RESEARCH ARTICLE

Development of metoclopramide hydrochloride orodispersibal tablets using taste masking tulsion 339

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ABSTRACT

In the present work, orodispersible tablets of Metoclopramide HCl were prepared by direct compression techniques using complex of drug with various superdisintegrant. Before formulation of tablets, the best superdisintegrant among Tulsion 339, Ac-Di-Sol, and Sodium starch glycolate was formulated with drug and tested. For taste masking ion exchange resin Tulsion 339 Drug: Tulsion339, 1:2.25 ratios was used. The blends were examined for pre-compression parameters. The result were complies with Pharmacopeial and non official limits. The prepared batches of tablets were evaluated for post compression parameters. Formulations were tested for *in vitro* drug release pattern (in pH 6.8 buffer), Batch F5 containing Tulsion 339 showed better disintegrating character along with the immediate release (100.32% within 6 minutes). Optimized batch F5 and tablets containing different concentration of Tulsion were compared with available marketed commercial formulation.

Keywords: Metoclopramide HCl, Oral dispersible Tablet, Tulsion 339, Superdisintigrant.

INTRODUCTION

The growing importance of mouth dissolving tablet was underlined recently when European Pharmacopoeia adopted the term Orodispersible Tablet as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.[1,2] A solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water is known as fast dispersing dosage form mouth dissolving tablets. [3] When this type of tablet is placed into the mouth, the saliva will serve to rapidly dissolve the tablet. Most commonly used drugs under this formulation are the agents active against migraine. The tablets are designed to disintegrate as well as dissolve within one minute or some within 10 seconds of oral administration in limited quantity of saliva. They liquefy on tongue and patient swallows the liquid, without the need of water.

Metoclopramide is used to treat Gastroparesis, by stimulating stomach activity to empty the stomach. Complicating the matter of oral administration of Metoclopramide is the fact that patients with Gastroparesis often have symptoms such as vomiting and nausea as well as fullness and bloating, each of which can lead to patient discomfort with or unwillingness to swallow the available oral tablet and associated water. If vomiting takes place, the amount of Metoclopramide that remains in the stomach is unknown, and the result of treatment is even less predictable. The present invention provides an oral rapidly dissolving Metoclopramide formulation and administration of Metoclopramide of the oral immediate release formulation to abate the rapid onset of Gastroparesis. [4, 5]

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MATERIALS AND METHODS

Metoclopramide Hydrochloride was obtained as gift sample by Shalaks Pharmaceuticals, New Delhi, India. Tulsion339 was obtained as gift sample by Thermax Ltd. Mumbai All other materials and solvents used were of analytical grade.

Formulation of drug polymer complex

Tulsion-339 was weighed 45gm, transferred to container containing purified water and make up the volume 100 ml [6]. This mixture was stirred on mechanical stirrer for 15 minutes. Metoclopramide hydrochloride 20 gm was added to above solution and

this mixture was stirred for 3 h and kept overnight. After 24 h. the solution was filtered through muslin cloth and the precipitate was washed 2 to 3 times with water. All drug polymer complexes were kept for drying in oven at 70^{0}C for 3 h and weighed. Practical yield was obtained by dividing the practical weight obtained from the sum of the weight of Metoclopramide HCL and Tulsion 339 added by using the following calculation.

$$\% \text{ yield of Drug polymer complex} = \frac{\text{Weight of solid dispersion}}{\text{Sum of the Metoclopramide HCL and Tul.339 added}} \times 100$$

Formulation of mouth dissolving tablet of drug polymer complex

Selection of superdisintegrant

Before formulation of tablets, the best superdisintegrant among Tulsion 339, Ac-Di-Sol, and Sodium starch glycolate was evaluated for suitability in the formulations as per Table 1.

Table 1: Selection of Superdisintegrant

Batchs	Disintegrant	Disintegrant %w/w	Diluents %w/w	Disintegration time (sec.)
D1	---	---	100	64
D2	Tul 339	8	92	9
D3	Tul 339	10	90	11
D4	Tul 339	12	88	11
D5	Ac-Di-Sol	8	92	32
D6	Ac-Di-Sol	10	90	25
D7	Ac-Di-Sol	12	88	19
D8	SSG	8	92	43
D9	SSG	10	90	41
D10	SSG	12	88	33

Tablets were prepared in various batches containing a blend of microcrystalline cellulose and mannitol (1:1) as a diluents and superdisintegrant in various concentrations. The best superdisintegrant was screened and used for the final formulation. All materials were passed through sieve no. 40 # Drug polymer complex (1:2.25) was mixed with diluents and Superdisintegrants. Sweetener and flavor was added to above blend, lubricated with magnesium-stereate. Powder blend was compressed on eight station rotary compression machine using flat punches as shown in Table 2. Orodispersible tablets was prepared by using direct compression technique.

Table 2: Formulation of Orodispersible Tablet

Batches	Ingredients (mg)						
	DPC*	Micro Crystalline Cellulose	Mannitol	Tulsion339	Sod. saccharine	Magnesium stearate	Orange flavor
F1	35	160	--	--	1	1	3
F2	35	--	160	--	1	1	3
F3	35	80	80	--	1	1	3
F4	35	144	--	16	1	1	3
F5	35	--	144	16	1	1	3
F6	35	72	72	16	1	1	3

* Drug polymer complex (DPC) equivalent to 10 mg of Metoclopramide HCL.

Evaluation of formulated tablet

Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of blend were determined of powder blend. [7,8]

Hardness

Hardness or tablet crushing strength the force required to break a tablet in a diametric compression. [9, 10] It is expressed in kg/cm^2.

Thickness

The thickness of the tablets was measured using vernier calliper. It is expressed in mm.

Friability

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were

de dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula. [11]

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Wetting time & Water Absorption Ratio

A piece of paper folded twice was placed in Petri dish having internal diameter of 5 cm containing 6 ml of water. [12, 13] A tablet was placed on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed for % water absorption ratio.

It was determined using the equation

$$R = \frac{100(Wb - Wa)}{Wa}$$

Where, Wa = Weight of tablet before water absorption

Wb = Weight of tablet after water absorption.

In-vitro disintegration time

The in-vitro disintegration time was determined using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds. [14, 15] Tablet was added to phosphate buffer solution pH 6.8 (which correlates pH of saliva) at 37±0.5°c. Time required for complete disintegration of tablet was measured.

Drug Content

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 10 mg of anhydrous Metoclopramide hydrochloride, add 50 ml of 0.1M hydrochloric acid, heat on a water-bath at 70º for 15 minutes, cool, dilute to 100.0 ml with water and filter. To 20.0 ml of this solution add 15 ml of 1.25M sodium hydroxide and extract with three quantities, each of 30 ml, of chloroform, dry each extract with anhydrous sodium sulphate and filter. Dilute the combined extracts to 100.0 ml with chloroform and mix. Measure the absorbance of the resulting solution at the maximum at about 305 nm.

In-vitro dissolution study

In vitro drug release study of DPC of Metoclopramide HCl was performed in USP dissolution apparatus Type 2 (paddle).Phosphate buffer ph 6.8 was used as a dissolution media. The bowls of the dissolution tester was filled with 900 ml of phosphate buffer PH 6.8 and allows to attaining a temperature of 37±0.5ºc and 50 rpm. Dissolution apparatus was started. At predetermined time interval i.e.1, 2, 3, 4, 5, 6 min. 5ml sample withdrawal and addition of fresh dissolution media. The collected samples were filtered and absorbance of the solution was measured at 305 nm. The concentration of Metoclopramide HCl was calculated using slope of calibration curve and cumulative percentage release was calculated.

Drug Release from MDT and marketed

From the results of the tests, tablets of batch F5 were considered to posses the best physical properties accompanied with quick disintegration and, therefore, tested and compared with the marketed tablet for dissolution. The dissolution study of the optimized tablet revealed rapid release.

Characterization of DPC and Molecular Properties

Molecular properties on complexation were studied by x-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR). The X-ray powder diffractograms of the DPC (1:2.25), Metoclopramide HCl and Tulsion 339 were recorded using a Philips PW 1729 X-ray diffractometer (Legroupe Interconnection, Canada) with monocrotized Cu Kα radiation (1.314 A0), at a speed of 2θ min–1 from 10- to 60- (2θ) under the voltage and current of 40 Kv and 30 Kv respectively (Figure14, 15 and 16). Infrared (IR) spectra of these samples were obtained by KBr disc method (1800, Shimadzu Asia Pacific Pvt. Ltd, Singapore) in the range of 4000 to 400 cm–1. [16, 17]

RESULTS AND DISCUSION

The angle of repose for the entire formulations blend was found to be in the range of 26.12º to 33.21º. Compressibility Index was found to be in the range of 14.61%. Bulk density was found to be in range of 0.26

to 0.51. Tapped density and Hausner ratio was also carried out. And found in the range of 0.35 ± 0.35-0.60 ± 0.39, 1.10 ± 0.17-1.34 ± 0.16.Drug content in drug polymer complex was found 98.5 ± 0.5 [Table 3].

Table 3: Physical Properties of Tablet Blend

Parameters	Formulation					
	F1	F2	F3	F4	F5	F6
Angle of repose	42.1± 0.55	37.8± 0.32	34.1± 0.51	31.0± 0.44	27.5± 0.65	33.0± 0.47
Bulk density	0.26 ± 0.29	0.51 ± 0.24	0.49 ± 0.25	0.49 ± 0.36	0.46 ± 0.63	0.47± 0.19
Tapped density	0.35 ± 0.35	0.60 ± 0.39	0.54 ± 0.28	0.58 ± 0.19	0.50 ± 0.42	0.54± 0.23
% Compressibility	25.4± 0.13	15.0± 0.37	9.82 ± 0.23	14.4± 0.30	8.37 ± 0.17	11.4± 0.18
Hausner ratio	1.34 ± 0.16	1.17 ± 0.12	1.16 ± 0.14	1.17 ± 0.14	1.10 ± 0.17	1.12± 0.16

All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. The hardness of the table was found to be between 2.85 to 5.5 kg/cm^2. The maximum thickness of the formulation was found to be 4.19 mm and the minimum thickness of the formulation was found to be 4.10 mm. The average thickness of all the formulation was found to be 4.15 mm. The maximum friability of the formulation was found to be 0.23 % and the minimum friability of the formulation was found to be 0.15%. The friability was less than 1% in all the formulations ensuring that the tablet were mechanically stable.

The results of disintegration of all the tablets were found to be within prescribed limits and satisfied the criteria of Orodispersible tablet. The values were found to be in the range of 75± 1.32 to 131 ±.041 sec. The wetting time and water absorption ratio was also in acceptable limit i.e. between 52.34 ± 1.10 to 111.04 ±1.44 sec and 82.31 ± 0.35 to 84.62 ± 0.20. The maximum drug content for all formulation was found to be 100.84% and the minimum % drug content was found to be 98.89 % .The result were complies the Pharmacopeial limits [Table 4].

Table 4: Evaluation of Physical Parameter of Tablet

Parameter	Batches					
	F1	F2	F3	F4	F5	F6
Thickness (mm)	4.11± 0.03	4.16± 0.06	4.15±0.02	4.14± 0.05	4.18± 0.02	4.18± 0.03
Hardness (kg/cm^2)	3.1±0.62	4.1±0.38	3.5±0.16	4.3±0.39	2.85±0.22	3.8±0.16
Weight variation	199 ±1.50	201± 1.85	198±1.66	200 ± 1.33	198± 1.79	201± 1.45
Friability (%)	0.18± 0.59	0.17± 0.14	0.22±0.34	0.16± 0.19	0.12± 0.24	0.18± 0.29
Disintegration Time (Sec)	95± 1.12	131± 1.49	100± 1.67	127± 1.52	75± 0.32	128± 1.15
Assay (%)	98.89	99.58	99.25	99.45	100.84	100.65
Wetting time (sec)	70± 0.112	111± 0.80	86± 1.90	101± 0.10	52± 0.90	100± 1.44
% Water absorption ratio	84.62±0.32	83.27±0.20	84.2±0.21	82.87±0.35	82.31±0.51	82.5±0.40

Dissolution Study in 6.8 pH phosphate buffer: formulation of F1, F2, F3, F4, F5 and F6 have a recorded drug release 98.5%, 97.8%, 98.2%, 98.6%,100.32% and 98.5% at the end of 07 min the results was showed in [Figure 1].

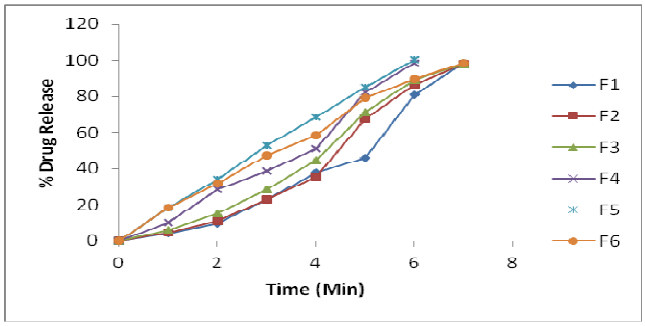

Figure 1: % Drug Release from Metoclopramide Orodispersible Tablet

The FTIR spectra of the pure drug were recorded in between 4000 to 400 cm^{-1}. Characteristics peak and chemical group present in IR spectrum of Metoclopramide was showed in[Figure 2,3,4] C-H Stretching of alkane at 2856-2939 cm^{-1}, C=O stretching of amide at 1650-1690 cm^{-1}, C=C stretching aromatic at 1550 cm^{-1}, N-H stretching of amine at 3249-3323 cm^{-1}, C-N stretching at 1275 cm^{-1} Can be seen in spectra of individual drugs as well as in spectra of physical mixture. So there is no interaction between Metoclopramide and Tulsion 399.

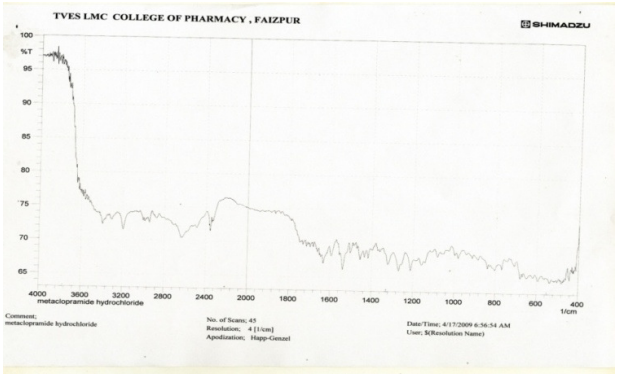

Figure 2: IR Spectrum of the Metoclopramide Sample

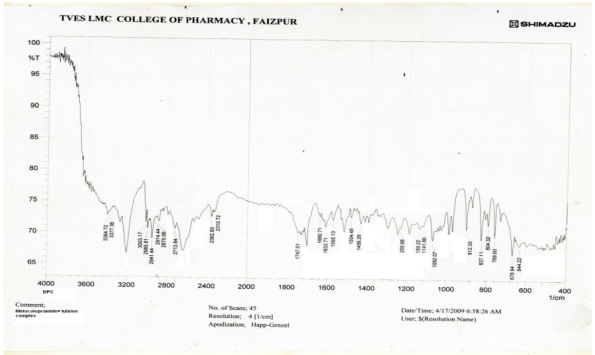

Figure 3: IR Spectrum of the Metoclopramide Tulsion complex

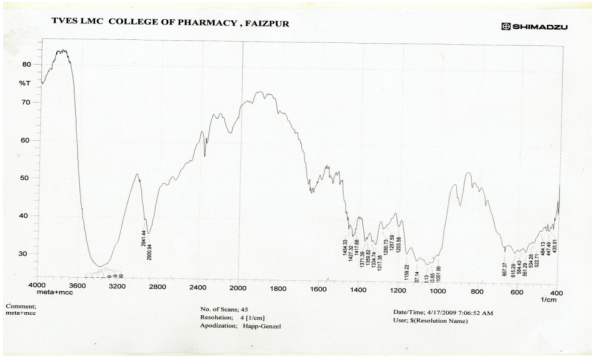

Figure 4: IR Spectrum of the Physical mixture

The x-ray diffractogram of Metoclopramide HCl confirms its crystalline nature, as evidenced from the number of sharp and intense peaks [Figure 5, 6,7]. The diffractogram of polymer (Tulsion 339) showed diffused peaks, indicating its amorphous nature while the diffraction pattern of the drug polymer physical mixture showed simply the sum of the characteristic peaks of pure drug and the diffused peaks of polymer, indicating presence of drug in the crystalline state. However, the diffraction pattern of DPC represents complete disappearance of crystalline peaks of drug**.** These findings suggest the formation of a new solid phase with a lower degree of crystallinity due to complexation.

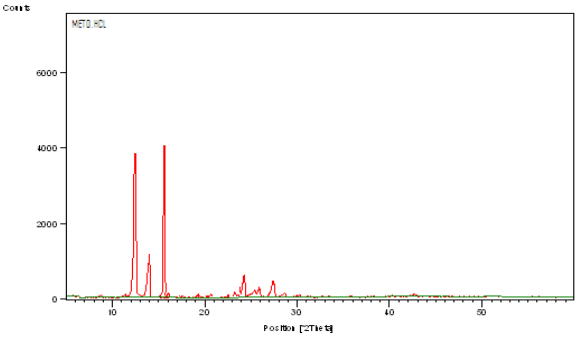

Figure 5: XRD of Metoclopramide Hydrochloride

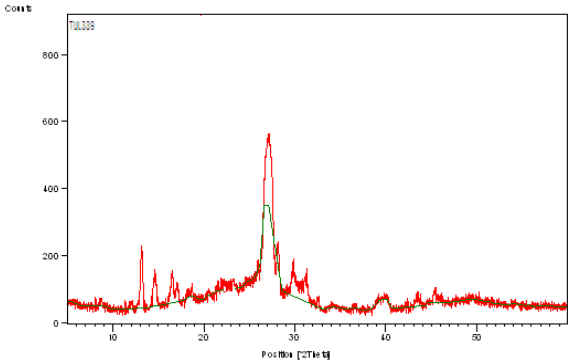

Figure 6: XRD of Tulsion 339

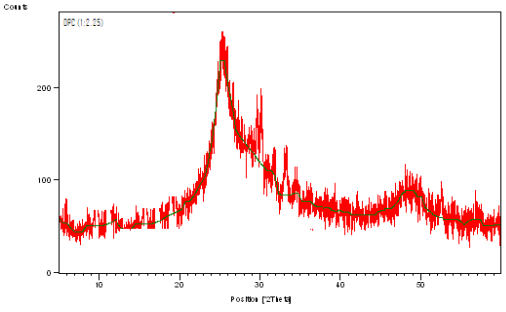

Figure 7: XRD of Metoclopramide:Tulsion complex

Effect of increasing concentration of Tulsion 339 on dissolution of Metoclopramide hydrochloride orodispersibletablets compared with marketed conventional tablet. Formulations which contained increasing concentrations of Tulsion 339 from 6%, 8% and 10%, were recorded 100% dissolution of drug within 7 min., 6 min. and 5 min. respectively. Given in [Figure 8].

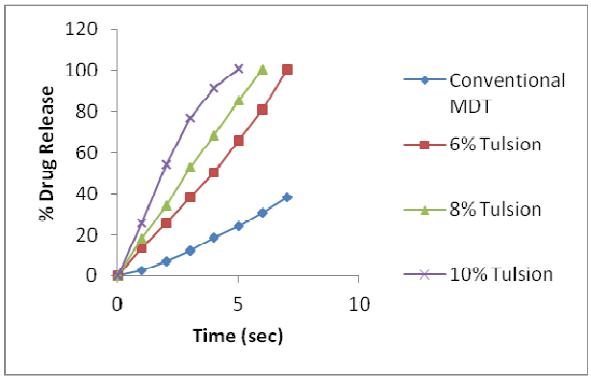

Figure 8: Comparison with Marketed Conventional Tablet

CONCLUSION

The Present study was undertaken with an aim to formulate and evaluated Taste masked orodispersible tablets of Metoclopramide Hydrochloride using direct compression method with the addition of super disintegrating agents Tulsion 339. Preformulation study was carried out initially with study of selection of superdisintegrants was done and different formulations were prepared using superdisintegrants Tulsion339 and different excipients. Results of all the physical and in-vitro dissolution data, *In-vitro* disintegration study was performed and from all evaluation data concluded that the F-5 formulation was the best one. From the present study it may be concluded that formulation of orodispersible tablet of Metoclopramide Hydrochloride containing superdisintegrants Tulsion339 and mannitol is suitable and can be taken as an ideal formulation.

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