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Research Article

Controlled Release of Ropinirole Hydrochloride from a Multiple Barrier Layer Tablet Dosage Form: Effect of Polymer Type on Pharmacokinetics and IVIVC

Nikhil Malewar,[1,3] Makarand Avachat,[1] Varsha Pokharkar,[2] and Shirish Kulkarni[2]

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Abstract. The purpose of the present study was to control *in vitro* burst effect of the highly water-soluble drug, ropinirole hydrochloride to reduce *in vivo* dose dumping and to establish *in vitro–in vivo* correlation. The pharmacokinetics of two entirely different tablet formulation technologies is also explored in this study. For pharmacokinetics study, FDA recommends at least 10% difference in drug release for formulations to be studied but here a different approach was adopted. The formulations F8A and F9A having similar dissolution profiles among themselves and with Requip® XL™ (f_2 value 72, 77, 71 respectively) were evaluated. The C_{max} of formulation F8A comprising hypromellose 100,000 cP was 1005.16 pg/ml as compared to 973.70 pg/ml of formulation F9A comprising hypromellose 4000 cP irrespective of T_{max} of 5 and 5.75 h, respectively. The difference in release and extent of absorption *in vivo* was due to synergistic effect of complex RH release mechanism; however, AUC_{0-t} and $AUC_{0-\infty}$ values were comparable. The level A correlation using the Wagner–Nelson method supported the findings where R^2 was 0.7597 and 0.9675 respectively for formulation F8A and F9A. Thus, *in vivo* studies are required for proving the therapeutic equivalency of different formulation technologies even though $f_2 \geq 50$. The technology was demonstrated effectively at industrial manufacturing scale of 200,000 tablets.

KEY WORDS: controlled release polymer; *in vitro–in vivo* correlation (IVIVC); multiple barrier layer tablets; pharmacokinetics; ropinirole hydrochloride (RH).

INTRODUCTION

Drug release of highly soluble drug molecules pose significant challenges *in vitro* as well as *in vivo* while designing a control release tablet dosage form. These challenges are namely burst effect in *in vitro* and dose dumping in *in vivo* giving an early C_{max} and possible side effects. Controlled release tablets may be monolithic, functional film-coated or multilayer *viz*. bilayer, trilayer or pellets compressed into the tablets. Drug release can be controlled by placing an effective barrier for the drug movement. For retarding drug release, hydrophilic as well as hydrophobic polymers or combinations thereof may be used. The pattern of drug release from the designed tablets needs to be reproducible in *in vitro* and *in vivo*. Along with the physicochemical properties, the pharmacokinetic properties of the drug also influence the dosage form design. Usually, the drug release needs to be controlled over a period of 8 to 24 h depending on the pharmacological requirement (1,2). These are essential components of quality by design as well as needed for establishing IVIVC effectively which are the current focused areas of formulation development.

RH was selected as a model drug due to its high water solubility (133 mg/ml) and low dose. It is highly selective for the dopamine D2-like receptor subtype, with a negligible affinity for the D1-like receptor subtype or other neurotransmitter receptors used in the treatment of idiopathic Parkinson's disease and restless leg syndrome. RH is rapidly absorbed after oral administration, reaching peak plasma concentration within 1–2 h. Food does not affect the extent of absorption even though T_{max} is increased by 2.5 h and C_{max} is decreased by 25% when administered with high fat meal. The elimination half-life is approximately 6 h and is absorbed linearly up to 24 mg.

Initially, RH was introduced as immediate release tablet in market and later as an extended release tablet. The extended release marketed product Requip® XL™ of GlaxoSmithKline is a trilayer tablet with the active-containing slow release layer in the center and two placebo outer layers acting as barrier layers which control drug release surface area. The placebo layers control the *in vitro* burst effect of the highly water-soluble drug, ropinirole hydrochloride and *in vivo* dose dumping. The time to reach peak plasma level was extended from 6 to 10 h. (3). However, manufacturing process involves separate granule preparation for placebo and ropinirole, and requires a sophisticated trilayer tablet compression machine with greater precision to control the weight of each layer. Therefore, it is a more labor-intensive process and commercial yield is often lesser.

Various types of barrier layer control release tablet formulations have been studied for different drugs. The research work is however confined to only physicochemical evaluation

[1] Lupin Ltd. (Research Park), 46A/47A, Nande Village, Mulshi Taluka, Pune, 411 042, Maharashtra, India.
[2] Department of Pharmaceutics, Poona College of Pharmacy, Bharati Vidyapeeth University, Erandwane, Pune, 411038, Maharashtra, India.
[3] To whom correspondence should be addressed. (e-mail: nikhilmalewar@lupinpharma.com)

of developed formulations without *in vivo* performance study (4–7). pH modulating agents such as citric acid monohydrate, dicalcium phosphate, fumaric acid, sorbic acid, adipic acid have been used to modify the drug release. Release controlling polymers such as hypromellose, acrylic acid polymers, methacrylic acid polymers, various grades of alginates have been used synergistically to alter the release of weakly basic drugs. The developed formulations have modified the drug release *in vitro* but pharmacokinetics was not studied (8–11). The drug release was modified using purely hydrophilic matrix, triple layer, film-coated tablets for high dose, highly soluble drug substances. IVIVC has been attempted between developed formulations for absorbed drug. The information about the scalability of the developed formulations however is not explored (12–14). RH microspheres have been attempted instead of tablet to control the drug release but the comparative pharmacokinetics of microspheres with established tablets dosage forms were not reported (15).

Single, bilayer or three barrier layer tablet formulations for controlling release of RH in various configurations have been reported. RH release data is discussed without establishing pharmacokinetics of the formulations (16,17). In another study, monolithic as well as multiple layer formulations for RH release control have been discussed *viz*. single layer tablets, bilayer tablets comprising of immediate and controlled release layer of RH, both controlled release bilayers each containing RH are also reported. RH release was effectively controlled up to 10–12 h only. However burst release up to 47% within 1 h was observed across various formulations studied (18). Controlled RH release from various tablet formulations and bioequivalence data was discussed without any clear emphasis on the explored formulation and IVIVC (19). The support platform barrier layered tablets by manual as well as automatic machine as a technology has also been discussed. The effect of dosage form technology on the pharmacokinetics is lacking (20,21). A highly water-soluble, high-dose molecule was explored using the barrier layer-coated tablets but on relatively smaller scale using Weibull model and radar diagram. The research work still lacked the *in vivo* performance data on developed formulations (22).

The present study was thus aimed to establish an effective multiple barrier layer formulation technology which is scalable on commercial level. Further, the aim was to understand the exact mechanism of drug release through the multiple barrier layers and establish the technology through IVIVC which may also be replicated for drugs molecules of varying properties. In addition to this, the comparative pharmacokinetics is to be evaluated to understand the effect of different formulation components and technologies along with the established marketed product Requip® XL™. This is essential to understand the significance of similarity factor (f_2) as a tool to for deciding the therapeutic equivalency of formulations. RH was selected not only for its high water solubility but also due to its low dose and controlling its release over a period of 24 h could be a real challenge while establishing the IVIVC.

MATERIALS

Materials

RH was purchased from Ind-Swift Laboratories Ltd ; hypromellose of various viscosity grades *viz*. hypromellose 2208: hypromellose K4M P CR, hypromellose K15M P CR, hypromellose K100M P CR, hypromellose 2910: hypromellose E5 LVP were obtained from Dow chemical USA, lactose monohydrate (DCL 11®, DMV International); microcrystalline cellulose PH 102 (Avicel® PH102,FMC Biopolymer, Ireland); colloidal silicon dioxide (Aerosil® 200, Degussa, Germany); povidone (K30, BASF, Germany); magnesium stearate (Merck, Germany); ethylcellulose (N50, Aqualon—Hercules, USA) were purchased. All other reagents and solvents were of analytical grade and were used as received. Requip® XL™ Lot: X3118 of GlaxoSmithKline was procured from USA.

Excipients and Polymers Selection

As a soluble diluent, lactose monohydrate, and as an insoluble diluent, microcrystalline cellulose, were selected to understand the influence of excipient solubility over drug release (23,24). The polymers of highest viscosity *viz*. hypromellose 2208 NF: Methocel K100M P CR, Methocel K15M P CR, Methocel K4M P CR were considered due to well established manufacturing process by Dow Chemicals. Further, controlled release (CR) grade polymers were selected over the normal grade due to their fine particle size of 90%<14 μm (25). Colloidal silicon dioxide was used as a glidant and magnesium stearate as a lubricant. Ethylcellulose of N50 grade was chosen as insoluble film former. The hypromellose 2910 (Methocel E5 LVP) was used as a pore former in the ethylcellulose film.

METHODS

Saturation Solubility

An excess of RH was added to 10 ml of various media such as deionizer water, 0.1 N HCl (pH 1.2), acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) in a stoppered conical flask and shaken at 37°C±0.5°C. At equilibrium after 2 days, aliquots were withdrawn, centrifuged at 4,000 rpm for 10 min, filtered (0.45 μm nylon membrane filter) and analyzed using high-performance liquid chromatography (HPLC) for drug content at 254 nm. The method of analysis is covered in latter part.

Preparation of Controlled Release Tablets

All formulations were manufactured using wet granulation technology under similar sets of conditions to avoid processing variables. The formulation details are given in Tables I and II. Intragranular as well as extra granular excipients were separately sifted through a 600-μm sieve. Intragranular excipients were loaded into a high shear mixer granulator (Jaguar®, India) and mixed for 15 min at slow speed agitator and chopper off. RH was dissolved in methyl alcohol and gradually added onto the powder mass. Granulation was continued to get the mass of suitable consistency at high-speed agitator and chopper off. The resulting wet mass was air dried for 15 min in fluid bed dryer (Retsch® GmbH) at inlet temperature of 60°C until percent of loss on drying was less than 2.5%. The dried granules were sifted through 600 μm sieve and loaded into the octagonal blender (Gansons®, India) along with extragranular excipients and mixed for 20 min. This was further lubricated using magnesium stearate for three

Table I. Qualitative and Quantitative Composition of Extended Release RH Tablets—Core

Ingredient names	F1	F2	F3	F4	F5	F6	F7	F8	F9
Intragranular (mg/tablet)									
Ropinirole Hydrochloride equivalent to Ropinirole	2.28	2.28	2.28	2.28	2.28	2.28	2.28	2.28	2.28
Hypromellose 2208 (Methocel K100M P CR®)	453.00	–	–	300.00	300.00	200.00	300.00	150.00	–
Hypromellose 2208 (Methocel K15M P CR®)	–	453.00	–	–	–	–	–	–	–
Hypromellose 2208 (Methocel K4M P CR®)	–	–	453.00	–	–	–	–	–	150.00
Lactose monohydrate	17.22	17.22	17.22	160.22	112.07	–	–	–	–
Microcrystalline cellulose	–	–	–	–	48.15	160.22	160.22	160.22	160.22
Colloidal silicon dioxide	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Povidone (K30)	15.00	15.00	15.00	20.00	20.00	20.00	20.00	20.00	20.00
Methyl alcohol[a]	QS	QS	QS	QS	QS	QS	QS	QS	Q.S.
Extragranular (mg/tablet)									
Hypromellose 2208 (Methocel K100M P CR®)	–	–	–	–	–	100.00	–	150.00	–
Hypromellose 2208 (Methocel K4M P CR®)	–	–	–	–	–	–	–	–	150.00
Colloidal silicon dioxide	5.00	5.00	5.00	10.00	10.00	10.00	10.00	10.00	10.00
Magnesium stearate	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Total core weight	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00

QS Quantity sufficient
[a] Evaporates during processing and is not a part of the final product

minutes. The lubricated blend was compressed using 14 mm × 7 mm size modified oval punches on 16 station rotary tablet compression machine (Cadmach®, India).

The coating solution was prepared by dissolving ethylcellulose and hypromellose in isopropyl alcohol and methylene chloride mixture (30:70). The tablets were coated in a perforated coating pan (Ganscoater GAC-250/375 Model GMP Type FLP®, Gansons Ltd. India) at inlet temperature: 40–45°C; exhaust: 37°C; pan rpm: 10–12; bed temperature: 35°C–37°C, spray rate: 3–4 rpm, and atomizing pressure of 1.6 bar. The tablets were dried to eliminate residual solvents. The formulations F4 to F9 were different in terms of composition as well as quantity but the overall manufacturing process was the same.

For formulation F4, lactose monohydrate was used as a soluble diluent and hypromellose K100MP CR as a rate-controlling polymer. In formulation F5, the amount of soluble diluent, lactose monohydrate, was reduced and replaced with insoluble diluent, microcrystalline cellulose. In formulations F6 and F8, the entire quantity of the lactose monohydrate was replaced with microcrystalline cellulose and the release controlling polymer was added intra and extragranularly. In formulation F7 entire release controlling polymer was added intragranularly in comparison to F6 and F8. In F9, the formulation composition was

Table II. Qualitative and Quantitative Composition of Extended Release RH Tablets—Coated

Ingredient names	F4A	F5A	F6A	F7A	F8A	F9A
Intragranular (mg/tablet)						
Ropinirole Hydrochloride equivalent to ropinirole	2.28	2.28	2.28	2.28	2.28	2.28
Hypromellose 2208 (Methocel K100M P CR®)	300.00	300.00	200.00	300.00	150.00	–
Hypromellose 2208 (Methocel K15M P CR®)	–	–	–	–	–	–
Hypromellose 2208 (Methocel K4M P CR®)	–	–	–	–	–	150.00
Lactose Monohydrate	160.22	112.07	–	–	–	–
Microcrystalline cellulose	–	48.15	160.22	160.22	160.22	160.22
Colloidal silicon dioxide	5.00	5.00	5.00	5.00	5.00	5.00
Povidone (K30)	20.00	20.00	20.00	20.00	20.00	20.00
Methyl alcohol[a]	QS	QS	QS	QS	QS	Q.S.
Extragranular (mg/tablet)						
Hypromellose 2208 (Methocel K100M P CR®)	–	–	100.00	–	150.00	–
Hypromellose 2208 (Methocel K4M P CR®)	–	–	–	–	–	150.00
Colloidal silicon dioxide	10.00	10.00	10.00	10.00	10.00	10.00
Magnesium stearate	2.50	2.50	2.50	2.50	2.50	2.50
Total core weight	500.00	500.00	500.00	500.00	500.00	500.00
Coating						
Ethyl cellulose (N50)	5.50	5.50	6.875	7.50	7.50	7.50
Hypromellose 2910 (Methocel E5 LVP®)	4.50	4.50	5.625	7.50	7.50	7.50
Isopropyl alcohol[a]	72.00	72.00	90.00	108.00	108.00	108.00
Methylene chloride[a]	168.00	168.00	210.00	252.00	252.00	252.00
Total weight of coated tablets	510.00	510.00	512.50	515.00	515.00	515.00

QS Quantity sufficient
[a] Evaporates during processing and is not a part of the final product

kept same as formulation F8 with the exception of replacing K100M P CR by K4M P CR as a release controlling polymer. Formulation F9A was scaled up to 200,000 numbers.

EVALUATION OF TABLETS

Physical Evaluation

Quality control tests for the tablets, such as mass variation, thickness, friability and resistance to crushing were determined. Mass variation was determined by weighing ten tablets individually. Resistance to crushing on ten tablets was determined using digital hardness tester (Erweka®, GmbH, Type TBH 220, Germany). Thickness of tablets was measured using vernier caliper (Mitutoyo Absolute Thickness tester®, Japan). Friability was determined for 10 tablets using friability apparatus (Electrolab®, Friabilitator Machine EF-2, India). The adhesion strength of the film coat was determined axially by using texture analyzer on ten tablets (Stable Micro Systems, UK. Model:TAXT plus) . The tablet coating was removed from around the tablet circumference using scalpel. The tablet was secured at fixed place centrally with double sided adhesive foam tape in the lower cavity firmly. The tablet samples were tested using 0.5 in. diameter cylinder probe (P/0.5). The operational parameters were: pre-test speed: 1.0 mm/s, test speed: 0.5 mm/s, post-test speed: 10.0 mm/s, return distance: 10 mm, trigger type and force: auto and 799 g, data acquisition rate: 500 pps. The trigger force was applied for 10 s. During this, tablets got compressed into both cavities to receive full coating contact with foam tape. The upper fixture was withdrawn quickly to remove coating. The maximum force required to separate the tablet from its coating was measured as tablet coating adhesion force.

CHEMICAL EVALUATION

Assay Procedure for the Tablets Using High-Performance Liquid Chromatography

A validated HPLC procedure was used for RH content determination using Inertsil ODS 3 V column, 250×4.6 mm, 5 μm. The detection was done at 254 nm. The column and auto sampler temperature was maintained at 30°C and 10°C, respectively. Injection volume of 20 μl and the mobile phase flow rate of 1.5 ml/min was maintained. Buffer was prepared by dissolving 13.6 g/L potassium dihydrogen orthophosphate in 1,000 ml water and pH was adjusted to 7.0±0.05 with potassium hydroxide solution (10% *w*/*v* solution). This was further mixed with acetonitrile in the ratio 83:17. Standard preparation was done by dissolving an accurately weighed quantity of RH WS equivalent to about 50 mg (approx 57 mg) in 50 ml methanol and volume was made up to 100 ml in the volumetric flask. A 2.0-ml volume of this solution was further diluted to 100 ml with mobile phase. Test samples were prepared by transferring 10 tablets into approximately 500 ml of methanol, sonicated for 20 min with intermittent shaking and diluted to 1000 ml with mobile phase. The resulted suspension was mixed and centrifuged at 6,000 rpm for 5 min. Five milliliters of supernatant solution was diluted to 10 ml with mobile phase, mixed, filtered through 0.45 μm membrane filter and injected. The same chromatography conditions were used for the solubility study of RH. The coefficient of variation of the method was 0.23.

Plasma Sample Preparation for Assay and Analysis

The blood samples were collected in K_2EDTA vacutainers. The samples were centrifuged at 3,800 rpm for 10 min at 10°C. The plasma was separated, stored in polypropylene vials at −25±5°C up to last sample withdrawal and then stored in deep freezer at −75±5°C until analysis. Samples were processed by adding 50.00 μL of internal standard dilution (about 0.040 μg/mL of escitalopram oxalate except in the standard blank and pre-dose samples; without internal standard). Further samples were aliquoted with 500.00 μL of calibration curve standards, quality control samples and subject samples into pre-labeled tube. To this 500.00 μL of water was added to each sample and vortexed. Solid-phase extraction (Oasis hydrophilic–lipophilic balance, 30 mg, 1-cm^3 cartridges) was conditioned with 1 mL of methanol and equilibrated with l.00 mL of water. Plasma sample were then loaded onto pre-conditioned solid-phase extraction cartridge. Solid-phase extraction cartridge was washed with 1.00 mL of water (twice) followed by 1.00 mL of 30% methanol in water and eluted with 0.5 mL of eluent (100% methanol) by applying minimum pressure. Eluted samples were vortexed and transferred into pre-labeled auto sampler vial. RH in plasma was quantified using validated UPLC-MS/MS (WatersQuattro Premier XE) method. Betabasic 8 (100× 4.6 mm id, 5 μm) column was used. Electrospray ionization and detection of RH and escitolapram oxalate were carried out with multiple reaction monitoring of *m*/*z* 261.094/114.076 and 325.179/109.015, respectively, in positive ion mode $[M+H]^+$ using a triple quadrupole mass spectrometer. The data was acquired and calculated using Masslynx software. This method was validated and the linearity ranged between 29.5 and 3008.5 pg/ml.

Drug Release Using USP Dissolution Apparatus and Analysis by High-Performance Liquid Chromatography

Rate of drug release was determined by using USP dissolution apparatus Type I (Electrolab TDT-08L, India) and HPLC. The drug release test was done on 12 units at 100 rpm, in 500 ml citrate buffer (pH 4.0) and at temperature 37°C± 0.5°C. 10 mL of aliquots were withdrawn at predetermined time points of 1, 2, 4, 6, 9, 12, 16, 20 and 24 h and replenished by fresh citrate buffer maintained at the same temperature. The withdrawn samples were filtered through 0.45 μm membrane filter and analyzed using column Inertsil ODS 3 V, 150× 4.6 mm, 5 μm at the flow rate of 0.8 ml/min, wavelength: 250 nm, injection volume: 50 μl, column temperature: 30°C, auto sampler temperature: 10°C, run time: 6 min. Citrate buffer pH 4 was prepared using 2% *w*/*v* solution of citric acid and 0.8% *w*/*v* sodium hydroxide. The pH was adjusted to 4± 0.05 using dilute hydrochloric acid. The mobile phase was prepared by mixing 800 ml water, 200 ml of acetonitrile and 1 ml of triethylamine. The pH was adjusted to 3.0 with orthophosphoric acid and degassed. Standard stock solution was prepared by dissolving RH equivalent to 40 mg in 70 ml of water, sonicated and volume was made up to 100 ml in volumetric flask. One milliliter of this solution was diluted to

100 ml with a medium. The necessary system suitability was checked for the column efficiency for RH peak. The approximate retention time of RH peak is about 4.0 min. The method was validated and coefficient of variation was 0.22.

PHARMACOKINETIC STUDY IN HUMANS

Study Design

The pharmacokinetic studies were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (Seoul, 2008) and in compliance with ICH GCP, GLP, local guidelines of ICMR. All studies were initiated after approval from institutional review board and no. of both studies are IRB no. 08-094-RPR and IRB no.08-096-RPR. Further, the entire information about study is uploaded on http://clinicaltrials.gov/ (NCT01712568 and NCT01717235).

The pharmacokinetic study in fasting condition was done for formulations F8A and F9A along with marketed product Requip® XL™ Lot: X3118 of GlaxoSmithKline, USA. Both studies were planned separately as open label, balanced, randomized, two-treatment, two-period, two sequence, single dose, crossover, bioavailability studies in healthy, adult, male, human subjects under fasting conditions. After an overnight fast of at least 10 h, single oral dose was administered with 240 ±2 ml of drinking water in sitting posture. In each period, 23 blood samples were drawn. This includes 1 h prior to dosing followed by 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 14, 16, 20, 24, and 30 h after dosing. The post dose samples were collected within 2 min of scheduled time. The study was conducted on 12 volunteers. The wash out period was 7 days. In both pharmacokinetic studies, the volunteers were given a standard meal, snacks and dinner at 4, 8, and 12 h during housing.

RESULT

Solubility Classification

Table III records the solubility of RH across various physiological media of the gastrointestinal tract *viz*. 0.1 N hydrochloric acid, acetate buffer pH 4.5, phosphate buffer pH 6.8, phosphate buffer pH 7.5, and deionized water. The pH of the resulting solution dropped slightly to acidic side and the solubility was almost similar in all the media.

Evaluation of Tablet Properties

The resistance to crushing was acceptable in the range of 200 to 300 N. The friability was negligible and suitable to withstand rigors during coating process. The tablet thickness was in the narrow range of 5.9 mm to 6.3 mm reflecting controlled weight variation. Table IV shows that the assay was well within range of 95 to 105%, which is a generally accepted product quality range. The moisture content contributed by the excipients used in the formulation was in the range 6 to 7.5%. The axial adhesion strength of formulation F8A tablets was 1,768.964 g (±SD 45.731) and 1,697.421 g (±SD 95.698).

Table III. Solubility of RH in Various Physiological Media

Medium	pH of the medium before solubility study	Final pH	Solubility mg/mL
0.1 N HCl	1.2	1.09	136.86
Acetate buffer	4.5	4.13	157.09
Phosphate buffer	6.8	6.31	148.65
Phosphate buffer	7.5	6.77	146.06
Deionized water	5.5	3.62	155.29

In vitro RH Release

Figures 1 and 2 show the RH release from the uncoated as well as film-coated tablets in citrate buffer at pH 4.0. RH release was more controlled in film-coated tablets at initial, mid and final hours as compared to the uncoated tablets. The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percentage of dissolution between the two curves. Two dissolution profiles are considered similar when the f_2 value is ≥50. The RH release of formulations F1 to F9 were compared with Requip® XL™ for the similarity factor (f_2) and found to be 53, 43, 44, 43, 44, 57, 50, 57, 50 respectively. The f_2 of uncoated tablets F4, F5, F6, F7, F8, F9 and corresponding coated tablets F4A, F5A, F6A, F7A, F8A, F9A was 57, 46, 75, 51, 60, 47, respectively. The f_2 of coated formulations F4A, F5A, F6A, F7A, F8A, F9A were 52, 70, 63, 85, 77, 71 when compared with the Requip® XL™. The f_2 of developed formulations F8A and F9A used for pharmacokinetic study was also calculated and found to be 72. The similarity factor was calculated using the following equation (26,27). $f_2 = 50 \times \log\{[1 + (1/n)\sum_{t=1} n(R_t - T_t)2] - 0.5 \times 100\}$where R_t and T_t are the cumulative % RH release of reference and test respectively and n is a number of time points. f_2 value is a measure of similarity of the two release profiles from 0 to 100.

PHARMACOKINETIC STUDY

The pharmacokinetic data is given in Table V. In the pharmacokinetic study of F8A *vs.* Requip® XL™, the peak plasma level of the Requip® XL™ was observed between 3 to 24 h with a mean of 10.0 h whereas for formulation F8A, the peak plasma level was between 3 to 9 h with a mean of 5.2 h. The intrasubject variability was 25.94, 27.64, 35.20 for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, respectively. The graphical representation of the data

Table IV. Chemical Properties of Tablets

B. no.	Assay % (±SD)	%Moisture content (±SD)
F1	99.5 (1.31)	6.95 (0.05)
F2	100.5 (0.83)	7.05 (0.05)
F3	99.0 (0.95)	7.46 (0.05)
F4A	97.5 (1.18)	6.49 (0.09)
F5A	98.9 (1.85)	6.56 (0.04)
F6A	98.0 (0.45)	6.84 (0.05)
F7A	97.5 (1.46)	6.55 (0.05)
F8A	101.0 (1.50)	6.20 (0.10)
F9A	99.0 (1.04)	7.17 (0.06)

SD is a deviation of three determinations

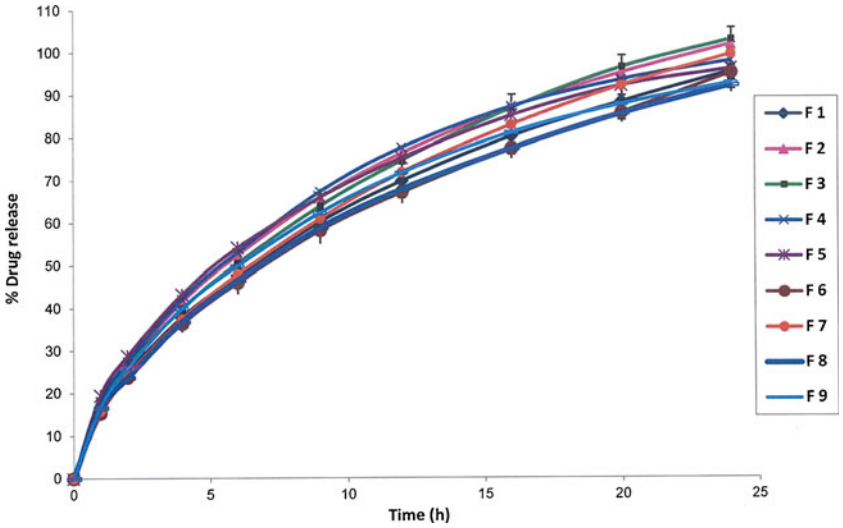

Fig. 1. % RH release from core tablet

is given in Fig. 3. The mean values of individual time points and plasma concentrations were plotted.

In the pharmacokinetic study of F9A *vs.* Requip® XL™, the peak plasma level of the Requip® XL™ was observed between 6 and 24 h with a mean of 10.4 h. whereas for formulation F9A, the peak plasma level was between 2 and 24 h with a mean of 8.7 h. Intra subject coefficient of variation determines the variability that is observed on repeating the experiments on the same subject under the same experiment condition which is due to biological or analytical measurement. The intra subject variability was 24.06, 25.78, and 47.28 for $C_{max,}$ AUC_{0-t}, and $AUC_{0-\infty}$, respectively. The graphical representation of the data is given in Fig. 4. The mean values of individual time points and plasma concentrations were plotted.

In the formulation F8A, the time required to achieve the C_{max} level was within narrow range of 3 to 9 h with a mean of 5.2 h in comparison to F9A which was 2 to 24 h with a mean of 8.7 h. The time required to achieve the C_{max} level was almost similar in both the studies for Requip® XL™. Therefore even though RH release of formulations in *in vitro* was similar to Requip® XL™, in *in vivo* RH release and absorption was rapid in case of F8A.

The pharmacokinetic analysis was done by non-compartmental method of analysis using the WinNonlin software version 5.3.

DISCUSSION

Solubility Classification

The gastrointestinal pH varies across the entire tract depending on the fasted as well as fed condition. RH is an acidic drug substance. The solubility of RH was determined over the entire pH range as the RH release in body is over a period of 24 h and the solubility study demonstrates similar solubility at different pH. This indicates that RH is highly

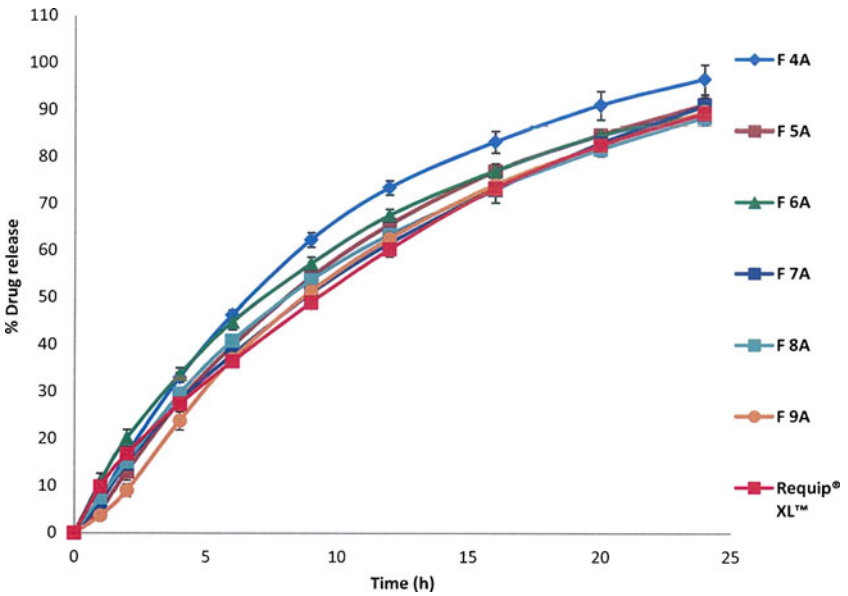

Fig. 2. % RH release from coated tablets along with Requip ® XL™

Table V. Pharmacokinetic Data of Extended Release RH Tablets F8A and F9A Vs Requip® XL™

Pharmacokinetic parameters	Least square means plasma concentration in pg h/mL					
	Requip® XL™ Lot:X3118	F8A	%ISCV	Requip® XL™ Lot:X3118	F9A	%ISCV
C_{max} (±SD)	1,231.51 (592.798)	1,005.16 (391.930)	25.94	864.02 (484.925)	973.70 (751.199)	24.06
AUC_{0-t} (±SD)	20,508.61 (12,149.800)	14,815.07 (8,276.804)	27.64	15,484.58 (9,683.202)	1,4953.49 (15,548.584)	25.78
$AUC_{0-\infty}$ (±SD)	21,912.23 (12,566.590)	20,189.14 (28,667.295)	35.20	17,186.85 (10,492.880)	20,779.04 (31,260.543)	47.28
T_{max} h (±SD)	8.00 (6.696)	5.00 (1.405)	–	9.00 (5.080)	5.75 (6.221)	–

ISCV intra subject coefficient of variation

soluble and unlikely to have any impact on the absorption due to varied pH in the gastrointestinal tract. Therefore as per FDA guidance (27), the RH is a highly soluble drug substance since highest dose dissolves in 250 ml of media. Further RH provides the opportunity to establish IVIVC.

Physical and Chemical Properties of the Tablets

The physical parameters were accepted based on the prior knowledge of the working on tablet dosage forms in general as well as were satisfactory to withstand the rigors of high-speed manufacturing process, handling , coating, packaging and shipping activities. The chemical properties such as assay, residual organic solvents content and water in the dried tablets were satisfactory.

In vitro RH Release

The USP apparatus I was chosen over apparatus II as one side of the tablet may not get exposed to the medium and thereby limiting the surface availability. Further, the office of generic drugs of the US FDA has also mentioned citrate buffer as a dissolution medium (28). The CR-grade hypromellose polymer was selected due to finer particle size for rapid hydration. RH is a highly soluble drug and its release is modulated by a combination of diffusion and erosion process from the tablets. The *in vitro* RH release of single layer tablets (core tablets) was evaluated. In F1, F2, F3 formulations, the hypromellose of varying viscosity but the same concentration of 90.6% *w/w* of the tablet weight was used. This larger concentration of hypromellose was used to get a better control over RH release due to its high solubility. RH release was rapid at first hour and almost similar at various time points across the dissolution profile of 24 h for all three formulations. RH release was greater than 90% at the end of 24 h. The RH release could not be controlled at first hour despite higher polymer concentration up to 90.6% *w/w* of the tablet weight and was independent of the hypromellose viscosity used across the range of 100,000 cP to 15,000 to 4,000 cP. The RH release was rapid as compared to Requip® XL™. This was due to trilayer tablets of Requip® XL™ where central active release controlling portion is covered by two non permeable placebo layers on either sides.

The larger polymer concentration in matrix did not give the effective control over RH release. Therefore, it was decided to reduce the polymer concentration to 60% from 90.6% of tablet weight. Based on the empirical knowledge, insoluble excipients in matrix tablets reduce the drug release and the soluble excipient attenuates the same. It was also decided to evaluate the influence of soluble excipient, lactose monohydrate as well as insoluble excipients, microcrystalline cellulose on RH release. In formulation F4, lactose monohydrate as a soluble diluent and hypromellose K100MP CR were used as a rate-controlling polymer but no significant change in RH release was observed. Further, partial replacement of soluble diluent lactose monohydrate with insoluble diluent microcrystalline cellulose in formulation F5 did not show significant change in the RH release in comparison to formulations F1 to F4. In formulations F6 and F8, the replacement of entire quantity of lactose monohydrate with microcrystalline cellulose and the addition of release controlling polymer (intra as well as extragranularly)

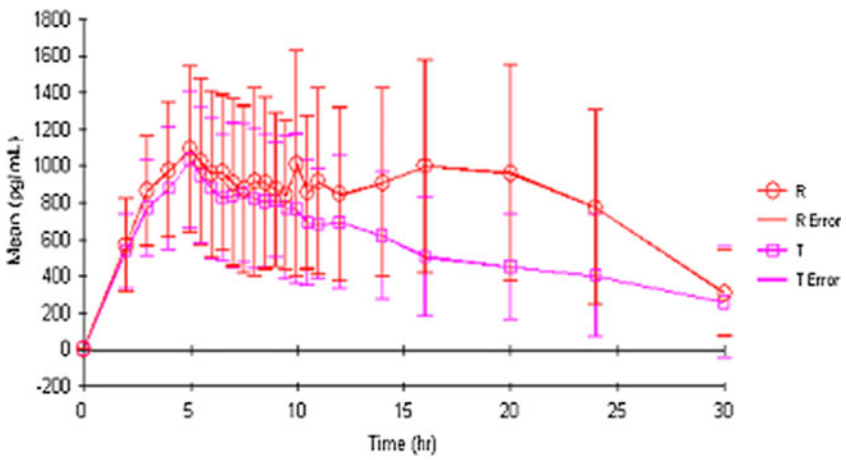

Fig. 3. Pharmacokinetics-linear mean plot of time (in hour) *vs.* plasma concentration on (in picogram per milliliter) of RH formulation F8A Vs Requip ® XL™ in fasting condition

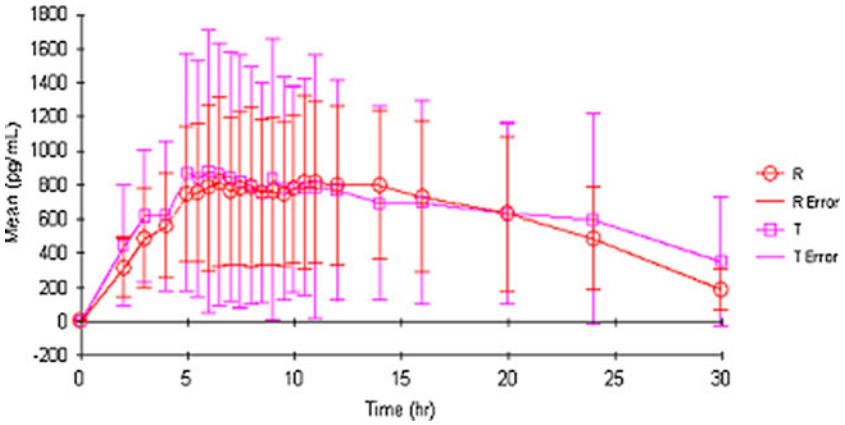

Fig. 4. Pharmacokinetics-linear mean plot of time (in hour) *vs.* plasma concentration on (in picogram per milliliter) of RH formulation F9A Vs Requip ® XL™ in fasting condition

did not have significant influence on RH release. Further, in formulation F7, the entire polymer quantity was added intragranularly for intimate contact with RH but this did not significantly changed RH release. The polymer viscosity was changed by replacing K100MP CR by K4MP CR in F9 while keeping the rest of the formulation of F8 the same also did not control the RH release. With all these formulations *viz*. F1 to F9, it was revealed that the polymer quantity, its viscosity as well as addition of soluble/insoluble excipients in the formulation has insignificant impact on RH release (Fig. 1). The f_2 values of all uncoated formulations were near to 50 when compared with Requip® XL™. Therefore, an effective barrier was still required to control the drug release.

It was decided to film coat the tablets of formulations F4 to F9 using ethylcellulose and hypromellose polymer in organic solvent system. The aqueous pseudolatex based polymeric systems like Surelease® and Aquacoat® ECD can also be used but however these were not considered due to shorter shelf life, curing requirement after coating, longer processing time and high coat build up. If curing is not done properly, the dissolution profile can change due to film aging during stability (29–31). The RH release was reduced by 4.6 to 14.7% across formulations F4 to F9 after film coating. Therefore, film coating acted as an effective barrier for controlling the burst effect in comparison to the single layer tablets during the initial hours. Overall RH release from coated tablets was slower in comparison to the single layer tablets in mid hours across all the sampling points and more than 85% RH released at the end of 24 h from all formulations (Fig. 2). The polymer concentration, its viscosity, and soluble or insoluble excipients in the formulations have almost similar impact on the drug release *in vitro* even in the film-coated tablets but the f_2 values of the coated tablets were improved with Requip® XL™ in comparison to corresponding uncoated tablets.

Mechanism of RH Release from Coated Tablets

The overall mechanism of controlled RH release from the tablet dosage form is shown schematically in Fig. 5 and can be explained as follows:

The film coating process was uniform and complete. In contact to aqueous medium, the hypromellose from the film coat hydrates and gets dissolved/leached in aqueous medium leaving behind a porous barrier (32–37). The water penetrates through the pores of film coat into the tablet matrix due to capillary action of the hypromellose and microcrystalline cellulose and the tablet core starts swelling. With the lapsed time, more pores are generated in the film which facilitates more and more water ingress through the pores. Further, the edge of tablets receives the least amount of coating deposition during the coating process and therefore is the weakest area of the film coat (38,39). The tablet volume expands due to swelling of the hypromellose and the film coat weakens, eventually cracking at the edges of the tablets. The coat started detaching at the edges of the tablets. More drug release was facilitated from this exposed area. With elapsed time, the lateral side of the coat detached from the core while leaving behind the tightly bound layer of the film coat on the top, bottom, and lateral sides of the core tablets. The drug release remains continued from the exposed area by diffusion and erosion mechanism (40–47). Further, tablets started losing definite geometry and became soft, palpable with the film coat still attached randomly to it. The pieces of the film coat were large or small at different places. This controlled the drug release over a long period of 24 h. This phenomenon was observed in the dissolution apparatus. But this phenomenon did not happen in *in vivo* due to cyclic pattern of gastric motility in interdigestive (fasted) as well as digestive (fed) state. The cyclic pattern of motility was characterized as phase I, II, III, IV, which involves the quiescent period with no contractions and electrical activities, random spike or intermittent contractions, regular bursts or contractions at the maximum frequency which travels distally and transition to normal phase respectively. These motions are of high frequency. Therefore, in *in vivo*, the film coat was not attached to the tablet surface and the entire release was governed by the matrix tablets itself. As RH is a highly soluble compound; the rate of release from the dosage form determined the absorption over the entire stretch of gastrointestinal tract.

Pharmacokinetic Study

The pharmacokinetic studies are very important to have the correlation between the drug release and therapeutic efficacy. It was decided to evaluate the formulations F8A and F9A by pharmacokinetic studies. FDA has recommended to test developed formulations which differ at least by 10% release to

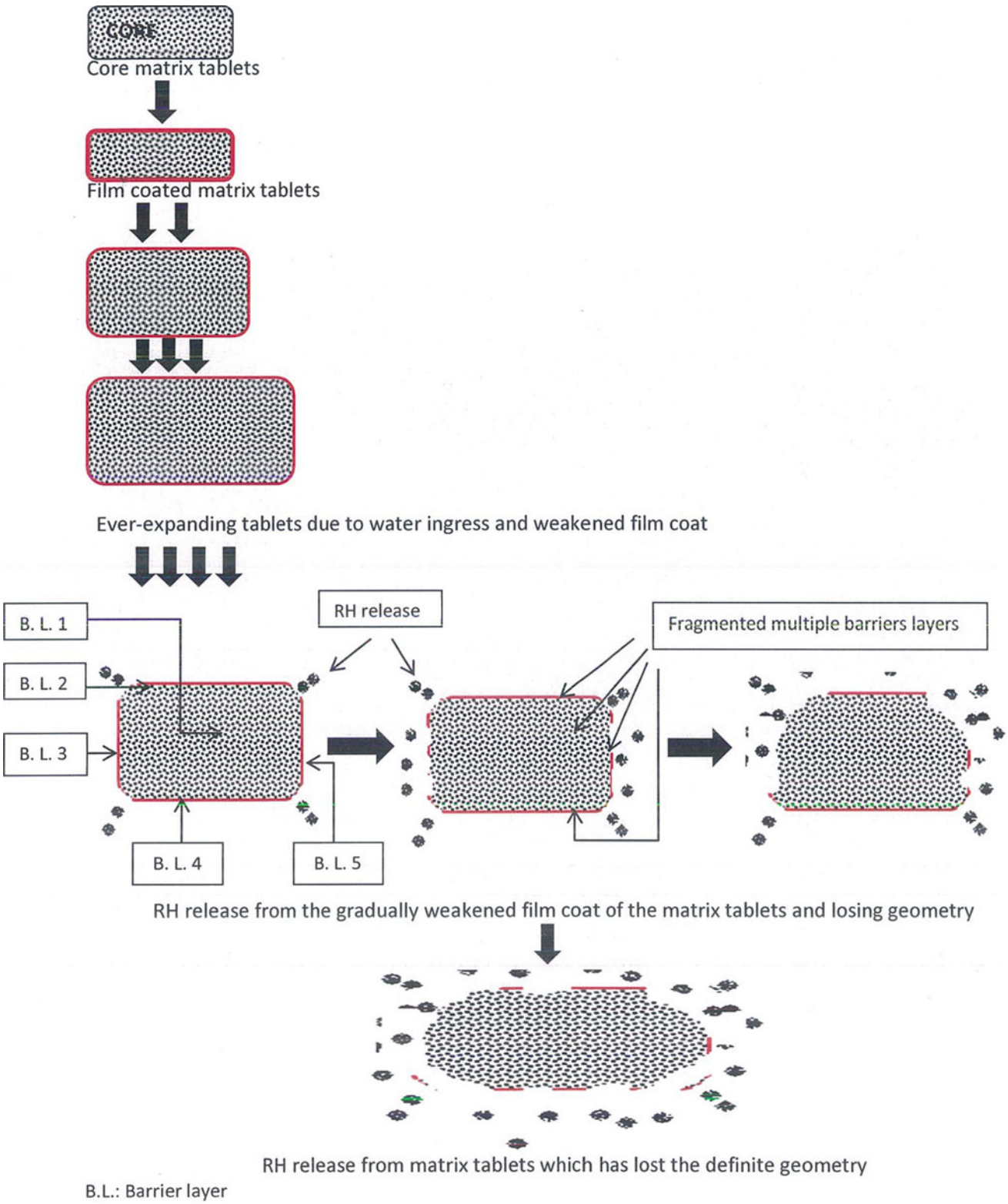

Fig. 5. Schematic representation of RH release

establish the IVIVC (48). A different approach was adopted by evaluating two different formulations of the same drug release profiles using the same manufacturing technology. These two formulations contained hypromellose 100,000 cP and 4000 cP, respectively which represented the extremes of commercially available viscosity grades used in the formulation development. It was expected that the hypromellose of viscosity 100,000 cP would give better control over RH release *in vitro* as well as *in vivo* and absorption as compared to 4,000 cP viscosity in *in vivo* due to greater viscosity.

Rapid RH release and absorption *in vivo* from formulation F8A was due to a longer hydration time required by the

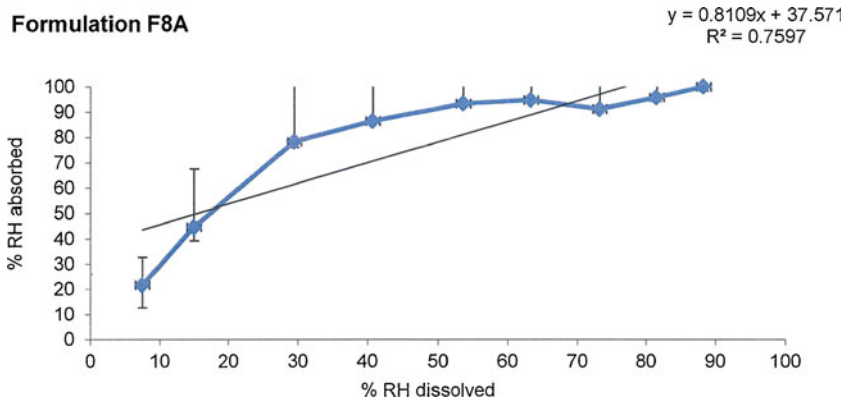

Fig. 6. Level A IVIVC correlation of formulation F8A by using Wagner–Nelson method

hypromellose of viscosity 100,000 cP. RH release was not controlled over extended period of time due to insufficient hydration of the polymer and inadequate barrier. This led to early C_{max} level or dose dumping in *in vivo* from the formulation and early elimination. This was effectively reflected in the AUC_{0-t} and $AUC_{0-\infty}$ in comparison to Requip® XL™. The mean values of individual subjects are given in Table V.

In case of formulation F9A, the RH release in *in vitro* was similar to Requip® XL™ and F8A. The RH release in *in vivo* was relatively slow in comparison to F8A. The slow RH release and absorption in *in vivo* was due to rapid hydration of the hypromellose of viscosity 4,000 cP in *in vivo*. Due to adequate hydrogel formation, sufficient barrier to release RH over the extended period of time was formed. This led to delay in T_{max} in comparison to F8A and delayed the early elimination. This was also effectively reflected in the AUC_{0-t}, and $AUC_{0-\infty}$ in comparison to Requip® XL™.

Despite the significant differences in the C_{max} of both the formulations F8A and F9A, AUC_{0-t}, $AUC_{0-\infty}$ were closer. This indicates that the extent of absorption was similar and independent of polymer type, drug release, and soluble/insoluble excipients. In two separate crossover studies, a difference in the pharmacokinetic parameters of Requip® XL™ was also observed. The mean RH level of 536.033 pg h/mL at 2 h and 254.794 pg h/mL at 30 h of formulation F8A and 444.550 pg h/mL at 2 h and 349.690 pg h/mL at 30 h of formulation F9A were observed. In Requip® XL™ , the mean plasma level of 569.957 pg h/mL at 2 h and 306.812 pg h/mL at 30 h and 313.931 pg h/mL at 2 h and 185.623 pg h/mL at 30 h were observed in both the pharmacokinetic studies. The RH absorption in both test formulations F8A and F9A differed significantly despite the closer T_{max} of 5.0 and 5.75 h, respectively, irrespective of the same formulation technology with the exception hypromellose viscosity. This concluded that the hypromellose viscosity is a major influencing variable in deciding the RH behavior *in vivo*. The T_{max} of 8 and 9 h of Requip® XL™ in two different pharmacokinetic studies had shown the different behavior. The half-life of 11.12 and 9.75 h of formulation F8A and F9A respectively and 6.55 and 5.80 h in Requip® XL™ in both different studies was observed. Therefore, RH being absorbed over a fairly long period of time throughout the gastrointestinal tract is proved (Figs. 3 and 4). Further, the study on 12 subjects in each of the study was sufficient to understand the pharmacokinetic aspects of the various RH formulations. The current emphasis was to also establish statistical *in vitro–in vivo* correlation. The level A correlation provides point to point relationship between *in vitro* dissolution and *in vivo* dissolution of the drug from the dosage form and is generally linear.

IVIVC for the formulation F8A and F9A was attempted by using the most meaningful level A correlation by deconvolution method. Wagner–Nelson method was adopted (49).

$$\% \text{ Absorbed} = (K_{el} \times AUC_{0\text{-}t} + Ct) \Big/ K_{el} \times AUC_{0\text{-}\infty}$$

Where K_{el} is the elimination rate constant for RH, AUC_{0-t} in picograms per milliliter is area under curve up to time t, Ct in picograms per milliliter is plasma concentration at

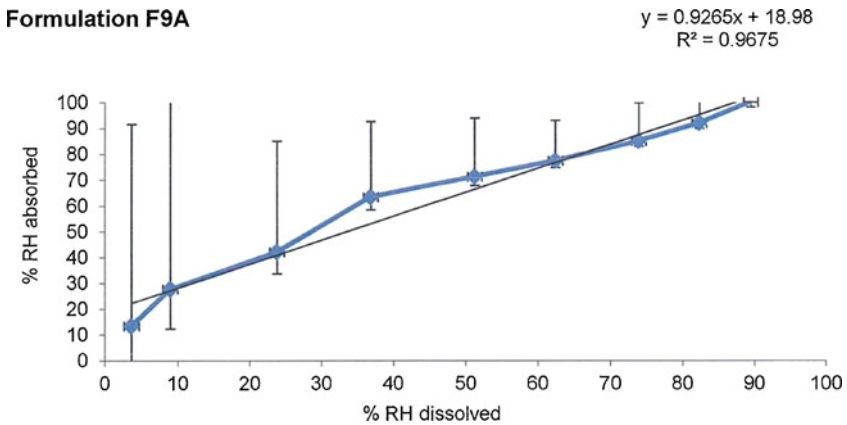

Fig. 7. Level A IVIVC correlation of formulation F9A by using Wagner–Nelson method

time t in h and $AUC_{0-\infty}$ in picograms per milliliter is area under curve up to time ∞ in h. This was done by a two-stage procedure: deconvolution followed by comparison of the fraction of RH absorbed to the fraction of RH dissolved. The graphical representation is shown in Figs. 6 and 7. In this, %RH absorbed as dependent factor was plotted against the independent factor %RH dissolved. Even though both the formulations had shown similarity factor more than 50 among themselves as well as with Requip® XL™, the *in vivo* observations were different. The above outcomes were supported by the correlation coefficient of 0.759 and 0.967 of F8A and F9A respectively. This study confirmed that f_2 factor matching does not necessarily mean the therapeutic equivalency of the various formulations unless evaluated in *in vivo*. Further, it was also concluded that dissolution conditions using citrate buffer pH 4.0 is suitable for establishing the IVIVC using level A method.

CONCLUSIONS

The burst release of ropinirole hydrochloride *in vitro* and dose dumping *in vivo* was effectively controlled due to synergistic effect of uniquely formed multiple barrier layers by leaching of the hypromellose, followed by cracks developed in eroding ethylcellulose–hypromellose film coat at the tablet edge and diffusion–erosion of hydrated hypromellose of the core tablets. Even though the similarity factor (f_2) was more than 50 among the tested formulations of F8A, F9A as well as with Requip® XL™, a significant difference in C_{max} level of ropinirole hydrochloride formulation F8A and F9A was observed due to different hypromellose viscosity used in core tablets even though overall release mechanism was same. The level A correlation using Wagner–Nelson method supported the findings where R^2 was found to be 0.7597 and 0.9675, respectively, for formulations F8A and F9A. Thus, pharmacokinetic study is mandatory to understand consequences of formulation technology and its component even though the f_2 factor is $\geq$50.

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