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Superdisintegrant Selection for Tramadol Dispersible Tablets

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ABSTRACT

The selection of a suitable superdisintegrant for a rapidly disintegrating dosage form is of the utmost importance, since disintegration time (DT) is a critical parameter. An experimental design was implemented, to find out the effects of superdisintegrants (sodium starch glycolate, crospovidone, croscarmellose sodium and methacrylic copolymer with divinyl benzene), at 2, 4, 6% w/w, on tablet hardness, with respect to DT. Methacrylic copolymer with divinyl benzene (at 4 wt%) was selected as the best superdisintegrant, adequate for the formulation of dispersible Tramadol tablets. With increasing hardness, there was a considerable increase in DT at all concentrations of superdisintegrants. A combination of crospovidone and methacrylic copolymer with divinyl benzene showed a remarkable drop in DT to 0.33 min. The stability of the batch with lowest DT was also tested under various conditions and the results suggested that there was no degradation over the test period.

Keywords: Tramadol. Sodium Starch Glycolate. Crospovidone. Croscarmellose Sodium. Superdisintegrants.

INTRODUCTION

The drug Tramadol hydrochloride is (±)cis-2-[(dimethylamino) methyl] -1- (3-methoxyphenyl) cyclohexanol hydrochloride. Tramadol is well established in the treatment of pain and is classified as a Step 2 compound on the World Health Organization ladder. Tramadol is a synthetic, centrally acting analgesic. Tramadol and its M_1 metabolite (O-desmethyltramadol) act as opiate agonists, through selective binding to the μ-opioid receptor, and weak inhibition of norepinephrine and serotonin uptake. This second mode of action is thought to increase analgesic activity by complementing opioid receptor binding. As Tramadol is effective and well tolerated, its use has increased substantially for a broad range of malignant and nonmalignant pain conditions. (British Pharmacopoeia, 2004; Puranik M et al., 2006)

Tablets are the most popular solid dosage forms available. However, many patient groups, such as the elderly, children and adults who are mentally retarded, uncooperative, nauseated or on reduced liquid intake diets, have difficulty in swallowing tablets (Amin, 2006). Among all the dosage forms developed to facilitate the ease of medication, dispersible tablets are one of the most widely employed (Koizumi et al., 1997).

Several methods are used to manufacture dispersible tablets (Parakh & Gothoskar, 2003; Aly, 2005; Bidar, 2006), but direct compression is the preferred option, affording cost effectiveness and ease of preparation. (Parakh & Gothoskar, 2003; Aly, 2005; Bidar, 2006)

While at first glance it would seem simple to formulate a tablet of a very water-soluble drug, there are, in fact, many inherent problems. Tablets containing high concentrations of water-soluble drug or drugs normally tend to erode, rather than disintegrate, which may result in slow disintegration and possible gastrointestinal irritation (Sheen & Kim, 1989).

The proper choice of disintegrant / superdisintegrant (excipients used to promote the rapid breakdown of solid oral dosage forms to aid dissolution *In Vivo*) and its consistency of performance are of critical importance to the formulation of a dispersible tablet. Hence, the objective of the present work was to prepare a rapidly dispersible tablet of Tramadol HCl and to find the best type and concentration of superdisintegrant, alone and in combination, for the formulation of Tramadol HCl tablets, as well as its effects on their hardness.

MATERIAL AND METHODS

Material

The tablets included the following ingredients: Tramadol HCl (Spic Ltd.), Avicel PH 102 (FMC

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Biopolymer), Pearlitol SD 200 (Roquette), Aspartame (Vita Sweet Co. Ltd.), colloidal silicon dioxide (Cabot Sanmar Ltd) and magnesium stearate (Amishi Drug & Chemicals). The four superdisintegrants studied were sodium starch glycolate (Hydrochloric Acid), crospovidone (BASF), croscarmellose sodium (Signet) and methacrylic copolymer with divinyl benzene - Polyflash® D (Doshion).

Experimental design

In this study, four superdisintegrants, *viz*. sodium starch glycolate (SSG), crospovidone (CRP), croscarmellose sodium (CCS) and methacrylic copolymer with divinyl benzene (MDB), were used in the formulation of the tablets and the concentration of superdisintegrant was chosen as the independent variable, while the dependent variables were hardness and disintegration time (DT).

Effect of content of superdisintegrant in formulation:

Four different superdisintegrants were selected and the effects on DT of varying their contents was studied by using 2, 4 and 6% w/w of each disintegrant in the tablets. The tablet weight was kept constant at 300 mg and hardness at 8-11 kg.

Effect of hardness on disintegration time:

In order to study the effect of hardness on DT, the formulations shown in Table 1 were compressed to 3 different hardnesses, namely 4-6 kg (Low), 8-10 kg (Medium) and 10-14 kg (High).

Effect of combining two superdisintegrants:

As a single superdisintegrant in the formulation may not be able to give the desired DT, a combination of superdisintegrants may be used. As shown in Table 2, CRP and MDB were used in different ratios in the formulations, to give a range of total contents of superdisintegrants from 4% to 12%. The same manufacturing procedure was used for all the tablets, which were compressed.

This study was carried out to find the effects of:

a) varying the total superdisintegrant content (combination of two superdisintegrants) (4, 6, 8, 10, 12 wt%),

b) higher MDB content (ratios 1:2, 1:3, 2:3) and

c) higher CRP content (ratios 2:1, 3:1, 3:2).

Stability tests were performed on the formulation containing a single superdisintegrant that showed the lowest DT.

Table 1: Formulation of Tramadol with various superdisintegrants (mg)

Ingredients	2% SSG	2% CRP	2% CCS	2% MDB	4% SSG	4% CRP	4% CCS	4% MDB	6% SSG	6% CRP	6% CCS	6% MDB
Tramadol HCl	50	50	50	50	50	50	50	50	50	50	50	50
Avicel PH 102	100	100	100	100	100	100	100	100	100	100	100	100
Pearlitol SD 200	128	128	128	128	122	122	122	122	116	116	116	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
Doshion/MDB	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
TOTAL (mg)	300	300	300	300	300	300	300	300	300	300	300	300

SSG – Sodium starch glycolate, CRP – Crospovidone, CCS - Croscarmellose sodium, MDB/Doshion - Methacrylic copolymer with divinyl benzene.

Table 2: Contents of two superdisintegrants in CRP:MDB combinations

CRP: Doshion/MDB	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

CRP = Crospovidone; MDB = Methacrylic copolymer with divinyl benzene

Manufacturing procedure

The ingredients for each formula (Table 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 the 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 on a 16-station tablet press (CADMACH CMD 4-16/MT) equipped with 9.5mm circular flat bevelled edge punches.

Tablet evaluation

Mass uniformity (Indian Pharmacopoeia, 1996)

Uniformity of weight was determined. The weights of the tablets were analysed for sample mean and standard deviation (n = 20).

Friability (Indian Pharmacopoeia, 1996)

Friability was calculated from the weight loss of tablets (n=20) tumbled for 100 revolutions in an Electrolab Friabilator (USP model: EF – 1W).

Disintegration Time (Indian Pharmacopoeia,1996)

Disintegration time was measured at 24-26ºC in water, in an Electrolab ED–2L disintegration tester, without disks (n=6).

Stability study (International Conference on Harmonization, 2003)

Temperature-dependent stability tests were carried out on the optimized batches. They were packed in Al foil blisters and stored under the following conditions

(i) 25 ± 2 °C and RH 60 % ± 5%
(ii) 30 ± 2 °C and RH 65 % ± 5%
(iii) 40 ± 2 °C and RH 75 % ± 5%.

The tablets were withdrawn after periods of 7, 14 days, 1, 2 and 3 months and tested for weight, hardness, thickness, DT and friability and assayed for drug content and the compatibility of drug and excipients were confirmed by IR spectroscopy.

RESULTS

Effect of superdisintegrant content on the disintegration time

Sodium starch glycolate (SSG), crospovidone (CRP) and croscarmellose sodium (CCS) all showed a steady fall in DT as their content increased from 2% to 6%. Methacrylic copolymer with divinyl benzene (MDB) showed a sharp drop in DT as its content rose from 2 to 4%. However, at 6%, the DT increased slightly. Hence, 4% MDB was selected as the most effective superdisintegrant and content for the Tramadol tablets.

Examining Fig. 1, it can be seen that DT rises in the order:

6% MDB < 6% CRP < 6% CCS < 6% SSG;
4% MDB < 4% CRP < 4% CCS < 4% SSG,
2% MDB < 2% CCS < 2% CRP < 2% SSG.

Overall, 4 – 6% CRP and MDB performed adequately, irrespective of the drug, while the other superdisintegrants did not. (Fig. 1)

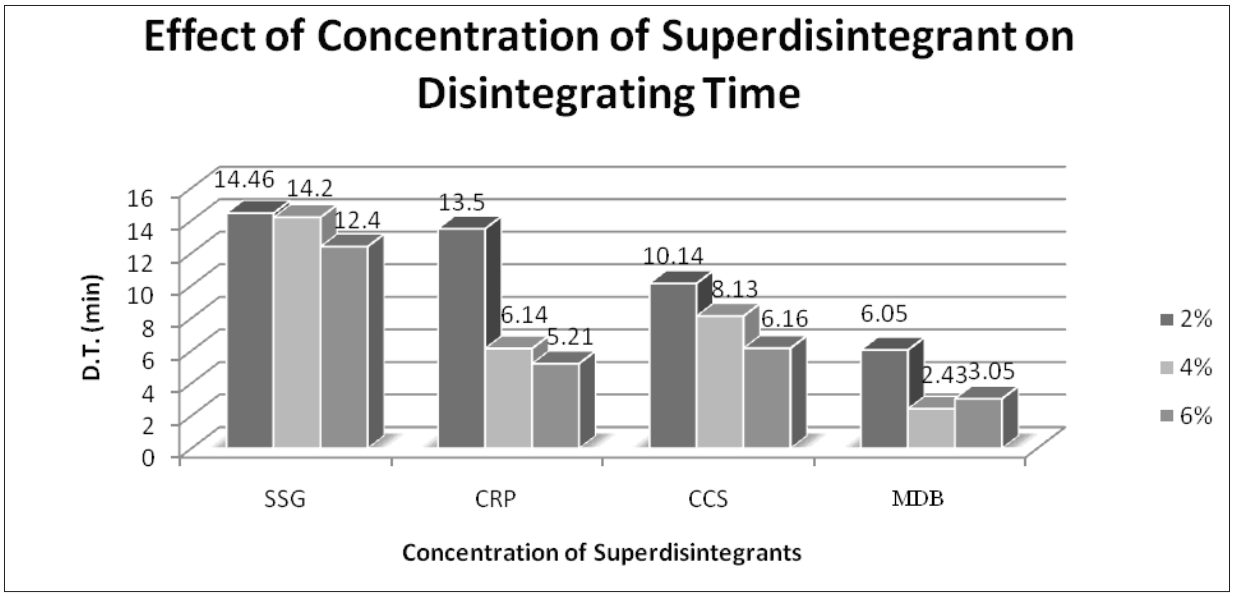

Fig. 1: Effect of Concentration of Superdisintegrants on Disintegration Time

Effect of superdisintegrant contents and hardness on disintegration time.

A clear tendency for DT to increase with increasing hardness was observed, irrespective of the content of the superdisintegrant used. (Fig. 2 – 4)

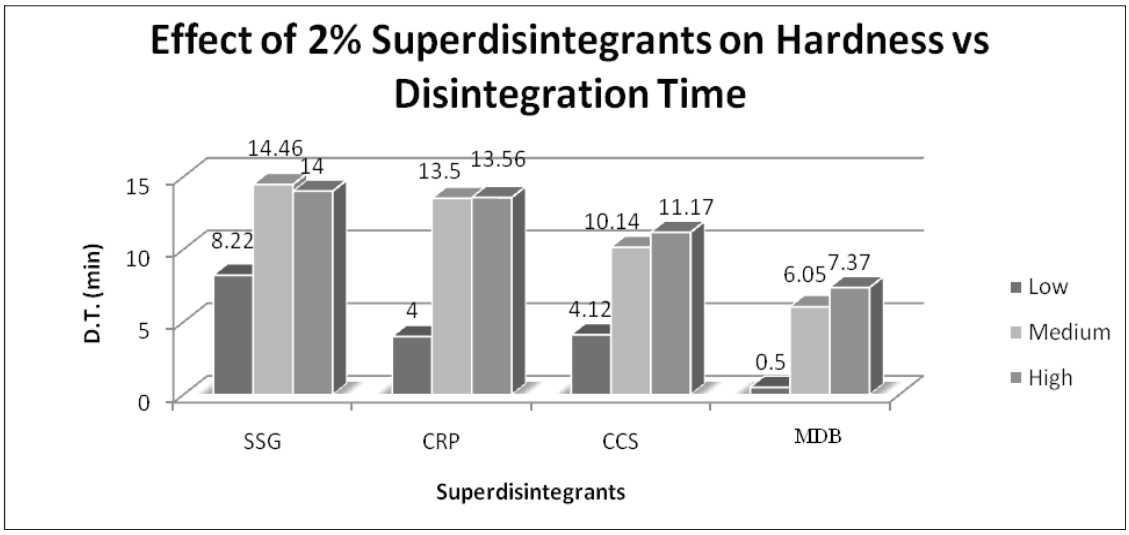

Fig. 2: Effect of 2% superdisintegrant vs Hardness vs. D.T.

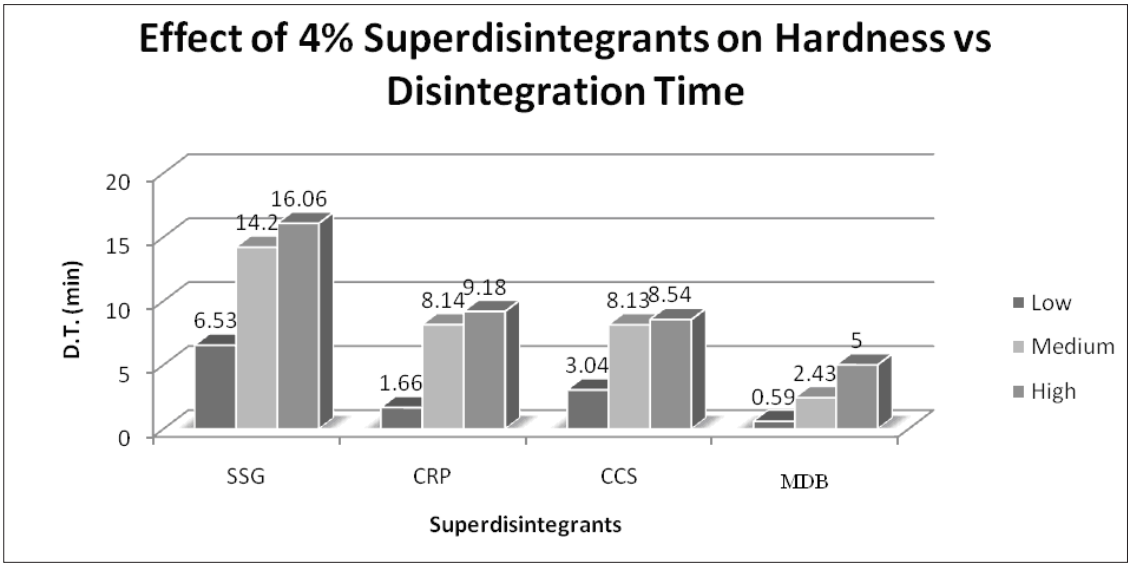

Fig. 3: Effect of 4% superdisintegrant and Hardness vs D.T.

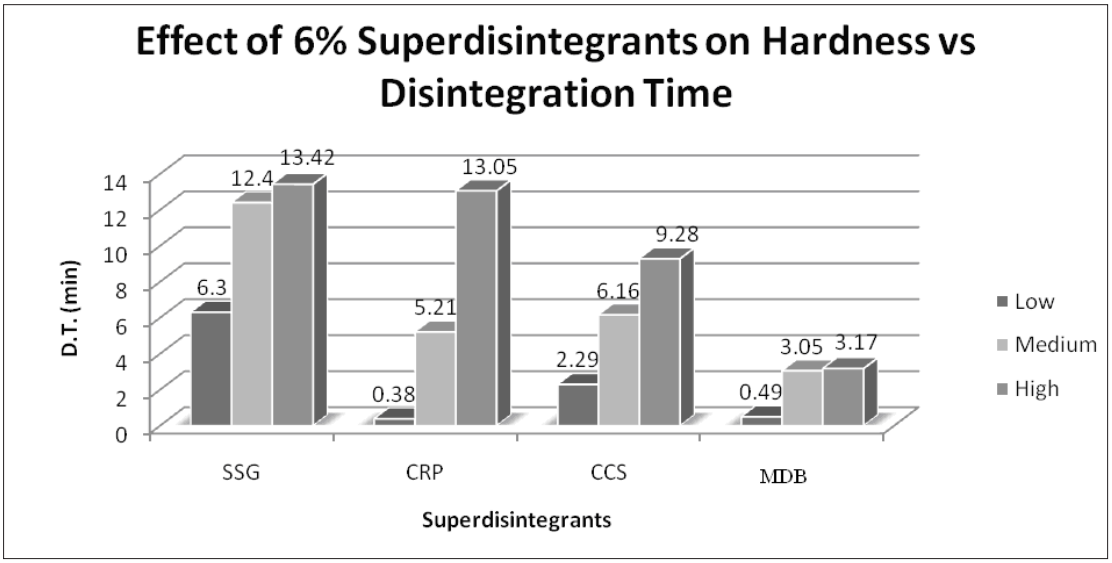

Fig. 4: Effect of 6% superdisintegrant and Hardness vs D.T.

Effect of combination of CRP and MDB on disintegration time.

The best result (shortest DT) was shown by TOD 09, i.e. 6% CRP and 6% MDB (Fig. 5, Table 3).

The batch 4% MDB, which showed the shortest DT (2.43 min) for a single superdisintegrant, was selected for the stability study. Stability tests on the formulation TOD-09 suggest that there was no degradation during the tests. (Fig. 6-7, Tables 4-6)

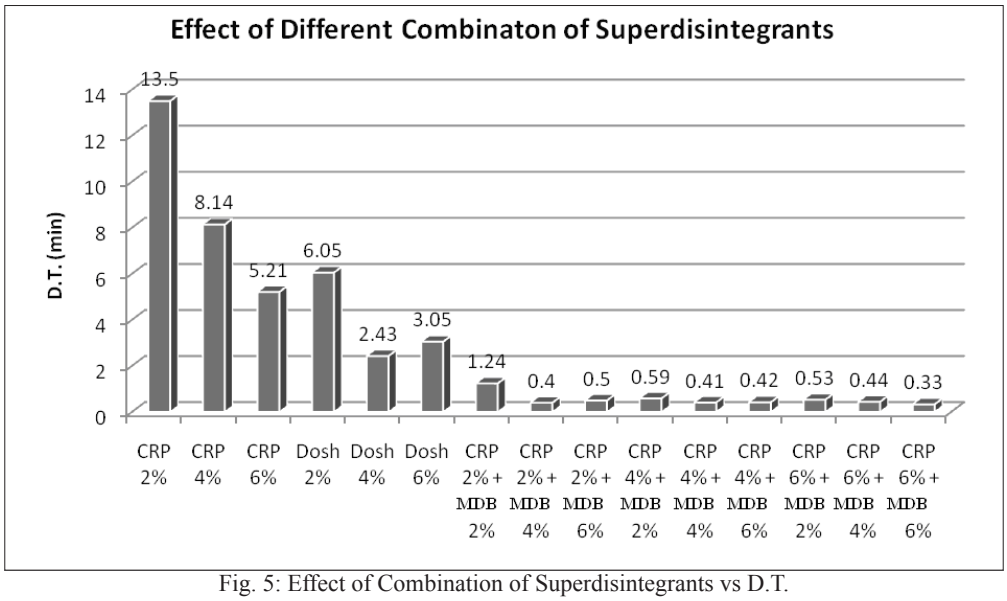

Fig. 5: Effect of Combination of Superdisintegrants vs D.T.

Table 3: Effects of Combination of Crospovidone (CRP) and Methacrylic copolymer with divinyl benzene (MDB) on Tramadol tablets

Parameters	CRP 2%+MDB 2%	CRP 2%+ MDB 4%	CRP 2%+MDB 6%	CRP 4%+MDB 2%	CRP 4%+MDB 4%	CRP 4%+MDB 6%	CRP 6%+MDB 2%	CRP 6%+MDB 4%	CRP 6%+MDB 6%
	TOD 14	TOD 15	TOD 16	TOD 17	TOD 18	TOD 19	TOD 20	TOD 21	TOD 22
Weight (mg)*	307.01 ± 0.43	304.97 ± 0.12	304.95 ± 0.33	305.47 ± 0.26	304.27 ± 0.27	302.06 ± 0.23	305.09 ± 0.29	305.53 ± 0.32	306.71 ± 0.25
Hardness (kg)**	9.8 ± 0.19	9.4 ± 0.32	8.43 ± 0.54	10.2 ± 2.43	8.7 ± 1.23	8.1 ± 0.34	9.3 ± 0.45	9.5 ± 0.34	8.5 ± 1.23
DT (min)**	0.57 – 1.24	0.35 – 0.40	0.48 – 0.50	0.55 – 0.59	0.36 – 0.41	0.36 – 0.42	0.37 – 0.53	0.41 – 0.44	0.26 – 0.33

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

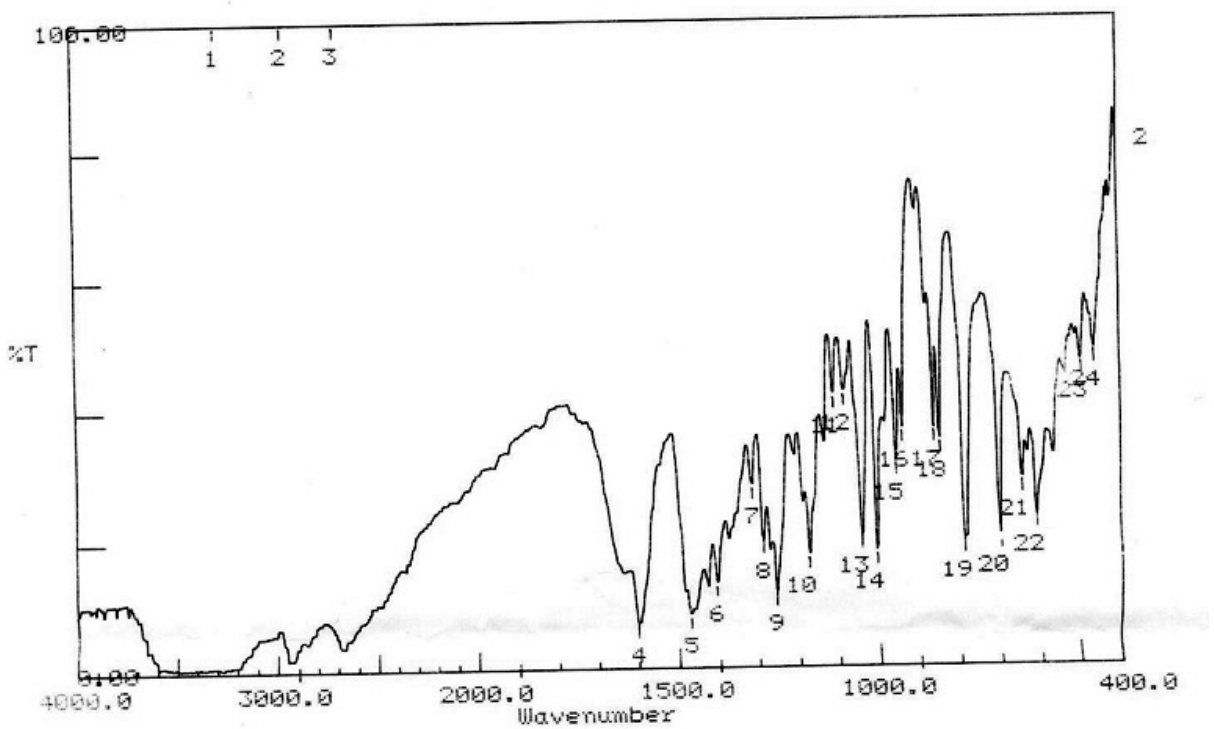

Fig. 6: IR Spectrum of Standard Tramadol HCl

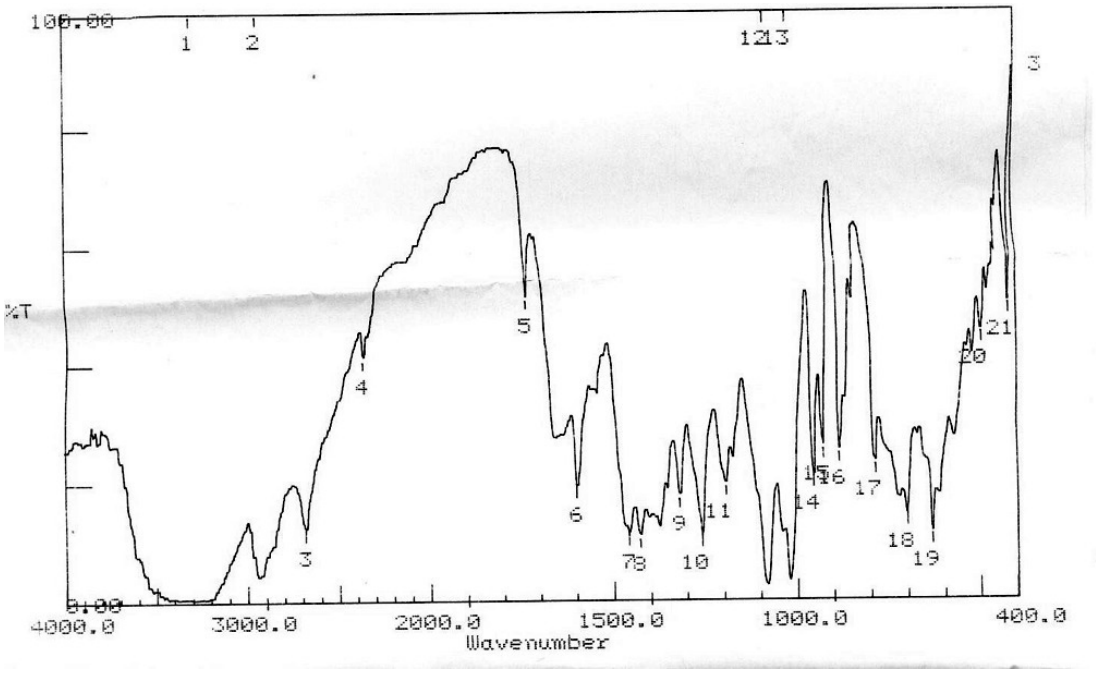

Fig. 7: IR Spectrum of Tramadol HCl Formulation with 4% MDB after stability studies.

Table 4: Accelerated Stability Tests – A: Tramadol Dispersible Tablets at 25ºC/ 60% RH

Parameters		Initial	7 days	14 days	1 Month	2 Month	3 Month
		TOD 09	TOD 09	TOD 09	TOD 09	TOD 09	TOD 09
Weight (mg)*		302.94±3.09	302.06± 3.30	301.71± 4.22	301.52± 4.04	303.04 ± 2.57	301.13 ± 4.91
Hardness (kg)**		8.39 ± 1.02	7.92 ± 1.49	7.87± 1.06	8.40 ± 1.64	7.27 ± 1.04	9 ± 0.2
Thickness(mm)**		3.43 ± 0.02	3.44 ± 0.06	3.42 ± 0.05	3.40 ± 0.02	3.42 ± 0.02	3.46 ± 0.02
DT (min)**		2.09 - 2.25	2.35 – 5.54	2.21 – 4.45	3.13 – 5.02	3.02 – 3.07	3.00 – 3.12
Assay %		103.43	100.75	101.94	100.29	103.78	114.61
Friabi-lity	100 rpm	0.07%	0.05%	0.02%	0.03%	0.04%	0.03%
	300 rpm	0.09%	0.01%	0.15%	0.17%	0.21%	0.22%

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

Table 5: Accelerated Stability Tests – B: Tramadol Dispersible Tablets at 25ºC/ 60% RH

Parameters		7 days	14 days	1 Month	2 Month	3 Month
		TOD 09	TOD 09	TOD 09	TOD 09	TOD 09
Weight (mg)*		303.74 ± 2.99	303.62 ± 3.25	301.22 ± 3.33	302.59 ± 2.23	301.12 ± 2.18
Hardness (kg)**		9.44 ± 1.51	9.36 ± 1.59	9. 5 ± 0.53	9.63 ± 1.31	9.68 ± 0.67
Thickness(mm)**		3.48 ± 0.04	3.47 ± 0.07	3.48 ± 0.02	3.51 ± 0.04	3.52 ± 0.02
DT (min)**		4.08 – 4.14	4.02 – 4.10	3.58– 4.13	3.34– 3.57	4.34 – 5.07
Assay %		109.40	96.12	91.01	94.28	106.42
Friabi-lity	100 rpm	0.13%	0.03%	0.04%	0.32%	0.34%
	300 rpm	0.02%	0.04%	0.46%	0.55%	0.60%

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

Table 6: Accelerated Stability Tests – C: Tramadol Dispersible Tablets at 25ºC/ 60% RH

Parameters		7 days	14 days	1 Month	2 Month	3 Month	0 - 2 ºC Month
		TOD 09	TOD 09	TOD 09	TOD 09	TOD 09	TOD 09
Weight (mg)*		302.45 ± 3.27	300.62± 4.15	300.6 ± 4.01	302.21± 2.68	301.3 ± 2.71	301.03± 2.72
Hardness (kg)**		9.86 ± 1.09	9.77 ± 1.22	9.41± 0.57	9.67± 0.56	9.67 ± 1.10	9.7 ± 1.10
Thickness(mm)**		3.48 ± 0.05	3.53 ± 0.05	3.58 ± 0.03	3.80 ± 0.10	3.40 ± 0.04	3.40 ± 0.05
DT (min)**		2.17 – 2.51	2.32 – 2.57	0.54 –1.35	0.43 – 0.59	0.30 – 0.54	1.33– 2.58
Assay (%)		101.49	102.31	99.98	102.15	101.49	103.21
Friabi-lity	100 rpm	0.14%	0.21%	0.32%	0.06%	0.02%	0.02%
	300 rpm	0.62%	0.78%	0.86%	0.89%	0.02%	0.01%

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

DISCUSSION

It has been observed that changing the quantity of superdisintegrants in a tablet changes the main parameters of drug absorption, namely solubility and availability to the body, which ultimately depend on hardness and disintegration time (DT) of the tablet. The DT is directly correlated with bioavailability of the drug: the shorter the DT, the earlier the drug is available to the body. In the present study, it was observed that for a single superdisintegrant to reduce the DT, a relatively high quantity of the superdisintegrant was required, whereas in combination the effect could be obtained at lower contents. This result of the study could be cost effective for the pharmaceutical industry.

Effect of varying contents of superdisintegrants on the disintegration time

As the concentration of superdisintegrant increased, the DT was found to decrease. This can be explained by the fact that although superdisintegrants may sorb liquid and cause swelling of the compact in proportion to the amount added, sufficient disintegrant must be present to expose primary particles upon disintegration. Too few disintegrant particles per unit volume of compact may only lead to the production of larger aggregates, which will have difficulty in further de-aggregation. This is the reason due to which the disintegration time decreases upto a concentration of super disintegrant after which there is stagnancy in the DT. (Wan & Prasad, 1990).

There was a major drop in DT when a combination of CRP and MDB was used in the Tramadol tablets, indicating a synergistic effect. A combination of 6% CRP: 6% MDB showed a remarkable fall in disintegration time down to 0.33 min.

Effect of varying hardness with different concentrations of superdisintegrants on disintegration time

As pressure increases the total porosity decreases and thus the DT also increases, as has been reported by Mufrod & Parrott (1990) and Ferrero & Munoz (1997).

MDB at 4% w/w gave an optimum disintegration time of 2.43min. An increase in DT with increasing hardness was observed, irrespective of the concentration of superdisintegrant.

The infrared spectra of standard Tramadol HCl and the formulation with 4% MDB clearly indicate that there are no changes in the major peaks of the drug, showing that there is no interaction between drug and superdisintegrant (Figs. 6 and 7). The present study has thus revealed a useful superdisintegrant (MDB), which improves the DT of tablets of Tramadol, an important class of drug that requires immediate release for its analgesic action.

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