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Selection of superdisintegrant for Famotidine rapidly disintegrating tablets

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Abstract

Patient groups such as elderly, children, and patients mentally retarded, uncooperative, nauseated, or on reduced liquid intake diets have difficulty in swallowing tablet dosage forms. For a rapidly disintegrating tablet, selection of superdisintegrant is of prime importance. This paper aimed in determining the optimum concentration of superdisintegrants and effect of hardness on disintegration time. 2, 4, 6% w/w concentration of superdisintegrants (sodium starch glycollate, crospovidone, croscarmellose sodium and Methacrylic copolymer with divinyl benzene) were used for this purpose. Famotidine which belongs to a class of medications called *H_2-antagonists* was selected as a suitable candidate. 4% Crospovidone was most effective as a superdisintegrant for Famotidine. It was seen that as hardness increased, the D.T. increased with all concentration of superdisintegrant. Superdisintegrants when used in combination did not show that much remarkable decrease in disintegration time as compared to the individual. Stability studies of the formulation suggest that there was no degradation with respect to time. IR data indicated no interaction of drug with the excipients.

Keywords: Zollinger-Ellison Syndrome, Ulcer, Famotidine, Sodium Starch Glycolate, Crospovidone, Superdisintegrant.

Introduction

Tablet is the most popular among all the solid dosage forms available. However, many patient groups such as elderly, children, and patients mentally retarded, uncooperative, nauseated, or on reduced liquid intake diets have difficulty in swallowing these dosage forms.[1] Among all the

dosage forms developed to facilitate the ease of medication, rapidly disintegrating tablets (RDT) is one of the widely employed common products. [2]

There are several methods for manufacturing RDT's [3-6] but direct compression was the preferred option resulting in cost effectiveness and ease of preparation [7].

For tablets and capsules which require rapid disintegration, the inclusion of the right superdisintegrant and in its optimum concentration is a prerequisite for optimal bioavailability. Superdisintegrants decrease disintegration time which in turn enhances drug dissolution rate. Thus, the proper choice of disintegrant / superdisintegrant and its consistency of performance are of critical importance to the formulation of rapidly disintegrating dosage forms.

Famotidine is chemically 3-[[[2-[(Diaminomethylene) amino] thiazol -4- yl] methyl] sulphanyl] -N- sulphamoyl propanimidamide. Famotidine belongs to a class of medications called H_2-*antagonists*. It is used to treat stomach and duodenal ulcers, gastroesophageal reflux disease (GERD), and conditions where too much stomach acid is secreted, such as Zollinger-Ellison Syndrome. It works by reducing the amount of acid secreted by the stomach. Famotidine is also used to prevent ulcers in certain circumstances. Thus, Famotidine was selected as a suitable candidate for preparation of RDT.

Material and Methods

Material

The tablets included the following ingredients: Famotidine (Zydus Healthcare Ltd.), Avicel PH 102 (FMC Biopolymer), Pearlitol SD 200 (Roquette), Aspartame (Vita Sweet Co. Ltd.), Colloidal silicon dioxide (Cabot Sanmar Ltd), Magnesium stearate (Amishi Drug & Chemicals). The four superdisintegrants studied were Sodium starch glycolate [SSG] (Shital Chemicals), Crospovidone [CRP] (BASF), Croscarmellose sodium [CCS] (Signet) and Methacrylic copolymer with divinyl benzene i.e. Polyflash® D 544 [Dosh] (Doshion).

Methods

The ingredients as per the respective formula (Table No.1) were weighed and then sifted through sieve no 40 (except magnesium stearate and colloidal silicon dioxide which were sifted through sieve no 60). All these ingredients except magnesium stearate were mixed in a double cone blender (Rimek Kalweka HD – 410) for 10 min at 10 rpm. Sifted magnesium stearate was then added to the blend and mixed in the double cone blender for another 2 minutes. The blend was compressed using a 16 station compression machine (CADMACK CMD 4-16/MT) using 9.5mm circular flat bevelled edge punches.

Evaluation

1. Uniformity of weight was determined. The weight data from tablets were analysed for sample mean and standard deviation.
2. Friability was calculated from the weight loss of tablets tumbled at 100 revolutions in Electrolab Friabilator (USP) model: EF – 1W.

3. Disintegration Time was performed at 24 - 26ºC in water using ELECTROLAB EL – 2L without disks.
4. Infra Red studies were done to check interactions between drug and excipients. They were carried out using KBr Discs. The reference standard was compared with that of the formulation.
5. Accelerated stability studies were carried out on the optimized batches. They were packed in Alu – Alu pouches and stored under the following conditions

(i) 25 $\pm$ 1 ^{o}C and RH 60 % $\pm$ 5%
(ii) 30 $\pm$ 1 ^{o}C and RH 65 % $\pm$ 5%
(iii) 40 $\pm$ 1 ^{o}C and RH 75 % $\pm$ 5%
The tablets were withdrawn after a period of 1, 2, 3 months and analyzed.

Table No. 1: Formulations

Batch No.	**2% SSG**	**2% CRP**	**2% CCS**	**2% Dosh-ion**	**4% SSG**	**4% CRP**	**4% CCS**	**4% Dosh-ion**	**6% SSG**	**6% CRP**	**6% CCS**	**6% Dosh-ion**
Ingredients	FM-01	FM - 02	FM - 03	FM - 04	FM - 05	FM - 06	FM - 07	FM - 08	FM - 09	FM - 10	FM - 11	FM - 12
Famotidine	40	40	40	40	40	40	40	40	40	40	40	40
Avicel PH 102	100	100	100	100	100	100	100	100	100	100	100	100
Pearlitol SD 200	138	138	138	138	132	132	132	132	126	126	126	116
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
SSG	6	0	0	0	12	0	0	0	18	0	0	0
CRP	0	6	0	0	0	12	0	0	0	18	0	0
CCS	0	0	6	0	0	0	12	0	0	0	18	0
Kyron	0	0	0	0	0	0	0	0	0	0	0	0
Doshion	0	0	0	6	0	0	0	12	0	0	0	18
Colloidal silicon dioxide	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	6	6	6	6	6	6	6	6	6	6	6	6
TOTAL (mg)	306	306	306	306	306	306	306	306	306	306	306	306

Experimental design

Three concentrations of superdisintegrants (Sodium Starch Glyclolate, Crospovidone, Croscarmellose Sodium, Methacrylic copolymer with divinyl benzene) were used to study effect of superdisintegrants on disintegration time keeping weight of tablet 306 mg and hardness 8 – 10 kg. Hardness of all these batches of three concentrations of superdisintegrants were varied at three ranges (4-5kg, 8-10kg and 13-14kg) keeping the other constraints constant. From observations, two best superdisintegrants i.e. Crospovidone and Methacrylic copolymer with divinyl benzene were used combinations as per Table No 2, were compressed and the effect of concentration on disintegration time was determined, keeping hardness 8 - 10 Kg.

Table No. 2: Effect of concentration of two superdisintegrants

CRP: Doshion	Total	Ratio
2:2	4%	1:1
2:4	6%	1:2
2:6	8%	1:3
4:2	6%	2:1
4:4	8%	1:1
4:6	10%	2:3
6:2	8%	3:1
6:4	10%	3:2
6:6	12%	1:1

Results and Discussion

Beyond expectation from the fact, an increase in concentration of superdisintegrant decreases the disintegration time, the results observed were different.

From Fig. 1, 6% Sodium starch glycolate showed a remarkable increase in disintegration time as compared to 2 and 4%. It was observed that sodium starch glycolate is effective at 4%. The mechanism of disintegration of sodium starch glycolate is swelling. In the beginning it swells very fast and later on it levels gradually, probably due to confinement of the tablet and also due to viscosity change of the penetrating liquid. This exceptional behavior could also be due to the higher concentration of sodium starch glycolate which may act as a binder instead of swelling which causes gelling. Thus, causing a viscous barrier (8) and so the disintegration time increases.

Crospovidone too shows a similar trend here, but there is a slight increase in D.T. at 6%. At 6% Crospovidone showed an increase in disintegration time because rapid penetration of the largest capillaries isolates other areas of finer pore structure which air cannot escape. These areas make no contribution to the overall uptake of liquid. Thus, 4% Crospovidone shows the best disintegration time.

Croscarmellose Sodium showed a low D.T. initially and then a sudden rise at which 4 and 6% are almost equal. Its disintegration action when used in low concentrations in tablet is thought to be due to its fibrous nature, which allows wicking of water into tablet matrices. Later on, swelling causes a smoothening of the particle edges as a result of which the perimeter length per unit area decreases. Thus, at lower concentrations the fibrous nature is more pronounced and smoothens gradually with time. At high concentrations, there is a probability that wicking and swelling occurs simultaneously thus, smoothening the particles and the width of the pore decreases. Thus, disintegration time decreases. Croscarmellose Sodium as a disintegrant is not that effective as Crospovidone or Methacrylic copolymer with divinyl benzene. Methacrylic copolymer with divinyl benzene however shows a decrease in D.T. as concentration increases. This is seen upto 4%. After this, there is no increase in D.T. A plateau is formed. This is because Methacrylic copolymer with divinyl benzene's trend of decrease in D.T. with increase in concentration is only upto a point (critical concentration). After that, it does not show a drastic change. All the above data suggest that 4% Crospovidone was most effective as a superdisintegrant for Famotidine. (Fig. 1)

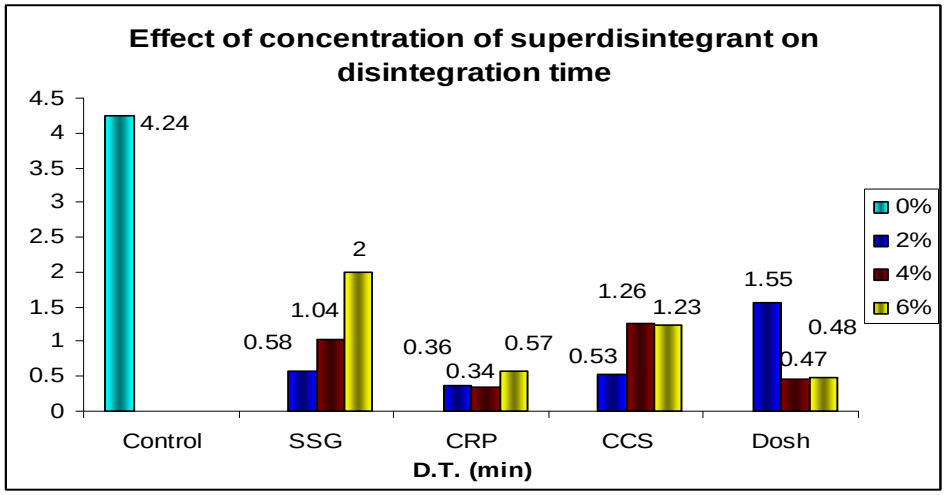

Fig. 1: Effect of concentration of superdisintegrants on disintegration time

Hence, the order was:

6% Methacrylic copolymer with divinyl benzene < 6% Crospovidone < 6% Croscarmellose Sodium < 6% Sodium Starch Glycolate,

4% Crospovidone< 4% Methacrylic Copolymer with Divinyl Benzene< 4% Croscarmellose Sodium < 4% Sodium Starch Glycolate,

2% Crospovidone < 2% Croscarmellose Sodium < 2% Sodium Starch Glycolate, <2% Methacrylic Copolymer with Divinyl Benzene.

It was observed that as hardness increases, the D.T. increases with all concentration of superdisintegrant. (Fig. 2-4)

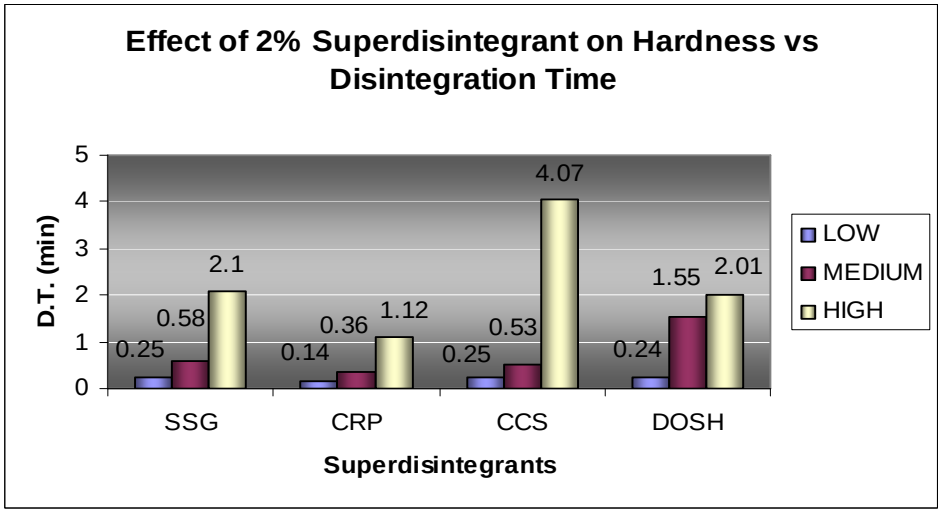

Fig. 2: Effect of 2% superdisintegrant on hardness vs. disintegration time

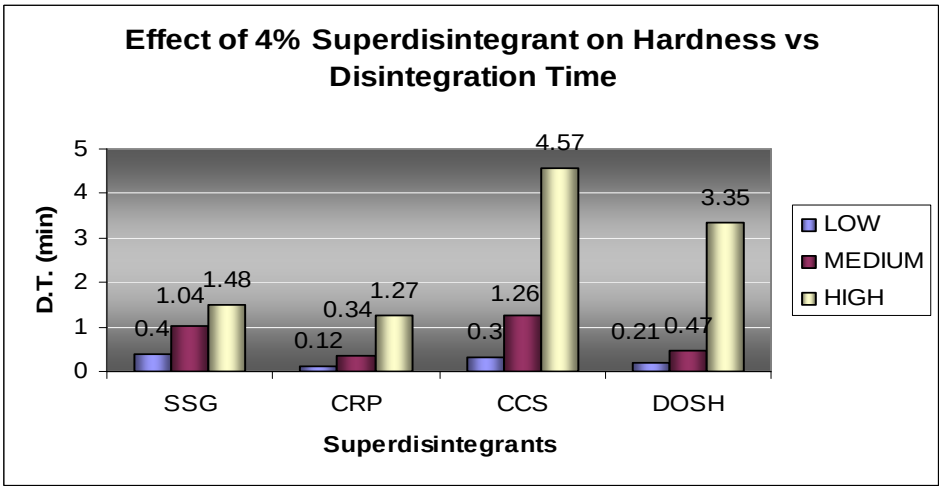

Fig. 3: Effect of 4% superdisintegrant on hardness vs. disintegration time

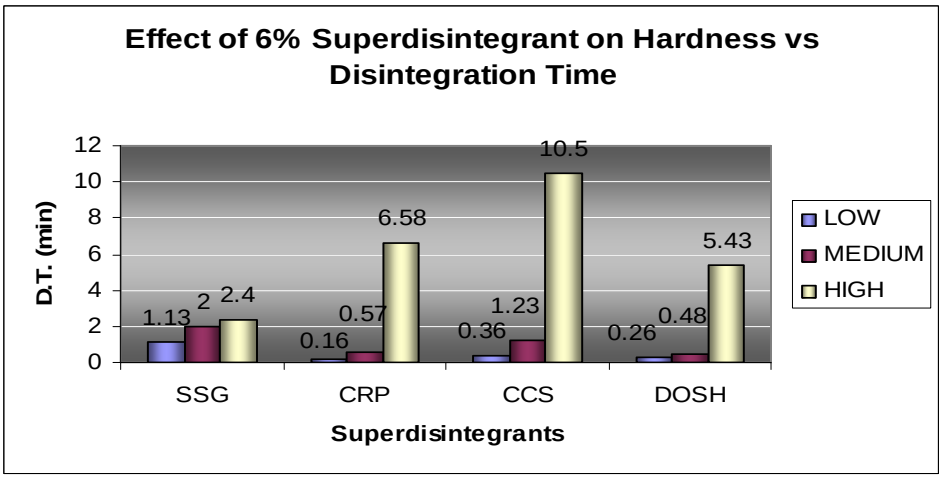

Fig. 4: Effect of 6% superdisintegrant on hardness vs. disintegration time

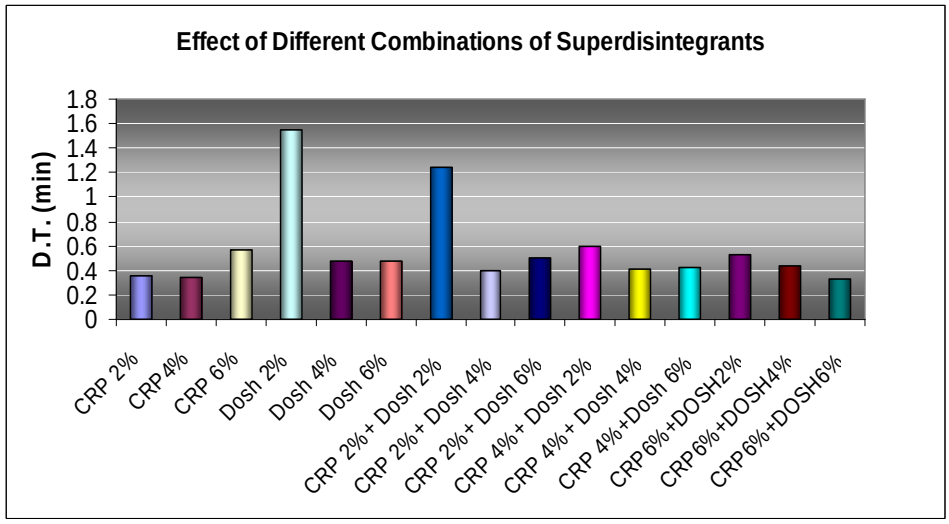

Fig. 5: Effect of different combinations of superdisintegrant

The optimized batch FM-06 (4% CROSPOVIDONE) with the lowest disintegration time (30 sec) was selected.

Stability Studies of the formulation upto 3 months suggest that there was no degradation with respect to time.(Table No 3)

Table No. 3: Accelerated Stability Studies

Note: * implies n = 10, **implies n = 6

Parameters	Initial	1 Month 25ºC/ 60% RH	2 Month 25ºC/ 60% RH	3 Month 25ºC/ 60% RH	1 Month 30ºC/ 65% RH	2 Month 30ºC/ 65% RH	3 Month 30ºC/ 65% RH	1 Month 40ºC/ 75% RH	2 Month 40ºC/ 75% RH	3 Month 40ºC/ 75% RH	0–2ºC Month 40ºC/75 % RH
	FM-06 S1	FM-06 S2	FM-06 S3	FM-06 S4	FM-06 S5	FM-06 S6	FM-06 S7	FM-06 S8	FM-06 S9	FM-06 S10	FM-06 S11
Weight (mg)*	308.58 ±3.71	307.76 ± 4.27	308.45 ± 3.28	307.2 ± 2.47	307.15 ± 3.34	308.61 ± 3.51	308.00 ± 2.12	308.62 ± 4.01	306.80 ± 4.11	309.79 ± 4.11	309.07 ± 2.36
Hardness (kg)**	8.9 ±1.51	9.48 ±0.54	9.3 ±1.33	9.41 ±1.51	9.5 ±0.53	9.4 ±0.4	9.38 ±2.36	9.4 ±0.57	9.19 ±0.90	9.1 ± 1.02	9.9 ± .45
DT (min)**	0.20 –0.30	0.27 –0.29	0.28 –0.30	0.29 –0.34	0.28 –0.29	0.27 –0.29	0.34 –0.35	0.29 –0.35	0.28 –0.34	0.41 – 0.35	0.19 –0.33
Assay (%)	101.15	98.34	98.08	98.01	98.28	98.05	99.91	98.98	98.65	99.15	98.63

IR data (Table No 4, Fig. 6, 7) indicated that the major peaks of drug has not changed, this implies that there is no interaction of drug with the excipients.

Table No. 4: IR range of Famotidine

Groups	Range (1/cm)
N-H amine stretching (b)	~3500
Primary amine N-H	1650 - 1550
C-N, aromatic	1340 - 1250
C=N	1660 - 1630
S=O, stretching vibrations	1070 - 1160

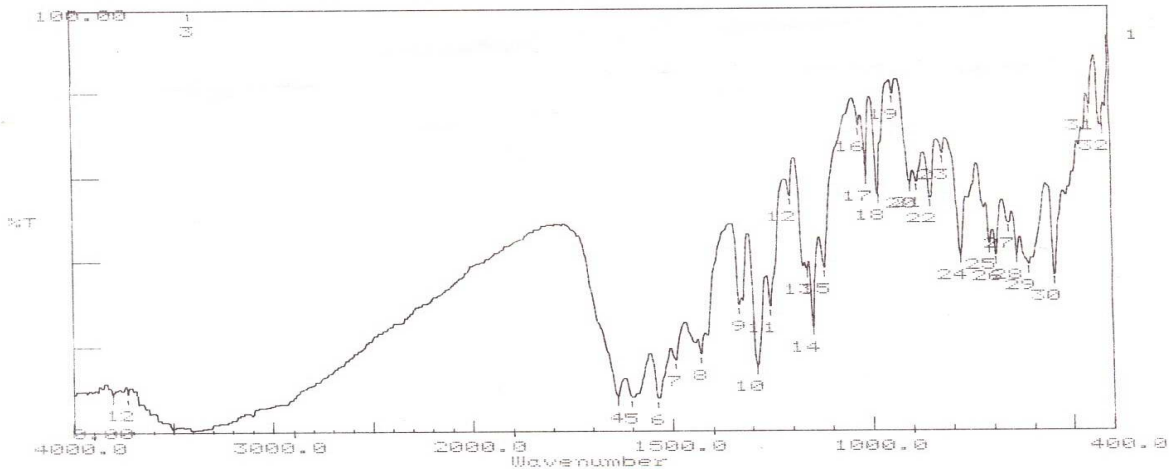

Fig. 6: Famotidine Standard – IR Spectrum

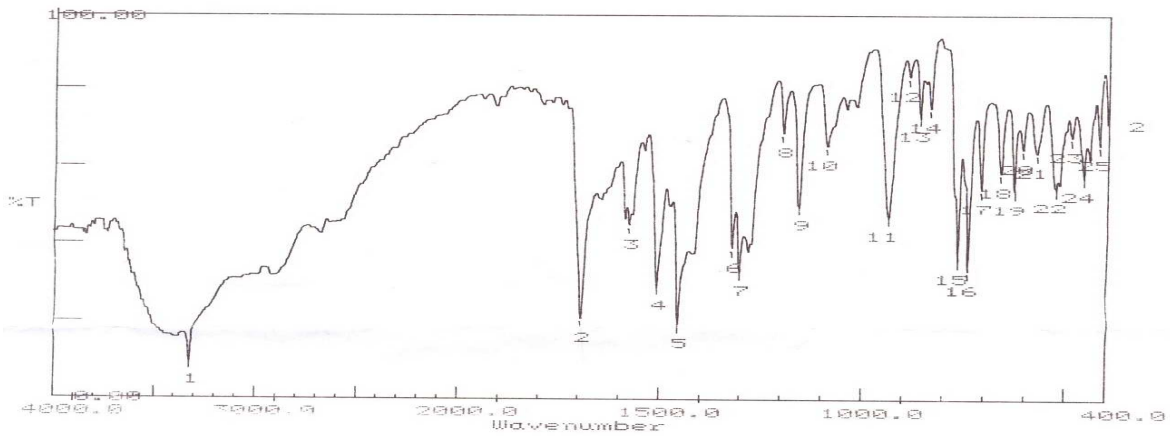

Fig. 7: Famotidine Formulation with 4% CRP – IR Spectrum

Conclusion

4% w/w of Crospovidone gave an optimum disintegration time of less than 30 sec. This may be further used for formulations with a modest dose and a low solubility drug. An increase in disintegration time with increase in hardness irrespective of the concentration of superdisintegrant was observed. Crospovidone and Methacrylic copolymer with divinyl benzene in combination did not show a remarkable fall in disintegration time. The formulation was stable and the IR data suggested no drug – excipient interaction.

Abbreviations:
SSG – Sodium starch gylcolate,
CRP – Crospovidone,
CCS - Croscarmellose sodium,
Dosh - Methacrylic copolymer with divinyl benzene.

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