

**Original Article**

**DESIGNING AND EVALUATION OF FLURBIPROFEN SODIUM SUPPOSITORIES**

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**ABSTRACT**

**Objective:** The present investigation was aimed to develop Flurbiprofen Sodium suppositories by using different suppository bases with a view to avoid loss of drug by first pass effect and to minimize toxic effects, thereby producing safe and effective dosage form which will improve the solubility and absorbability of poorly soluble drug.

**Methods:** Fusion method was used for the preparation of suppositories. Pre formulation studies of the drug was done by determining its physical appearance, melting point, IR spectrum, UV spectrum and solubility studies of Flurbiprofen sodium were carried out in different Solvents.

**Results:** Melting point of Flurbiprofen sodium was found to be in the range 114 °C-117 °C. UV spectrum of Flurbiprofen sodium in ethanol at pH7.4 was determined at 273 nm. Calibration curve of Flurbiprofen sodium in pH 6.4 phosphate buffer were constructed in the concentration range of 0-20 µg/ml. The prepared suppositories of each batch was evaluated for their physio-chemical properties like weight variation, Hardness, Friability, length and width, melting point, breaking strength, disintegration test, content uniformity, *in vitro* drug release and stability studies. The prepared suppositories were smooth and fine in texture with mechanical strength (hardness) i.e. can tolerate less than 5.0 kg. The friability was found to be within acceptable limits (less than 1%).

**Conclusion:** Suppositories were successfully formulated and evaluated. The type of base employed for the preparation of suppositories influenced the release of the drug during the dissolution studies. They can be arranged in order of release rate as-PEG 4000>PEG 6000>Cocoa butter. The use of Sodium lauryl sulphate also influenced the release rate of the drug and the release rate patterns of all formulations.

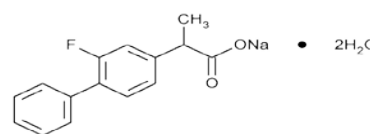
**Keywords:** Cocoa butter, Flurbiprofen sodium, *In vitro* release study, PEG 4000 and 6000, Rectal dosage form, Suppository

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**INTRODUCTION**

The rectal route is commonly used as an alternative when oral administration is inconvenient because of the inability to swallow or because of gastrointestinal side effects such as nausea, vomiting and irritation [1]. More important, rectal drug administration has the advantage of minimizing or avoiding hepatic first-pass metabolism [2]. Therefore the potential for oral dosage form development is severely limited for active agents that are poorly absorbed in the upper gastrointestinal tract and unstable to proteolytic enzymes. It's well known that the rectal route can deliver 60%-70% of the administration drug directly into systemic circulation. The lymphatic circulation also helps in absorbing a rectally administered drug from liver. The most common dosage form used for drug administration via rectal route is solid suppositories [3]. Flurbiprofen is an NSAID having prominent anti-inflammatory, analgesic and antipyretic properties. Flurbiprofen is an arylpropionic acid derivative. Similar to other NSAIDs Flurbiprofen also exerts its therapeutic effects largely by its ability to inhibit the biosynthesis of prostaglandins in all cells through inhibition of cyclooxygenase, thus inhibiting the gastro-protective prostaglandin's, which leads to gastric intolerance. Absorption after rectal doses may be more rapid. It is about 99 % bound to plasma proteins and has a plasma half-life of about 3 to 6 h. It is extensively metabolized mainly by hydroxylation. Minor symptoms of ocular irritation including transient burning and stinging, have been reported following the instillation of Flurbiprofen Sodium eye drops; there may be increased bleeding from ocular surgery and wound healing may be delayed. Local irritation may also follow rectal use and local effects including a sensation of Flurbiprofen lozenges. A sensation of warming, transient burning sensation, local irritation, in conjunction with surgery there is an increase in the bleeding tendency of ocular tissue. It is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in soft-tissue disorders such as sprains and strains, for postoperative pain, in mild to moderate pain including dysmenorrhoea and migraine,

as lozenges in the symptomatic relief of sore throat, in eye drops to inhibit intra-operative miosis and to control postoperative inflammation of the anterior segment of the eye [4-7].



**Fig. 1: Chemical structure of flurbiprofen sodium**

The objective of the study is to develop suppository of Flurbiprofen Sodium by using a different type of suppository bases with a view to avoid loss of drug due to first pass effect and to minimize toxic effects and produce safe and effective dosage form, which will improve the solubility and absorbability of the poorly soluble drug.

**MATERIALS AND METHODS**

**Materials**

Flurbiprofen Sodium, Glycerine, PEG 400, PEG 4000, PEG 6000, Cocoa butter, Menthol, HCl, Monobasic sodium phosphate, Dibasic sodium phosphate and Sodium lauryl sulphate were used for the preparation of suppositories. For analytical testing UV Spectrophotometer, IR Spectrophotometer, Tablet dissolution tester USP (XXIII), Suppository mould, Hardness Tester, Friabilator USP EF-2 were used.

**Methods**

**Preformulation studies**

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an

investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

#### Identification

Identification of Flurbiprofen Sodium was carried out by Infra-Red Absorption Spectrophotometry.

#### Melting point determination

Melting point was determined according to the USP pharmacopeia using a capillary tube with close end filled with Flurbiprofen Sodium to measure the melting point using an electrical melting point apparatus, where the melting point was recorded [8, 9].

#### Solubility studies

The solubility of Flurbiprofen Sodium was determined in distilled water, in various organic solvents and aq. Solution of alkali hydroxide and carbonates.

#### UV spectroscopy

The first step in preformulation is to establish a simple analytical method so that all future measurements can be quantitative. Most drugs absorb light in the ultraviolet wavelengths (190-390 nm) region, since they are generally aromatic or contain double bonds. Twenty-five milligrams of Flurbiprofen Sodium was dissolved in a 100 ml ethanol to prepare a 0.25 mg/ml stock solution. From this stock solution, 4 ml were transferred to 100 ml volumetric flask and diluted with phosphate buffer solution of 7.4 pH, then scanned by the UV spectrophotometer at the range of 200-400 nm, in order to determine the wavelength of the maximum absorbance ( $\lambda_{max}$ ) of Flurbiprofen Sodium [10].

#### Preparation of suppositories

Suppositories of Flurbiprofen Sodium were prepared by fusion method employing PEG 4000, PEG 6000 and cocoa butter as suppository bases, PEG 400 as a plasticizer and sodium lauryl

sulphate as a surfactant. The suppositories bases were accurately weighed and melted on water bath. Finely divided drug powder was thoroughly incorporated in the melted base with continuous stirring. The melted mass was poured in the appropriate suppository mould (0.9 gm). Suppositories were kept in refrigerator, at 4 °C to avoid the development of cracks [11] and the exposure to room temperature was limited to less than 24h before use in *in vitro* release studies. The details of the formulations are given in table 1.

#### Evaluation of suppositories

Every batch of suppositories manufactured or formulated must be tested to ensure that the required standards are met or not. The suppository containing medicaments in each batch should be evaluated for the following:

#### Visual characterization

The randomly selected suppositories (six suppositories from each batch) were cut longitudinally and examined with the naked eye (subjective evaluation) to assess the verified homogeneity of surface appearance and color of suppositories by

- Absence of fissuring.
- Absence of pitting.
- Absence of fat blooming.
- Absence of exudation.
- Absence of migration of the active ingredients.

This last test is best accomplished by taking a longitudinal section of the suppository to verify the homogeneity of the active ingredient(s) within the mass [6, 12].

#### Length and width

The width and length of the randomly selected suppositories (six suppositories from each batch) were measured for their physical dimension. After that, the same number of suppositories were selected and cut longitudinally and the surface was examined with the naked eye (subjective evaluation) for homogeneity.

Table 1: Code and composition of formulations

Composition		F1	F2	F3	F4	F5	F6
Bases (%) (Based on mould capacity)	PEG 4000	60	-	-	60	-	-
	PEG 6000	-	60	-	-	60	-
	Cocoa butter	-	-	60	-	-	60
Drug(mg)	Flurbiprofensodium	100	100	100	100	100	100
Plasticizer (%)	PEG 400	30	30	30	30	30	30
Surfactant (%)	SLS	-	-	-	0.25	0.25	0.25

#### Mechanical strength (Hardness)

The physical characteristic, such as mechanical strength (hardness test) was determined. The hardness of a cylindrical portion (9.6 mm thickness) of the suppository, which was obtained by cutting the middle portion of the suppository, was measured in its diameter direction with a Monsanto hardness tester [9].

#### Uniformity of weight (Weight variation)

Twenty suppositories were weighed and the average weight was calculated. Each suppository was then individually weighed by using a digital balance. Not more than 2 of the individual masses deviate from the average mass by more than 5%, and non-deviate by more than twice that %.

#### Friability

Twenty suppositories were weighted and placed in the plastic chamber of Roches Friabilator. The chamber was then rotated for 4 min at 25 rpm (a total of 100 revolutions). During each revolution, suppositories fall from a distance of 6 inches. After 100 revolutions, the suppositories were removed and weighed again.

$$\text{Friability (\%)} = \frac{W_i - W_f}{W_i} \times 100$$

Where  $W_i$  was the initial weight of the suppositories before friability testing,  $W_f$  was the weight of suppositories after the testing [3, 9].

#### Melting point

The melting time is a critical factor in the determination of the release rate of the active ingredient(s) from the suppository. This test is also known as macro melting range test. During this test, the time taken for the entire suppository to melt or disperse is measured when immersed in a water bath maintained at a constant temperature (37 °C ± 1 °C). The time required for the whole suppository to melt or disperse in the surrounding water was noted.

#### Breaking strength

The breaking strength or crushing strength was determined for measuring the fragility or brittleness of suppositories, which assess whether the suppositories will be able to withstand the hazards of packing, transporting and normal handling or not. A plastic disc was fixed horizontally on to one end of the iron rod to which weight are

applied and other end had been reduced to sharp point. The sample suppository was placed between the metal plate and the sharp end of the iron rod and placing 600 g weights on to the pan. After 1 min time intervals, 200 g weights are added, and the weight at which the suppository collapses in the breaking point, or the force that determined the fragility of brittleness characterization of the suppositories [8, 9].

#### Liquefaction or softening time

This important element indicates the physical behavior of a suppository subjected to its maximum functional temperature (37 °C). It consists of a U-tube partially submerged in a constant-temperature water bath. A constriction on one side holds the suppository in place in the tube. An iron rod is placed on the top of the suppository and the time for the rod to pass through to the constriction is recorded as the "softening time". This can be carried out at various temperatures from 35.5 to 37 °C, as a quality control check and can also be studied as a measure of physical stability over time. The softening test measures the liquefaction time of rectal suppositories. In this, to measure the time necessary for a suppository to liquefy under pressure similar to those found in the rectum in the presence of phosphate buffer pH 7.4 (5.0 ml) surrounding the water at body temperature.

#### Disintegration time

Disintegration time (D. T.) is the test carried out to measure the time taken for the entire suppository to melt, dissolve or disintegrate in the medium used at constant temperature and speed. Here tablet dissolution tester apparatus type 1 (basket type) is used and the time taken by the suppository to disintegrate completely and go into solution is observed. The medium used is pH7.4 phosphate buffer containing 2% Tween 80. The temperature was kept constant at 37 °C±0.5 °C and the speed at 50 rpm. The observations are shown in the table 3.

#### Drug content evaluation

Content uniformity test was determined by spectrophotometric method. The suppository was individually melted, subsequently

dissolved in phosphate buffer pH 6.8. After necessary dilutions the solutions were subjected to UV spectroscopy (Shimadzu UV1800) at 273 nm wavelength. The observations are shown in the table 4.

#### Dissolution rate studies

The USP basket method was employed for all the *in vitro* dissolution studies (USP-XXVI, Veeco Scientific, Mumbai). In this method 900 ml of Phosphate buffer solution pH 7.4 was used as the dissolution medium. The rate of stirring was 100 rpm. The suppositories were placed in basket and the temperature of the dissolution medium was maintained at 37°C±1°C for a period of 220 minute. All different time intervals 5 ml of the sample was taken and filtered. The dissolution medium was replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. The samples were filtered through 0.45 m membrane diluted suitably and assayed at 247 nm using an UV visible spectrophotometer (Thermospectronic UV-1).

#### Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order ( $Q$  v/s  $t$ ), first-order [ $\text{Log}(Q_0-Q)$  v/s  $t$ ], Higuchi's square root of time ( $Q$  v/s  $t^{1/2}$ ) and Korsmeyer peppas double log plot ( $\text{log } Q$  v/s  $\text{log } t$ ) respectively, where  $Q$  is the cumulative percentage of drug released at time  $t$  and  $(Q_0-Q)$  is the cumulative percentage of drug remaining after time  $t$ . [3, 8, 9, 12].

#### RESULTS AND DISCUSSION

Suppositories were formulated by fusion method and evaluated for their physicochemical characterization followed by *in vitro* evaluation through spectrophotometrically. The formulations were designed to overcome the gastric irritation of flurbiprofen and to prevent hepatic first-pass metabolism after oral administration. Suppositories are dosage forms for use in unavoidable circumstances such as comatose, nauseous or vomiting. The physical appearance was determined by visual examination; details are mention in table 2.

Table 2: Physical appearance of the drug flurbiprofen sodium

S. No.	Properties	Observation
1	Appearance	White crystalline powder
2	Physical State	Solid
3	Form	Powder
4	Taste	Slightly bitter
5	Odor	Practically Odorless

The flurbiprofen sodium drug was identified using IR spectrum and it was found to be similar to the standard spectrum of flurbiprofen sodium fig. 2. Melting point of flurbiprofen sodium was determined by capillary method. The melting point of flurbiprofen sodium was found to be in the range 114 °C to 117 °C, which complied with IP standards thus indicating purity of the drug sample. Suppositories of flurbiprofen sodium were prepared by fusion method employing different bases such as PEG 4000, PEG 6000 and cocoa butter, plasticizer such as PEG 400 and surfactant such as SLS. The results of visual and physicochemical characterization are shown in table 3 and 4. All the formulations were found to have homogeneous drug distribution. The width and length of the randomly selected suppositories was found to be uniform. The formulated rectal suppositories were smooth and fine in Texture with mechanical strength i.e. can tolerate less than 5.0 kg. The friability was found to be within acceptable limits (less than 1%).

With respect to melting range, the suppositories or different bases containing flurbiprofen sodium can be arranged in the order of PEG 4000>PEG 6000>cocoa butter. All the formulations were found to have sufficient mechanical strength to withstand abrasive forces causing disintegration of drug-loaded formulation. All the

formulated batches of suppositories showed to disintegrated within 30 min, which comply with the standards.

The drug content of all the formulations was determined spectrophotometrically at 273 nm. it was found to be in range from 95.23% to 98.98%, which is within the acceptable limits. Percentage cumulative drug release from suppositories of F3, F2, F1, F6, F5 and F4 were found to be 64.10, 68.85, 71.15, 73.57, 78.82 and 83.84 %, respectively at the end of 220 min. It was found that the PEG 4000 base containing SLS should have maximum release of flurbiprofen sodium from suppositories followed by PEG 4000, PEG 6000 and cocoa butter simple and containing SLS with PEG 6000 and cocoa butter. PEG base are water soluble; hence, they are dissolved more rapidly, releasing the drug into the dissolution medium and used of SLS showed to help for enhanced the release rate of formulation. On the other hand, the hydrophobic nature of drug and its high affinity for the fatty base (cocoa butter), the release rate from this baseless. This may be due to two reasons. Firstly though the cocoa butter can melt easily at 37 °C (melting range 33.5-35 °C). It may not readily disperse the drug throughout the dissolution medium because of high affinity of the drug towards the fatty base and secondly, drug partitioning may not be favored into aqueous medium of pH 7.4.

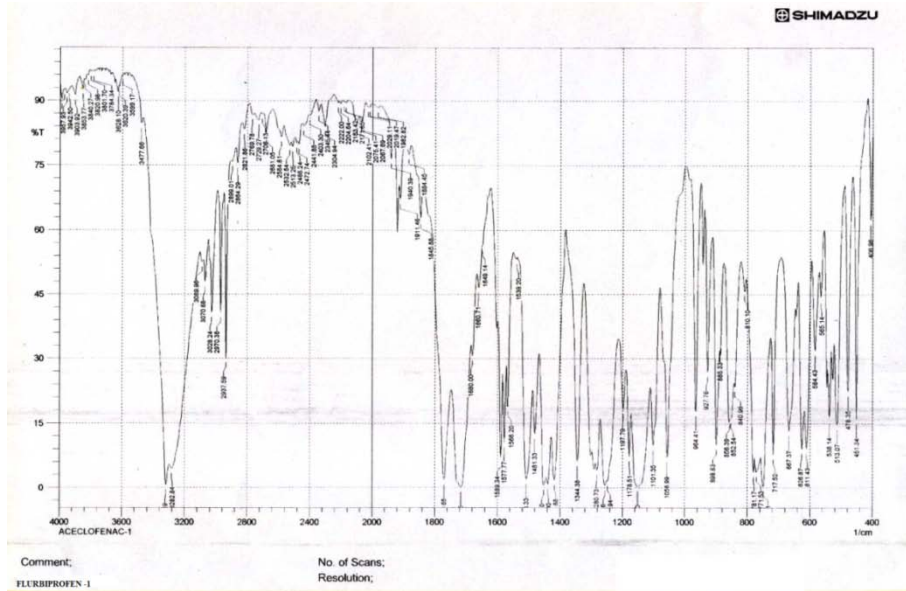


Fig. 2: IR spectrum of flurbiprofen sodium

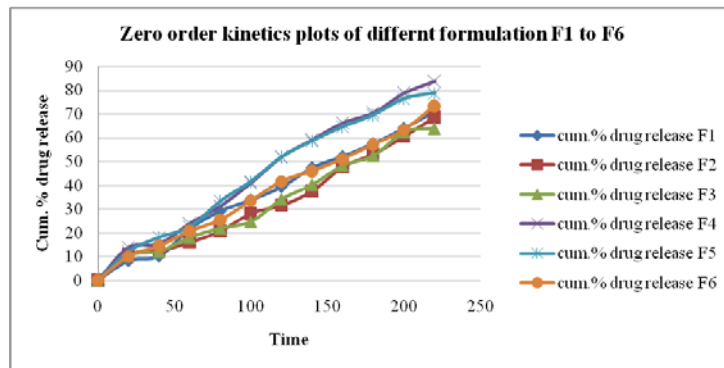


Fig. 3: Zero order drug release profile

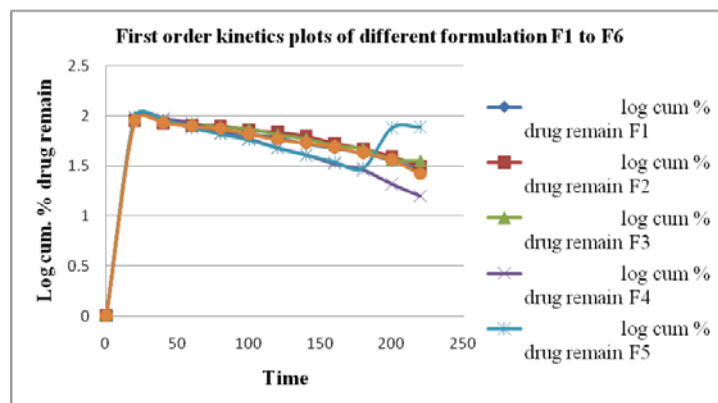


Fig. 4: First order drug release profile

Table 3: Physical characterization of formulations

Formulations	F1	F2	F3	F4	F5	F6
Color and appearance	White and opaque	White and opaque	Creamy (off-white) and opaque	White and opaque	White and opaque	Creamy (off-white) and opaque
Surface texture	Smooth	Smooth	Smooth and slightly sticky	Smooth	Smooth	Smooth and slightly sticky
Fissuring	No	No	No	No	No	No
Pitting	No	No	No	No	No	No
Exudation	No	No	No	No	No	No
Migration of active ingredients	No	No	No	No	No	No

Table 4: Physio-chemical characterizations of formulated suppositories

Formulation	F1	F2	F3	F4	F5	F6
Length (cm)	2.18±0.007	2.18±0.006	2.18±0.003	2.18±0.004	2.18±0.006	2.18±0.006
Width (cm)	0.96±0.005	0.96±0.007	0.96±0.004	0.96±0.005	0.96±0.007	0.96±0.004
Hardness (kg/cm <sup>2</sup> )	3.9	3.2	1.5	3.9	3.5	1.5
Weight variation (mg)	1.4117±0.02	1.4395±0.017	1.1458±0.024	1.1427±0.2	1.4108±0.08	1.1419±0.02
Friability (%)	0.48±0.04	0.45±0.03	0.54±0.02	0.37±0.05	0.41±0.03	0.46±0.05
Melting time	40.5°C	43.0°C	36.7°C	40.5°C	44.5 °C	36.7°C
Breaking strength(gm)	855±10.488	765±10.954	335±13.78	750±12.649	848±8.1649	338±8.1649
Liquefaction time(min)	2:28±0:0408	3:35±0:879	1:58±0:0007	2:28±0:0408	3:33±0:7389	1:56±0:0071

## CONCLUSION

The type of base employed for the preparation of suppositories of Flurbiprofen Sodium, influenced the release of the drug during the dissolution studies and dependent upon the condition. They can be arranged in order of release rate as-PEG 4000>PEG 6000>Cocoa butter as well as used of SLS also influenced the release rate of drug and release rate patterns of all formulations can be arranged in following order-F4>F5>F6>F1>F2>F3. It would be better if the suppositories are prepared for sustained release of the drug for a longer period of time is desired with PEG bases, whereas suppositories prepared with cocoa butter would be a better choice for the fast-release action of drug.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICT OF INTERESTS

Declared none

## REFERENCES

- Robert EK. Dispensing of medication. 9<sup>th</sup> ed. Easton PA: Mack Publishing Company; 1984. p. 87-99.
- El Majri MA, Sharma RK. Formulation and evaluation of piroxicam suppositories. Int J Drug Delivery. 2010;2(2):108-12. doi: 10.5138/ijdd.2010.0975.0215.02019.
- Lachman L, Liberman HA, Kanig JL. The theory and practice of Industrial Pharmacy. 3<sup>rd</sup> ed. Bombay: Varghese Publishing House; 1987. p. 564-88.
- Brooks CD, Linet OI, Schellenberg D, Turner LF, Defesche CL, Teoh KW. Clinical safety of flurbiprofen. J Clin Pharmacol. 1990 Apr;30(4):342-51. doi: 10.1002/j.1552-4604.1990.tb03604.x, PMID 2187910.
- Devi PN, Bonthu S, Neerukonda V, Pasha SI, Poloju Deepthi AMD, Rajeev KM. Flurbiprofen microbeads for controlled release. Int J Pharm Chem Biol Sci. 2013;3(3):586-94.
- Varshney Himanshu M, Tanwar YS. Designing, release characteristics and *in vitro* evaluation of flurbiprofen sodium suppositories. Int J Pharm Clin Res. 2009;1(1):31-4.
- Barar FSK. Essentials of pharmacotherapeutics. S. Chand and company Ltd. New Delhi; 2003. p. 127.
- The United States pharmacopoeia (USP) 30. NF 25. The United States Pharmacopeia Convention Inc: USA; 2006. p. 276.
- Carter SJ. Cooper and Gunn's-dispensing for pharmaceutical students. 12<sup>th</sup> ed. CBS publishers and distributors. Delhi; 1987. p. 232-52.
- Pugunes S, Ugandar RE. Formulation and evaluation of natural palm oil-based diclofenac sodium suppositories. Int J Pharm Sci Res. 2013;4(2):617-21.
- Ibrahim SA, El-Faham TH, Tous SS, Mostafa EM. Formulation, release characteristics and evaluation of ibuprofen suppositories. International Journal of Pharmaceutics. 1990;61(1-2):1-7. doi: 10.1016/0378-5173(90)90037-5.
- Gulzar Md A, Venkatesh GK, Udupa N. Formulation and evaluation of compressed suppositories of indomethacin. Indian J Pharm Sci. 2000;62(3):196-9.