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Research

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. Indion 414, 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.

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

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.

MATERIALS AND METHODS

Milnacipran HCL Procured From Mylan Laboratories Ltd., New Delhi. Provided by SURA LABS, Dilsukhnagar, Hyderabad, Indion 414 from Shreya Life Sciences, Aurangabad i, India, Polyplasdone XL 10 from Shreya Life Sciences, Aurangabad i, India.

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 for Milnacipran Hydrochloride

Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in 6.8 phosphate buffer UV spectrum was taken using Lab India Double beam UV/VIS spectrophotometer (Lab India UV 3000+). The solution was scanned in the range of 200 – 400 nm.

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 1: 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.

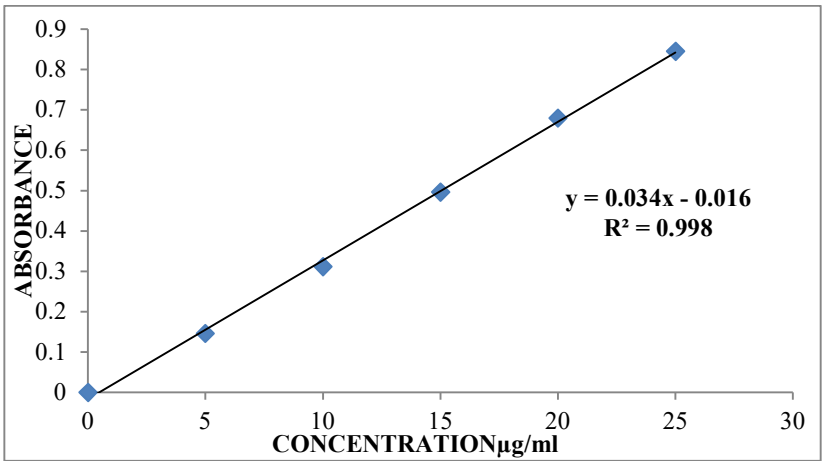
RESULT AND DISCUSSION

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 2: Calibration curve data of Milnacipran 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 3: 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 HYDROCHLORIDE ODTs

Table 4: 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 roche friabilator and the results are shown above. The average percentage friability for all the formulations was between 0.21 to 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 (97.52 to 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 3.15 to 5.56 Minutes. The F2 Formulation showed Very Less *In vitro* Disintegration Time i.e., 3.15 Minutes.

***In vitro* drug release studies of milnacipran hydrochloride**

Table 5: 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

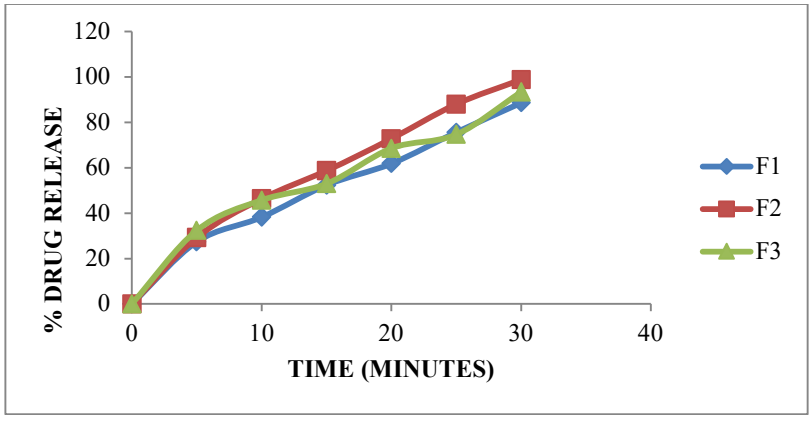


Fig 1: Dissolution profile of formulations F1, F2, and F3

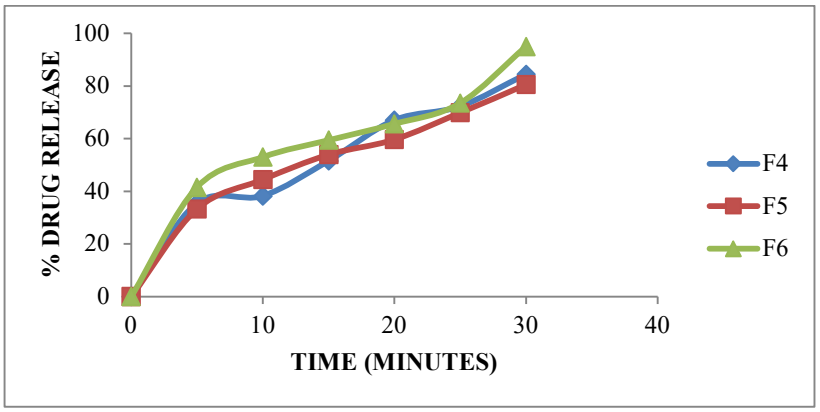


Fig 2: Dissolution profile of formulations F4, F5, and F6

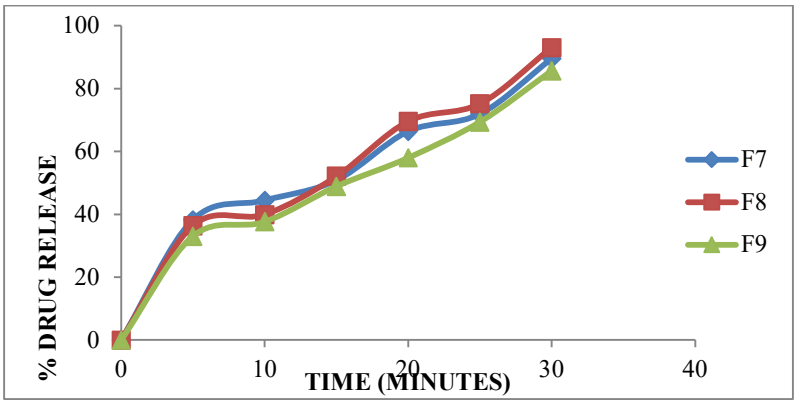


Fig 3: Dissolution profile of formulations F7, F8 and F9

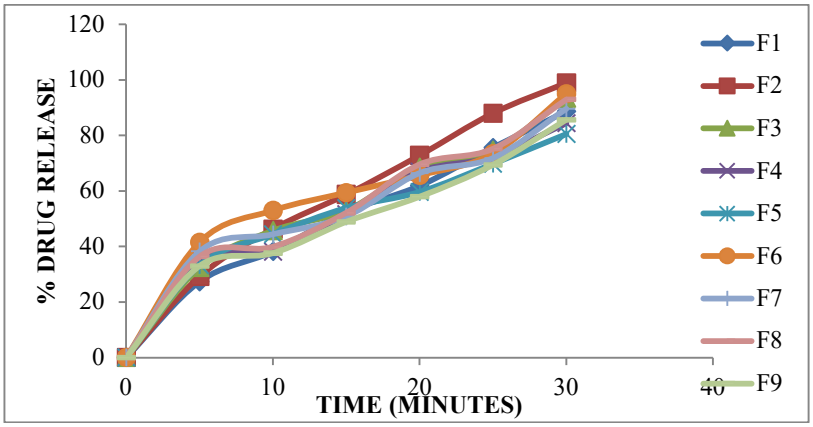


Fig 4: Dissolution profile of all formulations F1- F9

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

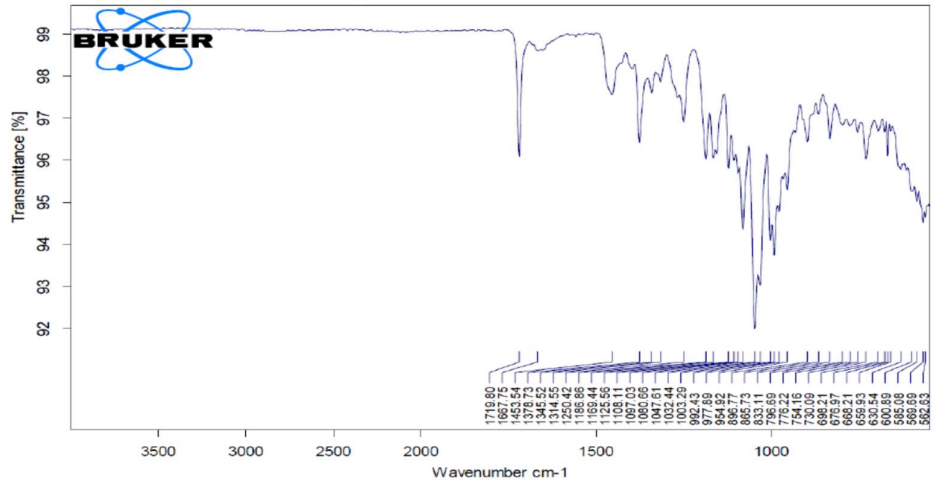


Fig 5: FTIR of Milnacipran Hydrochloride Pure drug

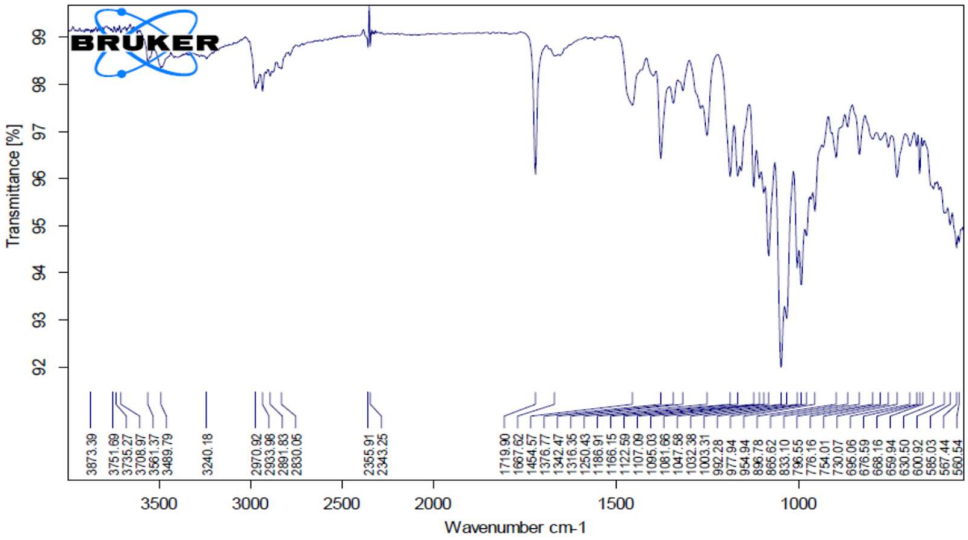


Fig 6: FTIR of Milnacipran Hydrochloride optimized Formulation

Milnacipran Hydrochloride was 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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