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Research

FORMULATION AND EVALUATION OF EXTENDED RELEASE OSELTAMIVIR CAPSULES 75 MG

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Abstract

The current research work predicts the applicability of QbD in manufacturing Oseltamivir Capsules 75 mg ER Capsules by using rate delaying polymers. From the outcomes it was clearly apparent that as the polymer concentration increases, there was a decline in the release of drug. Grouping of polymers with other excipients do not interact with drug and vice versa, which information to sustained delivery of drug for longer periods. The enhanced formulation from factorial design can be used as a single dose per day in the organization of HIV/AIDS.Wet granulation procedure was the chosen technology for the preparation of Oseltamivir phosphate capsule. Based on the preliminary studies, different formulation trials (F1-F7) were carried out with different concentrations of disintegrants, diluents. From the various formulations it was decided that the formulation batch of F7 was finalized as the optimized formula. Formulation F7 showed satisfactory results with various physicochemical evaluation parameters like Disintegration time, Dissolution profile, Assay when matched with that of the marketed product. The stability studies at all condition, indicates that the formulated capsules were found to be stable. Hence, it is finally concluded that, Oseltamivir phosphate capsules are pharmaceutically comparable, low cost, quality improved and stable formulation.

Keywords: Oseltamivir Capsules, Formulation, Evaluation, Extended release, HIV/AIDS.

INTRODUCTION

Many drugs can be administered orally as liquids, capsules, tablets, or chewable tablets. Because the oral route is the most convenient and usually the safest and least expensive, it is the one most often used. However, it has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption may begin in the mouth and stomach. However, most drugs are usually absorbed from the small intestine. The drug passes through the intestinal wall and travels to the liver before being transported via the bloodstream to its target site. The intestinal wall and liver chemically alter (metabolize) many drugs, decreasing the amount of drug reaching the bloodstream. Consequently, these drugs are often given in smaller

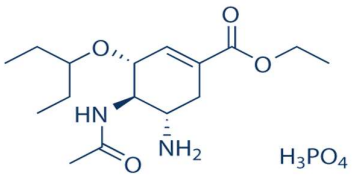
doses when injected intravenously to produce the same effect.When a drug is taken orally, food and other drugs in the digestive tract may affect how much of and how fast the drug is absorbed. Thus, some drugs should be taken on an empty stomach, others should be taken with food, others should not be taken with certain

Viral Infections and Antiviral Drugs: Viral infections are caused by pathogenic viruses that invade host cells and replicate, leading to disease. Viruses can infect various tissues and organs in the body, causing a wide range of symptoms and health complications.
Transmission: Viruses can spread through various routes, including respiratory droplets, direct contact with infected individuals, contaminated surfaces, or through vectors such as mosquitoes or ticks.
Antiviral Drugs: Antiviral drugs are medications that inhibit the replication of viruses or suppress their ability to infect host cells. They are used for the treatment and prevention of viral infections.
Mechanism of Action: Antiviral drugs target specific steps in the viral replication cycle, such as viral attachment, entry, genome replication, protein synthesis, or viral release. By interfering with these processes, antiviral drugs can inhibit viral replication and reduce viral load in the body.
Design of Experiment (DoE): Design of Experiment (DoE) is a systematic and statistical method used to plan, conduct, analyze, and interpret controlled tests to evaluate the factors that may influence a particular outcome or process. DoE aims to identify cause-and-effect relationships and optimize processes by systematically varying the input variables and analyzing their effects on the output.Anti-viral drug Oseltamivir is a neuraminidase inhibitor used in the treatment and prophylaxis of both influenza A and influenza B.
Extended Release Formulations: Extended release tends to release the active substance over a long period of time. Maintaining theplasma-drug concentration in the body. Theseextendedrelease dosage forms might take time to kick in when compared to it's immediate release oral dosage forms but maintain a more consistent level in the body. This ensures better treatment outcomes for longer periods of time with reducing the chances of side effects.
Advantages of Extended Release Dosage Formulations: It improves patient compliance, because a patient doesn't have to remember to consume multiple pills over the course of a day.
It may reduce adverse side effects or even the risk of seizures by limiting the intensity of the drug after the initial dose.

MATERIALS AND METHODS

Materials: Oseltamivir Phosphate Pregelatinized starch,
Povidone, talc**,** Sodium Stearyl Fumarate, Dehydrated Alcohol, Sifter, RMG, FBD, Multi millOctagonal blender, Pharma **Capsule** Fillers, Capsule dedusting Machine and polishing machineMetal detector, Moisture analyzer, Bulk density apparatus

DRUG PROFILE
Oseltamivir, commonly known by the brand name Tamiflu, is an antiviral medication used to treat and prevent influenza A and B. The 75 mg capsule is the standard dosage form for adults and adolescents.



Chemical Name: Oseltamivir phosphate, **Molecular Formula:** C16H28N2O4 (oseltamivir base), **Molecular Weight:** 312.4 g/mol (oseltamivir base), 410.4 g/mol (oseltamivir phosphate)
Experimental Methodology:
Representation of the in process test during the formulation and manufacturing of the product:
Selection of Raw materials during formation of the product: All the excipient used are well known and widely used as pharmaceutical Excipients in oral solid formulations and comply with the relevant pharmacopoeia monographs. Compatibility studies were conducted to investigate and predict physicochemical interaction between drug substance and excipients and consequently excipient.
Manufacturing Process: Steps involves in manufacturing process:Following steps are involves in the manufacturing process involving usage appropriate equipments: Dispensing of the raw material, Dry mixing and granulation, Blending Lubrication, Filling
Environmental condition: Like temperature, relative humidity and differential pressures needs to monitored during the entire manufacturing activity before giving line clearance and during activity. The observations were

found within the limits mentioned in batch record .(i. NMT Temperature NMT 25 ºC , RH NMT65 % and Pressure difference .0-4.0 mm of wc)

Dispensing: All raw material are used un the batches are dispensed as per the approved standard procedure and defined batch record and each stage is recorded in the batch record .
Sifting: Sifting of raw material is done as per the batch record using the mesh #20 during activity and same is recorded in the batch record. Integrity of the batch is cheeked before and after sifting.
Dry Mixing: Dry mixing is done in rapid mixture granulator for 20 minutes with impeller slow speed and chopper at "OFF" mode
Wet granulation: Is done addition of the purified water into the RMG to form the granules and get the desired content of mass and drug.
Drying: The wet mass air dried for 10 minutes to ensure fluidization in FBD. Dried at the inlet temperature of 60± 5ºC till the loss of drying reached in the range of NMT 2.0% at 105ºC in the moisture analyzer.
Sifting and Milling: The dried granules are sifted through mesh #30 and the retension are milled through Multimill with 1.5 mm screen at slow/ speed/ knives forward direction and sifted through mesh # 30.
Lubrication: Extra granular material – magnesium stearate sifted through mesh # 60 and loaded into the octagonal blender and rotated at 10 minute at 10 RPM and after blending sample is tested from 10 different location for the blend uniformity
Capsule filling: Fill the blend in the capsule cap and body
Following steps are involves in the manufacturing process involving usage appropriate equipments: Sifting, Dry Mixing, Paste preparation and Granulation, Drying, Milling, Lubrication, Capsule filling.

EXPERIMENTAL DESIGN FOR THE FORMULATION
Pharmaceutical Assessments: Determination of Bulk and Tapped Density :Tapped density : Tapped density of a powder is the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time. The tapped density of a powder represents its random dense packing. Tapped density can be calculated using equation :
where M=mass in grams, and Vf=the tapped volume in milliliters.
Tapped **Density(g/mL)=M / Vf**

Bulk density: The term bulk density refers to a measure used to describe a packing of particles or granules and the term Tapped density refers to the true density of the particles or granules

$$Bulk\ Density = \frac{Weight\ of\ power\ taken}{Bulk\ Volume\ of\ powder} = \frac{10}{\pi r^2 h_s}$$

Determination of Carr,s Compression Index
Flow Properties according to angle of repose comes under that range 0–90º. Carr Index of any solid is calculated for compressibility of a powder which is based on true density (ρT) and bulk density
(ρB), CI=100[(ρT–ρB)/ρB].
Determination The Hausner Ratio
The Hausner Ratio of a material is calculated with the following formula :
H = ρ tapped /ρ bulk
H : Hausner Ratio , ρ tapped : the tapped bulk density of the material (kg/m3) , ρ bulk : the loose bulk density of the material (kg/m3)

Interpretation and relation to flowability of Carr index and Hausner
Procedure for Wet Granulation Method:
Weighing of Ingredients: Weigh the required amounts of oseltamivir phosphate active pharmaceutical ingredient (API), binder (Povidone K-30), and other excipients according to the formulation recipe.
Mixing: Blend the Oseltamivir API, binder, and other excipients in a Rapid misture granulator until homogenously mixed.
Preparation of Binder Solution: Prepare a binder solution by dissolving the binder (e.g., hydroxypropyl cellulose) in purified water or an appropriate solvent (e.g., isopropyl alcohol) under stirring until complete dissolution.
Wet Massing: Slowly add the binder solution to the blended powder mixture while mixing continuously until a damp, granular mass is formed. Adjust the addition rate to achieve optimal granulation.**Wet Screening:** Pass the wet granules through a wet screen or sieve with an appropriate mesh size (e.g., 10-20 mesh) to break up large aggregates and obtain uniformly sized granules.

Drying: Spread the wet granules evenly on trays and dry them in a fluid bed dryer at a controlled temperature (40-60°C) until the moisture content is reduced to the desired level.
Milling: Mill the dried granules using a multi mill to achieve the desired particle size distribution and improve flow properties.
Sieving: Pass the milled granules through a sieve with an appropriate mesh size #20 to remove any oversized or undersized particles and ensure uniformity.
Lubrication (Optional): If necessary, add a lubricant (e.g., magnesium stearate) to the granules and blend them in a suitable mixer (e.g., double cone blender) until homogeneously distributed.
Compression: Finally, compress the lubricated granules into extended-release oseltamivir 75 mg capsules using a suitable tablet compression machine equipped with appropriate tooling (e.g., capsule filling machine, rotary tablet press).
Quality Control: Perform quality control tests on the finished capsules, including weight variation, disintegration time, drug content uniformity, and dissolution rate, to ensure they meet specified quality standards.
Packaging: Package the finished capsules in suitable containers (e.g., blister packs, HDPE bottles) and label them with necessary information, including dosage strength, batch number, expiration date, and storage conditions.
Evaluation Tests: Weight Variation Test, MethodWeighing the Capsules, Weighing Empty, ShellsCalculating Net Content Calculating Average Net Content
Acceptance Criteria: The capsules pass the weight variation test if: The weight of the active ingredient (oseltamivir) falls within a specified percentage range of the average weight (usually ±10% for capsules with an active ingredient content of 25 mg or more).No more than two of the individual capsule weights deviate by more than the specified percentage from the average weight. None of the individual capsule weights deviate by more than twice the specified percentage from the average weight

Disintegration Test Method
Apparatus:Disintegration Tester: Comprising a basket-rack assembly with six open-ended transparent tubes held vertically, each about 77.5 mm long.
Temperature-controlled water bath: Maintained at 37 ± 2°C.
Timer: To measure the time for disintegration.
Reagents
Disintegration Medium: Typically, distilled water or a specified buffer solution at 37 ± 2°C.
Procedure
Preparation: Preheat the disintegration medium to 37 ± 2°C.Place the required volume of the medium in the beaker of the disintegration tester.
Loading: Place one oseltamivir 75 mg capsule in each of the six tubes of the basket-rack assembly.If the capsules float, a small, perforated plastic disc can be placed on top of each capsule to prevent floating.
Testing: Lower the basket-rack assembly into the medium in the disintegration tester.Start the timer and allow the basket-rack assembly to move up and down at a constant frequency (28–32 cycles per minute) for the specified duration, typically 30 minutes unless otherwise specified in the monograph.
Observation: Observe the capsules at regular intervals. The capsules are considered to have disintegrated if no residue remains on the screen of the tube, or if there is a residue, it consists only of fragments of shell.
Recording Results: Note the time at which each capsule completely disintegrates. If any capsule does not disintegrate within the specified time, the test can be repeated with another set of six capsules.
Evaluation: All six capsules must disintegrate completely within the specified time to meet the requirements of the test.If one or two capsules fail to disintegrate, the test can be repeated with another 12 capsules. At least 16 out of the 18 capsules must disintegrate to pass the test.

Dissolution Test Method
Apparatus:
Dissolution Tester: USP Apparatus 1 (basket).
Dissolution Vessels: Typically, 1000 mL capacity.
Basket: Mesh size of 40 (40 openings per inch).
Water Bath: Maintained at 37 ± 0.5°C.
Timer: To measure the dissolution time.
UV-Vis Spectrophotometer or HPLC: For quantifying the dissolved drug.
Reagents:
Dissolution Medium: 900 mL of 0.1 N hydrochloric acid (HCl) or a phosphate buffer (pH 6.8), as specified in the monograph.
Standard Solution: Prepared using pure oseltamivir phosphate reference standard.

Procedure:
Preparation: Preheat the dissolution medium to 37 ± 0.5°C.Degas the medium if necessary to remove air bubbles.
Loading: Attach a basket to the shaft.Place one oseltamivir 75 mg capsule in the basket.
Testing: Rotate the basket at 100 rpm.Lower the basket into the dissolution medium and start the timer.
Sampling: Withdraw samples (typically 5 mL) from the dissolution medium at specified time intervals (e.g., 10, 20, 30, 45, and 60 minutes).Filter the samples immediately to remove any undissolved particles (using a 0.45 µm filter).Replace the sampled volume with fresh, pre-warmed dissolution medium to maintain a constant volume.
Analysis: Measure the absorbance of the filtered samples using a UV-Vis spectrophotometer at a specific wavelength (typically around 225 nm for oseltamivir).Alternatively, use High-Performance Liquid Chromatography (HPLC) if specified, following the specific chromatographic conditions provided in the monograph.
Calculation: Calculate the amount of oseltamivir dissolved at each time point by comparing the absorbance of the samples to that of the standard solution. Plot the percentage of drug dissolved versus time to obtain the dissolution profile.
Acceptance Criteria: Typically, a certain percentage (e.g., not less than 80% of the labeled amount) of oseltamivir should dissolve within a specified time (e.g., 45 minutes) to meet the acceptance criteria outlined in the monograph.

RESULTS AND DISCUSSION

Different Trail were taken for the optimizing the formula. Same has been determined in table 1 Different quantity of ingredient were change for the formulation to optimized the formula.

Conclusion: From the above table all in process control and parameter is observed well within criteria for Trail batches Trail 6 and Trail 7.

Blend Uniformity	Trail 1	Trail 2	Trail 3	Trail 4	Trail 5	Trail 6	Trail 7
Granulation Stage : Blend Uniformity Acceptance Criteria Individual values 90-110.0 with the RSD not more than 5.0%							
Location 1	88.0	88.0	88.0	89.0	88.2	99.5	95.8
Location 2	87.0	90.3	70.8	90.0	88.3	99.3	96.1
Location 3	72.0	98.0	86.5	78.0	88.2	99.2	96.0
Location 4	73.0	100	87.2	89.0	98.2	100.3	96.4
Location 5	88.0	89.0	78.0	80.1	85.4	100.3	96.1
Location 6	80.0	90.0	74.8	87.0	99.3	101.1	99.9
Location 7	78.0	78.0	86.1	86.4	89.1	100	99.9
Location8	71.8	70.8	96.1	86.1	88.2	99.1	99.8
Location 9	84.0	93.1	83.3	86.3	82.2	100.3	99.7
Location10	82.0	84.0	99.1	88.2	99.3	100.3	99.2
RSD %	6.112	5.28	5.18	4.26	4.92	2.95	2.893

Conclusion: From the above table blend uniformity is observed well within criteria for Trail batches Trail 6 and Trail 7.

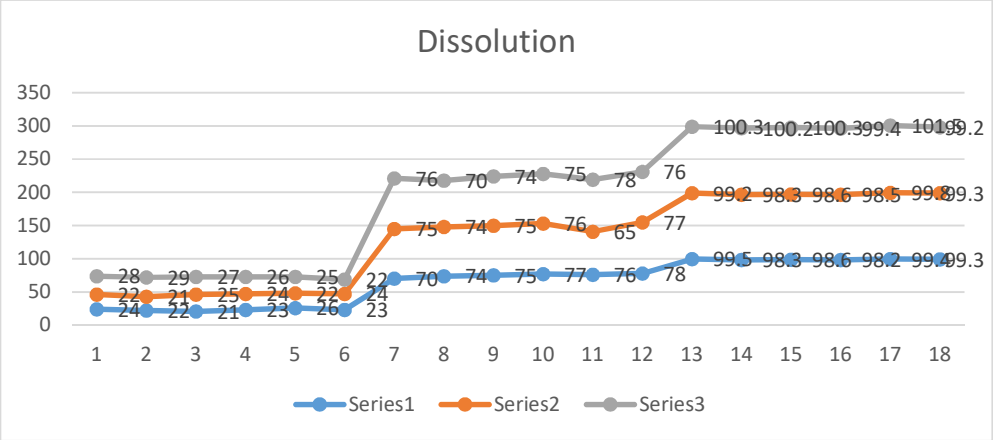
Blend Uniformity	Criteria	Trail 1	Trail 2	Trail 3	Trail 4	Trail 5	Trail 6	Trail 7
Granulation Stage :								
Description	White to off white granules	White to off white granules	White to off white granules	White to off white granules	White to off white granules	White to off white granules	White to off white granules	White to off white granules
Assay by HPLC	95-1025 % labelled claim	85.0	87.3	87.8	93.4	96.3	98.5	98.4
Particle size analysis : For information								

#30	19.49	20.49	24.49	28.89	25.39	24.49	26.49	23.92
#40	32.00	22.00	29.00	32.00	34.00	32.00	35.00	31.83
#60	38.54	28.83	38.59	35.55	37.53	38.53	38.59	37.83
#80	43.09	25.83	41.09	42.09	45.03	41.09	39.09	39.92
#100	46.05	32.92	45.00	47.03	43.02	45.00	46.00	43.21

Conclusion: From the above table control parameter is observed well within criteria for Trail batches Trail 6 and Trail 7.

Dissolution Profile of Capsule

Assay	Trail 7A	Trail 7B	Trail 7C
1	99.2	97.3	99.9
2	99.3	96.7	99.8
3	98.1	97.6	99.7
4	99.3	95.7	99.2
5	96.7	67.2	99.9
6	97.6	97.3	96.5
Mean	95.7	96.7	96.2
SD	1.12	0.84	0.26
%RSD	0.15	0.87	0.27
HPLC	QC-HPLC001	QC-HPLC001	QC-HPLC001
Column	QC-COL-005	QC-COL-005	QC-COL-005



SUMMARY AND CONCLUSION

The current research work predicts the applicability of QbD in manufacturing Oseltamivir Capsules 75 mg ER capsule by using rate delaying the polymers. From the outcomes it was clearly apparent that as the polymer concentration increases, there was a decline in the release of drug. Grouping of polymers with other excipients do not interact with drug and vice versa, which informations to sustained delivery of drug for longer periods. The enhanced formulation from factorial design can be used as a single dose per day in the organization of HIV/AIDS.Wet granulation procedure was the chosen technology for the preparation of Oseltamivir phosphate capsule. Based on the preliminary studies, different formulation trials (F1-F7) were carried out with different concentrations of polymers, diluents. From the various formulations it was decided that the formulation batch of F7 was finalized as the optimized formula. Formulation F7 showed satisfactory results with various physicochemical evaluation parameters like Disintegration time, Dissolution profile, Assay when matched with that of the marketed product. The stability studies at all condition, indicates that the formulated capsules were found to be stable. It was concluded that concentration of polymer had play a possible effect over various process parameters and in-vitro drug release studies (dissolution) suggested that formulated capsule had shown a sustained release up to 16 hrs when compared with marketed product.

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