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FORMULATION AND EVALUATION OF ORODISPERSIABLE TABLET OF PYRIDOSTIGMINE BROMIDE

Tushar S. Chormale[1], Pratik B. Bhanage[2], Dr. Megha T. Salve[3]

Department of Bachelor of Pharmacy
Shivajirao Pawar College of Pharmacy, Pachegaon, Ahilyanagar-413725
Email ID- chormaletushar53@gmail.com
*Corresponding Author- Tushar S. Chormale

1. ABSTRACT:

Pyridostigmine bromide is a cholinesterase inhibitor primarily used in the treatment of myasthenia gravis. Patients with myasthenia gravis, particularly those experiencing bulbar muscle weakness, often face difficulties in swallowing conventional tablets. This research aimed to formulate and evaluate orodispersible tablets (ODTs) of pyridostigmine bromide to provide a more convenient and rapidly dissolving dosage form, potentially improving patient compliance and onset of action. Different formulations were prepared using various super disintegrants and evaluated for their physicochemical properties, in-vitro disintegration time, wetting time, drug content uniformity, in-vitro dissolution profile, and stability. Optimized formulations exhibited rapid disintegration, acceptable drug content, and promising dissolution characteristics, suggesting the potential of pyridostigmine bromide ODTs as a viable alternative to conventional tablets.

KEYWORDS: Pyridostigmine bromide, Orodispersible tablets, Superdisintegrant, Formulation, Dysphagia.

2. INTRODUCTION:

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease characterized by weakness of the skeletal muscles, caused by an impairment in the transmission of nerve impulses to the muscles. This impairment occurs at the neuromuscular junction, where acetylcholine (ACh), a neurotransmitter, binds to its receptors on muscle cells to trigger muscle contraction. In MG, the body's immune system mistakenly produces antibodies that block or destroy these ACh receptors, leading to muscle weakness that fluctuates and worsens with activity and improves with rest. Pyridostigmine bromide is a well-established and commonly prescribed anticholinesterase medication used in the symptomatic treatment of myasthenia gravis.

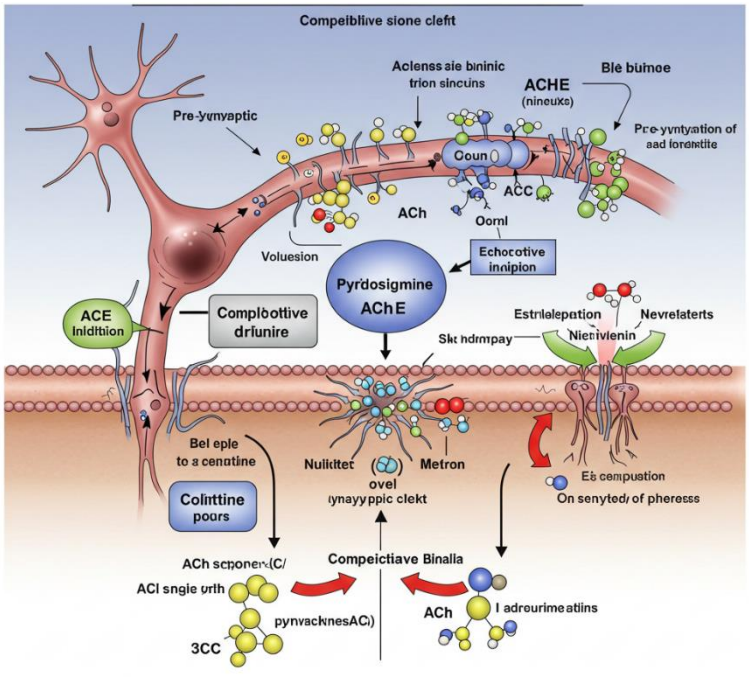


Fig 1. Mechanism of pyridostigmine in Myasthenia gravis.

By inhibiting the enzyme acetylcholinesterase, pyridostigmine reduces the breakdown of ACh in the synaptic cleft, thereby increasing its availability for binding to the remaining functional receptors and improving neuromuscular transmission, ultimately alleviating muscle weakness.

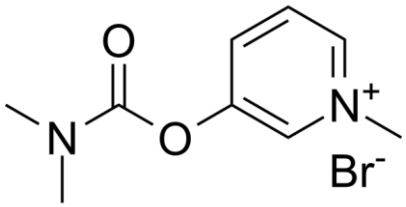
Traditionally, pyridostigmine bromide is administered orally in the form of tablets or syrup. However, patients with MG, particularly those with bulbar muscle weakness affecting swallowing, may experience difficulties in ingesting these conventional formulations. This can lead to inconsistent medication adherence and potentially compromise treatment efficacy.

To address this challenge, orodispersible tablets (ODTs) offer a promising alternative. ODTs are solid dosage forms designed to rapidly disintegrate or dissolve in the mouth within seconds, eliminating the need for water. This unique characteristic provides several advantages:

1. **Ease of Administration:** ODTs are particularly beneficial for patients with swallowing difficulties, the elderly, and those who may have trouble handling conventional tablets.
2. **Rapid Onset of Action:** The disintegration of ODTs in the mouth allows for faster drug absorption compared to tablets that require swallowing and subsequent disintegration in the gastrointestinal tract.
3. **Enhanced Patient Compliance:** The convenience and ease of use of ODTs can significantly improve medication adherence, especially for patients with chronic conditions like M.

This research aims to develop and evaluate an ODT formulation of pyridostigmine bromide. By leveraging the advantages of ODT technology, this formulation aims to improve the management of MG, particularly for patients with swallowing difficulties. The study will involve the formulation of ODTs using suitable excipients and superdisintegrants, followed by a comprehensive evaluation of their physicochemical properties and in vitro drug release characteristics. The findings of this research are expected to provide valuable insights into the feasibility and potential benefits of an ODT formulation of pyridostigmine bromide for patients with MG.

Drug profile-

Drug name	Pyridostigmine bromide
Indication	Pyridostigmine is commonly used to treat myasthenia gravis.
Mechanism of action	works by inhibiting acetylcholinesterase, the enzyme that breaks down acetylcholine, thus increasing the availability of acetylcholine at the neuromuscular junction and enhancing nerve impulse transmission to improve muscle strength
Chemical name	(1-methylpyridin-1-ium-3-yl) *N*,*N*-dimethylcarbamate;bromide
Chemical Structure	
Route of administration	Oral administration is effective.

Interaction	There are no known interactions between pyridostigmine and foods or drinks. It is unknown if drinking alcohol will affect pyridostigmine.
Side Effect	Pyridostigmine may cause allergic reactions, which can be serious. Breathing problems or wheezing, Racing heart, Fever or general ill feeling, Swollen lymph nodes, Swelling of the face, lips, mouth, tongue, or throat

3. MATERIAL AND METHOD:

Materials- Pyridostigmine bromide was obtained as a gift sample from Festiva Pharma, Gujrat and other all excipient obtained from Shivajirao Pawar College of Pharmacy, Newasa.

- Pyridostigmine bromide (Active Pharmaceutical Ingredient)
- Microcrystalline cellulose (MCC)
- Mannitol
- Crospovidone (CP)
- Sodium starch glycolate (SSG)
- Croscarmellose sodium (CCS)
- Aspartame (Sweetener)
- Mint flavor
- Magnesium stearate (Lubricant)
- Talc (Glidant)

3.1. Formulation of Orodispersible Tablets:

Pyridostigmine bromide ODTs were prepared by the direct compression method. The composition of different formulations (F1-F5) is shown in Table 1.

Table 1. Composition of Orodispersible Tablets

Ingredient	F1	F2	F3	F4	F5
Pyridostigmine Bromide	60	60	60	60	60
MCC	65	55	70	60	50
Mannitol	40	40	40	40	40
Crospovidone (CP)	-	-	5	10	15
Sodium Starch Glycolate (SSG)	25	35	5	10	15
Croscarmellose Sodium (CCS)	-	-	10	20	30
Aspartame	3	3	3	3	3
Mint Flavor	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3
Talc	2	2	2	2	2
Total Weight (mg)	200	200	200	200	200

Procedure:

1. Pyridostigmine bromide, MCC, mannitol, and the respective superdisintegrant (crospovidone, sodium starch glycolate, or croscarmellose sodium) were accurately weighed and passed through a #60 mesh sieve.
2. Aspartame and mint flavor were added and mixed uniformly.
3. Magnesium stearate and talc (previously passed through a #80 mesh sieve) were added as lubricant and glidant, respectively, and mixed gently for 2-3 minutes.
4. The powder blend was directly compressed into flat-faced tablets of 200 mg weight using a manual compression machine. A batch size of 10 tablets was prepared for each formulation.

3.1. Evaluation of Orodispersible Tablets:

The prepared ODTs were evaluated for the following parameters:

- **Physical Appearance:** Tablets were visually inspected for their shape, size, color, and surface defects.
- **Weight Variation:** Twenty tablets were randomly selected from each batch and their individual weights were recorded using an analytical balance. The average weight and percentage weight variation were calculated. The percentage deviation of each tablet weight should be within ±7.5% of the average weight.
- **Hardness:** The hardness of ten tablets from each batch was determined using a monsanto hardness tester. The average hardness was calculated and expressed in Kiloponds (Kp) or Newtons (N).
- **Friability:** Twenty tablets were accurately weighed and placed in a friability tester. The apparatus was operated at 25 rpm for 4 minutes (100 rotations). After the test, the tablets were dedusted and reweighed. The percentage friability was calculated using the formula:

  Friability (%) = [(Initial weight - Final weight) / Initial weight] × 100

  A friability value of less than 1% is generally considered acceptable.
- **Wetting Time:** The wetting time was determined by placing a tablet on a folded tissue paper placed in a Petri dish containing 6 ml of distilled water containing a water-soluble dye (methylene blue). The time taken for the water to completely wet the tablet surface was recorded. The test was performed in triplicate for each formulation.
- **In-vitro Disintegration Time:** The in-vitro disintegration time was determined using a disintegration test apparatus as per USP specifications, but without the use of a disc. Six tablets from each batch were placed individually in the tubes of the apparatus containing 10 ml of phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C. The time taken for the complete disintegration of the tablet into fine particles with no palpable mass remaining on the screen was recorded.
- **Drug Content Uniformity:** Ten tablets were randomly selected from each batch, individually powdered, and dissolved in a suitable volume of phosphate buffer (pH 6.8). The solution was filtered, and the drug content was analyzed spectrophotometrically at a predetermined λmax using a validated UV-Vis spectrophotometer. The average drug content and percentage deviation were calculated. The drug content should be within 85% to 115% of the labeled amount, with a relative standard deviation of not more than 6%.
- **In-vitro Dissolution Study:** The in-vitro dissolution study was carried out using a USP Type II dissolution apparatus (paddle method). The dissolution medium was 900 ml of phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C and stirred at a speed of 50 rpm. Samples (5 ml) were withdrawn at predetermined time intervals (5, 10, and 15 minutes), filtered through a 0.45 µm membrane filter, and analyzed spectrophotometrically at the predetermined λmax. The volume of the dissolution medium was maintained by replacing the withdrawn samples with fresh medium. The percentage drug release was calculated at each time point.
- **Stability Studies:** The optimized formulation was subjected to accelerated stability studies as per ICH guidelines. Tablets were packed in airtight containers and stored at 40 ± 2 °C and 75 ± 5% RH for a period of 15 days. At the end of each time point, the tablets were evaluated for physical appearance, drug content, disintegration time, and dissolution profile.

4. RESULT AND DISCUSSION:

4.1. Physical Properties of Tablets: All the prepared formulations exhibited acceptable physical appearance with uniform shape and color. The average weight of the tablets was found to be within the pharmacopoeial limits, indicating uniformity in tablet weight. The hardness of the tablets ranged 5-6 Kp, which was sufficient for handling and packaging. The friability values for all formulations were below 1%, indicating good mechanical strength and resistance to abrasion during handling.

Table 2: Physical Properties of Pyridostigmine Bromide Orodispersible Tablets.

Formulation	Average Weight (mg)	Weight Variation (%)	Hardness (Kp)	Friability (%)
F1	198	6.95%	5.2	0.012
F2	199	3.76%	5.6	0.030
F3	200.5	5.25%	5.3	0.100
F4	198.5	4.89%	5.7	0.024
F5	200	3.15%	5.1	0.063

4.2. Wetting Time and In-vitro Disintegration Time:

The wetting time and in-vitro disintegration time for different formulations are presented in Table 3.

Table 3: Wetting Time and In-vitro Disintegration Time of Pyridostigmine Bromide Orodispersible Tablets.

Formulation	Wetting Time (s)	In-vitro Disintegration Time (s)
F1	40 ± 0.5	189 ± 2.5
F2	55 ± 0.5	196 ± 2.5
F3	41 ± 0.5	190 ± 2.5
F4	32 ± 0.5	201 ± 2.5
F5	45 ± 0.5	188 ± 2.5

4.3. Drug Content Uniformity:

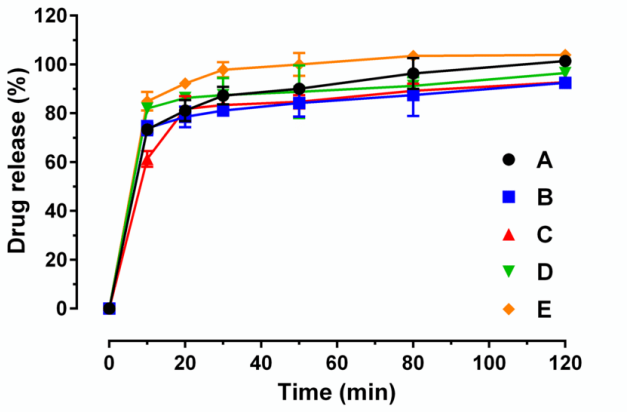
The drug content analysis revealed that all the formulations contained pyridostigmine bromide within the acceptable limits of 85% to 115% of the labeled amount. The percentage drug content for all batches ranged from 81% - 96 % with a relative standard deviation of less than 75%, indicating good drug content uniformity.

Table 4: Drug Content Uniformity of Pyridostigmine Bromide Orodispersible Tablets.

Formulation	Drug Content (%)
F1	96
F2	83
F3	81
F4	90
F5	95

4.4. In-vitro Dissolution Study:

The in-vitro dissolution profiles of the prepared formulations are shown in Figure 1. The % drug release at different time intervals is presented in Table



5.

Fig 2. In-vitro Dissolution Profiles of Pyridostigmine Bromide Orodispersible Tablets (F1-F5) in Phosphate Buffer (pH 6.8)

Table 5: Percentage Drug Release of Pyridostigmine Bromide from Orodispersible Tablets at Different Time Intervals.

Time (min)	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)
1	1	1.5	1.7	1.1	1
2	5.6	5.1	6	6.1	5.8
3	9.4	8.9	10	9.6	9.5
5	12	14	16	12.9	13.6
10	45.5	48	42	44.9	45
15	65.4	68.3	66	65.1	67

5. CONCLUSION:

The present study successfully formulated and evaluated orodispersible tablets of pyridostigmine bromide using the direct compression method. The incorporation of different superdisintegrants, namely crospovidone, sodium starch glycolate, and croscarmellose sodium, at varying concentrations significantly influenced the disintegration characteristics of the tablets. Formulations containing higher concentrations of superdisintegrants generally exhibited faster wetting and in-vitro disintegration times. All the prepared formulations met the pharmacopoeial requirements for weight variation, hardness, friability, and drug content uniformity, indicating acceptable physical properties and consistent drug distribution. The in-vitro dissolution studies revealed that the optimized formulation also exhibited rapid drug release, with a significant percentage of pyridostigmine bromide dissolved within the initial few minutes, suggesting the potential for faster onset of action compared to conventional tablets. The accelerated stability studies conducted on the optimized formulation showed no significant changes in physical appearance, drug content, disintegration time, and dissolution profile over the studied period, indicating the stability of the formulation under accelerated storage conditions.

In conclusion, this research demonstrates the feasibility of formulating pyridostigmine bromide into orodispersible tablets with rapid disintegration and dissolution characteristics. The optimized formulation offers a promising alternative to conventional tablets, potentially improving patient compliance, particularly in individuals with dysphagia associated with myasthenia gravis, and may contribute to a faster therapeutic response. Further in-vivo studies are warranted to evaluate the bioavailability and clinical efficacy of the developed pyridostigmine bromide ODTs in myasthenia gravis patients.

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