Effects of Magnesium Hydroxide on Disintegration Time and Dissolution Rate of Diclofenac Sodium Plain Tablet

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The objective of this study was to evaluate the effects of magnesium hydroxide (MH) on disintegration time (DT) and dissolution profile of diclofenac sodium (DS) plain tablet. The tablets of DS were formulated with conventionally used excipients and investigational agent $Mg[OH]_2$. Different parameters of tablets like hardness, thickness, friability, and disintegration time and dissolution rate were determined to assess the effects of MH on these parameters. The physical resistance against abrasion or shock of DS-MH tablets had been noticed by the results of hardness and friability test which were within the limits of standard specification. The disintegration times of tablets of the experimental batches except one, found 2.0 to 25 minutes were also within the limits of standard specification. The release rates of DS in simulated gastric fluid (SGF) at 30 minutes were inspiring about batches FO3: 84.78% and FO4: 90.38%. A positive correlation of coefficient determined between quantity of $Mg(OH)_2$ in different batches of tablets and their effects on dissolution rate was found statistically significant (r = 0.66). The t_{max} of DS was not affected by the presence or increment of MH as evident in $r_{tmax} = 0.50$. The overall study indicated that Magnesium hydroxide didn't affect the different physical parameters of plain tablet rather it in certain quantity while present in some batches assisted rapid disintegration and release profile of active content Diclofenac sodium. The DS-MH plain tablet to provide rapid disintegration, dissolution and absorption hence fastest anti-inflammatory action with acid neutralizing benefits by MH, might be considered sincerely

Key words: Diclofenac Sodium; Magnesium Hydroxide; Disintegration; Dissolution

Introduction

Rheumatoid arthritis and other inflammatory disorders have worldwide significance. Osteoarthritis causes up to 10% of adult population and inflammatory arthropathies about 2-3%. These diseases are responsible for up to 30% of physical disabilities and 60% of the burden of severe disabilities [1]. Rheumatic disease affects the people of all ages and ethnic groups. In UK, more than 40% over the year 65 have some kind of rheumatic disease, and 20 million people experience rheumatic complaints in each year. The NSAIDs, corticosteroids, opioiod analgesic, chloroquine, penicillamine, gold salt, sulphasalazine are major drugs for anti-inflammatory and analgesic action. Costicosteroids are highly selective but have adverse; osteoporosis, fluid retention, dermis arthropaties effect and increases susceptibility to infection. Dyspepsia, gastric or peptic ulceration induced by NSAIDs limit their use. Thus searching for better GI-safe agents were continued and once succeeded to popular COX-2 inhibitors. Merck, the Rofecoxib manufacturer, in September 2004, withdrew the popular new anti-inflammatory drug Rofecoxib after a study that long-term use of these drugs doubled the risk of heart attack and stroke. Thus,

exploration of safer anti-inflammatory drugs yet to be continued. Diclofenac sodium, one of the earliest NSAIDs member and first drug of phenyl acetic acid series has a wide range of therapeutic utility. It is the highly prescribed drug and has 30% prescription coverage from all NSAIDs market. It is used to treat osteoarthritis, rheumatic arthritis, chronic juvenile arthritis, low back pain, ankylosing spondylitis, post operative pain, renal pain, and pain in dental and other surgical operation. Diclofenac inhibits synthesis of prostaglandin by blocking the non-specific enzyme Cyclo-oxygenase (COX). Like other NSAID it has also GIT related adverse effects. However, bioavailability profile, anti-inflammatory dose, therapeutic efficacy and relatively low ulcerogenic effect [2] (make this agent more suitable to investigate.

Antacids are defined by their neutralizing capacity of HCl that can bring to pH 3.5 in 15 minutes and are used to anticipate for symptomatic management of pain caused by dyspepsia or ulcer, reflux oesophagitis & hyperacidity by neutralizing hydrochloric acid. Hydroxide of Ca^{2+}, Al^{3+} & Mg^{2+} are relatively insoluble. Thus gastric OH^- ion doesn't accumulate to corrosive level. MH reacts comparatively rapid with H^+, and Aluminum hydroxide is relatively slow. Presence of food elevates pH to above 5.0 after one hour and prolongs the neutralizing effect for 2.0 hours. In general sufficient antacids maintain pH 4.0 in adequate therapy. Partial neutralization of gastric HCl increases the peptic activity of enzyme four times more in pH 2.0 than at pH 1.3. Commercial milk of magnesia contained 390mg $Mg(OH)_2$ per 5 ml have 14 meq acid neutralizing capacity. Moreover antacid in very low dose (88mmol per day) for 8 weeks was as effective as 800mg of Cimetidine in healing ulcers [3].

To overcome the problems associated with NSAIDs related peptic ulcer and their life threatening complications prophylactic anti-ulcerant eg missoprostol, H_2-receptor blockers, proton-pump inhibitors had been used since before [4]. Antisecretory dose of prostaglandin analogue such as misoprostol, abraprostil,

enprostil and risoprostil have shown to be more effective than placebo but costly & less effective than H_2-antagonist [5]. The antisecretory actions of Famotidine and Cimetidine have weak androgenic effect and hence Gynecomastia, impotence [6] lessened the interest for these agents. Proton pump inhibitors (Omeprazole, Lansoprazole, Pentoprazole, Rabeprazole or Esomeprazole) are being used but are not economic in treating NSAIDs associated hyper-acidity. Besides the rebound hyper secretion of widely used omeprazole in about more than 82% in 15 days post treatment of H pylori negative patients and maximal basal acid output 28% [7] is one of the major objections. Antacids appear to be superior to placebo and equivalent to H_2-receptor in releasing ulcers symptom [8,9]. MH as antacid in diclofenac may be one of the best investigational agents in plain tablets.

Methods

For manufacturing of tablets the BP & USP specifications were followed. Ethical Drugs (Bangladesh) Ltd. provided the facilities to manufacture as many as the 20000 tablets of different formulation categories sufficient to conduct the study as required quality. Major machines, instruments and reagents used in the experiments are stated in Table: I and II.

Table – I: Depicts instruments used for analysis of various parameters of tablets

Instruments	Specification of instruments
1. Friabilator	Electro Lab EF (USP)
2. Hardness Tester	Pfizer Hardness Tester
3. Electronic Balance	Electronic Digital Balance 4 digit
4. P^H meter	Denver Instruments
5. Disintegration Testing Machine	Electro lab
6. Dissolution (USP) Type II	ERWEAKA, Germany
7. UV-Spectrophotometer	SHIMADZU UV 1201, UV VIS
8. Tablet Compression Machine	City Rotary Tablet Machine
9. Others	Unspecified

Table – II: Ingredients, sources, justifications and percent (%) of ingredients used in different batches of experimental tablets. Per tablet contains same 50 mg diclofenac sodium BP (Square).

Ingredients & Specification	Justification	Source	Quantity of Ingredients				
			FOI	FO2	FO3	FO4	FO5
Diclofenac sodium (mg)	Active ingredient	Square	50	50	50	50	50
Mg(OH)2 (mg)	Experimental agent	Ethical Drugs	0	200	300	350	400
Povidone USP XXIII (%)	Granulating agent	BASF, Germany	3.53	1.46	1.13	1.11	1.02
Maize Starch BP 1993 (%)	Diluents	Paradize, Roquette	35.34	14.64	11.33	11.07	10.17
Lactose BP 1993 (%)	Diluents	New Zealand	13.07	5.42	4.19	4.10	3.76
Talc Purified BP 1993 (%)	Lubricant	Local	2.12	0.88	0.68	0.66	0.61
Magnesium Stearate (%)	Lubricant	Remo Chemicals (BD) Ltd.	3.53	1.46	1.13	1.11	1.02
Avicel PH 101 BP 1993 (%)	Disintegrating agent	Ming Tai Chemical, Taiwan	7.07	2.93	2.27	2.21	2.03
Magnesium Hydroxide BP (%)	Experimental agent	Fuji Kasei Co Ltd. Osaka Japan	00	58.57	67.95	88.59	71.21

Preparation of simulated gastric fluid (SGF): The SGF was prepared for pH 1.2, which was considered equivalent to the gastric environment. Sodium chloride of 2 grams was used against 7.0ml of 36.4% HCl and finally added sufficient distilled water to prepare 1000ml solution.

Determination of hardness, thickness, friability and weight variation: Crushing strength for hardness was the scale reading to break and was recorded for each time of six tablets and was used for the purpose of hardness test. The Vernier micrometer scale was used to determine the tablet thickness. Roche Friabilator was used to assess the effect of abrasion and shock by utilizing a plastic chamber at 25rpm and accelerated to 100rpm. The difference between the pre and post operation weight were determined after dedusting and the percent changes were recorded. All these operations were conducted as per British Pharmacopoeia 1988. Weight variation was done as per USP specification. Determination of disintegration time: disintegration method type II as per standard USP specification (six glass tube, 3 inches long 10mesh screen) in SGF of pH 1.2 at 37 ± 2 0C was used for this purpose. Construction of calibration curve: A calibration curve was constructed by plotting absorbance at 274nm against amount of diclofenac (reference standard) present in 0.1 (N) HCl solutions [10]. Determination of dissolution rate: USP dissolution calibration was done before starting the experiment. Dissolution test was done at temperature 37 ^{0}C in Rotating Basket-1 in solution 0.1 N HCl, with 50rpm. The solutions were drawn 0 min 05 min, 10 min, 15min, 30 min, 60min, 75 min, 90min and 120min. The spectrophotometric readings were taken for solutions at 274nm through Quartz cell. The standard USP XXII/NFXVII apparatus was used for this operation. The dissolution media was used 900ml. The amount of diclofenac sodium was determined as per standard curve constructed.

Results

In the results, hardness, thickness, friability, weight variation, disintegration time and, dissolution rates are presented in Table – III.

Table – III: DS-MH combination preparations and overall evaluation result of the study. * No tablet was found intake after friability test.

Properties	FO1(Control)	FO2	FO3	FO4	FO5
Hardness (Kg) SD (±1.4)	1.5-2	6-8	5.5-6.5	4.0-5.0	6.5-8
Thickness (mm)	3.50	4.00	4.90	5.60	5.90
(%) Friability	100*.00	0.11	0.62	1.14	0.05
Weight Variation (%)SD (±0.5)	0.20	-1.40	-3.10	-0.30	-4.00
Disintegration time (DT) (min) (±SD)	25.24 (±5.08)	42.38 (±3.19)	6.27 (±1.07)	2.04 (±0.06)	4.88 (±2.28)
% Dissolved (30 min) (±SD)	68.92 (±0.54)	60.00 (±4.55)	84.78 (±0.54)	90.38 (±4.67)	58.36 (±3.47)
tmax (min)	25	87.5	36.67	52.55	85

Table – IV: Average disintegration time (minutes) of different batches with six individual tablets and standard deviations

| | Average DT (min) of 6 tablets | | | | | | | |
Formulation	1	2	3	4	5	6	Average DT (min)	SD
FO1	20.35	21.23	23.38	24.89	27.53	34.15	25.26	5.06
FO2	38.06	39.11	42.89	43.33	44.67	46.22	42.38	3.18
FO3	4.88	5.47	5.98	6.44	6.99	7.87	6.272	1.07
FO4	1.94	2	2.06	2.06	2.06	2.11	2.038	0.06
FO5	2.8	3.55	3.82	4.94	6.57	7.82	4.917	1.93

The average thickness values of each tablet for five formulations were 3.5mm (Control), 4.0mm, 4.9mm, 5.6mm, and 5.9mm. Hardness data are 1.5-2.0kg (control, FO1), and 6-8kg, 5.5-6.5kg, 4.0-5.0kg, and 6.5-8kg for tablets of batches FO2, FO3, FO4, and FO5 respectively. Losses on friability are 0.11%, 0.62%, 1.14%, and 0.05% from four experimental formulations and 100% tablets were friable in case of control (FO1). Disintegration time (±SD) were 25.24 minutes (±5.08), 42.38minutes (±3.19), 6.27minutes (±1.07), 2.04minutes (±0.06), and 4.88minutes (±2.28) for tablets of batches FO1, FO2, FO3, FO4, and FO5 respectively.

Dissolution rates (±SD) at 30 minutes were 68.9% (±0.54), 60.0% (±4.55), 84.78% (±0.54), 90.38% (±4.67) and 58.36% (±3.47) of the five batches. In the Table – IV, the Disintegration times (DT) for each 6 tablet of different batches were shown.

In the Table–V, a profile of average dissolution rate at time interval 10, 15, 20, and 30 minutes are mentioned. Within 10 minutes, 71.85% DS was released from the formulation FO3 and 52.68% from FO1 (control), 27.15% from FO2, 28.51% from FO5. The release rate increase gradually with time and becomes maximum at 30 minutes.

Table – V: Dissolution rate (%) in simulated gastric fluid (0.1N HCl solution) of DS tablet at 10 to 30 minutes for different batches of tablets. The table also shows the correlation between changes of time with increasing % of release of active drug DS.

	Formulations				
Time (min)	FO1	FO2	FO3	FO4	FO5
10	52.68	27.15	71.85	28.51	36.55
15	68.16	33.33	74.73	86.2	32.85
20	74.77	39.89	73.08	73.13	42.89
30	68.92	59.87	84.78	90.38	58.36
r		0.1319	0.3952	0.7249	0.5394

Figure–1 shows FO1, the dissolution rate was below than that of FO2, where each tablets of FO1 contains 200mg Mg $(OH)_2$ and FO1 contains no. The dissolution rate decreases in FO3 and FO4 that contains 300mg and 350mg Mg(OH)2 respectively.
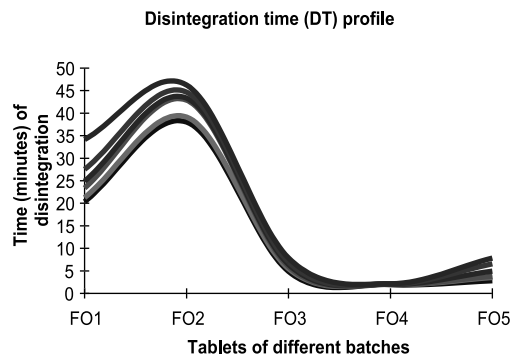

Disintegration time (DT) profile

Figure - 1: Average disintegration time of 1 to 6 diclofenac magnesium hydroxide tablets of five different batches.

Figure–2 shows the trend line that indicates lowest DT with maximum MH and vise versa. The dissolution rate of DS at different time period was determined and presented in Table – IV.

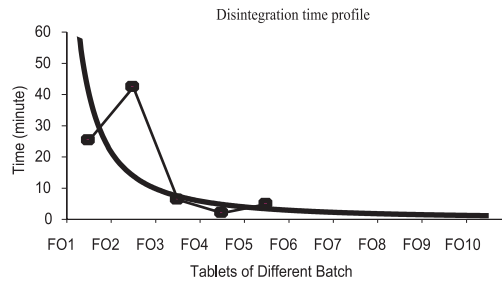

Disintegration time profile

Figure – 2: Trend line of disintegration time of diclofenac magnesium hydroxide plain tablets

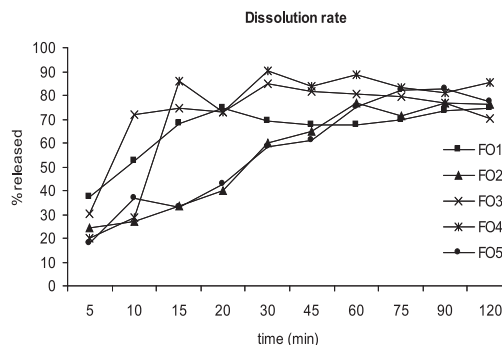Figure–3 is the schematic presentation for 6 formulations between % DS dissolved in SGF with times (min).

Dissolution rate

Figure - 3: Dissolution rate (%) diclofenac sodium from uncoated diclpfenac-antacid plain tablet : figure depicts the release rate (%) of diclofenac sodium at time 05 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, and 120 minutes.

Discussion

With the increment of any agent the average diameter (thickness) of tablet will be increased; thus average thickness increased 0.5mm, 1.4mm, 2.1mm and 2.4mm where MH increased in 200mg, 300mg, 350mg and 400mg in batches FO2, FO3, FO4 and FO5 respectively, it is rationale. A perfect positive correlation (r @1.0) between the changes of quantity of MH & average diameter (mm) of per tablet indicated

no variation of excipients present in batch-to-batch preparation. With the addition of MH, hardness increased (table 3) that indicated the binder quality of MH.. A strong negative correlation (r= -0.9) exists between the friability and dissolution rate of this study explains that the higher the rate of friability, the lower is the rate of dissolution. A correlation exists between friability, hardness and in-vitro dissolution rate[11]. And release characteristics vary considerably among different manufacturers and that even identical formulation. MH might have a positive impact on hardness and in our study it is evident by r=0.49, calculated between the hardness and disintegration time (Table-III). With time the rate of dissolution increases in SGF. Strong positive correlation (r= 0.725) between changes of time and rate (%) of release (Table-V) was observed in formulation FO4, containing 350mg experimental agent indicates the excellent combination of $Mg(OH)_2$ and starch . Levy & Hayes [12] stated that certain tablet formulations and processing factors apparently affect the dissolution rate of drug contained in the tablets. The DT 42.4min (±3.18), of FO2 is beyond the limit of standard specification which indicates poor combination of DS-MH. Average disintegration time was minimum and highly precise among the six tablets for batch FO4, as we see a sharp line in Figure-1 and parallel to x-axis (time-line) in Figure-3. The trend line of DT (Figure-2) shows that upon addition of MH disintegration time reduced dramatically. The trend line when is extrapolated prospectively to further formulations as shown up to 10 batches in Fig-2, considering the addition of rationale quantity of $Mg(OH)_2$; the DT value (min) wouldn't be increased. Starch is typically used in a concentration 5% to 20% of the tablet weight and as a convention starch 5% as disintegrating agent is recommended; and If rapid disintegration is desired this amount may be increased 10 or 15% [13]. The starch contents in our test products were within the range of 10-14.6% in the four

batches. As $Mg(OH)_2$ quantity increases the overall weight increases and thus, %age of starch is reduced (Table-II). Among tablets in this study with 10-11% starch showed excellent DT profile, that are present in FO3, FO4, and FO5 batches. Moreover, size of the tablets exposed to GSF may have contributory role in reduction of disintegration time of the three batches as with increasing size the exposing surface area increases. From the data stated in Table-V it is evident that because of MH in any quantity, the dissolution rates were not affected rather then improvement (Figure-3). The rate of absorption and availability of many drugs that are administered orally in solid forms are the functions of their rate of dissolution in gastro-intestinal fluids [14, 15]. The drug moieties, which are acidic in nature, absorb better in upper GIT [16] but one should not automatically expect a correlation between the disintegration time and dissolution rate and absorption through biological membrane. The researches conducted earlier demonstrated the possible variation of in-vitro dissolution of drug when composition of dosage form were altered [17, 18, 19]. This study showed diversified results but some were very much potential. It is established that the surface area of stomach is small compared to intestine (200m2), however some enteric coated preparation may resist dissolution in the intestine and very little portion of the drug is absorbed in gastric zone [20]. But release of active drug content at gastric zone instead of intestine will definitely provide additional area for absorption. Moreover, as of pH partition hypothesis [21] acidic drugs in acidic pH is favored the absorption; this is because of the fact that unionized portion of acidic drug will be predominating.

Diclofenac sodium is an acidic drug of pKa 4.0, and it is predicted that it will have favorable bio-availability profile if released at gastric zone. The standards limits of specification mentioned in this presentation indicate USP [22].

Conclusion

Not all, some DS-MH preparations of this study were potential and indicated that MH was the key players in improving the disintegration time dissolution profile. The excellent DT profile of batch FO4 having 50mg DS with 350mg MH should be one of the best candidates for further study.

However the formulation approach 'Diclofenac sodium - Magnesium hydroxide' (DS-MH) plain tablet with the intention to early disintegration and dissolution of active Diclofenac sodium, in gastric zone to provide rapid absorption hence fastest anti-inflammatory action with acid neutralizing benefits by MH, might be considered sincerely. Further, bioequivalence studies may be necessary for commercial standpoint.

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