Bilayer tablets of Paliperidone for Extended release osmotic drug delivery

To cite this article: K Sunil Chowdary and A A Napoleon 2017 *IOP Conf. Ser.: Mater. Sci. Eng.* **263** 022020

IOP Conf. Series: Materials Science and Engineering **263** (2017) 022020 doi:10.1088/1757-899X/263/2/022020

Bilayer tablets of Paliperidone for Extended release osmotic drug delivery

K Sunil Chowdary and A A Napoleon
Chemistry Department, SAS, VIT University, Vellore - 632014, Tamil Nadu, India

E-mail : aanapoleon@vit.ac.in, napoleonaa@gmail.com

Abstract. The purpose of this study is to develop and optimize the formulation of paliperidone bilayer tablet core and coating which should meet *in vitro* performance of trilayered Innovator sample Invega. Optimization of core formulations prepared by different ratio of polyox grades and optimization of coating of (i) sub-coating build-up with hydroxy ethyl cellulose (HEC) and (ii).enteric coating build-up with cellulose acetate (CA). Some important influence factors such as different core tablet compositions and different coating solution ingredients involved in the formulation procedure were investigated. The optimization of formulation and process was conducted by comparing different in vitro release behaviours of Paliperidone. In vitro dissolution studies of Innovator sample (Invega) with formulations of different release rate which ever close release pattern during the whole 24 h test is finalized.

1. Introduction

OROS (Osmotic [Controlled] Release Oral [Delivery] System) is a progressed controlled delivery oral medication in a tablet form with a semi-porous external layer and at least one little laser penetrated openings in it. As the tablet goes through the body, water is assimilated through the semipermeable layer by means of osmosis, and the subsequent osmotic pressure is utilized to drive the dynamic medication through the opening(s) in the tablet. OROS is a trademarked name claimed by ALZA Corporation, which spearheaded the utilization of osmotic pumps for oral medication release. [1-3]. In order to achieve a high pressure and procure a smooth release for the poor solubility drugs such as the former model drug PAL, Malaterre carried out the pushe pull osmotic pump (PPOP) which consists of a bi-layer core encircled by a semipermeable membrane with a laser-pierced orifice [4]. The boost layer polymer swelled and the drug suspension was driven out through the release orifice.

Among the PPOP showed great advantages which could not only provide a steady and slow drug release rate avoiding the high initial plasma concentration to keep effective, tolerant and safe, but also maintain a smooth, controlled and prolonged therapeutic window decreasing the adverse effects and drug excitation and improving the compliance [5]. The commercial product Invega® (6 mg) which was chosen as the reference preparation in this study is a tri-layer ascending release tablet [6]. When it comes to the coating of Osmotic Pump Tablet (OPT), different semipermeable membranes coating materials are in combination, such as cellulose acetate and hydroxy ethyl cellulose. The semipermeable membrane is an important aspect of the osmotic pump thanks to its role upon controlling the permeation rate of the water. Assumption that the same core tablets are prepared and coated with hydroxy ethyl cellulose and cellulose acetate respectively. Also, the in vitro dissolution

behaviors of the different ratio of semi permeable membrane coats of different percentage build-up studied and evaluated for proving the equivalence with Innovator sample.

2. Materials and methods

2.1. Materials

Paliperidone was synthesized by Mylan Laboratories Ltd, Telangana, India. Commercially available Paliperidone extended-release tablets Invega® (6 mg) which acted as the reference preparation in this study were purchased from ALZA Corporation, Mountain View, CA & Distributed by Janssen, L.P. Titusville, NJ., Povidone K30 by BASF, Butylated Hydroxytoluene by Merck, Polyethylene oxide (Polyox WSR N80K-LEO),(Polyox WSR Coagulant & (Polyox WSR 303-LEO) were a gift sample from Dow Europe GMBH, Ferric Oxide Red by Neelikon Food Dyes, Stearic Acid by Merck, Hydroxy ethyl Cellulose (Natrosol) by Ashland, Polyethylene Glycol from Dow, Houston, US, Stearic Acid by Merck Cellulose acetate (CA) was from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Acetone, ethanol and Sodium chloride (NaCl) were analytical grade. UPLC-grade methanol was purchased from Fisher Scientific (Pittsburgh, PA).

2.2. Design and theory of bilayer drug release oral osmotic tablet

OROS Push –Pull drug delivery system was designed to be a bilayer tablet. It consisted of an osmotically active bilayer core containing drug concentration layer and an osmotic push layer, surrounded by a hydroxy ethyl cellulose and cellulose acetate semipermeable membrane. Drug was released through a laser-drilled hole which stands on drug layer dome of the tablet. In the aqueous environment of the gastrointestinal tract (GIT), water is imbibed by osmosis activity gradient which controlled by osmotic excipients across the semipermeable membrane into the system core. The composition and thickness of the membrane also determined the rate of water absorbed to the core. Then the drug layer was hydrated, becoming a gel-like suspension and the push layer started to swell at the same time. As a result, the drug was driven out through the orifice by the expanding bottom layer. A theory can be used to describe the drug releasing process [7-9]. Generally, the drug release rate (dm=dt) of a single drug core and the volume imbibition rate of water (dv=dt) of oral osmotic tablet can be described like this:

$$\left(\frac{dm}{dt}\right) = \left(\frac{dv}{dt}\right) \cdot C_s \qquad (1)$$

$$\left(\frac{dv}{dt}\right) = \left(\frac{A}{h}\right) k\pi \qquad (2)$$

where Cs is the mass concentration of the drug in suspension, A is the membrane area, k is the osmotic membrane permeability, h is the membrane thickness, p is the osmotic pressure.

Kinetics of drug release

Zero order kinetics**:** Drug dissolution from pharmaceutical dosage form that does not disaggregate and drug release in slow manner represented by,

Wo-Wt =K0t Where,
Wo =Initial amount of drug concentration in solution.
Wt = Amount of drug release dissolved in time t.
K0t= Zero order rate constant.

At the point when the information was plotted as aggregate % release verses time, if the plot is directly linear then information obeys zero order kinetics with slope equivalent to Ko. This model speaks to a

perfect drug delivery profile keeping in mind the end goal to accomplish the delayed pharmacological activity. [10-11].

2.3. Preparation of the formulations

The formulation of core tablets was consisted of drug layer of paliperidone, Povidone K30, polyethylene oxide & stearic acid and Push layer of polyethylene oxide, sodium chloride, stearic acid and ferric oxide red. Active pharmaceutical ingredient (API) and all the excipients were passed through 40-mesh sieve before use, respectively. The drug layer blend was prepared by mixing paliperidone and other excipients in blender (white layer). The push layer blend was prepared by mixing all push layer excipients in blender (red color layer). Core tablets were compressed by a bilayer tablet machine (Eliza Press EP-400) equipped with a particular standard concave punch (7 mm diameter) (ACG Palm, India). The compress process was as follows: Firstly, drug layer follows push layer of red color get compress with hardness range of final tablet 7-9 killo pascals.

Compressed tablets continue for sub coating and follows enteric coating in optimization approach. Sub-caoting suspension prepared by adding hydroxy ethyl cellulose (HEC) & polyethylene glycol in purified water under stirring. Sub-coating build up carried for 3-5% of core tablet weight and optimized for further enteric coating process. Enteric coating suspension prepared by adding of cellulose acetate (CA) & polyethylene glycol in Acetone and purified water (95:5) under stirring. Enteric coating build up carried for 12-16% of sub-coat tablet weight and optimized the formulation. Coating process (both sub coating & enteric coating) carried by a traditional coating pan (Ganscoater-GAC-250).

Table 1: Summarized Paliperidone formulation details.

Ingredients	**P01**	**P02**	**P03**	**P04**	**P05**	**P06**	**P07**	**P08**	**P09**	**P10**
Drug Layer										
Paliperidone	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
Polyox WSR N 80 (200K)	88.40	88.40	88.40	88.40	88.40	88.40	88.40	88.40	88.40	88.40
Povidone K30	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
Butyl Hydroxy Toluene	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Stearic Acid	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Total Wt. (Drug Layer)	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***
Push Layer										
Polyox Coagulant	49.00	24.50	14.00	7.00	….	….	….	….	….	….
Polyox WSR 303	……	24.50	35.00	42.00	49.00	49.00	49.00	49.00	49.00	49.00
Sodium Chloride	49.80	49.80	49.80	49.80	49.80	49.80	49.80	49.80	49.80	49.80
Ferric Oxide Red	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Stearic Acid	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total Wt. (Push Layer)	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***
Total Weight (Core)	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**
Subcoating %	4%	4%	4%	4%	3%	4%	5%	4%	4%	4%
Hydroxy Ethyl Cellulose	7.2	7.2	7.2	7.2	5.4	7.2	9	7.2	7.2	7.2
Polyethylene Glycol 3350	0.8	0.8	0.8	0.8	0.6	0.8	1	0.8	0.8	0.8
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total Weight (Subcoated)	**208.00**	**208.00**	**208.00**	**208.00**	**206.00**	**208.00**	**210.00**	**208.00**	**208.00**	**208.00**
Cellulose Acetate Coat %	14%	14%	14%	14%	14%	14%	14%	12%	14%	16%
Cellulose Acetate	28.88	28.88	28.88	28.88	28.88	28.88	28.88	24.75	28.88	33.00
Polyethylene Glycol	0.289	0.289	0.289	0.289	0.289	0.289	0.289	0.248	0.289	0.33

3350										
Acetone: Water (97:3)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total Wt.(Cellulose Acetate)	**237.17**	**237.17**	**237.17**	**237.17**	**235.17**	**237.17**	**239.17**	**233.00**	**237.17**	**241.33**

For sub-coating maintain bed temperature at about 38～42^{0}C, rotating rate of the pan was 5～8 rpm, spraying rate was 5ml/min. For enteric coating maintain bed temperature at about 22～27^{0}C, rotating rate of the pan was 5～8 rpm, spraying rate was 15 ml/min. Under this circumstance, the core tablets & sub-coated tablets were sprayed and covered a homogeneous coating membrane of dissimilar material, respectively. To clear away the residual solvent and aging the membrane, the coating tablets were dried for 1 h at 40ºC in the coating pan for each coating in inching mode. Summarized paliperidone extended release tablets formulation details are compiled in Table 1. Comparative paliperidone extended release tablets Dissolution data of Time vs % drug release in Table 2.

3. Results and Discussion

The formulation of extended-release osmotic drug delivery by bilayer (PPOP) approach successfully achieved required dissolution (of Innovator) which matching & in similar approach in batch no. P06 and same is reproduced in batch no. P09. Here the final polymer in Push layer (49 mg/Tablet), sub-coating optimum percentage build-up (i.e 4%) and enteric coating optimum percentage build-up (i.e 14%) are key formulation optimized parameters which are giving reproducible results and dissolution matching with Innovator product (*In-vitro* approach). It is a cost effectiveness formulation.

Table 2: Comparative Paliperidone Dissolution data of Time vs % drug release

Dissolution In Modified SGF, pH 1.0 /media volume 500 ml/50 rpm speed/Paddle (USP – II) apparatus											
Time	**Innovator (15GG423)**	**Batch no. with dissolution data (% Drug Release)**									
		P01	**P02**	**P03**	**P04**	**P05**	**P06**	**P07**	**P08**	**P09**	**P10**
1 hr.	1	0	0	0	0	0	0	0	0	0	0
2 hr.	1	3	2	2	2	1	0	0	0	0	0
4 hr.	4	16	11	10	9	7	5	4	7	4	2
6 hr.	10	26	21	19	17	15	13	8	14	11	6
8 hr.	17	38	32	28	24	22	19	15	23	19	9
10 hr.	28	55	50	40	35	33	31	24	36	30	20
12 hr.	38	67	62	53	46	45	42	36	46	39	29
14 hr.	49	78	71	64	58	56	51	44	57	48	42
16 hr.	62	89	83	77	70	67	65	58	70	63	55
18 hr.	74	98	95	88	79	79	75	68	80	75	68
20 hr.	81	100	99	100	91	85	80	87	87	82	75
22 hr.	92	101	99	101	98	96	92	96	99	91	82
24 hr.	97	100	99	101	99	101	99	100	101	100	88

4. Conclusion

Presently, an extensive variety of medications are planned to develop as prolonged delivery systems. But, just those which result in a huge decrease in number of administrations, patient convenience and a decrease in toxicity from drug accumulation in the blood or gastrointestinal tract are probably going to enhance beneficial results. To be an effective prolonged delivery item, the medication must be

delivered from the dosage form at a foreordained rate, disintegrate in the gastrointestinal liquids, keep up adequate gastrointestinal residence time, and might be ingested at a rate and will supplant the extent of drug being eliminated.

Acknowledgments
The authors were honestly grateful to the administration of VIT University, Vellore, Tamil Nadu, India for their relentless inspiration, care and Mylan Laboratories Ltd, Telangana, India providing all the needed facilities for carrying out this study.

References

[1] Gurny N, 2009, Oral osmotically driven systems: 30 years of development and clinical use, *European Journal of Pharmaceutics and Biopharmaceutics.* **73** (3): 311–23.
[2] Theeuwes, F; Yum, S I, Haak R; Wong, P, 1991, Systems for triggered, pulsed and Programmed drug delivery, *Annals of the New York Academy of Sciences.* PP 428–440.
[3] Conley R, Gupta, S K, Sathyan, G, 2006, Clinical spectrum of the osmotic-controlled release oral delivery system (OROS), an advanced oral delivery form, *Current medical research and opinion*. **22** (10): 1879–92.
[4] Canuso C M, Schooler N, Carothers J, 2010, Paliperidone extended-release in schizoaffective disorder: a randomized, controlled study comparing a flexible dose with placebo in patients treated with and without antidepressants and/or mood stabilizers. *J. Clin Psychopharmacol*, **30**: 487-495.
[5] Owen R T, 2007, Extended-release paliperidone: efficacy, safety and tolerability profile of a new atypical antipsychotic. *Drugs Today*, **43**, 249-258.
[6] Janicak P G, Winans E A, 2007, Paliperidone ER-A review of the clinical trial data. *Neuro psychiatry.Treat*, **3**: 869-872.
[7] Michael J R, Jonathan H, Michel S R, 2003, Modified-release drug delivery technology, vol. 1, *CRC Press*; PP 110-130.
[8] Charman S A, Charman W N, 2002, Oral modified-release delivery systems. *Modified release drug delivery Tech*, **1,** PP 1-19.
[9] Ikegami K, Tagawa K, Osawa T, 2006, Bioavailability and in vivo release behaviour of controlled-release multiple-unit theophylline dosage forms in beagle dogs, cynomolgus monkeys and gottingen minipigs. *J Pharm Sci*, **95,** 1888-1895.
[10] Pundir S, Badola A, Sharma D, 2013, Sustained release matrix technology and recent advance in matrix drug delivery system- A review. *International Journal of Drug Research and Technology*, **3**(1), 12-20.
[11] Hadi Md. A, Lokeswara V B., Pal N, Rao S A, 2012, Formulation and evaluation of sustained release matrix tablets of montelukast sodium. *International Journal of pharmacy*, **2**(3), 574-582.