Effects of various excipients on tizanidine hydrochloride tablets prepared by direct compression

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Abstract: This study was conducted to assess the effects of various excipients in 10 different Tizanidine hydrochloride tablet dosage forms that were prepared by direct compression method (DC). Various excipients are available for DC method; we selected those excipients that are used commonly in tablet manufacturing. The excipients used included lactose anhydrous, di-basic calcium phosphate anhydrous, starch, talc, sodium carboxy methyl cellulose, polyvinyl pyrrolidone (PVP), silicon dioxide (Aerosil), stearic acid, magnesium stearate and microcrystalline cellulose (Avicel). These tablets were then evaluated by performing different pharmacopoeial and non-pharmacopoeial tests (i.e. diameter, hardness, thickness, weight variation, disintegration and assay). It was observed that Formulations B, D and H of Tizanidine hydrochloride gave best results within USP specified limits for the tests employed among all the formulations whereas Formulations F and G showed poor friability, disintegration and dissolution profiles rendering starch in combination of talc and sodium carboxy- methyl cellulose unsuitable for Tizanidine hydrochloride tablet formulations. With the present approach, more studies can be designed using other active ingredients and excipients to get an optimal and cost effective product.

Keywords: Tizanidine hydrochloride, excipients, diluents, direct compression, tablets.

INTRODUCTION

Tizanidine hydrochloride is an imidazoline derivative acting as agonist on centrally located α_2 receptors; has myotonolytic effects on skeletal muscles (Wagstaff AJ and Bryson HM, 1997). More than 50% of the dose administered orally is being absorbed through the gastrointestinal tract and drug is widely distributed. It undergoes swift and widespread first-pass metabolism in the liver leading to lower bioavailability (Moffat AC, 2006). Tizanidine hydrochloride may also be a useful adjunct to NSAIDs in the treatment of analgesic rebound headache (Smith TR, 2000).

Experimental design studies (EDS) are generally used in pharmaceutical industry for formulation of drugs or process optimization (Goutte *et al*., 2002). Though pharmaceutical research has been focused on development of new and more amenable dosage forms, tablets are still trendy due to their stability, ease of handling and ease of dosing (Jivraj *et al*., 2000). Direct Compression (DC) is useful in tablet manufacturing which involves fewer unit operations, thus low cost and less time utilization, producing optimal possible bioavailability, little microbial level and producing quicker dissolution rates for some compounds (Jivraj *et al*., 2000; Yasmeen *et al*., 2005). DC offers high efficiency in tablet manufacturing (Zhang *et al*., 2003). The tablets prepared by DC disintegrate into API particles in place of granules, which directly come into contact with the dissolution medium and demonstrate a relatively quicker dissolution (Gohel MC, 2005).

A simple formula for tablet preparation includes an active ingredient, a diluent and a lubricant 9 (Martino *et al*., 2004). For present study those excipients were selected that are used frequently in tablet preparations so as to have combination of materials that may produce an optimal dosage form of Tizanidine hydrochloride. Microcrystalline cellulose (Avicel) can be used as filler and showed excellent compressibility of the Ibuprofen tablets. It is self-lubricating (Omray and Omray, 1986) and provided compactness and strength to the tablets to much extent (Hernier and Teleman, 1997). The use of combination of Microcrystalline cellulose (Avicel) and lactose in preparations give better average effectiveness as compared to microcrystalline cellulose and dicalcium phosphate anhydrous combination (Morris *et al*., 2009). Tablets containing lactose demonstrate fast disintegration (Kamp *et al*., 1986). Starch, as indicated by many workers, is commonly used as binder; it is abundant, cost effective, fairly inert and does not react with most of the active drug substances (Haware *et al*., 2009; Elvira *et al*., 2002). A good swelling property of corn starch may promotes faster disintegration as compared to poor swelling ability of Avicel (Hisakadzu S and Yunxia B 2002). Starch is a commonly used disintegrant, which is available in various grades and tailored forms (Sheth, *et al*., 1980; Marshall K and Rudnic EM 1990), since tablet disintegration has been a first step for achieving swift bioavailability of the active ingredients.

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The use of lubricants may affect many properties of the formulated tablets i.e. tablet weight, friability, disintegration time, etc (Roberts *et al*., 2004; Michael *et al*., 2009). Magnesium stearate has been found to be a very efficient lubricant based on LPEF-lubricant (low punch ejection force) concentration profile (Turkoglu *et al*., 2005). Cellulose derivatives have the property to move smoothly over the inner surfaces of the dies for tablet compaction but for some formulation excipients and drugs, the use of lubricants is essential so as to have smooth fabrication on the production lines. Stearic acid is mainly used in oral formulations as a tablet lubricant; it may also be used as a binder (Kibbe, 2000).

The use of glidants in direct compression formulations improves powder flow and manage weight of tablets i.e. silica-type glidants are mainly proficient amid a number of other groups (Sheth *et al*., 1980). Colloidal silicon dioxide such as Aerosil has been used widely in the tablet manufacturing i.e. as a moisture adsorbent, free-flow agent and glidant (Jonat *et al*., 2006). In theophylline-loaded lipid microparticles, it was also used as a thickening/suspending agent (Albertini *et al*., 2004).

MATERIALS AND METHODS

Tizanidine HCl (hydrochloride) active was gifted by Novartis Pharma, Jamshoro Sindh, Pakistan. Ten different tablet formulations were designed with different excipients (table 1). Tablets were prepared using direct compression method on single punch machine with average weight of 160mg. Pharmacopoeial and non-Pharmacopoeial tests were performed i.e. uniformity of weight, hardness, uniformity of diameter, friability, assay, disintegration and dissolution to evaluate the effects of various excipients on Tizanidine HCl formulations.

Physicochemical testing

All the trial batches of Tizanidine HCl were evaluated using USP 28/NF 23 (USP 28/NF 23, 2005) and by non pharmacopoeial tests.

Uniformity of weight

20 tablets from each of the formulation were taken and weighed using the analytical balance (Mettler Toledo B204-S, Switzerland). The average weight of the tablets as well as percent deviation was calculated.

Hardness

Ten tablets were taken from each formulation to determine the hardness and percent standard deviation were calculated using OSK Fujiwara Hardness Tester, Tokyo, Japan.

Diameter and thickness

A random sample of 10 tablets was selected from each formulation to determine the diameter and thickness using vernier calipers.

Friability

The loss in weight indicates the ability of the tablets to withstand this type of wear (British Pharmacopoeia, 2004). Friability test for the tablets was performed on Digitek friabilator, China. 20 tablets from each formulation were selected randomly for the test and percent friability was calculated.

Assay of tizanidine tablets

20 tablets were selected randomly from each formulation which were weighed and crushed to powder. The reference and test samples were prepared using a mixture of 0.1N Sulphuric acid and Methanol (80:20) and filtered through Watman filter paper (No. 41). The absorbance of the resulting solutions was measured at 317nm spectrophotometrically (UV-Spectrophotometer 150-02, Schimadzu corporation, Kyoto, Japan), taking the same solvent mixture as blank.

Disintegration test

6 tablets from each formulation were selected randomly to perform the disintegration test (ERWEKA ZT-3 Husenstamm, Germany) using 900ml distilled water at temperature $37^{o}C \pm 2^{o}C$.

Dissolution test

The dissolution test was performed using ERWEKA DT700, Husenstamm, Germany, having 6 replicates. 0.01N Hydrochloric acid was used as dissolution medium and apparatus was run with a speed of 50 rpm at $37^{0}C \pm 0.5^{0}C$. The samples were taken at regular time intervals and sink conditions were maintained by adding fresh dissolution medium in the vessel. Test samples were filtered by Watman filter paper no 41 and analyzed spectrophotometrically (UV-Spectrophotometer 150-02, Schimadzu corporation, Kyoto, Japan) using 0.01N Hydrochloric acid as blank at 320 nm.

RESULTS

The tablets were evaluated for different physical parameters such as hardness, friability, drug content, disintegration and dissolution (table 2). All the tablets maintained hardness in the range of 3.30 to 7.50 kg/cm^2 except for formulation C, having highest hardness value of 11.71 kg/cm^2. It can be seen from table 2 that result of weight variation test, diameter and thickness of all the tablets prepared are satisfactory. The loss in total weight of the tablets due to friability was in the range of 0.003 to 0.6% except for Formulations F, G and J (table 2). Disintegration is assessed to make sure that the drug substance is completely available for dissolution and absorption from the gastrointestinal tract (Block and Yu, 2001). Disintegration time for all formulations lies in the range of 13 to 55 seconds except for Formulations F and G showing higher disintegration time from 197 to 217 seconds (table 2). The drug content in different formulations was quite consistent and within range i.e. 97% to 102.55% (table 2).

Table 1: Various formulations of Tizanidine HCl

S. No	Material	Formulation A		Formulation B		Formulation C		Formulation D		Formulation E		Formulation F		Formulation G		Formulation H		Formulation I		Formulation J	
		% ratio	Qty/tab (mg)	% ratio	Qty/tab (mg)	% ratio	Qty/tab (mg)	% ratio	Qty/tab (mg)	% ratio	Qty/tab (mg)	% ratio	Qty/tab (mg)	% ratio	Qty/tab (mg)	% ratio	Qty/tab (mg)	% ratio	Qty/tab (mg)	% ratio	Qty/tab (mg)
1	TizanidineHCl	1.4	2.3	1.4	2.3	1.4	2.3	1.4	2.3	1.4	2.3	1.4	2.3	1.4	2.3	1.4	2.3	1.4	2.3	1.4	2.3
2	Avicel 102	35.5	56.8	39.5	63.2	37.5	60.0	40.5	64.8	25.5	40.8	25.5	40.8	25.5	40.8	45.5	72.8	45.5	72.8	45.5	72.8
3	Talc	3.0	4.8	3.0	4.8	3.0	4.8	3.0	4.8	3.0	4.8	3.0	4.8	3.0	4.8	-	-	3.0	4.8	-	-
4	Starch	10.0	16.0	-	-	-	-	-	-	-	-	60.0	96.0	60.0	96.0	-	-	-	-	-	-
5	Lactose	50.0	80.0	50.0	80.0	50.0	80.0	50.0	80.0	-	-	-	-	-	-	50.0	80.0	50.0	80.0	50.0	80.0
6	Sodium CMC	-	-	6.0	9.6	-	-	5.0	8.0	10.0	16.0	10.0	16.0	10.0	16.0	-	-	-	-	-	-
7	PVP	-	-	-	-	8.0	12.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8	Di- calcium phosphate	-	-	-	-	-		-	-	60.0	96.0	-	-	-	-	-	-	-	-	-	-
9	Silicon dioxide	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.0	3.2	-	-	-	-
10	Stearic acid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.0	1.6	-	-	-	-
11	Magnesium stearate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.0	4.8

DISCUSSION

It can be seen from table 2 that formulation A has suitable combination of the excipients; the results for tests employed for it were all within USP specifications. Formulation A showed 89.23% rate of dissolution which may be due to the use of starch and it was found by (Levy GJ, 1963) that if starch is used in ratio of 5% to 20%, the dissolution rate can increase to three folds. The dissolution of Formulation B was higher than that of formulation A though it had hardness (7.30 kg) more than that of formulation A. This may be due to sodium carboxy-methylcellulose (CMC), which was used instead of cornstarch. When tablets are made using sodium CMC, it acts as super disintegrant; tablet self disintegrates and requires little lubricant. Cross-linked sodium CMC is a carrier for dissolution rate improvement of drugs (Sangalli *et al*., 1989). The results of various tests employed are within specifications for Formulation B as well. Formulation D also showed similar results like formulation B with minor change in the percentage of CMC used as excipient. Formulation C showed better dissolution rate (table 2) than formulation A, but the tablets prepared were the hardest (11.71 kg) among all the formulations. In this formulation starch and sodium CMC are not used while PVP has been used in this formulation in combination with other excipients. The main application area for Polyvinylpyrrolidone (PVP) is as a binder in tablets and granulates. Improvement in solubility can be achieved by adding a solubilizer such as Povidone because with many active substances, Povidone forms soluble complexes and this might be the reason for increased hardness for this formulation. Other test results are satisfactory for formulation C (table 2) (Chowdary KPR and Rao KSPA, 2012)

Formulation E gave best dissolution profile (table 2) among all the formulations, which may be due to the use of combination of di calcium phosphate and sodium CMC while lactose anhydrous was not included in these tablets. Di-calcium phosphate produces disintegrating effect which decreases the disintegration time (Carstensen and Ertell, 1990) whereas sodium CMC acts as super disintegrant and improves dissolution rate of drugs in Cross-linked form (Sangalli *et al*., 1989)

Formulation F and G showed poor disintegration, dissolution and friability profiles. Such poor results may be due to the presence of combination of starch and sodium CMC with omission of lactose anhydrous in Formulation F. The presence of starch in higher concentration works as binder instead of disintegrator

Table 2: Various quality control tests performed for tizanidine hcl tablets

Formulation	Average weight mg (S.D) n=20	Diameter mm (S.D) n=20	Hardness kg (S.D) n=20	Thickness mm (S.D) n=20	Dissolution % (S.D) n=6	Disintegration seconds (S.D) n=6	Assay % (S.D) n=20	Friability % n=20
A	160.08 (2.940)	7.401 (0.007)	3.31 (3.153)	3.131 (0.035)	89.23 (0.248)	13.00 (0.021)	99.04 (0.044)	0.434
B	160.56 (3.408)	7.386 (0.008)	7.30 (3.339)	3.123 (0.017)	99.62 (0.024)	28.00 (0.021)	97.04 (0.056)	0.003
C	162.07 (2.933)	7.393 (0.008)	11.71 (4.709)	3.131 (0.009)	92.17 (0.064)	51.00 (0.035)	97.25 (0.151)	0.058
D	162.66 (3.445)	7.391 (0.007)	7.45 (4.681)	2.921 (0.007)	99.68 (0.132)	54.00 (0.042)	100.81 (0.173)	0.161
E	160.96 (2.473)	7.416 (0.010)	6.76 (4.620)	2.405 (0.010)	102.79 (0.014)	20.93 (2.220)	98.30 (0.163)	0.528
F	162.91 (3.144)	7.410 (0.012)	6.46 (4.320)	2.756 (0.010)	75.52 (0.029)	197.90 (2.121)	102.55 (0.341)	1.745
G	162.76 (2.986)	7.445 (0.010)	3.48 (3.924)	3.108 (0.007)	68.84 (0.034)	217.0 (0.001)	99.20 (0.109)	2.012
H	165.47 (2.986)	7.405 (0.010)	4.99 (4.252)	3.263 (0.008)	97.54 (0.012)	24.00 (0.056)	97.85 (0.131)	0.605
I	169.32 (2.584)	7.413 (0.010)	6.98 (4.314)	3.298 (0.007)	94.21 (0.026)	29.00 (0.035)	98.58 (0.068)	0.331
J	157.52 (1.622)	7.398 (0.007)	2.95 (3.574)	3.361 (0.007)	85.91 (0.012)	15.00 (0.007)	97.84 (0.089)	3.535

(Cunningham 1999; Anastasiades, 2002). Higher contents of sodium CMC with cornstarch in Formulation G with absence of lactose anhydrous affected the results badly though % assay results are satisfactory. Starch is one of the most extensively used pharmaceutical excipients but its physicochemical and functional characteristics can differ immensely even among its samples of like source (Autamashih *et al*., 2011; Ramdayal *et al*., 2011).

In formulation H, silicon dioxide and stearic acid were used instead of talc (table 1). The effect of addition of lubricants such as stearic acid is expected to produce a lessening of drug dissolution as the proportion of the lubricant increases (Kranz and Wagner, 2006). It has been reported that stearic acid behaves as an inert material that modifies metronidazole dissolution which increases with increasing proportions of stearic acid (Belem *et al*., 2009).

Formulation I and J had simplest formulae with talc and magnesium stearate as excipients respectively (table 1). In Formulation J, use of magnesium stearate was found unsuitable rendering the formulation very friable (table 2). From recent studies on tablet formulation, it was found that lubricants like magnesium stearate and talc produce a few undesirable characteristics to tablets e.g. considerable diminution in crushing strength (Shibata *et al*., 2002) and noteworthy decline in disintegration time (Aoshima *et al*., 2005). It should also be noted that some studies show that the addition of magnesium stearate noticeably improved the blending characteristics of the milled batches (Mackin *et al*., 2002).

CONCLUSION

Since Tizanidine Hydrochloride tablets are used for the relaxation of smooth muscles hence require rapid release of the drug to produce the effects. Varied excipient combinations can alter not only the preparation but also the bioavailability of Tizanidine Hydrochloride tablets; most suitable and cost effective excipient selection can render the dosage forms optimal for patients' use and compliance.

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