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Formulation Development, Preparation and Evaluation of Taste Masking Orodispersible Tablet of Tiemonium Methylsulfate by using HPMC as Taste Masking Agent

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Abstract

This project is developed because patients have modest taste expectations for drug product-they need to be palatable. Palatable drug products generally have moderate attributes – not too bitter, hard, gritty, chalky or irritating. Taste masking of drug by coating of granules preparations of oro-dispersible tablet *in-vivo* study of taste and *in-vitro* drug release study is enhance rapid bioavailability and rapid onset of action, improve patient comfort and compliance. Tiemonium methylsulfate prevents the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle of GI tract 2 but it is a very bitter drug and slightly soluble in water. So the objective of the present work is to formulate dispersible or orodispersible tablets of this highly bitter drug, where in which its bitter taste is masked. Several techniques are available for the design of taste masking dosage forms as indicated in the introduction chapter. In the present study, the taste masking is done by using ion exchange resin complexation technique. It was preferred over other taste masking methods, as the drug releases occur only in the acidic environment without being released in saliva where by the bitterness of the drug get taste masked. All pre-formulation data compiled the idea property of taste masking oro-dispersible property of tablet. All formulations disintegrate within 60 sec and drug dissolution data showed that all formulation gives around 90% drug release within 120 seconds. Finally we can conclude that this experimental work may be a good way for the development of taste masking and oro-dispersible tablet.

Keywords: Oro-dispersible tablet; Tiemonium methyl sulfate; HPMC; Formulation

Introduction

More than 50% of pharmaceuticals products are used as oral dosage form for several reasons. This route of administration is considered as the 9H used route as it offers advantages like ease of administration, versatility, compliance and accurate dosing. Many pharmaceutical drugs have an unpleasant taste, often very bitter. The major consequence of the bitter taste is restricting greatly the further development of oral preparations and clinical applications of these drugs. People wish to take effective drugs that have a nice taste and can be administered easily [1]. In recent years, the importance of patient compliance, not only in drug efficacy per se but also in overall economics of healthcare, has been increasingly recognized. Efforts to improve patient compliance have included attempts to improve the palatability of orally administered pharmaceutics agents especially for pediatrics and geriatric patients. In particular, a bitter taste is known to decrease patient compliance, and thus reduce effective pharmacotherapy [2]. Hence taste masking of oral pharmaceuticals has become important tool to improve patient compliance and the quality of treatment especially in pediatrics. Hence formulation of taste masked products is a challenge. Patients have modest taste expectations for drug products – they need to be palatable. Palatable drug products generally have moderate attributes – not too bitter, hard, gritty, chalky or irritating. Many active pharmaceutical ingredients are bitter and require some form of taste masking to yield a palatable drug product. Occasionally, the API needs to be "sequestered" from the taste receptors using encapsulation, complexion, or other technology to yield a palatable drug product. However, most APIs can be effectively masked with a properly constructed excipient system [3]. The materials for taste masking purpose have often been classified depending up on the basic taste that is masked. Flavoring and perfuming agents can be obtained from either natural or synthetic sources. Natural products include fruit juices, aromatic oils such as peppermint and lemon oils, herbs, spices and distilled fractions of these. They are available as concentrated extracts, alcoholic or aqueous solutions, syrups or spirit. Apart from these conventional materials many compositions have been found to show effective taste masking abilities with improved flavor such as alkaline earth oxide, alkaline earth hydroxide or an alkaline hydroxide. Another composition includes phosphorylated amino acid such as phosphotyrosine, phosphoserine, and phosphothreonine md mixtures* Anethole effectively masked bitter taste as well as the aftertaste of zinc, which is roe in treating the common cold [4]. Clove -H and calcium carbonate, which has been found to be particularly useful to mask the unpalatable active in formulations which are intended to be chewed or dissolve in mouth prior to ingestion in solution [5]. When an ionisable drug reacts with a suitable ion exchange resin, the drug-resin complex formed is known as a drug-HPMC. Since the drug HPMC is insoluble in saliva, it has virtually no taste. So that even very bitter drugs lose their taste when converted into a drug HPMC with the correct selection of the ion exchange resin. The drug HPMC can be made sufficiently stable that it does not break down in the mouth so that the patient does not taste the drug when it is swallowed. However, when the drug-HPMC comes in contact with gastrointestinal fluids usually the acid of the stomach, the complex is broken down quickly and completely. The drug is released from HPMC directly into the solution and then absorbed in the usual way. The resin passes through the gastrointestinal tract without being absorbed. Drug delivery systems are becoming

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increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their higher performance [6]. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance [7]. In some cases such as motion sickness, sudden episode of allergic attack or coughing and unavailability of water, swallowing of tablet or capsules may become difficult. In order to assist these patients, several fast-dissolving drug delivery systems have been developed [8]. 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 or orodispersible tablets. When this type of tablet is placed into the mouth, the saliva will serve to rapidly disintegrate the tablet [9]. Oro-dispersible tablets disintegrate or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within few seconds and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. Tiemonium methylsulfate is a quaternary ammonium antimuscarinic agent with peripheral effect similar to those of atropine and is used in the relief of visceral spasms. It prevents the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle of GI tract [10].

Materials and Methods

Preparation of granules

This is done in a series of steps, in the laboratory, which are listed as follows: Firstly, the active drug (TMS), diluents (Starch), and ¾ stated amount of super disintegrants are passed through a 20 mesh sieve to obtain fine particles Table 1. Then, the active drug, super disintegrants and the Diluent under current investigation are appropriately weighed and mixed together for 10 mins in a motar. Then the binding solution is prepared by dissolving the above stated amount of povidone k-30 in sufficient amount of water. This solution is then added drop by drop to the dry mixture in the motar. During this addition the mixture is continuously mixed in clockwise direction an action. Which is continued for a further 10 mins after all the binding solution has been added. At the end of this mixing, a uniformly mixed wet mass is obtained. The wet mass is then dried in an oven for 30 mins at 600°C. Then dry mass is then passed through a 12 mesh sieve to obtain very fine particles. Finally, these fine particles are then mixed with the above declared quantities of MCC-140 gm, 1/4 Super disintegrant and mg stearate to obtain granules with the pre-requisite flow properties. The active drug and all the other excipients were taken in such amounts that at least 20 tablets of each formulation could be prepared (Tables 2-4 and Figure 1).

Ingredients	Purpose	Amount/tablet	Amount for 200 tablet
Tiemonium methylsulfate	API	50 mg	10 gm
Starch	Diluent & Binder	120	24 gm
MCC	Disintegrating Agent	100	20 gm
Aspartame (5%)	Sweetening agent	15	3 gm
Talc (2%)	Lubricant & Glidant	6	1.2 gm
Povidone K30 (3%)	Binder	9	1.8 gm
Total		300 mg	60 gm

Table 1: Preparation of Granules.

Formulation	F 1	F2	F3	F4	F5	F6	F7
Bulk density (g/cm3)	0.58	0.62	0.61	0.65	0.59	0.59	0.62
Tap density (g/cm3)	0.67	0.72	0.71	0.75	0.61	0.79	0.79
Compressibility index (%)	9.63	11.35	10.2	9.29	10.88	10.29	12.53
Angle of repose(Θ)		28.25	29.74	28.77	29.62	31.15	31.34

Table 2: Evaluation of Pre-formulation study (granules).

Formulation	F1	F2	F3	F4	F5	F6	F7
Weight (mg)	303.7	304.61	304.16	302.59	301.64	301.98	301.69
Thickness (mm)	2.15	2.007	2.022	2.033	2.11	2.05	2.14
Hardness (kg/cm2)	3.78	3.36	3.82	3.4	3.41	3.4	3.51
Diameter (mm)	7.06	7.063	7.121	7.8	7.14	7.82	7.11
% Friability	0.6655	0.6211	0.6247	0.6036	0.609	0.6047	0.6916

Table 3: Taste masking coating of Granules formulation.

Formulation	F1	F2	F3	F4	F5	F6	F7
Weight (mg)	303.7	304.61	304.16	302.59	301.64	301.98	301.69
Thickness (mm)	2.15	2.007	2.022	2.033	2.11	2.05	2.14
Hardness (kg/cm)	3.78	3.36	3.82	3.4	3.41	3.4	3.51
Diameter (mm)	7.06	7.063	7.121	7.8	7.14	7.82	7.11
%Friability	0.6655	0.6211	0.6247	0.6036	0.609	0.6047	0.6916

Table 4: Evaluation profile of Tablet.

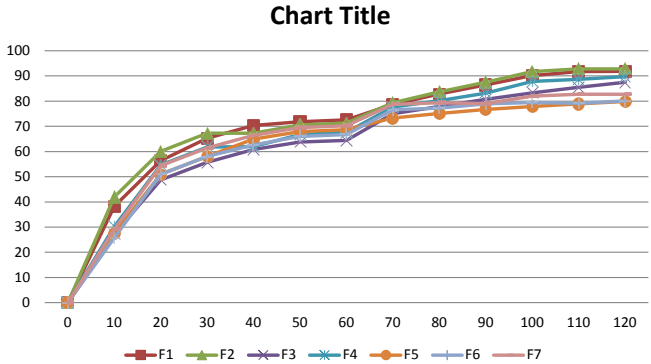

Figure 1: Dissolution Profile in Graph (*In-vitro* Dissolution).

Evaluation of prepared granules

Angle of repose is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal plane. Such a measurement gives a qualitative assessment of the internal cohesive and frictional effects observed within the granules under low levels of external loading, as might be observed in powder mixing, or in tablet die or capsule shell filling operations. It was measured by the fixed funnel and free standing cone method. Accurately weighed granules of each formulation were carefully poured through the funnel stationed of a clamp with its tip of the funnel. The mean diameter, 2R of the base of the powder cone was measured and the angle of repose (Ø) was calculated using the following equation: TanØ=H/R (Table 5).

Results and Discussion

Bulk and tapped densities were estimated using the following formula:

Bulk density = M\Va, Tapped density = M\Vf

Where Va = poured volume, Vf = final volume after tapping, M= Mass of the granules.

Weight variation test

For evaluating the uniformity of weight, twenty tablets were selected at random, weighed together and then individually. The mean and the standard deviation were determined.

Pre-formulation study

To design tablets and later monitor tablet production quality, physical properties must be studied. The following parameters were carried out to determine the quality of experimental tablets (Tables 6-11).

Formulation	F1	F2	F3	F4	F5	F6	F7
Labeled amount of drug/tablet (x)	50	50	50	50	50	50	50
Actual drug/tablet (y)	49.37	48.2	48.17	48.18	49.2	49.28	50.13
% drug content (y/x)100	98.74	96.4	96.34	96.36	98.4	98.56	100.26

Table 5: Drug content uniformity test.

Sr. no.	Formulation		Bulk density	Tap density	Compressibility	Angle of repose(Θ)
1	F1		0.58	0.67	9.63	26.89
2	F2	0.62		0.72	11.35	28.25
3	F3		0.61	0.71	10.2	29.74
4	F4		0.65	0.75	9.29	28.77
5	F5		0.59	0.61	10.88	29.62
6	F6		0.59	0.79	10.29	31.15
7	F7		0.62	0.79	12.53	31.34

Table 6: Pre-formulation study (average).

Sr.no	Formulation no	Weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Diameter (mm)	%Friability
1	F1	303.7	2.15	5.78	7.06	0.065586
2	F2	304.61	2.007	5.36	7.063	0.211411
3	F3	304.16	2.022	5.82	7.121	0.247321
4	F4	302.59	2.033	5.4	7.8	0.036645
5	F5	301.64	2.11	5.41	7.14	0.090339
6	F6	301.98	2.05	5.4	7.82	0.047167
7	F7	301.69	2.14	5.51	7.11	0.916297

Table 7: Formulation study (average).

Sr. No.	Batch code	Lebeled amount of drug in each tablet (x)	Actual drug content (mg) in each tablet (y)	% drug content (y/x)*100
1	F1	50	50.37	100.75
2	F2	50	50.2	100.41
3	F3	50	50.17	100.36
4	F4	50	50.18	100.37
5	F5	50	50.2	100.41
6	F6	50	49.2	100.41
7	F7	50	50.13	100.26

Table 8: Drug content uniformity (average).

Formulation	F1	F2	F3	F4	F5	F6	F7
Bulk density (g/cm3)	0.58	0.62	0.61	0.65	0.59	0.59	0.62
Tap density (g/cm3)	0.67	0.72	0.71	0.75	0.61	0.79	0.79
Compressibility index (%)	9.63	11.35	10.2	9.29	10.88	10.29	12.53
Angle of repose(Θ)	26.89	28.25	29.74	28.77	29.62	31.15	31.34

Table 9: Pre-formulation study (granules).

Formulation	F1	F2	F3	F4	F5	F6	F7
Labeled amount of drug/tablet (x)	50	50	50	50	50	50	50
Actual drug/tablet(y)	49.37	48.2	48.17	48.18	49.2	49.28	50.13
% drug content (y/x)100	98.74	96.4	96.34	96.36	98.4	98.56	100.26

Table 10: Uniformity of dispersion (In the test for uniformity of dispersion all these tablets (F1, F2, F3, F4, F5, F6, and F7) fulfilled the official (I.P) requirement. The dispersion produced in water passed through the table).

Formulations	Mouth Feel			
	10 Sec	30 Sec	60 Sec	120 Sec
F1	0	x	x	xx
F2	0	0	x	x
F3	0	0	0	x
F4	0	0	0	0
F5	0	0	0	0
F6	0	0	0	0
F7	0	0	0	0
0= No bitterness, x= Threshold bitterness,				
xx= Threshold bitterness, xxx= Threshold bitterness				

Table 11: Taste evaluations (F1,F2, F3,F4 F5, F6, F7formulations were given to panel of healthy human volunteers for taste masking evaluation using time intensity method which shows the masking of taste and also tablet gave a pleasant felling shown in table).

Conclusion

In the work under taken an attempt was made to explore the use of ion exchange resins as taste masking agents and Super Disintegrant Crospovidone (CP) as disintegrating agent in orodispersible tablets. The purpose was to enhance patient compliance and provide rapid onset of action. Tiemonium methylsulfate drug prevents the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle of GI tract 2, regardless of their function and innervations. But it is a very bitter drug and slightly soluble in water. As there are no reports on the development of taste masked dosage forms for Tiemonium methylsulfate by using HPMC polymer, an attempt was made for the development of taste masked tablets of Tiemonium methylsulfate. In the present study HPMC used as a polymer and alcohol as a solvent were used for taste masking purpose. The drug polymer were prepared by mixing the drug and polymer in different ratios and evaluated for the extent of complexion. The maximum amount of complexion was observed with 1:7 ratio (drug: polymer) for both the resins. The polymer of this ratio was used for the further study. These drug polymers coating were then converted into granules. They exhibited satisfactory values of angle of repose, bulk density a compressibility index. Finally it can conclude that this experimental work may be a good way for the development of taste masking and oro-dispersible tablet.

Conflicts of Interest

There are no conflicts of interest for any author of this manuscript. The preparation of the manuscript and the conduct of the study plans are considered a coincident function of employment.

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