**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Applicant: | VATS *et al.* | Attorney Docket No.: | RLL-1628USBYP |
| Serial No.: | 15/012,775 | Examiner: | TRUONG, Quanglong N. |
| Filing Date: | 02/01/2016 | Group Art Unit: | 1615 |

Title: CAPSULE DOSAGE FORM OF METOPROLOL SUCCINATE

Mail Stop Amendment
Commissioner for Patents
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**RESPONSE TO OFFICE ACTION**

In response to a March 21, 2016 Office Action, please amend the application as follows.

**Amendments to the claims** are reflected in the listing of claims, which begins on page **2** of this document.

**Remarks** begin on page 5.

**AMENDMENTS TO THE CLAIMS:**

The Listing of Claims will replace all prior versions, and listings, of claims in the application.

**LISTING OF CLAIMS**

1. (Currently amended) An extended-release capsule dosage form of metoprolol succinate in the form of coated discrete units, wherein the capsule dosage form comprises metoprolol succinate in an amount of about 30% to about 70% by the total weight of the dosage form and is bioequivalent to the marketed ~~Toprol-XL®~~ extended release tablet of metoprolol succinate.

2. (Original) The extended-release capsule dosage form according to claim 1, wherein the capsule is in the form of a sprinkle capsule.

3. (Original) The extended-release capsule dosage form according to claim 1, wherein the coated discrete units have a particle size from about 0.2 mm to 2.5 mm.

4. (Original) The extended-release capsule dosage form according to claim 1, wherein the coated discrete units are coated inert core in the form of plurality of pellets, granules, minitablets, or beads.

5. (Original) The extended-release capsule dosage form according to claim 1, wherein the coated discrete units comprise

a) inert cores;

b) a drug layer over the inert cores comprising metoprolol succinate; and

c) an extended release layer over the drug layer coated cores.

6. (Original) The extended-release capsule dosage form according to claim 5, wherein the inert cores are water-soluble or water-swellable.

7. (Original) The extended-release capsule dosage form according to claim 6, wherein the water-soluble or water-swellable inert cores are made up of sugar, microcrystalline cellulose, cellulose, starch, modified starch, or mixtures thereof.

8. (Original) The extended-release capsule dosage form according to claim 7, wherein the sugar is selected from the group consisting of glucose, mannitol, lactose, xylitol, dextrose, and sucrose.

9. (Original) The extended-release capsule dosage form according to claim 5, wherein the extended-release layer comprises an extended-release polymer in an amount of about 5% to about 20% based on the weight of drug layer coated cores.

10. (Original) The extended-release capsule dosage form according to claim 9, wherein the extended-release polymer is selected from the group consisting of water-soluble/swellable polymers, water-insoluble polymers, and mixtures thereof.

11. (Original) The extended-release capsule dosage form according to claim 10, wherein the water-soluble polymer is selected from the group consisting of hydroxypropyl methyl cellulose, hydroxyethyl cellulose, polyethylene glycol, poly(ethylene oxide), hydroxypropyl cellulose, carboxymethyl cellulose, xanthan gum, starch, and mixtures thereof.

12. (Original) The extended-release capsule dosage form according to claim 10, wherein the water-insoluble polymer is selected from the group consisting of cellulose ethers, cellulose esters, polymethacrylic acid esters copolymers, aminoalkyl methacrylate copolymers, copolymers of polyvinyl acetate and polyvinyl pyrrolidone, and mixtures thereof.

13. (Original) The extended-release capsule dosage form according to claim 12, wherein the cellulose ether is ethyl cellulose.

14. (Original) The extended-release capsule dosage form according to claim 12, wherein the water-insoluble polymer further comprises a pore-former.

15. (Original) The extended-release capsule dosage form according to claim 14, wherein the pore-former is selected from the group consisting of low viscosity grade hydroxypropyl methylcellulose, sodium alginate, sugars and sugar alcohols, low molecular weight polyethylene glycol, polyvinyl alcohol, and mixtures thereof.

16. (Original) An extended-release sprinkle capsule dosage form of metoprolol succinate comprising coated discrete units, having a particle size from about 0.2 mm to 2.5 mm, wherein

the capsule dosage form releases not less than 15% of metoprolol succinate after 4 hours, when measured in a United States Pharmacopeia (USP) type 2 dissolution apparatus, paddle at 50 rpm, at a temperature of 37°C ±0.5°C in 500 mL of pH 7.5 phosphate buffer.

17. (Original) The extended-release sprinkle capsule dosage form according to claim 16, wherein the capsule dosage form releases about 15% to about 45% of metoprolol succinate after 4 hours, when measured in a United States Pharmacopeia (USP) type 2 dissolution apparatus, paddle at 50 rpm, at a temperature of 37°C ±0.5°C in 500 mL of pH 7.5 phosphate buffer.

18. (Original) An extended-release sprinkle capsule dosage form of metoprolol succinate comprising coated discrete units, having a particle size from about 0.2 mm to 2.5 mm, wherein the capsule dosage form exhibits the following *in-vitro* dissolution profile, when measured in a United States Pharmacopeia (USP) type 2 dissolution apparatus, paddle at 50 rpm, at a temperature of 37°C ±0.5°C in 500 mL of pH 7.5 phosphate buffer: a) not less than 15% of metoprolol succinate is released after 4 hours; and b) not less than 60% of metoprolol succinate is released after 12 hours.

19. (Original) The extended-release sprinkle capsule dosage form according to claim 16 wherein the capsule dosage form comprises metoprolol succinate in an amount of about 30% to about 70% by the total weight of the dosage form.

## REMARKS

Applicants request reconsideration in view of the amendments above and the remarks below. Claim 1 is amended to improve its form. No new matter is added.

Claims 1-19 are pending.

**Claim Rejections under 35 U.S.C. § 112**

Claims 1-15 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the claim 1 contains trademark "Toprol XL". Applicants have amended claim 1 such that it no longer recites the trademark "Toprol XL," thus overcoming this rejection.

**Claim Rejections under 35 U.S.C. § 103**

**Claims 1-15**

Claims 1-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dharmadhikari *et al.* (WO 2009/087663) in view of Moodley *et al.* (US 2008/0113031). Specifically, the Examiner asserts that Dharmadhikari discloses an extended-release coated discrete units of metoprolol formed by mixing and granulating metoprolol succinate, hydroxypropyl methyl cellulose, lactose, povidone and Eudragit E. Further, the Examiner asserts that Example 1 of Dharmadhikari is bioequivalent to the Toprol® XL tablets and Table 1 discloses metoprolol succinate in an amount of 34.42%. The Examiner acknowledges that Dharmadhikari does not explicitly disclose the extended release dosage form is a capsule. However, the Examiner contends that Moodley discloses a formulation that comprises a capsule containing a plurality of minicapsules; and therefore, it would have been obvious to one of ordinary skill on the art at the time of the invention to modify the extended-release dosage form of Dharmadhikari to be in the form of an extended-release capsule dosage form, as disclosed by Moodley. Applicants traverse.

Dharmadhikari discloses a single-unit system for controlling the release of metoprolol succinate. The single-unit system of Dharmadhikari are produced by compressing uncoated granules into a tablet dosage form and then coating tablet dosage form with water insoluble polymer such as ethyl cellulose.

In contrast, the claimed invention is directed to a multi-unit system (coated discrete units) for controlling release of metoprolol succinate. These coated discrete units deliver active ingredient as independent subunits releasing the active ingredient at a controlled rate. Further, these coated discrete units provide many advantages over single-unit systems because of their small size. If there is damage to the coating of a tablet comprising a sustained release formulation, this can lead to "dose dumping" and result in dramatic side effects. In contrast, in multi-unit system such as coated discrete units, the release characteristics are incorporated into every single subunit and any damage only affects the release behavior of the subunit involved, which represents a small part of the total dose, reducing the likelihood of safety problems.

Table 1 of Dharmadhikari discloses metoprolol succinate in an amount of 34.42 % by weight of drug formulation layer (core weight) and about 22% based on the total formulation weight. The "total weight of the dosage form" in the claimed invention means "weight of core and coating of discrete units, and other excipients present in the capsule" (capsule shell weight is not included in the total weight of formulation). Therefore, the amount of metoprolol succinate in the claimed invention is in the amount of 30-70% by total weight of the formulation, which is higher than the Dharmadhikari tablet. This is further explained in the accompanying Declaration under 37 C.F.R. §1.132 by Dr. Romi Singh ("the Singh Declaration"), an inventor of the instant application.

Dr. Singh states that the amount of metoprolol in the claimed invention (Example 1) is 48.1% based on the total weight of the formulation, which is substantially higher than that of Dharmadhikari. Higher drug content in the formulation would lead to better patient compliance since formulation can be filled in small sized capsule (capsule size 4) and can be easily swallowed. The Singh Declaration, ¶¶ 5-8.

Hence, a person of ordinary skill in the art would not have been motivated to modify the extended release single unit formulation having low drug content of Dharmadhikari to the claimed formulation comprising coated cores, having high drug content.

Moodley is no help. Moodley discloses minicapsules/microcapsules formed by entrapping solubilized/suspended drug particles in a liquid, emulsion, or semi-solid phase inside

the encapsulating medium. These minicapsules are then coated with rate-controlling polymer. Further, Moodley discloses that "drug is released in an already solubilised form which aids absorption" (Moodley at [0214].

The claimed coated discrete units are different from Moodley's minicapsules. The claimed coated discrete units do not involve entrapping drug particles in liquid phase inside the shell, such as gelatin.

Thus, there is no teaching in the cited prior art references that would have motivated the skilled person to change a formulation comprising extended release single unit system to multi-unit system, with a reasonable expectation of success.

Moreover, it is impermissible for an obviousness analysis to use the claimed invention as "a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) (citing *In re Rouffet*, 149 F.3d 1350, 1357-58 (Fed. Cir. 1998)); *Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) (Care must be taken to avoid ***hindsight reconstruction*** by using 'the patent in suits a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit. (Emphasis added)') (quoting *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983)). But the Examiner has done exactly that: neither Dharmadhikari nor Moodley identifies the problem associated with currently available marketed dosage form of metoprolol. The currently marketed product and Dharmadhikari formulation cannot be given to patients having dysphagia since formulation cannot be crushed/chewed due to presence of outer extended release coating. Also, the cited prior art references do not provide any teaching that would lead the skilled artisan to formulate the multi-unit dosage form comprising claimed amount of metoprolol, and thereby reducing the amount of excipients in the formulation and improving patient compliance. ***Thus there is no motivation for a person of ordinary skill in the art to combine the cited references.*** There is also nothing in the disclosure of the cited references that would allow the person skilled in the art to have a reasonable expectation of success of making and using the claimed invention.

Claims 2-15 depend from claim 1 and are patentable over Dharmadhikari in view of Moodley for at least the same reasons that claim 1 is patentable over Dharmadhikari in view of Moodley.

**Claims 16-19**

Claims 16-19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dharmadhikari *et al.* (WO 2009/087663) in view of Moodley *et al.*(US 2008/0113031) and further in view of US 6156342 (Sriwongjanya). The Examiner acknowledges that Dharmadhikari does not disclose sprinkle capsule, wherein the coated discrete units have a particle size from about 0.2 mm to about 2.5 mm. Also, Dharmadhikari does not disclose claimed dissolution profile. However, the Examiner contends that Moodley discloses a formulation that comprises the capsule containing a plurality of minicapsule, wherein minicapsule have a particle size from about 0.2 mm to about 2.5 mm. Hence, the Examiner contends that it would have been obvious to one of the ordinary skill in the art at the time of invention to modify the dissolution profile of extended release sprinkle capsule dosage form as disclosed by Dharmadhikari and Moodley to the dissolution profile as disclosed by Sriwongjanya, with the motivation that this simulates intestinal fluid. Applicants traverse.

A person skilled in the art would not have been motivated to combine the teachings of Dharmadhikari with the teachings of Moodley in view of Sriwongjanya. None of these references discloses the claimed extended-release sprinkle capsule dosage form of metoprolol succinate comprising coated discrete units having the claimed dissolution profile. Moreover, Sriwongjanya discloses *in-vitro* profile of ***tramadol, which belongs to different chemical class of drug***. Unfortunately, what is learned about one controlled release formulated active does not allow the skilled artisan to improve the dissolution rate of another controlled release formulated active. And thus the skilled artisan would ***not*** be motivated to use the disclosure of Sriwongjanya to arrive at the claimed invention with a reasonable expectation of success.

The claimed sprinkle dosage form provides improved patient compliance for geriatric and pediatric patients. Patient compliance is more critical for chronic disease such as hypertension. Hence, the present inventors were surprisingly able to formulate a coated discrete units having

claimed particle size, which can be easily sprinkled and swallowed by the patients having difficulty in swallowing, and the said coated discrete units does not produce bad taste in the mouth when consumed with the soft foods.

Further, the claimed sprinkle capsule produces the desired *in-vitro* extended release profile, without any damage to the extended release coat.

There is a long felt need in the art since the marketed extended release tablet of metoprolol succinate cannot be given to dysphagic or pediatric patients, as the extended release tablets cannot be crushed/chewed, due to extended release coating on the tablet dosage form. Physician Desk Reference of the marketed formulation (Toprol-XL®) mentions "do not crush or chew" the extended release tablets. There is currently no alternate dosage form marketed in the U.S. for these patients.

For at least the foregoing reasons, claims 1-19 are not obvious over the cited references.

**Conclusion**

Authorization is hereby given to charge any fees due or credit any overpayment in connection with this response to Deposit Account No. 500912.

Respectfully submitted,

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