

An Overview of Mini Tablets Encapsulated with Natural Disintegrants

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ABSTRACT:

Key to this work is the development of rapid-release and sustained-release capsules. Mini-tablets are used to treat patients with coronary syndromes at risk of gastrointestinal bleeding. Hence gastric acid secretion inhibitor is administered jointly. Oral dosage forms are considered to be most preferred dosage forms for patients of various age groups. However traditional solid dosage form (Tablets and Capsule) are associated with problems; such as fluctuations in plasma drug concentration and difficulty swallowing in some patients. This advantage need for continuous development and improvement of tablets and Capsule for therapeutic enhancement. Increasing efficacy and patient's acceptance. Mini-tablets technology has been developed to reduce these difficulties. Superdisintegrants are incorporated in MDT in appropriate amounts to promote rapid disintegration and enhanced bioavailability. Different types of superdisintegrants are available depending on the source. They are co-processed, natural, semi-synthetic and synthetic. The various natural superdisintegrants employed in MDT, their mechanisms and applications are the primary focus of this paper. Natural polymers remain attractive due to their inherent properties as plant-derived substances that are cost-effective, easily accessible, and amenable to extensive chemical alterations. *Hibiscus rosa-sinensis* Linn, a member of the Malvaceae family, with leaves that contain a significant amount of mucilage. This characteristic renders them valuable for use into medicinal preparations. The objective of this work was to isolate mucilage from the leaves of *Hibiscus rosa-sinensis* and assess the ability of the dried mucilage to degrade, in order to identify its potential as a therapeutic ingredient.

Key words: Mini-tablets, Natural superdisintegrant, compression, Encapsulation, Extraction, *Hibiscus*, capsule, pellets.

1. INTRODUCTION:

A tablet in Capsule is multifunctional and multiunit system is which is versatile. A Mini-tablet in hard gelatin Capsule. It can be developed by formulating rapid-release Mini-tablets and sustained release Mini-tablets. Tablets pulsatile Mini-tablets and delayed on set sustained release tablets each with various interval time of release and Encapsulating in Capsule.[1] Mini tablets (diameter 2-3 mm equal or smaller) or several smaller standard Mini-tablets.. These can be filled capsules after doctor substitutes or weak cogs Multilayer tablets are usually made up of two three or more layers, same or different substance and or excipient. The most important reason for multi layer tablets that produces controlled release effect of active ingredients.

This dosage form provides a biphasic delivery system. This dosage form offers rapid release for drugs that require a rapid onset of therapeutic effects. An extended release phase ensues, maintaining consistent rates of release. A hard or soft-soluble shell encloses the drug in capsules, which are solid dosage forms. Shells are usually made of gelatin. Capsule containers, also known as drug delivery systems, can be used to fill tablets and capsules. The development of these containers was motivated by their significant potential to enhance therapeutic outcomes. Efficacy, patient compliance, and dosing regimens. The system is multifunctional and is made of gelatinized hard materials. [6]

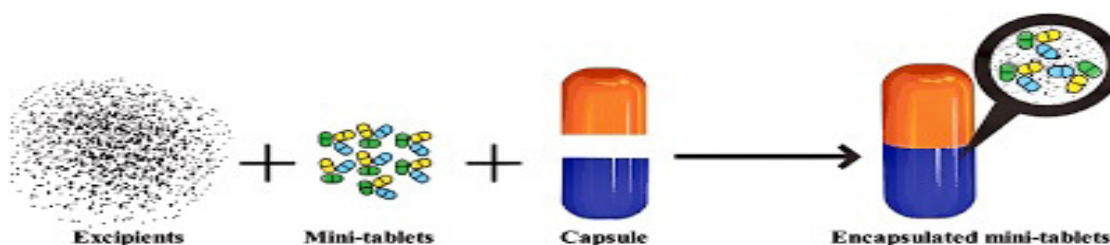


Figure 1: Encapsulation of minitabets

Encapsulation of minitabets that represent in the (fig-1) Minitablet encapsulation offers several benefits. Firstly, it allows for precise dosing, as each minitabets contains a specific amount of medication. This can be especially useful for drugs that require accurate dosage control. Secondly, encapsulation can enhance stability and protect the minitabets from external factors such as moisture or light, thereby extending their shelf life. It also improve the taste and appearance of minitabets, making them more palatable for patients.

It is possible to create multifunctional systems such as delayed-onset sustained-release minitabets (DSMTs), pulsatile minitabets (PMTs), sustained-release minitabets (SMTs), and rapid-release minitabets (RMTs) that are made of gelatinized hard capsules containing minitabets.[18]

Significance of Mini-tablets in Capsule:

- They can be manufactured relatively easily.
- They offer flexibility during development.
- They have excellent shape and uniformity, regular shape. And a smooth surface there by acting as an excellent coating substrate.

- They are great alternatives to tablets and granules, because of their relative ease of production and dosage form of equal dimensions weight.
- A smooth regular surface can be constructed in a producible and continuous way.
- They have risk of dose dumping.
- They have low intra and inter subject variability.
- They provide high degree of dispersion in the GI tract. This reduces risk of high topical medication concentration.
- They offer high drug loading wide range of release.
- Rate pattern and fine tuning of release rates.[3][4]

Application Mini-tablets in Capsule

- Improved and target (even-site specific) drug release and delivery.
- More predictable pharmacokinetics with less or inter subject variability.
- More homogeneous distribution in physical environment.
- Stable fixed dose combination of drug.
- Dose titration and reduced dose dumping.
- Patient-centred through better compliance (eg Patient with dysphagia and adherence)
- Individualized therapy (Ex: for paediatric or generics population)
- Separation of components to ensure better compatibility.
- It can produce rapid onset release of drug.[8]

Table No: 1 Marketed Minitablets Drug formulation Information:

S.no	Formulation Type	API	Year	Category/Treat
1.	Tablet in capsule	Acelofenac and misoprostol	2012	Rheumatoid Arthritis
2	Microtablets	lipase Amylase	2019	Enzyme Supply
3	Mini tablets	Omeprazole	2022	Proton pump Inhibitor
4	Mini tablets	Mycophenolatemo efil	2022	Suppress immune response
5	Mini tablets	Tracolumus	2022	Dermatitis
6	Mini tablets	Gabapentin	2022	Seizures
7	Mini tablets	Hydrochloride thiazide	2022	edema
8	Mini tablets	Flecainide	2022	Arrhythmias
9	Mini tablets	Amlodipine	2022	Treat high Blood pressure
10	Mini tablets	Levodopa/Carbidopa	2022	Parkinson Disease
11	Mini tablets	Captopril	2022	Hypertension

12	Mini tablets	Riboflavin	2022	Mouth ulcer
13	Mini tablets	Phenytoin sodium	2022	epilepsy
14	Mini tablets	Bosenton	2022	PHA(Pulmonary arterial Hypertension
15	Mini tablets	Indomethacin	2022	Osteoarthritis and rheumatoid arthritis
16	Tablet in capsule	Theophylline	2017	Asthma
17	Tablet in capsule	Ranitidine HCL	2017	GORD(Gastro oesophageal reflux disease
18	Tablet in capsule	Acetyl salicylic acid	2017	Reduce Fever
19	Tablet in capsule	Clopidogrel besylate	2017	Prevent Heart attack

1.1 Limitations

1. Aceclofenac and misoprostol is not recommended during pregnancy and breastfeeding. Should not be given to children as safety has not been established.[17]
2. OTC Omeprazole should be taken for only 14 days in row.
3-4kg: 2.5 mg 10 -19kg: 10mg
5-9kg: 5mg 20 kg or greater: 20mg
3. Patient with a body surface area 1.25 to 1.5m may be prescribed Mycophenolatemofetil capsule at a dose of 750 mg twice daily (1.5 daily dose)
4. Tacrolimus avoids excessive intake of high potassium foods (Bananas, orange, orange juice, Potatoes, Spinach)
5. Gabapentin Adult for epilepsy Initial dose: 300mg orally 3 times a day Maintenance dose: 300 to 600mg orally 3 times a day Maximum dose: 2400 to 3600 mg/day
6. Hydrochlorothiazide Adult dose for edema Usual dose: 25mg to 100 mg orally once or twice a day
7. Flecainide PSVT 50 mg PO BID; may increase by 50mg every 4 days; do not exceed 300mg/day
8. Amlodipine Adult dose for Hypertension Initial dose: 5mg orally once a day Maintenance dose : 5 to 10 mg orally once a day, Maximum dose: 10 mg/day
9. Levodopa and carbidopa Sustained-release tablet Initial dose; 50mg-200mg orally twice a day. Initial dosage should be given at intervals of more than 6 hours.[25]
10. Captopril Initial dose: 25 mg orally every 8-12 hours Maintenance dose : 25-150mg orally every 8-12 hours 450mg 1 day Maximum.[24]
11. Riboflavin Males: 1.3mg/day Females: 1.1mg/day Pregnant: 1.4mg/day 1.6mg/day[31]
12. Phenytoin sodium Tablet 100mg PO TID Maintenance: 300-400mg/day; increase to 600mg/day if necessary, May adjust dose no sooner than 7-10 day intervals when indicated.[16]
13. Bosentan Adult dose PAH Initial dose: 62.5mg orally twice a day for 4 weeks Maintenance dose: Following Initial dose increase to 125 mg orally twice a day.
14. Indomethacin for Rheumatoid Arthritis [16]
Intermediate release: 25mg to 50mg PO/PR q8-12hr; not exceed 200mg/day
Extended release: 75-150mg/day PO in single daily dose or divided q12hr; not exceed 150mg/day[7]

15. Theophylline For Asthma Initial dose: 300mg per day given as evenly divided dose every 6 to 8 hours
After 3 days if starting dose was tolerated: 400mg per day given as evenly divided dose every 6-8 hours.[1]
16. Ranitidine HCL Treatment dose:150mg orally 2 times a day or 300mg orally once a day after evening meal or at bed time.[9]Maintenance dose: 150 mg orally once a day at bedtime
17. Acetylsalicylic acidInitial dose: 3g orally per day in divided dose Maintenance dose: Adjust dose as needed for anti-inflammatory efficacy.
18. Clopidogrel besylate
<75 year 300mg loading dose followed by 75mg for 14 days up to 12 mo(if no bleeding)
>75 No loading dose
75 mg for 14 days up to 12 months (if no bleeding)

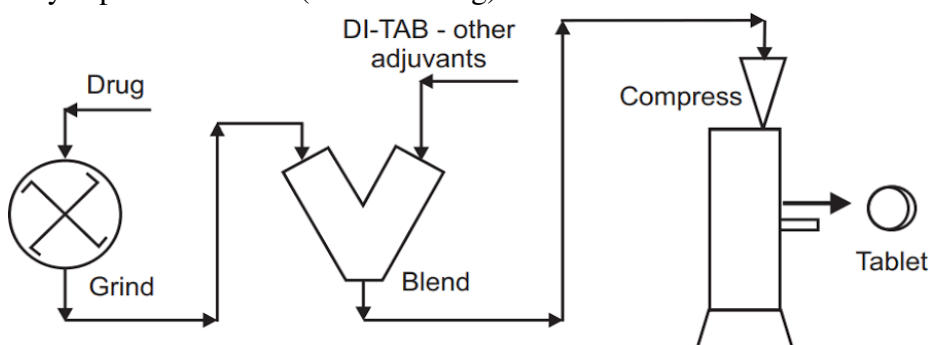


Figure 2: Direct compression technique

1.2 Methodology for manufacturing of mini tablets:

1. Direct compression technique:

In this method excipients and active pharmaceutical ingredients are directly compressed to form mini tablets.

- Direct compression method totally depends upon the excipients.
- A powder mixture flow is good to the top and bottom punches the mini tablets into die machine compress material under the high pressure and create a mini tablets.
- The particle size of all ingredients must be uniform.
- Direct compression method is commonly used because it takes less cost less time consumed mostly effective and least complex way to create mini tablets.[27]
- The stability problems are less as compared to wet granulation.
- Large dose drug may present problem with direct compression but these mini tablets are smaller in diameter so it is directly compressible. Active pharmaceutical ingredient + excipients premixed. Powder mixture flow should be good top to bottom. Particle size of all ingredients must be uniform. Powder mixture put bottom punches compress into die machine. Mini tablets [12][13]

2. Dry granulation technique:

- The dry granulation technique is a valuable method to manufacturing the mini tablets

- In this technique the effective dose of drug is too much for compaction drug is sensitive to heat moisture or both.[21]
- When the initial mixture of powders is formed into dies of alarge compacted mass is called compacted mass in association with capacity press and oral punches.
- On a large-scale compression granulationcan be performed on specially designed machines called roller compactor
- Roller compactor is capable for producing a mini tablet.[15]

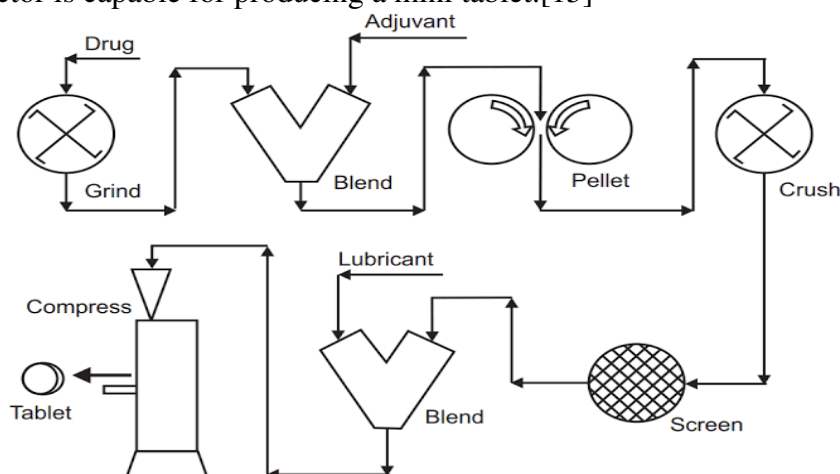


Figure3:Dry granulation technique

3. Wet granulation technique

- Wet granulation technique in which the screening or milling and mixing a all ingredients.
- The wet granulation technique employs a solution, suspension or slurry containing binder and incorporated into powder to form the mini-tablet by compression.
- The equipment are used for wet granulation is not highly effective to drying and more time consuming.[14]



Figure 4: Wet granulation Process

Table No: 2 Marketed Minitablets formulations:

Sr.no.	Brand name	Manufacturing company	Dose (mg)	Located country
1	Minitabs	ADARE Pharma solution	Flexible	India
2	Accolate	Astrazeneca group of companies	10,20	India
3	Zontivity	Merck	2.08	India
4	Ultrasea	Aptalis Pharma US	20,700 USP units of lipase	USA
5	Rozadyne	Ortho-MCNeilJassen Pharmaceuticals inc	4,8,12,16,24	USA
6	Exalgo	Mallinckrodt Inc	8,12,16,,32	USA
7	Trilipix	AbbvieInc	45,135	USA,Japan,Germany
8	Aricept	EISAI INC	5,10,23	USA
9	Effient	Daiichi sankyo and US firm Eli Lilly and company	5,10	USA
10	Zyprexa	Lilly medical	5,10,7.5	USA
11	Alesse	Pfizer medical information	0.1/0.02	Canada
12	Treximet	Curran Pharmaceuticals LLC	85,50,,10mg/60	England

4. Naturaldisintegrants are used in the Mini Tablets:

1. Hibiscus Rosa -sinesis
2. Banana
3. Mango peel

4.1. Hibiscus (Mucilage) Mucilage from Hibiscus rosa-sinensis and treated agar

It belongs to the family Malvaceae and is sometimes known as the Chinese hibiscus, shoe blossom plant, or China rose. Mucilages are used as disintegrants, suspending agents, thickeners, and water maintenance agents. Only you, L-rhamnose produces mucilage of D-gactose, D-galacturonic acid and D-glucuronic acid extracts. Processed for a day is called agar.[2] [28]

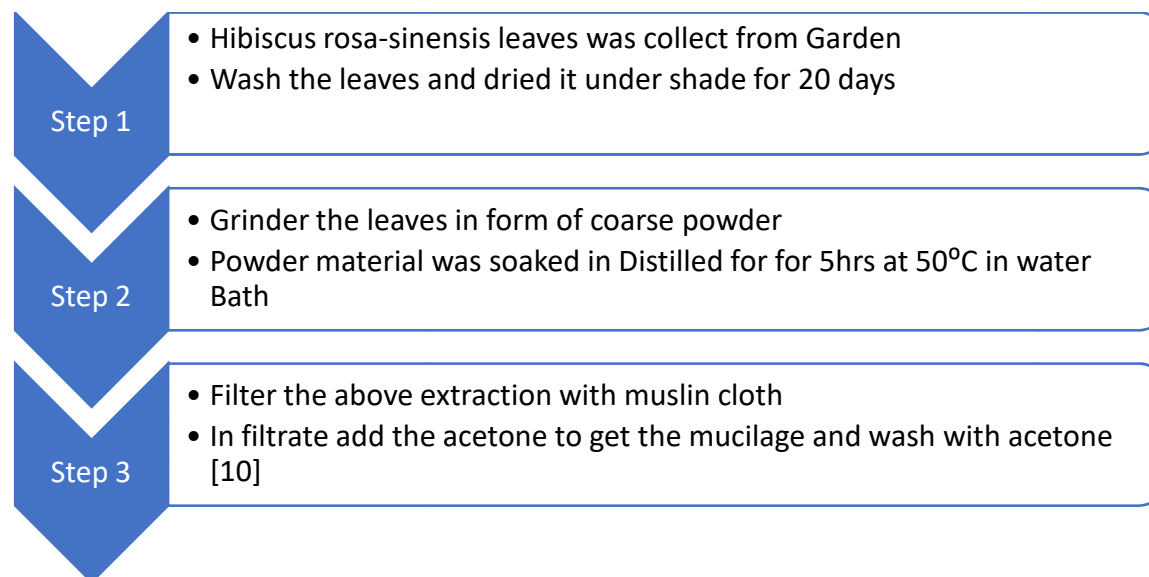
Extraction process of Hibiscus rosa-sinensis mucilage:**Figure5: Schematicrepresentation of extraction of Hibiscus mucilage**



Figure 6: Hibiscus Rose Sinensis leaves was collected, Dried leaves under shade for 20 days, collected coarse powder, Powder leaves was soaked in water bath for 5-6 hrs at 500 c, Filtered and collected Hibiscus Rose Sinensis Mucilage

4.2. Banana Fruit:

Plantain is another name for banana. DBP belongs to the Musaceae family and is a type of banana called Ethan and Nenthran (Nenthrawaza). As it contains vitamin A, it is used to cure loose stools and stomach ulcers. In addition, it contains vitamin B6, which helps to reduce elasticity and monotony. Its high content of carbohydrates and potassium can make it a particularly good source of energy. Potassium can lead to more dominating brain function.[2]



Figure 7: Banana Fruit

4.3. Mango peel:

Mango peel which constitutes 20-25% of the mango preparing squander was found to be a great source for the extraction of pectin of great quality, well suited for the planning of film, and satisfactory jam. Malviya et al. (2011) explored and found that mango peel pectin stands as a great candidate as superdisintegrant, in spite of the fact that not as more solid than manufactured superdisintegrants, due to its great dissolvability and higher swelling file, it may be utilized within the detailing of quick dispersible tablets.[29][2]



Figure 8: Peel of Mango

Extraction process of Pectin from mango:

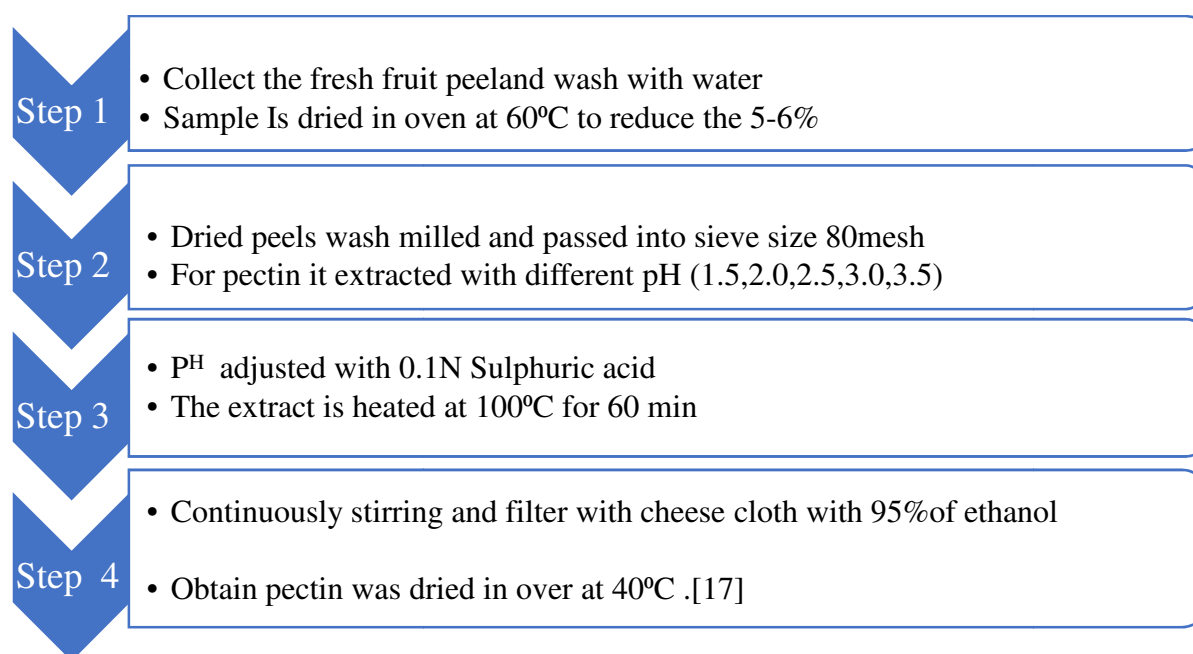


Figure 14: Schematic representation of extraction of mango from pectin

5. CONCLUSION:

This review concludes that pharmaceutical mini tablets are superior to single unit dosage forms in several ways. A precise medication dosage can be presumed to Patients in order to increase productivity. Comparing single unit dose forms with mini tablets, pellets and granules are an option. That being said, manufacturing factors need to be carefully considered in order to guarantee proper flow, accurate and thorough die filling, and apparatus destruction. By using small pills, local irritation and dose dumping can be prevented. Mini tablet dose forms are useful for drugs whose absorption occurs mostly in the small intestine because they easily pass through the duodenum without affecting intestinal motility or stomach emptying. Mini bioadhesive pills convey adhesion and improved effect than that of single unit bio adhesive tablets. They are fit for Pediatric and geriatric patient groups compare to single unit Dose forms and also good substitutes for pellets and granules. In this review we also concluded that the natural superdisintegrant gives more benefits and less or no adverse effects as compared to the synthetic

superdisintegrant. We use the hibiscus rosa-sinensis leaves as a superdisintegrant it saving the best activities as compared to other natural superdisintegrant.

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7. REFERENCES:

- 1.Mohammad F. Bayan¹, Hala M. Sbaih¹ and Mohamed J. Saadh²Faculty of Pharmacy, Philadelphia University, Amman, Jordan, ²Faculty of Pharmacy, Middle East University, Amman, Jordan Pharmaceutical Mini-Tablets Overview Indian Journal of Forensic Medicine & Toxicology, January-March 2021, Vol. 15.
- 2.Philippe; Philippe. Utilization of natural superdisintegrants in mouth dissolving tablet: A simplified review. Pharma Excipients. <https://www.pharmaexcipients.com/disintegrant-superdisintegrant/natural-superdisintegrants-in-mouth-dissolving-tablets>.
3. Bhatti S, Kaushik M. Utilization of natural superdisintegrant in mouth dissolving tablet: A simplified review. Innov Pharm Pharmacother 2020;8(2):32-38
- 4.Reddy L. H, Ghosh B, and Rajneesh. Fast dissolving drug delivery systems: a review of the literature, Indian Journal of Pharmaceutical Sciences, 2002; 64(4):331- 336
- 5.Chirani S, Lebig Mo, Bouameur S, Mouffok M, Chirani N, Chafi N et al. Elaboration of Microspheres' Capsules Based on Ethylcellulose and Synthesized Poly (Butylsuccinate) as Biodegradable Matrices for Drug Delivery of an Antithyroidian Agent. Indian Journal of Pharmaceutical Education 2017; 51: s79–s90.
6. Tawfeek HM, Saleem IY, Matthew Roberts, dissolution enhancement and formulation of rapid-release lornoxicam mini-tablets, pharmaceutics, drug delivery and pharmaceutical technology, 2470-2483.
- 7.Kiran V. Mahajan et.al. Designing and evaluation of compressed mini-tablets of ramipril as abiphasic delivery system. Indo American Journal of Pharm Research.2013;3(9).
- 8.Lengyel, M.; Kállai-Szabó, N.; Antal, V.; Laki, A.J.; Antal, I. Microparticles, Microspheres, and Microcapsules for Advanced Drug Delivery. Sci. Pharm. 2019, 87, 20. <https://doi.org/10.3390/scipharm87030020>.
- 9.Nyol S, Gupta M. Immediate release dosage forms:A review. J Drug Delivery Thera, 2013; 3(2): 155-161.
10. RajniBala, *ReechaMadaan, Vibhu, Aneesh and Dr.SandeepArora,Isolation and Evaluation of Hibiscus Rosa- Sinensis Leaf Mucilage as Superdisintegrant, EJPMR, 2016,3(8), 434-440.
- 11.Indian Pharmacopoeia, ministry of health and familywelfare, Govt. of India 4th ed. New Delhi: thecontroller of Publications; 1996
- 12.Bhuvaneshwari S, Umashankar M, Damodharan N. Mini Tablets: Pediatric Drug Delivery System. Research Journal of Pharmacy and Technology. 2020;13(6): 2985-2991.
- 13.Khankari R, Umale S. A Review on Pulsatile Drug Delivery System. Asian Journal of Pharmacy and Technology. 2020;10(2): 121-124.

14. Stoltenberg I, Breitzkreutz J, Orally disintegrating Minitablets : A novel solid oral dosage form For pediatric use, *European Journal of Pharmaceutics and Biopharmaceutics*. 2011; 78(3): 462–469.
15. Shobha Rani Hiranmanth R. Text book of Biopharmaceutics and Pharmacokinetics. Page: 178.
16. Priyanka P, Deepak T. A comprehensive Review on pharmaceutical mini tablets. *J Drug Deliv Ther*. 2018; 8(6):382-390.
17. Iolascon G, Giménez S, Mogyórosi D. A Review of Aceclofenac: Analgesic and Anti-Inflammatory Effects on Musculoskeletal Disorders. *J Pain Res*. 2021 Nov 30; 14:3651-3663. doi: 10.2147/JPR.S326101.
18. Rao N, Hadi M, Panchal H. A Novel Approach To Sustained Montelukast Sodium Release: Differentially Coated Mini-Tablets in HPMC Capsules. *International Journal of Pharmaceutical And Biomedical Sciences*. 2011; 2(2): 90-97.
19. National Institute for Health and Clinical Excellence [Online] Osteoarthritis: The care and Management of osteoarthritis in adults.
20. British Pharmacopoeia, Stationery Office, London, Vol 1, 1998, 414.
21. Hitesh Patel P, Preeti Karwa, Nitesh Patel J, A Novel Approach To Sustained Zolpidem Tartrate Release: Compressed Mini-Tablets, *International Journal of Pharmaceutical Sciences Review and Research*, 7(2), 2011, 53-55.
22. Dey NS, Majumdar S, Rao MEB, Multiparticulate Drug Delivery Systems for Controlled Release, *Trop J Pharm Res*, 7(3), 2008, 1067-1075.
23. Abdul S, Poddar SS. A flexible technology for modified release of drugs: Multi layered tablets. *J Control Release*. 2004; 97(3):393–405.
24. Efentakis M, Peponaki C. Formulation study and evaluation of matrix and Three-layer tablet sustained drug delivery systems based on Carbopols With isosorbitemononitrate. *AAPS PharmSciTech*. 2008; 9(3):917–923.
25. Chien Yie W (ed.). *Novel drug delivery systems*. 2nd ed. New York: Marcel Dekker, Inc; 1992: p. 139.
26. Jayanthi B, Manna PK, Madhusudhan S, Mohanta GP, Manavalan R. Per oral extended Release products -An overview. *Journal of Applied Pharmaceutical Science* 2011; 1(2):50-55.
27. Punna Rao Ravi, Sindhura Ganga, Ranendra Narayan Saha. Design and study of Lamivudine oral controlled release tablets. *American Association of Pharmaceutical Scientists PharmSciTech* 2007; 8(4):167-175.
28. Chang RK, Guo X, Burnside BA, Courch RA. Fast dissolving tablets. *Pharm Tech*, 2000; 24: 52-54.
29. Ashish Masih, Amar Kumar, Shivam Singh, Ajay Kumar Tiwari, 2017, “Fast dissolving Tablets: A Review”, *International Journal of Current Pharmaceutical Research*, 2: 8-18.
30. Arijit Gandhi. Mouth Dissolving Tablets: A New Venture in Modern Formulation Technology. *Pharma Innovation* 2012; 1(8):14-31.