

EXTENDED RELEASE ROPINIROLE TABLET FORMULATION PREPARED BY MELT GRANULATION TECHNIQUE

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ABSTRACT

The present work was aimed to develop an extended release matrix tablet formulation of Ropinirole hydrochloride (ROH) using polymers like polyox WSR 301, carbopol 71G, kollicoat SR 30 D and waxes like cetyl alcohol (CA), carnauba wax (CW), glyceryl monostearate (GMS). Wet granulation, direct compression and melt granulation techniques were adopted for tableting of ROH using aforesaid excipients. The granules were evaluated for micromeritic properties and tablets evaluated for weight variation, hardness, friability, drug content and in-vitro drug release. The granules showed satisfactory flow and acceptable pharmacotechnical properties, whereas, tablets demonstrated compliance with compendial requirements. Results of dissolution studies showed that matrices containing polyox WSR 301 and carbopol 71G prepared by direct compression and kollicoat SR 30 D (wet granulated) could not sustain the release of ROH effectively. However, hybrid matrix formulation (melt granulated) having different proportions of ROH: wax and polyox WSR 301 exhibited satisfactory release profile. Especially, formulation F6 (drug: CA; 1:5), F8 (drug: CW; 1:2), F10 (drug: GMS; 1:5) could extend ROH release for >20 hrs following zero order release with R^2 0.974, 0.966, 0.948 respectively. In conclusion, melt granulation using polyox WSR 301 showed potential to develop extended release tablets of ROH, necessitating scale-up studies.

Keywords: Ropinirole hydrochloride, Release retarding polymers, Polyox WSR 301, Melt granulation, Wax.

INTRODUCTION

Ropinirole hydrochloride (ROH) is an anti-parkinsonian agent, selective dopamine D_2 -receptor agonist, widely used in the treatment of Parkinson's disease and restless legs syndrome^{1,2}. It is water soluble drug (solubility, 133mg/ml in water and above 100mg/ml in various buffer solutions of pH range 1.2-10) getting rapidly absorbed from the gastrointestinal tract after oral administration, reaching peak plasma concentration in approximately 1-2 hours. However, its elimination half-life in humans is short ($t_{1/2} = 6$ h) and therapeutic dose needs to be administered three times a day. To reduce the dosing frequency and improve patient compliance, extended-release (ER) formulations of ROH are desirable, which will release drug for 24 hours³.

The literature survey on ROH has revealed its formulation as nanoemulsions (Azeem et al, AAPS, 2009), nanoparticles (Vinay kumar et al, AAPS Annual Meet, 2008) and ER microspheres (Avachat et al, AAPS Annual Meet, 2009). Attempts to enhance drug flux/permeation by iontophoretic delivery of ROH have been noted (Luzardo-Alvarez et al, Pharmaceutical Research, 2001). Recently, Upadhyay et al have formulated ER tablet formulation employing ethyl cellulose and hypromellose polymer coat (ER coat) on drug loaded core consisting of lactose monohydrate etc. In vitro dissolution studies have demonstrated drug release up to 24 hours. Another work on ROH tablet formulation depicts preparation of multilayered (trilayer) tablet formulation of ROH, extending release for 24 hours⁴. Means, the present formulations and technology are a bit complex and cumbersome; hence, the need has been felt to have ER formulation of ROH, which is quiet simple, consistent and reproducible. Fortunately, all these attributes can be met with simple matrix tablets.

In present work, commonly used methods of extending the drug release, like preparation of matrix system of hydrophilic and lipophilic polymers or hydrophobic waxes have been adopted^{5, 6}. ROH matrix tablets have been prepared using various polymers like polyox WSR 301⁷, carbopol 71G⁸, kollicoat SR 30 D⁹ and waxes like cetyl alcohol, glyceryl monostearate, carnauba wax¹⁰. Wet granulation of ROH using polymer kollicoat SR 30 D, direct compression using polyox WSR 301 and carbopol 71G and melt granulation using drug: wax in combination with polyox WSR 301 has been carried out. Drug release kinetics from tablet matrices has been explained with the help of mathematical models. Zero-order equation, first-order equation, Higuchi equation and Korsmeyer-

Peppas simple exponential equation models are used to elucidate the mode of release from matrices¹¹.

MATERIALS AND METHODS

Materials

Ropinirole hydrochloride was provided by Sandoz Pharmaceutical Ltd. (Mumbai, India) as a gift sample. Kollicoat SR 30D (KSR), polyox WSR 301 and carbopol 71G were obtained as a gift samples from BASF India Ltd. (Mumbai, India), Colorcon (Mumbai, India) and Lubrizol Advanced Materials (Mumbai, India) respectively. Microcrystalline cellulose (MCC), anhydrous dibasic calcium phosphate (ADCP), glyceryl monostearate were procured from SD fine chemicals, Mumbai (India). Cetyl alcohol, carnauba wax, colloidal silicon dioxide (CSD) and magnesium stearate (MS) were of analytical grade. All other chemicals and reagents used in the study were of analytical grade.

Methods

ROH extended release tablets were prepared by direct compression, wet and melt granulation of powder blend of ROH along with various excipients like polyox WSR 301, carbopol 71G, kollicoat SR 30 D, cetyl alcohol, glyceryl monostearate, and carnauba wax. A total ten number of batches were prepared (F1 to F10) and details of compression process have been described subsequently.

Direct compression

All ingredients of tablet formulation, F1 and F2, as given in Table 1, were sifted through # ASTM 40 sieve. ROH was mixed with MCC, anhydrous dibasic calcium phosphate, colloidal silicon dioxide and 30 % w/w of polymers i.e. polyox WSR 301 or carbopol 71G and then lubricated with 0.5 % w/w of magnesium stearate. The lubricated blend obtained was subjected to tableting.

Wet granulation

All ingredients of tablet formulation, F3 and F4, as given in Table 1, were sifted through # ASTM 40 sieve. ROH, MCC and anhydrous dibasic calcium phosphate were mixed and granulation was done with Kollicoat SR 30D (15% and 25% w/w) followed by drying in hot air oven at 50°C to achieve LOD of not more than 1.5% w/w. Dried granules were passed through a 22 mesh sieve and the collected granules were further lubricated with colloidal silicon dioxide and 0.5 % w/w of magnesium stearate and subjected to compression.

Melt granulation technique

Waxes i.e., CA, CW and GMS were melted on a water bath at temperature higher than their melting points (approximately 52°C for CA, 90°C for CW, 70°C for GMS). To the molten mass, ROH was gradually added with continuous stirring and whole mass was allowed to cool to ambient temperature. The cooled waxy mass was passed through a 22 mesh sieve and to it pre-sifted (through 40

mesh) MCC, anhydrous dibasic calcium phosphate and selected polymers were added in the proportion given in table no. 1 and then mixed. The resultant blend was lubricated with pre-sifted colloidal silicon dioxide and 0.5 % w/w magnesium stearate and subjected to compression.

Total six tablet formulations (F5 to F10), were manufactured using different proportions of ROH and waxes as stated in table 1.

Table 1: Composition of Ropinirole ER tablets

Formulation Code	ROH	MCC	ADCP	KSR	Polyox WSR 301	Carbopol 71G	CA (wax)	CW (wax)	GMS (wax)	CSD	MS
F1	9.1	36.8	23.3	-	30	-	-	-	-	0.5	0.3
F2	9.1	36.8	23.3	-	-	30	-	-	-	0.5	0.3
F3	9.1	51.8	23.3	15	-	-	-	-	-	0.5	0.3
F4	9.1	41.8	23.3	25	-	-	-	-	-	0.5	0.3
F5	9.1	32.7	23.3	-	25	-	9.1	-	-	0.5	0.3
F6	9.1	2.8	16.7	-	25	-	45.6	-	-	0.5	0.3
F7	9.1	32.7	23.3	-	25	-	-	9.1	-	0.5	0.3
F8	9.1	23.5	23.3	-	25	-	-	18.3	-	0.5	0.3
F9	9.1	32.7	23.3	-	25	-	-	-	9.1	0.5	0.3
F10	9.1	2.8	16.7	-	25	-	-	-	45.6	0.5	0.3

All values are expressed as percent of tablet weight

Micromeritic properties of lubricated blend

The bulk density (BD) and tapped density (TD)¹² of lubricated blend were determined by tap density tester USP (Campbell Electronics, India). The data was subsequently processed to get Hausner's ratio and compressibility index¹³. The flowability of the granules was determined by measuring the angle of repose (θ) using fixed funnel free standing cone method¹².

Preparation and Evaluation of tablets

All powder blend and granules were compressed by using 7 mm round flat, bevelled tooling on single rotary compression machine (Mini press II MT, Karnavati engineering, Gujarat, India). The composition of the tablets with their codes is given in Table 1. Evaluation of tablets was carried out for all batches for the tests given below.

Tablet weight variation

10 tablets were randomly selected from a batch of 250 tablets and accurately weighed using an electronic balance (AUX-220, Shimadzu) and results were expressed as mean of 10 tablet weight values.

Tablet thickness

Thickness of 10 randomly selected tablets was determined using Vernier callipers (Mitutoyo, India) and the average values of 10 tablets were calculated.

Tablet hardness

The hardness of 10 randomly selected tablets was determined using Monsanto hardness tester (Cad-mach, Ahmedabad, India). Results were calculated as mean of 10 tablet hardness values.

Tablet Friability

According to pharmacopoeial specifications, 6.5 g tablets were subjected to tablet friability test using Roche friabilator (Campbell Electronics, Mumbai, India). The drum was adjusted to rotate 100 times in 4 min after which the tablets were removed from the drum, dedusted and accurately weighed. The percent weight loss was calculated. The test was run twice for each tablet formulation¹⁴.

Drug content

Ten tablets of each formulation (F1 to F10) were weighed individually, crushed in porcelain mortar. Powder equivalent to 10 mg of ROH was transferred to distilled water and subsequently extracted. The fine dispersion was filtered through a 0.45 μ whatman

filter paper and filtrate was assayed spectrophotometrically using UV visible spectrophotometer (lambda 25, Perkin- Elmer) at λ_{max} of 250 nm after appropriate dilution with water¹⁵.

In-vitro ROH release kinetics

In-vitro drug release of ROH tablet formulations was carried out using USP type II dissolution test apparatus (TDT-08L, Electro lab, India) at 100 rpm in 900 ml of citrate buffer (pH 4.0) at 37°C \pm 0.5°C. Multi-point dissolution profiles were obtained over 24 hours and percent drug release was calculated from absorbance determined spectrophotometrically at λ_{max} of 250nm. The dissolution data analysis was carried out using PCP Disso v2.08 software (Poona college of Pharmacy, Pune, India) which studies mechanism of drug release from the prepared matrix tablets using zero order ($Q_t = Q_0 + K_0 t$), first order ($\ln Q_t = \ln Q_0 + K_1 t$), Higuchi ($Q_t = K_H \sqrt{t}$), and Korsmeyer-Peppas ($Q_t/Q_\infty = K_k t^n$) equations¹⁶.

RESULTS AND DISCUSSION

Design of extended release formulation requires numerous manufacturing process considerations along with appropriate selection of excipients. Being the simplest and economical method for tablet manufacturing, initial development of ROH extended release tablet was started with direct compression method. Since extended release was not obtained with direct compression method, wet granulation trials were carried out with Kollicoat SR 30D which also failed to give desired release pattern over the period of time. But, melt granulation technique using waxes could achieve it.

Micromeritic properties of lubricated blend

Angle of repose (θ), compressibility index and Hausner's ratio have been used frequently to study the flowability of blend. Results of BD and TD ranged from 0.368 g/ml \pm 0.01 to 0.477g/ml \pm 0.005 and 0.447 g/ml \pm 0.01 to 0.551 g/ml \pm 0.01. Results of angle of repose and compressibility index ranged from 14.27 $^\circ$ to 22.54 $^\circ$, and 12.4 % to 22.22%. HR values of all formulations (F1 to F10) were < 1.3, evidence of blends having excellent flowability. There was no difference observed in the values of CI and θ for all batches studied (Table 2)

Evaluation of tablets

The results of analysis of physico-chemical properties of the manufactured tablets have been shown in Table 3. Weight and thickness of the formulations ranged from 146.73mg \pm 0.034 to 152.2 mg \pm 0.028 and from 3.04 mm \pm 0.009 to 3.22 mm \pm 0.009, respectively. Tablet hardness and friability are measures of tablet strength. In the present study, the percentage friability for all the

formulations was found to be below 1% w/w and tablet hardness ranged from 4 to 5 kg/cm². The drug content was found to be uniform amongst different batches of tablets and ranged from 95.9% ± 0.3 to

101.75% ± 0.15. All the tablet formulations showed acceptable pharmaco-technical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability.

Table 2: Micromeritic properties of lubricated blend of Ropinirole

Formulation Code	Bulk density(g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner ratio	Angle of repose (°)
F1	0.426 (0.004)	0.496 (0.004)	14.11 (0.173)	1.16 (0.002)	14.31(0.04)
F2	0.401 (0.030)	0.483 (0.03)	17.04 (0.212)	1.21(0.003)	22.54 (0.05)
F3	0.477 (0.005)	0.551 (0.01)	13.42 (0.333)	1.16(0.004)	14.75(0.03)
F4	0.378 (0.010)	0.486 (0.01)	22.22 (0.364)	1.29 (0.006)	16.68 (0.08)
F5	0.400 (0.010)	0.480 (0.01)	16.66 (0.324)	1.20 (0.005)	22.23 (0.09)
F6	0.368 (0.010)	0.447 (0.01)	17.61 (0.196)	1.21 (0.003)	18.51 (0.05)
F7	0.398 (0.020)	0.466 (0.02)	14.53 (0.213)	1.17 (0.003)	14.27(0.03)
F8	0.405 (0.020)	0.462 (0.02)	12.40 (0.087)	1.14 (0.001)	20.17 (0.08)
F9	0.412 (0.010)	0.468 (0.01)	11.97 (0.448)	1.14 (0.006)	19.35 (0.05)
F10	0.404 (0.010)	0.469 (0.01)	13.87 (0.280)	1.16 (0.004)	15.10 (0.05)

Table 3: Physico-chemical properties of Ropinirole ER tablets

Code	Average weight* Mg (+ SD)	Thickness* (mm)	Hardness* kg/cm ²	Friability# (%w/w)	% Assay#
F1	146.73 (0.34)	3.12 (0.007)	4.1 (0.16)	0.56 (0.05)	97.0 (0.50)
F2	148.77 (0.57)	3.22 (0.009)	5.0 (0.24)	0.68 (0.05)	95.9 (0.30)
F3	150.12 (0.28)	3.22 (0.007)	4.2 (0.34)	0.21 (0.02)	100.85 (0.35)
F4	150.45 (0.46)	3.20 (0.004)	5.1 (0.21)	0.18 (0.02)	99.05 (0.45)
F5	149.22 (0.33)	3.20 (0.003)	4.0 (0.16)	0.44 (0.02)	96.65 (0.25)
F6	152.20 (0.28)	3.18 (0.007)	5.1 (0.32)	0.34 (0.03)	98.87 (0.23)
F7	148.18 (0.29)	3.20 (0.003)	4.9 (0.21)	0.33 (0.04)	99.36 (0.10)
F8	150.90 (0.26)	3.22 (0.005)	5.0 (0.16)	0.19 (0.01)	101.75 (0.15)
F9	150.0 (0.25)	3.04 (0.009)	5.0 (0.28)	0.48 (0.03)	96.78 (0.08)
F10	148.98 (0.40)	3.18 (0.007)	5.2 (0.34)	0.30 (0.04)	99.32 (0.43)

*n=10, # n=2

In vitro release

A suitable sustained-release formulation should release the required amount of drug in the initial hour, followed by slow release to achieve desired release pattern. The drug release mechanism is a dynamic process controlled by several variables. Few systems release drug by either purely diffusion or erosion controlled while other systems exhibit a combination of these mechanisms^{17,18}. The target release profile for sustained release product has been reported as follows: After 1 h: 0-15%; After 4 h: 25-50%; After 9 h: 50-75% and 24 hrs: NLT 85 %¹⁹.

In vitro study of tablets prepared by direct compression (F1 and F2) showed burst release in initial hours while extended release profile has been observed in tablets prepared by wet granulation method. In direct compression method, preliminary experiments carried out with 20% and 25 % w/w concentration of Polyox

WSR 301 and carbopol 71G showed burst drug release pattern. Further batches containing 30 % w/w concentration (F1 and F2) of both polymers also showed similar release pattern in which 65-70 % ROH was released within 2 hrs as shown in Figure 1. This burst release is probably due to faster dissolution of the highly water-soluble drug from the core tablet and its diffusion out of the matrix though the pores formed for the entry of solvent molecules. In wet granulation, initial experiments conducted with 10%, 15% and 20% w/w of Kollicoat SR 30D showed that 50- 65 % drug was rapidly released within 1 hr. However, tablet containing 25 % w/w Kollicoat SR 30D showed 41% drug release in 1 hr which was further retarded upto 24 hrs to release 86 % of drug. Since, initial burst release and deviations in the release profile were observed in previous formulations (F1 to F4) there is need for further development of formulation to mimic the desired release pattern.

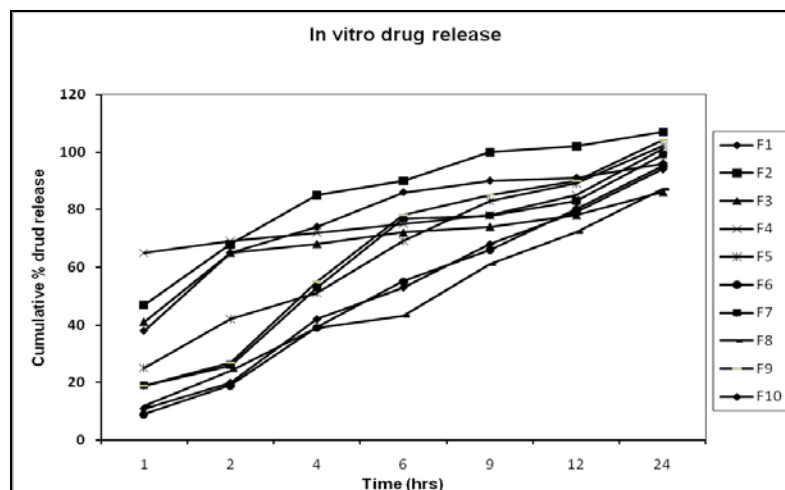


Fig. 1: Cumulative % drug release of formulations F1-F10

Conclusively, use of single polymer by either direct compression or wet granulation method is not adequate to prepare extended release drug matrices of ROH. Therefore, to control initial burst drug release from matrices and to achieve desired release pattern, melt granulation technique has been used to prepare hybrid matrices. Preliminary experiments carried out showed encouraging results with polyox WSR 301 than carbopol 71G with various proportions of cetyl alcohol. Amongst these formulations, the release rate was observed in the following order: Drug: CA (1:1) > Drug: CA (1:2) > Drug: CA (1:3) > Drug: CA (1:5), indicating decrease in release rate with increase in the lipophilicity of matrices. This can be explained by decrease in the wettability of matrices which further reduces rate of water penetration into the matrix and hence sustained drug release. Subsequent ROH tablets formulated with polyox WSR 301 and other waxes like CW and GMS showed sustained drug release pattern as shown in table 1. It was observed that formulation containing 1:5 ratio of drug: CA (F6), 1:2 ratio of drug: CW and 1:5 ratio of drug: GMS gave desired release profile over the period of 24 hrs as compared to other drug: waxes ratio studied.

The ROH release from the prepared matrices showed zero order release. The correlation coefficient (R^2) obtained for the batches F6, F8, F10 were 0.974, 0.966 and 0.948 respectively. The data output of the PCP disso software showed zero order as a best fit model.

CONCLUSION

The hydrophilic matrices of polymers like Polyox WSR 301, carbopol 71G and Kollicoat SR 30D alone could not control Ropinirole release effectively up to 24 hours. It is evident that Ropinirole hybrid matrix tablets prepared by combination of Polyox WSR 301 with various waxes could extend drug release for more than 20 hrs. Optimised formulations containing 1:5 ratio of drug:CA, 1:2 ratio of drug: CW, 1:5 ratio of drug: GMS along with 25 % polyox WSR 301 showed zero order release and hence can be considered promising, necessitating need of scale up studies. Subsequent studies on scale-up will focus on factors which may impact product quality and performance.

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REFERENCES

- Adler CH, Sethi KD, Hauser RA. Ropinirole for the treatment of early Parkinson's disease. *Neurology* 1997; 49:393-399.
- Tulloch IF. Pharmacologic profile of Ropinirole: a nonergoline dopamine agonist. *Neurology* 1997; 49 Suppl 1:S58-62.
- GlaxoSmithKline Ltd. Requip (Ropinirole hydrochloride) tablets prescribing information NDA 20-658/S-020, S-018 and S-021. Research Triangle Park, NC, USA; 2007.
- Atkinson GF; SmithKline Beecham Corporation. Use of Multi-layer Controlled Release tablet comprising Ropinirole. United States patent US 20040247676. 2004.
- Lordi GN. Sustained release dosage forms. In: Lachman L, Liberman HA, Kanig JL, editors. *The Theory and Practice of Industrial Pharmacy*. Mumbai, India: Varghese Publishing House; 1987. p. 430-456.
- Timmins P, Dennis BA, Vyas KA. Bristol-Myers Squibb Co. Biophasic Controlled Release Delivery Systems for High Solubility Pharmaceuticals and Method. United States patent US 6475521. 2002.
- Cappello B, Del Nobile MA, La Rotonda MI, Mensitieri G, Miro A, Nicolais L. Water soluble drug delivery systems based on a non-biological bioadhesive polymeric system. *Farmaco* 1994; 49(12):809-818.
- Jelena P, Djuric Z, Jovanovic M, Ibric S, Kilibarda V, Jovanovic D, Evic IK. Biopharmaceutical characterization of sustained release matrix tablets based on novel carbomer polymers: formulation and in vivo investigation; *Eur J Drug Metab Pharmacokinet* 2005; 30(1-2):99-104.
- Shao Z, Moralesi L, Diaz S, Mohammadi N. Drug Release From Kollicoat SR 30D- Coated Nonpareil Beads: Evaluation of Coating Level, Plasticizer Type, and Curing Condition. *AAPS PharmSciTech* 2002; 3(2): article 15.
- Abdelbary GA, Tadros MI. Design and in vitro/in vivo evaluation of novel nicorandil extended release matrix tablets based on hydrophilic interpolymer complexes and a hydrophobic waxy polymer. *Eur J Pharm Biopharm* 2008;69(3):1019-1028.
- Paulo C, Lobo JMS. Modelling and comparison of dissolution profiles. *Eur. J. Pharm. Sci* 2001; 13:123-133.
- Cooper J, Gunn C. Powder flow and compaction. *Tutorial Pharmacy*. New Delhi, India: CBS Publishers and Distributors; 1986. p. 211-233.
- Aulton ME, Wells TI. *Pharmaceutics: The science of dosage form design*. London, England: Churchill Livingstone; 1998. p. 647-649.
- The British Pharmacopoeia, British Pharmacopoeia Commission, HMSO, London. 2008
- Shete Y, Pimpodkar N, Nalawade RS, Pore YV and Kuchekar BS. Spectrophotometric Estimation of Ropinirole Hydrochloride in Tablets. *Indian Journal of Pharmaceutical Sciences* 2009; 71(1): 61-62.
- Korsmeyer RW, Gurny R, Docler E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm* 1983; 15:25-35.
- Mandal U, Gowda V, Ghosh A, Selvan S, Formulation and optimization of sustained release matrix Tablet of Metformin Hcl 500mg using surface response technology. *The Pharmaceutical society of Japan* 2007; 127(8):1281-1290.
- Chavhan S, Anantwar S, Derle D. Design and Evaluation of once daily sustained release matrix tablets of Nicorandil. *International Journal of Pharmacy and Pharmaceutical Sciences* 2011; 3 (2): 13- 18.
- Upadhyay A, Bang G, Malewar N, Avachat M. Lupin Ltd. Novel controlled release compositions of Ropinirole. WO2010/023693. 2010.