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Formulation Development of Tolperisone Hydrochloride Film Coated Tablet

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Abstract

Among all the different routes of administration, oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. Likewise, among all dosage forms tablet is the most popular dosage form existing today because of its convenience of self-administration, compactness and easy manufacturing. Sometimes immediate onset of action is considered obligatory immediate release tablets are the final option. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer and lead to better patient compliance. In the present work, we engage in discussion about formulation, development, and evaluation of immediate release tablets. An immediate release dosage form allows a manufacturer to extend market exclusivity. They are also a tool for expanding markets, extending product life cycles and generating opportunities. pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Tolperisone Hydrochloride Film Coated Tablets 50 mg was prepared using various excipients listed as in formula. The tablets were prepared by wet granulation method using concave plane punch on multi-station compression machine. The formulations were evaluated for their physical characteristics like thickness, hardness and friability, weight variation, content uniformity study was carried out. Evaluated for chemical analysis like Assay, disintegration and dissolution. In-vitro comparative dissolution study was performed with the help of U.S.P dissolution test apparatus-II with 900 ml of 0.1 N HCL, Acetate buffer pH 4.5 & 0.1 M HCL Acid at the 75 rpm for 45min.

1. Introduction

Among all the different routes of administration, oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. Likewise, among all dosage forms tablet is the most popular dosage form existing today because of its convenience of self-administration, compactness and easy manufacturing. Sometimes immediate onset of action is considered obligatory immediate release tablets are the final option. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer and lead to better patient compliance. In the present work, we engage in discussion about formulation, development, and evaluation of immediate release tablets. An immediate release dosage form allows a manufacturer to extend market exclusivity. They are also a tool for expanding markets, extending product life cycles and generating opportunities.

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption [1-8]. Immediate release drug delivery systems are designed to provide immediate drug levels in short period of time. In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms considering quality of life, most of these efforts have been focused on ease of medication. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities. Superdisintegrants are first choice of excipients which are extensively used for the formulation development of the immediate release tablets as they effectively result into the immediate disintegration, release and absorption of the drug after administration into the body. Cross carmellose sodium which is commonly known as Ac-di-sol is cross linked carboxy methyl cellulose sodium and sodium starch glycolate is a carboxy methyl starch and both of which are stable through hygroscopic material.

2. Materials and Methods

Materials: Tolperisone HCl (Active), Hypromellose, Lactose Monohydrate, Croscarmellose Sodium, PVP K- 30, Microcrystalline Cellulose, Colloidal Anhydrous Silica, Purified Talc, Magnesium Stearate, Opadry white excipient used in formulation development. Weighing balance (sartorius lab), UV-Spectrophotometer (U.V. i1900 Shimadzu, Japan), Dissolution apparatus (Electrolab), Tablet machine (Chamunda Pharma), Hardness tester (Pfizer type), Roche Friabilator (electro lab), pH Meter (Lab India), FTIR (Shimadzu, Japan.)

Methods

Preformulation Study: Study of Organoleptic properties of pure drug

Tolperisone Hydrochloride was tested for organoleptic properties such as appearance, solubility, odour, colour, melting point etc.

Determination of λmax and calibration curve of drug

Prepration of diluent

Mixed water and methanol in the ratio of 20:80 v/v mix well.

Determination of λmax

Weigh and transfer 160 mg of Tolperisone Hydrochloride into 200 ml volumetric flask add 150 ml diluent sonicated to dissolve. Make up with dilent mix well. Further transfer 5 ml of above solution into 50 ml volumetric flask make up with diluent mix well, to obtain the concentration of 80µg/ml. It was scanned for maximum absorbance by UV-spectrophotometer (Shimadzu, Japan) in range of 200-400 nm using diluent as a blank.

Preparation of standard calibration curve of Tolperisone Hydrochloride

Weigh and transfer 160 mg of Tolperisone Hydrochloride into 200 ml volumetric flask add 150 ml diluent sonicated to dissolve. Make up with dilent mix well. This solution was used as stock solution. Further transfer of 1 ml, 2.5 ml, 3.7 ml, 5 ml and 6 ml of stock solution were transferred in to series of 50 ml volumetric flask. Make up with diluent. The concentration of these solution was 16 µg/ml 40 µg/ml, 59 µg/ml, 80 µg/ml, 96 µg/ml. Finally, the absorbance of each sample was measured at 259 nm against blank phosphate buffer of pH 6.8. Standard curve of concentration vs. absorbance was plotted.

Compatibility study

The compatibility of the active substance with excipients: Compatibility studies of all active ingredients were carried out with the commonly used excipients under stressed conditions of 60oC for 6 hours and 80oC for 30 minutes. This aided in ruling out apparently incompatible excipients. The drug and the excipients were mixed in the 1:1 ratio (drug: excipients) to make a binary mixture. To analyze the compatibility of drug and polymer the FTIR spectrum of pure drug and combination of drug with polymer was recorded by using Fourier transform infrared spectroscopy and the spectrum analysis was done.

Following formulations of Tolperisone Hydrochloride film coated tablets were used for developmental work.

Table 6.3: Formulation development batches for Tolperisone HCl tablet

Sr. No.	Ingredients	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
I		**For Dry Mix**								
1	Tolperisone Hydrochloride	50	50	50	50	50	50	50	50	50
2	Hypromellose	20	20	20	40	40	35	35	35	35
3	Lactose Monohydrate	35	40	40	35	35	38	38	38	38
4	Croscarmellose Sodium(Ac-di-sol SD 711)	3	5	10	6	6	6	7	7	7
II		**For Paste Preparation**								
5	Povidone (PVP K 30)	5	3	5	8	8	8	8	8	8
6	Purified water	--	--	q.s	q.s	q.s	q.s	q.s	q.s	q.s
7	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
III		**For Lubrication**								
8	Microcrystalline cellulose (PH 102)	--	--	20	25	25	15	20	21	21
9	Croscarmellose Sodium (Ac-di-sol SD 711)	3	3	6	6	6	-	-	-	-
10	Colloidal Anhydrous Silica	-	-	-	-	-	1	1	1	1
11	Purified Talc	--	--	1	1	1	1	1	1	1
12	Magnesium Stearate	1	1	1	1	1	1	1	1	1
	Total weight of Core tablet	**117**	**122**	**153**	**173**	**172**	**155**	**161**	**162**	**162**
IV		**Film Coating**								
13	Opadry white	2	2	2	4	5	5	5	5	5
14	Isopropyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
15	Dichloromethane	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total weight of Coated Tab	**119**	**124**	**155**	**176**	**177**	**160**	**166**	**167**	**167**

Manufacturing Procedure & In process control

General Processing Instructions

- Line clearance checks shall be carried out before carrying out any operations of manufacturing as per current updated SOP.
- All equipment and machines are to be cleaned and operated as per Standard Operating Procedure for individual equipments and machines.
- Ensure the environmental conditions (Temperature, Pressure differential & Humidity) as per specific product requirement.
- Ensure wearing of gloves and masks in the manufacturing area.
- Use calibrated balance only.
- Use appropriate balance depending upon the quantity to be dispensed.
- Carry out dispensing of raw materials in dispensing area as per current updated SOPs.
- All materials selection, weighing and additions to be carried out under supervision of Approved staff.
- In-process checks shall be carried out wherever necessary.

Table 6.6: List of Key Equipments used in manufacturing

No.	Name of Key Equipment
1	**Weighing Balance**
2	Vibratory Sifter
3	Rapid Mixer Granulator
4	Mechanical Stirrer
5	Multimill
6	**Fluid Bed Dryer**
7	Steam Jacketed Kettel
8	Double Cone Blender / Octagonal Blender
9	Compression Machine B-Tooling
10	Punch Set, Upper Punch: Circular, Shallow concave and Plain. Lower Punch: Circular, Shallow concave and Plain.
11	Coating Pan with Spray Gun (Bullows)
12	Ganscoater with Spray Gun (Spraying System)
13	Inspection Belt

Manufacturing Procedure

Weighing and Dispensing

Weigh accurately active and inactive raw materials and dispense as per the formula.

Stage- 1.0 SIFTING:

Sift below ingredients through specified mesh with the help of Vibratory Sifter:

№	Ingredients	Sieve size
1	Tolperisone Hydrochloride IH	30#
2	Hypromellose	30 #
3	Lactose Monohydrate BP	30 #
4	Croscarmellose Sodium USPNF (Ac-Di-Sol SD- 711)	30 #

Collect the sifted material separately in prelabeled polybags.

Stage- 2.0 DRY MIXING:

Load the previously sifted material from Stage- 1.0 to RMG and mix for 30 min with slow speed of Impeller. Chopper off

Stage- 3.0 BINDER PREPARATION:

Take **Purified Water** in a Steam Jacketed Vessel & heat it to 50°C- 55°C.

Then transfer heated **Purified water BP** in another S.S Vessel & add slowly **Povidone BP (PVP K 30)** in it under continuous stirring and dissolve it completely.

Then add and mix **Isopropyl Alcohol BP** to above solution under continuous stirring and mix it completely and use this solution for binding

Stage- 4.0 WET GRANULATION:

Add Stage 3.0 to Stage 2.0 under continues mixing.

If required use extra quantity of **Purified Water BP and Isopropyl Alcohol BP** (1:1) to form wet mass of desired consistency.

Note down the extra quantity of **Purified Water BP and Isopropyl Alcohol BP used.**

Stage- 5.0 WET MILLING (If required)

Pass the wet mass obtained from Stage 4.0 through 10 mm screen

of multimill with knife forward direction & at a medium speed.

Stage- 6.0 DRYING:

Initially air dries the wet mass for 20 minutes in Fluid Bed Dryer (without temperature) & then at Inlet temperature 50ºC & Outlet temperature: 45ºC – 50ºC.

Record the Inlet and Outlet temperature of the FBD and drying time.

Rake the granules after every 30 min. interval.
Check the LOD on Moisture analyzer at 80ºC (Limit: 2 % to 3 % w/w)

Stage- 7.0 DRY SIFTING/ SIZE REDUCTION:

Sift the dried granules from Stage 6.0 through 20# sieve by using Vibratory Sifter. Pass the oversized granules through 2.0 mm screen of multi mill with knife forward direction, at fast speed and again sift through 20# sieve of sifter.

Storage of dried granules:

Storage Condition: Store the dried granules in duly labeled double polybag inside an airtight HDPE container at temperature 20 ºC - 25ºC and Relative Humidity 45% to 55%.

Storage period: Not more than 48 hrs.

LUBRICATION:

Load the dried & sifted granules from stage 7.0 to Double Cone Blender/Octagonal Blender.

Sift the following ingredients separately with the help of Vibratory Sifter.

№	Ingredients	Sieve size
1	Microcrystalline Cellulose (PH 102) BP	30 #
2	Colloidal Anhydrous Silica BP along with Croscarmellose Sodium USPNF (Ac-Di-Sol SD- 711)	30 #
3	Purified talc BP	30#
4	Magnesium Stearate BP	30 #

Load above sifted ingredients (**without Magnesium Stearate BP**) to Double Cone Blender/Octagonal Blender & mix as per limit mentioned in the below table

Add previously sifted **Magnesium Stearate BP** to Double Cone /Octagonal Blender, close the blender. Mix as per limit mentioned in the below table.

Table 6.7: Blending time

Equipment Name	Equipment Capacity	RPM	Mixing time before addition of Magnesium Stearate	Mixing time after addition of Magnesium Stearate
Double cone Blender	50.0 L	35	5 min	5 min
Octagonal Blender	500 L	15	10 min	5 min

Storage of blend: Store the blend in duly labeled double polybag inside an airtight HDPE container at temperature 20 ºC -25ºC and Relative Humidity 45% to 55%.until released for compression.

COMPRESSION:

Transfer the blend to Compression cubicle.
Note the No. of containers transferred to the compression in BMR.

Set the Compression machine using punch sets
Upper punch : Circular, shallow concave, plain
Lower Punch: Circular, shallow concave, plain

Operate the Compression machine as per current updated SOP and Compress the lubricated granules. Certify it after compliance with the Compression Parameters and record the results.

Table 6.8: In-process Checks during compression

No.	Parameter	Limits
1	Description	White to off-white colored, Circular, biconvex uncoated tablet plain on both sides.
2	Weight of 20 tablets	3.24g ± 10% (2.91 g to 3.56g)
3	Average weight per tablet	167 mg ± 10% (145.8 mg to 178.2mg)
4	Uniformity of Weight	± 10% of average weight
5	Hardness	NLT 3 kg/cm²
6	Friability	NMT 1 % w/w
7	Thickness	3.8 mm ± 0.2 mm (3.6 mm to 3.10 mm)
8	Diameter	9.0 mm ± 0.1 mm (8.9 mm to 9.1 mm)
9	Disintegration Time	NMT 15 minutes at 37°C ± 2°C

Storage of compressed tablets:

Storage condition: Store the compressed tablets in duly labeled double lined polybag inside an airtight HDPE container at temperature 20ºC-25ºC and Relative Humidity 45% - 55% until it is released for coating.

FILM COATING SUSPENSION PREPARATION:

Film coating suspension should be freshly prepared &used within 24 hrs from preparation.

Take **Isopropyl Alcohol BP** in clean S. S. Vessel & stir it to form a vortex. Add **Opadry white**

slowly in it. If require increase the speed of stirrer to form vortex.

Add **Dichloromethane BP** and stir it for 40 min.

Filter coating suspension through 100# nylon cloth.

FILM COATING PROCESS:

Load the dedusted tablets in Coating Pan, carry out the pre-warming of the tablet at 50ºC for 10 min. Inch the pan during prewarming.

Maintain the tablet bed temperature as mentioned in film coating parameters with respect to coating pan at the time of coating. Start the coating pan, commence and continue the coating.

Spray the coating suspension on the rolling tablet bed till weight gain is achieved. The film coating suspension in the vessel should be stirred slowly during coating.

Carry out the in-process checks as per parameters given in table of **In-process Checks Parameters.**

After completion of film coating dry the film coated tablet in the coating pan with the hot air for 10 min. Then transfer it in to in duly labeled double polybag inside an airtight HDPE container.

Table 6.9: Coating in-process checks parameters

Parameter	Limit
Description	Yellow colored, circular, biconvex, film coated tablet, plain on both sides.
Weight of 20 tablets	3.34 g □ 7.5% (3.0 g to 3.67 g)
Average Weight	167 mg □ 7.5% (150 mg to 183 mg)
Uniformity of Weight	± 7.5% of average weight
Thickness	3.4 mm □ 0.2 mm (3.2 mm to 3.6 mm)
Diameter	9.5 mm ± 0.2 mm (7.3 mm to 8.7bmm)
Disintegration Time	NMT 30 minutes at 37°C ± 2°C

Then transfer the film coated tablets in a double lined poly bag in HDPE container.

3. RESULTS AND DISCUSSION

7.1 PREFORMULATION STUDY

7.1.1 Organoleptic properties of drug

The sample of Tolperisone Hydrochloride received was studied for its organoleptic characteristics such as colour, odour, appearance. The results are given in Table 7.1

Table 7.1: Physical characteristics of drug

Characters	Inference
Appearance	White, Crystalline powder, it has slight characteristic odor, hygroscopic powder
Solubility	Very soluble in acetic acid (100%), freely soluble in water and in ethanol (95%), soluble in acetic anhydride, slightly soluble in acetone, practically insoluble in diethyl ether
Colour	White
Odour	characteristic odor
Melting point	167 OC - 174OC

7.1.2 Preparation of standard calibration curve of Tolperisone Hydrochloride

Calibration curve was plotted by taking values of concentration and absorbance

Table 7.2: Concentration and absorbance of Tolperisone Hydrochloride

Sr. No.	Concentration (µg/ml)	Absorbance (at 259 nm)
1	0	0.00
2	16	0.1653
3	40	0.3883
4	59	0.5727
5	80	0.7766
6	96	0.9319

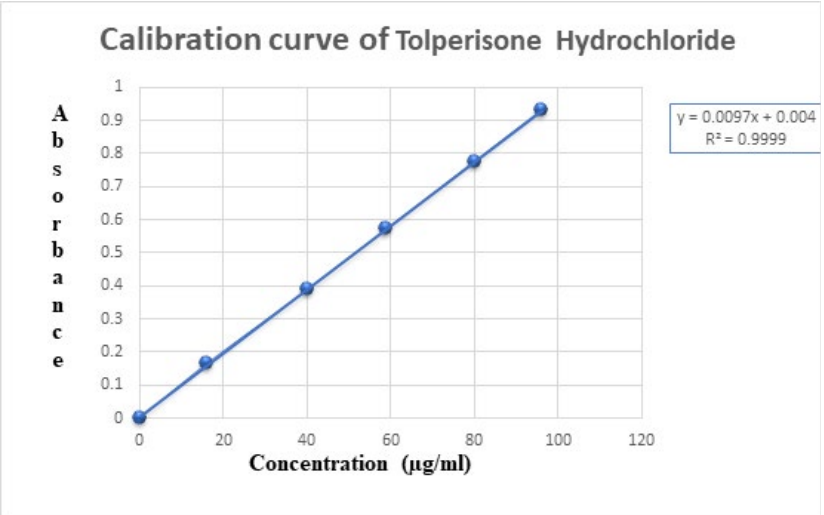

Fig. 7.1: Calibration curve of Tolperisone HCl

The correlation coefficient (R^2) = 0.999
From the graph it is showed that it follows Beer-Lambort's law.

7.1.3 Compatibility studies

Tolperisone HCl IH + Excipients	Observations on Appearance		
	Initial (Color)	60oC for 6 hours	80oC for 30 mins.
Hypromellose	White Powder	No Change	No Change
Lactose Monohydrate	White Powder	No Change	No Change
Croscarmellose Sodium (Ac-Di-Sol SD- 711)	White Powder	No Change	No Change
Povidone (PVP K- 30)	White Powder	No Change	No Change
Microcrystalline Cellulose (PH 102)	White Powder	No Change	No Change
Colloidal Anhydrous Silica	White Fluffy Powder	No Change	No Change
Purified Talc	White Powder	No Change	No Change
Magnesium Stearate	White Powder	No Change	No Change
Opadry white	Yellow Powder	No Change	No Change
Purified Water	Clear Solution	No Change	No Change

7.1.3.1 FTIR spectra of Tolperisone Hydrochloride

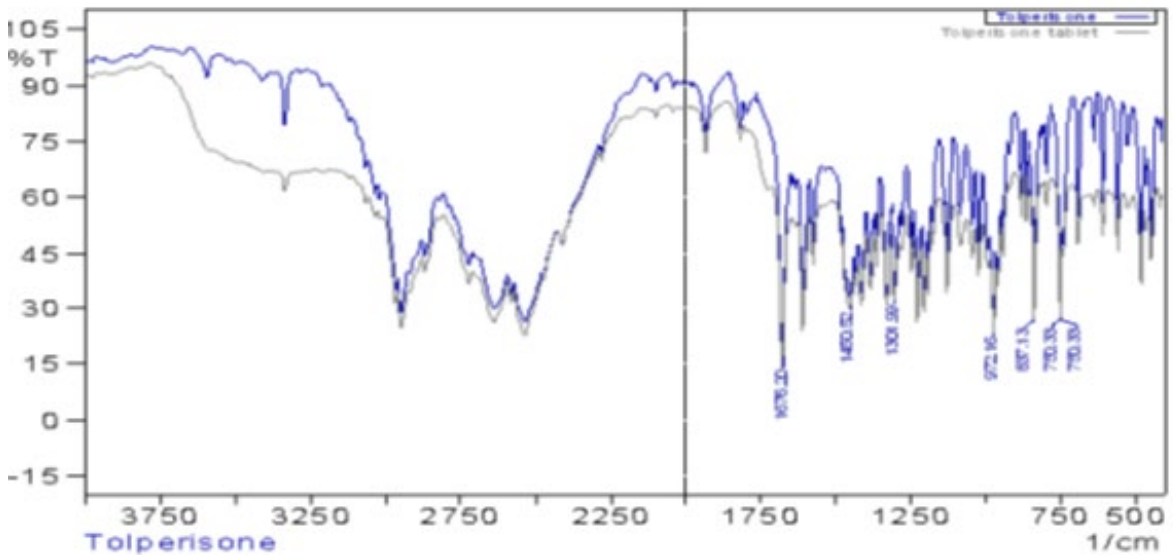

Figure 7.2: FTIR spectra of Tolperisone Hydrochloride

.1.3.2 FTIR spectra of physical mixture Tolperisone HCl and excipients

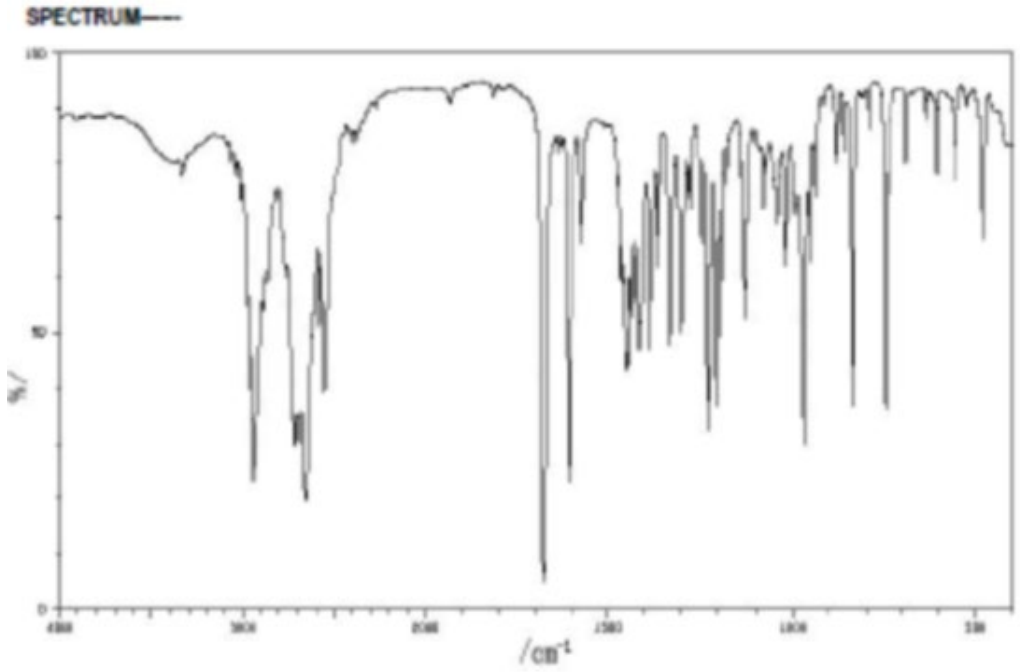

Figure 7.3: FTIR spectra of physical mixture Tolperisone HCl and Excipients

Summary:

No evidence of physical change was found between the active drug with excipients indicating that **Tolperisone Hydrochloride IH** and all excipients are compatible with each other. From the FTIR study of drug and polymer it was clear that drug and polymer are compatible.

7.2 EVALUATION PARAMETER

7.2.1 Precompression parameter

The powder blend of each formulation were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose and result obtained are shown in Table 7.3

Table 7.3: Precompression parameter of formulations

Formulation	Bulk density (gm/cm³)	Tapped density(gm/cm³)	Carr's index	Hausner ratio	Angle of repose (θ)
F1	0.44±0.017	0.51±0.017	13.72	1.15	30º.55'±0.36
F2	0.41±0.011	0.47±0.023	12.76	1.14	28º.80'±0.33
F3	0.47±0.023	0.58±0.028	12.96	1.14	27º.99'±2.01
F4	0.43±0.020	0.49±0.020	13.04	1.15	29º.40'±1.01
F5	0.46±0.025	0.53±0.024	12.95	1.14	28º.80'±1.20
F6	0.42±0.018	0.48±0.020	13.47	1.15	27º.95'±1.01
F7	0.44±0.021	0.51±0.022	12.86	1.14	28º.10'±1.02
F8	0.45±0.023	0.54±0.023	13.55	1.15	30º.75'±0.67
F9	0.45±0.023	0.55±0.017	13.54	1.15	30º.77'±0.68
*Values are expressed in mean ±SD (n=3)					

7.2.1.1 Bulk density

The bulk density values less than 1.2 gm/cm3 indicate good packing and values > 1.5 gm/cm3 are indicates poor packing. The bulk density values for all formulation of powder bulk varied in the range of 0.41±0.011gm/cm3 to 0.47±0.023gm/cm3. The values obtained lies within acceptable limits.

7.2.1.2 Tapped density

The tapped density values for all formulation of powder bulk varied in the range of 0.47±0.023 gm/cm3 to 0.58±0.028 gm/cm3. The values obtained lies within acceptable limits.

7.2.1.3 Carr's index

The percent compressibility of formulation of powder bulk was determined by Carr's compressibility index. The percent compressibility for all formulation lies within the range of 12.76 % to 13.72 % indicates acceptable flow property

7.2.1.4 Hausner's ratio

Hausner's ratio was found to be in the range of 1.14 to 1.15 which shows acceptable flow property and good packing ability.

7.2.1.5 Angle of repose

The of angle of repose for all formulation of powder blend were found to be in the range of 270.90'±2.01to 300.77'±0.68 indicating good flow property. It can be concluded that the powder blend for all batches possess good flow characteristic.

7.2.2 Post compression parameter

All the formulations evaluated for the postcompression parameters, result obtained were shown in Table7.4. The average weight from all the formulation were found be in the range 150.62 mg to 183.12 mg, indicates that the all batches have the average weight as per the official standards. The drug contents in all the batches in the range of 95.56 to 105. All the batches have good hardness and friability as per standards. Surface pH of the tablets were found in the range of 5.72±0.04 to 6.78±0.05 that indicates no risk of mucosal damage or irritation. The thickness of the tablet was in the range of 3.2 ±0.04 mm to 3.6± 0.02 mm.

Table 7.4: Post compression parameter of formulation

Formulation	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Weight variation (mg)	Drug content (%)	Surface pH
F1	2.67+0.20	3.08 +0.02	0.57+0.04	117.86+1.89	98.59	5.89+ 0.04
F2	3.43+0.35	3.18 + 0.05	0.64+0.02	122.61+3.42	99.44	5.72+ 0.04
F3	4.53+ 0.30	3.48 + 0.04	0.61+0.03	153.66+4.87	100.08	6.66+ 0.05
F4	5.97+ 0.41	3.53 + 0.02	0.67+0.03	173.66+4.56	98.19	5.43+ 0.06
F5	5.48+0.21	3.82 + 0.02	0.59+0.03	172.66+4.16	99.81	5.64+ 0.03
F6	5.10+0.34	3.80 + 0.03	0.60+0.03	155.66+2.94	99.67	5.70+ 0.09
F7	4.86+ 0.64	3.27 + 0.05	0.57+0.03	161.66+3.41	99.06	5.37+ 0.03
F8	4.60+ 0.41	3.63 + 0.04	0.39+0.03	162.66+5.68	99.97	5.90+ 0.04
F9	4.61+0.20	3.60 + 0.04	0.37+ 0.02	162.31+5.72	100.40	6.08+ 0.05
*Values are expressed in mean ±SD (n=3)						

Table7.9: Average cumulative percentage of drug released of formulations

Media	900ml of 0.1 N HCl at 75 rpm in USP Type I apparatus (basket)								
Time (min)	% Cumulative Drug Release (%CDR)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
05	76	71	58	5	8	10	15	14	15
10	84	80	63	18	16	24	28	30	28
15	92	89	79	27	31	43	45	48	51
20	96	92	89	34	39	57	60	63	65
30	98	96	95	52	56	69	78	84	88
45	100	98	99	69	75	78	88	98	99
60	101	100	101	82	86	89	94	100	100

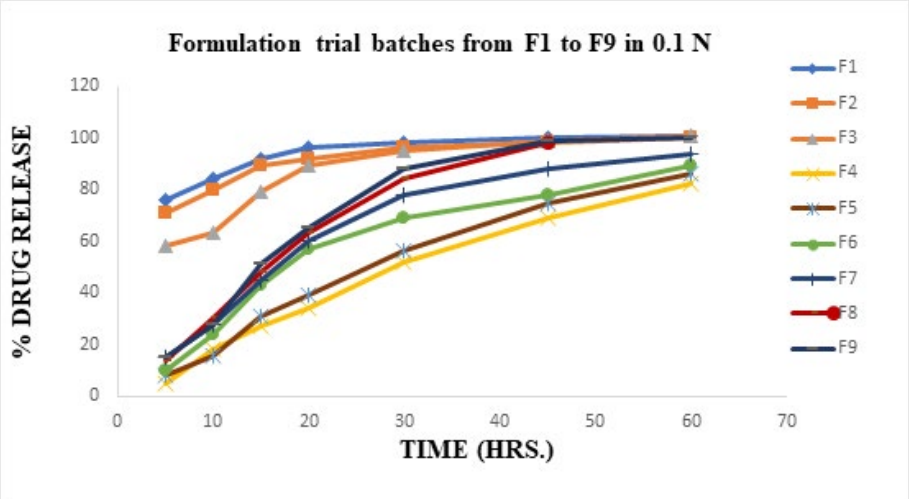

Figure:Comparative dissolution profile of F1 to F9 in 0.1N HCl

Acceptance Criteria:

In case where more than 85% of the drug is dissolved within 15 min for at least 3 media, the dissolution profiles may be accepted as similar without further mathematical evaluation.

4. Conclusion

Considering more than 85 % drug release of sample & innovator within 15 min in 3 media (0.1 m HCl, pH0 4.5 & pH 6.8), The product Tolperisone HCl Tablets 50 mg is comparable with innovator sample (Mydocalm 50) in dissolution profile in different dissolution media as per WHO guideline reference sphate buffer pH 6.8

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