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A REVIEW ON DIFFERENT FORMULATIONS OF BACLOFEN FOR SPASTICITY

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INTRODUCTION

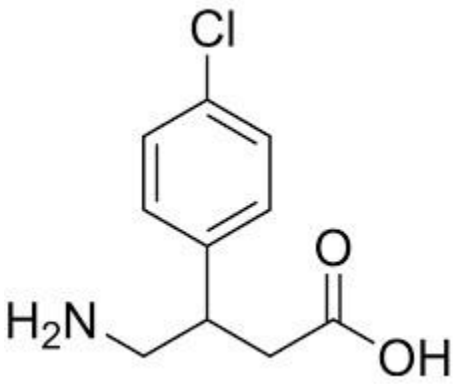
Spasticity is a medical term that refers to a condition characterized by involuntary muscle stiffness, tightness, or spasms. It is often caused by damage to the central nervous system, particularly the brain or spinal cord. Conditions such as cerebral palsy, multiple sclerosis, stroke, and certain spinal cord injuries can lead to spasticity. In spasticity, the muscles affected by increased tone may become rigid, making movement difficult and causing discomfort. The increased muscle tone is a result of abnormal signaling from the nervous system, leading to exaggerated reflexes and muscle contractions. Physical therapy, medications, and sometimes surgical interventions are common approaches to managing spasticity and improving the affected individual's mobility and quality of life.

Chewable tablets necessitate being fractured and chewed between the teeth before consumption. Administered to children facing challenges in swallowing and to adults averse to swallowing, these tablets are chewed and fragmented into smaller pieces before being ingested, emphasizing that they should not be swallowed whole. This process diminishes disintegration time and potentially accelerates the absorption rate of the medication. Mannitol serves as the foundational component in the formulation of chewable tablets. It is imperative for these tablets to exhibit an agreeable taste and flavor, disintegrate rapidly, and impart a refreshing sweet taste.[1]

Baclofen functions as a muscle relaxant and antispastic agent. Baclofen is a derivative of gamma-amino-butyric acid (GABA) employed as a skeletal muscle relaxant. Baclofen activates GABA-B receptors, resulting in a reduction in both the frequency and amplitude of

muscle spasms. It proves particularly effective in addressing muscle spasticity linked to spinal cord injury. Its primary mode of action seems to be centered at the spinal cord level, where it hampers spinal polysynaptic afferent pathways and, to a lesser degree, monosynaptic afferent pathways. The Baclofen USP variant appears as crystalline powder, ranging from white to off-white, with no discernible odor or practically no odor. This powder exhibits slight solubility in water, very slight solubility in methanol, and is insoluble in chloroform. Baclofen's chemical designation is 4-amino-3-(4-chlorophenyl)-butanoic acid. It holds a molecular weight of 213.66, and its empirical formula is C10H12C1NO2.[2],[5]

- The structural formula is



Advantages

- Enhanced bioavailability by circumventing disintegration and potentially improving dissolution.
- Increased patient convenience by eliminating the necessity for water during ingestion (chewable tablets can be consumed anywhere, even in the absence of water).
- Potential substitution for liquid dosage forms when a swift onset of action is required.
- Reduced first-pass effect.
- Elevated patient acceptance, particularly in pediatric cases, due to a pleasing taste and distinctive product characteristics.
- Given the challenges faced by children up to young teens in swallowing tablets and capsules for both physiological and psychological reasons, chewable tablets are preferable due to their palatability and enhanced stability.
- Easily reachable for self-administration.
- Feasible achievement of effective taste masking paired with a pleasant mouthfeel.

Different formulations of Baclofen[7]

S.No	Brand Name	Strength	Dosage Form	Formulation	Manufacturer
1	Baclof-10	10mg	Tablet	Immediate-Release	INTAS PHARMACEUTICALS LTD.
2	Baclof od 20	20mg	Tablet	Extended-Release	INTAS PHARMACEUTICALS LTD.
3	Gablofen	50mcg/ml	Injection	Injection	PIRAMAL CRITICAL CARE

Excepients used in formulations[1][7][15]

Pharmaceutically inactive components, aside from active pharmacological ingredients or prodrugs, incorporated during the assembly process or included in the actual pharmaceutical product. Excipients play a crucial role in the production of pharmaceutical dosage forms.

Bulking Agent/Diluent[1]

These substances are incorporated into formulations of chewable tablets to augment the tablet volume. When combined with the drug substance, the end product attains a sufficient weight and size, facilitating handling and manufacturing processes.

Mannitol[1]

Mannitol is a commonly employed diluent, serving as an appealing filler in tablet formulations. Particularly when the taste of a chewable tablet holds significant importance, mannitol proves to be an advantageous choice. This material exists in a pure and crystalline state, featuring odorless or free-flowing granules, thereby being essentially inert and non-hygroscopic. Its utilization as a diluent in the development of chewable tablet formulations is commonplace due to its negative heat of solution, imparting sweetness, and contributing to a pleasant mouthfeel. Furthermore, mannitol functions as a taste-enhancing agent, purportedly exhibiting about 70% of the sweetness found in sucrose. In its powder form, mannitol is suitable for wet granulation when combined with an auxiliary binder. It is also available in a granular structure for direct compression processes. Being inherently non-hygroscopic, mannitol is particularly advantageous in moisture-sensitive drug formulations. The combination of mannitol's attributes, including sweetness, mouth-feel, and non-hygroscopic nature of the powder, confers significant benefits for the formulation of chewable tablets.

Sorbitol[2]

Sorbitol is a polyol found in an odorless, white, or nearly colorless, crystalline, and hygroscopic powder form. In tablet formulations prepared through either the wet granulation method or direct compression, sorbitol serves as a diluent. For direct compression, it is commercially available as SorbTab (ICI Americas) and Crystalline Tablet Type (Pfizer Chemical).

In the creation of chewable tablet formulations, sorbitol is often employed due to its pleasant, sweet taste and its ability to impart a cooling sensation. It represents a slightly sweeter and significantly more hygroscopic isomer of mannitol. In comparison to mannitol, sorbitol is notably more hygroscopic.

Dextrose[7]

Dextrose is employed in tablet formulations as a diluent, serving as a colorless substance. These substances lack any discernible odor and present a sweet taste. Dextrose is derived through enzymatic or acid hydrolysis of starch, typically maize or corn starch. In the context of wet granulation, dextrose functions as a diluent and binder. In direct compression formulations, it acts as both a diluent and binder, predominantly in the creation of chewable tablets. The sweetness level of dextrose is approximately 70% of sucrose. It is available in both monohydrate and anhydrous forms. When compared as a tablet diluent with lactose, tablets formulated with dextrose monohydrate necessitate more lubricant and have a tendency to solidify in the initial hours post-compression.

Lactose[7]

Lactose, also known as milk sugar, is a disaccharide commercially derived from the milk of cows. It constitutes the remaining liquid after the production of cheese and casein. Lactose is frequently employed as a diluent in the formation of tablets and is a common excipient in tablet manufacturing. In the context of chewable tablets, the role of lactose is limited due to its low sweetness, which is approximately 20% compared to sugar. This deficiency necessitates the inclusion of an artificial sweetener with sufficient potency to overcome lactose's lack of sweetness. Chewable tablets containing lactose are unsuitable for patients with lactose intolerance.

Sucrose[15]

Sucrose is commonly utilized in tablets as both a sweetener and a diluent in sugar formulations. It is also employed as a component in wet granulation technology. While simple compacted sucrose crystals have not proven successful, variations involving modified sucrose have been integrated into direct compression routines. These modifications may include compositions such as (90-93% sucrose + 7-10% modified sugars) and NuTab (2% each of 95% sucrose, 4% converted sugars, and 0.1-0.0% from cornstarch and magnesium stearate). All diluents and binders based on sucrose are implemented in the direct compression tableting process, specifically for the production of chewable tablets. It is advisable to steer clear of counterfeit sweeteners in such formulations. Sucrose, when employed as a bulking agent, comes with several drawbacks. It is soluble and not a reduced sugar. Over time, it tends to darken and exhibits hygroscopic properties, leading to the formation of a textured cake when left undisturbed.[4]

Flavouring agent[3]

Flavoring agents play a pivotal role as essential components in chewable tablets. These agents are typically employed to impart a pleasant taste, enhance flavor, and often introduce a fragrance to chewable tablets. They are introduced in solid forms, such as spray-dried beadlets, and oils. The incorporation of flavoring agents typically occurs in the oil step of the process, mainly because these substances are sensitive to moisture and have a tendency to evaporate rapidly when subjected to heat, such as during the drying of wet granules. Water-soluble (aqueous) flavors have seen limited acceptance due to their diminished stability post-aging. Oxidation reactions contribute to a reduction in flavor consistency. In many cases, oils are emulsified with dried acacia and then sprayed. Dry flavors are convenient to handle and exhibit greater stability compared to oils. Oils are usually thinned with alcohol and sprayed into the granules as they descend into a lubrication tub. Various types and categories of flavors for general taste profiles are detailed in the table below.

Flavours	Group for Tasting Types
Sweet	Vanilla, fruits, maple, stone fruits, berries, grape
Sour(Acidic)	Raspberry, anise, cherry, root beer, cherry, strawberry
Salty	Mixed citrus, butterscotch, maple, nutty, buttery, spice, mixed fruits, butterscotch
Bitter	Coffee, cherry, Liquorice, grapefruit, wine fennel, peach, mint
Metallic	Grape, burgundy, lemon-lime
Alkaline	Chocolate, Mint, cream, vanilla

Sweeteners or taste enhancing agent[3]

Sweetening agents play a crucial role as essential components in chewable tablets. These agents are primarily incorporated into chewable tablets when commonly used carriers, such as lactose, sucrose, mannitol, and dextrose, fail to completely mask the taste of the active drug substance or components. In such instances, formulation scientists often resort to the use of artificial sweetening enhancers to enhance the overall sweetness impact. Due to concerns about the potential carcinogenic nature of artificial sweeteners, such as cyclamates and saccharin, pharmaceutical formulators typically strive to design their tablet products without these agents. The taste-masking method stands out as the primary and simplest approach to taste masking, especially in the case of pediatric formulations, chewable tablets, and liquid formulations. However, this method may not be highly effective for extremely bitter and highly water-soluble drugs. To improve the efficacy of taste-masking strategies, artificial sweeteners and flavors are commonly used in conjunction with other taste-masking techniques.

Aspartame[4]

Aspartame, also recognized as NutraSweet, serves as a non-pharmaceutical sweetening artificial agent. It boasts a sweetness potency approximately 200 times that of sucrose. The intensity of sweetness provided by Aspartame surpasses that of natural sugars. Approved for incorporation in desserts, beverages, and tea or coffee preparations, Aspartame enhances and prolongs the taste of citrus flavors. It exhibits excellent stability in dry conditions at room temperature and 50% relative humidity. However, Aspartame may induce discoloration in the presence of tartaric and ascorbic acid, prompting a reduction in its usage in certain formulations. In chewable tablets, Aspartame is typically employed at a dosage range of 3 to 8 mg per tablet.

Saccharine[6]

Saccharin is a commonly employed sweetening agent in chewable tablets. Approved by the Food and Drug Administration (FDA), saccharin possesses a sweetness intensity that is five hundred times greater than sucrose. One notable drawback of saccharin is its unpleasant delayed flavor impression. However, this drawback can be mitigated by introducing a minor quantity (1%) of sodium chloride. The delayed flavor impression associated with saccharin is particularly noticeable in approximately 20% of the population. The overall sweetness of saccharin diminishes as the sweetness level is enhanced. For instance, when the amount or

concentration of saccharin is increased, the degree of bitterness in the aftertaste also increases.

LITERATURE REVIEW

1. **Raj K. Keservani and Surya Prakash Gautam, 2020** Aims to provide a comprehensive understanding of the rationale, methodologies, and outcomes associated with the formulation and evaluation of baclofen (25mg) liposome vesicles utilizing lecithin as a crucial component. Lecithin, being a natural phospholipid, plays a crucial role in the formulation of liposomes. The review delves into the various aspects of this formulation, examining the rationale behind using lecithin and the potential benefits it brings to the liposomal vesicles. They develop five formulations of baclofen and encapsulation efficacy of each baclofen liposome formulation (RLP1, RLP2, RLP3, RLP4, and RLP5) was assessed. Among these formulations, RLP5 exhibited the highest percentage of encapsulation efficiency (58.67±0.81%), surpassing the values observed for RLP1, RLP2, RLP3, and RLP4 formulations.
2. **Muaadh A. et al. 2017** aims to provide a comprehensive understanding of the formulation and evaluation of baclofen mucoadhesive buccal films, offering insights into both laboratory-based assessments and potential clinical applications. They develop seven formulations and data clearly shows that indicated that the baclofen percentage release was at its peak (95.09% - 97.31%) in formulations B4 and B5. Conversely, B6 exhibited the lowest in vitro drug release, with only 67.34% of the drug being released within an 8-hour period. Where the greatest in vivo duration within the body was observed for B4 and B6, where mucoadhesion played a predominant role in extending the in vivo residence time of mucoadhesive films.
3. **A. Arunachalam, 2014** formulation and in vitro drug release studies of baclofen conventional tablets aims to provide a comprehensive understanding of the formulation strategies, performance characteristics, and potential improvements in the development of baclofen(20mg) tablets. Including overview of existing formulations of baclofen, including immediate-release and extended-release formulations and comparative analysis of different delivery systems for baclofen. They develop five formulations and every set exhibited favorable to acceptable characteristics of free-flowing attributes, hardness, thickness, weight consistency, and friability, with values falling within the specified pharmacopeial standards. In vitro investigations revealed that among the various formulations, FB-5 demonstrated the most optimal drug release.

4. **Gande S and Rao YM. 2011** aims to provide a comprehensive understanding of the development and evaluation of sustained-release effervescent floating matrix tablets containing baclofen, offering insights into both in vitro and in vivo performance. Lioresal (25 mg tablets, batch number 82001 P, Novartis Pharma, India) was purchased from market, Baclofen was a generous gift from Natco P harmaceuticals,(Hyderabad, India), Hydroxy propyl methyl cellulose (HPMC K15M, 100M, 6cps) were obtained from Colorcon Asia Private Limited (India), PVPK 30 was obtained from BASF (Germany). All excipients were of USP/NF grades and all other chemicals used were of analytical grades. They developed eight formulations of baclofen in formulation F-7 and F-8 the percentage of drug release was 105.8% and 101.5%.
5. **Nitin G. Sampat et al. 2003** aims to provide a comprehensive understanding of the current challenges associated with thrice-daily baclofen immediate-release formulations and assess the feasibility and benefits of once-daily sustained release or gastro-retentive systems as viable alternatives. Ninety patients with chronic neurogenic muscular spasticity were enrolled requiring 10-20 mg of baclofen IR every eight hours. The patients were randomized to two treatment arms: SR (n = 46) or GRS (n = 44) at the same once-daily dose for four weeks. Efficacy was measured by Ashworth score for muscle tone, spasm score, reflex score, 30-item functional independence score, and patient's diary score for three most affected activities of daily life.
6. **Abdelkader et al.**, the focus is on the formulation of a controlled-release matrix tablet containing 25 mg baclofen. The study investigates varying concentrations of hydrophilic matrixing agents, namely methylcellulose (MC), sodium alginate (Alg), and sodium carboxymethylcellulose (CMC). The tablets are produced using a wet granulation process. The study concludes that the formulation with MC and Alg as matrixing agents shows favorable characteristics for modified-release baclofen tablets, with sustained release, reproducibility, and stability over an extended period.
7. **Makwana et al.**, the focus is on developing a bilayer drug delivery system for the treatment of spasticity. The goals are to achieve a rapid peak plasma concentration and sustain that concentration. The research involves the analysis of pre- and post-compression values for drug-loaded bilayer tablets, investigation of the promising formulation's stability, and the use of wet granulation and direct compression processes for tablet production. The study concludes that the developed bilayer tablet system shows promise in achieving both immediate and sustained drug release, providing potential advantages for the treatment of spasticity.

8. **Ibrahim et al.**, the focus is on developing a modified-release formulation of baclofen in the form of floating beads to reduce unwanted side effects associated with quick absorption and immediate release. Alginate is utilized for bead formation, and coatings with Eudragit RS100, Eudragit L100, and cetyl alcohol are applied. The study evaluates various parameters, including encapsulation efficacy, buoyancy, shape, in vitro release, oral bioavailability, and potential adverse effects in live animals. The study concludes that the developed modified-release floating beads of baclofen show promise in reducing side effects and providing controlled release characteristics, with positive outcomes observed in both in vitro and in vivo evaluations.
9. **Mathivanan et al.**, the focus is on addressing spasticity, a condition characterized by abnormal tightness in certain muscles, using Baclofen. The existing once-daily extended-release GRS tablet for Baclofen is effective but comes at a high cost. The primary objective is to develop a cost-effective, once-daily, gastro-retentive floating system for Baclofen using high-molecular-weight cellulose (HPMC) and natural gums. The study concludes that the developed once-daily, gastro-retentive floating tablets of Baclofen, especially the optimized formulation (Formula 11), provide an effective and more affordable alternative to the existing commercially available GRS tablet for managing spasticity.

CONCLUSION

Chewable tablets represent adaptable dosage forms that amalgamate the manufacturability and stability advantages inherent in solid products, concurrently delivering advantageous Organoleptic and Administration benefits. The rising focus on patient-centered formulation in drug delivery has not only spurred advancements in specific demographics like pediatrics and specialized pharmaceuticals but has also extended to other sectors, including nutritional products, dietary supplements, and veterinary drugs. The healthcare market, therefore, presents a plethora of opportunities for the utilization of Chewable Tablets.

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