

## **A Prospective, Blinded, Monadic Comparative Sensory Study of Three Topical Pain Relief Spray Formulations**

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### **ABSTRACT**

**Introduction:** Oral drugs are commonly prescribed for the treatment of acute pain. Other than these agents, certain anticonvulsants and antidepressants are also prescribed for chronic pain. Although being effective in providing pain relief, oral administration frequently results in systemic adverse drug reactions (ADRs), which may prevent their ongoing use and result in their discontinuation. Topical analgesics are useful to provide symptomatic benefits seen with oral agents but devoid of the systemic ADRs. Essential oils extracted from plants, some of which are known analgesic compounds like methyl salicylate, eucalyptus oil, clove oil, menthol, turpentine oil which form contents of the newly launched Iodex rapid action spray along with excipients. The aim of this study was to evaluate the sensorial profiling of newly launched Iodex rapid action spray in meeting the consumer expectations as topical pain relief spray. The other objective was to validate consumer perception of the product's sensorial claims and appeal.

**Methods:** This study was a prospective, blinded, monadic comparison, consumer sensory study conducted in 3 different cities in India. Participants were pre-recruited to try 3 different pain relief spray formulations, 30 min session per day. One product to be tested each day. The participants had to use the product and answer the questionnaire online. Only Sensorial aspects were checked.

**Results:** Comparing the market sample 1 (Iodex rapid action spray) vs other formulations, all 3 products got very high level of consumer agreement. For the monadic score, market sample 1 was equal to if not better to than the other two i.e., market sample 2 and market sample 3 in regard to the sensory and participant liking claims.

**Conclusion:** Market sample 1 (Iodex rapid action spray) got very high level of consumer agreement. Market sample 1 (Iodex rapid action spray) is equal to if not better to than the other two i.e., market sample 2 and market sample 3 regards to the sensory and liking claims.

**KEYWORDS:** Analgesic, Essential oil, Iodex, Sensory, Spray

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### **INTRODUCTION**

The International Association for the Study of Pain defines pain as a multidimensional entity that involves nociception, afferents to the central nervous system, modulation, affective responses, endogenous analgesia, behavioral adjustments, and changes of social roles. While pain trigger factors are endured, pain degenerates to an independent response, manifesting even when it is possible to eradicate the primary stimulus. While pain trigger factors are endured, pain

degenerates to an independent response, manifesting even when it is possible to eradicate the primary stimulus.<sup>1</sup>

Oral drugs, including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, are commonly prescribed for the treatment of acute pain. Other than these agents, various types of oral neuromodulators such as certain anticonvulsants and antidepressants are also prescribed for chronic pain. Although being effective in providing meaningful pain relief, oral administration of these agents frequently results in adverse drug reactions (ADRs), which may prevent their ongoing use

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and result in their discontinuation.<sup>2, 3, 4, 5</sup> For example, oral opioids are associated with a wide variety of ADRs that affect both, the central and peripheral nervous systems, including potentially fatal respiratory depression, addiction, nausea, constipation and pruritus.<sup>2,5</sup> Use of oral NSAIDs can also result in serious ADRs, including gastrointestinal bleeding, cardiovascular complications (such as increased risk for myocardial infarction and hypertension), urticaria, itching, liver damage and renal dysfunction or failure.<sup>4, 6, 7</sup> Also, aspirin has been closely linked to the development of Reye syndrome, although rare but often fatal pediatric syndrome.<sup>8</sup> As the understanding of pain pathophysiology and treatment increases, new routes of drug delivery are being discovered with the objective of attempting to block pain at peripheral sites, with maximum active drug and minimal systemic effects. Topical formulations are the result of such exploration.<sup>1</sup>

Topical analgesics are useful, in part, to provide the symptomatic benefits seen with oral agents but devoid of the ADRs seen with oral analgesics. Topical administration of analgesics can produce clinical benefit by providing drug concentrations at a peripherally located site of injury or inflammation, without the high systemic concentrations that may increase the likelihood of ADRs.<sup>9, 10, 11</sup>

Topical analgesic therapy is thus useful in the management of a variety of conditions associated with acute or chronic pain, including acute soft tissue injuries, chronic musculoskeletal pain, and various neuropathic pain disorders.<sup>12, 13, 14</sup>

In addition, the intention of applying localized treatment within the lay population may be a means of enhancing the efficacy of the placebo element of topical agents. Such mechanisms are of limited value if the area of soreness is large, nevertheless, it is well known that placebo interventions may influence reported outcomes, especially pain, nausea, and other subjective complaints that are subject to context.<sup>15</sup>

The ultimate goal that motivates the development of topical preparations is the improvement of patient compliance to medical treatment, by providing effective pain relief with less central nervous system effects and minimal drug regimen burden. Topical preparations can potentially be useful in pediatric population too, whose chronic pain management is just as challenging as in adults.<sup>1</sup>

Topical analgesics are defined as liquids, gels, powders, creams, semisolids, emulsions, patches, foams, or aerosols containing an analgesic or anesthetic agent applied on or around the painful site.<sup>1</sup>

Essential oils extracted from plants are highly concentrated mixtures of chemicals, both volatile as well as hydrophobic. Monoterpenes, sesquiterpenes, and phenylpropanoids being the main chemical constituents present in essential oils.<sup>16</sup>

Many of the compounds of essential oils have already been used as topical analgesics for varied indications since decades, some even being part of traditional medicine since longer. Some of these known analgesic compounds are

Methyl salicylate,<sup>17</sup> Eucalyptus oil,<sup>18</sup> Clove oil,<sup>19</sup> Menthol,<sup>20</sup> Turpentine oil,<sup>22</sup> which form the main contents of the newly launched Iodex rapid action spray.

The aim of this study was to evaluate the sensorial profiling of newly launched Iodex rapid action spray in meeting the consumer expectations as topical pain relief spray. The other objective was to validate consumer perception of the product sensory claims and appeal (Understand product appeal versus existing competitors regarding warming, cooling sensation and other sensorial attributes).

### Study design

This study was a prospective, blinded, monadic comparison, consumer sensory study conducted in 3 different cities in India. Participants were pre-recruited to try 3 different pain relief spray formulations per day, 30 min session each day.

Iodex is a brand marketed by GlaxoSmithKline (GSK CH, India subcontinent). Iodex rapid action spray was compared with two others already marketed products in India. The formulations were referred to as Market sample 1 which was the Iodex rapid action spray, Market sample 2, and Market sample 3 respectively.

Market Sample 1 (Iodex rapid action spray) contains: Gandhapura Taila (Methyl salicylate) 20%, Peppermint Sattva (Menthol) 5%, Nilgiri Taila (Eucalyptus oil) 3%, Tarpin ka taila (Turpentine Oil) 4%, Lavang Taila (Clove oil) 2%.

Market Sample 2 contains: Wintergreen oil 15.0%, Mint extract (pudina ka phool) 5.0%, Eucalyptus oil 2.0%, Turpentine oil (Tarpin ka tel) 3.0% and Cinnamon oil 0.4%.

Market Sample 3 contains: Wintergreen oil 20%, Karpura 10%, Turpentine oil 10.0%, Nilgiri ka tel 6.0%, Pudina ka phool 4.0%, Lavang ka tel 1.0%, and Cinnamon oil 0.5%.

Survey kit was delivered to the participants individually. Each survey kit contained consent form (signed before taking the survey), instruction sheet clearly detailing product disposal post use, three different marketed spray formulations used for the study which were blinded and had a product code and pin code mentioned on them and a rotational plan. Products were rotated and randomized across participants. One product was to be tested each day. The participants had to use the product and answer the questionnaire online. Only Sensorial aspects were checked, and participants rated the products on a 1-9 hedonic scale, 1-5 agreement/ meets expectation scale, Just About Right (JAR) scale and preference questions.

Product application was done on typical area. A note was made to apply all the three formulations on the same area for all days of the survey. Comparative application/usage preference like ease of application, ease of use, convenience of use and comparative sensorial preference like fragrance, cooling attributes, warming attributes, post application attributes was observed and recorded. Other claim like preference over usual product was also evaluated.

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Inclusion criteria were individuals between 18 – 45 years of age; open to topical solutions for pain relief; participants with active lifestyle who were on the move/with a fitness regime; regular body pain sufferers (except headache and persistent joint pains) who experienced body pain within the past 6 months and experiences at least 1 pain occasion every 2-3 weeks, last occasion in the previous 2 weeks; used pain relieving medicines to treat their body pains in the past 6 months, at least once a month.

Exclusion criteria included individuals who had participated in market research project in last 3 months for pain relief; healthcare professional dealing with pain relief/management; rejecters of topical pain reliver brands, cooling and warming sensation on topical products, herbal ingredients like clove, camphor, capsaicin, mint, eucalyptus oil, wintergreen oil; pregnant/nursing mothers; with medical condition that needs hospitalization, or medical supervision; history of allergies to topical pain relief products (sprays, gels, creams); open wounds/lesions in application site.

**Statistical analysis:** Data was collected by ConfirmIt, exported to Microsoft Excel and analyses was done using Statistical Package including T-test and Z-test from MMR. Descriptive statistics such as mean and standard deviation (SD) for variables, frequency and percentage for categorical variables were determined. All tests were conducted on means and percentages. Test used was ANOVA at alpha = 5%

### RESULTS

**Demographic distribution:** There were a total of 467 participants included in the study, across 3 cities, 157 from Delhi, 163 from Mumbai and 147 from Chennai. There were 225 males and 242 females. Out of the total participants, 155 belonged to the 18 to 25 age group, 159 belonged to the 26 to 36 age group and 153 to the 36 to 45 age group. Almost half i.e., 232 belonged to the Socio-Economic Class (SEC) A whereas 235 belonged to SEC B. The baseline demographic findings given in Table 1.

**Table 1. Baseline demographic distribution.**

<b>Cities</b>	<b>Delhi</b>	<b>34%</b>
	Mumbai	35%
	Chennai	31%
<b>Sex</b>	Males	48%
	Females	52%
<b>Age</b>	18-25	33%
	26-35	34%
	36-45	33%
<b>SEC</b>	A	50%
	B	50%
<b>User Type</b>	Spray Users	50%
	Gel + Balm Users	50%

**Claims:** All the claims got very high level of consumer agreement for Market sample 1 with at least 90% across total participants in the 3 cities. The highest agreement scores to

Showcase market sample 1's sensory benefits were ease of application, fast to absorb, being non-sticky and providing a soothing cooling sensation as can be seen in Table

**Table 2. Monadic Score for different claims in the respondent using Market Sample 1 (Iodex rapid action spray)**

<b>Claims</b>	<b>Market sample 1 Top 2 box agreement % (T2B%)</b>
I can feel it starts to cool in 5 seconds	90%
I can feel the cooling in 10 seconds	90%
Starts to cool faster than other sprays	90%
Fast and long-lasting cooling action	91%
Easy and convenient to use	94%
Easy to apply	97%
Quick drying	92%
Fast to absorb	96%

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Non-sticky	95%
Non-greasy	91%
Doesn't leave skin dry	91%
Provides soothing cooling feeling	96%
Provides fast cooling sensation	90%
Provides long-lasting warming sensation	91%
Provides a comforting warming sensation	90%
Provides a comforting warm feeling so I feel it works deep and long lasting	91%
Provides dual sensation of cooling and warming	92%

Market sample 1 was better than market sample 2 and market sample 3 on 'easy to apply', 'quick drying', 'fast to absorb', 'non-sticky', 'provides soothing cooling feeling' and 'provides long-lasting warming sensation' claims. Market sample 1 was on par with market sample 2 and better than market sample 3 on 'non-greasy' claim. Market sample 1 was on par with market sample 3 and better than market sample 2

on 'starts to cool faster than other sprays' claim. Whereas market sample 2 was better than the other two samples in 'doesn't leave skin dry' and 'provides dual sensation of cooling and warming' claims and market sample 3 was better than the other 2 in 'provides fast cooling sensation' claim as depicted in Table 3.

**Table 3. Score for different claims in the respondent using three formulation sprays (monadic score) (T2B%)**

Claims	Market Sample 1	Market Sample 2	Market Sample 3
Starts to cool faster than other sprays	90%	89%	90%
Easy to apply	97%	96%	96%
Quick drying	92%	89%	91%
Fast to absorb	96%	94%	92%
Non-sticky	95%	88%	94%
Non-greasy	91%	91%	90%
Doesn't leave skin dry	91%	92%	90%
Provides soothing cooling feeling	96%	94%	94%
Provides fast cooling sensation	90%	92%	93%
Provides long-lasting warming sensation	91%	89%	90%
Provides dual sensation of cooling and warming	92%	94%	91%

### Overall liking:

Market samples were rated as to how much they were liked or disliked by the participants, 1 being strong dislike and 9 being strong like. Market sample 1 and 3 performed on par with each other in almost all categories, with market sample

1 being better in 'intensity of cooling sensation' category and market sample 3 being better in 'intensity of warming sensation' and 'speed of absorption' categories. While both performed better than market sample 2 in rest of the categories, as depicted in Table 4.

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Table 4. Mean Appeal for different claims in the respondent using three spray formulations

Mean Appeal (1-9)	Market Sample 1	Market Sample 2	Market Sample 3
Fragrance	7.5	7.4	7.5
Clove likeness (n=414)	7.6	7.5	7.6
Cooling sensation on skin on application (n=452)	7.6	7.5	7.6
Speed of cooling sensation	7.6	7.5	7.6
Lastingness of cooling sensation	7.5	7.4	7.5
Intensity of cooling sensation	7.6	7.5	7.5
Warming sensation on skin on application (n=417)	7.5	7.4	7.5
Lastingness of warming sensation	7.5	7.4	7.5
Intensity of warming sensation	7.5	7.4	7.6
Speed of the product drying	7.5	7.4	7.5
Speed of absorption	7.4	7.3	7.5

**Adverse drug reaction:** No ADRs were reported by any participants.

### DISCUSSION

Topical route of administration is one of the modes of drug administration preferred over oral and injections. This is due to its distinct advantages such as avoidance of first pass metabolism relating to oral administration, improvement of patient adherence and prevention of potential systemic adverse effects among others. The skin provides a large surface area suitable for absorption and the non-invasive procedure for the topical route that enables a continuous intervention with the applied medication. The amount of drug delivered through the topical route and the obtained therapeutic effect depends on the ability of the drug to permeate through the various layers of skin, which is usually helped by the active ingredients or excipients.<sup>23, 24</sup>

Topical spray is believed to have superiority over the conventional topical formulations in the light of its safety and tolerability. As compared to conventional formulations like patches, gel and ointment, sprays are readily available for application, provides flexible drug dosage delivery, and reduces the occurrence of skin irritation and no need for the patients to clean their hands after the application making them more convenient for use. Because of volatile solvent content, spray creates a fast drying and non-occlusive layer on the skin after its application and helps rapid drug permeation through the skin. Sprays offer many benefits and has a wide potential to be developed as the preferred topical formulation over gels, patches, and ointment in order to avoid skin irritations and improved patients' compliance. However, its efficacy is majorly dependent on the selection of appropriate excipients that will help improve the transdermal flux of the drug. Another advantage of sprays is that they reduce the chance of contamination or transfer of organism as compared to other topical formulations.<sup>23, 24</sup>

With a lack of studies conducted comparing different analgesic spray formulations, from this study, we can deduce that the said advantages of market sample 1 over the other 2 samples is either due to the individual ingredient or due to their synergistic action. Market sample 1 (Iodex rapid action spray) contains Gandhapura Taila (Methyl salicylate) 20%, Peppermint Sattva (Menthol) 5%, Nilgiri Taila (Eucalyptus oil) 3%, Tarpin ka taila (Turpentine Oil) 4%, Lavang Taila (Clove oil) 2%.

Methyl salicylate, a counter-irritant acts as an analgesic and anti-inflammatory. Its analgesic effects are presumed to result from its NSAID action as well as dilation of blood vessels in the skin, thereby increasing localized blood flow and thus tissue temperature resulting in a feeling of warmth. A recent study reported that it modifies a nonselective cation channel, transient receptor potential vanilloid 1 (TRPV1) found in sensory neurons, a process that may interrupt the transmission of pain signals. Another study suggests that although topical methyl salicylate can inhibit cyclooxygenase (COX) pathway, its association of inhibiting COX pathway is 100 folds lower than acetylsalicylic acid and the analgesic effect has been attributed to activation and desensitization of cutaneous nerves.<sup>17, 25</sup>

Menthol, another counter-irritant, produces a cooling sensation through the activation of a specific thermo-receptor, it causes tingling sensation and a feeling of coolness due to stimulation of 'cold' receptors by activation of transient receptor potential cation channel subfamily M member 8 (TRPM8) and TRPA1 channels by inhibiting Ca<sup>++</sup> currents of neuronal membranes. Ca<sup>++</sup> solutions cause a diffuse sensation of warmth by increasing the frequency of warm-receptor discharge whereas a decrease of external Ca<sup>++</sup>



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concentration increases the discharge of cold receptors. It has also been reported that modulation of Ca<sup>++</sup> currents is involved in the regulation of pain threshold. Vasodilatory effects produced by menthol can result in increase in local circulation and tissue temperature. Alternatively, menthol may also disrupt the intercellular lipid structure of the skin, thereby also aiding permeation of other ingredients.<sup>17, 21, 25</sup> Eucalyptus oil known for its pleasant smell, contains citronellyl acetate (CAT), eucalyptol. Its analgesic effect is attributed to CAT, although its mechanism of action isn't clear, at least in part is attributed due to involvement of the following receptors, protein kinase C (PKC) and protein kinase A (PKA), TRPV1, TRPM8, acid-sensing ion (ASIC) and glutamate receptors. It is also speculated that eucalyptus oil may be linked to processes involved in the prevention of sensitization of the nociceptor, down-regulation of the sensitized nociceptor and/or blockade of the nociceptor at peripheral and/or central levels. One of the well characterized signalling systems believed to participate in this mechanism(s) is the arachidonic acid metabolic pathway. In this regard, it has been previously shown that at least eucalyptol, one of the major components of eucalyptus oils, inhibits the production of prostaglandins, leukotrienes, thromboxanes and other cytokines similar to acetylsalicylic acid.<sup>16, 18, 21</sup>

Turpentine Oil with unknown mechanisms have shown a reduction in muscular pain in lumbar region and found to have an emergent effect to improve blood circulation and neuropathic pain reduction.<sup>22, 26</sup>

Clove oil has a volatile phenolic constituent, eugenol, which is a dimer. Eugenol is the main active component which acts by suppressing the expressions of COX enzyme. It can inhibit the expression of cytokines in macrophages, which are stimulated by polysaccharides. Eugenol also has an inhibitory effect on cell proliferation via suppression of NF-Kappa B (NF-kB). Macroscopic studies are suggestive of clinical evidence that it may have inhibitory effects on mononuclear cell as well as lowered the levels of cytokines such as TNF- $\alpha$ , interferon gamma and TNF- $\beta$  which causes inflammation and pain.<sup>16, 19, 21, 27</sup>

### CONCLUSION

Market sample 1 (Iodex rapid action spray) vs other formulations, all 3 products got very high level of consumer agreement. Market sample 1 is equal to if not better to than the other two i.e., market sample 2 and market sample 3 in regard to the sensory and liking claims. The active ingredients of Iodex rapid action spray have synergistic action of their analgesic activity as well as for improved absorption. Topical formulations have the advantages over oral dosage forms by having a more localized action with reduced systemic ADRs. Spray formulations are also readily available for application, provides flexible drug dosage delivery, and reduces the occurrence of skin irritation and more convenient to use.

**DISCLOSURE:** All the authors are on the payrolls of GSK Consumer Healthcare. This sensory study was sponsored by GSK Consumer Healthcare, India subcontinent.

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