Pakistan Journal of Pharmaceutical Sciences
Vol. 18, No.1, January 2005, pp.47-51

COMPARATIVE STUDY OF DIFFERENT FORMULATIONS OF ATENOLOL

RIFFAT YASMEEN, M. HARRIS SHOAIB AND HALIMA KHALID
Department of Pharmaceutics, Faculty of Pharmacy
University of Karachi, Karachi-75270, Pakistan

Tablets are the most common dosage form. Tablets can be prepared by dry method and wet methods, both methods have their own significance as well as disadvantages. Dry method and particularly *direct compression* is most simplest method of tablet manufacturing. On the other hand granulation is a multiple processing method which add complexity and make validation and control difficult.
For comparative study of atenolol tablets a new formulation was designed and compressed by *direct compression* method. Then it's physical parameters including hardness, friability, diameter, thickness, disintegration time, dissolution test were performed and finally assay carried out for evaluation and characterization of this new formulation against other formulation available in the market.

Keywords: Direct compression, wet granulation, atenolol, physical parameters.

INTRODUCTION

The oral route is the most frequently used route for drug administration. Oral dosage forms are intended for systemic effects resulting from drug absorption through gastro intestinal tract (Aulton, 1988).

The most common solid dosage forms in contemporary practice are tablets, which may be defined as "Unit forms of solid medicaments prepared by compaction". Most consists of a mixture of powders which has been compacted in a die to produce a single rigid body (Banker, 1990).

There are several reasons for the popularity of this group of dosage form

1. They employ the oral route of drug administration, which is generally the most acceptable route.
2. They permit a high degree of accuracy.
3. The dose of the active drug is contained in a relatively small volume. Thus a concentrated dosage form is produced, leading to the ease of packaging, transport, storage and administration (The Pharmaceutical Codex, 1994).

Tablets are divided into two general classes, whether they are made by compression or molding. Compressed tablets are usually prepared by large-scale production method, while molded tablets are generally involves small-scale production method (Remington, 1995).

The manufacturing of tablets can be divide to:

- Dry method
- Wet method

Dry method includes direct compression (d.c.), slugging and roller compaction, wet method includes wet granulation (Aulton, 1988).

Direct compression is a method of tablet making in which (1) crystalline drugs with intermediate to large doses are directly compressed without a prior granulation step, or (2) powdered drug is combined with a granulated or coarse particulate diluent and the mixture is directly compressed. The great advantages of direct compression are the simplicity of the process, avoidance of moisture and drying steps, minimal materials handling, rapidity of the total process, and optimum possible bioavailability of drug(s) from the resulting tablets. The process has no major disadvantages, but it has distinct limitations.

For drugs with potential in regard to bioavailability on oral administration, tablets may be more difficult to design and manufacture than capsules or a liquid oral form. It is often found that direct compression interferes less with drug availability than either wet granulation or slugging, because the latter methods require double compaction or the use of liquid adhesives which may (and frequently do) inhibit drug release (Sprowl's American Pharmacy, 1974).

Granulation

The purpose of the granulation stage is primarily to improve the flow properties of the mixture and also to improve its compression properties (Seager *et al*., 1979).

The wet granulation method of tablet production is a process of size enlargement, sticking particles of drug and excipient together by using an adhesive to produce a granular product with improved free-properties and an increased ability to cohere under pressure (The Pharmaceutical Codex, 1994).

Wet granulation or agglomeration of powders proceeds by agitation of a powder or powder mix in the presence of a liquid, usually an aqueous binder or solution or water if the binder has been premixed with the dry powder. Granule formation and growth proceed because of effects of mobile-liquid bondings formed between the primary particles (Encyclopedia of Pharmaceutical Technology, 1993).

Wet granulation has a number of advantages over the other granulation methods, but it is not suitable for hydrolysable and/or thermolabile drugs such as antibiotics (Aulton, 1988).

Direct compression

Direct compression is the process by which tablets are compressed directly from mixtures of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure, thus making pretreatment such as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality, but a number of materials are available which are directly compressible and which can serve as tablet diluents (Shangraw *et al*., 1981)

Most direct compression formulations consist of three basic types of ingredients

- An inert carrier (e.g., lactose) to provide volume for final dosage;
- A filler (e.g., microcrystalline cellulose) to form tablets; and
- The active ingredient(s).

These ingredients are mixed in a blender (Prescott and Hossfeld, 1994).

One of the most comprehensive study was that undertaken by Sangekar and his coworkers (Sangeker *et al*., 1972) who evaluated 24 d.c. formulations.

Another wide range study was that reported by Bolhuis and Lerk (1973) and by Lerk *et al.* (1974) who found that among the 11 excepients they used, Avicel, emcompress S and extrafine crystalline lactose had the best overall performance (Modern Pharmaceutics, 1990).

According to survey by Shangraw and Demarest (1993) direct compression is the preferred manufacturing process for pharmaceutical tablets (Shangraw and Demarest, 1993).

A wide range of literature is available regarding the comparative study of direct compression and wet granulation.

The results of the testing of calcium acetate tablets, produced by direct compression and by wet granulation are presented. Tablet hardness, friability and disintegration were determined. The best properties were observed in the tablets produced with maize starch. This procedure is fast and simple, and compound tablets of calcium acetate fulfill the current requirements for this type of preparation (Obrenovic *et al*., 2000).

The results of quality testing of lozenges made by direct compression and by wet granulation procedure are presented. The aim was to determine hardness, friability and disintegration of the lozenges. Considering the fact that the produced tetracaine hydrochloride lozenges were not transported, but were made according to the needs of the Clinic of Gastroenterology, Military Medical Academy, time of disintegration, not hardness and friability, was the priority in making a choice of formulation. That is why tetracaine hydrochloride lozenges made with 3.5% solution of carmellose sodium, which have the longest disintegration were chosen, which made possible the longest contact of the local anesthetic with mucous membrane of mouth and throat (Gazikalovic *et al*., 2002).

Advantages

The advantages of this process are obvious. Very few stages are involved, with a consequent reduction in appliance and handling costs. Furthermore is heat and water are not involved, stability is not affected. Also though additives such as lubricant and disintegrant are usually necessary, some direct compression diluents such as micro crystalline cellulose need neither, and hence costs are further reduced (Aulton, 1988).

Atenolol is β_1 – selective adrenergic receptor antagonist which was first synthesize in 1968 and is now widely used in the treatment of hypertension, angina pectoris, cardiac dysrhythmias and myocardial infarction (Dolley, 1991).

EXPERIMENTAL

In order to design a new formulation a thorough study is required to meet all specifications and ensure safety and efficacy of the newly formulated product. The specifications for pharmaceutical tablets usually include appearance, weight, thickness, hardness, friability, disintegration, dissolution, content uniformity, assay etc. These specifications are established to ensure that the tablet will have sufficient mechanical strength to withstand packaging, shipping, handling and are physically and chemically stable to deliver the accurate amount of drug at the desired dissolution rate when consumed by a patient. Any changes in these characteristics may significantly affect the safety and efficacy of the product. Therefore it is very important to keep a check on each and every step during the formulation and manufacturing of a drug product.

Reagents

Pure "atenolol" powder ($C_{14}H_{22}N_2O_3$) was donated by Zafa Laboratories (Pvt.) Ltd. Methanol (Merck Grade), sodium acetate (Merck), glacial acetic acid (Merck), Sodium hydroxide (Merck) were used during the course of work. Different brands of atenolol tablets were purchased from the market.

Formulation

A new formulation of atenolol was designed and tableting carriedout by *direct compression*. Table 1 lists the component of formulation and their percentages.

Table 1
Composition of formulations

S. No.	Ingredients	Qty/ Tab	% age
1	Atenolol	50mg	16.66
2	Avicel pH 101	100mg	33.33
3	Lactose D.C	100mg	33.33
4	Starch	20mg	6.66
5	Talc	20mg	6.66
6	Magnesium Stearate	10mg	3.33
	Total Qty	300mg	99.97

After compression of the physical parameters including hardness, friability, diameter, thickness, disintegration time, dissolution test were determine and finally its assay was performed for evaluation and characterization of newly formulated drug against standard and other formulations collected from the market.

Assay of atenolol by U.V. spectroscopy

Content of $C_{14}H_{22}N_2O_3$ was determined by using U.V. spectroscopy (Double-beam spectrophotometer, Model: 150 – 02). Method was taken from B.P. 2002; consisted of random sampling of 20 tablets, crushed and dissolved in 500ml methanol with the help of gentle heat and shaking for 15 min. after filtration the filtrate was diluted to 0.01% w/v of atenolol. The absorbance of the resulting solution was

determined, taking 53.7 as the value of A (1%cm) at the maximum at 275nm. Standard was also treated in the same manner and its absorbance was taken at 275nm (British Pharmacopoeia, 2002).

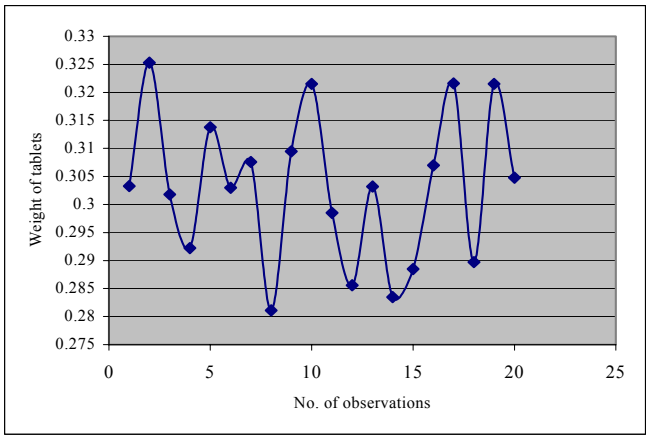

Fig. Uniformity of weight of 20 tablets compressed by direct compression.

Dissolution test

Dissolution test was adopted from USP27 (2004). Method consisted of buffer medium pH 4.6, prepared by mixing 44.9 parts (v/v) of 0.1 N sodium acetate with 55.1 parts (v/v) of 0.1N acetic acid solution. In 900ml buffer (pH 4.6) one tablet was operated at 50rpm. for 30minutes; using apparatus II. At the end of dissolution time the *test solution* (about 20ml) was filtrated and diluted to produce 0.01mg/ml of atenolol. For *standard preparation* an accurately weighed quantity of atenolol powder RS was dissolved in buffer medium to obtain a solution having a known concentration, about 0.01mg/ml of atenolol (United State Pharmacopoeia, 2004). Absorbance of test solution and standard preparation was taken at 275nm.

RESULTS AND DISCUSSION

On analysing the data of atenolol d.c. 50mg tablets it was found that 4 tablets crossing the 1st upper control limit and 4 tablets crossing the 1st lower control limit but no tablet is lying beyond the pharmacopoeial specified percentage weight limit, i.e. ± 7.5%.

As shown in the table 2 there is a significant decrease in the disintegration time of the newly formulated tablets of atenolol d.c. 50mg tablet with an increased in the percentage friability as compare to the other brands available in the market but the value of friability of tablets is 0.8-1.0% quoted as the upper level of acceptability for pharmaceutical products that's why the percentage friability of the newly formulated directly compressed tablets is satisfactory. It was also noticed that the diameter of the atenolol d.c. 50mg tablet is much greater and its thickness is much lesser than the other available brands, but according to pharmacopoeial specifications it lies within the acceptable limit.

The results indicate that atenolol d.c. 50mg tablet being as antihypertensive, antianginal and antiarrythmic should be formulated in such a way to produce its desired therapeutic

Table 2

The physical parameters of newly formulated atenolol d.c 50mg tab and other available brands were assessed. Data average and standard deviation were calculated

Brands Name	Wt. of 20 tabs(gm)	Friab. (%)	Dis. T (min)	Diam. (mm)	Thickness (mm)	Hardness (kg)	Diss. test (n.l.t 80%)	Assay 90-110%
*Atenolol d.c tab S.D	6.0581 ± 0.0134	0.490	15 Sec	12.35 ± 0.1369	2.06 ± 0.022	4.42 ± 0.284	95.95	94.84
Brand 1 S.D	4.0345 ± 0.0050	0.355	13 min	8.112 ± 0.033	3.74 ± 0.0601	3.50 ± 0.500	99.54	104.98
Brand 2 S.D	4.2630 ± 0.0038	0.161	5min	8.08 ± 0.0273	4.06 ± 0.0223	7.07 ± 0.3327	98.52	97.21
Brand 3 S.D	2.799 ± 0.0023	0.089	7min	8.12 ± 0.0273	3.95 ± 0.0707	3.31 ± 0.1550	94.92	98.44

* Directly compressed atenolol 50mg tablets.

Table 3

Weight of randomly selected 20 tablets, compressed by direct compression

No. of tab	1	2	3	4	5	6	7	8	9	10
Weight (gm)	0.3033	0.3253	0.3018	0.2922	0.3138	0.303	0.3076	0.2811	0.3095	0.032
No. of tab	11	12	13	14	15	16	17	18	19	20
Weight (gm)	0.2985	0.2856	0.3032	0.3048	0.2853	0.2885	0.307	0.3216	0.2897	0.3215

effects with minimum time period i.e. its onset of action must be very fast because in emergency conditions it is likely to administer such formulation which will effectively and quickly overcome the hazardous situations. Therefore in the light of observed data it is suggested that atenolol should be formulated by *Direct Compression* not only to produce quick action but also to remove processing complexities.

A number of research articles are available which are evident that direct compression is the preferred method of tableting than wet granulation method, some are given below.

In this research the influence of two lubricants-magnesium stearate and pruv--on the tablets elaboration of cimetidine, ranitidine, famotidine and pirenzepine by direct compression were studied. The presence of 0.5% of lubricants improved the flow of all the formulations, but especially the famotidine's formulation. The formulations with magnesium stearate had the worst results in tests of friability and tensile strength. All tablets with drugs and pruv had high data in indentation hardness. The tablets of cimetidine, famotidine and pirenzepine with magnesium stearate had less time of disintegration (Garcia-Marquez *et al*., 1992).

The paper studies the effect of the type of the disintegrating substance and the lubricant on the destruction heat of tablet materials and tablets. Destruction heat was determined by means of isoperibolic calorimetry. Tablet materials and tablets contained Avicel pH 101 as the dry binder, 10% of primojel, Ac-Di-Sol, or polyplasdone XL as disintegrating substances, and 5% of magnesium strearate or sodium laurylsulfate as the lubricants. The sum of destruction heats of the individual auxiliary substances equalled the found values in tablet materials and tablets. In tablets, in contrast to tablet materials, values of destruction heat higher by 57.9% were found. In the disintegrating substances and lubricants tested, the found values of destruction heats were dependent on the values of destruction heats of the individual auxiliary substances. In the disintegrating substances, a linear dependence of the total destruction heat (CDT) on the destruction heat of the disintegrating substances (DTR) was found, given by the relationship CDT = 0.797.DTR + 17.666 with the correlation coefficient r = 0.986 (Rehula *et al*., 2001).

REFERENCES

Aulton ME (1988). The Science of Dosage Form Design, 1st ed., pp: 4, 304, 309, 654.

Banker GS and Rhodes CT (1990). Modern Pharmaceutics, 2nd ed. Marcel Dekker Inc., pp.404-405.

British Pharmacopoeia (2002). Stationary Office London.

Dittert LW. Sprowl's American Pharmacy (1974). An Introduction to Pharmaceutical Techniques and Dosage Forms, 7th ed., JB Lippincott Company, pp.369-370.

Dolley SC (1991). "Atenolol", Therapeutic Drugs. 2nd ed. Vol 1. A-154.

Garcia-Marquez MA, Munoz A and Jimenez-Castellanos MR (1992). The effect of two lubricants (magnesium stearate and pruv) in the formation of tablets of four anti-ulcer agents by means of direct compression. *Pharm. Acta. Helv.,* **67**(2): 50-56.

Gazikalovic E, Obrenovic D, Nidzovic Z and Colic O (2002). Manufacture of tetracaine hydrochloride tablets using direct compression and moist granulation. *Vojnosanit Pregl*., **59**(6): 621-624.

Obrenovic D, Gazikalovic E, Ognjanovic J and Nidzovic ZZ (2000). Formulation of calcium acetate tablets *Vojnosanit. Pregl*., **57**(4): 427-430.

Omray A and Omray P (1986). Evaluation of Microcrystalline Cellulose as a glident. Indian *J. Pharm. Sci.,* **48**: 20-22.

Prescott JK and Hossfeld RJ (1994). Maintaining product uniformity and uninterrupted flow to Direct-Compression tableting process. *Pharm. Tech*., **18**(6): 99-114.

Rehula M, Lavicka J, Musilova M and Farm CS (2001). Calorimetric evaluation of directly compressed tablets. *Katedra farmaceuticke technologie Farmaceuticke fakulty Univerzity Karlovy*., **50**(1): 35-37.

Remington (1995).The Science and Practice of Pharmacy, 19th ed. Vol. II, p.1615.

Sangekar SJ, Sarli M and Sheth PR (1972). *In:* Banker GS and Rhodes CT (1990). Modern Pharmaceutics, 2nd ed. Marcel Dekker Inc., p.404.

Seager H, Burt I and Ryder J (1979). *In:* The Pharmaceutical Codex. (1994), 12th ed. London Pharmaceutical Press, p.6.

Shangraw RF, Wallace JW and Bowers FM (1981). *In:* The Pharmaceutical Codex. (1994), 12th ed. London Pharmaceutical Press, pp. 9-10.

Shangraw RF and Demarest Jr DA (1993). A survey of current industrial practices in the formulation and manufacture of Tablets and Capsules. *Pharm. Tech.,* **17**: 1, 32.

Swarbrick J and Boylan CJ (1993). Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc. Vol.7, p.126.

The Pharmaceutical Codex (1994). 12th ed. London Pharmaceutical Press, pp. 2, 5.

United State Pharmacopoeia 27 (2004). The United State Pharmacopoeia Convention, Inc.