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Research paper

Formulation and Evaluation of Combined Dosage Form of Diclofenac Sodium (Mini Tablet) and Omeprazole Sodium in Capsule Devices

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ABSTRACT

The work investigates the formulation and evaluation of combined dosage form of diclofenac sodium (mini tablet) and omeprazole sodium in capsule devices. The design of effective and safe drug delivery systems has become an integral part for the development and formulating of new medicines. So, research continuously keeps on searching for new ways to deliver drugs over a long period of time or for a well-controlled release profile, to minimizing the loss of drug, to reduce the side effect. The continuous release mini matrix tablet of diclofenac sodium prepared by wet granulation using HPMC, the patients at risk for ulcer disease who require treatment for arthritis receive nonsteroidal anti-inflammatory drugs (NSAIDs) that are selective for cyclooxygenase-2 or the combination of a nonselective NSAID with a proton-pump inhibitor. We assessed whether celecoxib would be similar to diclofenac plus omeprazole in reducing the risk of recurrent ulcer bleeding in patients at high risk for bleeding.

Keywords: *Diclofenac sodium; Omeprazole sodium; Controlled release; Ulcer disease; Arthritis; NSAID; Proton-pump inhibitor*

Introduction

Rates of ulcer perforation, hospital admission, and death are usually regarded as the best available measures of the frequency of severe peptic ulcer disease. Overall admission rates have tended to decline, which almost certainly reflects the widespread adoption of effective outpatient therapy. The overall incidence of ulcer perforation and death may also have fallen. Bleeding and perforation are common, may occur in the absence of warning symptoms, and are associated with a high mortality rate. In some countries, other factors, including smoking and diet, may be equally important. It is difficult to determine the relative contribution of each factor, though the widespread perception that the gastrointestinal tolerance of NSAIDs is poor, particularly in the elderly, may be well founded. In the United States, an estimated 107,000 patients are hospitalized and 16,500 die each year as a result of NSAID-related ulcer complications [0]. Current evidence indicates that concurrent therapy with NSAIDs and proton-pump inhibitors or misoprostol reduces the risk of ulcers and ulcer complications. Because proton-pump inhibitors are well tolerated, their use as prophylaxis has been recommended for patients at high risk for ulcer complications. However, lack of compliance may limit the usefulness of this strategy, especially in elderly people who are already receiving multiple drugs [2].

Whether COX-2–selective NSAIDs are similar to the combination of a nonselective NSAID plus a proton-pump inhibitor for patients at high risk for ulcer complications has not been investigated. Sustained release (SR), Controlled release (CR) pharmaceutical products have increasingly gained medical acceptance and popularity. Regulatory approval for marketing and their pharmaceutics advantage and clinical benefits over immediate release pharmaceutical products have been increasingly standard. The controlled release formulation overcome many of the drawback (Figure 1) [3].

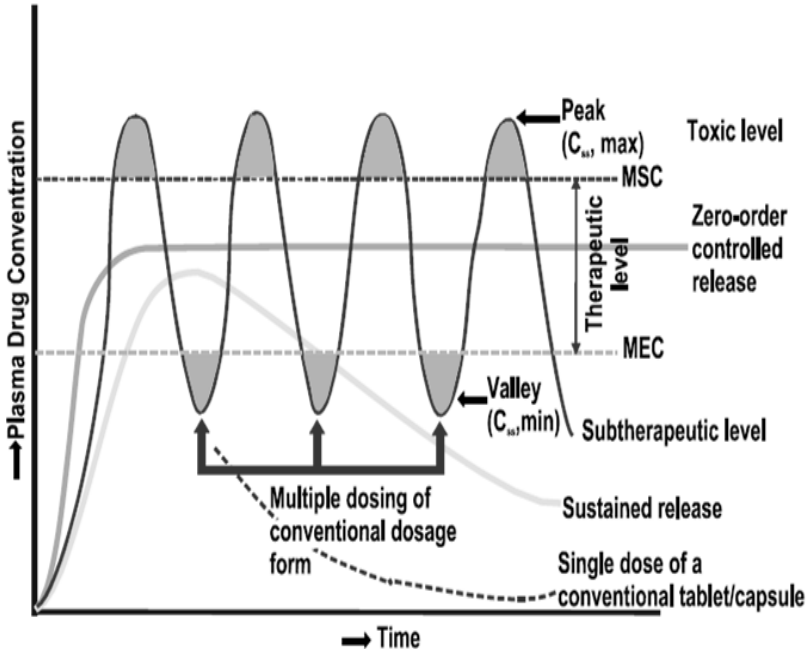

Figure 1: Plasma drug concentration time profile.

Materials and Methods

Diclofenac sodium, Omeprazole sodium pellet were procured from R. K. Enterprises, Meerut. Hydroxy propyl methyl cellulose, Polyvinyl Pyrrolidone, Microcrystalline Cellulose, Aerosol, Magnesium stearate were procured from Central Drug House, India and Empty Hard Gelatin Capsule Shell were procured from Biogem Healthcare, India.

Preparation of Sustained Released Diclofenac Sodium:

Matrix tablets each containing 50 mg of Diclofenac sodium were prepared by wet Granulation method. The tablets prepared were as per the formulations given in the Table 2. In the formulations of sustained release mini tablet of diclofenac sodium HPMC (10%, 50%, 80%) and PVP K30 (level 55%, 56%, 58%.) were used taken accurately and blended thoroughly. The blend was moistened with distilled water to get moist mass. The moist mass was then passed through sieve no 30 and the granular mass found were dried in hot air oven at 60ºC for 1hr.The dried granules were passed over sieve no 50 to get free flowing and uniform sized granules. The granules were lubricated with aerosol and magnesium stearate were additional which is previously passed through sieve no 100.

The resulting combination was compressed by Cadmac single station tablet punching machine to a hardness of 7.5-8 kg/sq.cm using flat punches [4,5].

Preparation of enteric coated Omeprazole Sodium pellets

Enteric coated Omeprazole a pellet was directly purchased from R. K. Enterprises, Meerut.

Filling the Diclofenac Sodium tablet and Omeprazole Pallets in capsule shell

The one mini-tablet of 50 mg diclofenac sodium sustained release and 20 mg of Omeprazole pallets were filled in a capsule shell (Size 0) to form caplet.

Results

Characterization of granules:

The results are shown in tables 2 and 3.

Table 1: Formula for sustained release mini tablet of diclofenac sodium.

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Diclofenac Sodium	60	60	60	60	60	60	60	60	60
HPMC	24	24	24	48	48	48	72	72	72
PVP	7	12	16	7	12	16	7	12	16
MCC	66	61	57	57	42	37	18	14	9
Aerosol	2	2	2	2	2	2	2	2	2
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Total Weight	160	160	160	160	160	160	160	160	160

Table 2: Pre-compression study of granules.

Formulation Code	**Bulk Density (gm/cm3) Mean±SD**	**Tapped Density (gm/cm3) Mean±SD**	**Hausner Ratio (Hr) Mean±SD**	**Carr's Index (%) Mean±SD**	**Angle of Repose (Ɵ) Mean±SD**
F1	0.59±0.012	0.66±0.01	1.15±0.01	12.24±1.52	21.7±0.18
F2	0.52±0.015	0.60±0.01	1.23±0.02	10.19±1.85	19.3±0.22
F3	0.58±0.010	0.64±0.02	1.17±0.01	14.63±0.98	24.9±0.77
F4	0.54±0.007	0.62±0.01	1.13±0.02	10.15±1.07	19.7±0.42
F5	0.57±0.010	0.62±0.02	1.15±0.02	13.83±1.23	21.4±0.82
F6	0.51±0.017	0.65±0.02	1.18±0.01	9.13±0.58	18.7±0.24
F7	0.57±0.010	0.65±0.01	1.14±0.01	11.65±1.17	20.5±0.42
F8	0.58±0.017	0.62±0.02	1.11±0.01	10.09±0.22	19.9±0.50
F9	0.53±0.015	0.64±0.01	1.16±0.02	14.19±1.74	52.8±0.23

Table 3: Post compression evaluation parameter.

Formulation Code	**Thickness (mm)**	**% Drug Content**	**Average Weight Variation (n=20)**	**Hardness (Kg/cm^2)**	**% Friability**
F1	5.06 ± 0.425	97.057 ± 0.355	160.03 ± 0.227	6.5 ± 0.099	0.11 ± 0.01
F2	5.13 ± 0.057	98.89 ± 0.589	158.8 ± 0.135	6.23 ± 0.578	0.15 ± 0.01
F3	5.13 ± 0.115	97.00 ± 0.987	161.7 ± 0.642	6.12 ± 0.996	0.42 ± 0.01
F4	5.03 ± 0.254	98.12 ± 0.987	160.26 ± 0.275	6.78 ± 0.587	0.47 ± 0.02

F5	5.06 ± 0.607	98.25 ± .0987	161.16 ± 0.546	6.58 ± 0.687	0.24 ± 0.02
F6	5.14 ± 0.157	96.65 ± 0.974	161.3 ± 0.223	6.48 ± 0.124	0.19 ± 0.01
F7	5.2 ± 0.997	96.94 ± 0.658	158.46 ± 0.716	5.5 ± .092	0.29 ± 0.02
F8	5.23 ±0.057	97.58 ± 0.658	161.79 ± 0.185	7.26 ± 0.658	0.20 ± 0.01
F9	5.23 ± 0.057	99.89 ± 0.651	161.79 ± 0.782	7.12 ± 0.528	0.38 ± 0.02

***In-vitro* release profile of diclofenac sodium in pH 6.8 phosphoric buffer**

The *in-vitro* dissolution of all the 9 batches of diclofenac sodium sustained release mini-tablets were accepted out and the outcome are given in table 4.

Table 4: In-vitro drug release data of diclofenac sodium in pH 6.8 phosphoric buffer.

Time (hrs)	**Percentage (%) Drug Release**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	1.94 ± .0124	1.78 ± .098	3.27 ± 0.10	1.94 ± .068	1.74 ± .068	1.62 ± .89	2.89 ± .054	2.12 ± .014	1.95 ± 0.58
4	22.71 ± .059	22.87 ± .067	22.98 ± 0.03	22.70 ± .068	22.58 ± .29	22.82 ± .088	23.78 ± .457	21.65 ± .078	22.78 ± 0.147
8	60.5 ± .087	61.97± .024	62.96 ± .052	60.81 ± .078	60.00 ± .689	62.43 ± .057	60.14 ± .45	61.28 ± .87	62.31 ± 0.58
10	77.43 ± .054	78.66 ± .147	83.50 ± 0.40	77.43 ± .067	78.24 ± .987	78.62 ± .98	77.25 ± .36	81.68 ± .258	80.25 ± 0.47
12	93.24 ± .064	92.31± .068	97.84 ± 0.63	92.24 ± .058	92.02 ± .54	96.08 ± .12	93.47 ± .19	94.57 ± .64	91.00 ± 0.47

***In-vitro* release profile of Omeprazole sodium in 0.1N HCl**

The *in-vitro* dissolution of all the 9 batches of Omeprazole sodium enteric coated pellets were accepted out and the outcome are given in table 5.

Table 5: In-vitro drug release data of Omeprazole sodium in 0.1 N HCl.

Time (hrs)	**Percentage (%) Drug Release**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
2	2.56 ± .016	1.99 ± .058	1.17 ± .009	2.13 ± .079	2.55 ± .070	2.10 ± .21	1.78 ± .090	1.62 ± .057	1.39 ± .69

***In-vitro* release profile of Omeprazole sodium in pH 6.8 phosphoric buffer**

The *in-vitro* dissolution of all the 9 lots of Omeprazole sodium enteric coated pellets were known out and the outcome are given in table 6.

Table 6: In-vitro drug release data of Omeprazole sodium in pH 6.8 phosphoric buffer.

Time (hrs)	**Percentage (%) Drug Release**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	91.66 ± .056	90.34 ± .088	93.07 ± .018	89.03 ± .127	90.88 ± .080	92.05 ± .076	90.22 ± .120	91.68 ± .099	91.39 ± .38

Comparative *In-Vitro* Dissolution Study of Diclofenac Sodium from Tablet and Caplet of F3 Batch

In this relative *in-vitro* dissolution study of tablet and caplet of F3 batch was done for defining the result of Omeprazole sodium on dissolution of diclofenac (Table 7).

Table 7: Drug Release of Diclofenac Sodium from F3 Batch of Tablet and Caplet.

Time (hrs)	Diclofenac Sodium Release from Tablet (F3)	Diclofenac Sodium Release from Caplet (F3)
1	3.27	2.52
4	22.98	26.82
8	62.96	61.96
10	83.91	83.98
12	97.84	98.99

Discussion and Conclusion

The goal in development of caplet is to develop systems that are safe, reproducible and effective. Combination of diclofenac sodium sustained release [DIC-SR] and Omeprazole sodium-enteric coated [EC] was designed developed for the minimizing the gastric side effect as well as decreasing the frequency of drug administration because diclofenac sodium has short half-life [6,7]. DIC-SR matrix was formulated by wet granulation method using HPMC polymer to release drug over 12 hrs. The concentrations of HPMC were evaluated at levels of 10%, 50%, 80% and PVP K-30 level of 55%, 56%, 58% were used.

The diclofenac sodium showed the peak at λ max 276 nm and the omeprazole sodium showed the peak at λ max 302 nm, which confirms the presence of diclofenac. The prepared mini-tablets were evaluated for number of parameters like thickness, weight variation, hardness, friability, drug content and in-vitro drug release studies.

All the batches of tablet were found to be under the acceptable range in pharmacopoeia limits. The in vitro drug release study of prepared diclofenac mini-tablet was done for 12 hours (USP dissolution rate test apparatus-II, 50 rpm, 37ºC ±0.5ºC) using phosphate buffer, pH 6.8 as a dissolution medium (900ml). The maximum drug release was found to be 97.84% over the period of 12 hrs.

The in vitro drug release study of enteric coated Omeprazole pallets was done in 0.1N hydrochloric acid for first 2hrs (USP dissolution rate test apparatus-I, 100 rpm, 37ºC ±0.5ºC) phosphate buffer, pH 6.8 as a dissolution medium (900ml) for the next 1 hr. In 0.1N HCl Omeprazole sodium percentage drug release was found less than 10%. The maximum drug release was found to be 1.17% in acidic medium and 93.07% in buffer medium.

Consent for Publication

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

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