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Design and Evaluation of Naproxen Tablet Formulations Prepared By Wet Granulation and Direct Compression Methods

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Summary: *The tablet formulation of naproxen, which is a nonsteroidal antiinflammatory agent, was studied. Twelve different formulations were prepared by wet granulation and direct compression technique. The effect of various adjuvants on the physico-pharmaceutical properties and release profiles of the substance were investigated. The dissolution data were fitted to several kinetic equations by employing a program (DISSOL) written for this purpose. It was seen that the wet granulation method was better than direct compression for poorly soluble naproxen. Primogel and CLD-2 were also found to be the best disintegrants.*

Keywords : *Naproxen, tablet formulation, kinetic assessment*

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Yaş Granülasyon ve Direkt Basım Yöntemleri ile Hazırlanan Naproksen Tablet Formülasyonlarının Tasarım ve Değerlendirilmesi

Özet: *Bir nonsteroidal antienflamatuar madde olan naproksenin tablet formülasyonu üzerinde çalışıldı. Yaş granülasyon ve direk basım yöntemi kullanılarak on iki farklı formülasyon hazırlandı. Tabletlerin fiziko-farmasötik özellikleri ve salım profilleri üzerine değişik yardımcı maddelerin etkileri incelendi. Çözünme verileri bu amaçla yazılmış bir program kullanılarak (DISSOL) değişik kinetik denklemlere uygulandı. Sonuçta, zor çözünen naproksen için yaş granülasyon yönteminin doğrudan basım yönteminden daha uygun olduğu görüldü. Pirimojel ve CLD-2 en iyi dağıtıcılar olarak bulundu.*

Anahtar sözcükler : *Naproksen, tablet formülasyonu, kinetik değerlendirme*

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Introduction

Naproxen USP XXI is a nonsteroidal-antiinflammatory agent. It is particularly used in the treatment of rheumatic diseases, as it has a powerful anti-inflammatory and analgesic action, associated with low local and general toxicity[1,2]. It is generally administrated as tablet, suppository and gel forms. In tablet formulations, the addition of excipients and the method of incorporation have often been shown to influence such tablet properties as their hardness, friability, disintegration and dissolution times[3,4]. The effect of formulations and processing factors on the dissolution rate of active ingredients from compressed tablets have been the subject of a number of reports[5-7].

The aim of the present study was to investigate the effect of some disintegrants and preparation techniques on the physical properties of naproxen tablet formulation. For this purpose, five different disintegrating substances were used: Maize starch, Esma-Spreng, Primogel, CLD-2 and STA-Rx 1500. Wet granulation and direct compression techniques were employed to prepare the tablets. In addition to the disintegrating agents, the methods were also compared.

Material and Methods

Chemicals: Naproxen(Syntex), polyvinlypyrrolidone(PVP, Kollidon 25, BASF AG), microcrystalline cellulose(Avicel^{R} PH 101, FMC Corp.), soluble starch(STA-Rx 1500, Staley Mfg. Co.), sodium starch glycolate(Primogel, Avebe), cross linked sodium carboxymethyl cellulose(CLD-2, Buckeye), casein

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formaldehyde(Esma-^{S}preng^{R}, Edelfettwerke), talc (BDH), colloidal silicium dioxide(Aerosil R200, Degussa) lactose, corn starch and other chemicals were of pharmaceutical grade.

Wet Granulation Method:
The naproxen granules were prepared using the 5 % w/w PVP solution as binder. The doughty mass produced was granulated through a 2 mm. sieve and dried at 50°C and then passed through a 0.8 mm. sieve.

Direct Compression Method:
The powders were mixed by geometric dilution in a jar for one hour. Then the mixture of talc-Aerosil 200 was added and mixed for ten minutes.

The tablets were compressed using flat face punches, whose diameter was 10 mm (Korsch EK-O). Their compositions are seen in Table 1.

Physical Properties of the Tablets:
The prepared tablets were evaluated for uniformity of weight(USP), and thickness (micrometer, NSK-Nippon), hardness(Strong-Cobb Hardness Tester), friability(Roche Friabilator), and disintegration time (USP).

Dissolution Rate Determination:
The USP XXI paddle method was used with 900 mL pH 7.4 Sorensen buffer solution as dissolution medium and stirring rate was 50 rpm. The temperature of 37°C was followed. The absorbance of the samples were determined spectrophotometricaly(Pye Unicam SP 200) at 239 nm. The results were the mean of three determinations. The data were evaluated kinetically using a computer program written for this purpose[8].

Results and Discussion

Physical Characteristics of the Tablets:
All tablets were found to satisfy the USP XXI requirements for weight uniformity and thickness. They also show good mechanical properties as regards both hardness and friability. The results are given in Table 2. While the hardnessess of the tablets prepared by wet granulation were between 11.4-12.1 s.c.u.(6.8-7.3 kg), it was found to be between 14.4-18.1 s.c.u.(8.6-10.9 kg) in directly com-

Table 1. Tablet Formulations[a]

Ingradients	Wet Granulation						Direct Compression					
Codes	NY1	NY2	NY3	NY4	NY5	NY6	ND 1	ND2	ND3	ND4	ND5	ND6
Naproxen	250	250	250	250	250	250	250	250	250	250	250	250
Corn strach	30.4	30.4	30.4	30.4	30.4	30.4						
Lactose	78.7	78.7	78.7	78.7	78.7	88.2						
Avicel PH 101							109.1	109.1	109.1	109.1	109.1	118.6
Corn starch	9.5						9.5					
Primogel		9.5						9.5				
Sta-Rx 1500				9.5						9.5		
Esma Spreng			9.5						9.5			
CLD-2					9.5						9.5	
PVP	47	4.9	5.1	4.8	5.1	4.7	4.7					
Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.6	7.6	7.6	7.6	7.6	7.6
Aerosil-200	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.8	3.8	3.8	3.8	3.8
Total weight	384.5	385.7	384.9	384.6	384.9	384.5	380.	380.	380.	380.	380.	380.

Table 2. Physical Properties of Naproxen Tablets

Codes	Weight (mg)* Mean	C.V.***	Thickness (mm)	Hardness (s.c.u.)** Mean	C.V.***	Friability %	Disintegration time (min.) Mean	C.V.***
NY1	383	0.767	4.30	11.8	8.33	0.99	61.3	3.04
NY2	384	0.264	4.27	11.5	7.67	1.06	43.8	4.19
NY3	383	0.483	4.26	11.4	10.29	0.78	38.8	6.10
NY4	383	0.368	4.26	11.7	9.06	0.82	45.8	10.7
NY5	384	0.574	4.35	12.1	6.1	0.61	38.7	2.11
NY6	385	0.685	4.38	11.1	6.20	1.04	52.0	4.03
ND1	384	1.75	4.25	17.9	8.25	0.56	9.41	27.9
ND2	378	0.51	4.25	14.4	6.11	1.07	0.54	8.6
ND3	381	2.19	4.19	15.1	8.52	0.71	1.45	3.47
ND4	381	1.69	4.22	17.5	11.9	0.56	2.10	35.2
ND5	380	1.10	4.34	18.1	8.01	0.17	0.41	6.16
ND6	380	0.87	4.25	16.4	11.9	0.30	21.8	7.78

* : Avarage of 20 determination
** : Avarage of 10 determination
*** : Coefficient of variation

pressible tablets. In the literature, a friability of less than 1 % is considered good. Therefore, the friabilities were found to be under the literature limit[9].

According to TF 1974[10], the tablets must disintegrate within 15 minutes. However, this interval is given as 30 minutes in the naproxen monograph of the USP XXI[11]. When we evaluated the results, all the tablets prepared by wet granulation method disintegrated within one minute. On the other hand, in the direct compression samples, the effect of the disintegrating agents have been seen easily . The ND 6 coded tablet, which does not contain any disintegrant, disintegrated in 21 minutes. Therefore, it was outside the range defined by TF 1974 requirements. Besides this, the disintegration time was found to be 9.41 min. in the ND 1 coded tablet, which contains corn starch as disintegrant. Other direct compression formulations disintegrated in 2 minutes. So, we have observed significant differences in disintegration times between the two methods. We can explain this situation as the dissolution of poorly soluble naproxen, which has a small particle size, was improved by using PVP solution as binder in the wet granulation method. Generally, the disintegration times are related to hardness. In the literature it was cited that, when the hardness increases, the disintegration time increases and the dissolution rate also delays[12]. However, contrary results were observed with ND5 coded tablets. Although the tablets have the highest hardness value among others, they gave the shortest disintegration time as 24. sec. The ND5 coded tablet followed the ND 2 tablet in disintegration time. So, these results indicate that, Primogel, which shows the disintegrating action by way of swelling and CLD-2, which has both swelling and capillary action, aren't influenced by the tablet hardness. Avicel also improves the disintegrating action through the capillarity action of water penetration[13,14].

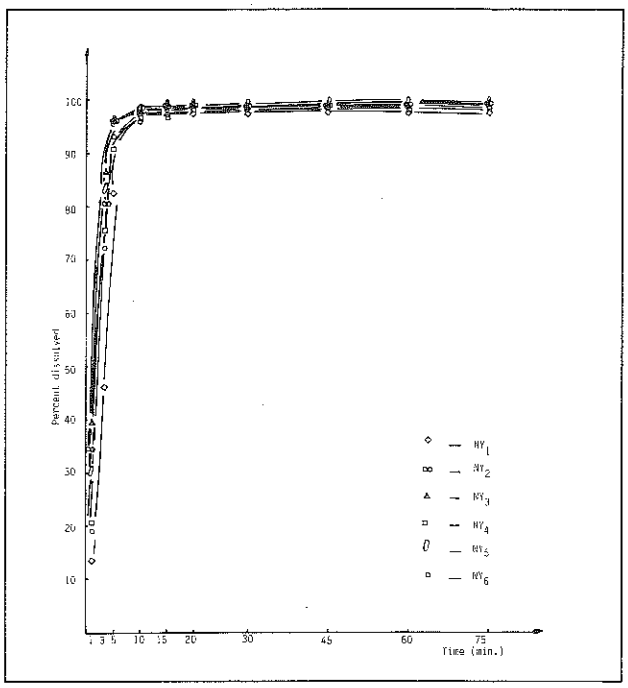

Figure 1. The release dissolution profiles of the tablets prepared by wet granulation

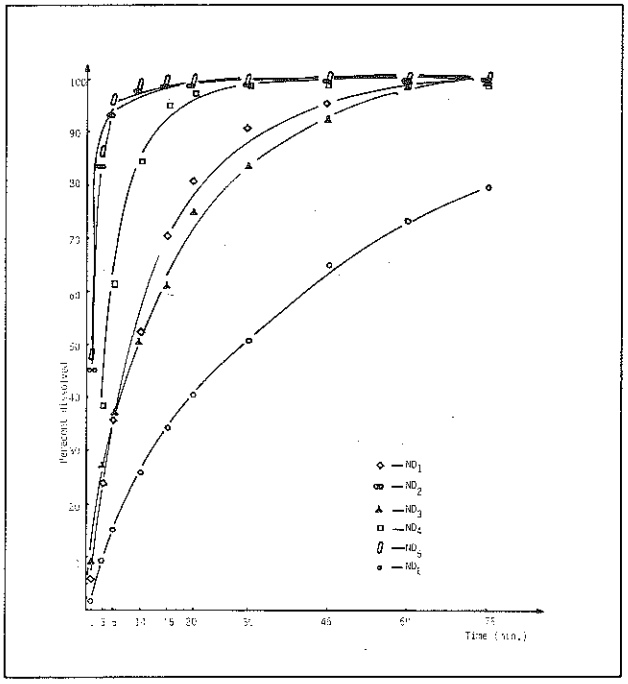

Figure 2. The release dissolution profiles of the tablets prepared by direct compression

The dissolution profiles of the tablets are seen in Fig 1 and Fig 2. Upon checking the release profiles, it is immediately seen that there is no difference among the wet granulated tablets. All of them released 90 % of the active substance in the first five minutes. On the other hand, significant differences were observed among the directly compressed ones. In the latter, the best results were obtained with ND2 and ND5 formulations. The ND4 coded tablets prepared with STA-Rx 1500 followed them. As indicated in the literature, using STA-Rx 1500 gave better results than the corn starch[15]. The dissolution rate of the tablets without disintegrant (ND6) were slower than the others. In these tablets, after 45 minutes 60 % of the active substance was released. Our experiments showed that, it is necessary to add a proper disintegrant into the formulations, because naproxen is a very hydrophobic substance, and Avicel PH 101 is not sufficient as a disintegrating agent. The $t_{90\%}$ and $t_{50\%}$ values obtained from the dissolution curves to characterise the dissolution rates were also found to be the best with Primogel and CLD-2.

The results of the kinetic assessment of the release data appear in Table 3. The best fits were obtained with RRSBW distribution in all the samples prepared with wet granulation processes[17,18]. Actually, we have expected these results. It is known that, this kinetic model fits the data of the tablets better, which quickly disintegrate. Modified Hixson-Crowell equation[16] and first-order reaction kinetics model follow.

Conclusion

The wet granulation technique as a method of manufacturing the tablets is suitable for production. Tablets prepared by the wet method exhibit good mechanical properties in hardness and disintegration time since naproxen takes in approximately 66 % of the tablet weight. Also the best results were obtained by Primogel and CLD-2 as disintegrating agent in both methods.

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Table 3. The Kinetic Assessment of Release Data[a]

KINETICS		FORMULATIONS					
		NY1	NY2	NY3	NY4	NY5	NY6
Zero[b]	$k_r o$	571	523	314	427	369	444
Order	r^2	0.649	0.519	0.425	0.485	0.432	0.489
First[c]	kr	12.8	17.7	13.5	11.4	21.8	12.5
Order	r^2	0.889	0.854	0.859	0.858	0.969	0.830
Modified[d]	a	0.933	9.673	0.532	0.722	0.667	0.773
Hixson-	b	$5.19x10^{-2}$	$6.82x10^{2}$	$5.19x10^{-2}$	0.051	$6.34x10^{-2}$	$5.53x10^{-2}$
Crowell	r^2	0.922	0.890	0.849	0.841	0.866	0.845
	T	4.39	2.04	1.00	3.03	2.13	3.08
RRSBW[e]	ß	1.15	0.914	0.593	0.919	0.981	0.990
	r^2	0.952	0.933	0.913	0.893	0.949	0.896
Hixson[f]-	K	10.7	15.7	12.5	11.2	13.5	11.6
Crowell	r^2	0.814	0.732	0.686	0.724	0.768	0.707
		ND1	ND2	ND3	ND4	ND5	ND6
Zero[b]	$k_r o$	164	300	161	246	280	149
Order	r^2	0.702	0.493	0.822	0.557	0.462	0.928
First[c]	k_r	3.84	17.2	4.12	8.38	21.4	1.27
Order	r^2	0.986	0.907	0.959	0.931	0.973	0.995
Modified[d]	a	0.812	0.512	0.705	0.834	0.501	0.873
Hixson-	b	$1.40x10^{-2}$	$5.38x10^{-2}$	$1.03x10^{-2}$	$3.04x10^{-2}$	$5.77x10^{-2}$	$5.78x10^{-2}$
Crowell	r^2	0.968	0.923	0.981	0.930	0.922	0.984
	T	13.1	1.55	14.0	6.15	1.44	40.9
RRSBW[e]	ß	0.971	0.780	0.858	1.06	0.806	0.930
	r^2	0.991	0.973	0.972	0.976	0.985	0.990
Hixson [f]-	K	2.99	13.1	2.84	5.94	13.6	1.41
Crowell	r^2	0.914	0.744	0.979	0.808	0.794	0.982

[a]Summary of output obtained from the program DISSOL(8); [b]kro: Zero order release rate constant, [c]kr: First order release rate constant; [d]a: Parameter is associated with the shape of the dissolution curve, b: Parameter is the apparent dissolution rate constant[16]; [e]T: The value stands for the time 63.2 % release of the drug, ß: The shape factor[17,18]; [f]K: The dissolution rate constant calculated from the Hixson-Crowell plot for sink conditions[19,20].

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