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FORMULATION EVALUATION AND OPTIMIZATION OF NOVEL TABLET FOR COMBINATION THERAPY

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ABSTRACT

The main objective of the present research work was to develop a bilayer tablet of famotidine (FMT) and diclofenac sodium (DS) in separate layers thus to maximize the efficacy of both drugs in combination for the effective treatment of joint pain. Famotidine layer was formulated as fast release layer and DS layer was formulated as sustained release layers. Composition of both the layers was optimized in a separate set of experiments and then formulated as bilayer tablet. The individual layers as well as the bilayer tablets were evaluated for *in vitro* dissolution behavior. Kinetic studies of an optimized (D10) batch of DS in both sustained release layer and as bilayer tablet has shown good linearity of regression coefficient 0.9773 (first order equation). The results reveal that an optimized immediate release layer (F5) of famotidine and a sustained release layer (D10) of diclofenac sodium might be suitable for the treatment of joint pain by sequential release of the two drugs in a bilayer tablet.

Key Words:- Bilayer tablet, Diclofenac sodium, HPMC K100M, Famotidine.

INTRODUCTION

Bilayer tablets are prepared with one layer of one drug for immediate release with a second layer designed to release a second drug later, either as second dose or in an extended release manner. Bilayer tablets are suitable for the sequential release of two drugs in combination, to separate two incompatible drugs, and also for sustained release tablets, in which one layer is for immediate release as initial dose and second layer is a maintenance dose (Gunsel WC, 1989; Shiyani B *et al*., 2008). Joint pain is moderate to severe intensity associated with gastrointestinal (GI), neurological, and autonomic symptoms. Therefore, in joint pain, a combination of pretreatment with antacid for example, Famotidine (FMT) 15 to 30 min prior to abortive therapy of a non-steroidal ant i- inflammatory drug (NSAID) such as diclofenac sodium (DS), is required for symptomatic treatment, in cases when nausea and vomiting are severe. In addition to its antacid effect, the prokinetic agent FMT is more effective to counteract gastric stasis associated with migraine and enhances the rate of absorption of the NSAID. The main rationale behind the development of a bilayer tablet of FMT (immediate release layer) and DS (sustained release layer) is that after oral administration of DS, well over 60% of the dose is absorbed from the GI tract (mainly the intestine) (Wells BG *et al*., 2006). DS has shorter plasma half-life (1–1.5 h), thus a sustained release formulation is preferred to prevent frequent administration.

The combination of FMT and DS into a single tablet is preferred by patients for the treatment of joint pain. An immediate release formulation of FMT allows immediate action of this active ingredient and enhanced absorption of NSAID agents, whose absorption is slower due to gastric stasis, especially in joint pain. FMT is one of the more potent antacid drugs, which apparently

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antagonizes H2 Receptor. FMT is used at low doses (i.e., 10 mg) and has a half-life of 5 h and a bioavailability of about 76%. Thus, FMT increases the absorption of concomitantly administered NSAIDs, whose absorption would be less due to the gastric stasis that occurs in joint pain. Thus, it is required to formulate FMT in immediate release layer (Pitre D, Stradi R, 2009) if it is used for this purpose. DS, or 2-[(2,6-dichlorophenyl) amino] benzene acetic acid monosodium salt, is a NSAID having potent anti-inflammatory, analgesic, and antipyretic effects. It is an inhibitor of prostaglandin synthetase. It has an unpleasant taste and causes gastric irritation. DS is mainly absorbed from the gastrointestinal tract. Chemically, DS is a phenyl acetic acid derivative with a pKa value of 4.0; it is practically insoluble in acidic solution but dissolves in intestinal fluid and water. The maximum average concentration in blood is between 0.7 and 1.5 mg/L after a dose is taken. The oral bioavailability is around 60% with an excretion half-life between 1.1 and 1.8 h. Thus, sustained release formulations are preferable to avoid frequent administration. Combining FMT and DS maximizes the drugs' potential for the treatment of joint pain (Adeyeye CM, Li P, 2001; Martindale, 2002; Goodman and Gillman's, 1996; Bagul US *et al*., 2006; Acıkgo ZM *et al*., 1994).

In this study, an immediate release layer of FMT was formulated with various superdisintegrants like HPMC K100 M. A sustained-release layer of DS was formulated by using a hydrophilic matrix (HPMCK100M). The effect of hydrophilic polymer (HPMC K100M) concentration was studied on in vitro release of DS from hydrophilic matrix. The aim of the present study was to design and evaluate a bilayer tablet to avoid chemical incompatibility between FMT and DS, in which the immediate release layer was fabricated to release the FMT within 30 min in the stomach, followed by sustained release of DS in the small intestine.

MATERIALS AND METHODS

Materials

Famotidine was obtained as a gift sample from Ipca Laboratory (Mumbai, India). Diclofenac sodium was obtained as a gift sample from Merck Pharmaceutical (Mumbai, India). HPMC K100 M, carbopol 934, magnesium stearate, colloidal silicone-dioxide and microcrystalline cellulose were procured from S.D. Fine chemicals Mumbai, India. All reagents used in these experiments were of analytical grade.

Methods

Preparation of Immediate Release Tablets of FMT

FMT, HPMC K100 M and Car 934 were mixed with super disintegrants for 15 min in a porcelain mortar and passed through a #60 sieve. The blend was mixed with colloidal silicon dioxide and magnesium stearate for 5 min and processed for direct compression by using a 7 mm round flat-faced punch rotary tablet machine (Minipress I, Karnavati Eng, Mehsana, Gujarat, India). Compression force was kept constant for all formulations. Superdisintegrants were used up to 8% in tablets. Compositions of the all batches are represented in Table I.

Preparation of Sustained Release Tablets of DS

Sustained release tablet was prepared by direct compression method. Initially DS and HPMC K100M were mixed together in poly bag then MCC was added and mixed for 5 min in a porcelain mortar. Then magnesium stearate and colloidal silicon dioxide was added and mixed for 5 min in a porcelain mortar and processed for direct compression by using 9 mm round flat-faced punch of a rotary tablet machine. Compositions of all batches are represented in Table II.

Preparation of Bilayer Tablets of FMT and DS

An optimized batch of FMT (batch F5) and DS (batch D10) was selected for formulation of the bilayer tablet. As a previously reported procedure, the powder blend of FMT and the DS layer were prepared separately. Initially the powder blend of a sustained release layer (batch D10) was filled in the die cavity of the rotary tablet machine and compressed one time by giving a single rotation, then the immediate release layer (batch F5) was filled over the sustained release compressed layer and both layers were compressed to form bilayer tablet through direct compression by using the 9 mm round flat-faced punch of the rotary tablet machine. Composition of the optimized batch of bilayer tablets is represented in Tables I.

Evaluation of the FMT Tablet

The tablets were evaluated for *in vitro* dissolution study by using USP type II dissolution apparatus. In addition to this the fast release tablets of FMT were evaluated for wetting time and maximal water uptake capacity

In Vitro Dissolution Tests

Dissolution tests of FMT tablets were performed using simulated gastric fluid with USP dissolution apparatus II at 50 rpm and 37 $\pm$ 0.5 °C. A test sample (5 ml) was withdrawn at particular time intervals (5, 10, 15, 30, 45, and 60 min) and replaced with fresh dissolution media maintained at 37 $\pm$ 0.5 °C. The test sample was filtered (membrane filter, 0.45 µm) and the concentration

of dissolved drug was determined using a UV spectrophotometer at λ max 273 nm. This test was performed on six tablets and the mean ± SD calculated.
The *in vitro* dissolution studies for SR tablets of DS were carried out using USP apparatus type II at 50 rpm. The dissolution medium (900 mL) consisted of simulated gastric fluid (pH 1.2 HCl buffer) was used for the first 2 h and then replaced with phosphate buffer (pH 6.8) for 3 to 12 h (900 ml), maintained at 37 ± 0.5 °C. The drug release at different time interval was measured by UV-visible spectrophotometer at 276 nm. The release studies were conducted on six tablets in each batch, and the mean values were plotted versus time ± SD.

Wetting Time

The tablet was placed at the centre of two layers of absorbent paper fitted into petri dish. The absorbent paper was thoroughly wetted with simulated gastric fluid; excess fluid was completely drained out of the petri dish. The time required for the fluid to diffuse from the wetted absorbent paper into the entire tablet was recorded using a stopwatch. This test was performed in triplicate and mean ± SD calculated (Mutasem M, Rawas Q, 2006).

Maximal Water Uptake Capacity

A modified method and apparatus were used for the water uptake study. The apparatus consisted of a sample holder and a liquid holding vessel (petri dish) set on an electronic digital balance. The tablet was placed into perforated sample holder, then fluid was passively withdrawn in to the tablet. The loss of weight from the liquid holder was noted from the digital balance. The test was performed in triplicate. All results were reported as mean ± SD (Zhao N, Augsburger LL, 2005).

Drug Release Kinetics

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order, first order and Higuchi's model.

RESULTS AND DISCUSSION

FMT was formulated as immediate release layer using HPMC K100 M and CARBOPOL 934.. Higher swelling and hydration capacity of Carbopol 934 lead to faster disintegration of batch F5. The results of disintegration and dissolution tests of all batches (F1–F6) demonstrated that batch F5 containing Carbopol 934 released 100% drug within 15 min. This is required for the sequential release of FMT in the combinatorial treatment of joint pain as well as it treat the acidity. The pre-compression and post-compression parameters of the immediate release layer indicate that batch F5 was suitable for bilayer preparation. DS is a weak acid (pKa 4.01), making it more soluble in basic conditions (unionized condition). Hence, DS was formulated as sustained release layer by using hydrophilic matrix polymer HPMC K100M. Composition of FMT Immediate Release Tablet (Values Represented in Milligrams)

Drug Release Kinetics

The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (R2) was determined. It was found that the in vitro drug release of the DS sustained release tablet was best explained by first-order equation (R2 ± 0.9773) and Higuchi's equation (R2 ±0.9772).

Preparation of Diclofenac Sodium

Sustained release tablet was prepared by direct compression method. Initially DS and HPMC K100M were mixed together in poly bag then MCC was added and mixed for 5 min in a porcelain mortar.

Drug Release

Drug release from the optimized batch (D10) was found follow first-order kinetics. It can also be proved from the Korsmeyer Peppas equation; the n values are in between 0.45– 0.59, indicating that the release seemed to be predominantly a diffusion-controlled mechanism. The results of regression values of first-order and Higuchi equations in drug release kinetics of optimized batch D10 was revealed that D10 follows a diffusion mechanism. Generally HPMC polymers show a diffusion mechanism, but the above results indicate a predominantly diffusion-controlled mechanism (Avachat A, Kotwal V, 2007).

Dissolution test of DS sustained release tablet batches D1–D10 to compression, the blend of all batches of FMT and DS were evaluated for various pre-compression parameters such as angle of repose, bulk density (i.e., lose bulk density, tapped bulk density), compressibility index, and Hauser's ratio. Results showed that all parameters were within limits. Hauser's ratio 1.25 for both optimized batches indicated good flow properties. The results of all the batches of both FMT and DS are shown.

***In Vitro* Dissolution Test**

Dissolution study data demonstrated that as the amount of HPMC K 100M decreased, the release of drug from the matrix increased. DS is a weak acid (pKa _ 4.01), making it more soluble in basic conditions. All studied parameters indicated that batch D10 was suitable as a sustained release layer for the preparation of a bilayer tablet. The graphical representations of dissolution study

of all batches are represented in Figure. The dissolution profile of all batches showed almost 99–100% drug release within 30 min, except the F5 batch showed 100% release within 15 min, as represented in Figure 3. Cumulative percent of drug released at 5, 10, and 15 min showed positive correlation between the maximal water uptake and the cumulative percent of drug dissolved at 5, 10, and 15 min. Higher water uptake leads to faster disintegration and dissolution of tablets. Wetting time of tablet was in the following decreasing order HPMC K100 M. Above all studied parameters indicated batch F5 was suitable as an immediate release layer for preparation of the bilayer tablet.

Evaluation of the Bilayer Tablet of FMT and DS

The parameters of the bilayer tablet such as weight variation, thickness, hardness, friability, and drug content were checked and are represented in Table V. Weight variation of the bilayer tablet (308.57 _ 5.72mg) was found to be within limits (100 _ 5%). Friability of the bilayer tablet (0.40%) was found to be less than 1%. Hardness was found to be 4.58 kg/cm2, and thickness variation (4.30 _ 0.14) was found to be less than 5%.

Dissolution of FMT and DS bilayer tablet

Bilayer tablet was found to be 101.2 _ 0.80 and 100.70 _ 0.58, respectively. The disintegration time (25 _1.3 s) of six tablets of the optimized batch was found to be same as that of immediate release FMT tablet.

***In Vitro* Dissolution Test**

The dissolution study suggested that FMT was released within 10 min in simulated gastric fluid, while DS was released in much smaller amount (1.71–1.91%) within 2 h. Subsequent to replacing media with phosphate buffer (pH 6.8), DS dissolution was found to be increased. The graphical representations of cumulative percent drug release vs time lot for FMT and DS in bilayer tablets are represented in Figure 1.

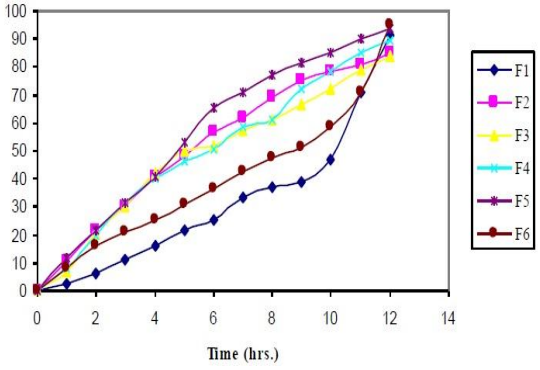
Stability Study of the Bilayer Tablet

Bilayer tablets in 1, 2, and 3 month stability studies were evaluated for properties like weight variation, friability, hardness, thickness, drug content, and disintegration; they followed pharmacopoeial limits, as shown in Table V. The results of stability study indicate that no change was found in percent cumulative release from the bilayered tablet, as represented in Figures 2.

Table 1. FMT indicates Famotidine

Ingredients	F1	F2	F3	F4	F5	F6
Famotidine	40	40	40	40	40	40
HPMC k100 m	30	50	-	-	-	-
Carbopol 934	-	-	30	50	-	-
Sod. Bicarbonate	12	12	12	12	12	12
Citric acid	12	12	12	12	12	12
Lactose	36	16	36	16	36	16
PVP k30	15	15	15	15	15	15
Talc	2	2	2	2	2	2
Mg.sterate	3	3	3	3	3	3
Binder (EC)	5% solution of EC in IPA					
Total	150	150	150	150	150	150

Figure 1. Cumulative % drug release for tablet bilayer



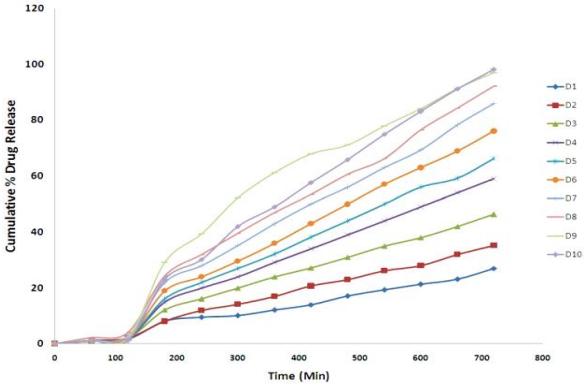
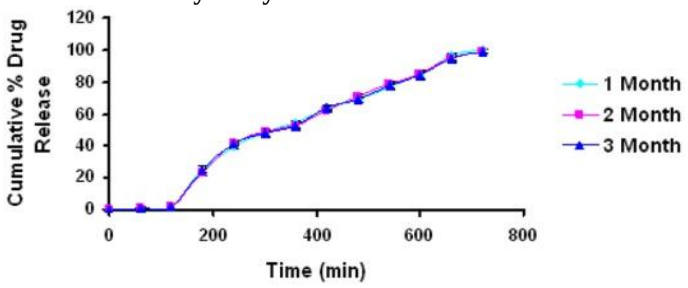


Figure 2. Dissolution test of DS bilayer tablet before and after stability study



CONCLUSION

We have developed a bilayer tablet with an optimized immediate release layer of FMT and a sustained release layer of DS. The tablet shows satisfactory pre and post-compression parameters. Our data shows that bilayer tablets of FMT and DS might be a suitable treatment for joint pain because they allow sequential release of the two drugs. The aim of the present study is to formulate and evaluate the combination therapy for the diseases like joint pain and acidity.

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