Formulation development of sugar free antacid chewable tablets for diabetes induced acidity in patients

Mehwish Khan[1], Hina Rehman[2], Rafia Usman[3], Sultan Ayaz[4], Fatima Qamar[5], Aymen Owais[6], Aisha Sana[4] and Safila Naveed[4]

[1]Department of Pharmacognosy, Faculty of Pharmacy, Jinnah University for Women, Karachi Pakistan
[2]Department of Pharmacy Practice, Institute of Pharmaceutical Sciences, Jinnah Sindh Medical University, Karachi Pakistan
[3]Department of Chemistry, N.E.D University of Engineering and Technology, Karachi Pakistan
[4]Department of Eastern Medicine, GC University, Faisalabad Pakistan
[5]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jinnah University for Women Karachi Pakistan
[6]College of Eastern Medicine, Jinnah University for Women, Karachi, Pakistan

Abstract: Sugar free chewable tablets are considered to be desired medication for diabetic population having acid reflex problems. The main objective of this study is to develop a patient complaint tablet dosage form which is sugar free, chewable and easy to use. The formulation is designed for hyperglycemic and dysphasic patients along acidity or stomach ulcer. For manufacturing Aluminum Hydroxide (Kyowa Japan), Magnesium Hydroxide (Taurus chemicals India) Simethicone, Povidone (JRS Pharma) Sorbitol powder, Magnesium stearate, Dilcalcium phosphate anhydrous, SSG (JRS Pharma) and Aspartame were used. The granules are formed by wet granulation method and tablets are compressed by rotary compression machine. The pre-formulation studies of granules (Angle of repose, Bulk/Tapped density, Carr's compressibility index and Hausner's ratio), uniformity of content (assay), acid neutralizing capacity, Identification by FTIR spectroscopy all are found within the limits as per USP specifications. All three formulation batches are stable under accelerated and ambient stability conditions for 6 months and 24 months respectively. The formulation development of sugar free oral chewable antacid tablet is pharmaceutically stable and can further analyze for safety and efficacy studies.

Keywords: Sugar free, acidity, chewable tablet, diabetes mellitus, antacid.

INTRODUCTION

Indigestion (Malavade and Hiremath, 2017) is a typical sign often leads towards heartburn, a condition where a portion of the gastric contents are constrained back up into the esophagus. It produces a burning sensation in the lower side of the chest (Soscia NP-Paeds and Friedman, 2011).Gastroesophageal reflux disease (GERD) is the disease in which persistent acid reflux taken place more than two times per week. Acid reflux or heartburn is a common effect of Gastroesophageal reflux disease (GERD) (Katz *et al*., 2013).

Patients with diabetes have high amounts of (glucose) in blood. That high glucose levels can harm the nerve (vagus nerve) which controls the gastric movements. Due to vagus nerve damage, the stomach muscles unable to perform regular function. The condition is called gastroparesis or delayed gastric emptying. Type 2 diabetes is known for gastroparesis (Association, 2014, Camilleri *et al*., 2013).

People with type II diabetes are obese and have frequent complain of GERD. As per World Journal of Gastroenterology 2008, GERD affects 40% of individuals with diabetes. Scientists observed that GERD effects with diabetes and creates complication including neuropathy extra pyramidal effects and neuropathies etc (Westerberg, 2013).

Various antacids are commercially available to relief hyperacidity and heart burn such as sodium bicarbonate, magnesium bicarbonate, Milk of magnesia, Sodium alginate, Calcium carbonates etc. The mentioned salts are available solely and in combination in market. The general mechanism of action of all antacids is neutralizing the acid content in stomach. The symptoms of heart burn characterized by a burning sensation in the chest after eating and lasts a few minutes to several hours or feeling of burning in the esophagus (Zerbib *et al.*, 2012). For the relief of heart burning in the stomach the use of antacid formulation are quite common (Lødrup *et al.,* 2013). Antacids neutralize stomach acids which relives the acid reflux (Camilleri *et al*., 2013). As antacids are quickly leaves from the stomach about one hour after a meal. Calcium-based antacids are only good for occasional symptoms because they may stimulate even more acid build-up if used regularly. Also, aluminum-based antacids may cause constipation, while magnesium-based may trigger diarrhea (Lødrup *et al.,* 2014). A combination of Aluminum hydroxide along with magnesium hydroxide and simethicone is very effective for the relief of

*Corresponding author: e-mail: drhinarehman@hotmail.com

heartburn but along with sugar content which is not suitable for diabetes patients. The aim of this study is to design chewable tablet same combination of salt along with sugar free ingredients which are suitable for a diabetes patient who is suffering from indigestion, heartburn or GERD.

MATERIALS AND METHODS

Chemicals/Ingredients

We have used Aluminium Hydroxide (Kyowa Japan), Magnesium Hydorixde (Taurus chemicals India) Simethicone, Povidone (JRS Pharma) Sorbitol powder, Magnesium stearate, Dilcalcium phosphate anhydrous, SSG (JRS pharma) and Aspartame for the manufacturing of sugar free chewable tablets. All reagents and equipment's used for formulation of tablets are of USP standard.

Manufacturing method

Wet granulation method was selected for the formulation development of chewable antacid tablets for validation and accuracy. We have manufactured three batches with the same formulation. First, by dissolving Povidone in hot purified water it acts a binding agent and sorbitol solution by dissolving sorbitol powder in purified water. After, we have make a dry blend of powder by mixing in a planetary mixer first we have added all three active pharmaceutical ingredients i.e. Aluminum hydroxide, Magnesium hydroxide and Simethicone and mixed for 2-3 mins after blending of API. Then added lactose monohydrate in dry blend. Now poured sorbitol solution followed by granulating fluid by continuous mixing. Kneaded it so that uniform homogenous mixture is formed.

Dry the granules in an oven or tray dryer at 60˚C. After drying sieve, the granules by S.S sieves for uniform sizing of granules. Added Magnesium stearate, after passing through sieve in to dried granules after that add Diacalcium phosphate anhydrous, Sodium starch glycolate and Aspartame and mix the granules for 5 mins.

Pre-formulation studies

Pre-formulation study is defined as the evaluation of the physical and chemical properties of Active pharmaceutical ingredient alone and when combined with the other excipients. The evaluation was done before the finished dosage form. The commonly evaluated pre-formulation parameters include angle of repose, bulk density/tapped density, pour density, Carr's compressibility index and Hausner ratio.

Angle of repose

Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion)-excipient blend allow to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation:

$\tan \Theta = h/r$

Where h and r are the height of cone and radius cone base respectively. Angle of Repose less than 30° shows the free flowing of the material.

Bulk density

Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. Bulk density can be calculated by using following formula:

Bulk density = Weight of the powder / Volume of the packing.

Tapped density

It is determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted. Tapped density can be calculated by using following formula:

Tapped Density = (Weight of the powder / volume of the tapped packing)

Hausner's ratio

A similar index to indicate the flow properties can be defined by Hausner's ratio. Hausner's ratio can be calculated by using following formula:

Hausner's ratio = (Tapped density x 100)/ (Poured density)

Compressibility index

The Compressibility Index of the blends is determined by compressibility index. Compressibility Index can be calculated by using following formula:

Compressibility Index (%) = [(TD-BD) X 100] / TD]

After pre-formulation studies granules are compressed in the form of tablets. The formed tablets are evaluated under USP specification. The commonly evaluated physical tests include weight variation, Friability, Thickness, and Hardness.

Identification Tests: Identification of Aluminum Hydroxide and Simethicone by FT-IR spectroscopy as per United States Pharmacopoeia (USP) monograph.

Assay of compressed chewable tablets is performed as per USP specification. Aluminum hydroxide and magnesium hydroxide is assayed by complexometric titration method as per USP specification (See USP monograph of Alumina, Magnesia and Simethicone tablets). The

percentage of label claim and content is calculated by the following formula

$$\text{mg/tablet} = \frac{\text{Titre vol x Titre factor x 200 x 3.900 x Avg.wt of tablet}}{\text{(Aluminum Hydroxide)} \quad \text{Wt of spl (mg) x 10}}$$

$$\text{mg/tablet} = \frac{\text{Titre vol x Titre factor x 200 x 2.916 x Avg.wt of tablet}}{\text{(Magnesium Hydroxide)} \quad \text{Wt of spl (mg) x 10}}$$

$$\text{mg/tablet} = \frac{\text{Weight of beaker (a - b) x Avg. wt of tablet x 1000}}{\text{(Simethicone) Wt of spl (mg) x 0.96}}$$

$$\text{\% age} = \frac{\text{mg/Tablet X 100}}{\text{(Aluminium Hydroxide) Label claim}}$$

Acid neutralizing capacity

Acid neutralizing capacity or acid consuming capacity is basically the capacity of antacid to neutralize acid (strong acids). We have performed ANC/ACC as USP monograph. The ANC value is calculated by the following formula.

Total mEQ= (30 x Normality of HCL)-(Volume of NaOH x Normality of NaOH)

Stability testing

Stability studies has been performed under ICH guidelines on all the 3 batches at accelerated conditions (40±2ºC/75±5% RH) for 6 months and at ambient conditions (30 ± 2 ºC/65±5% RH) for 24 months.

STATISTICAL ANALYSIS

The statistical values of Mean, Standard deviation and S.E.M have calculated by IBM SPSS Software 20.

RESULTS

Ratio and ingredients of chewable table has mentioned (see table 1). Pre-formulation studies have been performed successfully to determine the flow property of granules. For this purpose, we have performed angle of repose, bulk density/tapped density, pour density, Carr's compressibility index and Hausner ratio (see table 2). The mean and S.D value for Angle repose is 25.58 and 0.64, Bulk density 0.654 and 0.012, Tapped Density 0.848 and 0.021, Carr's Compressibility index 24.8 and 0.415 and for Hausner's Ratio is 1.243 and 0.020 respectively.

Compressed tablets of all the 3 batches show appropriate results in physical tests i.e. they exhibit good friability (Mean =0.02%), hardness (Mean=7 Kp), thickness (Mean=4.5mm) and weight variation.

Initial chemical testing of tablets of all three batches has performed. The Mean results of all 3 batches are 5.22%. They show positive FTIR spectrum as shown in fig.(a) (b) and (c). The Means Assay results of Aluminium hydroxide, Magnesium hydroxide and Simethicone are 201.54 mg per tablet, 203.15 mg per tablet and 21.450mg per tablet respectively. The mean acid neutralizing capacity is found to be 14.146 mEq per tablet. All results are within the required limits as per USP specification (see table 3).

Stability studies of all 3 batches has been performed and found satisfactory results under both climatic conditions i.e. accelerated conditions (40±2ºC/75±5% RH) for 6 months and at ambient conditions (30±2ºC/65±5% RH) for 24 months.

The mean values of % moisture content for F1, F2 and F3 at accelerated stability testing are 5.65%, 5.14% and 5.30% respectively while the mean values of % moisture content for F1, F2 and F3 at ambient stability testing are 5.28%, 5.19% and 5.54% respectively.

The mean values of acid neutralizing capacity for F1, F2 and F3 at accelerated stability testing are 15.29, 14.41, 14.95 respectively while The mean values of acid neutralizing capacity for F1, F2 and F3 at ambient stability testing are 14.77, 14.35, 14.62 respectively. The reference range as per USP specification the value of ANC is not less than 5 mEq per tablet the mean results are found to be satisfactory.

The mean assay results of Aluminium hydroxide, Magnesium hydroxide and Simethicone at accelerated climatic conditions stability testing (40±2ºC/75±5% RH) of F1 tablet formulation are found to be 202.960mg /tab (101.48%), 202.985mg/tab (101.492%) and 20.22mg/tab (101.1%) respectively. The mean results of F2 formulation are found to be 201.950mg /tab (100.97%), 200.36mg/tab (100.18%) and 20.385mg/tab (101.925%) respectively while F3 formulation shows means assay results of 201.180mg/tab (100.59%), 202.55 mg/tab (101.27%) and 20.62mg/tab (103.12%). These results are within the reference limits as mentioned in USP monograph.

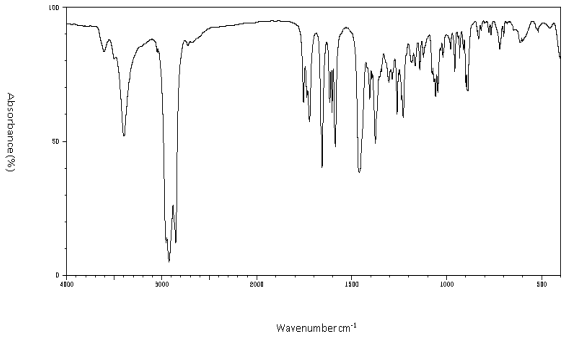
The mean assay results of Aluminium hydroxide, hydroxide and Simethicone at ambient stability testing (30±2ºC/65±5% RH) of F1 tablet formulation are found to be 202.45mg/tab, 201.664 mg/tab and 20.39 mg/tab respectively whereas for F2 formulation the results are found to be 200.79mg/tab, 200.82mg/tab and 20.27 mg/tab and F3 formulation shows results are 201.36mg /tab, 200.99mg/tab and 20.36mg/tab. These results are within the reference limits as mentioned in USP monograph.

Table 1: Formulation of antacid chewable tablets and their role of ingredients

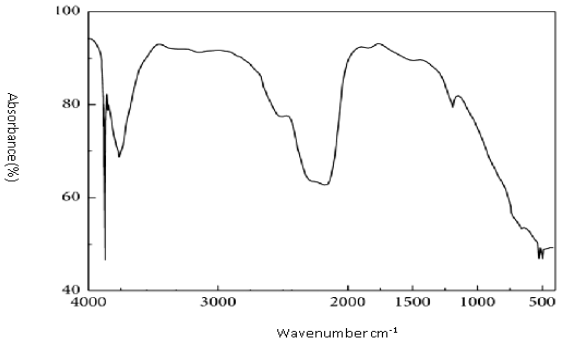
S. No	Ingredients	mg / % per unit tablet	Role of Ingredients
1	Aluminium Hydroxide	200 mg	API
2	Magnesium Hydroxide	200 mg	
3	Simethicone	25 mg	
4	Povidone	3.5%	Binding agent
5	Sorbitol Powder	14%	Sweetening agent
6	Magnesium Stearate	1 -2 %	Lubricant
7	Dicalcium Phosphate anhydrous	0.5%	Filler
8	Sodium starch glycolate	3%	Disintegrant
9	Aspartame	0.2%	Sweetening agent
10	Lactose Monohydrate	16%	Filler

Table 2: Pre-formulation studies of Granules (Evaluation of granules)

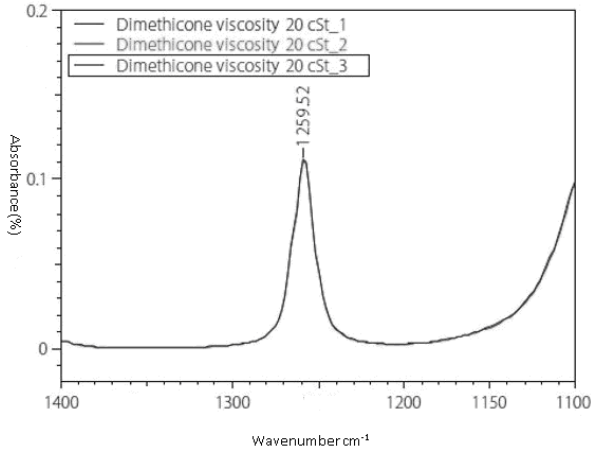
Formulation No.	Angle of repose	Bulk density (g/ml)	Tapped Density (g/ml)	Carr's Compressibility index	Hausner ratio
F1	24.93 ± .03	0.652	0.853	24.81	1.26
F2	25.60± 0.03	0.643	0.824	25.21	1.25
F3	26.21± 0.03	0.667	0.867	24.38	1.22
Mean	25.580	0.654	0.848	24.800	1.243
S.D	0.640	0.012	0.021	0.415	0.020
S.E.M	0.369	0.007	0.012	0.239	0.012



(a): FT-IR of Aluminum Hydroxide



(b): FT-IR of Magnesium Hydroxide



(c): FT-IR of Simethicone

Tablet 3: Chemical analysis of sugar free chewable antacid tablets

Formu-lation No.	Moisture content (By IR)	Identification by FTIR (Aluminium Hydroxide, Magnesium hydroxide, Simethicone)	Assay Aluminium hydroxide 200 mg per tablet (180mg-230 mg per tablet) (90.0%-115.0% of label claim)	Assay Magnesium hydroxide 200mg per tablet (180mg-230 mg per tablet) (90.0%-115.0% of label claim)	Assay Simethicone 20mg per tablet (16.25mg-23.75mg per tablet) (85.0%-115.0% of label claim)	Acid neutralizing capacity NLT 5 mEq per tablet
F1	5.88%	Positive	202.56 mg /tab 101.280%	205.79 mg/ tab 102.890%	22.92 mg/tab 114.6%	15.21 mEq per tablet
F2	4.56%	Positive	201.45 mg /tab 100.725%	200.56 mg /tab 100.28	20.20 mg/tab 101%	13.04 mEq per tablet
F3	5.23%	Positive	200.63 mg /tab 100.315%	203.10 mg /tab 101.55%	21.23 mg/tab 106.15%	14.19 mEq per tablet
Mean	5.22%	-	201.54 mg /tab 100.773%	203.15 mg /tab 101.573%	21.450 mg /tab 107.25%	14.146mEq per tablet
S.D	0.660	-	0.45	1.305	6.870	1.08
S.E.M	0.466	-	0.260	0.753	3.966	0.62

DISCUSSION

As we know that indigestion or acid reflux disease is a condition of gastric discomfort which is accompanied by heart burn or gastric mucosal burning. The relationship of diabetes and gastro paresis is very known (Rao *et al*., 2015).Various studies has been performed on diabetes and its effect on gastric motility (Marathe *et al*., 2016). Long term diabetes mellitus of both type 1 and type 2 can causes impairment of gastric motor function and cause significant upper gastrointestinal symptoms which significantly harm effect on quality of life, cause nutritional deficits, and degrade healthcare resource use (Lee and Hasler, 2017). For this Purpose, we have formulated those type of chewable tablets which are easy to intake due to its sugar free activity as it contains sorbitol powder and aspartame instead of sugar which are suitable for diabetes patients who are suffering from Gastroesophageal reflux disease (GERD) or heartburn symptoms. We have formulated three batches of same formulation and perform stability studies of 24 months. According to the results obtain by the stability studies of 2 years at accelerated and real time zones the results found satisfactory in the acceptable limits of all the 3 batches. In F1 and F2 formulation the moisture content of tablets is higher at 3 months of accelerated stability studies which is gradually decrease throughout the whole 2 years of study. Three similar formulation batches are prepared for the reason to find out the accuracy and precision of results. The assay of Magnesium hydroxide, Simethicone and aluminum hydroxide the results are not seen beyond the 100%. In F2 formulation at 9^{th} month and 18^{th} month the results of Aluminium hydroxide are found less than 100% which were 99.98% and 99.79% respectively while the results of Magnesium hydroxide showed 99.93% and Simethicone shows 99.9% of assay at 24^{th} months of stability studies. In F3 formulation assay of Aluminium hydroxide at 18^{th} and 24^{th} month of accelerated stability studies the results are less than 100% which are 99.78% and 99.93% respectively while magnesium hydroxide shows 99.78% and 99.925% at 12 and 24 month of accelerated stability studies. The results of Simethicone are less than 100% which is 99.9% at 9 months of stability studies. All results are found in acceptable limits according to USP specification.

CONCLUSION

The ease of chewable tablet is already known now days in the field of pharmaceutical business, as hyperglycemic patients can not take sugar containing chewable tablet due to medical cause. The need of the development of sugar free antacid to relieve acidity in stomach ulcer, hyper acidity and in diabetes induced acidity is very essential. The developed formulation is patient complaint due to increase palatability. All the chemical analysis and stability testing shows that the developed sugar free formulation is pharmaceutically stable and further analyzed for safety and efficacy.

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