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Formulation Development of Uncoated Metformin Tablet and it's *in vitro* Bioequivalence Study for Biowaiver

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ABSTRACT

The purpose of this research work is to prepare metformin hydrochloride immediate release tablets by wet granulation technique and study the possibility of bio-waiver by *in-vitro* dissolution studies by comparing the marketed formulation. In order to obtain the best, optimized product eight different formulations were developed by varying the concentration of binder and disintegrants. Weight variation, thickness, hardness, friability, and *in-vitro* release, were studied as response variables. The formulations F2 and F3 were selected as optimized formulation for comparing with the reference product. The *in-vitro* release profile in different media like 0.01 N hydrochloric acid (pH 2), phosphate buffer (pH 4.5), and phosphate buffer (pH 6.8) were studies, the results shows that both the formulation had shown the similarity factor (f2) more than 50% but it does not satisfy the WHO criteria for bio-waiver because none of the formulation including the marketed formulation had not shown 85% or more dissolved within 15 min in standard dissolution media at pH 1.2, 4.5, and 6.8.

Introduction

Oral drug delivery is the most preferred route for the drug administration because of ease of administration, convenience, and non-invasiveness method. Still the oral drug delivery system is the largest and oldest segment of the total drug delivery market [1]. Metformin hydrochloride is biguanide, which is widely used in the management of type-II diabetes in the form of oral formulation [2]. One of the major advantages of using metformin HCl is that unlike other anti-diabetic drugs, it does not induce hypoglycaemia at any reasonable dose, and hence it is called as an anti-hyperglycaemic rather than a hypoglycaemic drug [3].

Metformin is highly hydrophilic drug having oral bioavailability of 50 to 60% [4] and it is having a plasma elimination half-life of 6.2 hours [5-7] with a peak plasma concentration of 4.8 hours. Metformin is on the world health organization's list of essential medicines [8]. Generic drugs are produced only when the patents get expired and it is simply the copies of innovator drug products. In developing countries like India the generic versions are promoted for use in practice because they are usually less expensive than the innovator products and it improves the access to life-saving drugs. Generic drug products can only be interchangeable with innovator products when they are pharmaceutically and therapeutically equivalent [9].

In vivo bioequivalence (BE) studies are commonly used to assess therapeutic equivalence, but these studies are often costly and involve invasive procedures [10]. A less costly and ease method like *in vitro* dissolution tests based on BCS are nowadays acceptable surrogates for establishing the bioequivalence of generics with the innovator products.

According to FDA [11] and WHO [9], a bio-waiver for *in vivo* studies can be obtained for BCS Class I drugs that are very rapidly dissolving (≥85% dissolved within 15 min) or are rapidly dissolving (≥85% dissolved within 30 min) with f2 ≥ 50 in three dissolution media ranging in pH from 1.2 to 6.8. [11]. WHO also recommends bio-waiver for Class 2 and 3 drugs that are very rapidly dissolving [9]. Metformin hydrochloride is BCS Class III drug which is highly soluble with low permeability; it is therefore and is eligible for a bio-waiver based on the WHO criteria [12] according to the WHO bio-waiver testing procedure for Class 3 drugs [9], a bio-waiver can be considered only if both the generic and the innovator products dissolve very rapidly (i.e., 85% or more dissolved within 15 min in standard dissolution media at pH 1.2, 4.5, and 6.8).

The objective of the present study was to develop and prepare different formulations of Metformin HCl 500 mg uncoated tablet by varying different excipients, which is best comparable with the innovator product. This study is also sought to apply the BCS bio-waiver requirements.

Materials and Methods

Materials

Metformin hydrochloride (Active pharmaceutical ingredient), Starch (Diluent), Starch Fluid Paste

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(Thickening agent), Gelatin (Thickening agent), Methyl paraben (Preservative), Propyl paraben (Preservative), Talc (Lubricant) and sodium starch glycolate (Super disintegrant) were used in the preparation of the tablet. Metformin HCl was obtained from Pharmafabrikon, Madurai. All reagents and solvents used were of analytical grade satisfying pharmacopoeial standards.

Preparation of Metformin HCl Tablets [13, 14, 15]

The formulation design is given in table 1. Wet granulation technique will ensure uniform distribution of drug as well as improve flow property. Therefore, this approach was applied in the formulation development of metformin Tablets.

Table 1: Formulation of Metformin Tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Metformin	500	500	500	500	500	500	500	500
Starch	10	20	30	40	50	60	70	80
Sodium starch glycolate	20	20	20	20	30	30	30	30
Gelatin	5	5	5	5	5	5	5	5
Methyl paraben	3	3	3	3	3	3	3	3
Propyl paraben	2	2	2	2	2	2	2	2
Talc	1%	1%	1%	1%	1%	1%	1%	1%
Magnesium Stereate	2%	2%	2%	2%	2%	2%	2%	2%
SFP(10%w/v)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total	650	650	650	650	650	650	650	650

Wet Granulation

The active pharmaceutical ingredients and the excipients are weighed and it is sieved through the 22#mesh and it is dry mixed with pre-gelatinized starch which is passed through 40#mesh, then it is load in to rapid mixture granulator for about 15min at low speed. The binder solution was added to this powder mixture and the mixing was continued at slow speed for 5-15 min. Then it is rotated at fast speed for 5-15 min till required end point was achieved. Then the material is dried using the Fluidized bed dryer for 30 minutes until the loss on drying was not more than 0.5%. The dried granules were passed through the #14/150 mesh and the uniform sized granules were collected.

Final mixing and Tablet compression

The Screened granules were finally blended with lubricants using a suitable mixer with a revolution of 10 rpm for about 15 min. The granules are finally compressed into tablets using a suitable rotary tablet press using 14 mm flat faced circular punches with the target weight is 650 mg containing metformin HCl (500 mg).

Evaluation of Tablets

The prepared tablets were evaluated for weight variation, hardness, thickness, friability, and disintegration [16]. Hardness of the tablets was tested using a Monsanto hardness tester (Tab-machine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by verniercaliper. Weight variation test was performed according to the official method [17]. Drug content was analyzed by measuring the absorbance of standard and samples at λ=233 nm using UV/Vis spectrophotometer (Shimadzu 1601, Kyoto, Japan).

***In vitro* drug release studies** [18]

Drug release studies were conducted using USP- type 2 dissolution apparatus, paddle type (Electrolab, Mumbai, India) at a rotational speed of 50 rpm at 37±0.5°C using the 900 ml of dissolution media of 0.01 N HCl for 2hrs. Sink condition was maintained for the whole experiment. Samples (10 ml) were withdrawn at regular intervals and the same volume of pre-warmed (37±0.5°C) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 µ membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 233 nm [19]. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (min) curve.

***In vitro* Bioequivalence study**

The *in vitro* dissolution profile of the prepared eight formulation F2 and F3 was compared with the marketed formulation of metformin HCl (GLYCIPHAGE 500 uncoated tablet).

A volume of 900 mL of each of the following media was employed: 0.01 N hydrochloric acid (pH 2), phosphate buffer (pH 4.5), and phosphate buffer (pH 6.8). Dissolution testing was performed using USP Apparatus type 2 (Electrolab, Mumbai, India) at 50 rpm for all the products [20]. The dissolution system met the USP performance verification test requirements. Nine dosage units of each product were evaluated in all the three media. Samples were withdrawn at specified time intervals (10, 20, 30, 40, 50 and 60 min) of about 10 ml and the same volume of pre-warmed (37±0.5°C) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 µ membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 233 nm.

Comparison of Dissolution Profile

The dissolution profiles were compared using the similarity factor (f2) derived from the dissolution profiles. The dissolution profiles can be compared using two model independent parameters: the difference factor (f1) and the similarity factor (f2) derived from the dissolution profiles. The f1 factor measures the percent of difference between two dissolution profiles and the f2 factor shows similarity between them over all time points. The f1 is zero and f2 is 100 when the test and reference drug profiles are

identical. The dissimilarity proportionally increases if the f1 increases or f2 decreases. Two dissolution profiles are verified if f2 is between 50 and 100. f1and f2 can be calculated from following equations:

$$f2 = 50 \log \{[1+ \Sigma (R_t - T_t)^2]^{-0.5} X\ 100\}$$

Where R_t and T_t are the cumulative percentage of dissolved drug for the reference and test formulation at time t, respectively, and n is the number of time points. The dissolution results have served as a means to evaluate different formulations and determine final dissolution qualifications for pharmaceutical dosage form. [21, 22, 23]

Results and Discussion

All the tablet formulations had shown acceptable pharmaceutical properties and complied with in the range specified by IP Pharmacopoeia like weight variation (250mg or more is ± 5%) , hardness (4 – 6 kg/cm^2), thickness, and friability (not more than 1.0%) (Shown in Table 2)

Table 2: Physical Properties of the Prepared Metformin Tablet

Formulations	Parameters			
	Weight variation (mg)*	Hardness (kg/cm^2)#	Thickness (mm)#	Friability %
F1	652 ± 18	4.15 ± 0.24	4.32 ± 0.08	0.90
F2	656 ± 19	4.30 ± 0.42	4.44 ± 0.12	0.89
F3	658 ± 16	4.35 ± 0.34	4.49 ± 0.14	0.90
F4	652 ± 17	4.65 ± 0.34	4.60 ± 0.14	0.61
F5	652 ± 17	5.05 ± 0.37	4.52 ± 0.19	0.60
F6	649 ± 17	6.00 ± 0.41	4.48 ± 0.18	0.30
F7	651 ± 19	6.10 ± 0.32	4.61 ± 0.23	0.30
F8	648 ± 15	6.15 ± 0.24	4.59 ± 0.18	0.30

* Mean ± SD (n = 20 Tablets) # Mean ± SD (n = 10 Tablets)

In vitro drug release studies:

Dissolution profiles of different formulation are summarized in Figure 1. The Formulation F1 to F8 had showed delayed in dissolution profile with increase in starch and decrease in Sodium starch glycolate concentration. Formulation F2 and F3 had better dissolution profile because it had shown a dissolution of 78.6% and 69.3% within 30 minutes respectively and entire drug was release within 60 min. Both the F2 and F3 Batch had been selected for bioequivalence study.

In vitro Bioequivalence study

The *in vitro* dissolution profile of Metformin hydrochloride (BCS Class III) of in house prepared F2 and F3 formulation and leading marketed formulation Glyciphage 500mg uncoated tablet on various pH solutions like 0.01 N hydrochloric acid (pH 2), phosphate buffer (pH 4.5), and phosphate buffer (pH 6.8) is shown in figure 2 – 4.

Figure 1: in vitro drug release studies of in house Metformin Tablet

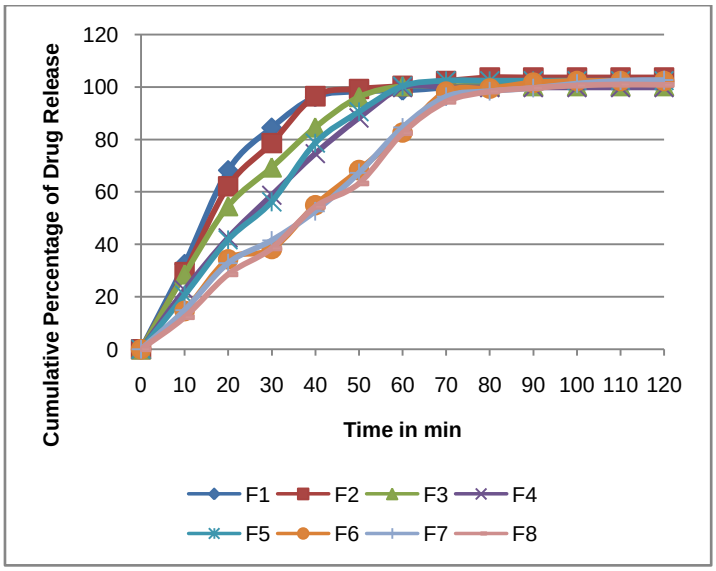


Figure 2: Comparative in vitro dissolution profile in house prepared F2 and F3 formulation and Glyciphage 500mg on 0.01 N hydrochloric acid (pH 2)

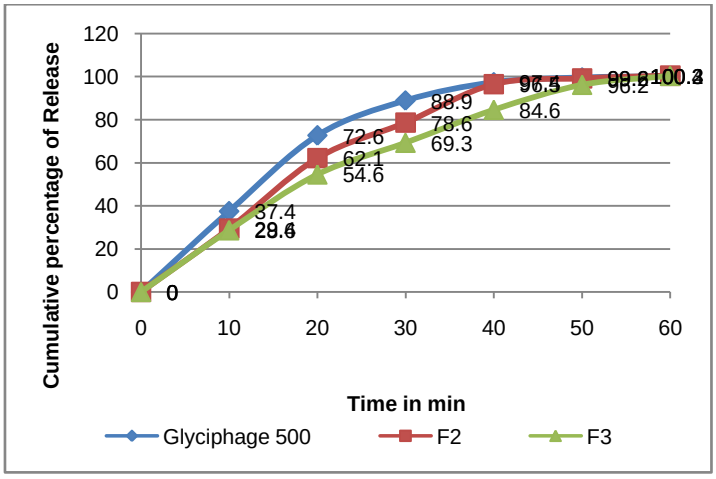


Figure 3: Comparative in vitro dissolution profile in house prepared F2 and F3 formulation and Glyciphage 500mg on phosphate buffer (pH 4.5)

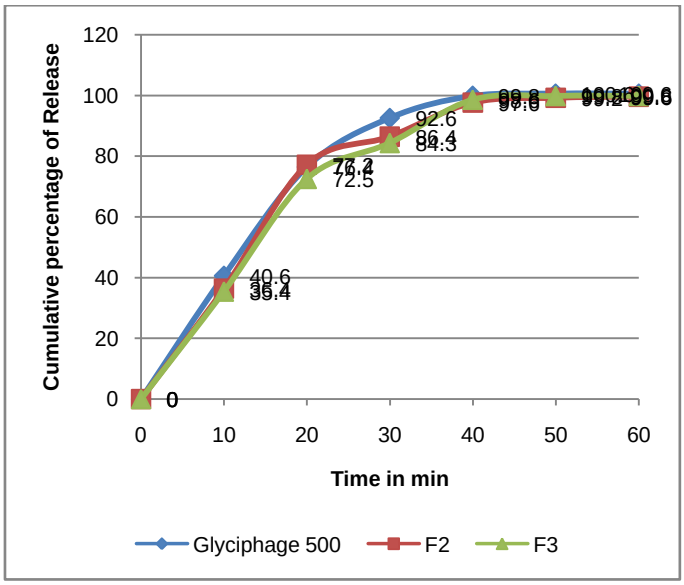
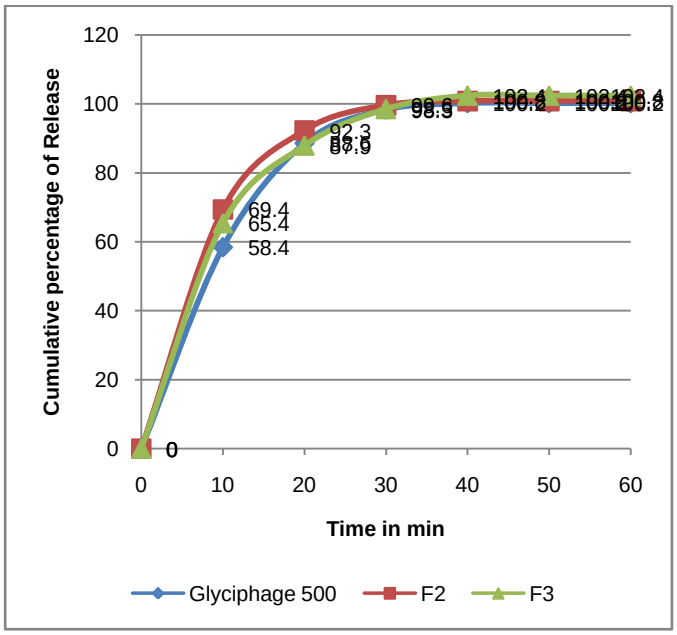


Figure 4: Comparative in vitro dissolution profile in house prepared F2 and F3 formulation and Marketed Formulation on phosphate buffer (pH 6.8)



The in house prepared F2 and F3 was compared with the leading brand of marketed sample of uncoated tablet, The results shows that marketed formulation Marketed Formulation and prepared formulation F2 and F3 were not very rapidly dissolving (≥85% of labelled amount not released within 15 min) and doesn't qualify for a bio-waiver according to WHO criteria (Figures 2–4 and Table 3).

Only generic drug products that are therapeutically equivalent to the innovator products will be approved by the appropriate regulatory bodies in respective countries may be marketed as appropriate for substitution [24]. Metformin HCl is a BCS Class III drug [25] and characterized by high solubility and low permeability. For the immediate-release formulation of this class it is assumed that if their dissolution behaviour in various physiological pH conditions can be considered acceptable for bio-waivers under WHO criteria (i.e., both the test and reference products are very rapidly dissolving). That is, dissolution of 85% or more of the labeled amount of API should be achieved within 15 min under all physiological conditions [9]. None of our formulation F2 and F3 of metformin tested met this requirement because the innovator product did not achieve 85% dissolution in 15 min (Table 3). The f2 values of both the formulation F2 and F3 were greater than 50 in all physiologic pH conditions, showing a similarity in dissolution (Table 3). The possible effect of excipients on the dissolution of metformin was not evaluated.

Table 3 Results of f2 Calculations for Metformin Hydrochloride Tablets in Different pH Media

Time (min)	Marketed Formulation	F2	F3
	% Dissolved	% Dissolved	% Dissolved
pH 2			
10	37.4	29.4	28.6
20	72.6	62.1	54.6
30	88.9	78.6	69.3
40	97.4	96.5	84.6
50	99.6	99.2	96.2
60	100.2	100.4	100.3
f2		57.99	44.82
pH 4.5			
10	40.6	36.4	35.4
20	76.4	77.2	72.5
30	92.6	86.4	84.3
40	99.8	97.6	98.6
50	100.6	99.2	99.8
60	100.6	99.6	99.8
f2		73.25	67.49
pH 6.8			
10	58.4	69.4	65.4
20	88.6	92.3	87.9
30	98.3	99.6	98.5
40	100.2	100.8	102.4
50	100.2	100.8	102.4
60	100.2	100.8	102.4
f2		65.54	73.32

Conclusion

This study shows that the in house developed products F2 and F3 formulation have shown better *in vitro* dissolution profile when compared to other formulations. Moreover both the formulation have better similarity factor f2 value more than 50% when *in vitro* dissolution profile compared with the marketed product. An effort was also made that the metformin can qualify for biowaiver as per WHO guidelines but the results indicate that even the marketed formulation also do not qualify that *in vitro* data can be used as an alternative to *in vivo* BE studies.

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Reference

1. Lachmann L, Liberman HA,Kanig JL. The theory and practice of Industrial pharmacy. 3rd edition, Varghese publishing house Bombay. 1991; 453: 317-320.
2. Stith BJ, Goalstone ML, Espinoza R, Mossel C, Roberts D, Wiernsperger N. The antidiabetic drug metformin elevates receptor tyrosine kinase activity and inositol 1, 4, 5-triphosphate mass in Xenopus oocytes. Endocrinology. 1996;137:2990-2999.
3. Wiley A. Insulin and oral hypoglycemic drugs. In: Williams DA, Lemke TL editors. Foyes Principle of medicinal chemistry. Lippincott Williams and Wilkins.New York. 2002: 641-648.
4. LilianBeatiz, Aguayo Rojas, Marilia Brito Gomes. Metformin: an old but still the best treatment for type2 diabetes. Diabetology& Metabolic Syndrome. 2013; 5: 5-6.
5. Bristol-Myers Squibb. U.S. Food and Drug Administration. Glucophage (metformin hydrochloride tablets) Label Information. 2008.
6. Choudhury PK. Controlled release metformin hydrochloride microspheres of ethyl cellulose prepared by different methods and study on the polymer affected parameters. J Microencapsul. 2009; 26: 46-53.
7. Soni ML. Sodium alginate microspheres for extending drug release, formulation and *in-vitro* evaluation. International journal of drug delivery. 2010; 2: 64- 68.
8. "WHO Model List of Essential Medicines (19th List)" (PDF). World Health Organization. April 2015. Archived (PDF) from the original on 13 December 2016.
9. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Proposal to waive *in vivo* bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms; WHO Technical Report Series, No. 937, Annex 7; World Health Organization: Geneva, Switzerland, 2006. http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf (accessed May 15, 2019).
10. Cook JA,Bockbrader HN. An Industrial Implementation of the Biopharmaceutics Classification System. Dissolution Technol. 2002; 9 (2): 6–8.
11. Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 2000.
12. Lindenberg M, Kopp S,Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur. J. Pharm. Biopharm. 2004; 58 (2): 265–278.
13. The Merck Manuals online.http://www.merck.com/mrkshared/m manual_home.
14. SastrySV, Nyshadham JR, FixJA. Pharmaceutical Science and Technology Today, Vol. 3: 138.
15. Gilbert, BankerGS, RhodesCT. Modern Pharmaceutics, 4th edition, Marcel Dekker Inc., New York.2002: 198-216.
16. Wells J. Pharmaceutical preformulation: The physiochemical properties of drug substances. In: Aulton ME, editor, Pharmaceutics the science of dosage form design Churchill Livingstone, London. 2002: 247.
17. Indian Pharmacopoeia. Government of India, Ministry of health and family welfare. 4th edition. New Delhi: The Controller of Publications; 1996.
18. RenatiDamodar, BabjiMovva. Preparation and *in-vitro*evaluation of metformin HCl tablets containing sustained release beads for increasing therapeutic window. Journal of Bioequivalence & Bioavailability. 2014;6(3): 91-95.
19. Basak SC, Rahman J, Ramlingam M. Design and *in vitro* testing of a floatable gastroretentive tablet of metformin hydrochloride. Pharmazie. 2007;62:145-148.
20. Shargel L. Drug product performance and interchangeability of multisource drug substances and drug products. Pharma Forum. 2009; 35 (3): 744–749.
21. Anderson NH, Bauer M. An evaluation of fit factors and dissolution efficiency for the comparison of *in vitro* dissolution profiles. J Pharm Biomed Anal. 1998; 17(4-5): 811-822.
22. Pillay V,Fassihi R. Evaluation and comparison of dissolution data derived from different modified release dosage forms: an alternative method. J Control Release. 1998; 55(1): 45-55.
23. Menegola J, Steppe M. Dissolution test for citalopram in tablets and comparison of *in vitro* dissolution profiles. Eur J Pharm Biopharm. 2007; 67(2): 524-530.
24. Cheng, CL, Yu LX, Lee HL, YangCY,Lue CS, Chou C. H. Biowaiver extension potential to BCS Class III high solubility–low permeability: bridging evidence for metformin immediate-release tablet. Eur. J. Pharm. Sci. 2004, 22 (4), 297–304.
25. Lindenberg M, Kopp S,Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur. J. Pharm. Biopharm. 2004; 58 (2): 265–278.