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FORMULATION AND DEVELOPMENT OF FAST DISSOLVING TABLET OF METOCLOPRAMIDE: AN ANTI-EMETIC DRUG

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ABSTRACT:

Aim: The main of the study is to formulate and develop orally disintegrating fast dissolving tablet of Metoclopramide hydrochloride.

Material & Methods: Before formulation and development of selected drug, the standard curve in buffer was prepared and absorbance at selected maxima was taken. Then two different disintegrating agents were selected and drug was mixed with disintegrating agents in different ratio. Various Preformulation parameters and evaluation of tablet i.e. disintegration time, dissolution time, friability, hardness, thickness were measured by standard procedure.

Result & Discussion: The angle of repose for all the batches prepared. The values were found to be in the range of 30.46 to 36.45, which indicates good flow property for the powder blend according to the USP. The bulk density and tapped density for all the batches varied from 0.49 to 0.54 g/mL and 0.66 to 0.73, respectively. Carr's index values were found to be in the range of 23.33 to 25.88, which is satisfactory for the powders as well as implies that the blends have good compressibility. Hausner ratio values obtained were in the range of 1.22 to 1.36, which shows a passable flow property for the powder blend based on the USP. The results for tablet thickness and height for all batches was found to range from 4.45 to 4.72 mm and 3.67 to 3.69 mm, respectively. Hardness or breaking force of tablets for all batches was found to range from 32.8 to 36.2 N. Tablet formulations must show good mechanical strength with sufficient hardness in order to handle shipping and transportation. Friability values for all the formulations were found to be in the range of 0.22 % to 0.30 %.

Conclusion: Orally disintegrating tablets were compressed in order to have sufficient mechanical strength and integrity to withstand handling, shipping and transportation. The formulation was shown to have a rapid disintegration time that complied with the USP (less than one minute). The data obtained from the stability studies indicated that the orally disintegrating mini-tablets of MTH were stable under different environmental storage conditions.

Keywords: Formulation & Development, Fast Dissolving Tablet, Metoclopramide, Anti-Emetic Drug, Oral Disintegrating Tablet

Introduction:

Tablet production can deliver the maximum output per manufacturing hour and is the most economical, particularly if one considers modern industrial methods including the process of direct compression.

Direct Compression represents the simplest and most cost-effective tablet manufacturing technique. This technique can now be applied to orally disintegrating tablets because of the availability of improved tablet excipient, especially tablet superdisintegrants and sugar-based excipient [1].

Orally disintegrating tablets (ODTs) can be defined as solid single-unit dosage forms that are intended to be placed in the mouth, and then swallowed without the need of water [2]. The tablet will disperse or dissolve in the saliva instantaneously, within seconds and swallowed easily as residue with no difficulty [3]. The faster the drugs disintegrate and dissolution occurs, the quicker the absorption and onset of clinical effect.

Metoclopramide Hydrochloride, the systematic (IUPAC) name known as, 4-amino-5-chloro-N-[2-(diethylamino) ethyl]-2 methoxybenzamide monohydrochloride monohydrate [4]. It has a chemical formula of C14H22ClN3O2·HCl and a molecular weight of 354.27 g/mol. According to the USP, Metoclopramide Hydrochloride contains not less than 98.0% and not more than 101.0% of metoclopramide hydrochloride (C14H22ClN3O2·HCl·H2O), calculated on the anhydrous basis [5]. Metoclopramide Hydrochloride is a white, crystalline powder, odorless substance, very soluble in water and freely soluble in alcohol, and sparingly soluble in methylene chloride.

Such anti-emetic drug, after oral dosing undergoes extensive gastric and first pass effect. This results in low bioavailability which therefore, will not minimize the rate of vomiting. In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as fast dissolving tablets. Fast dissolving tablet of anti-emetic drugs are designed for rapid and complete absorption in the body and for achieve therapeutic success.

MATERIAL & METHODS

Preparation of Standard Calibration Curve of Metoclopramide HCl

Preparation of Standard Stock Solution

Standard stock solution was prepared by accurately weighed 10 mg of MTH using digital balance and transferred to a 500 ml volumetric flask. 250 mL of simulated gastric fluid was added to the same volumetric flask and swirled for solublization.

Preparation of Sample Solutions

5 mL sample solutions were prepared to have a concentration of 2, 4, 6, 8, 10, 15, and 20 µg/mL. The standard stock solution was used as the highest concentration of the linearity range study.

Measurement of Absorbance and Calibration Curve

The absorbance of solutions containing 10µg/ml was determined in UV range 200-800 nm using SGF as blank. The λmax was found to be at 272 nm. At this wavelength maximum, calibration curve was drawn by plotting graph between absorbance and concentration.

Preparation of MTH Powder Mixtures with Superdisintegrants

Preparation of MTH orally disintegrating tablets was occurred by using two superdisintegrants excipient Sodium starch glycolate and Crospovidone.

Physical Evaluation of Prepared Blend for Compression

Angle of Repose

The angle of repose was determined according to a recommended procedure described in USP 36. The peak of the cone may be misshaped by the strength of the powder flowing from the funnel. [6].

Loose Bulk Density (LBD)

This is the ratio of the total mass of powder to the bulk volume of powder [7]. Accurately weigh a portion of powder mixture (40 g) and transfer it to a 100 ml graduated cylinder. [8].

Tapped Bulk Density (TBD)

This is the ratio of total mass of the powder to the tapped volume of the powder [7].

Compressibility Index (Carr's Index)

Standard equation describes the calculation of the Compressibility Index of the powder mixture by using bulk density and tapped density. It measures the powder flow ability and is expressed in percentage [8].

Hausner Ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. [8]. It is an indirect index to measure the ease of powder flow [7].

Evaluation of Orally Disintegrating Tablets of MTH

Tablet Appearance

Twenty tablets of each formulation were tested to check any discoloration or surface roughness in tablet formulation.

Weight Variation

Ten (10) tablets of each batch formulation were selected randomly and weighed in grams individually and accurately using digital balance. Figure 8-8 illustrates an Intelligent Weighing Technology's model PM-300 balance, Intelligent Weighing Technology, Inc. (Camarillo, CA).

Tablet Hardness and Thickness

It is the force required to break the tablet into halves by compression in the diametrical direction. Ten (10) tablets were selected randomly and

measured individually for thickness and hardness using Sotax Hardness Tester [9]. The tablets measured in mm for the thickness and Newton (N) for the breaking force using USP Standard method.

Tablet Friability

The tablet friability test determination was achieved accodring to the United States Pharmacopeia and National Formulary (USP 36-NF 31) using an Erweka Friability Apparatus [8, 10, 11].

In-vitro Disintegration Time Test

The test was carried out on six tablet using DI water at 37±5 °C as a medium and Erweka disintegration apparatus according to USP 36-NF 31standard basket method with disks [10]. Each tablet should be placed in each of the six tubes of the disintegration basket apparatus, one disc was added to each tube, and run for disintegration time [12]. The time was measured in seconds for complete disintegration of the tablet with no palpable mass remaining in the apparatus. In case if one or two tablets fail to disintegrate completely, the test must be repeated at least on 12 additional tablets. The USP requires at least 16 of the total of 18 tablets that tested are disintegrated [13].

In-vitro Dissolution Test

In-vitro dissolution test of metoclopramide hydrochloride ODT was performed triplicate for each batch using simulated gastric fluid (SGF) and AT 7smart Dissolution Apparatus from SOTAX. It is a dissolution apparatus that compliant with all pharmacopeia methods including USP 1,2,5,6, [14]. 900 mL of the hydrochloric acid buffer of pH 1.2 was used as dissolution medium. The paddle speed was adjusted to rotate at 50 rpm. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment.

Accelerated Stability Study of Optimized Batch

Accelerated stability studies for orally disintegrating tablets were established according the ICH guidelines. The change in in-vitro release profile on storage was determined for the optimized batch. It was subjected to the stability studies for eight weeks on both packaging systems and stored under the following conditions:

✓ 25 ± 2°C and the relative humidity (RH) should be 60% ± 5.

✓ 40 ± 2°C/ and the relative humidity (RH) should be 75% ± 5.

Relative humidity chambers were established by creating an excess of water soluble salt in contact with its saturated solution in baby food jars according to the CRC Handbook of Chemistry and Physics [15-18], and the temperature of 40±2°C was achieved by keeping the baby food jars in the oven. The tablets were withdrawn after weeks 1, 2, 3, 4, 5, 6, 7, and 8 to analyze the physical-chemical properties such as appearance (any color change or visual defect), hardness, and dissolution release test.

RESULT & DISCUSSION

Metoclopramide HCl (MTH) orally disintegrating mini-tablets were prepared using various ratios of superdisintegrants by direct compression. The superdisintegrants Primojel and Polyplasdone XL were used in various concentrations, namely 3%, 5%, and 7% to formulate the orally disintegrating mini-tablets of MTH.

The absorbance of the diluted solutions for MTH was measured using UV-Vis and the concentrations were extrapolated from the calibration curve [19].

Table 1: Linearity range study of MTH at 272 nm

S No	Dilution (μg/mL)	Absorbance
1	2	0.056
2	4	0.146
3	6	0.222
4	8	0.296
5	10	0.356
6	20	0.732

For direct compression, the flow ability of the powder blend is very important. Therefore, two methods were used for powder flow ability measurements. The bulk density and tapped density for the powder blends were determined to calculate the Hausner ratio and Carr's index. The second method for flow ability characterization was to determine the angle of repose.

Table 2 showed the data obtained for the angle of repose for all the batches prepared. The values were found to be in the range of 30.46 to 36.45, which indicates good flow property for the powder blend according to the USP.

Table 2: Flow properties of the powder blends angle of repose value

S No	Formulation	Angle of Repose
	F1	30.46±0.32
	F2	33.44±0.81
	F3	34.53±0.44
	F4	34.86±1.55
	F5	35.74±1.32
	F6	36.45±1.55

Table 3 provides the data obtained for the Carr's index and Hausner ratio for all the formulation batches. The bulk density and tapped density for all the batches varied from 0.49 to 0.54 g/mL and 0.66 to 0.73, respectively. Carr's index values were found to be in the range of 23.33 to 25.88, which is satisfactory for the powders as well as implies that the blends have good compressibility. Hausner ratio values obtained were in the range of 1.22 to 1.36, which shows a passable flow property for the powder blend based on the USP.

Table 3: Flow properties of the powder blends: bulk and tapped density, Carr's index, and Hausner ratio.

Formulation	Density (g/ml)		Flow Properties	
	Bulk	Tapped	Carr's Index	Hausner ratio
F1	0.49	0.66	23.33	1.22
F2	0.47	0.61	23.84	1.35
F3	0.49	0.68	24.21	1.37
F4	0.53	0.72	24.62	1.31
F5	0.56	0.74	24.78	1.39
F6	0.54	0.73	25.88	1.36

The all readings are in average of triplicate.

Table 4 represents the evaluation parameters for Metoclopramide hydrochloride orally disintegrating mini-tablets such as appearance, weight variation, thickness, height, hardness, friability, disintegration time, and drug content (dissolution time test).

Oral fast dissolving tablets of selected drug were prepared and examined visually for shape and color. A white color and concaved surface with circular shape was observed after compressing the formulations. All tablets passed the weight variation test and were found to be within the acceptable limit according to the USP. The results for tablet thickness and height for all batches was found to range from 4.45 to 4.72 mm and 3.67 to 3.69 mm, respectively. Hardness or breaking force of tablets for all batches was found to range from 32.8 to 36.2 N. Tablet formulations must show good mechanical strength with sufficient hardness in order to handle shipping and transportation. Friability values for all the formulations were found to be in the range of 0.22 % to 0.30 %. The results obtained were found to be within the acceptable range (<1%), indicating sufficient mechanical integrity and strength for the prepared tablets according to the USP. The disintegration time test was used based on the USP. According to the test, all of the tablet formulations should disintegrate completely within one minute which indicates faster disintegration. The percent drug content for all the formulations were calculated by measuring the absorbance at the wavelength 272 nm, and were found to be between 98.65% to 99.53%, which is within the acceptable limits as per USP.

Table 4: Evaluation parameters of Metoclopramide orally disintegrating tablets

Formulation	Weight variation (mg)	Thickness (mm)	Height (mm)	Hardness test (N)	Friability test (%)	Disintegration time (Sec)	% Drug content
F1	103.5±2.12	4.45±0.31	3.67±0.03	32.8±3.44	0.22	18.0±1.11	98.65±3.11
F2	104.5±1.22	4.45±0.01	3.55±0.04	40.5±2.77	0.28	14.4±1.44	95.11±1.34
F3	103.5±1.14	4.48±0.07	3.67±0.07	38.4±2.14	0.21	12.4±1.14	97.11±1.22
F4	104.2±1.56	5.34±0.06	3.22±0.04	41.3±2.81	0.20	37.7±3.29	97.22±1.44
F5	102.3±1.34	4.71±0.08	3.68±0.07	34.5±2.22	0.22	26.4±2.71	96.11±2.27
F6	104.5±1.56	4.72±0.09	3.69±0.05	36.2±3.55	0.30	49.7±2.44	99.53±2.78

Based on data analysis for the tablet evaluation, the various impact on the flow properties for blend, friability, disintegration time, wetting time, and drug release behavior of the tablets lead to selecting an optimized formulation for the batch. Eventually, Formulation 6 was selected for accelerated stability studies. Table 5 showed the evaluation parameters for the optimized batch that used amber cello blister package upon storage condition at 25°C/ RH 60% for eight weeks. The evaluation of the short-term stability studies included physical appearance, weight variation, thickness, hardness, disintegration time, and drug content.

Table 5: Stability studies evaluation parameters for the optimized batch

Time in week	Physical Appearance	Weight variation (mg)	Thickness (mm)	Hardness (N)	Disintegration Time (Sec)	Drug Content
1	No Change	98±2.22	4.34±0.02	27.3±2.33	31.3±2.21	99.2±2.23
2	No Change	99±1.12	4.22±0.03	24.4±2.12	32.4±2.31	96.18±1.22
3	No Change	99.2±2.11	4.44±0.01	25.4±2.22	31.2±3.12	97.13±2.45
4	No Change	98±1.22	4.45±0.01	26.1±2.22	30.3±2.13	99.2±2.11
5	No Change	97±2.13	4.21±0.21	23.2±2.34	28.2±2.11	92.34±1.48
6	No Change	99±1.23	4.32±0.12	25.1±1.11	27.3±2.44	98.15±2.31

CONCLUSION

The orally disintegrating mini-tablets of MTH were prepared using the above superdisintegrants excipients and evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. Post-compression parameters such as weight variation, hardness, friability, disintegration time, wetting time, dissolution analysis, drug content uniformity, and finally accelerated stability studies for the optimized batch were also evaluated.

In the beginning, the powder blends for the formulations were evaluated using their flow ability property. Carr's index values were found to be satisfactory for the powders as well which suggest that the blends had good compressibility. Hausner ratio values obtained were shown to be a passable flow property for the powder blend based on the USP.

Orally disintegrating tablets were compressed in order to have sufficient mechanical strength and integrity to withstand handling, shipping and transportation. The formulation was shown to have a rapid disintegration time that complied with the USP (less than one minute). The mixing of powders and compression yielded an acceptable limit for the percent drug content. An optimized batch was achieved and it was determined to contain Polyplasdone XL 7% because it showed a faster drug release in the dissolution profile and a rapid disintegration time. Accelerated stability studies were accomplished in order to optimize the batch using two different packaging systems with two temperatures and relative humidity conditions for eight weeks. The data obtained from the stability studies indicated that the orally disintegrating mini-tablets of MTH were stable under different environmental storage conditions.

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