ENHANCING THE DISSOLUTION PROFILE OF CARBAMAZEPINE EXTENDED-RELEASE TABLETS FOR THE TREATMENT OF CONVULSIONS BY USING VARIOUS SOLID DISPERSION TECHNIQUES

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Abstract

Carbamazepine (CBZ) is an anti-epileptic drug (BCS Class Ⅱ) and is widely used in the treatment of epilepsy and neuropathic pain. This drug is having low solubility in biological fluids, which results poor bioavailability (BA) after oral administration. So, the aim of present work is to enhance the solubility and dissolution rate of CBZ by using solid dispersion techniques. CBZ improves the solubility by Melting method, Solvent evaporation method and co-grinding method of solvent dispersion technique. These methods were prepared by using PEG 6000 in different concentrations i.e,(1.01, 1:03,1:05,1:07,1:09). FTIR and DSC are used to determine any compatibilities present in between drug and excipients. For the developed formulations evaluation parameters like %weight variations, Hardness, Friability was performed. FTIR and DSC show that the drug was stable in solid dispersions and there was no interaction. The *In-vitro* drug release for F3 formulations was found to be 80.13% in 12 hrs which was prepared by melting method. The *In-vitro* drug release for marketed tablet (Tegretol) was found to be 77% in 12 hrs. The obtained best formulation shows better release than marketed tablet i.e, (Tegretol ER). *In-vitro* drug release kinetics of best formulation follows the zero order and non-fickian transport mechanism. The prepared solid dispersions were observed that increased in the saturation solubility and dissolution rate of CBZ than that of pure drug. The present study concluded that formulation of CBZ extended-release tablets by melting method in solid dispersion technique were is highly effective for enhancing solubility of the drug.

Keywords: Solubility, Carbamazepine, melting method, solvent evaporation method, co-grinding.

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1. Introduction

An oral route of drug administration is the most preferred route of drug delivery due to convenience and ease of ingestion. A solid dosage form is a comfortable and familiar means of taking medication. Hence, a patient compliance and drug treatment are usually more effective with orally administered medications than other routes of administration.[1] At least 40% of the new chemical molecules tested are drugs having poor aqueous solubility. Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization, and addition of solvent or surface-active agents. Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. [2] Solid dispersion technology is one of the most promising and extensively performed approaches to improve the dissolution rate of insoluble compounds. Ease of scalability, its conversion to solid dosage forms such as capsules, tablets, taste masking strips and implants are some of the advantages offered by solid dispersion over other approaches. [3]

CBZ is considered a first line drug in the treatment of epilepsy and trigeminal neuralgia [4]. It is practically insoluble in water. It has at least four different polymorphs (I, II, III and IV) and the dihydrate form [5].

The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of CBZ by preparing solid dispersions with various polymers such as PEG6000 by various methods and prepared as an extended release tablets. The prepared tablets were evaluated various parameters and in vitro dissolution rate studies.

2. Materials and methods

Carbamazepine pure drug was generous gift sample from SRCP, PEG6000 were obtained from BASF, Mumbai, HPMCK15, Povidone K30, Starch, Lactose monohydrate, magnesium stearate, Talc from Sd fine chemicals. All other chemicals used were of analytical grade.

Methods of preparation:

Melting Method:[7]

- All formulation contents were properly weighed using a calibrated analytical balance.
- Drug was dissolved in excess amount of methanol.
- Different concentrations of PEG 6000 were melted at temperature below 70^0c.
- To the Melted PEG 6000 the mixture of drug and methanol was added.
- Melt in solidified ice bath with stirring.
- Solid mass was crushed and sieved.
- Later, it is prepared in to damp mass by using Isopropyl alcohol (IPA) and later granules are prepared by passing through sieve no.22.
- Granules are mixed with lubricating agents, diluents and later these mixtures weighed and punched by using punching machine.

Solvent evaporation method:[6]

- All formulation contents were properly weighed using a calibrated analytical balance.
- Drug was dissolved in excess amount of methanol.
- CBZ and different concentration of PEG 6000 were dissolved in methanol. By stirring and gently heating until a clear solution formed Drug, polymer, and solvent combinations were dried by evaporating on a water bath set to 70^OC until completely dry.
- After cooling, the obtained solid dispersions were crushed in a mortar and passed through a 0.355 mm sieve.
- Later, it is prepared in to damp mass by using IPA and later granules are prepared by passing through sieve no.22.
- Granules are mixed with lubricating agents, diluents and later these mixtures weighed and punched by using punching machine.

Co-Grinding method:

- All formulation contents were properly weighed using a calibrated analytical balance.
- Pure CBZ powder and PEG6000 carriers in various concentrations were physically combined for 10 minutes in a blender at a speed of 20 rpm.
- After that, the mixture was loaded into the chamber of a vibration ball mill.
- A specific number of steel balls were added so that the total volume of powder mixture and balls equaled $1/3^{rd}$ of the volume of the ball mill chamber.
- Later, it is prepared in to damp mass by using IPA and later granules are prepared by passing through sieve no.22.
- Granules are mixed with lubricating agents, diluents and later these mixtures weighed and punched by using punching mechanisms.

Evaluation tests:
Preformulation studies of granules were evaluated by various parameters like angle of repose, bulk density, tapped density, Hausner's ratio, carr's index.

General appearance:
The entire appearance of a tablet, its identity, and general attractiveness are critical for customer acceptability, as well as the management of lot-to-lot and tablet-to-tablet consistency. The measurement of size, shape, colour, presence or absence of odour, taste, and so on is part of the management of general appearance.

Size and Shape:
It can be described and controlled in three dimensions. The thickness of a tablet is simply one of several variables. Digital Vernier callipers can be used to measure the thickness of tablets. Tablet thickness should be kept within a 7.5% of the normal value.

Weight variation:
To verify for weight differences, 20 tablets were chosen at random from each formulation and weighed separately. The United States Pharmacopeia allows for some variance in tablet weight.

Hardness:
To withstand mechanical shake during manufacturing, packing, and shipping, tablets must have a particular amount of strength or hardness as well as resistance to friability. The strength of a tablet's crushing is measured by its hardness. Monsento hardness tester was used to test the hardness of all the formulations. The hardness of ten tablets from each batch was measured and reported.

Friability:
The friability of a tablet may be determined in the laboratory using the Roche Friabilitor. This consists of a plastic chamber that spins at 25 revolutions per minute, dumping tablets weighing not less than 6.5 g over a six-inch distance in the Friabilator, which is then operated for 100 revolutions. The tablets are weighed again. Compressed tablets containing less than 0.1 to 0.5 percent of the tablet weight are acceptable. The formula was used to calculate the % friability.

Drug content:
For this test, a stock solution was produced by dissolving 10 mg of carbamazepine in 100 mL of methanol, and a standard solution containing 10g/mL was obtained from the stock solution. A test solution of the fifteen formulations was prepared at the same carbamazepine concentration of 10.00 g/ml. The absorptions of these solutions were measured at 284 nm using methanol as a blank. The carbamazepine concentration in the sample may not be less than 92 percent or greater than 108 percent.

In-vitro dissolution studies: The in vitro dissolution was carried out utilizing USP II disintegration contraption. The dissolution test was performed utilizing 7.4 pH phosphate buffer as dissolution medium (900 mL) kept up at 37 ± 0.5^{O}C at 100 rpm. The examples (5 mL) of the arrangement were pulled back from the dissolution mechanical assembly for 12 h, and the examples were supplanted with new dissolution medium each an ideal opportunity to keep up the sink condition. Pulled back examples were investigated utilizing UV-VIS twofold pillar spectrophotometer at 284 nm against appropriately built alignment bend. All estimations were completed in triplicate, and normal qualities were plotted.

Dissolution kinetics:
Various models like zero-order, first-order, Higuchi models, Korsemeyer and Peppas were tested for explaining the kinetics of drug release.

Results and discussion:
The Carbamazepine extended-release tablets were prepared by Solvent evaporation, Melting method and Co-grinding methods. The formulation was carried out by using the ingredients such as PEG6000, HPMC, PVP K30, Isopropyl alcohol, talc and magnesium stearate.

Preformulation studies:
Preformulation were carried out for the powder. The results are within the limits showed good flow property, it shown in table 2.

The FTIR studies were carried out to determine the compatability studies. Spectra for the pure drug showed observed frequencies at 764.4cm^{-1}, 1384.82cm^{-1}, 1599.74cm^{-1}, 1675.117cm^{-1}, 3162.17cm^{-1} which determines the presence of C-H, C-H, C=N, N-H, O-H respectively. FTIR graph for mixture shown frequencies at 1466.3cm^{-1}, 1112.2cm^{-1}, 1599.6cm^{-1}, 1675.07cm^{-1}, 2885.6cm^{-1}representing the presence of C-H, C-O, N-H, C=C and C-H functional groups.

The values of weight variation and friability were found to be within the limits of CBZ extended release tablets stated in the Indian Pharmacopoeia. Thickness of the tablets varied from 4.20 mm to 4.50 mm. Hardness of the tablets varied from 4.70-6.0 which is within the limits only. The % friability and disintegration time values varied from 0.818%

to 0.954 % and after 5min also within the limits of CBZ – ER tablets. Results were shown in table 3. Dissolution studies were performed to determine the amount of drug release. Drug release for all formulations was found to be in the range of 58-80%. 3rd formulation produced through melting method showed drug release of 80.5%. Kinetic results showed that it followed zero order kinetics

Table No.1: Composition table for preparation of solid dispersion of CBZ Extended release tablets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**
Method	**Melting method**					**Solvent evaporation method**					**Co-grinding method**				
CBZ	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
PEG 6000	20	60	100	140	180	20	60	100	140	180	20	60	100	140	180
Solid dispersion powder Qty/tablet	213.3	250	293.3	333.3	366.6	212.8	253.3	290	336.6	373.3	218.6	257.3	313.3	333.3	373.3
HPMC K15	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Povidone K30	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Lactose	239.2	202.5	159.2	119.2	85.9	239.7	199.2	162.5	115.9	79.2	233.9	195.2	139.2	119.2	79.2
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Methanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total Qty/tablet	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500

All quantities taken in 'mg'

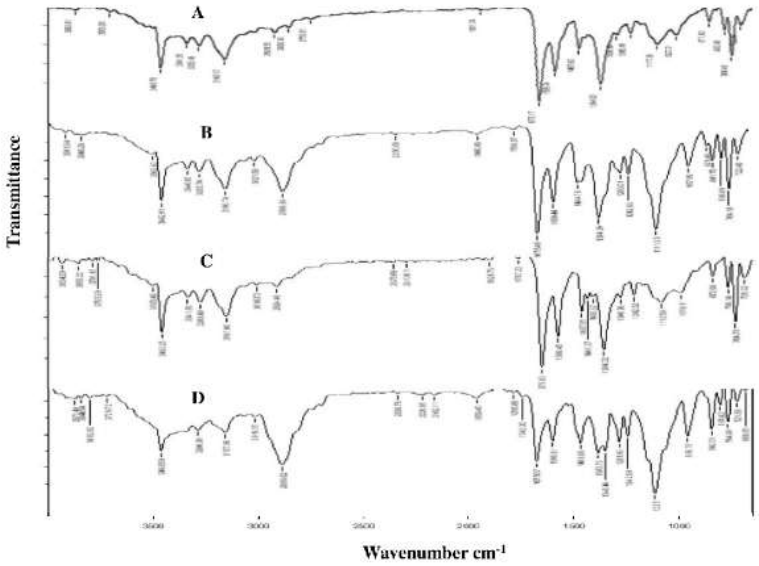

Figure No.1: FTIR Spectrum of A) Pure CBA, B) CBZ with PEG6000 C) CBZ with HPMC K15 D) Mixture of all ingredients

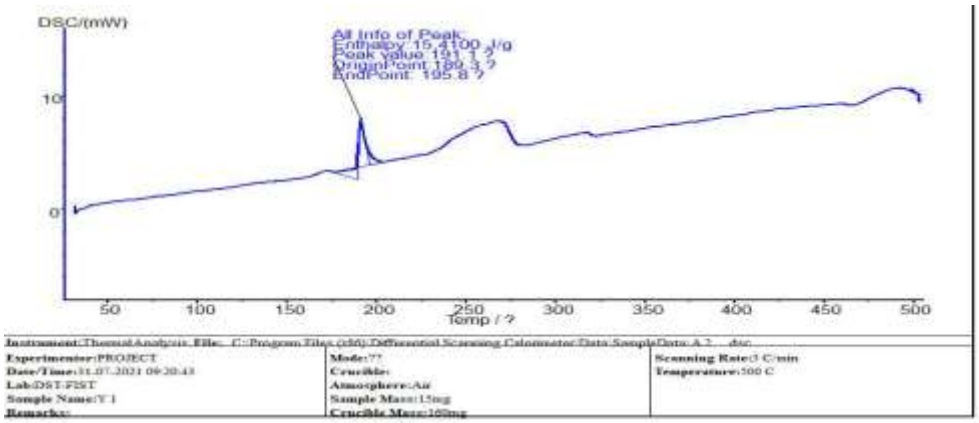

Figure No.2: DSC graph of Pure CBZ

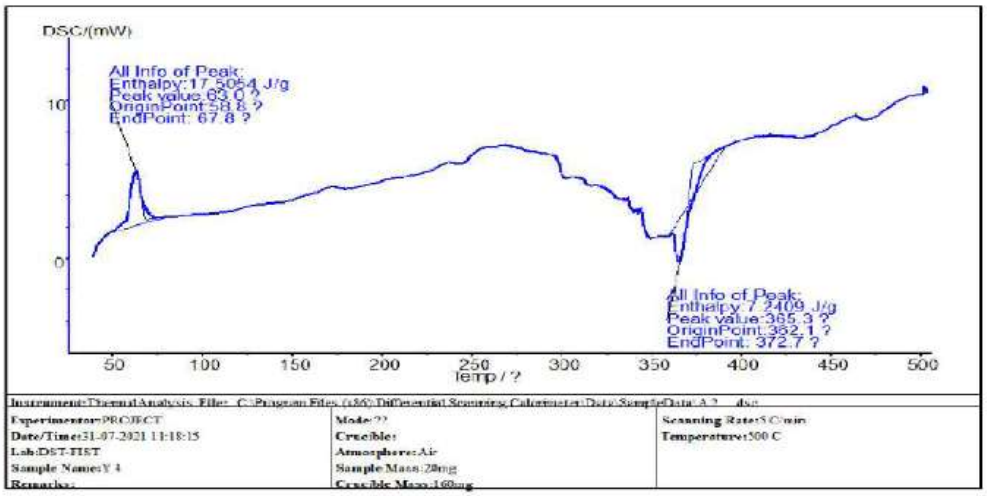

Figure No.3: DSC graph of CBZ with excipients

Table No.2: Powder properties of Formulation of Carbamazepine extended release tablets:

Formulation code	**Bulk density (g/cc)**	**Tapped density(g/cc)**	**Car's Index (%)**	**Hausner's ratio**	**Angle of repose(θ)**
F1	0.5	0.535	6.542	1.07	22.14
F2	0.454	0.483	6.159	1.06	24.32
F3	0.468	0.480	2.5	1.04	25.34
F4	0.468	0.477	1.88	1.01	28.28
F5	0.454	0.480	5.41	1.05	24.92
F6	0.441	0.454	2.868	1.02	29.48
F7	0.483	0.5	3.24	1.03	25.34
F8	0.468	0.480	2.5	1.025	26.07
F9	0.460	0.474	2.95	1.030	22.14
F10	0.454	0.480	5.41	1.05	28.28
F11	0.477	0.510	6.470	1.069	30.14
F12	0.471	0.510	7.64	1.082	24.32
F13	0.465	0.480	3.125	1.032	21.09
F14	0.457	0.474	3.586	1.037	24.92
F15	0.443	0.465	2.795	1.049	22.14

Table No.3: Evaluation studies of prepared tablets

Formulation code	**Weight variation (mg)**	**Friability (%)**	**Diameter (mm)**	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Drug content (%)**
F1	487	0.822	12.2	4.2	5.9	96.3
F2	499	0.818	12.01	4.45	5.8	97.2
F3	501	0.954	12.05	4.50	6.6	99.1
F4	494	0.901	12.06	4.4	5.3	96.2
F5	508	0.923	12.07	4.23	4.8	97.5
F6	504	0.855	12.02	4.20	5.4	97.3
F7	489	0.876	12.01	4.33	5.3	95.67
F8	499	0.912	12.1	4.35	4.7	98.01
F9	501	0.901	12.08	4.22	5.6	96.4
F10	492	0.928	12.2	4.2	5.1	95.5
F11	505	0.868	12.01	4.20	6.1	96.9
F12	501	0.899	12.07	4.33	4.9	98.6
F13	499	0.857	12.02	4.35	5.2	97.7
F14	492	0.869	12.01	4.2	5.7	96.5
F15	496	0.933	12.1	4.20	5.2	95.8

Table No.4: In-Vitro Dissolution studies for Formulations F1-F5 (Melting method)

Time (hrs)	**F1**	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
0.5	4.32	4.93	5.55	4.93	5.55
1	5.55	5.55	6.16	6.84	7.27
2	6.47	7.09	7.09	7.64	8.14
3	7.77	7.95	7.95	8.57	9.62
4	8.94	8.32	10.36	12.21	10.97
5	13.87	15.10	14.67	14.05	15.97
6	18.31	17.69	21.33	23.30	21.08
7	19.23	19.23	24.53	24.53	23.36
8	24.29	22.44	30.08	28.91	28.91
9	29.71	29.53	38.22	39.21	45.99
10	41.79	42.41	55.17	52.34	51.72
11	55.11	47.10	67.19	65.34	61.40
12	67.19	62.26	80.14	68.42	62.26

Table No.5: In-Vitro Dissolution studies for Formulations F6-F10 (Solvent evaporation method)

Time (hrs)	**F6**	**F7**	**F8**	**F9**	**F10**
0	0	0	0	0	0
0.5	4.31	5.55	5.55	6.23	6.23
1	7.08	6.60	7.03	7.03	7.03
2	7.58	6.97	7.95	7.95	7.64
3	9.00	8.51	8.38	8.57	8.57
4	10.35	9.74	9.12	9.12	9.12
5	11.65	10.42	11.03	11.03	11.03
6	16.15	17.82	17.20	17.20	16.58
7	19.97	20.65	22.38	23.98	23.98
8	26.07	29.59	33.84	36.92	36.92
9	33.65	35.51	39.39	43.09	40.01
10	42.34	48.02	45.86	48.95	48.95
11	55.23	58.32	52.15	55.23	51.35
12	61.64	67.19	63.49	61.64	61.34

Table No.6: In-Vitro Dissolution studies for Formulations F11-F15 (Co-Grinding method)

Time (hrs)	**F11**	**F12**	**F13**	**F14**	**F15**
0	0	0	0	0	0
0.5	4.93	4.93	5.54	5.54	4.93
1	7.02	6.84	6.41	7.21	7.02
2	7.89	7.45	7.45	7.89	7.52
3	8.56	8.56	8.81	8.81	8.81
4	8.75	8.63	9.80	9.67	9.49
5	10.66	9.73	12.20	10.97	10.97
6	14.73	14.73	15.34	14.11	15.16
7	21.08	23.30	23.30	22.68	22.06
8	35.07	28.78	29.83	29.83	29.83
9	40.00	35.07	35.07	33.22	35.63
10	48.94	48.94	42.41	40.93	40.00
11	50.11	52.27	51.28	53.13	53.13
12	59.48	62.26	61.08	58.37	59.54

Table No. 7: Comparison of best formulation (F3) with marketed drug

Time (hrs)	**% CDR Tegretol**	**% CDR F3**
0	0	0
0.5	5	5.54
1	10	6.16
2	20	7.08
3	31	7.95
4	36	10.35
5	42	14.67
6	49	21.32
7	53	24.53
8	59	30.08
9	64	38.21
10	71	55.17
11	75	67.19
12	77	80.13

Table No.8: In-Vitro Release Kinetics of F3 Formulations

Code	**Zero order**		**First order**		**Higuchi**		**Korsmeyer – peppas**		**Release mechanism**
	Slope	**R^2**	**Slope**	**R^2**	**Slope**	**R^2**	**n**	**R^2**	
F3	5.07	0.93	0.03	0.74	13.74	0.82	0.56	0.77	Non-fickian diffusion

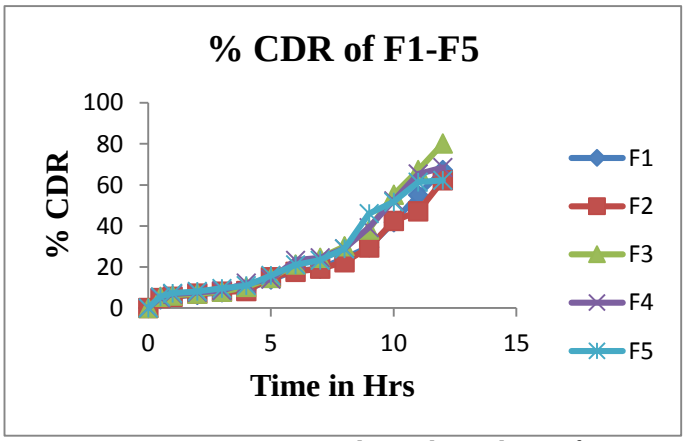

Figure No.4: Percentage cumulative drug release of F1-F5

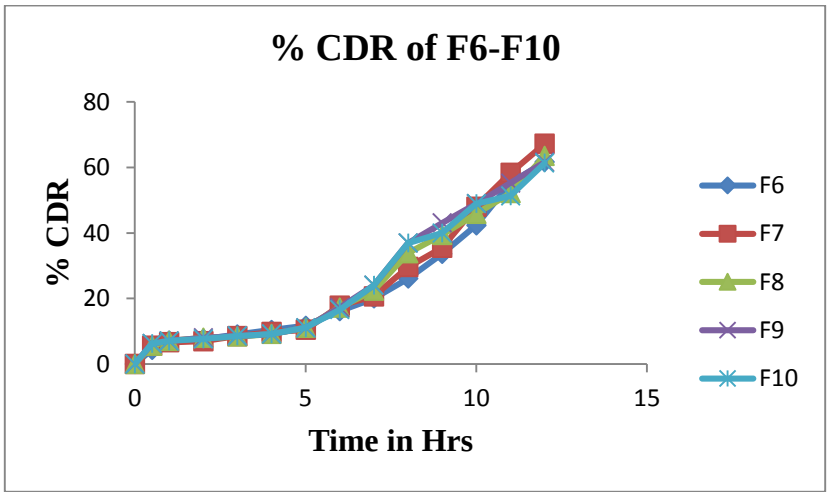

Figure No.5: Percentage cumulative drug release of F6-F10

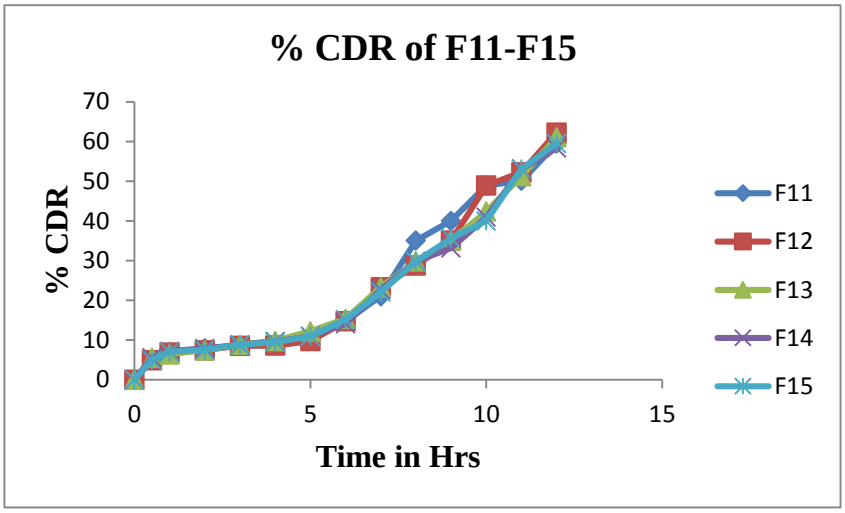

Figure No.6: Percentage cumulative drug release of F11-F15

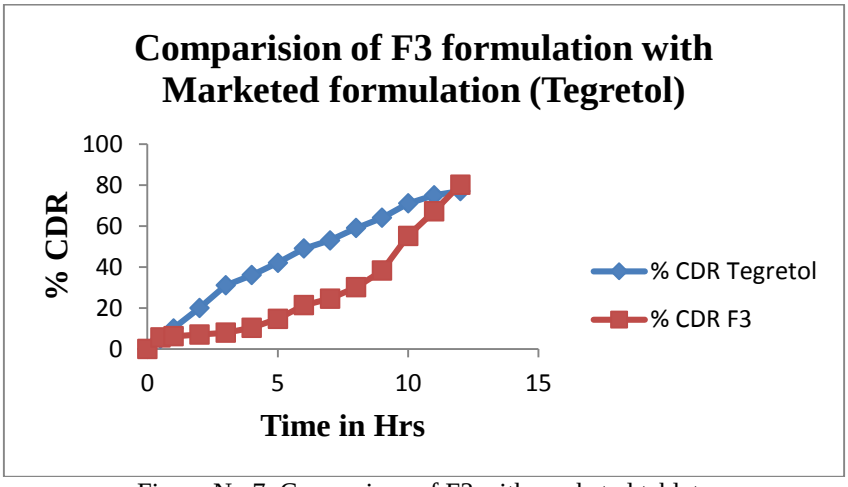

Figure No.7: Comparison of F3 with marketed tablets

3. Conclusion

In conclusion, our study showed that melting method of solid dispersion in Carbamazepine: PEG 6000 at 1:05 ratios enhanced dissolving rate, had high physicochemical properties, was characterised by dissolution release kinetics, and was chosen as the best formulation.

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4. References

Patil A, Kumar S. Formulation and evaluation of solid dispersions of an anthelmintic drug for enhancement of dissolution rate. JIPBS. 2017; 4 (3):71-74.

AppaRao B, Shivalingam MR, Kishore Reddy YV, Rao S, Rajesh K, Sunitha N. Formulation and Evaluation of Aceclofenac Solid Dispersions for Dissolution Rate Enhancement. International Journal of Pharmaceutical Sciences and Drug Research. 2010; 2(2): 146-150.

Enose AA, Dasan P, Sivaramakrishanan H, Kakkar V. Formulation Characterization and Pharmacokinetic Evaluation of Telmisartan Solid Dispersions. J Mol Pharm Org Process Res. 2016; 4(1): 131.

Tayel SA, Soliman II and Louis D (2008). Improvement of dissolution properties of carbamazepine through application of the liquisolid tablet technique. European Journal of Pharmaceutics and Biopharmaceutics, 2008;69 (1):342-347.

Ali W, Badawi A, Mahdy M and El-Nahas H (2013). Formulation and evaluation of carbamazepine 200 mg controlled release tablets using different HPMC grades. British Journal of Pharmaceutical Research,2013;3(4):632-647.

Sheikh Tasnim Jahan, Md. Saifur Rahman Khan, Md. Moniruzzaman, Md. Rezowanur Rahman, Sams Mohammad Anowar Sadat and Reza-ul Jalil, American journal of scientific and industrial research, 2011, 2(1): 112-115.

Nikghalb LA, Singh G, Singh G, Kahkeshan KF. Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs. Journal of Applied Pharmaceutical Science. 2012;2(10):170-5.

Barzegar-Jalali M, Valizadeh H, Dastmalchi S, SiahiShadbad MR, Barzegar-Jalali A, Adibkia KH, Mohammadi GH. Enhancing dissolution rate of carbamazepine via co-grinding with cros-povidone and hydroxy propyl methylcellulose. Iranian Journal of Pharmaceutical Research. 2007; 20(3):159-65.

YeHuang, Kavita H Khanvilkar, Angela D Moore, Marquetta Hilliard-Lott, effect of manufacturing process variables on invitro dissolution characteristics of extended-release tablets formulated with hydroxy propyl methylcellulose. Drug.Dev.Ind.Pharm.2006; 29 (1):79 – 88.