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FORMULATION AND OPTIMIZATION OF FLURBIPROFEN MATRIX TABLETS FOR COLONIC DRUG DELIVERY

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Abstract
The present study is the development of colon targeted matrix tablets of the drug flurbiprofen,A Nsaids class of drug that is designed to for sustained effect.Different formulation(F1 TO F9) batches were made with the help of different polymers and their different proportions (Guar gum,Eudragit RL,Eudragit RS) with the help of Wet granulation technique.The prepared matrix tablets were evaluated in terms of their pre-compression parameters, physical characteristics like hardness, friability, uniformity of weight, uniformity of drug content, invitro drug release.The in vitro release study had been done into simulated gastric and intestinal fluid with a new method. From this study we concluded that the batch F7 shows good results then the other batches.The batch F7 shows maximum prolong release upto 12 hrs.

Keywords: - Flurbiprofen, Colon, Sustained release, Guar gum, Eudragit RL, Eudragit RS.

Introduction
Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs.[1,2] The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon.[3] The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability.[4]

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And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.[5]

Oral route is the most convenient and preferred route but other routes for CDDS may be used. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal.[6] Drug preparation for intrarectal administration is supplied as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity.[7]

Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of

most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage i.e. glycosides.[8] These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules such as insulin by oral administration.Target sites, colonic disease conditions, and drugs used for treatment are shown in Table [9]

Table Colon targeting diseases, drugs and sites

Target sites	Disease conditions	Drug and active agents
Topical action	Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease. Chronic pancreatitis	Hydrocortisone, Budenoside, Prednisolone, Sulfaselazine, Olsalazine, Mesalazine, Balsalazide.
Local action	Pancreatactomy and cystic fibrosis, Colorectal cancer	Digestive enzyme supplements 5-Flourouracil.
Systemic action	To prevent gastric irritation	NSAIDS
	To prevent first pass metabolism of orally ingested drugs	Steroids
	Oral delivery of peptides	Insulin
	Oral delivery of vaccines	Typhoid

MATERIAL AND METHOD:-

Material:- The drug Flurbiprofen was obtained as a gift sample from Panacia biotech Baddi. All other ingredients used in the preparation and Instruments are of Analytical Pharmacopoeial grade.

Preparation of granules

All the powdered ingredients were weighed, mixed and granulated with the binder solution/paste prepared as above. This mixture was thoroughly blended manually and passed through a sieve with a nominal aperture of 1 mm. The granules prepared were dried in a tray drier at a temperature between 30 and 40 °C for 4 h. The dried granules were screened, mixed with lubricants and stored for tableting.[10]

Preparation of Flurbiprofen matrix tablets

Matrix tablets of Flurbiprofen were prepared by wet granulation technique using 10% PVP paste as binder. Microcrystalline cellulose was used as diluent and mixture of talc and magnesium stearate at 2:1 ratio was used as lubricant. Flurbiprofen matrix, tablets containing Guar gum, Eudragit RS-100 Eudragit RL-100 were prepared. The composition of different formulations used in the study containing 100 mg of Flurbiprofen in each case is shown in table Polymers were sieved through a mesh (250 μm) and mixed with Flurbiprofen (149 μm) and MCC (250 μm). The powders were blended and granulated with 10% PVP paste. The wet mass was passed through a mesh (1190 μm) and the wet granules were dried at 50 °C for 2 h. The dried granules were passed through a mesh (1000 μm) and were lubricated with a mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed with a maximum force of compression (4000–5000 kg) using 11 mm round, flat and plain punches on single station tableting machine.[11]

Formulation of Flurbiprofen tablets.

S.No	Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Flurbiprofen	100	100	100	100	100	100	100	100	100
2	Eudragit RL 100	50	---	---	100	----	---	50	50	---
3	Eudragit RS 100	---	50	---	---	100	---	50	---	50
4	Guar gum	---	---	50	---	---	100	---	50	50
5	PVP K 30	3	3	3	3	3	3	3	3	3
6	MCC	138	138	138	88	88	88	88	88	88
7	Magnesium stearate	3	3	3	3	3	3	3	3	3
8	Talc	6	6	6	6	6	6	6	6	6
	Total	300	300	300	300	300	300	300	300	300

EVALUATION STUDIES

Evaluation Of Granules

Determination of bulk density and tapped density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (vo) was measured. then the graduated cylinder was closed with lid, set into the density determination apparatus (bulk density apparatus, electrolab, Mumbai). The density apparatus was set for 500 taps and after that ,the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density,and tapped density were calculated using the following formulas.

Bulk density $= W/V_o$

Tapped density $= W/V_f$

Where,

V_o = initial volume

V_f = final volume.

Compressibility index

The Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio.The compressibility index and Hausner ratio may be calculated using measured values for bulk density ***(bulk***) and tapped density ***(tapped***) as follows:

$$Compressibility\ Index = 100 \times \left(\frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \right)$$

$$Hausner\ \ Ratio = \left(\frac{\rho_{tapped}}{\rho_{bulk}} \right)$$

Loss on drying

Determination of loss on drying of granules are important drying time during granulation was optimized depending LOD value. LOD of each batches were tested at 105oc for 2.5 minutes by using "Sartorius" electronic LOD apparatus.

Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\theta = h/r$

$\theta = \tan^{-1} h/r$

Where h = height of pile

r = radius of the base of the pile

θ = angle of repose

EVALUATION OF TABLET

All the prepared Sustained release tablets were evaluated for following official and unofficial parameters.

Weight Variation

Thickness

Hardness Test

Friability Test

Drug content

Dissolution Study

WEIGHT VARIATION:

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table and none deviate by more than twice the percentage shown.

Table- Percentage deviation allowed under weight variation

Percentage deviation allowed under weight variation test.	
Average weight of tablet (X mg)	**Section 1.01 Percentage deviation**
X < 80 mg	10
80 < X < 250 mg	7.5
X > 250 mg	5

Thickness

Twenty tablets were randomly selected form each batch and there thickness and diameter was measured by using digital vernier caliper.

Friability:

Twenty tablets were weighed and placed in the Electrolab friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = friability in percentage

W = Initial weight of tablet

Wt = weight of tablets after revolution

Tablet Hardness

The crushing strength Kg/cm2 of prepared tablets was determined for 10 tablets of each batch by using Monsanto tablet hardness tester. The average hardness and standard deviation was determined.[12]

Uniformity of Weight

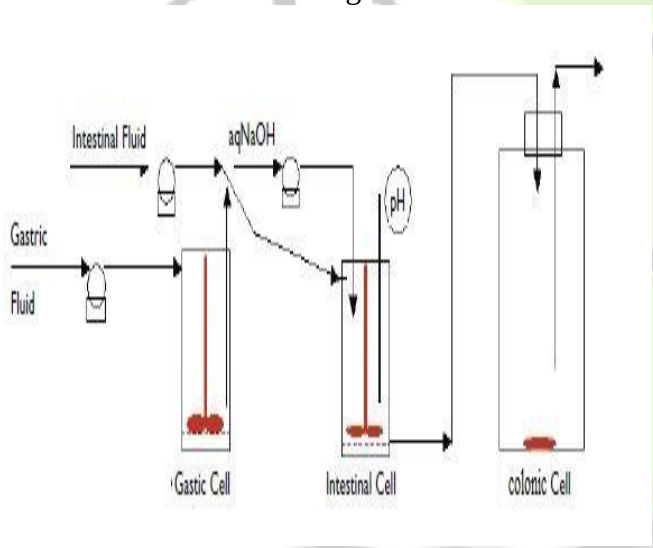
Twenty tablets were individually weighed and the average weight was calculated. From the average weight of the prepared tablets, the standard deviation was determined.

In vitro Dissolution studies

In Vitro dissolution study was carried out using new equipment design as described below.

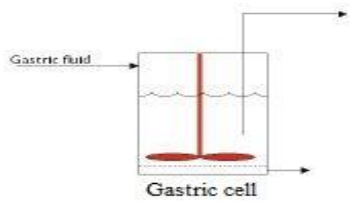
Equipment Design

The equipment is shown schematically in figure, comprises three continuous, stirred cells connected in series. Simulated gastric fluid is pumped into the first cell (gastric cell).The effluent from the gastric cell is fed into cell 2 (intestinal cell) together with simulated intestinal fluid and some sodium hydroxide (to neutralize the gastric acid). The effluent from the intestinal cell is fed into the third cell (colonic cell). All three cells are operated at constant volume. The dosage form to be tested is added to the first cell. Details of cell are shown in figure



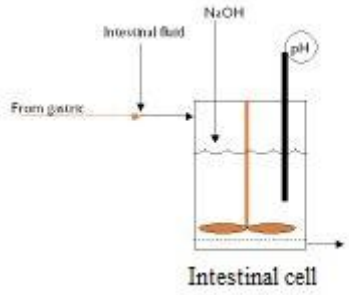
Gastric Cell:-

The gastric cell includes a dip tube as one of the outlets. This dip tube allow both solution and fine solids to exit the gastric cell. This simulates the transfer of undissolved solids from the stomach to intestine-a transfer which is known to be particle size dependent. The gastric cell also contains a filter through which fluid can be removed for analysis.



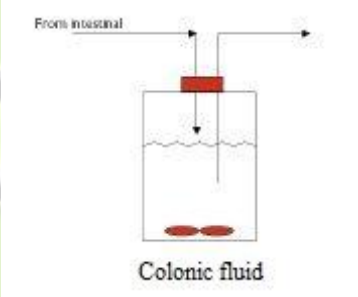
Intestinal Cell:-

The intestinal cell includes a pH probe linked to the supply of sodium hydroxide so that the pH can be controlled at any desired value. This cell also contains a filter. Fluid must pass through this filter to exit the cell, so that only dissolved drug can go on to the colonic cell. The fluid can be analyzed in line.



Colonic Cell:-

The colonic cell contains no filter or other additions. It is simply a constant volume stirred cell.



WORKING:-

The operation of the equipment is as described. The dosage form is added to the gastric cell where it disintegrates and starts to dissolve. As soon as particles get small enough they will start to transfer to intestinal cell, just as small particles will start to leave the stomach in vivo. The fluid transferring from the gastric cell to the colonic cell will therefore be a mixture of drug dissolved in gastric fluid and undissolved drugs and excipients. During this transfer, the fluid is mixed with simulated intestinal fluid. In the intestinal cell the pH is controlled at typical intestinal pH, and the undissolved drug will continue to dissolve. The undissolved drug cannot leave this cell, so that the overall effect is that dissolved drug is removed. This is equivalent to intestinal absorption, and the rate of removal will be first order in drug concentration – a very good approximation of the in vivo absorption kinetics. Finally the dissolved drug enters the colonic cell. In this cell the kinetics of removal will also be first order, and can be considered equivalent to clearance from blood plasma. Although this kinetic

model is not as universal as the first order absorption kinetics is still a good approximation in many cases.In summary, all of the processes – gastric disintegration, gastric dissolution, solids transfer, intestinal dissolution, intestinal absorption and plasma clearance are all incorporated under bio-relevant conditions

There are simulated gastric fluid, simulated intestinal fluid & colonic fluid are made. Matrix tablet is put into the gastric cell where its disintegration takes place and further dissolution had been done. The samples were taken out at different time intervals as measured at a λ_{max} 247 nm using UV visible spectrophotometer. The pharmacokinetic parameters of Flurbiprofen were used to calculate a theoretical drug release profile for 12 hr oral dosage form. The immediate release part for sustained release Flurbiprofen was calculated.

Results and discussion:- In the present study flurbiprofen matrix tablets were prepared with the help of different polymers by wet granulation method.After preparation of the matrix tablets. Evaluation studies were done with different parameters and the results were shown below.

Study of preformulation studies

Parameters> Batch	Bulk Density	Tapped Density	Carrs Index	Hausners Ratio	Angle Of Repose(degree)
F 1	0.488	0.526	7.22	1.08	22.14±0.03
F 2	0.512	0.574	10.80	1.12	19.16±0.06
F 3	0.486	0.526	7.22	1.08	24.18±0.057
F 4	0.502	0.581	13.60	1.16	18.16±0.042
F 5	0.523	0.602	13.12	1.15	19.14±0.02
F 6	0.543	0.592	8.47	1.09	21.14±0.026
F 7	0.499	0.564	11.52	1.13	20.42±0.01
F 8	0.544	0.601	9.48	1.10	18.21±0.02
F 9	0.561	0.611	8.19	1.08	24.14±0.042

Physico-chemical evaluation of matrix tablets

Thickness:- The results of the thickness of tablet are shown in Table.

The mean tablet thickness was found to vary from. 3.0 to 3.5

Parameter Batch	Thickness*	Hardness (Kg/cm3)*	Friability (%)	Disintigration Time(sec)*
F 1	3.3	5.0±	0.52	190±
F 2	3.1	6.1	0.58	210
F 3	3.3.	6.8	0.62	145
F 4	3.3	5.5	0.55	205
F 5	3.2	5.9	0.64	250
F 6	3.3	6.3	0.59	197
F 7	3.1	6.6	0.67	240
F 8	3.2	5.8	0.70	300
F 9	3.2	5.3	0.66	243

Mean weight variation

The results of the weight variation of tablets are shown in Table

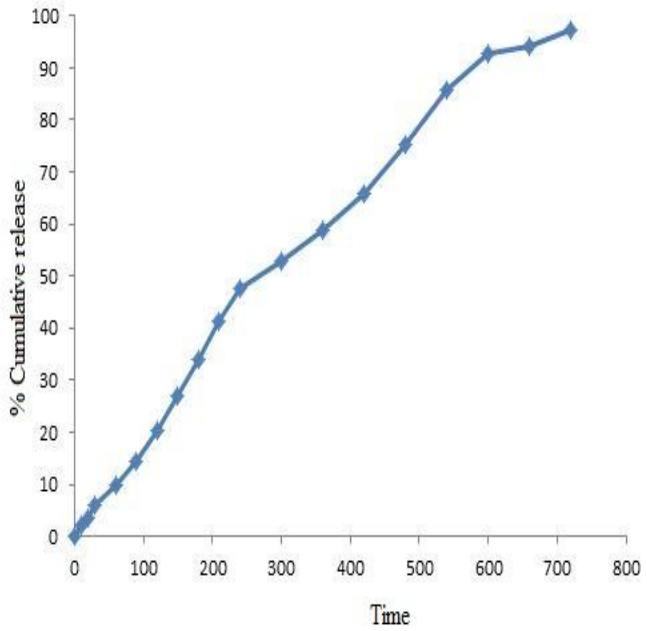
Parameter Batch	Weight Variation
F 1	200.1
F 2	198.9
F 3	202.1
F 4	201.4
F 5	199.3
F 6	198.4
F 7	200.7
F 8	201.5
F 9	199.3

Drug content uniformity

The results of drug content of ocular tablets are shown in Table. The drug content of ocular tablet was found to vary between 97.2% to 99.9% .

*Values are Mean ± SD (n=3)

BATCH	DRUG CONTENT (%)
F1	99.50
F2	92.89
F3	100.02
F4	99.59
F5	99.38
F6	97.05
F7	99.60
F8	91.69
F9	95.62



In Vitro studies:-

The data was taken in different time intervals in gastric, intestinal and colonic fluid.

TIME	% Cumulative release
10	1.989654
20	3.675895
30	5.874526
60	9.985247
90	14.22199
120	20.25681
150	27.04722
180	34.08456
210	41.48743
240	47.50086
300	52.99685
360	58.86223
420	65.65948
480	75.25489
540	85.66549
600	92.68041
660	94.26594
720	97.36554

Conclusion:-

From this study we concluded that Flurbiprofen matrix tablets with the help of ph dependent polymers prove to be a better drug delivery for colon targeting drug delivery. The new design of in vitro dissolution method is also better for simulated fluids determination of the sustained release tablets.

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