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MANGIFERA INDICA PECTIN AS A DISINTEGRANT IN DESIGN OF FAST DISSOLVING TABLETS

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Abstract:

Objectives: *The aim of the present work was to prepare and evaluate fast dissolving tablets of furosemide with a view to enhance patient compliance and minimizes the side effects.*

Methodology: *In this study, fast dissolving tablets of furosemide were formulated by direct compression method using such as pectin of mango peel (mangifera indica) was used as natural disintegrants and crospovidone as a synthetic superdisintegrant in different ratios with directly compressible mannitol (Pearlitol SD 200) as a diluent to enhance the mouth feel. The prepared formulations were evaluated for hardness, friability, drug content, in vitro dispersion time, wetting time, water absorption ratio, in vitro drug release studies, stability studies and excipients interaction studies.*

Results: *Among all the formulation, the formulation (FMP_3) containing 8% w/w pectin of mango peel (mangifera indica) is the overall best formulation ($t_{50\%}$ 5.2 min) based on in vitro drug release studies. Stability studies on the formulations indicated that there are no significant changes in drug content and in vitro dispersion time ($p<0.05$).*

Conclusion: *From the above studies, it can be concluded that fast dissolving tablets of Furosemide can be prepared using different natural super disintegrant for faster dispersion and disintegration in the mouth.*

Keywords: *Fast dissolving tablets, Furosemide, Crospovidone, mangifera indica, Natural disintegrants.*

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INTRODUCTION:

Recent advances in novel drug delivery system (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. Formulation one such approach is fast dissolving tablet of furosemide, an antidiuretic drug which is given by mouth in treatment of hypertension and edema[1]. Many patient express difficulties in swallowing tablet and hard gelatin capsules, leading to non-compliance and ineffective therapy [2]. Other problems experienced in using conventional oral dosage forms include patients with mental illness, uncooperative behavior and the one suffering from nausea, motion sickness, sudden episodes of allergic attack and coughing.[3-5]. Thus, the concept of formulating fast dissolving tablets of furosemide evolved, which offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with potential increased bioavailability.

Mucilage and pectin is most commonly used as adjuvant in the manufacture of different pharmaceutical dosage form. They possess a variety of pharmaceutical properties, which include binding, disintegrating, suspending, emulsifying and sustaining properties at different proportion in different pharmaceutical dosage form the synthetic polymer used as excipients suffer from any disadvantages such as high cost, toxicity, non-biodegradability and environmental pollution caused during their synthesis[6-9]. Natural mucilage , pectin, pulps are preferred over semi-synthetic and synthetic materials, due to their non-toxic, low cost, free availability, emollient and non-irritating nature.[10,11] *Magnifera indica contains* 16% to 20% tannin, namely protocatechuic acid, kinic acid and catechin. it also contains mangiferine, alanine, shikimic acid and astringent and contains resinous gum , it is used as a vermifuges and astringents used in treatment of rheumatism

In the present study, the fast dissolving tablets of furosemide were prepared by direct compression method using natural and synthetic disintergrants to compare the efficiency of different natural and synthetic disintegrants.

MATERIALS AND METHODS:

Furosemide was a gift sample from Strides Arco Labs, Bangalore. Crospovidone was gift sample from Wockhardt Research centre, Aurangabad, Maharashtra; India.Micro-crystalline cellulose was gift sample from Alkem Labs Pvt. Ltd., Mumbai,

Maharashtra, India.All the other chemicals were of analytical grade.

Mango Peel Extraction:

Ripe mango peels were obtained as a waste from local fruit shop selling orange juice. Peels were carefully washed and dried under shade for 24 h, further dried at 30-40ºC until constant weight was obtained. Dried fruit peel was cut into pieces and powdered in to electric grater. Powdered peel was further passed from sieve # 20 and stored in air tight container until used [12].

Step:-1 Extraction of pectin

Pectin was extracted under reflux in a condensation system using acidified water with citric acid to pH 2. Temperature of extraction media was maintained at 70ºC and duration of extraction was adjusted about 6 h. The extractor thimble was a Whatman cellulose thimble with 33 mm internal diameter and 80 mm external length. Orange peel powder was taken in soxhlet and process is repeated to obtain using fresh powder to obtained desired amount of pectin.

Step:-2 Isolation of Pectin

Dried mango peel powder was used for extracting pectin using soxhlet apparatus. Round bottom flask containing acidified (ph.2) using 0.5 N citric acid was heated continuously at 75º c for 7-8 hour after start of first siphon cycle , powder to solvent ratio was 1:8. After heating period was over mixture was passed through 2 fold muslin cloth and cooled to room temperature. Double amount of ethyl alcohol was added to solution with continuous stirring for 15 min. Mixture was kept for 2hour without stirring allow pectin floatation. Using this procedure, it is easy to filter pectic substances because pectin remains float on the surface of alcohol–water mixture. Floating pectin coagulate was filtered through cheesecloth, washed with 95% alcohol and pressed. Pressed pectin was further dried to constant weight at 35-45ºC.Hard pectin cake was ground and sieved through sieve # 20, stored in desicator and further used.

Extraction of pectin by using Soxhlet apparatus

Formulations of Furosemide Fast Dissolving Tablets:

Fast dissolving tablets of Furosemide were prepared by direct compression method, using pectin of *Magnifera indica as a* natural disintegrant and crospovidone (CP) as a synthetic superdisintegrant in different ratios and directly compressible mannitol as diluent to enhance the mouth feel. All the ingredients were passed through #60mesh separately. The drug and mannitol were mixed by small portion of both each time and blending it to get a uniform mixture and kept aside. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed at 8 mm size to get a tablet of 200 mg weight using a (Clit pilot press 10 station rotary tablet compression machine)[13] The tablets were prepared according to the formulae shown in Table 1.

Evaluation of Tablets:

The prepared batches of formulations were evaluated for the pre-compression parameters like bulk density, tapped density, angle of repose, carr's index shown in Table 2 and post compression parameters such as drug content uniformity, weight variation, hardness, friability, thickness, *in vitro* dispersion time, *in vitro* drug release and stability studies [14,15] (given in Table 3).

Weight Variation:

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by, twenty tablets were selected at random and weighed individually, and the individual weights were compared with average weight for the determination of weight variation.

Tablet Hardness:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using digital hardness tester. The hardness was measured in terms of kg/cm^2. Three tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

Friability:

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. Ten tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded. Percentage friability was calculated by using the formula:

% Friability= Initial weight of the tablets- Final weight of the tablets/ Initial weight of the tablets X 100

Tablet thickness:

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of three tablets of each formulation.

Drug Content Uniformity:

Ten tablets were weighed and powdered; a quantity of powder equivalent to 5 mg of furosemide was transferred to a 50 ml volumetric flask and dissolved in 40 ml methanol. The drug is extracted into the methanol by vigorously shaking 15 minutes. Then the volume is adjusted to 50 ml with methanol and the liquid is filtered. The furosemide content was determined by measuring the absorbance at 274.5 nm after appropriate dilution with methanol. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

Wetting Time and Water Absorption Ratio:

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed [16] (given in Table 3).

Water absorption ratio 'R' was determined using following equation:

$$R = 100 \times (Wa - Wb|Wb)$$

Where,

W_a = weight of tablet before water absorption,

W_b = weight of tablet after water absorption.

***In vitro* Dispersion Time:**

Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37±0.5°C. Time required for complete dispersion of a tablet was measured [17] (given in Table 3).

***In vitro* Dissolution Study:**

In vitro dissolution of Furosemide fast dissolving tablets was studied in USP XXII type-II dissolution apparatus (Electrolab USP TDT-06T) employing a paddle stirrer. 900 ml of phosphate buffer pH 6.8 was

used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution media was previously warmed to 37±0.5° and was maintained throughout the experiment. One tablet was used in each test, 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 274.5 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.[18]

Accelerated Stability Studies:

Stability studies on the promising formulation (FMP_3) were carried out by storing 15 tablets in amber coloured screw- capped bottle at elevated temperature of 40 $\pm 2^0$C/75%RH (Stability chamber, Oswald) for 3 months. At an interval of one month, the tablets were visually examined for any physical changes, percent drug content and *in vitro* dispersion time.

RESULTS AND DISCUSSION:

In the present work fast dissolving tablets of Furosemide were prepared by direct compression method, employing as pectin of mango peel powder (*Magnifera indica*) as a natural disintegrant and crospovidone as a synthetic superdisintegrant in different ratio using mannitol as a diluent, to enhance the mouth feel. A total of 10 formulations and a control formulation FC_0 (without superdisintegrant) were designed. All the blends were free flowing having angle of repose< 30^0, Carr's index <15%, tapped density <0.640, bulk density <0.570 and hausner's ratio<1.15 indicating all the blends have values within the IP limits (given in Table 2).

Tablets obtained were of uniform weight (due to uniform die fill) with acceptable variation as per IP specification i.e. below ±7.5%. Drug content, hardness, water absorption ratio and wetting time were found to be in the range of 96.08 to 99.45%, 2.6 to 2.9 kg/cm^2, 41.58% to 97.6% and 18.52 to 70.16 sec respectively (given in Table 3). Friability value of prepared tablets was found to be less than 1% (an indication of good mechanical resistance of tablets).

Among all the designed formulations, the formulation FMP_3 (containing 8% w/w of *magnifera indica* was found to be promising. The *in vitro* dispersion time, wetting time and water absorption ratio of FMP_3 were found to be 41.93sec, 43.33 sec and 75.41% respectively (given in Table 3).The experimental data also revealed that the results obtained from the *magnifera indica* pectin powder are better than those of conventional commercial formulation.

In vitro dissolution studies of the control formulation (FC_0), Commercial conventional formulation (CCF) and promising formulations (FMP_3, FCP_3) were carried out in pH 6.8 phosphate buffer and the various dissolution parameters values viz percent drug dissolved in 5 min, 10 min & 15 min (D_5, D_{10} and $D_{15,}$) dissolution efficiency at 10 min (DE_{10}), $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are shown in Table 4 and dissolution profile depicted in Figure 1. This data reveals that overall formulation FMP_3 as shown in more than two folder faster drug release ($t_{50\%}$ 5.2 min) when compared to CCF ($t_{50\%}$ 11.6 min) tablet formulation of furosemide .

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of FMP_3 and FCP_3 showed all the characteristics peaks of furosemide pure drug. Thus conforming that no interaction of drug occurred with the component of the formulations. Stability studies of the FMP_3 formulation presented in Table 5 and Table 6 indicated that there is no significant changes in drug content and *in vitro* dispersion time at the end of three months period ($P<0.05$).

CONCLUSION:

In the present work, it can be concluded that fast dissolving tablets of furosemide prepared by using pectin powder of *magnifera indica* shows better drug release and disintegration time as compared to tablets prepared from other natural and synthetic disintegrants.

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- Conflict of interest- None

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Table 1: Formulations of Furosemide Fast Dissolving Tablets Prepared by Direct Compression Method

Ingredients	Formulation Code						
	FCP_0	FMP_1	FMP_2	FMP_3	FCP_1	FCP_2	FCP_3
Furosemide	40	40	40	40	40	40	40
Pectin of mango peel powder (*magnifera indica*)	-	4	8	16	-	-	-
Crosspovidone	-	-	-	-	4	8	16
MCC PH102	40	40	40	40	40	40	40
Aspartame	4	4	4	4	4	4	4
Flavour	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4
SSF	2	2	2	2	2	2	2
Mannitol SD200	108	104	100	92	104	100	92
Total weight	200	200	200	200	200	200	200

FCA- Formulation containing pectin of mango peel powder (*magnifera indica*)
FC_0- (Control) Formulation without superdisintegrant
FCP- Formulation containing crosspovidone

Table 2: Pre-compression Parameters of Formulations Prepared by Direct Compression Method

Parameters	Formulation Code						
	FCP_0	FMP_1	FMP_2	FMP_3	FCP_1	FCP_2	FCP_3
Bulk density(gm/cc)	0.57	0.50	0.53	0.52	0.529	0.562	0.494
Tapped density(gm/cc)	0.64	0.58	0.59	0.61	0.576	0.629	0.550
Angle of repose(º)	30.10	30.02	30.12	30.81	29.54	28.54	28.290
Carr's index (%)	15.55	14.52	14.46	14.50	8.15	10.72	10.23
Hausner's ratio	1.12	1.10	1.13	1.16	1.08	1.11	1.11

Table 3: Post-compression Parameters of Formulations Prepared by Direct Compression Method

Parameters	Formulation Code						
	FCP_0	**FMP_1**	**FMP_2**	**FMP_3**	**FCP_1**	**FCP_2**	**FCP_3**
Hardness (Kg/cm^2)	2.6± 0.070	2.7± 0.070	2.8± 0.O99	2.7± 0.070	2.8± 0.17	2.7± 0.2	2.9± 0.15
Thickness (mm)	2.64± 0.020	2.7± 0.070	2.72± 0.020	2.69± 0.010	2.13± 0.02	2.19± 0.08	2.16± 0.02
Friability (%)	0.62± 0.010	0.61± 0.026	0.62± 0.010	0.59± 0.029	0.64± 0.19	0.61± 0.27	0.50± 0.14
***In-vitro* dispersion time (sec)**	110.23 ±0.9	69.12 ±0.010	54.62± 0.586	41.93 ± 1.32	43.7± 2.30	34.12±1.55	17.0±1.946
Wetting time (sec)	112.13±1.0	70.16± 1.01	55.87± 1.02	43.33± 1.05	44.6± 1.74	35.42±1.50	18.52±1.01
Water absorption ratio (%)	56.20±0.99	41.58± 0.100	68.11± 1.005	75.41± 1.012	73.3± 1.26	80.27±1.64	97.6± 1.02
Percent drug content (%)	98.64± 0.020	96.96± 0.0200	96.08± 0.0199	96.73± 0.6119	99.4± 1.01	99.2± 0.82	99.35±1.32
Weight variation	(148 to 155 mg) within IP limits of ±7.5%						

*Average of three determinations

Table 4: Comparative *in-vitro* Dissolution Parameters of Promising Fast Dissolving Tablet Formulations, Control and Commercial Conventional Formulation (CCF) in pH 6.8 Phosphate Buffer

Formulation Code	Dissolution Parametres						
	D_5 (%)	**D_{10} (%)**	**D_{15} (%)**	**DE_{10min} (%)**	**$t_{50\%}$ (min)**	**$t_{70\%}$ (min)**	**$t_{90\%}$ (min)**
FC_0	16.5%	29%	33%	14.98%	6.6min	13min	>30min
FMP_3	48%	74%	85%	47.6%	5.2min	9min	19min
FCP_3	74%	100%	--	68.25%	1.8min	4.5min	7.8min
CCF	25%	45%	62%	24.64%	11.6min	18.5min	>30min

Table-5: Stability Data of FMP_3 Formulation at 40°C/75% RH

Sl. No.	Time in days	Physical changes	Percent drug content ±SD*	*In-vitro* dispersion time*
1.	1st day (initial)	--	96.73±1.53	41.93±2.28
2.	30th day (1 month)	No changes	96.61±1.23	41.99±2.81
3.	60th day (2 month)	No changes	96.52±1.08	42.21±1.46
4.	90th day (3 month)	No changes	96.46±0.26	42.48±1.87

* Average of three determinations

Table-6: Statistical Analysis for Drug Content Data of FMP_3 Formulation

Sl. No.	Trials	1st day (A)	90th day (B)	A – B
1.	1	96.38	96.10	0.28
2.	2	96.63	96.44	0.19
3.	3	97.18	96.82	0.36
4.	Mean percent drug content	96.73	96.46	0.27
5.	± SD	0.409	0.294	0.115

t=1.354 ($p<0.05$)

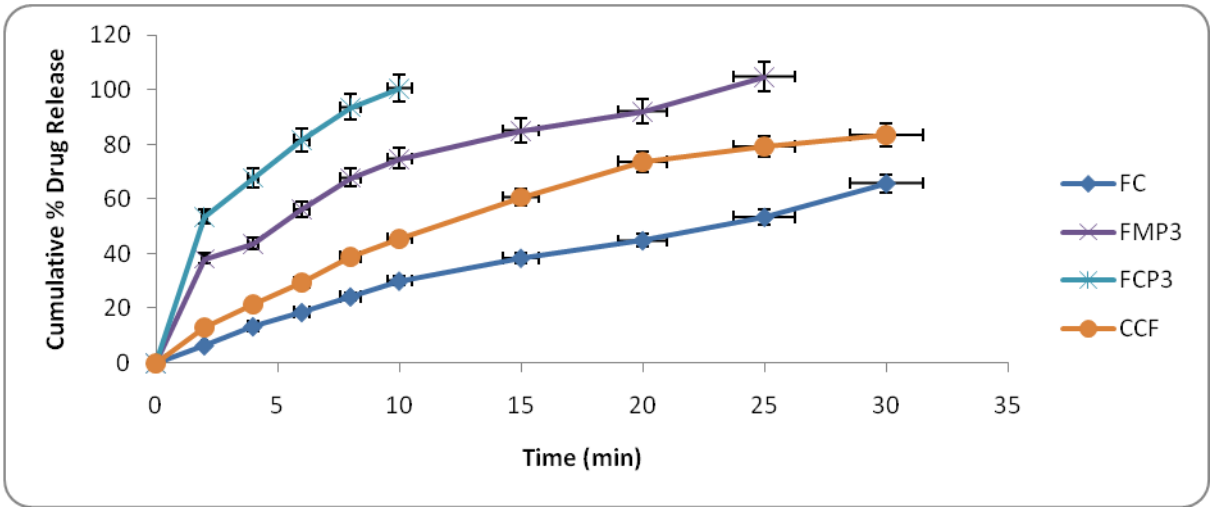

Fig 1:Comparative Cumulative % Drug Release Versus Time Plots (Zero-order) of Promising Fast Dissolving Tablet Formulations, Control and Conventional Commercial Formulations (CCF) in pH 6.8 Phosphate