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Oro-Dissolving Systems of Papaya Extract – Liquisolid Compacts and Lozenges

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Abstract : Objective: To develop oro- dissolving systems of *Carica papaya* leaf extract by various techniques to enhance its therapeutic effects.
Methods: Fresh *C. Papaya* leaf extracts were prepared by the cold extraction and maceration methods. The components of the extract were analysed by GC-MS technique. The concentrated extract was further formulated into liquisolid granules and soft lozenges by the liquisolid compaction and molding methods respectively. Various quality control tests such as weight variation, hardness, thickness and diameter and disintegration were carried out to evaluate the commercial feasibility of the formulations. An XRF and Microbial load analysis was done for the optimized set of tablets and lozenges and the yield calculated.
Results: Both the formulations showed an 80% yield and acceptable flow properties satisfying the required standards for quality. The GC-MS reported the presence of 12 major compounds with a similar spectrum. The XRF results gave the presence of high amounts of potassium(K) and trace amounts of copper and molybdenum. The microbial limit tests showed a total aerobic and fungal count within limits as per Indian pharmacopoeia.
Conclusion: The formulations were found to be stable and within the standard pharmacopoeial limits, satisfying conditions for effective release and action of the active drug.
Keywords: *Carica papaya*, oro-dissolving, liquisolid, soft lozenge.

Introduction:

Herbal medicines are plant's seeds, bark or flowers used for medicinal purposes which have stood the test of time for their safety, efficacy, cultural acceptability and lesser side effects. The chemical constituents present involves in the physiological functions of living flora which contributes to better compatibility in the biological system. Carica papaya L. is a soft wooded single-stemmed perennial tree which belongs to the family Caricaceae (1). The leaf barks of the plant produces natural compounds possessing anti-tumour and pesticidal properties (2). In the recent times the leaves of papaya showed the presence of many active components such as papain, chymopapain, glucosinolates, tocopherol, ascorbic acid, flavonoids, cyanogenic glucosides and cystatin which is responsible to increase the total antioxidant power in blood and reduction in lipid peroxidation level (3). The young leaves possess antibacterial activity and can be used in the treatment of jaundice (fine paste), urinary complaints, gonorrhoea (infusion) and dressing wounds (fresh leaves). Carpine, an alkaloid with an intensively bitter taste has strong depressant action on the heart was obtained especially from papaya leaves (4).

The leaf extract acts as a potent tumour-destroying agent which consists of various phytoconstituents such as cardiac glycosides, tannins, saponins and alkaloids (such as carpaine, pseudocarpaine and dehydrocarpaine I and II) that prevents the destruction of the bone marrow thereby increasing its ability to produce platelets. Further, they can increase the life of platelet in circulation by preventing platelet destruction in the blood (5,6). The liquisolid compaction technique is applied for the conversion of free flowing mass into a compacted, single unit dosage form which enhances the rate of dissolution of drugs, in suitable non-volatile

solvents. The process involves simple blending of the liquid drug or mixture with excipients like carriers such as microcrystalline cellulose and coating material like colloidal silica which results in the formation of damp mass of apparently dry, readily compressible powder. The concentrations of the carriers, coating materials, disintegrants, lubricants and glidants influence on the non-sticky, easily compressible blend, which can be directly compressed. The present modified liquisolid technique involves the compaction of the herbal extract into a powder mass that facilitates in enhancing the solubility/dissolution and stability of the active ingredients.

Lozenges are solid dosage forms that dissolve slowly in the mouth which contains the active ingredient along with sweetening agents to enhance their taste ensuring that the medication is in contact with the mouth tissues for a certain period of time which in turn enhances absorption(7). Soft lozenges have a smooth texture which is typically made of ingredients such as polyethylene glycol (PEG), chocolate, or a sugar-acacia base. These lozenges can be hand rolled and then cut into pieces which contain the required amount of active ingredient or they can be made by pouring the warm mass into a plastic troche mold as well(8). The liquisolid compacts as well as lozenges are oro-dissolving systems intended for faster and complete absorption. The aim of the study is to design the oro-dissolving system using Carica papaya extract for enhancing its therapeutic effects.

Materials and Methods

Green Carica papaya leaves were collected from Thirumalaisamudiram (Thanjavur). Mannitol, Lactose Monohydrate, Cellulose Micro Crystalline, Magnesium Stearate, Talc, PEG 4000, PEG 600, and Acacia was purchased from SD Fine chemicals Ltd, Mumbai, India. All buffer reagents were of analytical grade.

Preparation of Extracts

Cold extraction

The collected green Carica papaya leaves were washed with distilled water from which 50 grams of the leaves were crushed and grounded in a blender using 200 ml of distilled water in order to obtain the juice from the fresh leaves (9).

Maceration

An aqueous extract of Carica Papaya was prepared with 100% distilled water by adding 50g of fresh cut leaves in to 200 ml of distilled water. The mixture was kept in the room temperature for two days. At the end of the first day the water containing the extract was filtered and collected, then it was resuspended with 200ml fresh distilled water and the maceration was continued again for the next day. Finally both extracts were combined.

Concentration of Extract

The mixture was heated at 50-60˚ C for 48 hours. The procedure involves simple decoction process of the aqueous extract from which the soluble compounds further heated at a higher temperature of 70-75˚C for 3 hours until the solvent gets evaporated completely. Temperature was maintained to avoid the charring of the product. The obtained dry product was weighed and the yield was noted (10,11).

Preparation of Liquisolid Granules

Table 1. Preparation of liquisolid granules

Ingredients	Maceration method(g)	Cold extraction (g)
Dried leaf extract	5	3
Lactose monohydrate	4.25	4
Mannitol	4.25	4
Cellulose	4.25	4
Total weight	**17.75**	**15**
Magnesium Stearate	1.99%	-
Talc	1.99%	-

The concentrated extract of Carica papaya was mixed with the excipients such as microcrystalline cellulose, lactose monohydrate and mannitol (1:1:1 ratio) in order to increase its bulkiness and to convert in to a powder mass with passable flow property and compressibility. It was passed through sieve no: 25 in order to break the lumps to get uniform granules in which talc and magnesium stearate were added finally. The total weight of the granules was noted (12, 13). (Table 1)

Pre-Formulation Evaluation of Granules (14, 15)

Angle of repose

The flow property of the granules was assessed by funnel method. The weighed granules were passed through a funnel which was placed at a height of 5cm from the base. The height and diameter of the pile was noted from which the angle of repose was calculated using the formula,

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

Where, θ = Angle of Repose
h = Pile height
r = Radius of pile

Bulk density

The granules were accurately weighed and the height was measured in a 100 ml graduated cylinder after it was levelled from which the unsettled volume (Vo) was noted. The bulk density was calculated as,

$$\textbf{Bulk Density } (\rho o) = \frac{M}{Vo}$$

Where, M = Mass of powder taken; Vo = Apparent unsettled volume (Bulk volume)

Tapped density

The accurately weighed granules was transferred to a graduated cylinder from which the tapped density was determined by tapping the measuring cylinder containing pre-weighed granules (M) gently on a wooden plane from 1 inch (h) above, at regular intervals of 2 s for 500 times. Tapped density is the ratio of weight of sample to tapped volume.

$$\textbf{Tapped density } (\rho t) = \frac{M}{Vt}$$

Where, M = Weight of granules; Vt = Tapped volume of granules in cm^3

Carr's index

Carr's index also called as compressibility index, is an expression for porosity of the granules which is a simple indication for good flow of a material. Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined using the formula,

Preparation of Tablets

The liquisolid granules were compacted as tablets by direct compression method with uniform average weight using the single punch tablet machine (Khera Instruments, New Delhi). The machine was adjusted accordingly to get the desired size and weight (16, 17).

Evaluation of Liquisolid Tablets (18, 19, 20)

Weight variation test

The weight variation test was carried out for 20 tablets randomly by weighing each tablet individually and their average weight was calculated.

Thickness and diameter

The thickness and diameter of the five tables was determined by using Vernier calipers.

Friability

10 tablets were weighed and placed in the Roche friabilator test apparatus which is then subjected to rolling for repeated shocks, resulting from free falls within the apparatus. After 100 revolutions the tablets were de-dusted and weighted again. The tablets that loose less than 1% weight were considered to be compliant. The friability was determined from the expression,

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \text{ x } 100$$

Hardness

Hardness of the tablets was determined using Monsanto hardness tester. The tablet to be tested was placed between the spindle and anvil, and a desired pressure was needed to hold the tablet in position followed by moving the screw knob in clockwise direction untill the tablet was broken. The reading was noted, that indicates the pressure needed to break the tablet which was indicated in Kg/cm^2.

Disintegration time

Disintegration time of six tablets was calculated using disintegration test apparatus (Lab India DT100). Each tablet was subjected into the tube of the basket rack assembly of the disintegration apparatus without disc. The assembly was positioned in the beaker containing disintegration media (water) maintained at 37±2°C and the time required for complete disintegration, was recorded as disintegration time.

Soft Lozenge Formulation Procedure

Soft lozenges were prepared from PEG 600 and 4000 in the ratio of 1:1 (10 g each), with gum acacia base (0.5g) which provided texture and smoothness to the lozenge. The formulation procedure required heating process of about 50˚C (21, 22). The PEG was melted in a water bath to which acacia was added and mixed well. Then the raw extract was immediately poured into moulds and then cooled, which was placed in freezer for complete solidification and then the lozenges were removed from it.

Evaluation of Lozenges

The average weight of 20 lozenges prepared by both cold extraction and maceration techniques were calculated. The thickness, diameter and the disintegration time were measured in a procedure similar to that performed for tablets. The results were tabulated.

Gcms Protocol

In order to find the individual components present in the aqueous extract of Carica papaya leaves, GC Clarus 500 Perkin Elmer system was interfaced to a Mass Spectrometer. The conditions employed were, Column: Elite 5 MS (5% phenyl 95% dimethyl polysiloxane), Dimensions: 30 x 250 µm, Carrier gas: Helium, Constant flow rate of 1ml/min, Injection volume: 10µl, Injector temperature: 270°C, Ion-source temperature : 200°C, Oven programming: 50°C at 8°C / min to 200°C for 5 min and to 280°C for 10 min and MS range: 40 – 600 amu using electron ionisation. Also the temperature conditions for transfer line and source were 200°C and 180°C, respectively. The data obtained was correlated with the existing data in NIST (National Institute of Standards and Technology).

XRF Analysis

XRF study was performed for the optimized tablet to estimate the percentage of metal ion concentration in the formulation. The elemental analysis was done for components such as calcium, iron, silica, titanium, sodium, lead, nickel, magnesium, etc. Aluminium cups were filled with boric acid and then 1 gram of tablet sample was used to finely cover the boric acid. The aluminium cups were pelletized using a hydraulic press at 25 tons to obtain 34 mm diameter pellets. The sample was analyzed under vacuum conditions in oxide mode using XRF spectrometer (Model: Bruker S8 Tiger) equipped with a 4 KW, Rh anode X-ray tube. The concentration of the elements was expressed in ppm.

Microbial Load

The microbial load was estimated for the selected batch of tablets to determine its sterility and stability. The formulations were checked for the presence of colonies due to the presence of microorganisms such as E.Coli, Salmonella species, Shigella species and Streptococci. 1gm of powdered tablet sample was taken and added to 9 ml of sterile distilled water for preparing the serial dilution. The samples in the flask were kept in a mechanical shaker for few minutes to obtain the uniform suspension. 1 ml of the 10^{-1} dilution solution was transferred to 9 ml of sterile distilled water. This dilution was 1: 100 or 10^{-2}. This procedure was repeated up to 10^{-7} dilution. 0.1 ml of serially diluted samples was inoculated into the sterile plate containing Nutrient agar, Salmonella Shigella Agar (SSA) and Potato Dextrose Agar (PDA) medium by spread plate method. Nutrient agar and SSA plates were incubated at 37ºC for 24 hours and PDA plates were incubated at room temperature for 3-5 days. Bacterial and fungal colonies were counted using colony counter and checked for its standard limits.

Results and Discussion

Pre Formulation Studies for Liquisolid Granules

Table 2: Pre-formulation evaluation of granules

Parameters	Maceration	Cold extraction
Angle of Repose (˚)	29.43±1.10	25.26±1.34
Bulk density (g/ml)	0.638	0.551±0.06
Tapped density (g/ml)	0.869±0.0185	0.755±0.01
Compressibility index (%)	36.20	36.89
Percentage Yield (%)	89.43	83.06

The percentage yield was found to be greater than 80% for both granules which was prepared using maceration method and cold extraction of Carica papaya leaves, respectively.Flow properties of the powder and resistance of particle to particle movement can be judged by using angle of repose. The angle of repose was greater than 25%, indicating acceptable flow properties. The compressibility index falls in the range of 36% for both granules prepared using different extraction methods. Also the prepared blends showed good compatibility properties. All the tablets were prepared under similar conditions and were found to satisfy the required standard qualities. The values of pre-compressional parameters evaluated were found to be within prescribed limits, indicating the suitability for compression process (15).

Evaluation of Tablets

As per pharmacopoeial limits, a deviation of 7.5 % is allowed for approximately 300 mg average weight compact granules. The weight of the tablets was within the range of 274.45 to 318.95 mg. The compacts, prepared with maceration extracts were found to show uniform hardness of 2 Kg/ cm^2 whereas the cold extraction method showed an average hardness of 2.16 Kg/ cm^2, indicating good mechanical strength. Diameter and thickness were found to be 8.6 mm and 4.9-5.5 mm, respectively. In all the formulations the friability value was less than 0.25% giving an indication that the tablets formulated were mechanically stable. The percentage weight variation was within the limits. The disintegration time was less than 15 minutes for different formulations (15, 19) (Table 3)

Table 3: Evaluation of tablets

Parameters	Maceration	Cold extraction
Weight variation (mg)	348±17.4	284.42 ±11.94
Thickness(mm)	5.45±0.055	4.91± 0.06
Diameter (mm)	8.69±0.011	8.66± 0.03
Hardness(kg/cm²)	2±0	2.16±0.28
Disintegration time (min)	10-11	7
Friability (%)	0.23	0.23

Evaluation of Soft Lozenges

The average weight, thickness, diameter and disintegration time were calculated for the soft lozenges prepared by both cold extraction and maceration methods, and the results obtained were tabulated. (Table 4) Since the mold used for both maceration and cold extraction were same, hence their diameter and thickness differences were negligible .The average weight was more in the tablets prepared by cold extraction (818.05mg) than maceration (770.33 mg), due to the high density of cold extract when compared to the extract prepared by maceration. The same reason could be attributed for longer disintegration time in the former (3-4 minutes) compared to the latter (1.05 minutes).

Table 4: Evaluation of Soft Lozenges

Parameters	Maceration	Cold extraction
Average Weight(mg)	770.33	818.05
Thickness (mm)	4.97±0.35	5.07±0.04
Diameter(mm)	14.11±0.31	14.13±0.11
Disintegration time(min)	1.05	3-4

Gas Chromatography and Mass Spectroscopy

Analysis of Compounds Present in Plant a by GC-MS

The molecular analysis of compounds in alcoholic extract of Carica papaya was studied using Gas Chromatography Mass Spectroscopy Analysis and the identified compounds were listed in table 5 and the spectrum is shown in figure1. Around 24 compounds were identified in the GC-MS spectrum of Carica papaya leaves extract. From the GC-MS analysis, it was observed that 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, cis,cis,cis-7,10,13-Hexadecatrienal, n-Hexadecanoic acid and 2-Pyrrolidinone were present in higher composition and had a maximum peak area of 24.70% ,29.044%, 16.73% and 12.96 % respectively, while the other peaks had an area lesser than 4% indicating the lower concentration. The GC-MS analysis of already existing data reported that, the presence of 12 major compounds consisting of one piperidine alkaloid, two organic acids, six malic acid derivatives, and four flavonol glycosides with a similar spectrum (23).

Table 5: List of fragmented compounds

S. No.	Peak Name	Molecular Formula	Molecular weight	Retention Time	Peak Area	% Peak area
1.	Ethane, 1,1-diethoxy-	$C_6H_{14}O_2$	118	0.7675	3.68	1436283
2.	Diglycerol	$C_6H_{14}O_5$	166	2.1357	10.65	3996790
3.	2-Pyrrolidinone	C_4H_7NO	85	12.9651	11.82	24262978
4.	7-Hexadecene, (Z)-	$C_{16}H_{32}$	224	0.2368	16.66	443203
5.	6,11-Dimethyl-2,6,10-dodecatrien-1-ol	$C_{14}H_{24}O$	208	0.0188	17.83	35176
6.	Phenol, 2,4-bis(1,1-dimethylethyl)-	$C_{14}H_{22}O$	206	0.9331	19.01	1746271
7.	3-Octadecene, (E)-	$C_{18}H_{36}$	252	0.5217	19.84	976310
8.	Phthalic acid, ethyl pentyl ester	$C_{15}H_{20}O_4$	264	0.1445	20.20	270421
9.	2(1H)-Pyridinethione, 3-hydroxy-	C_5H_5NOS	127	0.1118	20.35	209273
10.	3-Eicosene, (E)-	$C_{20}H_{40}$	280	0.3072	23.10	574842
11.	2-Hexadecene, 3,7,11,15-tetramethyl-, [R-[R*,R*-(E)]]-	$C_{20}H_{40}$	280	1.3809	23.88	2584184
12.	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	$C_{20}H_{40}O$	296	24.7080	24.05	46238744
13.	3,7,11,15-Tetramethyl-2-	$C_{20}H_{40}O$	296	3.8675	24.64	7237650

	hexadecen-1-ol					
14.	4,8,12-Tetradecatrien-1-ol, 5,9,13-trimethyl-	$C_{17}H_{30}O$	250	0.2103	26.20	393501
15.	5-Hexen-3-ol, 2,2,4-trimethyl-	$C_9H_{18}O$	142	0.1614	26.44	302124
16.	3-Undecene, (E)-	$C_{11}H_{22}$	154	0.9397	27.43	1758534
17.	n-Hexadecanoic acid	$C_{16}H_{32}O_2$	256	16.7326	27.89	31313546
18.	1-Hexadecanol	$C_{16}H_{34}O$	242	0.4681	30.21	875978
19.	3-Eicosene, (E)-	$C_{20}H_{40}$	280	0.4083	30.55	764042
20.	Phytol	$C_{20}H_{40}O$	296	1.8689	30.65	3497463
21.	cis,cis,cis-7,10,13-Hexadecatrienal	$C_{16}H_{26}O$	234	29.0445	31.68	54354232
22.	Farnesol isomer a	$C_{15}H_{26}O$	222	0.3991	34.86	746857
23.	1,3-Cyclopentadiene, 5-[3-(dimethylamino)propyl]-	$C_{10}H_{17}N$	151	1.4115	36.42	2641488
24. Y	All-trans-Squalene	$C_{30}H_{50}$	410	0.2571	43.41	481199

XRF Analysis

From the XRF results of the Carica papaya leaf extract tablets, it was observed that, elemental potassium (K) was present in high amount which was around 54.65 %, followed by Magnesium (Mg) 12.10 %, Elemental copper and molybdenum which were present in low quantity in the range of 0.08 %. In terms of oxide compounds, silicon-di oxide was found in high percentage of about 25.21 % followed by Potassium oxide (K_2O – 21.46%) and Copper (II) oxide which has the least present oxide compound at 0.11 %(Table 6).From the previous studies, it was found that, sodium was present in the highest quantity followed by potassium, while phosphorous was found in least quantity. Among micro elements, Iron was found in highest quantity while Boron was found to be the least (24).

Table 6: Element and oxide form using XRF analysis

Element Form		**Oxide Form**	
Formula	**Concentration (%)**	**Formula**	**Concentration (%)**
K	54.65	SiO_2	25.21
Mg	12.10	K_2O	21.46
Si	11.79	MgO	20.07
Ca	9.29	CaO	13.00
Cl	4.36	SO_3	6.05
P	2.49	P_2O_5	5.71
S	2.42	Cl	4.36
Fe	1.24	Fe_2O_3	1.77
Na	0.59	Al_2O_3	0.90
Al	0.47	Na_2O	0.79
Pb	0.42	PbO	0.45
Cu	0.08	MoO_3	0.12
Mo	0.08	CuO	0.11

Microbial Limit Test of Carica Papaya Leaf Extract Tablets

From the obtained results of microbial limit test, it was found that total viable aerobic count and total fungal count are within the limits as per the standard Indian Pharmacopoeia. All the three microorganisms such as E Coli, Salmonella and Shigella were absent in the extract and hence it was proved that the herbal formulation was safe to administer orally. (Table 7) Also the stability of the formulation and sterility of processing conditions were identified to be satisfactory.

Table 7: Microbial limit test of Carica papaya leaf extract tablets

S. No.	Tested Microbial	Results	Indian Pharmacopoeia	Inference
1.	Total viable aerobic count	$3.5x10^5$ CFU/g	$<10^7$ CFU/g	Within limits
2.	Total fungal count	<10 CFU/g	$<10^4$ CFU/g	Within limits
3.	E.Coli	Absent/g	Absent/g	Absent/g
4.	Salmonella	Absent/g	Absent/g	Absent/g
5.	Shigella	Absent/g	Absent/g	Absent/g

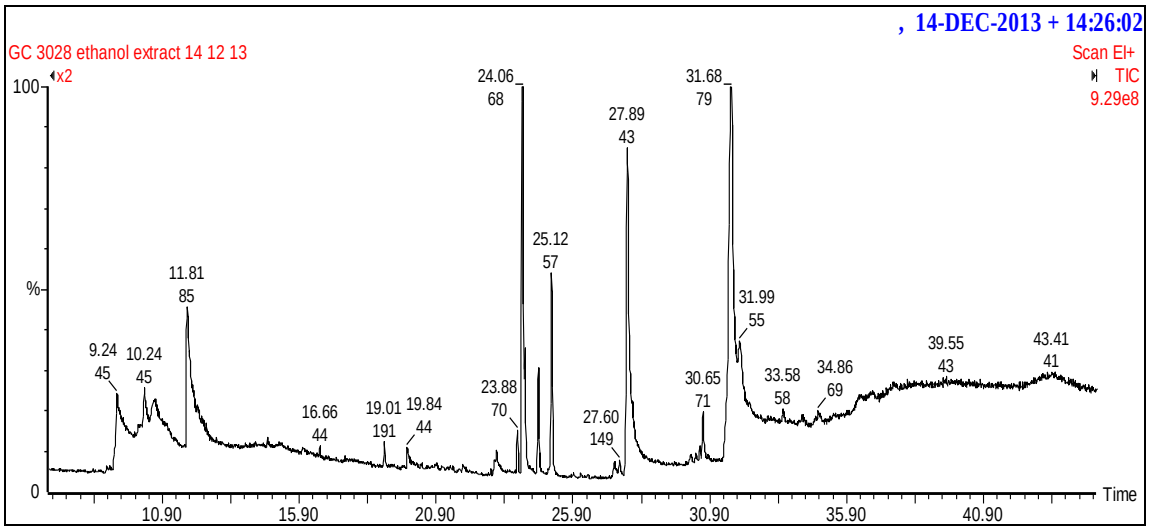

Figure 1. GC-MS of aqueous extracts of Carica papaya leaves

Conclusion

The study involves the formulation of fresh leaf extracts of *Carica papaya* into a liqui-solid compaction and soft lozenge formulation by both maceration and cold extraction methods. The pre compression and post compression parameters of the tablets were found to be desirable. The results of uniformity in weight, hardness test and friability test indicates its aptness for effective packing, transport and marketing. The disintegration time within the standard limits ensures perfect release of the active components *in-vivo*. Scale up studies can be performed for application at industrial scale.

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