



Taste masking of Metoclopramide Hydrochloride by Novel Melt Granulation.

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Abstract

The purpose of this research was to mask the intensely bitter taste of metoclopramide HCl by complexation with glycerol monostearate. Drug- glycerol monostearate complex was prepared by melt granulation technique in the ratio of 1:1, 1:2, 1:3,1:4. The optimum drug: glycerol monostearate ratio required for complexation was determined. The drug: glycerol monostearate complex were evaluated for the drug content, *in-vivo*, *in-vitro* taste evaluation study. The complex was characterized by FTIR, differential scanning calorimetry. The taste evaluation depicted the successful taste masking of metoclopramide HCl with drug: glycerol monostearate 1:4 ratio.

Keywords: Metoclopramide HCl; Glycerol monostearate; Melt granulation; Taste masking.

Introduction

Majority of the drugs have a natural bitter taste that can create a burning feeling in the throat or in the mouth. In particular, a bitter taste can decrease the patient compliance and thus reducing an effective pharmacotherapy. In order to achieve an acceptable palatability, the addition of flavors or sweeteners is limited and may not be efficient enough to mask the taste buds of drugs and requires the use of technological processes [1, 2]. Recent years have seen a tremendous progress in the technique of masking the unacceptable taste of an orally administered pharmaceuticals, such as filling in capsules [3], coating with water in soluble polymers or pH dependent water soluble polymer, adsorption on ion-exchange resin (IER), micro encapsulation with various polymers, complexing with cyclodextrin [4], viscosity modifications [5] and melt granulation [6] have been described.

Metoclopramide HCl is an intensely bitter drug, highly soluble in water soluble and is rapidly absorb from oral administration. It has a short biological half life 5-6 hr [7].

Metoclopramide hydrochloride is recommended in dose of 10 to 15 mg four times a day [8]. Metoclopramide HCl is a gastrointestinal stimulant used to treat gastro esophageal reflux, erosions or ulcers of esophagus [9], nausea, vomiting, heartburn, prolonged fullness after meals and loss of appetite in patients with diabetes [10]. The major problem occurs with this is its bitterness. Taste masking with lipophilic vehicles like lipids and lecithins: Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents. Melt granulation is a process by which pharmaceutical powders are efficiently agglomerated by

the use of a binder which can be a molten liquid or a solid that melts during the process [11]. Melt granulation has been successfully applied to develop sustained release formulations, taste masked formulations with lipophilic melting binders, such as glycerol monostearate, a combination of a hydrophobic materials, a starch derivative and stearic acid among others [12-15]. The objective of present work is to explore the utility of glycerol monostearate in the masking bitter taste of Metoclopramide HCl by novel melt granulation technique.

Materials and methods

Metoclopramide HCl was obtained from Aanjanya Biotech Ltd., Mumbai, India, Glycerol monostearate was a gift from Alpha Chemicals, Panvel, India, Kyron T-314 was a gift from Corel Pharmachem, Ahemdabad, Crosscarmellose sodium, Crosprovidone, Pearlitol SD 200 was a gift from Signet Chemicals, Mumbai, Tween 80 and Aerosol was purchase from Modern Scientific, Nasik, Aspartame and Magnesium stearate was purchase from SD Fine Chemicals, Mumbai, India.

Methods

Melt Granulation

The required quantity of glycerol monostearate was weighed. It was melted in porcelain dish at 50-60 C for 5 min and the tween 80 was added to the melted glycerol monostearate. Finally, a mixture of metoclopramide HCl and superdisintegrants was added to the molten mixture, which was then allowed to cool. Solidified



mass was crushed in mortar and passed through a 16 mesh sieve and thus granules were prepared.

Determination of Threshold Bitterness

Pure drug was subjected to sensory evaluation by the panel of six healthy volunteers using time intensity method. The bitter taste threshold value of metoclopramide HCl was determined based on the bitter taste recognized by six volunteers (four males and two females). A series of metoclopramide HCl aqueous solutions were prepared at different concentrations as standard solutions, i.e. 10, 20, 30, 40, 50 $\mu\text{g/ml}$ respectively. From standard solution 1 ml of each was placed on the center of the tongue, it was retained in the mouth for 15 seconds and then the mouth was thoroughly rinsed with distilled water. The threshold value was correspondingly selected from the different metoclopramide HCl concentrations as the lowest concentration that had a bitter taste.

Characterization of Complex

FTIR Spectroscopy

The IR spectrums of pure drug, glycerol monostearate, granules which are prepared by melt granulation method were recorded in the stretching frequency range $400\text{--}4000\text{ cm}^{-1}$. The samples were prepared by KBr press pellet technique.

Differential Scanning Calorimetry

The DSC thermogram of pure drug, glycerol monostearate, granules which are prepared by melt granulation method were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10 C per minute over a temperature range of $40\text{ C to }250\text{ C}$.

Drug Content

Drug content was determined by dissolving the melt granules equivalent to 10 mg of metoclopramide HCl in 100 ml of distilled water and analyzing sample after appropriate dilution by UV-Visible Spectrophotometer at $\lambda_{\text{max}} 272\text{ nm}$ using distilled water as a blank. The results are shown in Table 1.

In-vitro Taste Evaluation

Complex containing about 10 mg metoclopramide HCl were put into a test tube containing 10 ml of pH 6.8. The mixture was immediately vibrated for 15 seconds and then filtered. The clear solution was analyzed in a spectrophotometer at $\lambda_{\text{max}} 272\text{ nm}$ to determine the drug concentration in pH 6.8 after the appropriate dilutions, which was then compared with the threshold value. The calibration curve between absorbance (A) and concentration (C) was $A = 0.0676 C + 0.0123$ ($r = 0.9996$, $n = 5$) which was used for determination of concentration. Drug concentrations of binary systems were determined spectrophotometrically and were compared with the threshold bitterness and it was found to be below the threshold value of bitterness i.e $50\mu\text{g/ml}$.

In-vivo Taste Evaluation

Gustatory sensation test was carried out by panel of human volunteers. Six healthy human volunteers, of either sex, in the age

group of 22–25 years were selected for the study. Granules equivalent to 10 mg of metoclopramide HCl were dispersed in 10ml of distilled water for 15 seconds. Immediately after preparation, each volunteer kept about 1 ml of the dispersion in the mouth for 30 seconds. After expectoration, bitterness level was recorded. A numerical scale was used with the following values: 0 =Tasteless, 0.5=Very slightly bitter, 1=slightly bitter, 1.5=Slight to moderate bitter, 2=moderately bitter, 2.5=Moderate to strong bitter, 3=strongly bitter, 3+ =Very strong.

Results and Discussion

Characterization of complex

Fourier Transform Infra-Red Studies

The characterization complex was carried out by Fourier Transform Infra-Red Study. The IR spectrum of pure drug, glycerol monostearate and its ratio of complex i.e. 1:4 (as shown in Figure No. 1-3) and from the graph of IR spectra some peaks of glycerol monostearate overlap the peaks of metoclopramide HCl and hence, broaden of intensity of peak as compared to pure drug, indicating formation of complex.

Differential Scanning Calorimetric study

The DSC thermograms of pure drug, Glycerol monostearate its ratio of complex i.e. 1:4 are shown in Figure 4-6 and Table 2. In complex, the Metoclopramide HCl with Glycerol monostearate, the endothermic peak of Metoclopramide HCl was completely diminished and endothermic peak of Glycerol monostearate is shifted towards lower side 56.24 C , representing complete possible complexation. The efficiency of glycerol monostearate was tested for the purpose of taste masking with the possible method of melt granulation. Taste masking by melt granulation is achieved by decreasing the surface area of the drug by increasing its particle size. *In-vitro* taste evaluation study was carried out and compared with that of threshold bitterness value. Tastes of all complexes were assessed by panel of six human volunteers by time intensity method which revealed the actual taste sensation of complexes with drug. Complex of glycerol monostearate showed the acceptable taste at the drug: glycerol monostearate ratio of 1:4 for granules prepared by melt granulation technique.

Prepared granules were evaluated for *in-vitro* drug release with reference to threshold bitterness concentration of $50\mu\text{g/ml}$ at the end of 15 seconds. The physical mixture of drug and glycerol monostearate in the ratio of 1:4 showed $44.12\pm 0.06\text{ }\mu\text{g/ml}$ drug concentration, whereas the melt granules of drug and glycerol monostearate in the ratio of 1:4 showed $41.40\pm 1.15\text{ }\mu\text{g/ml}$ compared with threshold bitterness value $50\mu\text{g/ml}$. Hence from the results, the ratio of melt granules of drug and glycerol monostearate showed less threshold bitterness value as compared with physical mixture of drug and glycerol monostearate.

In-vivo evaluation of bitterness score of binary systems containing metoclopramide HCl and glycerol monostearate was carried out by six human volunteers using time intensity method which are shown in Table 3.



Conclusion

From the above results, it can be concluded that, complete taste masking of bitter metoclopramide HCl is achieved by granulating drug with glycerol monostearate by novel melt granulation technique. The efficiency of glycerol monostearate was tested for the purpose of taste masking with the possible method of melt granulation. Taste masking by melt granulation is achieved by decreasing the surface area of the drug by increasing its particle size. Polymers that serve as binders and taste-masking agents may be incorporated, which reduce the perception of taste.

List of abbreviations

IER - Ion-Exchange Resin
 GMS- Glycerol monostearate
 HCl - Hydrochloric acid
 DSC - Differential scanning calorimetry
 FTIR- Fourier transform infrared spectroscopy

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Author's contributions

Mr. S. B. Ahire - Carried out experimental part of study.
 Ms. P.D. Gaikwad and Dr.V.H. Bankar -Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data, also involved in drafting or revising it critically for important intellectual content and given final approval of the version to be published.

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Table 1 Drug Content and *in-vitro* Taste Evaluation of Complex of Drug:GMS

Sr. No.	Drug:GMS ratio	% drug content	Drug concentration ($\mu\text{g/ml}$)
1	1:1	98.30	47.14 \pm 1.34
2	1:2	99.46	44.19 \pm 1.20
3	1:3	99.70	43.97 \pm 1.32
4	1:4	101.20	41.40 \pm 1.15

Mean_S. D. (n_3).

Table 2 Thermal Transition and Enthalpy Values of Metoclopramide HCl, Glycerol monostearate and Melt Complex

Sr.No.	Chemical	DSC Thermal Transition ($^{\circ}\text{C}$)	Enthalpy (J/g)
1.	Metoclopramide HCl	177.38	(-) 204.37
2.	Glycerol monostearate	60.11	(-) 127.21
3.	Melt Complex		
	(A) Metoclopramide HCl	(A) -	(A) (-) -
	(B) Glycerol monostearate	(B) 56.24	(B) (-) 89.11

Table 3 Results of Bitterness Score of pure drug and Melt complex of Metoclopramide HCl and Glycerol monostearate

Volunteer	1	2	3	4	5	6
Pure drug	3+	3+	3+	3+	3+	3+
Drug:GMS ratio 1:1	2.5	2.5	3	2.5	2.5	2.5
Drug:GMS ratio 1:2	2	2	2.5	2	2	2
Drug:GMS ratio 1:3	1.5	1.5	1	1.5	1.5	1
Drug:GMS ratio 1:4	0.5	0	0	0	0	0

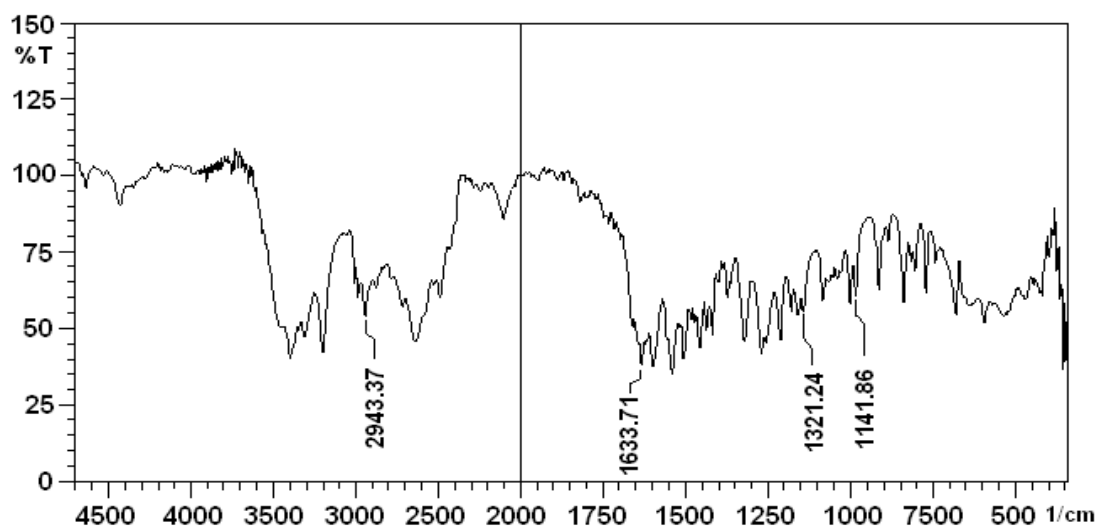


Figure 1 FTIR Spectra of Metoclopramide hydrochloride

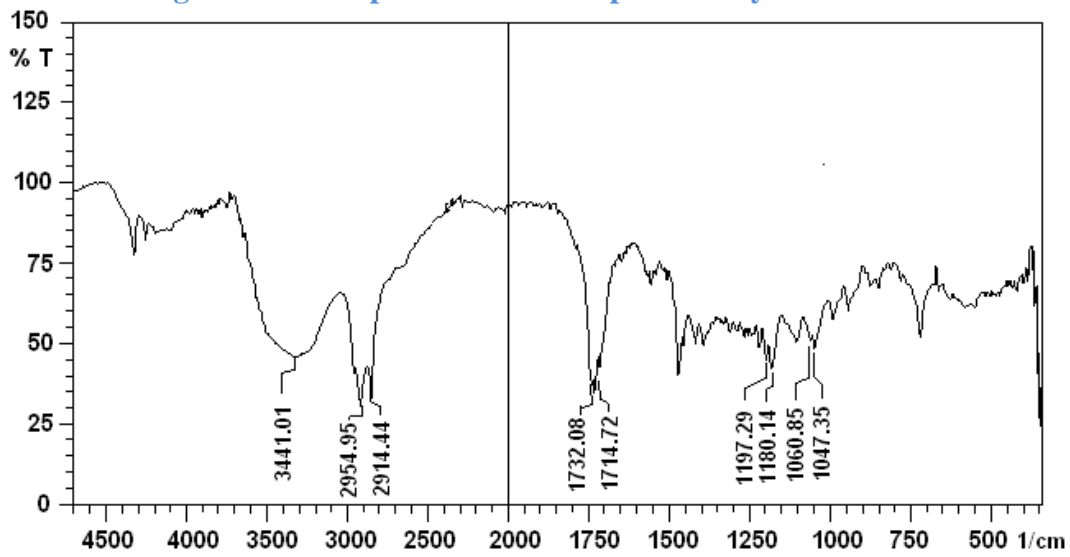


Figure 2 FT-IR Spectra of Glycerol monostearate

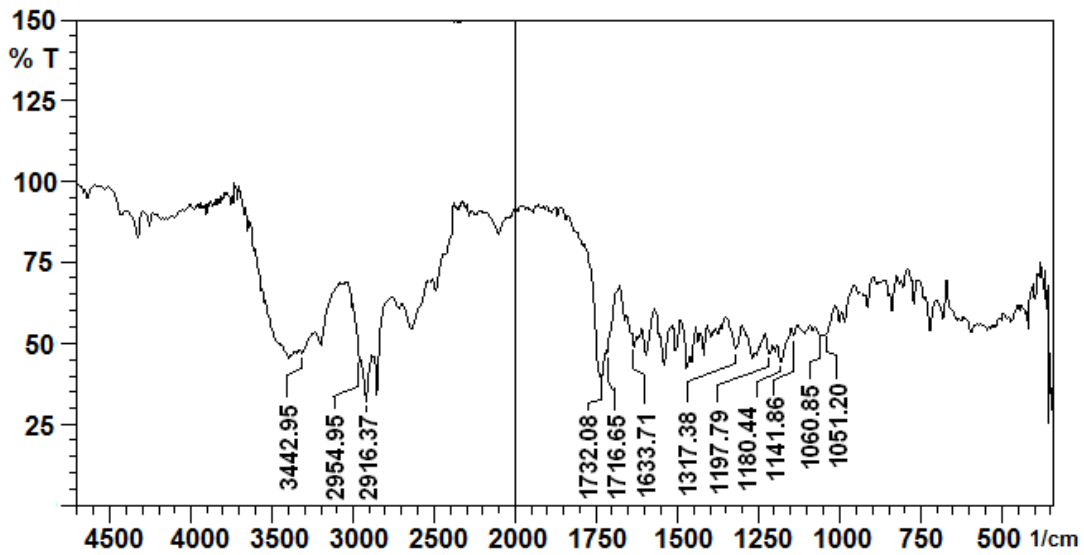


Figure 3 FT-IR Spectra of Melt Complex



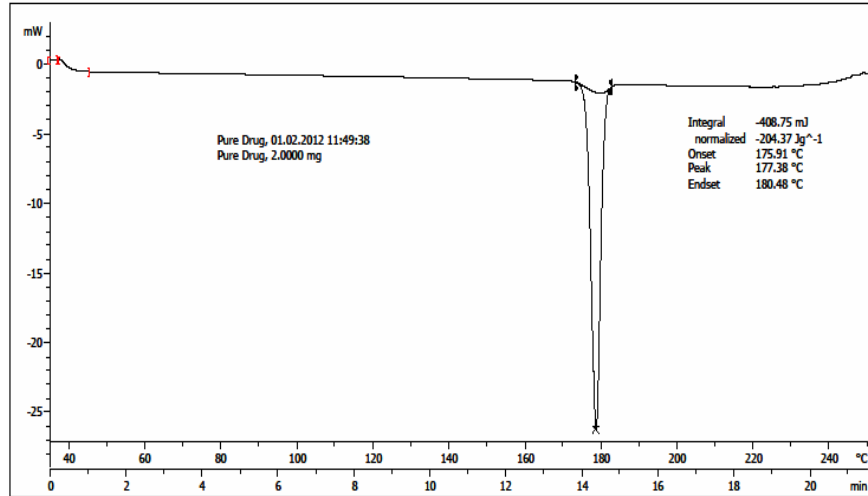


Figure 4 DSC Thermogram of Metoclopramide HCl

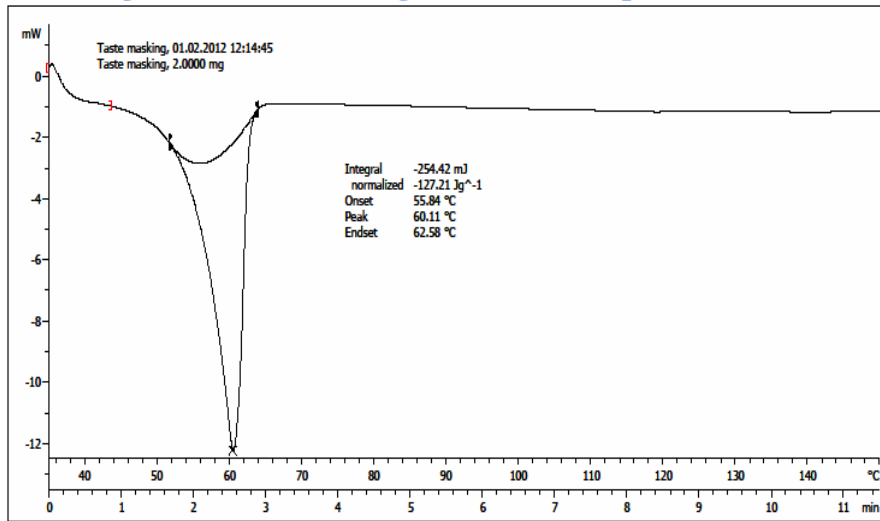


Figure 5 DSC Thermogram of Glycerol monostearate

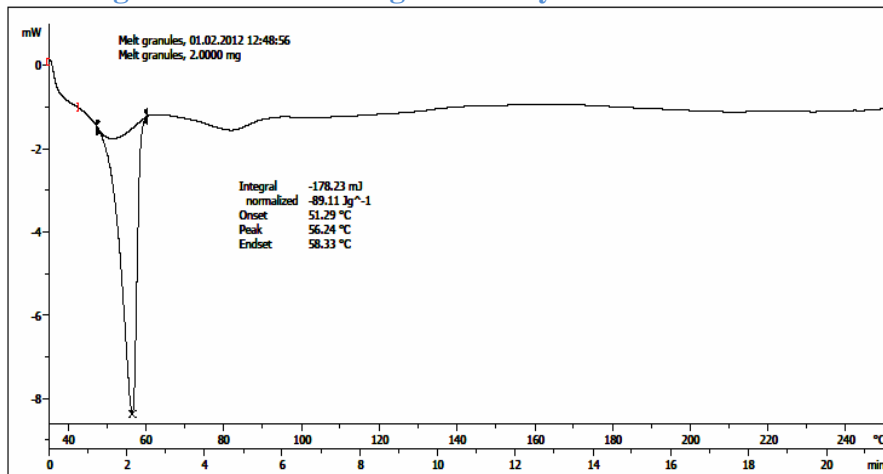


Figure 6 DSC Thermogram of Melt Complex

