Global Journal of Pharmacology 7 (2): 138-142, 2013
ISSN 1992-0075

DOI: 10.5829/idosi.gjp.2013.7.2.73146

Development of *In vitro/In vivo* Correlation for Oxcarbazepine Granules

[1]A. Prameela Rani and [2]Hema Veesam

[1]Department of Pharmaceutics, University College of Pharmaceutical Sciences,
Acharya Nagarjuna University, Guntur-22002, India
[2]Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences,
Vijayawada-520010, India

Abstract: Oxcarbazepine was formulated as granules in order to provide rapid disintegration and drug release than tablets, have combined properties of chemical and microbiological stability, usually more stable to the effects of atmosphere, furthermore extended to estimate good degree of *in vitro* and *in vivo* correlation (IVIVC). Oxcarbazepine had poor aqueous solubility, available as tablet dosage form, thus the solubility was increased by hydrotropes then formulated into granules. These granules were observed for *in vitro* dissolution profile and studied for *in-vivo* pharmacokinetic profile, from the obtained values, a level A IVIVC modeling was observed. Interestingly from the results attained granule showed almost 97% drug release (FDR) and 80% drug absorbed (FDA) in 90min. fascinatingly, from the correlation between FDR and FDA, slope and regression co-efficient obtained nearer to 1.0 indicating good linearity. In conclusion, a point-to-point link from level A which was a keystone of acceptable and reliable correlation was achieved.

Key words: Oxcarbazepine · Granules · Dissolution Study · Pharmacokinetics · IVIVC

INTRODUCTION

Oxcarbazepine is 10,11-dihydro-10-oxo-5*H*-dibenz(b,f)azepine-5-carboxamide derivative of carbamazepine with low (0.08g/L) aqueous solubility [1] and 1.31 partition co-efficient. It generally acts as sodium channel blockade, calcium channel blockade. It is rapidly absorbed from GI region and 40% of drug is bound to plasma proteins. It is mainly metabolized by glucuronic acid conjugation and is excreted by renal excretion. Granules are solid unit dosage form agglomerates of smaller particles of medicament in which powdered drug was mixed with excepients which may be irregular in shape [2]. Sometimes it is difficult to find a satisfactory preparation for a solid medicament with a large dose as tablets as impracticable because of size required per dose [3]. Formulating of oxcarbazepine into granules is a challenging aspect because of the poor flow characteristics of pure drug. The aspiration in observing pharmacokinetics is to quantitatively account for the amount which has entered the body from the instant of administration until it has been completely cleared [4]. Generally pharmacokinetic parameters are not measured directly but are determined experimentally from a set of dependent (concentration) and independent (time) variables. *IVIVC* can be established from four different levels of correlation [5]. Among all the correlations, level A was most suggested for accuracy on poor water soluble drugs [6,7]. The objective of the design and manufacture of granules is to deliver orally the correct amount of drug in proper form at over the proper time and the possibility of developing a level A correlation between percent drug released and percent drug absorbed for oxcarbazepine granules was investigated.

MATERIAL AND METHODS

Oxcarbazepine active pharmaceutical ingredient (OXC-API), polyvidone and primellose were obtained as a gift samples from Novartis, Mumbai, India and FMC biopolymer, USA resp. Remaining all other excipients, chemicals and solvents are procured from local suppliers.

Corresponding Author: Hema Veesam, Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, D-No: 41-1/2-18, Dwarakanagar-III line, Vijayawada-520013, Andhra Pradesh, India
Tel: +91-9440014336.

Formulation of Oxcarbazepine Granules: Firstly oxcarbazepine solubility was enhanced by formulating into solid dispersion using hydrotropic agents such as urea, sodium acetate and trisodium citrate. Granules were prepared by wet granulation method where all the ingredients were weighed and passed through 40#. A binder solution of different concentrations was prepared and the mixture of drug blend, spray dried lactose and croscarmellose sodium was blended together and granulated using aqueous solution of polyvinyl pyrrolidone. The wet mass was passed through 8mm screen and granules were dried using micro-wave oven. The dried granules were then passed through 20#. Later they are preserved in containers for further studies.

Determination of Flow Characteristics of Granules

Bulk Density: Bulk density was determined by pouring gently 20gms of sample through a glass funnel into 50mL-graduated cylinder. The volume occupied by the sample was recorded.

Tapped Density: Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed.

Hausner Ratio and Compressibility Index: Both the compressibility index and the Hausner ratio were determined by using bulk density and the tapped density and the tapped density of the powder.

Angle of Repose [8]: Drained angle of repose is determined by allowing an excess quantity of material positioned above a fixed diameter base to drain from the contained. Formation of a cone of powder on the fixed diameter base allows determination of the drained angle of repose

Dissolution Test: Dissolution test was carried out using USP type II (paddle) apparatus for 1h. The stirring was kept at 50rpm, 0.75% SLS as dissolution medium (900mL) and temperature was maintained at 37 ± 1°C. 5mL of samples were collected at regular time intervals of 0, 5, 10, 15, 20, 30, 45 and 60min and were assayed spectrophotometrically at 256nm. Triplicate number of experiments was performed for each formulation.

Experimental Design: Albino rats (National Institute of Nutrition, Hyderabad, India) of either sex, weighing 180-210g were selected [9]. Animals were maintained under standard laboratory conditions. The experimental protocol has been approved by Institutional Animal Ethical Care Committee (IAEC) of BITS-PILANI, Hyderabad. The approved IAEC protocol number is IAEC/RES/06/03 in accordance with animal experimentation and care guidelines provided by IAEC/CPCSEA. Human dose was extrapolated to animal dose using USFDA dose calculator [10]. In the study design for pharmacokinetics assessment a number of six wistar rats were selected for drug administration with three animals for each formulation (vehicle and granules).

Assessment of Pharmacokinetic Data and Data Analysis: All the animals in every group were administered orally at a dose of 62mg/kg bodyweight using 1ml of polyethylene glycol (vehicle). Blood was collected from retro-orbital sinus after anesthetizing animal with anesthetic ether. 0.1mL of 2.8% sodium citrate was used as anticoagulant. Blood samples were taken at regular time intervals from 0h till 12hrs following drug administration. Plasma was separated by centrifugation and stored at -20°C until further analysis. Plasma OXC (oxcarbazepine) and MHD (active metabolite of oxcarbazepine) concentration [11] was determined using a validated HPLC method with minor modifications. The various other pharmacokinetic parameters [12] were calculated by the optimal descriptive extra-vascular model fit utilizing the less available data and help to predict even most basic parameters. The best model was chosen based on statistical and goodness-of-fit criteria. The amount drug absorbed was calculated through wagner-Nelson model using Try kinetica PK-PD version 5.0 program.

***In vitro* and *Invivo* Correlation:** Out of four modeling methods, level A is mostly used and the typical mathematical process of developing a level A IVIVC [13] involves assessment of cumulative percent drug released from dissolution studies and includes deconvolution of *in-vivo* plasma profile by model independent method such as wagner-Nelson method to estimate the *in vivo* percent drug absorbed from cumulative area under curve, followed by comparison if *In-vivo* fraction of drug absorbed to *In vitro* fraction of drug dissolved. Further linear correlation between FDR and FDA were established for pooled mean data of formulations from $Y=aX+b_0$ where Y is FDA; X is FDR; a and b_0 are regression parameters. For the model r was determined.

RESULTS AND DISCUSSION

The drug blend of solid dispersions consists of 150mg of OXC-API and 600mg of mixture of urea, sodium citrate and sodium acetate thus has enhanced solubility of upto 0.8mg/mL was observed. For further formulation into granules, these solid dispersions were used and formula was given in Table 1. 850mg of granules was made for single dose formulation with 150mg of drug. Granules prepared with synthetic hydrophilic binder as PVP with water as granulating liquid till capillary or funicular stage was obtained and droplet stage was avoided as if powder mixture is over wetted, the granules will be hard and if they are not wetted sufficiently, the resulting granules will be soft [14] thus PVP K-30 binder concentration was important that contribute to reduce friability of granules [15]. Povidone and primellose selected as per acceptable daily intake (ADI) and is Regulatory Authorities (GRAS) listed [16]. All the prepared formulations were evaluated for flow properties and shown in Table 2. Formulation F3 showed poor flow character probably due to high binder concentration. Remaining all formulations showed almost good flow characteristic. The dissolution data of granules were represented in Table 3 where F5 showed highest drug release but those formulations with low binder concentration and high disintegrate (F2) showed higher drug release and similarly formulation with high binder concentration and low disintegrate showed lower drug release. Thus F5 was selected due to excellent flow properties and higher dissolution rate than remaining formulations and was used for further studies. The pharmacokinetic study was conducted till 12h and observed for plasma drug concentration. The maximum concentration reached was about 20.37µg/mL at 4h as shown in Table 4. The percent drug absorption in-vivo depends on two important factors, solubility and intestinal permeability as given by Guidance for Industry, FDA [17]. Level A provides a linear correlation with percent drug released from dissolution studies to percent drug absorbed from animal plasma studies. The percent drug released *vs* percent drug absorbed was studied for 90min where 97% of drug was released from *in vitro* dissolution studies to 80% of drug absorbed from *in vivo* studies under level A correlation to obtain point-to-point correlation between dissolution studies and drug

Table 1: Formulation table of oxcarbazepine granules

Formulation code (mg)	Drug blend	Polyvidone	Primellose	Fruit flavor	Spray dried lactose
F1	750	17	8.5	2.12	72.36
F4	750	17	25.5	2.12	55.36
F5	750	42.5	8.5	2.12	46.84
F8	750	42.5	25.5	2.12	29.84
F5	750	29.76	17	2.12	51.12

Table 2: Flow properties of granules

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Compressibility index	Angle of repose
F1	0.542	0.603	1.112	10.18	31 ± 2.01
F2	0.559	0.629	1.125	11.06	34 ± 1.23
F3	0.553	0.625	1.30	21.55	29 ± 0.85
F4	0.542	0.608	1.122	10.89	28 ± 1.88
F5	0.549	0.602	1.096	8.8	27 ± 1.32

Table 3: Dissolution data of OXC granules

	Percent drug dissolved (mean ± SD)				
Time (min)	F1	F2	F3	F4	F5
0	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
5	17.19 ± 0.03	19.61 ± 0.07	13.51 ± 0.12	9.22 ± 0.03	46.76 ± 0.07
10	30.02 ± 0.07	38.45 ± 0.06	27.51 ± 0.08	20.68 ± 0.08	63.33 ± 0.15
15	42.68 ± 0.07	54.72 ± 0.1	40.47 ± 0.07	32.60 ± 0.06	78.84 ± 0.3
20	53.14 ± 0.07	74.20 ± 0.16	50.56 ± 0.08	46.06 ± 0.07	84.43 ± 0.73
30	65.12 ± 0.06	84.26 ± 0.15	62.33 ± 0.09	61.06 ± 0.08	87.44 ± 2.02
45	77.33 ± 0.15	88.86 ± 0.16	73.51 ± 0.15	79.07 ± 0.16	93.12 ± 3.02
60	89.40 ± 0.15	92.69 ± 0.13	83.82 ± 0.17	86.33 ± 0.16	96.95 ± 0.15

Table 4: Pharmacokinetic profile of OXC granules on albino rats

	Plasma drug concentration (μg/mL)	
	OXC granulated blend	
Time (h)	OXC	MHD
0	0.0 ± 0.0	0.0 ± 0.0
0.25	0.58 ± 0.02	15.23 ± 0.2
0.5	1.28 ± 0.01	15.7 ± 0.2
1	1.46 ± 0.05	17.1 ± 0.26
1.5	1.25 ± 0.01	18.4 ± 0.2
2	1.20 ± 0.03	19.2 ± 0.2
3	0.95 ± 0.01	20 ± 0.17
4	0.60 ± 0.07	20.37 ± 0.15
6	0.40 ± 0.09	19.37 ± 0.32
8	0.35 ± 0.01	18.4 ± 0.32
10	0.30 ± 0.02	16.4 ± 0.35
12	0.25 ± 0.05	15.5 ± 0.36

OXC: oxcarbazepine parent drug; MHD: Active metabolite of oxcarbazepine

Table 5: Level A correlation between % drug released *vs* % drug absorbed of oxcarbazepine

	OXC granules	
Time (h)	%ADR	%ADA
0.25	78.84	64.2
0.50	87.44	68.02
1.0	96.95	75.5
1.5	97.12	80.01
In vitro In vivo Correlation modeling		
Slope	0.776	
Intercept	1.99	
R^2	0.905	

** % ADR- percent drug release from in vitro dissolution study; % ADA- percent drug absorbed from in vivo study*

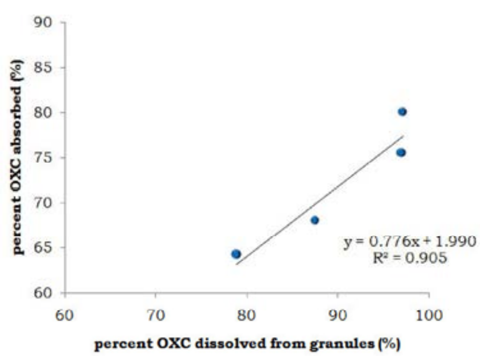

Fig. 1: *In-vitro* percent drug dissolved *vs In-vivo* percent drug absorbed

absorption studies was successful in achieving the favored target of good correlation as given in Table 5 and Fig. 1. Thus the dissolution test may serve as proxy for bioequivalence studies [18] and an appropriate dissolution conditions based on *in vivo* performance could be adapted for routine and in-process quality control of oxcarbazepine granules [19]. It was interest, therefore, to explore if condition of dissolution of this study, which is very akin to what is proposed by FDA, correlates with serum plasma profiles already obtained by performing in-vivo studies for immediate release dosage forms [20]. The level A modeling showed very good linear correlation between percent drug dissolved and percent drug absorbed for oxcarbazepine granules. 97% Percent drug dissolved was used designed for the study along with 80% of drug absorbed from plasma studies. Amazingly, slope and regression co-efficient obtained for the correlation was nearer to 1.0 indicating good correlation from level A modeling. A point-to-point link from level A which is a keystone of an acceptable and reliable correlation was achieved.

CONCLUSION

In conclusion, a point-to-point link from level A which is a keystone of an acceptable and reliable correlation was achieved. From the results of the current study, IVIVC developed by level A correlation makes oxcarbazepine dissolution profile meaningful, as it allows predicting in-process quality control of oxcarbazepine granules.

REFERENCES

1. Amidon, G.L., H. Lennernas, V.P. Shah and J.R. Crison, 1995. A theoretical basis for a biopharmaceutical drug classification: The correlation of *in vitro* drug dissolution and *in vivo* bioavailability. Pharm. Res., 12: 413-419.
2. Cooper and gunns, 2000. Dispensing for pharmaceutical students. Delhi, CBS Publishers and Distributors, pp: 217.
3. Shobhit, K., K.G. Satish and P.K. Sharma, 2012. A review on recent trends in oral drug delivery: fast dissolving formulation technology. Adv. Biological Res., 6(1): 6-13.
4. Notari, R.E., 1987. Bio-pharmaceutics and clinical pharmacokinetics, Marcel Dekker, pp: 300.
5. Nattee, S. and N.D. Eddington, 2002. *In vitro/ In vivo* correlation, definition and regulatory guidance. Int. J. Generic drugs, 2: 1-11.
6. Reppas, C. and B.J. Dressman, 2000. IVIVC for lipophilic, poorly water soluble drugs. Eur. J. Pharm. Sci., 11: 73-80.

7. Nainar, S., R. Kingston, S. Angamuthu, D. Prabhakaran and K. Ravi, 2012. BCS in *In vitro In vivo* Correlation: Concept and development in strategies in drug delivery. Trop. J. Pharm. Res., 11: 319.
8. Carr, R.L., 1965. Evaluation of flow properties of solids. Chem. Eng., 72: 163-168.
9. Lincy, J., M. George, S. Abhishikha and N. Gopal, 2011. Antipyretic and analgesic effects of aqueous extract of *Prosopis cineria*. Global J. Pharmacol., 5(2): 73-77.
10. Guidance for industry, 2005. estimating the maximum safe starting dose in initial clinical trials therapeutics in adult healthy volunteers. Pharmacology and Toxicology. US Department of health and human services, FDA, Rockville, MD. July 2005.
11. Matar, M., J. Nicholls, Tekle Asgedom, A. Bawazir and I. Al-Hassan, 1999. Liquid chromatographic determination of six antiepileptic drugs and two metabolites in microsamples of human plasma. Therapeutic Drug Monitoring, 21: 559.
12. Shubha, R., V. Mounica, Shivprakash and P. Harish, 2006. Formulations dependent variability in pharmacokinetics: A case study with metformin. W. J. Med. Sci., 1(1): 9-13.
13. Emami, J., 2006. *In vitro In vivo* correlation: From theory to application. J. Pharm. Pharm. Sci., 9: 169-189.
14. Joseph, P.R., 2006. Oral solid dosage forms. In Science and practice of pharmacy. Eds., M.R. Edward and B.S. Joseph, Pharmaceutical manufacturing, Lippincott Williams and Wilkins, pp: 889-899.
15. Tejas, B.P., L.D. Patel, T.B. Patel, H.M. Sunil and T.R. Patel, 2010. Influence of process variables on physicochemical properties of granulation mechanism of diclofenac sodium. IJPSRR, 3(1): 61-65C.
16. Raymond, R., 2006. Monographs of polymers, in Handbook of pharmaceutical excipients, 5^{th} ed., American Pharmaceutical Association, USA.
17. Guidance for industry, 1997. Extended release oral dosage forms: development, evaluation and application of IVIVC, FDA, Center for Drug Evaluation and Research.
18. Olaniyi, A.A., C.P. Babbalola, F.O. Oladeinde and A.O. Adegoke, 2001. Towards quality assurance of drugs: Biopharmaceutical methods. University of Ibadan, pp: 7-23.
19. Bhabani, N.S. and N.K. Udaya, 2009. Lamivudine loaded microspheres for oral use. Asian J. Pharm. Clin. Res., 2: 55-60.
20. Dressman, J.B., G.L. Amidon, C. Reppas and V.P. Shah, 1988. Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms. Pharm. Res., 15: 11-22.