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Original Research Article

Exploiting lemon peel extract in orodispersible granule formulation using green banana flours as natural superdisintegrant

Afroj Ayyaj Shaikh[1]*, **Sayali G Zambare**[1], **Digvijaysingh R. Kale**[1], **Ahamefula Anslem Ahuchaogu**[1]

[1] *Dept. of Pharmaceutics, Shri. Siddhivinayak Institute of Pharmacy, Jamunavata, Uttar Pradesh, India*

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ABSTRACT

Background: Amidst the global COVID-19 pandemic, there is an urgent need to bolster immunity. This study endeavors to address this necessity by formulating orodispersible herbal granules enriched with lemon peel extract, recognized for its immune-boosting attributes.
Materials and Methods: The extraction of lemon peel was facilitated through ultrasound, followed by meticulous evaluations encompassing color, solubility, and yield. Disintegrants, ranging from 2% to 6% concentrations of banana flour, were incorporated into granule formulations. The compatibility of lemon peel extract with other constituents was scrutinized via FTIR and DSC analyses. Utilizing a design-of-experiment (DoE) strategy employing a 32 full factorial design, formulations were synthesized and assessed for various parameters, including flow properties, density, disintegration time, and release attributes.
Results: Analysis revealed lemon peel extract's significant phenolic content (185 mg Gallic acid equivalent/gm) and flavonoid content (170 gm Quercetin equivalent/gm of extract). The orodispersible granules exhibited favorable flow properties, demonstrating rapid dissolution within 45 to 59 seconds. In vivo assessments showcased heightened immune-boosting efficacy. Moreover, the optimized batch displayed superior in-vivo bioavailability, attaining a peak plasma concentration at 1 hour (88.47 ng/ml).
Conclusion: The successful development of herbal granules amalgamating lemon peel extract and banana flour underscores their potential to enhance immunity during the COVID-19 pandemic. These formulations exhibit commendable attributes of quality, consistency, and stability, promising substantial benefits in augmenting immune response.

1. Introduction

In the food industry, citrus fruits are widely used to make drinks, concentrates, jams, jellies, juices, and preservatives. The main component of citrus waste is lemon peels, which make up about 50% of the fruit's mass.[1] Despite being rich in a range of bioactive metabolites, the peel waste produced following the usage of fruit pulp is primarily disposed of as waste. Peels contain abundant bioactive compounds like flavonoids, phenolic acids, and natural antioxidants. These elements are commonly utilized in healthcare preparations and contribute to averting chronic ailments. As a result, there is an increasing demand in the market for these enhanced-value products.[2]

Lemon, or citrus limonum, is one of them. Lemon essential oils shown potent antioxidant and anti-proliferative properties against HeLA cell line. It was discovered that the peel extracts have antimicrobial and antifungal qualities, as well as decreased blood vessel permeability and potential use in phlebitis treatments. They even inhibited the formation of atypical skin growths and reduced the incidence of squamous cell skin melanoma.[3]

* *Corresponding author*.
E-mail address: afrojs952@gmail.com (A. A. Shaikh).

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There are now several orodispersible medication formulations available on the market. The therapeutic choices have been enhanced by the use of oral lyophilisates and orodispersible granules, pills, or films. The benefits such as easy use, no swallowing, and comfortable administration may be especially beneficial to the juvenile and geriatric populations. Because the research and production of innovative products are typically more expensive than those of standard oral medicine dosage forms, such as tablets or capsules, only a small number of them have reached the market to date. [4,5]

Orodispersible granules (ODGs) represent a form of multi-particulate medication format where multiple small-sized carriers combine to form a singular dosage of active pharmaceutical ingredient (API). The carriers are made using granulation techniques and are either sprinkled on soft food prior to oral administration or given directly into the patient's mouth. ODGs disperse after delivery throughout the oral mucosa. As a result, the make it simple to administer and customize the dose, which is particularly helpful for populations that are younger and older. [6]

In the present study formulation of ODGs are formed by using extrusion and spheronization techniques. The granules of lemon peel extract are prepared using green banana flours as natural superdisintegrant.

2. Material and Methods

Lemon (Citrus limon) sample was collected from the local market. The peels were dried and powdered. Green bananas (Musa acuminate) were bought from the local market. Lactose was procured from Loba Chem Pvt Ltd Mumbai.

The general procedures and animal usage protocol for conducting this study underwent scrutiny and received approval from the Institutional Animal Ethics committee. All aspects related to animal experimentation adhered strictly to the recommendations outlined in the Guide for the Care & Use of Laboratory Animals and complied with the guidelines set by the Committee for Control and Supervision of Experiments on Animals (CCSEA). Every ethical practice specified in the CCSEA guidelines for animal care was followed meticulously during the procedures. (CCSEA Registration No.: 2105/PO/RcBt/S/20/CPCSEA)

2.1. Preparation of lemon peel extract

The lemons were washed using tap water and afterwards using distilled water. Following the cutting of lemons into small segments, the peel and pulp were segregated, and subjected to drying in a hot air oven at 80 °C. The dehydrated peels underwent mill processing to achieve a fine powder consistency. Only the material that cleared an 80-mesh sieve was kept safe for usage. The extraction of lemon peel powder was done using the ultrasound assisted extraction (USAE) technique. All during the process, the temperature was kept at 40 °C. Filtration was done on the extract obtained. The filtrate was evaporated at 40 °C in a rotating evaporator. After achieving concentration, the resultant substance was dried for formulation by evaporating it in porcelain. [7,8]

2.1.1. Preparation of banana flours

Unripe bananas underwent a cleaning process and were rinsed with water. These green banana fruits were utilized to create two varieties of thin slices: one comprising both the banana pulp and peel, while the other solely consisted of the banana peel. In order to maintain consistent moisture levels, each slice was subjected to an 8 hour drying period at 70°C within a controlled laboratory oven. The resultant dried substance was finely ground into banana flour. This powder was then tightly sealed and kept at room temperature for subsequent analysis and study. [9–11]

2.1.2. Characterization of lemon peels extract

Phytochemical screening of lemon peels extract

Standard protocols were employed to conduct tests for carbohydrates, tannins, flavonoids, alkaloids, and glycosides.

2.1.3. Total phenolic content (TPC)

The total phenolic content of the lemon peel was assessed using the Folin-Ciocalteu reagent. Test tubes containing different sample aliquots along with Gallic acid (ranging from 0.2 to 1.0 ml) were prepared. To each tube, 3 ml of distilled water was added, followed by the introduction of 0.5 ml of Folin- Ciocalteau reagent. Subsequently, 2 ml of a 35% Na2CO3 solution was added to each tube and thoroughly mixed after a 3-minute interval. The mixture was then subjected to a precisely timed one-minute boiling water bath. After cooling, the absorbance at 725 nm was measured in comparison to a blank reagent. A standard curve was established by using various concentrations of Gallic acid. [8]

2.1.4. Determination of total flavonoids

1 ml of lemon peel extract was placed in a 10 ml volumetric flask. To this, 0.30 ml of 5% sodium nitrite and 4 ml of distilled water were added. After a 5-minute interval, 0.3 ml of aluminum chloride was introduced, followed by the addition of 2 ml of 1 N sodium hydroxide after an additional 6 minutes. The solution was then diluted up to a total volume of 10 milliliters with distilled water. The absorbance was measured at 510 nm using a UV-Visible spectrophotometer to determine the concentration of flavonoids. The concentrations were determined using a quercetin standard curve and expressed as mg Quercetin Equivalents (CE)/100 g of the sample. [11,12]

2.1.5. Fourier transform infrared (FTIR) spectroscopy

FTIR spectroscopy analysis was conducted on lemon peel extract, banana flours, and granules utilizing an FTIR spectrophotometer (FTIR 1-S Affinity) within the range of 400–4000 cm' (-1). Spectra were obtained and subsequently examined for analysis. [13]

2.1.6. Differential scanning calorimetry

Differential scanning calorimetry (DSC 3/500, Mettler Toledo, USA) was employed to investigate the heat-related characteristics of lemon peel extract, banana flour, and granules. The samples underwent heating within a sealed aluminum pan, with an empty sealed pan utilized as a reference. This heating process occurred between 30 and 400 °C under a nitrogen flow of 50 ml/min at a rate of 10 °C/min [14]. Preparation of orodispersible granules. [15–17]

An extruder and spheronizer were used to create herbal granules with lemon peel extract. To create plastic mass, precisely weighed amounts of lactose, banana flours, and lemon peel extract were triturated in a mortor with the aid of pastel. As granulation liquid, an adequate amount of distilled water was added. The extruder was used to pass the prepared bulk through. After that, the extrudates were spheronized using a spheronizer. After being made, the granules were dried and kept in an airtight container.

3. Experimental Design

Utilizing the Design-Expert software (Version-11, State-ease, Inc., Minneapolis, MN, USA), a complete 3^2 factorial design was formulated to explore the separate and combined impacts of independent formulation variables on the crucial quality attributes of ODGs. This approach involved the examination of two independent variables across three distinct levels. Table 1 demonstrates the studied independent formulation variables: banana peel concentration (X1) and superdisintegrants concentration (X2). Table 2 displays the entire design matrix that the software produced. The percentage of drug release after 15 minutes (Y2) and the disintegration time (Y1) were selected as the dependent responses. The various test findings were displayed as mean ± standard deviation (SD). The data were statistically analyzed using the ANOVA test using Design Expert 11 software. P-value was less than 0.05, which deemed statistically significant.

Table 1: Independent formulation variables

Coded Levels	Concentration of banana peelpowder (%) X1	Concentration ofSuper disintegrant (%) X2
-1	0.5	2
0	1	4
+1	2	6

−1: factor at low level; 0: factor at medium level; 1: factor at high level.

Table 2: A full matrix of 32 full factorial design for orodispersible formulations

Batch Codes	Levels in Coded Form X1	X2
G1	1	2
G2	2	2
G3	0.5	2
G4	1	4
G5	2	4
G6	0.5	4
G7	1	6
G8	2	6
G9	0.5	6

4. Characterization of Orodispersible Granules

The flow properties of the ODG formulations were examined based on their specific characteristics. Assessments were conducted by analyzing various parameters including the, bulk density, tapped density, Carr's index, angle of repose and Hausner's ratio.

4.1. Particle size analysis

Dry sieving method was utilized for the analysis of particle size. The test powder (50g) was placed on the top sieve after the sieves were stacked on top of one another according to the method. After agitating the sieve nest for a predetermined amount of time (20 minutes), the weight of the material retained on each sieve was precisely calculated to provide the weight % of powder in each sieve size range and average particle size. [18]

4.1.1. In vitro disintegration test

A USP disintegration tester was employed to ascertain the Disintegration Time of the prepared granules. The disintegration process occurred within a medium of 900 mL distilled water, maintained at a temperature of 37 ± 0.5 ∘C. The duration taken for complete breakdown of the granules was measured and recorded in seconds. [19]

4.1.2. Dissolution study

The granules dissolution investigation was carried out using the USP class II dissolve test apparatus. A phosphate buffer dissolving media (900 ml) with a pH of 6.8, 37 °C, and 50 rpm was used for the dissolution test. To maintain a consistent volume, 5 ml of a sample was withdrawn every minute and then added back. After passing the sample through Whatman filter paper, the absorbance at 725 nm was measured. Next, using an already-created calibration, the amount of drug delivered was estimated [14].

4.1.3. In-vivo pharmacokinetics and immunomodulatory animal study

The purpose of this study was to assess the pharmacokinetics and immunomodulatory effect of granules made from extracts of lemon peel in lab animals. Swiss albino mice were given cyclophosphamide (100 mg/kg s.c.) to induce immunosuppression. The mice were then given a formulation of granules containing extracts from lemon peels for the next ten days in a row. Every animal receiving treatment was monitored for any death or illness, and on the fifth and tenth days of the course of treatment, body weight was measured. When the treatment period was over, the animals were put to sleep, and blood samples (platelets, red blood cells, and white blood cells) were taken for haematological study. An incision was performed in the abdomen, the spleen and thymus were removed, and their relative weights were determined using the body weight and absolute weight. The tissue from the spleen and thymus was preserved in a 10% formalin solution before being further processed for a histological analysis. In the pharmacokinetic study, Sprague Dawley rats were given a single dose of lemon peel extract and a formulation of lemon peel extract granules. Blood samples were taken at 5, 10, 15, 30, minutes, 1 hour, and 2 hours intervals. The blood samples were centrifuged at 5000g, and the supernatant serum samples were taken and processed further for HPLC analysis. [20,21]

5. Result and Discussion

5.1.

5.1.1. Phytochemical screening of lemon peel extract

The results obtained after phytochemical evaluation are shown inTable 3.

Table 3: Preliminary phytochemical screening for the evaluation of extract

Test	Observation	Result
Carbohydrates	Brown color	-
Tannins	Dark blue	+
Saponins	No foam	-
Flavonoids	Pale yellow	+
Alkaloids	Yellow	-
Cardiac glycosides	Brown ring	+
Terpenoids	Light red brown color	+
Phenols	Pale yellow	+

5.2. Total phenolic content (TPC)

By employing the Gallic acid standard curve (y = 0.0257x + 0.1869 R^2 = 0.9774), the total phenolic content within the ethanolic extract derived from lemon peel was measured at 185 mg GAE/g of the lemon peel extract.

5.2.1. Determination of total flavonoids

Using the standard curve of Quercetin (y = 0.0121x + 0.0018, R^2 = 0.987), the flavonoid contents of, ethanolic extract of lemon peel was found to be 170 mg Quercetin equivalent/g of lemon peel extract.

5.3. Fourier transform infrared (FTIR)

FTIR investigations were conducted to detect potential molecular interactions between Lemon peel extract and Banana flour. The FTIR spectra of Lemon peel extract, Banana flour, and orodispersible granules formulated using these components are depicted in Figure 1. The prominent cellulose peak within the fingerprint area of 1100–1200 cm–1 in the FTIR spectra suggests the fundamental skeleton of lemon peel extract as cellulose. Bands observed at approximately 1650 and 1750 cm-1 signify the presence of free and esterified carboxyl groups, which aid in identifying pectin within the Lemon peel extract. Additionally, a broad peak spanning between 3000 cm-1 and 3600 cm–1 indicates the stretching vibrations of free or hydrogen-bonded hydroxyl groups found in phenols, alcohols, carboxylic acids, cellulose, pectin, lignin, and similar components. [22]

5.3.1. Differential scanning calorimetry

The DSC graphs presented in Figure 2 illustrate the thermal behavior of Lemon peel extract, Banana flour, and Orodispersible granules. Specifically, the DSC plot of Lemon peel extract displays an endothermic peak at 75.56 °C, signifying its melting point. Meanwhile, the DSC curve of banana flour reveals a prominent and broad endothermic effect occurring between 58–128 °C (with a peak Tmax = 89.81 °C), likely attributed to dehydration processes. Furthermore, the expansive endothermic peak observed at 107 °C suggests a robust interaction or bonding between the extract and banana flour [13,23]

5.3.2. Formulation of orodispersible granules

The natural superdisintegrant banana flours in varying concentrations (2-6%) were used to develop different formulations of lemon peel extract by extrusion and spheronization method as shown in Table 4.

5.4. Optimization by factorial design

3^2 factorial design was selected and as required 9 batches were prepared. The ranges of Y1 and Y2 are 45- 59 sec and 96.2-98.1 % respectively as shown in Table 5. For all the responses observed for 9 formulations prepared were simultaneously fitted to Quadratic, linear, 2FI, cubic models using Design Expert (Version- 11, State-ease, Inc., Minneapolis, MN, USA) It was observed that the best fitted model for disintegration time and % drug release was Quadratic. It is evident that all the two independent variables, namely the concentration of banana peel powder

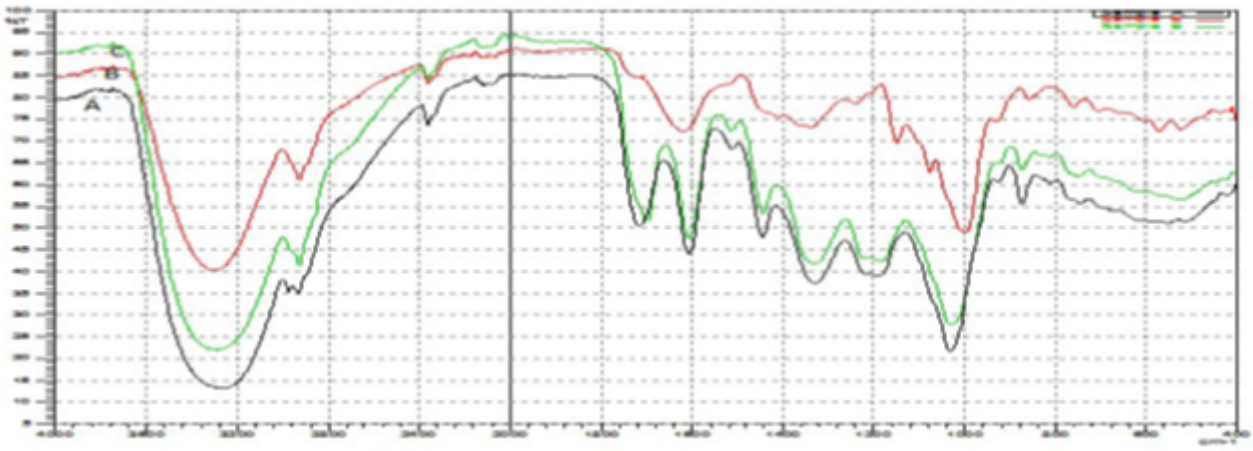

Figure 1: FTIR spectra of A Lemon peel extract, B Banana flour, and C Orodispersible granules

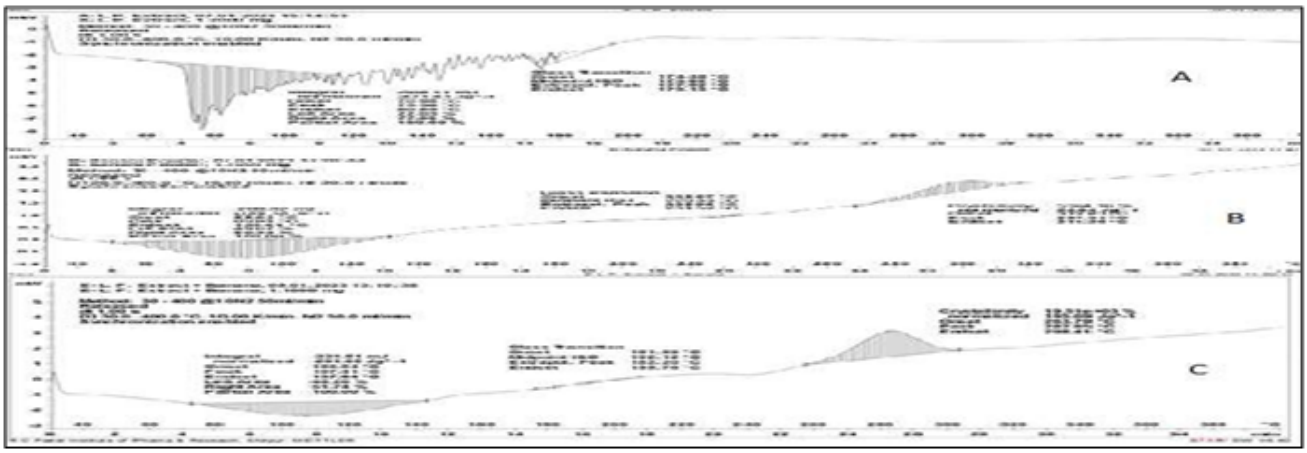

Figure 2: DSC thermo grams of A) Lemon peel extract, B) Banana flour and C) Orodispersible granules

Table 4: Formulations of orodispersible granules of lemon peel extract.

Ingredients	G1	G2	G3	G4	G5	G6	G7	G8	G9
Lemon peel extract	200	200	200	200	200	200	200	200	200
Banana peel powder	3	4	2	6	8	4	9	12	6
Whole banana powder	3	2	4	6	4	8	9	6	12
Lactose	94	94	94	88	88	88	82	82	82

Table 5: 32 Full factorial design layout (Odgs)

Batch Codes	Levels in Coded Form		Disintegration Time	% Drug Release
	X1	X2	(s)	(%)
G1	1	2	50	97.4
G2	2	2	49	97.5
G3	0.5	2	52	97.0
G4	1	4	47	97.9
G5	2	4	45	98.1
G6	0.5	4	48	97.7
G7	1	6	56	96.7
G8	2	6	54	96.9
G9	0.5	6	59	96.2

and % of banana flour respectively have interactive effects on the two responses, Y1(disintegration time) and Y2 (% drug release). A positive value represents an effect that favors the optimization, while negative values indicate an inverse relationship between the factor and the response. Hence, the goals were set for responses Y1 and Y2 in Design Expert software.

5.5. Contour plots and response surface analysis

Two dimensional contour plots were prepared for both the responses and are as shown in Figure 3 for responses Y1 and Y2 respectively. The 3D surface plots for both responses are depicted in Figure 4 for responses Y1 and Y2 respectively. These plots are known to study the interaction effects of the factors on the responses.

Figure 3: Contour plot A. Disintegration time B. Drug release

6 and 7 display both the observed and anticipated values for the response variable. Consequently, it can be inferred that the model is highly appropriate, given the minimal disparity between the experimental and predicted values.

Regression Equation of Response

Final Equation in Terms of Coded Factors

Disintegration time = +45.85-1.83X1+2.95X2-0.4821X1X2+0.8750X12+6.67X22

Regression Equation for response

% Drug release =+98.08+0.2667X1-0.3446X2+0.0482X1X2-0.2125X12-0.9500X22

5.5.1. Evaluation of granules (Angle of repose, bulk and tapped density and Carr′s index)

Table 8 Displays the findings of the flowability investigation. According to the findings, all formulae exhibited good flow characteristics.

5.6. Average particle size

The particle size analysis was done using sieve analysis method and was found in the range 500-750 μm for all the formulations. The mean diameter of the granules was found to be 502 μm approximately.

5.6.1. In vitro disintegration time

A key necessity for orodispersible granules is rapid disintegration. The findings from the in vitro disintegration study can be observed in Table 9[13].

5.7. Dissolution study

The % amount of drug released after 10 min obtained for the nine formulations of herbal granules of lemon peel extract are presented in Table 6. The results show that all formulas had a good release profile within 10 minutes. The good release profile of all formulations may be attributed to the presence of natural superdisintegrant banana flour.

Table 9: In-Vitro disintegration time and amount of drug released from granules

Batch code	disintegration time(sec)	Amount of drug released (%)
G1	50±0.32	97.4±0.92
G2	49±0.43	97.5±0.69
G3	52±0.51	97±0.90
G4	47±0.62	97.9±1.62
G5	45±0.46	98.1±0.68
G6	48±0.58	97.7±0.46
G7	56±0.61	96.7±0.52
G8	54±0.65	96.9±0.69
G9	59±0.39	96.2±0.54

5.8. In-vivo pharmacokinetics and immunomodulatory animal study

Lemon peel extract granules formulation and lemon peel extract, systemic Hesperidin concentration were monitored up to 2 hours of time interval. Lemon peel extract granules formulation shows immediate release of hesperidin and gradual increase systemic concentration were observed shown in Table 10. Peak plasma concentration of Hesperidin (granules formulation) were observed at 1hours (88.47ng/ml), of time interval as shown in Figure 5.

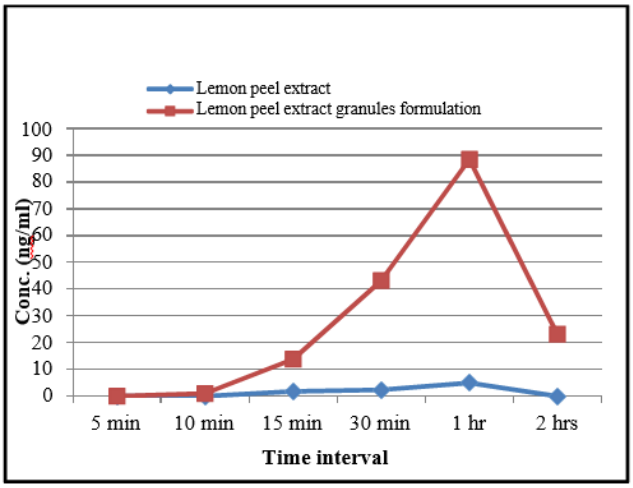

Figure 4: Pharmacokinetics of hesperidin in lemon peel extract & lemon peel extract granules formulation

In this investigation, an in vivo method was employed to assess the impact of the plant extract on the immune system of mice.Figure 6 A illustrates the normal architecture of the white pulp of the spleen under a microscope, devoid of any lymphocyte depletion. A close look at the spleen in Figure B reveals a significant decrease of lymphocytes throughout the white pulp. In Figure C microscopic examination of moderate lymphocyte depletion in white pulp of spleen multifocal.

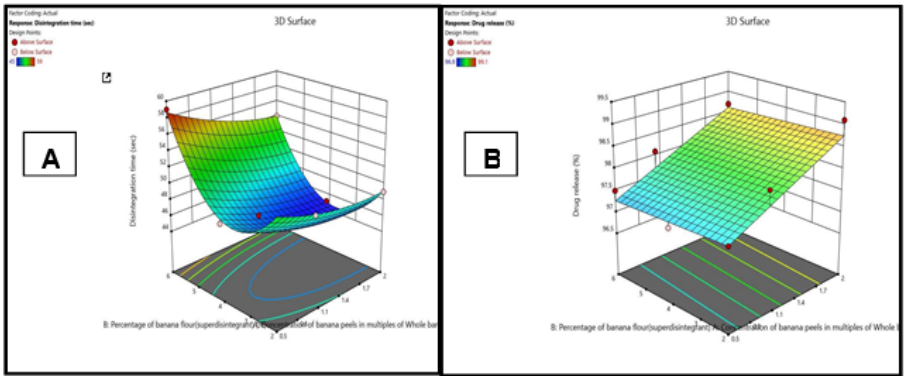

Figure 3: 3D Surface graph A. disintegration time B. Drug release.

Table 6: Experimental and predicted value for the response

Run Order	Actual Value	Predicted Value	Residual	Predicted error (%)
1	50.00	50.12	-0.1151	-0.334
2	49.00	49.09	-0.0913	-0.183
3	52.00	51.79	0.2063	0.403
4	47.00	46.56	0.4444	0.936
5	45.00	44.89	0.1111	0.244
6	48.00	48.56	-0.5556	-1.166
7	56.00	56.33	-0.3294	-0.589
8	54.00	54.02	-0.0198	-0.037
9	59.00	58.65	0.3492	0.593

Table 7: Experimental and predicted value for the response

Run Order	Actual Value	Predicted Value	Residual	Predicted error (%)
1	97.40	97.38	0.0226	0.0205
2	97.50	97.48	0.0202	0.0205
3	97.00	97.09	-0.0429	-0.0927
4	97.90	97.97	-0.0667	-0.0715
5	98.10	98.13	-0.0333	-0.0305
6	97.70	97.60	0.1000	0.102
7	96.70	96.66	0.0440	0.0413
8	96.90	96.89	0.0131	0.0103
9	96.20	96.26	-0.0571	-0.0623

Table 8: Results for the angle of repose, bulk density, tapped density, and carr's index

Formulation Codes	Parameters			
	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Angle of Repose (^{o})
G1	0.571±0.012	0.685±0.013	6.604±1.330	24.34±1.363
G2	0.508±0.015	0.536±0.012	5.621±1.233	23.19±1.221
G3	0.583±0.023	0.585±0.021	4.556±1.422	25.35±1.007
G4	0.387±0.004	0.521±0.002	5.623±1.221	24.49±1.126
G5	0.506±0.013	0.527±0.005	6.792±1.012	25.95±1.096
G6	0.503±0.025	0.533±0.006	6.076±1.231	23.57±1.132
G7	0.509±0.034	0.536±0.014	6.422±1.086	26.53±1.165
G8	0.584±0.013	0.505±0.017	5.432±1.097	26.35±1.136
G9	0.596±0.017	0.624±0.023	7.601±1.242	25.28±1.432

Table 10: Individual animals auc & concentration measurement

Time interval	AUC of Hesperidin in extract formulation Animal No.			Average AUC	Conc. (ng/ml)
	1	2	3		
5 min.	0	0	0	0	0
10 min.	6.2341	4.6231	5.3721	5.4097	0.96
15 min.	14.5267	12.5347	16.8237	14.6283	13.78
30 min.	39.4237	33.5379	34.3972	35.7862	43.20
1hour	71.5193	64.5372	68.9543	68.3369	88.47
2hour	23.5491	20.3641	18.6497	20.8543	23.19

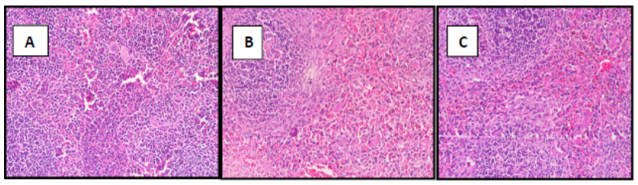

Figure 5: A. Group I: Negative control B. Group II: Positive Control (Cyclophosphamide 100mg/kg s.c.) C. Group III: Lemon peel extracts granules formulation (200mg/kg p.o.)

Figure 7 A illustrates the normal architecture of the cortex and medulla in the thymus tissue under a microscope. Figure B's microscopic view of the thymus reveals a moderate amount of lymphocyte apoptosis in the cortex. A microscopic view of a modest lymphocyte depletion in the thymus cortex is shown in Figure C.

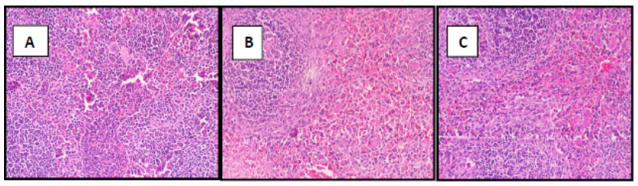

Figure 6: A. Group I: Negative control **B.** Group II: Positive control (Cyclophosphamide 100mg/kg s.c.) **C.**Group III- Lemon peel extracts granules formulation (200mg/kg p.o.)

5.9. HPLC analysis of lemon peel extract

HPLC (High Performance Liquid Chromatography) evaluation of lemon peel extract was done for further quantification of bioactive component as shown in. The experimental conditions are given inTable 11.

Table 11: Chromatographic conditions

HPLC	Agilent (1100) Gradient systemVWD detector with manual injector
Software	Chemstation (10:01)
Column	Id 4.6 x 250mm length
Particle size packing	5.0μm
Stationary phase	RP C-18 (AGILENT)
Compound	Lemon peel extract (Hesperidin)
Mobile Phase	Isocratic HPLC grade water, column temperature kept 40^{o}C during analysis
Detection wavelength	345nm
Flow rate	1ml/min
Temperature	Ambient
Sample size	10μl

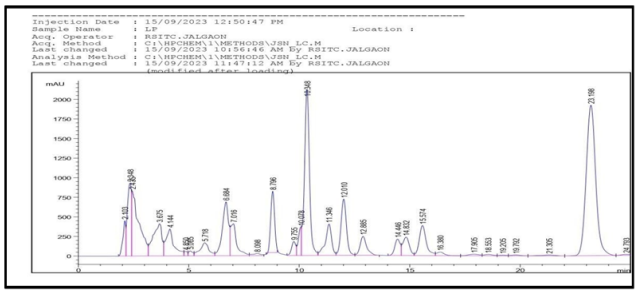

Figure 7: Chromatograph of Lemon peel extract granules formulation

6. Conclusion

Successfully, orodispersible granules containing dried extract of citrus limon were formulated using banana flours as a superdisintegrating agent. The granules underwent assessment for various parameters including bulk density, tapped density, Carr's index, angle of repose, and Hausner's ratio. FTIR analysis indicated no interaction between banana flours and lemon peel extract, confirming their suitability for granule preparation. Statistical analysis using ANOVA with Design Expert 11 software yielded a P-value less than 0.05, signifying statistical significance. The optimized formulation, achieved through extrusion spheronization, demonstrated acceptable disintegration time and percentage drug release. In vivo immunomodulatory testing revealed immune-boosting activity. This research establishes a foundation for employing lemon peel extract as an effective supplemental immunopotentiating treatment. The peak plasma concentration of the granules occurred at 1 hour.

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8. Source of Funding

None.

9. Conflict of Interest

The author declares that they have no conflict of interests.

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Author biography

Afroj Ayyaj Shaikh, Professor https://orcid.org/0000-0001-9189-9848

Sayali G Zambare, Professor

Digvijaysingh R. Kale, Principal

Ahamefula Anslem Ahuchaogu, Professor

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