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DESIGN, DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS OF TORSEMIDE

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Abstract

The purpose of the research was to develop, manufacture, and evaluate the Torsemide fast-dissolving tablet, which was designed to be a stable and reliable dosage form for the "Torsemide drug." The main goal was to create a generic version of the inventor's fast-dissolving torsemide tablets. Fast-dissolving tablets with a similar dissolution profile and bioequivalence to the reference product have been created as a safe, effective generic alternative. The problem of creating a torsemide tablet that dissolves quickly required the employment of a super disintegrate in order to quickly achieve bioavailability.

Keywords: Fast dissolving tablet, Disintegrate, bioavailability, Torasemide, HPLC method.

Introduction

Pharmaceuticals have made a major contribution to improving the health status of patients over a past few decades. At the same time, its expenditure has increased rapidly, with spending on medicines outpacing economic growth in many countries. Many economists have speculated that, if spending on healthcare continues to increase at the current rate, the economies of most countries will be severely affected. Most governments have, therefore, begun to implement cost-containment measures to slow the rate of healthcare spending and have concentrated to a larger degree on pharmaceutical spending. Since generics are usually marketed at substantially lower prices than the original brand- name products and, with the rising cost of healthcare; this has made them an attractive option to healthcare providers and governments.

Generic drug

Generic medicines are those where the original patent has expired and which may now be produced by manufacturers other than the original innovator (patent-holding) company. The term “generic drug” a or “generic medicine” can have varying definitions in different markets, however the term is commonly understood, as defined by the World Health Organization (WHO), to mean a pharmaceutical product which is usually,

- Intended to be interchangeable with an innovator product
- Is manufactured without a license from the innovator company, and
- Is marketed after the expiry date of the patent or other exclusive rights.

Torasemide

Torasemide, also known as torsemide, is a diuretic medication used to treat fluidoverload due to heart failure, kidney disease, and liver disease and high blood pressure. It is a less preferred treatment for high blood pressure. It is taken by mouth or by injection into a vein. Torasemide belongs to BCS class I drug classified as high permeability and high solubility drug.

Physicochemical properties Structure

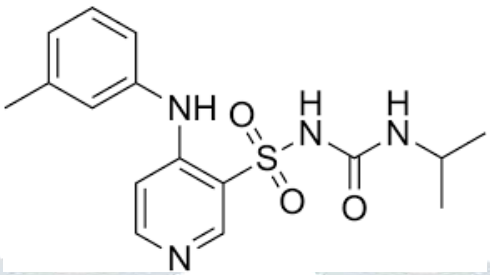

Fig. No. 1 Structure of Torasemide

Category: Anti-Hypertension

IUPAC Name: 1-({4-[(3-methylphenyl)amino]pyridin-3-yl}sulfonyl)-3-(propan-2-yl)urea

Molecular formula: $C_{16}H_{20}N_4O_3S$

Molecular Weight: 348.42

Appearance: white to light brown colour.

Solubility: Freely soluble in methanol, Ethanol, Water, HCl, Phosphate buffer.

Melting point: 163◦c -165◦c

BCS Class: I (High solubility, High permeability)

Half-life:

The average half-life of torasemide is 3.5 hours.

Clinical PharmacologyMechanisms of action

It is widely known that administration of torasemide can attenuate renal injury and reduce the severity of acute renal failure. This effect is obtained by increasing urine output and hence, facilitating fluid, acid-base and potassium control. This effect is obtained by the increase in the excretion of urinary sodium and chloride. Several reports have indicated that torasemide presents a long-lasting diuresis and less potassium excretion which can be explained by the effect that torasemide has on the renin-angiotensin-aldosterone system. This effect is very similar to the effect observed with the administration of combination therapy with furosemide and spironolactone and it is characterized by a decrease in plasma brain natriuretic peptide and improved measurements of left ventricular function. Above the aforementioned effect, torasemide presents a dual effect .in which the inhibition of aldosterone which donates torasemide with a potassium-sparing action. Torasemide has been shown to reduce extracellular fluid volume and blood pressure in hypertensive patients suffering from chronic kidney disease. As well, some reports have indicated that torasemide can reduce myocardial fibrosis by reducing the collagen accumulation. This effect is suggested to be related to the decrease in aldosterone which in order has been shown to reduce the production of the enzyme procollagen type I carboxy-terminal proteinase which is known to be overexpressed in heart failure patients. As

mentioned above, torasemide is part of the loop diuretics and thus, it acts by reducing the oxygen demand in the medullary thick ascending loop of Henle by inhibiting the Na+/K+/Cl- pump on the luminal cell membrane surface. This action is obtained by the binding of torasemide to a chloride ion-binding site of the transport molecule. Torasemide is known to have an effect in the renin-angiotensin-aldosterone system by inhibiting the downstream cascade after the activation of angiotensin II. This inhibition will produce a secondary effect marked by the reduction of the expression of aldosterone synthase, TGF-B1 and thromboxane A2 and a reduction on the aldosterone receptor binding.

Absorption:

Torasemide is the diuretic with the highest oral bioavailability even in advanced stages of chronic kidney disease. This bioavailability tends to be higher than 80% regardless of the patient condition. The maximal serum concentration is reported to be of 1 hour and the absorption parameters are not affected by its use concomitantly with food

Distribution: he volume of distribution of torasemide is 0.2 L/kg.

Metabolism:

Torasemide is extensively metabolized in the liver and only 20% of the dose remains unchanged and it is recovered in the urine. Metabolized via the hepatic CYP2C8 and CYP2C9 mainly by reactions of hydroxylation, oxidation and reduction to 5 metabolites. The major metabolite, M5, is pharmacologically inactive. There are 2 minor metabolites, M1, possessing one-tenth the activity of torasemide, and M3, equal in activity to torasemide. Overall, torasemide appears to account for 80% of the total diuretic activity, while metabolites M1 and M3 account for 9% and 11%, respectively.

Elimination

Torasemide is mainly hepatically processed and excreted in the feces from which about 70-80% of the administered dose is excreted by this pathway. On the other hand, about 20-30% of the administered dose is found in the urine.

Adverse effect:

- Chest Tightness
- Difficulty swallowing
- Dry mouth
- Heart Throbbing
- Stomach Cramps

Excipient Profile

Microcrystalline Cellulose

Non-proprietary Names:

BP: Microcrystalline Cellulose

USP-NF: Microcrystalline Cellulose

Synonyms:

Avicel PH; Cellets; Celex; cellulose gel; hellulosummicrocristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

Chemical Name: Cellulose

CAS Registry Number: 9004-34-6

Structural Formula:

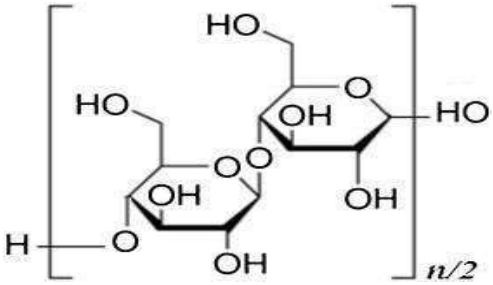

Fig. No. 2 Structure of Microcrystalline Cellulose

Empirical Formula: (C6H10O5) n where n ≈220.

Molecular Weight: 162.1406 g/mol per glucose unit

Functional Category: Adsorbent; suspending agent; tablet and capsulediluent; tablet disintegrate.

Description:

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Material used:

Table 1: List of API, excipients with grade and source

Sr. No	Ingredient	Functions	Grad	Source
1	Torsemide	Active ingradient	-	Laurus Lab
2	Lactose monohydrate	Binder	Supertab11D	DEF pharma
3	Microcrystallinecellulose	Diluent	Avicel 102	FMC biopharm
4	Cross carmellosecellulose	Super disintegrant	Ac-di-sol	Hyqual
5	Pregelatinized Starch	Super disintegrant	Primogel	Hyqual
6	Magnesium stearate	Lubricant	-	Avantor

Instrument used:

Table 2: List of instrument with make

Sr. no	Instruments/ Apparatus	Make
1	Analytical Balance	Sartorius BT2245
2	Moisture analyzer	Sartorius MA150
3	Octagonal blender	Karnawatieng. Ltd
4	Compression machine	Cadmach

5	Tablet hardness tester	Dr. Schleuniger
6	Disintegration test apparatus	Electrolab
7	Friability test apparatus	Electrolab
8	Density measurement apparatus	Electrolab
9	Tablet coating machine	Neocoata
10	U V spectrophotometer	Analytik Jena (specord 210)
11	Dissolution test apparatus	Electrolab
12	HPLC	waters

Result and Discussion

Physiochemical properties of drug:-

Organoleptic properties:

Table 3: Organoleptic properties of API

Properties	Observation
Colour	White to off white
Taste	Bitter
Odour	Odourless
Appearance	White Powder

Melting point determination:-

Melting point of API was found to be, which is in range as given inliterature (163-165ºC). Hence the drug can be stated as pure.

Table 4: Melting point determination

Sr. No.	Melting point [˚C] (observed)	Average [˚C]
1	165	165
2	164	
3	165	

Solubility:-

The solubility of the received sample of API was examined in various solvents (aqueous and organic). It is an only qualitative analysis. The resultsthus obtained were as follows-

Table 5: Details solubility of API

Sr. No.	Solvent	Solubility
1	Alcohol and Water	Freely soluble
2	Methylene chloride	Very slightly soluble

Loss on drying:-

Loss on drying was carried out by using halogen moisture analyzer and itwas found to be 0.58% at 105ºC.

Ultraviolet absorption spectroscopy:Wavelength Selection

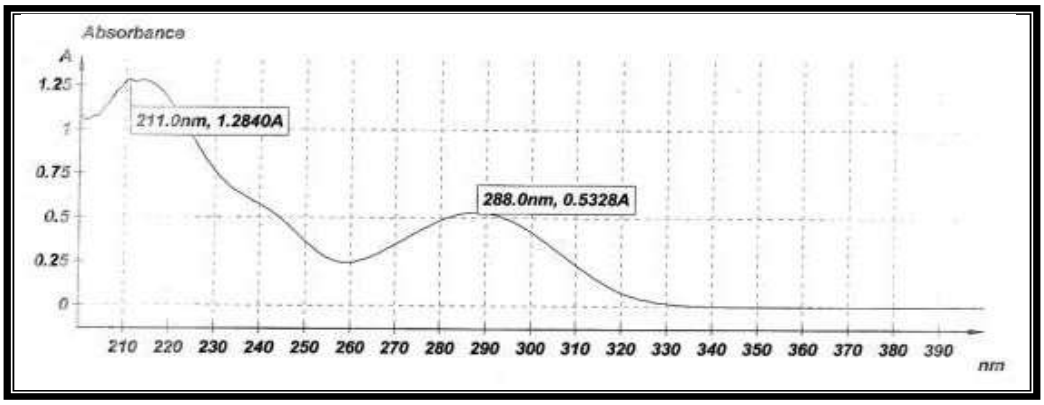

Figure 3: UV Spectrum of API

An absorption maximum was found to be at 288 nm. Hence 288 nm wasselected as λ max for further studies.

Calibration curve:

The solution containing different concentration of Torsemide was prepared and scanned at 288 nm by using UV spectrophotometer. Graph of absorbance vs. concentration was plotted and found to be linear over the range of 2.5-7.5 µg/ml indicating its compliance Lambert's-Beer's law.

Table 6: Absorbance at various conc. of API

Sr. No.	Concentration (ug/ml)	Absorbance
1	**0**	0
2	**2.5**	0.2661
3	**4**	0.4257
4	**5**	0.5323
5	**6**	0.6308
6	**7.5**	0.7983

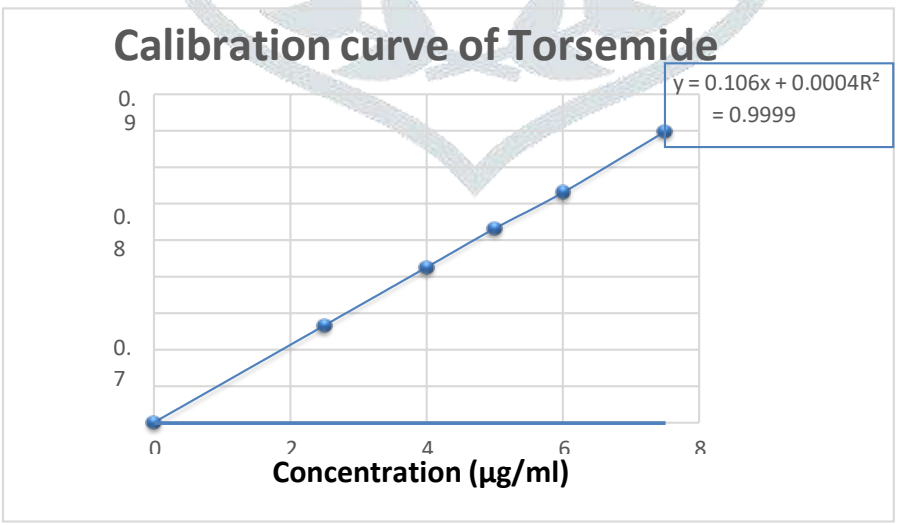

Figure 4: Calibration curve of drug

Table 7: Parameters found in calibration curve

Sr. No.	Parameter	Finding
1	Wavelength detection	288nm
2	Regression equation	y = 0.106x+0.0004
3	Correlation coefficient	R = 0.9999

BCS solubility study:-

Table 8: BCS solubility data of API in different media

Sr. No	Media	250ml mg/
1	Purified Water	865.0
2	0.01N HCl	1752.2
3	0.001N HCl	1536.5
4	0.1N HCl	2069.5
5	pH 6.8 phosphate buffer	632.01
6	pH 4.5 Acetate buffer	1056.5
7	pH 7.5 phosphate buffer	436.2

Micrometrics properties evaluation:

Table 9: Micrometrics properties of API

Sr. No	Parameters	Results	Flow properties
1	Bulk density(g/ml)	0.48	-
2	Tapped density(g/ml)	0.78	-
3	Carr's index (%)	35.25	Very Poor
4	Hauser's ratio(HR)	1.27	Very Very poor

Drug-excipients compatibility result:

Physical compatibility:

Table No. 10: Result of physical compatibility of Drug

Sr. No.	API/ Excipients Name with Grade	Drug ExpientsRatio	Condition	Observations on appearance	Assay(%)
01	API	1	Initial	White	100.2
02	API + Microcrystalline Cellulose	1:1	Initial	White	99.5
03	API + Lactose Monohydrate	1:1	Initial	White	99.9
04	Croscarmellosesodium	1.1	Initial	White	100.0

05	+ PregelatinizedStarch	1:1	Initial	White	100.1
06	I + Magnesiumstearate	1:0.5	Initial	White	99.7
08	API + All excipient	1:1	Initial	No colour change	99.8

Conclusion:

No loss in assay was observed in any of these mixtures at Initial. Hence no degradation products also not at Initial condition. All results were found are within specification. There is no incompatibility with the selected excipients.

Pre compression parameter: -

Table 11: Evaluation of lubricated blend

Formulation. no	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner ratio
F1	0.602	0.723	20.35	1.5
F2	0.614	0.759	20.65	1.21
F3	0.607	0.747	19..98	1.23
F4	0.620	0.780	23.00	1.26
F5	0.631	0.791	22.65	1.24
F6	0.626	0.774	20.98	1.25
F7	0.610	0.759	21.67	1.27
F8	0.589	0.765	21.30	1.28

Conclusion:

In the above table characteristic of the powder blend from F1 to F8 is given. From values of Compressibility index and Hauser's ratio we can conclude that blend of the above formulation have passable flow properties and compressibility index.

Post compression Parameter:

Table 12: Evaluation of Post compression Parameter.

F. No	Weight Variation (mg)	ardness(N)	Thickness (mm)	Disintegration Time	Friability (%)	Assay (%)
F1	201	89	3.90	2min 56sec	0.5	98.8
F2	202	88	3.93	2min 21sec	0.6	97.3
F3	203	85	3.95	2min 40sec	0.5	98.3
F4	202	85	3.91	2min 15sec	0.6	98.8
F5	197	85	3.84	1min 53sec	0.5	98.2
F6	202	86	3.92	1min 56sec	0.4	98.1
F7	204	88	3.97	2min 56sec	0.4	98.21
F8	201	89	3.91	1 min 28sec	0.4	98.6

Conclusion:

From among all the eight comparison batches with the variable Disintegrates formulation batch no F8 was found to be satisfactory as compared to other formulation. In this the thickness, hardness and disintegration time of prepared tablet was found to be satisfactory as that of Marketed Formulation tablet. In friability test the maximum weight loss should be not more than 1%. The result revealed that the tablets passed the friability test.

Dissolution study:

In vitro release study of reference product:-

Table 13: In vitro drug release study of reference product

Sr. no.	Time	900 ml of 0.1N HCl at 50 RPM by using USP type II (Paddle) apparatus
		% Drug Release of Innovator
1	0	0
2	5	99
3	10	99
4	15	99
5	20	100
6	30	100

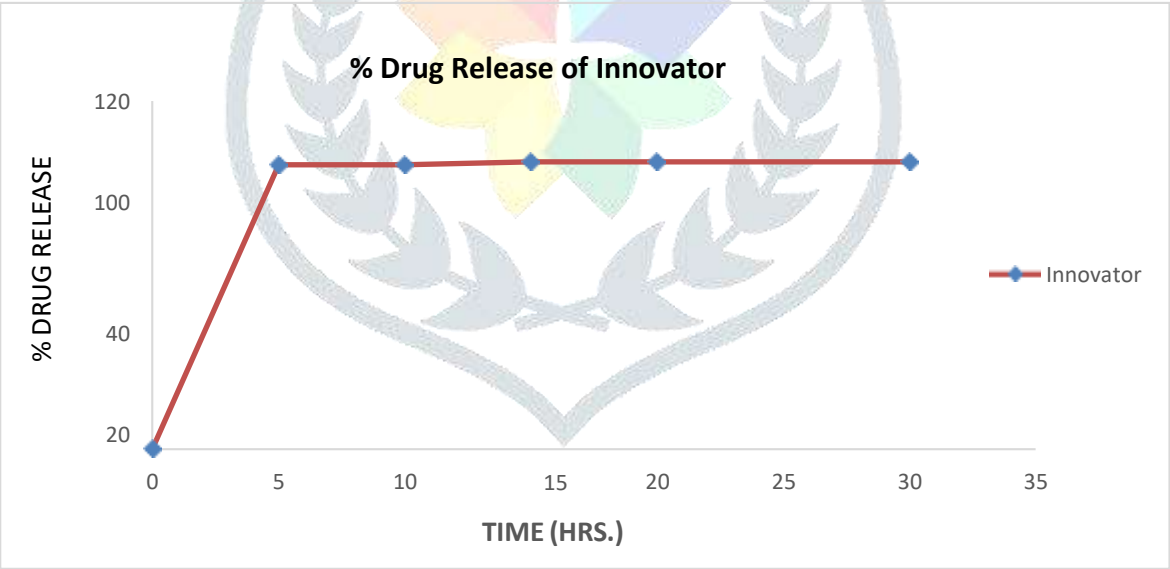

Figure 5: Reference Product Dissolution profile

Conclusion:

From the above result it was observed that the innovator can meet the Q point. i.e. 85% drug release within the 15 min.

Multimedia Dissolution of Reference Product:-

Table 14: Multimedia dissolution study of reference product

Apparatus: USP Type II (Paddle)	lume: 900 ml, Speed: 50 rpm		
Time(min)	1 N HCl	Phosphate buffer pH 6.8	Acetate buffer pH 4.5
5	98	73	83
10	99	88	91
15	99	92	93
20	100	95	95
30	100	96	97

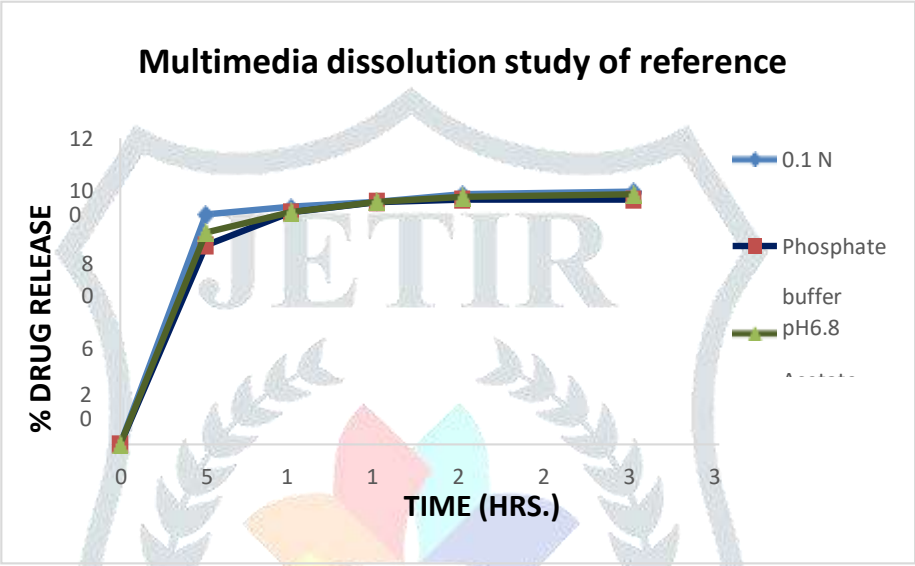

Figure 6: Multimedia dissolution profile of reference product

In vitro Dissolution Study:

Table 15. %Comparative dissolution profile of innovator with allFormulation batches in 0.1N HCl

Media	900ml of 0.1 N HCl at 100 rpm in USP Type I apparatus (Paddle)								
Time	% Drug Release								
	Innovator	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0	0
5	99	58	63	64	66	71	79	81	98
10	99	66	71	68	70	80	83	91	99
15	99	71	73	74	76	85	87	94	99
20	100	74	75	78	80	89	89	96	99
30	100	76	78	80	82	91	92	97	100

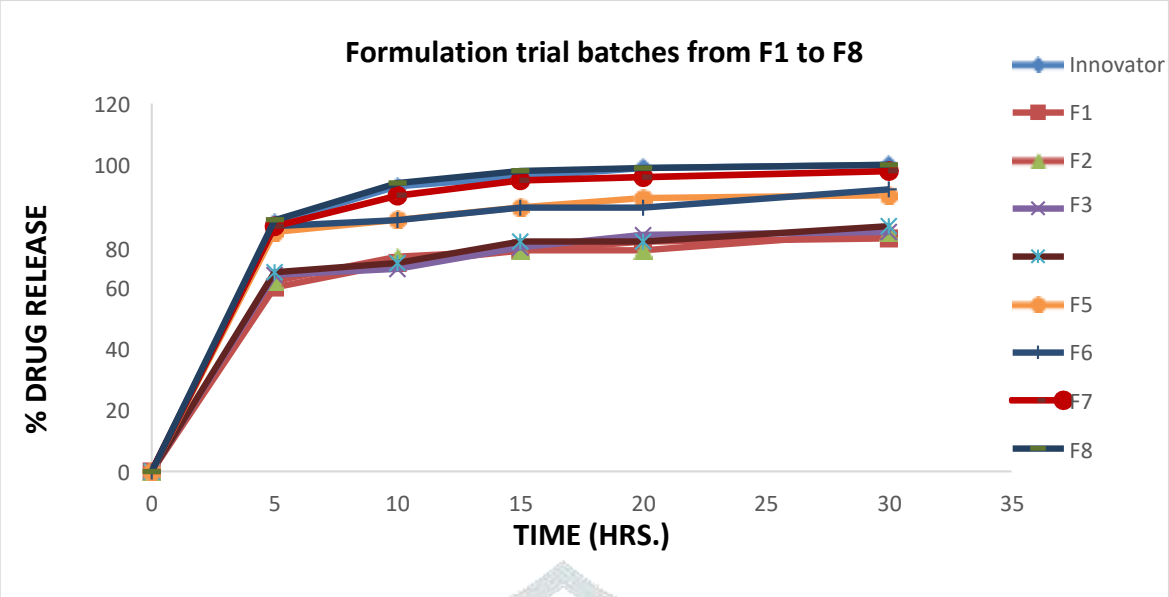

Figure 7: Comparative dissolution profile of all the formulationbatches with reference product in OGD media

Multimedia dissolution study:-

Table 16: Comparative multimedia dissolution data

Apparatus	**USP Type-II**	**Volume**	**900 mL**	
		Speed	100 RPM	
% Drugrelease				
Medium	**pH 4.5 Acetate Buffer**		**pH 6.8 PhosphateBuffer**	
Time Points (min)	**Innovator**	**F8**	**Innovator**	**F8**
0	0	0	0	0
5	83	82	73	73
10	91	91	88	88
15	93	94	92	92
20	95	94	95	94
30	97	96	96	95

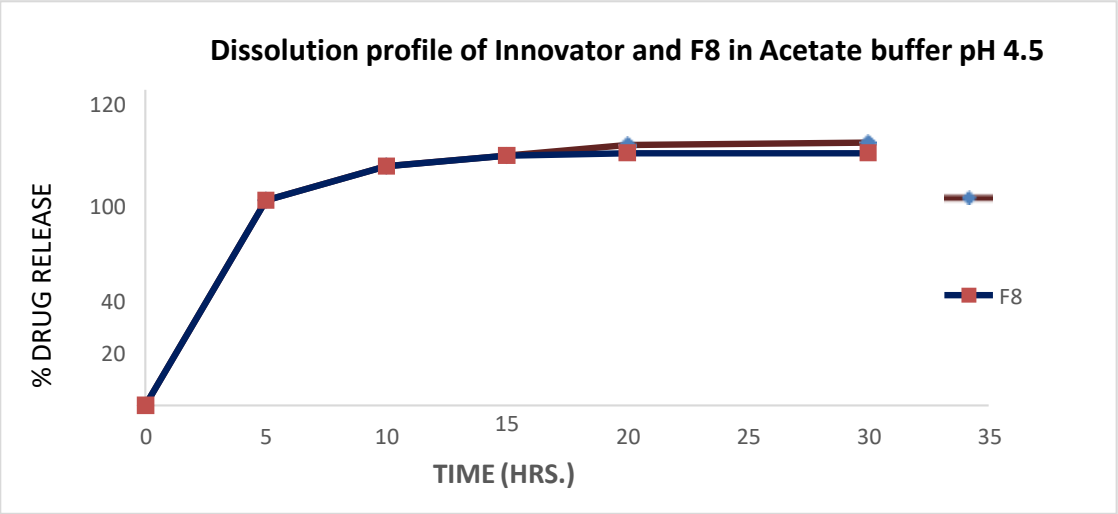

Figure 8: Dissolution profile of Innovator and F8 in Acetate bufferpH 4.5

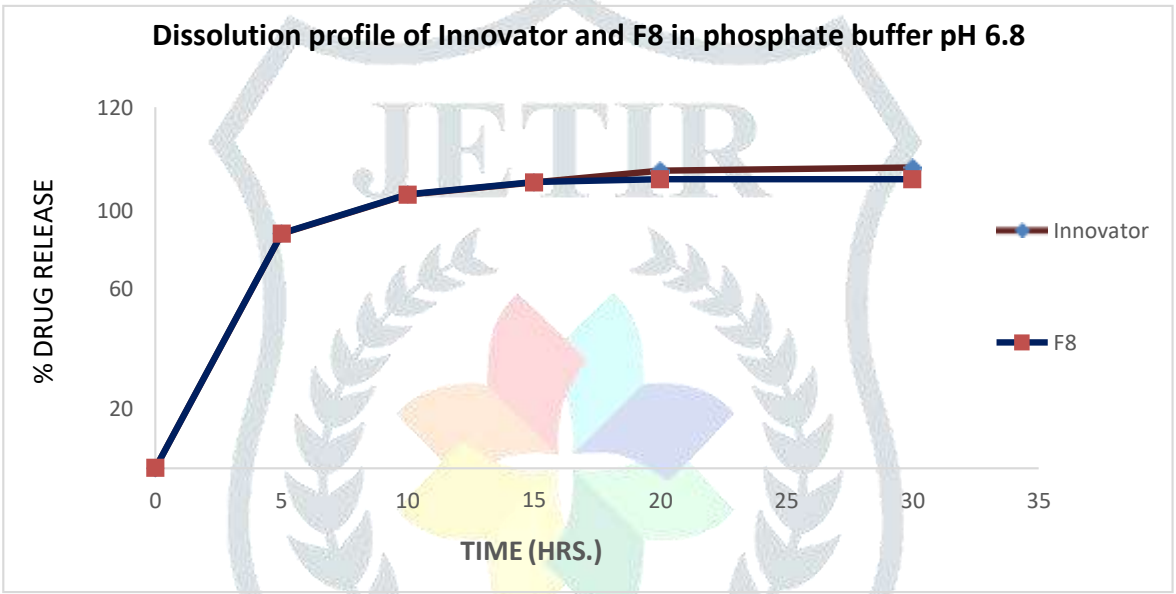

Figure 9: Dissolution profile of Innovator and F8 in phosphate buffer pH 6.8

Observation and conclusion:

Formulation batch F8 dissolution compiles as per reference product criteriaof Innovator in pH 4.5 acetate buffers and pH 6.8phosphate buffer.

Conclusion

The research work was aimed with formulation, development and evaluation of Torsemide fast dissolving tablet of "Torsemide drug" i.e. Torsemide fast dissolving tablet was formulated a stable as well as robust dosage form. The basic objective was to develop a generic version of fast dissolving tablets of torsemide in line with the innovator. A generic version of fast dissolving tablets was developed that is safe, efficacious and to get the comparable dissolution profile and also bioequivalent to the reference product. The task of developing the fast dissolving tablet of torsemide by using super disintegrant because to achieve the bioavailability within the short period. The drug powders were subjected to preformulation studies. The preformulation characteristics are within the pharmacopoeia specification. The preformulation studies were carried out and the results were found to be satisfactory. The drug and excipients compatibility were carried

out by HPLC method and physical observation showed there was no interaction between them. The drug assay was carried out by HPLC method. The various formulation of torsemide were prepared by using Direct compression method, being direct compression involve few step, offers commercial advantages and easy of manufacturability. The tablet was formulated by using excipients such as lactose monohydrate, MMC PH102, Cross carmellose sodium, Pregelatinized Starch and Magnesium stearate. The blend ready for compression was evaluated for bulk density, tapped density, compressibility index and hausner's ratio. It was found that blend had compressibility index from 18 to 22% and hausner's ratio from 1.20 to 1.24 which indicate that blend ready for compression. Total five formulations were prepared using different concentration of MCC PH102, Cross carmellose sodium and Sodium starch glycolate. The tablets were evaluated for weight variation, thickness, hardness, disintegration time, friability, drug release and assay. The weight of tablets found within limit. The thickness of tablets varied from 201 ± 0.21mm.

The designation time vary according to the concentration of excipients. The assays of different batches were found between 98-100% indicating uniformity in drugcontent within tablet.

All eight formulations were evaluated for in vitro drug release in 0.1N HCl, over a period of 30 min using USP type II (Paddle) dissolution apparatus at 50 RPM. The dissolution profiles of the batches were compared with that ofinnovator product. Among all F8 batch –showed comparable in vitrodissolution profile to that of innovator product. The multimedia dissolution were performed by using pH 4.5 acetate buffer and pH 6.8 phosphate buffer. From the result it was observed and it was satisfied for improving dissolution rate to that of reference product. It was found that the release rate of tablet influenced by the super disintegrant. Fast dissolving tablet prepared by direct compression showed comparable dissolution result with innovator. Form the above result it can be concluded that batch F8 showed comparable result with innovator and also shows improvement in dissolution rate by using super disintegrant that means improving dissolution ultimately improvement in bioavailability. Hence anti migraine drug i.e. Torsemide can be successfully formulated as an fast dissolving tablet.

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