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Formulation and In-vitro Evaluation of Bilayer Tablet of Pantoprazole Sodium and Diclofenac Sodium for NSAIDs Induced Gastrointestinal Side effects

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Abstract:- The aim of the present study was to develop and evaluate a bilayer tablet of pantoprazole and diclofenac sodium for immediate and sustained release, targeting a pharmacokinetic profile that reduces pain and side effects associated with NSAIDs. A 2^2 factorial design was employed, utilizing different polymer concentrations. The results showed that hollow beads containing diclofenac sodium exhibited excellent buoyancy in the acidic environment of the stomach. The immediate-release layer of pantoprazole sodium and sustained-release layer of diclofenac sodium were prepared using the wet granulation method. The prepared layers were evaluated for hardness, thickness, weight variation, friability, drug content, and in vitro disintegration time, all of which were within acceptable pharmacopeial specifications. The HPMC matrix's enhanced buoyancy makes it an excellent candidate for intragastric floating drug delivery, slowing down gastric emptying. Overall, the buoyant granules provided a lag phase while demonstrating gastroretention, beneficial for treating gastroesophageal acidity.
Key Words: Gastroretenstion, HPMC, factorial design, buoyancy

Introduction: - NSAIDs can cause serious side effects, including stomach ulcers and bleeding, stomach problems, pain, constipation, diarrhoea, Acidity, nausea, and peptic ulcers. Adults over 65 are particularly susceptible to stomach bleeding and ulcers. To mitigate these risks, strong proton pump inhibitors (PPIs) like pantoprazole and omeprazole are often prescribed. Conventional NSAID formulations, such as sustained-release (SR) diclofenac sodium, can cause severe ulceration when administered in doses of 75-100 mg/day. Therefore, concurrent use of PPIs is recommended to prevent excessive stomach acid production.

Oral drug delivery is the most preferable and flexible route, ensuring patient compliance. Sustained-release formulations consider various factors, including pH, transit rate, enzyme systems, and dosage form. Dissolution and diffusion mechanisms control the slow release of the drug in the gastrointestinal tract (GIT). Ideally, sustained-release formulations should follow zero-order kinetics to achieve a consistent blood level time profile, like intravenous administration. In this study following steps are involved to develop a bi-layer tablet formulation and evaluate of diclofenac sodium and pantoprazole sodium using different polymers &investigate the sustained-release effect through in vitro dissolution testing. It is an economical method for manufacturing bi-layer diclofenac sodium and pantoprazole sodium tablets.

Methods and Materials: - Preformulation may be defined as to investigate physical and chemical parameter of drug and excipients. These studies for Diclofenac sodium and Pantoprazole sodium include tests for identification, calibration curve and other studies. There were carried out and compared with the specifications as per the pharmacopeia and other official Books.

Formulation of bilayer tablet can be divided into following parts;

(a) Formulation and evaluation of immediate release of Pantoprazole granules with sodium starch glycolate using wet granulation method.
(b) Formulation and evaluation of immediate release of Pantoprazole granules with Cross Carmillose using wet granulation method.
(c) Formulation and evaluation of sustain release of diclofenac sodium granules with HPMC using wet granulation method
(d) Formulation of bilayer tablet by compression of immediate release and sustain release granules.

I. **Formulation and evaluation of immediate release bland of Pantoprazole sodium**: - Immediate release granules of Pantoprazole sodium are prepared by wet Granulation method. Weigh Pantoprazole sodium 20 mg and added excipients including diluent and disintegrate and mix it properly use binder solution screening through sieve # 8-12 and prepare dough and dry in drier up to 60°c again screening through sieve #20-25 and prepared granules.

II. **Formulation and evaluation of sustain release bland of diclofenac sodium**: - Sustain release granules of sodium are prepared by wet Granulation method. Weigh diclofenac sodium (75 mg) and added excipients including diluent and disintegrate and mix it properly use binder solution screening through sieve # 8-12 and prepare dough and dry in drier up to 60°c again screening through sieve #20-25 and prepared granules.

Compositions of Pantoprazole sodium immediate release granules: -

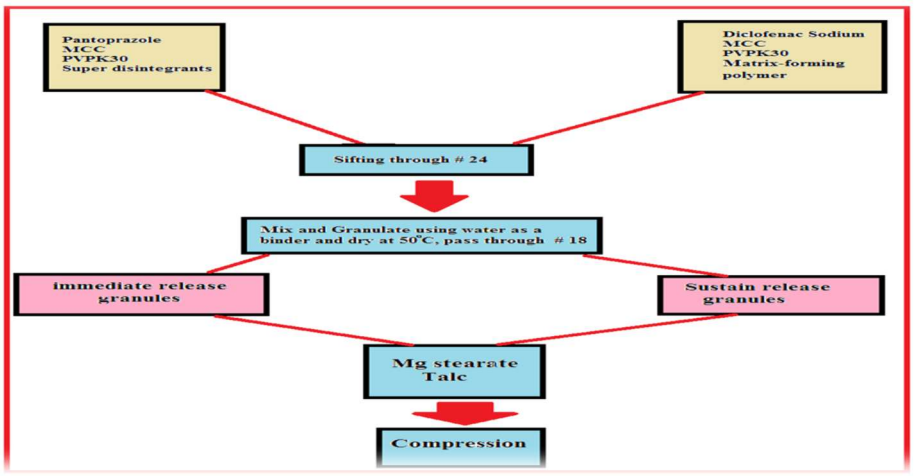
Ingredients	F_1	F_2	F_3	F_4
Pantoprazole	20	20	20	20
SSG	-	10	-	40
CC	2.5	-	25	-
MCC	412.5	405	390	375
PVPK30	15	15	15	15

Compositions of Pantoprazole sodium immediate release granules

Compositions of Diclofenac Sodium for sustain release: -

Ingredients	F_1	F_2	F_3	F_4
Diclofenac sodium	75	75	75	75
HPMC K_4M	-	40	-	80
HPMC $K_{100}M$	40	-	80	-
MCC	320	320	280	280
PVPK30	15	15	15	15

Compositions of Diclofenac Sodium for sustain release



Result and Discussion: -

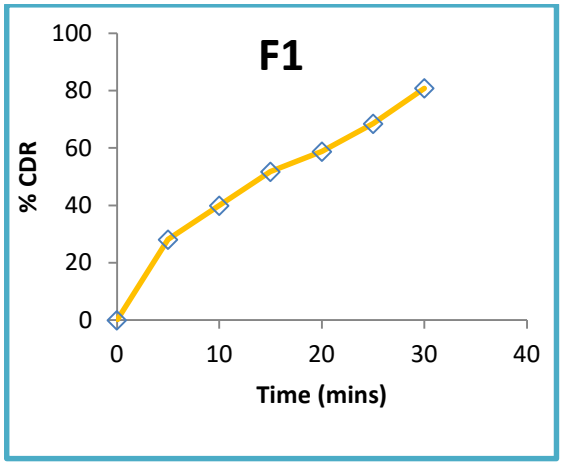
I. **Evaluation test of Granules: -** To assess physicochemical properties and release characteristics of the granular blend, Preformulation included bulk density, tapped density, angle of repose, compressibility index, Harsner's ratio.

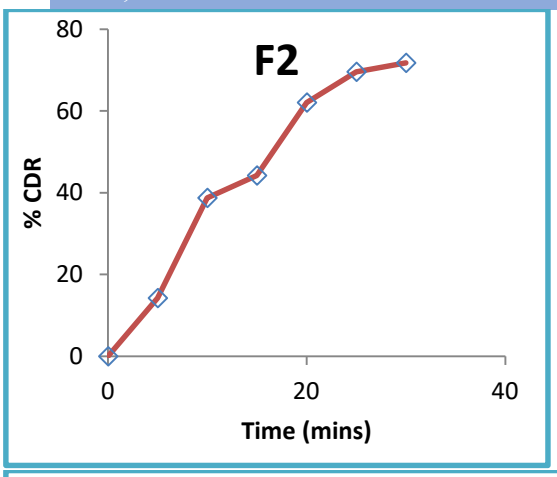
Formulation	Bulk density	Tapped density	Horne's ratio	Compressibility index	Angle of repose	Flow Character
F_1	0.4	0.416	0.961	3.8	24.44	Excellent
F_2	0.476	0.5	0.952	4.8	14.03	Excellent
F_3	0.5	0.526	0.950	4.94	12.52	Excellent
F_4	0.434	0.5	0.868	13.2	12.80	Excellent

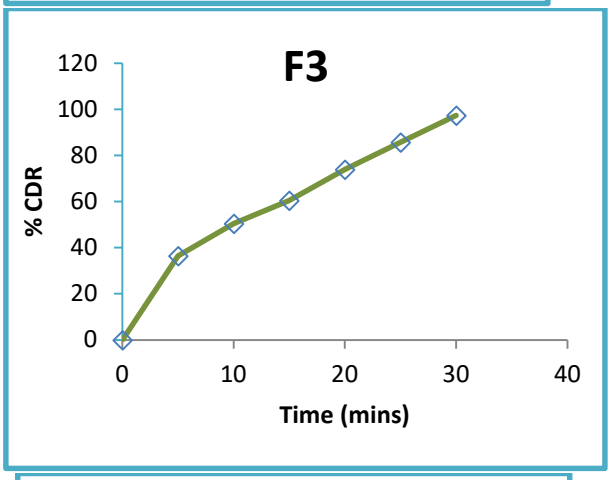
Table 6.6 Evaluation test of pantoprazole Granules

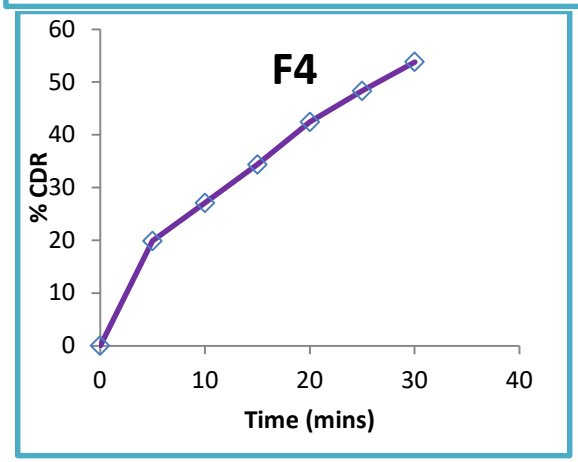
Post Compression study of bilayer tablet:-

1. **Dissolution of IR layer of Pantoprazole sodium:**

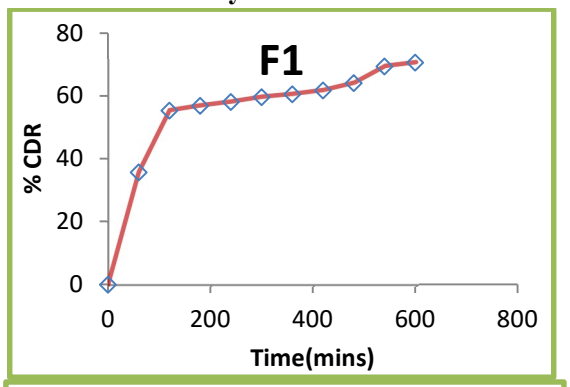


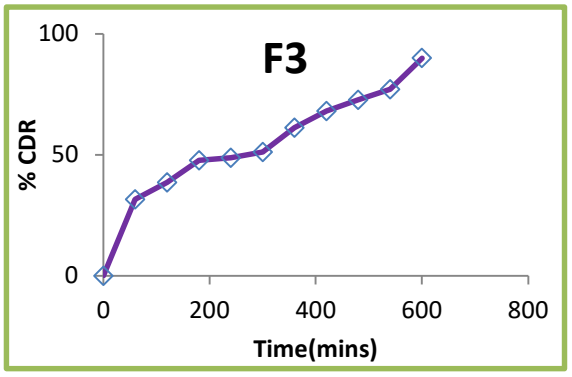

F2
% CDR
Time (mins)
0
20
40
60
80

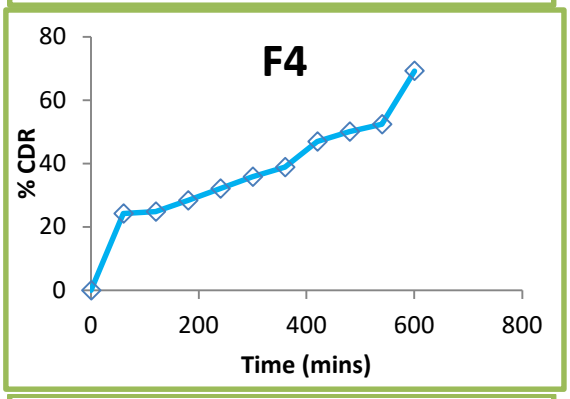

F3
% CDR
Time (mins)
0
10
20
30
40
80
100
120

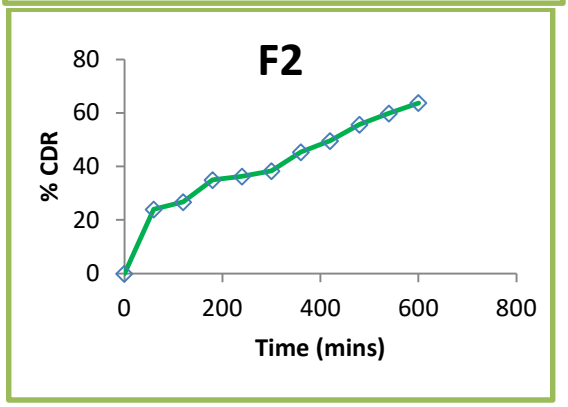

F4
% CDR
Time (mins)
0
10
20
30
40
50
60

Dissolution of SR layer of Diclofenac Sodium:-









All the formulations satisfactorily showed drug release of more than 60%. The formulation F3 showed the best drug release (90% in pH 6.8) on the other side the formulation F3 of Pantoprazole sodium IR also showed the resembling drug release (97% in pH 1.2) when compared to the best drug released formulation.

For mul atio ns	B u l k D e n	T a p p e d D	H au sn er ’s ra tio	Co mp res sibi lity Ind ex	A n g l e o f	low aracter

	sity (gm/ml)	ensity (gm/ml)		(%)	Repose	
F_1	0.392	0.465	1.186	15.70	23.1	Excellent
F_2	0.392	0.454	1.158	13.66	24.76	Excellent
F_3	0.392	0.454	1.158	13.66	27.13	Excellent
F_4	0.385	0.4	1.179	15.20	27.1	Exce

	5 4	l l e n t

Evaluation test of Diclofenac Granules

Post compression study of pantoprazole sodium IR tablet

	F1	F2	F3	F4
Weight variation(in mg) (n=20)	485	495	501	503
Thickness(in cm) (n=5)	4.21	4.35	4.25	4.35
Hardness(in kg/cm^2) (n=5)	2.7	3.3	3.0	3.5
% Friability (n=5)	0.33	0.50	0.53	0.30
Wetting time(in min) (=5)	4	5	4	5
Percentage drug content (n=5)	96.96	95.33	98.33	97.55
Disintegration time (in seconds) (n=6)	57	55	53	56

Post compression study of pantoprazole sodium IR tablet

Post compression study of pantoprazole sodium IR & diclofenac sodium SR and tablet

	F1	F2	F3	F4
Weight variation (in mg) (n=20)	485	495	500	501
Thickness (in cm) (n=5)	4.2	4.3	4.2	4.3
Hardness (in kg/cm^2) (n=5)	2.6	3.0	2.9	3.0
% Friability (n=5)	0.31	0.52	0.54	0.34
Percentage drug content (n=5)	97	95	99	96

Buoyancy Time (n=mins)	60	66	65	62
Disintegration time (in seconds) (n=6)	59	60	59	56

Post compression study of Diclofenac sodium SR tablet

Conclusion

The present study was carried out to develop and evaluate single Bilayer tablet in which combination of Pantoprazole sodium (Proton Pump inhibitor) and Diclofenac (NSAIDs) are used to improve patient's compliance by effective management of long-term treatment of rheumatoid arthritis related problems. The bilayer tablet was prepared by single compression method in which immediate layer was formulate by using Sodium starch Glycolate and cross carmillose as super disintegrates in different concentration and sustain release layer of diclofenac sodium using matrix forming material like HPMC K100M, HPMCK4M in different combinations. First the drug was subjected to different Preformulation studies which included identification of drug, physical characterization, melting point determination, and spectrophotometric analysis, development of calibration curve, stability study, and solubility study. Immediate release layer of Pantoprazole sodium and Sustain release layer of diclofenac sodium were prepared by wet granulation method using 2^n factorial designing with different concentration of polymers. The formulated granules showed accordance for different physiochemical parameters viz bulk density, tapped density, Hausner's ratio, Carr's compressibility index and angle of repose of both layers separately and were within acceptable limit of Pharmacopeial specifications.

Immediate layer of Pantoprazole sodium and Sustain release layer of Diclofenac sodium were prepared by wet granulation method and prepared layer were evaluated for Hardness, thickness, weight variation, friability, drug content, in vitro disintegration time of both layer were in acceptable limit of Pharmacopeial specifications.

the study it was concluded that the hollow beads containing diclofenac sodium showed excellent buoyancy in acidic environment of stomach. The enhanced buoyancy of HPMC Matrix makes them excellent candidate for intra gastric floating drug delivery, by slowing down the gastric emptying. Overall, the buoyant granules provided a lag phase while showing gastro retention that would be beneficial for Gastro acidity.

Bilayer Tablet was prepared by Single compression using Different amount granules of both layers in single punching machine. The physical parameters of bilayer tablet were within acceptable range of good mechanical and handling properties.

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