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EFFECTS OF PROCESS VARIABLES AND EXCIPIENTS ON TABLETTING PARAMETERS OF NORFLOXACIN TABLETS

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ABSTRACT

A study was conducted to evaluate the tabletting parameters of Norfloxacin (NFX) tablets. The effects of method of tabletting, e.g., direct compression, dry granulation and wet granulation, moisture content and water soluble/insoluble additives on final hardness, disintegration and dissolution of the tablets were investigated.

INTRODUCTION

Norfloxacin, a fluoroquinolone derivative, inhibitor of bacterial DNA synthesis, tends to form hemihydrate on exposure to moisture[1] and it is very difficult to achieve a desired moisture content for obtaining suitable tablet parameters. A number of articles have been published on the effect of moisture present during compaction of tablets[2-4]. Anomalous compression result, attributed to electrostatic effects, was eliminated by humidifying the material[5]. Wolff et al[6] observed that nonlubricated granules could not be compressed when the moisture content was more than 4%, although the results of Train[7] and the Shotton and Rees[8] showed that the die wall friction may be reduced in the presence of moisture. It has been reported that free moisture exists in solids state and the significant decrease in tablet strength could be due to the presence of capillary water thru which interparticular bonds are removed by dissolution[9].

The disintegrating agents exert forces by capillary action or by swelling in presence of water and rupture the tablet into smaller particles[10]. This eventually speeds up the dissolution of the drug. The disintegrating agent can be used as intragranular or intergranular form[10]. In tablets with water soluble diluent, the dissolution of diluent may enhance the effectiveness of disintegrating agent while in tablets with water insoluble diluent, action of the disintegrating agent is the primary mechanism of drug release. Disintegration can take place by rapid water uptake, swelling of disintegrating particles, mechanism of effervescence or enzymatic action[11].

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The efficient swelling promotes a rapid water uptake into the compacts[12-15]. A number of reports have discussed the effects of disintegrating agents, but insufficient information is available for characterization of different disintegrating agents based on:

- suitability of specific disintegrating agent for specific physicochemical properties of the drug,
- effect of disintegrating agents in combination with various polymeric excipients used in the tablet.

The present study was conducted to evaluate the effects of the method of granulation, moisture content, water soluble/insoluble excipients on the disintegration and dissolution of NFX tablets. NFX was selected as a model drug considering its direct compressibility, high disintegration rate at normal hardness, hardness dependent dissolution, low solubility and moisture content affecting disintegration and dissolution.

MATERIALS

Norfloxacin B.P., Starch, pregelatinized starch, Magnesium stearate, Talc, Lactose BP, Dicalcium phosphate BP, Indion® (ion exchange resin), AcDisol® (internally crosslinked Na-carboxymethyl cellulose), and Disigel®(sodium starch glycolate), Mannitol, Dextrose and Microcrystalline cellulose. All were procured commercially.

EQUIPMENTS

Comminuting fitz mill, Fluidized bed dryer, Cadmac® 35 stationary tabletting machine, Hardness tester, Tablet disintegration apparatus USP, Dissolution apparatus USP.

METHOD

Preparation of Tablet

Wet granulation of NFX was carried out using water as granulating liquid, starch and pregelatinized starch as the binders. The wet mass was passed thru comminuting fitz mill (front knife, sieve QS 1/2). The granules were dried on fluidized bed dryer at 65° C inlet and 45°C outlet temperature. The drying was carried out till the required moisture content (monitored by Karl Fisher apparatus) was attained. The dried granules were sifted thru sieve #20 and lubricated with 0.5 % magnesium stearate. During sifting and lubrication, the humidity of processing area was controlled to be 60 % RH.

Dry granulation and direct compression were carried out using one or more of the excipients Lactose, Mannitol, Dextrose, Microcrystalline cellulose and Dicalcium phosphate. Final compression of tablets was done using Cadmac® CMB35 stationary machine. The compression pressure (130MPounds) and speed of the machine were kept constant for all experimental batches.

Tensile Strength Measurement

Hardness of the tablet was measured using Erweka Hardness Tester. Average hardness of the five tablets was recorded.

Disintegration Test

Disintegration was carried out as per the USP XXI.

Dissolution Test

Dissolution test was carried out as per the USP XXI using 750 ml dissolution medium at pH 4, at 50 rpm.

RESULTS AND DISCUSSION

Tablets prepared by different method were evaluated for their tensile strength, disintegration and dissolution and the results are presented in table 1. Tablets prepared by wet granulation with water only showed better dissolution characteristics which is attributed to the absence of any binding agent, allowing maximum free surface area for smaller granular dissolution. However, no correlation between disintegration and dissolution was observed. In case of direct compression, tensile strength was higher which could be due to smaller particle size causing an increase of the cohesive and frictional forces, resulting in stronger tablets so that tablet strength is a function of the total binding area.

In the wet granulation process, the tablets having different moisture contents of granules ranging from 6% to 20% were prepared. Tensile strength, disintegration and dissolution of the tablets were evaluated. Specific tabletting problems like sticking or picking was not observed even with high moisture content of 20%. Fig 1 depicts a gradual decrease in tensile strength of the tablet as the moisture content increases. This may be attributed to decrease in binding strength between particles as the added water forms a film around the particles. It has been reported earlier that hardness of lactose tablets decreases as moisture content increases[10]. At high moisture content (more than 17%), the tensile strengths of tablets were minimum as shown in fig 1. This can be explained as the compression load increases, water is driven out of the void spaces forming a continuous film at the die wall. This film acts as a lubricant and results in reducing the contact between the tablet granules and the die wall. As shown in fig 2, at 6% moisture content the amount dissolved in 30 minutes is 55% and on increasing the moisture content to 18% and 20%, the percentage of drug dissolved increased to 100%. This improvement in dissolution would be due to increased number of porous channels in the granules at higher moisture content, which permits water to penetrate into the granules.

Effect of Tablet Manufacturing Process on Disintegration :

Effect of tablet manufacturing process on disintegration and dissolution was evaluated and presented in table 1. It was observed that the tablets prepared by wet granulation method (without the binder to omit the binder effect on disintegration and dissolution) showed instant disintegration in 30 seconds and 100% dissolution in 30 minutes. This phenomenon is attributed to,

- formation of microchannels in solid particles that permits the water to penetrate into the particles,
- water in wet granulation leaves hydrophilic moieties on solid particles on drying which shows affinity for water during disintegration and dissolution[1].

The disintegration time for directly compressed and slugged tablets were same as 3 mins but they differ in the percent drug dissolved as 90% and 84%, respectively. As the tablets prepared using slugging method disintegrates into bigger lumps (which pass thru disintegration sieve # 10) it takes longer time for dissolution.

TABLE 1 Effect of Method of Granulation on Tablet Properties

	Wet Granulation			Dry Granulation	Direct Compression
	Water	Pregel-Starch	Starch		
Hardness, kg/sq.cm	6.0	8.0	8.0	8.0	10.0
Disintegration, min	0.6	5.0	5.0	3.0	3.0
Dissolution, %	100	65	75	78	90

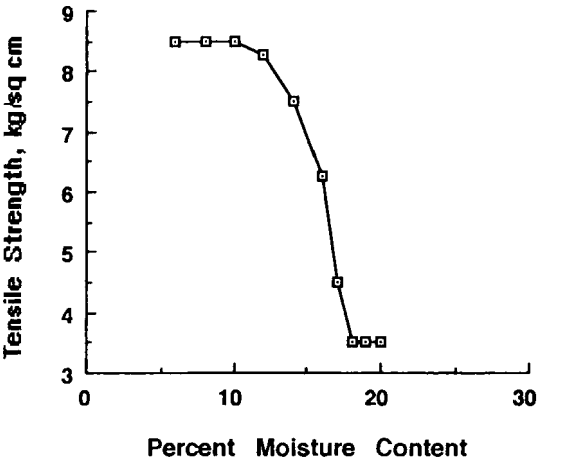

FIGURE 1

Effect of moisture content on tensile strength of tablets

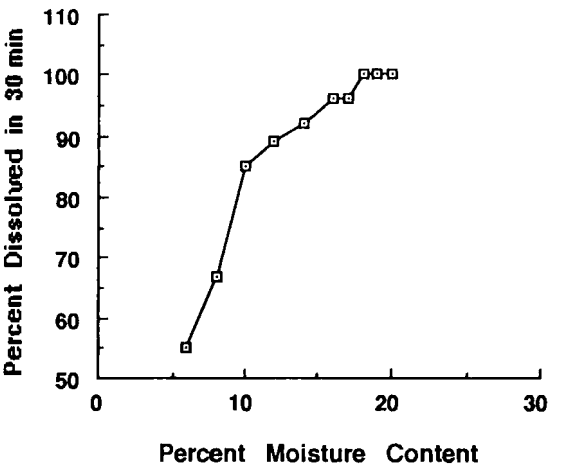

FIGURE 2

Effect of moisture content on percent dissolved

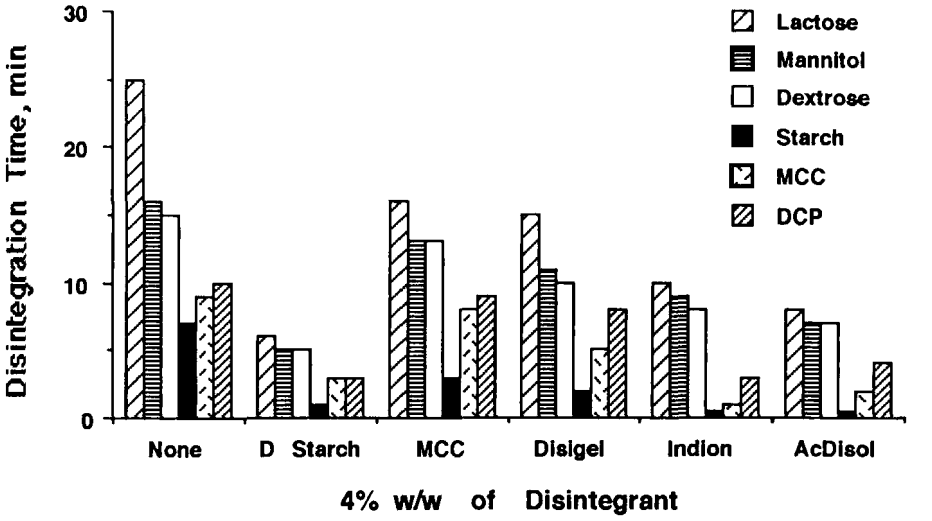

FIGURE 3

Effect of different disintegrating agents on disintegration of tablets

Effect of the Excipients on Disintegration:

In comparing the disintegration of tablets prepared by direct compression or dry granulation with water soluble/insoluble additives, it was observed that disintegration with water soluble additives took place by surface erosion, while disintegration and dissolution taking place simultaneously. Disintegration with water soluble Lactose, Mannitol and Dextrose took place by surface erosion of the tablet[9]. This may be due to that fact that dissolution of excipients was faster than the swelling or wicking process of disintegration and consequently, the disintegrant did not remain in contact with the tablet matrix and did not exert force thru the tablet matrix. This resulted in longer disintegration time. A preferable disintegrant acts by bursting mechanism (capillary mechanism with Starch or Sodium starch glycolate) with water soluble additives. In case of insoluble diluents, dissolution did not occur simultaneously with disintegration. As the disintegrating agent was always in contact with the tablet matrix, continuously exerting forces to rupture the tablet, disintegration action was more rapid with an insoluble additives than with a soluble excipient as depicted in fig 3.

Effect of Disintegrating Agents

The combined measurement of force developed and water uptake simultaneously affected the same compact and provided a novel parameter to quantify the efficacy of disintegrating agents. In this study different disintegrating agents; dried starch, Microcrystalline cellulose, Disigel, Indion, and AcDisol were evaluated as shown in table 2. The disintegration efficacy of different disintegrating agents with water soluble or insoluble excipients is shown in fig 4. All disintegrating agents showed lower

TABLE 2 Effect of Different Disintegrants on Tablet Disintegration and Dissolution

Disintegrating agents	Percentage w/w	Lactose*		Mannitol*		Dextrose*		Starch*		MCC*		DCP*	
		DT	DIS	DT	DIS	DT	DIS	DT	DIS	DT	DIS	DT	DIS
None	0	25	60	16	70	15	75	7	94	9	90	10	90
Dry Starch	4	6	87	5	90	5	92	1	100	3	100	3	100
MCC	4	16	56	13	72	13	70	3	100	8	77	9	72
Disigel	1	20	60	15	70	13	76	7	94	9	90	9	90
	2	17	60	15	70	13	76	6	94	9	90	9	90
	3	15	70	13	70	13	80	4	96	7	93	8	90
	4	15	70	11	66	10	82	2	96	5	95	8	93
Indion	1	13	72	11	75	11	77	3	100	5	95	8	93
	2	12	74	10	77	11	80	2	100	4	100	4	100
	3	10	80	9	82	8	62	0.5	100	2	100	3	100
	4	10	80	9	82	8	85	0.5	100	1	100	3	100
AcDisol	1	14	85	13	69	13	70	3	100	3	100	5	95
	2	10	72	11	72	10	72	3	100	3	100	5	95
	3	8	78	7	75	7	75	0.5	100	2	100	4	98
	4	8	78	7	75	7	75	0.5	100	2	100	4	98

* Diluent; DT : Disintegration time, min; DIS : Percent dissolved in 30 min

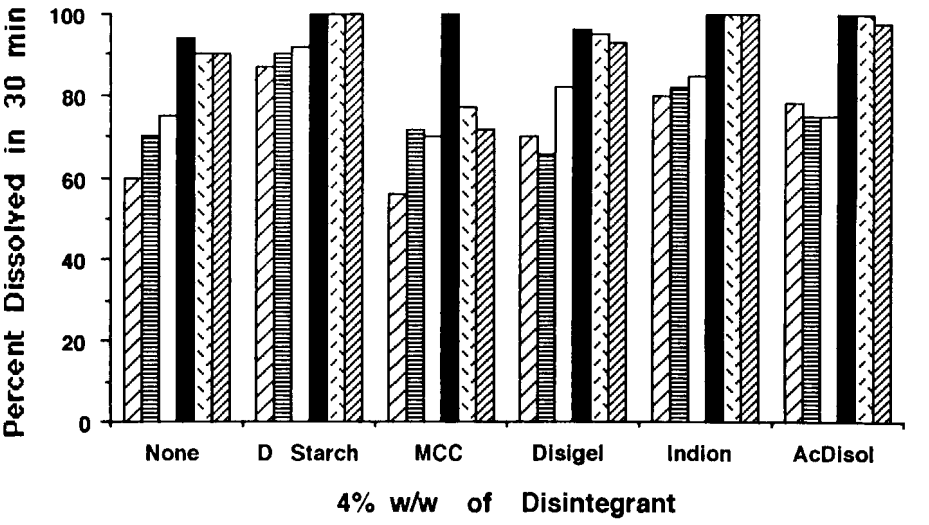

Figure 4

Effect of different disintegrating agent on dissolution of tablets

disintegration time and higher percentage of dissolution in combination with water insoluble excipient rather than with water soluble excipients.

REFERENCES

1. Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Company, pp 1221
2. Z. T. Chowhan and L. Palagyi, J. Pharm. Sci., 67, 1385 (1978)
3. T. Eaves and T. M. Jones, J. Pharm. Pharmacol., 25, 729 (1968)
4. P. L Sheth and K. Muenzel, Pharm. Ind., 21, 9 (1959)
5. J. Jaffe and N. E. Foss, J. Amer. Pharm. Assoc. Sci. Ed., 48, 26 (1959)
6. J. E. Wolff and H. G. Dekay, J. Amer. Pharm. Assoc. Sci. Ed, 36, 407 (1947)
7. D. Train., Ph.D. Thesis, University of London (1956)
8. E. Shotton and J. E. Rees, J. Pharm. Pharmacol. Suppl, 18, 1960 (1966)
9. L. Lachman, H. A. Lieberman and J. L. Kanig, The Theory and Practice of Industrial Pharmacy, 3rd Edition, Lea & Febiger
10. Mufrod and E. L. Parrot, Drug Dev. Ind. Pharm., 16, 1081 (1990)
11. C. Caramella, F. Ferrari, M. C. Bonferoni and M. Ronchi, Drug Dev and Ind. Pharm, 16, 2561 (1990)
12. G. K. Bohluis, H. V. vanKamp, C. F. Lerk and F. G. M. Sessink, Acta Pharm. Technol, 28, 111 (1982)
13. A. M. Guyot-Hermann and J. Ringard, Drug Dev. Ind. Pharm, 7, 155 (1981)
14. D. Gissinger and A. Stamm, Drug Dev. Ind. Pharm., 6, 511 (1980)
15. E. M. Rudnic, C.T. Rhodes, S. Welch and P. Bernardo, Drug Dev. Ind. Pharm, 8, 87 (1982)