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FORMULATION AND *IN-VITRO* CHARACTERISATION OF MILNACIPRAN HYDROCHLORIDE ORODISPERSIBLE TABLETS

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Abstract:

Present study is aimed at the development of oral dispersible tablets of Milnacipran Hydrochloride using natural superdisintegrants.Indion414 , Polyplasdone XL 10, Primogel for the preparation of oraldispersible tablets by direct compression method. The blends were evaluated for the pre-compression parameters and all the formulations were found to possess good flow properties. Tablets were compressed by direct compression technique, evaluated for weight variation , hardness, thickness, friability , water absorption, disintegration time, dispersion time drug content and dissolution studies. The drug release profiles of the three superdisintegrants were compared. The optimized formulation F2 was showed good results disintegrated in 3.15 min with 98.89 % drug release.

Key words :*Oral dispersible tablets , Milnacipran Hydrochloride , Indion 414 ,Polyplasdone XL 10, Primogel super disintegranrts , direct compression tablets.*

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INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.[1]

For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oral dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.[2]

A Fast dissolving tablet (FDT)is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT.

US FDA defined FDT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue".

Recently European Pharmacopoeia used the term 'Fast dissolving tablet' as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing.

Orally disintegrating tablets are also called as mouth-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, Fast dissolving tablets, rapimelts, porous tablets, quick dissolving tablet[3].

The US Food and Drug Administration responded to this challenge with the 2008 publication of Guidance for Industry: Orally Disintegrating Tablets [4].Three main points stand out in the final guidance:

- FDTs should have an *in vitro* disintegration time of approximately 30sec or less.
- Generally, the FDT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an FDT for both patients and regulators.
- The guidance serves to define the upper limits of the FDT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an FDT.

The concept of orodispersible tablet emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus without the need for water during administration, an attempts that makes them highly attractive for pediatric and geriatric patients[5] . Difficulty in swallowing conventional tablets and capsules is common among all age groups, especially in elderly and dysphagic patients. This disorder of dysphagia is associated with many medical conditions including stroke, Parkinson's disease, AIDS etc. One study showed that 30% out of 1600 patients experienced difficulty in swallowing tablets due to their large size and by their surface, shape and taste. Elderly patients may find the administration of the conventional oral dosage forms difficult as they regularly require medicines to maintain a healthy life. Children may also have difficulty in ingesting because of their underdeveloped muscular and nervous systems. The problem of swallowing tablets is also evident in travelling patients. Above mentioned problems can be resolved by means of orodispersible Tablets (ODTs)[6]. ODTs are known by various names such as "fastmelting, fast-dissolving, mouth disintegrating Tablet or (MDTs)". Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics. ODTs disintegrate and/or dissolve rapidly in saliva; therefore, water is not required during administration. Some tablets are designed to dissolve in saliva within few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed as fast-disintegrating tablets, as they may take about one minute to disintegrate completely. ODTs offers several advantages over other dosage forms like effervescent tablets, dry syrups and chewing gums or tablets, which are commonly used to enhance patient's compliance[7]. Administering effervescent tablets/granules and dry syrups involve unavoidable preparation that include the intake of water. Elderly patients cannot chew large pieces of tablets or gums and sometimes experience the bitter or unpleasant taste of the drug in the dosage form if the taste masking is not done in proper way.[8]

First-generation ODTs 12,13,14,15

While first-generation ODT technologies produce tablets that dissolve rapidly in the mouth, provide convenience and ease of swallowing, and have had success in the market, som of them fall short in terms of taste masking and the accommodating high doses

and because most first-generation technologies can h andle only low amounts of APIs, their therapeutic applications are limited and are used only in immediate-release applications. A table 2 list today's major ODT technologies.

First-generation ODTs are commonly characterized b y high porosity, low density, and low hardness, making them brittle and difficult to handle. As a result, they often require blister packagi ng, which is less

convenient for patients than bottles and entails high p roduction costs. Fre ze-dried ODTs are especially friable, making them difficult to package conventionally and raising questions about storage stability. Furthermore, it's difficult to use traditional flavous and sugars to mask poor-tasting APIs with first-generation ODTs, which restricts their ap lication to nonbitter APIs. The common approach is to use flavouring and sweetening agents to overpower the taste rather than neutralize it. Today, there are only a few technologies on

the market that provide effective tastemasking capabilities, which requires a physical barrier between the API and the taste buds. One such technique is coacervation (encapsulation). As the ODT market

matures, pharmaceutical companies are seeking addit ional capabilitiesfrom these dosage forms. These include higher API loading, more effective taste masking, controlled-release capability, low friability, cost-effective development, and more packaging options.

New generation of ODTs

New generation of ODTs available today, is one that can be combined with a proprietary process to improve taste masking, allow a modified-release profile, and enhance bio-availability. As a result, formulators can taste-mask even extremely poor-tasting drugs, use high doses of API, and expand the range of therapeutic

applications. These ODTs comprises of rapidly disper sing microgranules, a direct-compression blend, and an external

tablet lubrication method. The result is an ODT with excellent physical robustness,mouth-feel, and

disintegration properties. The tablets dissolve in 15 to 30 seconds (depending on dosage strength)and produce a smooth, pleasant tasting mixture of API granules andcarrier

that is easy to swallow. The tablets are made on standard presses, accept printing on both sides, typically have a friability of less than 0.5 percent, and can be

packaged in bottles or blister packs.

Combining micro-encapsulation with ODT technolog y effectively can

masks bitter APIs and can be applied

to soluble and poorly soluble substances, as well as to high-dose products. One technology is based on coacervation, a coating technique that encapsulates individual drug particles completely and provides superior taste masking. The coacervation process places a uniform coating of polymeric membranes of varying thicknesses and porosities directly onto dry crystals or granules, creating particles that are typically 150 to 300 microns. The membranes creat an inert barrier between the API and the taste buds and a stabilization barrier between the API and the tablet excipients.

Controlled release Combining ODTs with specialized functional polymers and coating processes can lead to ODTs with sustained-, modified-, and customized-release profiles. It is even possible to combine release profiles in a single dose. Typical of these approaches are micro-encapsulation and multiparticulate coating technologies, which allow formulators to create modified-release polymer layers around API particles. These particles are flexible enough for compression without breakage or loss of the modified- release properties and small enough to provide good mouth-feel. Adjusting the coating parameters (thickness, composition, porosity, pH modifying agents, and number of layers) changes the desired plasma profile. Some technologies provides sustained release by layering active drugs onto a neutral core (bead), followed by one or more

rate-controlling, functional membranes

Allowing up to 6 hours of delayed release as given in figure 2, these layered beads ca n be less than 500 microns in very robust ODTs. figure 3 compares a sustained-release potassium chloride (KCl) ODT that maintains its rate of release as long as 12 hours to a standard non-ODT sustained- release KCl tablet. Incorporating bead populations with different release profiles into the dosage form enables formulators to optimize the in vivo release profile. For example, the ODT could release the API as either a burst or sustain the release with a lag time of at least 4 hours.

IDEAL PROPERTIES OF ORODISPERSIBLE TABLETS

- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds
- High drug loading

- Be compatible with taste masking and other excipients
- Have a pleasing mouth feel
- Leave minimal or no residue in the mouth after oral administration
- Exhibit low sensitivity towards environmental conditions such as humidity and temperature.
- Be adaptable and amenable to existing processing and packaging Machinery.

Advantages Of Orodispersible Tablets

- Administration to patients who cannot swallow, like the elderly, stroke victims and bedridden patients; patients who should not swallow, like renal failure patients; and patients who refuse to swallow, such as pediatrics, geriatric and psychiatric patients
- Patient's compliance fordisabledbedriddenpatientsandfor traveling and busy people, who do not have ready access to water
- Good mouth feel property helps to change the basic view of medication as "bitter pill," particularly for pediatric patients due to improved taste of bitter drugs
- The convenience of administration and accurate dosing as compared to liquid Formulations
- Benefit of liquid medication in the form of solid preparation
- More rapid drug absorption from the pre-gastric area, i.e., mouth, pharynx and esophagus which may produce rapid onset of action.
- Pregastric absorption can resultin improved bioavailability, reduced dose and improved clinical performance by reducing side effects New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent life extension.

Disadvantage Of Orodispersible Tablets

- Orodispersible is hygroscopic in nature so must be keep in dry place
- Sometime it possesses mouth feeling
- ODT requires special packaging for properly stabilization and safety of stable product
- Dose uniformity is a technical challenge.

SELECTION OF THE ODTS DRUG CANDIDATES

Several factors must be considered when selecting drug candidates for delivery as ODT dosage forms:

- The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form. E.g., selegiline, apomorphine, buspirone, etc.
- The drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT
- Drugs are having the ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for ODT formulations
- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs
- Patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for ODT formulations
- Drugs which are having a short half-life and needs frequent dosing, which are very bitter or either having unacceptable taste whose taste masking cannot be achieved or which require controlled or sustained release are inappropriate for ODT formulation.

CHALLENGES IN THE FORMULATION OF ODTS

Mechanical strength and disintegration time

ODTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many ODTs are fragile, and there are many chances that such fragile tablet will break during packing, transport or handling by the patients. It is very natural that increasing the mechanical strength will delay the disintegration time. Hence, a good compromise between these two parameters is always essential.

Tastes masking

Many drugs are bitter in taste. A tablet of bitter drug dissolving disintegration in the mouth will seriously affect patient compliance and acceptance for the dosage form. Hevce, effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.

Aqueous solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented using various matrix-forming excipients such as mannitol that can induce

crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablets

The degree of ease when taking tablets depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Amount of drug

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. According to USP generally, the ODT tablet weight should not exceed 500 mg. For lyophilized dosage form, the drug dose should be lower than 400 mg for insoluble drug and <60 mg for soluble drug. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Hygroscopicity

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

Mouth feel

ODTs should not disintegrate into larger particles in the oral cavity. The particles generated after the disintegration of the ODTs should be as small as possible. Moreover, addition of flavors and cooling agents like menthol improve the mouth feel.

Good packaging design

For the protection of ODTs from moisture and other environmental hazards, the package design should be considered early in the development stages.

Freeze drying or lyophilization

Freeze drying or lyophilization is a process in which solvent is removed from a frozen drug solution or suspension containing structure forming excipients. Tablets formulated by this technique are usually very light and porous in nature which allows their rapid dissolution. The glassy amorphous porous structure of excipients, as well as the drug substance produced with freeze drying, results in enhanced dissolution. Freeze drying process normally consists of three steps:

- Material is frozen to bring it below the eutectic point
- Primary drying to reduce the moisture around 4% w/w of dry product
- Secondary drying to reduce the bound moisture up to required final volume.

Entire freeze drying process is carried out at non-elevated temperature; therefore, nullifying adverse thermal effects that may affect drug stability during processing.

Tablet molding

The major components of molded tablets typically are water-soluble ingredients. The powder mixture is moistened with a solvent (usually ethanol or water), and then the mixture is molded into tablets under pressures lower than those used in conventional tablet compression. (This process is known as compression molding). Then the solvent can be removed by air drying. Because molded tablets are usually compressed at a lower pressure than are conventional compressed tablets, a higher porous structure is created to enhance the dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen. Recently, the molded forms have also been prepared directly from a molten matrix in which the drug is dissolved or dispersed (known as heat molding) or by evaporating the solvent from a drug solution or suspension at ambient pressure (novacuum lyophilization).

Spray drying

Spray drying is a process by which highly porous, fine powders can be produced. Spray dryers are invariably used in the pharmaceutical industry to produce highly porous powders. Allen et al. have reported applying this process to the production of fast dissolving tablets [20.]

The main aim of drying is to obtain dry particles with desired properties. Orally disintegrating tablets are made up of hydrolyzed or unhydrolyzed gelatin as supporting agent for the matrix, mannitol as a bulk agent, and sodium starch glycolate and croscarmellose sodium as a disintegrating agent. Sometimes in order to improve the disintegration and dissolution, citric acid and sodium bicarbonate are used. Finally, the formulation is spray-dried in a spray drier. ODTs prepared through this method are disintegrated in <20 seconds . Maximum drug release and minimum disintegration time were observed with kollidon CL excipient base as compared to tablets prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique.

Sublimation

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (e.g., urea, ammonium carbonate, ammonium bicarbonate, hexamethelenetetramine, camphor, etc.) were added to the other tablet ingredients, and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structures. In addition, several solvents (e.g.,

cyclohexane, benzene) can also be used as pore forming agents [11].

Tablets manufactured by this technique are reported to usually disintegrate in 10-20 seconds. Mannitol and camphor were used, respectively, as tablets matrix and subliming material. Camphor was vaporized by subliming in vacuum at 80°C for 30 minutes to develop pores in the tablets.

Melt granulation

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to conventional granulation is that no water or organic solvents are needed. For accomplishing this process, high shear mixers are utilized, where the product temperature is raised above the melting point of the binder by a heating jacket or by the heat of friction generated by impeller blades. This approach to prepare FDT with sufficient mechanical integrity involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). Superpolystate© is a waxy material with a melting point of 33-37°C and an HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solublises rapidly leaving no residues.

Cotton candy process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. It is also known as the candy floss process [18]. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to ODT. This process can accommodate high doses of drug and offers improved mechanical strength. However, high process temperature limits the use of this process.

Mass extrusion

It involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using the heated blade to form tablets [18].

Phase transition

A novel method to prepare ODTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique, ODTs are produced by compressing and subsequently heating tablets that contain two sugar alcohols, one with high and other with a low melting point. The heating process enhances the bonding among particles leading to sufficient hardness of tablets which was otherwise lacking owing to low/little compatibility [23].

Nanonization

A recently developed Nanomelt technology involves a reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into ODTs. This technique is, especially advantageous for poorly, water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability, and wide range of doses (up to 200 mg of drug per unit).

MATERIALS

Milnacipran HCL-Procured From Mylan Laboratories Ltd., New Delhi. Provided by SURA LABS, Dilsukhnagar, Hyderabad, Indion 414-Shreya Life Sciences, Aurangabad i, India, Polyplasdone XL 10-Shreya Life Sciences, Aurangabad i, India, Primogel-Shreya Life Sciences, Aurangabad i, India, Aerosil- Shreya Life Sciences, Aurangabad i, India, Aspartame-Shreya Life Sciences, Aurangabad i, India, Avicel PH 102-Shreya Life Sciences, Aurangabad i, India.

METHODOLOGY:

Buffer Preparation:

Preparation of 0.2M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed

Preparation of pH 6.8 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 112.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Analytical method development forMilnacipran Hydrochloride:

a) Determination of absorption maxima

A solution containing theconcentration 10 µg/ ml drug was prepared in 6.8 phosphate buffer UV spectrum was taken using Lab India Double beam

UV/VISspectrophotometer (Lab India UV 3000+). The solution was scanned in the range of 200 – 400 nm.

b) Construction of standard graph

100 mg of Milnacipran Hydrochloride was dissolved in 100 ml of pH 6.8 phosphate buffer to give a concentration of 1mg/ml (1000 µg/ml).From the above standard solution (1000 µg/ml) 1ml was taken and diluted to 100ml with pH 6.8 phosphate buffer to give a concentration of 0.01mg/ml (10µgm/ml). From this stock solution aliquots of 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml,2.5 ml

were pipette out in 10 ml volumetric flask and the volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 5, 10, 15, 20 and 25 µg/ mL respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) i.e., 210nm.

Formulation Development:

- Drug and different concentrations of super Disintegrates (Indion 414, Polyplasdone XL 10, Primogel) and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes.
- The obtained blend was lubricated with Aspartame and glidant (Aerosil) was added and mixing was continued for further 5 minutes.
- The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Table :Formulation table showing various compositions

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Milnacipran HCL	25	25	25	25	25	25	25	25	25
Indion 414	25	50	75	-	-	-	-	-	-
Polyplasdone XL 10	-	-	-	25	50	75	-	-	-
Primogel	-	-	-	-	-	-	25	50	75
Aerosil	6	6	6	6	6	6	6	6	6
Aspartame	3	3	3	3	3	3	3	3	3
Avicel PH 102	91	66	41	91	66	41	91	66	41
Total weight	150	150	150	150	150	150	150	150	150

The tablets were prepared by using Tablet Compression machine. The hardness of the tablets was maintained as 2.15±0.14 to 2.33±0.64 kg/cm^2.

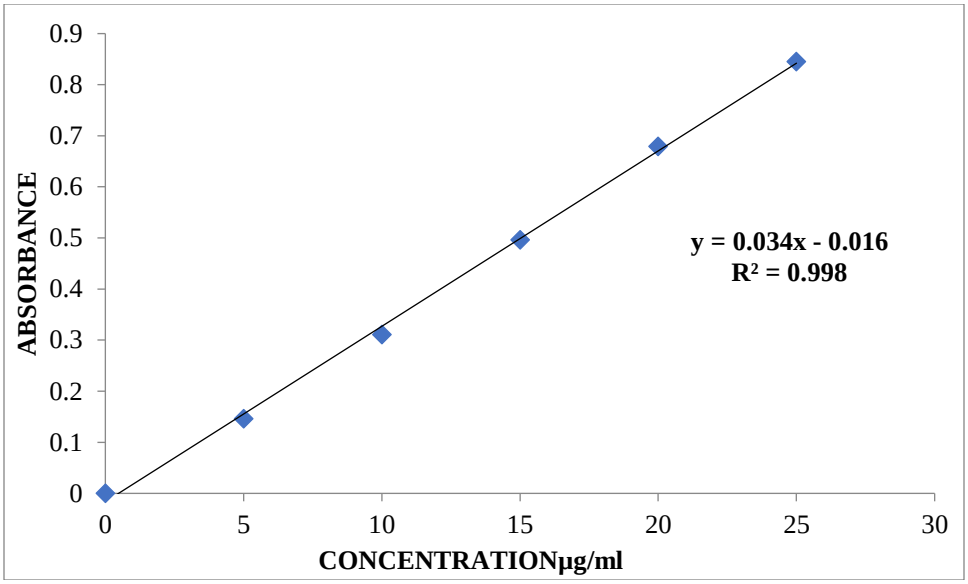
RESULTS AND DISCUSSION:

Preparation Of Calibration Curve Of Milnacipran Hydrochloride :

The Regression Coefficient was found to be 0.998 which indicates a linearity with an equation of y = 0.034x - 0.016. Hence beer - Lambert's law was obeyed.

Table :Calibration curve data ofMilnacipran Hydrochloride in ph 6.8 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
5	0.146
10	0.311
15	0.496
20	0.679
25	0.845



EVALUATION OF PRE - COMPRESSION PARAMETERS OF POWDER BLEND

Table: Evaluation of pre-compression parameters of powder blend

Formulation Code	Angle of Repose (°)	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	19.68 ± 0.22	0.632 ± 0.82	0.787 ± 0.92	20	1.28
F2	24.08 ± 0.38	0.621 ± 0.54	0.775 ± 0.67	20	1.26
F3	21.42 ± 0.31	0.612 ± 0.25	0.765 ± 0.88	16.83	1.18
F4	25.29 ± 0.25	0.598 ± 0.42	0.747 ± 0.36	19.89	1.25
F5	26.44 ± 0.9	0.618 ± 0.85	0.772 ± 0.67	20	1.25
F6	27.33 ± 0.77	0.602 ± 0.31	0.762 ± 0.81	21.04	1.26
F7	21.01 ± 0.2	0.619±0.22	0.725 ± 0.75	14.62	1.17
F8	29.89 ± 0.18	0.638 ± 0.37	0.785 ± 0.83	18.20	1.22
F9	24.08 ± 0.26	0.618 ± 0.85	0.772 ± 0.67	20	1.25

- For each formulation blend of drug and excipients were prepared and evaluated for various pre compression parameters described earlier in methodology chapter.
- The bulk density of all formulations was found in the range of (0.602 ± 0.31 -0.638 ± 0.37**)** and tapped density was in range of (0.725 ± 0.75 -0.787 ± 0.92).
- The carr's index and hausner's ratio was calculated from tapped density and bulk density.

EVALUATIONS OF POST COMPRESSION PARAMETERS OF MILNACIPRAN HYDROCHLORIDEODTs

Table :Evaluation of post compression parameters of Milnacipran Hydrochloride Fast dissolving tablets

Formulation codes	Average Weight (mg)	Hardness(kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* Disintegration Time (min)
F1	149.36	2.15±0.14	0.59	1.12±0.32	98.89	5.56
F2	150.72	2.29±0.28	0.21	1.35±0.65	99.16	3.15
F3	152.65	2.33±0.64	0.28	1.23±0.44	97.52	5.38
F4	147.26	2.18±0.33	0.35	1.30±0.76	99.37	4.12
F5	149.39	2.23±0.49	0.39	1.28±0.23	98.65	3.36
F6	148.53	2.25±0.54	0.41	1.33±0.82	98.75	4.28
F7	151.86	2.26±0.88	0.56	1.18±0.21	97.92	4.29
F8	148.73	2.28±0.61	0.33	1.22±0.48	99.43	5.20
F9	146.96	2.17±0.46	0.45	1.26±.38	98.71	5.32

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown above.The average tablet weights of all the formulations were noted down.

Hardness and friability: All the FDT formulations were evaluated for their hardness, using monsanto hardness tester and the results are shown above.The average hardness for all the formulations was found to be between (2.15±0.14 to 2.33±0.64)Kg/cm^{2}which was found to be acceptable.

Friability was determined to evaluate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the FDT formulations were evaluated for their percentage friability using rochefriabilator and the results are shown above.The average percentage friability for all the formulations was between **0.21to 0.59**, which was found to be within the limit. Addition of Aerosil resulted in appreciable decrease in friability.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown above.The assay values for all the formulations were found to be in the range of **(97.52to 99.43).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

***In vitro* disintegration time:** *In vitro* disintegration studies showed from 3.15to 5.56Minutes. The F2 Formulation showed Very Less *In vitro* Disintegration Time i.e., 3.15Minutes.

***IN VITRO* DRUG RELEASE STUDIES OFMilnacipran Hydrochloride**

Table: Dissolution data of Milnacipran Hydrochloride

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	27.32	29.22	32.37	35.44	33.26	41.48	38.24	36.36	32.99
10	38.21	46.31	45.72	38.18	44.39	52.98	44.36	39.88	37.63
15	52.33	58.68	52.96	51.54	53.87	59.37	50.82	52.07	48.86
20	61.83	72.76	68.53	66.98	59.62	65.59	66.37	69.56	57.94
25	75.56	87.95	74.65	72.25	69.77	73.43	71.85	75.15	69.37
30	88.62	98.89	93.37	84.39	80.51	94.94	89.52	92.94	85.58

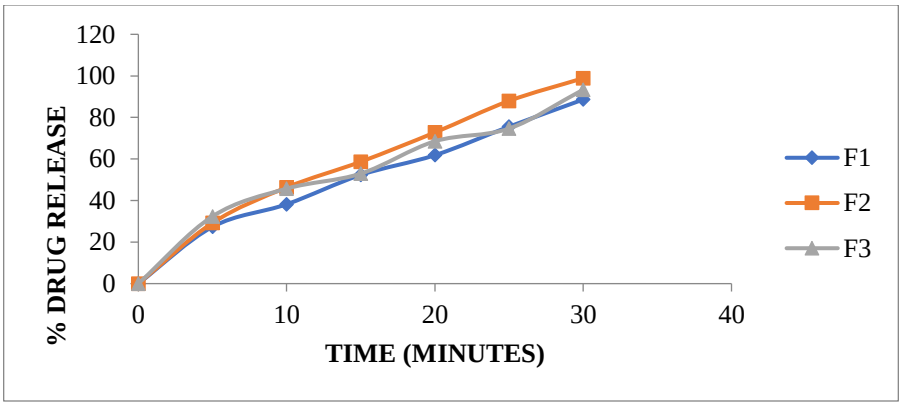


Fig: Dissolution profile of formulations F1, F2, and F3

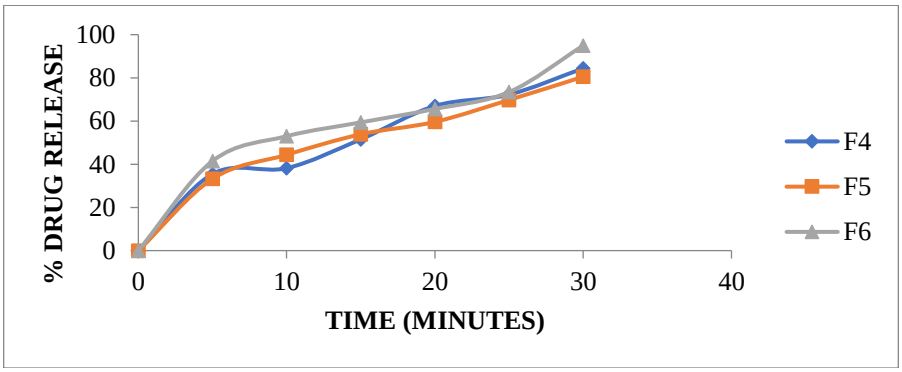


Fig : Dissolution profile of formulations F4, F5, and F6

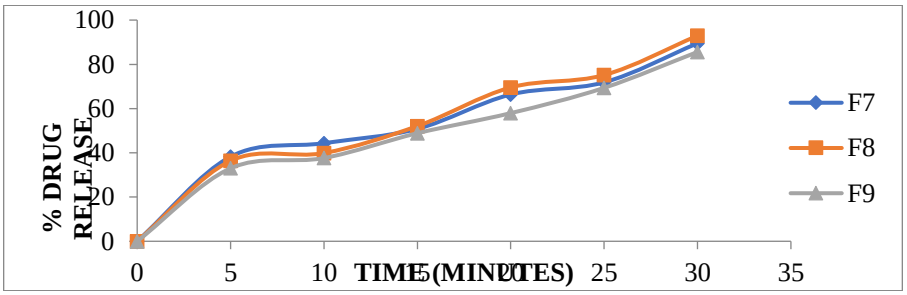


Fig : Dissolution profile of formulations F7, F8 and F9

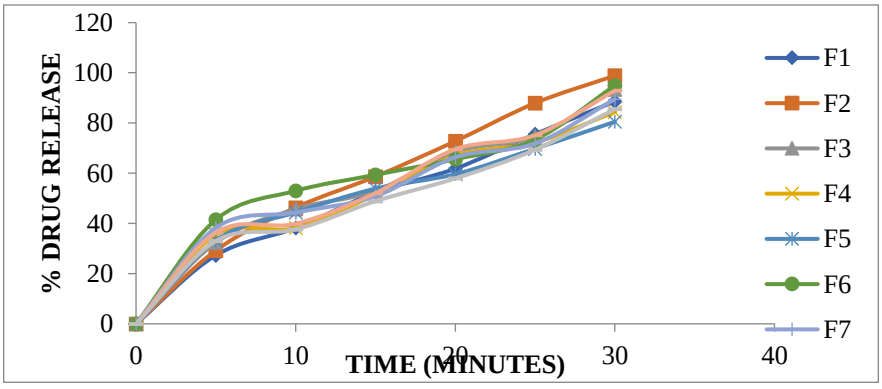


Fig : Dissolution profile of all formulations F1- F9

Indion 414. finally concluded that F2 formulation was optimised better formulation. It shows good drug release with 98.89% than the other polymers. F2 formulation was consider as optimized formulation.

FTIR RESULTS:

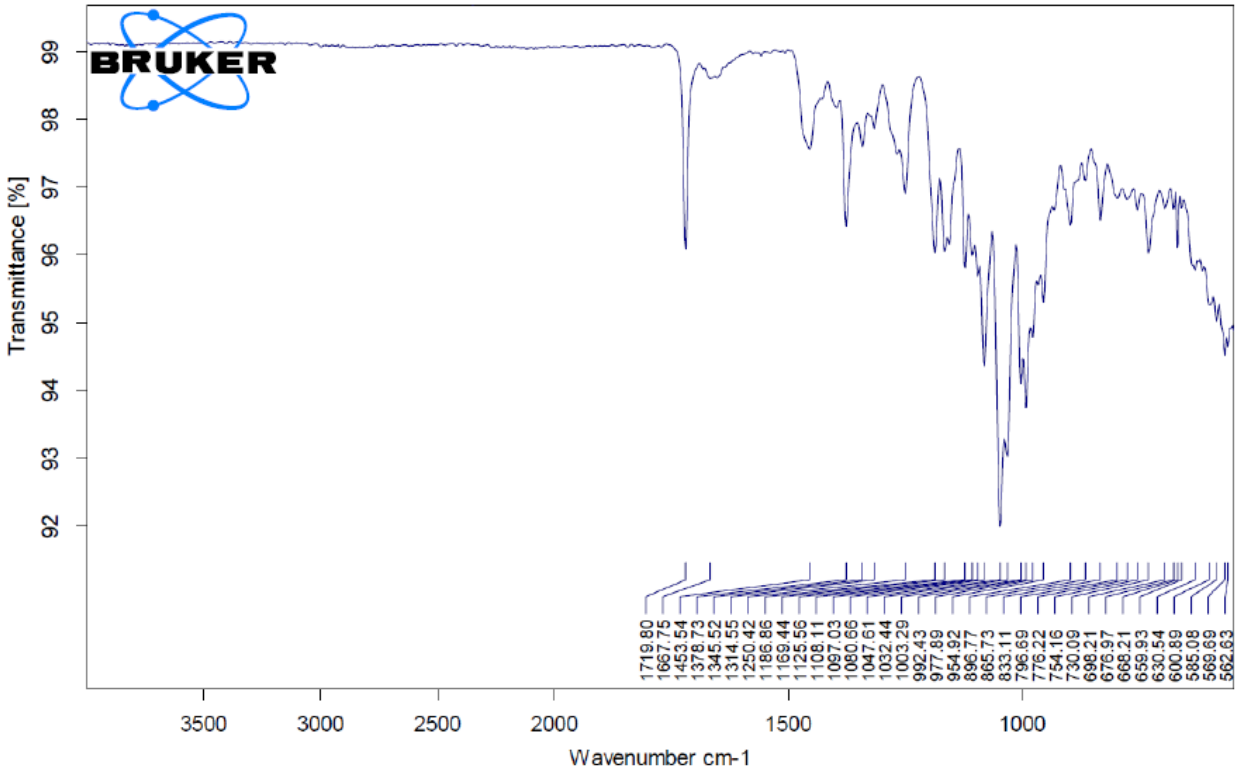


Fig:FTIR of Milnacipran Hydrochloride Pure drug

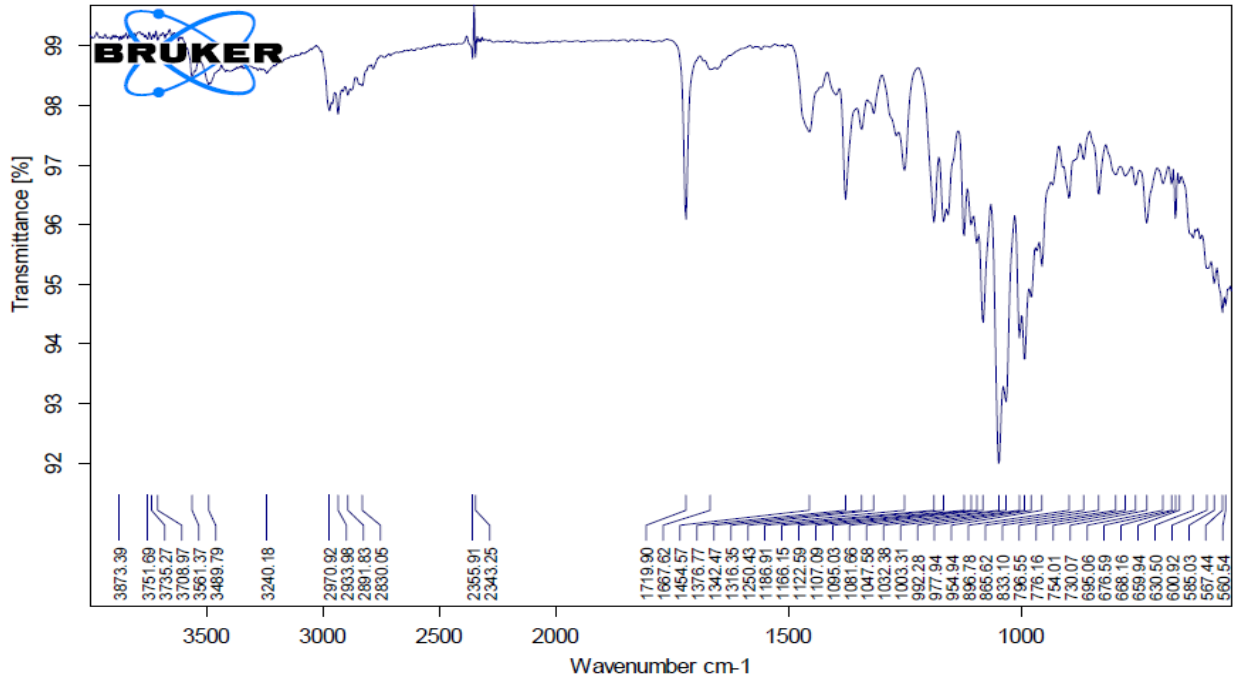


Fig :FTIR of Milnacipran Hydrochlorideoptimized Formulation

Milnacipran Hydrochloridewas mixed with various proportions of excipients showed no colour change, providing no drug-excipient interactions.

CONCLUSION:

The study clearly demonstrates that oral dispersible tablets of Milnacipran Hydrochloride could be successfully prepared by direct compression method in a cost effective manner employing Indion 414. It was evident from the results that rate of drug release can be optimized using disintegrates for oral dispersible formulations. From the developed formulations that release of Milnacipran Hydrochloride was best in F2 formulation that in vitro study and in vitro dispersion time study. From the FTIR study it was confirmed that the drug and excipients in the formulations were compatible with each other. Hence the availability of various technologies and the manifold advantages of oral dispersible tablets will surely enhance the patient complicance providing rapid on set of action.

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