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Formulation and Evaluation of Risedronated Sodium 150mg Tablet, Optimization at Development Stages of Tablet

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ABSTRACT: Risedronate sodium, a third-generation bisphosphonate used to treat Paget's disease and prevent osteoporotic fractures, will be the subject of this research report. Risedronate decreases bone turnover, increases bone density, and lowers the incidence of non-vertebral and vertebral fractures in individuals with osteoporosis. Treatments for osteoporosis in men, postmenopausal osteoporosis, and osteoporosis caused by glucocorticoids have all been proven to be effective. In order to enable the evaluation, optimisation, and confirmation of the critical product / process parameter identified during the formulation's developmental stage, the process optimisation plan's goal is to monitor the risedronate sodium tablet manufacturing process. This will ensure that the final product, when produced at pilot scale or test batch, will yield consistent results.

KEYWORDS: Nanoprecipitation, osteoporosis, PLGA, polymeric nanoparticles, risedronate sodium.

I. INTRODUCTION

This essay discusses the use of active pharmaceutical ingredients, or "drugs," in the prevention or treatment of illness. An API (active pharmaceutical ingredient) might be liquid, semisolid, or solid. They are seldom given to patients "as is," that is, without additional recipients, because there's a chance the intended outcome won't materialise. It was once believed that recipients were inert in nature; but, in more recent times, it has become widely recognised that recipients can significantly alter the intended effect of a medication. In the pharmaceutical industry, the API and excipient are appropriately processed to create dosage forms as tablets, capsules, suspensions, solutions, etc.Just as crucial as the actual API is the recipients' selection and the way the drug excipient mixture is processed..

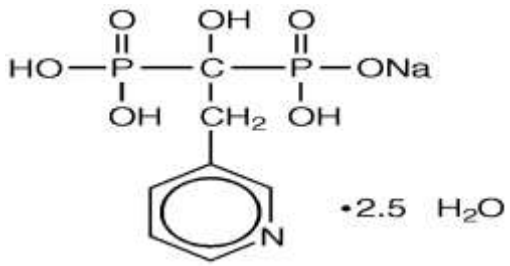
It is possible to increase patient acceptability by managing the organoleptic characteristics. The dosage form delivers the medicine at the appropriate therapeutic level.

The process of selecting the optimal component from a range of accessible options is known as optimisation. Word optimisation in pharmacy is found in the lettarutere, which refers to any research off formula. Pharmacists typically experiment in development projects by following a set of rational processes, meticulously regulating the variables and making adjustments one at a time until desired outcomes are achieved. This is the method used in the pharmaceutical sector for optimisation..

II. DRUG PROFILE

Risedronate Sodium:

Structure:



Systemic (IUPAC) name:[1-hydroxy-2-(3-pyridinyl) ethylidene]bis[phosphonic acid] mono sodium salt.

Chemical data:

Molecular formula - C7H10NO7P2Na •2.5 H2O
Molecular weight - 305.10
Melting point - 252 - 262°C

Physical Description:

Risedronate sodium is a fine white to off-white crystalline powder. Risedronate sodium is present in the form of hemi-pentahydrate with small amounts of monohydrate.

Solubility:

Risedronate sodium is soluble in water, pH 7.0 potassium phosphate dibasic solutions and 0.1 N sodium hydroxide; very

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slightly soluble in 0.1 N hydrochloric acid, practically insoluble in ethanol and insoluble in isopropanol.

Dosing:
One 150 mg tablet orally, taken once-a-month.

Storage:
Store at controlled room temperature 20° to 25° C (68° to 77° F).Store in a safe place out of reach of children's.

Mechanism of action:

The action of risedronate on bone tissue is based partly on its affinity for hydroxyapatite, which is part of the mineral matrix of bone. Risedronate also targets farnesyl pyrophosphate (FPP) synthase. Nitrogen-containing bisphosphonates (such as pamidronate, alendronate, risedronate, ibandronate and zoledronate) appear to act as analogues of isoprenoid diphosphate lipids, thereby inhibiting FPP synthase, an enzyme in the mevalonate pathway. Inhibition of this enzyme in osteoclasts prevents the biosynthesis of isoprenoid lipids (FPP and GGPP) that are essential for the post-translational farnesylation and geranylgeranylation of small GTPase signalling proteins. This activity inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.

Pharmacokinetics

Absorption and bioavailability:

Based on simultaneous modelling of serum and urine data, peak absorption after an oral dose is achieved at approximately 1 hour (Tmax) and occurs throughout the upper gastrointestinal. The fraction of the dose absorbed is independent of dose over the range studied (single dose, from 2.5 mg to 30 mg; multiple dose, from 2.5 mg to 5 mg). Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean absolute oral bioavailability of the 30 mg tablet is 0.63% (90% CI: 0.54% to 0.75%) and is comparable to a solution.

Distribution:

The mean steady-state volume of distribution for risedronate is 13.8 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was in the range of 0.001% to 0.01%.

Metabolism and Excretion:

There is no evidence of systemic metabolism of risedronate. In young healthy subjects, approximately half of the absorbed dose of risedronate was 52 mL/min (CV = 25%), and mean total clearance was 73 mL/min (CV = 15%). excreted in urine within 24 hours, and 85% of an intravenous dose was recovered in the urine over 28 days. Based on simultaneous modelling of serum and urine data, mean renal clearance was 105 mL/min (CV = 34%) and mean total clearance was 122 mL/min (CV = 19%), with the difference primarily reflecting nonrenal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. In osteopenic postmenopausal women, the terminal exponential half-life was 561 hours, mean renal clearance.

Adverse Effects:

Gastrointestinal Adverse Events: A greater percentage of patients experienced diarrhea with Risedronate sodium 150 mg once-a-month compared to 5 mg daily (8.2% vs. 4.7%, respectively). The Risedronate sodium 150 mg once-a-month group resulted in a higher incidence of discontinuation due to abdominal pain upper (2.5% vs. 1.4%) and diarrhea (0.8% vs. 0.0%) compared to the Risedronate sodium 5 mg daily regimen. All of these events occurred within a few days of the first dose. The incidence of vomiting that led to discontinuation was the same in both groups (0.3% vs. 0.3%).

Ocular Adverse Events: None of the patients treated with Risedronate sodium 150 mg once-a-month reported ocular inflammation such as ureitis, scleritis, or iritis.

Laboratory Test Findings: When Risedronate sodium 5 mg daily and Risedronate sodium 150 mg once-a-month were compared in postmenopausal women with osteoporosis, the mean percent changes from baseline at 12 months were 0.1% and 0.3% for serum calcium, -2.3% and -2.3% for phosphate, and 8.3% and 4.8% for PTH,

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respectively. Compared to the Risedronate sodium 5 mg daily regimen, Risedronate sodium 150 mg once-a-month resulted in a slightly higher incidence of hypocalcaemia at the end of the first month of treatment (0.2% vs. 2.2%). Thereafter, the incidence of hypocalcemia with these regimens was similar at approximately 2%.

III. EXCIPIENT PROFILE

Microcrystalline cellulose:

Synonyms:

Avicel 101and 102, Pharmacel, Tabulose, celex, crystalline cellulose

Non Proprietary Name:

BP: Microcrystalline cellulose

Ph Eur: Cellulosam microcrystalline cellulose

JP: Microcrystalline cellulose

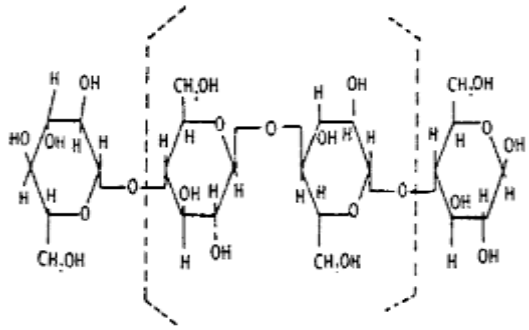
USPNF: Microcrystalline cellulose

Chemical Name: Cellulose

Empherical Formula: $(C_6H_{10}O_5)_n$ (n=220)

Molecular Weight: 3600

Structure:



Functional Category: Tablet and capsule diluents, Tablet disintegrants.

Application:

Widely used in pharmaceuticals primarily as binder or diluents in oral tablets and capsules, in both wet granulation & direct compression process. Also have some lubricant &disintegrants properties that make it useful as tablet.

Tablet disintegrants - 5 – 15% concentration

Tablet binder or diluents - 20- 90 % concentration

Description: Purified, white, odourless, tasteless, crystalline powder composed of porous particles.

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution. Practically insoluble in water, dilute acid in most organic solvents.

Properties: Bulk density: 18-19 lb/ft3

PH: 5- 7

Stability and Storage conditions: Stable through hygroscopic materials. Bulk material should be stored in a well container.

Handling precautions: May be irritant to eyes. Gloves, dust masks eye protections are recommended

CROSPOVIDONE XL:

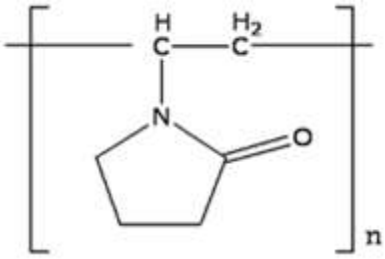
Synonyms:

Crospovidone, crospovidonum, insoluble polyvinyl pyrrolidone and cross linked PVP.

Chemical Name: Cross-linked homopolymer of 1-ethenylpyrrolidin-2-one.

Molecular Formula: $(C_6H_9NO)_n$

Structure:



Description: White, free flowing, compressible powder. A synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidone.

Solubility: Completely insoluble in water, acids, alkalis, and all organic solvents. Hygroscopic. Swells rapidly in water. Rapidly disperses in water, but does not gel even after prolonged exposure.

Chemical Activity: Chemically inert. Has a high adsorptive capacity, forms reversible physical complexes with many molecules without the formation of covalent chemical bonds.

Physical Characteristics:

PH (10% slurry): 5.0 – 8.0

Moisture (Karl-Fisher): £ 5.0%

Parameter of different Polyplasdone XL

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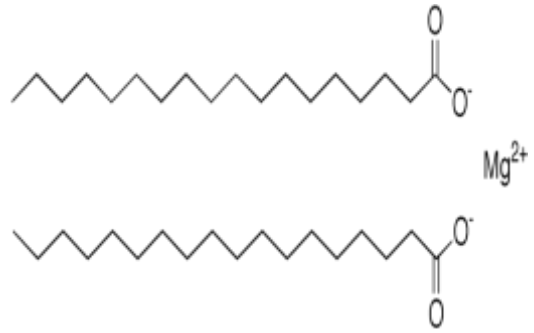
Product	Typical Average Particle size (microns)	Tap Density (g/cc)	Bulk Density (g/cc)
Polyplasdone XL	100	0.3	0.2
Polyplasdone XL-10	30	0.5	0.3
Polyplasdone INF-10	11	0.5	0.4

Applications of cross povidone

Wet granulation	Disintegrant/super-disintegrant
Dry granulation	Greatest rate of swelling compared to other disintegrants
Direct compression	Greater surface area to volume ratio than other disintegrants typically used at a level of 1 to 3%
	Dissolution aid for tablets, capsules and pellets

Magnesium stearate:
Synonyms: Octadecanoic acid, magnesium salt.
Linear Formula: [CH3 (CH2)16CO2]2Mg.
Molecular Weight: 591.24.

Structure:



Functional Category: Tablet and capsule lubricant.
Description: It is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteric taste.

Solubility: Practically insoluble in water, ethanol (~750 g/l), and ether R; slightly soluble in hot ethanol (~750 g/l).

Applications:
Magnesium stearate is often used as an anti adherent in the manufacture of medical tablets, capsules and powders.
In this regard, the substance is also useful, because it has lubricating properties, preventing ingredients from sticking to manufacturing equipment during the compression of chemical powders into solid tablets; magnesium stearate is the most commonly used lubricant for tablets.
Studies have shown that magnesium stearate may affect the release time of the active ingredients in tablets, etc., but not that it reduces the overall bioavailability of those ingredients. As a food additive or pharmaceutical excipient.
Magnesium stearate is also used to bind sugar in hard candies like mints, and is a common ingredient in baby formulas.

IV TRAILS AND EVALUATION

TRIAL 1
Sifting
Sieve Risedronate sodium hemipentahydrate, microcrystalline cellulose USNF (PH 101) and the crospovidone separately through # 30(ASTM, 600µm)
Dry mixing:
Sifted materials loaded to rapid mixer granulate and dry mixing was carried out up to 15 min with impeller at slow speed. 6 point unit dose samples collected in duplicate after 5, 10 and 15 minutes of mixing interwels and submitted for analysis.
Granulation:
The granulating fluid 42%was added over a period of 4 min with impeller at slow speed for 4 min 30 sec, followed by impeller and chopper at slow speed for 1min 30 sec.
Drying:
Drying was carried out at an inlet temperature of 60oc ± 5Oc.in fluidised bed dryer till the loss on drying of granules is 7.5 – 8.5% w/w.
Sifting and Milling:
Dried granules are sifted through #25 (ASTM 710 µm) mesh and retentions milled through multi mill using 1.5 mm screen at slow speed knifes forward action milled granules were sifted through #25(ASTM 710 µm) mesh and retention were milled through 1.0 mm screen at medium speed, knifes forward direction and sifted through #25 mesh(ASTM 710 µm).

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Extra Granular Material Sifting:

Microcrystalline cellulose USNF (PH 102) sifted through #40 mesh (ASTM 710µm).Magnesium stearate was sifted through #60 mesh (ASTM 250 µm).

Blending (Pre lubrication):

Lode the sifted and Milled granules into Octagonal Blender and mix up to 10 min. 10 point unit dose sample collected and duplicated 5,10,15 min of mixing intervel and submitted for analysis.

Blending (Lubrication):

Lode Magnesium stearate to the pre lubricated materials in Octagonal blender and blend for 3, 5 and 7 min.

TRIAL 2

Sifting

Sieve Risedronate sodium hemipentahydrate, microcrystalline cellulose USNF (PH 101) and the crospovidone separately through # 30(ASTM, 600µm)

Dry mixing:

Sifted materials loaded to rapid mixer granulate and dry mixing was carried out up to 15 min with impeller at slow speed. 6 point unit dose samples collected in duplicate after 5, 10 and 15 minutes of mixing intervels and submitted for analysis.

Granulation: The granulating fluid of about 36% was added over a period of 4 min with impeller at slow speed. Kneading was done with impeller at slow speed for 4 min 30 sec, followed by impeller and chopper at slow speed for 1min 30 sec.

Drying :

Drying was carried out at an inlet temperature of 60oc ± 5Oc.in fluidised bed dryer till the loss on drying of granules is 7.5 – 8.5% w/w.

Sifting and Milling:

Dried granules are sifted through #25 (ASTM 710 µm) mesh and retentions milled through multi mill using 1.5 mm screen at slow speed knifes forward action milled granules were sifted through #25(ASTM 710 µm) mesh and retention were milled through 1.0 mm screen at medium speed, knifes forward direction and sifted through #25 mesh(ASTM 710 µm).

Extra Granular Material Sifting:

Microcrystalline cellulose USNF (PH 102) sifted through #40 mesh (ASTM 710µm).Magnesium stearate was sifted through #60 mesh (ASTM 250 µm).

Blending (Pre lubrication):

Lode the sifted and Milled granules into Octagonal Blender and mix up to 10 min. 10 point unit dose sample collected and duplicated 5,10,15 min of mixing intrawel and submitted for analysis.

Blending (Lubrication):

Lode Magnesium stearate to the pre lubricated materials in Octagonal blender and blend for 3, 5 and 7 min.

TRIAL 3

Sifting

Sieve Risedronate sodium hemipentahydrate, microcrystalline cellulose USNF (PH 101) and the crospovidone separately through # 30(ASTM, 600µm)

Dry mixing:

Sifted materials loaded to rapid mixer granulate and dry mixing was carried out up to 15 min with impeller at slow speed. 6 point unit dose samples collected in duplicate after 5, 10 and 15 minutes of mixing interwels and submitted for analysis.

Granulation:

The granulating fluid of about 44% was added over a period of 4 min with impeller at slow speed. Kneading was done with impeller at slow speed for 4 min 30 sec, followed by impeller and chopper at slow speed for 1min 30 sec.

Drying:

Drying was carried out at an inlet temperature of 60oc ± 5Oc.in fluidised bed dryer till the loss on drying of granules is 7.5 – 8.5% w/w.

Sifting and Milling:

Dried granules are sifted through #25 (ASTM 710 µm)mesh and retentions milled through multi mill using 1.5 mm screen at slow speed knifes forward action milled granules were sifted through #25(ASTM 710 µm) mesh and retention were milled through 1.0 mm screen at medium speed, knifes forward direction and sifted through #25 mesh(ASTM 710 µm).

Extra Granular Material Sifting:

Microcrystalline cellulose USNF (PH 102) sifted through #40 mesh (ASTM 710µm).Magnesium stearate was sifted through #60 mesh (ASTM 250 µm).

Blending (Pre lubrication):

Lode the sifted and Milled granules into Octagonal Blender and mix up to 10 min. 10 point

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unit dose sample collected and duplicated 5,10,15 min of mixing intervel and submitted for analysis.

Blending (Lubrication):
Lode Magnesium stearate to the pre lubricated materials in Octagonal blender and blend for 3, 5 and 7 min.

TRIAL 4
Sifting
Sieve Risedronate sodium hemipentahydrate, microcrystalline cellulose USNF (PH 101) and the crospovidone separately through # 30(ASTM, 600µm)
Dry mixing:
Sifted materials loaded to rapid mixer granulate and dry mixing was carried out up to 15 min with impeller at slow speed. 6 point unit dose samples collected in duplicate after 5, 10 and 15 minutes of mixing interwels and submitted for analysis.
Granulation: The granulating fluid of about 42% was added over a period of 4 min with impeller at slow speed. Kneading was done with impeller at slow speed for 4 min 30 sec, followed by impeller and chopper at slow speed for 1min 30 sec.
Drying:
Drying was carried out at an inlet temperature of 60oc ± 5Oc.in fluidised bed dryer till the loss on drying of granules reaches below 7.5

Sifting and Milling:
Dried granules are sifted through #25 (ASTM 710 µm) mesh and retentions milled through multi mill using 1.5 mm screen at slow speed knifes forward action milled granules were sifted through #25(ASTM 710 µm) mesh and retention were milled through 1.0 mm screen at medium speed, knifes forward direction and sifted through #25 mesh(ASTM 710 µm).

Extra Granular Material Sifting:
Microcrystalline cellulose USNF (PH 102) sifted through #40 mesh (ASTM 710µm).Magnesium stearate was sifted through #60 mesh (ASTM 250 µm).
Blending (Pre lubrication):
Lode the sifted and Milled granules into Octagonal Blender and mix up to 10 min. 10 point unit dose sample collected and duplicated 5,10,15 min of mixing intervel and submitted for analysis.
Blending (Lubrication):
Lode Magnesium stearate to the pre lubricated materials in Octagonal blender and blend for 3, 5 and 7 min.

TRIAL 5
Sifting
Sieve Risedronate sodium hemipentahydrate, microcrystalline cellulose USNF (PH 101) and the crospovidone separately through # 30(ASTM, 600µm)

Dry mixing:
Sifted materials loaded to rapid mixer granulate and dry mixing was carried out up to 15 min with impeller at slow speed. 6 point unit dose samples collected in duplicate after 5, 10 and 15 minutes of mixing interwels and submitted for analysis.

Granulation:
The granulating fluid of about 42% was added over a period of 4 min with impeller at slow speed. Kneading was done with impeller at slow speed for 4 min 30 sec, followed by impeller and chopper at slow speed for 1min 30 sec.

Drying:
Drying was carried out at an inlet temperature of 60oc ± 5Oc.in fluidised bed dryer till the loss on drying of granules is >8.5% w/w.

Sifting and Milling:
Dried granules are sifted through #25 (ASTM 710 µm)mesh and retentions milled through multi mill using 1.5 mm screen at slow speed knifes forward action milled granules were sifted through #25(ASTM 710 µm) mesh and retention were milled through 1.0 mm screen at medium speed, knifes forward direction and sifted through #25 mesh(ASTM 710 µm).

Extra Granular Material Sifting:
Microcrystalline cellulose USNF (PH 102) sifted through #40 mesh (ASTM 710µm).Magnesium stearate was sifted through #60 mesh (ASTM 250 µm).

Blending (Pre lubrication):
Lode the sifted and Milled granules into Octagonal Blender and mix up to 10 min. 10 point unit dose sample collected and duplicated 5,10,15 min of mixing intervel and submitted for analysis.

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Blending (Lubrication):
Lode Magnesium stearate to the pre lubricated materials in Octagonal blender and blend for 3, 5 and 7 min.

TRIAL 6
Sifting
Sieve Risedronate sodium hemipentahydrate, microcrystalline cellulose USNF (PH 101) and the crospovidone separately through # 30(ASTM, 600µm)

Dry mixing:
Sifted materials loaded to rapid mixer granulate and dry mixing was carried out up to 15 min with impeller at slow speed. 6 point unit dose samples collected in duplicate after 5, 10 and 15 minutes of mixing interwels and submitted for analysis.

Granulation:The granulating fluid of about 42% was added over a period of 4 min with impeller at slow speed. Kneading was done with impeller at slow speed for 6 min , followed by impeller and chopper at slow speed for 1min 30 sec.

Drying:
Drying was carried out at an inlet temperature of 60oc ± 5Oc.in fluidised bed dryer till the loss on drying of granules is 7.5 – 8.5% w/w.

Sifting and Milling:
Dried granules are sifted through #25 (ASTM 710 µm)mesh and retentions milled through multi mill using 1.5 mm screen at slow speed knifes forward action milled granules were sifted through #25(ASTM 710 µm) mesh and retention were milled through 1.0 mm screen at medium speed, knifes forward direction and sifted through #25 mesh(ASTM 710 µm).

Extra Granular Material Sifting:
Microcrystalline cellulose USNF (PH 102) sifted through #40 mesh (ASTM 710µm).Magnesium stearate was sifted through #60 mesh (ASTM 250 µm).

Blending (Pre lubrication):
Lode the sifted and Milled granules into Octagonal Blender and mix up to 10 min. 10 point unit dose sample collected and duplicated 5,10,15 min of mixing intervel and submitted for analysis.

Blending (Lubrication):
Lode Magnesium stearate to the pre lubricated materials in Octagonal blender and blend for 5 min.

TRIAL 7
Sifting
Sieve Risedronate sodium hemipentahydrate, microcrystalline cellulose USNF (PH 101) and the crospovidone separately through # 30(ASTM, 600µm)

Dry mixing:
Sifted materials loaded to rapid mixer granulate and dry mixing was carried out up to 15 min with impeller at slow speed. 6 point unit dose samples collected in duplicate after 5, 10 and 15 minutes of mixing interwels and submitted for analysis.

Granulation:
The granulating fluid of about 42% was added over a period of 4 min with impeller at slow speed. Kneading was done with impeller at slow speed for 3min, followed by impeller and chopper at slow speed for 1min 30 sec.

Drying:
Drying was carried out at an inlet temperature of 60oc ± 5Oc.in fluidised bed dryer till the loss on drying of granules is 7.5 – 8.5% w/w.

Sifting and Milling:
Dried granules are sifted through #25 (ASTM 710 µm)mesh and retentions milled through multi mill using 1.5 mm screen at slow speed knifes forward action milled granules were sifted through #25(ASTM 710 µm) mesh and retention were milled through 1.0 mm screen at medium speed, knifes forward direction and sifted through #25 mesh(ASTM 710 µm).

Extra Granular Material Sifting:
Microcrystalline cellulose USNF (PH 102) sifted through #40 mesh (ASTM 710µm).Magnesium stearate was sifted through #60 mesh (ASTM 250 µm).

Blending (Pre lubrication):
Lode the sifted and Milled granules into Octagonal Blender and mix up to 10 min. 10 point unit dose sample collected and duplicated 5,10,15 min of mixing intrawel and submitted for analysis.

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Blending (Lubrication): Lode Magnesium stearate to the pre lubricated materials in Octagonal blender and blend for 3, 5 and 7 min.

TRIAL 8

Sifting

Sieve Risedronate sodium hemipentahydrate, microcrystalline cellulose USNF (PH 101) and the crospovidone separately through # 30(ASTM, 600µm)

Dry mixing:

Sifted materials loaded to rapid mixer granulate and dry mixing was carried out up to 15 min with impeller at slow speed. 6 point unit dose samples collected in duplicate after 5, 10 and 15 minutes of mixing interwels and submitted for analysis.

Granulation: The granulating fluid of about 42% was added over a period of 4 min with impeller at slow speed. Kneading was done with impeller at slow speed for 4 min 30 sec, followed by impeller and chopper at slow speed for 1min 30 sec.

Drying:

Drying was carried out at an inlet temperature of 60oc ± 5Oc.in fluidised bed dryer till the loss on drying of granules is 7.5 – 8.5% w/w.

Sifting and Milling:

Dried granules are sifted through #25 (ASTM 710 µm)mesh and retentions milled through multi mill using 1.5 mm screen at slow speed knifes forward action milled granules were sifted through #25(ASTM 710 µm) mesh and retention were milled through 1.0 mm screen at medium speed, knifes forward direction and sifted through #25 mesh(ASTM 710 µm).

Extra Granular Material Sifting:

Microcrystalline cellulose USNF (PH 102) sifted through #40 mesh (ASTM 710µm).Magnesium stearate was sifted through #60 mesh (ASTM 250 µm).

Blending (Pre lubrication):

Lode the sifted and Milled granules into Octagonal Blender and mix up to 10 min. 10 point unit dose sample collected and duplicated 5,10,15 min of mixing intervel and submitted for analysis.

Blending (Lubrication):

Lode Magnesium stearate to the pre lubricated materials in Octagonal blender and blend for 3, min.

TRIAL 9

Sifting

Sieve Risedronate sodium hemipentahydrate, microcrystalline cellulose USNF (PH 101) and the crospovidone separately through # 30(ASTM, 600µm)

Dry mixing:

Sifted materials loaded to rapid mixer granulate and dry mixing was carried out up to 15 min with impeller at slow speed. 6 point unit dose samples collected in duplicate after 5, 10 and 15 minutes of mixing interwels and submitted for analysis.

Granulation:

The granulating fluid of about 42% was added over a period of 4 min with impeller at slow speed. Kneading was done with impeller at slow speed for 4 min 30 sec, followed by impeller and chopper at slow speed for 1min 30 sec.

Drying:

Drying was carried out at an inlet temperature of 60oc ± 5Oc.in fluidised bed dryer till the loss on drying of granules is 7.5 – 8.5% w/w.

Sifting and Milling:

Dried granules are sifted through #25 (ASTM 710 µm)mesh and retentions milled through multi mill using 1.5 mm screen at slow speed knifes forward action milled granules were sifted through #25(ASTM 710 µm) mesh and retention were milled through 1.0 mm screen at medium speed, knifes forward direction and sifted through #25 mesh(ASTM 710 µm).

Extra Granular Material Sifting:

Microcrystalline cellulose USNF (PH 102) sifted through #40 mesh (ASTM 710µm).Magnesium stearate was sifted through #60 mesh (ASTM 250 µm).

Blending (Pre lubrication):

Lode the sifted and Milled granules into Octagonal Blender and mix up to 10 min. 10 point unit dose sample collected and duplicated 5,10,15 min of mixing intervel and submitted for analysis.

Blending (Lubrication):

Lode Magnesium stearate to the pre lubricated materials in Octagonal blender and blend for 3, 5 and 7 min.

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V RESULTS AND DISCUSSIONS:

PHYSICAL PROPERTIES OF GRANULES FOR DIFFERENT TRAIL BATCHES RISEDRONATE SODIUM TABLETS 150 mg (US/CANADA):

BATCH NO	MESH SIZE							BD (g/ml)	TD (g/ml)	CI (%)	HR
	20	40	60	80	100	120	200				
	% CUMULATIVE RETENTIONS										
RST01	5.30	5.90	33.50	45.50	54.80	55.80	57.80	0.573	0.786	27.143	1.372
RST02	8.00	9.00	32.00	44.30	52.30	64.60	66.20	0.559	0.750	25.373	1.340
RST03	12.60	13.90	44.90	56.50	65.10	66.10	67.10	0.526	0.802	28.125	1.391
RST04	2.77	15.93	24.02	24.94	63.81	63.73	73.19	0.593	0.787	24.657	1.327
RST05	5.50	19.25	28.25	32.75	64.75	65.75	75.00	0.588	0.754	22.059	1.028
RST06	4.25	12.50	34.50	44.75	56.25	56.75	73.50	0.571	0.769	25.714	1.34
RST07	13.50	15.25	39.00	26.00	43.75	44.00	58.00	0.594	0.759	21.739	1.278
RST08	8.25	20.75	37.50	40.00	61.50	76.25	88.50	0.579	0.769	24.638	1.327
RST09	8.50	23.00	37.75	47.75	62.25	71.25	88.50	0.579	0.769	24.638	1.327

DISCUSSIONS

The physical properties of granules were studied performing Bulk Density, Tapped Density ,Carr's Insex Hausner,s Ratio and partile size distrubution

The flow properties and sticking nature of tablets is cleared by increasing the kneeding time and increasing the fluid uptake

BLEND UNIFORMITY

DRY MIXING OPTIMIZATION FOR DIFFERENT TRAIL BATCHES

LOCATION	TRAIL 1			TRAIL 9
	5MIN	10MIN	15MIN	10MIN
1	100.7	101	102.1	97.6
2	102.8	101.5	101.5	98.1
3	102.7	101.5	100.7	98.7
4	100.7	102.0	101.0	98.7
5	101.2	101.4	102.8	97.9
6	101.8	100.8	100.9	98.5
AVERAGE	101.7	101.4	101.5	98.3
MINIMUM	100.7	100.8	100.7	97.6
MAXIMUM	102.8	102.0	102.8	98.7
R S D	0.94	0.42	0.81	0.45

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DISCUSSION:

In the trail 1 the prelubrication is carried out for 5, 10, 15 min . based on the R s d The prelubrication was optimized to 10min

In these the trails 1 and 9 were represented where trail 1 shows the results of various timing for optimisation and trail 9 which shows the best pre lubrication time

PRE LUBRICATION

Pre lubrication optimisation for different trail batches

LOCATION	TRAIL 1			TRAIL 9
	5MIN	10 MIN	15MIN	10 MIN
1	99.5	100.6	99.1	98.5
2	98.6	101.2	99.2	99.7
3	101.1	100.2	99.3	99.9
4	99.9	99.5	99.6	100.1
5	99.1	100.3	99.8	99.9
6	101.2	99.7	99.7	99.8
7	99.6	99.7	99.3	100.6
8	100.9	99.7	99.8	99.7
9	100.1	99.9	100.0	97.9
10	100.2	100.6	99.9	100.7
AVERAGE	100.02	100.14	99.57	99.88
MINIMUM	98.6	99.5	99.1	97.9
MAXIMUM	101.2	101.2	100	100.7
R S D	0.86	0.54	0.32	0.59

DISCUSSION

In trail1 the prelubrication is carried out or 5, 10, 15 min . Based on the R s d The pre lubrication time is optimised to 10 min

In the table 18 the trail 1 and 9 were represented Where trail 1 shows the results various timing for optimisation and trail 9 which shows the best pre lubrication time

LUBRICATION

LUBRICATION OPTIMIZATION FOR DIFERENT BATCHES

S NO	TRAIL 1			TRAIL 9
	3MIN	5 MIN	7 MIN	5 MIN
1	97.7	105	108	103
2	99.3	101.2	105	100.8
3	100.1	103	103	103
4	99.7	93	93	94
5	100.9	102.2	102.2	101.2
6	100.7	95	95	96
7	97.1	104.4	104.4	103
8	100.4	100.4	100.4	100.4
9	97.4	103.1	103.1	99.3
10	99.3	93	96	102
AVERAGE	99.3	100.3	101.71	99
MINIMUM	97.1	93	103	94
MAXIMUM	100.9	104.4	108	103
R S D	1.39	4.62	5.3	4.57

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DISCUSSION:

In trail 1 the lubrication is carried out for 3, 5, 7 min. Based on the R s d the lubrication time is optimized to 5 min In the Table 19 The trail 1 and 9 were represented where trail 1 shows the results of various timing for optimization and the trail 9 which shows the best lubrication time

TABLET COMPRESSION PARAMETERS OF DIFFERENT TRAILS

Discussions

Hardness studies were performed to check the minimum and maximum limits of the various parameters like average weight ,weight uniformity hardness thickness Friability and DT

RISEDRONATE SODIUM TABLETS 150 mg (US/CANADA): HARDNESS

BATCH NO		1	2	3	4	5	6	7	8	9	10
RST01	US	15.2	15.4	15.3	16.4	15.8	17.0	16.5	14.5	17.1	16.4
	CANADA	14.5	15.3	15.4	15.8	17.1	17.5	16.2	16.5	15.3	14.6
RST02	US	14.5	14.2	14.8	15.8	15.3	17.1	16.9	15.1	16.3	15.5
	CANADA	15.1	14.6	15.2	15.8	15.3	16.3	14.3	17.7	15.2	16.2
RST03	US	14.4	14.4	12.1	13.5	15.2	13.3	14.8	14.7	13.4	13.6
	CANADA	13.7	14.2	14.3	14.7	15.2	14.4	14.3	14.1	13.9	14.3
RST04	US	15.2	15.4	15.3	16.4	15.8	17.0	16.5	14.5	17.1	16.5
	CANADA	14.5	15.3	15.4	15.8	17.1	17.5	16.2	16.5	15.3	14.6
RST05	US	14.5	14.2	14.8	15.8	15.3	17.1	16.9	15.1	16.3	15.5
	CANADA	15.1	14.6	15.2	15.8	15.3	16.3	14.3	17.7	15.2	16.4
RST06	US	15.4	15.6	15.7	15.8	16.7	18.3	15.7	17.1	16.2	15.5
	CANADA	14.9	15.7	16.3	15.0	15.0	16.9	15.5	14.1	15.4	15.5
RST07	US	14.4	14.4	12.1	13.5	15.2	13.3	14.8	14.7	13.4	13.3
	CANADA	13.7	14.2	14.3	14.7	15.2	14.4	14.3	14.1	13.9	14.2
RST08	US	16.4	16.7	17.0	14.9	16.1	16.5	17.6	17.4	17.4	18.0
	CANADA	14.0	15.1	15.2	15.1	14.0	16.0	15.6	14.5	14.8	13.9
RST09	US (OPTIMUM)	16.4	16.7	17.0	14.9	16.1	16.5	17.6	17.4	17.4	18.0
	LOW	11.2	11.5	10.9	10.5	11.2	10.5	11.9	11.0	12.0	11.1
	HIGH	18.9	19.2	19.1	18.5	18.6	19.2	19.6	20.1	20.5	19.5
	CANADA (OPTIMUM)	14.0	15.1	15.2	15.1	14.0	16.0	15.6	14.5	14.8	13.9
	LOW	10.9	11.2	11.3	11.6	12.0	11.9	11.9	11.6	11.9	11.5
	HIGH	18.9	19.6	19.9	18.6	17.9	20.0	20.0	19.9	19.8	20.0

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RISEDRONATE SODIUM TABLETS 150 mg (US/CANADA): THICKNESS

BATCH NO		1	2	3	4	5	6	7	8	9	10
RST01	US	3.66	3.56	3.52	3.55	3.59	3.58	3.62	3.62	3.59	3.67
	CANADA	3.81	3.77	3.79	3.78	3.79	3.80	3/74	3.75	3.73	3.76
RST02	US	3.56	3.56	3.51	3.55	3.56	3.54	3.52	3.59	3.55	3.56
	CANADA	3.57	3.60	3.59	3.64	3.69	3.71	3.69	3.67	3.68	3.71
RST03	US	3.65	3.65	3.64	3.66	3.63	3.65	3.63	3.58	3.64	3.62
	CANADA	3.71	3.64	3.68	3.68	3.67	3.67	3.65	3.76	3.64	3.73
RST04	US	3.62	3.51	3.56	3.56	3.55	3.58	3.60	3.62	3.56	3.57
	CANADA	3.80	3.77	3.80	3.79	3.79	3.81	3.78	3.74	3.72	3.75
RST05	US	3.49	3.41	3.46	3.42	3.45	3.54	3.51	3.46	3.45	3.47
	CANADA	3.57	3.60	3.59	3.64	3.69	3.71	3.669	3.67	3.68	3.71
RST06	US	3.65	3.65	3.64	3.66	3.63	3.65	3.63	3.58	3.64	3.62
	CANADA	3.78	3.79	3.72	3.76	3.76	3.76	3.75	3.72	3.76	3.76
RST07	US	3.53	3.52	3.52	3.52	3.56	3.53	3.51	3.51	3.50	3.50
	CANADA	3.71	3.64	3.68	3.68	3.67	3.67	3.65	3.76	3.64	3.73
RST08	US	3.60	3.56	3.57	3.51	3.56	3.54	3.55	3.54	3.53	3.62
	CANADA	3.82	3.78	3.75	3.81	3.82	3.77	3.85	3.81	3.83	3.79
RST09	US (OPTIMUM)	3.79	3.75	3.76	3.77	3.77	3.77	3.78	3.76	3.77	3.82
	LOW	3.79	3.80	3.81	3.79	3.81	3.78	3.76	3.79	3.80	3.79
	HIGH	3.45	3.44	3.53	3.46	3.53	3.47	3.45	3.51	3.45	3.46
	CANADA (OPTIMUM)	3.80	3.79	3.81	3.77	3.81	3.80	3.79	3.80	3.75	3.79
	LOW	3.86	3.88	3.89	3.91	3.82	3.86	3.85	3.81	3.86	385
	HIGH	3.56	3.62	3.65	3.58	3.60	3.59	3.61	3.59	3.58	3.62

DISSOLUTION RATE PROFILE
Dissolution profile of RSDT10001

DISCUSSION

In these trail there is no effect on the dissolution rate Flow properties is less so it can be increased by increasing or decreasing fluid up take

Invitro dissolution studies

S No	TIME	%CDR
1	5	92
2	10	97
3	15	98

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4	20	99
5	30	100
6	45	101
7	60	102

DISSOLUTION PROFILE OF RSDT10002

In vitro dissolution studies of risedronate sodium

S No	TIME	%CDR
1	5	46
2	10	58
3	15	80
4	20	93
5	30	99
6	45	101
7	60	102

DISCUSSION

In these trail the dissolution studies are studied due to less fluid up take

In these trail flow properties of granules is less hence the release of drug is retarded

Hence fluid up take should be increased

RSDT1003

TIME	%CDR
5	36
10	64
15	93
20	98
30	101
45	101
60	102

DISCUSSION

In these trails The fluid content is more

The granules obtained are moistened in nature

DISSOLUTION PROFILE OF RSDT10004

S No	TIME	%CDR
1	5	32
2	10	38
3	15	45

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4	20	50
5	30	63
6	45	86
7	60	98

DISCUSSION
In These work is done on Loss on drying Physical parameters are effected

DISSOLUTION PROFILE OF RSDT10005

S No	TIME	%CDR
1	5	69
2	10	84
3	15	91
4	20	97
5	30	102
6	45	102
7	60	103

DISCUSSION
In these trail is performed by incresin the lod Moisture content is more No effect in dissolution

DISSOLUTION PROFILE OF RSDT10006

TIME	%CDR
5	73
10	80
15	92
20	98
30	101
45	102
60	103

VI CONCLUSION

After completion the data generated during the process optimazation of Riscdronate Sodium 150 mg studied and results shows that critical parameters identified at development stages of formulation were reproducing at process optimazation batches how ever following changes are recommended

- Drymix prelubriation and lubrication time optimized
- Kneeding times was increased to over sticking problems
- LOD must be with in the limits 7-8.5% to prevent physical disappearance

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