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Fabrication and evaluation of taste masking sachets of tizanidine HCL

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ABSTRACT

Tizanidine hydrochloride is an Imidazoline derivative which acts as agonist on centrally located α 2 receptors and this leads to myotonolytic effects on skeletal muscle. The dosage of 2-4 mg is given. Tizanidine's bioavailability is about 34-40% and its half-life is about 2.5 hours. It is subjected to a metabolism in the first step (approximately 95% of the dose) of the liver which allows the imidazole state, the aromatic system and the sulphur atom to be oxidated. This leads to reduced bioavailability and a bitter taste of Tizanidine hydrochloride. The application of various carriers including β-cyclodextrin, mannitol and povidone to enhance the bioavailability of the flavor and to mask the strong dispersion technique. Results of prepared solid Tizanidine HCL dispersions by the solvent method of evaporation, including solubility, melting point determination, uniformity in drug content, entrapment efficiency and studies of in vitro-dissolution were discussed. Characterization in solid state was done by various analytical techniques such as FT-IR studies. Ultimately, by comparing in different ratios all the formulations i.e.,F1-F9 with Tizanidine HCL, povidone, β-cyclodextrin & Mannitol. By Solvent evaporation method at the end of 90 min with drug release of 93.99 %, Formulation F9 containing β-cyclodextrin (1:3) showed better results. This is why it was selected optimized formulation. Through comparing the release kinetic studies of Tizanidine HCL with zero order and first order, the better formulations are replaced by the kinetic studies of first order.

Keywords: Tizanidine HCl, Povidone, β-Cyclodextrin and Mannitol.

INTRODUCTION

Kids, the elderly and many other individuals, including patients with disabilities and disorders, often have difficulty swallowing tablets or capsules. In these cases, it is preferable to provide the medication either in a chewable solid form or in a liquid delivery form [1].

The unpleasant taste of certain medicines is one of several major problems with formulation. The oral administration of bitter medications with an acceptable degree of palatability is one key problem in the health care providers, particularly for pediatric patients. The masking of bitter medicinal taste is an important element of patient compliance. The current situation is that a pharmacist is confronted by the issue of salty and irritating drug taste in pediatric and geriatric formulations [2].

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. Methods commonly used for taste masking involves various physical and chemical method that prevent the interaction of taste bud with drugs, Two approaches are commonly utilized to overcome bad taste of the drug [3-5].

1. By reducing the solubility of drug in the pH of saliva (5.6 - 6.8).
2. By altering the affinity and nature of drug which will interact with the taste receptor.

An ideal taste masking process and formulation should have the following properties [6-8].

1. Less machinery and storage procedures must be included.
2. Masking flavor easily with as few financial and easy to use excipients.
3. No effect on bioavailability of pharmaceutical products.
4. Minimum cost of production.
5. Can be done at room temp.
6. Requiring high-security excipients.
7. Quick to plan easily and simply.

Factors that are taken into consideration during the taste-masking formulation process include: Extent of the bitter taste of the API [9-11].

- Dose load required.
- Application of product particulate type and weight.
- Solubility of medications and ionic properties.
- Disintegration and breakdown of the finished product required.
- Bioavailability needed.
- Release profile you like. Required dosage form.

Factors affecting selection of taste masking technology Conventional taste masking techniques such as the use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs such as quinine, celecoxib, etoricoxib, antibiotics like levofloxacin, Sweeteners could not achieve taste masking of oral formulation of ibuprofen due to its dominating taste. Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique. Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid oral suspensions [12, 13].

MATERIALS AND METHODS

Tizanidine HCl was obtained as gift sample from Dr. Reddy's Laboratories. Other excipients (Mannitol, povidone, β-cyclodextrin) were purchased from SD Fine chemicals.

PREFORMULATION STUDIES

Determination of melting point

A small amount of drug on one end in a capillary tube scale was used to measure the drug melting point. The capillary tube was positioned electrically operated in a melting point system and at the temperature at which the material melts. Three times this was achieved and the average value was measured.

Solubility studies

The solubility of Tizanidine HCl has been measured in several buffers. Saturated formulations are prepared by adding drug to vehicles and shaken on the shaker at a temperature of 25 ° C for 24 hours. A suitable buffer was diluted sufficiently to filtered samples (1ml) and Tizanidine HCl was calculated with 230 nm of spectrophotometric solubility.

Drug–polymer compatibility studies

Drugs and polymers are in close contact with each others, which can help to improve drug toxicity, which could interfere in the preparation of tablet formulation. Therefore, drug-polymer-interaction preformulation experiments are very important in selecting the correct polymers. The stability of the chosen polymers around Tizanidine HCl was determined with FT-IR spectroscopy by KBR pellet method.

Formulation of Tizanidine HCl Taste Masking Sachets by Solvent evaporation method

In this process, carriers are properly measured and transported in the specified proportions into boiling test tubes. Different concentrations of medications are added and dispersed. These substances were weighed. The solution was transferred to petridish, then solvent was evaporated at room temperature and the dispersion was dried at 65^{o}C for 6hrs. The gathered mass was

compiled, pulvarized and tampered with into 100 mesh in each case.

Evaluation Studies

Drug Content

Weight equivalent to 10 mg of drug was accurately calculated and transferred into a 100 ml VF. Volume was adjusted with 0.1N HCl, further shaken to ensure solubility of drug in it. Then the specimen was cleansed. The same normal solution concentration was prepared by the dissolution of 10 mg generic product in 0.1N HCl (pH 1.2 Acid buffer). Absorption of both the sample and natural solutions of Tizanidine HCl has been measured at 230 nm in UV-Visible spectrophotometers.

In Vitro Dissolution Studies

Tizanidine HCl was poured into a capsule and held in a dissolution medium with solid dispersion of 4 mg. Dissolution analysis of USP Systems I (basket methods) at 900 ml pH 1.2 HCl buffer was conducted at 37±0.5^{o}C and 50 RPM frequency. 5 ml Aliquot was taken out at a fixed time period and a fresh equal amount was replaced to maintain a constant volume after each sampling & analysed at 230 nm with an adequated UV-visible spectrophotometer (T60 PG Instruments).

Evaluation of taste of complexes

A five-member jury evaluated the dynamic substance β-CD experiment against the bitter taste and graded the bitter taste into the next five classes.

Class 5: Very strong bitter taste
Class 4: Strong bitter taste
Class 3: Moderately bitter taste
Class 2: Slightly bitter taste
Class 1: No bitter taste

The raw material with a mean bitter taste of 5.0 was used as a standard strength. The panelists sought written consent and the procedure was explained that the complex seasoning should be tested. Every client, i.e. the pure substance, was given control.

The bitterness of each of the substances with that of the controls was asked to compare, indicating their predicted bitterness. The panel members are asked to gargle and wait 20 minutes for a further test. Depending on the bitterness levels of each panel member, the mean bitterness value of each ratio was determined.

RESULTS AND DISCUSSION

Determination of melting point

The Melting point for Tizanidine HCl was calculated by capillary approach was found in the range 286-290^{o}C.

Solubility Studies

From the solubility studies in different buffers, 0.1N HCl (pH 1.2 Acid buffer) can be shown to be more soluble than other buffer solutions.

Drug and Excipients compatibility studies

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Tizanidine HCL) and optimized formulation (Tizanidine HCL: excipients) which indicates there are no physical changes.

Evaluation Stuides

The entrapment efficiency of formulations F1-F9 were found to be in the range of 62.28-90.19%. The drug content formulations F1-F9 were found to be in the range of 55.48-94.10%. The percentage yield of formulations F1-F9 were found to be in the range of 52.22-96.62%.

Invitro dissolution studies

Total nine formulations of Tizanidine HCL taste masking sachets were formulated by solid dispersion technique with different ratios of Drug: Carriers.

Invitro drug release of Tizanidine HCL solid dispersions with Povidone in various ratios were observed which shows at the end of 90 mins, the formulation F1 releases 64.96, formulation F2 releases 69.71, F3 releases 72.91%.

Invitro drug release of Tizanidine HCl solid dispersions with mannitol in various ratios were observed which shows at the end of 90 mins the formulation F4 releases 78.21, formulation F5 releases 81.16, formulation F6 releases 88.96%.

Invitro drug release of Tizanidine HCl with β cyclodextrin in various ratios were observed which shows at the end of 90 mins the formulation F7 releases 86.27, formulation F8 releases 90.99, formulation F9 releases 93.99%.

Finally by comparing all the formulations F1-F9 formulation F9 containing Tizanidine HCl: β-Cyclodextrin (1:3) shows better results at the end of 90 min with drug release of 93.99%, hence it was selected as the best formulation among all the formulations.

By comparing the release kinetics studies of best formulation with zero order and first order we can say that the best formulation follows first order release kinetics studies having R^2 value 0.945 were as zero order release kinetics studies having R^2 value 0.849, hence we can say that the best formulation follows first order release kinetics.

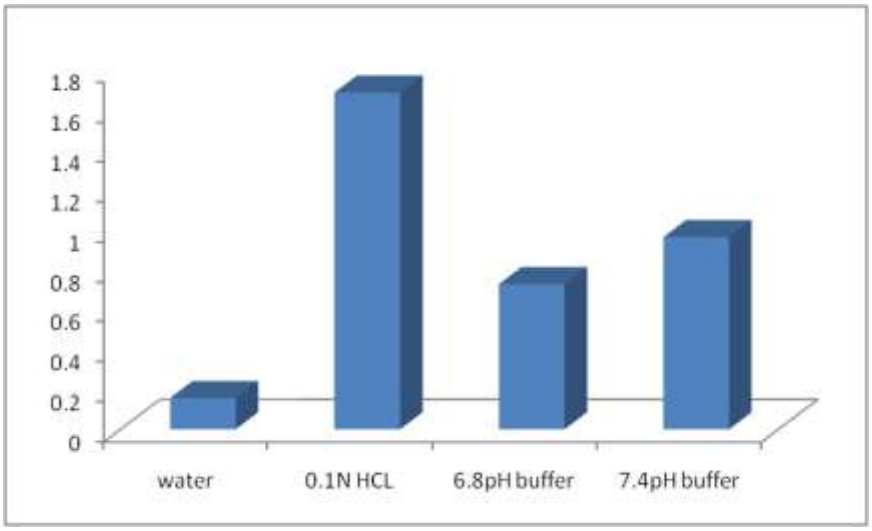

Fig no. 1: Solubility studies of Tizanidine HCl in different mediums

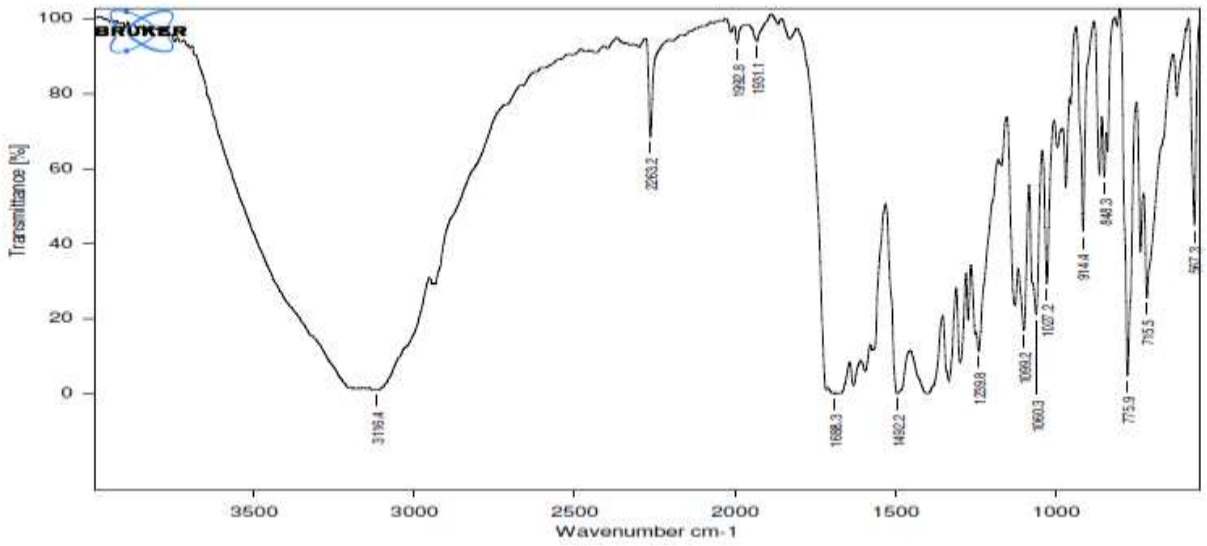

Fig no. 2: IR spectrum of pure Tizanidine HCl

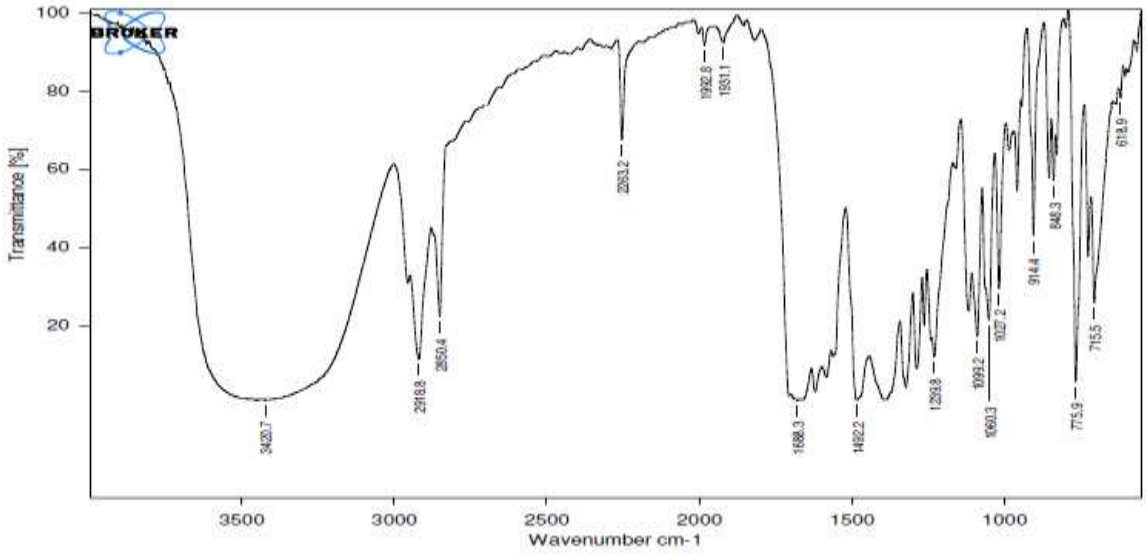

Fig no. 3: IR spectrum of Tizanidine HCl Optimised Formulation

Table 1: Formulation of Taste masking sachets of Tizanidine HCL with Povidone

Formulation code	Drug: polymer	Drug : polymer ratio
F1	Tizanidine HCl: Povidone	1:1
F2		1:2
F3		1:3

Table 2: Formulation of Taste masking sachets of Tizanidine HCL with Mannitol

Formulation code	Drug: polymer	Drug : polymer ratio
F4	Tizanidine HCl: Mannitol	1:1
F5		1:2
F6		1:3

Table 3 : Formulation of Taste masking sachets of Tizanidine HCL with β-cyclodextrin.

Formulation code	Drug: polymer	Drug : polymer ratio
F7	Tizanidine HCl: β-cyclodextrin	1:1
F8		1:2
F9		1:3

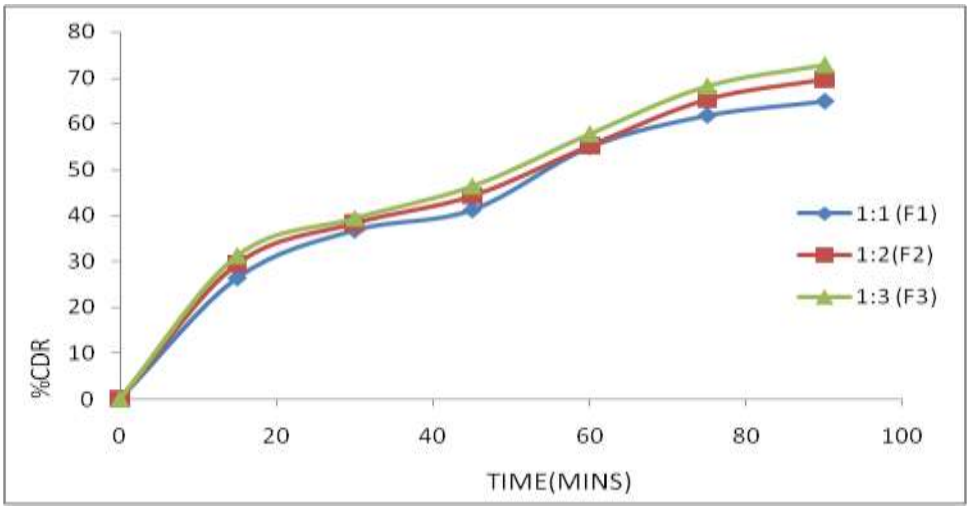

Fig no. 4: *Invitro* drug release profile for Tizanidine HCL: Povidone (F1-F3)

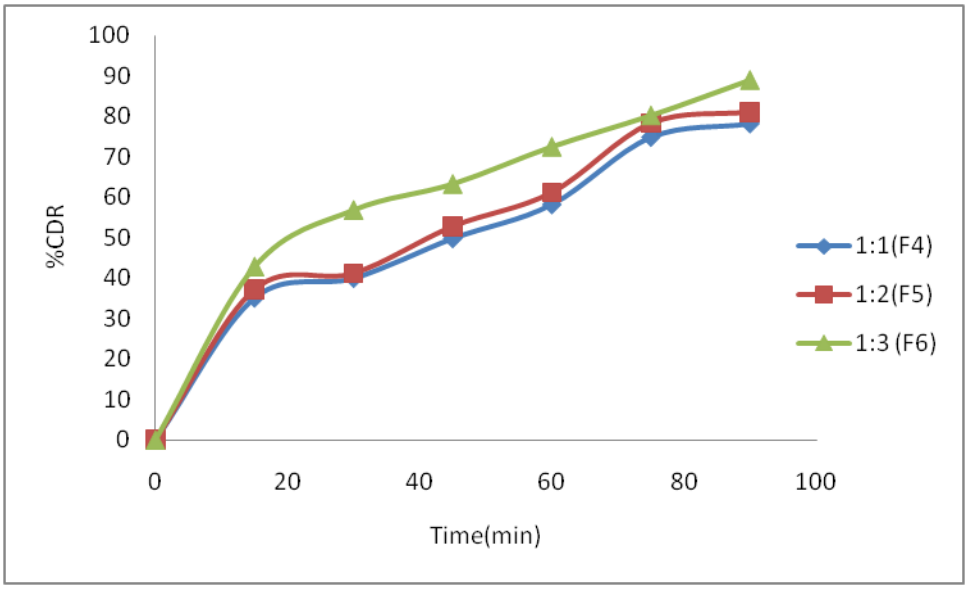

Fig no. 5: *Invitro* drug release profile for Tizanidine HCl: Mannitol (F4-F6).

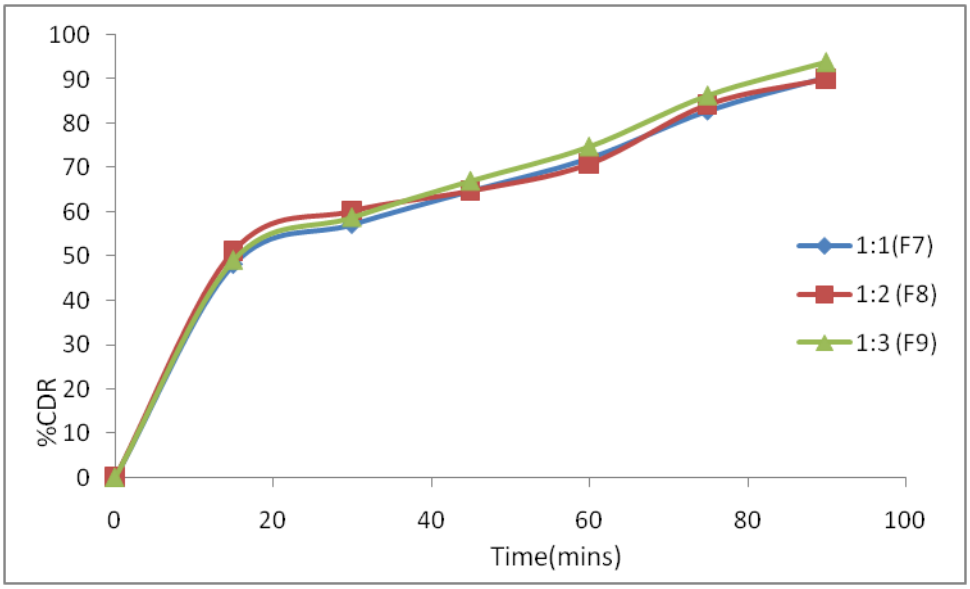

Fig no. 6: *Invitro* drug release profile for Tizanidine HCl: β-Cyclodextrin (F7-F9)

Table 4: Taste evaluation of the complexes.

	Mean bitterness value			
Formulations	**Pure drug**	**Povidone**	**Mannitol**	**β-Cyclodextrin**
1:1	5	5	4	4
1:2		4	3	2
1:3		3	2	1

CONCLUSIONS

Povidone, β-Cyclodextrin, Mannitol was used in the preparation of solid dispersions for taste masking by solvent evaporation method. The *invitro* dissolution studies of Tizanidine HCL was performed including the release kinetics studies. Among the all nine formulations formulation with β-Cyclodextrin (1:3) shows better drug release than the other formulations. Taste evaluation of the complexes also revealed that the β-Cyclodextrin (1:3) along with Tizanidine HCl was found to be taste masked successfully by using solid dispersion technique. So it was concluded that the β-Cyclodextrin was used as a carrier for enhancing the taste of Tizanidine HCl.

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