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FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF PERAMPANEL IMMEDIATE RELEASE TABLETS

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ABSTRACT

The aim of the present study is to develop and evaluate the immediate release tablet of Perampanel by direct compression method. The superdisintegrant crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG) were used for immediate release of drug from tablet. The prepared tablets were evaluated for all pre-compression parameters and post-compression parameters. The drug excipients interaction was investigated by FTIR. All formulation showed compliances with Pharmacopoeial standards. The study reveals that formulations prepared by direct compression F3 exhibit highest dissolution using crospovidone showed faster drug release 99.13 % over the period of 45min.

INTRODUCTION

Oral route is the most convenient and extensively used for drug administration. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance suitable for industrial production, improved stability and bioavailability. The concept of immediate release tablets emerged from the desire to provide patient with more conventional means of taking their medication when emergency treatment is required. Recently, immediate release tablets have gained prominence of being new drug delivery systems. The oral route of administration has so far received the maximum attention with respect to research on physiological and drug constraints as well as design and testing of product, Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. Several orally disintegrating tablet (ODT) technologies based on direct compression. In pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation is at least 70% (preferably 80%) of active ingredient within 4 hours, such as within 3 hours, preferably 2 hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes) of administration. In Formulation of immediate release, the commonly Superdisintegrants used are Croscarmellose, sodium, Sodium Starch glycolate and Crospovidone.[1] Oral route of administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance.

Also, solid oral delivery systems does not need sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. There is requirement for new oral drug delivery system because of poor patient acceptance for invasive methods, requirement for investigation of new market for drugs and combined with high cost of disease management. Developing new drug delivery techniques and that utilizing in product development is critical for pharma companies to survive this century.[2,3,4]The term 'immediate release' pharmaceutical formulation is the formulation in which the rate of release of drug and/or the absorption of drug from the formulation, is neither appreciably, nor intentionally, retarded by galenic manipulations. Immediate release dosage form is those which break down quickly and get dissolved to release the medicaments. In the present case, immediate release may be provided of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not delay, to an appreciable extent, the rate of drug release and/or absorption.[5,6,7] Immediate release drug delivery is suitable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life. But main requirement for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat undesirable imperfection or disease.[8]

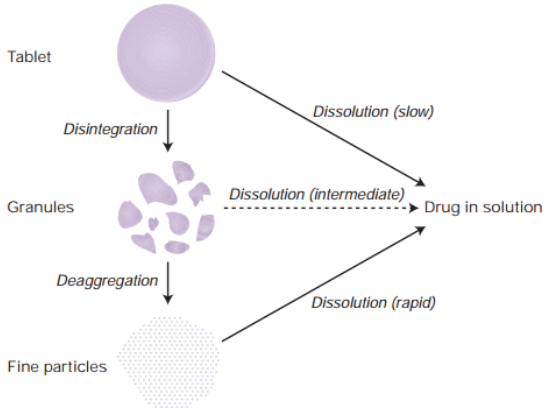


FIG-1. Drug release and dissolution process of an oral tablet

Desired Criteria for Immediate Release Drug Delivery System

Immediate release dosage form should in the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.

- ✓ In the case of liquid dosage form it should be compatible with taste masking.
- ✓ Have a pleasing mouth feel.
- ✓ No residue in the mouth after oral administration.
- ✓ Exhibit low sensitivity to environmental condition as humidity and temperature.
- ✓ Be manufactured using conventional processing and packaging equipment at low cost.
- ✓ Rapid dissolution and absorption of drug, which may produce rapid onset of action.

Merits:

- ✓ Unit dose system and Long shelf life.
- ✓ Cost effective.
- ✓ Improved stability, bioavailability.
- ✓ Accuracy and uniformity of drug content.
- ✓ More Economic and Ease of administration.
- ✓ Tastelessness and Elegance.
- ✓ Patient compliance.
- ✓ They are in general the easiest and cheapest to package.
- ✓ Optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use [15]

Demerits:

- ✓ Posses swallowing difficulty.
- ✓ Onset of action is slow and depends on disintegration and dissolution. Some drugs resist compression, due to their amorphous nature or low-density.
- ✓ Drugs having bitter taste, objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating of tablet Bioavailability problems.

MATERIALS:

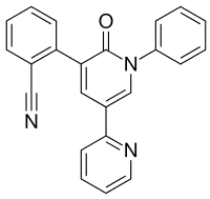
Chemicals: Perampanel, Crospovidone, Croscarmellose Sodium, Sodium starch glycolate, MCC, Mannitol, Aspartame, Mg stearate, Talc.

Drug Profile:

Perampanel

Chemical name/ Nomenclature / IUPAC Name: 2-{6'-oxo-1'-phenyl-1',6'-dihydro-[2,3'-bipyridine]-5'-yl} benzonitrile

Structure:



Mechanism of action: The exact mechanism of action of perampanel in seizures is not yet determined, but it is known that perampanel decreases neuronal excitation by non-competitive ihibition of the AMPA receptor.

Therapeutic efficacy/ Indications: Used in patients over 12 years old for the treatment of partial-onset seizures that may or may not occur with generalized seizures.

Adverse effects/Side effects: dizziness, somnolence, vertigo, aggression, anger, loss of coordination, blurred vision, irritability, and slurred speech.

METHODS:

Direct compression method is a novel approach in which drug materials and excipients are formed into tablets. It has the steps of blending and compression and there is no need for granulating the powder. This method does not involve pretreatment of active ingredients as required in granulation and physical nature of ingredients remain unchanged in direct compression.

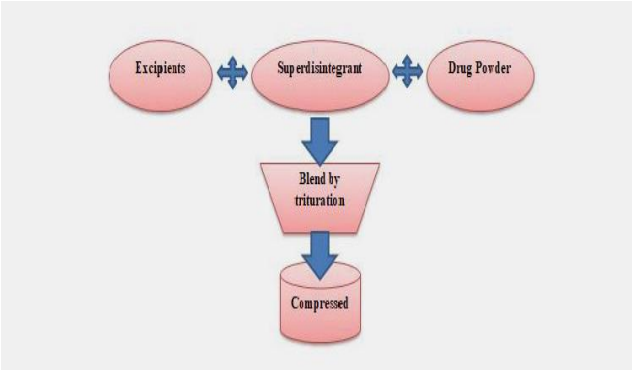


FIG-2. Steps involved in direct compression method

Buffer Preparation:

Preparation of 0.2M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm sodium hydroxide pellets were dissolved 10 1000ml of distilled water and mixed.

Preparation of pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium

Dihydrogen ortho phosphate and 112.5 ml 0.2M NaOH was taken into the 1000ml volumetric flask. Volume was made up to 1000ml with distilled water.

Pre formulation Studies

Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Analytical method development for Perampanel:

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λmax was found to be 227nm. Hence all further investigation were carried out at the same wavelength.

b) Preparation of Standard graph in pH 6.8 phosphate beffer

100 mg of Perampanel was dissolved in 100ml volumetric flask make upto 100ml of Phospatebeffer of pH 6.8., form primary stock 10ml was transferred to another volumetric flask made up to 100ml with Phosphate buffer of pH 6.8, from this secondary stock was taken separately and made up to 10 ml with Phosphate buffer of pH 6.8, to produce 2, 4, 6, 8 and 10µg/ml respectively. The absorbance was measured at 227 nm by using a UV spectrophotometer.

Formulation Development:

- Drug and different concentrations for super Disintegrates and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes.
- The obtained blend was lubricated with Magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes.
- The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Perampanel	2	2	2	2	2	2	2	2	2
Crospovidone	4	8	12	-	-	-	-	-	-
Crosscarmellose sodium	-	-	-	4	8	12	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	4	8	12
MCC	116	112	108	116	112	108	116	112	108
Mannitol	15	15	15	15	15	15	15	15	15
Aspartame	5	5	5	5	5	5	5	5	5
Mg stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total weight	150	150	150	150	150	150	150	150	150

Total weight of tablets = 150 mg

Table 1: Formulation of Immediate Release tablets.

The tablets were prepared by using 7mm flat surfaced punch. The hardness of the tablets was maintained as 3.0-3.9 kg/cm^2.

Evaluation parameters:

Pre compression parameters: 1. Angle of repose, 2. Bulk density, 3. Tapped density, 4. Compressibility Index, 5. Hauser's ratio were evaluated results were seen in Table 3.

Post compression parameters: a) Thickness, b) Weight variation, c) Friability, d) Assay, e) Disintegration test, f) Wetting Time, g) Water Absorption Ratio, h) *In vitro* dispersion time, i) Dissolution test of Perampanel tablets, j) Drug -Excipients compatibility studies were performed, results were seen in Table 4.

RESULTS AND DISCUSSION

Calibration curve of Perampanel :

The standard curve of Perampanel was obtained and good correlation was obtained with R^2 value of 0.998 the medium selected was pH 6.8 phosphate buffer.

Concentration (µg/ml)	Absorbance
0	0
2	0.124
4	0.251
6	0.371
8	0.472
10	0.594

Table 2: Standard graph values of Perampanel at 227 nm in pH 6.8 phosphate buffer.

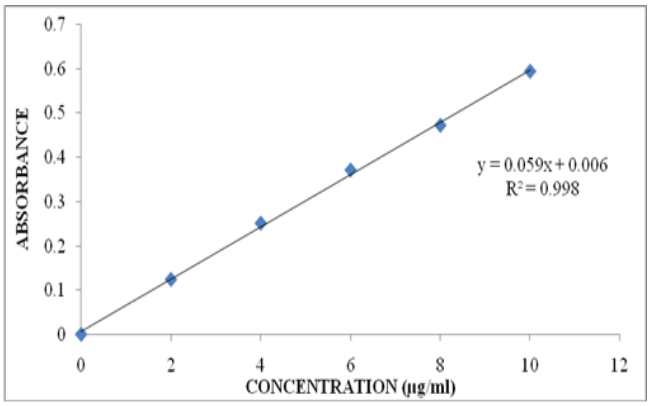


FIG-3. Standard curve of Perampanel

Characterization of pre compression blend:

Formulation code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	37.6	0.3217	0.3911	17.74	1.21
F2	36.7	0.3439	0.4244	18.96	1.23
F3	35.5	0.3911	0.4639	15.6	1.18
F4	36.6	0.3117	0.3836	18.7	1.02
F5	32.5	0.5937	0.6785	12.5	1.14
F6	28.5	0.5588	0.6064	7.84	1.08
F7	37.8	0.2977	0.3562	16.41	1.19
F8	36.5	0.4830	0.5937	18.64	1.22
F9	27.7	0.5699	0.6125	6.95	1.07

All the values represent n=3

Table 3: Physical properties of Precompression blend

The precompression blend of Perampanel were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 37.8˚, Carr's index values were less than 18.96 for the precompression blend of all the batches indicating good to fair floability and compressibility. Hausner's ratio was less than 1.23 for all batches indicating good flow properties.

Physical evaluation of Perampanel immediate release tablets: The results of the weight variation, hardness, thickness, friability, and drug content of tablets are given in table. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit. The hardness of the tablets ranged from 3.0 – 3.9 kg/cm^2 and the friability values were < than 0.69 % indicating that the tablets were compact and hard.

The thickness of the tablets ranged from 2.15 - 2.95 cm. All the formulations satisfied the content of the drug as they contained 97.46 - 99.58 % of Perampanel and good uniformity in drug content was observed. Thus, all physical attributes of the prepared tablets were found to be practically within control limits.

Formulation code	Average Weight (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)	Disintegration Time (sec)
F1	150.02	2.36	3.6	0.32	98.62	15
F2	149.65	2.15	3.4	0.62	97.36	29
F3	148.32	2.54	3.5	0.25	99.15	10
F4	149.59	2.33	3.1	0.41	98.31	34
F5	147.83	2.95	3.8	0.53	99.58	52
F6	149.78	2.46	3.7	0.49	97.46	46
F7	148.37	2.57	3.2	0.58	99.33	29
F8	149.25	2.75	3.0	0.15	98.52	20
F9	146.57	2.93	3.9	0.69	97.84	17

Table 4: Physical evaluation of Perampanel

Invitro release studies:

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 ˚C. Samples of 5 ml were collected at different time intervals up to 1 hr and has analyzed after appropriate dilution by using UV spectrophotometer at 227nm.

TIME (MIN)	% DRUG RELEASE		
	F1	F2	F3
0	0	0	0
5	19.35	16.18	25.97
10	27.65	33.96	36.62
15	36.41	45.58	57.34
20	52.85	53.72	69.12
25	57.75	67.63	78.87
30	69.95	73.87	83.54
45	75.35	81.67	99.13

Table 5: In vitro data for formulation F1-F3

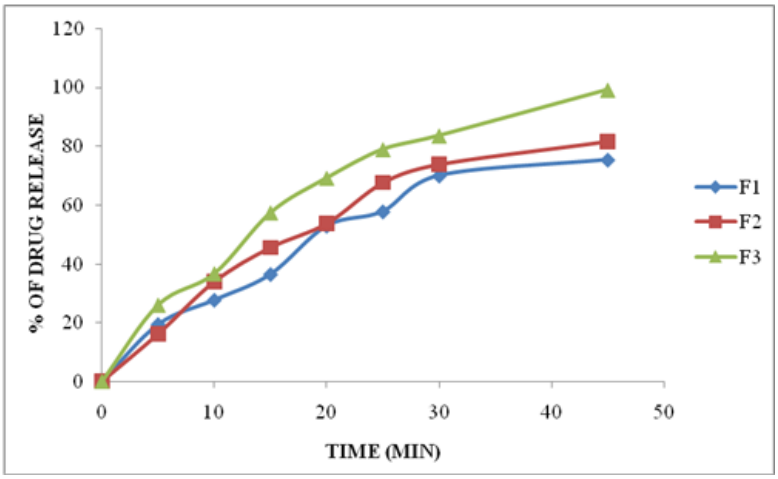


FIG-4: In vitro dissolution data for formulation F1-F3

TIME(MIN)	% DRUG RELEASE		
	F4	F5	F6
0	0	0	0
5	13.62	23.28	29.72
10	20.81	38.63	35.15
15	34.97	49.12	47.34
20	47.52	50.79	59.52
25	59.82	64.28	72.34
30	63.52	79.52	84.97
45	79.12	83.96	96.26

Table 6: In vitro dissolution data for formulations F4-F6

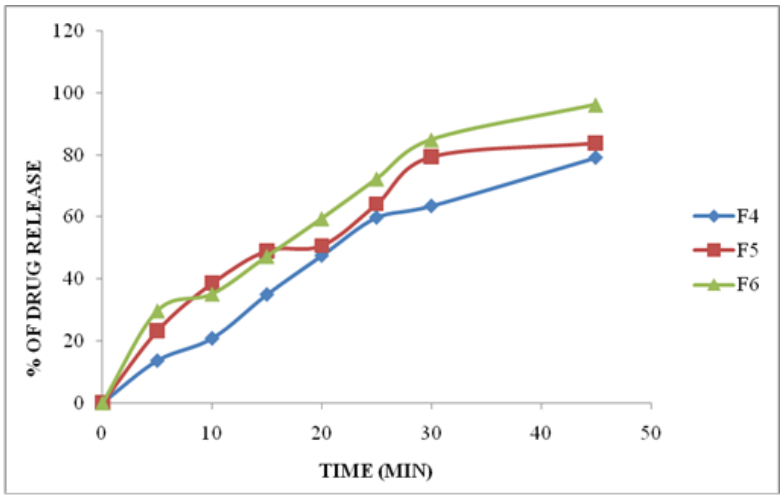


FIG-5: In *vitro* dissolution data for formulations F4-F6

TIME (MIN)	% DRUG RELEASE		
	F7	F8	F9
0	0	0	0
5	15.62	26.34	30.43
10	22.84	39.48	45.58
15	46.97	44.19	58.33
20	59.25	56.76	62.49
25	67.62	75.25	68.34
30	89.97	79.97	75.61
45	98.25	87.35	80.25

Table 7: In *vitro* dissolution data for formulations F7-F9

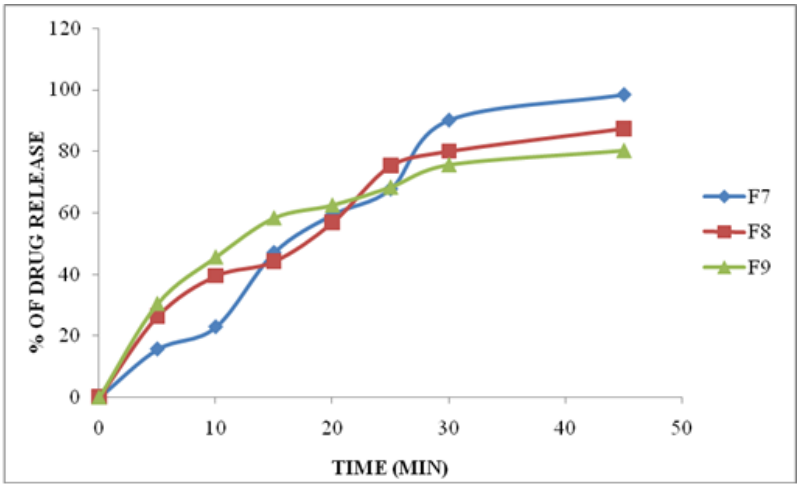


FIG-6: In *vitro* dissolution data for formulations F7-F9

Among all the formulations F3 formulation containing drug and Crospovidone showed good result that is 99.13 % in 45 minutes, at the concentration of 12 mg. Hence from all the formulations it is evident that F3 formulation is the better formulation.

Drug-Excipient compatibility studies by FTIR studies:

Perampanel was mixed with various proportions of excipients showed no color change at the end of two months, providing no drug –excipient interactions.

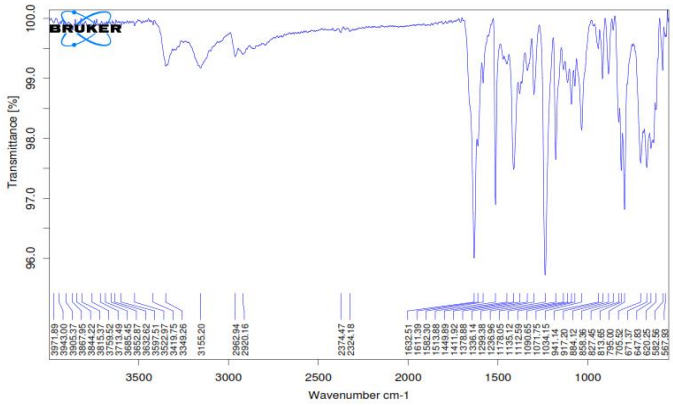


FIG-7: FTIR spectra of pure drug

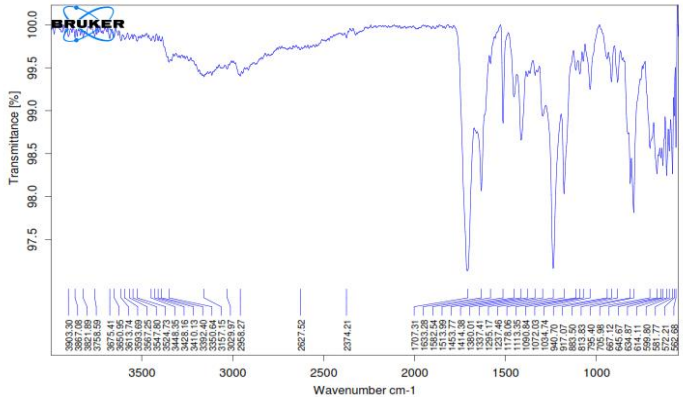


FIG-8: FTIR spectra of optimized formulation

Perampanel was mixed with proportions of excipients showed no colour change providing no drug-excipient interactions.

CONCLUSION:

Preformulation studies of Perampanel were performed; the FT-IR analysis revealed that thesuperdisintegrants and excipients used were compatible with Perampanel. Immediate releasetablets of Perampanel is to be prepared by direct compression technique using superdisintegrants,namely crospovidone, sodium starch glycolate and croscarmellose sodium.Amongst all the formulations, formulation containing Crospovidone as superdisintgrants isfulfilling all the parameters satisfactorily. It has shown excellent *in vitro* disintegration comparedto other superdisintegrants. Combines multiple mechanisms to achieve disintegration at lowlevels without forming gel i.e. require slow dissolution, disintegration and provides rapiddisintegration in direct compression tablet as well increases tablet breaking force and reducesfriability; enhances the dissolution of poorly soluble drugs. Apart from all the formulations, F3 formulation showed maximum drug release (99.13%) at the end of 45 min.

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