ISSN 2349-7203

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

HUMAN

Human Journals
Research Article
June 2015 Vol.:3, Issue:3

Dissolution Enhancement of Haloperidol Tablets using pH Modifier and Co-Solubilizer

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
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Submission: 7 June 2015
Accepted: 14 June 2015
Published: 25 June 2015

Keywords: Haloperidol, Solubility, Dissolution rate, pH modifier, Co-solubiliser

ABSTRACT

Improvement in solubility behavior is the most challenging aspect for various new chemical entities, more than 60% of these molecules exhibit poor solubility, leading to the unsatisfactory dissolution profile, consequently, the bioavailability. Haloperidol is butyrophenone series antipsychotics drug and belongs to BCS Class II. There are various techniques to enhance the solubility of the drug, such as particle size reduction, nanosuspension, use of surfactants, salt formation, pH modifier, solid dispersion etc. Various formulations of Haloperidol were tried using different combinations of citric acid as pH modifier, where 1:5 (Haloperidol: Citric acid) ratio showed maximum release of 84% in 3 h. When this ratio was employed with different concentrations of Propylene Glycol (PG) used as co-solubilizer, Haloperidol: citric acid: PG in the ratio of 1:5:0.6 showed the enhancement in drug release and was increased to 93% in 3 h. This formulation was found to be stable under accelerated stability conditions (40°±20 C and 75± 5% RH) for six months as per ICH guidelines.

INTRODUCTION

Haloperidol is widely used as antineuroleptic drug, chemically it is 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one and belongs to BCS class II drug. Govind K. et al. [1] and Sajal Kumar Jha et al. [2] had prepared the mouth disintegrating tablet using combination of superdisintegrats in different percentage. All the formulations had disintegration time less than 30 sec. Ravi kumar et. al.[3] had prepared melt in mouth tablet using camphor as subliming agent by sublimation technique. The disintegration time was 70 sec. A common approach to improve dissolution of a compound is by forming salts. Earlier work on improvement in dissolution rates by formation of pharmaceutical salts and its impact on bioavailability have been reviewed by Berge et al. [4]. Shoufeng Li et. al. [5] had prepared the Hydrochloride and Mesylate salts, it was observed that mesylate salt exhibit the higher solubility between pH 2 and 5 as compare to hydrochloride salt. Mesylate salt also showed higher dissolution due to common ion effect as compare to hydrochloride salt or base. Atul Ayur et. al. [6] had used citric acid in the ratio of 1:15 to 100, and in another examples malic acid in the ratio of 1:4 to 7, to improve the solubility of haloperidol. We have used citric acid in our formulations to improve the solubility due to the common ion effect and to further enhance the solubility PG was incorporated in the formulation as co-solubiliser.

MATERIALS AND METHODS

Materials

Haloperidol (RPG life science, Mumbai), citric acid (Vasa pharma chem., Beharmpura), microcrystalline cellulose (Ankit Pulps & Boards, Nagpur), cross carmellose sodium (Gujrat microwax, Ahmedabad), Maize starch (Universal starch-chem Allied, Dhule), colloidal anhydrous silica (Wacker chemi AG, Germany), magnesium stearate (VASA pharma chem., Beharmpura), purified talc (Ankit Pulps & Boards, Nagpur), titanium dioxide (Sachtleben chemie GmbH, Finland), dibutyl phthalate (KLJ plasticizer ltd., Daman), Eudragit L-100 (Vikram Thermo., Ahmedabad), isopropyl alcohol (E. Merk) and propylene glycol (Shell chemicals, Singapore). All other chemicals and reagents used were of analytical grade.

Methods

Preparation of Haloperidol Tablets by Wet granulation method

All dry mixing stage materials were sifted through sieve #40 were weighed and placed in RMG; PG was added in dry mixing stage (Table 1) and blended in RMG for about 15 min at 150 rpm. Starch paste was added to the above mixture and granulated in the rapid mixture granulator (PRISM Pharma, Mumbai) for 15 min. The granules obtained were dried in FLP (Chang zhou jiafa equipment, China) for 20 min. After milling and sifting through #16, lubricant and part of disintegrate were added in the lubrication stage and compressed to form tablets of 140 mg using 7 mm punches. All the tablets were placed in the pan coater and the coating solution was the sprayed over the tablets to provide the uniform coat. The coat deposition on tablets was 8%. The coating solution used, was prepared by dissolving Eudragit L-100 in isopropyl alcohol (2.5%) containing dibutyl phthalate, titanium dioxide and purified talc 0.5% each. Compositions of various formulations are shown in Table 1. The optimized batch was kept under Accelerated condition 40°C±2^0 C and 75% ± 5% RH.

Table 1: Formulations of Haloperidol Tablets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Dry mixing Stage	Quantity in mg						
Haloperidol	1	1	1	1	1	1	1
Citric acid	3	4	5	6	5	5	5
Microcrystalline Cellulose	16.7	15.7	14.7	13.7	15	14.7	14.3
Croscarmellose Sodium	3	3	3	3	3	3	3
Propylene Glycol	--	--	--	--	0.3	0.6	1
Binding Stage							
Maize Starch	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Lubrication Stage							
Croscarmellose Sodium	1.2	1.2	1.2	1.2	0.6	0.6	0.6
Colloidal anhydrous silica	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Magnesium Stearate	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Maize Starch	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Purified Talc	0.4	0.4	0.4	0.4	0.4	0.4	0.4

Evaluation

Pre-compression parameter

All the batches were evaluated for various parameters like bulk density, tapped density, Carr's compressibility index and Hausner ratio by conventional methods [7] (Table 2).

Post-compression parameter

All the batches were evaluated for various parameters like weight variation, hardness, drug content and *in vitro* dissolution test (Table 3).

Content uniformity test

Ten tablets were weighed and powdered, 10 mg equivalent of Haloperidol was weighed and dissolved in suitable quantity of methanol, the solution was filtered, suitably diluted and the drug content was analyzed using UV spectrometer at 254 nm.

In vitro dissolution test

Dissolution study was conducted using USP type-I apparatus (Electrolab), and the test was performed using 900 ml of 0.1 N HCl for 2 h and 900 ml of phosphate buffer pH 6.8 for next 1 h, at 100 rpm and 37±0.5°C. A 10 ml sample was withdrawn at 2 h and 3 h and filtered. The absorbance of the sample was measured at 254 nm after suitable dilution if necessary; using appropriate blank and the drug release was estimated (Table 3).

Stability Study

Samples from stability studies were withdrawn after 1, 2, 3 and 6 months and evaluated for appearance, drug content and drug release.

RESULTS AND DISCUSSION

The Haloperidol granules F1 to F4 were evaluated for their pre-compression parameters were found to have good flow properties (av. compressibility index 12.79% and Hausner ratio 1.14). Addition of PG adversely affect the above values., When the ratio of 1:5:1 PG was added compressibility index value has increase to 15.76% while the Hausner ratio value has increased to 1.18, indicating the retardation in flow properties of the granules.

Table 2: Physical Parameter of Haloperidol Granules

Formulation	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner ratio	Compressibility index (%)
F1	0.555	0.628	1.13	11.62
F2	0.555	0.632	1.13	12.18
F3	0.555	0.641	1.15	13.41
F4	0.555	0.645	1.16	13.95
F5	0.564	0.657	1.16	14.15
F6	0.561	0.657	1.17	14.61
F7	0.561	0.666	1.18	15.76

Weight variation was found to be within limits. Drug content of all the batches were about 99-101%. The dissolution studies of Haloperidol Tablets prepared using different concentration of citric acid (F1 to F4) as pH modifier showed different percentage of drug release depending upon the concentration of citric acid. The maximum release of 84% in 3 h was observed when the citric acid ratio was 1:5 (Haloperidol: Citric acid) as compared to 77.82% from F1 when the ratio was 1:3. Further increase in the citric acid ratio to 1:6 showed no further enhancement in drug released. This improvement in the drug release pattern could be due to the improvement in solubility of the drug due to the favorable acidic environment provided by the citric acid. After achieving the optimum concentration of citric acid, further increase in citric acid concentration provided no further enhancement in solubility profile.

The dissolution pattern of the Haloperidol was improved further by using propylene glycol as co-solubilizer, in different ratio (F5 to F7). Increase in concentration of PG favorably reflected on dissolution pattern, the drug release was increased to 88.48% and 93.21% in 3 h by incorporating the ratios of 1:5:0.3 and 1:5:0.6 of PG respectively. Further increase in the PG concentration to 1:5:1, leads to the production of oily spots on tablets hence it was not evaluated.

Table 3: Evaluation Parameter of Haloperidol coated Tablets

Formulation		**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
% Drug Release	Acidic Stage (%)	3.11	3.44	3.21	2.48	3.01	2.34
	Buffer Stage (%)	77.82	80.29	84.12	84.22	88.48	93.12
Drug content		99.67	99.98	99.86	100.63	99.85	100.58

Stability study

Under Accelerated Stability study the Haloperidol Tablets were found to be stable for six months (Table 4).

Table 4: Accelerated stability study of Haloperidol Tablets

Storage condition- Accelerated 40°C±2^0 C and 75% ± 5% RH		**AFTER MONTHS**				
TEST		**INITIAL TESTING**	**1 Month**	**2 Months**	**3 Months**	**6 Months**
Description		Complies	Complies	Complies	Complies	Complies
% Drug release	Acidic Stage (%)	2.36	2.85	3.02	3.25	3.29
	Buffer Stage (%)	94.01	93.75	93.34	93.21	92.99
Drug Content (%)		101.87	101.45	100.32	99.95	99.65

CONCLUSION

It was found that the use of citric acid as pH modifier in the ratio of 1:5 improved the dissolution of Haloperidol in neutral condition, which was further enhanced by addition of propylene glycol in the ratio of 1:5:0.6 to more than 90% of haloperidol dissolution.

ACKNOWLEDGEMENT

We are thankful to the management of ZIM laboratory Kalmeshwar, Nagpur for providing all the facilities and chemicals to conduct these experimentation and allowing us to publish this data.

REFERENCES

1. Chandile GK, Kumar JA, Kakade SM, Rajasekar S, Jadhav RT. Development and evaluation of haloperidol orally disintegrating tablets using novel co-processed superdisintegrants. Int.J.Res.pharm.Sci.,2011:2(3):348-352.
2. Jha SK,Vijayalakshmi P, Karki R, Goli D. Formulation and evaluation of melt-in-mouth tablets of haloperidol. Asian J.pharm., 2008:2(4):255-260.
3. Kumar R, Patil MB, Patil SR, Paschapur MS. Development and characterization of Melt-in-mouth tablets of haloperidol by sublimation technique. Int. J. pharm. Pharm. Sci., 2009: 1(1).
4. Berge SM, Bighley LD, Monkhouse DC.Pharmaceutical salts. J. pharm. Sci., 1977:74:815-820.
5. Li S, Wong SM, Sethia S, Almoazen H, Joshi YM, Serajuddin TM. Investigation of solubility and dissolution of a free base and two different salt forms as a function of pH. Pharm Res.,2005:22(4):628-635.
6. Ayer A, Theeuwes F, Wong PSL.Process for increasing solubility of drug. United state patent, 1988:4, 732, 915.
7. Rockville MD.The Unit States Pharmacopeial Convention. United States of Pharmacopeia-National Formulary, USP 30–NF 25., 2007:1:634-645.