DEVELOPMENT OF BIORELEVANT DISSOLUTION MEDIA FOR ABACAVIR DISPERSIBLE TABLETS

*** Gudimetla Karthik , **Dr. Pabba Parameshwar**

*Research Scholar, School of Pharmacy, Career Point University, Kota Rajasthan

**Research Supervisor, School of Pharmacy, Career Point University, Kota, Rajasthan

Corresponding authors: *Gudimetla Karthik , **Dr. Pabba Parameshwar

ABSTRACT

The main objective to establishment of biorelevant dissolution media for Abacavir Dispersible tablets is a useful technique for qualitative forecasting of the *in vivo* behavior of formulations. Dissolution tests that can predict the *in vivo* performance of Pharmaceutical drug products are usually called biorelevantdissolution tests. Biorelevant dissolution testing can be used to guide formulation development, to identify food effects onthe dissolution and bioavailability of orally formulation.To develop a biorelevant dissolution media for Abacavir Dispersible tablets for oral dosage forms, the physiological conditions in the gastrointestinal(GI) tract that can affect drug dissolution are taken into consideration according to the properties of the drug and dosageform. A variety of biorelevant methods in terms of media and hydrodynamics to simulate the contents and the conditionsof the GI tract are presented. The use of biorelevant media can have a great impacton the pharmacokinetic studies performed to optimizedosing conditions and product formulation. In addition,biorelevant dissolution testing could be used to assessbioequivalence of post-approval formulation changes in certain kinds of drugs.

Key words: Abacavir Dispersible tablets, Zeigen tablets 300 mg, biorelevant dissolution

INTRODUCTION:

Abacavir Sulfate (BCS Class 3 drug) is a nucleoside reverse transcriptase inhibitor (NRTI) used for treatment of human immunodeficiency virus (HIV) infection. HIV infection is usually treated with antiretroviral therapy (ART) regimens, which consist of three or more different drugs used in combination. Typical antiretrovirals used in these regimens include NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase strand inhibitors (InSTIs). Abacavir makes an ideal addition to these types of combination therapies due to its dosing flexibility

DRUG SUBSTANCE -BIORELEVANT DISSOLUTION DEVELOPMENT

During Drug product development, oral dosage formulations are selected to assess their safety. Biorelevant dissolution plays an important role in the selection of appropriate drugformulations for development. During development, biorelevant dissolution can be of value in:

- Selecting appropriate drug substance phases and forms for formulation development.
- Developing toxicology formulations with adequate bioavailability
- Method development to evaluate batch-to-batch consistency.

API physical and chemical properties can significantly impact formulation dissolution and bioavailability. Consideration of chemical and physical stability, processibility, and bioavailability needs to be balanced in API phase selection. Salt formation and particle size reduction are mechanisms that can enhance dissolution and bioavailability. Biorelevant dissolution of various drug substance phases can facilitate the selection of appropriate salt forms, polymorphs, and particle sizes.

The amount of drug substance is based on the compound potency and projected human doses. The primary goal of drug substance dissolution is to examine the impact of drug substance attributes on the rate and extent of dissolution in biorelevant media. The salt forms of basic compounds can have higher solubility in gastric pH, and precipitation to neutral forms can occur at intestinal pH. The salt forms of weakly acidic compounds can disproportionateto the neutral forms at gastric pH and re solubilize in intestinal pH. For neutral compounds, reducing particle size can lead to dissolution enhancement. However, very small particles can form large aggregates, which lead to slow dissolution. Sonicating drug suspensions or dispersing drug with excipients can break agglomerates before biorelevant dissolutions. Understanding API dissolution in biorelevant median also builds a solid foundation for further formulation development. The goal of dosage form development is to solubilize the maximum amount of API and maintain it in solution for the longest period of time within the absorption window. Biorelevant dissolution helps to assess the challenges of dissolving all the doses required in the GI tract. The higher the challenges are the higher the bioperformance risk and the greater the development efforts that are likely needed.

Biorelevant dissolution also informs where the drug will be most solubilized in the GI tract and guides pharmaceuticalscientists in achieving the desired bioavailability with different formulations. For example, using soliddispersions, pre-dissolving the drug in lipids, or reducing

particle size can enhance the apparent solubility. Use of excipients such as surfactants, water-soluble fillers, and Superdisintegrants leads to faster dissolution rates. Polymers and antinucleation agents can be used to maintain salts in solution and delay precipitation to neutral forms.

Dosage Form Considerations:

For Abacavir Dispersible Tablets IR dosage forms comes under BCS Class III compounds.Dissolution profile is rapidly dissolving due to dispersible tablets ; a disintegration test can predict dissolution behavior because disintegration of the dosage form is the rate-limiting step to dissolution. Formulation properties have a substantial effect on *in vitro* and *in vivo* dissolution. *In vitro* dissolution profiles in biorelevant tests (biorelevant media in combination with biorelevant hydrodynamics according to the formulation properties) should be evaluated during development, and an IVIVC can be established between the *in vitro* dissolution and *in vivo* performance. *In vivo* drug release from these formulations occurs according to a specific predefined delivery pattern, and environmental factors should not influence the release. Oral bioavailability is limited by intralumenal release, and the selection of an appropriate biorelevant dissolution test can lead to prediction of *in vivo* performance. The use of a pH gradient and sequential changes of media) can be valuable during drugdevelopment to expose the dosage forms to the different conditions across the GI tract. The biorelevant dissolution test should be designed according to the dosage-form release pattern and the simulated fasted-or fed-state conditions.

Biorelevant media simulate the gastrointestinal fluids by containing the physiological surfactants, bile salt and lecithin. Biorelevant intestinal media simulate intestinal fluidssecreted under fasted- (FaSSIF) or fed-state conditions (FeSSIF). Food intake alters the physiochemical properties and composition of intestinal fluids for digestion. That is why separate intestinal media are defined for fasted and fed-state conditions. This can help detect food effects and optimize formulation performance by using Biorevalent dissolution media are FaSSIF and FaSSIF-V2 are the two most frequently used compositions for biorelevant intestinal media reflecting fasted-state conditions.

MATERIALS:

Abacavir sulfate was obtained as a gift sample from Hetero labs, Sodium starch Glycolate gifted from JRS Pharma, microcrystalline cellulose gifted from FMC Pharma, Croscarmellose

Cellulose (Primellose), Magnesium stearate, Sucralose and strawberry flavor gifted sample from Signet Chemicals Ltd, Mumbai. All other chemicals and reagent were of analytical grade.Sodium taurocholate gifted by Sigma–Aldrich, lecithin were gifted by BASF, Hydrochloric acid were received by Ashland supplier. All other chemicals and reagents were of analytical grades.

Preparation of dispersible tablets using wet granulation method:

The drug, other excipients were sifted through ASTM mesh no 40. The dry mix blend was then granulated with respective granulation fluid. The wet granules were dried at 600c until the complete evaporation of granulation fluid from the granules. The dried granules were again sifted through ASTM mesh no 30.The dried and sifted granules were then pre lubricated and flavoring with respective excipients and then lubricated with magnesium stearate. The lubricated granules were compressed on 5 station tablet compression machine using respective punches (Cadmach Machinery Co, Ahmedabad, India).

Table 1: Formulation and physical characteristics of designed dispersible tablets of Abacavir sulfate

Ingredients	F1	F2	F3
Abacavir sulfate	60.00	60.00	60.00
Microcrystalline cellulose (PH 102)	32.40	30.00	30.00
Croscarmellose sodium (Primellose)	8.00	10.00	8.00
Povidone K90	8.00	10.00	8.00
Sucralose	6.00	6.00	6.00
Purified Water	QS	QS	QS
Microcrystalline cellulose (PH 112)	15.00	15.00	15.00
Sodium starch Glycolate (Type A)	8.60	7.10	5.60
Strawberry flavor	0.50	0.50	0.50
Magnesium stearate	1.50	1.50	1.50
Total tablet weight (mg)	**140.00**	**140.00**	**140.00**

Preparation of *In-vitro* dissolution media (USP Official dissolution media Test 3)

***In-vitro* drug release studies:**

Dissolution studies were performed using the USP II, paddle-rotating method (Electrolab dissolution tester,TDT-08, India) at 37 °C ± 0.5 °C and 50 rpm using 0.1 N HCl , 900ml as the dissolution media. Is solution studies were carried out in triplicate. A 2 ml aliquot of sample was withdrawn at regular time intervals, filtered and then these samples were diluted 10 folds with distilled water and then assayed spectrophotometrically at 246 nm. (Data tabulated in table no. 3 and graph 1 representing the comparative dissolution release between references and test product)

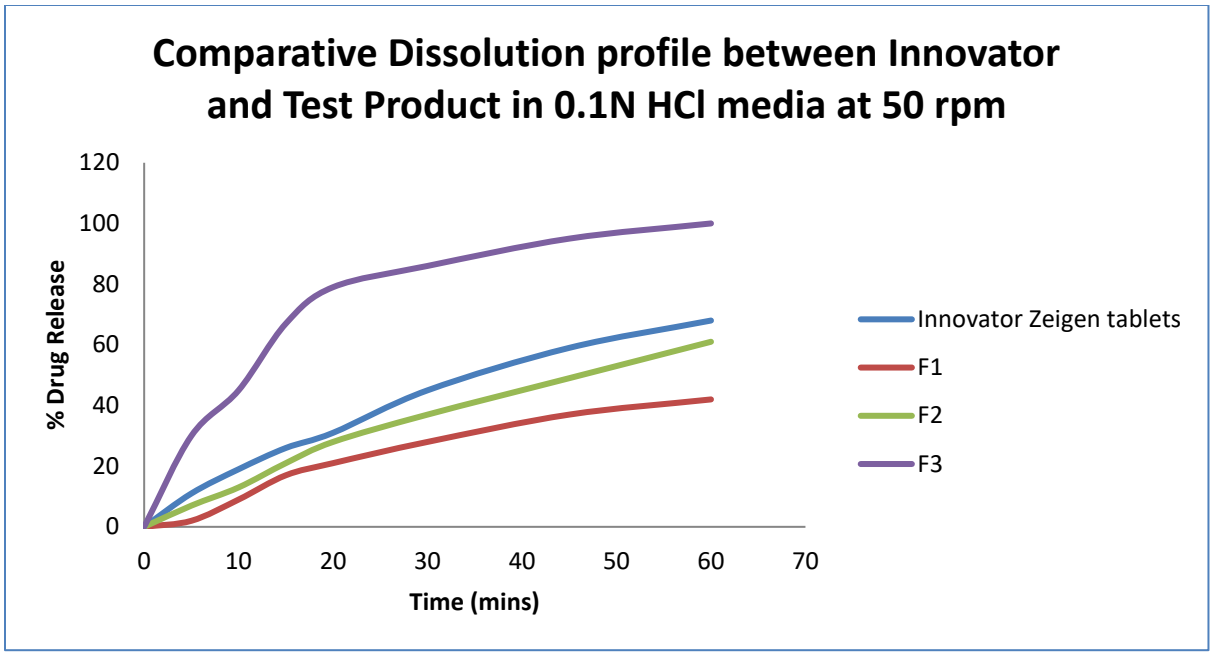
Preparation of Biorelevant Dissolution Medium:

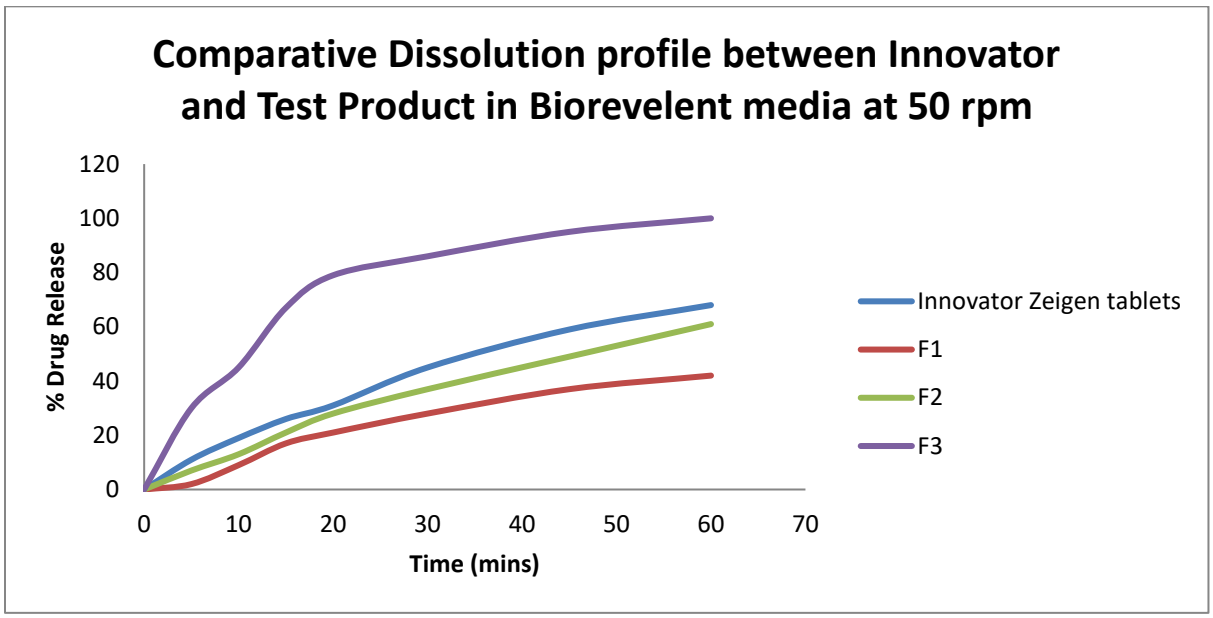
Dissolution studies were performed using the USP II, paddle-rotating method (Electrolab dissolution tester,TDT-08, India) at 37 °C ± 0.5 °C and 50 rpm using the composition of the simulated intestinal fluid, Fasted state simulating intestinal fluids was made of sodium taurocholate and lecithin. The FaSSIF contains 3mM sodium taurocholate and 0.75mM lethicin make up the volume to 900ml A 2 ml aliquot of sample was withdrawn at regular time intervals, filtered and then these samples were diluted 10 folds with distilled water and then assayed spectrophotometrically at 246 nm. (Data tabulated in table no. 4 and graph 2 representing the comparative dissolution release between references and test product)

Table 2: Dissolution profiles of marketed product (Zeigen tablets 300 mg vs the dispersible tablets) vs different formulation in 0.1N HCl

(The cumulative % drug release was calculated for the formulations and the drug release data were curve fitted)

Type of Formulation	***In vitro* dissolution using 0.1 N HCL, 900ml, Apparatus 2 and 50 RPM**				**Biorevalent dissolution medium** (Sodium taurocholate& lecithin), **900ml, Apparatus 2 and 50RPM**			
Time (Hours)	**Innovator Zeigen tablets**	**F1**	**F2**	**F3**	**Innovator Zeigen tablets**	**F1**	**F2**	**F3**
5	34	23	39	67	11	2	7	30
10	67	38	59	70	19	9	13	45
15	76	47	68	89	26	17	21	67
20	87	56	78	97	31	21	28	79
30	98)	70	91	96	45	28	37	86
45	101	87	98	100	59	37	49	95
60	100	90	101	100	68	42	61	100
F2		**31**	**59**	**42**	**F2**	**41**	**60**	**24**


Comparative Dissolution profile between Innovator and Test Product in 0.1N HCl media at 50 rpm
% Drug Release
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Time (mins)
Innovator Zeigen tablets
F1
F2
F3


Comparative Dissolution profile between Innovator and Test Product in Biorevelent media at 50 rpm
% Drug Release
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Time (mins)
Innovator Zeigen tablets
F1
F2
F3

CONCLUSION:

This work focuses on studying the correlation between the *in vitro* dissolution of USP official media and Biorelevant dissolution medium of BCS class III drug.Formulation F2 tablets exhibited similar release profiles to that of Zeigen tablets in the FDA-recommended dissolution medium, significant variations in drug release profiles were observed in the different dissolution media. Our findings highlight the importance of studying the effect of the physiological properties of GI fluids on the rate of drug release from tablets prepared using different types of Disintegrants and Binder attaining similar release profiles in a compendial- or FDA-recommended dissolution medium. Understanding these effects can be crucial to prevent along the intestinal fluid, maximize drug bioavailability and help predict more accurate *in vitro–in vivo* correlations.

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