ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 7, Issue, 11, pp. 14359-14366, November, 2016

International Journal of Recent Scientific Research

Research Article

FORMULATION AND PROCESS DEVELOPMENT OF KETOROLAC TROMETHAMINE FAST DISSOLVING ORO-DISPERSIBLE FILM AS PER QUALITY BY DESIGN GUIDELINE

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ARTICLE INFO

Article History:

Received 17th August, 2016
Received in revised form 21th September, 2016
Accepted 28th October, 2016
Published online 28th November, 2016

Key Words:

Quality by Design, ICH guideline, Target Product profile, Critical Process Parameters, CQA, NSAID's, oral fast dissolving, solvent casting.

ABSTRACT

A Quality by design a common understanding of the concept of ICH guideline Q8, Q9 and Q10 and treated as an essential in the process of formulation. The present investigation starts with the identification of TPP and CQA which involves risk assessment in their final selection process.
In the product design space the product characteristic involves identification of critical product attributes which ultimately resulted in the selection of CPP that is process design space. This identified control strategy requiring continuous monitoring and updating the process requirements. Validation is one of the important steps in achieving and maintaining the quality of the final product which has been taken into consideration in the present research work. Important parameters were validated. The dosage form in the present research work is a new generation NSAID's which is commonly used for relief of pain caused during post operative surgical procedure. Therefore in selecting target product profile risk of incomplete bioavailability due to tablet or oral dosage form as taken into consideration. The quality by design principle and tools demonstrated in the present research work will play an important role in understand- ing and creating opportunities for investigation and developing control strategy in pharmaceutical development process.

INTRODUCTION

Oro-dispersible film [(1)]**:-**Films as dosage forms have gained relevance in the pharmaceutical area as novel, patient friendly, convenient products. The introduction of fast dissolving dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patients. Fast dissolving films are gaining interest as an alternative of fast dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as tongue, within few seconds, meaning the consumer can take the product without the need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance.

Ketorolac Tromethamine Film[(3)]

Ketorolac Tromethamine (KT) is one of the most potent non steroidal anti-inflammatory drugs that is known to have potent analgesic. It has been found effective in the treatment of trauma-related pain as well as pain associated with cancer. Ketorolac tromethamine is used for post operative pain, as an alternative to opioid agents, and is administered intramuscularly, intravenously, or orally. Typical oral dose for oral doses are 5 to 30 mg.

MATERIAL

Ketorolac trometamine is purchase for gift sample of Sahyadri Scientific Research, Islampur

Experimental Work

Identification of Target Product Profile [(4-7)]

The target product profile (TPP) has been defined as a "Prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized".

Table No 1 Ketorolac Trometamine Orodispersible Film

Sr.No.	Test	Specification/Limits
1	Description	A thin, transparent film
2	Dosage form	Oro-dispersible film
3	Strength	10 mg per strip
4	Category	NSAID's
5	BCS class	Class I
6	Thickness	NLT 0.1 mm±5%
7	Disintegration	5-30 sec.
8	Folding endurance	NLT 100
9	Size	6 cm2
10	Packaging and storage	Packed in aluminum pouch and Protected from light and moisture.

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Risk Assessment

This drug is used to postoperative pain for short term treatment only. It is not used for minor or chronic pain, therefore its immediate release in the system is important. Hence oro-dispersible film which liberates the drug fast has been selected and specification was fixed accordingly.

Critical Quality Attributes (Cqas) [6]

Ketorolac tromethamine Oro-dispersible film

Table no 2 ketorolac tromehamine orodispersible film

Sr.No.	Test	Specification/Limits	Method
1	Description	A thin, transparent film	Attached (I)
2	Identification	Complies	Attached (II)
3	Content	10 mg per strip	IP-Modified
4	Dissolution	Dissolution media : 300ml pH of dissolution media :6.8 Speed: 100 Rpm; Time: 5min. DissolutionNLT75%	Attached(III)
5	Uniformity of content	NLT 85% & NMT 115% of 1mg	IP
6	Assay	90 to 110 % of 10 mg	IP
7	Moisture content	NMT 2%	Attached(V)
8	Appearance	Transparent	Attached(I)
9	Thickness	NLT 5%	Attached(II)
10	Disintegration	5-30 sec.	Attached(XII)
11	Folding endurance	NLT 100	Attached(IV)
12	Weight variation	NLT 90.0-110 %	IP (III)
13	Surface pH	6.5-7.0	Attached(IX)

Test Method [7-8]:

Appearance:[36]

All prepared films were checked for their appearances either they are transparent or opaque.

Acceptance criteria: Transparent and free from foreign particle by necked eye.

Thickness: [36]

It is measured by micrometer screw gauge or calibrated digital vernier calliper at 5 different strategic locations.(center and four corners)

Acceptance criteria: The maximum variation in the thickness of the film is 0.1 mm ± 5%.

Weight Variation: [37]

Weight variation is studied by individually weighing 10 randomly selected films and by calculating the average weight.
Acceptance criteria: ± 5%.

Folding endurance: [38]

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.NLT 100

Acceptance criteria: ± NLT 100

Moisture content: [39]

Weigh the film and keep in a desiccators containing calcium chloride at room temperature for 24 hrs. dry it to constant weight.

$$\% \text{ moisture content} = \frac{\text{initial weight} - \text{final weight} * 100}{\text{Final weight}}$$

Moisture uptake:[40]

Weighted films are kept in desciccator at room temperature for 24 hrs. then films are exposed to 84 % relative humidity using saturated solution of potassium chloride in desciccator until a constant weight is achieved. % moisture uptake is calculated as given below.

$$\text{Moisture uptake} = \frac{\text{final weight} - \text{initial weight} * 100}{\text{Initial weight.}}$$

Acceptance criteria: NMT 2%

Tensile strength: [41]

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below.

$$\text{Tensile strength} = \frac{\text{load at failure} * 100}{\text{Strip thickness} * \text{strip width}}$$

Percent elongation: [41]

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases.
Acceptance criteria: NMT 10%

Surface pH: [42'43]

The film to be tested was placed in a Petri dish and was moistened with 0.5ml of distilled water and kept for 30sec.The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1msin. The average of three determinations for each formulation was done.
Acceptance criteria: pH 6.5 -7.0

Drug content Uniformity determination: [38]

This parameter was determined by dissolving one film of dimension 3 x 2cm by homogenization in 100 ml of stimulated saliva of pH 6.8 for 30 min with continuous shaking. From this, 10 ml was diluted to 50 ml with simulated salivary fluid. The absorbance was measured using an UV spectrophotometer. The experiments were carried out in triplicate for the films of all formulations and average values were recorded.
Acceptance criteria: 90 %-110%

In vitro dissolution studies: [44]

Dissolution profile of fast dissolving films was carried out using USP type II (paddle apparatus) with 300 mL of simulated salivary fluid (pH 6.8) as dissolution medium maintained at 37 ± 0.50C. Medium was stirred at 100 rpm. Samples were withdrawn at every 30 sec interval, replacing the same amount with the fresh medium. Amount of drug in the withdrawn samples was determined by UV spectrophotometer. The percent drug released was plotted against time.

Acceptance Criteria: Not less than 75% of stated amount of ketorolac tromethamine.

Disintegration time: [45, 46]

Disintegration of orally fast dissolving films requires US disintegration apparatus. The disintegration time limit of 30 seconds or less for orally disintegrating tablet described in Centre for Drug Evaluation and Research (CDER) guidance can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation.

Acceptance Criteria: Disintegration range from 5 to 30 seconds.

Risk Assessment: [59]

All the above test methods were based on the quality of target product profile and keeping in mind the critical quality attributes with the help of technical literature and available knowledge.

Product Design Space[8]

Table no 3 Master Manufacturing and Control Record

Sr.No.	Name of Ingredient	Unit	Quantity per 100 film	Category
1	Ketorolac tromethamine IP	mg	1000	NSAIDs
2	Polyvinyl alcohol IP	mg	1875	Polymer
3	Polyethylene glycol 400 USP	mg	30	Plasticizer, solvent
4	Sodium starch glycolate IP	mg	600	Disintegrant
5	D-Mannitol IP	mg	2500	Sweetener, solubalizer
6	Purified water IP	ml	62.5	Solvent

Theoretical weight per film 60 mg

Risk Assessment

The product was design on the basis of several sources of information and the specification were finalized according to built quality into the product.

Process Design Space[9]

Method of manufacturing

Step I -Weigh all the ingredient accurately.

Step II -Dissolved the film forming polymer polyvinyl alcohol (PVA) in purified water with the help of magnetic stirrer at 200 rpm for two hours. Check the clarity

Step III -Add Ketorolac tromethamine to the aqueous polymeric solution and add PEG 400. Check the clarity and weight

Step IV-Add mannitol and sodium starch glycollate and dissolve and stir well.

Step V-The above solution was sonicated for 20 min for removal of air bubbles and casted on glass plates with d marketed 3x2 cm areas. dried at clean room temperature 27-300 C. (moisture content more than 5%)

Step VI -Carefully remove the strips from the glass plate. Check for any foreign particle or defects.

Cut into 3x2 cm pieces by using proper machine. Collect Q.C sample and retention sample.

Step VII-The film samples are stored, in properly packed condition away from moisture in a cool place.

Optimization: Basic Concept and Technology [54]

Optimization has been defined as the implementation of systemic approaches to achieve the best combination of product and/ or process characteristic under a given set of conditions. The word optimization simply means to make as perfect, effective or functional as possible. The term optimized has been used in the past to suggest that a [product has been improved to accomplish the objective of the development scientist. However, today the term implies that the computers and statistics have been utilized to achieve the objectives. With respect to drug formulation or pharmaceutical processes, optimization is a phenomenon of finding "the best" possible composition or operating condition.[56]

Variables

Design and development of drug formulation or pharmaceutical process usually involve several variables. The input variables, which are directly under the control of the product development scientist, are known as independent variables, e.g. compression force, excipient amount, mixing time, etc. Such variables can either be quantitative or qualitative. Quantitative variables are those that can take numeric values e.g. amount of disintegrating agent, suspending agent, temperature, time, etc. Instances of qualitative variables, on the other hand, include the type emulgent, solubilizer or tableting machine. Their influence can be evaluated by assigning dummy values of them. Accordingly, a drug formulation with respect to optimization techniques can be consider as a system, whose output (Y) is influenced by set of controllable (X) and uncontrollable (U) inputs variables via a transfer function (T). The nomenclature of T depends upon the predictability of the output as an effect of change of the input variables. If the output is totally unpredictable from the previous studies, T is termed as black box. The term white box is used for a system with absolutely true predictability, while the term, grey box is used for moderate predictability.

Experimental designs

The design used for simultaneous methods are frequently referred to as response surface designs. Various experimental designs frequently involved in the execution of RSM can broadly classified as:

A. Factorial design and modifications
B. Central composite and design modifications
C. Mixture designs
D. optimal designs

Table No. 4 Variable of 32 Factorial Design

Independent Variables	Coded Levels		
-1		0	1
		Actual level	
X 1=PVA	200	300	400
X 2=SSG	2	4	6
Response variable			
Y1 Tensile strength (gm/cm2)			
Y 2 disintegration time (sec)			

Table no 5 Experimental Runs for 32 Factorial Design

Batches	PVA	SSG
F 1	-1	-1
F 2	-1	0
F 3	-1	1
F 4	0	-1
F 5	0	0
F 6	0	1
F 7	1	-1
F 8	1	0
F 9	1	1

RESULT AND DISCUSSION

Target Product Quality Profile

It meets the identity, assay, dosage form, purity and stability of the label claim.

Table no 6 specification of ketorolac tromethamin film

Sr. No.	Test	Specification/Limits	Observation	Method
1	Description	A thin, transparent film	A thin, transparent film	Attached (I)
2	Identification	Complies specification	Passes Test	Attached (II)
3	Content	10 mg per strip	9.8 mg per strip	IP-Modified
4	Dissolution	NLT 75%	98.19%	Attached(III)
5	Assay	90 to 110 % of 10 mg	98.61 %	IP
6	Moisture content	NMT 5%	Nil	Attached
8	Thickness	NLT 0.1mm ± 5%	0.110±0.003 SD	Attached
9	Disintegration	5-30 sec.	16.03±0.52	Attached
11	Folding endurance	NLT 100	Passes Test	Attached
12	Weight variation	NLT 90.0-110 %	45-47 mg	IP
14	Surface pH	6.5-7.5	6.70±0.03	Attached

Product Design Space

Name of Product: Ketorolac Tromethamineoro-dispersible film

Table No 7 Bill of Material

Sr.No.	Name of Ingredient	Unit	Quantity per 1000 film	Category
1	Ketorolac tromethamine IP	Gm	10	NSAIDs
2	Polyvinyl alcohol IP	Gm	18.750	Polymer
3	Polyethylene glycol 400 USP	Gm	0.3	Plasticizer, solvent
4	Sodium starch glycolate IP	Gm	6	Disintegrant
5	D-Mannitol IP	Gm	25	Sweetener, solubalizer
6	Purified water IP	ml	625	Solvent

Compatibility Study FT-IR

Drug- Excipient interaction study Infrared spectroscopy was used as means of studying drugexcipients interactions. It was found that there was no chemical interaction between ketorolac tromethamine and excipients used because there were no changes in the characteristic peaks of ketorolac tromethamine in the IR spectra of mixture of drug and excipients as compared to IR spectra of pure drug.

Fig 1 FTIR spectra of Ketorolac tromethamine (API)

Calibration Curve

Preparation of standard curve of ketorolac tromethamine in phosphate buffer

Spectrum of Ketorolac tromethamine indicated the value for λ max at 323 nm

Table no 8 calibration curve for ketorolac tromethamine in phosphate buffer.

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.2902
3	10	0.6311
4	15	0.9213
5	20	1.1879
6	25	1.5154

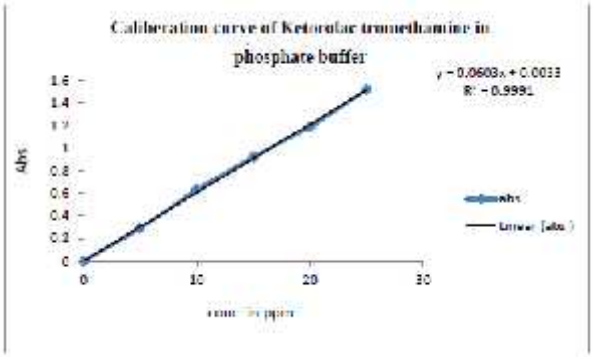

Fig No. 2 Calibration curve for ketorolac tromethamine in phosphate buffer pH 6.8

Define Product Design Space

Method of manufacturing

Note

A. Ambient room temperature is required for manufacturing.
B. All Manufacturing activities should be carried out in a specified department.
C. Necessary BOP's and SOP's and cleaning procedures should be strictly followed.

Direction

Step I -Weigh all the ingredient accurately.

Step II -Dissolved the 200mg film forming polymer polyvinyl alcohol (PVA) in purified water with the help of magnetic stirrer at 200 rpm for two hours. Check the clarity

Step III -Add 160mg of Ketorolac tromethamine to the aqueous polymeric solution and add 1ml of PEG 400. Check the clarity and weight

Step IV -Add 25mg of mannitol and 6 mg of sodium starch glycollate and dissolve and stir well.

Step V -The above solution was sonicated for 20 min for removal of air bubbles and casted on glass plates with d marketed 3x2 cm areas. dried at clean room temperature 27-300 C. (moisture content more than 5%)

Step VI -Carefully remove the strips from the glass plate. Check for any foreign particle or defects.

Cut into 3x2 cm pieces by using proper machine. Collect Q.C sample and retention sample.

Step VII -The film samples are stored, in properly packed condition away from moisture in a cool place.

Optimization of Ketorolac Tromethamine Film

Optimization of formulation variables for preparation of oro-dispersible film of ketorolac tromethamine by using 32 factorial design. To study the effect of variables, we applied the

32 factorial design. The amount of PVA (X1) and SSG (X2) were kept as independent variable and Tensile Strength and Disintegration time selected as dependent variables.

Y= ß0 + ß1X1 + ß2X2+ ß11X12 + ß22X12 + ß12X1X2
Where, Y= measured response, X= level of factors, ß= coefficient computed from the response of the formulation. Total 9 batches of Ketorolac tromethamine containing polymeric film were prepared and these batches were evaluated for Tensile Strength and Disintegration time.

Table no 9 Experimental Runs for 32 Factorial Designs

Batches	PVA	SSG	Tensile*Strength (gm/cm2)	Disintegration Time* (sec)
F 1	-1	-1	398.00±4.53	19.23.03±0.24
F 2	-1	0	375.45±3.52	18.23±0.28
F 3	-1	1	378.41±1.41	20.08±0.19
F 4	0	-1	465.32±1.74	17.33±0.21
F 5	0	0	462.66±2.52	19.46±1.6
F 6	0	1	488.23±3.52	16.03±0.52
F 7	1	-1	449.32±2.43	21.16±0.49
F 8	1	0	480.53±3.87	24.69±0.29
F 9	1	1	508.92±4.22	25.32±0.33

Table no 10 Variable of 32 factorial

	Design		
dependent Variables	Coded Levels		
-1	0		1
Actual level			
X 1=PVA	200	300	400
X 2=SSG	2	4	6
Response variable			
Y1 Tensile strength (gm/cm2)			
Y 2 disintegration time (sec)			

the high levels of the factors are coded as +1 and the low levels of the factors are coded as -1. The Model F-value of 570.38 implies the model is significant. There is only a 3.22% chance that an F-value this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant.

Response 1 Tensile Strength

The P value 0.0322 is significant..Values greater than 0.1000 indicate the model terms are not significant. The positive effect of X1 increases the in Tensile Strength of polymeric film

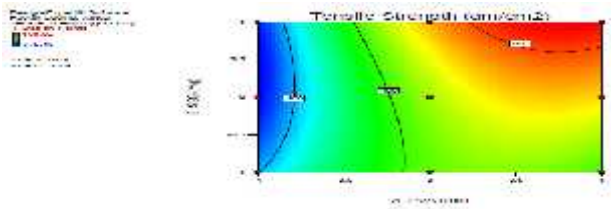

Fig 3 surface response graph for tensile strength contour

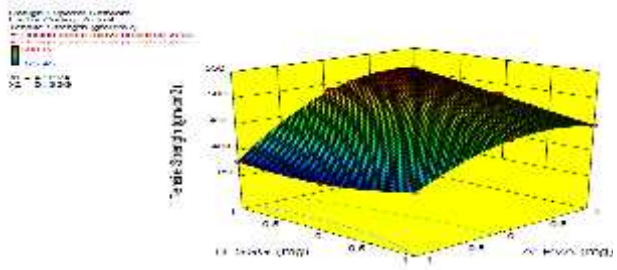

Fig 4 Surface Response Graph For Tensile Strength 3d

Response 2 Disintegration Time

The P value is 0.0293 significant .The Model F-value of 689.33 implies the model is significant. There is only a 2.93% chance that an F-value this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant.

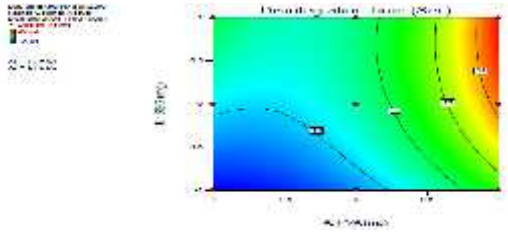

Fig 5 surface response graph for disintegration time contour

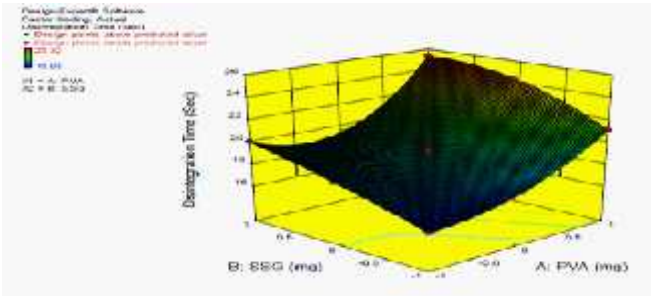

Fig 6 surface response graph for disintegration time 3D

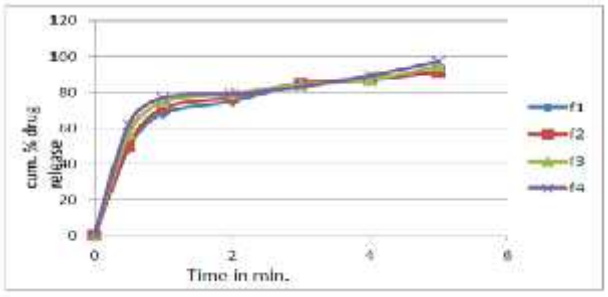

Fig 7 Drug release profile of f1-f4 Batches

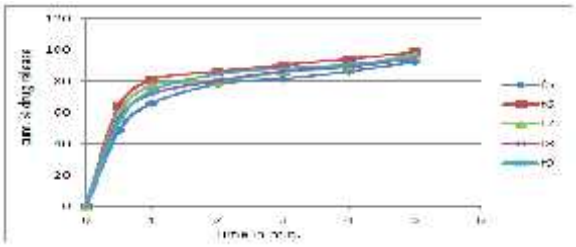

Fig 8 Drug release profile of F5-F9 Batches

CONCLUSION

The present research work was undertaken with the view that develop ketorolac tromethamine film oral dosage form with increase emphasis on performance qualification focusing of critical quality attributes. This resulted to follow the modern concept of quality by design approach for the manufacturing of pharmaceutical dosage form.

In this research work the identification of target product profile and its critical quality attributes considering the risk factors were done systematically.

Table 11 In vitro cumulative % drug release in phosphate buffer pH 6.8

Time (min)	f1	f2	f3	f4	f5	f6	f7	f8	f9
0	0	0	0	0	0	0	0	0	0
0.5	48.9479	49.8403	56.9495	62.0621	48.3277	64.1042	58.9008	55.8756	53.6823
1	68.3092	71.1680	74.6168	77.0369	65.7226	80.8184	77.3092	71.6067	73.7395
2	75.1008	77.2789	79.3058	78.9731	78.0958	86.1277	79.8050	80.1226	84.3579
3	84.3428	85.0991	84.3579	83.0873	81.3479	90.2571	85.7042	86.1731	88.0487
4	88.0336	86.9294	86.9294	89.2285	86.1579	94.0689	89.2285	89.1226	90.3932
5	91.5882	91.2857	94.5226	97.1848	92.2840	98.1983	97.1848	94.2504	95.1579

Product design space which is related to the specification and process design space which is related to the manufacturing process has also been developed keeping in mind the critical control parameters. Control strategies are also listed.

Validation is an important step in achieving and maintaining the quality in final product batch after batch also were taken into account.

This research work gives complete comprehensive requirements for the quality by design manufacturing techniques.

Amongst nine batches the film composed of PVA (300 mg) and SSG (6 mg) (F6); representing the lowest significant DT with the highest significant drug dissolution rate and satisfactory physico-mechanical properties.

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How to cite this article:

Mangal Gahandule, Gadhave.M.V.2016, Formulation And Process Development of Ketorolac Tromethamine Fast Dissolving Oro-Dispersible Film As Per Quality By Design Guideline. *Int J Recent Sci Res.* 7(11), pp. 14359-14366.