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EFFECT OF GRANULATION METHODS ON CIPROFLOXACIN FILM COATED TABLETS

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Abstract:
Tablet dosage forms remain popular because of the advantages to the patient like accuracy of dosage, compactness, portability, blandness of taste, and ease of administration. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Ciprofloxacin, an antibacterial agent, a flouroquinolones derivative was used for this study. In this study, work was done to evaluate the ciprofloxacin film coated tablets prepared by different granulation techniques, wet granulation and dry granulation. Dry granulation was conducted on a press using a chilsonator, which offers a wide range of pressure and roll types to attain proper densification. In wet granulation method, solutions of the binding agent were added to the mixed powders before compression. Tablets prepared by both granulation methods were film coated and evaluated for tablet thickness, tablet weight, friability testing, hardness testing, disintegration and dissolution. Though both the formulations passed all tests for evaluation, tablets prepared by wet granulation method showed better results in hardness test, friability test, disintegration test and dissolution test than the tablets prepared by dry granulation method. Accelarated stability studies, conducted for a period of three months, proved that the tablets prepared by wet granulation method showed better stability than the tablets prepared by dry granulation method.
Keywords: *Tablet dosage form, film coated tablets, antibiotics, ciprofloxacin, granulation method.*

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INTRODUCTION:

Tablets are solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and have been traditionally prepared by either compression or molding methods [1]. They differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. Compressed tablets usually are prepared by large scale production methods while molded tablets are generally produced in small scale [2]. Tablets remain popular as a dosage form because of its advantages like simplicity and economy of preparation, stability, convenience in packaging, shipping, and dispensing, accuracy of dosage, compactness, portability, blandness of taste, ease of administration.

The various tablet types are compressed tablets, sugar coated tablets, film-coated tablets, enteric coated tablets, multiple compressed tablets, controlled release tablets, compressed tablets for solution, effervescent tablets and compressed tablets. Three general methods typically used for commercial tablet preparation are wet-granulation method, dry granulation method, and direct compression method. The method of preparation and the added ingredients give the tablet formulation, the desirable physical characteristics allowing the rapid compression of tablets [3]. After compression, the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics, and uniformity, which also are influenced both by the method of preparation and by the added materials present in the formulation. In addition to the active or therapeutic ingredient, tablets contain a number of inert materials called excipients. The ingredients diluents, binders, glidants, and lubricants help to impart satisfactory processing and compression characteristics to the formulation whereas disintegrants, surfactants, colors, flavours and sweetening agents help to give additional desirable physical characteristics to the finished tablets.

Antibiotics are drugs used to treat infections caused by bacteria and other microorganisms [4]. Originally, an antibiotic was a substance produced by one microorganism that selectively inhibits the growth of another. The quinolone antibacterial drugs, the flouroquinolones are strong inhibitors of DNA gyrase and topoisomerage. The flouroquinolones possess activity against gram positive, gram negative and the atypical organism. The older fluoroquinolones, namely, ciprofloxacin, norfloxacin and ofloxacin are highly active against gram negative pathogens.

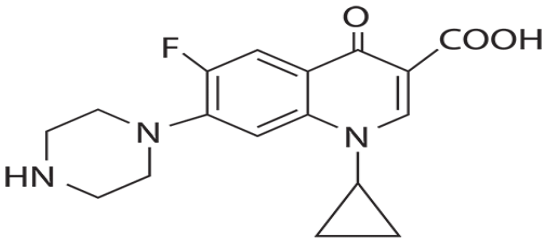

Fig 1: Structure of ciprofloxacin

Ciprofloxacin is an antibiotic used to treat a number of bacterial infections [5]. Ciprofloxacin remains the fluoroquinolone with the most potent in vitro activity against *P.aeruginosa*. Resistance to one fluoroquinolone usually confers resistance to all other quinolones, but not to other classes of antimicrobial drugs. Fluoroquinolones are all effective orally but also may be administered parenterally. They have large volumes of distribution and reach therapeutic concentrations in most tissues. They have long half lives and may be administered only once or twice a day. Ciprofloxacin tablets can be prepared by two methods, dry granulation and wet granulation. Wet granulation was done by using binding agents whereas dry granulation without binders.

MATERIALS AND METHODS:

Ciprofloxacin was obtained as gift sample from Dr.Miltons Laboratories, Puducherry. Sodium starch glycollate and povidone were purchased from HiMedia Laboratories Pvt Ltd. All the other ingredients used are of high standard analytical grade.

Pre-Formulation Studies

Drug-excipients compatibility studies:

Compatibility of the drug with other excipients was studied by using FT-IR technique in the wavelength of 4000-400cm^{-1}.

Method of preparation

In dry granulation method, formulation F_1 sufficient quantity of ciprofloxacin, colloidal silicon dioxide and micro crystalline cellulose powder were sifted through mesh [6]. The mixed granules were passed through sifter. Granules were prepared using purified tale, colloidal silicon dioxide, sodium starch glycollate and dried starch. The sifted ingredients were mixed with magnesium stearate in a mass mixer. The lubricated granules were transferred to the punching machine for compression. The compliance of the parameters like average weight, hardness, thickness, disintegration time and friability for the compressed tablets were ensured. The tablets were loaded and coated in a coating pan. The tablets were checked for uniformity of film formation edge coverage and color. Wet granulation method

formulation F_2 was performed by the same procedure with the addition of binding agent, starch paste.

Evaluation of coated ciprofloxacin tablets

Weight variation:

The weight of the tablets was evaluated with the help of electronic balance [7]. 50 tablets were taken randomly from both F_1 and F_2 Formulation during compression process and weighed individually. The average weight of the tablets and their standard deviation from the mean value were obtained.

Table 1: Weight variation of ciprofloxacin tablets

Formulation	F_1	F_2
Theoretical average weight (mg)	714.00	714.00
Average weight of tablets (mg)	714.46	714.82
S.D of weight of tablets (mg)	$\pm$ 1.7	$\pm$ 5.96

Tablet thickness:

The thicknesses of the tablets were evaluated with the help of the Vernier Caliper after calibrating to zero. and each individual tablets were checked for their thickness. 20 tablets from each of both F_1 Formulation and F_2 Formulation were taken for evaluation. The standard deviation from their average thickness was calculated [8].

Table 2: Thickness of ciprofloxacin tablets

Formulation	F_1	F_2
Theoretical thickness of tablet (mm)	5.700	5.700
Average thickness of tablets (mm)	5.672	5.784
S.D of thickness of tablets (mm)	$\pm$ 0.03	$\pm$ 0.038

Friability:

The friability of the ciprofloxacin tablets were evaluated by using a friabilator. 20 tablets were taken from both F_1 Formulation and F_2 Formulation and their total weight were noted. The tablets were placed in the rotating chamber of the friabilator and the friabilator was allowed to rotate for 100 times. The tablets remained after rotations were taken and weighed again. The difference between the weights before and after rotation was found out and the percentage of weight loss was calculated and tabulated.

Table 3: Friability Test of Ciprofloxacin Tablets

Formulation	B_1 (%)	B_2 (%)	Limits (%)
F_1	6.0	6.32	NMT 1.0
F_2	6.0	6.12	NMT 1.0

Hardness:

A hardness tester was used for testing the hardness of the tablet. 20 tablets were taken for testing and the hardness of each tablet was checked and their deviation from required hardness was calculated and tabulated [9].

Table 4: Hardness of Ciprofloxacin Tablets

Formulation	F_1	F_2
Theoretical hardness of tablet (kg/cm^2)	6.0	6.32
Average hardness of tablets (kg/cm^2)	6.0	6.12
S.D of hardness of tablets (kg/cm^2)	$\pm$ 0.29	$\pm$ 0.36

Disintegration:

Six ciprofloxacin tablets from each formulation were taken for testing the disintegration. DM water was taken as medium and maintained at a constant temperature of 37$\pm$0.5ºC. Six tablets were placed in the basket as one in each and the time taken for the tablets to disintegrate was noted and tabulated [10].

Table 5: Disintegration Test of Ciprofloxacin Tablets

Formulation	B_1 (sec)	B_2 (sec)
F_1	746	740
F_2	535	526

Dissolution of Ciprofloxacin tablets:

Dissolution of ciprofloxacin was studied by using USP II apparatus (paddle type) with 900ml DM water as dissolution medium. Paddle was rotated at 50rpm at 37$\pm$0.5ºC for 30 min. 5ml of aliquots was withdrawn at predetermined time interval and an equal amount of the medium was replaced to maintain sink conditions. Three samples (sample 1, sample 2 and sample 3) were taken in the initial middle and final stage respectively, for analysis. The amount of drug released was determined spectrophotometrically. The absorbance of standard and sample was measured at the wave length 276nm, by using dissolution medium as a blank on UV-spectrophotometer [11].

Table 6: Dissolution Profile of Ciprofloxacin Tablets

Test	F_1 (%)	F_2 (%)	Limits (%)
Sample 1	99.15	97.37	NLT 80
Sample 2	98.82	96.72	NLT 80
Sample 3	97.89	96.12	NLT 80

Stability studies:

Since the drug substances are naturally reactive, some additives may react with drug molecules on long storage. So accelerated stability studies are performed. Tablets are stored at a temperature of 37±2ºC at relative humidity 70±5ºC after blister packing for three months. They were periodically (1 month, 2 months and 3 months) evaluated by assay.

Table 7: Assay of Ciprofloxacin Tablets

Test	F_1 (%)	F_2 (%)	Limits (%)
Sample 1	99.19	99.89	95-105
Sample 2	99.52	100.01	95-105
Sample 3	99.09	99.79	95-105

Table 8: Accelerated Stability Data

B.No	Period	Description	Assay(in mg)	%
F_1	Initial	A pale yellow colored round shaped slightly biconvex film coated tablets, plain on both sides	499.52	99.90
	After 1 month		497.06	99.41
	After 2 months		496.52	99.30
	After 3 months		494.38	98.81
F_2	Initial	A pale yellow colored round shaped slightly biconvex film coated tablets, plain on both sides	498.26	99.65
	After 1 month		496.06	99.21
	After 2 months		495.86	99.17
	After 3 months		493.40	98.60

RESULTS AND DISCUSSION:

Preformulation studies results did not show any drug-excipients interaction. From the results of analysis, the physical stability studies showed the formulation of F_1 was better compared with F_2. Mostly all the physical parameters were good in F_1 formulation when compared with F_2.

The weight variation studies showed that there is less deviation in the weight of the tablets in formulation F_2 which was within the acceptable limit, which does not cause any problem during packing, whereas in formulation F_2, there was a great deviation in the weight of the tablets (Table 1). The reason is because, in formulation F_1 there is uniformity in the size of the granules, which helped in flow property of the granules during compression. But in formulation F_2, the size of the granules is not uniform which directly affected the flow property and indirectly caused weight variation of the tablets.

When performed the tablet thickness test the tablets in formulation F_1 was closer to the required thickness (Table 2). Due to the presence of uniform granules, the compression was perfect, so desired thickness is obtained. In formulation F_2 the ununiformity of the granules failed to flow uniformly and the compression was affected and the thickness was increased beyond the desired thickness.

In the hardness test the tablets of formulation F_1 were hard enough to withstand the effects caused during shipping (Table 3). Though formulation F_2 produced required hardness there was a greater variation in the hardness between the tablets. Due to the less hardness of formulation F_2, its friability loss was more than formulation F_1.

The tablet containing Ciprofloxacin was determined UV-Spectrophotometrically in stability studies. The Ciprofloxacin content showed slight difference between F_1 formulation and F_2 formulation which was within acceptable limit.

CONCLUSION:

Ciprofloxacin coated tablets were formulated in two different methods like wet granulation and dry granulation. These two formulations were named as F_1 and F_2 respectively. The evaluation and stability of the Ciprofloxacin coated tablets in the two formulations were determined analytically. From the results of this study it was conclude that the formulation F_1 prepared by wet granulation was found to be better than the formulation F_2 prepared by dry granulation method.

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