"BCS BASED BIOWAIVER (US - ANDA) AND COMPARATIVE ANALYSIS OF GLOBAL REGULATORY GUIDELINES"

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We wish her better achievements in her future endeavors.

Thanking You.

Yours faithfully,
For Cadila Healthcare Ltd.

Nishan Patel
Human Resource

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Table of Contents

Chapter No.	Chapter Name				Page No.
1	Introduction				1
	1.1	Biowaiver			
	1.2	BCS Based Biowaiver			
2	Aim & Objective				3
3	Literature Review				8
4	Dissertation Work				
	4.1	Types of Biowaiver and Comparison between Global Guidelines			10
	4.2	Comparative Analysis of Different BCS based Biowaiver Guidelines			19
	4.3	United States – Abbreviated New Drug Application			30
	4.4	In-Vitro Permeability and Laboratories			37
	4.5	Biowaiver Monograph of Anti-inflammatory Drug XYZ			52
	4.6	Dossier Compilation for Anti-inflammatory Drug Product based on BCS based Biowaiver	4.6.1	Module 1: Administrative	62
			4.6.2	Module 2: Quality Overall Summary	63
			4.6.3	Module 3: Quality	98
			4.6.4	Module 5: BCS based Study Summary Tables	129
5	Summary				143
6	Conclusion				144
	References				
	Annexure				

List of Tables

Table No.	Table Name	Page No.
1.1	Biopharmaceutical Classification System	4
4.1	Comparison of Availability of Types of Biowaiver in Different Guidelines	17
4.2	Comparison of Key Factors for BCS Based Biowaiver	20
4.3	List of Laboratories	41
4.4	Reagents Used in Permeability study	47
4.5	Calibration Data of Permeability Study	48
4.6	Sampling Data of Permeability Study	50
4.7	Mean Data of Permeability experiment	50
4.8	Anti-inflammatory Drug Dose-Solubility Ratio	55
4.9	Dissolution Study Data of Anti-inflammatory Drug	58
4.10	Impurities	69
4.11	Genotoxic Impurities	69
4.12	Drug Substance Specification	70
4.13	Specification of Impurities	73
4.14	Testing Frequency	77
4.15	Storage Condition	77
4.16	Composition of Anti-inflammatory Drug Product	78
4.17	IID Evaluation of Anti-inflammatory Drug Product	79
4.18	Comparison of Formulation	80
4.19	Critical Characteristics of Drug Substance	80
4.20	Excipient Compatibility	81
4.21	Direct Compression Formulation	82
4.22	Wet Granulation Formulation 1	82
4.23	Wet Granulation Formulation 2	83
4.24	Direct Compression Formulation-Unit Operation	85
4.25	Wet Granulation Formulation 1-Unit Operation	87
4.26	Wet Granulation Formulation 2-Unit Operation	87
4.27	Reconciliation Data	88
4.28	Specification of Inactive Ingredients	88
4.29	Test and Acceptance Criteria for Anti-inflammatory Drug Product	89
4.30	Stability Specification	95
4.31	Stability Study Data	96
4.32	Impurities-Module 3	109
4.33	Specification of Drug Substance-Module 3	112

List of Tables

Table No.	Table Name	Page No.
4.34	Reference Standards or Material	114
4.35	Testing Frequency-Module 3	116
4.36	Testing Data-Module 3	117
4.37	Composition of Anti-inflammatory drug product	118
4.38	Proposed packaging configuration of Anti-inflammatory drug product	118
4.39	Formulation trials and functionality of Raw materials selected	119
4.40	Composition of Anti-inflammatory Drug Product-Module 3	120
4.41	Finished Product Specifications-Module 3	120
4.42	Manufacturing Steps, Possible Variables and Controls	122
4.43	Batch formula for the Anti-inflammatory Drug Product	123
4.44	Control of Critical Steps	123
4.45	Process Validation and/or Evaluation	124
4.46	Specifications of Excipients	124
4.47	Batch Analysis Data	126
4.48	Packing Material Specification	126
4.49	Method Validation for Solubility Testing	129
4.50	Solubility Data for Anti-inflammatory Drug in Different Buffered Media at Different pH	130
4.51	Pivotal Permeability Study Information	131
4.52	Materials and Methods for Validation of Permeability Study	132
4.53	Standard Operating Procedures	133
4.54	Analytical Method Validation (For Pivotal Permeability Study)	134
4.55	Pivotal Permeability Study Design	134
4.56	Pivotal Permeability Study: Apical-to-Basolateral (A to B) Permeability of Test Compound and Internal Standards	135
4.57	Pivotal Permeability Study: Basolateral-to-Apical (B to A) Permeability of Test Compound and Internal Standards	136
4.58	Pivotal Permeability Study: Ratio of B-to-A Papp Vs. A-to-B Papp.	136
4.59	Gastrointestinal Tract Instability Data	137
4.60	Dissolution Method Information	138
4.61	Information of Analytical Method Used to Analyze Dissolution Samples	138
4.62	Dissolution Data	140
4.63	Formulation Data	142

List of Figures

Figure No.	Figure Name	Page No.
1.1	Criteria for BCS based Biowaiver	5
4.1	Types of Biowaiver	10
4.2	Structure of Anti-inflammatory Drug	52
4.3	D/S versus pH graph	56
4.4	Drug Substance Synthesis-Stage I	100
4.5	Drug Substance Synthesis-Stage II	101
4.6	Drug Substance Synthesis-Stage III	101
4.7	IR Spectrum	103
4.8	^{13}C NMR Spectrum	104
4.9	^{1}H NMR Spectrum	105
4.10	Mass Spectra	107
4.11	Diffractogram	108
4.12	TGA graph	109
4.13	IR Spectra of Packing Material	115

List of Abbreviations

Short Name	Abbreviation
USFDA	United States Food and Drug Administration
EU	European Union
ICH	International conference on Harmonization
WHO	World Health Organization
ASEAN	Association of Southeast Asian Nations
RLD	Reference Listed Drugs
BA/BE	Bioavailability/Bioequivalence
BCS	Biopharmaceutical Classification System
USP	United States Pharmacopoeia
$/USD	United States Dollar
eCTD	Electronic Common Technical Dossier
CFR	Code of federation Rule
GDUFA	Generic Drug User Fee Act
RA	Regulatory Affairs
DMF	Drug Master File
R&D	Research and Development
F&D	Formulation & Development
CAS	Chemical abstract Service
IIG/IID	Inactive Ingredient Guideline/Database
CDER	Central Drug Evaluation and Research
RH	Relative Humidity
FEI	Facility Establishment Identifier
DUNS	Data Universal Numbering System
NMT	Not More Than
NLT	Not Less Than
SUPAC	Scale Up and Post Approval Changes
CoA	Certificate of Analysis
CMC	Chemistry, Manufacturing and Control
TPP	Target Product Profile
QTPP	Quality Target Product Profile
CMAs	Critical Material Attributes
CPPs	Critical Process Parameters
USP-NF	United States Pharmacopoeia-National Formulary
MSDS	Material Safety Data Sheet
Ml	Milliliter
Mm	Millimeter
Cm	Centimeter
Mg	Milligram
M	Molar
w/v	Weight by Volume

Sec	Second
Min	Minute
Hr	Hour
ºC	Degree Celsius
§	21CFR

"BCS Based Biowaiver (US-ANDA) and Comparative Analysis of Global Regulatory Guidelines"

Abstract:

To waive a complete and systemic Bioequivalence (BE) study, Biowaiver or Request for a Biowaiver is a fast track approach to boost the drug development. Over the past three-four years the biowaiver market shows greater number of biowaiver submissions and the wider use of In-vitro permeability study. Biowaiver is a beneficial approach for getting approval of ANDA while, BCS based biowaiver is the novel approach to gain approval for NDA as well as ANDA. A BCS based Biowaiver is an exemption from conducting human bioequivalence studies when active ingredient and dosage form meet criteria of solubility, permeability and dissolution. This Dissertation work covers different kind of biowaiver approaches and the criteria for the applicability of BCS based biowaivers in the different geographic scopes with regard to global development strategy. There is a comparison of global guidelines on provisions availability for different types of Biowaiver approaches. From comparison of different global guideline for the requirement criteria of BCS based biowaiver application it is reviewed that most of the guidance conforms to the USFDA, EU and WHO guidelines because most of the countries are following the BCS based biowaiver concept as one of the three main guidance documents (USFDA, EMA, WHO) or a combination of specific requirements. In addition, dossier of BCS based biowaiver requires less data then general ANDA dossier. It includes data that supporting high solubility, high permeability, rapid and similar dissolution and some additional data on excipients and CMC assessment.

Chapter 1

Introduction

1. Introduction

Drug development and approval are challenging and time consuming process for pharmaceutical companies. Thousands of once-promising compounds wash out in the preclinical phase and hundreds more fail in clinical trials and only one are likely to be approved for marketing. Hundreds of millions of dollars are spent on pharmaceuticals or biologics that fail to make it to market. The new drug development takes approximately 12-15 years to reach the market. One of the approaches is to concentrate on developing products for niche markets that may have smaller market potential, but that can lowers cost and time consumption used for development. Moreover, for Generic drug approval unnecessary time and money consumed to perform BE study to prove bioequivalence for more than one formulation designed at development. To fasten the drug approval process "**request for biowaiver"** is novel and effective approach**,** i.e. in-vivo bioequivalence and bioavailability study waivers in accordance to the principles of the Biopharmaceutical Classification System (BCS) as well as other kind of biowaiver approaches that can significantly save time and cost.

Biowaiver is a kind of ANDA filing, which applies

- To reduce cost and time consumption from complete, systemic BE study.

BCS based Biowaiver is applicable to ANDA as well as NDA filing which applies,

- To exempt in-vivo Bioequivalence (BE) study
- To reduce cost and time of BE study

So, BCS based Biowaiver is a novel and beneficial approach for industries to avoid unnecessary expense and time consumption from in-vivo BE study.

1.1 Biowaiver

Simply, Biowaiver is considered as waiver of clinical bioequivalence studies or exemption of BE study.

As per WHO guidance, "The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than In-vivo bioequivalence test".

In other words, biowaiver means an exemption for In-vivo bioequivalence studies. By applying biowaiver approaches whenever possible generic companies can save a lot of resources. With regard to global development strategy it is important to know the criteria for the applicability of biowaivers in the different geographic scopes.
There are mainly seven types of biowaiver application:

- Biowaiver for Specific Dosage Forms
- Biowaiver for Additional dosage Strengths
- Biowaiver for Other Strengths
- Biowaiver for Scale up and Post Approval Changes
- Biowaiver for Same Product
- Bridging – Biowaiver for national bioequivalence study based on bioequivalence study versus foreign reference product
- Biowaiver based on BCS

In further chapters all types are described briefly while BCS based biowaiver are described in detail.

1.2 BCS based Biowaiver

A Biowaiver can currently be requested for solid orally administered immediate release product containing the drug having high solubility and high permeability (BCS based Biowaiver).

Statistics on generic drug products approved between 2000 and 2011 by USFDA based on

BCS classification include 263 approvals, [34]

- 110 approvals of BCS Class I
- 55 approvals of BCS Class II
- 98 approvals of BCS Class III

This shows BCS based biowaiver is new, beneficial and fast track approach for getting approval.

It is estimated that the In-vivo bioavailability and bioequivalence studies cost up to $ 250,000 each and require up to 2 months completing, whereas the In-vitro laboratory tests are rather inexpensive and fast. However, the regulations on BCS based biowaiver differ between the FDA, EU and WHO. The FDA allows the biowaiver only for BCS class I drug substances whereas current WHO and EMA guidance allow products containing Class III drug substances to be considered for the biowaiver.

Other countries following the BCS based biowaiver concept as one of the three main guidance documents (USFDA, EMA, WHO) or a combination of specific requirements are Brazil, Australia, Association of Southeast Asian Nations (ASEAN) countries, South Africa, Canada, India, Argentina, Saudi Arabia. While Switzerland, Japan have not yet implemented the BCS based biowaiver as a means to ensure bioequivalence of different drug products in any shape or form.

What is BCS based Biowaiver?

A BCS based Biowaiver is an exemption from conducting human bioequivalence studies when active ingredient meets certain solubility and permeability criteria In-vitro and when the dissolution profile of the dosage form meets the requirements for an immediate release oral dosage form.

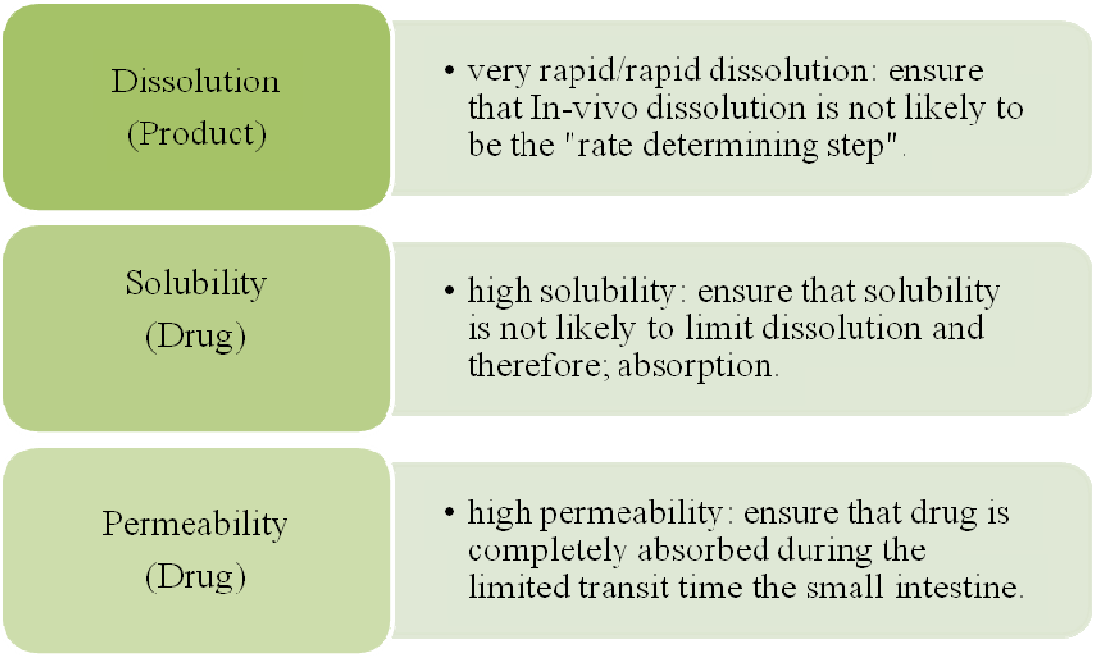


Figure1.1 Criteria for BCS based Biowaiver

For drug substances belonging to a Particular specified BCS class (as per guidance), a complete biowaiver for bioequivalence studies might be possible if criteria of solubility, Permeability and dissolution are met.

BCS based biowaiver are intended only for BE studies. They do not apply to the food effect bioavailability studies or other pharmacokinetic studies.

As per Biopharmaceutics Classification System (BCS), Drugs are classified into four classes having different solubility and permeability criteria described in Table 2.1.

Table 1.1 Biopharmaceutical Classification System

BCS Class I High Solubility High Permeability	**BCS Class II** Low Solubility High Permeability
BCS Class III High Solubility Low Permeability	**BCS Class IV** Low Solubility Low Permeability

Different regulatory authorities have different BCS class requirement for approving BCS based biowaiver. Most of the authorities allow biowaiver for the drug substances belong to BCS class I or BCS class III which is discussed in further chapter.

Chapter 2

Aim & Objective

2. Aim & Objective of Work

As per survey of FDA, Every year only 18 – 26 New Chemical Entities (NCEs) get approved as a New Drug Application (NDA). Whereas, pharmaceutical companies file thousands of Abbreviated New Drug Applications (ANDAs) to get an approval as a generic version of innovators every year.

To get an approval for ANDAs, generic formulation should be proven bioequivalent to that of Reference Listed Drug (RLD). For market authorization of generics, instead of non-clinical and clinical studies, only Bioequivalence (BE) study is required.

At drug development stage, only one formulation become eligible for marketing from many of formulations. In that case, Biowaiver concept comes into picture to reduce unnecessary time and expense of BE study for each formulation.

Biowaiver is a kind of ANDA filing, which applies to reduce cost and time from Complete, Systemic BE Study while, BCS based Biowaiver is applicable to ANDA as well as NDA filing which applies, to exempt in-vivo BE study.

Dossier filing of BCS based Biowaiver include data in form of different modules. It consists of Module 1, Module 2, Module 3 and Module 5. It exempts Data of Module 4 as it is an ANDA filing.

Thus, the Aim of the Dissertation work was to compare Global Regulatory Guidelines on Biowaiver as well as BCS based Biowaiver and Compilation of Dossier for BCS based Biowaiver.

The objective of the present work was…….

- Comparison of availability of provisions for different types of Biowaiver
- Comparative analysis of global regulatory guidelines for BCS based Biowaiver
- Preparation of Monograph from literature search
- To finalize laboratory for In-vitro permeability study
- Dossier Compilation for BCS based Biowaiver

Chapter 3

Literature Review

3. Literature Review

Volpe Donna A. et al [11] has studied examples with cells, intestinal tissue, and artificial membranes demonstrate the applicability and feasibility of method suitability for evaluating permeability models. An assay with established method suitability, standard compounds and criteria for classifying drugs improves the reliability for such assays for regulatory applications.

Xinyuan Zhang et al [12] has analysed the intracellular distribution and transcellular transport characteristics of a test set of molecules, together with more general physicochemical space plots covering all possible combinations of pKa, logPn and logPd, sixteen a priori classes of lysosomotropic behavior for monobasic amines were defined.

Paton David M et al [13] has studied that clinical pharmacokinetic data on the H_1 receptor antagonist, commonly referred to as the antihistamines. Despite their widespread use over an extended period, relatively little pharmacokinetic data is available for many of these drugs.

Dahan Arik et al [14] has studied that the BCS scientific framework and impact on regulatory practice of oral drug products and review the provisional BCS classification of the top drugs on the global market. One notable finding of the Provisional BCS classification is that the clinical performance of the majority of approved IR oral drug products.

Cristofoletti Rodrigo et al [16] has studied that the final outcome of a bioequivalence study is strongly influenced by the solubility of the drug, but not by its intestinal permeability or extent of metabolism. Also, as the estimated risks were similar between the comparisons of classes 1 and 3 versus class 2 of both systems, BDDCS could be considered as adequate as BCS in the classification of drugs with a view to applying the biowaiver.

Nair Anil K. et al [34] has studied classification of drug substances based on aqueous solubility and intestinal permeability. The objective of this study was to use the World Health Organization Model list of essential Medicines to determine the distribution of BCS Class 1, 2, 3 and 4 drugs in Abbreviated New Drug Applications (ANDA) submissions. The literature search indicated a trend of more ANDA approvals of BCS Class I drugs than Class 3 or Class

2 drugs. Antiallergic drugs in Class 1, drugs for pain relief in Class 2 and antidiabetec drugs in Class 3 have reviewed the largest number of approvals during this period.

Shozo Miyazaki et al [39] has determined 3 pharmaceutical hydrochloride salts in sodium acetate hydrochloride acid buffer. The results of this study substantiated that salt formation does not always result in an enhancement of solubility characteristics. The decrease in solubility at lower pH value is attributed to the common ion effect of chloride on the solubility product equilibrium of the hydrochloride salts.

Kortejarvi H. et al [40] has reviewed that currently biowaivers are determined based on solubility, permeability and dissolution but the factors related to the gastrointestinal tract and the dynamic nature of drug dissolution and systemic pharmacokinetics are not taken into account.

MANZO R.H. et al [56] has studied in his study that literature data relevant to the decision to allow a waiver of In-vivo bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing amitriptyline hydrochloride. Literature data indicates that amitriptyline hydrochloride is a highly permeable active pharmaceutical ingredient (API). Data on the solubility according to the current Biopharmaceutical Classification System (BCS) were not fully available and consequently amitriptyline hydrochloride could not be definitively assigned to either BCS Class I or BCS Class II.

Hassan. Y et al [58] has reviewed all the previous studies which have been done for anti-inflammatory drug related to description, physical properties, synthesis, metabolism and method of analysis.

Pallicer Juan M et al [59] has reviewed from literature that previously reported chromatographic method to determine the 1- octanol/water partition coefficient (log Po/W) of organic compounds is used to estimate the hydrophobicity of bases, mainly commercial drugs with diverse chemical nature and pKa values higher than 9.

Chapter 4

Dissertation Work

4. Dissertation Work

4.1 Types of Biowaiver and Comparison between Global Guidelines

Different Drug regulatory authorities approve biowaiver for different conditions, which are summarized in Figure 4.1 and described below in brief.

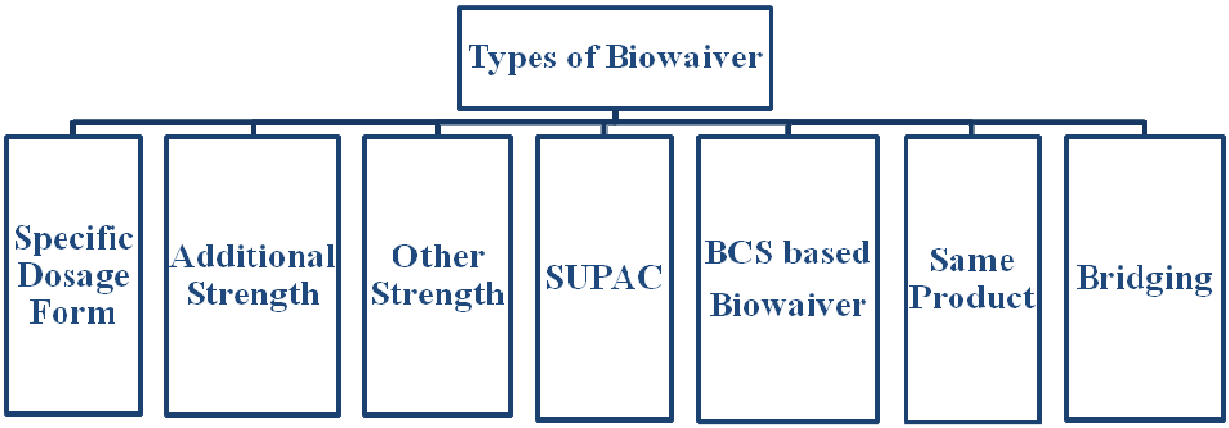


Figure 4.1 Types of Biowaiver

1) **Biowaiver for Specific Dosage Forms**

   Due to certain characteristics of some specific formulations, BE study is not required to perform. In that case, bioequivalence between the test and the reference product can be presumed without any further In-vivo experiments. This kind of biowaiver can be possible for aqueous oral solutions, parenteral solutions and topical solutions (e.g. eye drops). One of the major prerequisite is that the excipients should not influence the bioavailability of the active drug substance. The conditions for this biowaiver are identical in most countries.

2) Biowaiver for Additional Dose Strengths

If several strengths of a generic drug product are developed for the same formulation then under this approach, it can be sufficient to demonstrate bioequivalence of test versus the reference product only with one or two strengths depending on certain product characteristics rather than performing BE study for all strength designed. Also for this biowaiver the basic requirements are identical in most countries.

For this type of biowaiver, BE study is performed either for highest strength or lowest strength among several strengths in case of linear Pharmacokinetic profile. Highest or Lowest strength study is based on pharmacokinetic profile of different strength means if there is linear relationship between dose Vs response of several strengths then only BE study can be performed either for highest or lowest strength.

Choice of strength for BE study: (In case of Additional Strength) *(54)*

Highest Strength: Mostly highest strength is used for BE study. Moreover, if lowest strength is undetectable by analytical method then also highest strength is used to perform BE study.

Lowest Strength: When highest strength is not tolerated by patient or if the highest strength is the issue of patient safety in that case lowest strength is used for BE study.

When highest and lowest both strengths are issue in that case, strength other than highest and lowest is used for BE study among several strengths.

If there is some deviation from quantitatively proportional composition then apply below criteria to the strength used in the bioequivalence study and the strength(s) for which a waiver is to be granted. *(54)*

- The amount of the active substance(s) is less than 5% of the tablet core weight, the weight of the capsule content.

- The amounts of the different core excipients or capsule content are the same for the concerned strength and the amount of active substance is changed.
- The amount of filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths.
- Appropriate In-vitro dissolution data should confirm the adequacy of waiving additional In-vivo bioequivalence testing.

3) Biowaiver for Other Strengths

If several strengths (which are already approved) are designed for same formulation then it is called "Biowaiver based on Other Strength". Mostly highest or lowest strength (In case of linear pharmacokinetic) are used for BE study.

There are two approach comes under Biowaiver for other strengths.

First approach called "Look a Like" is used under Biowaiver for other strength, where difference of total weight and size of different strengths is minor.

Waiver of In-vivo studies for different strengths of a drug product can be granted under 21CFR 320.22 (d) (2) when

- The drug product is in the same dosage form, but in a different strength;
- This different strength is proportionally similar in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an appropriate In-vivo study;
- The composition of strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, color agents and flavors are not required to follow this rule).

Another second approach is called “Dose Proportional”. For that guidance defines proportionally similar in the following ways:

- All active and inactive ingredients are in exactly the same proportion between different strengths (e.g., a tablet of 50 mg strength has all the inactive ingredients, exactly half that of a tablet of 100 mg strength, and twice that of a tablet of 25 mg strength).
- Active and inactive ingredients are not in exactly the same proportional between different strengths as stated above, but the ratios of inactive ingredients to total weight of the dosage form are within the limits defined by the SUPAC-IR and SUPAC-MR guidance up to and including Level II.
- For high potency drug substances, where are amount of the active drug substance in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within ± 10% of the total weight of the strength on which a biostudy was performed), the same inactive ingredients are used for all strengths and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-IR and SUPAC-MR guidance up to and including Level II.

4) Biowaiver based on BCS

For drug substances belonging to a BCS class (Mostly Class I or Class III) a complete biowaiver for bioequivalence studies might be possible if criteria of solubility, permeability and dissolution are met. The eligibility criteria for BCS based biowaivers differs between USA, EU and WHO as well as in other countries which have been compared in Chapter 4.2 on basis of solubility, permeability, dissolution and BCS Classification.

5) Biowaiver for Scale Up and Post Approval Changes

During the life cycle of a medicinal product, there is usually several post approval changes occurred which require a new bioequivalence study to prove the equivalence of the new generic medicinal product to the reference product. However, under this approach there is no need of additional BE study as the applicant can justify that certain preconditions are fulfilled or comparable in different geographical scopes. This kind of biowaiver is applicable to mostly minor post approval changes and few of the moderate changes.

Information of the types of In-vitro dissolution testing in the presence of specified post approval changes are provided in an FDA guidance for industry entitled SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale Up and Post Approval Changes: Chemistry, Manufacturing and Controls, In-vitro Dissolution testing. For post approval changes, we recommended that the In-vitro comparison be made between the pre change and post change products. In instances where dissolution profile comparisons are suggested, we also recommended an f2 test be used. An f2 value of >50 suggests a sufficiently similar dissolution profile and no further In-vivo studies are needed. When In-vivo BE studies are called for, we recommend that the comparison be made for ANDAs between the post change and reference listed drug products.

6) Biowaiver for Same Product

Biowaiver for same product can be granted if the generic medicinal product is a 1:1 copy of the reference product, bioequivalence between the test and reference product can be presumed based on demonstration of identity and comparative In-vitro dissolution data. The basis for this biowaiver approach is the sameness of the test and reference product. It is not officially described in regulatory guidance documents, but in theory it is possible only if the generic applicant knows exact quantitative and qualitative composition (with regard to active substance(s) and excipients) as well as the galenical characteristics and manufacturing process of the reference product. In

practice however, it is often not feasible due to patent issues to develop quantitatively and qualitatively the same product like the innovator. Altogether, this approach is not very common but sometimes it possible. (e.g. simple gelatin capsules filled only with the active ingredient without any excipients) Regulatory authorities worldwide must be convinced of this biowaiver approach on a case by case basis.

7) **Bridging – Biowaiver for National Bioequivalence Study based on Bioequivalence Study versus Foreign reference Product**

There is the so called "Bridging" approach which is used to waive unnecessary national bioequivalence studies. Many countries require so called – local bioequivalence studies that are bioequivalence studies of test product versus the local reference product and very often with subjects from the local population. Especially, Asian countries (for instance China, South Korea, Thailand and Japan) usually require such local bioequivalence studies. Moreover, Russia, Canada, Australia, Brazil, Mexico and other countries require bioequivalence studies versus the corresponding local reference product. In the case of ethnic sensitivity relating to the metabolism of the drug substance, it makes sense to demonstrate bioequivalence in different ethnic populations. However, the need to use the local reference product is not always justified, because innovator products are very often identical in different countries around the world.

Under this "Bridging" biowaiver concept regulatory authorities accept the results of bioequivalence studies which have been performed for test versus a foreign reference product rather than national reference product approved in the country where the application is made. The study results versus the foreign reference product are "bridged" via product likeness to the locally/nationally approved reference product. If the foreign and local/national reference products are essentially same, an additional bioequivalence study may not be required. Although, one prerequisite is that general study requirements like GCP are fulfilled and that potential ethnic differences in pharmacokinetics can be excluded.

Above described biowaiver approaches are compared for global regulatory authorities based on provision available in Table 4.1. Where, (+) “Plus” indicates availability of provision in that guideline and (-) “Minus” indicates absence of provision in that guideline.

From comparison of biowaiver in table 4.1 it can be seen that provisions of specific dosage form, BCS based Post Approval Changes, Same Product based biowaiver and Additional Strength biowaiver (Highest or Lowest) are available in each country or guideline mentioned in comparative analysis. Whereas, biowaiver for other strengths and based on bridging are allow by few of the regulatory authorities. In addition, different regulatory authorities require different BCS class drug to grant BCS based biowaiver.

Table 4.1 Comparison of Availability of Types of Biowaiver in Different Guidelines

Parameter / Country	Specific Dosage Form	Other Strengths	Additional strengths -Lower -Higher	BCS Based	Post Approval Changes	Same Product	Bridging
USA	+	+	+	+ Class I	+	+	+
EU	+	+	+ Highest & Lowest	+ Class I & Class III	+	+	+
WHO	+	-	+	+ Class I, Class III & Class II weak acid	+	+	-
ASEAN	+	+	+ Highest & Lowest	+ Class I	+	+	-
Australia	+	+	+ Highest & Lowest	+ Class I & Class III	+	+	-
Brazil	+	-	+ Highest & Lowest	+ Class I	+	+	-
Canada	+	-	+	+ Class I & Class III	+	+	-

Parameter / Country	Specific Dosage Form	Other Strengths	Additional strengths -Lower -Higher	BCS Based	Post Approval Changes	Same Product	Bridging
China	Guidance from Regulatory Authority of China is not available in Translated Language or English Language.						
India	+	-	+	+ Class I	+	+	-
Japan	+	-	+	Not Available	+	+	-
Malaysia	+	+	+ Highest & Lowest	+ Class I	+	+	+
Russia	+	-	+	+ Class I	+	+	-
Saudi Arabia	+	-	+	+ Class I	+	+	+
South Africa	+	-	+	+ Class I	+	+	-

4.2 Comparative Analysis of Different BCS based Biowaiver Guidelines

Quantities of data to support a request for biowaivers have to be submitted. The drug substance for which a waiver is being requested should be highly soluble and highly permeable. Sponsors requesting biowaivers based on the BCS should submit the information or data on solubility, permeability and dissolution.

Different guidelines have their own requirements and criteria for submitting dossier to get BCS based biowaiver. Comparison between requirements of data supporting BCS based biowaiver is given below for different guidelines. Different regulatory authorities have given guidance for carrying out biowaiver study. The biowaiver approval criteria differ for region vise regulatory authorities but most of the guidance has same requirements for permeability, solubility and dissolution because most are adopted from USFDA, EMEA and WHO guidance on BCS based biowaiver. Difference between requirements of study criteria for solubility, permeability and dissolution are kept in bold fonts in Table 4.2.

Table 4.2 Comparison of Key Factors for BCS Based Biowaiver

	Solubility of Drug Substance	**Permeability of Drug Substance**	**BCS Class of Drug Substance**	**In-vitro Dissolution Similarity of Test and Reference Product**
USA[52]*	Highest dose strength is soluble in ≤ 250 ml of buffers **pH range:** **1-7.5** **Temp.:** 37 ±1°C **Methodology:** • Shake Flask Method, • Acid or Base Titration	**Highly Permeable:** Extent of absorption in humans is **≥ 90%** **Methodology:** • Absolute Bioavailability study • Mass Balance study • In-vivo perfusion study • In-vitro excised human or animal Intestinal study • In-vitro epithelial cell culture study	**Class I**	**Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance dissolves within 30 minutes. **Apparatus:** USP Type I at 100 rpm or Type II at 50 rpm **Dissolution Media**: 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12
EU[47]	Highest dose strength is soluble in ≤ 250 ml of	**Highly Permeable:** Extent of absorption in humans is **≥ 85%**	**Class I, Class III**	**Class I** **Rapidly Dissolving:** ≥85% of the

	buffers **pH range:** **1-6.8** **Temp.:** 37 ±1°C **Methodology:** • Shake Flask Method	**Methodology:** • Absolute Bioavailability study • Mass Balance study		labeled amount of the drug substance dissolves within 30 minutes. **Class III** **Very Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance dissolves within 15 minutes. **Apparatus:** USP Type I at 100 rpm or Type II at 50 rpm **Dissolution Media:** 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12
WHO[48]	Highest dose strength is soluble in ≤ 250 ml of buffers **pH range:** **1-6.8**	**Highly Permeable:** Extent of absorption in humans is **≥ 85%** **Methodology:** • Absolute Bioavailability study	**Class I, Class III and Class II weak acid**	**Rapidly Dissolving:** **Class I:** ≥85% of the labeled amount of the drug substance dissolves within 30 minutes.

	Temp.: 37 ±1°C **Methodology:** • Shake Flask Method	• Mass Balance study		**Class III:** ≥85% of the labeled amount of the drug substance dissolves within 15 minutes. **Class II(Weak Acid):** ≥85% of the labeled amount of the drug substance dissolves within 30 minutes at pH 6.8 **Apparatus**: USP Type I at 100 rpm or Type II at 75 rpm **Dissolution Media:** 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12
ASEAN[35]	Highest dose strength is	**Highly Permeable:** Extent of	**Class I**	**Rapidly Dissolving:** ≥85% of the

	soluble in ≤ 250 ml of buffers **pH range:** **1-7.5** **Temp.:** 37 ±1°C **Methodology:** • Shake Flask Method • Acid or Base Titration	absorption in humans is **≥ 90%** **Methodology:** • Absolute Bioavailability study • Mass Balance study • In-vivo perfusion study • In-vitro excised human or animal Intestinal study • In-vitro epithelial cell culture study		labeled amount of the drug substance dissolves within 30 minutes. **Apparatus:** USP Type I at 100 rpm or Type II at 50 rpm **Dissolution Media:** 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12
Australia[47]	Highest dose strength is soluble in ≤ 250 ml of buffers **pH range:** **1-6.8** **Temp.:** 37 ±1°C **Methodology:** • Shake Flask Method	**Highly Permeable:** Extent of absorption in humans is **≥ 85%** Methodology: • Absolute Bioavailability study • Mass Balance study	**Class I,** **Class III**	**Class I** **Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance dissolves within 30 minutes. **Class III** **Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance dissolves within 15 minutes. **Apparatus:** USP Type I at 100 rpm

				or Type II at 50 rpm **Dissolution Media:** 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12
Brazil[45]	Highest dose strength is soluble in ≤ 250 ml of buffers **pH range:** **1-6.8** **Temp.:** 37 ±1°C **Methodology:** • Shake Flask Method	**Highly Permeable:** Extent of absorption in humans is **≥ 85%** **Methodology:** • Absolute Bioavailability study • Mass Balance study • In-vitro epithelial cell culture study	**Class I**	**Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance dissolves within 30 minutes. **Apparatus**: USP Type I at 100 rpm or Type II at 50 rpm **Dissolution Media:** 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

				N = 12
Canada[6]	Highest dose strength is soluble in ≤ 250 ml of buffers **pH range:** **1-6.8** **Temp.:** 37 ±1°C **Methodology:** • Shake Flask Method, or similar method with justification.	**Highly Permeable:** Extent of absorption in humans is **≥ 85%** **Methodology:** • Absolute Bioavailability study • Mass Balance study	**Class I and Class III**	**Class I** **Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance dissolves within 30 minutes. **Class III** **Very Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance dissolves within 15 minutes. **Apparatus:** USP Type I at 100 rpm or Type II at 50 rpm **Dissolution Media:** 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12
China	Guidance from Regulatory Authority of China is not available in Translated Language or English Language.			
India[4]	Highest dose strength is	**Highly Permeable:** Extent of	**Class I**	**Rapidly Dissolving:** ≥85% of the

	soluble in ≤ 250 ml of buffers **pH range:** **1-7.5** **Temp.:** 37 ±1°C **Methodology:** • Shake Flask Method • Acid or Base Titration	absorption in humans is **≥ 90%** **Methodology:** • Absolute Bioavailability study • Mass Balance study • In-vivo perfusion study • In-vitro excised human or animal Intestinal study • In-vitro epithelial cell culture study		labeled amount of the drug substance dissolves within 30 minutes. **Apparatus:** USP Type I at 100 rpm or Type II at 50 rpm **Dissolution Media**: 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12
Japan[3]	Regulatory Authority of Japan has introduced the concept of BCS based biowaiver but it hasn't particular guideline for that.			
Malaysia[5]	Highest dose strength is soluble in ≤ 250 ml of buffers **pH range:** **1-6.8** **Temp.:** 37 ±1°C	**Highly Permeable:** Extent of absorption in humans is **≥ 85%** **Methodology:** • Absolute Bioavailability study • Mass Balance study	**Class I**	**Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance dissolves within 30 minutes. **Apparatus:** USP Type I at 100 rpm or Type II at 75 rpm **Dissolution Media:** 900 ml of following media

	Methodology: • Shake Flask Method or similar method with justification			(1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12
Russia[48]	Highest dose strength is soluble in ≤ 250 ml of buffers **pH range:** **1-6.8** **Temp.:** 37 ±1°C **Methodology:** • Shake Flask Method or similar method with justification	**Highly Permeable:** Extent of absorption in humans is **≥ 85%** **Methodology:** • Absolute Bioavailability study • Mass Balance study • In-vivo perfusion study • In-vitro excised human or animal Intestinal study • In-vitro epithelial cell culture study	**Class I**	**Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance dissolves within 30 minutes. **Apparatus:** USP Type I at 100 rpm or Type II at 75 rpm **Dissolution Media:** 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12
Saudi Arabia[2]	Highest dose strength is soluble in ≤ 250 ml of	**Highly Permeable:** Extent of absorption in humans is **≥ 85%**	**Class I**	**Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance

	buffers **pH range:** **1-6.8** **Temp.:** 37 ±1°C **Methodology:** • Shake Flask Method or similar method with justification	**Methodology:** • Absolute Bioavailability study • Mass Balance study • In-vitro epithelial cell culture study		dissolves within 30 minutes. **Apparatus:** USP Type I at 100 rpm or Type II at 75 rpm **Dissolution Media:** 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12
South Africa[1]	Highest dose strength is soluble in ≤ 250 ml of buffers **pH range:** **1-7.5** **Temp.:** 37 ±1°C **Methodology:** • Shake Flask Method or similar method	**Highly Permeable:** Extent of absorption in humans is **≥ 90%** • Absolute Bioavailability study • Mass Balance study • In-vitro epithelial cell culture study	**Class I**	**Rapidly Dissolving:** ≥85% of the labeled amount of the drug substance dissolves within 30 minutes. **Apparatus:** USP Type I at 100 rpm or Type II at 50 rpm **Dissolution Media:** 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer;

	with justification			(3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. **N** = 12

(Note: * indicates amended draft guidance on "Waiver of In-vivo Bioavailability and Bioequivalence studies for Immediate Release Solid Oral Dosage Forms based on a Biopharmaceutics Classification System – Guidance for Industry, May 2015. As per this guidance allow BCS class I as well as BCS class III for getting approval for BCS based Biowaiver. Moreover, pH range for solubility study, extent of absorption and dissolution criteria have been changed same as EU guidance.)

4.3 United States – Abbreviated New Drug Application

This chapter includes information on content and format of Abbreviated New Drug Application for United States. It emphasizes how and what data should be submitted in different modules to USFDA for ANDA.

4.3.1 US – ANDA (US – Abbreviated New Drug Applications) [7]

An Applicant submits an ANDA based on a previously approved drug product on which the ANDA relies is officially known as the reference listed drug (RLD). A reference listed drug (RLD) is defined as the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application (§314.3(b)). FDA lists approved drugs that may be referenced in an ANDA in the Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book). The Orange book is updated by a monthly cumulative supplement.

CTD Format

The CTD format was developed by the International Conference on Harmonization (ICH) in an attempt to streamline the variability of submission requirements among Japan, European Union and the United States. The CTD collate information of quality, safety and efficacy into a common format that has been adopted by ICH regulatory authorities. Only ANDA submissions made electronically, following the eCTD format on the date of submission will be subject to the review metric goals described in the GDUFA commitment letter.

The CTD is comprised of the following modules:

- Module 1: Administrative Information
- Module 2: CTD Summaries
- Module 3: Quality
- Module 4: Nonclinical Study Reports
- Module 5: Clinical Study Reports

But ANDA dossier includes data only of Module 1, Module 2, Module 3 and Module 5 except Module 4 because ANDA doesn't require non-clinical data.

Module 1 contains administrative information and is not considered part of the "common" application. Each regulatory authority that accepts the CTD uses its own Module 1. The information described for Module 1 in this guidance applies only to ANDAs submitted to the USFDA. Modules 2 to Module 5 of the CTD are common for all the regions.

Detailed information on content and format of Abbreviated New Drug Application can be obtained from Guidance for Industry ANDA Submissions — Content and Format of Abbreviated New Drug Applications, June 2014, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm400630.pdf

Module 1 – Administrative Information [7]

1. Forms and Cover Letter
2. Administrative Information
3. References
4. Other Corresponds
5. Labeling

Module 1 includes information on above listed requirements. Checklist for module 1 requirements is given in Chapter 4.6.

Module 2 – CTD Summaries [7]

1. Quality Overall Summary

2.3 Contains the Quality Overall Summary (QOS), which provides an overview of the chemistry, manufacturing, and controls (CMC) section of the application (§ 314.50(c)(2)(iv)). The QOS summarizes what is known about the drug substance (the active pharmaceutical ingredient (API)) in section **2.3.S** and the drug product in section **2.3.P.** Applicants should provide separate information on each drug substance contained in the

product in section 2.3.S. All information provided in the summary needs to be accurate and supported by information, data, or justification included in Module 3 or other parts of the application.

Applicants should use the Question-Based Review (QbR) model when writing their summaries. FDA introduced the QbR initiative in 2005 as a tool for the review of the CMC — Drug Substance and Drug Product Quality — sections of the ANDA and updated the QbR model to include additional CMC questions from microbiology in 2011. The QbR model assists applicants in developing their QOS by providing specific questions that, when answered, ensure adequate information is submitted for FDA review. FDA has posted the QbR-QOS outlines designed for simple dosage form products (solution or immediate-release solid oral dosage forms).

FDA recommends that the QOS be submitted in MS Word and text-based PDF file. If the applicant provides a scanned PDF copy of the QOS, FDA requests that the applicant also submit the QOS in Microsoft Word.

2. Clinical Summary

Note: For BCS based biowaiver, Clinical summary part include only summary of In-vitro permeability study.

Module 3 – Quality *(7)*

1. **Drug Substance**

   3.2.S.1 Contains general information about the drug substance

   3.2.S.2 Contains information related to each drug substance manufacturer and manufacturing

   3.2.S.3 Contains characterization information for the API

   3.2.S.4 Contains all information about the control of the drug substance

   3.2.S.5 Contains information about the reference standards or materials

   3.2.S.6 Contains information about the container closure system

3.2.S.7 Contains stability data including the retest date or expiration date of the API

2. **Drug Product**

3.2.P.1 Contains the description and composition of the drug product

3.2.P.2 Contains the information on the pharmaceutical development of the drug product

3.2.P.3 Contains information about the manufacture of the drug product

3.2.P.4 Contains information on the controls of excipients including the identity of the source of inactive ingredients and the grades

3.2.P.5 Contains information supporting the controls of the drug product

3.2.P.6 Contains information about the reference standards or materials

3.2.P.7 Contains information on the container closure system

3.2.P.8 Contains the stability data

3. **Appendices**

4. **Regional Information**

5. **Literature References**

Module 4 – Nonclinical Study Reports

ANDAs generally do not contain data that are required for Module 4.

Module 5 – Clinical Study Reports

Module 5 contains all of the clinical study report data needed to support the application and demonstrate that the generic is bioequivalent to the RLD (§ 314.94(a)(7)). To facilitate the submission of complete data, FDA develops product specific guidance, summary data tables and multiple guidelines on biopharmaceutics. Applicants should use an eCTD study Tagging File for each study submitted.

Specifically for BCS based biowaiver, Module 5 contains data only on permeability study, Dissolution study and its validation data in tabular form only.

4.3.2 BCS based Biowaiver (US – ANDA) [52]

Especially for BCS based biowaiver, which is Abbreviated New Drug Application (ANDA) for USFDA contains following data in different modules except Module 4. Module 5 of BCS based biowaiver contains only permeability data other than clinical data like normal ANDA.

The following information should be included in the application:

1. **Data Supporting High Solubility**

The following information should be included in the application:

- A description of test methods, including information on analytical method and composition of the buffer solutions
- Information on chemical structure, molecular weight, nature of the drug substance (acid, base, amphoteric, or neutral), and dissociation constants (pKa(s))
- Test results (mean, standard deviation, and coefficient of variation) summarized in a table under solution pH, drug solubility (e.g., mg/ml), and volume of media required to dissolve the highest dose strength
- A graphic representation of mean pH-solubility profile

2. **Data Supporting High Permeability**

The following information should be included in the application:

- For human pharmacokinetic studies, information on study design and methods used along with the pharmacokinetic data.
- For direct permeability methods, information supporting the suitability of a selected method that encompasses a description of the study method, criteria for selection of human subjects, animals, or epithelial cell line, drug concentrations in the donor fluid, description of the analytical method, method used to calculate extent of absorption or permeability, and where appropriate, information on efflux potential (e.g., bidirectional transport data).

- A list of selected model drugs along with data on extent of absorption in humans (mean, standard deviation, coefficient of variation) used to establish suitability of a method, permeability values for each model drug (mean, standard deviation, coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean ± standard deviation or 95% confidence interval) with identification of the low/high permeability class boundary and selected internal standard. Information to support high permeability of a test drug substance should include permeability data on the test drug substance, the internal standards (mean, standard deviation, and coefficient of variation), stability information, data supporting passive transport mechanism where appropriate, and methods used to establish high permeability of the test drug substance.

3. Data Supporting Rapid and Similar Dissolution

For submission of a biowaiver request, an IR product should be rapidly dissolving. Data supporting rapid dissolution attributes of the test and reference products should be developed. The following information should be included in the application:

- A brief description of the IR products used for dissolution testing, including information on batch or lot number, expiry date, dimensions, strength, and weight
- Dissolution data obtained with 12 individual units of the test and reference products using recommended test methods in section III.C. The percentage of labeled claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included.
- Data supporting similarity in dissolution profiles between the test and reference products in each of the three media, using the f_2 metric

4. Additional Information

- The manufacturing process used to make the test product should be described briefly to provide information on the method of manufacture (e.g., wet granulation vs. direct compression).
- A list of excipients used, the amount used, and their intended functions should be provided. Excipients used in the test product should have been used previously in FDA-approved IR solid oral dosage forms.

4.4 In-Vitro Permeability Study and Laboratories

For BCS based Biowaiver Permeability Data should be submitted to get approval. There are different types of permeability studies provided in respective guideline on BCS based Biowaiver. Different methods are described below.

Methods for Permeability Study

Unlike the straightforward methods for solubility, dissolution and gastric stability, the BCS guidance recommends several methods to determine the permeability class membership of a drug substance.

1. **Human Methods**
   Mass Balance Studies
   Absolute Bioavailability

2. **In-vivo Intestinal Perfusion**
   Animal Methods In-vivo Intestinal Perfusion
   In situ Intestinal Perfusion

3. **In-vitro Methods**
   Flux across Excised Human or Animal Tissue
   Transport through Epithelial Cell Monolayers

Among different permeability studies, In-vitro methods are mostly preferred by pharmaceutical companies for BCS based Biowaiver approval.

In-vitro Permeability Study

Permeability Study:

In-vitro permeability studies can assess the oral absorption potential and characteristics of drug candidates. Typically Caco-2 and/or Madin-Darby Canine Kidney (MDCK) cells grown as Monolayers in Transwells are used for In-vitro permeability studies. PAMPA is also very useful assay method for permeability study.

4.4.1 Methods Used for Permeability Study:

1. PAMPA

PAMPA (Parallel Artificial Membrane Assay) is a method which determines the permeability of substances from a donor compartment, through a lipid-infused artificial membrane into an acceptor compartment. [25]

It is one of the In-vitro ADME screening services.

- The Parallel Artificial Membrane Permeability Assay (PAMPA) is used as an In-vitro model of passive, transcellular permeation.
- PAMPA avoids the complexities of active transport, allowing test compounds to be ranked based on a simple permeability property alone.
- The ability of this assay to evaluate permeability over a large pH range is valuable for an early understanding how new oral compounds might be absorbed across the entire gastrointestinal tract.

2. Caco-2

The Caco-2 cell line is a continuous cell of heterogeneous human epithelial colorectal adenocarcinoma cells.

The Caco-2 monolayer is widely used across the pharmaceutical industry as an In-vitro model of the human small intestine mucosa to predict the absorption of orally administered drugs.

The Caco-2 permeability assay is an established method for predicting the In-vivo absorption of drugs across the gut wall by measuring the rate of transport of a compound across the Caco-2 cell line. [25]

The Caco-2 system is preferred over other systems, for the study of oral absorption because

- It uses human-derived cells,
- Both disappearance of the compound from the apical (Luminal) side and appearance of the compound on the basolateral (Serosal) side can be monitored,
- Good correlation can be obtained between permeability across Caco-2 cell Monolayers and absorption in humans for a large variety of chemical series, and
- The system is at risk for elucidated factors (e.g., efflux transporters, metabolism, and para cellular transport) associated with poor transport of drug molecules.

Applications of Caco-2 Permeation Screens

- Transport mechanisms-passive diffusion
- Transport mechanisms-carrier mediated
- Assessments of prodrugs
- pH effects on transport
- Cytotoxicity Vs absorption enhancement
- Chemotherapeutics
- Rapid absorption screen

Features of Caco-2 cell Monolayers

- From tight junctions between cells
- Express many of the transporters found in the small intestine (bile acid, amino acid, dipeptide, tri-peptide etc)
- Express the p-glycoprotein efflux pump
- Exhibit metabolizing enzymes on the brush border membrane and in the cytosol

3. MDCK Cells

MDCK cells are a well established polarized epithelial cell line that, like Caco-2 cells, have been used to differentiate when cultured on semi permeable membranes. As a result of their more rapid growth rate, MDCK cells offer the advantage of higher throughput than Caco-2 cells, which are limited by both a 3-week growth period and regular maintenance feeding requirements. MDCK cells provide information about the passive permeability of a chemical class and therefore are a more simplistic system. Also, specific cell lines have been generated that possessed single expressed transporters, such as the MDR1 construct, for use in a more defined experiment.

Suitability of compound is determined by using MDR1-MDCK permeability assay to identify intestinal or CNS permeability, characterize P-gp substrates or investigate P-gp efflux.

MDR1- MDCK permeability is one of the portfolios of In-vitro ADME screening services and it is used in the identification of P-gp substrates. [25]

Advantages of MDCK (Madin-Darby Canine Kidney) Cells

- Easy to use and clean analytically, with good reproducibility and viability
- Passive diffusional transport information at the cellular level
- Lack of p-glycoprotein pumps or substantial levels of metabolizing systems

Among all types of permeability studies mostly Caco-2 assay method is preferred by pharmaceutical companies for In-vitro permeability study. In my project work also for BCS based biowaiver application Caco-2 permeability study has been chosen and Permeability study data are obtained from Caco-2 permeability assay. For that many laboratories are searched with locations, Affiliations and their quotations worldwide. The laboratories which perform Caco-2 permeability study are as follows.

4.4.2 List of Laboratories

Following are the chosen laboratories based on quotations for Caco–2 permeability study from many laboratories enlisted in table 4.3. From these three laboratories given below, Cyprotex Ltd. was finalized for Caco–2 permeability study as a part of my dissertation work.

4.3 List of Laboratories

Laboratories for Caco – 2 Permeability Study			
	Absorption System	**Cyprotex**	**Gentronix (Innovation & Services)**
Location:	**1. USA Headquarter** Exton, PA- 19341 Tel: 610-280-7300 Fax: 610-280-9667 **2. Western USA** San Diego, CA 93111 Tel: 858-560-7300 Fax: 858-560-9006	**1. United Kingdome (HQ)** 15 Beech Lane, Macclesfield, Cheshire SK102DR United Kingdom, Tel: +44(0)1625 505100 Fax: +44(0)1625 505199 enquiries@cyprotex.com **2. United States** 313 PeasantSt., Watertown, MA02472, USA Tel: +1-888-297-7683 Fax: +1-617-812-0712 enquiries@cyprotex.com **3. United States** 4717 CampusDrive, Kalamazoo, MI49008, USA	**1. Gentronix Limited** BioHubat Alderley Park Alderley Edge Cheshire SK104TG United Kingdom **2. Scientific Enquiries** Professor Richard Walmsley Tel: +44(0)1625238743 Fax: +44(0)1625238701 Richard.walmsley@gentronix.co.uk **3. North America** Gentronix Limited Dorothy Zelent Tel: +1(0)484-612-3424 Dorothy.zelent@gentronix.us

		Tel: +1-269-353-5555 Fax: +1-269-544-1077 enquiries@cyprotex.com	**4. Japan** Intralink (Tokyo) CharlesCielo T: +81355799280 F: +81355799291 Charles.cielo@intralink.jp.com
Affiliation	➢ American Association for Cancer Research (AACR) ➢ American Association for Laboratory Animal Science (AALAS) ➢ American Association of Advancement of Science ➢ American Association of Pharmaceutical Scientists (AAPS) ➢ American Board of Toxicology (ABT) ➢ American Chemical Society (ACS) ➢ American College of	➢ Cyprotex supply a range of services to assess the potential toxicity of chemicals. 2D and 3D In-vitro skin and ocular models are available. Cyprotex are also able to offer endocrine disruption is also able to offer endocrine including compliance with the US EPA endocrine disruption screening programme (EDSP). Many of our services follow GLP, OECD, REACH, US EPA and the EU Cosmetics Directive.	➢ GLP, OECD guidelines ➢ OECD guidelines ➢ Gentronix is GLP compliant and offers regulatory assays to OECD and other test guidelines.

	Toxicocology (ACT) ➢ American Society for Pharmacology & Experimental therapeutics (ASPET) ➢ California Analytical Chemists Organization (CACO) ➢ CACO Pharmaceutical & Bioscience Society (CACO-PBSS) ➢ Controlled Release Society (CRS) ➢ Delaware Valley Drug Metabolism Discussion Group (DVDMDG) ➢ Delaware Valley Mass Spectrometry Discussion Group (DVMSDG) ➢ Drug Information Association (DIA)		

	➢ Eastern Technology Council (ETC) ➢ European federation for Pharmaceutical Sciences (EUFEPS) ➢ Federation of American Societies for Experimental Biology (FASEB) ➢ Globalization of Pharmaceutics Education Network, Inc. (GPEN) ➢ Institute for In Vitro Sciences, Inc ➢ International Society for the Study of Xenobiotics (ISSX) ➢ Mid-Atlantic Pharmacology Society (MAPS) ➢ New England Drug Metabolism Discussion Group (NEDMDG) ➢ New Jursey Biobreak		

	➢ New Jursey Drug Metabolism Discussion Group (NJDMDG) ➢ OCTANE ➢ PA Biotech (PABio) ➢ Philadelphia Biobreak ➢ Regulatory Affairs Professional Society (RAPS) ➢ Society for Neuroscience ➢ Society of Toxicology		
Facility Credentials	➢ AAALAC Accredited ➢ USDA registered ➢ NIH registered	**---**	**---**
Quotation for Caco – 2 Permeability Study	**$ 3000**	**£ 900**	**£ 1600**

Here, in section 4.4.3, example of Caco-2 permeability study is given which include protocol and detailed study data.

4.4.3 Example of Caco-2 Permeability Study

Purpose:

To measure directional Caco-2 permeability of test compounds in cultured Caco-2 monolayer. [15]

Instruments	Reagents
Tissue culture CO2 incubator with humidity control	Ringers buffer solution (pH 7.4 at 25°C)
Liquid handler	Ringers buffer with 1% Methanol
Orbital shaker	Blk solution: Ringers buffer: Methanol=2:1 (v/v)
EVOM Epithelial Volt-ohmmeter (World Precision Instruments, Sarasota, FL)	100% Methanol including internal standard (IS)
Bench top centrifuge with 96-well plate adaptor	10 mM stock dosing solution in DMSO
Caco-2 cells (Human colorectal adenocarcinoma, ATCC #37-HTB, passage 30-45)	100 µM dosing solution in buffer
Becton Dickinson plates, Part # 351181, Fisher Scientific, Inc.	

Protocol summary

- Caco-2 permeability: 20-23 day/ Passage 30-45
- 24-well format transwell: 0.31 cm^2 surface area
- Donor conc: 100 µM including 1% DMSO
- A: 300 µL pH 7.4/ B: 1200 µL pH 7.4 Ringers buffer
- Directionality: A B and B A (N=4)

- Donor side sampling: 20 µL at beginning and end (90 min)
- Receiver side sampling: 100 µL at 30, 50, 70, and 90 min
- Incubation at 50 oscillations per minute, 37 °C, 5%CO2, 95% humidity
- Analysis: LC-UV, LC-MS, or LSC
- Output: Peff (cm/sec) = (dX/dt)/(A*Co*60), dX/dt: transported amount (nmole) *versus* time (minute) profile in the receiver chamber; A: surface area (cm^2); and Co: initial donor concentration (µM)
- Positive control: Drug 1 and Drug 2
- Membrane integrity: TEER >200 Ocm^2
- Amount required: Approximately 1 mg or 100 µL of 10 mM test compound in DMS
- Throughput: 6 compounds / 2 Caco-2 plates/1 FTE/ day

Preparation of Ringers with Glucose (Isotonic = 290 mOsm/kg)

Table 4.4 Reagents Used in Permeability study

Chemical	Molecular wt.	Concentration	Mass (g) for 1 L	Mass (g) for 4 L	Mass (g) for 4 L
Ca SO4 2H2O	172.2	1.25 mM	0.2152	0.4305	0.861
MgSO4 7H 2O	246.5	1.1 mM	0.2712	0.5423	1.0846
KCl	74.55	5 mM	0.3728	0.7455	1.491
Na2HPO4	142.0	1.15 mM	0.1633	0.3266	0.6532
NaH2PO4 H2O	138.0	0.3 mM	0.0414	0.0828	0.1656
NaHCO3	84.01	25 mM	2.100	4.200	8.401
Glucose($C_6H_{12}O_6$)	180.2	25 mM	4.505	9.01	18.02
NaCl	58.44	110 mM	6.428	12.86	25.71

Preparation of 4 L Solution

- To 3.5 L distilled water; add Calcium Sulfate and Magnesium Sulfate.
- Adjust the final volume of the solution to 4 L with distilled water, with continuous stirring.
- Adjust final solution to a pH of 7.4 using 1N HCl or 1N NaOH.

- Make the buffer iso-osmotic using NaCl. Measure tonicity of the solution using a tonometer. Given that an isotonic solution is equivalent to 0.9% NaCl (290 mOsm/L), Y= {(290-x)/290} x 9mg x 4000 mL, where y = NaCl required (in mg) to make the solution isotonic and x = observed tonicity of solution (reported as mOsm/L).

Preparation of Dosing Solution in 15 Ml Pp Tube

- 100 µM dosing solution in RG: 140 µL 10 mM stock + (14 mL – 140 µL) RG

Preparation of Calibration in 96 Shallow Well

- Prepare 10 µM standard: 100 µL of 100 µM dosing solution + 0.9 mL Ringers with 1% Methanol.
- Prepare analytical standard solutions 10, 5, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.02, 0.01, and 0 µM.

Table 4.5 Calibration Data of Permeability Study

1	2	3	4	5	6	7	8	9	10	11	12
0	20 µL of 0.1 µm	20 µL of 0.2 µm	20 µL of 0.5 µm	20 µL of 1 µm	20 µL of 2 µm	20 µL of 5 µm	20 µL of 10 µm	40 µL of 10 µm	100 µL of 10 µm	200 µL of 10 µm	Source solution
180 µL	180 µL	180 µL	180 µL	180 µL	180 µL	180 µL	180 µL	160 µL	100 µL	0	1 % MeOH in Buffer
Blk	0.01 µm	0.02 µm	0.05 µm	0.1µm	0.2µm	0.5µm	1 µm	2 µm	5 µm	10 µm	

Transport Studies

Dosing and Sampling

- Equilibrate both sides of the monolayers for 10 minutes with prewarmed (37°C) drug-free Ringers buffer (300 µL apical side, 1,200 µL basolateral side) supplemented with glucose (25 mM).
- Measure TEER under 37°C water bath conditions.
- When studying A to B transport: Fill basolateral side with 1,200 µL of Ringers buffer. Initiate transport experiments by transferring test drug dosing solution (320µL) to apical side.
- When studying B to A transport: Fill apical side with 300 µL of Ringers buffer. Initiate transport experiments by transferring test drug dosing solution (1,220 µL) to basolateral side. Transport studies for each direction (A to B, B to A) are performed in quadruplicate for each test drug.
- Start timer after dosing last donor well.
- Remove 20 µL aliquots from the donor wells at 0 minutes (D_0) and transfer these aliquots to the donor site of the 96-well plate containing 180 µL buffers with 1% Methanol. This step effectively dilutes the D_0 ten times.
- Initiate transport studies by placing plate on orbital shaker maintained inside a prewarmed (37°C) and humidified (5% CO2) incubator. Studies are performed under stirring conditions at 50 oscillations per minute.
- Remove 100 µL aliquots from the receiver side of the monolayer at 30, 50, 70, and 90 minutes postdosing and transfer these aliquots to the corresponding 96-well sample plate (See Table 26). Replace with an equivalent volume of prewarmed buffer.
- Remove 20 µL aliquots from the donor side of the monolayer at 90 minutes postdosing (D_f) and transfer these aliquots to a donor site of a 96-well plate containing 180 µL Ringers buffer with 1% Methanol. This step effectively dilutes the D_f ten times.
- Replace both sides of monolayer with fresh, drug-free, prewarmed Ringers buffer (300 µL apical sides, 1,200 µL basolateral side) and equilibrate for 10 minutes.
- Measure TEER under 37°C water bath conditions.

Table 4.6 Sampling Data of Permeability Study

0 µM	0.01 µM	0.02µM	0.05 µM	0.1µM	0.2µM	0.5µM	1 µM	2 µM	5 µM	10 µM	
Blk	Blk	Blk	Blk	A to B			B to A	Blk	Blk	Blk	Blk
1-30	2-30	3-30	4-30					5-30	6-30	7-30	8-30
1-50	2-50	3-50	4-50					5-50	6-50	7-50	8-50
1-70	2-70	3-70	4-70					5-70	6-70	7-70	8-70
1-90	2-90	3-90	4-90					5-90	6-90	7-90	8-90
1-Do	2-Do	3-Do	4-Do					5-Do	6-Do	7-Do	8-Do
1-Df	2-Df	3-Df	4-Df					5-Df	6-Df	7-Df	8-Df

Table 4.7 Mean Data in Table Represent the Mean Value from 12 Separate Inter-day Experiments

Peff (x E-6 cm/sec) in pH 7.4 Caco-2		
	A to B	**B to A**
Drug 1		
Mean	1.08	2.29
Range	0.69-1.80	1.69-1.80

4.5 Biowaiver Monograph of Anti-inflammatory Drug XYZ

About 30 biowaiver monographs have been documented up to date by the joint effort of FIP and WHO which are working on a running biowaiver monograph project. These monographs have a great impact on the approval of drug products as many applicants have submitted dossiers which refer to the results summarized in the monographs, without being asked by the regulatory agencies to repeat the studies, thus saving the applicants time and money. [29]

For BCS based Biowaiver monograph of that drug molecule is required as per WHO to support biowaiver application, [29] which includes data on solubility, permeability, dissolution and other important parameter from literature available. Monograph of Anti-inflammatory drug is prepared by literature available on Anti-inflammatory drug molecule and salt. Literatures searched are covered in reference part.

4.5.1 Biowaiver Monograph for Immediate Release Solid Oral Dosage Forms: Anti-Inflammatory Drug (XYZ)

Abstract

Literature data relevant to the decision to allow a waiver of in-vivo bioequivalence (BE) testing for the approval of Immediate release (IR) solid oral dosage forms containing Anti-Inflammatory drug are reviewed. Its therapeutic uses, its pharmacokinetic properties, the possibility of excipient interaction and reported Bioequivalence (BE)/Bioavailability (BA) problems are also taken into consideration. Some literature data indicates that Anti-inflammatory drug is a highly permeable active pharmaceutical ingredient (API) [59] but there is not any reported value permeability as per biopharmaceutical Classification system (BCS) guidance of FDA. Data on the solubility according to the current BCS criteria are available based on experimental solubility data that says it is “highly soluble”. Consequently, Anti-inflammatory drug could not be definitively assigned to either BCS class I or BCS Class II.

Keywords: Anti-inflammatory drug; Biopharmaceutical Classification system (BCS); Permeability; Solubility; Absorption; Biowaiver

Introduction

The bioequivalence (BE) of generic drug products can be determined in various ways, the most common of which is a comparative study with a suitable reference product in healthy volunteers under standardized conditions. Over the past 10 years, it has also become possible in many countries to determine bioequivalence using in-vitro methods – the so called biowaiver approach and over 30 biowaiver monographs on this subject have already been published, each addressing the pros and cons of applying the in-vitro bioequivalence test procedure to a specific Active Pharmaceutical Ingredient (API). In this Monograph, the possibility of extending the biowaiver procedure to the approval of generic products of Anti-inflammatory drug, an effective H_1 receptor antagonist is discussed. This monograph is based on available information from the literature, together with some additional experimental data, which have been used to address the Biopharmaceutical Classification System (BCS) classification, biopharmaceutical properties, and the risk associated with waiving in-vivo BE testing for Anti-inflammatory drug. Briefly, the aims of the present study are to evaluate all pertinent data available from literature sources to assess the appropriateness of such a biowaiver from the biopharmaceutical point of view and also from the perspective of public health.

Methods

Literature data were obtained from Web of Science, PubMed, Drugs.com and Drug Bank Databases up to November 2014. The Keywords used for searching Histaminic drug, absorption, bioavailability, bioequivalence, Log P, solubility, permeability and dissolution. Information was also obtained from regulatory documents published by WHO, USFDA and EMA.

GENERAL CHARACTERISTICS

Description

It is sesquihydrate of XYZ. The structural formula of the anhydrous salt is given in figure 4.2. Anti-inflammatory drug is a white to slightly yellowish crystalline solid.

_____XYZ_____

Figure 4.2 Structure of Anti-inflammatory drug

Stereoisomer, Salts and Polymorphs

Anti-inflammatory drug is mostly present in the form of chloride salt. Such salts have improved solubility in intestine [38] therefore it is possible to use them for the preparation of drug products. Anti-inflammatory drug doesn't exhibit any polymorphs, but is also presented anhydrous and sesquihydrate form.

There is not any kind of isomer reported in literature for Anti-inflammatory drug.

Therapeutic Indication, Dose, Therapeutic Index and Toxicity

Anti-inflammatory drug is an antihistaminic and antiserotonergic agent. It has a wide range of anti-allergic and anti-pruritic activity and can be used successfully in the treatment of acute and chronic allergies and pruritus, such as: dermatitis, including neurodermatitis, neurodermatitis circumscripta, eczema, eczematoid dermatitis, dermatographism, mild local allergic reactions to insect bites, hay fever and other seasonal rhinitis, perennial allergic and vasomotor rhinitis, allergic conjunctivitis due to inhalant allergens and foods, urticaria, angioneurotic oedema, drug and serum reactions, anogenital pruritus of chickenpox. Anti-inflammatory drug may be used as therapy for anaphylactic reactions, adjunctive to adrenalin and other standard measures after the acute manifestations have been controlled.

There is no recommended dosage schedule for children, < 2 years of age. While for children of 2-6 years dosage be initiated with 2 mg two or three times a day adjusted as necessary but the total dosage is not to exceed 12 mg a day. For children between 7-14 years of age the usual dosage is 4 mg three times a day. This dosage may be adjusted as necessary but the dosage is not to exceed 16 mg a day. For adults, the therapeutic range is from 4 mg to 20 mg a day, the majority of patients requiring 12 mg to 16 mg a day. An occasionally patient may require as much as 32 mg a day for adequate relief. It is suggested that dosage be initiated with 4 mg three times a day and adjusted according to the size and response of the patient but the dosage is not to exceed 32 mg a day.

Over dosage may produce hallucination, central nervous system depression or stimulations to convulsions respiratory and cardiac arrest, and death especially in infants and children. Also, atropine-like signs and symptoms (dry mouth; fixed, dilated pupils; flushing, etc.) as well as gastrointestinal symptoms may occur. The oral LD50 of Anti-inflammatory drug is 123 mg/kg, and 295 mg/kg in the mouse and rat, respectively. [41]

Solubility

Anti-inflammatory drug is soluble in water to the extent of about 4mg per ml, freely soluble in methanol, sparingly soluble in ethanol, soluble in chloroform and practically insoluble in ether. [41]

All solubility values reported in Table 4.8 on the basis of solubility study using Shake Flask method USP for 24 hours and estimated by UV. In Shake Flask method conditions and procedures are following as per USP in which 250 ml of media is prepared over the pH range of 1-7.5 at 37 ± 1 ℃ Temperature. As per USP, drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. A plot that reflects the dependence of various solubility and pH values is shown in figure 4.3. According to solubility study data as per given in table 1 Anti-inflammatory drug is highly soluble drug substance.

Decrease in solubility of anti-inflammatory drug at lower pH is attributed to the common ion effect of chloride ions which produce equilibrium with the hydrochloride salts. [38]

Table 4.8 Anti-inflammatory drug solubility values, Together with the Dose-Solubility Ratios (D/S) for 4 mg dose.

pH	Medium	Solubility $(mg/ml)^{pH}$	D/S [ml (4 mg)]	Acceptance Criterion (D/S≤250 ml) for Drugs (Yes/No)
	Water	3.296	1.213	Yes
	0.1 N HCl	0.609	6.568	Yes
4.5	Acetate Buffer	4.387	0.911	Yes

5.0	Phosphate Buffer	3.589	1.114	Yes
5.5	Phosphate Buffer	3.900	1.025	Yes
6.0	Phosphate Buffer	2.835	1.410	Yes
6.8	Phosphate Buffer	1.515	2.640	Yes
7.5	Phosphate Buffer	0.843	4.744	Yes

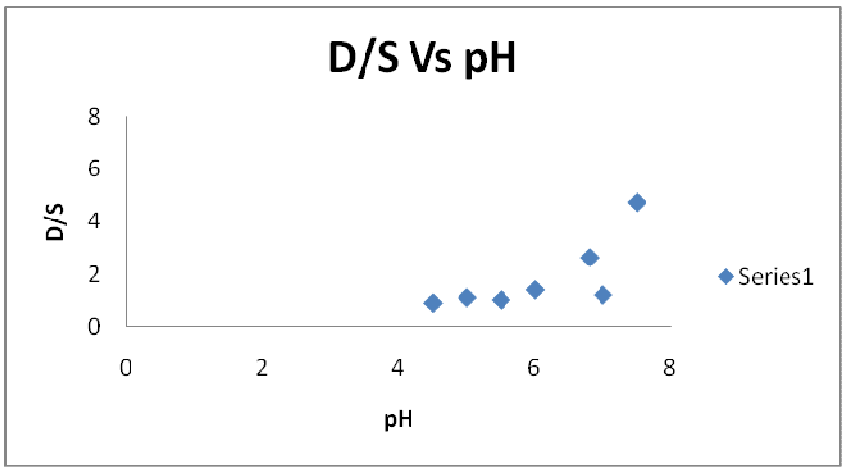


Figure 4.3 D/S Values (ml) in relation to the pH at a dose 4 mg Anti-inflammatory drug. The critical D/S limit is 250 ml

Partition Coefficient

Anti-inflammatory drug is a highly lipophilic molecule having a Log P (Octanol/Water) of 4.92. Log P value is determined by chromatographic method based on the polarity model that describes retention in RP-HPLC as a function of the polarity of the neutral solute [(59)] , It is a highly lipophilic molecule based on the acceptance criteria (Log P > 1.72 called highly permeable). [(55)]

Pka

The aqueous Pka of Anti-inflammatory drug has been reported as 8.87. [(59)]

Dose Strength of Marketed Drug Products

Anti-inflammatory drug is not mentioned in the WHO Model List of Essential Medicines (EML). For marketing Authorizations (MA) in US for tablet that consists 4 mg of Anti-inflammatory drug. [42]

While in Australia tablet and syrup formulations (XYZ®) are available for 4 mg of Anti-inflammatory drug.

PHARMACOKINETIC PROPERTIES

Absorption and BA

Drugs those have extensive metabolism are highly absorbed. [58] According to literature [57], initially "extensive metabolism" was defined as ≥50% metabolism of an oral dose in-vivo whereas now "extensive metabolism" be pushed to ≥70%. Anti-inflammatory drug is metabolized about 60% (2-20% excreted in stool and 40% in urine) according to literature. [41]

Permeability

<Data will be included after Caco-2 permeability study>

Metabolism and Excretion

After a single 4 mg oral dose of 14C-labelled Anti-inflammatory drug in normal subjects, given as tablet or syrup, 2-20% of the radioactivity was excreted in the stools. Only about 34% of the stool radioactivity was unchanged drug, corresponding to less than 5.7% of the dose. At least 40% of the administered radioactivity was excreted in the urine. No significant difference in the mean urinary excretion exists between tablet and syrup formulation. No detected amounts of unchanged drug were present in the urine of patients on chronic 12-20 mg daily doses of a XYZ® syrup formulation. The Principle metabolite found in human urine has been identified as a quaternary ammonium glucuronide conjugate of Anti-inflammatory drug. Elimination is diminished in renal insufficiency.

DOSAGE FORM PERFORMANCE

Excipients present in Anti-inflammatory drug tablet USP 4 mg with the MA in USA (ABC Pharmaceuticals) are microcrystalline cellulose, Lactose Monohydrate, Sodium Starch

Glycolate and Magnesium stearate. There is not any kind of interactions between excipients reported.

Dissolution

The USP specification for Anti-inflammatory drug tablets is NLT 80% (Q) of the labeled amount of _____ in 30 minutes in 900 ml of 0.1 N HCl. As shown in table 2, experimentally dissolution of Anti-inflammatory drug tablet is performed using USP apparatus type II at 50 RPM in different three media which shows more than 80% drug release within 30 minutes.

Table 4.9 Dissolution Study Data

Apparatus	Media (900 ml)	Time (Min.)	Drug Release (%)
USP Type II, 50 RPM	0.1 N HCl	30	91
	4.5 Acetate Buffer	30	95
	6.8 Phosphate Buffer	30	86

DISCUSSION

Solubility

The FDA defines "highly soluble" if highest single dose completely dissolved over the pH range 1-7.5 [(52)], while the EU [(47)] and the recently revised WHO guidelines [(48)] limit the requirements to the pH range 1-6.8 in 250 ml of media at 37±1° C. As per experimental report (Table 4.8) Anti-inflammatory drug is having D/S≤250 ml therefore, as per FDA guidance Anti-inflammatory drug molecule is a highly soluble drug substance.

Permeability

According to FDA BCS guidance, API is classified as "Highly Permeable" if the administered dose absorbed ≥90% or more. While as per EU guidance and recently revised WHO guidance API should be absorbed more than 85% or more. According to pharmacokinetics (Mass Balance Study) of Anti-inflammatory drug molecule after a single 4 mg oral dose of 14C-labeled anti-inflammatory drug molecule in normal subjects, about 34% of the stool radioactivity is unchanged drug. While 2-20% of the radioactivity is excreted in the stools and

40% of the administered radioactivity is excreted in the urine. Permeability of Anti-inflammatory drug molecule drug molecule is also supported by Log P value which is 4.42.

Surrogate Techniques for In-vivo BE Testing

For Anti-inflammatory drug molecule, it is unlikely that bioequivalence between two IR solid oral dosage forms would arise from differences in permeability produced by formulation differences.

Bioequivalence between formulations, if any exists, would most probably be caused by differences in in-vivo dissolution, which is expected to be the most critical parameter in the absorption process, at least in the neutral pH range. Consequently, for Anti-inflammatory drug molecule IR solid oral dosage forms, comparative in-vitro dissolution testing as per BCS guidance; [52] is an appropriate surrogate technique for in-vivo BE testing. The dissolution test USP 37 for Anti-inflammatory drug tablets uses dilute hydrochloric acid (0.1N HCl) as test medium.

Risks with respect to Excipient and/or Manufacturing Variations

The lack of reports of BA/BE problems supports the view these common excipients will have no effect on the BE of a test product, as long as they are incorporated in amounts currently used in IR tablet formulations.

An indication of the amounts usually present in dosage forms for drug products with a MA in the USA can be obtained from the FDA Inactive Ingredients Database.

Risk of Bioequivalence in Terms of Therapeutic Outcome

The USFDA Classified Antihistaminic drug as Perennial and seasonal allergic condition and as therapy for anaphylactic reactions which means that eventual complications of the sickness and/or adverse reactions arising from plasma concentrations outside the therapeutic window of the drug are not necessarily serious, and are unlikely to compromise the integrity of the individuals or be life threatening.

BCS Classification and Biowaiving

Salt of Anti-inflammatory drug is "highly soluble" but solid permeability data (based on particular permeability study as per FDA guidance) are lacking. Although some literature says Anti-inflammatory drug is highly permeable by having Log P 4.42[(59)] (Acceptance criteria Log P>1.72[(55)]), no definitive conclusion can be drawn as to whether Anti-inflammatory drug is "highly permeable" Or not until appropriate experimental data are available, Anti-inflammatory drug must be regarded as lying at the interface of BCS class I/II. Dissolution study data from experiment puts Anti-inflammatory drug in BCS class I. Moreover, some literatures have classified Anti-inflammatory drug as BCS class I, but this classification is reached on the basis of calculated Log P data.

CONCLUSION

Despite the relative uncertainty of the BCS classification for Anti-inflammatory drug, a biowaiver is scientifically justifiable for this API, provided that the test product is formulated with such excipients and in amounts currently used in IR tablet formulations and shows rapid In-Vitro dissolution, according to the criteria as defined in the BCS guidance. [(47, 48, 52)]

4.6 Dossier Compilation for Anti-inflammatory Drug Product based on BCS based Biowaiver

Dossier of BCS based Biowaiver includes,

- Module 1 (Administrative)
- Module 2 (Quality Overall Summary)
- Module 3 (Quality)
- Module 5 (BCS Summary Tables)

Here, dossier of BCS based Biowaiver is a kind of US-ANDA filing dossier. Thus, it excludes Module 4. Whereas, Module 5 consists BCS summary tables which include data on solubility study, permeability study, dissolution of dosage form (tablet) and permeability validation data.

Following dossier is for Anti-inflammatory product (tablet), which includes BCS class I drug substance. While dossier consist content write-up as required in the guidance of content and format for ANDA. Those requirements are already described in chapter 4.3.

4.6.1 Module 1: Administrative

Checklist for Module 1[18]

1.1	1.1.2	Signed and Completed Application Form (356h)
		Form FDA 3794
1.2		Cover Letter
	1.2.1	Form FDA 3674
		Table of Contents (Paper Submission only)
1.3	1.3.1	Contact/Sponsor/Applicant Information
	1.3.2	Field Copy Certification
	1.3.3	Debarment Certification
	1.3.4	Financial Certifications
	1.3.5	Patent and exclusivity 1.3.5.1 Patent Information 1.3.5.2 Patent Certification 1.3.5.3 Exclusivity Claim
1.4	1.4.2	Statement of right of references
1.12	1.12.24	Request for Comments and Advice
	1.12.11	Basis for Submission
	1.12.12	Comparison between Generic Drug and RLD
	1.12.14	Environmental Analysis
	1.12.15	Request for Waiver
1.14	1.14.1	Draft Labeling 1.14.1.1 Draft carton and container labels 1.14.1.2 Annotated draft labeling text 1.14.1.3 Draft labeling text 1.14.1.4 Labeling Comprehension Studies
	1.14.3	Listed Drug Labeling

4.6.2 Module 2: Quality Overall Summary (QOS)

For ANDAs, Quality Overall Summary (QOS) is a summary module of dossier which includes summarized data of Module 3 and Module 5. Here, QOS is presented in Question based Review format. [19]

The Office of Generic Drugs (OGD) has developed a question-based review (QbR) for its Chemistry, Manufacturing, and Controls (CMC) evaluation of Abbreviated New Drug Applications (ANDAs) that is focused on critical pharmaceutical quality attributes. The QbR is a concrete and practical implementation of the underlying concepts and principles outlined by the FDA's cGMPs for the 21st Century and PAT initiatives.

What is Question based Review (QbR)?

QbR is a general framework used for CMC assessment of ANDAs, which includes important scientific and regulatory review questions that mainly emphasize on critical pharmaceutical attributes essential for ensuring generic drug product quality.

The QbR serves two purposes for the CMC assessment of ANDAs. [10]

- It provides a guide to the reviewer in the evaluation of dossier whether a product is of high quality and in the assessment of the level of risk associated with the manufacturing process and design of the product.
- It provides transparency to sponsors about the logic that reviewers invoke in their CMC reviews.

Quality Overall Summary

2.3 Introduction to the Quality Overall Summary

- **Reference Listed Drug:**
- **Non-Proprietary Name of the drug product:** Anti-inflammatory drug (XYZ) Tablets USP
- **Non-Proprietary Name of the drug substance:** Anti-inflammatory drug (XYZ)
- **Sponsor Company:** Cadila Healthcare Ltd.
- **Dosage Form:** Tablets
- **Strengths(s):** 4 mg
- **Route of Administration:** Oral
- **Proposed Indication:** Perennial and seasonal allergic rhinitis, Vasomotor rhinitis, Allergic conjunctivitis due to inhalant allergens and foods, Mild, uncomplicated allergic skin manifestations of urticaria and angioedema, amelioration of allergic reactions to blood or plasma, Cold urticarial, Dermatographism, As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula and molecular weight?

Nomenclature:

INN Name:	Anti-inflammatory drug (XYZ)
Compendial Name:	Anti-inflammatory drug (XYZ)
Chemical Name:	----------

CAS No.	[41345-29-4]

Structure:

Molecular Structure	**----------**
Molecular Formula	**----------**
Molecular Weight	**----------**

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as a function of pH), hygroscopicity, melting points and partition coefficient?

Physical Description	White to slightly yellow, odorless or practically odorless, crystalline powder.
Aqueous solubility	Slightly soluble in water, freely soluble in methanol, soluble in chloroform, sparingly soluble in alcohol, practically insoluble in ether.
Polymorphism	Not reported in literature. However, Anti-inflammatory drug Hydrochloride manufactured by Paras is crystalline in nature. XRD diffractograms of three consecutive batches are provided in section 3.2.S.3.1 to show the consistency.
Chirality	There is no chiral center in Anti-inflammatory drug.
Isomerism	Anti-inflammatory drug does not exhibit isomerism
Hygroscopicity	Not a hygroscopic molecule
Melting point	257.5 – 261.5 ºC

pKa	9.3
Partition Coefficient (Log P)	4.7

2.3.S.2 Manufacture

Who manufacture the drug substance?

Anti-inflammatory drug is manufactured by Paras Pharma Chem Ltd.

Corporate Office:

Paras Pharma Chem Ltd,

78/A, Vengalrao Nagar,

Hyderabad – 500038

Telangana State, India

Phone: +91 40 44763666/23711717

Fax: +91 40 23811576

Email: paras@paraspharma.com

Website: www.paraspharma.com

Manufacturing Site:

Paras Pharma Chem Limited,

Unit-1, Plot No.39, A&B, Phase-I, IDA, Jeedimetla,

Hyderabad – 500 055,

Telangana state, India

Phone: +91 40 4475 4545/23095056

Fax: +91 40 44754555

Contact Person at Paras:

Mr. N V Chalam

Head Corporate Quality,

Phone: +91 40 44763666/23711717

Fax: +91 40 238 11 576

Email: venkatachalam.cq@paraspharma.com

rah@paraspharma.com

The manufacturing facility has been inspected and approved by USFDA, Mexican MOH (COFEPRIS) and Korean FDA.

How do the manufacturing processes and controls ensure consistent production of drug substance?

Paras Pharma Chem Limited has developed and validated the manufacturing process for Anti-inflammatory drug. The bulk drug substance Anti-inflammatory drug manufactured by Paras Pharma Chem Limited is well established and reproducible; the specification of Anti-inflammatory drug ensures that the product fully meets the USP requirement. No significant changes have been made to the manufacturing process during scale up.

Batch analysis from production scale process validation batches are available in closed part of DMF which ensures consistency in manufacturing.

2.3.S.3 Characterization

How were the drug substance elucidated and characterized?

The structure of Anti-inflammatory drug hydrochloride has been confirmed by its synthesis. Further the molecular structure confirmed by spectroscopic studies like elemental analysis, Infrared spectrum, NMR spectrum and Mass spectrum for Anti-inflammatory drug Hydrochloride.

How were potential impurities identified and characterized?

Table 4.10 Impurities

Sr. No.	Chemical Name	Structure	Specification	Type
Organic Impurities				
1	Anti-inflammatory drug related compound A	-----	NMT 0.15 %	Process related Impurity

2	Amitriptyline related compound A	-----	NMT 0.15 %	Process related Impurity
3	Amitriptyline related compound C	-----	NMT 0.15 %	Process related Impurity
4	Any individual unknown impurity	-----	NMT 0.10 %	-----
5	Total impurities	-----	NMT 0.5 %	-----
Inorganic Impurities				
1	Toluene	-----	NMT 890	Residual Solvents
2	Methanol	-----	NMT 3000	
3	Tetra hydro furan	-----	NMT 720	
4	Isopropyl alcohol	-----	NMT 5000	
5	Residue on Ignition	-----	NMT 0.1 % w/w	Reagent/ Catalyst
6	Heavy Metals	-----	NMT 30 ppm	

Organic Impurities:

Anti-inflammatory drug Hydrochloride monograph is available in USP. Related substances formed during manufacturing process of drug substance are controlled as per USP monograph specification.

Inorganic Impurities (Residual Solvents):

The solvents used in the synthesis of Anti-inflammatory drug are Toluene, Methanol, Tetra hydro furan and Isopropyl alcohol. The limits for residual solvents are proposed in accordance with ICHQ3C guideline requirements. The In-house GC validated (as per ICH Q2) analytical method has been adopted for routine testing as well as characterization.

Inorganic Impurities (Reagents/Catalysts):

The reagents and catalysts are washed out during routine manufacturing process through various works up activities like washing to organic layer and centrifugation/isolation of material. These are controlled as per USP method.

Genotoxic Impurities:

All the reagents, raw materials, intermediate and by products (if any) from starting materials manufacturing process to final API have been explored for genotoxic potentiality and found following compound could leads to genotoxicity which is characterized by GC method.

Table 4.10 Genotoxic Impurities

	Source	**LOD**	**LOQ**
Ethyl Bromide	Raw Material	2 ppm	6 ppm

2.3.S.4 Control of Drug Substance

What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

Table 4.12 Drug Substance Specification

Quality Attributes		**CQA Yes/No**	**Specifications**	**Analytical Procedure**	**Justification**
Appearance		No	White to slightly odorless, or practically colorless, crystalline powder	Visual Inspection	NA
Identification	By IR	Yes	To match with working/ reference standard	IR	USP <197k>
	By HPLC		The retention time of the anti-inflammatory drug peak of the sample solution corresponds to that of the standard solution as obtained in the test for organic impurities.	HPLC	USP monograph
	Chemical Test		A bright blue fluorescence should be observed		USP monograph
Impurities (Related	Anti-inflammatory drug related	Yes	NMT 0.15 %	HPLC	USP monograph

Substance)	compound A				
	Amitriptyline related compound A		NMT 0.15 %		
	Amitriptyline related compound C		NMT 0.15 %		
	Any individual unknown impurity		NMT 0.10 %		
	Total impurities		NMT 0.5 %		
Residual solvents	Toluene	Yes	NMT 890	GC	(In-house) To control the residual solvent in the final API and also to meet the ICH requirement. The limits are proposed as per ICHQ3C guideline
	Methanol		NMT 3000		
	Tetra hydro Furan		NMT 720		
	Isopropyl alcohol		NMT 5000		
Heavy Metals		Yes	NMT 30 ppm	USP <231> Method II	USP Monograph

Residue on Ignition	Yes	NMT 0.1 % w/w	USP <281>	USP Monograph
Water Content	Yes	7.0 – 9.0 %w/w	By KF	USP Monograph
Acidity (0.05 % as HCl)	Yes	NMT 0.15 ml should be required		

There is an official monograph in USP for Anti-inflammatory drug substance and tests from the USP monograph are performed. Limits for these tests are those found in the monograph. Specifications are justified above by USP monograph.

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary validated? What is the justification for the acceptance criterion?

Appearance

The drug substance is visually inspected to verify that it is a white, crystalline powder.

Identification

The identification tests, a specific IR test, HPLC test, and chemical test by using UV light are performed as per the USP monograph for anti-inflammatory drug.

Assay

In accordance with the USP monograph, the assay limit is set at 98.5% to 100.5% w/w. Assay is determined by the USP method which is a potentiometry titration method.

Impurities (Related Substance)

Related substances are analyzed by HPLC method as per USP monograph. Related compounds potentially present in the drug substance are as below:

Table 4.13 Specification of Impurities

Name of Impurity	**Limit**	**Linearity**	**Precision**	**Accuracy (% Recovery)**	**LOD (%)**	**LOQ (%)**
Anti-inflammatory drug related compound A	NMT 0.15%	$R^2 = 0.9989$	NMT 5 % RSD = 2.10	99.10 %	0.0004	0.001
Amitriptyline related compound A	NMT 0.15%	$R^2 = 0.9979$	NMT 5 % RSD = 1.99	98.10 %	0.0007	0.002
Amitriptyline related compound C	NMT 0.15%	$R^2 = 0.9992$	NMT 5 % RSD = 1.87	99.63 %	0.0004	0.001
Any individual	NMT	$R^2 = 0.9982$	NMT 5	101.38 %	-----	-----

unknown impurity	0.10%		% RSD = 2.01			
Total impurities	NMT 0.5%	R^2 = 0.9996	NMT 5 % RSD = 1.96	95.82 %	-----	-----

Impurities (Residual Solvents)

The solvents used in the synthesis of Anti-inflammatory drug are Toluene, Methanol, tetra hydro furan and Isopropyl alcohol. The limits for residual solvents are proposed in accordance with ICHQ3C guideline requirements. The In-house GC validated (as per ICH Q2) analytical method has been adopted for routine testing as well as characterization.

Residual Solvents	**Limit**	**Linearity**	**Precision**	**Accuracy (%Recovery) (85%-115%)**	**LOD (%)**	**LOQ (%)**
Toluene	NMT 890	R^2 = 0.9999	NMT 15 % RSD = 2	111.7 %	0.5	1.6
Methanol	NMT 3000	R^2 = 0.9975	NMT 15 % RSD = 3.8	105.8 %	3.5	11.6
Tetra hydro Furan	NMT 720	R^2 = 0.9996	NMT 15 % RSD = 1.2	97.1 %	0.7	2.4
Isopropyl alcohol	NMT 5000	R^2 = 0.9987	NMT 15 % RSD = 3.4	106 %	7.0	16.6

Impurities (Inorganic)

As per USP monograph of Anti-inflammatory drug, Heavy Metals Test by USP method II, with a limit of NMT 20 ppm and Residue on Ignition test with a limit NMT 0.1% w/w is performed.

2.3.S.5 Reference Standards

How were the primary reference standards certified?

Primary Reference Standard:

The reference standard of Anti-inflammatory drug hydrochloride has been procured from USP. The lot no. is H1L349. The IR spectrum for USPRS lot no H1L349 has been recorded.

Working Standard:

The working standard of # WS/FP/CYP/1401 has been qualified against primary reference standard USPRS lot no. H1L349.

2.3.S.6 Container Closure System

Anti-inflammatory drug hydrochloride is packed in double polyethylene bags (linear low density polyethylene), inner transparent and outer black.

The polyethylene bags (Inner transparent & outer black are placed in HDPE container and material shall be poured in the transparent polyethylene bag, tied individually using plastic fastener (Pilfer Proof) and outer one (Black Polyethylene Bag) with pilfer proof fastener embedded with company logo. One label shall be pasted on black polyethylene bag. The HDPE drum is closed with the metallic ring and sealed with a tamper proof metallic seal embedded with company logo. One label shall be pasted on container.

2.3.S.7 Stability

What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?

Stability Summary and Conclusions

1. **General**

   Anti-inflammatory drug is being manufactured from the year 2008 at Paras, Unit-II, and Vizag location. The stability studies have been initiated with process validation batch samples (CYP/002/08, CYP/003/08 & CYP/004/08) in the year 2008.

   In addition to the above site, the same product without any change in process has been transferred to Paras, Unit-I, at Hyderabad in the year 2011. The stability studies have been initiated with process validation batch samples (CYP/11/001, CYP/11/002 & CYP/11/003) in the year 2011. The following are the stability conditions selected for study and its current status.

2. **Stress Testing**

   The stress studies on Anti-inflammatory drug Hydrochloride #XXX/G1-35/S-III/WS/01 were carried out.

   1. The results indicate that there was significant degradation under oxidation condition. Minor degradation was observed under acidic and base degradation condition. No degradation was observed under UV-light, Heat, Humidity and Aqueous conditions.
   2. Stability Indicative Nature: the above observations conclude that this test method is able to detect the degradation in Anti-inflammatory drug samples. Hence the above test method is stability indicative.
   3. Hidden Peaks: Also, spectral data from HPLC analysis utilizing diode array option has shown that there are no hidden and degraded peaks masked by the Anti-inflammatory drug peak.

   From the above results it could be conducted that, the In-house (Ph. Eur) HPLC method for related compounds is able to detect degradation products and hence could be used as a stability indicating method.

   Supporting analytical data for the above study is discussed in section no. 3.2.S.4.3 under analytical method validation report for related substance by HPLC.

Testing Frequency

The following table gives the frequency of testing of stability samples.

Table 4.14 Testing Frequency

Study	Duration
Accelerated stability studies	6 months (Initial 1,2,3 & 6)
Long term stability studies	5 years (Initial 3,6,9,12,18,24,36,48 & 60 months)

Storage Conditions

The storage conditions are given below.

Table 4.15 Storage Condition

Study	Duration
Accelerated stability studies	6 months (Initial 1,2,3 & 6)
Long term stability studies	5 years (Initial 3,6,9,12,18,24,36,48 & 60 months)

Statement/Labeling

1. **Storage Conditions:** Preserve in well closed containers. Store at 25 ºC, excursions are allowed between 15 ºC and 30 ºC.
2. **Expiry Date:** 5 years

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition

What are the components and composition of the final product? What is the function(s) of each excipient?

Following are the components and composition of Product Anti-inflammatory drug, 4 mg

Table 4.16 Composition of Anti-inflammatory Drug Product

Name of Ingredient	Unit Composition (mg/tab)	Exhibit Batch Composition (kg)	Quantity (% w/w)	Intended Commercial Batch Composition (kg)	Quantity (% w/w)
Anti-inflammatory drug	4.00				3.33
Lactose Monohydrate	40.00				33.33
Microcrystalline Cellulose	70.00				58.33
Sodium Starch Glycolate	5.00				4.17
Magnesium Stearate	1.00				0.83
Total	120.00				100.00

Function of Excipients:

Ingredients	Functions
Lactose Monohydrate	Diluent
Microcrystalline Cellulose	Diluent
Sodium Starch Glycolate	Disintegrant
Magnesium Stearate	Lubricant and Glidant

Does any excipient exceed the IID limit for this route of administration?

Table 4.17 IID Listing and Evaluation for Excipients used in Anti-inflammatory Drug Product

Ingredients	Listing in IID	Maximum level of excipient reported in IID (mg)	Amount per unit of Tablet (% w/w)	IID level or other applicable limits (mg/day)
Lactose Monohydrate	Yes	1020	40.00	320
Microcrystalline Cellulose	Yes	1385.3	70.00	560
Sodium Starch Glycolate	Yes	876	5.00	40
Magnesium Stearate	Yes	400.748	1.00	8

Do the differences between this formulation and RLD present potential concerns with respect to therapeutic equivalence?

There is no major difference in terms of type of excipients used for RLD and the test formulation. The difference may be in the grades of excipients used between RLD and test formulation. So, there is no potential concern with respect to therapeutic equivalence.

Table 4.18 Comparison of Formulation

Innovator	**Zydus**
Lactose Monohydrate	Lactose Monohydrate
Microcrystalline Cellulose	Microcrystalline Cellulose
Sodium Starch Glycolate	Sodium Starch Glycolate
Magnesium Stearate	Magnesium Stearate

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the Product

2.3.P.2.1.1 Drug Substance

Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

Description, Solubility, Assay, Bulk density, Tapped density, Residual solvents, related substance, Heavy metals, Water content, Phosphate content, Optical Rotation, Polymorphism, Particle size are the control specification tests for the Anti-inflammatory drug substance.

Among all above mainly particle size distribution, polymorphism, and assay are critical control parameters affecting the product development; process and performance refer Table for more information.

Table 4.19 Critical Characteristics of Drug Substance Affecting Drug Product Development

Critical Characteristics	Justification

2.3.P.2.1.2 Excipients

An excipient comparability study was carried out for excipient intended to be finalized/used for Anti-inflammatory drug Tablet formulation. The compatibility study indicated that there were minimal interactions observed between all excipients and drug substance at dry state. The selected excipients demonstrated compatibility with the drug substance in dry state except xanthan gum; however the unknown impurity in drug product. For the wet state in drug substance, the total impurities were detected at 0.80% after one month under stress conditions as given in table.

The compatibility study indicated that relative degradation of drug substance is higher in wet state compared to dry state. Looking at the excipient compatibility data, it is not advisable to use talc, sodium stearyl fumarate and microcrystalline cellulose with active ingredient in wet state and these can be used extra granularly in Anti-inflammatory drug tablets with wet granulation technology. Anti-inflammatory drug shows high impurity level with crosscarmellose sodium when used in ratio of 1:1. Hence lower levels of crosscarmellose sodium as one of the excipient.

Table 13 contains data results of related substances test for 4 weeks stage in wet state at 50 ℃/80% RH. Complete report on drug-excipient compatibility is available in this application <Confirm pages of ANDA application>

Table 4.20: Related Substance data at 50 ºC/80% RH %RH;

Combina-tions of Excipients	Ratio	Related Substances					
		Anti-inflammatory drug related compound A	Amitriptyline related compound A	Amitriptyline related compound C	Any individual unknown impurity	Maximum Unknown Impurity	Total

2.3.P.2.2 Drug Product

What attributes should the drug product possess?

Data are not available.

How was the drug product designed to have these attributes?

1. Assay of Anti-inflammatory drug
2. Dissolution of Finished Product
3. Weight variation of Finished Product

Were alternative formulations or mechanisms investigated?

Yes, initially three formulations were investigated. Based on API nature ----- was selected for formulation development. Looking at the excipient compatibility data of Anti-inflammatory drug in hydrated state wet granulation approach using two different solvents as granulating fluid were planned.

Table 4.21 Approach 1: Direct Compression

Sr. No.	Ingredients	Range
1	Anti-inflammatory drug	

2	Lactose Monohydrate	
3	Microcrystalline Cellulose	
4	Sodium Starch Glycolate	
5	Magnesium Stearate	

Table 4.22 Approach 2: Wet Granulation – Drug in dry mix

Sr. No.	**Ingredients**	**Range**
Intragranular		
1	Anti-inflammatory drug	
2	Lactose Monohydrate	
3	Microcrystalline Cellulose	
4	Purified Water	
Extragranular		
5	Sodium Starch Glycolate	
6	Magnesium Stearate	

Table 4.23 Approach 3: Wet Granulation – Drug in Solution

Sr. No.	**Ingredients**	**Range**
Intragranular		
1	Anti-inflammatory drug	
2	Lactose Monohydrate	
3	Microcrystalline Cellulose	
4	Methanol	
5	Purified Water	
Extragranular		
6	Sodium Starch Glycolate	

7	Magnesium Stearate	

How were the excipients and their grades selected?

Excipients selection was based on the reverse engineering of RLD, previous experience, published literature and formulation development studies conducted in the drug product of the below mentioned excipient, reliability of the supplier source, their recommendations, and their compliance with USP/NF standards. Excipients used were same as reference listed drugs (RLD).

Lactose Monohydrate:

Povidone K29/32: Povidone is widely used hydrophilic binder in solid orals. Povidone K29/32 USP grade is used as binder for anti-inflammatory drug Tablets, USP.

Microcrystalline Cellulose:

Magnesium Stearate:

Sodium Stearyl Glycolate: Sodium stearyl Glycolate is widely used lubricant for solid orals. Sodium Stearyl Glycolate NF grade is used as lubricant for Anti-inflammatory drug Tablets USP.

How was the final formulation optimized?

Optimization of Formula:

Formulation optimization was carried out Design of Experiment Tool. Full factorial design was applied for optimizing the prototype formulation. Based on initial development and risk assessment following factors were considered for optimizations. Please refer Module 3.2.P.2 for detailed PDR.

2.3.P.3 Manufacture

Who manufacture the drug product?

Drug Product Manufactured By:

Nesher Pharma, USA (a subsidiary of Cadila Healthcare Ltd.)

13910 St.Charles Rock Road,
Bridgeton, Missouri (MO)
63044, United States (USA)
FEI Number: 1922352
Duns Number: 969028351

Drug Product Packaged by:

Legacy Pharmaceutical Packaging
13333 Lakefront Drive, Earth City,
Missouri (MO) 63045,
United States (USA)
FEI Number: 3004453700
DUNS Number: 969852743

Responsible Regulatory Contact:

What are the Unit Operations in the drug product manufacturing process?

Table 4.24 Direct Compression

Ingredients/Inputs	Step	Process	In-Process Control
Sifting: API, Lactose Monohydrate, Microcrystalline cellulose, Sodium Starch Glycolate	**1**	Sifting (----)	Integrity of Sieve
Blending:	**2**	Blending	1. Blending time

Material of Step 1		(----)	2. Blend Uniformity
Lubrication: Blend of step 2 & Magnesium Stearate	**3**	Lubrication (----)	1. Lubrication Time 2. Blend Uniformity
Compression: Compress lubricated blend of step 3 using appropriate tooling	**4**	Compression (----)	Complete Analysis

Table 4.25 Wet Granulation – Drug in Dry Mix

Ingredients/Inputs	Step	Process/Equipment	In-Process Control
Sifting & Mixing: API, Lactose Monohydrate Microcrystalline Cellulose	**1**	Sifting (----) Mixing (----)	Integrity of Sieve
Binder Solution: Purified Water	**2**	Granulation (----)	1. Granulation Time 2. Amperage
Drying:	**3**	Drying (----)	1. Drying time 2. Loss on Drying
Milling: Mill dried granules of step 3	**4**	Sizing (----)	1. Integrity of screen
Blending: Sized granules of step 4 & sodium starch Glycolate	**5**	Blending (----)	1. Blending time 2. Blend Uniformity

Lubrication: Blend of step no.5 & magnesium stearate (Presifted)	**6**	Lubrication (----)	1. Lubrication Time 2. Blend Uniformity
Compression: Compress lubricated blend of step 6 using appropriate tooling	**7**	Compression (----)	Complete Analysis

Table 4.26 Wet Granulation – Drug in Solution

Ingredients/Inputs	Step	Process/Equipment	In-Process Control
Sifting & Mixing: Lactose Monohydrate, Microcrystalline Cellulose	**1**	Sifting (----) Mixing (----)	1. Integrity of sieve 2. Blend Uniformity
Binder Solution: Dissolve API in methanol, Purified water as additional solvent	**2**	Granulation (----)	1. Granulation Time 2. Amperage
Drying:	**3**	Drying (----)	1. Drying Time 2. Loss on Drying
Milling: Mill dried granules of step 3	**4**	Sizing (----)	1. Integrity of screen
Blending: Sized granules of step 4 & Sodium Starch Glycolate	**5**	Blending (----)	1. Blending time 2. Blend Uniformity

Lubrication: Blend of step no.5 & magnesium stearate	**6**	Lubrication (----)	1. Lubrication Time 2. Blend Uniformity
Compression: Compress lubricated blend of step 6 using appropriate tooling	**7**	Compression (----)	Complete Analysis

What is the reconciliation of the exhibit batch?

<This information should be included from exhibit batch data and this text to be confirmed at the time of submission>

Table 4.27 Reconciliation Data

Packaging	Batch	Target	Yield	OOS Limit

Does the batch formula accurately reflect the drug product manufacturing process? If not, what are the differences and the justification?

Yes, the batch formula reflects the drug product manufacturing process accurately. <This information should be included from exhibit batch data and this text to be confirmed at the time of submission>

What are the in-process tests and controls that ensure each step is successful?

<This information should be included from exhibit batch data and intended batch records>

2.3.P.4 Control of Excipients

What are the specifications for the inactive ingredients and are they suitable for their intended function?

Table 4.28 Specification of Inactive Ingredients

Ingredients	Manufacturer	Complies with-
Lactose Monohydrate		
Microcrystalline Cellulose		
Sodium Starch Glycolate		
Magnesium Stearate		

Each ingredient used in formulation meets the compendia standard and they are suitable for their intended use as shown in above table.

2.3.P.5 Control of Drug Product

What is the drug product specification? Does it include all the critical drug product attributes?

Assay, Related substance, related solvents, Drug Dissolution, Water Content and Dosage Uniformity are the critical drug product attributes available in table__ as follows:

Table 4.29 Test and Acceptance Criteria for Anti-inflammatory Drug Product

Test	Acceptance Criteria	Analytical Procedure	Results	Justification
Assay				
Related Substance				
Residual Solvents				
Drug Dissolution				
Water Content				

Dosage Uniformity				

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

Assay:

The proposed drug product assay acceptance criteria for both Release as well as Stability are same that is 90.0-110.0%. Assay of Anti-inflammatory drug can be performed using HPLC method by injecting a blank solution (Diluent) followed by five replicate injections of respective working standard solution. Inject bracketing standard after every 10 injections of sample solutions.

Assay is determined via the chromatographic conditions summarized below:

HPLC Conditions

HPLC Conditions	
Column	X-Bridge BEH C8, (150 mm × 4.6 mm), 2.5 µm, Column XP
Mobile Phase	620 ml Buffer Solution, 245 ml Methanol 135 ml Acetonitrile
Flow Rate	0.65 ml/min
Column Temperature	50 ºC
Detector Wavelength	207 nm
Injection Volume	10 µL
Typical Retention Time	Anti-inflammatory drug – 13.0 minutes
Typical Run Time	20.0 Minutes

System Suitability in Assay is achieved by following criteria:

1. The relative standard deviation (RSD) of the Anti-inflammatory drug peak area responses in standard preparation from five replicate injections is not more than 2.0%.
2. The tailing factor (T) for the Anti-inflammatory drug peak in the working standard is not more than 2.0.
3. The theoretical plates for the Anti-inflammatory drug peak in the working standard are not less than 2000.

Uniformity of Dosage (By Weight Variation)

Though, a tablet fill machine which performs a 100% weight check as an in-line monitor. However, Acceptance content uniformity (Uniformity of Dosage) of the drug product is ensured by weight variation method based upon testing of individual tablets using the drug

product assay test method and acceptance criteria in USP <905> will be performed to confirm acceptable Anti-inflammatory drug content uniformity in the finished dosage form.

Dissolution Test:

The proposed dissolution method used for Anti-inflammatory drug Tablet is USP method II. Dissolution Conditions kept in dissolution test are given below.

Dissolution Condition	
Dissolution Media	Deaerated 0.1 N Hydrochloric acid
Media Volume	900 ml
Apparatus	Paddle (Apparatus 2) with 3-prong sinker
Speed	50 rpm
Sample Volume	Sample 10 ml from each vessel at the intervals
Sampling Intervals	20 minutes or as requested

HPLC Conditions

HPLC Conditions	
Column	Inertsil C8-3 (100 mm × 4.6 mm), 5 µm
Mobile Phase	550 ml Buffer Solution 230 ml Methanol, 220 ml Acetonitrile
Flow Rate	1.2 ml/min
Column Temperature	50 ºC
Detector Wavelength	225 nm
Injection Volume	20 µL
Typical Retention Time	Anti-inflammatory drug – 3.0 minutes
Typical Run Time	6.0 Minutes

Acceptance criteria are proposed using different numbers of units and dissolution time points which are as follows:

Acceptance Criteria:

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5 %
S_2	6	Average of 12 Units (S1 + S2) is equal to or greater than Q.
S_3	12	Average of 24 units (S1 + S2 + S3) is equal to or greater than Q, and not more than 2 units are less than Q – 15% and no unit is less than Q – 25%

Related Compounds:

Here impurities (Related Compounds) are determined using HPLC method by inject a blank solution (Diluent), Placebo solution, Sensitivity Solution, Resolution Solution and six replicate injections of working standard solution. Inject bracketing standard after every 6 injections of sample solutions. Impurities with their acceptance criteria are given below which follows USP monograph.

Impurities	Acceptance Criteria	Complies with
Impurity A	NMT 2.0 %	USP Monograph
Impurity A	NMT 2.0 %	
Impurity A	NMT 2.0 %	
Individual Unidentified Impurity	NMT 2.0 %	
Total Unidentified Impurity	NMT 2.0 %	
Total Impurities	NMT 2.0 %	

Impurities (degradants) are determined via the HPLC chromatographic test conditions as given below.

HPLC Conditions

HPLC Condition	
Column	X- bridge BEH C8, (150 mm × 4.6 mm), 2.5 µm Column XP
Mobile Phase	620 ml Buffer Solution 245 ml Methanol 135 ml Acetonitrile
Flow Rate	0.65 ml/min
Column Temperature	50 ºC
Detector Wavelength	207 nm
Injection Volume	10 µL
Typical Retention Time	Anti-inflammatory drug – 13.0 minutes
Typical Run Time for Standard and Resolution	20.0 minutes
Typical Run Time for Diluent, Sample, Placebo	60.0 minutes

System suitability in assay of related compounds is achieved by following criteria:

1. % RSD for six replicate injections of standard preparation calculated for Anti-inflammatory drug peak is NMT 10.0%
2. Resolution between 5-Acetyl acid and anti-inflammatory drug acid in resolution solution is NLT 1.5
3. The signal to noise (S/N) of the Anti-inflammatory drug peak in the Sensitivity solution must be greater than or equal to 10.

The Relative Retention Time and Limit of Quantification of impurities are given below in table to achieve system suitability.

Name	Relative Retention Time (Approx)	LOQ (%)	RRF
Impurity – A (Anti-inflammatory drug)	0.25	0.02	0.95
Impurity – B (Anti-inflammatory drug)	0.52	0.02	2.63
Impurity – C (Anti-inflammatory drug)	1.37	0.02	0.95
Anti-inflammatory drug	1.0	0.02	-

Residual solvents

Solvents are not used in the manufacture of Anti-inflammatory drug tablet, USP and the maximum daily dose of the drug product is less than 10 g. No solvents are used in manufacture of any ingredient of the drug product, and for the API from Class 1. Class 2 and Class 3 solvents are 'likely to be present' (as this term is defined in USP <467>) in the API at NMT 3000 ppm and 5000 ppm respectively. These solvents are monitored and controlled in

the API raw material at levels below the respective individual USP <467> limits. Therefore, direct testing of finished Anti-inflammatory drug tablet for residual solvents is not required.

Water Content

Water content is determined using Karl-Fischer method by mixing the contents of not less than 4; Tablets and accurately weigh about 200 mg and transfer into the vessel and proceed as per the specification of USP monograph.

All analytical methods used are above are suitable for intended use and among them assay, related substance and dissolution are validated.

2.3.P.6 Reference Standards and Materials

How are the primary reference standards certified?

<This information should be included from exhibit batch data>

2.3.P.7 Container Closure System

What container closure system(s) is proposed for packaging and storage of the drug product? Has the container closure system been qualified as safe for use with this dosage form?

For packaging purpose of Anti-inflammatory drug product (tablets, 4 mg) following packaging strategy is used.

- 100 in a 1 bottle
- 1000 in a 1 bottle
- Blister Pack
- Bulk

2.3.P.8 Stability

What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?

Table 4.30 Stability Specification

Test	Release	Stability	Method
0			

All attributes used to confirm the quality of the finished drug product at batch release are evaluating during stability testing, with the exception of identity and Uniformity of Dosage as these are not expected to change overtime.

What drug product stability studies support the proposed shelf life and Storage Conditions?

Table 4.31 Stability Study Data

Test (Acceptance Criteria)	Accelerated (40ºC/75% RH)	Room Temperature (25ºC/60% RH)

What is the Post Approval Stability Protocol?

The post approval stability protocol/commitment requires that the first three commercial production batches (packaged in the smallest and largest configurations) be placed on stability (25ºC/60% RH) and tested at intervals of 0,3,6,9,12,18,24 months and 36 months (if applicable) until the desired expiration date is reached. Yearly thereafter, a minimum of one production batch (packaged in the smallest and largest configuration of each container/closure) will be placed on the long term stability program. Expiration dates may be

extended based upon acceptable room temperature stability data from a minimum of three production batches. If during the post approval stability studies, any lots are found to fall outside the approved specifications these may be reported to the FDA under 21CFR 314.81 (b) (1)(ii). For additional details regarding the post approval stability protocol refer to Module 3.2.8.2. <This text to be confirmed at the time of submission>

4.6.3 Module 3: Quality - Chemistry, Manufacturing and Control

3.2.S Drug Substance

3.2.S.1 Description

3.2.S.1 Physicochemical and Biological Property

1.	**Generic Name**	Anti-inflammatory drug (XYZ)
2.	**Patent Status**	
3.	**Approximate Expiry Date**	
4.	**Inventor**	
5.	**Molecular Formula**	**----------**
6.	**Molecular Weight**	350.9
7.	**Chemical Structure**	**----------**
8.	**Chemical Name (IUPAC)**	**----------**
9.	**General Characteristics**	White to slightly yellow, odorless or practically odorless, crystalline powder
10.	**Melting Pint**	254.5 – 257.5 ºC
11.	**pKa**	9.3
12.	**Solubility**	Slightly Soluble in water, Freely soluble in methanol, soluble in chloroform, sparingly soluble in alcohol, Practically insoluble in ether.
13.	**log P**	4.7
14.	**Indication**	Perennial and seasonal allergic rhinitis, Vasomotor rhinitis, Allergic conjunctivitis due to inhalant allergens and foods, Mild,

		uncomplicated allergic skin manifestations of urticaria and angioedema, amelioration of allergic reactions to blood or plasma, Cold urticarial, Dermatographism, As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.
15.	**Polymorphism**	Not reported in literature. However, Anti-inflammatory drug Hydrochloride manufactured by Paras is crystalline in nature. XRD diffractograms of three consecutive batches are provided in section 3.2.S.3.1 to show the consistency.
16.	**Chirality**	There is no chiral center in Anti-inflammatory drug.
17.	**Isomerism**	Anti-inflammatory drug does not exhibit isomerism
18.	**Hygroscopicity**	Not a hygroscopic molecule
19.	**Mechanism of Action**	**--**
20.	**Pharmacokinetics and Metabolism**	
21.	**Sensitivity**	**--**
22.	**Side Effects**	

3.2.2 Manufacture

3.2.S.2.1 Manufacturer of the Drug Substance

Anti-inflammatory drug is manufactured by Paras Pharma Chem Ltd.

Corporate Office:

Paras Pharma Chem Ltd,

78/A, Vengalrao Nagar,

Hyderabad – 500038

Telangana State, India

Phone: +91 40 44763666/23711717

Fax: +91 40 23811576

Email: paras@paraspharma.com

Website: www.paraspharma.com

Manufacturing Site:

Paras Pharma Chem Limited,

Unit-1, Plot No.39, A&B, Phase-I, IDA, Jeedimetla,

Hyderabad – 500 055,

Telangana state, India

Phone: +91 40 4475 4545/23095056

Fax: +91 40 44754555

Contact Person at Paras:

Mr. N V Chalam

Head Corporate Quality,

Phone: +91 40 44763666/23711717

Fax: +91 40 238 11 576

Email: venkatachalam.cq@paraspharma.com

rah@paraspharma.com

The manufacturing facility has been inspected and approved by USFDA, Mexican MOH (COFEPRIS) and Korean FDA.

3.2.S.2.2 Method of Preparation of the Drug Substance Synthesis

Manufacturing of Preparation of the Drug Substance Synthesis

Stage – I:

N-methyl-4-chloropiperidine reacts with Dibenzosuberenone in presence of Magnesium turnings, Tetra Hydro Furan, Ethyl Bromide, Lithium Bromide, Ammonium Chloride, Toluene, Water and Methanol to form 5-(1-methylpiperidine-4-yl)-5H-dibenzo[a,d][7] annulen-5-ol.

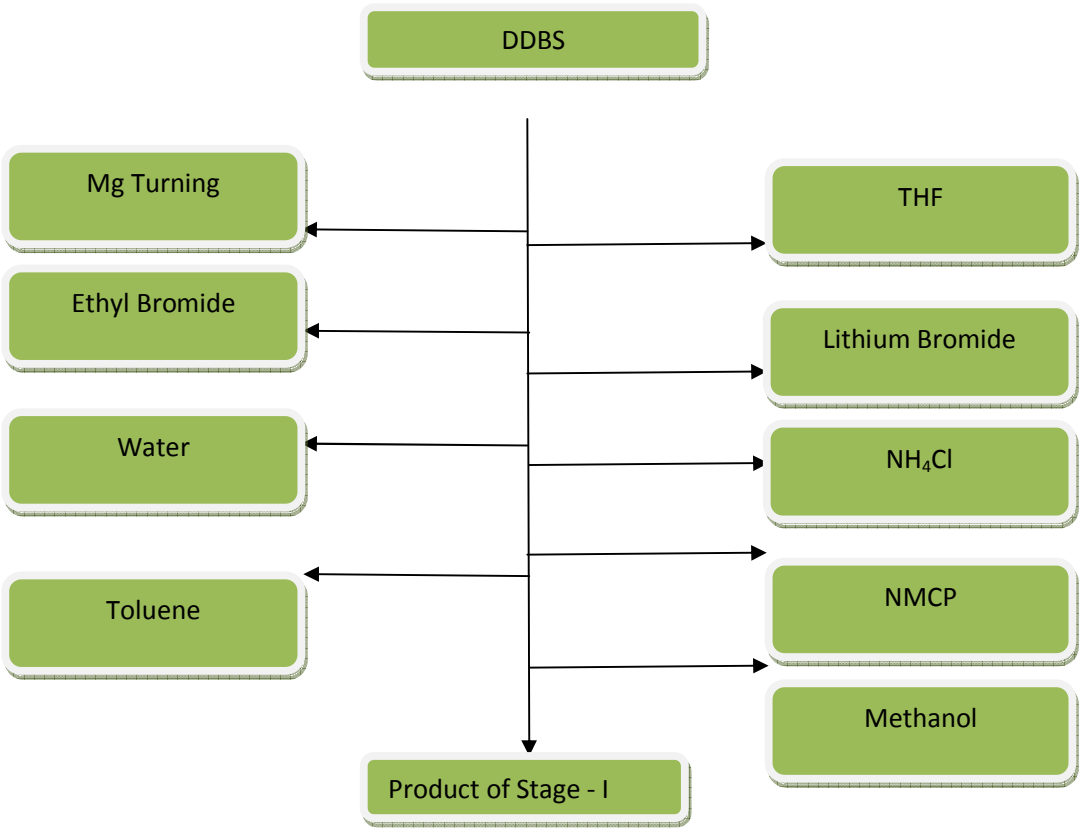


Figure 4.4 Drug Substance Synthesis-Stage I

Stage – II

5-(1-methylpiperidin-4-yl)-5H-dibenzo [a,d][7]annulen-5-ol reacts with Hydrochloric acid in presence of water to form 4-(5H-dibenzo[a,d][7]annulen-5ylidenne)-1-methylpiperidine hydrochloric crude (Stage II)

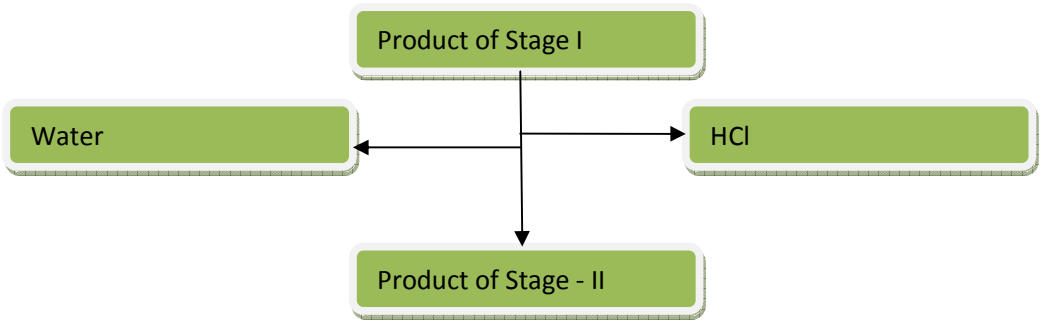


Figure 4.5 Drug Substance Synthesis-Stages II

Stage – III:

4-(5H-dibenzo [a,d][7] annulen-5ydilene)-1-methylpiperidine hydrochloride crude is purified with Carbon, Isopropyl Alcohol, Water and Hydrochloride (CP grade) to form pure Anti-inflammatory drug Sesquidrate.

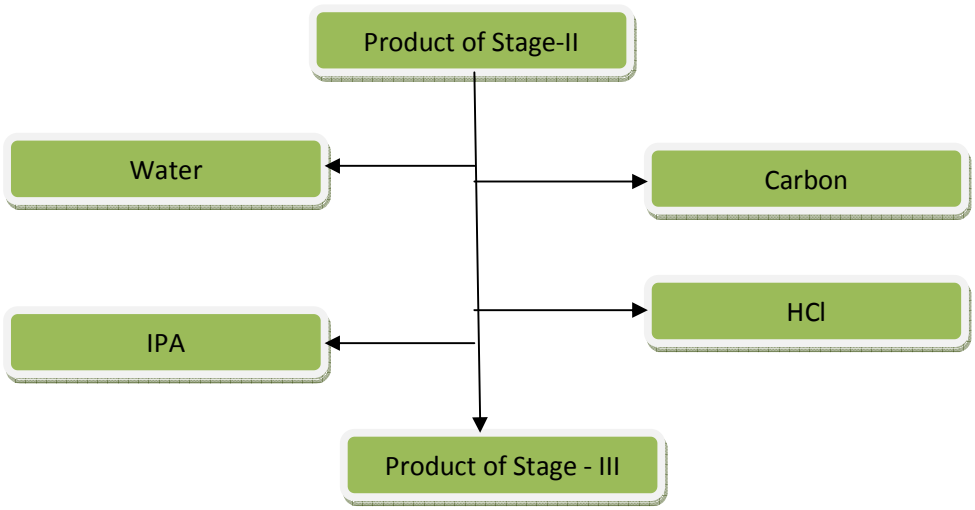


Figure 4.6 Drug Substance Synthesis-Stage III

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and Other Characteristics

The structure of Anti-inflammatory drug Hydrochloride has been confirmed by its synthesis. Further the molecular structure confirmed by spectroscopic studies like elemental analysis, Infrared spectrum, NMR spectrum and Mass spectrum for Anti-inflammatory drug B.No.XYZ/11/011 has been provided as follows.

Structure:

_____

Elemental Composition:

For confirmation of elemental composition, a comparison was done for Anti-inflammatory drug theoretical elemental values against three tested batches and found that meeting the criteria.

Element	***Theoretical Value (%)**	**Obtained Value (%)**		
		XYZ/1101001	**XYZ/1101002**	**XYZ/1101003**
Carbon	**71.88**	**72.33**	**72.34**	**72.34**
Hydrogen	**7.18**	**7.08**	**7.17**	**7.18**
Nitrogen	**3.99**	**3.91**	**3.94**	**3.97**
Chlorine	**10.10**	**9.83**	**9.80**	**9.77**
Oxygen	**6.84**	**6.68**	**6.77**	**6.60**

*Theoretical values are calculated against the molecular weight of Anti-inflammatory drug Hydrochloride Sesquihydrate.

IR Spectrum:

IR spectrum of XYZ/11/001 was recorded on a Thermo FTIR, and was compared with that of Anti-inflammatory drug **USPRS lot No.H0I002**. It exhibited peaks at the same wave numbers as exhibited by the Anti-inflammatory drug **USPRS Lot No.H0I002**.

Further, three prospective process validation batch samples have been analyzed and the values of IR have been compared with USPRS Lot H0I002. All the results are similar and complying with the requirements.

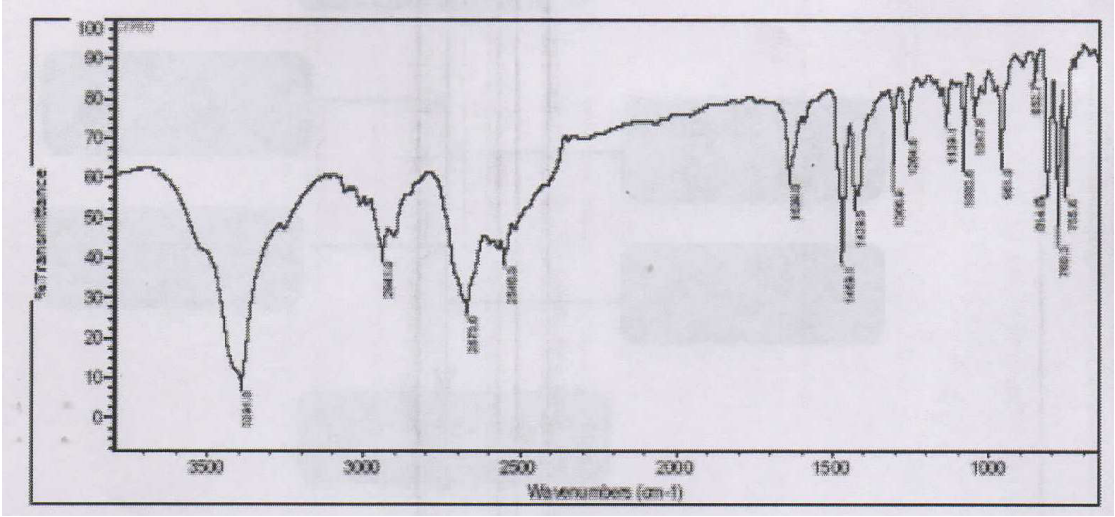


Figure 4.7

1H NMR Spectrum:

The structural interpretation of Anti-inflammatory drug, 1H NMR is given below.

Location of Protons	**Chemical Shift**	**No. of Protons**	**Multiplicity**	**Assignment**
Aliphatic Protons				
7	2.925-3.034	3	Doublet	N-Methyl Protons
2,3,5,6	2.251-2.862	8	Multiplet	Piperidine Ring Protons
11,12	3.289-3.543	2	Doublet	$-CH_2=CH_2-$ (Cycloheptene Ring Protons)

Aromatic Protons				
15,16,17,18,19,20,21, 22	6.880-7.352	8	Multiplet	Aromatic Protons in Benzene Ring

A typical proton NMR spectrum of Anti-inflammatory drug is given below.

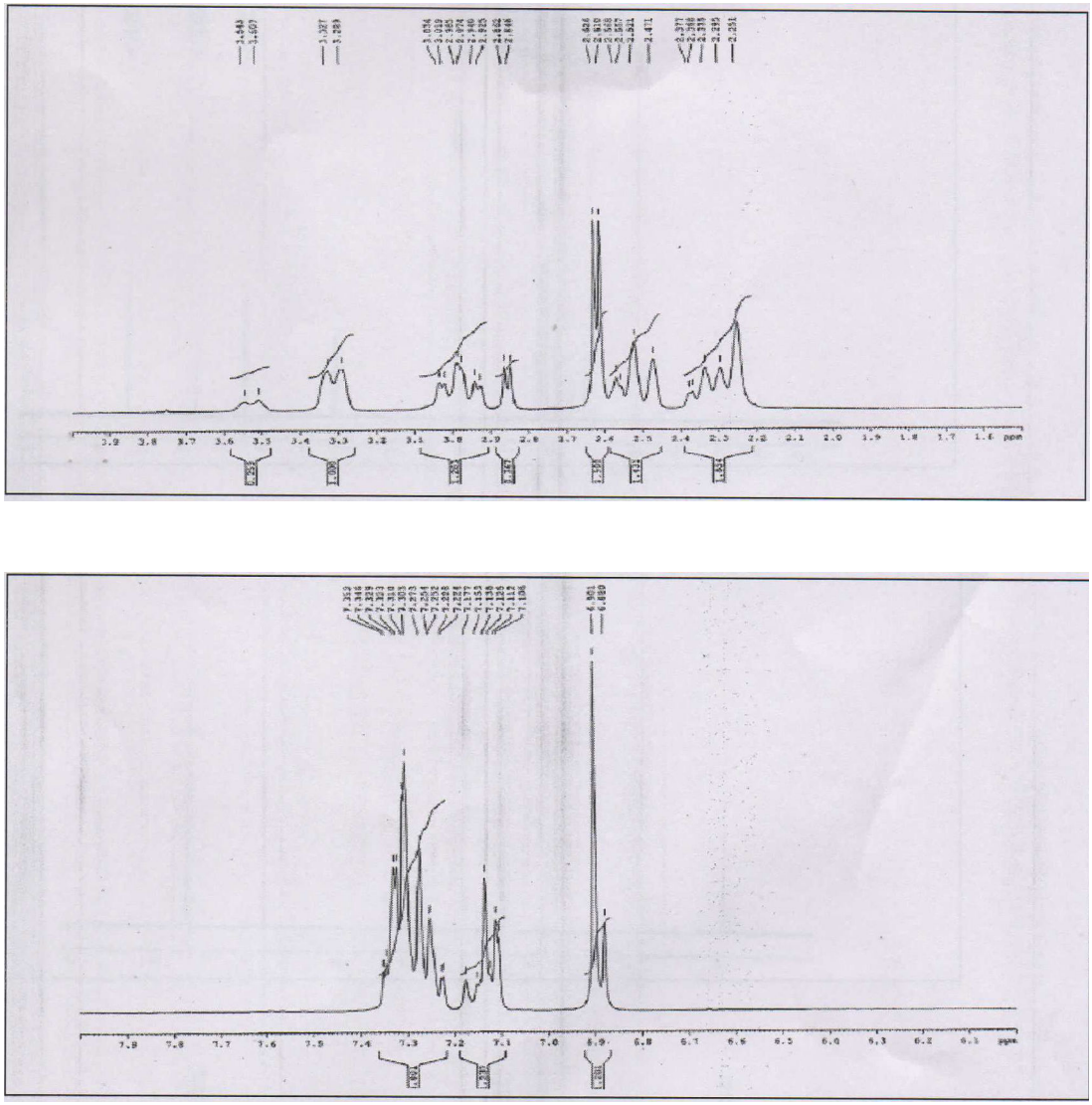


Figure 4.8

^{13}C NMR Spectrum:

The structural interpretation of Anti-inflammatory drug, ^{13}C NMR is given below.

Chemical Shift	Location of Carbon	Assignment
Aliphatic Carbons		
43.536	7	-CH_3 (N-Methyl Carbon)
26.621-26.732	3,5	Piperidine Ring
55.206-55.557	2,6	Piperidine Ring
Aromatic Carbons		
130.882-130.946	11,12	-CH2=CH2- (Cycloheptene ring)
134.350-137.455	8,9,10,13,14	Cycloheptene Ring and attached carbon
127.077-128.692	15,16,17,18,19,20,21,22	Aromatic Carbons in Benzene Ring

Typical ^{13}C NMR spectrums of Anti-inflammatory drug are provided below

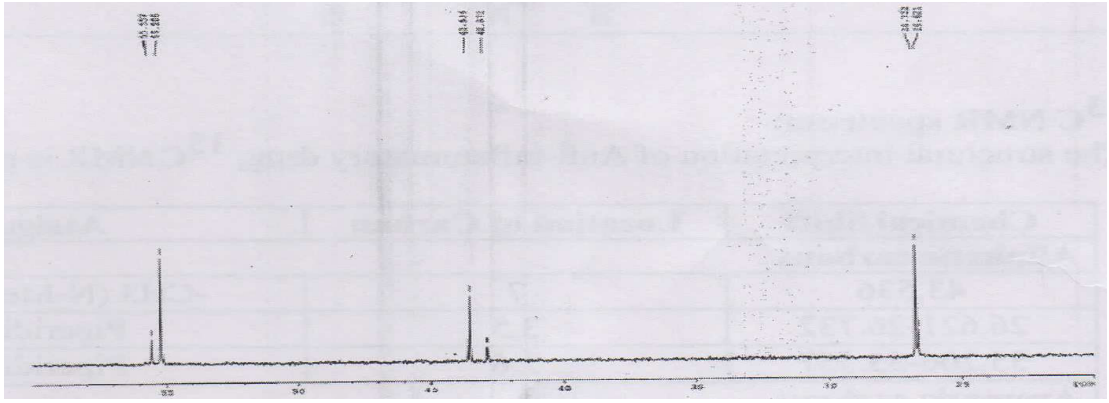


Figure 4.9

Mass Spectrum:

The molecular ion $[M+H]^+$ of Anti-inflammatory drug (free base was detected at 288.9 (molecular weight 287.4) as a very significant peak which correlates with Anti-inflammatory drug. The Fragmentation pattern and molecular assignment is given on the following page, confirming the structure of Anti-inflammatory drug.

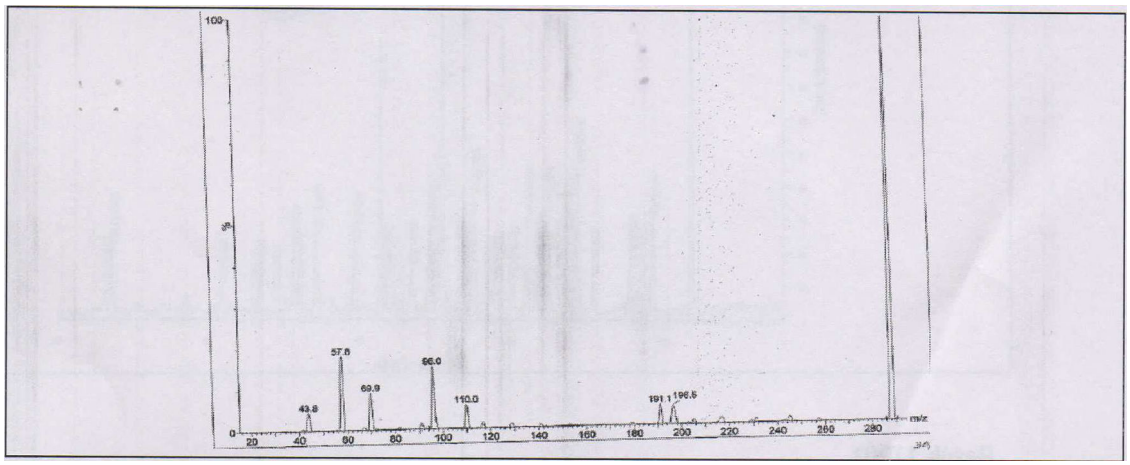


Figure 4.10

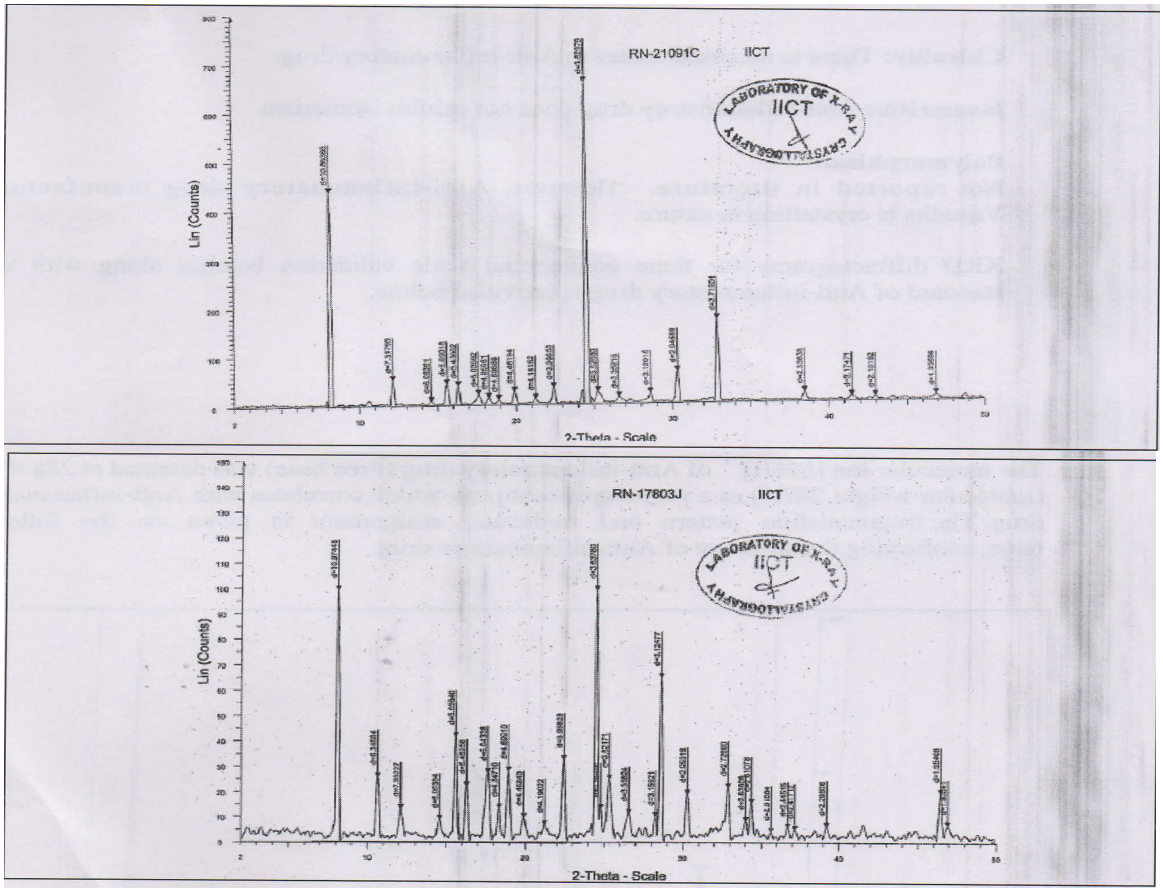
Chirality: There is no chiral center in Anti-inflammatory drug.

Isomerism: Anti-inflammatory drug does not exhibit isomerism.

Polymorphism: Not reported in literature. However Anti-inflammatory drug manufactured by Paras is crystalline in nature.

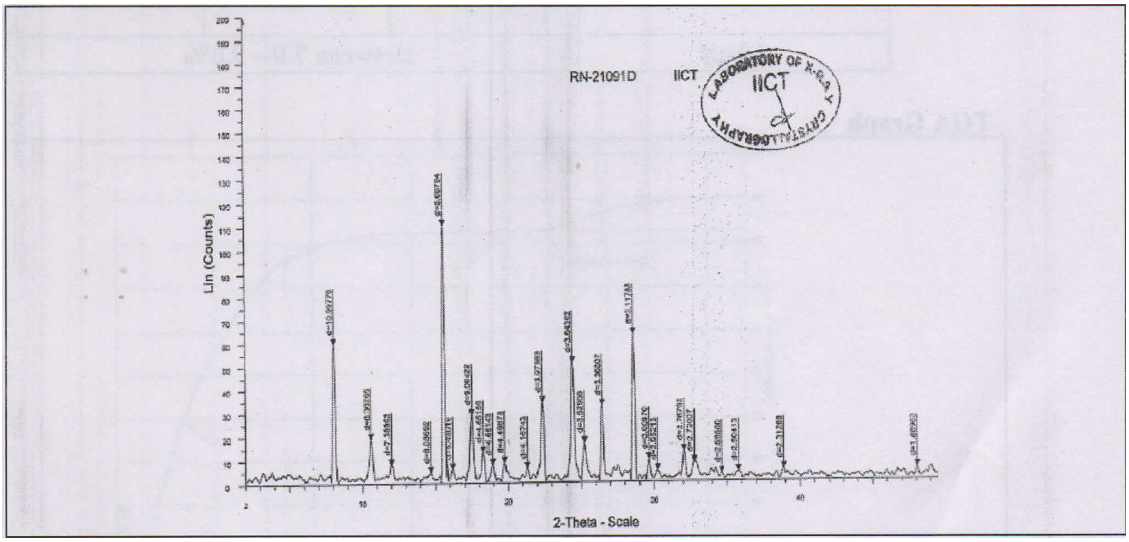
XRD Diffractograms for three commercial scale validation batches along with working standard of Anti-inflammatory drug is provided below.

Diffractogram for Working Standard:



Batch 11001

Batch 11002



Batch 11003

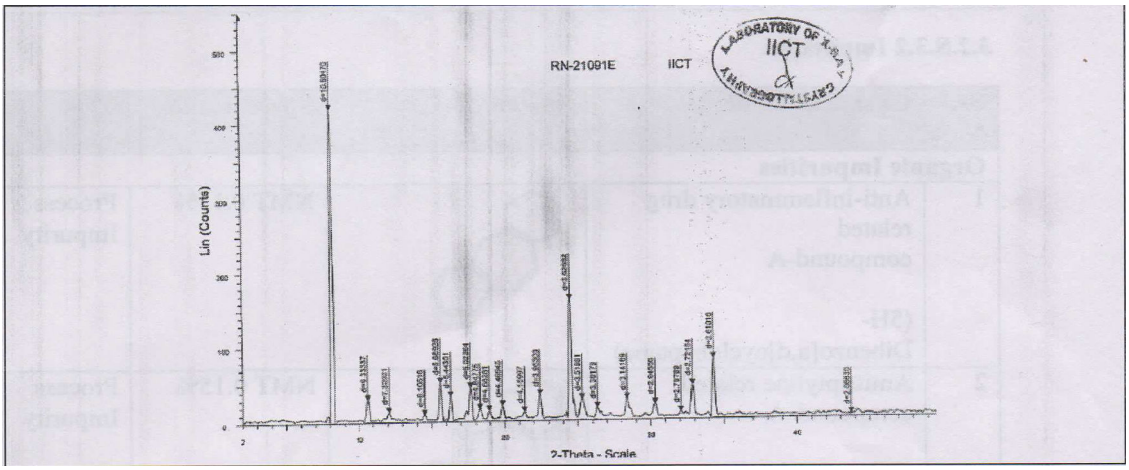


Figure 4.11

Thermo Gravimetric Analysis:

The samples of commercial Anti-inflammatory drug were tested for Thermo Gravimetric Analysis (TGA) to conform sesquihydrate nature. Based on the result the water content present in Anti-inflammatory drug being manufactured by Paras is "sesquihydrate". The results are compared with the USP Pharmacopoeial water content test results and conforming the same.

Test/Batch No.	XYZ/11/001	XYZ/11/002	XYZ/11/003
TGA result	7.226	7.409	7.224

Water Content by KF	7.52	7.47	7.47
Limit	**Between 7.0 – 9.0 %**		

TGA Graph

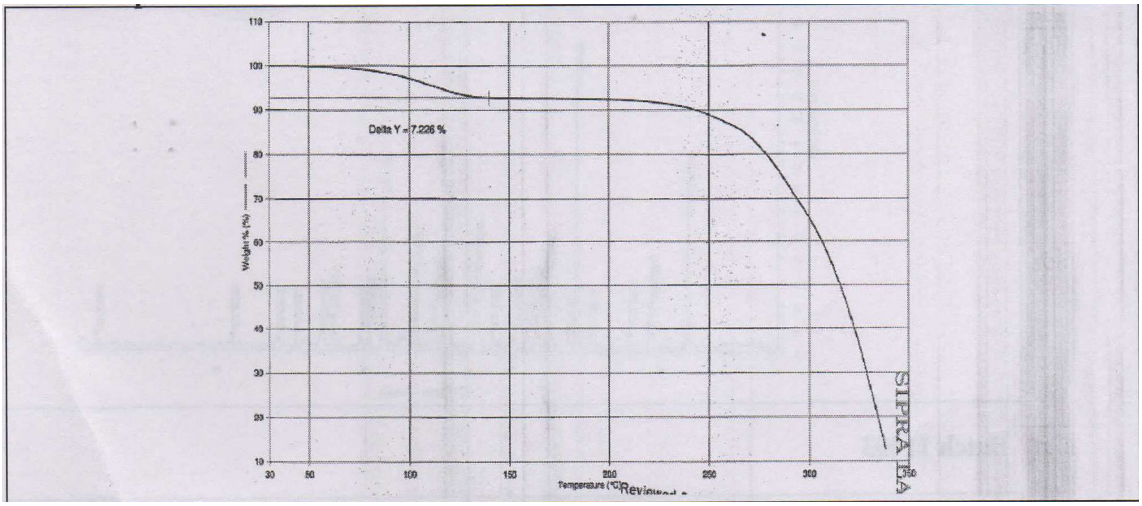


Figure 4.12

3.2.S.3.2 Impurities

Table 4.32 Impurities

Sr. No.	Chemical Name	Structure	Specifications	Type
Organic Impurities				
1	Anti-inflammatory drug related compound A	-----	NMT 0.15%	Process Related Impurity
2	Amitriptyline related compound A	-----	NMT 0.15%	Process Related Impurity
3	Amitriptyline related compound C	-----	NMT 0.15%	Process Related Impurity
4	Any individual unknown impurity	-----	NMT 0.10%	--
5	Total impurities		NMT 0.5%	--
Inorganic Impurities				

1	Toluene	-----	NMT 890 ppm	Residual Solvents
2	Methanol	-----	NMT 3000 ppm	
3	Tetra hydro furan	-----	NMT 720 ppm	
4	Isopropyl alcohol	-----	NMT 5000 ppm	
5	Residue on Ignition	-----	NMT 0.1 % w/w	Reagents/Catalyst
6	Heavy Metals	-----	NMT 30 ppm	

Organic Impurities:

Anti-inflammatory drug monograph is available in USP. Related substances formed during manufacturing process of drug substance are controlled as per USP monograph specification.

Inorganic Impurities (Residual Solvents):

The solvents used in the synthesis of Anti-inflammatory drug are Toluene, Methanol, Tetra hydro furan and Isopropyl alcohol. The limits for residual solvents are proposed in accordance with ICHQ3C guideline requirements. The In-house GC validated (as per ICH Q2) analytical method has been adopted for routine testing as well as characterization.

Inorganic Impurities (Reagents/Catalysts):

The reagents and catalysts are washed out during routine manufacturing process through various works up activities like washing to organic layer and centrifugation/isolation of material. These are controlled as per USP method.

Genotoxic Impurities:

All the reagents, raw materials, intermediate and by products (if any) from starting materials manufacturing process to final API have been explored for genotoxic potentiality and found following compound could leads to genotoxicity which is characterized by GC method.

	Source	**LOD**	**LOQ**
Ethyl Bromide	Raw Material	2 ppm	6 ppm

3.2.S.4 Control of Drug Substance

Tests performed for quality control are given in table with their specifications and analytical procedures which are used to perform tests.

Table 4.33 Drug Substance Specification

Quality Attributes		CQA Yes/No	Specifications	Analytical Procedure	Justification
Appearance		No	White to slightly odorless, or practically colorless, crystalline powder	Visual Inspection	NA
Identification	By IR	Yes	To match with working/reference standard	IR	USP <197k>
	By HPLC		The retention time of the anti-inflammatory drug peak of the sample solution corresponds to that of the standard solution as obtained in the test for organic impurities.	HPLC	USP monograph
	Chemical Test		A bright blue fluorescence should be observed		USP monograph
Impurities (Related Substance)	Anti-inflammatory drug related compound A	Yes	NMT 0.15 %	HPLC	USP monograph
	Amitriptyline related compound A		NMT 0.15 %		
	Amitriptyline related		NMT 0.15 %		

	compound C				
	Any individual unknown impurity		NMT 0.10 %		
	Total impurities		NMT 0.5 %		
Residual solvents	Toluene	Yes	NMT 890	GC	(In-house) To control the residual solvent in the final API and also to meet the ICH requirement. The limits are proposed as per ICHQ3C guideline
	Methanol		NMT 3000		
	Tetra hydro Furan		NMT 720		
	Isopropyl alcohol		NMT 5000		
Heavy Metals		Yes	NMT 30 ppm	USP <231> Method II	USP Monograph
Residue on Ignition		Yes	NMT 0.1 % w/w	USP <281>	USP Monograph
Water Content		Yes	7.0 – 9.0 %w/w	By KF	USP Monograph
Acidity (0.05 % as HCl)		Yes	NMT 0.15 ml should be required		

There is an official monograph in USP for Anti-inflammatory drug substance and tests from the USP monograph are performed. Limits for these tests are those found in the monograph. Specifications are justified above by USP monograph.

3.2.S.5 Reference Standards and Materials

The reference standard of Anti-inflammatory drug has been procured from USP. The lot no. is H1L349. The IR spectrum for USPRS lot no H1L349 has been recorded.

The working standard WS/FP/XYZ/1401 has been qualified against primary reference standard USPRS lot no H1L349.

Table 4.34 Reference Standards

Sr. No.	Reference Standards/Materials	Make	Batch No./Lot No.
Primary Reference Standard:			
1	Anti-inflammatory drug hydrochloride	USPRS	H1L349
Working Standard:			
2	Working Standard	In-house	WS/FP/XYZ/1401
Impurity Standards: The impurity standards developed In-house are well characterized and their molecular structures have been elucidated by using spectroscopic studies [IR, ^{1}H NMR, ^{13}C NMR & Mass] The spectral data of impurity standards along with their CoAs are provided in the following pages.			
3	Anti-inflammatory drug related compound A	USP	FIL356
4	Amitriptyline related compound A	In-house	WS/RM/DBS/1402
5	Anti-inflammatory	In-house	WS/IMP-

	drug related		C/XYZ/1201

Overlaid IR spectrum of working standard with USPRS lot no H1L349 has been provided.

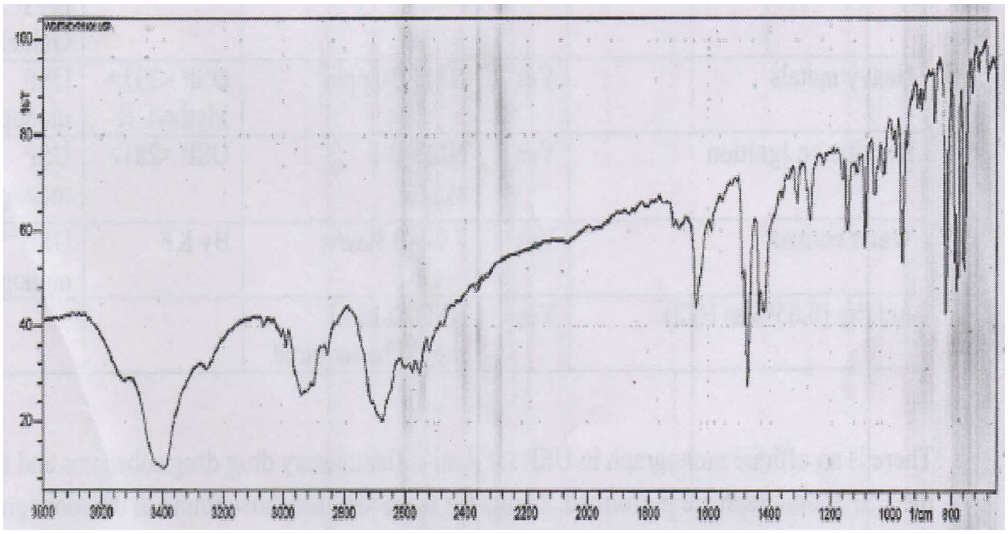


Figure 4.13 IR Spectra of Packing Material

Anti-inflammatory drug is packed in double polythene bags [Linear low density polyethylene], inner transparent and outer black.

The polythene bags [inner transparent & outer black] are placed in HDPE container and material shall be poured in the transparent polyethylene bag, tied individually using plastic fastener [pilfer proof] and outer [black polyethylene bag] with pilfer proof fastener embedded with company logo. One label shall be pasted on black polythene bag. The HDPE drum is closed with the metallic ring and sealed with a tamper proof metallic seal embedded with company logo. One label shall be pasted on container.

The specification and testing procedures along with CoA of primary packaging material and food grade certificate for polyethylene bag are provided by manufacturer.

Stability Summary and Conclusions

3. **General**

   Anti-inflammatory drug is being manufactured from the year 2008 at Paras, Unit-II, and Vizag location. The stability studies have been initiated with process validation batch samples (CYP/002/08, CYP/003/08 & CYP/004/08) in the year 2008.

   In addition to the above site, the same product without any change in process has been transferred to Paras, Unit-I, at Hyderabad in the year 2011. The stability studies have been initiated with process validation batch samples (CYP/11/001, CYP/11/002 & CYP/11/003) in the year 2011. The following are the stability conditions selected for study and its current status.

4. **Stress Testing**

   The stress studies on Anti-inflammatory drug Hydrochloride #XXX/G1-35/S-III/WS/01 were carried out.

   The results indicate that there was significant degradation under oxidation condition. Minor degradation was observed under acidic and base degradation condition. No degradation was observed under UV-light, Heat, Humidity and Aqueous conditions.

   Stability Indicative Nature: the above observations conclude that this test method is able to detect the degradation in Anti-inflammatory drug samples. Hence the above test method is stability indicative.

   Hidden Peaks: Also, spectral data from HPLC analysis utilizing diode array option has shown that there are no hidden and degraded peaks masked by the Anti-inflammatory drug peak.

From the above results it could be conducted that, the In-house (Ph. Eur) HPLC method for related compounds is able to detect degradation products and hence could be used as a stability indicating method.

Supporting analytical data for the above study is discussed in section no. 3.2.S.4.3 under analytical method validation report for related substance by HPLC.

Testing Frequency

The following table gives the frequency of testing of stability samples.

Table 4.35 Testing Frequency

Study	Duration
Accelerated stability studies	6 months (Initial 1,2,3 & 6)
Long term stability studies	5 years (Initial 3,6,9,12,18,24,36,48 & 60 months)

Storage Conditions

The storage conditions are given below.

Table 4.36 Storage Data

Study	Duration
Accelerated stability studies	6 months (Initial 1,2,3 & 6)
Long term stability studies	5 years (Initial 3,6,9,12,18,24,36,48 & 60 months)

Statement/Labeling

3. **Storage Conditions:** Preserve in well closed containers. Store at 25 ºC, excursions are allowed between 15 ºC and 30 ºC.
4. **Expiry Date:** 5 years

Note: <The Product of Anti-inflammatory drug is still at development scale. Hence, data of Exhibit batches are not available.>

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

1. **Description of the drug product**

   Exhibit batch data are not available.

2. **Composition of the dug product**

   Exhibit batch data are not available.

The composition of Anti-inflammatory drug product along with the respective function is provided below in Table.

Table 4.37 Composition of Anti-inflammatory drug product

Sr.No.	Ingredients	Spec	Quantity/Unit (mg/ml)	Function

3. **Container Closure System**

   Anti-inflammatory drug product is being marketed in ----------. A package leaflet is included in each carton. The proposed packing specification of Anti-inflammatory drug product is given in Table below.

Table 4.38 Proposed packaging configuration of Anti-inflammatory drug product

Primary Pack		
Secondary Pack		

The detailed information regarding the proposed container closure system of Anti-inflammatory drug product is presented in **Section 3.2.P.7.**

3.2.P.2 Pharmaceutical Development

The product development studies of Anti-inflammatory drug product are carried out in R&D centre of Cadila Healthcare Limited.

The objective of developmental activities was to manufacture a stable, robust formulation of Anti-inflammatory drug product.

3.2.P.2.1.1 Drug Substance

Anti-inflammatory Drug substance used in manufacture of Anti-inflammatory drug product complies with USP. The physicochemical characteristics of the drug substances Anti-inflammatory Drug USP, as reported in the literature is described in Module 3.2.S.1.

Drug and Excipients Compatibility Study:

3.2.P.2.1.2 Excipients

Exhibit batch data are not available.

3.2.P.2.2 Drug Product

Exhibit batch data are not available.

3.2. P.2.2.1 Formulation Development

The **Table 4.39** below indicates the content of the finished product along with the functionality of each ingredient.

Table 4.39 Formulation trials and functionality of raw materials selected

Sr. No.	Ingredients	Specification	Quantity mg/ml	Functionality

Conclusion:

The pre-formulation and formulation studies performed have yielded a stable formulation. This formulation when subjected for further stability has given satisfactory results.

Final Formula and Manufacturing Process

Based on the stability study of primary batches of **Anti-inflammatory Drug Product (Tablets)** in proposed pack the following composition as stated in Table 4.40 was finalized.

Table 4.40 Composition of Anti-inflammatory Drug Product

Sr. No.	Ingredients	Specification	Quantity (mg/ml)

Proposed Specifications for Anti-inflammatory Drug Product

The finished product specifications proposed for Anti-inflammatory Drug Product on USP monograph are summarized in **Table 4.41**.

Table 4.41 Finished Product Specifications

Sr.No.	Finished Product Tests	In-house Limits

Sr.No.	Finished Product Tests	In-house Limits	
	Assay Anti-inflammatory Product	Release	
		Regulatory	
Additional Tests:			

3.3.P.2.2.2 Overages

3.3.P.2.2.3 Physicochemical Properties

3.2.P.2.3 Manufacturing Process Development

Objective

The manufacturing process comprises of bulk manufacturing, mixing, granulation, compression, coating following critical parameters of manufacturing process were studied:

I. Selection of manufacturing process

II. Optimization of manufacturing process

After the above studies, the formulation was also studied for stability studies.

III. Stability studies

Proposed steps in the manufacturing of anti-inflammatory drug product

The proposed steps in the manufacturing of anti-inflammatory drug product along with the possible variables and the controls are listed in Table 4.42.

Table 4.42 Manufacturing Steps, Possible Variables and Controls

Stage of Manufacturing	Possible Variables	Measured/Recorded Parameters

Brief Manufacturing Process

The manufacturing process, briefly described below was finalized for anti-inflammatory drug product based on the process optimization studies, the manufacturing process, briefly described below was finalized for anti-inflammatory drug product. The manufacturing process consists of following steps:

I.

II.

3.2.P.3. Information about the Manufacture of the Drug Product

Exhibit Batch data are not available.

3.2.P.3.1 Manufacturer

Anti-inflammatory drug is used in manufacturing of Anti-inflammatory drug product (Tablet USP).

Manufacturer:

Cadila Healthcare,

Bavla, Ahmedabad

3.2.P.3.2 Batch Formula

Batch formula for the Anti-inflammatory Drug Product Injection given below**.**

Table 4.43 Batch formula for the Anti-inflammatory Drug Product

Sr.No.	Ingredients	Spec	Quantity/Unit (mg/ml)	Quantity/ Batch

3.2.P.3.4 Controls of Critical Steps and Intermediates

The various in-process controls during the manufacture of Anti-inflammatory drug product are listed in the batch manufacturing records and the quality of the drug product is controlled by the product specifications and the in-process tests carried out during and at end. The in-process monitoring tests as per the Batch Manufacturing Records are listed in Table 4.44.

Table 4.44 List of Possible Variables and Measured/Recorded parameters

Stage of Manufacturing	Possible Variables	Measured/Recorded Parameters	Set Values/Limits

3.2.P.3.5. Process Validation and/or Evaluation

Retrospective Process validation report of Anti-inflammatory drug product ten batches is attached overleaf. The batch on which the validation was carried out was manufactured using the formulation details as given in earlier section 3.2.P.3.2 and the manufacturing process as given in section 3.2.P.3.3. The batch no. and the batch size of the Anti-inflammatory drug product on which the process validation studies were carried out is provided in the table 4.45.

Table 4.45 Process Validation and/or Evaluation

Product Name	Batch No.	Batch Size	Mfg. date	Exp. Date

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

All the Excipients listed in the table below comply with the specification of USP monograph. Additionally few in-house tests are performed for better quality control of the Excipients. The Excipients are sourced from only those vendors that can supply Excipients in compliance with the required specifications.

Table 4.46 Specifications of Excipients

Sr. No.	Excipients	Reference
1.		
2.		
3.		

The specifications of the respective raw materials used during the manufacturing of Anti-inflammatory drug product are attached overleaf.

3.2. P.4.2 Analytical procedures

All the excipients are tested as per the methodology described in the current USP monographs. The standard testing procedures for all excipients are provided in the section 3.2.P.4.2. Additionally few in-house tests are performed for better quality control of the Excipients.

Sr. No.	Excipients	Reference

The standard testing procedure of the respective raw materials used during the manufacturing of Anti-inflammatory drug product is attached overleaf.

3.2.P.4.4 Justification of specifications

The certificates of analysis (COAs) of all Excipients used in the manufacture of Anti-inflammatory drug product, from the manufacturer of the drug product are attached overleaf.

3.2.P.4.5 Excipients of human or animal origin

The relevant TSE/BSE free certificates from the manufacturer of the Excipients used in the Anti-inflammatory drug product are attached overleaf.

3.2.P.5 Information Supporting the Controls of the Drug Product

3.2.P.5.1 Specifications

The release specification of Anti-inflammatory drug product is attached overleaf.

3.2.P.5.2 Analytical procedures

Exhibit Batch Data are not available.

3.2.P.5.3 Validation of analytical procedures

Exhibit Batch Data are not available.

3.2.P.5.4 Batch analysis

Batch analysis reports for 3 exhibit batches of Anti-inflammatory Drug Product are presented. The batch details are as mentioned below.

Table 4.47 Batch Analysis Data

Anti-inflammatory Drug Product			
Batch No.	**Batch Size**	**Mfg. Date**	**Exp. Date**

3.2.P.5.5 Characterization of impurities

3.2.P.5.6 Justification of specifications

Anti-inflammatory Drug is official in the USP. The specifications of Anti-inflammatory Drug Product are based on the USP monograph.

3.2.P.6 Reference Standards or Materials

3.2.P.7 Container Closure System (Name, Dosage form)

Packing Materials Specification

Table 4.48 Packing Material Description

Primary Pack	1.	
	2.	
Secondary Pack	1.	
	2.	
	3.	
Tertiary Pack	1.	
	2.	

Specifications of Primary Packaging Components

Specifications for the primary components used in the packaging of batches of Anti-inflammatory drug product are listed in table.

No.	Test	Specification

3.2.P.8 Stability Data

Exhibit Batch Data are not available.

3.2.R Additional information

Exhibit Batch Data are not available.

3.2.R.1 Process validation scheme for drug product

The manufacturing process of Anti-inflammatory Drug Product has been validated on ten batches. The Retrospective process validation report of which is included in Module 3.2.P.3.5

3.2.R.2 Medical device

Not applicable

3.2.R.3 Certificate(s) of suitability

Not applicable

3.2.R.4 Medicinal products containing or using in the manufacturing process materials of animal and/or human origin

No materials of animal origin are present in the product. The relevant TSE / BSE certifications for the Excipients are attached in Module 3.2.P.4.5

4.6.4 Module 5: BCS Based Study Summary and Formulation Tables

Table 4.49 Method Validation for Solubility Testing

Information Requested	For Anti-inflammatory Drug
Bioanalytical method validation report location	
Study Report Number	
Analyte	Anti-inflammatory drug
International Standard (IS) (if applicable)	NA
Method Description	By UV method (USP dissolution method)
Limit of Quantitation	-
% Recovery (and % CV) at each concentration tested (if applicable)	-
Average recovery of IS (%) (if applicable)	NA
Standard curve concentrations (units/ml)	0.026 mg/ml
QC concentrations (units/ml)	-
QC precision range (units/ml)	-
QC accuracy range (units/ml)	-
Stability (hrs) (if applicable)	-
Dilution Integrity (if applicable)	-
Selectivity	Specific; USP disso method
Stability Indicating for the testing period? Y/N	Stable

Table 4.50 Solubility Data for Anti-inflammatory Drug in Different Buffered Media at Different pH

Sr. No.	Buffer	Volume	Mean Drug Solubility	Initial Drug Concentration Used for Solubility	pH after Solubilization	Number of Replicates	SD	%RSD
1	0.1 N HCl	250 ml	0.609 mg/ml	-	1.3	2	0.003	0.89
2	4.5 Acetate Buffer	250 ml	0.387 mg/ml	-	4.4	2	0.025	4.32
3	6.8 Phosphate Buffer	250 mL	1.515 mg/ml	-	6.75	2	0.021	10.44
4	7.5 Phosphate Buffer	250 mL	0.843 mg/ml	-	7.6	2	0.007	6.49

Table 4.51 Pivotal Permeability Study Information

Study No.	**-**
Method (i.e. In-vivo mass balance/absolute BA/intestinal permeability)	In-vitro permeability study
Rationale for method selection	To check extent of absorption
Study Title	Caco-2 Permeability study
Study Objective	To measure directional Caco-2 permeability of test compounds in cultured Caco-2 monolayer
Permeability Study Site & Address	**Cyprotex Laboratories.** **Address:** **United Kingdome (HQ)** 15 Beech Lane, Macclesfield, Cheshire SK102DR United Kingdom, Tel: +44(0)1625 505100 Fax: +44(0)1625 505199 enquiries@cyprotex.com
Analytical Site & Address	**-**
Study Dates	Starting from 26th Dec, 2014

Table 4.52 Materials and Methods for Validation of Permeability Study

Description	
Reagents & Materials	➢ Ringers buffer solution (pH 7.4 at 25°C) ➢ Ringers buffer with 1% Methanol ➢ Blk solution: Ringers buffer: Methanol=2:1 (v/v) ➢ 100% Methanol including internal standard (IS) ➢ 10 mM stock dosing solution in DMSO ➢ 100 µM dosing solution in buffer
Cell Culture	**-**
Permeability Assay Buffer (PAB)	**-**
Quality Control of Cell Monolayers	**-**
Permeability Assay	Caco-2 Assay
Analytical Methods for Test Compounds	**-**
Permeability and Recovery Calculation	**-**

Table 4.53 Standard Operating Procedures

SOP No.	Effective Date of SOP	SOP Title

*For all tests and their method validation studies conducted to support the current BCS based waiver request (e.g. permeability, Solubility, Dissolution, Gastric stability tests etc)

Table 4.54 Analytical Method Validation (For Pivotal Permeability Study)

Study No.	
Study Title	
Study Objective	
Analytical Site	
Analytical Site Address (Permeability Lab)	
Analytical Site Address (Bioanalytical Lab)	
Study Dates	
Information Location	
Analyte Name	
Internal Standards	
Analytical Method	
Standard Curve Range	
Limit of Quantitation	
Average recovery of Drug from Top Chamber (%)	
Average recovery of Drug from Bottom Chamber (%)	

Average recovery of IS from Bottom Chamber (%)	
Average recovery of IS from Bottom Chamber (%)	
QC concentrations (units/ml)	
QC Intraday Precision Range (%)	
QC Intraday Accuracy Range (%)	
QC Interday Precision Range (%)	
QC Interday Accuracy Range (%)	
Bench top Stability (hrs)	
Stock (Refrigerator) stability (hrs)	
Processed (Auto sampler) stability (hrs)	
***Freeze thaw stability (cycles)**	
***Long term storage stability (days)**	
Dilution Integrity	
Specificity	
SOPs Submitted	
Bioanalytical method is acceptable	

Table 4.55 Pivotal Permeability Study Design

Study Information	
Study Number	
Study Title	
Testing Site	
Study Monitor	
Analytical Site	
Study Director	
Study/Analysis Dates	
Storage Period (No. of days from the first day of sample collection to the last day of sample analysis)	

Testing Conditions	
SOP	
Sample Analysis	
Internal Control Compounds	
Permeability Buffer	
Plates	
Cell Culture	
Cell Culture Certification	
Dosing Solutions	
Replicates	
Permeability Direction	
Permeability Test Conditions & Sampling Time Points	
Permeability and Recovery Calculation	

Table 4.56 Pivotal Permeability Study: Apical-to-Basolateral (A to B) Permeability of Test Compound and Internal Standards

Drug	Parameter	Nominal Dosing Concentration (units)		
Test Compound	**Papp (mean ± SD)**	**Conc. 1**	**Conc. 2**	**Conc. 3**
	Recovery (%)			
High Internal Standard	**Papp (mean ± SD)**			
	Recovery (%)			
Low Internal Standard	**Papp (mean ± SD)**			
	Recovery (%)			

Table 4.57 Pivotal Permeability Study: Basolateral-to-Apical (B to A) Permeability of Test Compound and Internal Standards

Drug	Parameter	Nominal Dosing Concentration (units)		
Test Compound	Papp (mean ± SD)	Conc. 1	Conc. 2	Conc. 3
	Recovery (%)			
High Internal Standard	Papp (mean ± SD)			
	Recovery (%)			
Low Internal Standard	Papp (mean ± SD)			
	Recovery (%)			

Table 4.58 Pivotal Permeability Study: Ratio of B-to-A Papp Vs. A-to-B Papp.

Drug	Papp (mean ± SD)	Nominal Dosing Concentration			Ratio (B-toA)/ (A-to-B)
		Conc. 1	Conc. 2	Conc. 3	
Test Compound	A-to-B				
	B-to-A				
High Internal Standard	A-to-B				
	B-to-A				
Low Internal Standard	A-to-B				
	B-to-A				

Table 4.59 Gastrointestinal Tract Instability

File Location:					
Medium	**Time of Incubation**	**Incubation Temperature**	**Concentration**		**% Degradation**
Gastric Fluid/Simulated Gastric Fluid					
Intestinal Fluid/Simulated Intestinal Fluid					
File Location of SOP					

Table 4.60 Dissolution Method Information

Dissolution Method	As per USP monograph
Deaeration/Degassing of the medium (Yes/No)	No
Filter Description (if used in dissolution testing)	0.45 micron Nylon/PVDF
Sinker Description (if used in dissolution testing)	NA
Mesh Size Description (if basket used in dissolution testing)	NA
Sampling (Manual/Auto/Fiber Optics)	Auto
CoA of Test Product (location in the submission)	--
CoA of Reference Product (location in the submission)	--

Table 4.61 Information of Analytical Method Used to Analyze Dissolution Samples

HPLC Parameters (if applicable)	
Mobile Phase	**-**
Column	**-**
Flow Rate	**-**
Wavelength	**-**
Injection Volume	**-**
Column Temperature	**-**
Run Time	**-**
UV Parameters (if applicable)	
Wavelength	**285 nm**
Cell Path Length	**50 mm**
Analytical Method Validation Report and Date	**-**
Submission of SOP for Method Validation (Yes/No, Effective Date)	**-**
Address of Method Validation Site	**-**
Address of Dissolution Testing Site	**-**
Submission of Dissolution Method Transfer Report (if the dissolution testing site is different from the method validation site) (Yes/No, Location of the Report)	**-**
Analyte	**-**
Method Description	**-**
Specificity/Placebo Interference	**-**
Linearity and Range	**-**

Accuracy/Recovery	**-**
Precision	**-**
Repeatability (%RSD)	**-**
Intermediate Precision (%RSD)	**-**
Filter Equivalency (% Difference)	**-**
Robustness	**-**
Standard and Sample Solution Stability	**-**

Table 4.62 Dissolution Data

Dissolution Condition	**Apparatus:**	2									
	Sinker:	Yes/No – No									
	Speed of Rotation	50									
	Medium:	0.1 N Hydrochloric Acid									
	Volume:	900 ml									
	Temperature:	37± 0.5 ℃									
Firm's Proposed Specifications		As per USP (NLT 80% (Q) in 30 minutes (Is it acceptable for IRA, Please confirm)									
Dissolution Testing Site (Name, Address)		Cadila Healthcare Limited, Ahmedabad, India									
Study Ref. No.	**Testing Date**	**Product ID/Batch No. (Test-Manufacture Date) (Reference-Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units***		**Collection Times**					**Study Report Location**
						min.	**min.**	**min.**	**min.**	**min.**	

Study Report.	Batch Number	Test Product		12 (Individual Unit tested only)	Mean						
					Range						
					% CV						
Study Report.		Reference Product		12	Mean						
					Range						
					% CV						

Table 4.63 Formulation Data

Anti-inflammatory Drug Tablets USP, 4 mg	**Strength (4 mg) Tablet**	
	Amount (mg)	**Amount (%)**
Anti-inflammatory drug	4.00	3.33
Lactose Monohydrate	40.00	33.33
Microcrystalline Cellulose	70.00	58.33
Sodium Starch Glycolate	5.00	4.17
Magnesium Stearate	1.00	0.83
Total	**120.00**	**100.00**

Chapter 5

Summary

Summary

From the comparison of types of biowaiver in chapter 4.1 it can be seen that provisions of specific dosage form, biowaiver based on Post Approval Changes, Same Product based biowaiver and Additional Strength biowaiver (Highest or Lowest) are available in each country or guideline mentioned in comparative analysis. Some guideline (EU, ASEAN, Australia, Brazil, Malaysia) allow both the strengths (Highest or Lowest) while most of the guidelines allow only highest strength to perform BE study. Moreover, biowaiver for BCS based biowaiver are not available in all countries or guidelines mentioned above (like Japan, Switzerland). In addition different authorities have different BCS class (Mostly BCS Class I) requirement for granting biowaiver. Provision for getting biowaiver based on other strength is available only at USA, EU, ASEAN, Australia and Malaysia. While provisions for "Bridging Approach" is available in only USA, EU, Australia, Malaysia and Saudi Arabia.

Comparison of criteria of BCS based biowaiver in chapter 4.2 shows that Most of the countries like Brazil, Australia, Association of Southeast Asian Nations (ASEAN) countries, South Africa, India, Saudi Arabia have adopted the BCS based biowaiver concept as one of the three main guidance documents (USFDA, EMA, WHO) or a combinations of specific requirements. Guidance of India, ASEAN and South Africa closely resembles to USFDA guidance. Moreover, Australia (TGA) has adopted EU guideline as it is so they both have same requirements for BE study and Biowaiver. Thus, most of the requirements for BCS based biowaiver are identical for solubility, permeability and dissolution study except pH range for solubility study, extent of permeability and BCS class requirement which are kept in bold fonts in table 4.2.

For getting BCS based biowaiver different authorities require different BCS class of drugs. But, most of the authorities require BCS class I (USA, ASEAN, Brazil, India, Malaysia, Russia, Saudi Arabia and South Africa). Whereas EU, Australia and Canada require either BCS Class I or BCS Class III. As per WHO guidance, BCS based biowaiver can be granted either for BCS Class I or Class III or Class II weak acids.

Chapter 6

CONCLUSION

Conclusion

It can be concluded that the Biowaiver is a blessing for generic companies as it exempts BE study. In addition, Biowaiver is a time and cost saving fast track approach for ANDA filing. BCS based Biowaiver is employed to waive In-vivo BE testing for new as well as generic drugs application. Granting biowaivers under systems such as the BCS, eliminates unnecessary drug exposures to healthy subjects and provides fast approval, while maintaining the high public health standard for therapeutic equivalence. Using the rationale of BCS, it can be argued that biowaivers can also be granted on the basis of standard pharmacokinetic data, if a drug exhibits dose linear pharmacokinetics and a sufficiently fast dissolution profile.

However, BCS based biowaiver do not apply to food effects bioavailability studies and other pharmacokinetic studies as they are intended only for BE studies. Thus, BCS based biowaiver is not applicable to waive all type of clinical studies.

Research is ongoing in this field by exploring more ways to increase the utilization of this biowaiver approach (mostly BCS based biowaiver). In the future, the Biowaiver monograph project will extend to fixed dose combinations and science based risk calculations. However, for best science practice in the area of biowaiver there should be global harmonization for biowaiver regulations and guidelines on biowaiver.


Reference &
Resources

References

1. 2007. SADC guideline for Bioavailability and Bioequivalence, South Africa. http://www.ich.org/fileadmin/public_Web_site/ABOUT_ICH/Organization/SADC.pdf (accessed January 8, 2015).

2. Guideline for Biowaiver based on Biopharmaceutics Classification System (BCS) for Immediate Release (IR) Solid Oral Dosage forms, Saudi Food & Drug Authority, Saudi Arabia. http://www.ich.org (accessed January 12, 2015).

3. 2012. Guideline on Bioequivalenvce studies of Generic Products, Japan. http://www.nihs.go.jp/drug/be-guide(e)Generic/GL-E_120229_BE_rev140409.pdf (accessed January 21, 2015).

4. 2005. Guideline on Bioavailability and Bioequivalence studies, CDSCO, India. http://cdsco.nic.in/html/be%20guidelines%20drafts%ver10%20march%2016,%2005.pdf (accessed november 28, 2014).

5. 2013. Guidance on Biopharmaceutics Classification System (BCS)-Based Biowaiver National Pharmaceutical Control Bureau, Ministry of Health, Malaysia. http://portal.bpfk.gov.my/aeimags/file/guidanceonbiopharmaceuticalclassificationsystembcsbased biowaiver.pdf (accessed december 24, 2014).

6. 2014. Release of Guidance document: Biopharmaceutics classification system based biowaiver, Health canada, Canada. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guideld/bcs_guide_ld_scb-eng.php (accessed November 17, 2014).

7. 2014. Guidance for Industry - ANDA submissions - Content and Format of Abbreviated New Drug Applications, USFDA. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm400630.pdf (accessed december 30, 2014).

8. 2003. Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations U.S. Department of Health and Human Services Food and Drug Administration, CDER, USFDA. http://www.fda.gov/downloads/Drugs/guidances/ucm070124.pdf (accessed january 3, 2015).

9. www.ich.org. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M8/ICH_M8_eCTD_14_June_2011.pdf (accessed January 3, 2015).

10 Question Based Review (QbR) for Generic Drugs: An Enhanced Pharmaceutical Quality

. Assessment System. http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm120973.htm (accessed february 4, 2015).

11 Drug Permeability Studies in Regulatory Biowaiver Applications by Donna A. Volpe.
.

12 Simulation based cheminformatic analysis of organelle targeted molecules: lysosomotropic
. monobasic amines by Xinyuan Zyang. **2008**.

13 Clinical Pharmacokinetics of H1 receptor Antagonist (The Antihistamines) by David M. Paton,
. Department of Pharmacology and Clinical Pharmacology, University of Auckland.

14 2009. Prediction of Solubility and Permeability Class Membership: Provisional BCS
. Classification of the World's Top Oral Drugs by Arik Dahan. http://www.ncbi.nlm.nih.gov/pubmed/19876745 (accessed november 23, 2014).

15 Caco-2 cells, Biopharmaceutics Classification System (BCS) and Biowaiver by Smetanova,
. Institute of Experimental Biopharmaceutics. www.ncbi.nlm.nih.gov/pubmed/21542416 (accessed november 25, 2014).

16 2013. A Comparative Analysis of BCS and Biopharmaceutics drug Disposition Classification
. System: A cross sectional survey with 500 bioequivalence studies by Rodrigo Cristofoletti. wileyonlinelibrary.com (accessed november 15, 2014).

17 The complexity of intestinal permeability: Assigning the correct BCS classification through
. careful data interpretation by Moran Zur, Department of Clinical Pharmacology, and Ben-Gurion University of the Negev.

18 ANDA filing checklist. http://www.fda.gov/downloads/Drugs/./UCM320405.pdf (accessed
. january 22, 2015).

19 Example of Quality Overall Summary for Immediate Release oral Dosage forms.
. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120977.pdf (accessed december 20, 2014).

20 2013. Inactive Ingredient Database - FDA Update, by Robert Iser.
. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM375889.pdf (accessed january 1, 2015).

21 2014. Guidance for Industry ANDA Submissions - Prior approval supplements under GDUFA.

. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM404441.pdf (accessed December 28, 2014).

22. 2014. Citizen Petitions and petitions for stay of actions subject to section 505(q) of the Federal food, Drug and Cosmetics Act Guidances for Industry. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079353.pdf (accessed february 3, 2015).

23. Guidelines and Guidance Documents. http://bebac.at/Guidelines.htm (accessed January 23, 2015).

24. BCS based Study Summary and Formulation Tables. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM396512.pdf.

25. In-vitro permeability study and Caco-2 permeability assay. http://www.cyprotex.com/admepk/in-vitro-permeability/caco-2-permeability (accessed january 9, 2015).

26. 2014. ANDA submissions - Refuse to Receive Standards Guidance for Industry. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm370352.pdf (accessed January 11, 2015).

27. 2005. Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. http://www.fda.gov/downloads/drugs/Guidances/UCM078932.pdf (accessed january 25, 2015).

28. Guidelines on Drug Bioequivalence Study requirements in GCC Countries. http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisation/GCC/Topics_under_Harmonisation/Bioequivalence.pdf (accessed february 25, 2015).

29. Biowaiver Monographs 2004 - 2012, International Pharmaceutical federation. http://www.fip.org/centennial/files/static/press/FIP_centennialbook_biowaiver_webversion.pdf (accessed december 21, 2014).

30. 2014. Guidance for Industry Controlled Correspondence related to Generic Drug development. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm411478.pdf (accessed december 16, 2014).

31. 2014. Guidance for Industry- ANDA submissions - Ammendments and Easily correctable deficiencies under GDUFA. http://www.fda.gov/Drugs/guidancecomplianceRegulatoryinformation/guidances/default.htm

(accessed January 5, 2015).

32. 2001. Guidance for Industry - M4: Organization of CTD. http://www.fda.gov/cder/guidance.htm . (accessed december 11, 2014).

33. 2002. Guidance for Industry : Providing Regulatory submissions in electronic format - ANDAs. http://www.fda.gov (accessed November 30, 2014).

34. Nair, A. K. Statistics on BCS Classification of Generic Drug Products Approved Between 2000 and 2011 in the USA, 2012. www.ncbi.nlm.nih.gov/pmc/articles/PMC3475853/ (accessed Feb 12, 2015).

35. ASEAN countries, 2004. www.hsa.gov. http://www.hsa.gov.sgt/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_policies/Guidelines_on_Drug_Registration/ACTR_GuidelinesforConductofBioavailabilityandBioequivalenceStudies_Nov05.pdf (accessed January 13, 2015)

36. Health Canada., 2014. www.healthcanada.com. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guideld/bsc_guide_ld_scb-eng.php (accessed January 23, 2015).

37. www.fda.com. http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM247465.pdf . (accessed March 3, 2015).

38. 1980. Molecular properties of WHO essential essential drugs, Kasim NA. http://www.sciencedirect.com/science/article/pii/0378517380900319 (accessed november 13, 2014).

39. 2004. Unusual Solubility and dissolution behavior of Pharmaceutical hydrochloride salts in chloride containing media by faculty of Pharmaceutical Sciences. http://www.sciencedirect.com/science/article/pii/0378517380900319 (accessed november 14, 2014).

40. Pharmacokinetic Simulation of Biowaiver Criteria: The effects of gastric emptying, dissolution, absorption and eliminate rates by H. Korteja. *European journal of pharmaceutical sciences* **2007**.

41. Package insert: Product information of_____ Anti-inflammatory product. http://www.aspenpharma.com.au/product_info/pi/periactin_pi_17Nov11.pdf (accessed december 5, 2014).

42. Package insert of Anti-inflammatory Drug Tablets USP. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/087056s045lbl.pdf (accessed december 24, 2014).

43. Methodological recommendations for drug manufacturers on In-vitro equivalence test for generic drug products according to biowaiver procedure, Federal Service on Surveillance in Healthcare and Social Development, Russia. http://www/fip.org/files/fip/BPS/BCS/Biowaiver%20guidance%20(ru)%20-pdf.

44. Guidelines on Drug. http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisation/GCC/Topics_under_Harmonisation/Bioequivalence.pdf.

45. Guidelines for exemption and replacing relative bioavailability/bioequivalence, ANVISA Brazil. http://www.puntofocal.gov.ar/notificotrosmiembros/bra226t.pdf (accessed January 15, 2015).

46. Guidelines for exemption and replacing relative bioavailability/bioequivalence. http://www.puntofocal.gov.ar/notific_otros_miembros/bra226_t.pdf (accessed Jan 25, 2015).

47. 2010. Guideline on the investigation of Bioequivalence, EMEA. http://www.ema.europe.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf (accessed January 17, 2015).

48. Guideline on the Investigation of Bioequivalence, 2011. www.who.com. www.WHO.com (accessed Jan 15, 2015), 5.

49. Guideline on Bioequivalence Studies of Generic Products, 2012. http://www.nihs.go.jp/drug/be-guide(e)Generic/GL-E_120229_BE_rev140409.pdf (accessed Feb 3, 2015).

50. Guideline for Biowaiver based on Biopharmaceutics Classification System (BCS) for Immediate Release (IR) Solid Oral Dosage forms, 2012. http://www.sfda.gov.sa/En/Drug (accessed Jan 26, 2015).

51. Guidance on Biopharmaceutics Classification System (BCS)-Based Biowaiver National Pharmaceutical Control Bureau, 2013. http://portal.bpfk.gov.my/aeimages/file/guidance_on_biopharmaceutics_classification_system_bcs_based_biowaiver.pdf (accessed Feb 12, 2015).

52. 2007. Guidance for Industry: Waiver of In-vivo Bioavailability and Bioequivalence studies for Immediate Release Solid Oral Dosage Forms based on a Biopharmaceuticals Classification System,. http://www.fda/downloads/Drugs/guidances/ucm070246.pdf (accessed january 12, 2015).

53. Guidance for Industry: Waiver of In-vivo Bioavailability and Bioequivalence studies for Immediate Release Solid Oral Dosage Forms based on a Biopharmaceuticals Classification System, 2000. www.fda.gov. (accessed Jan 15, 2015).

54. Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations U.S. Department of Health and Human Services Food and Drug Administration, 2003. www.fda.gov. http://www.fda.gov/downloads/Drugs/Guidances/ucm070124.pdf (accessed Feb 20, 2015).

55. 2013. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Piroxicam. http://onlinelibrary.wiley.com/doi/10.1002.jps.23799/pdf (accessed November 18, 2014).

56. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Amitryptyline Hydrochloride by R.H.Manzo, 1 M.E. Olivera, 2006. http://onlinelibrary.wiley.com/doi/10.1002/jps.20615/pdf (accessed november 26, 2014).

57. 2007. Pharmacokinetic simulation of biowaiver criteria: The effects of gastric emptying, dissolution, absorption and elimination rates, European journal of pharmaceutical sciences. http://onlinelibrary.wiley.com/doi/10.1002/jps.20064/abstract (accessed january 5, 2015).

58. 2012. 5. Biopharmaceutical Drug Disposition Classification System: an extension of Biopharmaceutical Classification System, International Research Journal of Pharmacy,. http://onlinelibrary.wiley.com/doi/10.1002/jps.20064/abstract (accessed november 27, 2014).

59. 3. Lipophilicity assessment of basic drugs (log Po/w determination) by a chromatographic method by Juan M. Pallicer a, Joaquim Salesb, Marti Rosesa, Clara Rafolsa, Elisabeth Boscha, Spain.

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