International Journal of Pharmaceutical Research and Development

ISSN Print: 2664-6862
ISSN Online: 2664-6870
Impact Factor: RJIF 8
IJPRD 2023; 5(1): 01-07
www.pharmaceuticaljournal.net
Received: 01-11-2022
Accepted: 05-12-2022

UN Dungarwal
Department of Pharmaceutics, SNJB's Shriman Suresh Dada Jain College of Pharmacy, Chandwad, Nashik, Maharashtra, India

Dr. AS Mundada
Department of Pharmaceutics, SNJB's Shriman Suresh Dada Jain College of Pharmacy, Chandwad, Nashik, Maharashtra, India

Corresponding Author:
UN Dungarwal
Department of Pharmaceutics, SNJB's Shriman Suresh Dada Jain College of Pharmacy, Chandwad, Nashik, Maharashtra, India

Formulation and evaluation of immunomodulatory orodispersible herbal granules

UN Dungarwal and Dr. AS Mundada

DOI: https://doi.org/10.33545/26646862.2023.v5.i1a.28

Abstract
COVID 19 was declared as a global pandemic by World Health Organization (WHO). The significance of immunity boosters has grown in these demanding circumstances. The objective of the present study is to formulate herbal orodispersible granules by incorporating the extract of lemon peel (*Citrus limon*) having immunomodulatory activity. Better compliance can be achieved by orodispersible granules to pediatric, geriatric, and bedridden patients. The lemon peel extract was obtained by using the ultrasound-assisted extraction technique. The extract was subjected to preliminary organoleptic characterization for color, odor, solubility, and percent yield. Phytochemical screening was performed on lemon peel extract for the qualitative and quantitative analysis of flavonoids, phenolic compounds, etc. Banana flour was used in different concentrations (1-3%) to formulate various batches of orodispersible granules which act as superdisintegrant. The compatibility study was performed for lemon peel extract with excipients using FTIR and DSC. Herbal granules were prepared by extrusion and spheronization technique and evaluated for angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, *In vitro* disintegration time, and *In vitro* release characteristics. The total phenolic content of lemon peel extract was found to be 185 mg Gallic acid equivalent/ gm. While total flavonoid content was found to be 170gm Quercetin equivalent/gm of extract. Orodispersible granules of lemon peel extract were formulated. All batches had shown better flow properties. The granules dispersed rapidly in 39 to 87s. Lemon peel extract was successfully formulated and evaluated as herbal granules using banana flour. Results of the present study revealed that developed formulations may serve as herbal products with better quality, consistency, and stability.

Keywords: Lemon peel extract, phenolic compounds, extrusion and spheronization, orodispersible granules

1. Introduction
The World Health Organization declared COVID-19, a global pandemic. The significance of immunity boosters has grown in these demanding circumstances. Infection risk is higher in people with preexisting conditions such as diabetes, hypertension, and cardiovascular illnesses. Polyphenols benefit the body by improving health in several areas, such as digestion, cardiovascular health, and cognitive function. Flavonoids have hepatoprotective, antiviral, anti-allergic, anti-inflammatory, and anticarcinogenic properties [1, 2].
Phenolic antioxidants can significantly affect the development and prevention of a variety of diseases associated with oxidative stress [3]. Citrus species count among the most versatile sources of phenolic antioxidants. They have good health and nutritional benefits for humans. Additionally, they play a role in boosting the immune system [4]. Citrus peel, whole fruit, and pulp with seeds all contain phenolic chemicals. In comparison to the entire fruit and pulp, lemon peels have a higher concentration of phenolic compounds [5]. During the production of lemon juice, a lot of lemon peel waste is produced. The by-products of lemons are thought to be a cheap source of bioactive compounds that can be used commercially to increase the country's income in the industrial sector [6].
One of the most significant crops in the world is the production of bananas. The postharvest losses for green bananas that are rejected due to flaws and are not suitable for export fluctuate between 5% and 10% [7], resulting in very low-value products or even garbage. Due to their high carbohydrate, protein, high-fiber, and low-fat content, flours made from whole green bananas or their pulp have recently demonstrated their promise as functional ingredients through characterization and techno-functional qualities [8].

It acts as a natural superdisintegrant. Natural polymers and superdisintegrants can be used to create these dosage forms so that they dissolve in the least amount of water possible in less than a minute. The development of tolerance, cost, high toxicity, increased frequency of side effects, and decreased patient compliance due to variables like terrible mouth feel, throat irritation, etc. are all disadvantages of synthetic ingredients. Natural superdisintegrant has added advantages of biocompatibility, low cost of production, and more acceptability by patients. Therefore, the effective and easily available natural superdisintegrant from banana fruit offers secure and effective drug delivery with better patient acceptance [9].

A new class of formulations known as orodispersible drug delivery systems (ODDDS) combines the benefits of both liquid and traditional tablet formulations. These enable both the ease of ingesting offered by a liquid formulation and the comfort of a tablet formulation. When compared to primary choice oral liquids, ODDDS offers more precise dosing [10]. They are a great option for folks who are bedridden or on the go because they don't need water for administration. Psychotic people cannot conceal them in the mouth because when placed there, they just vanish [11].

Granules offer benefits such as faster disintegration and dissolution compared to tablets and capsules, greater acceptability in pediatrics and geriatrics due to lower risk of choking, and less time and money required for their manufacture compared to tablets. They are also more palatable than syrups and decoctions [12].

The aim of this study was the incorporation of dried lemon peel extract into orodispersible granules. Green banana fruit flour was used as a natural superdisintegrant in the formulation of orodispersible granules.

2. Materials and Methods

Lemon peels were obtained from the fruit processing industry to carry out this study. 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.

2.1 Preparation of lemon peel extract

The lemon peel extract was obtained using the ultrasound-assisted extraction (USAE) technique. The lemon peels were cleaned before being dried at 80 °C in a hot air oven (Labstar, LSI-21). The dried peels were processed in a mill and reduced to a fine powder. The substance preserved for use was that which passed through an 80-mesh sieve. Using an ultrasonicator, the powdered peel was defatted using organic solvent (Petroleum ether). The residue was filtered, and then extracted with ethanol (80%). The sample-to-solvent ratio was kept at 1:20. Temperature was maintained at 40 °C throughout the process. The obtained extract was filtered. In a rotary evaporator (Variac, TC 201), the filtrate was evaporated at 40 °C. For formulation, the concentrated extract that was produced following the evaporation of the organic solvent was employed [13, 14].

2.2 Preparation of Banana flour

Green bananas were cleaned and washed with water. Two different kinds of slices-one made of complete banana slices (pulp and peel) and the other from the peel (banana peel), of around 3 mm thickness were produced from green banana fruits. All slices were dried in a laboratory oven (Classis Scientific, India) at 60 °C for 6 h to maintain constant moisture levels. A fine powder was created by milling the dried substance. Before the further investigation, the powder was hermetically sealed and kept at room temperature [8, 15].

2.3 Characterization of lemon peel extract

2.3.1 Preliminary study of lemon peel extract

In the preliminary study, various parameters like color, odor, solubility, and percent yield of lemon peel extract have been studied.

2.3.2 Phytochemical screening of lemon peel extract

The extract so obtained was subjected to preliminary phytochemical screening for the detection of different phytoconstituents. Various chemical reagents were used for the qualitative and quantitative analysis of phenolic compounds, and flavonoids.

2.3.3 Total phenolic content (TPC)

According to the procedure outlined by A. Jagannath and Ravikumar Biradar [13], the total phenolic content of the lemon peel was calculated using the Folin-Ciocalteu reagent. Briefly, a 25 ml volumetric flask was filled with 1 ml of sample extract. After adding 4 ml of distilled water, 1 ml of the Folin-Ciocalteu phenol reagent, and waiting 5 mins, 10 ml of the 7% sodium carbonate solution was added. With distilled water, 25 ml of this was mixed up. The tubes were incubated for 90 mins at room temperature. The absorbance was then measured using a UV-Visible spectrophotometer (V-630Jasco, Japan) at 725 nm in comparison to a blank. The total phenolic content was determined and represented as mg Gallic Acid Equivalents (GAE)/100 g sample using a calibration curve for Gallic acid as a reference.

2.3.4 Gallic acid standard curve

By using a modified version of the Folin-Ciocalteu reagent method, a Gallic acid calibration curve was created. In water, gallic acid (3 mg) was dissolved (10 mL). It had a 300 mg/L concentration. Serial concentrations of 10, 20, 30, 40, and 50 mg/L were prepared by diluting with distilled water. For the Gallic acid standard, the same process was used as described above. All standard solutions had their absorbance determined using a UV spectrophotometer set to a constant wavelength of 725 nm [13].

2.3.5 Determination of total flavonoids

A 1 ml of lemon peel extract was placed in a 10 ml volumetric flask. To this 4 ml of distilled water and 0.30 ml of 5% sodium nitrite were added. Aluminum chloride (0.3 ml) was added after 5 min followed by the addition of 2 ml of 1 N sodium hydroxide after a further period of 6 mins. The solution was diluted by making up to 10 ml of distilled water. Absorbance was measured at 510 nm using a UV-Visible spectrophotometer (V-630Jasco, Japan). A Quercetin standard curve was used to quantify the flavonoid concentrations and expressed as mg Quercetin Equivalents (CE)/100 g sample [16, 17].

2.4 Preparation of orodispersible granules [18-19]

Orodispersible granules were prepared by extrusion and spheronization techniques. It involved various steps which were as follows-

1. Dry mixing and Granulation
Herbal granules containing lemon peel extract were prepared by using an extruder & spheronizer. Specified quantities of extract (200 mg), banana peel powder (0.3-1%), banana peel plus pulp powder (0.6-2%), and lactose (q.s) were accurately weighed and triturated in mortor with the help of pastel. A sufficient quantity of distilled water was added.

2. Extrusion: In this process, the wet mass was forced through the orifices of the extruder to shape into long cylindrical rods of uniform diameter.

3. Spheronization: In this step, the extruded cylinders were poured onto the spinning plate of the spheronizer, called the friction plate, in which the extrudate was broken up into smaller cylinders with an equal length to their diameter. These plastic cylinders were rounded due to frictional forces.

4. Drying: To achieve the desired moisture content in the final pellet, drying was done. The granules obtained in the above process were kept for drying at room temperature.

5. Screening: Screening of the granules was done to achieve the desired size distribution, and for this purpose, sieves were used.

2.5 Fourier transform infrared (FTIR) spectroscop
Lemon peel extract, banana flour, and granules were subjected to Fourier transform infrared spectroscopy studies using an FTIR spectrophotometer (FTIR 1-S Affinity). Spectra were recorded over the range 400–4000 cm-1. The obtained spectra were analyzed.

2.6 Differential scanning calorimetry
The thermal behavior of lemon peel extract, banana flour, and granules was examined using differential scanning calorimetry (DSC 3/500, Mettler Toledo, USA). The samples were heated in a sealed aluminum pan, using an empty pan sealed as a reference, over the temperature range from 30 to 400 °C, at a rate of 10 °C/min under a nitrogen flow of 50 ml/min.

2.7 Evaluation of granules [20]
The developed formulations were optimized and evaluated based on their flow properties. Parameters like the angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, *In vitro* disintegration time, and dissolution profile were evaluated and the optimum formulation was selected.

2.7.1 Angle of repose
The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The granules were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius of the base of the conical pile was measured and the angle of repose (θ) was calculated by using the following formula:

$$\tan\theta = h/r$$

Where, θ = Angle of repose, h = Height of the cone, and r = Radius of the cone base.

2.7.2 Bulk density
A dry 100 ml cylinder was filled with 15 g of granules without compacting them. The unsettled apparent volume, V_O, was measured after the powder was gently leveled without compacting. Using the following formula, the bulk density was determined:

$$\rho_b = M/Vo$$

Where, ρb=Apparent bulk density, M=Weight of sample, Vo= Apparent volume of powder.

2.7.3 Tapped density
Following the steps outlined in the measurement of bulk density, the sample-containing cylinder was initially tapped 500 times, then 750 times more, until the difference between the consecutive measurements was less than 2%. The tapped volume, V_t, was then measured to the nearest graded unit. The following formula was used to determine the tapped density, expressed as grams per ml:

$$\rho_{tap} = M/Vt$$

Where, ρ_{tap}= Tapped density, M = Weight of sample, Vt= Tapped volume.

2.7.4 Carr's index
The Carr's Index, which is determined using the following formulas, reflects these variations between the bulk and tapped densities:

$$\text{Compressibility Index} = [(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100$$

Where
ρ_b=Bulk density, ρ_{tap}= Tapped density.

2.7.5 Hausner's ratio
Hausner's ratio is a proximate indicator of powder flow simplicity. It is calculated as

$$\text{Hausner's Ratio} = \text{Tapped density } (\rho_{tap}) / \text{Bulk density } (\rho_b)$$

W here, ρ_{tap} is tapped density and ρb is bulk density

2.7.6 Particle size analysis
The average particle size of the granules was determined using the sieve analysis method [21].

2.7.7 *In vitro* disintegration time
One dose of the dispersible granules (500 mg) was added to a beaker with 50 ml of distilled water, at 37 °C±2 °C and the amount of time it took for all of the granules to disperse/disintegrate completely was noted [22].

2.7.8 Dissolution study
The USP class II dissolve test apparatus was used to conduct the granules dissolution study. The dissolution test was conducted using 900ml of a phosphate buffer dissolution medium with a pH of 6.8 at a temperature of 37 °C and 50 rpm. After every 1 minute, 5 ml of a sample was taken, and 5 ml was added back to keep the volume constant. The sample was then filtered through the Whatman filter paper,

and its absorbance was determined at 725 nm. The amount of medication released was then estimated using a calibration that had already been created [23].

3. Results and Discussion

The lemon peel extract and formulated granules were subjected to different evaluation tests. The results are as follows.

3.1 Characterization of lemon peel extract

3.1.1 Preliminary study

Organoleptic properties of lemon peel extract along with yield were recorded and summarized in Table 1.

3.1.2 Phytochemical screening of lemon peel extract

A preliminary phytochemical screening was performed on the lemon peel extract to determine its phenolic and flavonoid content. The results of the phytochemical screening of lemon peel extract are displayed in Table 2.

3.2 Total phenolic content (TPC)

Using the standard curve of Gallic acid ($y = 0.0258x + 0.1871$, $R^2 = 0.9774$), the total phenolic contents of, ethanolic extract of lemon peel was found to be 185 mg GAE/g of lemon peel extract. The calibration curve obtained for Gallic acid is shown in fig 1.

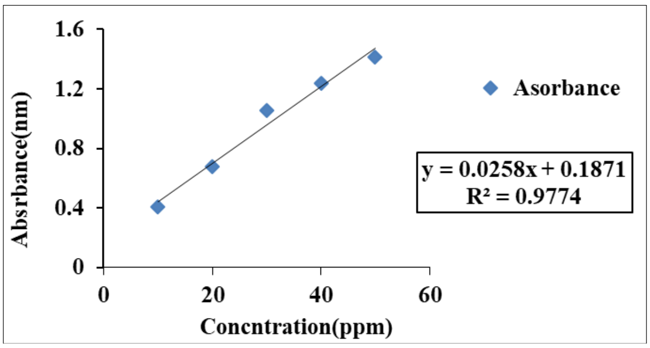

Fig 1: Calibration curve of gallic acid for estimation of total phenolic content

3.3 Total flavonoid content

Using the standard curve of Quercetin ($y = 0.0116x$, $R^2 = 0.979$), the flavonoid contents of, ethanolic extract of lemon peel was found to be 170 mg Quercetin equivalent/g of lemon peel extract. The calibration curve obtained for Quercetin is shown in figure 2.

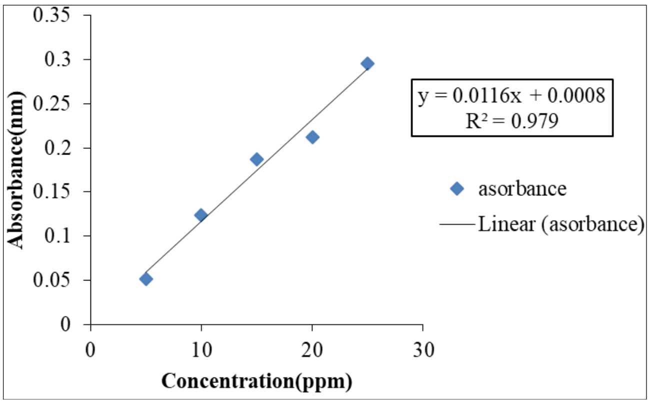

Fig 2: Calibration curve of Quercetin for estimation of total flavonoid content

3.4 Formulation and optimization of orodispersible granules

The natural superdisintegrant banana flours in varying concentrations (1-3%) were used to develop different formulations of lemon peel extract by extrusion and spheronization method as shown in Table 3.

3.5 Fourier transform infrared (FTIR) spectroscopy

FTIR studies were performed to detect the possible molecular interaction between Lemon peel extract and Banana flour. FTIR spectra of Lemon peel extract, Banana flour, and orodispersible granules formulated using lemon peel extract and banana flour are illustrated in Fig. 3. The FTIR spectra of Lemon peel extract exhibits characteristic cellulose peak in the fingerprint region of 1000–1200 cm^{-1}, which shows the main skeleton is cellulose. Bands around 1650 and 1750 cm^{-1} are indicative of free and esterified carboxyl groups which may be useful in identifying pectin [24] present in Lemon peel extract. The broad peak between 3200 cm^{-1} is indicative of the existence of hydroxyl groups of macromolecular association (cellulose, pectin, etc.). All characteristic peaks of lemon peel extract were retained in spectra of orodispersible granules indicating no interaction between lemon peel extract and excipients.

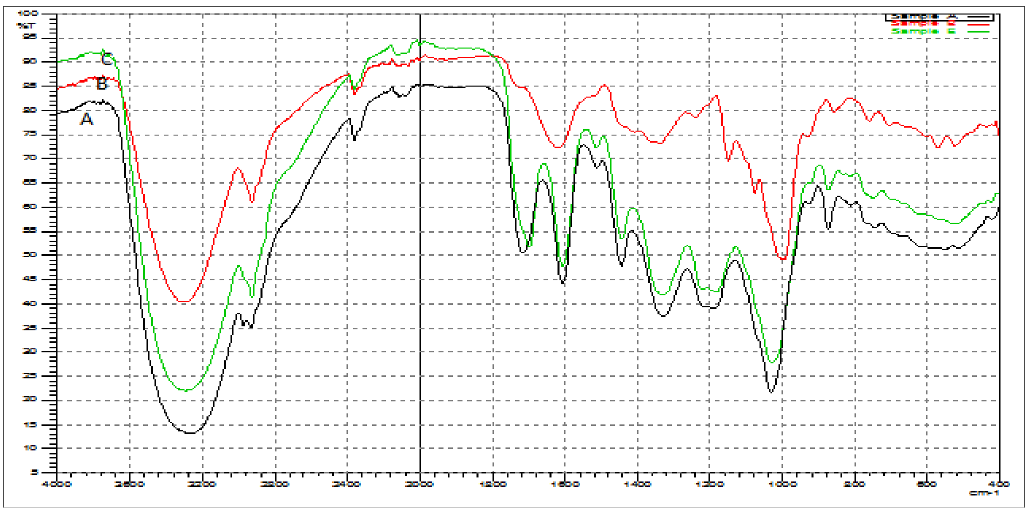

Fig 3: FTIR spectra of A Lemon peel extract, B Banana flour, and C Orodispersible granules

3.6 Differential scanning calorimetry

The DSC thermograms of Lemon peel extract, Banana flour, and Orodispersible granules are shown in Fig. 4. The DSC thermogram of Lemon peel extract exhibits an endothermic peak at 75.56 °C corresponding to its melting point. The DSC curve of banana flour displayed a wide and strong endothermic effect in the 58–128 °C interval (peak Tmax = 89.81 °C), which may be ascribed to dehydration. The broad endothermic peak at 107 °C indicates strong bonding between extract and banana flour [25].

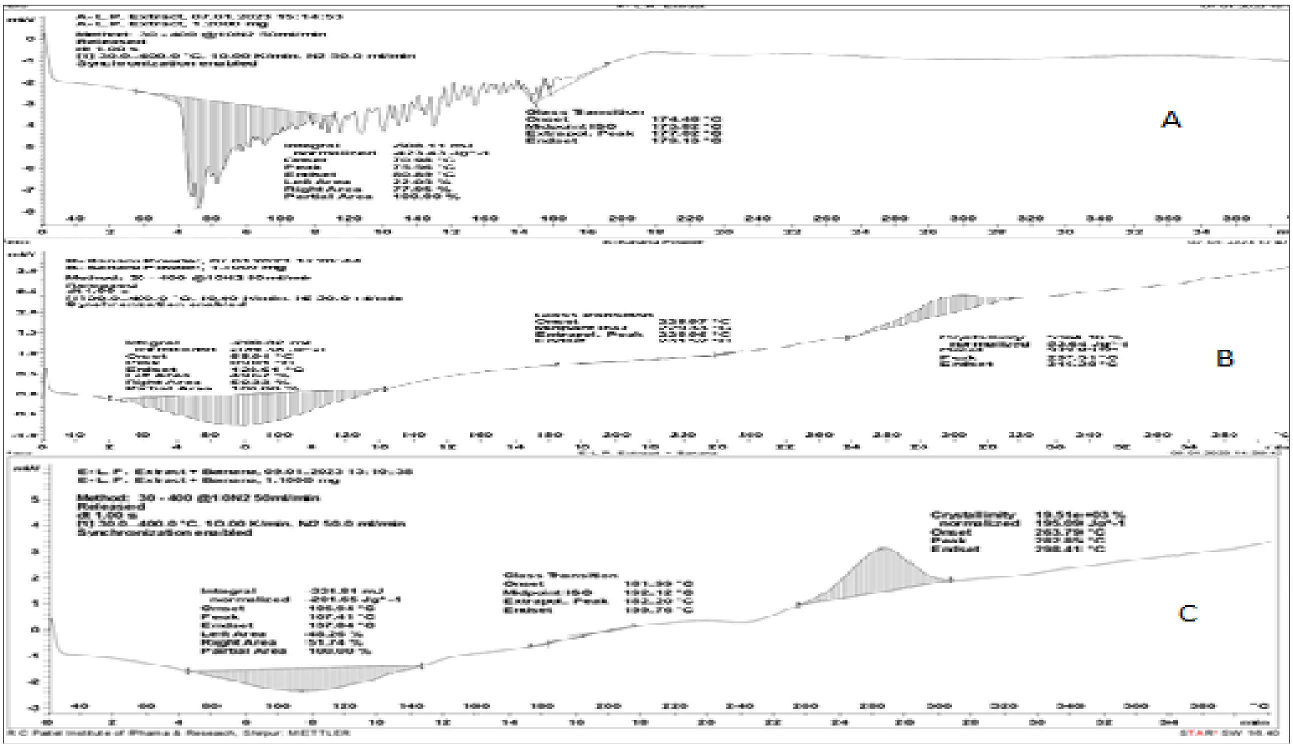

Fig 4: DSC thermograms of A Lemon peel extract, B Banana flour, and C Orodispersible granules

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

Table 4 displays the findings of the flow ability investigation. Bulk density measurements ranged from 0.53-0.57. The prepared granules' tapping density values ranged from 0.56 to 0.625. The angle of repose values were determined to be in the range of 23.3-24.4. The produced granules' Carr's index result ranged from 13.8 to 17.09, however. The values of Hausner's ratio were found to be between 1.055 and 1.097. According to the findings, all three formulae exhibited good flow characteristics.

3.8 Average particle size

The particle size analysis was done using the sieve analysis method and was found in the range of 500-700 µm for all the formulations as shown in Table 5. The mean diameter of the granules was found to be 502 µm approximately.

3.9 *In vitro* disintegration time

One of the primary requirements of orodispersible granules is faster disintegration. The results of *In vitro* disintegration study are shown in Table 6. *In vitro* disintegration time for different batches of ODGs was 39–87 s. The granule formulations containing banana flour at low concentration (3%) showed higher values of 87s for *In vitro* disintegration time. The minimum *In vitro* disintegration time for formulations containing 1% of banana flour was observed to be 35 s.

3.10 Dissolution study

The % amount of drug released after 5 min obtained for the three formulations of herbal granules of lemon peel extract are presented in table 7. The results show that all three formulas had a good release profile within 5 mins. F1 shows the highest percentage of drugs released, 99.7% within 5 mins. The good release profile of all formulations may be attributed to the presence of natural superdisintegrant banana flour.

Table 1: Organoleptic properties and yield of lemon peel extract

Sr. No.	Test	Observation
1.	Color	Yellowish brown
2.	Odor	Characteristic
3.	% yield	10%
4.	Solubility	Water soluble

Table 2: Preliminary phytochemical screening for the evaluation of phenolic content

Constiteuents, tests, reagents	Observation
Phenolic compounds	
FeCl3 Solution	+
Gelatin test	+
Flavonoids	
Shinoda test	+
Libermann test	+

Table 3: Formulations of orodispersible granules of lemon peel extract

Sr. No.	Ingredients(mg)	F1	F2	F3
1	Lemon peel extract	200	200	200
2	Banana peel powder	1.66	3.33	5
3	Banana pulp plus peel powder	3.33	6.66	10
4	Lactose	295	290	285
5	Total weight	500		

Table 4: Results for the angle of repose, bulk and tapped density, and Carr's Index

Batch code	Parameters				
	The angle of repose (θ)	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**Carr's Index**	**Hausner's ratio**
F1	22.75±0.25	0.57±0.016	0.625±0.019	15.07±2.15	1.093±0.003
F2	23.35±0.68	0.54±0.053	0.601±0.040	17.09±2.83	1.097±0.038
F3	24.46±0.86	0.53±0.044	0.566±0.024	13.87±2.26	1.055±0.045

Mean ± SD, n = 3

Table 5: Particle size analysis

Sieve used	Opening size(mm)	Wt. retained(gm)	%Retention
8	2	0.0	0
16	1	0.21	0.208
22	0.710	15.9	15.8
30	0.5	80.6	80. 20
60	0.250	2.8	2.78

Table 6: *In vitro* disintegration time

Batch code	Disintegration time(sec)
F1	39.3±0.39
F2	71.2±0.91
F3	87.1±0.57

Mean ± SD, n = 3

Table 7: Amount of drug released from granules

Sr. No.	Formulation	Amount of drugs released (%)
1	F1	99.7±0.152
2	F2	99.2±0.215
3	F3	98.8±0.143

Mean ± SD, n = 3

4. Conclusion

Solid oral formulations like tablets and capsules are not readily accepted by pediatric and geriatric patients due to the fear of choking. Thus, herbal granules formulated from a dried extract of lemon peel have good flow properties, and greater palatability and disintegrate within 39 seconds in the oral cavity without the use of water. Hence, it can be widely accepted by pediatric and geriatric patients. It can also be an ideal choice for traveling patients as it obviates the need for water for its administration. The cost of the formulation is reduced as it is easy to manufacture this formulation on a large scale.

5. Acknowledgments

The authors are thankful to the Principal, of SSDJ College of Pharmacy, Chandwad for providing the facilities to carry out research work.

6. Conflict of interest

All authors (U. N. Dungarwal, and A. S. Mundada) declare that they have no conflict of interest.

7. References

1. Rasouli H, Farzaei M, Khodarahmi R. Polyphenols and their benefits: A review. Int J Food Properties. 2017;20(21):1700-1741. https://doi.org/10.1080/10942912.2017.1354017
2. M'hiri N, Ioannou I, Ghoul M, Boudhrioua N. Phytochemical characteristics of Citrus peel and effect of conventional and non-conventional processing on phenolic compounds: a review. Food Rev Int; c2014. p. 1-48. http://dx.doi.org/10.1080/87559129.2016.1196489
3. Wang J, Zhai Y, Ou M, Bian Y, Tang C, *et al*. Protective Effect of Lemon Peel Extract on Oxidative Stress in H9c2 Rat Heart Cell Injury. Drug Des Devel Ther. 2020;15:2047-2058. https://doi.org/10.2147%2FDDDT.S304624
4. Diab KA. *In vitro* Studies on Phytochemical Content, Antioxidant, Anticancer, Immunomodulatory, and Antigenotoxic Activities of Lemon, Grapefruit, and Mandarin Citrus Peels. APJCP. 2016;17(7):3559-67.
5. Elkhatim KA, Elagib AA, Hassan AB. Content of phenolic compounds and vitamin C and antioxidant activity in wasted parts of Sudanese citrus fruits. Food Sci & Nutr. 2018;6(5):1214-1219. https://doi.org/10.1002%2Ffsn3.660
6. Suri S, Singh A, Nema PK. Current applications of citrus fruit processing waste: A scientific outlook. Appl. Food Res. 2022;2(1):100050. https://doi.org/10.1016/j.afres.2022.100050
7. Castillo V, Oliva R, Moncayo P, Viera W, Seraquive M. Fruit quality and postharvest losses of organic banana (*Musa acuminata*) in Ecuador Focus UTE. 2019;10(4):57-66. http://ingenieria.ute.edu.ec/enfoqueute/index.php/revista/about
8. Salazar Diego, Mirari A, Santiago C, Andrés V, *et al*. Green Banana (*Musa acuminata* AAA) Wastes to Develop an Edible Film for Food Applications. Polym. 2021;13(18):3183. https://doi.org/10.3390/polym13183183
9. Tausif A, Nayyar P, Sharma P. FDA-Approved Natural Polymers for Fast Dissolving Tablets. J Pharm. 2014;2014:1-6.
10. Hannan PA, Khan JA, Khan A, Safiullah S. Oral Dispersible System: A New Approach in Drug Delivery System. Indian J Pharm Sci. 2016;78(1):2-7. https://doi.org/10.4103%2F0250-474x.180244
11. Badgujar B, Mundada A. The technologies used for developing orally disintegrating tablets: A review. Acta Pharm. 2011;61:117-139. https://doi.org/10.2478/v10007-011-0020-8
12. Cornil ˘a A, Iurian S, Tomut˘a I, Porfire A. Orally Dispersible Dosage Forms for Paediatric Use: Current Knowledge and Development of Nanostructure Based Formulations. Pharmaceutics. 2022;14:1621. https://doi.org/10.3390/pharmaceutics14081621
13. Jagannath A, Biradar R. Comparative Evaluation of Soxhlet and Ultrasonics on the Structural Morphology and Extraction of Bioactive Compounds of Lemon (*Citrus limon* L.) Peel. JFCN. 2019;5(3):56-64. http://dx.doi.org/10.17756/jfcn.2019-072
14. Saini A, Panesar PS, Bera MB. Comparative Study on the Extraction and Quantification of Polyphenols from Citrus Peels using Maceration and Ultrasonic Technique. Curr Res Nutr Food Sci. 2019;07(3):678-685 http://dx.doi.org/10.12944/CRNFSJ.7.3.08
15. Desu P, Rao P, Gayathri D, Sagarika P, Prasanth N, *et al*. Formulation and Evaluation of Rapid Dissolving Films Of Zolmitriptan By Using Natural Polymer. Int J Pharm Res and Bio sci. 2016;5(3):39-48.
16. Khatiwora E, Adsul VB, Torane RC, Gaikwad S, Deshpande NR, *et al*. Spectroscopic determination of total phenol and flavonoid contents of citrus lemon peel

from the northeastern region of India. J Drug Des Devel Ther. 2017;7(1):21-24.
17. Saptarini N, Herawati I, Permatasari U. Total Flavonoids Content In Acidified Extract Of Flowers and Leaves Of Gardenia (Gardenia Jasminoides Ellis) Asian J Pharm Clin Res. 2016;9(1):213-215.
18. Muley S, Nandgude T, Poddar S. Extrusion-spheronization a promising pelletization technique: In-depth review. AJPS. 2016;11(6):684-699. https://doi.org/10.1016/j.ajps.2016.08.001
19. Nandi U, Trivedi V, Ross SA, Douroumis D. Advances in Twin-Screw Granulation Processing. Pharmaceutics. 2021;13:624. https://doi.org/10.3390/pharmaceutics13050624
20. M'hiri N, Ioannou I, Ghoul M, Boudhrioua N. Phytochemical characteristics of Citrus peel and effect of conventional and non-conventional processing on phenolic compounds: A review. Food Rev Int; c2014. p. 1-48. http://dx.doi.org/10.1080/87559129.2016.1196489
21. Dungarwal U, Patil S. Development of orodispersible tablets of taste masked rizatriptan benzoate using hydroxy propyl β cyclodextrin, J Pharm Investig. 2016;46(1):537-545. DOI:10.1007/s40005-016-0240-5
22. Amin R, Biswas S, Rahman R, Bhuiyan JR, Rana S. Study and Impact Evaluation of Particle Size Distribution on Physicochemical Properties of Three Different Tablet Formulations through Sieve Technology. IJPRS. 2014;3(1):448-463.
23. Szumilo M, Belniak P, Swiader K, Holody E, Poleszak E. Assessment of physical properties of granules with paracetamol and caffeine. Saudi Pharm J. 2017;25(6):900-905. doi: 10.1016/j.jsps.2017.02.009.
24. Rivera-Leyva JC, García-Flores M, Valladares-Méndez A, Orozco-Castellanos LM, Martínez-Alfaro M. Comparative Studies on the Dissolution Profiles of Oral Ibuprofen Suspension and Commercial Tablets using Biopharmaceutical Classification System Criteria. Indian J Pharm Sci. 2012;74(4):312-8. DOI: 10.4103/0250-474X.107062.
25. Arslanoglu H, Altundogan H, Tumen F. Preparation of cation exchanger from lemon and sorption of divalent heavy metals. Bioresour Technol. 2007;99(2008):2699-2705. https://doi.org/10.1016/j.biortech.2007.05.022
26. Oliveira TI, Rosa MF, Cavalcante FL, Pereira PH, Moates GK, *et al*. Optimization of pectin extraction from banana peels with citric acid by using response surface methodology. Food Chem. 2016;198:113-118. https://doi.org/10.1016/j.foodchem.2015.08.080