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Research

Formulation and evaluation of ketorolac tromethamine 10 mg tablets by qbd approach using novel technology

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Abstract

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. Compression method; evaluation of their compliance to various critical process quality parameters, i.e., weight variation, friability, hardness, thickness, moisture content, disintegration, assay, and dissolution; and their comparison with marketed brands for determination of pharmaceutical equivalency 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 tablet were found to be stable. Hence, it is finally concluded that, tablet are pharmaceutically comparable, low cost, quality improved and stable formulation.

Keywords: Formulation, Evaluation, Ketorolac Tromethamine, QBD, Novel Technology**,** Physicochemical evaluation parameter.

INTRODUCTION

Ketorolac Tromethamine is a non steroidal anti-inflammatory drug (NSAID) used primarily for its analgesic (pain-relieving) and anti-inflammatory properties. It is available in various forms, including oral tablets and as an injectable solution. Ketorolac is commonly prescribed for short-term management of moderate to severe pain, such as that associated with surgery or musculoskeletal injuries. It works by inhibiting the production of prostaglandins, which are chemicals in the body that contribute to inflammation and pain. Due to its potent analgesic effects, ketorolac is sometimes used as an alternative to opioids for pain relief, particularly in situations where opioid use is not ideal or desired. However, it's important to note that like all NSAIDs, ketorolac can have side effects, including gastrointestinal irritation, renal impairment, and in rare cases, serious cardiovascular events. Therefore, it should be used cautiously and according to the prescribed guidelines to minimize risks.

Ketorolac is typically prescribed for short-term use only (up to 5 days) due to its potential side effects, and long-term use is generally avoided. It is often used in hospital settings postoperatively or in emergency departments but may also be prescribed in outpatient settings for acute pain management when necessary. Ketorolac Tromethamine, commonly known simply as ketorolac, is a nonsteroidal anti-inflammatory drug (NSAID) used primarily for its potent analgesic (pain-relieving) and anti-inflammatory properties. It is chemically known as (+-)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1), and it belongs to the class of NSAIDs called pyrrolo-pyrrole derivatives.

This medication is available in several formulations, including oral tablets and as an injectable solution. It is widely used for the short-term management of moderate to severe pain, such as postoperative pain, musculoskeletal pain, and pain from various medical conditions. Ketorolac works by inhibiting the enzyme cyclooxygenase (COX), thereby reduces the production of prostaglandins, which are substances in the body involved in inflammation and pain signaling. Ketorolac Tromethamine is commonly used in hospital settings postoperatively or in emergency departments, but it may also be prescribed in outpatient settings when acute pain management is required. Its efficacy and safety profile make it a valuable option in pain management, though careful consideration of its potential risks is essential in clinical practice.

Tromethamine, also known as tris (hydrox ymethyl)amino methane or simply Tris, is an organic compound with the formula (HOCH2)3CNH2. It is often used in biochemistry and molecular biology as a buffering agent, particularly in the preparation of biological buffers for various applications like enzyme assays, cell culture media, and electrophoresis, Tromethamine is highly water-soluble and has a high buffering capacity in the range of pH 7-9, which makes it useful in maintaining a stable pH environment in many biochemical and biological processes.

Tromethamine, also known as tris (hydroxymethyl) aminomethane or Tris base, is a widely used chemical compound with important applications in various fields:

1. **Buffering Agent:** Tromethamine is primarily known for its buffering capacity. It can maintain a stable pH environment in aqueous solutions, particularly in the pH range of 7-9. This property is crucial in biochemical and biological experiments where maintaining a specific pH is essential for the activity and stability of enzymes, proteins, and other biomolecules.
2. **Biochemical and Biomedical Applications:** It is extensively used in biological and biochemical research laboratories as a component of buffer solutions. These solutions are used in techniques such as electrophoresis, cell culture, and protein purification, where precise pH control is necessary for optimal results.
3. **Pharmaceutical Formulations:** Tromethamine is utilized in pharmaceuticals as an excipient to adjust and stabilize the pH of formulations. It is commonly found in injectable drugs, eye drops, and topical creams where maintaining a specific pH range enhances stability.
4. **Veterinary Medicine:** It is also used in veterinary medicine for similar purposes, especially in formulations where a stable pH is critical for drug effectiveness and safety.
5. **Other Applications:** Beyond its primary uses, tromethamine finds applications in various industrial processes where pH control is crucial, such as in textile processing and dyeing.

Tromethamine is generally considered safe when used appropriately according to established guidelines and is widely available in high purity grades suitable for laboratory and pharmaceutical use. However, like any chemical compound, it should be handled with care and in accordance with safety protocols due to its alkaline nature.

Manufacturing process

Ketorolac Tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that is used for its potent analgesic (pain-relieving) and anti-inflammatory properties. Here's an overview of the manufacturing process for Ketorolac Tromethamine:

1. **Synthesis of Ketorolac:** The first step involves synthesizing the Ketorolac molecule itself. Ketorolac is chemically synthesized through a multi-step process that typically starts with readily available starting materials. The exact synthetic route can vary, but it generally involves reactions such as acylation, cyclization, and functional group transformations to form the Ketorolac structure.
2. **Formation of Ketorolac Tromethamine:** Once Ketorolac is synthesized, it is then converted into Ketorolac Tromethamine. This conversion involves reacting Ketorolac with tromethamine (tris(hydroxymethyl)aminomethane), which serves as a buffering agent and stabilizer. The reaction typically occurs under controlled conditions to ensure high yield and purity of Ketorolac Tromethamine.
3. **Purification:** After the formation of Ketorolac Tromethamine, the product undergoes purification steps to remove impurities and by-products from the reaction mixture. Purification may involve techniques such as crystallization, filtration, and recrystallization to obtain the compound in its pure form.
4. **Formulation:** Once purified, Ketorolac Tromethamine is formulated into its final dosage forms, which can include tablets, injectable solutions, or ophthalmic solutions, depending on the intended use. Formulation processes ensure that the drug is stable, bioavailable, and suitable for administration to patients.

5. **Quality Control:** Throughout the manufacturing process, rigorous quality control measures are implemented to ensure the consistency, purity, and safety of Ketorolac Tromethamine. This includes testing the raw materials, intermediates, and final product according to pharmacopeial standards and regulatory requirements.
6. **Packaging and Distribution:** After manufacturing and quality control testing, Ketorolac Tromethamine is packaged into appropriate containers and labeled according to regulatory guidelines. It is then distributed to healthcare facilities, pharmacies, and other points of distribution for use by healthcare professionals.

Overall, Ketorolac Tromethamine plays a crucial role in pain management across various clinical settings, offering an effective alternative or adjunct to opioid analgesics in appropriate situations.

Novel drug development technology

Novel drug development technologies are advancing rapidly, driven by innovations in science, engineering, and computational methods. These technologies aim to streamline the drug discovery and development process, enhance therapeutic efficacy, improve patient outcomes, and reduce costs. Here are some key technologies transforming the landscape of novel drug development:

High-Throughput Screening (HTS) and Automation

HTS allows researchers to rapidly test thousands to millions of chemical compounds against biological targets in a short time. Automated systems further accelerate this process, enabling efficient screening of potential drug candidates.

Computational Drug Design

Computational tools such as molecular modeling, virtual screening, and machine learning algorithms are used to predict the interaction of drug candidates with target molecules. This approach helps prioritize compounds for synthesis and testing, reducing time and cost.

Biotechnology and Genetic Engineering

Advances in biotechnology, including recombinant DNA technology, CRISPR-Cas9 gene editing, and synthetic biology, enable the development of biologics such as monoclonal antibodies, gene therapies, and cell-based therapies with targeted mechanisms of action.

Omics Technologies

Genomics, proteomics, metabolomics, and other omics technologies provide comprehensive insights into the molecular mechanisms of diseases and drug responses. They facilitate personalized medicine approaches by identifying biomarkers and patient stratification strategies.

Nanotechnology and Drug Delivery Systems

Nanotechnology enables the design of nanoparticles and nanostructures for targeted drug delivery, improving drug solubility, bioavailability, and therapeutic efficacy while reducing side effects.

Artificial Intelligence (AI) and Machine Learning

AI algorithms analyze large datasets, including genomic data, clinical records, and drug interactions, to identify patterns and predict drug efficacy, safety, and patient outcomes. AI also assists in optimizing clinical trial design and drug repurposing.

3D Printing and Personalized Medicine

3D printing technology allows for the precise fabrication of personalized dosage forms and medical devices tailored to individual patient needs. This technology has the potential to revolutionize drug manufacturing and patient care.

Continuous Manufacturing

Traditional batch manufacturing processes are being replaced by continuous manufacturing techniques that improve efficiency, reduce costs, and ensure consistent product quality throughout the production process.

Regenerative Medicine and Stem Cell Therapy

Advances in regenerative medicine and stem cell therapy offer novel approaches for tissue regeneration and repair, as well as the treatment of degenerative diseases and injuries.

Blockchain and Digital Health Technologies

Blockchain technology ensures secure data sharing and enhances transparency in clinical trials, supply chain management, and patient healthcare records. Digital health technologies, including telemedicine and wearable devices, enable remote monitoring and personalized treatment options.

These technologies are transforming the drug development landscape, facilitating the discovery of new therapies, accelerating the translation of research into clinical applications, and ultimately improving patient care and outcomes. As these innovations continue to evolve, they hold the promise of addressing unmet medical needs and shaping the future of healthcare.

Drug profile

Ketorolac Tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) with potent analgesic (pain-relieving), anti-inflammatory, and antipyretic (fever-reducing) properties. Here is a detailed drug profile of Ketorolac Tromethamine. Chemical formula C19H24N2O6, **Molecular weight:** 255.269 g/mol.

MATERIALS AND METHODS

Ketorol, *Octagonal blender* ac Tromethamine, Microcrystalline Cellulose USP NF, Lactose Monohydrates, Hydroxy Propyl cellulose, Magnesium Stearate,Vibratory Sifter, Tablet compression, Machine,Tablet deduster, Metal detector, Analytical balan, Moisture analyzer Coating Machine, Vernier caliper, Bulk density apparatus.

Representation of the in process test during the formulation and manufacturing of the product

Sr.No	Test	Methods
Granulation		
1.	Loss of Drying	Performed in moisture analyzer balance
2.	Bulk density	Measurement of Bulk density was done by pouring powder into a measuring cylinder through sieve # 20 and the initial weight was noted. The initial volume was termed as bulk volume.11
3.	Tapped density	Tapped density is defined as the ratio between aggregate weights of granules to the tapped volume of powder. Measurement of the volume was done by tapping the granules 750 times. If the variance in volume exceeds 2%, further tapping should be done for 1250 times. It was conveyed in g/ml
4.	Angle of Repose	Angle of repose was done by using powder flow tester. Angle of repose can be calculated by measuring the height and radius of the pile of granules
5.	Compressibility index	It demonstrates the flow properties of the granules. It is conveyed in the form of % and can be calculated using bulk density and tapped density.
6.	Hausner Ratio	Hausner ratio is an indirect way of accessing the ease of granules flow. It can be calculated by using bulk density and tapped density
Compression		
7.	Weight Variation	Randomly 20 tablets were selected and weighed using a single balance. Standard deviations were calculated and checked with the standard pharmacopeial limits.
8.	Thickness	Tablets were selected randomly from all batches and measurement of thickness was done by using Vernier Calliper.1
9.	Hardness	The strength of tablet is expressed in the form of tensile strength (Kg/cm2). The amount of force required to break the tablets was measured by using a hardness tester
10.	Friability	Randomly 20 tablets were selected and weighed from all the batches. The weighed tablets then placed in friabilator and then ran for 100 revolutions. After completion of 100 revolutions tablets were de-dusted, re-weighed and %friability was calculated.

Selection of the Raw material during formulation of the product

All the excipients used are well known and widely used as pharmaceutical excipients in oral soild 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 excipients.

Compatibility Testing

Method

The drug substance and excipients were mixed and filled in glass vails.The vails were kept in both closed and open condition at 40°C / 75% RH (open and closed condition), 60°C and UV light chamber. Sample was exposed to yhe different condition were evaluated

RESULTS

Table 1 : Different quantity of ingredient were change for the formulation to optimized the formula

Ingredient	**Quantity in batch per kg (mg/Tablets)**						
	Trail 1	**Trail 2**	**Trail 3**	**Trail 4**	**Trail 5**	**Trail 6**	**Trail 7**
Dry Mixing							
Ketorolac Tromethamine USP	10	10	10	10	10	10	10
Cellulose Microcrystalline USP NF	65.5	65.5	65.5	60	64.8	65.5	65.5
Lactose	117	118	116.1	121.6	116.8	116	116
Hydroxy Propyl cellulose	5	4	5.9	6	6	6	6
					Total	197.5	197.5
Extra Granular Ingredients							
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
						200	200
Coating							
Opadry white	6.00	6.00	6.00	6.00	6.00	6.00	6.00
Purified water	60	60	60	60	60	60	60
Total tablet weight						**206**	**206**
Flow Properties	Very Poor	Poor	Passable	Fair	Good	Excellent	Excellent

Manufacturing Process

Following steps are involves in the manufacturing process involving usage appropriate equipment

I. **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 ^{o}C , RH NMT65 % and Pressure difference .0-4.0 mm of wc)
II. **Dispensing:** All active and inactive 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 .
III. **Sifting**: Sifting of raw material Ketorolac Tromethamine , Lactose monohydrate , microcrystalline cellulose is done as per the batch record using the mesh #20 and Hydroxy propyl cellulose through mesh #20 , Magnesium stearate through mesh #30 during activity and same is recorded in the batch record. Integrity of the batch is cheeked before and after sifting.
IV. **Dry Mixing:** Load the material in the RMG and mixed for 5 minutes with impeller at slow speed and chopper off and record the amperage reading
V. **Lubrication**: Extra granular material – Magnesium Stearate sifted through mesh # 60 and loaded into the octagonal blender and rotated at 5 minute at 10 RPM and after blending sample is tested from 10 different location for the blend uniformity
VI. **Compression:** Compression is done at the compaction forces to active the desired results
VII. **Coating:** Coat the tablet

Granulation critical process parameter

Granulation control	Trail 1	Trail 2	Trail 3	Trail 4	Trail 5	Trail 6	Trail 7
Blender RPM	15	15	15	15	15	15	15
Blending time	12	12	12	12	12	12	12
Bulk density(g/ml)	0.551	0.532	0.525	0.525	0.589	0.553	0.558
Tapped density (g/ml)	0.642	0.617	0.692	0.631	0.621	0.654	0.643
Angle of Repose	35	46	47	34	33	27	27
Carrs Index	34	27	23	18	14	<10	<10
Hausner Ratio	1.26	1.16	1.15	1.2	1.2	0.7	0.8
Flow Properties	Very Poor	Poor	Passable	Fair	Good	Excellent	Excellent
Compressibility index (%)	31.809	37.997	29.597	67.698	37.994	38.805	38.805
Water Content by KF	2.26	2.84	2.65	2.53	2.32	2.60	2.61

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 of Granules

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	97.0	97.0	97.59	97.0	97.44	97.39	97.69
Location 2	97.0	100.3	97.55	90.0	97.56	97.49	97.59
Location 3	92.0	97.59	97.69	97.0	100.05	97.69	97.55
Location 4	96.0	97.55	97.65	97.0	97.66	97.65	97.39
Location 5	97.69	97.56	97.69	90.1	97.42	97.69	97.49
Location 6	97.65	100.05	97.59	96.0	97.64	97.59	97.69
Location 7	97.69	97.59	97.55	96.4	97.93	97.55	97.56
Location8	97.59	97.59	96.1	96.1	100.05	97.56	97.55
Location 9	97.0	97.0	97.59	97.0	97.44	97.39	97.69
Location10	97.0	100.3	97.55	90.0	97.56	97.49	97.59
RSD %	1.22	1.02	1.25	1.16	0.28	0.23	0.20

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

Granules Characteristics

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	95-105 %	97.3	98.3	96.8	99.54	97.3	99.5	101.4

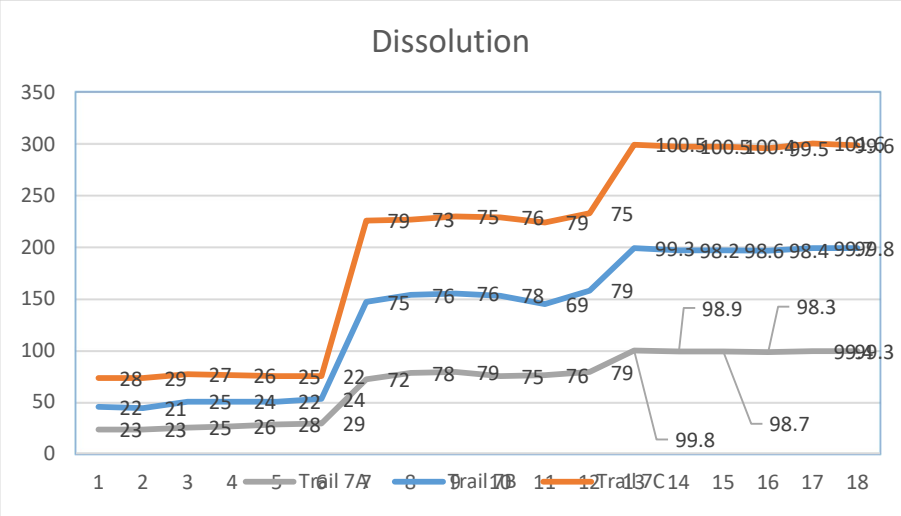
	labelled claim							
Particle size analysis : For information								
#20	0.32	0.18	0.20	0.17	0.20	0.19	0.20	0.19
#30	0.57	0.47	0.67	0.50	0.67	0.49	0.67	0.49
#40	1.62	1.45	1.56	1.36	1.56	1.46	1.56	1.46
#60	3.56	4.09	3.62	4.25	31.62	14.05	3.62	4.05
#80	16.41	14.85	16.55	15.80	36.55	24.80	16.55	14.80
#100	17.32	16.28	17.20	2419	42.20	38.19	38.5	36.58
#120	18.38	19.49	20.67	53.49	53.67	45.49	53.89	52.63

Dissolution Profile of film coated Tablets

Dissolution	**Trail 7A**	**Trail 7B**	**Trail 7C**
1	99.44	99.67	99.67
2	99.56	99.59	99.59
3	100.05	99.55	99.55
4	99.42	99.38	99.38
5	99.64	99.48	99.48
6	99.83	99.69	99.69
Mean	99.66	99.65	99.56
SD	0.24	0.12	0.12
%RSD	0.24	0.12	0.12
HPLC	QC-HPLC002	QC-HPLC002	QC-HPLC002
Column	QC-COL-009	QC-8COL-009	QC-COL-009

Dissolution:in pH 6.8 Phosphate buffer at 75 RPM USP 1 for film coated tablet

	Time	**Specification**	**Trail 5**	**Trail 6**	**Trail 7**
1	10minute	NMT 30%	25	27	26
2			21	26	26
3			20	26	27
4			26	25	26
5			25	27	25
6			22	26	26
1	20 min	Between 60-80%	69	72	73
2			73	73	70
3			70	70	74
4			74	74	73
5			73	69	70
6			70	72	74
1	30 minute	NLT 80 %	100.4	100.4	101.1
2			100.3	100.3	101.4
3			100.4	100.4	101.4
4			100.4	100.4	99.4
5			99.4	99.4	101.5
6			99.3	99.3	99.4



SUMMARY

Ketorolac Tromethamine 10 mg tablets were developed and evaluated using QbD approach by the novel technology. Summary of the study results states, it was concluded that concentration of disintegrater had play a possible effect over various process parameters and in-vitro drug release studies (dissolution) suggested that formulated tablets had shown a immediate release when compared with marketed product.

CONCLUSION

The current research work predicts the applicability of QbD in manufacturing Ketorolac Tromethamine 10mg Tablets by using rate delaying the polymers. From the outcomes it was clearly apparent that as the disintegrate concentration increases. Grouping of disintegrate with other excipients do not interact with drug and vice versa, which information's to sustained delivery of drug for longer periods. The enhanced formulation from factorial design can be used as a single dose per day. The experimental design gives a direction for further optimization. In the present study, Trail # 7 was identify as the formulation best satisfying all the criteria for an optimum formulated.

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