Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

Formulation and Evaluation of Taste Masked Granules for Oral Suspension

Kalyankar Tukaram[1]*, Shinde Nagoji[1], Upalkar Sapna[1], S. D. Deosarkar[2] and Karhale Mukesh[1]
[1]Department of Quality Assurance, School of Pharmacy, Swami Ramanand Teerth Marathwada University, Nanded, India.
[2]School of Chemical Sciences S.R.T.M.University Nanded 431066 India
Corresponding Author-Dr. Tukaram M Kalyankar,
Department of Quality Assurance, School of Pharmacy, Swami Ramanand Teerth Marathwada University Nanded.

(Received: 07 January 2024 Revised: 12 February 2024 Accepted: 06 March 2024)

KEYWORDS
Paracetamol
Mefenamic acid
granules,
Powder for
suspension

ABSTRACT:
The goal of this study is to determine the drug-excipient compatibility using FT-IR spectroscopy, evaluate the pre-formulation factors of paracetamol and mefenamic acid, and then formulate granules that contain paracetamol and mefenamic acid in order to carry out evaluation studies on the formulated granules. The combination of paracetamol and mefenamic acid is a very helpful medication for the treatment of moderate pain in children who suffer from rheumatoid arthritis, osteoarthritis, discomfort including muscle pain and dental pain, as well as fever and headaches. In the course of this research, a total of nine different formulations, denoted by the letters F1 through F9, were created and tested largely for taste and drug release profile. The taste of the F8 formulation was deemed suitable for oral administration. The percentage of drug release was 99.32 0.34% for Paracetamol and 98.91 0.12% for Mefenamic Acid, respectively. F8 Formulation was examined for stability study up to 3 M at 45 °C 2 °C/75% RH 5% accelerated condition and was analysed for % Assay & % drug release. The powder for oral suspension has been substituted for the traditional dose form. Receiving the correct dose in the form of an oral suspension or solution might be challenging.

1. Introduction

Patients find that taking their medication orally is the most effective and easiest method of drug delivery. Tablets (both conventional and controlled-release) and capsules (both hard and soft gelatin capsules) have emerged as the most common solid oral dose forms used today. This includes both conventional tablets and controlled-release tablets. On the other hand, many patients struggle with dysphagia, which means they have trouble swallowing tablets and hard gelatin capsules. As a result, they do not take their prescription as their doctors have instructed them to. It is believed that 35% of the general population, 30–40% of senior patients in nursing homes, and 25–50% of patients hospitalised for acute neuromuscular problems and head traumas have dysphagia. These percentages are based on estimates from previous research. The most common causes of dysphagia are disorders of the oesophagus, such as achalasia and gastroesophageal reflux disease (GERD), conditions of the cardiovascular system, such as aneurysms, autoimmune diseases, such as Sjogren's syndrome and auto immune deficiency syndrome (AIDS), surgery on the thyroid, radiation therapy to the head and neck or oral cavity, and other neurological conditions, such as cerebral palsy. A comprehensive survey was carried out to ascertain the percentage of patients who had difficulty swallowing pills and to investigate the factors that contributed to this problem. Over twenty-six percent of patients reported having difficulty in taking their medications by mouth. The size of the tablet was the primary concern voiced by customers, followed by the surface, shape, and flavour of the tablets. Problems with swallowing were reported by two times as many female patients as male patients. Individuals who were older than 70 years old had an easier time taking pills than patients who were younger than that. Patients who were either paediatric or geriatric, particularly those who were reclined in bed, as well as persons who were sick, encountered the most difficulty in swallowing pills. When developing a solid oral dosage form, organoleptic qualities are a crucial element to take into

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

account since they might impact the preferences of consumers. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, particularly for paediatric and geriatric patients. Taste is the most important parameter that governs patient compliance in the case of bitter drugs, and taste is the most important parameter that governs patient compliance. Several medications that are taken orally include components that have an unpleasant bitter taste. The consumer's desire for this product to have a more palatable flavour has led to the creation of a variety of formulas that have enhanced both performance and acceptance[33]. Oral medication delivery systems that dissolve or disintegrate within seconds to a few minutes after being placed in the mouth are referred to as quick-dispersing oral drug delivery systems (QD). Tablets, caplets, wafers, films, and granules are all included in the QD systems[13].

Disadvantages of Conventional Dosage Form:

• An increased risk of forgetting to take a dosage of a medication that has to be administered often because its half life is quite short.

• A change in the concentration of the drug in the plasma might result in an inadequate or excessive dose of treatment. This has the potential to hasten the onset of unpleasant effects, particularly in the case of a medicine that has a low therapeutic index (TI), whenever overmedication takes place.

• Poor patient's compliance.

Advantages of modified drug delivery system

• Decrease the amount of volatility in drug blood levels in order to improve effectiveness.

• A decrease in the number of dosage intervals.

• Improve patient compliance.

• Efficient in terms of costs.

Taste masking by granulation:

Granulating a bitter substance reduces the amount of the substance's surface area that comes into contact with the tongue during oral consumption. The technology of taste masking consists of two components: the first is the selection of an appropriate taste masking agent (such as sweeteners, polymers, flavours, or amino acids), and the second is the selection of an appropriate taste masking approach. A proper method of flavour masking may have a significant influence, not only on the quality of the taste masking but also on the efficiency of the procedure. The easiest method is to cover up unpleasant flavours using sweets and other flavours[33].

Basis of choosing flavor:

• Complementary to the already present taste of the medicine

• Known popularity of various flavours

• Age of patient

• Allergy

• Basis for choosing sweetener

• Complementary flavour connected with sweetness

• Soothing impact on the membrane of the throat

Granulation phenomenon:

Granulation is the act of, or the process by which, initial powder particles are made to stick to one another in order to produce bigger, multiparticle entities known as granules. This action or process takes place in the pharmaceutical business. It refers to the process of bringing separate particles into closer proximity with one another by forging links between them. Compression or the application of a binding agent are the two methods that may be used to establish bonds. Granulation is considered to have been successful if each individual granule has all of the components of the mixture in the appropriate amounts and there is no segregation of the granules.Many powders are cohesive and do not flow very well because of their tiny size, uneven form, or surface features. These factors contribute to their inability to flow. Granules produced using such a cohesive system will be bigger and more isodiametric, two characteristics that contribute to enhanced flow qualities.Granules of the same powders may often be compacted more easily than particles themselves, despite the fact that some powders are difficult to compress even when a readily compactable glue is included in the mixture. This is because of the way in which the adhesive is distributed throughout the granule, which is a result of the process that was used to create the granule.The following are some of the reasons why a medicinal ingredient should be granulated:

• To achieve a greater degree of consistency in the distribution of the medicine throughout the product.

• To make the material more dense.

• To improve the flow rates while maintaining a consistent flow rate.

• In order to make the metering or volumetric dispensing process easier.

• In order to lessen the amount of dust.

• To give the goods a more aesthetically pleasing look.

Immediate Drug Delivery System: In these formulations—that is, granules—medications are released into the environment by dispersion after fast disintegration. The rate of drug release and/or

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

absorption should not be noticeably slowed down by the use of any diluents or carriers that are not approved for use in the pharmaceutical industry. Immediate release might be achieved via the use of a suitable diluent or carrier in the pharmaceutical industry.Improved compliance, increased bioavailability, improved stability, and cost effectiveness are some of the benefits that come with using an immediate drug delivery system. It also beneficial to reduction in the amount of time required for disintegration and dissolution.

Various Granulation Techniques: Wet granulation, dry granulation (also known as roll compaction), and direct mixing are the three types of granulation techniques that are used the most often in the pharmaceutical industry for the creation of solid dosage forms. Given the significance of granulation in the manufacturing of oral dosage forms — the highest quality pharmaceutical compounds must undergo granulation in order to enhance their flowability and processing properties before they can be tableted — and the widespread application of the method in the business world, it is essential to have a solid understanding of the fundamentals as well as the available choices, which are outlined in the following paragraphs. Because roll compaction does not entail the use of any moisture in the process, it is an excellent method for processing substances that become either physically or chemically unstable when exposed to moisture. Additionally, it is not essential to dry the granules that are generated, and as a result, the process is often more energy efficient.

Dry Granulation: Granules may be formed by this procedure rather than by utilising a liquid solution. This is done because the product that is going to be granulated may be sensitive to heat and moisture, or it may not compress very well. The process of forming granules without the addition of moisture entails compacting and reducing the size of the mix in order to generate a granular mixture that is free flowing and consistent in size. Therefore, the original powder particles are aggregated by utilising swinging or high shear mixer-granulators in conjunction with high levels of pressure. Dry granulation may be accomplished in one of two ways: either a powder is compressed between two rollers in a roller compactor or chillonator, which results in a sheet of material, or a huge tablet (slug) is formed in a heavy duty tableting press. When a tablet press is used for dry granulation, the powders may not have sufficient natural flow to feed the product evenly into the die cavity, which results in variable degrees of densification. This may cause issues with the tablet's consistency. The roller compactor, also known as the granulator-compactor, makes use of an auger-feed system that distributes powder between the pressure rollers in a manner that is consistent and uniform. Between these rollers, the powders are compressed into a ribbon or into tiny pellets, and then the mixture is processed in a low-shear mill. After the product has been appropriately compacted, it may then be put through a mill and given a final mix before being compressed into tablets.

Wet Granulation: The process of adding a liquid solution to powders begins with the massing of a mix of dry primary powder particles with the help of a granulating fluid. After this step, the powders are added to the liquid solution. The fluid includes a solvent, and in order for it to be non-toxic, the solvent has to be volatile so that it may be eliminated by drying. Water, ethanol, and isopropanol are all examples of common liquids, and they may exist alone or in many combinations. Either an aqueous (preferred) or a solvent-based base may be used for the liquid solution. When water is added to powders, the powder particles may establish bonds with one another that are strong enough to hold them together when the powders are locked together. On the other hand, the granules can become unusable once the water has evaporated. As a result, it's possible that water doesn't have the necessary strength to form and maintain a relationship. In these kinds of situations, a liquid solution that contains a binder is necessary to be used. After the solvent or water has been evaporated and the powders have formed a mass that is held together more tightly, the granulation may then be milled. Depending on the qualities of the powders and the equipment that is readily accessible, the procedure may be quite straightforward or it may involve a great deal of intricacy. The wet mass is pressed through a sieve as part of the classic wet granulation procedure, which results in the production of wet granules that are then dried. In the succeeding screening step, granule agglomerates are shattered into their component parts. When water-sensitive pharmaceuticals need to be processed, organic solvents are employed instead of dry granulation. Organic solvents are also used in situations in which a short drying time is necessary. Wet granulation is still the technique of choice for many active compounds since direct compression is not the most effective technology for dealing with these

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

substances. Even if the active ingredient is susceptible to hydrolysis, concerns with wet granulation may be solved using sophisticated equipment such as a fluidized bed. In the last kind of granulation, known as wet granulation, the powder mixture is combined with liquid binders before being used to produce granules. The processes of continuous direct compression (CDC) and continuous mixing for the dry granulation involve the individual loading and accurate feeding of the active pharmaceutical ingredient (API) and a variety of excipients into a continuous blender. Both of these processes are known as continuous mixing for the dry granulation.

Granulation Mechanisms:

Granulation may be broken down into four fundamental mechanisms or rate processes. These processes include wetting and nucleation, coalescence or growth, consolidation, attrition or breakage, and wetting and nucleation. When compared to mechanical mixing, initial wetting of feed powder and existing granules by the binding fluid is greatly influenced not just by spray rate or fluid distribution but also by feed formulation parameters. Wetting encourages the nucleation of fine powders and also promotes coating in situations when the feed particle size is greater than the drop size. When dealing with inadequately wetting feeds, it is common practise to choose the appropriate wetting agents, such as surfactants. During the stage known as coalescence or growth, partly moist initial particles and bigger nuclei merge to produce granules that are formed of several particles. Coalescence is a more general term that refers to the successful collision of two granules to form a new, larger granule. The term nucleation is typically applied to the initial coalescence of primary particles in the immediate vicinity of the larger wetting drop. On the other hand, the term nucleation is typically applied to the initial coalescence of primary particles in the immediate vicinity of the larger wetting drop. In addition, the coalescence of granules with main feed powder is referred to as layering, which is another word for the process. The initial distribution of moisture, such as a drop, or the homogeneity of a fluid supply to the bed, such as with high-shear mixing, both encourage nucleation. Nucleation may occur as a result of any of these processes. The nucleation process is intricately connected to the wetting step of the process. As granules expand, they get denser as a result of compaction pressures brought on by the agitation of the bed. This consolidation step is responsible for controlling internal granule voidage, also known as granule porosity, and, as a consequence, end-use qualities such as granule strength, hardness, or disintegration. Granules that have been formed may be more prone to attrition if they are fragile to begin with or if defects appear as a result of the drying process. All of the many types of granulation units, from spray dryers to fluidized beds to high-shear mixers, are capable of concurrently exhibiting these rate mechanisms and processes. Nevertheless, some mechanisms could predominate in a certain production process. For instance, the wetting process has a significant impact on fluidized bed granulators, but the mechanical redistribution of binding fluid that occurs as a result of impellers and particularly high-intensity choppers has the effect of reducing the wetting process's contributions to the granule size produced by high-shear mixing. When granules are subjected to high shear mixing, as opposed to fluidized bed granulation, the consolidation process is far more prominent. These simultaneous rate processes, when taken as a whole and sometimes competing against one another, determine the final granule size distribution as well as the granule structure and voidage that are the result of a process, and therefore the final end-use or product quality attributes of the granulated product.

Granulation Technologies:

Single Pot: The term "single pot processor" refers to a mixer/granulator that may dry granules in the same equipment without discharging them (or one-pot processor). Granulation takes place in a typical high-shear processor; however, precautions must be taken to prevent the production of lumps, which cannot be broken up before drying. There are many different approaches of drying items in individual pots. The use of a vacuum in the bowl, which results in a decrease in the temperature at which the granulation liquid evaporates, is the fundamental component of the drying process. The heated dryer walls have traditionally been the source of heat in dryers; the rate of heat transmission is proportional to the surface area of the dryer walls and the amount of product that is being processed. Therefore, this approach of directly heating the organic solvent is most useful for working with modest volumes of binder fluids or organic solvents on a smaller scale.By adding stripping gas to the pot, one is able to get a very low total moisture content in the finished product (only required in particular applications). The effectiveness of the vapour removal process is improved by the introduction of a little

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

amount of gas at the very bottom of the piece of equipment. This gas then travels through the product bed. A linear scale-up is not conceivable due to the fact that the heated wall is the sole source of drying energy. This problem is made worse when the material that is going to be processed is heat sensitive (as this limits the wall temperature), when water is used as a granulation liquid (it has a relatively high boiling temperature under vacuum and a high heat of evaporation compared with organic solvents), and when it is used for larger-scale production (the surface/volume ratio gets worse as the volume increases).These constraints may be circumvented by the use of microwave energy. This not only provides an additional source of energy but also has the added benefit, when working with organic solvents that only pure organic vapours need to be treated on the exhaust side, as opposed to a mixture of solvent and large volumes of process gas, which would be required by the majority of the other wet granulation technologies.

Integrated High Shear Granulation and Fluid Bed Drying (Batch Granulation): This configuration is the one that is used on an industrial scale the majority of the time while manufacturing pharmaceutical granules. This technology not only enables complete integration with upstream and downstream machinery, but it also incorporates a wet mill in between the granulator and the dryer for added convenience. Because contemporary control systems make it simple, it is possible to load, mix, and granulate a second batch in the high shear granulator while simultaneously drying the batch that was processed in the fluid bed in preparation for discharge. A single automated technique may be used to clean all of the equipment while it is still in place.

Melt granulation: The binder solution used in a typical wet granulation process is replaced with a meltable binder in the melt granulation method, also known as melt granulation. However, the high shear approach has the advantage of enabling the binder to be added in its solid state, which is also a possibility when the binder is introduced in its molten form. The energy that is added throughout the melting process comes from the friction of the mixer as well as the heated jacket that surrounds the bowl.

Products that are effervescent: The pre-effervescent reaction is kicked off by adding a very trace amount of water; this results in the release of some of the carbon dioxide during the granulation process, but it also results in the production of water as a reaction product; this then functions as a granulation fluid, producing more carbon dioxide in addition to more water. This avalanche has to be halted at a particular point, and the best way to do it is to remove the water and get the drying process started. This may be accomplished with the help of a high-shear granulator and subsequent fluid drying by discharging the material at the conclusion of the granulation process into a fluid bed drier that has been heated in advance.

Fluid Bed Spray Granulation: Granulation may be accomplished with the use of fluid beds that have spray nozzles attached to them. Although the top-spray position was favoured for a good number of years, the benefits of tangential spray systems have become more and more apparent in recent years. The spray nozzle is placed in a region that has substantially greater shear forces than other areas, which makes it possible to process formulations that were previously only capable of being granulated in high shear processors. This is the primary benefit of the design. In recent years, as a direct reaction to the competition posed by single pot technology, fluid beds have seen a tremendous improvement. The handling of material may now be contained by using a closed connection with the equipment both upstream and downstream. In addition to this, completely automated cleaning in fluid beds with the use of stainless steel filters has now achieved a level that is on par with what is achievable in a single pot. This is a significant advancement.

Fluidized Spray Drying (FSD):FSD creates grains from a liquid in a one-step process. Granules may be produced of the active ingredient at the primary manufacturing stage. This allows the active ingredient to only need to be mixed with excipients that are suited for direct compression during the secondary processing stage. This is only possible with actives that are tacky (when they are wet), since any other actives would need the addition of a binder. To generate granules in a single step while simultaneously combining all of the components into a solution or suspension is yet another use that may be made of the FSD technology.A contemporaneous manner of atomization of the liquid feed takes place at the very top of the tower while the FSD process is carried out. Following the evaporation of the liquid, the newly produced particles are expelled from the drying chamber together with the air that is being exhausted. After being separated in a cyclone or filter, these particles are subsequently reintroduced into the drying chamber, where they make contact with moist droplets and form agglomerates. After reaching a

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

particular weight, these agglomerates are no longer able to exit the drying chamber at the top of the tower with the exhaust air. Instead, they fall into the integrated fluid bed located at the bottom of the drying chamber. After being dried and chilled here, they are then ready to be released. When switching to a different product, however, this kind of apparatus is difficult to clean, especially the pipe work that is exposed to the environment. As a result, there have been developments in technology that include systems in which the exterior pipework does not interact with the product.

Continuous granulation: There is a significant amount of interest in continuous processing as a consequence of the many regulatory measures that have been implemented to enhance product quality and to lower the risk of product failure. A typical system is comprised of three modules: a wet high shear granulation module, a segmented dryer module, and a granule-conditioning module. Each of these modules performs a specific function within the system. Dry components may either be dosed separately into the continuous high shear granulator in the granulation module, or they can be premixed beforehand. Following a brief period of dry mixing, the granulation liquid is introduced. This ensures that each particle gets the same quantity of liquid overall. The whole wet granulation process is completed in a matter of seconds, and there are only a few grammes of product being processed at any one moment; as a consequence, the start-up time is reduced, and there are no product losses. This results in a continuous flow of wet granules with a consistent quality and density that are delivered to the dryer; the particle size may be modified by altering the operating level in the granulator. Because there are no large agglomerates, the process of wet milling is not necessary.The continuous flow of grains is separated into individual 1.5-kilogram packages by the dryer module, which operates according to the fluid bed drying concept. These individual packages are then dried in various sections of the dryer. When the content of a segment has achieved the necessary level of moisture, the segment is emptied, moved to the granule-conditioning module, and then refilled with a fresh package of wet granules. This process continues until the content of the segment has reached the appropriate level of moisture. Monitoring is done on the drying curve of each individual package. In the granule-conditioning module, the dried granules may be analysed for important aspects of their quality, such as the distribution of their particle sizes, the level of humidity, and the consistency of their contents. Because there is only 6–9 kg in process at any one time, the amount of potential product loss is kept to a minimum. Because of its compact size and modular design, the system can be rapidly deployed, easily scaled up, and is simple to integrate with pre-existing infrastructure with relative ease.

2. Materials and Methods

Chemicals: Bidwai Chemicals Pvt. Ltd. (Nanded) was the company that provided the flavouring, paracetamol, and mefanamic acid. Maltodextrin and Pearlitol SD 200 were both products that were supplied by Signet Chemicals Corporation Pvt. Ltd. (Mumbai). S D Fine-Chem Ltd. (Mumbai) was kind enough to provide us with sucrose, povidone K30, and citric acid. Gangwal Chemicals Pvt. Ltd. (Mumbai) was the source for the sucralose that was used. The company Research-Lab Fine Chem Industries (Mumbai) was the one that provided the sodium chloride.

Formulation of granules:IP, NF and IH grade ingredients were used in different weights for optimization of formulation by nine batches. Weights of sucralose, maltodextrin and lemon flavour were increased by 5 mg, 50 mg and 5 mg respectively (Table 1).

Ingredients	**Pharmacopoeia Grade**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Paracetamol	IP	325	325	325	325	325	325	325	325	325
Mefenamic acid	IP	250	250	250	250	250	250	250	250	250
PearlitolSD 200	NF	300	300	300	300	300	300	300	300	300
Sucrose	NF	300	300	300	300	300	300	300	300	300
Sucralose	NF	10	15	20	20	20	20	20	20	20
Povidone K30	IP	20	20	20	20	20	20	20	20	20
Sodiu	IP	3	3	3	3	3	3	3	3	3

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

m chloride		0	0	0	0	0	0	0	0	0
Citric acid	IP	60	60	60	60	60	60	60	60	60
Purified Water	IP	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Maltodextrin	IP	50	50	50	100	150	200	200	200	200
Lemon Flavour	IH	10	10	10	10	10	10	15	20	25
Total Weight		1355	1360	1365	1415	1465	1515	1520	1525	1530

Table 1

Composition of the Formulation

Batch Manufacturing Process: Weigh out the following ingredients and add them to the mixture: mefenamic acid, paracetamol, pearlitol SD 200, citric acid, sodium chloride, sucrose, sucralose, and maltodextrin. Put the material through sieves with a 20-mesh opening. Mix the ingredients together for ten minutes using a mortar and pestle. After adding the Povidone K30 to the water (q.s.) and stirring it well to get a clear solution, add the clear solution to the dry mix that is being prepared in the mortar and pestle and mix it thoroughly. Run the wet bulk through sieves with a mesh size of 10, and then place the wet granules in an oven set to 50 degrees Celsius for two hours. Put the dried grains through sieves with a 20-mesh opening. After mixing for 20 minutes, add maltodextrin to the dry granules that were previously mentioned. Blend fill in sachet.

Evaluation of granules for taste masking property: Nine different batches of the taste-masking granules were tested throughout the formulation process.

• The APIs used in Batch F1 had an overpoweringly bitter flavour, which was a problem.

• The quantity of sucralose was raised by 5 mg in Batch F2 in an effort to improve the product's taste; nonetheless, the granules still have a bitter flavour.

• In Batch F3, the quantity of sucralose was raised once again by 5 mg in order to boost the sweetness of the granules; nonetheless, the bitter taste was not eliminated completely.

• In Batch F4 of this product, rather than increasing the total quantity of sucralose, here the total amount of maltodextrin has had 50 mg added to it.

• The quantity of maltodextrin in Batch F5 is once again raised by 50 mg due to the fact that the granules still have the same harsh flavour as they did in Batch F4.

• When compared to earlier batches, the bitter taste of the granules in Batch F6 was not as strong as it had been in earlier batches. To make the granules taste even better, an additional fifty milligrammes of maltodextrin was added to the mixture.

• The bitter taste of the granules was hidden in Batch F7, but the quantity of flavour added in that batch was insufficient since it did not display any flavouring property, so the amount of flavour was increased by 5 mg. Batch F6 was used to hide the bitter taste of Batch F7.

• The quantity of flavouring agent used in Batch F8 is raised once again by 5 mg in order to provide the formulation with an improved taste.

• The quantity of flavouring agent used in Batch F9 was raised by another 5 mg after the previous increase. However, as a consequence of this, the taste of the suspension became too strong; hence, the total quantity of flavouring ingredient in the formulation was maintained at 20 mg.

• It was determined that the Batch F8 had a flavour profile that was more amenable to the oral suspension's intended use. It was determined that the quantity of sweetener and flavouring agent needed to adequately cover up the APIs' naturally bitter taste in the oral solution was enough.

Preformulation studies: The term "preformulation" refers to a series of studies that concentrate on the physicochemical characteristics of a novel drug candidate and how those characteristics could have an impact on the creation of a dosage form for the medicine. This can give useful information for the formulation design process or provide credence to the idea that molecular change is necessary. Before developing a pharmaceutical formulation, it is necessary to take into account the inherent chemical and physical features that are present in each medicine. This feature lays the groundwork for the combination of medications and pharmaceutical substances in the

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

production of dosage form and offers the necessary framework. The purpose of the preformulation study is to develop a dosage form that is elegant, stable, effective, and safe. This will be accomplished by determining the kinetic rate profile of the new drug substance, determining its compatibility with the other ingredients, and determining its physicochemical parameters. In the preformulation research, the parameters of drug solubility, partition coefficient, dissolution rate, polymorphic forms, and stability all play key roles. Crystalline and amorphous forms are examples of polymorphism, which reveals distinct differences in the chemical, physical, and therapeutic characteristics of the drug molecule. In this article, certain preformulation assessment parameters of drugs are discussed, along with their corresponding qualities and methodologies.

Organoleptic properties: This entails the notation of the colour, smell, and flavour of the descriptive language. Drugs are often identifiable by their distinct appearance, smell, and taste. During subsequent stages of the formulation process, unpleasant ones are covered up.

Flow properties: For the purpose of determining the reason for poor flow, powder flooding or rate restrictions, segregation, or product non-uniformity, it is essential to have a comprehensive knowledge of the flow characteristics and flow ability of the bulk material in question.

(1) Bulk density: The ratio of the mass to the volume (including the volume of the inter particulate void) of an untouched powder sample is what is meant to be understood as the bulk density of a material. The density is expressed as grammes per millilitre. Both the density of the powder particles and the arrangement of the powder particles are important factors that influence the bulk density. The preparation of the sample material, how it is treated, and how long it is stored all have an impact on the bulk density. Using a dry graduated cylinder of 250 ml (readable to 2 ml), carefully inject, without compacting, about 100 g of the test sample (m) weighed with 0.1% accuracy. This will provide the bulk density. In the event that it is essential to do so, carefully level the powder without compacting it, and read the unsettled apparent volume (V0) to the closest graded unit. Utilizing the formula m/V0, get the bulk density in grammes per millilitre. In most cases, it is preferable to do repeat measurements when trying to determine the value of this attribute.The formula for calculating bulk density is as follows: quantity of powder taken apparent unstirred volume**Bulk density = mass of powder taken ÷ apparent unstirred volume**

(2) Tapped density: The enhanced bulk density that may be reached by tapping a container holding a powder sample with a mechanical tool is referred to as the tapped density. To acquire the tapped density, a graduated measuring cylinder or vessel that contains the powder sample is mechanically tapped in order to obtain the density reading. Following the observation of the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped, and measurements of the volume or mass are obtained until there is minimal further change in the volume or mass seen. The mechanical tapping is accomplished by first elevating the cylinder or vessel and then letting it to descend, under its own mass, a defined distance using one of the three ways that are detailed further down in this section. It is probable that devices that spin the cylinder or vessel while tapping down are preferable for the purpose of minimizing the possibility of mass separation when tapping down.Tapped density = Weight of sample taken ÷ tapped volume

(3) Compressibility/ Carr's Index (C.I.): It is a measurement that indicates how easily a powder may be compressed. In the field of pharmaceutics, the Carr's index is used rather often in order to determine the flow ability of a powder. Because the bulk density and the tapped density are likely to have comparable values in a powder that can be easily poured, Carr's index is likely to have a low value. On the other hand, the difference between the bulk density and the density measured after being tapped would be bigger in a powder that had poor flow because there would be more interactions between the particles. As a result, the Carr's index would be higher in this kind of powder. If the Carr's index is over 25, it is seen to be an indicator of poor flowability, and if it is below 15, it is thought to be an indication of high flow ability (Table 2).

Compressibility Index (C.I.)	Flow Properties
5-15	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Table 2
Scale of flowability by Compressbility Index

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

The formula for calculating the compressibility index is: Compressibility index = [(Tapped density - Bulk density) ÷ Tapped density] × 100

(4) Hausner ratio: The Hausner ratio is a statistic that is associated to the flow ability of a powder or granular material. The Hausner ratio may be written as "Hauser ratio." After determining the tapped density as well as the bulk density, the hausner ratio was computed with the use of the formula (Table 3);

Hausner ratio = Tapped density ÷ Poured density

Range	Flow Properties
1.1-1.3	Excellent
1.3-1.4	Good
1.4-1.5	Fair
1.5-1.6	Poor

Table 3

Scale of flowability by Hausner ratio

(5) Angle of Repose (θ): The term "Angle of Repose" (Θ) refers to the greatest angle that may exist between the surface of a pile of powder and a horizontal plane. The angle of repose is a useful tool for determining the amount of frictional force present in grains or loose powder. (Table 4)

Angle of repose (θ)	Flow Property
25-30	Excellent
30-35	Good
35-40	Fair
40-45	Poor
45-50	Very Poor

Table 4

Relationship between angle of repose and powder flow

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

Where,

θ - Angle of repose.

h - Height of pile.

r - Radius of the base of pile.

The brim was equipped with a funnel, and the test specimen was permitted to move freely through the aperture while gravity did its work. The area of the pile is measured using the cone that was generated on the graph sheet. This allows for an assessment of the granules' capacity to flow. In addition to that, the height of the pile is measured.

Solubility study:A investigation on the solvability of paracetamol revealed that it was soluble in hot water, as well as in methanol, ethanol, and ethyl acetate. The amount of solubility in water is 1400 mg/l. Mefenamic acid is soluble in solutions of alkali hydroxides, but it is only slightly soluble in chloroform and ether, and it has a solubility in water that is equal to 20 mg/l. The BCS categorises paracetamol as a class III drug, whereas mefenamic acid is included in the class II category.

Melting point: It was determined that the melting point of paracetamol is 168.61 degrees Celsius, although the published value is 168-170 degrees Celsius. The melting point of mefenamic acid was measured to be 229.19 degrees Celsius, while the number that is often given is between 229 and 231 degrees Celsius. As a result, the results of the offered sample coincide with those that were reported.

UV Spectroscopy:

(1) Determination of UV Absorption Maxima – Producing stock solutions at a concentration of 100 g/ml required the dissolution of 10 mg of paracetamol and 10 mg of mefenamic acid in corresponding volumes of 100 ml of 0.05M phosphate buffer 10.8. After further diluting 1 ml of these solutions to a total volume of 10 ml using the respective solutions, the resulting concentration of 10 g/ml was then scanned between 400 and 200 nm.

(2) Preparation of sample solution for calibration curve – The preparation of the sample solution for the calibration curve involves making various dilutions of stock solutions (100 g/ml) of paracetamol and mefenamic acid in 0.05M phosphate buffer pH 10.8 to obtain solutions with concentrations of 2, 4, 6, 8, 10, 12 and 5, 10, 15, 20, 25, 30 g/ml, respectively. The absorbance was measured at the respective max of each medication against the corresponding phosphate buffer that served as the blank.

IR Spectroscopy: The IR spectra of both drugs was recorded using a potassium bromide (KBr) pellet with a resolution of 4 cm-1 across a range of 4000 to 400 cm, and the primary peak was quantified using an IR affinity -1 shimadzu spectrophotometer. There has been a correlation established between the structural assignments of pure medicines and the standard band frequencies.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

Drug – Excipients compatibility studies: Studies to determine whether or not a drug and its excipients are compatible: In the process of systematically developing the granule formulation, the pharmaceutical development began with a research to determine whether or not a drug and its excipients are compatible. The mixtures of distinct therapeutic compounds and excipients were put through many different temperature and humidity settings, including 250 degrees Celsius with 60 percent relative humidity (RH), 300 degrees Celsius with 65 percent RH, and 400 degrees Celsius with 75 percent RH. The mixtures were stored in airtight transparent glass vials with tight-fitting caps. The first observation of the samples was performed, and then those samples were inspected once a week for a period of sixty days for any changes in their look, colour, or odour.

Differential Scanning Calorimetry (DSC): The DSC thermal analysis was performed for knowing thermo-mechanical characteristics, to discover any potential chemical interactions between drug and excipients. This was done in order to determine the efficacy of the formulation. The differential scanning calorimeter, or DSC, is a technique of thermal analysis that may be used to identify changes in the physical and/or chemical characteristics of the materials as a function of temperature. This is accomplished by measuring the changes in heat associated with the processes in question. The heat flow that was necessary to keep the sample and the reference at the same temperature was measured after the sample and the inert reference were put in a temperature-controlled chamber. The outcome of this is either an endothermic reaction, in which heat is absorbed, or an exothermic reaction, in which heat is released (exothermic reaction).

Formulation development of Mefenamic Acid and Paracetamol: The creation of a suitable formulation for mefenamic acid and paracetamol, the granules of mefenamic acid and paracetamol were made by passing the powder through sieves numbered no.20. Evaluation was place using the powder mixes first, before the granulation process began.

Evaluation of granules:

Appearance: Granules were examined visually to verify the condition of their surface.

Uniformity of weight: Weight Uniformity Twenty sachets were chosen at random and weighed separately to determine the weight of each one. A calculation was made to determine their average. The percentage of weight variance was computed based on the granules' average weight.

Drug Content/ Assay: Twenty individual packets were weighed and then pulverised. After vigorous shaking on an ultrasonic cleaner, a quantity of powder that was equal to 13 milligrammes of paracetamol and 10 milligrammes of mefenamic acid was dissolved in 100 millilitres of 0.05M phosphate buffer with a pH of 10.8. After being filtered and diluted, the concentrations of paracetamol and mefenamic acid were brought down to 13 g/ml and 10 g/ml, respectively, so that the absorbance could be brought up to the corresponding max value. The simultaneous equation approach was used in order to determine the concentration of both medications.

In vitro drug release studies (Dissolution test): In vitro drug release studies (Dissolution test) The in-vitro drug release research was carried out using a USP type II paddle equipment, 900 ml of filled fluid, paddle rotation of 50 rpm, and a temperature of 37 0.5 degrees Celsius. During the duration of 60 minutes, a sample of 5 millilitres was taken at regular intervals set in advance. The sample was filtered with whatmann filter paper, and then using a double beam UV spectrophotometer, the concentrations of paracetamol and mefenamic acid in the solutions were determined at 257.6 nm and 286 nm, respectively.

3. Results

API identification results: According to the organoleptic examination of paracetamol and mefenamic acid, both substances are in the solid form, are white in colour, have no discernible odour, and taste bitter.

Solubility: The drug paracetamol dissolves easily in a variety of solvents, including water, methanol, alkali hydroxides, and phosphate buffer 10.8. The solubility of mefenamic acid in water was quite low, but it was soluble in methanol and it was very easily soluble in alkali hydroxides and phosphate buffer 10.8.

API Characterization: Mefenamic acid is a white to off-white crystalline powder, and paracetamol has no discernible odour and a taste that is just mildly bitter. (Table 5).

Sr. No.	Parameters	Paracetamol	Mefanamic acid
1	Melting point	169-170ºC	230-231ºC
2	Bulk density	0.285gm/ml	0.166

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

			gm/ml
3	Tapped density	0.4gm/ml	0.222gm/ml
4	Carr's Index	28.75	25.32
5	Hausner's Ratio	1.403	1.33
6	Angle of repose	37.91º	33.1º

Table 5
Characterization of Paracetamol and Mefanamic acid

UV Spectroscopy: The maximal absorption, also known as the max, was determined to be 257.6 nanometers for paracetamol and 286 nanometers for mefenamic acid, respectively. In a 0.05M phosphate buffer with a pH of 10.8, it was discovered that the response to paracetamol was linear throughout a concentration range of 2-12 g/ml when measured at 257.6nm. The correlation coefficient for this experiment was 0.999. (Table 6). In a manner analogous, it was discovered that the response for mefenamic acid was linear in the concentration range of 5-30 g/ml at 286nm, with a correlation value of 0.998 in phosphate buffer with a pH of 10.8. (Table 7). There are provided examples of standard plots for both paracetamol (Figure 1) and mefenamic acid (Figure 2).

Concentration (µg/ml)	Absorbance (λmax 257.6)
2	0.160
4	0.315
6	0.456
8	0.638
10	0.782
12	0.955

Table 6
Linearity study data of Paracetamol in 0.05 M phosphate buffer pH 10.8

Concentration (µg/ml)	Absorbance (λmax 286 nm)
5	0.27
10	0.457
15	0.674
20	0.885
25	1.102
30	1.353

Table 7
Linearity study data of Mefenamic acid in 0.05 M phosphate buffer pH 10.8

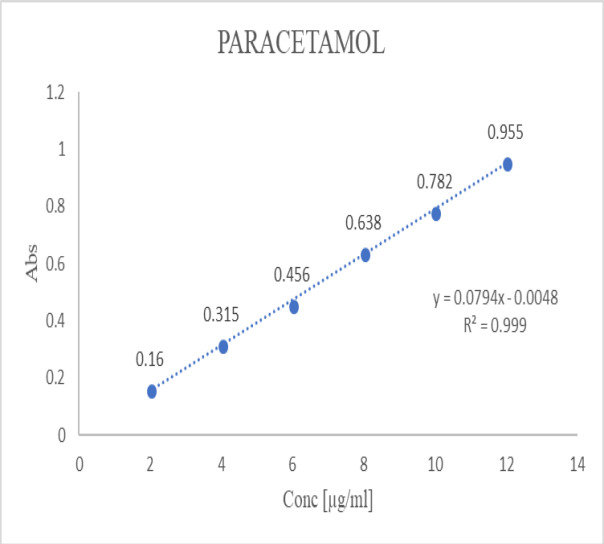


Figure 1: Calibration Curve of Paracetamol in 0.05 M Phosphate Buffer pH 10.8

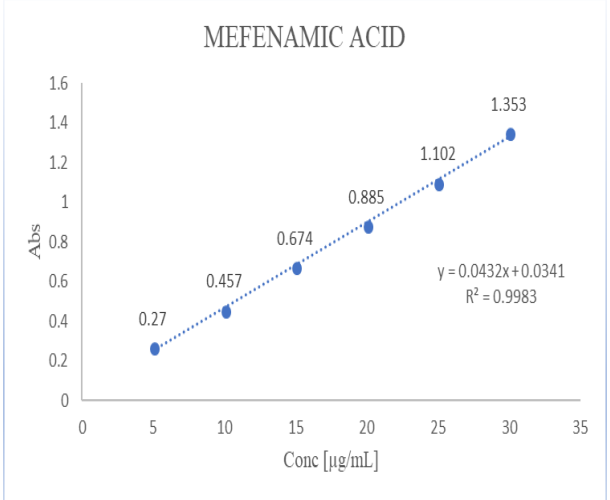


Figure 2: Calibration Curve of Mefenamic acid in 0.05M Phosphate Buffer pH 10.8

Infra-red Spectroscopy: After that, the sample of the medication was put into the FT-IR cuvette. On an FT-IR, the sample of the medication was examined over the wavelength range of 4000-400 cm-1. It was determined that the FT-IR spectra of the drug sample

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

were recorded (Figure 3, Figure 4).Analysis of Paracetamol and Mefenamic Acid Utilizing Fourier Transform Infrared Spectroscopy in (Table 8).

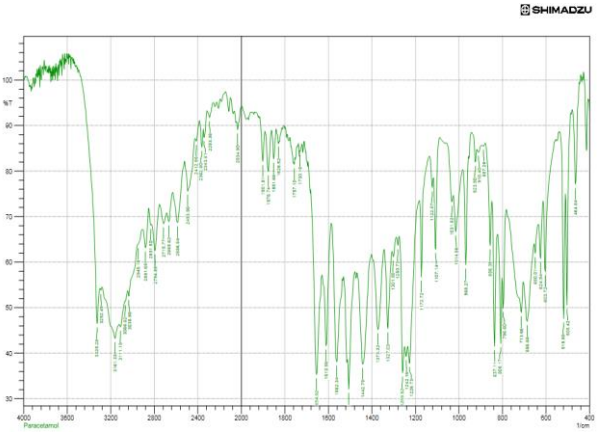


Figure 3: FT-IR of Paracetamol

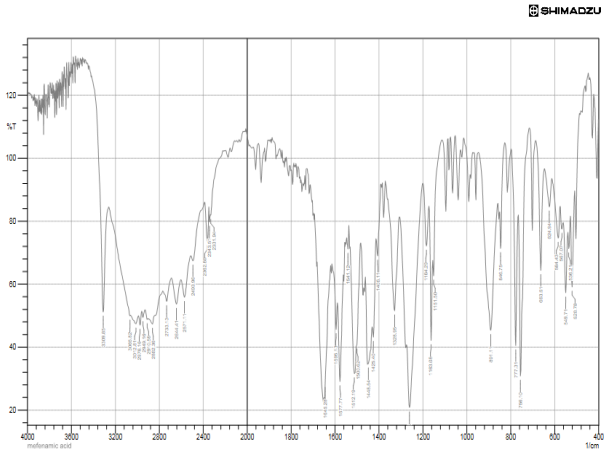


Figure 4: FT-IR of Mefenamic acid

IR Spectrum	Standard Peaks Value (cm^{-1})	Observed Peaks Value (cm^{-1}) of APIs	Groups
Paracetamol	1600 and 1475	1608	C=C Stretching (Aromatic)
	3500-3100	3325.28	N-H Stretching
	1680-1630	1651.07, 1635.04	C=O Stretching (Amide)
	3650-3600	3647.39	O-H Stretching (Phenolic)
Mefenamic acid	1600 and 1475	1471.69, 1595.13	C=C Stretching (Aromatic)
	3500-3100	3311.78	N-H Stretching
	3400-2400	2976.16	O-H Stretching (Carboxylic)
	1725-1700	1714.72	C=O Stretching (Carboxylic)

Table 8
Characteristic peaks of PAR and MEF

Drug Excipients compatibility study: The careful selection of excipients is essential to the successful formulation of a solid dosage form that is suited to the intended purpose and is also effective. Excipients are added to drugs in order to make their administration easier, to enhance the drug's steady release, and to increase its bioavailability. It is essential to investigate whether or not the medicine is compatible with the excipients. FT-IR spectroscopy was used in order to study and forecast any potential physicochemical interactions between the components of a formulation, as well as to choose appropriate excipients that were compatible with the formulation. Sodium Chloride, Sucrose, Sucralose, Citric acid, Pearlitol SD 200, Maltodextrin, Povidone K30, and Flavoring agent are the excipients that were employed in the formulation.The spectrum was collected in the wavelength band of 4000-400 cm-1 after FT-IR spectroscopy was carried out. The first step of the process involves mixing a sample of drug and excipients at a ratio of 1:1. This will be done in a cuvette. Spectra were obtained by placing the drug sample in a light path, scanning it using an FT-IR, and recording the results (Figure 5).All of these peaks have been seen in the formulation as well as the physical combination, which suggests that there was no chemical interaction between the drugs and the excipients. Additionally, it demonstrated that the drug's stability was maintained throughout the granulation process.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

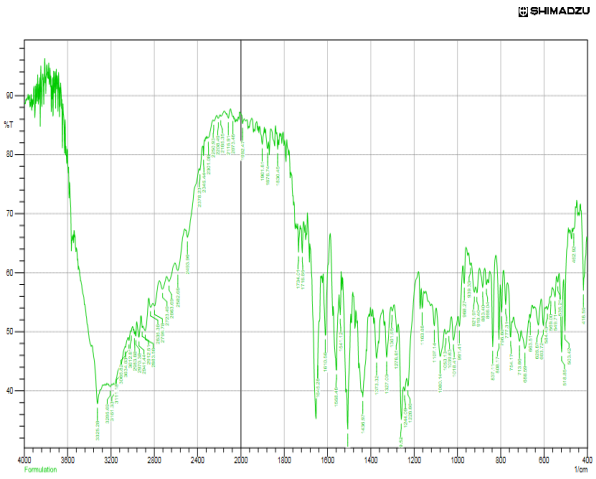


Figure 5: FT-IR of Drug+Excipients (1:1)

Differential Scanning Calorimetry: The thermograms of paracetamol and mefenamic acid both show a characteristic, sharp endothermic peak at 171.41 degrees Celsius (Figure 6) and 231.72 degrees Celsius (Figure 7), respectively. These temperatures correspond to the melting points of the drug paracetamol, which is 170 degrees Celsius, and mefenamic acid, which is 230 degrees Celsius.When the DSC thermograms of the medications and the thermograms of the formulation were evaluated alongside one another, it revealed that the formulation was having an endothermic peak that was equivalent to that of the pharmaceuticals. This leads one to the conclusion that the peaks were related to the drug's melting point, and it also points to the crystalline form of the substance, as seen in (Figure 8).DSC investigation of drug-polymer interaction in glutinous rice-based microbeads was performed and published by Sachan et al. (2012). The thermal analysis demonstrates the application of heat and the measurement of changes in heat; as a result, it refers to the temperatures of transitions or the flow of heat as the samples move through transition.

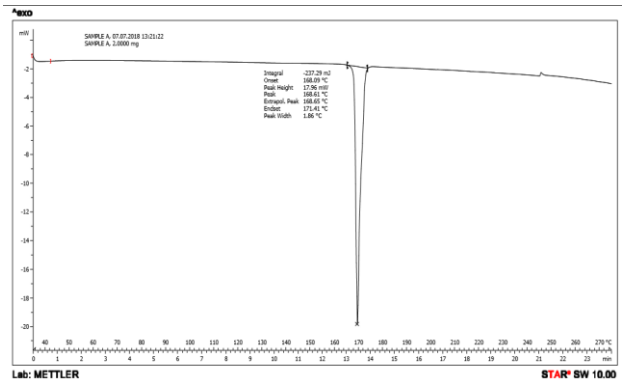


Figure 6: DSC of Paracetamol

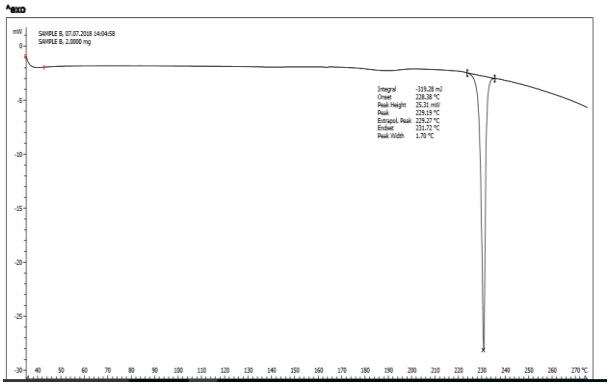


Figure 7: DSC of Mefenamic acid

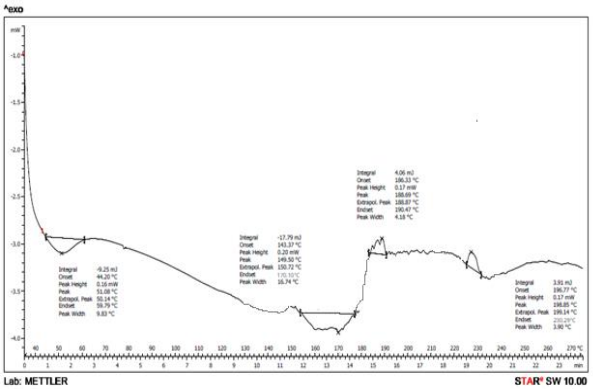


Figure 8 : DSC of Drug + Excipients

X-Ray diffraction (XRD) study: The powder X-ray diffraction patterns for the pure medication paracetamol (Figure 9) and mefenamic acid (Figure 10) as well as their excipients (Figure 11) are shown here. The majority of the distinctive lines that could be seen in the diffraction patterns were, on the whole, clear and distinct. Accurate peak locations for qualitative analysis may be more easily obtained with samples that have been properly prepared. Should the sample surface have been uneven, or should it have been moved away from the focusing circle, peak intensities and positions

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

will be different.The XRD patterns of both the drug and its formulation were analysed, and all of the high intensity peaks (relative intensity) that were found in each were compared. It was discovered that the medications exhibited XRD patterns that were comparable to those shown by the formulation. The location of peaks and the relative strengths of those peaks allowed for the identification of a structure based on the powdered diffraction pattern of the structure. The value of 2 and the ratio of the intensities of the strongest peaks, denoted as I/I0, were used to define each XRD pattern.

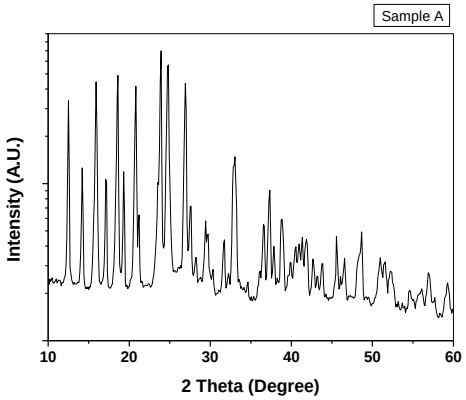


Figure 9: pXRD of Paracetamol

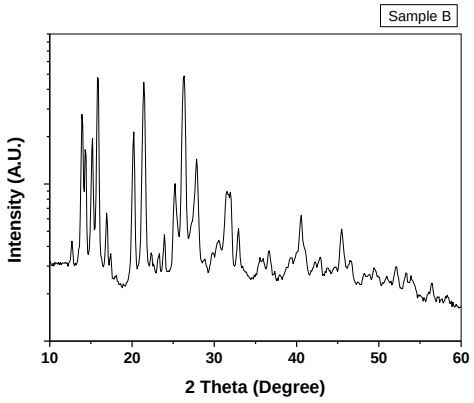


Figure 10: pXRD of Mefenamic acid

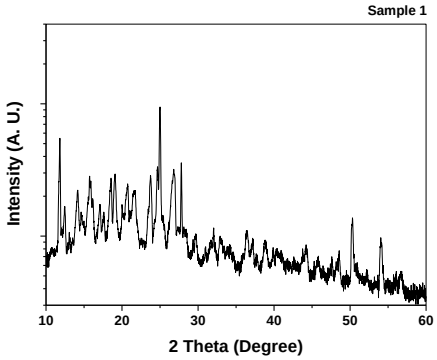


Figure 11: pXRD of Paracetamol, Mefenamic acid and Excipients composite

Formulation study: Selection of the Excipients:The excipients employed in formulation, which include sucrose, sucralose, pearlitol SD 200, and maltodextrin, are used as a sweetening agent since they cover up the medicinally unpleasant taste of the medications. Sucralose is used to hide the bitter taste of APIs since it is around 600 times sweeter than sugar and it is utilised in the same way. Povidone K30 is a binder that, when ingested orally, goes straight through the body without being broken down. Citric acid and sodium chloride work together to keep the dispersion's flavour consistent while also acting as osmotic agents and preserving the isotonicity of the solution. In addition to its role as a preservative, citric acid serves to keep active components in stable condition.

Drug and powder flow properties: The quality of the granules that are produced is directly proportional to the quality of the mix that is used to make them. As a result, it is essential to examine the powder in order to determine whether or not it has the acceptable level of quality. The sample of the blended substance that was being evaluated was passed through sieve no. 20, and the volume of the sample that was comparable to 5 grammes was measured out into a graduated cylinder containing 25 millilitres.

The formulation has an angle of repose in the range of 30-35 degrees, which indicates that it has acceptable flow characteristics. In addition, the value of Carr's index was between 5 and 15, which indicates outstanding flow ability. The material ratio calculated by Hausner falls between between 1.1 and 1.3, which indicates that it has excellent flow properties (Table 9).

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

Sr. No.	Batch code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index	Hausner's ratio	Angle of repose
1	**F1**	0.496 ± 0.005	0.614 ± 0.017	19.218± 0.043	1.238± 0.015	32.16º ± 0.824
2	**F2**	0.499 ± 0.01	0.598| ± 0.002	16.555± 0.04	1.198± 0.015	32.26º ± 1.22
3	**F3**	0.498 ± 0.002	0.580 ± 0.016	14.138± 0.04	1.165± 0.025	33.08º ± 0.885
4	**F4**	0.509 ± 0.010	0.597 ± 0.005	14.740± 0.020	1.173± 0.020	32.27º ± 1.108
5	**F5**	0.503 ± 0.015	0.607 ± 0.005	17.133± 0.026	1.207± 0.015	32.92º ± 1.27
6	**F6**	0.502 ± 0.015	0.601 ± 0.002	16.473± 0.04	1.197± 0.025	32.37º ± 0.967
7	**F7**	0.506 ± 0.012	0.593 ± 0.006	14.671± 0.03	1.172± 0.0208	32.57º ± 1.414
8	**F8**	0.501 ± 0.07	0.591 ± 0.010	15.228± 0.039	1.180± 0.015	33.54º ± 0.699
9	**F9**	0.506 ± 0.011	0.606 ± 0.007	16.501± 0.020	1.198± 0.02	33.13º ± 0.633

Table 9
Flow properties of formulation

In-vitro % Drug release profile from preliminary batches: The pattern of drug release was investigated in a phosphate buffer with a concentration of 0.05M and a pH of 10.8. The In-Vitro release profile indicated that F8 was the most promising formulation because the extent of drug release from this formulation was high in comparison to the other formulations. This formulation is suitable for an immediate release drug delivery system in accordance with the guidelines (Table 10, Table 11, Table 12, and Table 13). (Figure 12, Figure 13, Figure 14, Figure 15).

	Batch	Time (in min.)						
		0	**5**	**10**	**15**	**30**	**45**	**60**
% Drug Release	**F1**	0	25.97± 0.84	32.20 ± 0.35	44.22± 0.49	68.03± 0.96	79.21± 0.30	97.32± 0.63
	F2	0	26.29± 0.37	32.2± 0.23	43.15± 0.68	68.03± 0.97	80.18± 0.94	98.75± 0.45
	F3	0	25.7± 0.53	30.92 ± 0.14	43.93± 0.35	67.10± 0.15	79.07± 0.16	96.33± 0.44
	F4	0	26.16± 0.22	31.56 ± 0.57	44.22± 0.68	68.23± 0.70	81.49± 0.41	99.41± 0.63
	F5	0	25.75± 0.46	30.89 ± 0.35	42.95± 0.43	68.12± 0.13	80.27± 0.44	97.85± 0.26
	F6	0	25.81± 0.51	31.40 ± 0.52	44.03± 0.26	67.81± 0.50	81.3 ± 0.35	97.77± 0.40
	F7	0	26.38± 0.52	31.32 ± 0.52	42.84± 0.34	67.62± 0.73	81.42± 0.46	98.29± 0.12
	F8	0	26.28± 0.43	32.33 ± 0.34	44.11± 0.20	67.85± 0.27	81.32± 0.71	99.32± 0.34
	F9	0	25.59± 0.43	30.86 ± 0.33	42.91± 0.23	67.22± 0.33	79.15± 0.93	98.69± 0.49

Table 10
Drug release profile of Paracetamol

	Batch	Time (in min)						
		0	**5**	**10**	**15**	**30**	**45**	**60**
	F1	0	41.12± 0.29	44.98± 0.11	61.99± 0.44	75.07± 0.18	84.01± 0.56	97.93± 0.06
	F2	0	40.77±	44.95±	60.71±	74.93±	84.14±	96.66±

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

%Drug Release			0.47	0.12	0.50	0.37	0.60	0.49
	F3	0	41.12±0.34	46.24±0.28	61.36±0.45	74.75±0.23	83.96±0.122	97.87±0.29
	F4	0	42.26±0.38	45.61±0.46	62.22±0.28	75.03±0.06	85.07±0.15	96.32±0.29
	F5	0	40.79±0.31	45.48±0.44	62.30±0.41	73.96±0.29	85.11±0.15	97.64±0.19
	F6	0	41.48±0.39	44.74±0.43	61.24±0.25	73.79±0.33	83.78±0.29	96.96±0.19
	F7	0	40.87±0.11	45.20±0.38	62.17±0.23	75.12±0.23	84.83±0.17	98.77±0.46
	F8	0	41.02±0.22	46.59±0.53	60.33±0.31	73.75±0.36	84.63±0.4	98.91±0.12
	F9	0	42.14±0.22	45.91±0.18	61.3±0.37	74.8±0.46	83.66±0.20	97.93±0.13

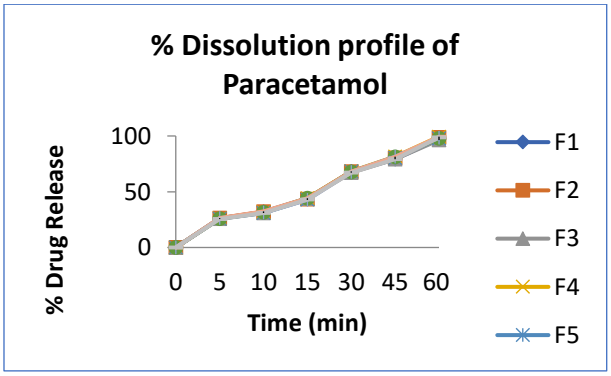
Table 11Drug release profile of Mefenamic acid

Time (Min)	% Drug Release	
	PAR	MEF
0	0	0
5	26.28±0.43	41.02±0.22
10	32.33±0.34	46.59±0.53
15	44.11±0.20	60.33±0.31
30	67.85±0.27	73.75±0.36
45	81.32±0.71	84.63±0.4
60	99.32±0.34	98.91±0.12

Table 12
In-vitro drug release of formulation containing PAR and MEF [Batch F8]

Time (Min)	% Drug Release					
	0 Month (25°C ± 2°C)		1 Month (45°C ± 2°C/75% RH±5%		3 Month (45°C ± 2°C/75% RH±5%	
	PAR	MEF	PAR	MEF	PAR	MEF
0	0	0	0	0	0	0
5	26.28 ± 0.43	41.02 ± 0.22	24.08 ± 0.43	39.23 ± 0.22	25.14 ± 0.43	40.92 ± 0.22
10	32.33 ± 0.34	46.59 ± 0.53	34.73 ± 0.34	49.12 ± 0.53	35.29 ± 0.34	48.79 ± 0.53
15	44.11 ± 0.20	60.33 ± 0.31	47.23 ± 0.20	62.18 ± 0.31	43.47 ± 0.20	63.48 ± 0.31
30	67.85 ± 0.27	73.75 ± 0.36	69.01 ± 0.27	76.19 ± 0.36	66.86 ± 0.27	77.11 ± 0.36
45	81.32 ± 0.71	84.63 ± 0.4	83.43 ± 0.71	81.19 ± 0.4	82.23 ± 0.71	82.73 ± 0.4
60	99.32 ± 0.34	98.91 ± 0.12	98.19 ± 0.34	97.46 ± 0.12	98.52 ± 0.34	98.01 ± 0.12

Table 13
In-vitro drug release profile of formulation after stability study [Batch No. F8]



Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

Figure 12: % Drug Release Profile of Paracetamol for F1 to F9 Formulation

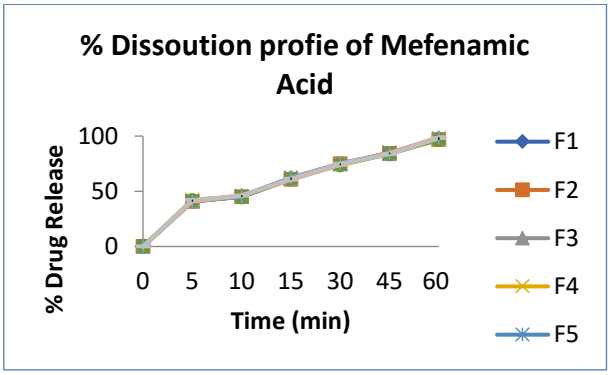


Figure 13: %Drug Release profile of Mefenamic acid for F1 to F9 Formulation

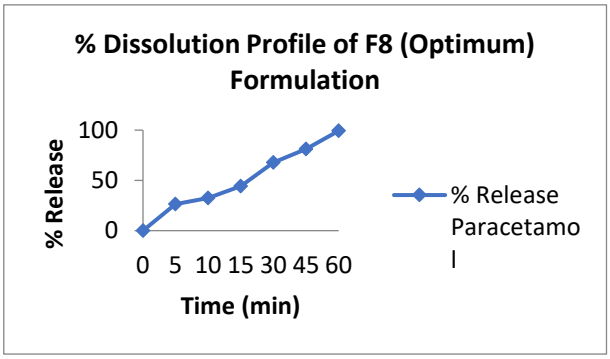


Figure 14: % Drug Release of Paracetamol of F8 Optimum Formulation

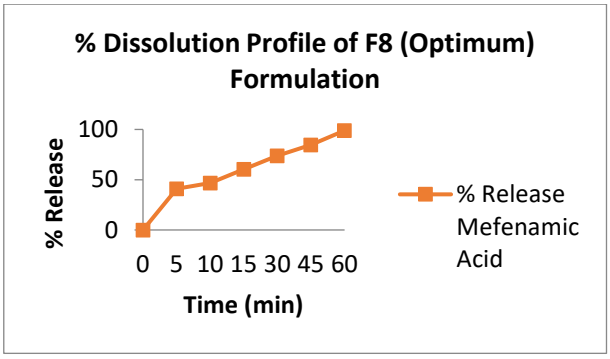


Figure 15: % Drug Release of Mefenamic acid of F8 Optimum Formulation

Stability study of Paracetamol and Mefenamic acid: At the time of usage, the data from the stability study of the dosage form are analysed and examined for safety, quality, and purity, as well as the in-vitro release rates that they claim to have. However, the drug release pattern and the content consistency were not determined to have undergone any substantial alterations with this formulation. During the course of the investigation, there were no discernible shifts in any of the parameters that were being monitored; hence, it was possible to draw the conclusion that the formulation was reliable (Table 14) and (Figure 16, Figure 17, Figure 18).

Specification	0 Month (25°C ± 2°C)	1 Month (45°C ± 2°C/75% RH±5%	3 Month (45°C ± 2°C/75% RH±5%
PAR	99.69±1.550	99.55±1.778	99.38±1.167
MEF	99.66±0.756	99.13±0.409	99.66±0.871

Table 14
Stability study data of Formulation Assay (%Content Uniformity) [Batch No. F8]

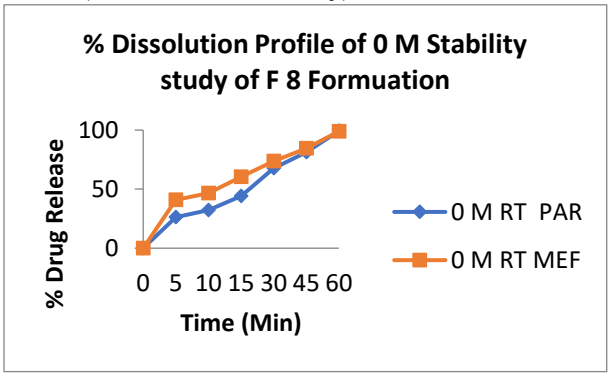


Figure 16: %Drug Release Profile at 0 Month Room Temperature (RT) Condition

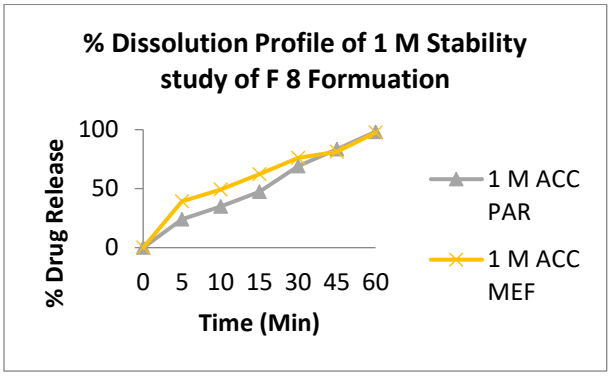


Figure 17: %Drug Release Profile at 1 Month Accelerated (ACC) condition

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

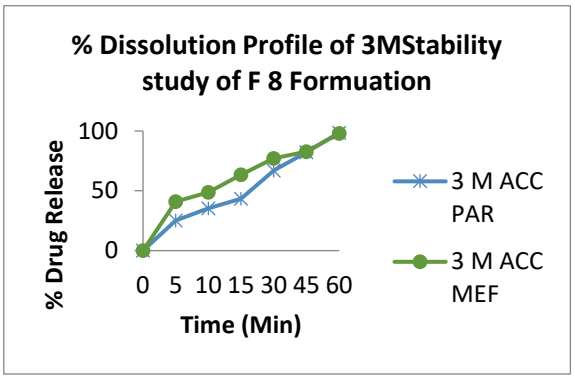


Figure 18: %Drug Release Profile at 3 Months Accelerated (ACC) Condition

4. Conclusion

A study of the available literature on fever management was carried out. It is a Class III drug according to the Biopharmaceutics Classification System (BCS), with high solubility and low permeability absorption characteristics, and oral dosing is the most common method of administration. Paracetamol is a non-prescription analgesic and anti-pyretic medication that is used to treat mild to moderate pain and fever. The medicine has a half-life that may vary anywhere from one to four hours, and its bioavailability can reach up to sixty to seventy percent. Mefenamic acid is the only derivative of Mefenamic acid that can cause analgesia in both the centralnervous system and the peripheral nervous system. It is a Class II medicine according to the Biopharmaceuticals Classification System (BCS), has poor solubility and high permeability absorption properties, and is quickly absorbed after oral administration. It is approved for the short-term alleviation of moderate discomfort and for primary dysmenorrhea. The medicine has a bioavailability of up to ninety to one hundred percent, and its half-life is somewhere in the vicinity of two hours.Following the collection of the sample of the medication, it was analysed for the purposes of identification using FT-IR and melting point. After the medications had been identified, their compatibility with the chosen excipients was evaluated using FT-IR and differential scanning calorimetry, respectively. It was discovered that the excipients chosen were suitable for use with the corresponding medications. In general, antipyretic and analgesic medications have a taste that is described as being bitter.The harsh flavour of the oral formulation makes it unpleasant to consume. Patients of all ages, but especially the elderly and the young, often struggle with swallowing. Patients suffering from a variety of diseases and ailments often resist taking medications. Both mefenamic acid and paracetamol have a bitter aftertaste and may be purchased on the market in tablet, capsule, and suspension form respectively. This study's objective was to find ways to hide the medications' unpleasant taste by granulating them, adding sweeteners and flavourings, and mixing them with other substances. It was discovered that the formed granules have an excellent flow quality. Studies using FTIR equipment demonstrated unequivocally that there was no interaction between the medication and the excipients. It was determined how the medicine would be released in vitro from the granules.The flow characteristics of the particular powder were determined to either fall within the range specified by the official pharmacopoeia or meet with its requirements. XRD was used to investigate both the physical characteristics of the medicines and the formulation. The In-Vitro release profile suggested that F8 was the most promising formulation. This was due to the fact that the extent of drug release from this formulation was high in comparison to other formulations, making it appropriate for use in an immediate release drug delivery system in accordance with the guidelines. In the end, granules made from the batch that had been optimised were created.Rapid relief from fever and discomfort may be attained by the use of a combination of the active chemicals paracetamol and mefenamic acid, which are both promptly released. Granules from the improved batch were used in a study of stability that was carried out over the course of three months. Granules were examined to determine the drug release pattern and the degree to which their contents were uniform. During the course of the investigation, there were no discernible shifts in any of the parameters that were being monitored; hence, it was possible to draw the conclusion that the formulation was reliable.The tables of the optimised batch have an excellent drug release pattern. After being subjected to a stability test for a period of three months, the formulation's dissolving profile and physical characteristics were found to have undergone no discernible shifts, according to the findings of the research.The effectiveness of sweetening and flavouring compounds was evaluated with regard to the objective of disguising the taste using granulation as one of the available methods. The aforementioned method of flavour concealment works by reducing the surface area of the medication while simultaneously

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2444-2463 | ISSN:2251-6727

increasing the particle size of the drug's constituents; this process was found to be quite straightforward.

Acknowledgement

Authors are thankful to Bidwai Chemicals Pvt. Ltd., Nanded. for providing us the gift sample of the pure drug and to the School of Pharmacy, S. R. T. M. U. Nanded, for providing research facilities.

References

1. Akiladevi D., Shanmugapandiyan P., Preparation and Evaluation of Paracetamol by Solid Dispersion Technique, *Int. J. Pharm. Pharma. Sci*.,**3(1),** 0975-1491 (2011)
2. Amelian A, Szekalska M, Ciosek P., Characterization and Taste Masking Evaluation of Microparticles with Cetirizine Dihydrochloride and Methacrylate-Based Copolymer Obtained by Spray Drying, *Acta Pharm*., **67(1)**, 113-124 (2017)
3. Basha D.M., Reddy A.K., Simultaneous Estimation of Mefenamic Acid and Paracetamol in Suspension Form by Using UPLC, *Int. J. Chem. Sci*., **12 (3)**, 1015-1022 (2014)
4. Bharadwaj G.,Singh L., Sharma V., Development of Taste Masked Oral Suspension of Mefenamic Acid and Paracetamol for Increase Acceptability, *Res J. Pharm. Bio. Chem. Sci*., ISSN:0975-8585, 775-784 (2015)
5. Bhowmik D., et al., Formulation and Evaluation the Oral Tablets Ibuprofen., *The Pharma. Innov*., **1 (9)**, 32-43 (2012)
6. British Pharmacopoeia, The British Pharmacopoeia Commission offices, London, **1**, 1-3500 (2008)
7. Cantor S.L., et al., Pharmaceutical Granulation Processes, Mechanism, and the Use of Binders. School of Pharmacy, University of Maryland, Baltimore, Maryland, U.S.A., 261-301, (2004) http://www.researchgate.net/publication/262049187_Pharmaceutical_Granulation_Processes_Mechanisms_and_the_Use_of_Binders
8. Chauhan H.K., Patel P., Formulation and Evaluation Effervescent Tablet of Paracetamol and Ibuprofen, *Int. J. Pharm. Res. Sch*., **1(2)**, 509-520 (2012) [accessed2020Jan25]https://www.ijprs.com/article/formulation-and-evaluation-of-effervescent-tablet-of-paracetamol-and-ibuprofen
9. Choudhari V.P., Bharande P.D., Chate S.G., Spectrophotometric Simultaneous Determination of Mefenamic acid and Paracetamol in Combined Tablet Dosage Form by Dual Wavelength, Area Under Curve and Absorbance Corrected Method. *Der. Pharma. Chemica*., **4 (3)**, 935-940 (2012)
10. Dinte E.,Bodoki E., Leucuta S., Compatibility Studies between Drugs and Excipients in the Preformulation Phase of Buccal Mucoadhesive Systems. *FARMACIA*, **61**, 4 (2013) [accessed 2020 Jan 25]https://www.researchgate.net/publication/256094226_Compatibility_studies_between_drugs_and_excipients_in_the_preformulation_phase_of_buccalmucoadhesive systems.
11. Dixit M., Kulkarni P.K., Enhancing Solubility and Dissolution of Mefenamic Acid by Freeze Drying,*Elixir Int. J*., 5026-5029 (2011)
12. Gangwal S., Sharma A.K., Simultaneous Spectrophotometric Determination of Mefenamic Acid and Paracetamol in Combined Pharmaceutical Dosage Forms, *Indian J. Pharm. Sci*., 216-218 (1996)
13. GhoshT.K., PfisterW.R., Drug delivery to the oral cavity: molecules to market, CRC Press, 1st Ed., 1-448 (2005)
14. Han X., Zhang D.K., Zhang F., Novel Strategy for Bitter Taste Masking of Gankeshuangqing Dispersible Tablets Based on Particle Coating Technology, *Pharmacognosy magazine*, **13**, 40-400 (2017)
15. Havaldar F.H., Dharmendra L., Simultaneous Determination of Paracetamol, Acetyl Salicylic acid, Mefenamic acid and CetrizineDihydrochloride in the Pharmaceutical Dosage Form. *E-J. Chem.*, **7 (S1)**, S495-S503 (2010)
16. Indian Pharmacopoeia. The controlled publication, New Delhi. 900-901 (2007)
17. Jain D.K., Darwhekar G.N., Choudhary N., Formulation and Evalution of Reconstitutable Oral Suspension of Ambroxol HCL and Azithromycin, *Int. J. PharmTech Res*., **3 (2)**,0974-4304 (2011) [accessed2020Jan25]. http://sphinxsai.com/vol3.no2/pharm/pharmpdf
18. Kato H., Ono Y., Yonezawa Y., Sunada H., The Effect of Binder Particle Size on Granule and Tablet Properties in High Shear and Extrusion Granulation. *J. Drug Deliv. Sci. Tech*., **16 (6)**, 461–6 (2006)

19. Lachmann L. and Libermann H., The Theory and Practice of Industrial Pharmacy.Varghese Publishing House, Bombay. 3rd Ed., 3-909.(1987)
20. Leuenberger H., et al., Granulation: Preparation, Evaluation & Control, 5th Annual Garnet E. Peck Symposium, West Lafayette IN., 1-59 (2007).
21. Maheshwari R.K., Rajagopalan R., Development of Formulation and Evaluation of Paracetamol Syrup made by Mixed Solvency Soncept, *Sch. Res. Library*., 4 (1), 170-174 (2012)
22. Nurhikmah W., Sumirtapura Y.C. and Pamudji J.S., Dissolution Profile of Mefenamic Acid Solid Dosage Forms in Two Compendial and Biorelevant (FaSSIF) Media, *Sci. Pharm*., **84 (1)**, 181–190 (2016)
23. Nusim S.H., Active Pharmaceutical Ingredients Development, Manufacturing, and Regulation, *Taylor & Francis Group*, **33**, 487-2742 (2005)
24. Parikh D.M., Handbook of Pharmaceutical Granulation Technology, Taylor & Francis Group, LLC. Synthon Pharmaceuticals Inc. Research Triangle Park, North Carolina, U.S.A. 2 Ed., 1-613 (2005)
25. Patil P.B., Gupta V.R., Development of Dissolution Medium for Poorly Water-soluble Drug Mefenamic Acid, *Res. J. Pharm. Bio. Chem. Sci*., **1 (4)**, ISSN:0975-8585 (2010)
26. Patel P., et al., Drug-Excipient Compatibility Studies: First Step for Dosage Form Development, *The Pharma Innov. J*., **4 (5)**, 14-20 (2002)
27. Pawar H.A., Joshi P.R., Development and Evaluation of Taste Masked Granular Formulation of Satranidazole by Melt Granulation Technique, *J. Pharma*. **7**, 1-7 (2014)
28. Rajniak P., Mancinelli C., Chern R.T., Stepanek F., Hill B.T., Experimental Study of Wet Granulation in Fluidized Bed: Impact of the Binder Properties on the Granule Morphology,*Int. J. Pharm*., **334 (1–2)**, 92–102 (2007)
29. Remington, The Science and Practice of Pharmacy, Lippincott Williams and Willkins, 315 West Canada Street, Baltimore, Maryland, USA. 20th Ed., 3-2039 (2002)
30. Sachan N., Ghosh S., Bhattacharya A., Differential Scanning Calorimetric Analysis of Drug-polymer Interaction in Glutinous Rice Based Microbeads. *Asian J. Chem*., **5**, 2207-2209 (2012)
31. Seedher N., Bhatia S., Solubility Enhancement of Cox-2 Inhibitors Using Various Solvent System, *AAPS Pharm. SciTech*., **4 (3)**,article 33, 1-8 (2003)
32. Sharma B.K., Instrumental methods of chemical analysis, Goel Publishing House, Krishna Prakashan Media Ltd., 193-333 (2004)
33. Sharma D., Kumar D., A Novel Approach for The Improvement of Organoleptic Properties of Pharmaceutical Active Substance, *Int. Res. J. Pharm.*, **3(4)**, (2012) [accessed 2020 Jan 25]. https://www.researchgate.net/publication/236152461_Taste_Masking_Technologies_A_Novel_Approach_for_the_improvement_of_Organoleptic_Property_of_Pharmaceutically_Active_Substance
34. Sohi H., Sultana Y., Khar R.K., Taste-masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches,*Drug Dev. Ind. Pharm*., **30 (5)**, 429-448 (2004)
35. Stahl H., Comparing Granulation Methods, GEA Pharma. Systems.,Kalscheurener Strasse 92, D-50354 Hürth, Germany, 1-1 (2004) [accessed 2020 Jan 25].hppt://www.gea.com/en/stories/compairing-granulation-techniques.jsp.
36. Tetsuya N., Tetsuo O., et al., Preparation of Bitter Taste-masking Granules of Lafutidine for Orally Disintegrating Tablets using Water-insoluble/soluble Polymer Combinations, *J. Drug Del. Sci. Tech*., **32 (A)**, 38-42 (2016)
37. USP 36NF 31, 1088, In-Vitro and In-Vivo Evaluation of Dosage Forms, Rockville, MD, 1-15 (2013)
38. Wang L., Sun Y., Kuang C., Preparation and Evaluation of Taste Masked Oral Suspension of ArbidolHydrochloride,*Asian J. Pharm. Sci*., 73-79 (2015)