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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE USING NATURAL SWEETENING AGENT OF STEVIA LEAF POWDER

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ABSTRACT

Taste masking becomes a pre-requisite for bitter drugs to improve the patient compliance especially in the pediatric and geriatric population. Metoclopramide hydrochloride is recommended in dose of 10 to 15 mg four times a day for getting relief from nausea, vomiting, stomach pain and reflux oesophagitis. It finds application in all the categories of patients.In the present study an attempt has been made to prepare bitterless fast dissolving tablet of Metoclopramide Hydrochloride using stevia leaf powder as a taste masking agent. Direct compression was the technique used for preparing taste masked tablets.
Keywords: Fast dissolving tablets, Metoclopramide hydrochloride, Steavia leaf, Direct compression, Taste masking.

INTRODUCTION

Patients, particularly pediatric and geriatric patients, have difficulty in swallowing solid dosageforms. These patients are unwilling to take these solid preparations due to a fear of choking. Inorder to assist these patients, several mouth dissolving drug delivery systems has been developed. Fast dissolving tablets can be prepared by direct compression, wet granulation, moulding, spray drying, freeze drying or sublimation methods [1]. Fast dissolving tablets dissolve rapidly in the saliva without the need for water, releasing the drug [2, 3].

Metoclopramide hydrochloride a derivative of paraaminobenzoic acid, is a commonly prescribed drug used for the management of gastrointestinal disorders such as gastric stasis, gastroesophageal reflux [4] and for the prevention of cancer chemotherapy- induced emesis [5]. 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 FDTs. Metoclopramide HCl is an intensely bitter drug; hence, if it is incorporated directly into an FDT the main objective behind formulation of such a dosage form will definitely get futile.

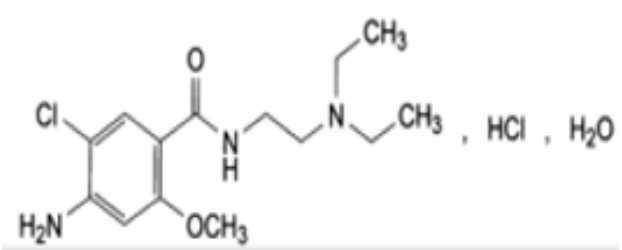

Fig. 1: Structure of Metoclopramide Hydrochloride

Taste masking of Metoclopramide HCl was carried out by using Stevia leaf powder (Sweetening method). These taste masked granules or complex was further formulated into the mouth-dissolving tablet by direct compression method using

sodium starch glycolate, crosscarmellose sodium and crospovidone as the superdisintegrants.

MATERIALS AND METHODS:

Metoclopramide hydrochloride was a gift sample from Rohini chemicals Haridwar (India). The Stevia leaf powder was a gift sample from Noida (India). Crosspovidone, sodium starch glycolate, magnesium stearate, and talc powder were obtained from School of pharmacy, Lloyd college Greater noida (India). All ingredients used were of pharmaceutical grade.

Method

Preparation of fast dissolving tablets by direct compression method

Fast dissolving tablets of Metoclopramide HCL were prepared by direct compression. All the ingredients were passed through # 60-mesh separately. Then the ingredients were weighed and mixed and compressed with 10mm flat face surface punches using single tablet punching machine. (7)

Assessment of the bitter taste of the metoclopramide hydrochloride (bitterness threshold)

The bitter taste threshold value of metoclopramide hydrochloride was determined based on the bitter taste recognized by six volunteers (three females and three males). A series of metoclopramide hydrochloride aqueous solutions were prepared at different concentrations as standard solutions, i.e. 5, 10, 15, 20, 25, 30, 35, 40 and 45 μg/ml, respectively. The test was performed as follows: 1 ml of each standard solution was placed on the center of the tongue, it was retained in the mouth for 30 s, and then the mouth was thoroughly rinsed with distilled water. The threshold value was correspondingly selected from the different metoclopramide hydrochloride concentrations as the lowest concentration that had a bitter taste.(8)

EVALUATION PARAMETERS

Preformulation studies:

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form. Hence, the following preformulation studies were performed on the obtained sample of drug.

Bulk Density (Db):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume iscalled the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M / Vb$$

Where, M is the mass of powder & Vb is the bulk volume of the powder.

Tapped Density (Dt):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted

Table 1: Composition of Fast Dissolving Tablets of Metoclopramide Hydrochloride

Ingredients (mg)	**Formulatios**				
	F1	**F2**	**F3**	**F4**	**F5**
Metoclopramide Hydrochloride	50	50	50	50	50
Mannitol	50	50	50	50	50
Sodium starch glycolate	10	20	30	40	50
Cross povidone	50	40	30	20	10
Stevia leaf powder	10	10	10	10	10
Magnesium stearate	10	10	10	10	10
Talc	5	5	5	5	5
Flavoring agant	15	15	15	15	15
Total weight of the tablet 200 mg					

if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M / Vt$$

Where, M is the mass of powder & Vt is the tapped volume of the powder.

Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose . It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\tan\theta = h / r \text{ therefore } \theta = \tan^{-1} (h / r)$$

Where,θ is the angle of repose, h is the height in cms & r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Table 2: Angle of Repose as an Indication of Powder Flow Properties

S.No.	Angle of Repose(θ)	Type of Flow
1.	<20	Excellent
2.	20-30	Good
3.	30-40	Passable
4.	>34	Very Poor

Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is give

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, Dt is the tapped density of the powder and

Db is the bulk density of the powder

Table 3: Relationship between % compressibility and flow ability:

S.No	%Compressibility	Flow ability
1.	5-12	Excellent
2.	12-16	Good
3.	18-21	Fair Passable
4.	23-35	Poor
5.	33-38	Very poor
6.	<40	Very Very Poor

Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Where, Dt is the tapped density.

Db is the bulk density.

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression Methods:

Tablet hardness

The strength of tablet is expressed as tensile strength (Kg/cm2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester).[9]

Thickness

Three tablets were selected randomly from each formulation and their thickness was measured with Vernier caliper. The mean ± SD values were also calculated.

Weight Variation Test

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation was calculated. IP limit for weight variation in case of tablets weighting up to 120 mg is ± 10%, 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%.

PD= (W**avg**) – (W **initial**) / (W **avg**) x 100

Where PD= Percentage deviation,

W**avg** = Average weight of tablet,

W**initial** = Individual weight of tablet.

Friability

Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed 20 tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed.[10]

Drug Content

Ten tablets were powered and the blend equivalent to 5 mg of metoclopramide hydrochloride was weight and dissolved in suitable quantity of pH 1.2 solutions. Solution was filtered and diluted and drug content analyzed spectrophotometrically at 239 nm using Shimadzu Corporation, UV-1601, Japan.

Disintegration Test

Disintegration time is very important for ODTs which is desired to be less than 60 seconds. This rapid disintegration assists swallowing of the tablet and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. In vitro disintegration time was determined using disintegration test apparatus (Electrolab, USP model ED-2L, Mumbai) without disk for six tablets. The disintegration medium was 900 mL of distilled water kept at 37 ± 0.5°C and stirred at a rate of 30±2 cycles/min. The time was measured in seconds for complete disintegration of the tablet with no palpable mass remaining in the apparatus. The test was carried out in triplicate.

Wetting Time and Water Absorption Ratio

A piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing 6 ml of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. The same procedure without amaranth was followed for determining the water absorption ratio.[11] The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation,

$$R = 100 (W_a - W_b)/W_b$$

Where, W**b** and W**a** were the weights of the tablet before and after study.

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and *in vitr*o dispersion time was performed.[12,13]

Dissolution Studies of Formulated Tablets

The *Invitr*o dissolution study was carried out in USP dissolution test apparatus type2(paddle)

Dissolution Medium	: 900ml of simulated gastric fluid
Temperature	: 37 ± 0.5^{0}C
RPM	: 50
Tablets taken for	: 2 tablets were weighed & taken study
Volume withdrawn & replaced	: 5 ml every five minutes.
λ max	: 273 n
Beer's range	: 2 –25 mcg /ml.

Accelerated stability studies

Atahe promising formulation were tested stability for a period of 3 months at accelerated conditions of a temperature 40^{0}C and a relative humidity of 75% RH,for their drug content.

RESULTS AND DISCUSSION

Powder mixture of all the formulations were evaluated for various precompression parameters like bulk density, tapped density, Carr's index and Hausner's ratio using tap density apparatus.Bulk density was found in the range of 0.53-0.56 g/cm3 and tapped density between 0.62-0.79 g/cm3 as shown in table 4. Compressibility index was found to lie in the range of 12.00-30.14% with fair to good flow properties. Flow properties of powder can be judged from the angle of repose. The angle of repose <30° indicates free flowing material and >40° with poor flow properties. The angle of repose were found in the range of 27.13°-32.68° as given in table 2 showing that the blend was free flowing and can be used for direct compression.

All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness was shown in the range of 3.00 ± 0.11 to 6.10 ± 0.17 Kg/cm2 in all the formulations. The friability of all formulations was determined. The friability values of none of the formulations exceeded 1%. The results of friability indicate that the tablets were mechanically stable and can withstand rigors of transportation and handling. Thickness of all tablets was between 2.15±0.04 – 3.02±0.05 mm

showing fairly uniform tabletting. The results of disintegration of all the tablets were found to be within prescribed limits and satisfied the criteria of Fast dissolving tablet. The values were found to be in the range of 22.00 ± 8.26 to 88.80 ± .015 sec. Wetting time was used as parameter to correlate with disintegration time. Wetting is related to the inner structure of the tablets and hydrophilicity of the excipients. SSG swells rapidly and enormously with gelling. This may be due to the fact that SSG is disintegrated by swelling mechanism leading to longer wetting time.the wetting time was ranged from 43.86±3.24 – 92.00±1.51sec. These values were represented in Table5. Sensory evaluation of the optimized tablet proved good palatability.

All the formulations showed angle of repose within 300 which indicates good flow. The values of loose bulk density and tapped bulk density help in calculating the % compressibility of the powder.

All formulations show good compressibility. The formulated tablets were elegant and almost uniform thickness. All the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness. The weight loss after friability test was found well within the approved range (<1%) in all the formulation, indicates the tablets possess good mechanical strength. All the tablets passed weight variation test as per the pharmacopoeial limits. All formulations showed quick wetting, this may be due to ability of swelling and also capacity of absorption of water. All superdisintegrants have high water absorption capacity and cause swelling. All formulations showed disintegration time less than 95 seconds, indicates the swelling of disintegration substance suggested mechanism of disintegration. The volunteers felt good taste in all the formulations. As the formulation was not bitter due to the presence of stevia leaf powder,

Table 4: The physicochemical properties of granules

Formulation	Angle of Repose (θ)	Bulk Density	Tapped Density	Compressibility (%)
F1	32.68±0.50	0.56	0.65	13.84
F2	30.83±0.54	0.55	0.71	22.50
F3	28.20±1.54	0.55	0.62	12.00
F4	27.13±0.78	0.53	0.79	30.14
F5	27.61±0.63	0.54	0.64	15.15

Table 5: Evaluation parameters of Tablets

Formulation	Hardness (kg/cm^3)	Thickness (mm)	Friability (%)	Wetting time (sec)	Disintegration Time (sec)
F1	4.13±0.24	2.40±0.05	0.78±0.12	90.04±1.44	57.52±0.41
F2	6.10±0.17	3.02±0.05	0.56±0.09	92.00±1.51	39.00±2.32
F3	3.20±1.23	2.17±0.01	0.43±0.02	43.86±3.24	41.46±1.64
F4	3.00±0.11	2.15±0.04	0.26±0.08	99.00±1.47	22.00±8.26
F5	4.19±0.29	2.50±0.08	0.73±0.36	90.95±1.31	88.80±0.15
Number of trials(n) =3					

which is 400 times sweeter than sucrose. In oral disintegration all the formulations showed rapid disintegration in oral cavity. By observing the above results use of sodium starch glycolate and cross Povidone, indirect compression method results in hydrophilicity and swelling which in turn causes rapid disintegration. Thus these disintegrants are suitable in preparing the rapidly disintegrating tablets. This rapid dissolution might be due to fast breakdown of particles of superdisintegrants.

In all formulations the drug release was nearer to 100% within 12 minutes. The optimized formulations F4 was selected for accelerated stability studies and the tablets possessed the same parameters even after the stressed conditions, indicates good stability properties of formulation.

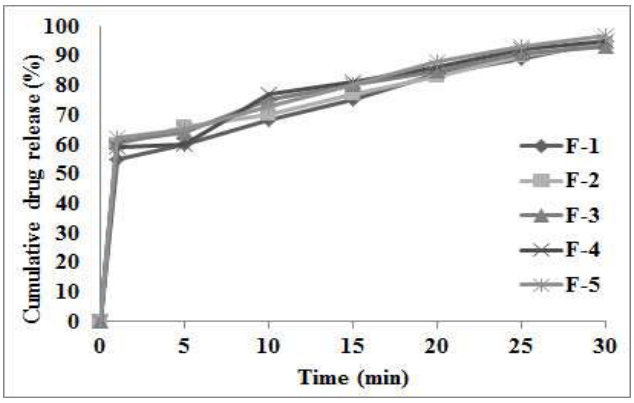

Fig2: *in-vitro* drug release profile of formulated tablets

CONCLUSION

The study achieved complete taste masking of metoclopramide HCL and rapid disintegration and dissolution of FDT. The prepared tablets disintegrate within few seconds without need of water,thereby enhance the absorption leading to its increased bioavailability and more palatable form during emesis.

Thus, the patient friendly dosage form of bitter drugs, especially for pediatric, geriatric, bedridden and co-operative patients, can be successfully formulated using this technology.

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