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FORMULATION DEVELOPMENT AND EVALUATION OF OXYMORPHONE HCL SOFT GELATIN CAPSULES

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ABSTRACT
The objective of this work is to develop simple, elegant, liquid-filled immediate release soft gelatin capsules containing Oxymorphone HCl intended for the management of moderate to severe pain in patients who require treatment with an oral opioid analgesic. The present work describes the design of formulation and manufacturing process of Oxymorphone HCl 30 mg capsules. Manufacturing of Oxymorphone HCl Capsules, 30 mg, consists of two concurrent manufacturing processes: gel mass and fill material, which converge during the encapsulation process. Capsule fill material was formulated using tartaric acid and low molecular polyethylene glycol 400 matrix system. The gel mass was prepared in gelatin as shell forming material, and glycerin was used as plasticizer at a 1: 0.5 ratio. The prepared soft gelatin capsules were evaluated for water content in fill material, loss on drying of shell, weight variation, burst strength, assay, and dissolution. The capsules had a fill weight of 350 mg, disintegration time less than 10 minutes, and drug release rate >95% in 20 minutes. Furthermore, Texture analysis showed the capsules had burst strength of 145.0 N with an elasticity value of 3.03 mm. With this we, conclude that Oxymorphone HCl immediate release soft gelatin capsules can be manufactured at commercial scale with similar composition and improved quality attributes of other existing solid dosage forms such as tablets.

KEYWORDS: Oxymorphone HCl, Soft Gelatin Capsules, Encapsulation.

INTRODUCTION
The one-piece softgel capsule features an easy-to-swallow shell that masks taste and smell, and available in a broad range of unique shapes and colors.

Wide varieties of hydrophilic based fill excipients are used to improve the bioavailability of poorly water-soluble compounds, reduce food effects, and improve drug stability. The wide range of shapes and colors available for the shell meet objectives for branding, line extension and lifecycle management. Additionally, softgel capsules offer unparalleled dosage-form flexibility: Encapsulation of a wide variety of fill formulations, wide array of sizes, shapes, colors and forms, oral, topical, ophthalmic and vaginal administration, and softgel capsules address a broad array of formulation challenges, often incorporating a variety of pharmaceutical-approved polar based excipients. Formulation flexibility is a hallmark of softgel formulation and manufacturing technology. Furthermore, it allows multi-fold improvement in bioavailability and reduction of food effect, assures dose uniformity, provides safe handling of low potency API, and constitutes a suitable dosage form for oxygen and/or light sensitive API.[1]

Oxymorphone is an opioid agonist whose principal therapeutic action is analgesia. Oxymorphone is white or slightly off-white, odorless powder and chemically it is a 4, 5α-epoxy-3, 14-dihydroxy-17- methylmorphinan-6-one hydrochloride, molecular formula $C_{17}H_{19}NO_4$ (mol. wt 337.8 g/mol). Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, fentanyl, codeine, hydrocodone, and tramadol. In addition to analgesia, other pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression. Like all pure opioid agonist analgesics, with increasing doses, there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

MATERIALS AND METHODS

Oxymorphone HCl, tartaric acid monohydrate, polyethylene glycol 400, gelatin, glycerin all are commercial grade and obtained from reputed vendors.

Preparation of Oxymorphone HCl Fill Material
Oxymorphone HCl fill material was prepared by dissolving in tartaric acid solution followed by mixing with pre-molted polyethylene glycol 400 and mixed continuously for 35-40 minutes under continuous nitrogen purging. The resultant clear solution was filtered through 10 micron filter and stored in a S.S. vessel until encapsulation. Oxymorphone HCl fill material was prepared with varying amount of tartaric acid, water and polyethylene glycol 400. Formulation details are given in Table 1.

Table 1: Composition of Oxymorphone HCl Fill Material for Oxymorphone HCl Softgel Capsules, 30 mg.

Ingredient(s)	Formulations Code			
	OXY-1 (mg/unit)	OXY-2 (mg/unit)	OXY-3 (mg/unit)	OXY-4 (mg/unit)
Oxymorphone HCl	30.00	30.00	30.00	30.00
Tartaric Acid	3.00	3.25	4.00	4.25
P.Water	60.00	60.00	60.00	60.00
PEG 400	257.00	256.75	256.00	255.75
Total	350.00	350.00	350.00	350.00

Preparation of Gel Mass

Gel formulation was prepared with gelatin and glycerin as a shell forming material and plasticizer at a concentration of 42% and 22%, respectively. Gel mass was prepared by cooking gelatin in a mixture of glycerin and purified water for approximately 65 ± 10 minutes at 80°C until a homogenous mass was obtained. Cooked gelatin mass was deaerated to remove air bubbles. Water content in the gel mass was maintained between 15% - 25% (Target 20%). After the desired water content was achieved, the gelatin mass was discharged to preheated gelatin holding tanks maintained at 60 ± 5°C till encapsulation.[2]

Encapsulation

Oxymorphone HCl soft gelatin capsules, 30 mg were prepared by using rotary die machine (Sky Pharma, Korea). Light mineral oil (Miglyol 812 N) was used for machine and ribbon lubrication as well. Capsules were dried in two stages: primary drying was carried out in tumbles using mineral oil-lecithin solution wetted towels at room temperature for 30-45 minutes in continuous motion and secondary drying was carried out in drying tunnel at controlled temperature (28°C±2°C) and humidity (NMT 25% RH) for 96 hours to achieve the desired moisture content.[3]

EVALUATION OF SOFT GELATIN CAPSULES

The soft gelatin capsules filled with Oxymorphone HCl fill material were subjected to different tests to evaluate for various parameters.[4]

Capsule Description

Physical appearance of the product was visually determined by spreading ten capsules on a clean white surface and inspected for their physical attributes.

Capsule Dimensions

The dimensions of the capsules were measured using a Vernier Caliper.

Weight Variation of Capsules

Weight variation was determined by cUSP general Test Method <95>.[5]

Capsule Shell and Fill Weight

The capsule was sectioned into halves, and the fill material was drained. The shell was wiped with lint free paper towels to remove any remaining fill material before weighing. Capsule fill weight was determined by subtracting the shell weight from the whole capsule weight.

Moisture Content

Moisture content for shell and fill material was determined as below.

Shell Moisture Content

Shell moisture content of softgels was determined according to Test Method FP131G. Softgel capsule shells were sectioned into small pieces, and heated at 105°C for 15 minutes (standard drying) using an O'HAUS Moisture Analyzer. Data was reported as Loss on Drying (LOD), percent weight/weight (%w/w).

Fill Material Moisture Content

The water content in the capsule fill material was determined by Karl Fischer Titration, cUSP <921> Method 1a. Data obtained by this method was noted as "KF".[5]

Capsule Shell Thickness

The capsule shell thickness was measured using a Vernier Caliper.

Capsule Burst Strength

Capsule burst strength (n=6) was performed with the CS225 Chatilon force measurement (Manufacturer: Ametek) fitted with a flat hardness probe 1.5 inch in diameter. The amount of force (N) and distance (mm) the probe traveled until the capsule burst was recorded.

Drug Content

Drug content was determined by opening ten capsules and the fill solution equivalent to 30.0 mg of Oxymorphone HCl, to a 100ml volumetric flask, and add 10 ml acetonitrile adjusted to pH 2.1± 0.05 with orthophosphoric acid then sonicate for 15 minuts. Allow the solution to equilibrate to room temperature. Then centrifuge a portion of sample for 15 minutes. The resulting solution was passed through a 0.45µm membrane filter. Finally drug content was estimated using HPLC (Agilent Technologies) at 280 nm (Mobile phase: Sodium 1-heptanesulfonate in acetonitrile adjusted to pH 2.1± 0.05 with orthophosphoric acid), Column: Zorbax XDB C18, 4.6 X 75 mm, 3.5 microns or equivalent, injection volume: 10 µl).

Dissolution Study

Drug release study was carried out using USP dissolution rate test Apparatus II. The study was carried out at 37±5°C and 50 rpm for 45 minutes in 900 mL of 0.1N HCl. After specified time interval, 10 mL of sample was withdrawn from the vessel. The sample was filtered through 0.45 µm filter and the drug contents were estimated using HPLC at 220 nm, Column: Xterra RP18, 4.6 X 250 mm, 5 microns or equivalent, injection volume: 25 µl).

RESULTS AND DISCUSSION

Evaluation of Oxymorphone HCl Soft Gelatin Capsules, 30 mg revealed that the 14.05 x 3.99 mm dimensional Oblong, transparent softgel capsule contains the active drug Oxymorphone HCl in clear liquid form at a concentration of 30 mg per average fill weight of 352 mg. Physical evaluation showed that the average weight of 10 capsules was 526 mg; shell weight and thickness were 176 mg and 0.85 mm respectively. The moisture content in the fill and shell was 4.00% and 10.0% respectively. Texture analysis showed that the capsules had a burst strength of 132.8 N with an elasticity value of 2.23 mm. Oxymorphone HCl Soft Gelatin Capsules, 30 mg had a potency of 99.6%, 0.04% related compounds. All four Softgel formulations containing varying amount of tartaric acid showed similar physicochemical properties. The drug release rate at 45 minutes was 98.2%. Results are presented in **Table 2**.

Table 2: Evaluation of Oxymorphone HCl Soft Gelatin Capsules

Attribute	Formulations Code			
	OXY-1	OXY-2	OXY-3	OXY-4
Description	Clear transparent oblong capsules containing clear liquid	Clear transparent oblong capsules containing clear liquid	Clear transparent oblong capsules containing clear liquid	Clear transparent oblong capsules containing clear liquid
Dimensions (mm)	14.05 X 3.99	14.15 X 3.89	14.00 X 3.89	14.05 X 4.01
Fill Weight (mg)	350.01	352.00	349.25	355.6
Shell Weight (mg)	175.00	173.25	176.00	175.85
Total Capsule weight (mg)	525.01	525.25	525.25	531.45
Burst Strength (N)	135.6	135.0	138.25	129.85
Elasticity (mm)	2.21	2.23	2.20	2.18
Disintegration Time (min)	<8	<8	<10	<15
Drug Content (%)	98.6	99.8	100.25	100.01
Dissolution (in 15 minutes)	>99	>95	>95	>94

CONCLUSION

The proposed formulation showed optimal drug release, implicating that this method can be used for treatment of moderate to severe pain in patients who required oral mediated opioid analgesic. Furthermore, the proposed formulation shows that Oxymorphone HCl soft gelatin capsules can be prepared on a commercial scale with great viability and improved patient compliance and bioavailability.

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