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COMPARATIVE STUDY ON THE DISSOLUTION PROFILES OF COMMERCIAL MODIFIED RELEASE FORMULATIONS OF NIFEDIPINE

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ABSTRACT

A controlled release formulation of Nifedipine (NF) was developed on modified pharmacokinetic principles where time of delivery is longer than dosing interval (Sood, 2001). Dissolution profile of NF was compared with all modified release formulations (Test) marketed in India. USP apparatus II (paddle type) at 50 rpm was employed to perform dissolutions studies. Phosphate buffer at pH 6.8 containing 1% w/v sodium lauryl sulphate (SLS) was used as dissolution medium. Samples were withdrawn at different time points over a period of 24 hours and percentage release of drug was calculated. The factor f_2 of Food and Drug Administration (FDA)'s guideline was applied for qualitative determination of similarity between pair dissolution profiles. Results indicated that no test formulations were similar to NF formulation (f_2 below 50). In order to show pharmacokinetic advantage of NF formulation over other, three best formulations were selected (based on similarity factor) and further subjected to dissolution testing at different pH. Along with NF formulation, all selected test formulations showed pH independent release (f_2 above 50). Finally, *in vivo* performance of all selected formulations were predicted and compared with *in vivo* performance of NF formulation.

KEYWORDS: Nifedipine (NF), sodium lauryl sulphate (SLS).

INTRODUCTION

Drug absorption after oral administration of a solid dosage form depends on release of drug from a formulation (dissolution of the drug) and permeation across GI tract. These two steps are very critical and rate determining, *in vitro* dissolution of a drug is of a relevance to predict

accurately *in vivo* performance of formulation. One of the main principles of *in vitro* dissolution testing is that it should be conducted under sink condition.[1] Dissolution studies of drug of low aqueous solubility create problems for scientists to maintain sink conditions during their dissolution studies using conventional dissolution methods and procedure. Various modification in dissolution test method such as use of large volume of dissolution medium, addition of surfactant in test medium, use of two phase test medium or modification of dissolution test equipment have been discussed. However, addition of surfactant in dissolution medium to provide sink condition is considered to simulate physiological environment more closely than other approaches.[2,3]

The main advantage of a sustained release (SR) or controlled release (CR) formulation is the maintenance of the drug blood concentrations at therapeutic level by means of controlled release of drug during a long period. Knowledge of drug release rate of a SR/CR formulation is a very important parameter as its variations could lead to lack of therapeutic effect or to toxicity level within a body. Release rate (calculated from dissolution study) was not be compromised if sink conditions are not maintained. Further, to analyze mechanism of release several models have reported in literature.[4]

Nifedipine (NFD) chemically belongs to a class of dihydropyridine derivative, which has been available for almost 25 years. NFD inhibits the influx of calcium into cardiac and vascular smooth muscle by blocking α type voltage operated and receptor operated calcium channel. This in turn, results in electromechanical decoupling of actin and myosin filaments and inhibition of contraction, which permits relaxation of cardiac or smooth muscle fibers.[5]

Conventional formulation of drug is highly effective in management of various cardiovascular disorders like angina, mild to moderate hypertension, myocardial infarction and Raynaud' phenomenon.[6] Rafflenbeul suggests that NFD also reduces primary progression and long-term survival after myocardial infarction.[7] NFD in conventional formulations is known to have a short elimination half-life with significant fluctuations in plasma drug concentrations.[8,9] Many attempts have been made to maintain a suitable plasma level of NFD for a long period of time with minimal frequency of administration. This results in introduction of various SR formulation of NFD into market and is recommended for once or twice-daily administration. Adverse effects of NFD are usually related to its vasodilatory action that includes headache, flushing, dizziness and lower leg oedema. Other adverse

effects are gastrointestinal symptoms and transient hypotension. In addition, the abrupt cessation of NFD therapy leads to coronary artery spasm, hypertensive crises and worsening of asthma symptoms. Atenolol reduces the vasodilatory adverse effects of NFD and conversely NFD also decrease the incidence of adverse effect resulting from atenolol. Hence, use of fixed sustained release NFD/atenolol combination has been associated with a better tolerability profile than either agent alone.[10]

NFD is extremely light sensitive drug and breaks down rapidly upon exposure to daylight to a nitrosophenylpyridine. Hence, assay and test should be performed in either dark or under golden fluorescent or other low-actinic light.[5] NFD being a class II of BCS has poor aqueous solubility hence, dissolution enhancing methods should be employed to maintain sink condition of such formulations. Surfactant, bile acids, bile salts and lecithin have shown to increase rate of dissolution of poorly water-soluble drugs.[11] A two-phase media or dissolution test at high agitation speed (100 rpm) has potential applicability for improved prediction of *in vivo* performance and IVIVC of NFD gastrointestinal therapeutic system (GITS) or similar pharmaceutical formulation of other poorly water-soluble drugs.[12]

In earlier study in this institute[13], a MR formulation of NFD based on multiple unit matrix based system was developed by using modified pharmacokinetic principle where time of delivery is longer than dosing interval (NF formulation). Present study was aimed to show pharmacokinetic advantage of NF formulation (reference formulation) over all other formulations available in India. Moore and Flanner proposed fit factors to compare release profiles.[14] Difference factor (f_1) measures the percent error between two curves over all time points whereas similarity factor (f_2) is a logarithmic transformation of the sum-squared error of difference between the test and reference products over all time points. FDA suggests that two dissolution profiles are declared similar if f_2 is between 50-100.

MATERIALS AND METHODS

Materials

Drug nifedipine was received as gift sample from Unichem. Laboratories Ltd., India. Sodium lauryl sulphate (96% Purity grade; Loba Chemie, India), syringe filter, cartridge (0.45µm pore size Minisart hydrophilic; Sartorious AG, Germany) was used as obtained. Modified release formulation of NFD marketed in India as (listed in Table 1) were purchased from a

local pharmacy. All other chemicals were used as received. Since NFD is light sensitive, all experiments were performed using low actinic glass ware and under subdue light.

METHODS

Aqueous drug samples from assay and drug release studies were analyzed using a UV/VIS spectrophotometer (DU 640i, Beckman). Absorbance values of NFD samples were recorded at 236 nm (λ_{max}). Each formulation was evaluated for content uniformity in which five units were selected and crushed separately. Crushed powder was transferred to 100 ml volumetric flask to which, methanol was added and contents were gently warmed using water bath (50-60^{o}C for 2 min). From this 1 ml of sample was withdrawn and filtered through 0.45 µm pore size filter (Minisart, Sartorious). After suitable dilutions with dissolution medium comprising of phosphate buffer (pH 6.8) with 1% w/v SLS, it was subjected to absorbance determination by using spectrophotometer (DU640i, Beckman) at 236 nm. Drug concentration was calculated from measured absorbance, which was further used to back calculate drug content in the formulation. Parallelly quality control samples were analyzed in order to check precision of method during each analysis. Each formulation (Twenty units) was individually weighed using electronic weighing balance (AG245, Mettler Toledo) and upper and lower limit of variation was calculated. Five units of each tablet formulations were evaluated for friability (EF-2, Electrolab). Five tablets of each formulation were separately evaluated for crushing strength using Erweka Hardness tester (TBH20, Elecrolab).[15]

Previously developed dissolution test method conditions were applied for drug release evaluation of all modified release formulations of NFD (13). Drug release studies were done in a USP XXI/XXII apparatus II (programmable dissolution tester TDT-0P, Electrolab). Phosphate buffer (900ml in each vessel) containing 1% SLS (95% purity) at pH 6.8 was used as dissolution medium. Dissolution medium was maintained at 37±0.5^{o}C during the study and paddles were rotated at 50 rpm. Samples (5 ml) were withdrawn at different time intervals over 24 hour.

Table 1: Modified release formulation of NFD marketed in India.

Drug products	Code	Grade if any; Source
Adalat retard OROS	N1	30 mg nifedipine tablets; Batch no.: N103; Bayer Ltd., India
Calbloc retard	N2	10, 20 mg nifedipine tablets; Batch no.: 12002 and 32007; Unichem. Ltd., India
Calcigard retard	N3	20 mg nifedipine tablets; Batch no.: 1202001; Torrent Ltd., India
Cardules retard	N4	10, 20 mg nifedipine hard gelatin capsules; Batch no.: P1003 and P0012; Nicholas Piramal Ltd., India
Depicor SR	N5	10, 20 mg nifedipine tablets; Batch no.: A202 and A1201; E.Merck Ltd., India
Depin retard	N6	20 mg nifedipine tablets; Batch no.: MA2595; Zydus Medica Ltd., India
Nicardia retard	N7	10, 20, 30, mg nifedipine tablets; Batch no.: 02037, 03022 and P300413; Unique Ltd., India
Nifedine SR	N8	10, 20 mg nifedipine tablets; Batch no.: 0F128 and 2A112; Sarabhai Piramal Pvt. Ltd., India
Nifelet retard	N9	20 mg nifedipine tablets; Batch no.: DJ2050; Cipla Ltd., India

period and the volume withdrawn was immediately replenished using fresh medium that was maintained at 37±0.5°C. Samples were filtered through 0.45 μm pore size filter (Minisart, Sartorius) and analyzed spectrophotometrically (DU640i, Beckman) at 236 nm. Further to study the influence of pH dissolution studies were performed at three-pH level (hydrochloric acid buffer at pH 2.0, phosphate buffer at pH 5.0, and 7.4). All dissolution studies were performed under darkness or subdued light or low actinic sodium vapor monochromatic light.

Mathematical comparison of dissolution curves obtained from different formulations provides an opportunity to test the similarity between two dissolution profiles. Fit factors (eq.1 and 2) proposed by Moore and Flanner were used for comparing the dissolution profiles.[14]

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100\,\% \qquad (1)$$

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

Where R_t and T_t are percent drug released at time point t for reference and test products respectively, n is the number of dissolution time points and w_t is the optional weight factor.

In addition to fit factors, S_d (eq. 3) value[16], mean dissolution time (MDT) (eq. 4) and dissolution efficiency (DE) (eq. 5) were also calculated for comparing drug release profiles.[17]

$$S_d = \frac{\sum_{t=1}^{n-1} \left| \log\left(\frac{AUC_{Rt}}{AUC_{Tt}} \right) \right|}{n-1} \quad (3)$$

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_J}{\sum_{j=1}^{n} \Delta M_j} \quad (4)$$

$$DE(\%) = \frac{\int_0^t y.dt}{y.t} x100 \quad (5)$$

where, AUC_{Rt} and AUC_{Tt} are the areas under the dissolution curves of the references and test formulations, respectively, at time t, *j* is the sample number, *n* is the number of dissolution sample times, $\hat{t}$ is the time at midpoint between t_j and t_{j-1} determined from $(t_j + t_{j-1})/2$, ΔM is the additional amount of drug dissolved between t_j and t_{j-1} and *y* is drug percent dissolved in time *t*.

Dissolution data obtained from selected formulations were fitted to Zero-order, First order, Higuchi and Hixon-crowell models and regression analysis was carried out. The criterion for selecting best model was based on goodness-of-fit. Zero order rate equation (eq. 6) shows drug release is independent of its concentration.[18] First order equation (eq. 7) describes drug release is proportional to the amount of drug remaining in delivery system.[19] Higuchi model (eq. 8) describes drug release from insoluble matrix as a function of square root of time[20] and Hixson-Crowell cube root law (eq. 9) describes drug release from erodible isometric geometry matrices.[21]

$$Q_t = K_0 t \quad (6)$$

$$InQ_t = InQ_0 - K_1.t \quad (7)$$

$$Q_t = K_H.\sqrt{t} \quad (8)$$

$$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = K_{HC}.t \quad (9)$$

where, Q_t is the amount of drug released in time *t*, Q_0 is the initial amount of the drug in tablet, K_0 , K_1, K_H, and K_{HC} are release rate constants for zero order, first order, Higuchi, and Hixson-Crowell rate equations, respectively. The detailed discussion of mechanism of drug release was reviewed by Sood and Panchagnula (4).

In vitro dissolution profiles are described by semi-empirical equation (eq. 10), so called power law.[22]

$$\frac{M_t}{M_\infty} = Kt^n \qquad (10)$$

Where, Mt and M_∞ are cumulative amounts of drug release at time t and infinite time respectively. k is a constant incorporating structural and geometric characteristics of release device, and 'n' is release exponent indicative of the release mechanism. Drug profiles up to 60% drug release were fitted to this equation by non-linear regression using Sigma stat, version 2.0.

Furthermore, the contribution of Fickian diffusional release and the case II erosional release over the first 60% of release profile were quantified according to Heuristic model (eq. 11) developed by Peppas and Sahlin.[23]

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \qquad (11)$$

Where the first term of the right hand side is the Fickian contribution and the second term being the case II erosional contribution. *m* is Fickian diffusion component for a devise of any geometrical shape that exhibits controlled release. The value of *m* for marketed formulations was determined from the plot of aspect ratio against diffusional exponent according to Peppas and Sahlin.[23]

Drug release parameters (R^0 and t_{del}) obtained from *in vitro* data of most similar release profile (Based on f_2 value) and drug's pharmacokinetic properties were used for predicting blood drug concentrations-time profiles from single dose and at steady state from multiple dosing.[24] Method of superposition was used for steady state concentration predictions. Values of C_{ssmax} and C_{ssmin} thus obtained were compared to the values obtained from actual plasma level profile of reference formulation.

The goodness of MR formulations was evaluated[25] from calculated dosage form index, DI (eq. 12) and %fluctuation (eq. 13) of formulations.

$$DI = C_{ssmax}/C_{ssmin} \quad (12)$$

$$\text{Fluctuations } (\%) = (C_{ssmax}-C_{ssmin})*100/C_{ssav} \quad (13)$$

Where, C_{ssmax} and C_{ssmin} are maximum and minimum blood drug concentrations at steady state, respectively and C_{ssav} is average blood drug oncentration at steady state.

RESULTS AND DISCUSSION

All the products were found to contain the labeled amounts of the drug. Weight variation within the same formulation was found less than 0.1% however, large difference in average weight among different formulations was observed that in turn indicate variation in total amount of excipient used by different manufacturer. Crushing strength of different formulations varied from 5-40 kilopascal (kP) that may be due to difference in technology used to manufacture. N 1 and N 4 are osmotic and multiunit matrix system respectively while rests of the formulations are single unit matrix system. Friability (%) was found less than 0.04.

Dissolution study development and setting specifications for a drug with low aqueous solubility create problems. As it is difficult to maintain sink conditions during their dissolution studies using conventional dissolution methods and procedures. Various modifications in dissolution test method such as use of large volume of dissolution medium, addition of surfactant in medium, use of two phase medium or modification of dissolution test equipment have been discussed.[26,27] However, addition of surfactant in dissolution medium to provide sink condition is considered to simulate physiological environment more closely than other approaches.[2,3]

Table 2 Similarity (f_2 and S_d), dissimilarity (f_1) factor, MDT and DE index values for drug release profiles obtained from modified release formulations of NFD marketed in India in comparison to NIPER formulation (reference) in dissolution medium containing phosphate buffer (pH 6.8) with1% w/v SLS

Test formulations	REFERENCE FORMULATION				
	f_2	f_1	S_d	MDT index[a]	DE index[b]
N1[c] 30mg	45.26	27.29	0.3881	1.22	1.09
N1[e] 30mg	48.31	19.23	0.0691	1.22	1.22
N2 10mg	17.81	99.11	0.5162	0.31	2.44
N2 20mg	21.16	77.34	0.2813	0.46	1.78
N3 20mg	18.68	95.42	0.5489	0.25	1.64

N4 10mg	13.05	125.35	0.6287	0.34	1.84
N4 20mg	22.95	78.82	0.4632	0.48	1.54
N5 10 mg	10.95	138.16	0.6784	0.20	1.92
N5 20 mg	16.95	102.88	0.5915	0.28	1.66
N6 20mg	13.04	124.81	0.6229	0.19	1.86
N7 10 mg	17.93	99.11	0.5681	0.33	1.65
N7 20 mg	19.15	94.90	0.5477	0.41	1.64
N7 30 mg	32.32	46.90	0.1675	0.84	1.48
N8 10mg	6.49	166.95	0.7575	0.07	2.06
N8 20 mg	9.88	143.68	0.7069	0.15	1.93
N9 20mg	20.02	83.92	0.3655	0.35	1.62
[a]MDT of test to reference; [b]DE of test to reference; [c]with lag time; [e]without lag time f_2 value more than 50 and S_d equal to zero were considered as similar profiles MDT and DE index equal to one indicates comparable profiles					

It was concluded from previous study that SLS concentration of 1% w/v in dissolution medium was sufficient to provide sink conditions for NFD products.[13] At the same time exhibited sufficient discriminatory power to differentiate various drug product categories (capsules, matrix tablets and osmotic tablets) that release the drug at different rates and mechanisms. Hence, dissolution studies of marketed MR formulation of NFD were performed in phosphate buffer containing 1% w/v SLS at pH 6.8.

An ideal MR formulation should release loading dosage in first hour and remaining maintenance dose at a constant rate. Drug release profiles from NF formulation with test formulations are shown in Figure 1. N-1 is an osmotic tablet and showed lag period of 2 hours. N-7 30 mg released about 30-40% whereas rest of the formulations released more than 70% in first four hours. In comparison to these, NF formulation released 25-30% in same time.

FDA recommends similarity factor f_2 for comparison of drug release profiles from different formulations and/or at different conditions, that was calculated from mean dissolution data using equation 2. For dissolution profile to be considered similar, value of f_2 should lie between 50 and 100.[28] Similarity factor of 100 suggests that test and NF formulation profiles are identical and, as the value becomes smaller, the dissimilarity between releases profiles increases. On the other hand, difference factor f_1 was also calculated using equation 1 to approximate the percentage error between two profiles. The value of f_1 is zero when test and reference formulation profiles are identical and increases proportionally with the dissimilarity between two profiles. Calculated f_1 and f_2 values are shown in Table 2. N1 (30 mg) shows a lag time of two hours, f_1 and f_2 values were calculated with and without lag time. Calculated f_2

value without lag time (48.31) was more close to 50 than with lag time (45.26). N7 (30 mg) has f_2 value 32.32 while rest of the formulations have less than 20. Correlation of f_2 to average difference (%) between reference and test profile is non linear where more than 90% similarity in profiles is indicated by f_2 value above 50.[14] However, f_2 value above 40 indicates that the profiles are more than 80% similar. Further, no test formulations have f_1 value less than 20 except N1 (19.23 without lag time). In addition to these, S_d value[16], MDT index and DE index were also calculated (Table 2). Both MDT index and DE index supported calculated f_2 values in ranking the similarity of test to reference formulation with respect to *in vitro* drug release. Further, large difference in S_d value of N1 with and without lag time was observed. However, S_d value without lag time (0.0691) was very close to zero indicated similarity to NF formulation.

Table 3 Similarity factor (f_2) and dissimilarity (f_1) values for drug release profiles obtained from selected modified release formulations of NFD marketed in India under different conditions of pH (2.0, 5.0 and 7.4)

	$f_2^{\#}$				$f_1^{@}$		
	pH 2.0	pH 5.0	pH 7.4		pH 2.0	pH 5.0	pH 7.4
N1 30 mg							
pH 2.0	-	58.10	71.90		-	11.21	5.60
pH 5.0	58.10	-	53.70		11.68	-	13.66
pH 7.4	71.90	53.70	-		5.31	12.43	-
N4 10 mg							
pH 2.0	-	64.88	71.65		-	4.20	2.99
pH 5.0	64.86	-	76.75		4.33	-	2.57
pH 7.4	71.65	76.75	-		3.01	2.51	-
N4 20 mg							
pH 2.0	-	58.94	74.78		-	6.20	2.79
pH 5.0	58.94	-	71.42		5.83	-	3.21
pH 7.4	74.78	71.42	-		2.71	3.31	-
N7 20 mg							
pH 2.0	-	61.49	57.91		-	6.59	7.31
pH 5.0	61.49	-	45.57		7.05	-	14.88
pH 7.4	57.91	45.57	-		6.81	12.95	-
N7 30 MG							
pH 2.0	-	60.96	45.76		-	6.29	13.08
pH 5.0	60.96	-	54.10		6.71	-	7.97
pH 7.4	45.76	54.10	-		15.05	7.85	-

[#]Value of 100 indicate completely similar profiles while value of 50 shows 90% similarity; [@]values less than 15 are accepted as similar profiles.

Table 4 Kinetic and statistical parameter obtained from drug release data of selected formulations

Release models	N1[#]	N7 30 mg	N4 20 mg	NF
Peppas - Sahlin				
K_1	-	0.109×10^{-9}	0.337	0.100
K_2	-	0.109	0.057	0.047
K_2/K_1	-	1×10^{9}	0.169	0.478
R^2	-	0.997	0.975	0.996
Korsmeyer - Peppas				
K	-	0.123	0.390	0.104
n	-	0.791	0.539	0.668
R^2	-	0.995	0.977	0.998
Zero order				
Slope	6.0557	8.0912	2.9299	3.3172
K	1.8167	2.4274	0.5860	1.3269
R^2	0.9857	0.9797	0.5914	0.9371
First order				
Slope	-0.074	-0.055	-0.076	-0.044
K	0.1709	0.3267	0.1764	0.1021
R^2	0.9279	0.9222	0.9561	0.9929
Higuchi				
Slope	24.105	26.222	18.442	21.884
K	24.105	26.222	18.442	21.884
R^2	0.9359	0.9646	0.8308	0.9827
Hixon - Crowell				
Slope	0.1392	0.2828	0.1602	0.8392
K	0.1392	0.2828	0.1602	0.8392
R^2	0.9842	0.9781	0.9372	0.9874

K is release rate constant with units mg/hr, hr^{-1}, $\%/(hr)^{1/2}$ and $(\%)^{1/3}$/hr for zero order, first order, Higuchi and Hixon - Crowell models respectively; n, release exponent; R^2, correlation coefficient.
[#]an osmotic system where Peppas - Sahlin and Korsmeyer - Peppas equations are not applicable.

This study was aimed to compare the NF formulation with that of available marketed formulations and prove its pharmacokinetic advantage over others. Based on f_2 value, N1 and N7 were selected to study the effect of pH on drug release. In addition, N4 was also selected for further study because of similarity in technology and dosage form with NF formulation. Formulations thus selected were evaluated for their drug release performance at different pH (Figure 2). In order to compare these profiles, f_1 and f_2 values were calculated (Table 3) and it was found that al selected formulations show pH independent release.

Dissolution data of selected formulations was fitted to basic release models. From the linear portion of the curves slope, intercept and correlation coefficient were calculated and data is summarized in the Table 4. The curvilinear nature of the cumulative % drug release versus

time plot (Figure.1) obtained from N4 suggests that it follow first order drug release kinetics, which is further confirmed by high correlation coefficient. Dissolution data obtained from both N1 and N7 30 mg (Figure. 1) showed zero order release kinetic with a release rate of 1.816 and 2.427 mg/hr (Table 4). In contrast to these, NF formulation follows first order release kinetics with release rate $0.1021hr^{-1}$.

Fickian diffusion, polymer relaxation and osmotic pressure are the basic drug transport mechanism, which control the release from *peroral* CR formulations. Dissolution data of selected formulations and NF formulation were treated with various mathematical models in order to elucidate the predominant mechanism of drug release. Being OROS system, N1 provide controlled release by the mechanism of push-pull osmotic pressure.[29] Mechanism of drug release from matrix-based formulations is described by a simple empirical equation proposed by Korsemeyer and Peppas (30). Where exponent 'n' indicates mechanism of drug release and its values lies between 0.45-0.89 for a cylindrical geometry. A value of n = 0.45 indicates Fickian diffusion, 0.45 < n < 0.89 indicates anomalous diffusion (non-Fickian) and n = 0.89 indicates case II relaxation process. N7 30 mg, N4 20 mg and NF formulation showed anomalous drug release mechanism (Table 4) i.e. combination of both diffusion and relaxation mechanism. NF formulation showed n = 0.67 indicates that both diffusion and relaxation mechanism are contributing equally to the overall drug release.

Further, to quantify the contribution of both mechanisms, Peppas and Sahlin[23] model was applied to about 60% drug release. The ratio of coefficient (k_2/k_1) values indicates that for N7 30 mg, relaxational process is predominating and for N4 20 mg diffusional mechanism is predominating. While for NF formulation k_2/k_1 ratio is 0.48 substantiating the result of equal contribution of both diffusional and relaxation mechanism.

With the help of superposition principle,[30] steady state plasma levels were calculated using drug release parameters (R^o and t_{del}) for selected formulations. Predicted steady state plasma drug concentrations (from *in vitro* data) for all.

Table 5: Predicted steady state plasma concentration level of NFD from in vitro drug release profiles and in vivo Pharmacokinetic data

FORMULATIONS	Dose (mg)	t_{del} (hr)	k	C_{ssmin} - C_{ssmax} (ng/ ml)	DI	Fluctuations (%)
N1[#]	30	14	1.8167[a]	2.32 - 74.31	31.97	131.09
N1[@]	30	-	-	17.16 - 23.69	1.38	30.69
N4 [#]	20	12	0.1764[b]	4.51 - 9.91	2.19	75.62
N4[#]	30	11	2.4274[a]	1.08 - 97.88	90.61	152.96
NF formulation[#]	40	22.56	0.1021[b]	13.28 - 22.35	1.68	50.91
NF formulation[@]	40	-	-	17.81 - 20.50	1.20	18.78

[#]steady state plasma levels are determined by superposition method (24)
[@]steady state plasma levels are determined for NIPER formulation from reference (13) and for N1 from single dose human pharmacokinetic study.[31]
[a]mg/hr; [b]hr^{-1}
C_{ssmax} and C_{ssmin} , maximum and minimum steady state concentration respectively; t_{del}, time of delivery; DI, dosage form indexk, release rate constant

selected marketed formulations lie out side the therapeutically desirable range. However, steady state blood levels of NF formulation were within the desired therapeutic range. DI and % fluctuations indicative of performance of CR formulations were also calculated (Table 5). Predicted DI and % fluctuations were high in all the cases except for NF formulation. While DI of N4 20 mg was less than other selected formulation but predicted steady state plasma drug concentrations did not reach therapeutically desired range. Further, multiple dose plasma concentration time profile was predicted from single dose human pharmacokinetic studies of NF formulation[12] and N1.[31] Blood levels predicted from *in vitro* drug release studies were significantly different from those predicted from *in vivo* pharmacokinetic for N1 while profiles are similar in case of NF formulation. Both DI and % fluctuations were less in case of NF formulation (Table 5).

CONCLUSIONS

Drug release from about 80% of marketed MR formulation was immediate and thus may not maintain therapeutic blood level for desired time. Assuming general absorbability throughout GI tract, *in vivo* blood levels were predicted by convolution from *in vitro* drug release for the selected formulations. None of the formulations showed therapeutic blood level for desirable time period. Further, predictive multiple dosing showed large % fluctuations with negligible accumulation after each dosing. Large difference in predicted steady state blood level from *in vitro* and *in vivo* data was observed in case of N1 (This is a very interesting result which need further investigation). NF formulation showed desirable blood levels with least fluctuations

(%) at steady state on multiple dosing. In nutshell, NF formulation showed therapeutic advantage over other marketed MR formulations.

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