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CONTENTS

EFFECT OF SELECTED BINDERS AND DISINTEGRANTS ON THE DISSOLUTION RATE OF TERBINAFINE HYDROCHLORIDE FROM TABLETS

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Abstract: Terbinafine hydrochloride is slightly soluble in water, therefore its oral absorption is limited by the dissolution rate. Poor aqueous solubility of the drug gives rise to difficulties in the formulation of dosage forms and may lead to variable dissolution rate and bioavailability. All samples of tablets containing 250 mg terbinafine were prepared by conventional wet granulation method. Varius type of disintegrants and binders as sodium starch glycolate (Primojel, Avebe Veendan); croscarmellose sodium (Vivasol, JRS); pregelatinized starch (Starch 1500, Colorcon); polyvinylpyrolidone (PVP, K-25); hydroxypropylmethylcellulose; hydroxypropylcellulose; microcrystalline cellulose (Vivapur 200, JRS) were used to prepared some series of tablets. HPMC as binder and croscarmellose sodium and pregelatinized starch as disintegrants showed higher dissolution rate.

Key words: Terbinafine hydrochloride, superdisintegrants, binders, improve drug dissolution

Introduction

Terbinafine hydrochloride (TH) is a potent antifungal agent of abbylamine which selectively inhibits fungal squalene oxidase (7). TH (pKa of 7.1),is slightly soluble in water, therefore its oral absorption is limited by the dissolution rate. Poor aqueous solubility of the drug gives rise to difficulties in the formulation of dosage forms and may lead to variable dissolution rate and bioavailabilities.

Binders are added to tablet formulations to add cohesiveness to powders, of widely varying particle sizes to granules, which may more uniformly flow the hopper to the feed system, to allow for normal processing (sizing, lubrication, compression and packing), yet allow the tablet to disintegrate and the drug to dissolve upon ingestion, releasing the active ingredients for absorption (4, 7).

Superdisintegrants have been proposed as insoluble and hydrophilic but strongly swelling carriers for solid deposition of hydrophobic drugs (6).

In the tablet formulation the inclusion of right disintegrant at the critical concentration is necessary for optimal bioavailability (2).

The increasing drug dissolution and thus improved bioavailability has resulted in the replacement of native starches by more active disintegrants such as the modified starches like sodium starch glycolate and pregelatinized starch and modified celluloses like croscarmellose sodium. Sometimes placed in water, they swell considerably. For that reason, at low concentration they contribute to the high and fast penetration of water into the whole tablet structure.

The choice of a superdisintegrant for a tablet formulation depends largely on the nature of the drug being used. For example, the solubility of the drug component could affect the rate and mechanism of tablet disintegration. Water-soluble materials tend to dissolve rather than disintegrate, while insoluble materials generally tend to disintegrate if an appropriate amount of disintegrant is included in the formulation (10).

Many new or recently discovered cationic drugs are poorly water soluble as TH.

The purpose of this work was to evaluate and compare the effect of some commonly used binders and superdisintegrants on the dissolution rate of TH from formulated tablets.

Materials and Methods

Materials

Terbinafine hydrochloride (Galena san Paulo); sodium starch glycolate (Primojel, Avebe Veendan); croscarmellose sodium (Vivasol, JRS); pregelati-

nized starch (Starch 1500, Colorcon); polyvinylpyrolidone (PVP, K-25); hydroxypropylmethylcellulose; hydroxypropylcellulose; microcrystalline cellulose (Vivapur 200, JRS); magnesium stearate; all excipients meet the requirements of Ph. Eur. 5.

Methods

Preparation of tablets

All samples of tablets containing 250 mg terbinafine were prepared by conventional wet granulation method according to the formulae in Table 2. One series of tablets (S1 – S5) were formulated with different binders and sodium starch glycolate and pregelatinized starch as disintegrants in concentration of 5 and 10 %, respectively. All the binders were used in the form of aqueous solution or mucilage of suitable strength. Another series of tablets (S6 – S8) were formulated with the same binders, but the pregelatinized starch as a disintegrant was in a concentration from 5 to 18%. The last series of tablets (S9 – S12) were formulated with the same binders, but the pregelatinized starch and croscarmellose sodium as disintegrants were in concentration 5 and 10 % respectively.

Rotary tabletting machine (Fette 1, Germany) with 11 mm normal faces punches was used to compress the tablets at a fixed compression load.

Hardness measurements

Ten tablets randomly selected from each batch were assessed for hardness using an Erweka electronic hardness tester.

Disintegration time studies

Disintegration time in distilled water was determined by using Erweka Tablet Disintegaration Test Machine, Eur. Ph.

Analysis of TH

The amount of drug in the investigated samples was determined by HPLC (1). The method was validated by determination of the following operational characteristics: linearity, range, precision, accuracy, limit of detection and limit of quantitation.

Dissolution testing

The dissolution rate of TH from tablets was studied in 900 ml of acid medium (pH 1,2) using Eur. Ph. Dissolution Rate Test Apparatus (Model Erweka 6DT) with paddle stirrers. One tablet containing 250 mg of TH (as base), a velocity 100 rpm and a temperature of 37 ±0,50 C were used in each test. Samples of dissolution medium were withdrawn through a filter at different time intervals, suitable diluted and assed for TH by measuring the amplitudes in mm between the maximum at 295 ± 1 nm and the minimum at 280 ± 1 nm of sample solution and of reference solution.

From the dissolution data dissolution efficiency (DE) was calculated as suggested by Khan (5). DE30 values, calculated on the basis of dissolution data, were statistically analyzed by Analysis of Variance (ANOVA). Test to test the significance of the observed difference due to various binders and disintegrants.

Results and Discussions

All the tablets prepared were found to contain TH (as base) whithin 250mg ±5% of the label claim. All batches prepared fulfilled the official (EP) test for uniformity of weight. Hardness of the tablets in all the batches was found to be in the range of 6 to 8 kP being satisfactory. The tablets formulated with all other binders fulfilled the official (EP) specification for disintegration time, variation were observed in their disintegration times in the range (to 6,0 min) (Tabl.1).

Dissolution profiles of all samples are shown in Table 3. Dissolution of TH from the tablets followed zero or first order kinetics. The correlation coefficient (r) between log per cent from 0,797 to 0,969 with various tablet formulations.

Many variations were observed in the dissolution characteristics of the tablets formulated with various binders (Tabl. 2) (6, 7).

Based on DE30 values the order of performance of binders was found to be HPMC = Na alginate > HPC > PEG 6000 > PVP. Analysis of variance (ANOVA) of SD values indicated highly significant ($P<0,01$) differences in the dissolution characteristics of tablets due to binders. Tablets formulated with HPMC and sodium alginate exhibited significantly highest dissolution rates and efficiency values. Tablets formulated with PEG 6000, PVP K 90F as binders showed very low dissolution rate and efficiency values. The rapid and higher dissolution observed with these binders may be due to their strong hydrophilic nature.

The effect of the disintegrants namely pregelatinized starch, Primogel and Vivasol on the dissolution rate of TH was studied in series of tablets prepared with different binders (Tabl. 3).

Table 1. *Physico-mechanical characteristics of tablets containing TH (± SD, n =12)*

	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12
Hardness, kP	6,6±0,8	7,8±0,6	5,6±0,9	9,5±0,5	7,3±0,5	6,5±0,3	8,7±0,8	7,6±0,7	8,4±0,5	7,5±0,7	7,6±0,6	7,3±0,9
Disintegration Time	1 min ±0,05	1 min ±0,07	22 sec ±0,05	5 min 32 sec n ±0,05	5 min 12 sec n ±0,09	1 min ±0,02	1 min 20 sec ±0,01	2 min ±0,07	33 sec ±0,02	25 sec ±0,07	32 sec ±0,01	1min 15sec ±0,08

Table 2. *TH tablets prepared with various binders*

Ingradiet (mg/tablet)	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**
Terbinafine HCL(as base)	250	250	250	250	250	250	250	250	250			
Sodium alginate	3,0											
HPC		3,0				3,0			3,0	3,0	3,0	
HPMC			3,0				3,0					3,0
PEG 6000				20,0								
PVPK30					20,0			20,0				
Primojel	20,0	20,0	20,0	20,0	20,0							
Pregelatinized starch	40,0	40,0	40,0	40,0	40,0	70,0	20,0				40,0	40,0
Vivasol									20,0	12,0	20,0	20,0

Table 3. *Dissolution characteristics of TH tablets formulated with different binders*

Formulation	**min**					**DE_{30} (%); X±SD**	**K, Ra**
	10	**20**	**30**	**45**	**60**		
S1	82,3	95,5	97,8	98,1	99,0	75,3 ± 1,95	Ra = 0,615 K = 0,0447
S2	54,2	80,6	98,5	98,6	99,1	61,0 ± 0,31	Ra = 0,865 K = 1,523
S3	75,6	91,8	98,2	98,3	99,2	72,5 ± 1,25	Ra = 0,733 K = 1,276
S4	58,2	77,3	90,7	95,3	97,3	60,0 ± 0,91	Ra = 0,834 K = 1,390
S5	40,6	69,8	87,2	96,3	96,2	50,1 ± 3,22	Ra = 0,891 K = 1,525
S6	64,2	82,3	90,7	95,3	97,3	63,6 ± 1,72	Ra = 0,801 K = 1,333
S7	46,1	57,9	71,6	87,7	94,2	46,5 ± 2,62	Ra = 0,925 K = 1,420
S8	47,6	64,9	80,4	97,1	98,7	51,0 ± 2,04	Ra = 0,912 K = 1,523
S9	71,1	85,6	91,9	97	98,6	67,3 ± 2,52	Ra = 0,774 K = 1,304
S10	57,4	71,0	81,2	94,7	99,5	56,1 ± 3,81	Ra = 0,876 K = 1,429
S11	71,9	93,5	98,4	98,8	99,7	71,0 ± 1,63	Ra = 0,745 K = 1,308
S12	86,3	94,5	95,8	96,1	97,0	76,1 ± 1,72	Ra = 0,664 K = 0,044

Ra = korelation coefficient
K = rate constant

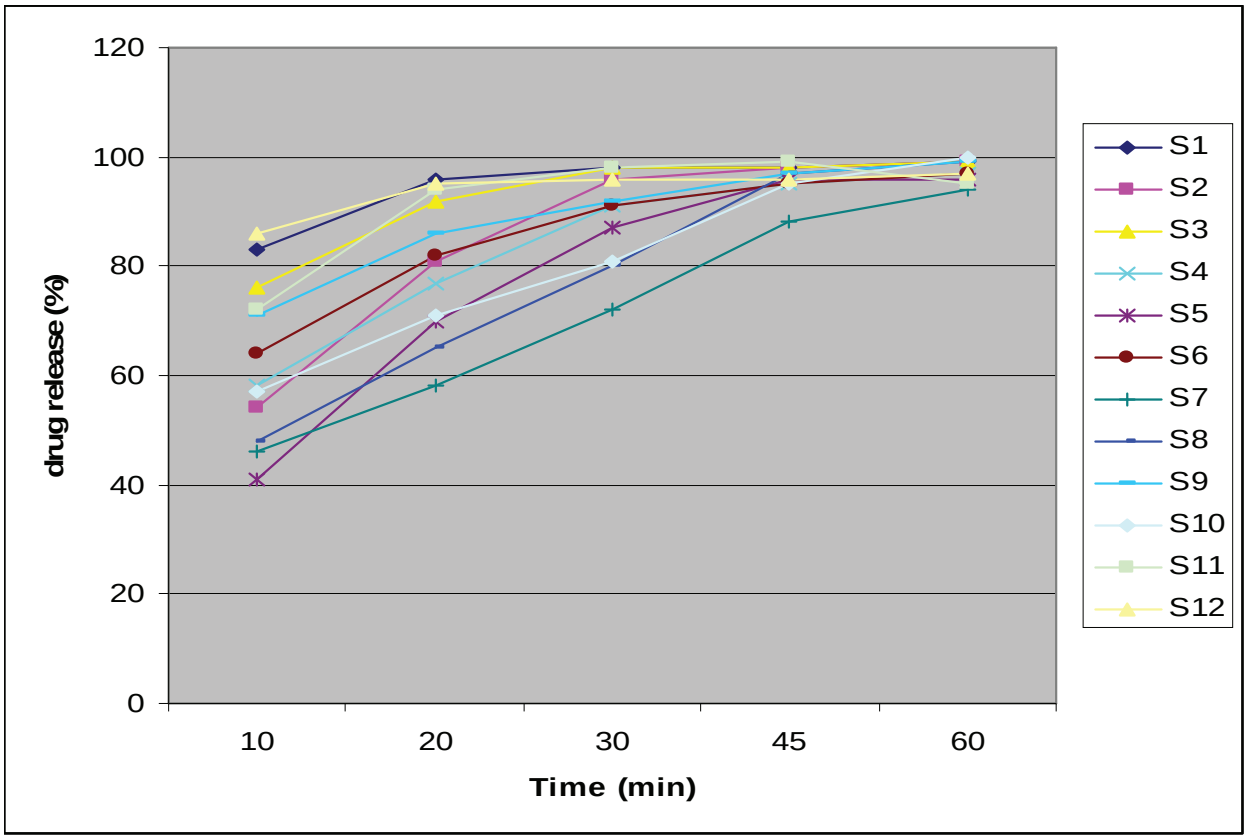

Fig.1 *Cumulative drug release profile of batch S12*

Based on DE30 values the order of performance of disintegrants was found to be Vivasol>Primogel>PEG with the binders HPMC, HPC and sodium alginate. Croscarmellose sodium is less affected by both pre-compression and prewetting (9). The efficiency of Primojel is highly dependent on their particle size. Due to the size increase following granulation, a higher addition level of super disintegrant is required to ensure fast and uniform disintegration of tablets prepared by granulation.When HPMC was used as binder, tablets formulated with Vivasol showed higher dissolution rate. With both the binders HPC and PVP, tablets formulated with PEG showed very poor dissolution of TH. Hence the corresponding binder-disintegrant combinations were suitable for TH tablets and the tablets fulfilled all the official requirements. Partially pregelatinized starches (Starch 1500) have a mixture of properties of both native and fully gelatinized starches; made them useful as both a binder and a disintegrant in wet granulated formulations (8).

Rate constant provides most accurate idea of the rate of release process. The process of dissolving a solid substance in corresponding solvent, without interaction is described by Nernst и Brunner equation based on the I Fick low of diffusion and Noyes – Whitney low of dissolution. Dissolution of TH from tablets followed first order kinetics and there is not the big difference between the samples. The correlation coefficient (r) between log per cent undissolved and time was in the range of 0,452 – 0,515 with in various tablet formulations.

Conclusion

Hence the corresponding binder – disintegrant combinations were considered suitable for TH tablets. HPMC as binder and croscarmellose sodium and pregelatinized starch as disintegrants showed higher dissolution rate. All tablet formulations fulfilled also the other official requirements.

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