RESEARCH ARTICLE

Formulation and evaluation of melt-in-mouth tablets of haloperidol

Sajal Kumar Jha, Vijayalakshmi P, Roopa Karki, Divakar Goli

Department of Pharmaceutics, Pharmaceutics Research Laboratory, ABMR College of Pharmacy, Soldevanahalli, Bangalore, India

Haloperidol, a butyrophenone, is widely used neuroleptic. Though haloperidol is well absorbed after oral dosing, there is a first pass metabolism leading to a reduced bioavailability of the drug (60-70%). Therefore, the present investigation is concerned with the development of melt-in-mouth tablets of haloperidol. Various formulations were prepared incorporating a combination of superdisintegrants, croscarmellose sodium, sodium starch glycolate, and crospovidone by direct compression method. The formulated melt-in-mouth tablets were evaluated for various physicochemical parameters, disintegration time and for *in vitro* drug release. All the formulations had disintegration time less than 30 s and release maximum amount of drug by 12 min. Formulation containing higher concentration of crospovidone decreases disintegration time and optimize the drug release. The most satisfactory formulation was found to be stable during the stability studies conducted as per ICH guidelines QIC, as it showed no significant changes ($P<0.05$) in the physicochemical properties, disintegration time and *in vitro* drug release.

Key words: *Direct compression, disintegration time, haloperidol, in vitro drug release, melt-in-mouth tablets, physicochemical parameters, stability studies*

INTRODUCTION

Difficulties with and resistance to tablet-taking are common in all patient groups and can exacerbate compliance problems and undermine treatment efficacy. Physical problems with swallowing (dysphagia) can occur at any age but are particularly prevalent in the elderly and those with dementia, whereas refusal to swallow is often encountered in geriatric, pediatric, and psychiatric patients. Nonetheless, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability. In recent years, rapid-dissolving oral drug formulations have been developed to overcome problems related to swallowing difficulties.[1]

A melt-in-mouth tablets (MMT) can be defined as an oral solid dosage form which when placed on tongue, disintegrates rapidly, releasing the drug, which dissolves or disperses in the saliva and then swallowed. Some drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down in to the stomach.[2]

Address for Correspondence:
Dr. Sajal Kumar Jha, Department of Pharmaceutics, Acharya and B.M. Reddy College of Pharmacy, Soldevanahalli, Bangalore - 560 090, India. E-mail: jha_sajal@indiatimes.com.

Poor compliance is a major concern in the treatment of depression. Between 30 and 68% of depressed patients, discontinue treatment within one month significantly increasing their risk of relapse. Poor compliance is promoted by many factors including aversion to antidepressant therapy. This aversion is mainly caused by the stigma associated with depression and drug-related effects, including the slow onset of action observed with conventional antidepressants.

The problem of patient compliance in the administration of oral antipsychotic drugs can be overcome by development of an appropriate dosage form. MMT are best suited and have gained popularity in the recent years in oral antipsychotic drug therapy.

This new formulation of psychotropics can offer advantages over older formulation in terms of convenience, side-effect profiles, efficacy, and/or a fast onset of action.[3]

Literature survey revealed haloperidol is a promising drug candidate to formulate MMT;[4] therefore an attempt has been made to develop and characterize its feasibility for MMT. Haloperidol is widely used neuroleptic which is a butyrophenone. Chemically it is 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one. Though haloperidol is well

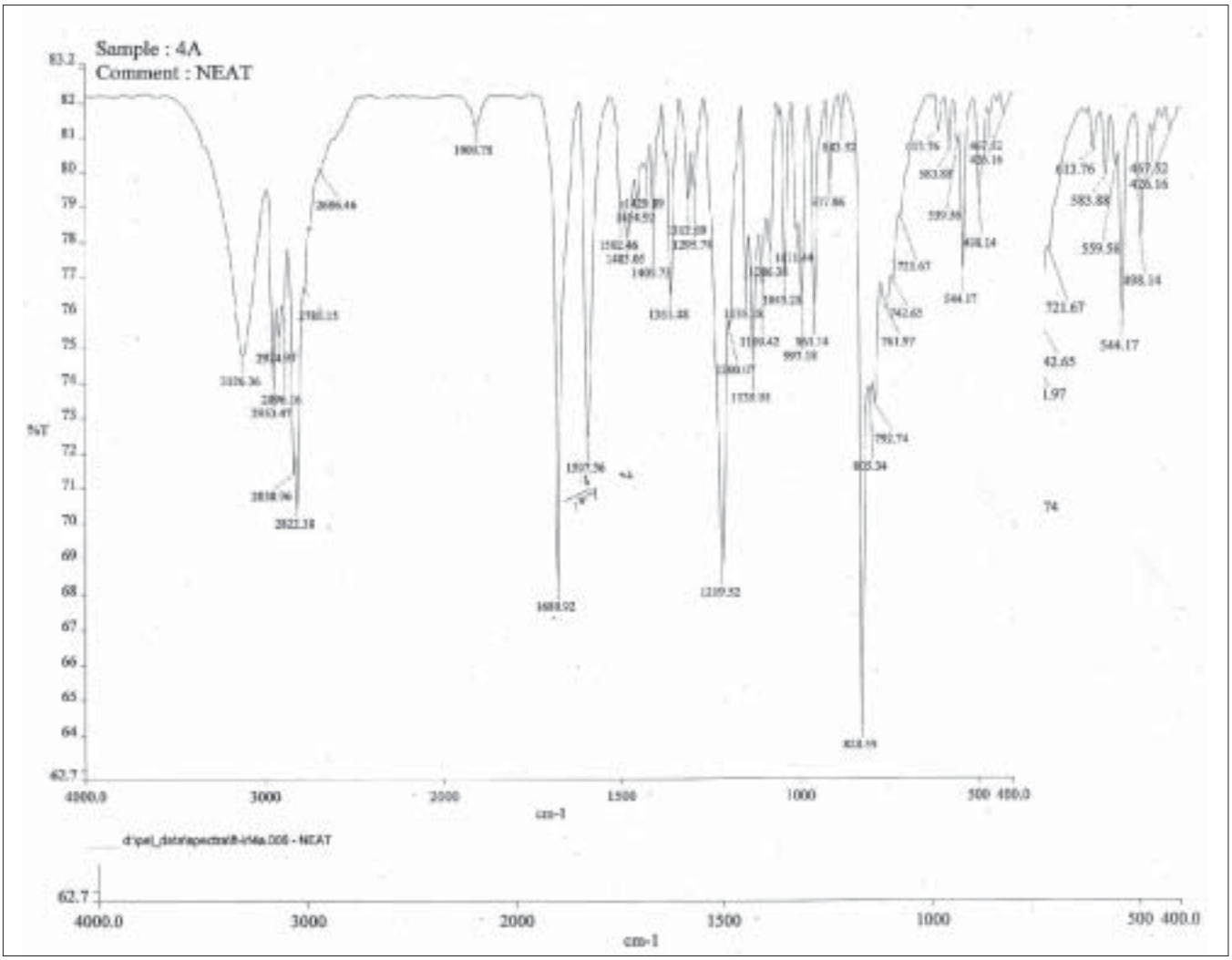

Figure 1: IR spectra of pure drug

absorbed after oral dosing, there is a first pass metabolism leading to a reduced bioavailability of the drug (60-70%). Therefore, the present investigation is concerned with the development MMT of haloperidol.

MATERIALS AND METHODS

Materials

Haloperidol obtained from Sun Pharmaceutical Industries (Mumbai, India), Croscarmellose Sodium, Crospovidone, Sodium starch glycolate, mint flavor were obtained as gift sample from Micro labs (Bangalore, India), Mannitol from Loba chemicals, (Mumbai, India), Microcrystalline Cellulose from Shrusti Pharmaceuticals, (Bangalore, India), Magnesium stearate, Purified Talc from S.D. Fine Chemicals (Mumbai, India). All other materials used were of pharmaceutical grade.

Table 1: Composition of MMT of haloperidol

Ingredients	Formulation code								
(mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Haloperidol	10	10	10	10	10	10	10	10	10
Mannitol	50	50	50	50	50	50	50	50	50
CCS	10	10	10	10	15	20	10	10	10
SSG	20	25	30	20	20	20	20	20	20
CP	10	10	10	10	10	10	10	15	20
MCC	20	15	10	20	15	10	20	15	10
Mg stearate	1	1	1	1	1	1	1	1	1
Purified talc	2	2	2	2	2	2	2	2	2
Mint flavor	2	2	2	2	2	2	2	2	2

All the formulations (F_1- F_9) contain 10 mg of haloperidol and the total weight 125 mg

Formulation of haloperidol MMT

Haloperidol MMTs were prepared by direct compression method according to the formula given in Table 1. A total number of nine formulations were prepared. All the ingredients were passed through 60-mesh sieve separately and collected, finally compressed into tablets after lubrication with talc (2%) and magnesium stearate (1%) by using 6 mm flat punch using RIMEK 10 station tablet compression machine.

Before tablet preparation, the mixture blend subjected for compatibility studies (IR), and pre-compression parameters

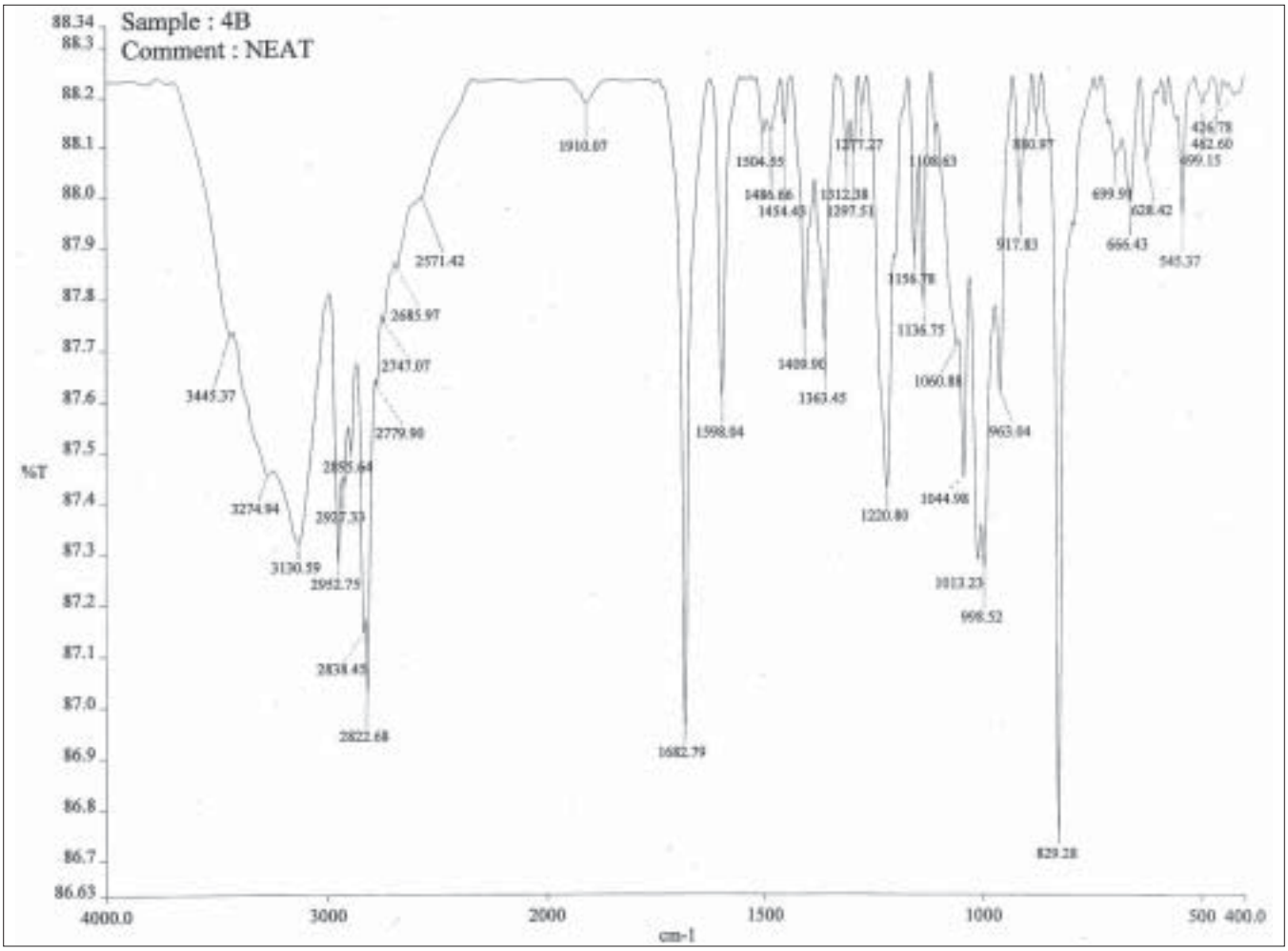

Figure 2: IR spectra of the drug and excipients

like angle of repose,[5] compressibility index, and bulk density.

The MMT prepared were subjected for post-compression parameters like uniformity of thickness, hardness, friability, weight variation, drug content uniformity, wetting time, and *in vitro* disintegration time.[6-8]

EVALUATION PARAMETERS

Wetting time

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 6 ml of simulated saliva pH (phosphate buffer pH 6.8). A tablet was put on the paper, and the time required for complete wetting was measured. Six trials for each batch were performed; average time for wetting with standard deviation was recorded.[9]

In vitro disintegration time

In vitro disintegration time was performed by apparatus specified in USP at 50 rpm. Phosphate buffer pH 6.8, 900 ml was used as disintegration medium, and the temperature of which maintained at 37 ± 2°C and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.[10]

Evaluation of *in vitro* dissolution studies

In-vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) [Electrolab (ETC-11L) Tablet

Table 2: Micromeritic properties of MMT of haloperidol

Blend	Angle of repose*	Compressibility index*	Bulk density*
F1	19.66 ±0.02	11.56 ±0.01	0.332 ±0.002
F2	19.98 ±0.01	15.40 ±0.0152	0.348 ±0.001
F3	20.60 ±0.0152	12.10 ±0.01	0.382 ± 0.001
F4	20.16 ±0.0152	13.50±0.01	0.421± 0.002
F5	21.41 ±0.01	13.24 ±0.01	0.465 ± 0.0015
F6	20.36 ±0.0152	18.15 ±0.01	0.523 ± 0.0015
F7	24.72 ±0.01	13.21±0.01	0.345± 0.001
F8	22.31 ±0.0152	15.82 ±0.0152	0.386 ±0.0015
F9	25.12±0.0152	16.26 ±0.0152	0.373± 0.001

*Each value is an average of 3 readings

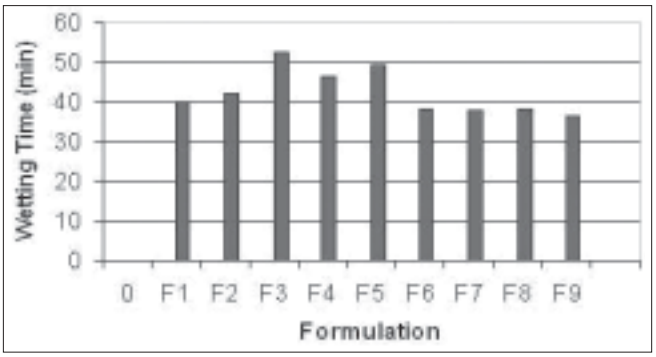

Figure 3: Wetting time of MMT of haloperidol

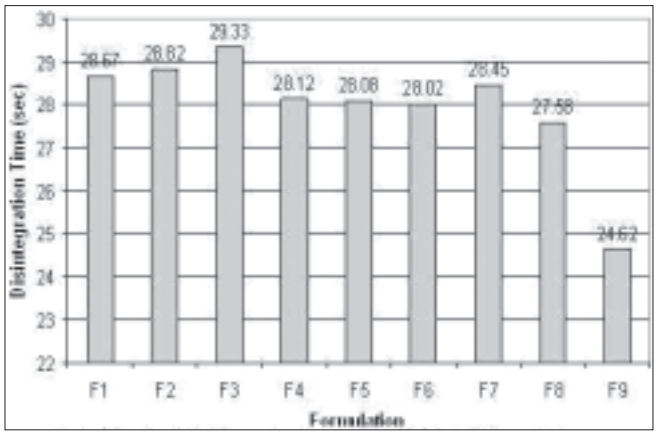

Figure 4: *In-vitro* disintegration time of MMT of haloperidol

Dissolution Tester] at 50 rpm. Phosphate buffer pH 6.8, 900 ml was used as dissolution medium which maintained at 37±0.5˚C. Aliquot of dissolution medium (10 ml) was withdrawn at specific time intervals (2 min) and was filtered. The amount of drug dissolved was determined by UV spectrophotometer (Shimadzu, Japan) by measuring the absorbance of the sample at 248.0 nm. Three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.[11]

RESULTS AND DISCUSSION

In the present study, haloperidol MMT were prepared by using croscarmellose sodium, sodium starch glycolate, and crospovidone as superdisintegrants. A total number of nine formulations were prepared by direct compression technique. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. IR spectroscopy was used as means of studying drug-excipient compatibility and confirmed undisturbed structure of haloperidol, which indicates no drug-excipient interaction [Figures 1 and 2]. The data obtained of post-compression parameters such as hardness, friability, weight variation, uniformity of content, thickness, wetting time, disintegration time are shown in Table 2. The hardness was found to be in the range of 3 to 4 kg/cm^2 in all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations the friability value is less than 1% and meets the IP (Indian Pharmacopoeia) limits.[12] All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits.[13] The weight of all the tablets was found to be uniform with low standard deviation values indicating efficient mixing of drug, superdisintegrants and excipients. The percentage drug content of all the tablets was found to be between 88.68 ± 0.1069% and 98.32 ± 0.02 % of haloperidol, Table 3 which was within the acceptable limits. The percentage drug release by each tablet in the *in vitro* drug release studies were based on the mean content of the drug present in respective tablet. The result of *in vitro* disintegration of all the tablets were found to be within prescribed limit and satisfy the criteria of MMT. The values were found to be in the range of 24.62 ± 0.0404 to 29.33 ± 0.0450 s [Figure 4]. It was observed that the increased concentration of crospovidone, decreases disintegration time and optimized the drug release. Crospovidone in the concentration of 20 mg acts as potential disintigrant and disintegrate the tablet within 24.62 ± 0.04 s fulfilling the criteria of MMT. Crospovidone when comes in contact with water it quickly wicks water into the tablet through capillary action to create internal pressure that disintegrates the tablet [Figure 3].

The concentrations used are 10, 15, and 20 mg, in that 20 mg acts as the best and can be employed in the formulation of the MMT. Though tablets prepared by croscarmellose sodium and sodium starch glycolate disintegrates in the mean time,

Table 3: Evaluation of physicochemical parameters of MMT of haloperidol

Formulation code	Hardness* (kg/cm^2)	Friability* (%)	Weight variation (mg)	Uniformity of content* (%)	Thickness of tablets* (mm)	Wetting time* (s)	Disintegration time (s)
F1	3.220 ± 0.1485	0.2469	125.2 ± 0.1527	88.68 ± 0.1365	2.50 ± 0.0153	40.05 ± 0.5629	28.67 ± 0.0251
F2	3.215 ± 0.1542	0.2540	122.5 ± 0. 6658	89.48 ± 0.2468	2.50 ± 0.01	42.25 ± 0.4746	28.82 ± 0.0208
F3	3.632 ± 0.2147	0.2283	124.3 ± 0.2081	90.22 ± 0.3324	2.65 ± 0.0153	52.51 ± 0.9497	29.33 ± 0.0450
F4	3.521 ± 0.1612	0.2540	126.4 ± 0.3	90.68 ± 0.07	2.50 ± 0.0157	46.28 ± 0.6939	28.12 ± 0.0305
F5	3.532 ± 0.1376	0.2338	125.8 ± 0.3605	91.76 ± 0.0721	2.25 ± 0.0389	49.38 ± 0.3353	28.08 ± 0.02
F6	3.536 ± 0.1712	0.2312	125.6 ±0.4163	92.88 ± 0.0611	2.25 ± 0.0342	38.10 ± 0.7067	28.02 ± 0.0351
F7	3.328 ± 0.0568	0.3987	126.2 ± 0.2081	89.32 ± 0.0208	2.5 ± 0.0115	37.82 ± 0.9497	28.45 ± 0.0351
F8	3.432 ± 0.1021	0.3019	125.4 ± 0.2516	95.15 ± 0.0152	2.5 ± 0.0153	38.23 ± 0.3424	27.58 ± 0.0305
F9	3.202 ± 0.0052	0.4506	125.9 ± 0.2516	98.32 ± 0.02	2.25 ± 0.0504	36.45 ± 0.3784	24.62 ± 0.0404

*Each value is an average of six determinations.

Table 4: *In vitro* dissolution profile data for MMT formulations of haloperidol

Time (min)	Formulation code*									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	MT
2	57.40 ± 0.1113	57.57 ± 0.1844	61.97 ± 0.0763	65.36 ±0.2119	76.22 ±0.1305	76.89 ±0.3659	58.21 ±0.0305	81.23 ±0.01	80.32 ±0.0115	26.49 ± 0.01
4	64.60 ± 0.1604	69.70 ± 0.2835	71.65 ± 0.1014	71.31 ±0.1357	80.55 ±0.1153	77.24 ±0.0702	65.35 ±0.0351	84.32 ± 0.0152	83.34 ± 0.02	32.40 ± 0.02
6	74.60 ± 0.1604	79.32 ± 0.1692	80.69 ± 0.1357	76.51 ±0.1417	83.31 ±0.1044	79.35 ±0.0458	75.62 ±0.0351	87.41 ±0.01	86.65 ± 0.02	35.76 ±0.0152
8	82.67 ± 0.2651	83.24 ± 0.1670	85.14 ± 0.2700	82.75 ±0.1350	85.10 ±0.0757	82.35 ±0.0458	82.18 ±0.0152	90.55 ±0.0152	89.16 ±0.0152	48.29 ± 0.02
10	86.21 ± 0.1069	88.41 ± 0.0650	89.36 ± 0.1808	86.68 ±0.0871	88.25 ±0.0351	86.66 ±0.0850	86.32 ±0.0152	92.21 ±0.01	93.24 ±0.0152	59.48 ± 0.01
12	88.68 ± 0.1069	89.48 ± 0.0702	90.22 ± 0.25	90.68 ± 0.07	91.76 ±0.0721	92.88 ±0.0611	89.32 ±0.0208	95.15 ± 0.0152	98.32 ± 0.02	65.42 ±0.01

*Average of six determinations, MT- Marketed Tablet

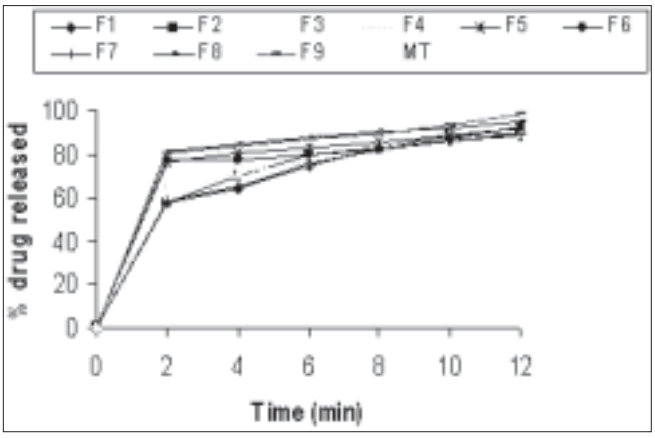

Figure 5: *In-vitro* dissolution profile of MMT of haloperidol

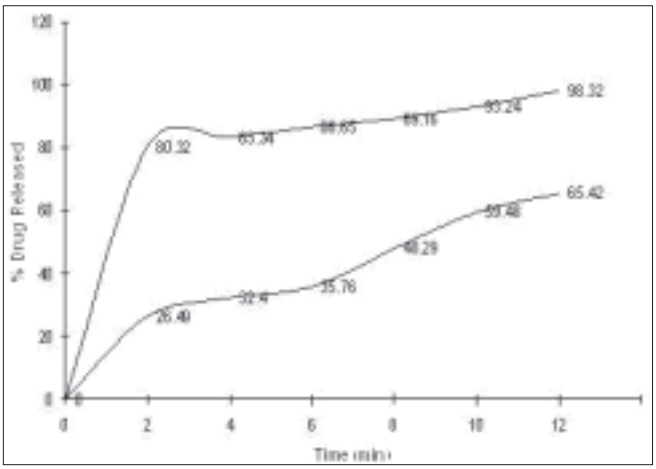

Figure 6: Comparison of dissolution profile of F9 and the marketed product

but in comparison with crospovidone they do impediment. All the tablets prepared were subjected for *in vitro* release profile [Figure 5].

Overall the MMT formulations of haloperidol showed an average of 88 to 98% drug release range at the end of 12 min which is as per IP specifications of 90-110% and it was also observed that formulations F_9 took shortest time to release the maximum amount of drug whereas the other formulations took more than 12 min to release the drug [Table 4].

In comparison with other formulations, F_9 shows a better drug release of 98.32% at the end of twelve minutes. Further the formulation F_9 was compared with marketed formulation (SENORM, Sun Pharmaceutical Industries) and found to be superior in terms of dissolution profile [Figure 6].

There was no significant variation in the physicochemical parameters, *in vitro* disintegration time, and *in vitro* dissolution profiles after two months stability [Tables 5 and 6] study as per ICH guidelines Q1C.[14]

Table 5: Result of evaluation for hardness, friability, disintegration time in stability studies of MMT formulations of haloperidol

Time (days)	Hardness (kg/cm^2)		Friability (%)		Disintegration time (s)	
	A	B	A	B	A	B
30	3.512±0.1612	3.516±0.1568	0.3578	0.3582	25.88± 0.0.0321	25.72± 0.04021
60	3.498±0.1021	3.506±0.1121	0.3589	0.3605	25.68± 0.03126	25.48± 0.04154

A= 30°C, 65% RH, B= 40°C, 75% RH, Each value is an average of 3 determinations

Table 6: *In-vitro* dissolution profile data for MMT formulations of haloperidol during stability studies

Temperature (°C)	Sampling interval (days)	2 min	4 min	6 min	8 min	10 min	12 min
30	30	80.64 ± 0.1123	84.46 ± 0.1456	87.84 ± 0.2358	90.25 ± 0.2354	94.39 ± 0.2578	98.35± 0.1547
	60	81.96 ± 0.1654	85.63 ± 0.2541	89.56 ± 0.2546	92.85 ± 0.3541	95.64 ± 0.3451	99.42± 0.1258
40	15	81.79 ± 0.2415	84.82 ± 0.3241	88.36 ± 0.1247	90.95 ± 0.2741	95.31 ± 0.2146	98.89± 0.1248
	30	82.16 ± 0.2415	86.29 ± 0.1484	89.93 ± 0.3241	93.67 ± 0.1879	96.78 ± 0.2415	99.95± 0.2748

Each value is an average of 3 determinations

CONCLUSION

Melt-in-mouth tablets (MMT) of haloperidol is successfully prepared by using different proportions of superdisintegrants, Undoubtedly the availability of various technologies and the manifold advantages of MMT will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability, and its popularity in the near future.

ACKNOWLEDGEMENTS

The authors are grateful to Sun Pharmaceutical Industries for providing gift sample of haloperidol and also Principal Acharya and B. M. Reddy College of Pharmacy, Bangalore for providing necessary facilities to carry out the research work.

REFERENCES

1. van Schaick EA, Lechat P, Remmerie BM, Ko G, Lasseter KC, Mannaert E. Pharmacokinetic comparison of fast-disintegrating and conventional tablet formulations of risperidone in healthy volunteers. Clin Ther 2003;25:1687-99.
2. Bi Y, Sunada H, Yonezawa Y, Dayo K, Otsuka A, Lida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in oral cavity. Chem Pharm Bull 1996;44:2121-7.
3. Keith S. Advances in psychotropic formulations. Prog uropsychopharmacol Biol Psychiatry 2006;30:996-1008.
4. Sharma S, Garg R, Naruka PS, Gupta GD. Fast dissolving tablet: The future of compaction. Pharmainfo.net, 2007.
5. Babu GV, Kumar NR, Himasankar K, Seshasayana A, Murthy KV. Nimesulide-modified gum karaya solid mixtures: Preparation, characterization and formulation development. Drug Dev Ind Pharm 2003;29:855-64.
6. Chowdary KP, Hemavathy R. Formulation and dissolution rate studies on dispersible tablets of ibuprofen. Indian J Pharm Sci 2000;63:213-6.
7. Rama Rao N, Chowdary KP. Improvement of dissolution rate and bioavailability of Piroxicam with pre-gelatinized starch. Indian J Pharm Sci 2001;63:36-40.
8. Rizk S. Investigation on a new modified USP Xanthan with tablet disintegration properties. Drug Dev Ind Pharm 1997;23:19-26.
9. Gohel M, Patel M, Amin A, Agarwal R, Dave R, Bariya N. Formulation design and optimization of mouth dissolving tablets of niimesulide using vacuum drying technique. AAPS Pharm Sci Tech 2004;5:36.
10. Panigrahi D, Baghel S, Mishra B. Mouth dissolving tablets: An overview of preparation techniques, evaluation and patented technologies. J Pharma Res 2005;4:33-8.
11. Kuchekar BS, Arumugam V. Fast dissolving tablets. Indian J Pharm Edu 2001;35:150.
12. Indian Pharmacopoeia. 4th ed. Controller of Publications. India, New Delhi: 1996. p. 80,
13. Chaudhary PD, Chaudhary SP, Lanke SD. Formulation and evaluation of taste masked Orodispersible dosage form of levocetrizine dihydrochloride. Indian J Pharm Edu Res 2007;41:319-28.
14. Available from: http://www.ich.org/cache/compo/363-272-1.html. 05/11/1996.

Source of Support: Nil, **Conflict of Interest:** None declared.