DOI: http://dx.doi.org/10.4314/star.v4i1.21
ISSN: 2226-7522(Print) and 2305-3372 (Online)
Science, Technology and Arts Research Journal
Sci. Technol. Arts Res. J., Jan-March 2015, 4(1): 124-128
Journal Homepage: http://www.starjournal.org/

Original Research

Effect of Combination of Superdisintegrants on the Dissolution Rate: Meclizine Hydrochloride Fast Dissolving Tablets

Sateesh Kumar Vemula*, Biniam Paulos and Selamu Kebamo

College of Medical and Health Sciences, Wollega University, P.O Box: 395, Nekemte, Ethiopia

Abstract

The aim of the present research is to develop the fast dissolving tablets and to study the effect of combination of superdisintegrants on the dissolution rate by using meclizine hydrochloride as a model drug. Development of oral fast dissolving tablets is mainly to achieve the following objectives; they are to give fast onset of action and to overcome difficulty in swallowing tablets and capsules that resulting in non-compliance. The prepared tablets were characterized for hardness, weight variation, friability, wetting time, water absorption ratio, and disintegration time. *In vitro* drug release studies were performed by using USP XXIV Type II dissolution apparatus in 0.1 N HCl. From *in vitro* dissolution studies, the formulation F3 (3% crosscarmellose and 3% crosspovidone) showed rapid dissolution of about 99.34% in 15 min, and disintegration time 39 sec when compared with others. The percent drug release in 15 min (Q_{15}) and initial dissolution rate for formulation F3 was 99.34±0.56%, 6.54%/min. These were very much higher compared to control tablets (36.48±0.82%, 2.43%/min). The dissolution efficiency was found to be increased by 3.5 fold with F3 formulation compared to control tablet. From the stability studies, the similarity index was found to be above 50 that indicates the stability of tablets. In conclusion, development of meclizine hydrochloride fast dissolving tablets using combination of superdisintegrants is showed improved results rather than the tablets with individual superdisintegrants. Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies.

Article Information

Article History:

Received : 18-01-2015

Revised : 27-02-2015

Accepted : 05-03-2015

Keywords:

Dissolution efficiency

Fast onset of action

In vitro dissolution studies

Initial dissolution rate

Superdisintegrants

***Corresponding Author:**

Sateesh Kumar Vemula

E-mail:
vemulasatish15@gmail.com

INTRODUCTION

Development of oral solid dosage forms using insoluble drugs with the help of different methods is not only to enhance the solubility and dissolution rate of poor soluble drugs but also to improve the therapeutic efficacy (Chaitanya *et al*., 2014; Vemula and Katkum, 2014). Development of fast dissolving tablets can be achieved by various conventional methods like direct compression, wet granulation, spray drying, freeze drying, and sublimation (Seager, 1998; Hirani *et al*., 2009; Daravath *et al*., 2014). Among the different methods, use of superdisintegrants is one of the easiest and successful methods to enhance the dissolution rate. Formulation of fast dissolving tablets by integrating superdisintegrants is a user friendly, convenient and industry feasible method (Neduri *et al*., 2013). One of the advantages of incorporating the superdisintegrants is to provide fast disintegration due to combined effect of swelling and water absorption. Due to swelling of superdisintegrant, the wetted surface of the carrier increases that promote the wettability and dispersibility of the system, leads to enhance the disintegration and dissolution (Vemula *et al*., 2011).

Meclizine hydrochloride (MCZ) is a first-generation antihistamine of the piperazine class drug, used in the treatment of motion sickness. MCZ is a H_1 receptor antagonist and practically insoluble in water (Vangala *et al*., 2014; Goyani *et al*., 2012). In the present study, fast dissolving tablets were prepared by direct compression method and studied the effect of various superdisintegrants and their concentration on the dissolution rate of MCZ. Some of the recent research examples on MCZ dosage forms are Meclizine hydro chloride mouth dissolving tablets (Nimisha *et al*., 2012), Cyclodextrin-meclizine HCl Inclusion Complexes (George and Vasudevan, 2012), Metabolism and pharmacokinetics of meclizine suspension (Wang *et al*., 2012), Meclizine HCl orally disintegrating tablets (Mahrous *et al*., 2011), Meclazine-maltodextrin oro-dissolving tablets (Elnaggar *et al*., 2010).

In the previous research carried i.e., formulation and evaluation of meclizine hydrochloride fast dissolving tablets (Vemula *et al*., 2014), successfully developed the fast dissolving tablets using superdisintegrants like crosspovidone, crosscarmellose and sodium starch glycolate. In this study, formulation F6 tablets containing 8%w/w crosspovidone showed complete drug release within 20 min and rapid dissolution when compared to other formulations i.e., 98.12±0.34% in 20 min. The current research was intended to develop MCZ fast dissolving tablets by direct compression method to study the effect of combination of superdisintegrants on the dissolution rate. In the present research, crosscarmellose and sodium starch glycolate were used in combination with crosspovidone to enhance the dissolution rate.

MATERIALS AND METHODS

Materials

Meclizine hydrochloride is obtained as a gift sample from Symed labs Ltd, India. Crosspovidone, crosscarmelose and sodium starch glycolate were gift samples from Matrix laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

Preparation of Fast Dissolving Tablets (FDTs)

Direct compression method was used to prepare the fast dissolving tablets (FDT's). MCZ, fixed ratio combination of superdisintegrants (Sodium starch glycolate: Crosspovidone and Crosscarmellose: Crosspovidone) other tabletting excipients were passed through a mesh 60. The drug was mixed with proper portion of superdisintegrant with care to facilitate the proper mixing of drug and superdisintegrant. Then excipients other than lubricant and glidant were added and mixed in a poly bag for 5-10 min. The obtained blend was lubricated with magnesium stearate and talc for another 5 min and the resultant mixture was directly compressed into tablets with 6 mm round flat punches using rotary tabletting machine. In a similar manner, conventional control tablets were prepared without using superdisintegrants. The final weight of the tablet was adjusted to 100 mg and the compositions of the tablets were given in Table 1 (Vemula and Veerareddy, 2011).

Table 1: Formulations of meclizine HCl fast dissolving tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	Control
Meclizine HCl	25	25	25	25	25	25	25
Crosspovidone	1	2	3	1	2	3	-
Crosscarmellose	1	2	3	-	-	-	-
Sodium starch glycolate	-	-	-	1	2	3	-
Starch	-	-	-	-	-	-	10
Sodium lauryl sulphate	1	1	1	1	1	1	1
Mannitol	25	25	25	25	25	25	25
Avicel PH102	43	41	39	43	41	39	35
Aspartame	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1
Total weight	100	100	100	100	100	100	100

Evaluation of Physical Parameters

After the preparation of tablets, all the formulations were evaluated for physical properties like weight variation, hardness and friability. For estimating weight variation, 20 tablets of each formulation were weighed using an Electronic weighing balance. The strength of tablet is expressed by measuring hardness and friability. The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was determined on ten tablets in a Roche friabilator for 4 min at 25 rpm (Veerareddy and Vemula, 2012). For estimation of drug content, ten tablets were crushed, and the aliquot of powder equivalent to 50 mg of drug was dissolved in suitable quantity of methanol/0.1 N HCl solution. Solution was filtered and diluted and drug content determined by UV-Visible spectrophotometer at 232 nm (Vemula and Vangala, 2014).

Determination of *In Vitro* Disintegration Time and Wetting Time

In this study, the *in vitro* disintegration time of FDT's was determined by using the Gohel procedure. 10 ml of water at room temperature was taken in a petridish of 10 cm in diameter. The tablet was then carefully placed in the centre of petridish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in triplicates (Gohel *et al*., 2004). Wetting time was determined as described in the literature elsewhere. Briefly, two circular tissue papers were placed in a petridish of 10 cm diameter. Ten milliliter of water containing 0.5 (% w/v) of phenol red was added to the petridish. The dye solution was used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of the paper in the petridish at room temperature. The time required for water to reach the upper surface of tablet and to completely wet them was noted as wetting time. Wetting time was recorded using stop watch and the measurements were carried out in triplicates (Bi *et al*., 1996).

In Vitro Dissolution Study

The *in vitro* dissolution study was carried out using USP XXIV Type II dissolution apparatus at a rotation speed of 50 rpm and a temperature of 37±0.5 °C for all the prepared FDT's. The drug release studies were carried out in 0.1N HCl buffer. An aliquot of 5 ml was collected at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered through 0.45 µm membrane filters and analyzed spectrophotometrically at 232 nm (Vaskula *et al*., 2012).

Calculation of Dissolution Parameters

Cumulative percent drug release was plotted as a function of time and percent drug release in 15 min (Q_{15}) was calculated. Initial dissolution rate (IDR) was calculated as percentage dissolved of drug over the first 15 min per minute. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the 15 min. Relative dissolution rate (RDR) is the ratio between amount of drug dissolved from best formulation and that dissolved from the marketed tablets at 15 min (Vemula and Veerareddy, 2011).

Stability Studies

According to ICH guidelines, stability studies were carried on F3 formulation to judge the drug and formulation stability. Best formulation (F3) was sealed in aluminum packaging coated inside with polyethylene, and three replicates were kept in the humidity chamber maintained at 40±2 ^{o}C and 75±5% RH for six months (Chaudhary *et al*., 2011). Samples were collected after six

months of storage and analyzed for the drug content and *in vitro* dissolution rate and they were subjected to statistical analysis using paired *t*-test to test the significance of difference at 0.05 level of significance (LS). Then the similarity index was calculated between dissolution rates of optimized tablets before and after storage to prove the stability of the dosage form (Vemula and Veerareddy, 2013; Vemula and Bontha, 2013).

RESULTS AND DISCUSSION

Evaluation of Physical Parameters

The evaluated different physical parameters of MCZ fast dissolving tablets were given in Table 2. In weight variation test, the pharmacopoeial limit for the tablets of not more than 7.5% of the average weight. The hardness of the tablets was found to be in the range of 2.8 to 3.1 kg/cm^2. Another measure of tablets strength is friability. The percentage friability for all formulations was below 1% i.e., 0.24 to 0.36, indicating that the friability is within the prescribed limits. The tablets were found to contain 98.64±0.59 to 99.78±0.32% of the labeled amount indicating uniformity of drug content.

Determination of *In Vitro* Disintegration Time and Wetting Time

The disintegration time of all formulations was found in the range of 39.52±0.38 to 58.21±0.42 sec. The wetting time of formulated tablets was found in the range of 59.24±0.45 to 79.68±0.27. From the results, the formulation F3 containing 3% crosscarmellose and 3% crosspovidone showed the fastest disintegration (39 sec) and less wetting time (59 sec) as compared to other formulations (Table 2).

Table 2: Evaluation of meclizine HCl fast dissolving tablets

Formulation	Weight variation* (mg)	Hardness$^{\$}$ (kg/cm^2)	Friability (%)	Drug content uniformity$^{\#}$ (%)	*In vitro* Disintegration Time$^{\#}$(sec)	Wetting Time$^{\#}$ (sec)
F1	99.28±0.34	2.8±0.12	0.32	98.64±0.59	50.29±0.76	71.32±0.21
F2	101.32±0.23	3.1±0.38	0.36	99.42±0.74	43.92±0.54	64.86±0.38
F3	100.28±0.49	3.0±0.42	0.24	99.78±0.32	39.52±0.38	59.24±0.45
F4	100.49±0.64	2.9±0.18	0.36	99.34±0.78	58.21±0.42	79.68±0.27
F5	98.97±0.72	3.0±0.24	0.24	98.27±0.24	44.16±0.23	75.18±0.49
F6	100.02±0.48	2.8±0.34	0.28	99.78±0.56	41.48±0.51	61.82±0.74
Control	101.24±0.45	3.0±0.14	0.32	99.16±0.82	298.92±0.68	246.38±0.42

*All results correspond to avg ± SD, n=20; $^{\$}$ All results represent avg ± SD, n=6; $^{\#}$ All results represent avg ± SD, n=3

In vitro Dissolution Study

Figure 1 demonstrated the MCZ release patterns from F1-F6 fast dissolving tablets. From the *in vitro* dissolution studies, tablets containing combination of crosscarmellose and crosspovidone showed fast dissolution rate than others. Among all the formulations, F3 tablets showed complete drug release within 15 min and rapid dissolution when compared to other formulations i.e., 99.34±0.56% in 15 min. Where as in the similar conditions, the control tablets of same dose was showed 36.48±0.82% drug release in 15 min (Figure 2). Similar type of results showed in a study i.e., piroxicam fast disintegrating tablets (Vemula *et al*., 2010). The possible reasons and mechanisms for increased dissolution rates are formation of porous structure on the surface of tablet due to sublimation and the presence of superdisintegrants enhance the water permeation (wicking action) in to the tablet leads to fasten the wetting action, disintegration time and finally causes the fast dissolution rate (Vemula *et al*., 2010).

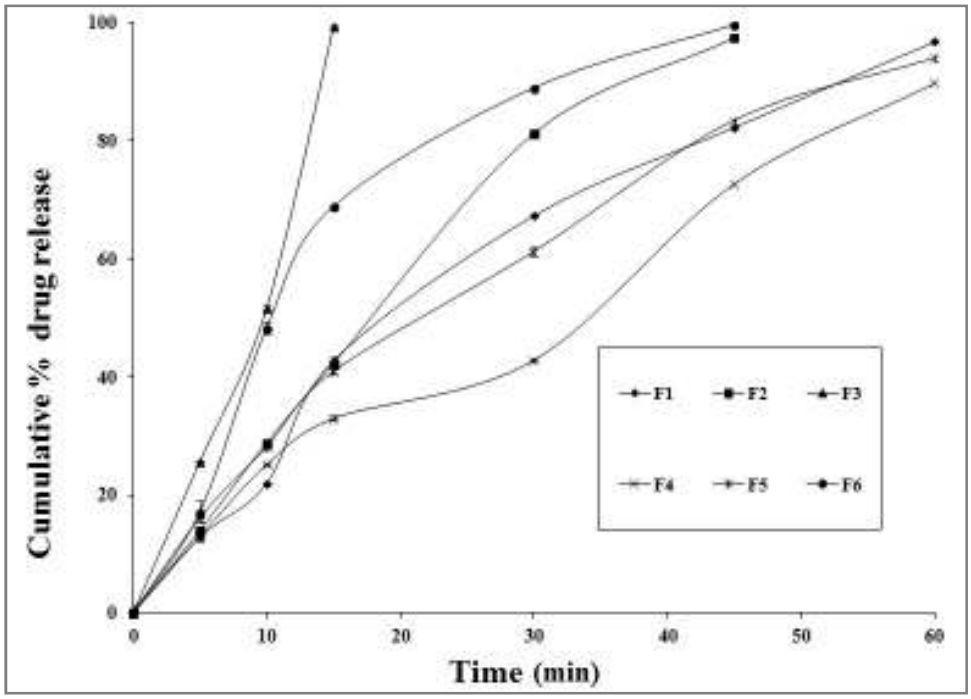

Figure 1: Release profile of MCZ from fast dissolving tablets (n=3)

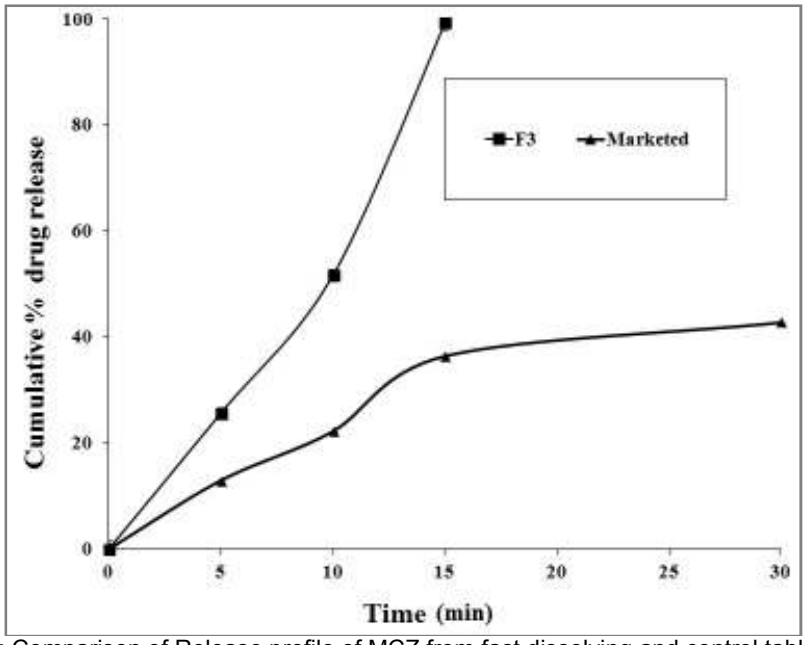

Figure 2: Comparison of Release profile of MCZ from fast dissolving and control tablets (n=3)

Calculation for Dissolution Parameters

The percent drug release in 15 min (Q_{15}) and initial dissolution rate (IDR) for formulation F_3 was 99.34±0.56 %, 6.54% per min. These were very much higher compared to marketed tablets (36.48±0.82 %, 2.43% per min). The improvement in the dissolution characteristics of a drug described in terms of dissolution efficiency (DE) and relative dissolution rate (RDR). The RDR was found to be 2.69. The DE was found to be 42.35 and it is increased by 3.0 fold with F6 FDTs compared to control tablets i.e., 17.82 (Table 3). Similar type of improvement in IDR, DE, RDR was reported in the study of Vemula *et al* i.e., flurbiprofen fast disintegrating tablets (Vemula and Veerareddy, 2011).

Table 3: Dissolution parameters of meclizine HCl F3 and control tablets

Formulation	(Q_{15})	IDR (%/min)	DE	RDR
F3 tablet	99.34±0.56	6.54	42.35	2.69
Control tablet	36.48±0.82	2.43	17.82	

* All results represent Avg ± SD, n=3

Stability Studies

After storage of six months, F3 tablets were subjected to drug assay and *in vitro* dissolution studies (Table 4) and from the statistical analysis there was no significant difference between before and after storage (P<0.05). The similarity index value between dissolution profiles of optimized formulation before and after storage was found to be 82.13, which is more than 50 indicates similarity between the dissolution profile before and after storage (Vemula *et al*., 2014a; Vemula *et al*., 2014b).

Table 4: Stability studies of meclizine HCl F3 fast dissolving tablets

Time (min)	Before storage	After 6 months storage	*t*-test at 0.05 LS	Similarity Factor (F2)
0	0.00±0.00	0.00±0.00		
5	25.67±0.28	22.34±0.78	Not Significant	82.13
10	51.71±0.56	49.67±0.84		
15	99.34±0.56	98.12±0.24		
% Assay	99.62±0.51	98.27±0.46	Not Significant	--

* All results represent Avg ± SD, n=3

CONCLUSIONS

An effort was made to develop the fast dissolving tablets of meclizine hydrochloride using combination of superdisintegrants to enhance the dissolution rate. Meclizine hydrochloride fast dissolving tablets were formulated using direct compression method and evaluated for different parameters, which were found in the acceptable range. From the dissolution studies of prepared tablets, F3 fast dissolving tablets containing 3% crosscarmellose and 3% crosspovidone showed rapid disintegration time and fast dissolution rate. The percent drug release in 15 min (Q_{15}) and initial dissolution rate (IDR) for formulation F_3 was 99.34±0.56 %, 6.54 % per min. These were very much higher compared to marketed tablets (36.48±0.82 %, 2.43 % per min). The DE was found to be increased by 3.0 fold with F3 FDTs compared to control. The similarity index value between dissolution profiles of optimized formulation before and after storage was found to be 82.13, which is more than 50 indicates similarity between the dissolution profile before and after storage In conclusion, development of fast dissolving tablets using combination of superdisintegrants by direct compression method is a suitable and feasible method to improve the dissolution rate of meclizine hydrochloride.

Acknowledgements

The authors acknowledge the Symed labs Ltd, India and Matrix laboratories India for gift samples. The authors also thank to Chaitanya College of Pharmacy Education and Research, Hanamkonda, India for providing facilities.

Conflict of Interest

Authors declared no conflict of interest.

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