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Formulation development and optimization studies of mouth dissolving tablets of tizanidine HCl

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Abstract: The purpose of this research was the development and optimization of mouth dissolving tablets (MDT) of Tizanidine hydrochloride using superdisintegrant. MDTs of Tizanidine (4mg) were manufactured by direct compression method. Formulations comprised of Tizanidine and excipients including croscarmellose sodium, Avicel PH 102, aspartame, orange flavor and magnesium stearate. Blends of powder were assessed for flow characterization and then compressed by direct compression. During post compression stage, a detail evaluation of tablets with respect to weight variation, hardness, thickness, disintegration time, wetting time, friability, drug content analysis, content uniformity, palatability and dissolution studies was carried out. All the formulations complied with the pharmacopeial requirements of weight, disintegration time and assay. Amongst the trial formulations F4 with concentration of croscarmellose sodium i.e. 5% was proved as best optimized due to satisfactory quality attributes such as least disintegration time and sufficient hardness. Hence, it was concluded that manufacturing of mouth dissolving tablets by addition of superdisintegrant is beneficial for treating patients with dysphagia.

Keywords: Tizanidine hydrochloride, croscarmellose sodium, mouth dissolving tablets (MDT)

INTRODUCTION

Many pharmaceutical and patient needs are addressed by mouth dissolving tablets. The USP has approved that dosage forms such as mouth dissolving, oro-dispersible tablets (ODTs), fast disintegrating tablets (FDTs), fast dispersible tablets are categorized as ODTs. This is a new technology, enhancing the quality of life and dosing convenience for patient with special need (Comoglu *et al*., 2016). In this novel dosage form after disintegration in oral cavity the drug is immediately released in mouth by saliva, and/or swallowed with little or no water (Dave *et al*., 2015). Oral administration of drug is the most convenient route for patients in many cases. However, there are some drawback associated with this route such as delayed absorption and delayed onset of drug action. For this reason, application of this new technology is in demand which immediately release the medicament. Other benefits associated with such formulations include unit dose system, fast onset of action, long shelf-life, cost effectiveness, stability, increased bioavailability etc. (Pande, *et al*. 2016). During the last ten years the demand of ODTs has been immensely increased in the pharmaceutical industries.

In the present study Tizanidine Hydrochloride was used as model drug. It is a centrally acting α-2 adrenergic agonist, widely prescribed as a muscle relaxant. Being a BCS II drug, it has good solubility in organic polar solvents with high *in-vivo* permeability. For absorption, dissolution is the rate limited step, hence it is ideal candidate for mouth dissolving formulation using superdisintegrant. Its usual recommended dose is 4 thrice a day, for 1 to 4 days only (Zaman *et al*., 2018; Rajashekhar *et al*., 2016). Its plasma protein binding is about 30%, 95% of the dose is metabolized by CYTP1A2 (cytochrome P1A2). Due to extensive first-pass metabolism, low bioavailability and bitter taste of the drug; Tizanidine was selected as the ideal candidate for making mouth dissolving tablet especially for treating the muscular spasm, muscular cramping and tightness among children and old age patients.

In the present study mouth dissolving tablets of *Tizanidine Hydrochloride* (4mg) were developed and optimized. Direct compression technique was utilized using variable concentrations of superdisintegrant to dissolve the tablet in mouth cavity. Quality evaluation of mouth dissolving formulations was carried out using several Pharmacopeial and non-Pharmacopeial methods.

MATERIALS AND METHODS

Chemicals and reagents

Tizanidine Hydrochloride (SAMI Pharmaceuticals Pvt. Ltd.), Aspartame (Lubon Industry Co. Ltd., China),

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Avicel PH102 (F.M.C., International product, USA), croscarmellose sodium sodium (Shree Vasai Enterprises, Mumbai, India), magnesium stearate (Jingjiang Chemical Co. Ltd., China).

Softwares used

Design Expert® version (7.0), Statistical software SPSS (17.0) (SPSS Inc), DD solver®.

Equipment

Analytical balance (Panther USA), Single punch Compression machine (TDP-1.5), sieve # 20, vernier caliper (Seiko, China), friability tester (Curio FB 2020, Pakistan), digital hardness tester, USP dissolution apparatus II (DA 6D, Veego, India), USP Basket-rack assembly (DA 6D, Veego, India), UV spectrophotometer (Shimadzu, Japan), Sonicator (LC60H, Elma, Germany)

Formulation design

Central composite design (CCD) with its origin at center point was employed through Design Expert® version (7.0) for Tizanidine formulations designing. Tizanidine hydrochloride (4mg) was used as a model drug. Excipients used as independent variable such as Croscarmellose sodium (2-7%) and Avicel (35-50%). Whereas, aspartame (1%) as a sweetening agent, orange flavor as flavorant and magnesium stearate as lubricant were added in fixed quantity. The effect of different concentrations of superdisintegrant was studied on tablet disintegration time. Composition of the formulations is given in table 1.

Micromeritic assessment of powder blend

The powder blend of all formulations was evaluated for micromeritic characterization. Hausner's ratio, angle of repose and Carr's Index were calculated in order to evaluate the flow properties. Powder blends that have shown conformity with USP values between fair to excellent flow were selected for compression procedure.

Compression of the tablets

Active and excipients were passed through mesh # 20 after weighing, and then mixed by tumbling action in a poly bag except magnesium stearate. In the last stage lubricant was added and mixed for five minutes. After micromeritic evaluation, the powder blends with excellent to fair flow properties were finally compressed by direct compression method using single punch tablet machine (TDP-1.5).

Post compression evaluation

Physical properties assessment

After compression of the tablets, random samples from each formulation were examined against Pharmacopoeial and non-Pharmacopoeial standards. Weight variation (N=20), thickness (N=10), hardness (N=10), disintegration time (N=6), friability (N=10), dissolution (N=6), assay and content uniformity (N=10) were evaluated for each trial formation (F1, F2, F4, F7 & F9). A sample of twenty tablets from each formulation was collected and their cumulative and average weight was determined and compared against official standard. A sample of 10 tablets was used to determine thickness using Vernier caliper (Seiko, China). The mechanical strength of the tablets was evaluated through hardness and friability potential of formulations. For friability testing a sample of ten tablets was exposed to friability tester for 100rpm. The disintegration time was calculated with USP Basket-rack assembly (DA 6D, Veego, India) using standard recommended conditions (BP, 2013). The test results were analyzed and tabulated graphically using Microsoft excel ®2010. Mean values with standard deviations are calculated. Percentage recoveries (assay) and uniformity of content were performed in triplicates in accordance to USP method (USP, 2013).

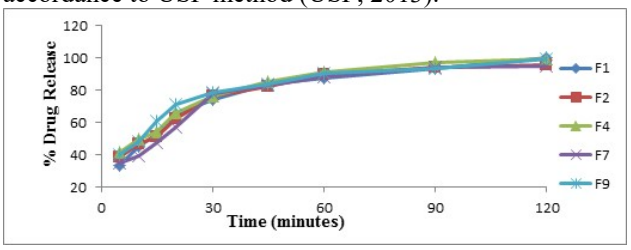

Fig. 1: Dissolution release profile of Tizanidine at pH 0.1N HCL

Evaluation of palatability

During the study the palatability of optimized formulation (F3) of Tizanidine oral disintegrating tablet was also determined. Ten healthy human male volunteers were selected for study and were assign volunteer code (A-J). Palatability evaluation feedback form was filled by each volunteer of the study (table 4-5). They were instructed to take one tablet (one dose) in to the mouth (Do not swallow the tablet) and wait for 30 seconds. After 30 seconds tablet content was spitted (mouth was not washed), record the feedback. After spitting the table, wait for 5 minutes and record the feedback again. At the end of study thoroughly wash the mouth cavity with water.

Dissolution profile comparison

On the basis of different proportion of superdisintegrant used in the formulations, it is recommended to statistically compare such products using similarity factor (f_2) to confirm that drug release patterns are not different considerably (FDA 2009). *In-vitro* profiles of trial products were observed at different time points with sample size of N=6 in 900ml of 0.1 N HCL as dissolution medium using USP dissolution apparatus II at 50 rpm (temp 37±0.5ºC). All test formulations of Tizanidine hydrochloride tablets and reference formulation were tested. After every 5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 minutes, samples were withdrawn and filtered using Whattman (41) filter paper and analyzed through UV-spectrophotometer at 228mn.

Table 1: Composition of Tizanidine hydrochloride mouth dissolving tablets using central composite design

Formulations	Type	Coded level Croscarmellose	Coded level Avicel PH102	Croscarmellose (%)	Avicel PH102 (%)	Aspartam (mg)	Avicel PH102 (mg)	Croscarmellose (mg)	Mg Stearate (mg)	Flavour (mg)	Active (mg)	weight (mg)
1	Fact	-1	-1	4	35	1.7	131.72	15.05	6.03	1.5	4	160
2	Fact	1	-1	5	35		114.90	32.83	5.07			
3	Fact	-1	1	4	50		137.77	11.02	4.01			
4	Fact	1	1	5	50		124.44	24.89	3.48			
5	Axial	-1.4142	0	2.757	42.5		138.77	9.00	5.03			
6	Axial	1.4142	0	11.242	42.5		117.64	31.12	4.04			
7	Axial	0	-1.4142	7	31.893		120.34	26.41	6.05			
8	Axial	0	1.4142	7	53.106		131.94	17.39	3.97			
9	Center	0	0	7	42.5		127.33	20.97	4.49			

Release kinetic analysis

Numerous models were utilized using *in-vitro* release data of designed formulations (F1, F2, F7, F9) and reference formulation (F4), including First Order, Higuchi, Hixson Crowell and Weibull kinetic models. Similarly model independent methods i.e. similarity factor (f_2) and difference factor (f_1) were also employed. These method have also been applied by other researchers to determine the similarity or difference between test and reference formulations (Zafar *et al*., 2015). For selected formulations the values of f_2 were determined by using DD Solver® program.

Ethical approval

Ethical and technical aspect of study were reviewed and approved by Graduate and Research Management Council of Federal Urdu University for Arts, Science and Technology, Karachi, Pakistan.

STATISTICAL ANALYSIS

Data was statistically analyzed using Microsoft excel program and different post compressional parameters were calculated with mean and SD values. Moreover release profile data was examined using DD Solver® an Add In program and best fit model was chosen on the basis of highest value of r^2.

RESULTS

In the present investigation, mouth dissolving formulations of Tizanidine hydrochloride were designed and optimized by CCD. During formulations design concentration of avicel PH 102 and croscarmellose were varied at 5 levels (1, 0, -1, α, -α). Total 9 formulations were designed (table 1). Powder blends were assessed by various parameters i.e. Hausner's ratio, compressibility index and angle of repose. The mean values of angle of repose were found between 25.62±1.26º-36.85±1.49º. The indicate values of Hausner's ratio were found in the range of: 1.09±0.32-1.23±0.7. Whereas average values of Carr's index were found in the range of: 9.68±0.59%- 17.9± 0.63%. On the basis of micromeritic results five formulations were selected for compression i.e., F1, F2, F4, F7 & F9. The results for pre-compression parameters of these trial formulations are shown in table 2. The average weight of all test formulations was found as per USP specification within ± 5%. The calculated thickness values of all formulations were found within ±5mm. Average hardness of all test formulations was observed to be acceptable i.e., ≥ 3Kg. The % friability was found less than 1%. The disintegration time of selected formulations was observed acceptable (not more than 3 minutes). Content uniformity and percentage recovery tests were executed according to the USP method and results were assessed in adequate limits i.e. 90-110%. The amount of drug release from all formulations was found to be more

Table 2: Pre-compressional properties of powder blends

Formulations	Angle of repose(ɵ) (±SD), n=3	Carr's index (%) (±SD), n=3	Hausner's ratio (±SD), n=3
F1	35.65 (±1.56)	13.7 (±1.32)	1.16 (±0.75)
F2	33.44 (±2.37)	12.1 (±1.08)	1.13 (±0.92)
F4	25.62 (±1.26)	9.68 (±0.59)	1.09 (±0.32)
F7	29.23 (±2.07)	13.5 (±0.84)	1.12 (±0.71)
F9	36.85 (±1.49)	17.9 (±0.63)	1.23 (±0.76)

Table 3: Post-Compressional parameters of reference and trial formulations

Parameters	F1	F2	F4	F7	F9
Hardness (kg) n=10	3.19± 0.11	3.58±0.11	3.46±0.15	3.71±0.12	3.79±0.07
Weight variation (mg) n=20	174.15±1.916	146.45±6.22	153.7±3.35	152.4±3.15	151.45±4.00
Thickness(mm) n=20	4.52±0.08	2.86±0.13	2.89±0.10	2.66±0.23	2.31±0.21
Friability(%) n=10	0.76±0.04	0.85±0.05	0.59±0.03	0.73±0.04	0.89±0.06
Wetting time (sec) n=5	23±0.32	22±0.32	20±0.08	25±0.01	27±0.02
Disintegration time (sec) n=10	28 ±1.21	25±0.08	21±0.09	26±0.05	29±0.07
Content uniformity n=10	101.58±0.94	98.81±0.63	101.55±0.54	99.94±0.99	98.95±0.75
Assay Test (%) n=3	99.76±0.12	99.88±0.04	100.22±0.49	100.16±0.70	99.95±0.30

Table 4: Palatability evaluation Scale

Score	Preliminary Taste (30 sec)		Subsequent Taste (5 min)		Mouth Feel	Flavor	On The Whole Acceptability
	Level of Bitterness	Level of Sweetness	Level of Bitterness	Level of Sweetness			
1	Exceptionally Bitter	Not At All Sweet	Exceptionally Bitter	Not At All Sweet	Very Gritty	Very Unpleasant	Worst
2	Highly Bitter	Very Slightly Sweet	Highly Bitter	Very Slightly Sweet	Gritty	Unpleasant	Poor
3	Acceptable /Tolerable	Acceptable /Tolerable	Acceptable /Tolerable	Acceptable /Tolerable	Acceptable /Tolerable	Acceptable /Tolerable	Acceptable /Tolerable
4	Very Slightly Bitter	Highly Sweet	Very Slightly Bitter	Highly Sweet	Creamy	Pleasant	Good
5	Not Bitter	Exceedingly Sweet	Not Bitter	Exceedingly Sweet	Exceptionally Creamy	Exceptionally Pleasant	Exceptionally Good

than ±80%. Post compressional parameters are mentioned in table 3. During palatability testing preliminary taste and subsequent taste of optimized formulation (F3) were determined with respect to level of bitterness and level of sweetness at two time point i.e., at 30 sec and 5min respectively in ten healthy volunteers. Furthermore mouth feel, flavor and over all acceptability of optimized formulation was also determined. Feedback form was filled by all volunteers and summarized as Table 4-5. Average value of level of bitterness and sweetness at initial test was found to be 4.2±0.788 and 3.7±0.823. While after taste values were in order of 4.2± 0.421 and 3.7±0.966. Drug release profiles of selected formulations at pH 0.1N HCl were presented in fig. 1. The similarity and differential factors i.e., f_2 and f_1 were also estimated. While the dissolution profile comparison showed the highest values of r^2 with Weibull model (table 6-7).

DISCUSSION

In current investigation mouth dissolving tablets of Tizanidine hydrochloride (4mg) were developed and optimized through Design Expert ®. Total 9 formulations were designed through Design Expert using 1 as the center point. Only five formulations were selected for compression based on appropriate weight and satisfactory micrometric characteristics. Tizanidine hydrochloride was selected as a model drug due to its bitter taste, poor solubility and no such formulation's availability in the market. Formulations comprised of croscarmellose sodium (2-5%) as superdisintegrant, avicel PH102 (35-50%) as bulking agent, magnesium stearate (2%) as lubricant and aspartame (1%) as sweetening agent. Technique of direct compression was used to compress trial formulations which is the customary choice for making oro-dispersible tablets (Rajashekhar *et al*., 2016). Croscarmellose sodium was incorporated as superdisintegrant to facilitate tablet mouth dissolving properties. The proposed mechanisms of this superdisintegrant are swelling, wicking and strain recovery mechanisms. Imbibitions' of water into the compact structure of tablet is the principal phase of the breaking down process and consequently affects all other activities of essential significance as it will influence the

Table 5: Taste evaluation results for the selected optimized formulation (F4)

Volunteer code	Preliminary Taste (30 sec)										Subsequent Taste (5 min)										Mouth Feel					Flavor					On The Whole Acceptability				
	Level of Bitterness					Level of Sweetness					Level of Bitterness					Level of Sweetness					Very Gritty To Exceptionally Creamy					Very unpleasant To Exceptionally Pleasant					Worst To Exceptionally Good				
	Exceptionally Bitter To Not Bitter					Not At All Sweet To Exceedingly Sweet					Exceptionally Bitter To Not Bitter					Not At All Sweet To Exceedingly Sweet																			
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
A	-	-	-	√	-	-	-	√	-	-	-	-	-	√	-	-	-	-	-	√	-	-	-	√	-	-	-	-	√	-	-	-	-	√	-
B	-	-	-	√	-	-	-	√	-	-	-	-	-	√	-	-	-	-	-	√	-	-	-	√	-	-	-	-	√	-	-	-	-	√	-
C	-	-	-	-	√	-	-	√	-	-	-	-	√	-	-	-	-	√	-	-	-	-	√	-	-	-	-	-	√	-	-	-	-	√	-
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J	-	-	√	-	-	-	-	√	-	-	-	-	-	√	-	-	-	√	-	-	-	-	-	-	√	-	-	-	-	√	-	-	-	√	-
Average	4.2					3.7					4.2					3.4					3.8					4.3					4.1				
SD	0.788					0.823					0.421					0.966					0.788					0.483					0.737				

various disintegrant mechanisms (Jemal and Tesfaye, 2019). Other studies have also included this excipients in the manufacturing of fast dissolving tablets (Jeevanandham, *et al*. 2014).

Flow properties estimation is an essential requisite for product development process. Because appropriate flow of powder blend minimizes the chance of non-uniform distribution of medicament and yield required weight of the unit dosage form (Maroof *et al*. 2016). So in this study various micromeritic assessments were done. The powder blends indicated smaller values of Hausner's ratio (the lowest with F4 1.09±0.3), Carr's index and angle of repose (least with F4 i.e. 9.68±0.59% and 25.62±1.26º respectively) showing excellent compressibility and flow characteristics.

The average weight of all formulations was found in the range of: 146.45mg - 153.7mg. The mean thickness of all formulations was found to be: 2.31-2.89mm. Friability and hardness of tablet formulations are extensively related to the mouth dissolving tendency of tablets. The recommended hardness for such formulation is 4kg (Shah, *et al*. 2011). Average hardness of tablets in this study was lying in the range of 3.19kg - 3.79kg (least with F1 and highest with F9) which exhibit the sufficient mechanical strength of the tablets. Mouth dissolving tablets should disintegrate quickly, because superdisintegrant is incorporated for this purpose. Disintegration time is the crucial parameter for making mouth dissolving tablets. The disintegration time of all test formulations was found in the range of 21-29 seconds. Formulations containing croscarmellose produce least wetting time due to high porosity which facilitates the water diffusion in tablets. This results in wicking, and helps in rapid disintegration of tablets (Varun and Ajaykumar, 2013). Wetting time of the trial formulations (n=5) was found in the range of 20±0.08 - 27±0.32 seconds.

Some researchers have also applied the use of superdisintegrants in combinations for quick breakup (Panigrahi, *et al*. 2012). Friability is used to evaluate the strength and crumbling potential of tablets during transportation, distribution and even at various steps of manufacturing. An appropriate value of friability for mouth dissolving tablets should be less than 1% (Hitesh *et al*., 2017). In the current study, the % friability was found to be 0.59-0.89%. The mean assay and content uniformity of all formulation were in order of 98.81% ±0.63 to 101.58%±0.94 and 99.76%±0.12 to 100.22% ±0.49 respectively. Taste is another important characteristic for mouth dissolving tablets. Tizanidine hydrochloride is a bitter medicament thus use of aspartame was employed to mask its bitterness. However, combination of diluents have also recommended to mask bitterness of the drug (Stange, *et al*. 2013; Yasmin, *et al*. 2019; Patel, *et al*. 2014). A panel of 10 human volunteers

Table 6: Application of kinetic models on different formulations of Tizanidine hydrochloride 4mg tablets at 0.1N HCl

Formulations	First order		Higuchi		Hixon Crowell		Weibull model		
	r^2	k_1 (h^{-1})	r^2	k_H ($h^{-1/2}$)	r^2	K_{HC} ($h^{-1/3}$)	r^2	β	α
F1	0.9260	0.080	0.8388	10.576	0.9963	0.012	0.9867	0.718	5.897
F2	0.7408	0.164	0.6744	7.851	0.9312	0.011	0.9919	0.522	2.193
F4	0.8141	0.187	0.6136	7.659	0.9304	0.011	0.9813	0.584	2.263
F7	0.8036	0.135	0.6712	8.452	0.9330	0.012	0.9794	0.573	2.799
F9	0.9340	0.146	0.5918	8.647	0.9252	0.012	0.9909	0.720	3.677

Table 7: Similarity and differential factors for Tizanidine tablets

Formulations	f_1	f_2
F1 & F4	11.77	61.36
F2 & F4	14.36	56.20
F7 & F4	9.58	73.29
F9 & F4	11.33	69.64

was organized to evaluate the taste of the trial formulation for presented study. They were asked to keep the particles of orally disintegrated tablet in the oral cavity for 30 sec and give their comments. Members of the panel reported that trial formulation has agreeable taste and mouth feel satisfactory to be used as oral disintegrating tablets. The results of palatability test were illustrated in table 4-5. Majority volunteers reported acceptable to good palatability values with respected to mouth feel, taste, flavor and over all acceptability. Only one out of ten volunteer reported level of sweetness subsequent to taste as slightly sweet. In mouth feel evaluation, all reported as acceptable and above grade. Hence, the results indicated that formulation F4 is having appropriate palatability. Ramana *et al*., also performed similar studies to determine the palatability efficiency of poorly soluble and bitter taste drug risperidone. Researchers reported that better taste masking and disintegration may be obtained from lyophilized and compressed tablet using appropriate taste enhancers as amberlite (Ramana *et al*., 2010).

Different kinetic models were used for formulation optimization and their data has been mentioned in table 6. All trial formulations and reference product showed compliance with Weibull model with highest value of R^2. Trial formulations (i.e. F1, F2, F7, F9) were compared with reference formulation (F4) using similarity and differential factors. Results of f_1 values for all trial formulations were found less than 15. Whereas f_2 values for trial formulations were lying in the range of 56.21 - 73.29 in 0.1N HCI solutions. Authors have reported similar findings in literature for Mefenamic acid and Flurbiprofen (Maroof *et al*., 2016; Yasmin *et al*., 2019).

CONCLUSION

Mouth dissolving tablets of Tizanidine Hydrochloride were successfully developed by direct compression technique. Formulation F4 with selected concentration of croscarmellose sodium i.e. 5% showed the least disintegration and wetting time with sufficient hardness and content uniformity, hence proved as the best optimized formulation. This study clearly demonstrates that mouth dissolving tablets of Tizanidine can be prepared using suitable concentration of superdisintegrant through direct compression method. Manufacturing of mouth dissolving tablets could be of great importance for the patients suffering from dysphagia in geriatric cohort.

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