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To Formulate Develop and Evaluate Sustained Release Matrix Tablet of Torsemide and also Carried out in Vitro Dissolution Studies.

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ABSTRACT

The aim of present study was formulation and development and evaluation of sustained release matrix tablet of Torsemide. The Torsemide is potassium sparing diuretic generally used in hypertension. The Torsemide has advantages over furosemide in treatment of Edema associated with congestive heart failure. The action of Torsemide can be mediated by several mechanisms operating within the thick, medullary segment of ascending loop of Henle. The Torsemide has a dose about 10mg twice a day, so to reduce dosing frequency it is formulated in sustained release formulation.

Torsemide sustained release tablet was prepared by using polymers HPMC K 100 as sustained release polymer and Kollidon VA64 as binder by direct compression method. A 3^2 full factorial design was used to formulate different batches containig different concentration of HPMC K 100 and Kollidon VA64. The prepared tablets were evaluated for different parameters like Hardness, Friability, and Dissolution.

Out of all factorial design batches F6 batch shows sustained release drug release for 24hr as compared to other all batches.

KEY WORDS: Torsemide, Sustained release matrix tablet, HPMC K 100, Kollidon VA64, Dissolution kinetics.

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1. INTRODUCTION[1, 2, 3, 4]

Over the past decades the treatment of acute and chronic illness has been accomplished by many conventional drug delivery systems such as tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories. These conventional drug delivery systems are still the primary pharmaceutical products commonly seen today in prescription. Oral route is the most commonly employed route of drug administration. Although different route of drug administration are used for the delivery of drugs, oral route remain the preferred route. Even for sustained release systems the oral route of administration has been investigated the most because of flexibility in dosage forms design that the oral route offers.

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Also in these types of systems, for achieving and maintaining concentration of drug within the therapeutic range, frequent dosing is required which result into see-saw pattern of the drug levels**.**

To overcome these problems sustained release systems were introduced three decades ago. Sustained release, sustained action, prolonged release, controlled release, extended action, timed release, depot and repository dosage forms are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The term “controlled release” has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rate over long period of time.

The basic goal of drug therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non-toxic for an extended period of time. To achieve better therapeutic action various types of drug delivery systems are available, out of which sustained release systems are gaining much importance because of their wide advantages over others like ease of administration, convenience and non-invasiveness. The vast majority of traditional dosage forms can be described as dump systems which deliver their active substances in a first order fashion, that is, release occurs at rates that are highest initially and then decline steadily thereafter. Clinically this peak and valley pattern results in a time dependent mix therapy. Drug side effects tend to predominate at the high peak concentration in blood, whereas, an inadequate therapeutic effect may prevail at the valley level. Use of controlled release systems provides an excellent tool to achieve precise control of rate standpoint, but also at a particular site

➢ Advantages of sustained release drug delivery[8]

Sustained release products have many advantages listed as follows.

1. These formulations reduce dosing frequency of drugs.
2. These formulations may maintain therapeutic concentrations.
3. Reduce the toxicity by slowing drug absorption.
4. The use of these formulations avoids the high blood concentration.
5. These formulations have the potential to IM side effects.
6. Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
7. Improvement in treatment efficacy.
8. Minimize drug accumulation with chronic dosing.
9. Improve the bioavailability of some drugs.
10. Usage of less total drug.
11. Improve the ability to provide special effects prove the patient compliance.

➢ Disadvantages of sustained release drug delivery

1. This formulation contains a higher drug load and thus leads to loss of integrity of the dosage form.
2. The larger size of sustained release products may cause difficulties in ingestion or transit through gut.
3. The release rates are affected by various factors such as food and the rate of transit through the gut.
4. Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
5. High cost of preparation
6. Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. The majority of oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug.

2. MATERIAL AND METHOD

API: Torsemide is obtained as a gift sample from Pure chem laboratories Ltd., Ankleshwar, Gujrat. Kollidon VA64 and HPMC K100 (matrix forming material), Micro crystalline cellulose (MCC) PH102 (filler), Talc (glidant) and Magnesium stearate (lubricating agent).

Instrument used for study:

1. UV spectrophotometer (Shimadzu UV-2450 Double Beam Spectrometer).
2. FTIR spectrophotometer (Shimadzu).
3. Pfizer hardness tester (Cadmach, India).
4. Roche Friabilator (Remi Electronics, Mumbai, India).
5. Single pan electronic balance (Shimadzu AUX 220)
6. Vernier calliper.
7. USP XXII Type II Dissolution apparatus DS 8000 (Lab-India, Mumbai, India).
8. UV spectrophotometer (Shimadzu UV-2450 Double Beam Spectrometer).
9. Differential scanning Calorimetry (PerkinElmer 4000)

Method:

2.1. Formulation study

2.1.1. Preliminary trial batches:

Composition of preliminary trials batches for sustained release formulation is shown in Table .In all the formulations dose of Torsemide 20 mg was taken. Torsemide matrix tablets were prepared by direct compression method. The excipients used were Kollidon VA64 and HPMC K100 (matrix forming material), Micro crystalline cellulose (MCC) PH102 (filler), Talc (glidant) and Magnesium stearate (lubricating agent).

2.1.2. Direct compression technique:

Torsemide, Kollidon VA64, HPMC K100 and MCC were mixed properly. The powder blends were lubricated using Magnesium stearate and Talc was added finally. Tablets were prepared using 10-station rotary compression machine. The prepared tablets were evaluated for hardness and *in vitro* drug release.

Table 1: Composition of trial batches

Ingredients (mg) / batch	T1	T2	T3	T4
Torsemide	20	20	20	20
HPMC K100	60	40	70	30
Kollidon SR	60	80	40	90
MCC 102	40	40	40	40
Mg. Stearate	15	15	15	15
Talc	5	5	5	5
Total	200	200	200	200

2.2.3. Formulation of Torsemide SR matrix tablets

In the given table the values of excipients are decided depending on the concentrations suggested as in Book of excipients. The values are given depending on particular role of that ingredient. HPMC here is used as sustained release matrix forming polymer, Kollidon VA 64 is binder, MCC 102 as diluents, talc and magnesium stearate as flow enhancers.

Table 2: Formulation of 3^2 Factorial Design Batches

Ingredients (mg) / batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Torsemide	20	20	20	20	20	20	20	20	20
HPMC K100	70	70	60	60	70	80	80	60	80
Kollidon VA64	40	30	50	40	50	50	40	30	30
MCC 102	50	60	50	60	40	30	40	70	30
Mg. Stearate	15	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5	5
Total	200	200	200	200	200	200	200	200	200

2.3. Preparation of Tablets:

The direct compression method was utilized for the preparation of tablets. The drug Torsemide, HPMC K100, Kollidon VA64 and MCC PH102 were mixed thoroughly in mortar and pestle for 5 min. The blends of the prepared powder were lubricated with Magnesium stearate and mixed with Talc. The tablets were compressed using 9 mm punches at on multiple punches 10 station tablet machine. The formulae of all factorial batches of Torsemide SR Matrix tablet are shown in the Table.

2.4. Evaluation of Torsemide (SR) matrix tablets

2.4.1. Appearance and thickness :

The thickness of tablet as a dimensional variable was evaluated. The tablet thickness was controlled within ±5% of average value. The colour, odour and any other flaws like chips, cracks, surface texture, etc. are other important morphological characteristics were observed.The thickness of tablet was measured in mm using micrometre screw gauge and diameter defined by die used in the preparation of tablets.

2.4.2. Hardness

Tablet hardness is defined as force required to crushing the tablet in diametric compression test. The hardness was measured with Pfizer hardness tester. The tablets were placed diametrically

between two plungers and the lower plunger is kept in contact of tablet to read as zero. The upper plunger is forced against a spring by turning the screw until tablet fractures.

2.4.3. Weight variation test

Twenty tablets were taken and weighed and average weight of the tablet was determined. The tablets were weighed individually and the weight variation was determined.

2.4.4. Friability

Twenty tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which revolves at 25 rpm for 4 min. dropping the tablets through a distance of 6 inch with each revolution. This process was repeated for all formulations and the percentage friability was calculated.

The % Friability was then calculated by,

$$\% \text{ Friability} = W_{initial} - W_{final} / W_{initial} \times 100$$

2.4.5. Drug Content

It is determined by ten random tablets were taken and one tablet was crushed powder equivalent to 20 mg was dissolved in 100 ml of 0.1N HCl and shaken for 20 min. solution will be filtered and after suitable dilution using 0.1N HCl, absorbance was measured spectrophotometrically against reagent as blank. Amount of drug present in one tablet was calculated.

2.4.6.* In vitro *drug release study

The drug release rate from Torsemide SR matrix tablets was determined using USP apparatus type II (lab India, India). The dissolution test was performed using 900 ml of 0.1N HCl at 37 ± 0.5°C and 50 rpm. A sample (10 ml) was withdrawn at a specific interval and replaced with fresh dissolution medium of same quantity. The samples were filtered through a Whatman filter paper. Absorbance of the solutions was measured at 237 nm by UV-Visible Spectrophotometer (UV-2450 SHIMADZU).The drug release and drug release kinetics was calculated.

2.5. Kinetics analysis of drug release:

In order to investigate the mode of release from the tablets the release data were analysed with the following mathematical models:

A. Zero-order kinetic:

$$Q_0 = Qt + k_0t$$

Where, Qt is amount of drug release at time t

K_0 is zero order release rate constant.

Q_0 is amount of drug present initially at t = 0

B. First-order kinetic:

$$\ln (100 - Q) = \ln Q0 - k_1 t$$

Where, Q = amount of drug release at time t

Q_0 = amount of drug present initially

K_1 = first order release rate constant

C. Higuchi equation:

$$Q = k_H\, t1/2$$

Where, Q = amount of drug release at time t

K_H = Higuchi dissolution constant

D. Korsmeyer-Peppas model:

$$Q = k_P t^n$$

Where, Kp is a constant incorporating the structural and geometric characteristics of the drug dosage form.

n is the release exponent indicative of the mechanism of release.

This equation was further simplified and proposed by Ritger and Peppas,

$$Mt/M = Kt^n$$

Where, Mt is the drug released at time t,

M is the amount of drug released at infinite time

K is a kinetic constant, and

n is the diffusional exponent.

The value of n indicates the drug release mechanism. For a slab the value n = 0.5 indicates Fickian diffusion and values of n between 0.5 and 1.0 or n = 1.0 indicate non-Fickianmechanism. In case of a cylinder n = 0.45 instead of 0.5, and 0.89 instead of 1.0. This model is used to analyse the release from polymeric dosage forms, when the release mechanism is not well known or when there is a possibility of more than one type of release phenomenon involved.

Table 3: Interpretation of diffusional release mechanism from polymeric films.

Release exponent (n)	**Drug transport mechanism**
0.5	Fickian diffusion
0.5 < n > 1.0	Anomalous transport(non-Fickian)
1.0	Case-II transport
Higher than 1.0	Super Case-II transport

3. RESULTS AND DISCUSSION:

3.1. Drug identification

The sample of Torsemide procured for study and was identified by melting point, UV spectrum, ATR spectrum and DSC thermograph.

3.1.1. Organoleptic characteristic of API

Table 4: Organoleptic characteristic

Parameter	Observation Result	Reported Standard
Colour	White	White
Odour	Odourless	Odourless
Appearance	Crystalline powder	Crystalline powder

Organoleptic properties of drug samples were in accordance with literature values.

3.1.2. Melting Point

Table 5: Melting Point

Sample	Observed value (^{0}C)	Reported value (^{0}C)
Torsemide	162- 165^{0}C	163-165^{0}C

3.1.3 Solubility studies:

Table 6: Solubility Studies

Solvent	Observed Solubility(mg/ml)	Reported Solubility(mg/ml)
Water	0.00156	0.001
DMSO	17	18

3.2. DSC Study:

3.2.1. DSC study of API

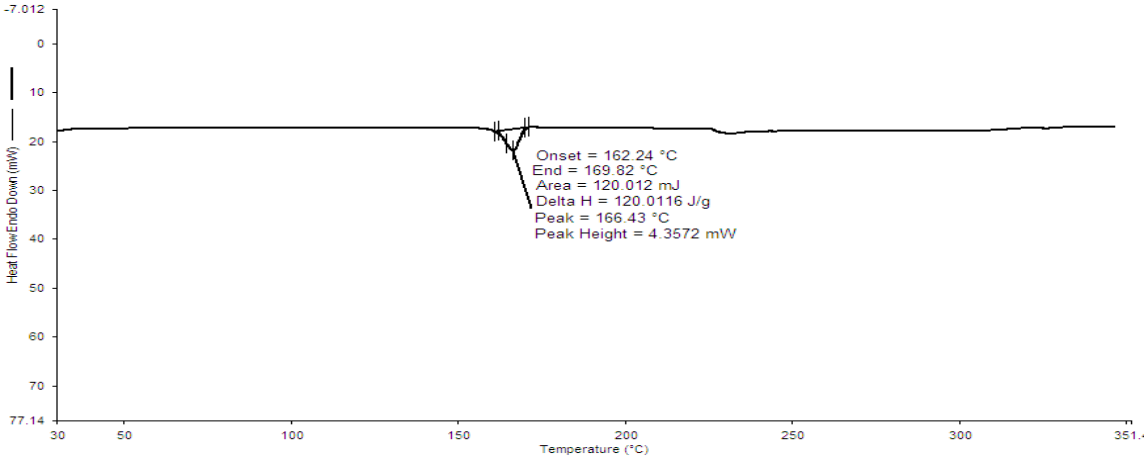

Fig1: DSC Thermogram of Torsemide

Here the DSC thermogram shows the melting point in range of 166-169^{0}C
This is in the standard reported range for pure Torsemide.

3.2.2 DSC study of Excipient and Drug Excipient Mixture

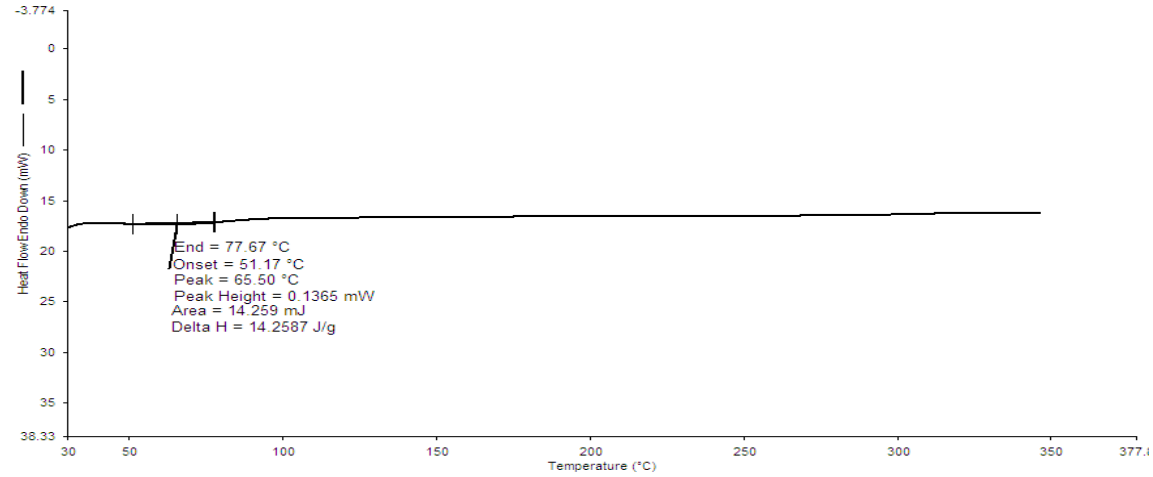

Fig2: DSC thermogram of HPMC K100

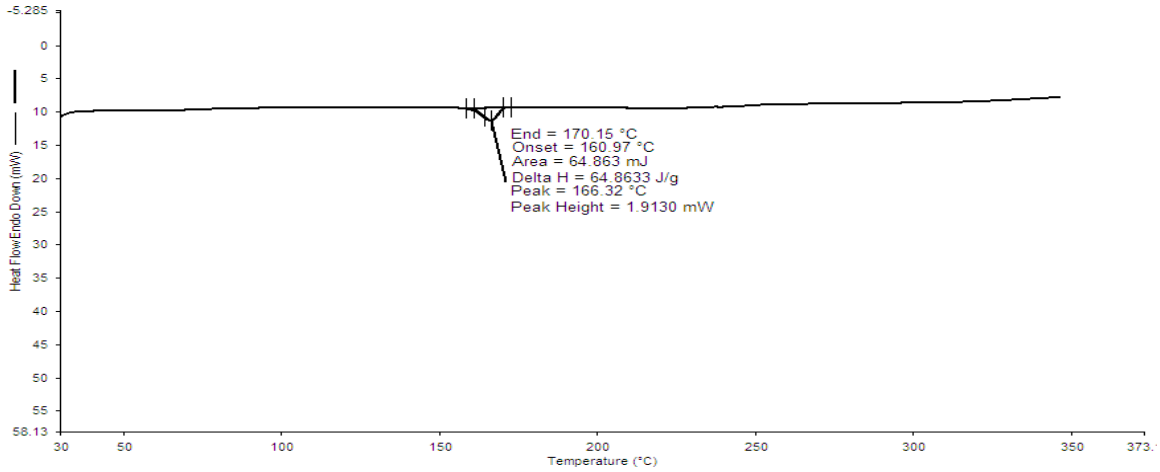

Fig3: DSC thermogram of Physical mixture

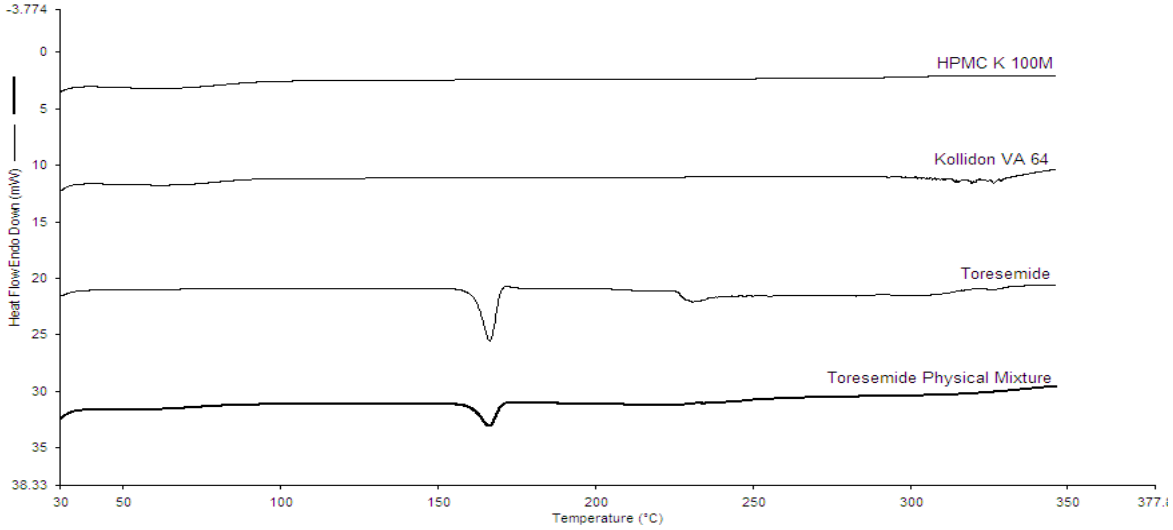

Fig4: DSC overlay plot

The melting point range observed in both thermogram is same indicating compatibility between drug and excipients.

3.3. Formulation Studies

3.3.1 Preliminary trial batches

Table7: Evaluation of preliminary trial batches

Time (hrs.)	% Drug Release of trial formulations			
	T1	T2	**T3**	T4
1	6.14	2.18	**5.10**	11.66
3	19.17	27.28	**16.32**	26.25
5	26.94	38.59	**23.51**	30.64
8	38.77	50.78	**33.56**	42.90
11	48.14	61.95	**43.44**	53.34
14	58.03	69.32	**53.87**	63.25
16	64.63	72.34	**59.43**	69.53
18	69.33	74.15	**65.28**	75.69
20	74.86	75.18	**71.87**	77.69
22	78.10	76.31	**76.59**	80.14
24	81.18	71.31	**82.42**	81.86

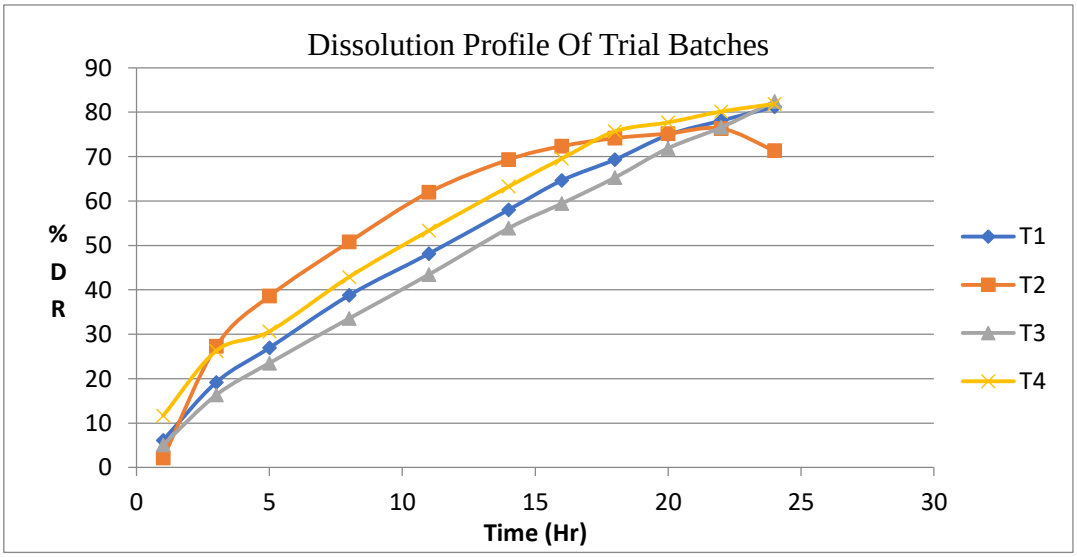

Fig 5: Drug Release of Preliminary trial batches

The release profile of trial formulations (T1 to T4) **given in Table18**. Formulation T1 to T4 drug release studied for 24 Hrs. T3 and T4 batch shows better drug release profile than others. Concentration of HPMC K100 shows impact on release of active ingredient in formulations.T3 shows 82.42 and T4 shows 81.86

Table 8: Evaluation of tablet

Batch	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug Content (%)
F1	200±1.8	7±0.11	0.59±0.01	3.2±0.05	98.45
F2	199±1.7	7.3±0.1	0.63±0.0111	3.3±0.15	98.13
F3	198±1.0	6.6±0.17	0.68±0.009	3.2±0.15	99.09
F4	200±1.8	7±0.2	0.49±0.016	3.3±0.15	99.31
F5	199±1.9	7.1±0.31	0.51±0.008	3.4±0.05	99.57
F6	201±1.8	7.5±0.05	0.54±0.017	3.3±0.1	98.90
F7	202±1.9	7.1±0.1	0.43±0.009	3.3±0.15	99.98
F8	200±1.8	6.6±0.15	0.67±0.012	3.2±0.1	100.12
F9	200±1.3	6.7±0.05	0.69±0.014	3.2±0.11	97.63

Mean ±SD n=20

3.4. In vitro drug release studies

Formulation containing combination of HPMC K100 and Kollidon VA64 retarded the drug release up to 24 Hrs.

Table 9: In vitro drug release studies

Time in hrs	Cumulative Drug Release Of Formulation (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	33.43	32.81	31.35	31.77	33.33	32.29	32.29	30.72	29.68
4	38.6	38.28	37.32	36.81	37.34	37.44	37.65	35.86	35.74
6	42.56	41.82	39.3	40.34	42.13	41.6	41.39	40.42	41.66
8	49.95	49.21	46.77	48.86	47.95	52.42	51.9	47.71	48.97
10	56.21	54.32	51.04	51.49	57.33	57.58	57.26	51.69	54.63
12	59.38	58.94	57.83	57.65	61.77	62.55	62.65	57.43	58.52
14	65.94	63.73	62.75	63.58	68.27	67.97	69.15	62.64	63.94
16	73.24	70.5	69.64	70.59	71.41	72.15	75.6	68.28	70.7
18	80.96	73.65	71.23	73.54	77.66	75.48	80.84	72.78	73.55
20	86.05	78.02	76.53	81.36	83.08	82.96	85.14	76.74	78.34
22	90.46	87.38	81.92	90.12	89.45	91.82	91.39	82.98	87.17
24	95.98	92.53	91.72	96.76	96.87	97.21	96.81	91.84	92.63

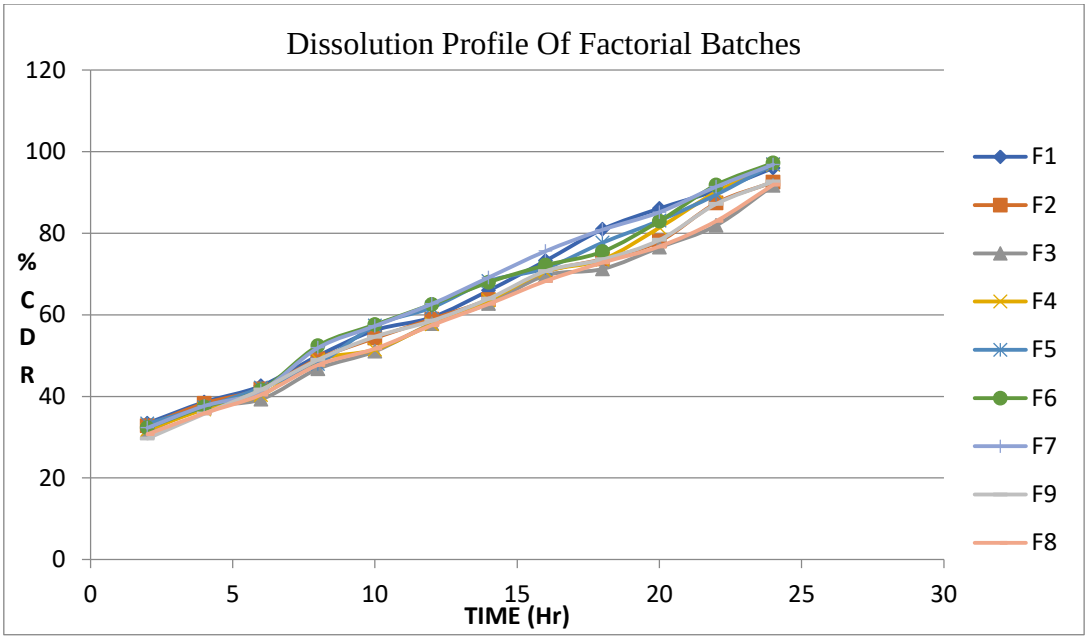

Fig 6: Drug Release of Factorial Batches

In case of trial batches the concentration was decided as suggested in the book of excipients. Depending on results obtained from those trials the final formulation concentration was decided. The T3 batch showed best results for the drug release and hence that point was considered to be centre point for optimisation.

Thus DOE suggested following batches having concentration in given range keeping trial optimized concentration as middle one.

Table 10: Experimental batches as per DOE

		Factor 1	Factor 2	Response 1	Response 2
Std.	Run	A:HPMC K 100	B:Copovidone	Drug release	Hardness
		Mg	Mg	%	Kg/cm2
11	1	70	40	95.98	7
5	2	70	40	95.98	7.1
2	3	70	30	92.52	6.5
10	4	70	40	95.98	6.9
7	5	60	50	91.72	7.2
4	6	60	40	96.76	7.4
8	7	70	50	96.87	7
9	8	80	50	97.21	6.7
6	9	80	40	96.81	6.8
1	10	60	30	91.84	7.3
3	11	80	30	92.63	6.8

3.5. Optimized Batch:

The optimized batch was suggested by the DOE software depending on the onses entered in software.

Table 11: Optimized batch as per DOE

Solutions						
Number	**HPMC K 100**	**Copovidone**	**Drug release**	**Hardness**	**Desirability**	
1	80.000	50.000	97.388	6.756	1.000	Selected

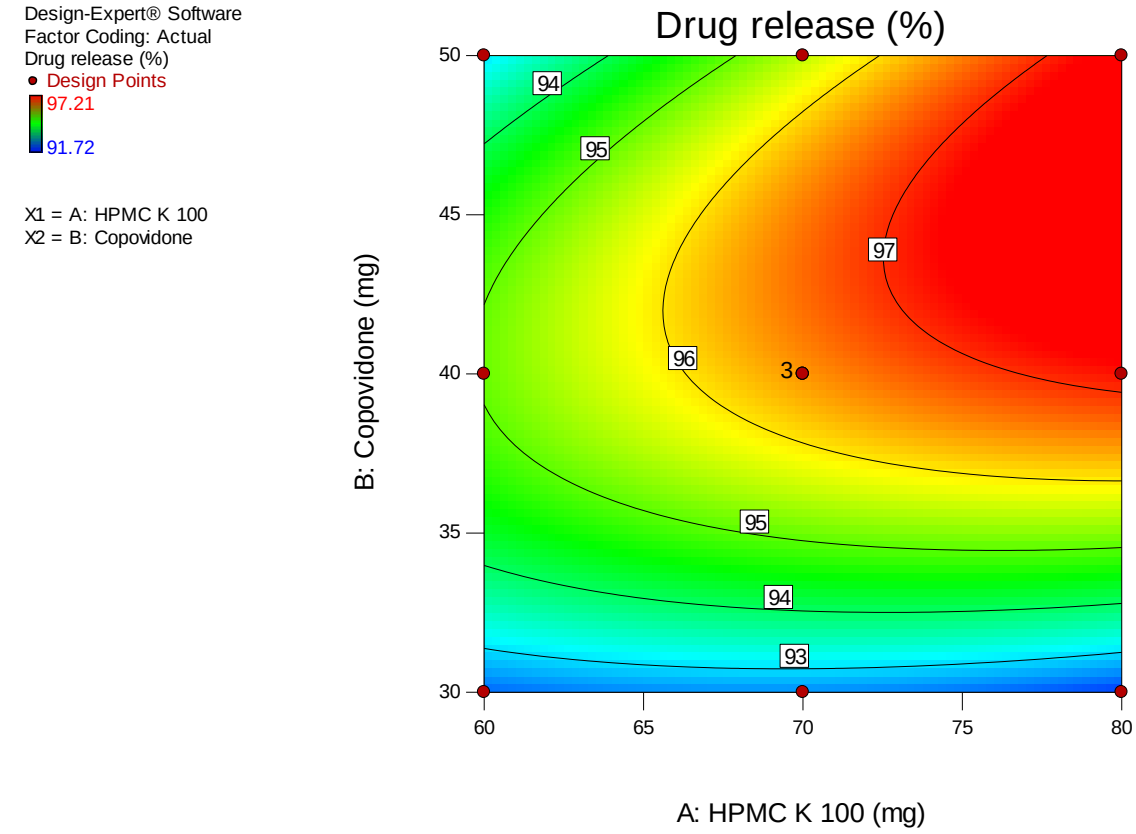

Fig 7: contour plot of Drug release

The above contour plot shows combined effect due to varying concentrations of Copovidone and HPMC K 100 on the drug release characteristic of tablet. It could be seen that as the concentration of copovidone increases there is proportional increase in the drug release at constant concentraton of HPMC k 100. Solely the increasing concentration of HPMC k 100 is directly proportional to effect only at higher concentrations of copovidone. Both these factors when increased simultaneously so combined effect on drug release. The curvature in the 3D plot clearly indicates that the increasing

copovidone increases drug release only up to a limit beyond which the drug release is further decreased.

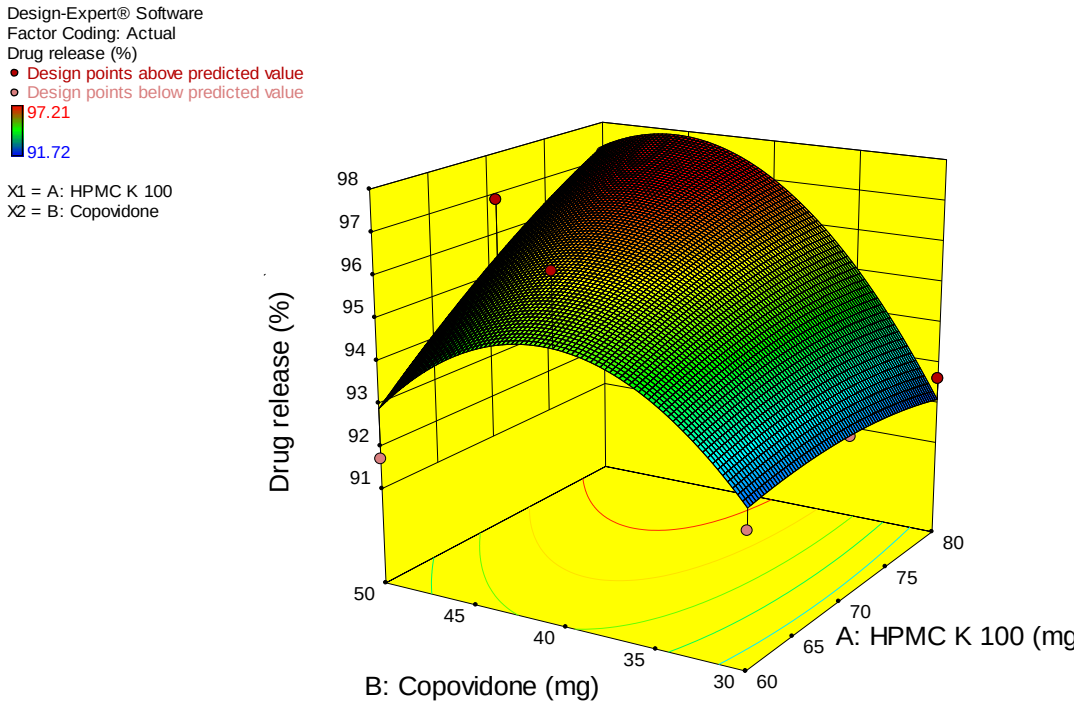

Fig 8: 3D plot of drug release

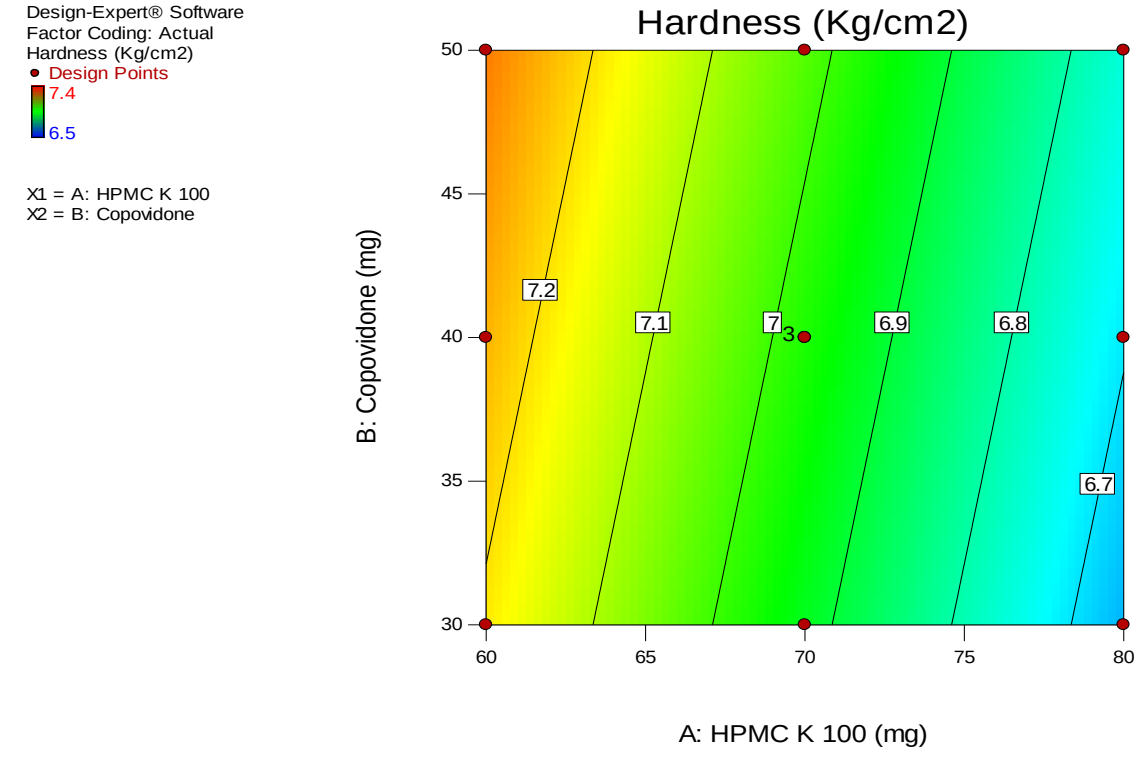

Fig 9: Contour plot for Hardness

Above contour plot shows effect of HPMC K 100 and Copovidone on Hardness of the tablet. It is seen that the HPMC K 100 is the dominant factor to have effect on Hardness. As HPMC increases the hardness decreases and copovidone has its effect only at extreme high and low values of HPMC K 100. To have higher hardness low concentration of HPMC and higher concentration of copovidone is suggested.

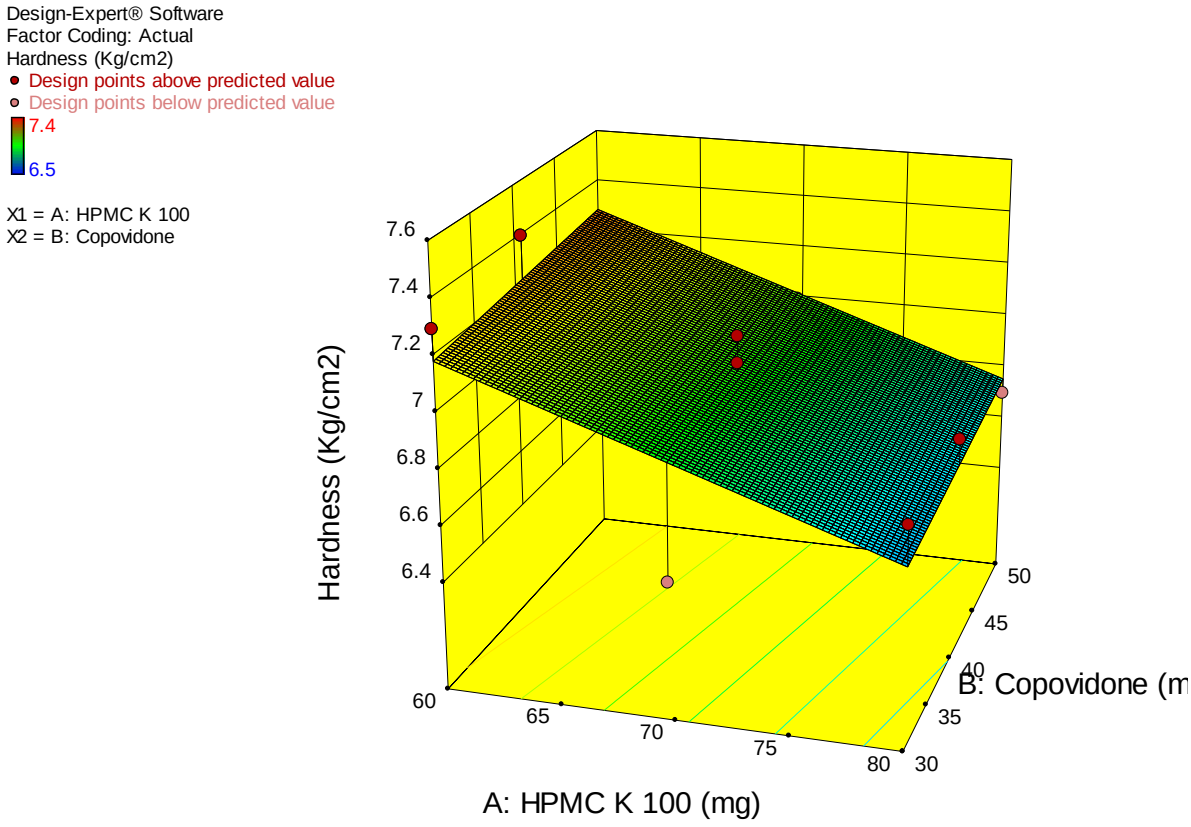

Fig 10: 3D plot for Hardness

To have all the responses within limits the overlay plot shows required input variable values. Thus it indicates a design space where all the responses are within acceptable limit at any value of input variable in that particular design space.

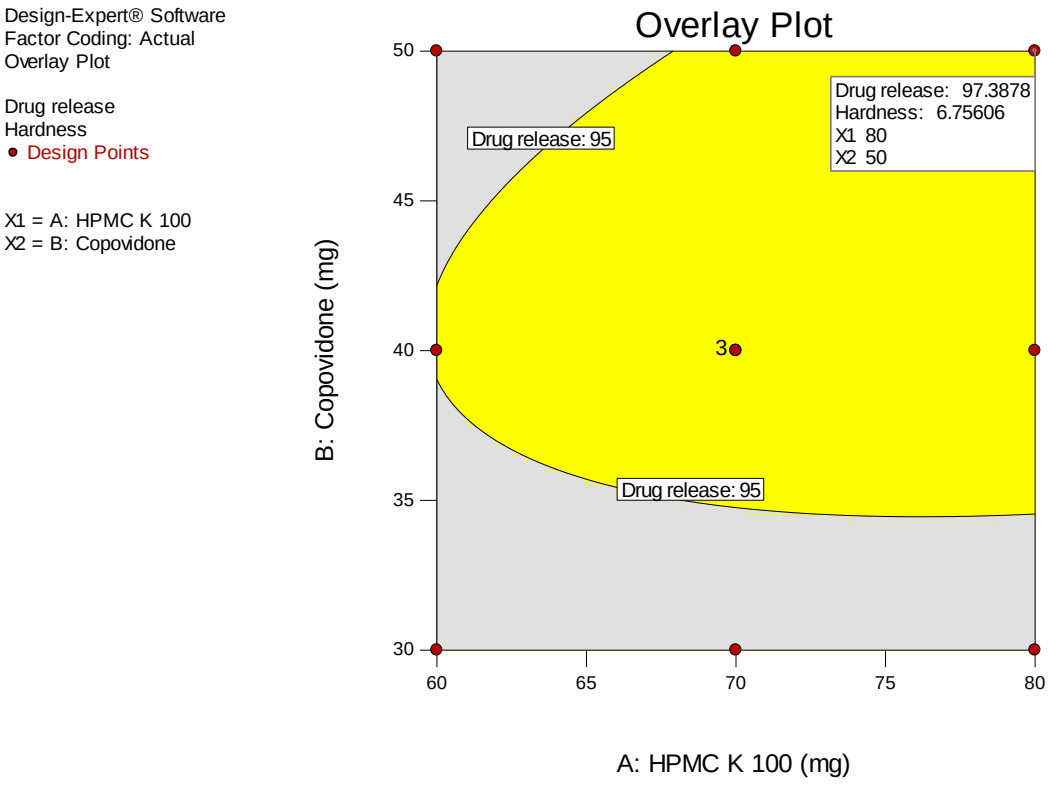

Fig 11: Overlay plot of all factors and responses

Dissolution models for the optimized batch (F6)

For the dissolution model to fit in any of the mentioned case we need to conditions to fit. We have to find a model wit least sum of square error value having higher regression value.

The above data suggests that KorsemayerPeppas model could be fitted more appropriately to the developed system as it has least error value and comparatively a good regression coefficient. Also it is mentioned prior that the developed system is swellable in nature which proves the suggested model good for fit.

Table 12: Dissolution Models

Sr. no	Model	Sum of squares of error	Regression
1	Zero Order	41142.9	0.995
2	Hiiguchi	4.918.40	0.969
3	First Order	38666.49	0.938
4	Hixon Crowel	11.8	0.995
5	KorsemayerPeppas	10.92	0.951

4. CONCLUSION

The oral route is most preferred route of administration of dosage forms. Controlled release dosage forms are advantageous over conventional dosage form because reducing dosing frequency and improved patient compliance. The work was carried out to design sustained release matrix tablet of Torsemide using combination of two polymers.

The conclusions drawn from the investigations were summarized below

- The polymer was selected for the sustaining the release i.e. HPMC K100 and Kollidon VA64 are compatible with the Torsemide.
- Sustained release matrix tablets of Torsemide were successfully prepared using HPMC K100(40%) , Kollidon VA64(25%) and other excipients.
- The tablets were evaluated for Pharmacopoeial and non-Pharmacopoeial tests.
- The 3^2 factorial design can be successfully applied for the optimization of the batches.The selected independent variable exhibits significant effect on dependent variables.
- The oral sustained release drug delivery system of Torsemide provides the drug release for 24 Hrs in a sustained manner to achieve the desired therapeutic profile with maximum drug utilization, improve patient compliance.
- In the trial batches the HPMC K100 (70mg) and Kollidon VA64(40mg) so the better results, according to that the levels for factorial batches decided.
- The formulation F6 shows the maximum drug release in 24hrs in sustained release manner.

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