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Taste Masking: Formulation and Development of Rapidly Disintegrating Tablets of Phenytoin Sodium

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Abstract

Aim: To Formulate and Develop of Rapidly Disintegrating Tablets of Phenytoin Sodium Taste Masking. **Objective:** The current work was focused to Formulate develop and evaluation of Rapidly Disintegrating Tablets of Phenytoin Sodium as taste masking. **Methods:** The Rapidly Disintegrating Tablets of Phenytoin Sodium were prepared by dry granulation method and direct compression method. Pre formulation studies have been performed for the Active Pharmaceutical Ingredient. **Results**: Drug excipient compatibility studies have been performed and the tablets have been prepared in seven different formulations with the change in the ratios of excipients. These tablets are evaluated for various parameters including the release of drug by using dissolution studies. **Conclusion:** Hence the study resulted in the Formulation and Development of Rapidly Disintegrating Tablets of Phenytoin Sodium comparable to the innovator product for Phenytoin Sodium which is stable.

Keywords
Disintegrating Tablets, Phenytoin Sodium, Taste Masking.

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INTRODUCTION:

The undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for paediatric patients. [1] Masking of bitter taste of drugs is an important parameter for the improvement of patient compliance. [2] The problem of bitter and obnoxious taste of drug in paediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. [3]

Chemoreceptors on the Tongue

Taste is the brain's interpretation of chemicals that trigger receptors on the tongue, which are housed in the taste buds. Molecule interacts with taste receptor on the tongue to give taste sensation when they dissolve in saliva. This sensation is the result of signal transudation from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste. [4,5]

Ion exchange resin complexes

Ion-exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups attached to water insoluble polymer backbone. These groups have an ability to exchange [16] for oppositely charged counter ions, thus absorbing the ions into the polymer matrix. Since most drugs possess ionic sites in their molecule, the resin's charge provides a means to weak ionic bonding so that dissociation of the drug- resin complex does not occur under the salivary pH conditions, thus resulting in taste masking. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug. [11]

MATERIALS AND METHODS:

Materials:

Phenytoin Sodium were taken Gift Sample from Harman Finochem, Aurangabad. (India) Indion 454 were taken from Ion Exchange ltd, Mumbai and other ingredient like Magnesium stearate, Avicel PH 102 , Aspartame , Hydrochloric Acid , Sodium Hydroxide , Sodium Starch Glycolate and Croscarmellose sodium, Potassium Dihydrogen Phosphate were used analytical grade.

Methods:

Identification and Characterization of Phenytoin sodium

Ultraviolet Spectrum

The λ_{max} of Phenytoin sodium, in Phosphate buffer pH 6.8, 0.1N hydrochloric acid and in deionized water was observed at 220.5 nm, 220 nm and 220 nm respectively and reported value is 222 nm. Peaks are shown in Figure 1, 2 and 3 respectively.

Infrared absorption spectra

The IR spectrum of Phenytoin sodium was recorded by using KBr pellet method. The drug was triturated in porcelain mortar pestle with dry potassium bromide in ratio (1:100). The pellets were prepared in KBr press at a pressure of 8 tones. The pellet was scanned over the range of 4000-600 cm^{-1} in FTIR (Series 4000) Jasco and the spectrum was obtained. Spectra are shown in Figure 4.

Preparation of granules and rapidly disintegrating tablets

Resinate had excellent flow properties therefore dry mixing and compression method was selected for making tablets. The Resinate complex, Aspartame and Avicel PH 102 were sieved through sieve # 60. Except lubricant, all ingredients were mixed in polyethylene bag for 10 min. After 10 min mixing, lubricant was added and mixed for 3 min by manual shaking. Resulting powder blend was then used for making tablets by direct compression method. (Table 1)

Table 1: Tablet formula (A1 Formulation)

Sr. No.	Ingredient	Quantity/tablet	Use
1	Drug Resinate	257mg (equivalent to100mg of drug).	Active ingredient and Taste masking agent
2	Avicel PH102	123mg	Diluent
3	Magnesium stearate	8 mg (2%)	Lubricant
4	Aspartame	8 mg (2%)	Sweetener
5	Talc	4 mg (1%)	Glidant
	Total Weight of tablet	400 mg	

Preliminary batches of formulation of ODT

After successful taste masking by complexation with IER, it was required to formulate drug in ODT. Since resinate had excellent flow, it was mixed with various excipients and then compressed into tablet. Total often preliminary batches were taken for formulation of ODT. Formula for these batches are as follows.

Table 2: Preliminary batches of formulation of tablet

Formulation Code	Drug-Resinate complex(mg) (Equivalent to 100 mg of drug)	MCC PH102 (mg)	Mannitol (mg)	Magnesium stearate (mg) (2%)	Talc (mg) (1%)	Aspartame (mg) (2%)
A1	257	123	_	8	4	8
A2	257	_	119	8	4	8
A3	257	_	111	8	4	8
A4	257	_	103	8	4	8
A5	257	_	119	8	4	8
A6	257	_	111	8	4	8
A7	257	_	103	8	4	8
A8	257	_	119	8	4	8
A9	257	_	111	8	4	8
A10	257	_	103	8	4	8

- Table below shows disintegrant and the concentration of disintegrant added to the formulation batches A1 - A10. Different concentrations viz 1%, 3 % and 5 % of the disintegrants cross povidone, Sodium Starch glycolate, Croscarmellose Sodium were used in different formulation batches given below.

Table 3: concentration of disintegrant added to the formulation batches

Formulation Code	Disintegrant added	Conc of disintegrant
A1	Avicel	-
A2	Cross povidone	1%
A3	Cross povidone	3%
A4	Cross povidone	5%
A5	Sodium Starch glycolate (SSG)	1%
A6	SSG	3%
A7	SSG	5%
A8	Croscarmellose Sodium (CS)	1%
A9	CS	3%
A10	CS	5%

From the above 10 formulations, A1 formulation batch was selected and optimized for making of rapidly disintegrating tablets of phenytoin sodium. The A1 formulation batches has disintegrating time 8-10 sec without the addition of any disintegrants which is within the standard limit and is economical.

Evaluation of Tablets

Tablets were evaluated for following parameters:

Appearance

The appearance of a tablet involves the measurement of number of attributes such as a tablets size, shape, and color.

Hardness

A significant strength of rapidly disintegrating tablet is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of crushing strength for rapidly disintegrating tablets is usually kept in a lower range to facilitate early disintegration in the mouth.

Tablet crushing strength (F_c) or hardness, the force required to break a tablet in a diametric compression, it was measured using Monsanto tablet hardness tester. (Result is given in Table 5.)

Friability

The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. Friction and shock are the forces that most often cause tablets to chip, cap or break. Friability of the tablets was determined using Roche Friabilator. Usually it should be below 1%, an indication of good mechanical resistance of tablets.

Pre-weighed sample of tablets was placed in the friabilator and subjected to 100 revolutions (25 rpm). The tablets were de-dusted using a soft muslin cloth and reweighed. (Result is given in Table 5.)

The friability (f) is given by the formula,

$$f = 1 - (W/W0) \times 100$$

Where, W_o is the weight of the tablets before the test. W is the weight of the tablets after the test.

Determination of drug content in tablet

Method used for determination of drug content is given below: Tablet was weighed and crushed; powder was added in 50ml of 0.1N Hydrochloric acid. It was filtered through Whatmann filter paper (no.41), suitably diluted with 0.1N hydrochloric acid and kept for 3 hrs. and assayed at 220 nm, using a UV-Visible spectrophotometer.

Wetting time

Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablet is another important parameter, which needs to be assessed to give an insight into capillarity and subsequently the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet.

To determine wetting time a piece of tissue paper folded twice was placed in a small Petri dish (I.D = 10 cm) containing 10 ml of water at room temperature. A tablet was put on the
tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded in second.

***In vitro* disintegration test**

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration time of tablets was determined in conventional disintegration test apparatus in accordance with the official European Pharmacopoeia monograph 'Oro-dispersible tablets' stating a maximum disintegration time of 3 minutes. The *in vitro* disintegration time of a tablet was determined using USP disintegration test apparatus as per I.P. specifications without using disc.

To test disintegration time- one tablet is placed in each tube and the basket arch is positioned in a 1 liter beaker of water at $37^0C \pm 2^0C$.A standard motor driven device is used to move the basket assembly up and down. (Result is given in Table 5.)

In *vitro* drug release study

The Drug release from rapidly disintegrating tablet was carried out in 0.1 N HCl and buffer pH 6.8, Determination of cumulative drug release from tablet.

Taste evaluation

Evaluation of taste masking by panel method

Taste evaluation carried out on a taste panel of healthy volunteers with organoleptic sense, with their prior consent. On placing the drug resin complex in mouth for 60 seconds, bitterness recorded against pure drug using a numerical scale. The numerical scale bears values as 0 = Good, 1 = Tasteless, 2 = slightly bitter, 3= bitter, 4=Very bitter.

Evaluation of taste masking by U.V method

The release of the drug from the drug resin complex was studied in phosphate buffer pH 6.8 to determine the amount of drug that would be released in mouth during the administration of formulation. The bitterness of the drug was related with amount of drug released in the mouth. Resinate equivalent to drug dose was transferred to test tube containing 15 ml phosphate buffer pH 6.8 and shaken for 60 sec. It was filtered by whatman filter paper (no. 41) and analyzed by U.V at 220 nm to determine concentration of unbound drug. These concentrations were compared with the concentration of pure drug which was determined by U.V. method.

Determination of Drug Content in Complexes

Drug content in complexes was determined by taking weighed amount of complex equivalent to drug dose 100 mg in 0.1N HCl for 2 hrs. It was stirred, Filtered and filtrate was analyzed by UV method at wavelength 220 nm.

RESULTS AND DISCUSSION

Identification and Characterization of Phenytoin sodium

IDENTIFICATION OF PHENYTOIN SODIUM

Ultraviolet Spectrum

The λ_{max} of Phenytoin sodium, in Phosphate buffer pH 6.8, 0.1N hydrochloric acid and in deionized water was observed at 220.5 nm, 220 nm and 220 nm respectively and reported value is 222 nm. Peaks are shown in Figure 7, 8 and 9 respectively.

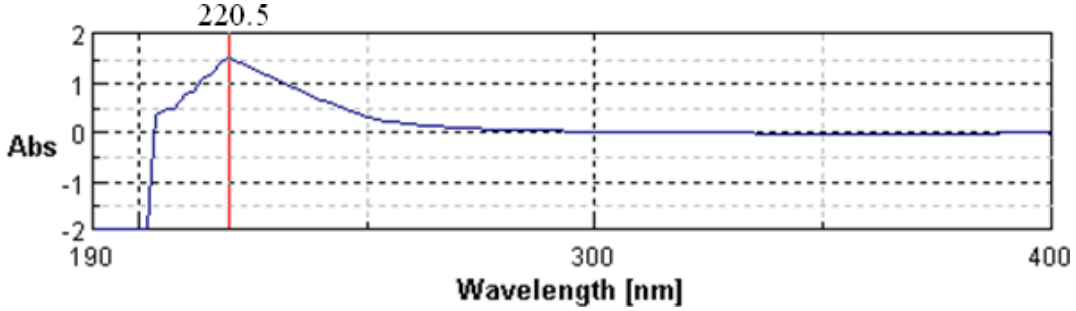

Figure 1: UV Spectrum of Phenytoin sodium in 0.1 N HCl

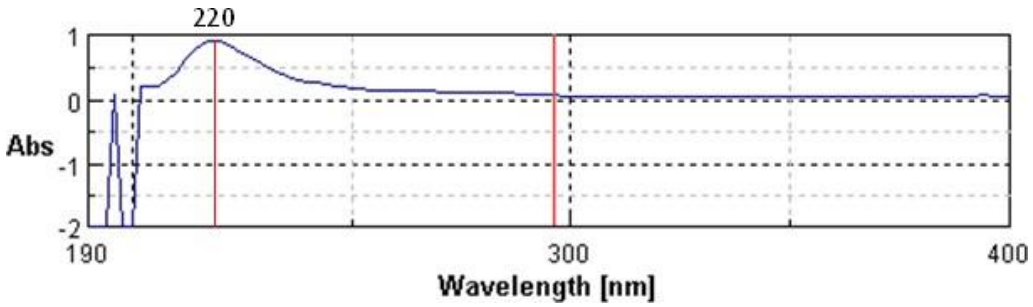

Figure 2: UV Spectrum of Phenytoin sodium in Phosphate Buffer pH 6.8

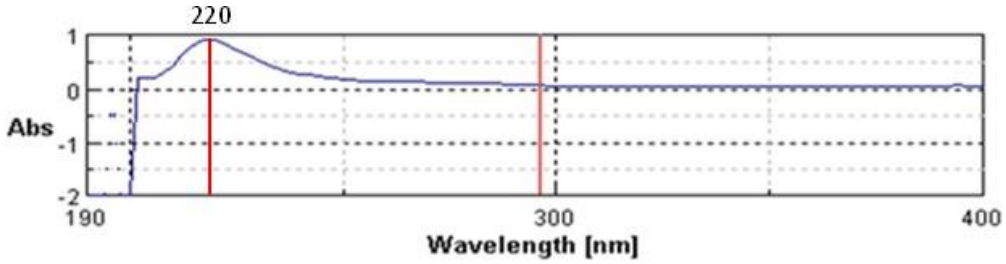

Figure 3: UV Spectrum of Phenytoin sodium in deionized water

Infrared Spectrum

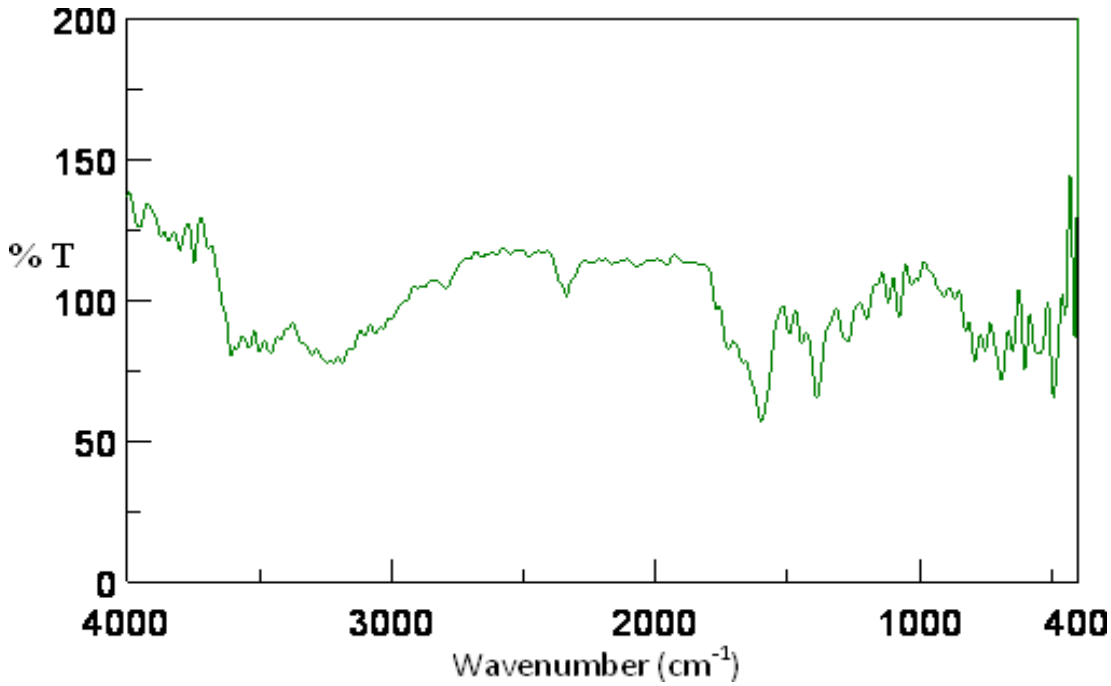

FIG 4: Infrared Spectrum of Phenytoin sodium

On the basis of UV spectrum, Infrared spectrum and DSC thermogram the procured sample of Phenytoin sodium was identified.

Identification and characterization of excipient
DSC study of Ion Exchange Resin Indion 454

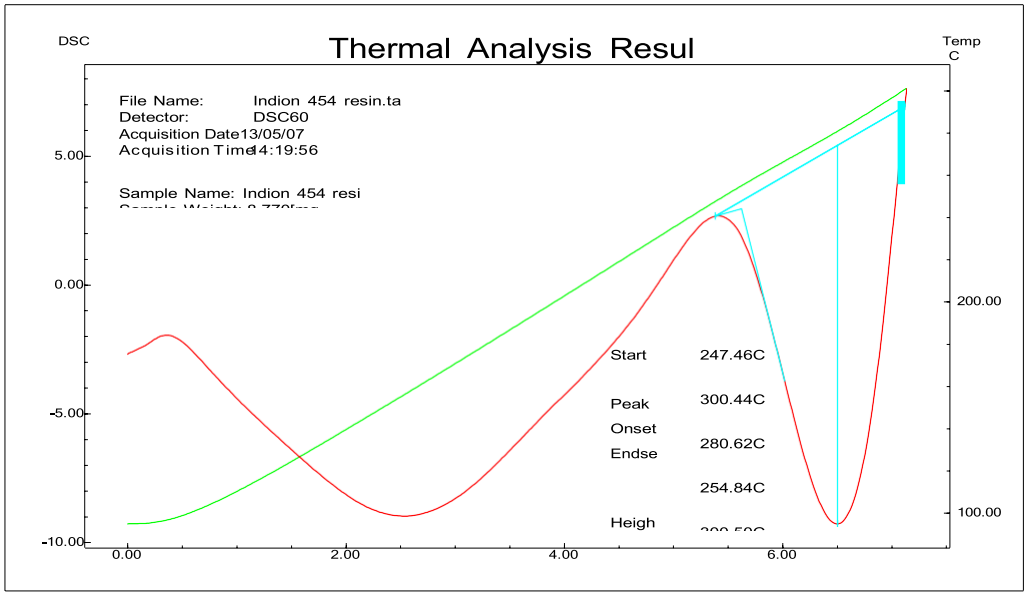

Figure 5: DSC of Resin Indion 454

DSC Thermogram of Ion Exchange resin Indion 454 showed one endothermic peak of fusion at 280.62° C.

Characterization of Phenytoin sodium

The physical characterization of drug was carried out and is reported in Table 4.

Table 4: Characterization of drug

Sr. No.	Test	Specification[44]	Result
1	Clour	White	Confirmed
2	Odour	Odourless	Confirmed
3	Melting point	290-299^{0}C	292^{0}C
4	Taste	Bitter	Confirmed
5	Hygroscopicity	-	5.5%
6	Loss on drying	-	2.3%
7	pH of 10% aqueous solution	10.0-12.3	11.6
8	Solubility	In Distilled water	21.56 mg/ml
		In 0.1NHCl	1.718 mg/ml
		In Phosphate Buffer pH 6.8	2.530 mg/ml
9	FT IR	-	Confirmed

Evaluation of Rapidly Disintegrating Tablets
Evaluation of Parameters

Various pharmacopoeias indicate various quality control tests for pharmaceutical tablets. The quality control tests performed on tablets showed following values.

Table 5: Evaluation of rapidly disintegrating Tablets

Sr. No.	Parameter	Result
1	Hardness	5.1±0.1 kg/cm^3
2	In vitro Disintegration time	11.03±1.60sec
3	Wetting time	8±1sec
4	Friability	0.72± 0.03%

The hardness of formulated batch was found to vary from 5.00 ± 0.1 kg/cm^2. According to compendial standards, the tablets comply with the friability test, as weight loss during the friability test was less than 1%. In addition, the tablets did not break or show any capping or cracking during the test. This indicated that the formulated tablets had good mechanical strength.

In wetting time study, it was observed that the tablet was fully hydrated before 10 seconds of contact with water and became soft throughout. Wetting time below 30 sec is important aspect for rapidly disintegrating tablet. To achieve percent friability within limits for a fast-disintegrating tablet was challenge to the formulator. The percent friability values for formulation batch were found to be within limit due to constant tablet press setting across all batches of design irrespective of weight variation.

The above formula showed good results in terms of friability, hardness, wetting time. Therefore, it was considered to be optimized formula. The tablets were further studied for drug release in various media & stability.

Drug Release of Tablet in Deionized Water

Taste Evaluation of Tablets by volunteers

The results for taste evaluation of rapidly disintegrating tablet by a panel of 5 healthy human volunteers are shown in Table 6. Volunteers reported response using mark scale which was constructed by formulator.

Two volunteers reported taste of rapidly disintegrating tablet (RDT) as good whereas 3 volunteers reported as tasteless. Moreover, all the volunteers experienced a good mouth feel of the rapidly disintegrating tablet of Phenytoin sodium - resinate. This shows that Phenytoin RDT has good palatability.

Table 6: Taste Masking Evaluation of Tablet by Volunteers

Sr. No.	Volunteer's code	Response by volunteer
1	A	1
2	B	0
3	C	1
4	D	1
5	E	0

Scale: 0= Good, 1= Tasteless, 2= Slightly Bitter, 3= Bitter, 4= Very Bitter

a. Stability Study of Rapidly Disintegrating Tablet

Stability results of final batch tablets are shown in Table 39.

Table 7: Stability study of Tablet

Duration / Parameter	1 Month	2 Month	3 Month
General Appearance	No change	No change	No change
Hardness (kg/cm^2)	5.0 ± 0.1kg/cm^2	5.03± 0.05kg/cm^2	5.02± 0.03kg/cm^2
Drug Content (%)	98.30± 1.0%	97.23± 0.29%	95.89± 1.30%
In vitro Disintegration time	12± 1sec	12-13± 0.57 sec	13± 1 sec
Taste of tablet	Acceptable	Acceptable	Acceptable
Drug release in 0.1N HCl at 60 min	84.11± 1.33%	82± 1.55%	81.32± 1.18%

Stability study was carried at 40^{0}C ± 2^{0}C/ 75% ± 5% RH for 3 months. Two-month stability data of rapidly disintegrating tablets reported with various parameters viz, general appearance, hardness, *In vitro* disintegration time, drug content, wetting time, taste of tablet, *In vitro* drug release.

Stability study of the tablets showed no significant drug loss or no significant changes in the mechanical strength of the tablets. It concluded that Rapidly Disintegrating Tablet are stable at 40^{0}C 75% RH for 3 months.

CONCLUSION:

Taste masking of bitter drugs has been a challenge to the scientist. We have tried to prepare and evaluated Rapidly Disintegrating Tablets of Phenytoin Sodium methods, which could be suitable for taste masking of bitter drug. There are number of technologies available which effectively mask the objectionable taste of drugs we used ion exchange resin method. The development of taste masking methodology is very well describing in this article.

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