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Taste and Efficacy Comparison of Two Paracetamol Preparations for the Treatment of Fever in Children

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Abstract

Objective: *The main objective of this study was to compare the taste-masking efficiency of LYOMATRIX Technology which was utilized in the development of Paracetamol Oral Solution (Taste Masked) i.e., NEXPAR with marketed suspension product to see any improvement in taste and therapeutic efficacy in paediatric population.*

Methods: *Children from the age of 2-12 years with fever of non-serious origin were randomized to receive either of the treatments. The paracetamol dose selected was 15mg/kg body weight. Armpit temperature was measured at various time-points till 24 hours. A second dose was administered only when at 6 hours the body temperature was still found to be 101.3ºF; or the child was not responding to the treatment. At the end of the study, parents were asked to subjectively rate the efficacy of the product. The primary endpoints were to; compare the taste acceptability; area under the temperature-time curve; and to compare reduction in fever after administration of two different formulations from baseline at various time points post-dosing. Secondary efficacy endpoints included a variety of objective and subjective measures.*

Results: *Statistically significant differences in all the primary endpoints were in favour of NEXPAR. Most of the secondary endpoints also showed some significant differences. Both agents were equally well tolerated. Significantly more parents in the NEXPAR group rated the drug as very efficacious.*

Conclusion: *NEXPAR was found to have better taste and greater formulation acceptance by the children, ensuring better compliance, correct dosing and better absorption of the drug resulting in better therapeutic outcome.*

Keywords: *Fever, Taste-mask, Bitter taste, Paediatric, Paracetamol, LYOMATRIX Technology, Solution, Suspension.*

Introduction

Medicine often tastes bitter, and because children are more bitter sensitive than are adults, this creates problems with compliance. The more bitter, the more likely the drug will be rejected. Paracetamol (PCM), is one such widely used analgesic and antipyretic, whose bitter taste is difficult to mask[1]. PCM also faces challenges in oral bio-availability, formulation, and extraction due to its low aqueous solubility[2]. Oral grittiness (i.e. rough mouthfeel) because of the solubility issue of a drug may arise from the presence of particles in the mouth, limiting palatability[3]. Formulating a suitable liquid dosage form of PCM for efficient drug delivery is challenging due to its low aqueous solubility. Whereas, formulating tablets and capsules often causes struggle for patients, including children, older adults, and disabled individuals, with swallowing them, and therefore, liquid oral dosage forms are preferred for these patients due to their ease of swallowing[4].

Liquid dosage forms often face issues with drug taste, making taste masking a major challenge[4]. A pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium[5]. The homogeneity of suspensions requires shaking before use. But most of the times people forget to do so[6], and this may have implications on the accuracy of dose administered. Taste masking agents though increase formulation viscosity, but, prevent the bitter drug from coming in contact with taste receptors[7], however, the enhanced viscosity slows gastric emptying, affecting absorption[4], especially when faster response is desired.

Additionally, in a dissolution study carried out by Zongming G, et al., it was observed that the release of the drug was very much delayed from a suspension leading to delayed dissolution and absorption. Since the drug is already solubilised in case of a solutions any delay is obviated[8]. This shows the difference in the physical property of both the liquid products. To overcome the challenges of suspension formulation Paracetamol Oral Solution (Taste Masked) i.e., NEXPAR (NTM) has been designed utilizing LYOMATRIX Technology.

The present study was undertaken to examine potential of LYOMATRIX Technology to improve the palatability of the PCM containing formulation without impacting the time taken to reduce the temperature at the currently recommended dose in children. The formulation, NTM, was compared with Marketed PCM Suspension (MPS) in children with fever.

Materials and Methods

A prospective, randomized, open label study was designed to compare the palatability, effectiveness and safety of NTM 125mg/5ml versus MPS 120mg/5ml, in children suffering from fever. Following the ethics committee's approval, the trial was prospectively registered (CTRI/2024/04/065184) and conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki 2013. Patients were recruited for the treatment from Department of Pediatrics, Maulana Azad Medical College & LN Hospital, New Delhi, between April and September 2024. Calculation of the sample size was based on a clinical trial in which febrile children were assigned randomly to receive either ibuprofen or PCM using SPSS Software (17.0 Version)[9]. To reach a predictive power of 90%, with an alpha (α) level of significance of $P < 0.05$; 180 patients in each treatment group were recruited. As a safeguard, it was decided to recruit 200 subjects per group in order to cope-up with any dropouts.

The study included subjects aged 2-12 years and those with a body temperature of at least 38.5°C/ 101.3°F, with an upper boundary of 39.4°C/ 103°F. The study excluded individuals with hypersensitivity to the study drug, history of conditions affecting drug absorption, hepatic failure, and patients who had received corticosteroids, immuno-suppressants, and non-steroidal anti-inflammatory agents. The study involved obtaining written informed consent from parents of all participants and patients aged 7-12 before enrollment. The study participants were randomly assigned into two treatment groups in a 1:1 ratio using R software version 4.3.2, as confirmed through a runs test. Patients in Group I were given a

single dose of MPS 120mg/5ml, while patients randomized to Group II were given a single dose of NTM 125mg/5ml which were supplied by Pulse Pharmaceuticals Pvt. Ltd., Hyderabad, India. The principal investigator decided to administer a second dose of medication if the child's body temperature remained above 38.5°C (101.3°F) even after 6 hours of the first dose, he or she was unresponsive, or he or she displayed discomfort. After 8 hours of observation and temperature recording, parents and children were permitted to leave the hospital.

Clinical Evaluation

At baseline, demographic data and the medical history of the child were obtained. Standard physical examination was conducted, and vital signs and temperature were recorded.

The armpit temperature was measured before and after drug administration at the time points of 0.50, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, and 8.00 hours, under investigator supervision to ensure uniformity of the procedure. Readings were recorded in case report form (CRF) and patient diary. A taste evaluation test was undertaken utilizing a 9-point Hedonic Rating Scale (HRS) immediately after administering the first dose of both the products. The child's temperature was measured again after 24 hours through a telephonic interview along with parents' global assessment (PGA) to assess an individual's preference for the product. Adverse events were also documented.

The PGA allowed for objective judgment of treatment efficacy. The first question referred to the parents' overall opinion of the treatment with four levels of qualitative answers: (1) very efficacious; (2) efficacious; (3) slightly efficacious; and (4) not efficacious. The second question was 'if your child develops a fever again in the future, would you give him/ her the same treatment?' There were two levels of answer; yes or no. Parents were also allowed to make comments.

The study primarily aimed to compare the taste acceptability, area under the temperature-time curve ($[AUC]_{0-6}$°F.hr), and fever reduction after administering two different formulations to children at various time points. Secondary endpoints included the number of subjects with temperatures below 101.3°F, those below 99.3°F (afebrile), and any need for a second dose.

Statistical Analysis

The data was analyzed using SPSS 18.0 expressed as Mean, SD and N, with a significance level of $P < 0.05$ for continuous and categorical data, and comparison of the data were carried out student's t test for numerical normal data.

Results

The study involved 400 subjects, with 200 receiving MPS 120mg/5ml and 200 receiving NTM 125mg/5ml. Both formulations were administered at a dose of 15mg/kg body weight, with no significant differences in demographics or temperature, as shown in table 1.

Table 1: Demographic data of patients in the study groups.

Parameters	**MPS Group (N=200)**	**NTM Group (N=200)**
Age (mean ± SD years)	5.83 ± 2.86	5.87 ± 2.92
Gender {N (%)}	M = 126 (63.0%) F = 74 (37.0%)	M = 120 (60.0%) F = 80 (40.0%)
Height (mean ± SD cm)	106.28 ± 16.54	105.67 ± 16.96
BMI (mean ± SD kg/m^2)	14.17 ± 2.37	14.63 ± 2.46
Body temperature (mean ± SD °F)	102.12 ± 0.64	102.07 ± 0.63

**Data was analysed by Student's unpaired t-test*

Patient Response

The NTM group overall scored higher than MPS group on the HRS and in specific parameters as well, indicating superior ratings across all sensory attributes compared to the MPS group. These differences were statistically significant (P <0.001) which is depicted in fig.1.

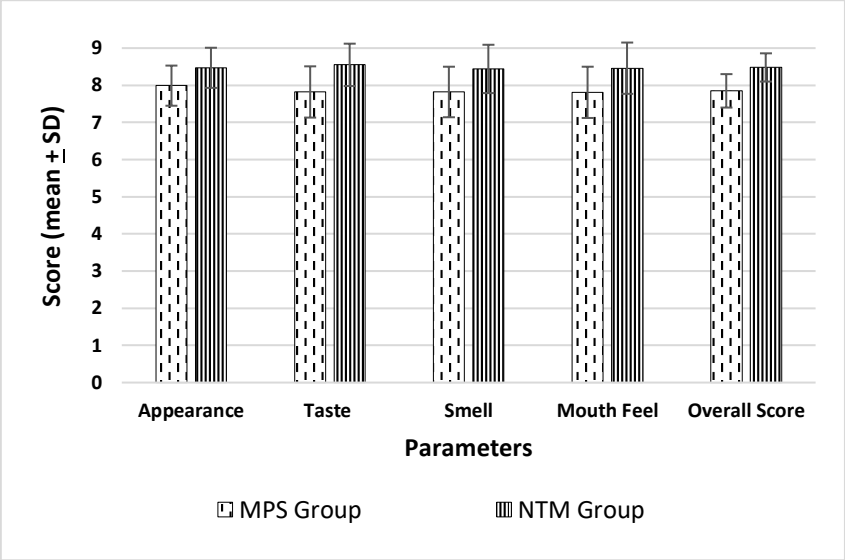

Fig.1: Mean score on the Hedonic Rating Scale (9-points) of Both Treatment Groups

Parents of the subjects in NTM group favoured the product administered to that group on all the items of the questionnaire. In the assessment following the drug administration, 50.5% (101) of parents of subjects in NTM group and 24.5% (49) parents in MPS group rated the treatment as very efficacious. Additionally, 47.5% (95) of the parents in NTM group and 64.5% (129) parents in MPS group rated the treatment as efficacious. A smaller percentage of parents (2.0%) in the MPS group, rated the treatment as slightly efficacious. None of the parents in any group rated the treatment as not efficacious. These differences were statistically significant (P < 0.001) and are depicted in in table 2, indicating the preference of the parents in terms of the efficacy.

Table 2: Comparison of PGA in both of the Treatment Groups

Parameters (PGA Categories)	**MPS Group (N=200)**	**NTM Group (N=200)**	**P value**
Very efficacious	49 (24.5%)	101 (50.5%)	P < 0.001
Efficacious	129 (64.5%)	95 (47.5%)	
Slight efficacious	22 (11.0%)	4 (2.0%)	
Not efficacious	0 (0.0%)	0 (0.0%)	

**Data were analyzed using Chi-square test.*

Temperature Reduction

The subjects in NTM group demonstrated significantly better mean temperature reduction from baseline at 1 hr, 2 hr and 3 hr (P<0.001) post-dosing. The mean temperature at repeated measures after drug administration are given in table 3 and the temperature reduction curve expressed as an absolute difference from baseline is plotted in fig.2.

Table 3: Comparison of Mean Temperature and its Extent of Reduction from Baseline in the Two Treatment Groups

Temperature (mean + SD, °F)			P value
Parameters	**MPS (n=200)**	**NTM (n=200)**	
Baseline	102.12 ± 0.64	102.07 ± 0.64	P=0.4
30 min	101.44 ± 0.77	101.30 ± 0.81	P=0.08
1 hr	100.58 ± 0.89	100.22 ± 0.83	**P<0.001**
2 hrs	99.65 ± 0.92	99.25 ± 0.91	**P<0.001**
3 hrs	99.01 ± 0.79	98.62 ± 0.73	**P<0.001**
4 hrs	98.53 ± 1.04	98.35 ± 0.63	**P=0.04**
5 hrs	98.50 ± 0.79	98.51 ± 0.75	P=0.9
6 hrs	98.63 ± 0.97	98.69 ± 0.84	P=0.5
8 hrs	99.02 ± 1.15	99.10 ± 1.02	P=0.5
24 hrs	98.55 ± 0.90	98.52 ± 0.84	P=0.8

**Data was analysed by Student's unpaired t-test*

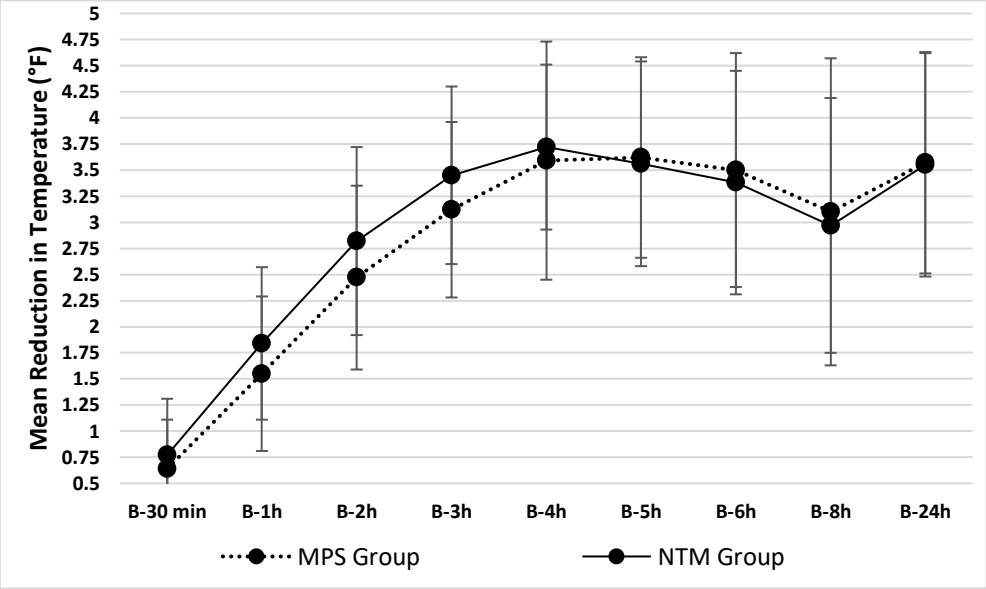

Fig.2: Comparison of Mean Temperature Reduction Curve from Baseline in the Two Treatment Groups

In the NTM group, a statistically significant (P<0.001) reduction in temperature was observed at 1, 2 and 3 hours post drug administration; the temperature reduced by 1.84°F, 2.82°F, 3.45°F compared to 1.55°F, 2.47°F, 3.12°F in MPS Group, respectively. Even at 4 hours, the NTM group exhibited a higher reduction (3.72°F) as compared to the MPS Group (3.59°F), but the difference was not found to be significant (P=0.2). The NTM group showed greater temperature reduction in the initial stages of treatment.

The mean temperature reduction $AUC_{0\text{-}4h}$ was 398.26°F.min in the NTM group and 399.63°F.min in the MPS group, this difference was significant (P < 0.001). The $AUC_{0\text{-}6h}$ had a mean value of 595.43 in the NTM group and 596.68 in the MPS group, again the difference was significant (P < 0.001). Additionally, the $AUC_{0\text{-}24h}$ had a mean value of 793.14 in the NTM group and 794.30 in the MPS Group (P < 0.001).

Thirty minutes post the administration of the treatment medication the number of patients with temperature < 101.3°F was found to be 89 (44.5%) in MPS Group whereas 99 (49.5%) in NTM Group. By the end of 1 hour, these numbers increased to 159 (79.5%) patients in the MPS group and 195 (91.5%) patients in the NTM group. This difference at 1 hour when compared in both the groups was found to be significant at P=0.001, in favour of the NTM group. The NTM group had more subjects with body temperature below 101.3°F at 2, 3, and 4 hours, but the difference was not statistically significant (Table 4). By the end of the 4-hour follow-up, 88.5% and 94.5% of patients in the MPS and NTM groups achieved a temperature reduction below <99.3°F, respectively. The second dose was required by an equal number of patients in both the groups.

Table 4: Number of Subjects with Temperature < 101.3 ºF and < 99.3 ºF at Each Time Point

Time-Points	Number of Subjects with Temperature <101.3 ºF			Number of Subjects with temperature <99.3 ºF		
	MPS Group [N (%)]	NTM Group [N (%)]	P value	MPS Group [N (%)]	NTM Group [N (%)]	P value
30 min	89 (44.5)	99 (49.5)	P=0.4	0 (0.0%)	2 (1.0%)	P=0.5
1 hr	159 (79.5)	182 (91.0)	**P=0.001**	14 (7.0%)	30 (15.0%)	**P=0.01**
2 hr	194 (97.0)	195 (97.5)	P=1.0	65 (32.5%)	101 (50.5%)	**P<0.001**
3 hr	197 (98.5)	199 (99.5)	P=0.6	139 (69.5%)	170 (85.0%)	**P<0.001**
4 hr	199 (99.5)	200 (100.0)	P=1.0	177 (88.5%)	189 (94.5%)	**P=0.047**

**Data was analysed by Student's unpaird t-test*

Safety

No adverse effects were reported in either of the study groups, indicating the therapy's potential as a safe option for larger patient populations.

Discussion

Ninety percent of pediatricians report that a drug's taste and palatability are one of the biggest barriers to completing treatment[10]. Children often refuse medication due to their lack of awareness of its importance as they find them "yucky". France's new recommendations for children's fever treatment emphasize that fever is only a symptom and the primary focus should be on the child's overall comfort. Fever, particularly in young children, can cause discomfort. As there is little evidence that fever (not hyperthermia) is harmful, therapy is usually aimed at promoting comfort rather than reducing temperature[11].

Keeping the above in perspective, this study was designed to evaluate the overall likeness of the NTM and to document any superiority in temperature reduction over the MPS. The evaluation of formulation likeness included the parameters of appearance, taste, odor, and mouth feel of the product utilizing an established and validated 9-point HRS. The NTM formulation scored much higher in all of the parameters overall, and individually as well. LYOMATRIX Technology was used to mask the taste of NTM formulation, enhancing the solubility of the poorly soluble PCM. Complexation of drugs with complexing agents modifies the biopharmaceutical parameters like drug dissolution rate and also helps to mask unpalatable taste. These complexing agents' form a host inclusion complex both in solution and in the solid phase. Molecules or functional groups that are responsible for unpleasant taste of the drugs are hidden from the sensory receptors by encapsulating them within the cavity of complexing agent[7]. Once the solution reaches the intestine, PCM is released from the liquid matrix by diffusion. Despite taste masking, the product's viscosity remains intact, enhancing drug solubility and facilitating rapid absorption, providing an added advantage in the treatment process. This could be seen in most of the efficacy endpoints of our study as well.

Significant reduction in temperature in the initial hours and faster peak temperature reduction, with the NTM than MPS indicates superior and rapid action

of NTM. More number of afebrile patients, temperature <99.3°F, in the NTM group indicates a faster and more robust outcome of the treatment.

Numerous studies have shown poor bioavailability in suspension-formulated drugs due to suboptimal dissolution, which are often due to the suspending agents added to the products[8]. Solutions are more stable than suspensions because the particles in a solution are dissolved properly hence, avoiding the step of dissolution and resulting in greater absorption and faster therapeutic outcome. This is what is implicated in this study through the temperature reduction data as well. The absorption of PCM from NTM was faster as compared to the MPS, as the PCM is already in a dissolved form, demonstrating a quicker onset of action, leading to faster and greater temperature reduction in children.

Stability issues in suspensions, such as sedimentation, particle aggregation, and particle size distribution, can impact the uniformity and efficacy of the suspension, potentially leading to overdosing or under-dosing[12]. This dosing regimen of PCM can also be risky due to dosing errors that may lead to overdoses, potentially causing hepatic or renal toxicity[13]. Suspensions need to be shaken before use and patients or caregivers frequently forget to do so. In an assessment of compliance study conducted in the year 2021 it was found that 80% of the patients in one group and 38% of the patients in another group forgot to shake the bottle even after being instructed [6]. This significant difference among the results of both the groups was seen in a hospital set-up, where the patients were under continuous observation of the investigators and the drug administration was also done after shaking the bottles properly and as per proper body weight. But in the real world scenario, irrespective of the countries, people usually make mistakes and do not comply with the given instructions. In such cases, the results might vary a lot and we could see larger difference in the results.

Many parents, however, view fever as a disease rather than a symptom, which often leads to unnecessary anxiety. Parental anxiety influences their judgment, their understanding of the condition, compliance with their child's treatment and subsequent recovery. Consequently, parental anxiety about their child's illness and treatment must be an integral part of a comprehensive strategy in the treatment of children[9]. The PGA in the study showed a significant difference in response, indicating that the NTM formulation was more effective and accepted by both parents and children.

Conclusion

The NTM formulation of the PCM at doses similar to those of the MPS demonstrates greater efficacy and similar tolerability in children with fever. On comparing both the treatment groups, the NTM group demonstrated a faster reduction in temperature and a greater acceptance of the formulation. Parents of the subjects in the NTM group rated the formulation as very efficacious and reported that they would use the formulation again. The greater acceptance of the NTM formulation, reducing medication rejection, may also address parental anxiety.

LYOMATRIX Technology by facilitating the solubilisation of PCM allows not only for correct dosing without any need to shake the bottle, but also ensures a rapid absorption of the drug. The molecular-level taste masking makes the formulation highly palatable for children thereby preventing any medication rejection.

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Conflict of Interest

The authors S.C., A.S. and H.C. are employees of Pulse Pharmaceuticals Pvt. Ltd.

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Contributor statement: [A.A.] contributed in experimental design, supervised and performed the

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Human Ethics: This study strictly follows the ethical guidelines established by ICMR; Ethical Guidelines for Biomedical Research on Human Participants (2017), International Conference on Harmonization Guideline-Good Clinical Practice (ICH-GCP) and WMA Declaration of Helsinki, 2013.

Ethics Committee Approval: The study was approved by the Ethics Committee of Maulana Azad Medical College and Associated Lok Nayak Hospital on 27th March, 2024 with reference letter no. F.1/IEC/MAMC/107/13/2023/No44.

Statement on Consent to Participate: Informed consent was obtained from all participants and their parents/ caregivers, and their confidentiality was maintained throughout the study.

Statement on Consent to Publish: All the authors, give their consent for the publication of identifiable details, which can include photograph(s) and all the details within the text to be published in the Journal "Indian Journal of Pediatrics".

Trial registry with date of registration: registered on CTRI: CTRI/2024/04/065184 on 04/04/2024.

Data availability statement: The data that support the findings of this study are openly available in Clinical Trials Registry – India, at https://ctri.nic.in/Clinicaltrials/login.php, with reference number CTRI/2024/04/065184.

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