Physico-chemical comparison of famotidine tablets prepared via dry granulation and direct compression techniques

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Abstract: Famotidine is generally employed for the treatment of gastric ulcer. The present study was conducted to fabricate famotidine tablets using various diluents. The binder was incorporated to the formulations in different proportions. Both the dry granulation and direct compression techniques were employed to develop the tablets. Physical evaluation of tablets i.e. tablets hardness, friability, weight variation, thickness and diameter was determined. In vitro dissolution studies of the prepared tablets were carried out for 60 min using the USP apparatus II and 900 ml 0.1 M HCl stirred at 37 ± 0.5°C with a speed of 50 rpm. Physical analysis of tablets prepared via direct compression showed satisfactory results regarding the weight variation, hardness and friability, since their respective values were within the BP limits. All the prepared famotidine tablets exhibited diffusion based mode of drug release. 100% release of drug occurred in less than 60 min. The drug release from all the formulated tablets has elaborated the involvement of diffusion (Higuchian drug release). This comparative study exhibited that physical parameters of tablets are affected by the technique of tabletting.

Keywords: Famotidine; dry granulation; direct compression; release kinetics.

INTRODUCTION

Good properties of tablet do not depend upon a tablet press; rather it is the tabletting process which improves compression properties resulting in the reduction in segregation, improvement in content uniformity, good yields, improved productivity, decreased tablet imperfections, and condensed time consumption. In short, the goal of method is to hold the excipients to prepare a quality tablet (Ohwoavorhua and Adelakun, 2005).

In case of substances which are thermal and moisture sensitive, dry granulation process is preferably employed to prepare granules since it does not involve the use of liquid solution as in case of wet granulation. Dry granulation process involves the compaction and densification of powders involving a roller compactor or tablet press that is employed as a slugging tool. The powders may not have sufficiently uniform stream into the die cavity which produces different degrees of densification, a tablet press is employed for dry granulation (Malonne *et al*., 2000). The roller compactor involves an auger-feed scheme i.e. constant and uniform delivery of powder between two pressure rollers forming a ribbon which is crushed using a mill. After removal of fine powder by sieving, granules are compressed into tablet. Compatibility of the products influences the successful compaction (Mahaparale *et al*., 2006). Fine powder is removed to avoid capping, laminating, weight, and hardness predicaments (Zang and Schwartz, 2003).

If ingredients (known as directly compressible or DC) can be mixed and then be compressed into perfect tablets without any chemical change by using a tablet press, direct compression technique is employed which is the shortest technique to prepare a tablet. This method does not involve the development of granules; however granulation should be preferred when the powders cannot be compressed to avoid the non-uniformity of content (Nanjwade *et al*., 2011).

Being a hydrophilic drug, famotidine absorption is rapid from the gastrointestinal tract (Martindale, 1993). It has a quite short biological half life (5 ± 1 h) and its immediate release formulations are typically administered as a peroral dose of 20 mg twice daily (Gulzeb *et al*., 2008).

Prior to implement a method to prepare a formulation, the best thing is to place the artifact on the tablet press to elaborate the turn out. Thus the objective of this study to was to formulate immediate release famotidine tablets using variable proportions of binder. Besides, the effect of the technique employed, that are dry granulation and direct compression, on the properties of tablets was also assessed. The physical characteristics, in vitro dissolution data and the relevant kinetics of tablets were determined.

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MATERIALS AND METHODS

Materials

Famotidine was purchased from Cadila Health Care (Kirala, India). Cellulose microcrystalline (CMC, Avicel pH 102) and potato starch were purchased from FMC international, NY, USA. Lactose DC (Directly Compressible) was obtained from ICN Biomedicals, New Zealand. Aerosil was purchased from Cabot GmbH & Co., Heidelberg, Germany.

Methods

Dry granulation technique (DGT)

Formula of famotidine tablets prepared by DGT is given in table 1. The weighed components [famotidine, avicel pH 102 (binder and disintegrant), lactose DC (diluent) and aerosol (glidant)] were blended for 5 min using a mixer (Erweka, Germany). The blend was compressed into slugs using a single punch tablet machine (Erweka, Germany) having 12 mm flat punches followed by the crushing of slugs into dry granules. The granules were passed via sieve (mesh size 16) and blended. Then the mixture was compressed by single punch tablet machine (Erweka, Germany) using 12 mm flat punches to prepare tablets (T1, T2 and T3). Tablet hardness was kept in a range of 6-10 kg. Another set of excipients (starch, lactose, talc and stearic acid) was also employed in a composition as mentioned in table 1 to prepare tablets (T4, T5 and T6) via dry granulation.

Direct compression technique (DCT)

Formula of famotidine tablets prepared by DCT is given in table 1. The weighed components [famotidine, avicel pH 102 (binder and disintegrant), lactose DC (diluent) and aerosol (glidant)] were blended for 20 min using a mixer (Erweka, Germany). The blend was directly compressed into tablets using a single punch tablet machine (Erweka, Germany) having 12 mm flat punches to prepare tablets (T7, T8 and T9). Tablet hardness was kept in a range of 6-10 kg.

Physical evaluation of tablets

Physical evaluation of tablets was done according to USP guidelines (USP 1998). Ten tablets were put to hardness testing using hardness tester (Erweka, Germany). The results of tablet hardness are narrated in table 1. Twenty tablets were put to friability testing using friability tester (Erweka, Germany). The results of tablet friability are given in table 1. Another set of twenty tablets was put to weight variation testing and the results are presented in table 1. Tablet thickness and diameter was also determined as listed in table 1.

In vitro dissolution studies

In vitro dissolution studies were conducted for 60 min by using USP apparatus II with following conditions: 900 ml 0.1 M HCl, stirring rate 50 rpm, dissolution medium temperature 37 ± 0.5°C. To each flask, single tablet of each of the developed formulations was put. Samples were taken at predetermined time intervals and the absorbance was taken at 265 nm (Gulzeb *et al*., 2008) using UV/Vis spectrophotometer (1601, Shimadzu, Japan). For each formulation, in vitro dissolution studies were carried out in triplicate. The cumulative drug released (%) was calculated as a function of time.

STATISTICS ANALYSIS

Data were analyzed by applying one-way ANOVA using the software SPSS version 13.0. Differences between various data values were deemed to be significant at $p < 0.05$.

RESULTS

A sum of 3 tablet formulations from each process and/or excipient combination were developed and assessed. Formulation T1-T3 and T7-T9 were prepared using same ingredients but different tabletting technique, while only dry granulation technique was applied to formulation T4-T6 using different excipients, compared to that of T1-T3, to elaborate any interference of the nature of excipients with the formulation characteristics. Famotidine tablets were fabricated employing various tablet making techniques using same and different sets of excipients (table 1). Physical analysis of tablets (table 1) prepared with direct compression showed satisfactory results regarding the weight variation, hardness and friability, since their respective values were within the USP limits (USP, 1998).

Tablet sticking was observed in the tablet formulations T1-T6 with a compression force greater than 140 N. Drug contents for all tablet formulation ranged between 99.91%-102.01%. The variations in the results of arbitrarily sampled tablet weight, thickness and diameter for each batch of each formulation were below 1.5%. The average thickness (n=3) of tablets was approximately consistent in all the tablet formulations. As compared to that dry granulation, the hardness was consistent in all the formulations prepared by direct compression which obviously show that the mixing was uniform. Tablets T7-T9 showed excellent mechanical force with adequate solidity and low friability (<1%), while the values of tablets T1-T6 were >1.0.

All the tablet formulations had weight variation within the compendial limits of ±7.5% of the weight. In all fabricated tablets, weight variation was found to be in a range of 199.92±1.6 - 201.84±1.27 mg, which was in compendia limits. The drug contents (%) of all the tablet formulations were observed to be in a range of 99.91±0.73% - 102.01±0.32%, which was within the

Table 1: Formula of famotidine tablets prepared by various approaches

Technique	Dry granulation						Direct compression		
Formulations	T1	T2	T3	T4	T5	T6	T7	T8	T9
Famotidine (mg)	20	20	20	20	20	20	20	20	20
Avicel pH 102 (mg)	125	100	75	-	-	-	125	100	75
Lactose DC (mg)	50	75	100	-	-	-	50	75	100
Aerosil (mg)	5	5	5	-	-	-	5	5	5
Starch (mg)	-	-	-	10	15	20	-	-	-
Lactose (mg)	-	-	-	168.8	163.8	158.8	-	-	-
Talc (mg)	-	-	-	1	1	1	-	-	-
Stearic acid (mg)	-	-	-	0.2	0.2	0.2	-	-	-
Physical attributes of the prepared tablets									
Drug contents (mg)	100.35 ± 0.33	99.91 ± 0.73	101.23 ± 0.72	102.01 ± 0.32	100.38 ± 0.68	100.91 ± 0.53	101.74 ± 0.69	101.39 ± 0.32	99.93 ± 0.79
Hardness	6.58 ± 1.01	6.81 ± 0.84	6.52 ± 1.09	6.19 ± 1.24	6.92 ± 1.89	6.52 ± 1.64	8.39 ± 0.37	8.75 ± 1.15	8.62 ± 1.23
Friability (%)	1.71 ± 0.02	1.52 ± 0.08	1.95 ± 0.05	1.10 ± 0.28	1.18 ± 0.59	1.21 ± 0.35	0.87 ± 0.09	0.65 ± 0.03	0.79 ± 0.07
Weight (mg)	201.19 ± 2.73	199.92 ± 1.6	200.91 ± 2.03	200.26 ± 2.18	201.84 ± 1.27	200.93 ± 2.64	201.05 ± 2.45	200.37 ± 1.17	199.92 ± 2.05
Diameter (mm)	9.00 ± 0.73	9.00 ± 0.32	9.00 ± 0.91	9.00 ± 0.67	9.00 ± 0.69	9.00 ± 0.72	9.00 ± 0.68	9.00 ± 0.79	9.00 ± 0.33
Thickness (mm)	3.66 ± 0.03	3.66 ± 0.04	3.66 ± 0.04	3.66 ± 0.06	3.66 ± 0.05	3.66 ± 0.08	3.66 ± 0.06	3.66 ± 0.02	3.66 ± 0.09

compendial limits. All the tablets were evaluated for *in vitro* disintegration time which varied from 3.0±0.09 min to 4.62±0.23 min in case of direct compression technique and 2.11±0.07 and 3.3±0.09 in case of dry granulation approach which indicate rapid disintegration of tablets which could be attributed to the quick uptake of the water from the dissolution medium resulting in the burst effect. The dissolution behavior of all formulations is presented in fig. 1. The n-values, as determined by linear regression of natural log of M_t/M_α versus natural log of time of various formulations, ranged between 0.229 and 0.341 for famotidine release for all the developed tablets. It elaborates that the mode of drug release involved diffusion only.

DISCUSSION

Many data sources are deemed in the rest of this article for drawing the appropriate conclusions. Firstly, a hunt of a proprietary database for the development of tablet formulations was employed to supply comparative figures for different types of materials like drugs, ingredients, granulations, mixtures, slugs and tablets, followed by the selection of precise instances of each of these kinds of substances for additional and thorough contemplation.

As evident from fig. 1, the segment of first 10 min represents the linear portion for all the dissolution plots in the acid medium indicating very fast initial release of drug in this phase. This comparatively faster rate of dissolution may be due to the fast disintegration of tablets resulting in the enhanced penetration of acidic medium into the tablets, and thus, promoting the release of famotidine (Leela *et al*., 2011).

The influence of tablet preparation approach is exhibited by fig. 1 and table 1. Fig. 1 reveals that the release of famotidine was non-significantly ($p>0.05$) faster from T4-T6 compared to all other formulations, which could be due to the lower compressibility of the excipients used in T4-T6 resulting in their rapid dissolution. The slowest release of famotidine was from tablets T7-T9 which were prepared via direct compression: as fine powder particles of various excipients were used, which might be resulted in the improved compressibility (supported by the hardness data as shown in table 1) and very diminutive void gap for dissolution media to penetrate primarily (Nanjwade *et al*., 2011). While, the granule solidity would be lesser in case of dry granulation method therefore, the media might entered rapidly and thus drug release from such tablets (T1-T6) was non-significantly ($p>0.05$) faster compared to that of T7-T9.

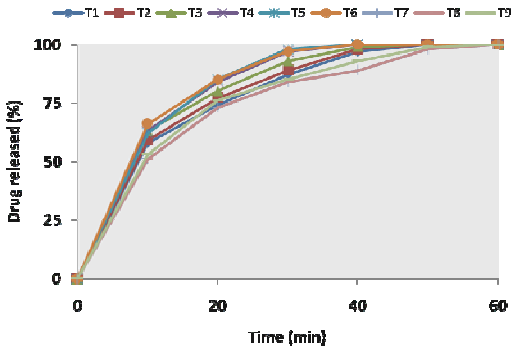

Fig. 1: Dissolution profiles of all nine formulations.

When the excipients were replaced with another set consisting of starch, lactose, talc and stearic acid (T4-T6) (table 1), it resulted in a non-significant ($p>0.05$) increase in famotidine release compared with that of T1-T3 prepared with the same method i.e. dry granulation. This non-significant ($p>0.05$) increase in famotidine release for tablets T4-T6 could be attributed to the difference the compressibility of the ingredients (Leela *et al*., 2011) as reflected by their lower hardness value (table 1). Tablet manufacturing method thus displayed considerable influence on the rate of drug release in an order as: dry granulation > direct compression. Complete release of drug from all the prepared tablets occurred in less than 60 min.

Zero order, first order, Higuchi's diffusion controlled release model and Korsmeyer-Peppas model were employed to elaborate the mode of release as well as to describe the best model fit drug release data on the basis of determination co-efficient, R^2 (Murtaza *et al*., 2010; Aamir *et al*., 2011). The equations of these models are as: Zero order kinetic model ($M_t=M_o+K_ot$), first order kinetic model ($\ln M_t = \ln M_o + K_1t$), Higuchi Kinetic Model ($M_t= M_o+K_Ht_{1/2}$) and Korsmeyer-Peppas Kinetic Model ($M_t/M_\alpha = K_kt^n$) (Khan *et al*., 2010; Higuchi, 1963; Rasool *et al*., 2010).

Where M_t represents the cumulative quantity of drug released at some particular time point and M_o is the early on quantity of drug in the formulation. K_o, K_1, K_H and K_k represent the rate constants for zero order, first order, Higuchi and Korsmeyer-Peppas models, correspondingly. M_t/M_α shows the portion of drug release at time t and n is the release exponent that describes different release modes. The n-value is determined from the slope of Korsmeyer-Peppas plot. If n= 0.5, dissolution data follows the Fickian diffusion where the rate of drug release depend on time, whilst $0.5< n <1.0$ designate anomalous (non-Fickian) release. The diffusion is Fickian when liquid diffusion occurs at slower rate than the rate of relaxation of polymeric chains, while the mode of drug release is called as case II transport when the relaxation process is very slow as compared to the rate of diffusion. The mode of release is anomalous (non-Fickian diffusion) when diffusion rate of liquid and relaxation rate of polymer chains are of the same order of magnitude (Murtaza *et al*., 2009; Korsmeyer and Peppas, 1983). When n = 1, the release follows the zero order.

The n-values ranged between 0.229 and 0.341 for famotidine release for all the developed tablets elaborating that the mechanism of drug release depended upon the diffusion process. The factor which affects the rate of drug release from non-swellable systems is the rate of diffusion of dissolution medium into the formulation (Korsmeyer and Peppas, 1983; Murtaza *et al*., 2009).

From pair wise procedures, difference factor (f_1) was opted for dissolution analysis. Based on FDA direction, value of f_1 in a range of 0-15 guarantees the similarity of the two compared dissolution data.

$$f_1 = \{[\sum_{i=1}^{P} |R_t-T_t|] / [\sum_{i=1}^{P} R_t]\}$$

Where, R_t and T_t symbolize the dissolution values at P time points of the reference and test formulations, respectively (Murtaza *et al*., 2009). The dissolution data has elaborated that the values of f_1 from all comparisons lie between 0-15 which means that there is no difference between the dissolution profiles of tablets. It ultimately argues that technique of manufacturing does not have significant influence on the dissolution behavior of the immediate release tablets.

CONCLUSIONS

These immediate release famotidine tablets were formulated using two different techniques for tablet making i.e. dry granulation and direct compression employing various ratios of excipients. This comparative study exhibited that physical parameters of tablets were affected by the technique of tabletting. However, the rate of drug release was unaffected by the method employed to fabricate the tablets. The tablets produced by direct compression were found to be according to the compendial prerequisites of hardness and friability. The drug release from all the formulated tablets has elaborated the involvement of diffusion.

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