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RESEARCH ARTICLE

Formulation and Evaluation of Sustained Release Tablet of Torsemide

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ABSTRACT:
The purpose of the present study was to formulate and evaluatesustained release tablet of Torsemide. Sustained release tablets of Torsemide were formulated with different concentrations of HPMC K4M and HPMC K100M by using wet granulation technique and evaluated for the different evaluation parameters such as thickness, hardness, drug content uniformity, friability, *in-vitro* drug releasestudies, release kinetic studies and stability studies were performed. All the evaluation parameters results were significant. *In-vitro* drug releasestudies were performed and drug release kinetics evaluated using the linear regression method was found to follow Zero order, First order, Matrix and Korsemeyer and Peppas' equation. The drug release mechanism was found Fickian type in most of theformulations. The prepared formulation shows better and significant results for all the evaluated parameters. The formulation F9 shows maximum percentage of drug release (98.2 %) and prolonged release fortime period of about 12 h, thereby improves the bioavailability and patient compliance.

KEYWORDS: Sustained Release Drug Delivery System (SRDDS), Torsemide, HPMC K4M, HPMC K100M, In-vitro drug release.

INTRODUCTION:
Sustained release dosage form releases drug continuously and steadily such that its appearance in the systemic circulation is prolonged and its plasma profile is for long duration.

Loop diuretics are generally administered to the patients to induce urinary output and play a very important in the treatment of fluid overload patients of congestive heart failure, chronic renal failure and acute pulmonary edema.[1, 2, 3]

Torsemide is a new high ceiling loop diuretic that has drastically changed the therapy of fluid overload disorders, it has higher bioavailability and greater potency with lesser side effects it produces larger diuresis, natriuresis and lesser kaluresis that results in the greater reduction in body weight and leads to reduction in edema,[1,2,3]

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the sustained release of Torsemide will result reduction of edema of post hospitalized patients as the non-compliance of drug result in their severity of the condition and patients feel unwell due to fluid accumulation to overcome this problem the need of this formulation is there which will make comfort to the already stressed person due to their renally compromised condition it will also be helpful to the patients of hypertension due to fluid overload, anuric patients.

MATERIALS AND METHODS:
1. MATERIALS:
Torsemide was obtained as a gift sample from the Hetero Drugs Pvt. Ltd., Hyderabad, Telangana, India and Medilux Laboratories Pvt. Ltd. Pithampur, MP, India. Hydroxypropylmethyl cellulose K4M and K100M was obtained as a gift sample from the Colorcon Asia Pvt. Limited, Goa, India. Another excipients and chemicals were obtaines as a gift sample from the Research Lab, Mumbai. All the ingredients used were analytical grade only.

Table no.1: Formulation of sustained release tablets (batch F1 to F9)

Name of material	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Torsemide	50	50	50	50	50	50	50	50	50
HPMC K100M	40	40	40	50	50	50	60	60	60
HPMC K4M	20	30	40	20	30	40	20	30	40
MCC 101	40	40	40	40	40	40	40	40	40
Mg. Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total	**160**	**170**	**180**	**170**	**180**	**190**	**180**	**190**	**200**

2. METHODS:

Sustained Release tablets containing Torsemide were prepared by wet granulation technique using varying concentration of different grades of polymer, binder and excipients.Torsemide was mixed with sustained release polymer as per formulae in mortar and pestle. To it added MCC as binderwere granulated by using Isopropyl alcohol as granulating agent using a glass mortar pestle for about 15 min. Granules were obtained by passing the sluggy mass through sieve no 12. Finally magnesium sterate and talc is added to the granules as a glidant. The mixed blend was then compressed into tablets by direct compression method using 8mm punches on a 10 station rotary tablet punching machine (MC-200, FLUID PACK MINIPRESS, C. I. P. MACHINERY, PVT. LTD.).The compositions of all formulations are given in Table no. 1

3. Pre-compression parameters:[6-9]

Prior to compression, the formulation powder blends were evaluated for their bulk and tapped density and from these values the compressibility index and Hausner ratio were calculated. The flow properties of the powder blend were ascertained from the angle of repose.

4. Post-compression parameters:

The prepared tablets were evaluated for quality control tests such as weight variation, hardness, thickness, friability and content uniformity.

5. Thickness:[10]

The thickness of the tablets was determined using a Vernier Caliper. Three tablets from each batch were used and average value was calculated.

6. Hardness [7,10]

Hardness of the tablets was tested using Pfizer hardness Tester.

7. Friability:[7,10]

Friability test was carried out using Roche Friability Tester. Ten whole tablets were placed in drum and rotated for 100 revolutions and % friability was determined. It should be less than 1%.

$$\% F = (1-W/W_0) \times 100$$

Where,

W_0 = weight of tablet before test,

W = weight of tablet after test.

8. Weight variation test:[7]

Twenty tablets were randomly selected from each batch and weighed individually to check for weight variation and results were compared with IP limits.

9. Drug Content:[9,11]

The tablets were weighed and taken in a mortar and crushed to powder. A quantity of powder equivalent to 10 mg of Torsemide was taken in a 100 ml volumetric flask and phosphate buffer pH 6.8 was added. It was then heated at 60ºC for 30 min. The solution was filtered using Whatmann filter paper and then its absorbance was measured at 288 nm. The amount of drug was calculated using standard calibration curve.

10. In-vitro drug release:[12]

The Torsemide released from different sustained release tablet formulations was determined using a USP Type II paddle apparatus under sink condition. The dissolution medium was 900 ml of Phosphate buffer pH 6.8, the temperature of dissolution medium was maintained at 37 ± 0.5ºC; paddle speed 100 rpm, to simulate *in vivo* conditions. The formulation prepared was subjected to dissolution tests for 12 h. At every 1 h interval, Sample was withdrawn, filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium. Drug content in the dissolution sample was determined at 288 nm by UV -visible Spectrophotometer. Cumulative percent drug release was found out at each time interval and graph was plotted between cumulative % drug released and time in hrs.

11. Treatment of dissolution data with different kinetic equation:

The dissolution data was kept for treatment with different kinetic equation for to check the release mechanism of the drug from the device.Here all the data analysis was done by using PCP Disso V-3 software, India .To describe the kinetics of drug release from prepared test formulation, mathematical model like zero order, first order, peppas, higuchi, hixon –crowell were used.

12. Accelerated Stability Study:

In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However, studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. Sustained release tablets of optimized batch F9 was selected for stability studies. The tablets were packed in aluminium foil and were placed in amber coloured glass container. The temperature was maintained at 40 ± 2^0C, and the humidity maintained was75% ±5% RH. The samples of stability study were withdrawn after one month and tested for appearance, hardness, and drug content and drug release.

RESULT AND DISCUSSION:

Pre-compression Parameters:

The bulk densities and tapped densities of all batches were found to be in the range of 0.15–0.20 gm/ml and 0.17–0.25 gm/ml respectively. This value of bulk density indicated good packing character of the final blend. The value of Hausner's ratio was less than 1.25 which indicated good flow properties. The compressibility index for all these formulation blends were found to be below 25% indicating fair to good flow properties. Angle of repose gave a qualitative assessment of the internal cohesive and frictional effect under low levels of external loading, as might apply in powder mixing or in tablet die filling operation. The values of angle of repose for all these formulation blends were found to be between $22.4^0\pm0.79$ to $27.3^0\pm1.25$. From these observations, values of angle of repose were found between good passable ranges.The results of pre-compression parameters of Torsemide sustained release tablets are given in Table no: 2.

Table no.2: Results of pre-compression parameters for batches F1 to F9.

Batch No.	Bulk density (gm/ml)*	Tapped density (gm/ml)*	Hausner's Ratio*	Compressibility index (%)*	Angle of repose*
F1	0.17±0.02	0.21±0.01	1.17±0.02	15.2±1.11	27.3±1.25
F2	0.16±0.02	0.18±0.03	1.12±0.01	11.3±0.73	25.5±0.83
F3	0.14±0.03	0.17±0.02	1.12±0.02	20.1±0.90	24.7±1.05
F4	0.13±0.01	0.15±0.01	1.14±0.03	12.3±0.96	25.7±0.6
F5	0.15±0.02	0.17±0.02	1.13±0.03	11.9±0.67	26.9±0.55
F6	0.16±0.03	0.20±0.02	1.23±0.07	20.2±0.97	25.6±0.79
F7	0.15±0.03	0.18±0.03	1.20±0.01	16.4±0.91	22.4±0.79
F8	0.16±0.01	0.19±0.01	1.18±0.02	14.3±0.65	24.4±0.79
F9	0.15±0.02	0.17±0.02	1.14±0.05	11.8±0.45	25.5±0.86

*Mean ± S.D. n=3

Table no.3: post-compression parameters for batches F1 to F9.

Batch No.	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Weight variation (mg)*	Drug content (%w/w)*
F1	3.2±0.05	5.2±0.1	0.25±0.02	170.6±0.4	97.50±0.9
F2	3.4±0.05	6.3±0.2	0.53±0.03	180.2±0.1	97.46±1.2
F3	3.5±0.06	5.3±0.1	0.72±0.03	190.7±0.2	97.70±0.8
F4	3.3±0.05	5.2±0.1	0.67±0.04	180.5±0.3	98.53±0.6
F5	3.5±0.05	6.2±0.2	0.62±0.03	190.5±0.3	97.93±0.5
F6	3.7±0.05	5.2±0.2	0.59±0.02	200.5±0.4	98.26±0.5
F7	3.5±0.1	6.2±0.2	0.68±0.02	190.5±0.4	97.70±0.8
F8	3.7±0.1	6.3±0.1	0.34±0.02	200.4±0.3	98.33±0.5
F9	4.1±0.05	5.2±0.1	0.65±0.04	210.3±0.2	99.43±0.4

*Mean ± S.D. n=3

Post-compression Parameters:

The mean thickness of formulation of Torsemide sustained release tablet was ranges between 3.2to 4.1 mm. The measured hardness of sustained release tablet of Torsemide was compressed at 5-6 kg/cm^2. The limits for hardness are 5-6kg/cm^2 for sustained release tablet, all batches showed hardness within limits. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. All tablets showed weight variation less than ±5% which complies with official limits. All the tablets passed weight variation test as the % weight variation was within the Indian Pharmacopoeia limits. The weights of all the tablets were found to be uniform with low standard deviation values. The drug content of all batches was found between 97.46±1.2% to99.43±0.4%.The results of post-compression parameters of Torsemide sustained release tablets are given in Table no: 3.

In-vitro drug release studies:

From the comparative dissolution data, it was observed that batches F1, F2, and F3 in which constant concentration of HPMC K100M and increasing

concentration of HPMC K4M was used. The total cumulative drug releases for these batches were 92.4, 92.6, &93.6 respectively.Comparative dissolution profile of batch F4, F5 and F6 containing concentration of HPMC K 100 M was more as compare to batch F1, F2 and F3 and HPMC K4M was added in same proportion as in batches F1, F2, F3. The total cumulative drug release from the batches F4, F5 & F6 were found to be 93.8, 94.2&94.6 respectively.Comparative dissolution profile of batch F7, F8, F9 containing concentration of HPMCK100M was more as compare to batch F1 to F6.HPMC K4M was added in same proportion as that of batches F1, F2, & F3 these all batches should retard release of drug more as compare to all other batches the total cumulative drug release from these batches were 94.7%, 97.8%, 98.2% respectively.

From in-vitro drug dissolution studies of the different batches of Torsemide, it was observed that with increasing the viscosity and content of HPMC K100M & HPMC K4M, the rate and extent of drug release from the tablets increases. This is because, as the molecular weight of the HPMC increase, the degree of entanglement of polymer chain increases. Thus the mobility of the drug molecule in the fully swollen system decreases.The hydrophilic polymer solubilized more and drug release was high. Thus the HPMC K100M with the combination of HPMC K4M provides the optimum drug release.The result of in-vitro drug release studies is given in Table no. 5while the plot of % cumulative drug release against time (hrs.) is depicted in Figure-2.

Table no. 4:In-vitro % cumulative drug release profile of batches F1 to F9

Batch no.	%CDR at the end of 12 Hrs.
F1	92.4±0.7
F2	92.6±0.6
F3	93.6±1.1
F4	93.8±0.9
F5	94.2±0.7
F6	94.6±1.1
F7	94.7±0.7
F8	97.4±0.8
F9	98.2±0.6

*Mean ± S.D. n=3

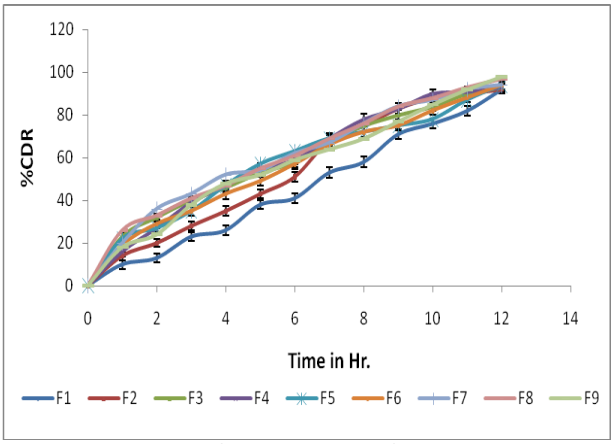

Figure-1: comparison of dissolution data of batch F1 to F9

DRUG RELEASE KINETICS:

The in-vitro drug release data of the all nine batches was fitted into different kinetic models to determine the mechanism of drug release. The model that best fits the release data was evaluated by correlation coefficient (r^2). The results obtained were shown in Table no. 6.

In that mechanism of drug release data obtained was fitted to all models that is zero order, First order, Matrix, Peppas model and Hixson –Crowell.

In dissolution study of all formulation it was observed that as concentration of polymer increases, rate of drug release is increases. The dissolution data was treated with different kinetic equation. Zero Order model was best fit model. This model was considered, as the release data of formulation F9 seem to fit better withZero Order model i.e. the release mechanism was Fickian diffusion. In this model the rate and extent of penetration sorption into the polymer are determined by the concentration gradient-controlled and or relaxation –controlled diffusion.

Table no.5: Correlation coefficient (r^2) values of different release kinetic models for all batches of Sustained release tablet.

Batch No.	Zero Order	First Order	Matrix	Korsemeyar Peppas	Hixson Crowel	Best fitting model
F1	0.9967	0.9145	0.9177	0.9876	0.9597	Zero Order
F2	0.9972	0.9858	0.8936	0.9940	0.9920	Zero Order
F3	0.9970	0.9714	0.9911	0.9397	0.9937	Zero Order
F4	0.9972	0.9968	0.9815	0.9566	0.9958	Zero Order
F5	0.9922	0.9575	0.9888	0.9338	0.9860	Zero Order
F6	0.9966	0.9361	0.9831	0.9626	0.9829	Zero Order
F7	0.9959	0.9676	0.9933	0.9250	0.9925	Zero Order
F8	0.9908	0.9323	0.9893	0.9412	0.9849	Zero Order
F9	**0.9843**	**0.8472**	**0.9387**	**0.9826**	**0.9486**	**Zero Order**

ACCELERATED STABILITY STUDY OF OPTIMIZED BATCH:

Stability is the essential factor for quality, efficacy and safety of drug product. The drug product with insufficient stability can result in change of their physical as well as chemical characteristics Present study was carried out to check the dissolution behaviour, and physical appearance of optimized batch F9.

An optimized batch tablets was wrapped in aluminium foil and stored at 40±2^{0}C temperature with relative humidity of 75±5%. The sampling was done after onemonth and evaluation was done for appearance, thickness, hardness, friability, drug content and cumulative % drug release. This all data showed in following table no.7.

Table no.6: Comparative study of optimized batch at initial and after 1 month of Stability study.

Sr. No.	Parameter	F7	
		Initial	After 1 Month
1	Appearance	White	No change
2	Hardness	5.2 ±0.1	5.1±0.6
3	Thickness	4.1 ±0.2	4.1 ±0.1
4	Weight variation	210.3 ±0.02	210.1 ±0.03
5	Friability	0.65 ±0.04	0.72 ±0.03
6	Drug content	99.4 ±0.4	98.6 ±0.1
7	%CDR	98.2±0.6	98.2 ±0.4

CONCLUSION:

The present work was formulation and evaluation of sustained release tablet of Torsemide drug. The main aim of this research work is to develop sustained release tablet of Torsemide with view to prolong the drug release and to give the action of drug for long duration and to avoid non-compliance of it.

In vitro release of sustained release tablets for batch F9 was found to be 98.2%. From the overall observation and study of physical properties, *In- vitro* study it complies with USP standard for extended release dosage form, tablet of batch F9 selected as optimized batch.

Stability study of optimized batch indicated that there were no significant changes in drug content as well as dissolution parameters.The advantage of sustained release tablet is to extend the release of drug and to prolong its action.The sustained release drug delivery system with sustained release tablet formulation can reduce dosing frequency, decrease side effect and improve patient compliance.

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