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Research Article

Annona reticulate Pulp Powder as a Disintegrant in Design of Fast Dissolving Tablets

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Abstract

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. In this study, fast dissolving tablets of furosemide were formulated by direct compression method using such as pectin of orange peel powder *(Citrus sinensis)*, custard apple pulp powder *(Annona reticulata)*, were used 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. Among all the formulations, the formulation (F_{CA3}) containing 8% w/w pulp of custard apple *(Annona reticulate)* was the overall best formulation (t_{50}%2.1 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 ($p<0.05$). 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, Natural disintegrants. *Annona reticulate, Citrus sinensis*

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 patients 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, pectin and pulp are 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]. Annona reticulata contains flavonoids, alkaloids, and acetogenins, It is used a vermifuge, in abscesses and ulcers. The unripe fruit is rich in tannin; is dried, pulverized and employed against diarrhea and dysentery. Fragments of the root bark are packed around the gums to relieve toothache. Annona reticulata are easily available having low cost and non toxic as compared to synthetic disintegrants.

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.

Extraction of Annona reticulate (custard apple pulp powder)

Custard Apples were purchased from the local market. The pulp of the fruits was scraped off gently. The pulp obtained was dried in sunlight. The dried mass was grinded in mixture to get fine powder and passed to mesh #60. The pulp powder was dried in oven at a temperature less than 60 ºC, powdered (#60 mesh), weighed and stored in air tight well closed container until further use [12].

Isolation and extraction of orange peel extraction

Ripe orange peels were obtained as a waste from local fruit shop selling orange juice. Peel were carefully washed with water and dried under normal room temperature for 24 h, further dried at 30-40 ºC until constant weight was obtained. Dried fruit peel was cut into pieces and powdered in to electric grater or electric mixer. Dry powdered peel was further passed from sieve # 20 and stored in air tight container until used.

Extraction of pectin includes two steps.

Step1: 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.

Step2: Isolation of pectin

Hot acid extract was pressed in cheese cloth bag and the concentrated juice was cooled to 4ºC. Pectin was precipitated by alcohol- juice treatment 2:1 (v/v) followed by continuous stirring for 15 min and this

mixture was further allowed to stand for 2 h to 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 35-45 ºC. Hard pectin cake was ground and sieved through sieve # 20, stored in desicator and further used.

Formulations of furosemide fast dissolving tablets

Fast dissolving tablets of furosemide were prepared by direct compression method, using pectin of *Citrus sinensis* and pulp of *Annona reticulate* natural disintegrants 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 as shown in Table 1.

Table 1: Formulations of furosemide fast dissolving tablets prepared by direct compression method

Ingredients	Formulation Code									
	FCP_0	FCA_1	FCA_2	F_{CA3}	FOP_1	FOP_2	FOP_3	FCP_1	FCP_2	FCP_3
Furosemide	40	40	40	40	40	40	40	40	40	40
Custard apple pulp powder*(Annona reticulata)*	-	4	8	16	-	-	-	-	-	-
Pectin of Orange peel powder *(Citrus sinensis)*	-	-	-	-	4	8	16	-	-	-
Crosspovidone	-	-	-	-	-	-	-	4	8	16
MCC Ph102	40	40	40	40	40	40	40	40	40	40
Aspartame	4	4	4	4	4	4	4	4	4	4
Flavour	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4
SSF	2	2	2	2	2	2	2	2	2	2
Mannitol Sd200	108	104	100	92	104	100	92	104	100	92
Total weight	200	200	200	200	200	200	200	200	200	200

FCA- Formulation containing custard apple pulp powder *(Annona reticulata)*
FC_o- (Control) Formulation without superdisintegrant
FOP- Formulation containing pectin of Orange peel *(Citrus sinensis)*
FCP- Formulation containing crosspovidone

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 were 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] as given in Table 3.

Table 2: Pre-compression parameters of formulations prepared by direct compression method

Parameters	FCP_0	FCA_1	FCA_2	F_{CA3}	FOP_1	FOP_2	FOP_3	FCP_1	FCP_2	FCP_3
Bulk density(gm/cc)	0.57	0.50	0.52	0.53	0.54	0.52	0.51	0.529	0.562	0.494
Tapped density(gm/cc)	0.64	0.63	0.62	0.60	0.59	0.55	0.57	0.576	0.629	0.550
Angle of repose(°)	30.10	29.12	28.15	28.59	29.68	29.52	29.72	29.54	28.54	28.290
Carr's index (%)	15.55	12.11	12.68	12.47	10.42	10.56	10.74	8.15	10.72	10.23
Hausner's ratio	1.12	1.16	1.15	1.14	1.11	1.16	1.12	1.08	1.11	1.11

Table 3: Post-compression parameters of formulations prepared by direct compression method

Parameters	FCP_0	FCA_1	FCA_2	F_{CA3}	FOP_1	FOP_2	FOP_3	FCP_1	FCP_2	FCP_3
Hardness (Kg/cm^2)	2.6± 0.070	2.7± 0.070	2.8± 0.099	2.9± 0.070	2.8± 0.099	2.9± 0.070	2.8± 0.070	2.8± 0.17	2.7± 0.2	2.9± 0.15
Thickness (mm)	2.64± 0.020	2.66± 0.020	2.70± 0.010	2.69± 0.010	2.69± 0.010	2.71± 0.020	2.70± 0.070	2.13± 0.02	2.19± 0.08	2.16± 0.02
Friability (%)	0.62± 0.010	0.58± 0.010	0.60± 0.011	0.59± 0.010	0.61± 0.010	0.62± 0.020	0.59± 0.014	0.64± 0.19	0.61± 0.27	0.50± 0.14
In-vitro dispersion time (sec)	110.23 ±0.9	54.16 ±1.01	40.2± 1.990	19.9 ± 2.35	44.8± 0.98	59.4± 1.989	27.5± 2.17	43.7± 2.30	34.12 ±1.55	17.0 ±1.946
Wetting time (sec)	112.13 ±1.0	55.2± 1.720	41..6 ±0.92	20.5± 1.10	45.7± 1.049	61.25 ±1.94	28.9± 1.02	44.6± 1.74	35.42± 1.50	18.52± 1.01
Water absorption ratio (%)	56.20± 0.99	68.1± 1.009	77.35± 0.98	92.62± 1.12	72.1± 1.990	65.7± 1.90	82.1± 1.05	73.3± 1.26	80.27 ±1.64	97.6± 1.02
Percent drug content (%)	98.6± 0.020	97.8± 0.034	98.1± 0.100	98.9± 0.009	97.16± 0.60	97.2± 0.569	97.8± 0.017	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

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:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \text{ X } 100$$

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 for 15 min. 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] as given in Table 3.

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

$$R = 100 \text{ x } (Wa - Wb/wb)$$

Where,

Wa = weight of tablet before water absorption,

Wb = 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] as 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 °C 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 (FCA3) were carried out by storing 15 tablets in amber coloured screw-capped bottle at elevated temperature of 40 ±2 °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 orange peel powder (Citrus sinensis), custard apple pulp powder (Annona reticulata), 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 FCo (without superdisintegrant) were designed. All the blends were free flowing having angle of repose< 30°, 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 as 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 97.16 to 99.45%, 2.6 to 2.9 kg/cm^2, 65.78% to 97.6% and 18.52 to 61.25 sec respectively as shown 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 FCA3 (containing 8% w/w of *Annona reticulata* was found to be promising. The *in vitro* dispersion time, wetting time and water absorption ratio of FCA3 were found to be 19.9 sec, 20.5 sec and 92.62% respectively (Table 3).The experimental data also revealed that the results obtained from the *Annona reticulate* Pulp powder are better than those of conventional commercial formulation (Figure 1).

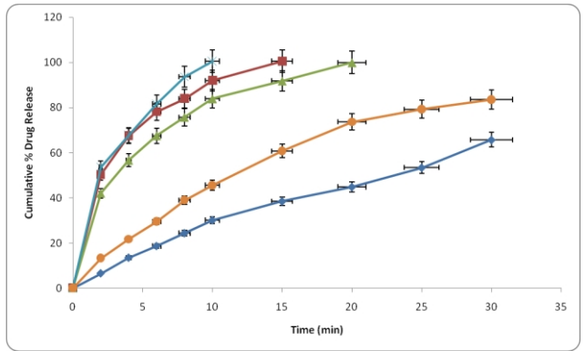

Figure 1: Comparative cumulative % drug release versus time plots (zero-order) of promising fast dissolving tablet formulations, control and conventional commercial formulations (ccf) in pH 6.8 phosphate

In vitro dissolution studies of the control formulation (FC_o), Commercial conventional formulation (CCF) and promising formulations (F_{CA3}, 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 and 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.

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	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
F_{CA3}	72%	93%	100%	64.86%	2.1min	4.3min	10min
FOP_3	63%	82%	91%	55.59%	3.1min	6.9min	14min
FCP_3	74%	100%	–	68.25%	1.8min	4.5min	7.8min
CCF	25%	45%	62%	24.64%	11.6min	18.5min	>30min

This data reveals that overall formulation FCA3 as shown in more than five and half fold faster drug release (t_{50}% 2.1 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 F_{CA3} and FCP3 showed all the characteristics peaks of furosemide pure drug. Thus conforming that no interaction of drug occurred to the component of the formulations (Figure 2,3,4).

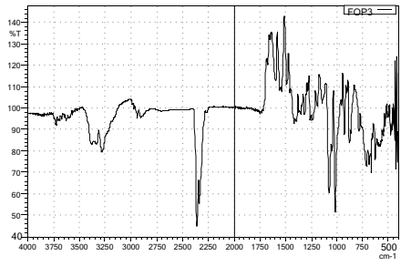

Figure 2: IR spectroscopic containing formulation of orange peel

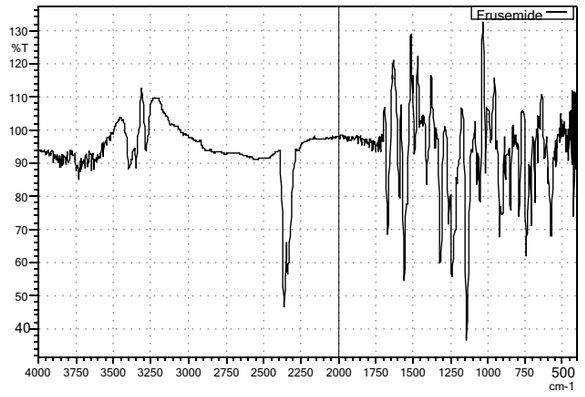

Figure 3: IR spectroscopic containing pure drug frusemide

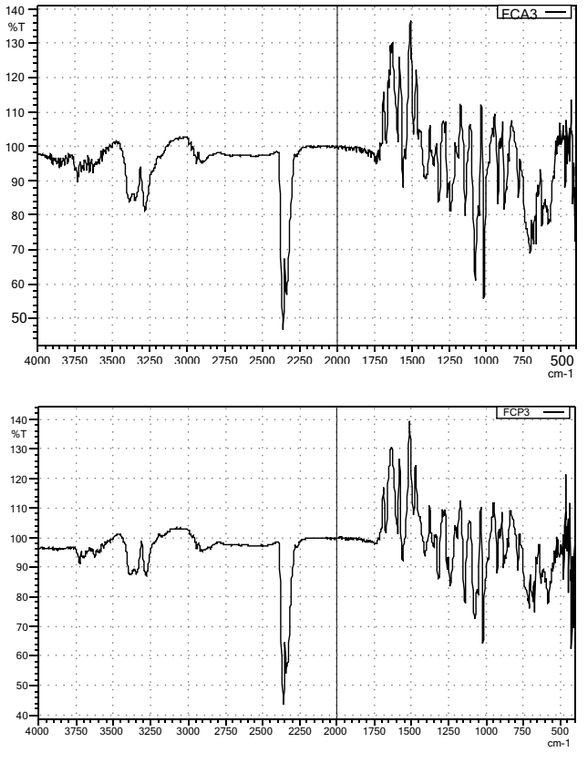

Figure 4: IR spectroscopic containing formulation of custard apple

Table 5: Stability Data of FCA3 Formulation at 40ºC/75% RH

Sl. No.	Time in days	Physical changes	Percent drug content ±SD*	*In-vitro* dispersion time*
1.	1st day (initial)	-	98.90±1.42	19.19±2.95
2.	30th day (1 month)	No changes	98.62±0.26	20.26±2.38
3.	60th day (2 month)	No changes	98.48±0.81	20.32±2.95
4.	90th day (3 month)	No changes	98.23±0.69	20.46±1.45

* Average of three determinations

Table 6: Statistical Analysis for Drug Content Data of F_{CA3} Formulation

Sl. No.	Trials	1st day (A)	90th day (B)	*A – B*
1.	1	98.92	98.90	0.02
2.	2	98.90	98.89	0.01
3.	3	98.88	98.89	0.01
4.	Mean percent drug content	98.90	98.89	0.01
5.	± SD	0.020	0.0057	0.0143
t=0.403	(p<0.05)			

Stability studies of the F_{CA3} 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 pulp of *Annona reticulata* shows better drug release and disintegration time as compared to tablets prepared from other natural and synthetic disintegrants.

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Declaration

The authors report no conflict of interest.

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