Journal of Research in Pharmacy

Research Article

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Formulation and *in vitro* evaluation of pramipexole orally disintegrating tablets for pediatric restless leg syndrome

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Received: 06 March 2023 / Revised: 20 March 2023 / Accepted: 20 March 2023

ABSTRACT: In this study, orally disintegrating tablets (ODT) of pramipexole dihydrochloride monohydrate (PPX) was developed with direct compression method by using ready-to-use excipients Parteck® ODT, Pharmaburst® 500, Ludiflash®, F-Melt®, and Prosolv® Easytab SP for pediatric restless leg syndrome (RLS). The formulated ODTs were circular in shape with a total weight of around 100 mg, which was appropriate for pediatric use. In spite of very low content of the drug, content uniformity could be obtained successfully in accordance to the pharmacopoeial specification with a satisfactory mechanical strength in terms of hardness and friability. However, formulations based on Parteck® ODT and Ludiflash® could not achieve a disintegration time <30 s according to *in vitro* disintegration test, which was also supported by the simulated wetting test. The optimal ODTs based on Pharmaburst® 500, F-Melt® and Prosolv® Easytab SP were further evaluated for *in vitro* dissolution study. A very fast release of the drug was observed with these formulations that reached a peak value in 10 min., which was superior than that of the reference conventional tablet formulation of PPX. As a result, pediatric orally disintegrating tablets of PPX were successfully formulated with Pharmaburst® 500, F-Melt® and Prosolv® Easytab SP by using direct compression method with suitable characteristics, which can be further studied to use in pediatric RLS.

KEYWORDS: Pramipexole; restless leg syndrome; pediatric; orally disintegrating tablets; direct compression; ready-to-use excipients

1. INTRODUCTION

Restless leg syndrome (RLS), also known as Willis-Ekbom disease, is a frequent sensory motor disorder characterized by a strong impulse to move the limbs during rest or is exacerbated by rest, and disappears during movement or is relieved after movement [1, 2]. The symptoms of RLS frequently worsen over time and generally deteriorate with aging [1-3]. Furthermore, RLS has been reported as the fourth most common cause of insomnia, particularly at the start of sleep [2]. Most of the population-based studies have reported a low prevalence in most Asian populations, which vary between 1% and 3%. However, a significantly higher prevalence has been found in Europe and North America, ranging from 5% to 13% [1].

The mean age for the onset of RLS symptoms has been reported to be 27 years [4]. Although approximately 38–45% of adults have been reported to have onset of symptoms before age 20 years, with 13% of patients reporting symptoms before the age of 10, most patients are not diagnosed for several years after their disease first manifests [2]. Since the diagnosis of RLS in childhood is complicated with defined symptoms based on previous studies, it may be more prevalent than estimated [5]. However, a prevalance of 2-4% in school-aged children and adolescents has been reported [6]. Due to difficulty sleep onset or staying asleep, children with RLS may exhibit conduct issues like aggression, inattention, hyperactivity, and daytime somnolence. These issues can cause serious affect on a child's school performance, social development, and interactions with others, resulting in incorrect diagnoses of a variety of psychiatric conditions, including attention deficit hyperactivity disorder (ADHD), among others [5, 6].

Currently, there is no broadly approved agents available for the treatment of RLS, and the treatment choice varies depending on severity of the disease. For instance, while levodopa or a dopamine agonist may be used to treat patients with intermittent RLS, those with severe symptoms may need to be treated with potent opioids. Additionally, benzodiazepines, which are hypnotic and anxiolytic drugs, as well as other

How to cite this article: Türkmen Ö, Pozharani LB, Moein A. Formulation and *in vitro* evaluation of pramipexole orally disintegrating tablets for pediatric restless leg syndrome. J Res Pharm. 2023; 27(5): 1808-1820.

ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.465

sedative medicines that may provide symptomatic relief, but have no effect on the course of RLS have traditionally been used in the treatment of RLS [7, 8]. Moreover, it was proposed that D_3 dopamine receptor agonists possess neuroprotective effects by increasing the secretion of dopamine neurotrophic factor in tissue culture [9]. Pramipexole (PPX), a non-ergot D3 autoreceptor agonist, is prescribed to treat idiopathic Parkinson's disease. Currently, it is labeled for the treatment of moderate to severe RLS [7, 8, 10, 11]. However, since PPX is available only as tablet form at various strengths which are not specified for pediatric use, there is a necessity for the more child-friendly dosage forms of PPX.

Modern medicine is dependent on patient-friendly dosage forms, which are also necessary for effective pediatric drug therapy. Experts have long suggested a paradigm shift away from traditional liquid medication forms and toward cutting-edge oral solid dosage forms for pediatric use [12, 13]. Pediatric orodispersible tablets stand out as the ideal dosage form for children among them, since they combine the benefits of oral and solid dosage forms, are well-tolerated even by newborns, and allow for personalized dosing [12-14].

Orally disintegrating tablets (ODTs) are solid pharmaceutical dosage forms that quickly dissolve in the mouth of the patient without the use of water [15-18]. It is a useful tool for patients who might have trouble taking traditional solid oral dosage forms because of a mental illness, a physical disability, a lack of access to water, or because they are too young or old. It can help to minimize the difficulty of treatment on patients and caregivers due to its easy administration. It has been demonstrated in numerous studies that patients prefer ODTs to conventional tablets [19, 20]. ODTs can be prepared by various methods as reported in the literature [15-17]. Among those, the direct compression method presents advantages such as simple technology with usually no necessary modifications to conventional compression apparatus; therefore, it is commonly utilized for the preparation of ODTs [12, 18]. ODTs prepared with this method generally possess satisfactory mechanical properties like good hardness and low friability [16]. Due to the critical effect of link between excipients and other formulation components as well as methods on these characteristics, the ready-to-use excipients stands out with many beneficial attributes for the direct compression of ODTs [12, 18].

Depending on the aforementioned requirements, the aim of this study was to develop and evaluate pediatric PPX orally disintegrating tablets for restless leg syndrome in children, based on ready-to-use excipients including Parteck® ODT, Pharmaburst® 500, Ludiflash®, F-Melt®, and Prosolv® Easytab SP by utilizing the advantages of direct compression method.

2. RESULTS AND DISCUSSION

2.1. Fourier transform infrared spectroscopy study

The chemical and physical incompatibility of drugs and excipients in solid state can significantly affect the critical formulation properties such as stability, dissolution rate, and bioavailability. There is not an availabile procedure that is universally used to estimate the compatibility of drugs with excipients. Thermoanalytical methods are utilized to routinely investigate and predict any physicochemical incompatibility between drugs and pharmaceutical excipients. These techniques are widely applied alone or in combination with with microscopy, spectroscopy (UV, IR), and X-ray powder diffractometry [21, 22]. Because of these reasons, FTIR analyses were conducted to examine possible drug excipient interactions before the formulation studies.

FTIR spectras of pure PPX and pure ready-to-use excipients as well as physical blends of PPX with these excipients are shown in Figures 1A and 1B, respectively. The characteristic absorption peaks of the pure PPX were obtained at the wavenumbers of 3412, 2958, 1587, 1365 and 761 cm^{-1} indicating, the functional groups of N-H stretching, C-H stretching, C=C stretching, C-N stretching and C-H bending, respectively (Fig 1A). All of the characteristic peaks for the pure drug were also observed in the spectrum of physical mixture (Fig 1B), indicating that the pure drug and the excipients did not interact chemically. This confirms the compatibility of PPX and the used excipients in the ODT formulations [23].

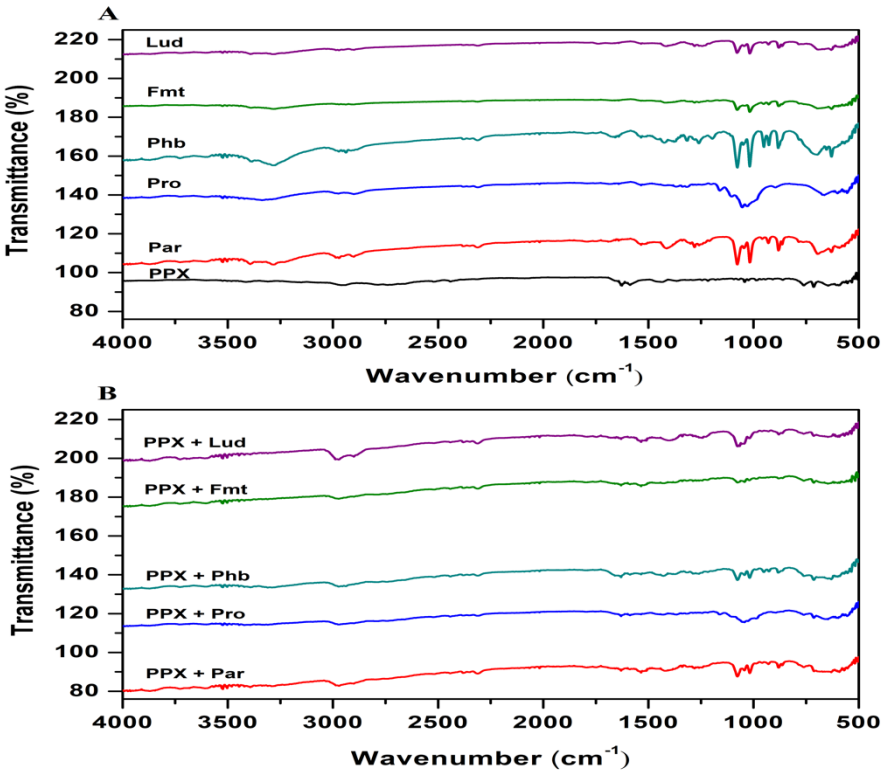

Figure 1. ATR-FTIR spectra of the pure drug, the tested excipients (A) and drug-excipient mixtures (B)
Abbreviations: PPX: Pramipexole dihydrochloride monohydrate, Par: Parteck® ODT, Pro: Prosolv® Easytab, Phb: Pharmaburst® 500, Fmt: F-Melt®, Lud: Ludiflash®

2.2. Differential scanning calorimetry study

Thermal analyses are used to asess a sample characteristic while the sample is heated or cooled at a constant rate of temperature change or maintained at a fixed temperature in a specified atmosphere. For this purpose, an indispensible thermal analysis method DSC was conducted in addition to FTIR analyses to examine possible drug excipient interactions [24]. The DSC thermograms of PPX, ready-to-use excipients and binary mixtures are demonstrated in Figures 2A and 2B. The DSC curve of PPX (Figure 2A) showed a peak (endothermic event) corresponding to the dehydration of monohydrate form drug at 120.68 °C, and melting occured in the range of 291.23°C to 307.3°C [25]. The DSC curves of excipients also showed the characteristic thermal behaviour of each excipient, which is composed co-processing of powders with special purposes (Table 1). The thermogram of excipients except for Prosolv® Easytab SP which containing microcrystalline cellulose (MCC) instead of mannitol (MAN) showed an endothermic peak at around between 165 °C and 169 °C because of the MAN, which constitutes the base of the co-processed excipient (pure MAN has a melting range from 166 to 168 °C). Furthermore, Prosolv® Easytab SP shows an endothermic peak at 89.02 °C corresponding to melting point of sodium starch glycolate (SSG) in the co-processed excipient. The thermograms of drug-excipient blends did not exhibit any new peaks without slight shifts, which was a indicative for absence of incompatibility between drug and excipients. However, the slight shifts in the peaks could occur due to mixing process, as it has been reported to cause a reducing effect on the purity of the components [26].

Table 1. Composition of ready to use excipients used for formulations of pramipexole dihydrochloride monohydrate orally disintegrating tablets

Excipient	Parteck® ODT	Prosolv® Easytab	Pharmaburst® 500	Ludiflash®	F-Melt®
Composition	Mannitol Croscarmellose sodium	Microcrystalline cellulose Sodium starch glycolate Colloidal silicon dioxide	Mannitol Crospovidone Sorbitol Precipitated silicon dioxide	Mannitol Crospovidone Polivinyl acetate dispersion	D-Mannitol Xylitol Microcrystalline cellulose Crospovidone Magnesium aluminometasilicate

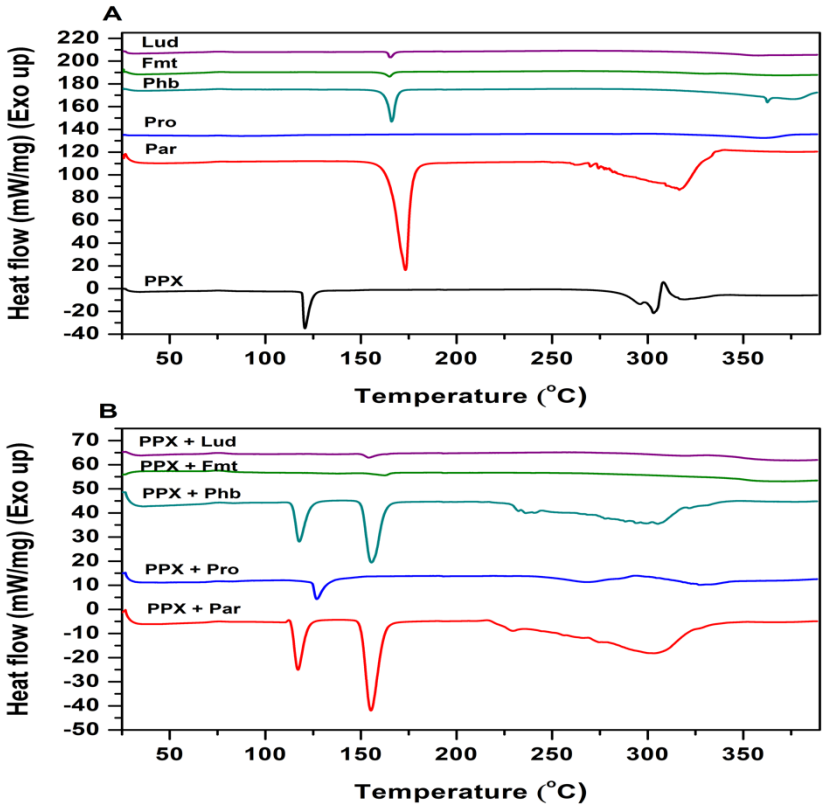

Figure 2. Differential scanning calorimetric (DSC) thermograms of the pure drug, the tested excipients (A) and drug-excipient mixtures (B)
Abbreviations: PPX: Pramipexole dihydrochloride monohydrate, Par: Parteck® ODT, Pro: Prosolv® Easytab, Phb: Pharmaburst® 500, Fmt: F-Melt®, Lud: Ludiflash®

2.3. Blending and tabletting

Direct compression is a relatively simple and less complicated technique for production of pharmaceutical tablets involving blending and compaction as primary processing steps compared to other methods including a dry granulation or wet granulation step [18, 27, 28]. The advantages of this method on mechanical strength of tablets makes it a commonly preferred method for production of ODTs. However, the main challenge of this method is the appropriate selection of excipients which are critical for a short disintegration time (less than 3 min – according to the European Pharmacopoeia 6.0, or less than 30 s – recommended by the FDA) [29]. Excipients should be chosen for ODT formulations depending on the properties of the material (plastic, elastic, or brittle) and the required functions, such as specified particle size distribution, improved flowability, and increased compactability or rapid disintegration. The components of each co-processed excipient are given in Table 1. Among the excipients, MAN is frequently used for fast dissolving pharmaceutical dosage forms. However, it has poor flowability, weak binding characteristics, and

poor compactability when utilized as untreated powder, which are barriers to the development of an acceptable formulation. Co-processing is the interaction of two or more excipients at the subparticle level achieved by co-spray-drying, co-spray-agglomerating, or co-granulating, which leads to increased functionality [12, 30]. Therefore, co-processed excipients based on MAN like Parteck® ODT, Pharmaburst® 500, Ludiflash® and F-Melt® used in the present work were selected based on this requirement. Additionally, another co-processed excipient, Prosolv® Easytab SP was also utilized, which was mainly composed of MCC, with an aim to compare the compression and post-compression characteristics of ODTs with this excipient to that of the MAN based co-processed excipients [18]. All of the powder blends represented an acceptable flow property which was suitable for direct compression method as well as all they improved the flowability of PPX (data not shown). This characteristic is very critical to achive an acceptable limit for content uniformity of an active pharmaceutical ingredient with very low quantity in a tablet formulation [31]. Moreover, all of the formulations with PPX could be successfully compressed into ODTs at a force of 1000 kg/cm^2.

2.3.1. Weight variation

The measured weights of ODTs are given in Table 2. There was no significant difference between the formulations ($p > 0.05$), which shows a good flowability of powders. This result was construed as all of the formulations meeting the pharmacopeial criteria [32].

2.3.2. Diameter and thickness

The diameters of ODTs are shown in Table 2. When the formulations compared with each other, a significant difference was observed between Par_PPX and Phb_PPX as well as Par_PPX and Fmt_PPX ($p < 0.05$). When the formulations compared with each other, there was a significant difference between Par_PPX and Pro_PPX, Par_PPX and Fmt_PPX, Phb_PPX and Fmt_PPX, and Phb_PPX and Lud_PPX ($p < 0.01$, $p < 0.01$, $p < 0.001$, $p < 0.001$, and $p < 0.01$, respectively). Tablet thickness is determined by various factors including the diameter of the die, the amount of powder allowed to be filled into the die cavity, the compaction characteristics of the fill material, and the compression force. As the diameter and the compression force were constant, these differences can clearly be attributed to material properties of fillers that dictate the post-compression characteristics of tablets, since the composition of the ready-to-use excipients was different [33, 34].

2.3.3. Crushing strength

The crushing strength or hardness values of ODTs are presented in Table 2. There was no significant difference between the formulations ($p > 0.05$), which indicated that all of the investigated formulations demonstrated a sufficient hardness. However, the different values obtained with different excipients clearly showed the effect of composition of co-processed excipients. For example, the good compactibility characteristic of Pharmaburst® 500 was a result of the effect of sorbitol, which possess plastically deforming feature with good binding properties. Furthermore, it can be seen from the results that combining MAN with MCC possessing mainly plastic deformation properties resulted in an excellent compactability [12, 30, 35]. Moreover, the obtained results showed the minor influence of superdisintegrants in the ready-to-use excipients on tablet compressibility, since they are used in small quantities [18].

2.3.4. Friability

The friability values of ODTs are given in Table 2. A friability value less then 1% is considered suitable for an ODT formulation when evaluated with the sufficient crushing values to maintain the mechanical strength against stress which may occur during usual handling [12, 18, 32]. The obtained results showed the acceptability of all of the formulations in terms of friability that could successfully maintain the mechanical strength of ODTs.

2.3.5. Simulated wetting time

The simulated wetting times (SWTs) of ODTs are given in Table 2. The Pro_PPX, Phb_PPX and Fmt_PPX achieved a SWT less than 30 s; but the SWTs of Par_PPX and Lud_PPX were only below 60 s. When the SWTs of formulations compared with each other, there was a statistically significant difference between the formulations (Figure 3). However, there was no significant difference between Pro_PPX and Fmt_PPX, and Phb_PPX and Fmt_PPX ($p > 0.05$). The change in appearance of tablets observed during the wetting test confirmed the disintegration mechanism of the different disintegrants in the ODTs (data not shown). The use of the superdisintegrants SSG and crospovidone (PVPP) decreased SWTs in most cases. However, Parteck® ODT, which contains croscarmellose sodium (CCS) as another superdisintegrant, was not able to achieve satisfactory results. Additionally, MCC improves liquid transfer into a tablet matrix in addition to the effect

of disintegrants by accelerating both diffusion and capillary effect [36] as observed with Prosolv® Easytab SP and F-Melt®. But the Ludiflash® behaved similar to Parteck® ODT, in spite of containing PVPP. Therefore, this result can be interpreted as the major of influence of co-processing type on SWTs of ODTs, as Pharmaburst® 500 showed a very short SWT, which findings were in agreement with previous studies [37, 38].

2.3.6. Disintegration time

The *in vitro* DTs of ODTs are represented in Table 2. When the DTs of formulations compared with each other, there was a statistically significant difference between the formulations (Figure 3). However, there was no significant difference between Par_PPX-Pro_PPX, Par_PPX-Fmt_PPX, Par_PPX-Lud_PPX, Pro_PPX-Phb_PPX, Pro_PPX-Fmt_PPX, and Phb_PPX-Fmt_PPX ($p > 0.05$). It has been indicated in previous studies that properties of the drug, type of the co-processed excipients as well as the compression forces utilized, which are all linked to characteristics of ODTs have a substantial impact on DT [29, 39]. However, since the amount of the PPX in the formulations is very low, there might be no effect of the drug on the DT of ODTs. ODTs typically disintegrate in less than a minute, and a person may experience disintegration times of between five and thirty seconds [40]. Although Pro_PPX and Fmt_PPX demonstrated a high hardness, they achieved to disintegrate below 30 s. The unique effect of MCC on ODT formulations with characteristics such as adequate mechanical strength and a decreased DT is demonstrated by this result, since depending on concentration it functions as both a disintegrant and a binder [41]. This characteristic results in ODTs with good mechanical strength and shorter DT as observed with Prosolv® Easytab and F-Melt®. The mechanism of disintegration of PVPP is through capillary effect that can also be seen in Phb_PPX, which possessed sufficient hardness and shortest DT with which a correlation between hardness and disintegration time was observed. Moreover, the DTs of Prosolv® Easytab, Pharmaburst® 500 and F-Melt® were higher than the SWTs of these excipients. This observation is a result of the dependence of quick wetting time of ODTs on the unique characteristics of components and co-processing type of the ready-to use excipients. In contrast, the decrease and increase in the DTs of Parteck® ODT and Ludiflash® supported by a previous study suggesting that determining the DT of ODTs only by SWT is not sufficient, and may cause biases [42]. Based on these results, the formulations Pro_PPX, Phb_PPX and FMelt_PPX were able to meet the specified DT (< 30 s) stated by FDA [40]. However, Par_PPX and Lud_PPX could not meet this criteria.

Table 2. The characteristics of pramipexole dihydrochloride monohydrate orally disintegrating tablet formulations

Formulation	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (N)	Simulated wetting time (s)	Disintegration time (s)	Acceptance Value
Par_PPX	100.6 ± 1.415	8.336 ± 0.193	3.604 ± 0.020	17.10 ± 5.109	56.33 ± 1.528	39.33 ± 2.944	4.51
Pro_PPX	98.82 ± 1.574	8.170 ± 0.130	3.374 ± 0.055	17.60 ± 2.591	9.000 ± 1.000	26.67 ± 4.033	2.49
Phb_PPX	100.4 ± 2.059	8.187 ± 0.169	3.814 ± 0.133	19.60 ± 4.812	15.33 ± 1.528	25.17 ± 1.472	2.95
Fmt_PPX	100.5 ± 1.864	8.148 ± 0.041	3.316 ± 0.176	22.70 ± 8.577	13.33 ± 1.528	28.00 ± 2.530	2.65
Lud_PPX	100.1 ± 2.521	8.168 ± 0.042	3.432 ± 0.030	15.10 ± 2.079	50.33 ± 2.517	209.7 ± 9.352	3.54

Note: Data are expressed as mean ± SD.

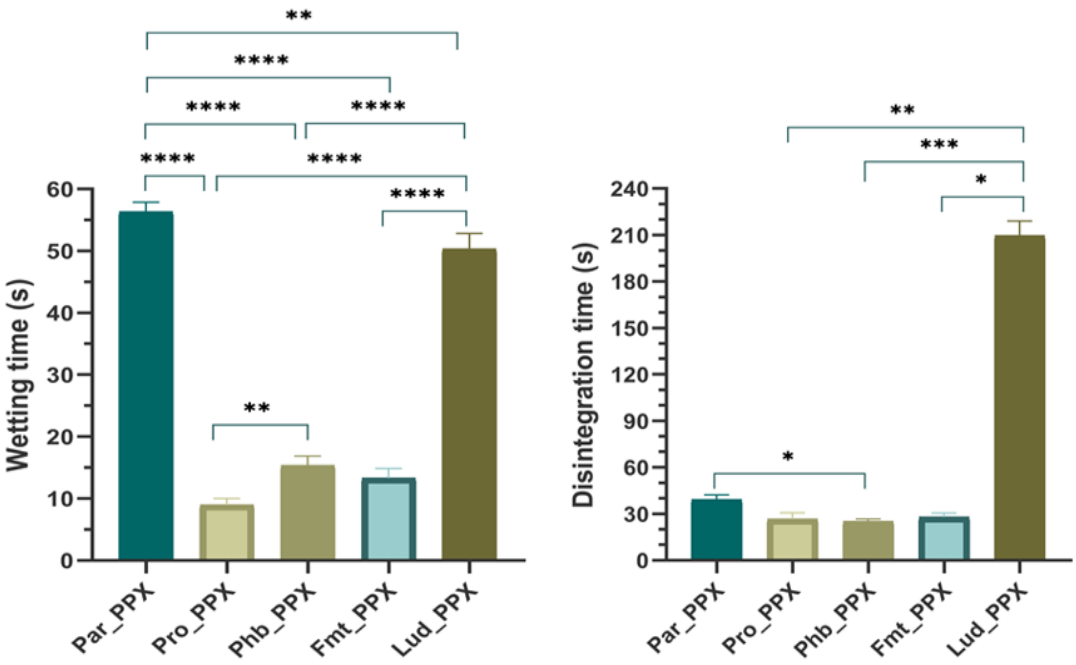

Figure 3. The comparison of wetting time (left) and disintegration time (right) of pramipexole dihydrochloride monohydrate orally disintegrating tablet formulations
Note: Data are expressed as mean ± SD. The statistical analysis of SWT and DT test was carried out using ANOVA and Kruskal Wallis test followed by Dunn's multiple comparison test, respectively (* $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$). The statistically not significant comparisons were not illustrated.

2.3.7. Content uniformity

For low-dose dosage forms, weight variation and content homogeneity are crucial quality factors that should be compared. As stated earlier, there was no statistically significant difference between the formulations in terms of weight variation ($p > 0.05$), which supported the successfull content uniformity of prepared ODTs. The investigated ODTs can be classified as low-dose dosage forms with a very low drug content of 125 µg. In direct compression method of such formulations, achieving good flowing properties might be critical for the uniformity of dosing [12]. The acceptance value (AV) of the Par_PPX, Pro_PPX, Phb_PPX, Fmt_PPX, and Lud_PPX are given in Table 2. All of the investigated formulations were in compliance with the the Ph. Eur. (AV < 15) with a relatively low AV value below 5. It is crucial to warrant a uniform distribution of API in a solid dosage form to guarantee acceptable final product quality. The challenge in distributing a low dose drug homogenously into a large mass of excipients is a commonly considered challenging, because as the quantity of API decreases, the variability of blend potency usually increases. Although a sufficient mixing is no doubt the first critical step, it is not a guarantee the quality of a good mixing, because the powder mass after the mixing may be segregated during the handling process [43]. The obtained findings in the present study reveals the evenly mixing behaviour of the PPX powder and the co-processed excipients without segregation, which result in an acceptable content uniformity along with a good weight variation as there was no significant difference between the formulations.

2.3.8. In vitro dissolution rate

The optimum ODTs were selected for *in vitro* dissolution test with regards to DT < 30 s, which was achieved with Pro_PPX, Phb_PPX, and Fmt_PPX, respectively. Additionally, a reference product of PPX was also tested for comparison. The test was performed over 30 min., as the complete drug release from ODTS, but not for reference product was attained before this time point, and the release profile was presented in Figure 4. A fast release of the drug from Pro_PPX was observed within 2 min., which reached the plateu at 5 min., with a total release of 86.22 ± 4.97%. The drug release from Phb_PPX was 85.38 ± 2.80% at 5 min., which reached the plateu at 10 min., with a total release of 95.90 ± 2.64%. Fmt_PPX showed a sharp increase in the drug release by reaching 59.70 ± 4.12% after 5 min., which reached the plateu at 10 min., with a total release of 101.53 ± 2.91%. All of the formulations achieved a drug release > 50% at 2 min. For the reference product, there was a slow and steady increase in the release profile over 30 min. The obtained results indicated a complete release of the drug from selected ODTs over 10 min, however, the reference product released only 69.37 ± 2.57% of the drug at the end of 30 min. Two-way ANOVA test revealed a significant difference between reference

product and Pro_PPX, Phb_PPX, and Fmt_PPX at all time points, which confirmed the superiority of ODTs than the conventional tablets in terms of fast drug release. Besides, there was a statistically significant difference between Pro_PPX and Fmt_PPX at 2 min ($p < 0.05$), between Pro_PPX and Fmt_PPX ($p < 0.01$), or Phb_PPX and Fmt_PPX ($p < 0.01$) at 5 min., and between Pro_PPX and Phb_PPX ($p < 0.05$) or Pro_PPX and Fmt_PPX ($p < 0.05$) at 10 min. These findings support the results obtained for SWT and *in vitro* DT tests also in which the components and co-processing type of each ready-to-use excipient also significantly effects the drug release [44, 45], though PPX is classified as Biopharmaceutics Classification System (BCS) class I active substance, which possess a high water solubility profile [46].

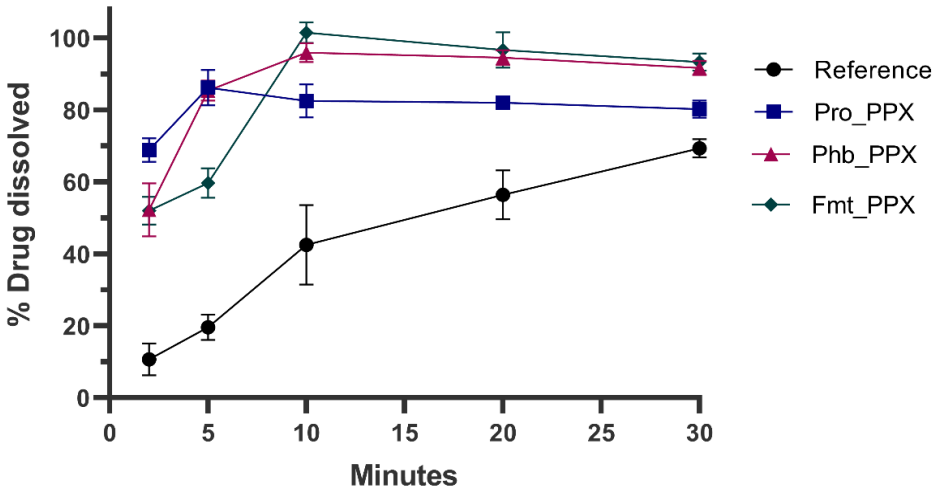

Figure 4. Dissolution rates of optimal pramipexole dihydrochloride monohydrate orally disintegrating tablet formulations
Note: Data are expressed as mean ± SD

3. CONCLUSION

In the present study, we presented the development of ODT formulations of PPX for pediatric RLS. For this purpose, the PPX ODTs were prepared by using ready-to-use excipients with conventional direct compression method. Then, the prepared ODTs were evaluated in terms of weight variation, diameter and thickness, hardness, friability, SWT, *in vitro* DT, content uniformity, and *in vitro* dissolution rate. The performed tests showed the appropriate characteristics for all formulations except the SWTs and DTs which were above 30 s for ODTs based on Parteck® ODT and Ludiflash® that failed to meet the FDA specifications for ODTs. The in *vitro* dissolution test was carried out with ODTs based on Prosolv® Easytab SP, Pharmaburst® 500 and F-Melt® demonstrated that ODTs achieved a complete drug relase within 10 min., which was superior compared to that observed with the reference tablet of PPX. The obtained results demonstrate the feasibility of PPX ODTs prepared in this study can be further evaluated for RLS in children.

4. MATERIALS AND METHODS

4.1. Materials

Pramipexole dihydrochloride monohydrate was kindly provided by Deva Holding A.S., Türkiye. Parteck® ODT (Merck, Germany), Prosolv® Easytab SP (JRS Pharma, Germany), Pharmaburst® 500 (SPI Pharma, USA), F-Melt® (Fuji Chem, Japan) and Ludiflash® (BASF, Germany) were used as ready-to-use excipients. Sodium stearyl fumarate (Pruv®; JRS Pharma, Germany), citric acid (Merck, Germany), aspartame (Sigma-Aldrich, USA), and vanillin (Sigma-Aldrich, Germany) were auxiliary ingredients used in the ODT formulations. HPLC grade acetonitrile was purchased from Merck, Germany. Double distilled water was used in all experiments.

4.2. Drug assay

PPX was quantitatively measured and confirmed in bulk and ODT formulations using a high-performance liquid chromatographic (HPLC) assay method that was performed according to a previously published study [47]. Chromatographic separation was carried out by using Agilent 1260 Infinity HPLC system (Wilmington, DE, USA) equipped with an Eclipse XDB-12 C18 column (150 mm x 4.6 mm, 5 µm particle size). The Agilent Chem Station software was also used to process the obtained data. A mixture of distilled water: acetonitrile (10: 90 v/v) was used as mobile phase, and the assay was performed at λ_{max} of 263 nm. The flow rate set at 1.0 mL/min with 10 µL injection volume and isocratic elution. 10 mg of PPX in was dissolved in 10 mL of mobile phase to prepare the stock solution, which was transferred to an ultrasonic bath (Selecta Ultrasound HD, Spain) for 30 minutes for complete dissolution. Linear calibration curve was obtained by fitting least-squares regression analysis of a series of concentrations (6.25, 12.5, 25, 50, 75, 125, and 225 µg.mL^{-1}) prepared by diluting stock solution with mobile phase. The assay method was validated in compliance with ICH guidelines involving linearity, limits of detection (LOD) and quantitation (LOQ), precision, accuracy, specificity, and selectivity (ICH, 2005). The calibration curve was linear (r^2 =0.999) in the range of 6.25-225.00 µg/mL. The mean retention time, detection limit, and quantification limit were 5.2 min., 4.18 µg/mL, and 12.66 µg/mL, respectively.

4.3. Fourier transform infrared spectroscopy study

Fourier transform infrared spectroscopy (ATR-FTIR) analysis of pure drug, the excipients (Parteck® ODT, Prosolv® Easytab SP, Pharmaburst® 500, F-Melt®, Ludiflash®, and the drug-excipient mixtures (1:1, w/w) were performed using Schimadzu IRAffinity-1 (Schimadzu, Japan) to determine the purity of PPX and a possible physicochemical interaction of it with the excipients. ATR-FTIR spectra were collected between 600 and 4000 cm^{-1}. The measurements were performed in triplicate [48].

4.4. Differential scanning calorimetry study

The differential scanning calorimetry (DSC) analysis of pure drug, the excipients (Parteck® ODT, Prosolv® Easytab SP, Pharmaburst® 500, F-Melt®, Ludiflash® and the drug-excipient mixture (1:1, w/w) were carried out with DSC (Setaram Labsys, DSC131 Evo, France) under a constant flow of argon gas with a flow rate of 100 mL min^{-1}. The samples of amount of 5-8 mg were weighted through an analytical balance (MT MS 105, Mettler Toledo, USA), the aluminum pans sealed hermetically, then heated at a rate of 10 °C min^{-1} between 25 °C and 400 °C, and as reference an empty pan was used [49].

4.5. Blending and tableting

The components of formulations were weighed using an electronic balance (MT MS 105, Mettler Toledo, USA), then added to a Cube Mixer KB (Erweka, AR 403, Erweka GmbH, Germany), except the tablet lubricant sodium stearyl fumarate (SSF), and the powder blend was mixed for 13 min at 45 rpm, which was based on the preliminary studies. After adequate mixing, the SSF was added to the powder blend, which was blended for an additional 2 minutes. For each formulation batch, a total of 150 g of powder blend was prepared. The blended powder compressed with a single punch tablet press (Erweka, EP 1, Erweka GmbH, Germany) instrumented with an 8 mm die to obtain tablets of 100 mg in weight. A compression force of 1000 kg/cm^2 was applied based on the preliminary experiments. 24 hours after compression, each set of samples was assessed. Table 3 shows the composition of formulations.

Table 3. Composition of various pramipexole dihydrochloride monohydrate orally disintegrating tablet formulations

Ingredients (mg/tablet)	Formulation				
	Par_PPX	Pro_PPX	Phb_PPX	Fmt_PPX	Lud_PPX
Pramipexole dihydrochloride monohydrate	0.125	0.125	0.125	0.125	0.125
Parteck® ODT	85	-	-	-	-
Prosolv® EasyTab SP	-	85	-	-	-
Pharmaburst® 500	-	-	85	-	-
F-Melt®	-	-	-	85	-
Ludiflash®	-	-	-	-	85
Aspartame	2.6	2.6	2.6	2.6	2.6
Citric acid	9	9	9	9	9
Vanilin	1.3	1.3	1.3	1.3	1.3
Sodium stearyl fumarate	1.975	1.975	1.975	1.975	1.975

Note: Each formulation was prepared at least in triplicate.

4.6. Evaluation of tablets

Weight variation, diameter and thickness, hardness, friability, simulated wetting time, *in vitro* disintegration time, content uniformity, and *in vitro* dissolution rate tests were performed to evaluate the characteristics of ODTs.

4.6.1. Weight variation

A total of twenty tablets were selected randomly per formulation, and each was weighed with an electronic balance (MT MS 105, Mettler Toledo, USA). The test was carried out according to the Ph. Eur. 2.9.5 [32].

4.6.2. Diameter and thickness

A total of twenty tablets were selected randomly per formulation, the diameters and thickness of tablets were measured by using digital vernier caliper with a sensitivity of 0.01 mm (Erweka, TBH 125, Erweka GmbH, Germany).

4.6.3. Tablet hardness

A total of six tablets were selected randomly per formulation, and the test was performed according to the Ph. Eur. 2.9.8 by using a hardness tester (Erweka, TBH 125, Erweka GmbH, Germany), and the readings were recorded in Newton units [32].

3.6.4. Tablet friability

A total of twenty tablets were selected randomly per formulation, and weighed using an electronic balance (MT MS105, Mettler Toledo, USA). The percentage friability was determined by tumbling the tablets for 4 min. at a rotation speed of 25 rpm in a friabilator (Erweka TAR 120, Erweka GmbH, Germany). The ODTs were weighed after the dust on the ODTs was gently removed, and percentage of weight loss was calculated. According to the Ph. Eur. 2.9.40, samples having a percentage friability value less than 1 were regarded as acceptable [32].

4.6.5. Simulated wetting test

The simulated wetting test (SWT) of the ODTs was evaluated using the method described by Park *et al*. [50]. Three tablets were selected randomly per formulation for the test. A Whatman filter paper disk (21 mm in diameter) was placed in each well of a 12-well polystyrene microplate (22 mm in diameter) and the dye solution 0.1% (w/w) Sensient Blue #1 with a volume of 1.25 mL was added into each well using an automatic pipettor. The amount of dye solution was determined by tablet weight which is presented in Table 4 [50]. Using a pair of forceps, each ODT was placed on top of the moist paper disk in each well to make the tablet face in contact with the filter paper. The tablet was not covered with dye solution. The total time for the blue dye solution to diffuse through the tablet, and completely cover the surface was measured using a chronometer was determined as SWT [42].

Table 4. Optimum volume of the blue dye solution for a given tablet size

Suggested volume of dye solution (mL)	Tablet size (mg)
0.75	<49
1.0	50-99
1.25	100-379
1.5	380-600
1.75	>800

4.6.6. Disintegration time

The disintegration test was carried out using a disintegration equipment (Erweka ZT 322, Erweka GmbH, Germany), which included a basket rack assembly with six tubes each was 7.75 mm long and 2.15 mm in diameter containing a 10 mesh screen at the bottom. Six tablets were selected randomly per formulation, and transferred the tubes. The tubes were raised and lowered 28–32 times per minute in disintegration media of 900 mL distilled water maintained at 37 ± 2 °C. The *in vitro* disintegration time (DT) was determined as the time needed for all fragments of tablets to pass through the sieve [40, 51].

4.6.7. Content uniformity

Ten tablets were selected randomly per formulation, which was pulverized with a mortar and pestle, then transferred into the test tubes, to which was added 5 mL mobile phase (as described in section 4.2.), and were horizontally agitated with a horizantal shaker (IKA HS 501, IKA, Germany) for 6 h to accomplish the complete extraction of drug. A 0.45 µm pore-sized membrane filter was used to filter aliquots of 1 mL from each tube. The samples were diluted with mobile phase for HPLC analysis. The experiment was performed according to the Ph. Eur. 2.9.40 [32].

4.6.8. In vitro dissolution study

The *in vitro* dissolution test of ODTs was carried by using an USP II paddle apparatus. Phosphate buffer (pH 6.8) at 37 ± 5 °C was used as dissolution medium, and the rotation speed was set at 50 rpm [52-54]. Ten tablets were selected randomly per formulation, and each tablet was placed on the beaker of apparatus (Erweka DH 1520, Erweka GmbH, Germany). Aliquots of 1 mL were taken at specified time intervals and the volume of dissolution medium was replenished with an equal volume of the fresh dissolution medium at 37 ± 5 °C. Comparative *in vitro* dissolution study was also conducted for optimized test formulation with reference product (Parkyn 0.125 mg Tablet, Abdi İbrahim, Türkiye). The obtained samples were filtered through 0.45 µm pore-sized membrane filters, diluted with mobile phase and analyzed with HPLC.

4.7. Statistical analysis

All data expressed as mean ± standard deviation (mean ± SD). Statistical analyses of data were carried out using one-way analysis of variance (ANOVA) or Kruskall Wallis followed by Tukey's and Dunn's multiple comparisons tests. The dissolution data was analysed by using two-way ANOVA test followed by Tukey's and Dunnett's multiple comparisons tests. The analyses were performed using the GraphPad Prism® 8.0.1. version program (GraphPad Software Inc., USA). The statistically significant difference was set at $p < 0.05$.

Author contributions: Concept – Ö.T., L.B.P.; Design – Ö.T., L.B.P.; Supervision – Ö.T., L.B.P.; Resources – Ö.T., L.B.P.; Materials – Ö.T., L.B.P.; Data Collection and/or Processing – Ö.T., L.B.P, M.A.; Analysis and/or Interpretation – Ö.T., L.B.P, M.A.; Literature Search – Ö.T., L.B.P, M.A.; Writing – Ö.T., L.B.P, M.A.; Critical Reviews – Ö.T., L.B.P.

Conflict of interest statement: The authors declare no conflict of interest in the manuscript.

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