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Stability Studies in Combine Dosage form of Etoricoxib and Thiocholchicoside using RP-HPLC

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Abstract: *The drugs are vital to health of an individual and it can be defined as all medicines for internal or external use of human beings or animals to be used for diagnosis, treatment, mitigation or prevention of any disease or disorder. Analytical chemistry is the science of chemical characterization by developing methods using enhanced analytical instruments and obtaining information about the qualitative information of matter. Accuracy, reproducibility and reliability are the basis of developing methods. Analytical chemistry may be defined as the science and art of determining, the composition of material in terms of the elements or compounds contained. The combination of etoricoxid and thiocolchicoside and has unique duel mode of action i.e in this combination, Etoricoxib is anti-inflammatory medicines used to relieve pain, swelling, other symptoms of inflammation and thiocolchicoside is used clinically for its muscle relaxant, Anti-inflammatory, and analgesic properties .It is used medically to treat orthopedic, traumatological and rheumatologic disorders as well as to treat muscular spasms. From the literature survey conducted it was found that there is not any analytical method reported for etoricoxib and thiocholchicoside in combination by single reverse phase HPLC method in pharmaceutical dosage forms. etoricoxib and thiocholchicoside in combination is increasingly finding use in treatment of pain and inflammations. So the objective of the present work is to develop simple, accurate, economical and rapid reverse phase HPLC method for the Stability study of etoricoxib and thiocholchicoside in solid dosage form this research work comprises to develop stability indicating assay method, to resolve the degradation products from mixture of stressed samples and to separate the degradation products observed under variety of conditions.*

Keywords: *Reproducibility, Reliability, Analytical method, Stressed, Degradation products.*

1. INTRODUCTION

The drugs are vital to health of an individual and it can be defined as all medicines for internal or external use of human beings or animals to be used for diagnosis, treatment, mitigation or prevention of any disease or disorder. Analytical chemistry deals with the methods for determining the chemical composition of samples of matter [10][16][30]. A qualitative method yields information about the atomic or molecular species or the functional groups that exist in the sample; a quantitative method in contrast, provides numerical information as to the relative amount of or more of these compounds [14][15]. Analytical chemistry may be defined as the science and art of determining the composition of materials in the forms of elements or components contained in manufacturing laboratories. Market is folded with combination of drugs in various dosage forms. Now a day the multi-components formulations have gained a lot of importance due to greater patient acceptability, increased potency, multiple action, fewer side effects and quicker relief[17][20].

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions [21]. The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of the EC, Japan and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. This guideline addresses climatic zones I and II [25]. The principle has been established that stability information generated in any one of the three regions of the EC, Japan and the United States would be mutually acceptable to the other two regions, provided the information is consistent with this guideline and the labeling is in accord with national/regional requirements.[5]

Before knowing its combination, we should need to know that how they work individually, so you know that Etoricoxib is anti-inflammatory medicines used to relieve pain, swelling, other symptoms of inflammation and thiocolchicoside is used clinically for its muscle relaxant, Anti-inflammatory, and analgesic properties .It is used medically to treat orthopedic, traumatological and rheumatologic disorders as well as to treat muscular spasms. It is used to control the pain and swelling suffered by individuals with different medical conditions. The combination of etoricoxid and thiocolchicoside and has unique duel mode of action i.e in this combination, etoricoxid used to treat orthopedic and thiocolchicoside used to control the pain and swelling. Drug interactions occur when it is taken with another drug or with food. Before you take a medication for a particular ailment, you should inform the health expert about intake of any medications including non prescription medications, over- the counter medicines that may increase the effect of etoricoxib and thiocolchicoside, so the doctor can warm you of any possible drug interactions. After combination of etoricoxib and thiocolchicoside we observed that etoricoxib is selective inhibitor of COX-2 that decreases GI toxicity and is without effects on platelet function. Thiocolchicoside is a muscle relaxant, which has been claimed to possess GABA (gamma- Amianobutyric acid) mimetic and glycinergic actions. It has been demonstrated by recent studies concomitant administration of an Etoricoxib and thiocolchicoside show significantly better symptoms relief compared with the modest improvement of inflammation with each of the treatment alone[1].

So the objective of the present work is to develop simple, accurate, economical and rapid reverse phase HPLC method for the Stability study of etoricoxib and thiocholchicoside in solid dosage form this research work comprises to develop stability indicating assay method, to resolve the degradation products from mixture of stressed samples and to separate the degradation products observed under variety of conditions.

2. METHOD

2.1. Literature Survey. We used PubMed, Elsevier and many more Literature resources to collect etoricoxib and thiocholchicoside analytical methods. From the literature survey conducted it was found that there is not any analytical method reported for etoricoxib and thiocholchicoside in combination by single reverse phase HPLC method in pharmaceutical dosage forms.

2.2. Method Development (To be Done by Reverse Phase HPLC)-

2.2.1. Preparation of Standard Solution

Stock solution of Thiocolchicoside (A) Transferred an accurately quantity 40.0 mg of Thiocolchicoside working standard in to a 100 ml volumetric flask added about 50 ml of diluent and sonicate to dissolve, made volume up to mark with diluent and mix.

Stock solution of Etoricoxib (B) Transferred an accurately quantity 60.0 mg of Etoricoxib working standard in to a 100 ml volumetric flask added about 50 ml of diluent and sonicate to dissolve, made volume up to mark with diluent and mix.

1 ml solution of Thiocolchicoside (A) and 10 ml solution of Etoricoxib (B) was together diluted with diluent (mobile phase) in 100 ml volumetric flask.

The resulting solution was sonicated for 10 min. 20 µl of the standerd solution was injected.

2.2.2. Preparation of Test Solution

Weight accurately 10 tablets and calculated the Average weight, after crushing tablet powder equivalent to 300mg of etoricoxib and 20mg of thiocolchicoside transferred in 250 ml volumetric flask. Added about 100ml diluent and sonicated for 30minutes with continuous shaking made up to the mark with diluent and mix. Filtered the solution through 0.45µm PVDF filter, collected the filtrate by discard first few ml of the filtrate. 5ml of that solution taken and again added in 100 ml of diluents.

Calculation Formula

% of Thiocolchicoside content

$$\frac{AT}{AS} \times \frac{WS}{100} \times \frac{1}{100} \times \frac{250}{Wt} \times \frac{100}{5} \times \frac{Avg.wt}{LC} \times \frac{P}{100}$$

AT = Peak area of Analyte of Sample Preparation

AS = Peak area of Analyte of Standerd Preparation

Wt. = Weight of sample taken for sample preparation.

WS = Weight of working standerd taken in mg for standerd preparation

P = Potency of working standerd on as such basis.

LC = Label Claim of Respective strength

Calculation Formula:-

% of Etoricoxib content -

AT WS 10 250 100 Avg.wt P
----- x ------x---------x-------x-------x-----------x-------x100
AS 100 100 Wt 5 LC 100

AT = Peak area of Analyte of Sample Preparation

AS = Peak area of Analyte of Standerd Preparation

Wt. = Weight of sample taken for sample preparation.

WS = Weight of working standard taken in mg for standard preparation

P = Potency of working standard on as such basis.

LC = Label Claim of Respective strength

2.2.3. Determination of Solubility

Solubility of ETORICOXIB AND THIOCHOLCHICOSIDE was performed in different solvents

Solubility of etoricoxib and thiocholchicoside

S.NO	SOLVENT	SOLUBILITY OF DRUG
1	Water	Freely Soluble
2	Methanol	Soluble
3	Acetonitrile	Soluble
4	Ethanol	Soluble

2.2.4. By HPLC

Column -: BDS Hypersil C18 (25cmx4.6mm)5µm.
Detection Wavelength -: 220nm
Temperature -: 30°C
Injection volume -: 20µl
Mobile Phase -: ACN: Buffer (750:250)
Flow Rate (ml/min.) -: 1.5 ml/min.
Diluents -: Mobile Phase

2.3. Accelerated Stability Study

40°C ± 2°C/not more than (NMT) 25% RH for 6 months

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf

Typical parameters used: .

Study	Storage condition	Minimum time period covered by data at submission
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

2.4. Monitoring of Stability Chamber

Temperature and Relative humidity of the chamber should be recorded using a calibrated continuous data logger. If the facility is not available or under maintenance it should be done

manually at least twice in a day. If the stability chamber is not rectified with in 24 hours, the stability sample shall be shifted to standby stability chamber

3. RESULT

Description:

A Round Biconvex film coated Tablets

Average Weight :

186 mg

Related Substances :

(Limit NMT 2.0%)

Assay: Each Film Coated tablet contain

Etoricoxib 60 mg

Limit - 90.0% to 110.0% label claim.

Thiocolchicoside IP 4mg

Limit - 90.0% to 110.0% label claim

Labeling

- Following are the minimum requirements on the label:-

Name of product Etoshine Tablet

Batch No. BSA3640

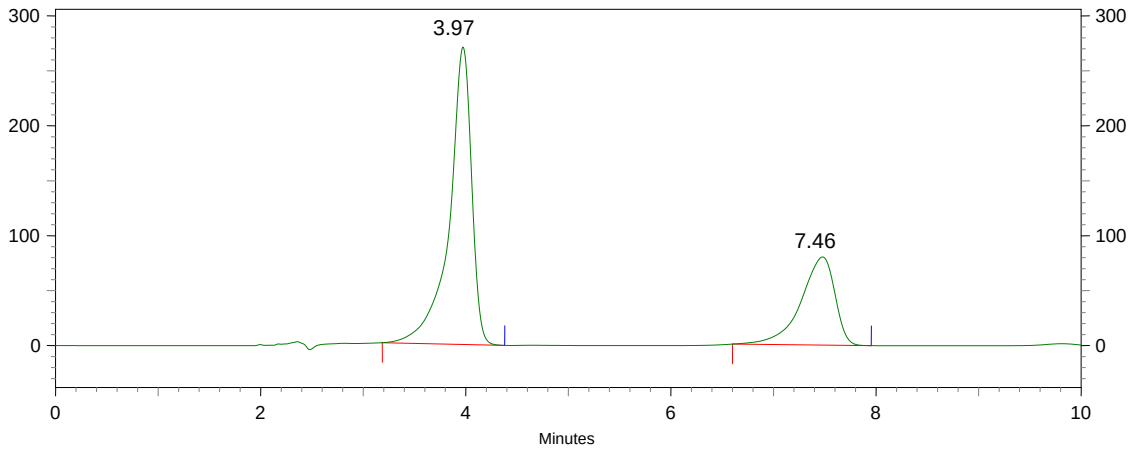
Storage condition: Temp.40°C±2°C 75 RH±5%RH

Sample kept on date 07/07/2012

Manufacturer :- Sun pharma

Std Wt.Etoricoxib	60.90 mg	
Std Wt.Thiocolchicoside	41.00 mg	
Potency Etoricoxib	99.5%	%
Potency Thiocolchicoside	99.8%	%
Spl.Wt.	928.5mg	Mg
Avg.wt of tablet	186.0mg	Mg
L.claim.Etoricoxib	60mg	Mg
L.claim.Thiocolchicoside	4mg	Mg

Assay Etoricoxib & Thiocolchicoside



DAD: Signal A, 220 nm/Bw:4 nm Results					
Pk #	Name	RT	Area	Area %	Asymmetry
1	Thiocolchicoside	3.97	8501844	68.855	0.7
2	Etoricoxib	7.46	3808933	31.145	0.7
Totals					
			12310777	100.000	

Data File : \\Dataserver\EZdata\Projects\2013\Data\Jun_2013\Finish Product\Etoshine\ Etoricoxib
& Thiocolchicoside_10.06.2013_001.dat

Injection Time: 6/10/2013 8:35:10 AM

Sample Name: Blank Solution

Method: \\Dataserver\EZdata\Projects\2013\Method\Jun_13\Finish product\ Etoricoxib & Thiocolchicoside .met

Sequence: \\Dataserver\EZdata\Projects\2013\Sequence\Jun_2013\Finish Product\ Etoricoxib &
Thiocolchicoside \Etoshine_10.06.13.seq

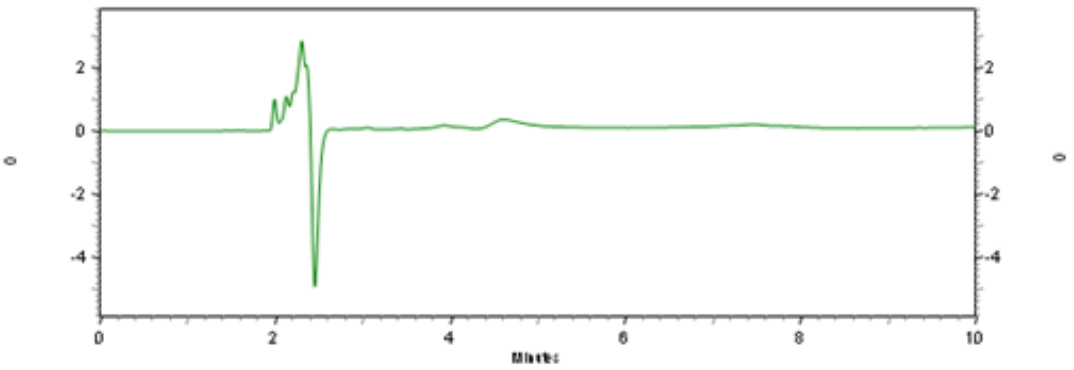
Instument No.: QCHP149 (Offline)

Operator: LCGC\Disha

Location: vial 1

Injection Volume: 20

Analysis : Assay Etoricoxib & Thiocolchicoside



DAD: Signal A, 220 nm/Bw:4 nm Results					
Pk #	Name	RT	Area	Area %	Asymmetry

Accelerated Stability study				Accelerated study-1	Accelerated study -3	Accelerated study -6
Etoshine MR Tablet	BSK3640	M.D.12/2011 E.D.11/2013	Description	A Round Biconvex film coated Tablets	A Round Biconvex film coated Tablets	A Round Biconvex film coated Tablets
			Average Weight	186 mg	186 mg	186 mg
			Related Substances	Not detected	Not detected	Not detected
			Assay Etoricoxib	99.79 %	99.48 %	98.70 %
			Assay Thiocolchicoside	99.21 %	98.78 %	98.29 %
Microbiological Testing:						
Total Aerobic Microbial Count			Limit NMT 100 cfu / g	NMT 100 cfu / g	NMT 100 cfu / g	NMT 100 cfu / g
Total combined yeast & molds count			Limit NMT 10 cfu / g	NMT 10 cfu / g	NMT 10 cfu / g	NMT 10 cfu / g
E.coli			Limit NMT 1 cfu / g	NMT 1 cfu / g	NMT 1 cfu / g	NMT 1 cfu / g
S.species			Limit Absent/10g	Absent	Absent	Absent
S. aureus			Limit Absent/1g	Absent	Absent	Absent
Ps. Aeruginosa			Limit Absent/1g	Absent	Absent	Absent

4. CONCLUSION

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug substance and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a re-test period applicable to all future batches of the drug substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period. The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested re-test period will be granted. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient. An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall re-test period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

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