

Department of Drug Administration
Requirements of Comparative Dissolution Studies for registration of Generic Products

PART_I: GENERAL REQUIREMENTS

S No	Test Parameters	Requirements
1	Temperature	37± 1 °C
2	Apparatus	Paddle (75 rpm) or Basket (100 rpm)
3	No of sample units	12 units
4	Dissolution media	For Immediate and Extended Release Products: 1. pH 1.2 hydrochloric acid, 2. pH 4.5 buffer and 3. pH 6.8 buffer For Delayed Release (Enteric Coated) Products: 1. pH 1.2 hydrochloric acid (for 2 hours), 2. pH 6.8 buffer
5	Dissolution media Volume	900 ml or less
6	Recommended Sampling Points	1. Immediate Release Products: 5, 10, 15, 20, 30, 45 and 60 minutes 2. 12-hour extended-release products: 1, 2, 4, 6, 8 and 12 hours; 3. 24-hour extended-release products: 1, 2, 4, 6, 8, 16 and 24 hours

Notes:

- Comparative Dissolution Tests with suitable justification is required if waiver of BA/BE tests for BCS Class II/IV drugs and Modified Release Dosage forms is requested from manufacturer.
- The dissolution measurements of the two finished pharmaceutical product (FPPs) (test and comparator) should be made under the same test conditions.
- Surfactants should be avoided in comparative dissolution testing. A statement that the API is not soluble in any of the media is not sufficient, and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.
- Dissolution profile comparison should be done with Innovator product. If Innovator product is not available in domestic market, manufacturer can apply for import recommendation to obtain Innovator product for testing purpose from international market. In special cases, when it is not possible to obtain Innovator product for reasons (like withdrawal from market) manufacturer shall submit an application to DDA to recognize other brand as comparator Brand. Department will identify suitable comparator brand and inform the manufacturer. Manufacturer are advised to consult with DDA if there is any confusion regarding the identification of Innovator brand. Dissolution profile comparison with comparator brands other than those authorized by Department will not be accepted.



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PART II: INTERPRETATION

- For immediate release products, if both the test and reference (comparator) products show more than 85% dissolution in 15 minutes the profiles are considered similar (no calculations required).
- Similarity of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f_2)

$$f_2 = 50 \cdot \log \left\{ \left[1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\}$$

where R_t and T_t are the mean per cent API dissolved in reference (comparator) and test product, respectively, at each time-point.

1. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar;
- A maximum of one time point should be considered after 85% dissolution of the reference (comparator) product has been reached;
 - In the case where 85% dissolution cannot be reached owing to poor solubility of the API or the release mechanism of the dosage form, the dissolution should be conducted until an asymptote (plateau) has been reached;
 - **At least 12 units** should be used for determination of each profile. Mean dissolution values can be used to estimate the similarity factor, f_2 . To use mean data the percentage coefficient of variation at initial time-points (e.g. up to 10 minutes for immediate release) should be not more than 20% and at other time-points should be not more than 10%;

References:

1. Medicine Registration Guidance, 2073
2. WHO TRS 1003 Annex 6: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability.



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ANNEXURE – I REPORT FORMAT OF COMPARATIVE DISSOLUTION STUDY

1. ABSTRACT

S. No.	Dissolution Medium	Media Volume	Apparatus	RPM	Temperature	Time Point
1						
2						
3						

2. PRODUCT DETAILS

S. No.	PRODUCT DETAILS	TEST PRODUCT	REFERENCE PRODUCT
1	GENERIC NAME		
2	BRAND NAME		
3	BATCH NO		
4	MFG DATE		
5	EXPIRY DATE		
6	MANUFACTURED BY		
7	STORAGE CONDITION		

3. RESULTS:

3.1 MEDIA – I (0.1 N HCl)

3.1.1 Test Product Dissolution data in Media-I

S NO	CUMULATIVE PERCENTAGE DRUG DISSOLVED (TEST PRODUCT)						
	time point 1 (eg 5 min)	time point 2 (eg 10 min)	time point 3 (eg 15 min)	time point 4 (eg 20 min)	time point 5 (eg 30 min)	time point 6 (eg 45 min)	time point 7 (eg 60 min)
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10							
11							
12							
MIN							
MAX							
AVERAGE							
% RSD							



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3.1.2 Reference Product Dissolution data in Media-I

S NO	CUMULATIVE PERCENTAGE DRUG DISSOLVED (REFERENCE PRODUCT)						
	time point 1 (eg 5 min)	time point 2 (eg 10 min)	time point 3 (eg 15 min)	time point 4 (eg 20 min)	time point 5 (eg 30 min)	time point 6 (eg 45 min)	time point 7 (eg 60 min)
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MIN							
MAX							
AVERAGE							
% RSD							

f2 calculation:

Graphical representation:

3.2 MEDIA ii (4.5 acetate buffer)

3.2.1 Test Product Dissolution data in Media-II

S NO	CUMULATIVE PERCENTAGE DRUG DISSOLVED (TEST PRODUCT)						
	time point 1 (eg 5 min)	time point 2 (eg 10 min)	time point 3 (eg 15 min)	time point 4 (eg 20 min)	time point 5 (eg 30 min)	time point 6 (eg 45 min)	time point 7 (eg 60 min)
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12							
MIN							
MAX							
AVERAGE							
% RSD							

3.2.2 Reference Product Dissolution data in Media-II

S NO	CUMULATIVE PERCENTAGE DRUG DISSOLVED (REFERENCE PRODUCT)						
	time point 1 (eg 5 min)	time point 2 (eg 10 min)	time point 3 (eg 15 min)	time point 4 (eg 20 min)	time point 5 (eg 30 min)	time point 6 (eg 45 min)	time point 7 (eg 60 min)
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MIN							
MAX							
AVERAGE							
% RSD							

f2 calculation:

Graphical representation:

3.3 Media III (pH 6.8 phosphate buffer)

3.3.1 Test Product Dissolution data in Media-III

S NO	CUMULATIVE PERCENTAGE DRUG DISSOLVED (TEST PRODUCT)						
	time point 1 (eg 5 min)	time point 2 (eg 10 min)	time point 3 (eg 15 min)	time point 4 (eg 20 min)	time point 5 (eg 30 min)	time point 6 (eg 45 min)	time point 7 (eg 60 min)
1							



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12							
MIN							
MAX							
AVERAGE							
% RSD							

3.3.2 Reference Product Dissolution data in Media-III

S NO	CUMULATIVE PERCENTAGE DRUG DISSOLVED (REFERENCE PRODUCT)						
	time point 1 (eg 5 min)	time point 2 (eg 10 min)	time point 3 (eg 15 min)	time point 4 (eg 20 min)	time point 5 (eg 30 min)	time point 6 (eg 45 min)	time point 7 (eg 60 min)
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7							
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9							
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12							
MIN							
MAX							
AVERAGE							
% RSD							

f2 calculation:

Graphical representation:

4.0 CONCLUSION:

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S. No.	Generic Name	Innovator/Comparator Products (Brand Name and Manufacturers)
1	Aceclofenac Sustained/Prolonged Release Tablets	HIFENAC SR Tablets, Intas
2	Aceclofenac Tablets	HIFENAC Tablets, Intas
3	Acetazolamide Tablets	Diamox Tablets, Pfizer
4	Amlodipine and Hydrochlorthiazide Tablets	AMLONG H Tablets, Microlabs
5	Aripiprazole Tablets	ARIP MT Tablets, Torrent; ARPIZOLE Tablets, SUN
6	Atorvastatin Tablets	AZTOR Tablets, Sun Pharma
7	Azithromycin Tablets	AZEE Tablets, Cipla
8	Bilastin Tablets	BILAXTEN Tablets, Menarini
9	Calcium and Vit D3 Tablets	SHELCAL Tablets, Torrent
10	Carbimazole Tablets	NEOMERCAZOLE Tablets, Abbott
11	Cefixime Tablets	SECEF Tablets, Novartis/Sandoz
12	Cefixime Dispersible Tablets	SECEF DT, Novartis/sandoz
13	Cefpodoxime Proxetil tablets	ZEDOCEF Tablets, Macleods; MICROCEF Tablets, Microlabs
14	Cefuroxime Axetil Tablets	CEFTUM Tablets, GSK; ZOCEF Tablets ALKEM
15	Cefuroxime axetil (powder for oral suspension)	ZOCEF (powder for oral suspension), Alkem
16	Cilnidipine Tablets	NULONG Tablets, Microlabs
17	Cinacalcet Tablets	PTH Tablets, Intas
18	Ciprofloxacin Tablets	BAYCIP Tablets, Bayer/Zydus/Encore; CIFRAN Tablets, Sun Pharma
19	Clarithromycin Tablets	ACEM Tablets, Emcure; CLARBACT Tablets, IPCA
20	Clonazepam Tablets	RIVOTRIL Tablets, Abbott /Roche
21	Clopidogrel Tablets	PLAVIX Tablets, Sanofi
22	Dabigatran Capsules	PRADAXA Capsules, Boehringer
23	Danazol Capsules	DANOGEN Capsules, Cipla
24	Deflazacort Tablets	DEZACOR Tablets, Aristo
25	Desvenlafaxine ER Tablets	VENTAB DXT Tablets, Intas; VENIZ Tablets, Sun Pharma
26	Dexlansoprole Delayed Release Capsules	DEXLANZOL DR Capsules, Cipla
27	Diacerin Capsules/Tablets	DURAJOINT Capsules, Abbott; JOINCERIN Tablets, Torrent
28	Divalproex Sodium Extended Release Tablets	DEPAKOTE XR Tablets, Sanofi
29	Drotaverine Tablets	DOVERIN Tablets, Intas
30	Duloxetine Capsules	MACXETINE Capsules, (Macleods) ; DUZELA Capsules, Sun Pharma
31	Duloxetine Tablets	DUVANTA Tablets, Intas
32	Dydrogesterone Tablets	DUPHASTON Tablets, Abbott
33	Escitalopram and Clonazepam Tablets	FELIZ S Tablets, Torrent
34	Esomeprazole Fast Release Tablets	NEXPRO FAST Tablets, torrent
35	Esomeprazole Gastroresistant Tablets	NEXIUM Tablets, Astrazeneca
36	Etoricoxib Tablets	NUCOXIA Tablets, Cadila
37	Febuxostat Tablets	ZURIG Tablets, Zydus

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38	Fenofibrate Tablets, Capsules	TGR Tablets, Intas; FENOLIP Tablets, Cipla; LIPICARD Capsules USV
39	Finasteride Tablets	FINAST/FINAX Tablets, Dr. Reddy's
40	Finerenone Tablets	KERENDIA Tablets, Bayer AG
41	Flavoxate Tablets	URISPAS Tablets, Martin&Harris; URELY Tablets Mapra Laboratories
42	Fluvoxamine Tablets	FLUOXIN Tablets, Sun Pharma
43	Folic Acid Tablets	FOLVITE Tablets, Wyeth
44	Glimepiride Tablets	AMARYL Tablets, Sanofi
45	Hydrchlorothiazide Tablets	AQUAZIDE Tablets, Sun Pharma
46	Hyoscine butylbromide	BUSCOGAST Tablets, sanofi; BUSCOSPАЗ Tablets Sunglow Lifesciences
47	Ibuprofen and Paracetamol Tablets/Suspension	COMBIFLAM, Sanofi ; FLEXON, Aristo
48	Ilaprazole Tablets	LUPILA Tablets, Lupin
49	Indomethacin SR Capsules	MICROCID SR Capsules, Micro Labs
50	Isotretinoin Capsules	SOTRET Capsules, Sun Pharma
51	Itopride SR Capsules	GANATON OD Capsules, Abbott
52	Itraconazole Capsules	SPORANOX Capsules, J&J ; CANDITRAL Capsules, Glennmark
53	Lansoprazole	LAN Tablets, intas; LANSPRO Tablets, Indchemie
54	Levetiracetam Extended Release Tablets	LEVERA XR Tablets , Intas
55	Losartan Potassium and Amlodipine Tablets	LOSAR A Tablets, torrent; REVAS AM Tablets, Alembic; AMLOZAR Tablets , Micro Labs; REPACE A Tablets, Sun Pharma
56	Losartan Potassium Tablets	REPACE Tablets, Sun Pharma; TOZAAR Tablets, Torrent
57	LosartanPotassium and Hydrochlorothizide Tablets	TOZAAR H Tablets, Torrent
58	Mesalamine Prolonged Release Tablets	VEGAZ OD, Dr. Reddy's
59	Metformin Extended Release Tablets	CETAPIN XR, Sanofi
60	Methylprednisolone	MEDROL, Pfizer
61	Metoprolol Extended Release Tablets	SELOKEN XL Tablets, Astrazeneca
62	Meveberine Hydrochloride Retard Capsules	COLOSPA RETARD Capsules, Abbott
63	Mirabegron Extended Release Tablets	MIRAGO Tablets, Sun Pharma
64	Mirtazapine Tablets	MIRTAZ Tablets, Sun Pharma
65	Montelukast Tablets	SINGULAIR Tablets, Intas/MSD; Montair, Cipla
66	Naproxen Tablets	NAPROSYN Tablets, RPG Lifesciences
67	Nebivolol tablets	NEBICARD Tablets , Torrent
68	Nimesulide Tablets	NIMULID Tablets, Panacea Biotech
69	Nimodipine Tablets	NIMODIP Tablets, Torrent
70	Olanzapine Tablets	ZYPREXA Tablets, Lily; OLEANZ Tablets Sun Pharma
71	Omeprazole Tablets/Capsules	Prilosec OTC, Astrazeneca; OMEZ Capsules, Dr. Reddy's

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72	Ondansetron Orally Disintegrating Tablets	ONDEM MD Tablets, Alkem
73	Ornidazole Tablets	DAZOLIC Tablets, Sun Pharma
74	Pantoprazole Gastro-resistant and Domperidone Prolonged Release Capsules	PANTOTAB DSR Capsules, Mircro Labs
75	Paracetamol and Chlorzoxazone Tablets	MYOSPAS Tablets, Win-Medicare
76	Paroxetine Extended Release Tablets	PEXCEP CR, Intas; PAXIDEP CR, Sun Pharma
77	Pentoxifylline Prolonged Release Tablets	TRENTAL Tablets, Sanofi India
78	PRAMIPEXOLE Extended Release Tablets	PRAMIROL SR Tablets, Intas
79	Propranolol Sustained Release Tablets	INDREAL LA Tablets, Abbott
80	Ramipril Tablets	CARDACE Tablets, Sanofi
81	Ribaroxavan Tablets	XARELTO Tablets, Bayer
82	Rifaximin Tablets	CIBOZ Tablets, Zydus Cadila
83	Risperidone Tablets	RISPERDOL Tablets, Janseen
84	Rosuvastatin Tablets	CRESTOR Tablets, Astrazeneca /IPR
85	Sacubitril Valsartan Tablets	VYMADA Tablets, Novartis
86	Sertraline Tablets	DAXID Tablets, Pfizer
87	Tadalafil Tablets	CIALIS Tablets, Lupin/Eli Lilly; FORZEST Tablets, Sun Pharma
88	Telmisartan	TELMA Tablets, Glennmark
89	Telmisartan and Amlodipine Tablets	TELMA AM Tablets, Glennmark
90	Telmisartan and Chlorthalidone Tablets	TELMA CT Tablets, Glennmark
91	Telmisartan and Hydrochlorothiazide Tablets	TELMA H Tablets, Glennmark
92	Tizanidine Tablets	TIZAN Tablets, Sun Pharma
93	Tranexamic acid	XAMIC Tablets, Torrent
94	Ursodeoxycholic acid	UDILIV Tablets, Abbott
95	Vitamin D3 Capsules	DV 60K Capsules, Indchemie
96	Voglibose Tablets	VOGLITOR Tablets, Torrent
97	Voriconazole Tablets	VFEND Tablets, Pfizer

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