by weight of dry film coating per 100 parts by weight of ranitidine HCl tablet core, with a more preferred range being from 3.0 to 4.0 parts by weight dry film coating per 100 parts by weight of the ranitidine HCl tablet core.

10 A variety of colorants or opacifiers may be employed in the coating solution including water soluble dyes, aluminum lakes of water soluble dyes, and inorganic pigments such as titanium dioxide and iron oxide. The recommended range of application for suitable colorants or opacifiers is from 5% to 65% w/w based on the dry weight of the hydroxypropyl methylcellulose, with the preferred range between 25% and 50% w/w.

15 The preferred solvent for the film coating components is purified water, but various classes of organic solvents commonly used in this art such as alcohols, ketones, ethers and chlorinated hydrocarbons, for example, ethanol, acetone, tetrahydrofuran, methylene chloride and the like, may also be used.

20 The HPMC film coating may be suitably applied by conventional art methods for film coating of pharmaceutical tablets. In general, the HPMC is dispersed in purified water or other suitable solvent until dissolved followed by addition and dispersion of the desired amount of triacetin. The colorant or opacifier may then be added and intimately mixed into the dispersion. Additional components such as flavourings, stabilizers, antioxidants, and preservatives may also be added to the coating dispersion. The coating dispersion is applied to the ranitidine HCl tablet cores using standard pharmaceutical tablet coating means. Suitable methods for applying the coating dispersion include the use of air atomization spray equipment and a perforated coating pan.

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EXAMPLES

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The following examples are presented to further illustrate the invention and should in no way be construed as a limitation thereof.

EXAMPLE 1

A. Cast Film Plasticizer Comparison Study

5 Cast film studies were performed using a typical film aqueous coating composition containing, on a per gram HPMC dry weight basis, plasticizer, 0.2 gm, and Opaspray (Colorcon, Inc., West Point, PA, USA - OPASPRAY is a Trade Mark) colorant solids 0.5 gm. Cast films were prepared by adding 1.5 g of a 15% solids solution to a uniform plate, 42 mm in diameter, and
10 drying at ambient temperature for at least 24 hours. Ranitidine HCl (1.5 gm), of particle size 50 to 200 μm , was then spread uniformly on the dried film coating and stored at 60°C / 78.9% relative humidity (RH) for approximately two weeks. The RH was controlled by using a desiccator jar and a saturated KBr solution, which was maintained at
15 60°C in a drying oven. This procedure was used to prepare films containing triacetin, triethyl citrate, polyethylene glycol (PEG) 400 and propylene glycol as the plasticizer. After two weeks, the cast films were removed and visually examined for discoloration. The results of this study are shown in Table 1.

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Table 1 - Summary of Ranitidine HCl/Plasticizer Study

5	Plasticizer	Molecular Weight (G/Mol)	Boiling Point (°C)	Ranitidine HCl Solubility mg/ml	Cast Film Discoloration
	Triacetin	218.20	258	0.042	1b
10	Triethyl citrate	276.28	294	0.183	3
	PEG 400	380-420	238 ^a	5.17	4
	Propylene glycol	76.09	188	196.5	2

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a Flash Point

b 1=least discoloration, 4=greatest discoloration

20 B. Retarding of Ranitidine HCl Tablet Discoloration with Triacetin

Four batches of ranitidine HCl tablet cores were coated using a procedure according to that described in Example 2, vide infra.

25 The coating composition of each batch contained Opaspray Pink M-1-1457 as the colorant, and the amount of triacetin varied from 0% to 15% (by 5% increments). All of the tablet cores were coated at the level of 2.5 parts dry film coating per 100 parts by weight of the ranitidine tablet core. Tablets were stored for 1 month in high density
30 polyethylene bottles at 60°C/78.9% RH and then visually examined for appearance changes, i.e., the darker the appearance, the greater the decomposition. The results of this study are shown in Table 2.

Table 2

Summary of triacetin level effects on HPMC coated tablet appearance after storage in HDPE bottles at 60°C/78.9% RH for 30 days.

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	<u>Triacetin Level</u>	<u>Appearance^a</u>
	0%	4
10	5%	3
	10%	2
	15%	1

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^a 1=least decomposition

4=greatest decomposition

EXAMPLE 2

20 Hydroxypropyl methylcellulose, 6 mPas, 24.24 g, was agitated in approximately 150.00 g of hot purified water. Cold purified water, 124.43 g, was added with agitation to dissolve the polymer. Upon complete dissolution of the hydroxypropyl methylcellulose, the solution was allowed to cool to ambient conditions. Triacetin, 3.65g, 25 was added to the polymer solution and dispersed. Colorant suspension, 31.01 g, in the form of an Opaspray White M-1-7120 colorant suspension (Colorcon Inc., West Point, PA, USA) which contains 39.1% solids by weight was then added and dispersed in the HPMC/triacetin solution. The resulting coating solution had the following composition:

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INGREDIENTS	% w/w
Hydroxypropyl methylcellulose 6 mPas	7.3
5 Triacetin	1.1
Colorant suspension	9.3
Purified Water	82.3
	100.0

10 Embossed (raised indicia), uncoated ranitidine HCl tablet cores containing the equivalent of 150 mg of the free base were prepared by mixing the active ingredient with a pharmaceutically suitable binder and lubricant and compressing the mixture into tablet cores weighing 300 mg each in a manner similar to that taught in U.S. Patent 4,128,658. One kg of the uncoated tablet cores were placed in an HCT 30 HI COATER perforated coating pan (Vector Corp., Marion, IA, USA). The coating solution was applied using an air atomizing nozzle.

20 Twelve milligrams of dry film coating were applied per tablet. The embossed indicia were essentially as distinct and easy to read as those on the uncoated table core. The tablets were found to be substantially free of discoloration after prolonged periods of storage under normal conditions.

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EXAMPLE 3

30 Hydroxypropyl methylcellulose, 27.6 g, 6 mPas was agitated in a combination of 136.9 g of isopropyl alcohol and 319.9 g of dichloromethane until dissolved. Triacetin, 4.1 g, was added to the polymer solution and dispersed. Colorant suspension (Opaspray Apricot K-1-1173), 22.5 g, containing 37% w/w solids was then added and

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dispersed in the solution. The resulting coating solution had the following composition:

5	INGREDIENTS	% w/w
	Hydroxypropyl methylcellulose	5.4
	Triacetin	0.8
10	Colorant suspension	4.4
	Isopropyl alcohol	26.8
	Dichloromethane	62.6
		100.0
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Engraved (indicia cut 0.254 mm into the surface), 300 mg ranitidine HCl tablet cores containing the equivalent of 150 mg of free base were prepared by the method described in Example 2. One kg of the uncoated tablets were placed in an HCT 30 HI COATER perforated coating pan. The coating solution was applied using an air atomizing nozzle. Twelve milligrams of dry film coating were applied per tablet. The engraving was substantially free of edge erosion and filling in and the coated tablets were found to be substantially free of discoloration after a prolonged period of normal storage.

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CLAIMS

1. A ranitidine hydrochloride tablet coated with a
5 polymeric film comprising hydroxypropyl methylcellulose
(HPMC) and triacetin.
2. A tablet as claimed in claim 1 wherein the
triacetin content of the polymeric film coating is 5% to
25% based on the weight of the HPMC.
- 10 3. A tablet as claimed in claim 2 wherein the
triacetin content of the polymeric film coating is 10% to
15%.
4. A tablet as claimed in any of claims 1 to 3
wherein the polymeric film coating also contains one or
15 more colorants or opacifying agents.
5. A tablet as claimed in claim 4 wherein the amount
of colorant or opacifying agent in the polymeric film
coating is 5% to 65% based on the weight of HPMC.
6. A tablet as claimed in any of claims 1 to 5
20 wherein the polymeric coating constitutes 2.1 to 5.0 parts
by weight of dry film coating per 100 parts by weight of
tablet core.
7. A tablet as claimed in claim 6 wherein the
polymeric coating constitutes 3.0 to 4.0 parts by weight
25 of dry film coating per 100 parts by weight of tablet
core.
8. A process for the preparation of tablets as
claimed in any of claims 1 to 7 which comprises applying a
polymeric film coating comprising HPMC and triacetin to
30 ranitidine hydrochloride tablet cores by a film coating
technique.
9. A process as claimed in claim 8 wherein the
polymeric film coating is prepared and applied under
aqueous conditions.
- 35 10. A process as claimed in claim 8 wherein the
polymeric film coating is prepared and applied using an
organic (non-aqueous) solvent.