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FORMULATION AND EVALUATION OF CAPECITABINE SUSTAINED RELEASE TABLETS

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ABSTRACT

The objective of the present investigation was to formulate and devaluate sustained release of Capecitabine tablets. Capecitabine sustained release tablets were developed different polymers HPMC K 100, Carbopo l974 and Xanthan Gum with different ratios. Totally 9 formulations were prepared. Sustained release tablets of Capecitabine were prepared by wet granulation technique. The prepared granules evaluated in terms of their Pre-compression studies like Tapped Density, Bulk Density, Angle of repose, Carr's Index and Hausner's ratio. The tablets were evaluated by Post-compression studies like hardness, thickness, friability and *in vitro* studies. The results of *in vitro* drug release studies showed that formulation-2 (API and HPMC and Xantham gum) has better drug release (98.44%) for 24hrs.

KEYWORDS

Capecitabine, HPMC, Xantham gum, Carbopol and *In vitro* study.

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INTRODUCTION[1]

For many decades treatment of acute diseases or chronic illnesses have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, liquids, aerosols and injectables. Even today these conventional dosage forms are the primary pharmaceutical vehicles commonly seen in the prescription and over the counter drug market. The oral conventional types of drug delivery systems are known to provide a prompt release of the drug. Therefore to achieve as well as to maintain the drug

concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in a significant fluctuation in drug levels often with a sub-therapeutic and or toxic levels and wastage of drug. Recently several technical advancements have resulted in the development of new systems of drug delivery capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a tissue. Sustained release drug delivery system consists of mainly two parts an immediate dose and sustaining part. The immediately available dose is normally added to the sustaining part of the tablet or alternatively incorporated in the core of the tablet i.e., a portion (initial priming) dose of the drug released immediately in order to achieve the desired therapeutic response promptly. The remaining dose of the drug (maintenance dose) is then released slowly thereby resulting in therapeutic drug tissue level, which is a prolonged. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

Advantages of sustained release dosage form

- The frequency of drug administration is reduced.
- Improved patient compliance and convenience Reduction in fluctuation in steady state levels.
- Drug administration is made more convenient as well.
- Better control of drug absorption can be attained.
- Increased safety margin of high potency drugs
- Maximum utilization of drug with minimum dose
- Minimize or eliminate local and systemic side effects.
- Minimize drug accumulation with chronic dosing.
- Improve efficacy in treatment.

MATERIAL AND METHODS[1]

Materials and Chemical

Capecitabine, HPMC K 100, Carbopol 974, Xanthan Gum Povidone K 30, MCC, Talc 2%, Magnesium Stearate 1%, and Lactose.

Method

Preparation of granules

Wet granulation

Wet granulation was carried to improve the flow properties for formulating sustained release tablets of drug. Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablets. Wet granulation is a process of using a liquid binder or adhesive to the powder mixture. Water may be used as a vehicle for granulation, but the active being a highly water soluble drug there are more chances of formation of highly densed areas of drug. To avoid formation of lumps a non-aqueous solvent like isopropyl alcohol can also be used. Here povidone (PVP K-30) is used as binder.

Procedure

1. All the ingredients mentioned in Table were weighed accurately.
2. API, polymers, binder were sifted through BSS # 40 sieve.
3. API, polymers were mixed in a poly bag for 15 mins ensure the uniformity of premix blend.
4. The binder was dissolved in water to get a clear solution.
5. The blend was wet granulated with binder solution.

6. The wet mass was passed through No.18 sieve. Wet granules were dried in a Rapid drier at 50°C for 60 minutes.
7. The dried granules were sifted through BSS # 24 sieve. The moisture content should not more than 15.
8. These granules were blended with lubrication mixture (1% w/w magnesium stearate and 2% w/w talc previously sifted through BSS # 60).
9. The blend of Step 8 was compressed into tablets by using 11.8 mm biconvex, round shaped punches.

Evaluation of Granules[2,3]

Bulk density

3gm of granules were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated according to the formula

Formula

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

Formula

Tapped density = Weight of granules/ Tapped volume of granules Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal.

Formula

$\theta = Tan^{-1}$ (h/r) Where, θ = Angle of repose, h = Height of the powder cone, r = Radius of the powder cone.

Compressibility Index or Carr's Index Carr's Index is measured using the values of bulk density and tapped density.

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where, TD = Tapped density**,** BD = Bulk density

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Formula

Hausner's Ratio = Tapped density/Bulk density

Evaluation of tablets[3,4,5]

Hardness or Crushing strength Test Hardness of the tablet was determined using the Monsanto hardness tester.

The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Sustained release tablets have a hardness of 10 -20 kg ; however, Oral disintegrating tablets normally have a hardness of 4 to 10 kg and hypodermic and chewable tablets have a hardness of 3 kg.

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Vernier calipers and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight F - Final weight the prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a Strong-Cobb hardness test. Friability of the tablets was determined in a Roche friabilator. The thickness of the tablets was measured by Vernier caliper. Weight variation test was performed according to the official method.

***In vitro* Dissolution test**

Drug release was assessed by using USP dissolution test apparatus type I (Basket). 900 ml of dissolution medium maintained at 37±0.5^{0}C was used. Basket was rotated at 50 rpm for 24 hrs. An aliquot (10ml of samples) were withdrawn at 1, 2, 4, 8, 12, 16, 20, 24 hours time intervals, replacing the same amount with the pre warmed fresh medium. The samples withdrawn were filtered and the amount of drug dissolved was analysed by a UV spectrophotometer (Shimadzu UV) at 303 nm.

RESULTS AND DISCUSSION

The tablets were evaluated for different parameters like weight variation, thickness, hardness, drug content and *in vitro* evaluation studies and stability studies. Observations of all the formulations form physical characterization have shown that the formulations show optimum results.

The formulation showed in Table No.1.

The pre compression results are shown in the Table No.2.

The post compression results were tabulated and shown in the Table No.3 and *in vitro* evaluation results are shown in the Table No.4.

The release kinetic data showed in Table No.5.

Table No.1: Formulation of capecitabine sustained formulations

S.No	Ingredients	F1mg	F2mg	F3mg	F4mg	F5mg	F6mg	F7mg	F8mg	F9mg
1	Capecitabine	150	150	150	150	150	150	150	150	150
2	Lactose	100	120	130	135	130	120	100	120	130
3	HPMC K 100	5	10	20	5	10	20	5	10	20
4	Carbapol974	--	--	--	--	--	--	5	10	20
5	Xanthan Gum	5	10	20	--	--	--	--	--	--
6	Povidone K 30	12	12	12	12	12	12	12	12	12
7	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8	MCC	90	90	90	90	90	90	90	90	90
9	Talc 2%	4	4	4	4	4	4	4	4	4
10	Magnesium Stearate 1%	4	4	4	4	4	4	4	4	4
11	Total Weight	400	400	400	400	400	400	400	400	400

Table No.2: Pre Compression Parameters

S.No	Formulation	Angle of repose(ɵ)	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Hausner's ratio	Carr's index (%)
1	F1	25.12±0.98	0.646±0.006	0.735±.009	1.137±.003	12.09±0.233
2	F2	24.78±.82	0.617±0.004	0.722±0.003	1.170±0.013	14.53±0.926
3	F3	26.89±0.80	0.634±0.005	0.720±0.008	1.136±0.022	11.99±1.739
4	F4	27.21±0.72	0.645±0.005	0.742±0.005	1.150±0.001	13.24±0.169
5	F5	25.62±0.53	0.652±0.012	0.740±0.003	1.134±0.021	11.89±0.562
6	F6	27.89±0.92	0.669±0.024	0.757±0.002	1.131±0.019	11.62±0.327
7	F7	26.58±0.94	0.654±0.011	0.728±0.003	1.130±0.009	12.16±1.202
8	F8	27.226±0.69	0.669±0.002	0.788±0.006	1.127±0.002	11.29±0.324
9	F9	26.32±0.72	0.660±0.002	0.750±0.011	1.135±0.001	11.93±0.084

Table No.3: Evaluation of Matrix Tablets

S.No	Formulation	Weight variation(mg)	Hardness (kg/cm2)	Friability (%)	Thickness (mm)	Drug content (%)
1	F1	400±0.82	3.42±.032	0.32	3.93±0.14	97.07±0.02
2	F2	398±0.19	3.65±0.21	0.105	3.89±0.21	98.7±0.007
3	F3	400±0.53	4.01±0.42	0.117	3.92±0.16	97.7±0..008
4	F4	402±0.35	3.54±0.13	0.305	3.95±0.05	98.15±0.028
5	F5	401±0.45	3.97±0.14	0.104	3.9±0.02	98.67±0.32
6	F6	397±0.26	4.12±0.33	0.111	4.01±0.012	97.63±0.65
7	F7	400±0.76	3.76±0.25	0.214	3.96±0.07	98.75±0.86
8	F8	400±0.64	4.29±0.18	0.125	3.94±0.14	99.08±0.28
9	F9	400±0.12	3.87±0.09	0.287	3.81±0.02	98.43±0.07

Table No.4: *In vitro* Dissolution Studies

S.No	Time (hrs)	%Drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	2	21.52±0.03	24.08±0.02	25.5±0.10	19.08±0.12	16.97±0.15	17.26±0.15	13.2±0.12	12.6±0.13	11.6±0.14
3	4	30.16±0.01	32.45±0.03	33.16±0.12	28.01±0.13	23.42±0.13	25.08±0.03	21.8±0.09	18.7±0.17	16.2±0.16
4	6	38.08±0.02	39.66±0.02	41.85±0.14	33.12±0.16	30.83±0.17	32.4±0.05	27.4±0.02	23.1±0.18	21.5±0.13
5	8	43.2±0.04	45.47±0.01	49.7±0.21	41.31±0.17	39.85±0.19	40.67±0.07	32.3±0.06	29.8±0.14	28.3±0.18
6	10	49.45±0.05	54.17±0.02	57.23±0.13	47.01±0.14	42.43±0.12	44.63±0.09	37.8±0.04	34.6±0.16	35.6±0.12
7	12	56.81±0.03	60.41±0.03	64.25±0.16	52.51±0.12	46.36±0.14	49.7±0.05	42.9±0.09	39.2±0.14	39.8±0.17
8	14	63.47±0.02	66.28±0.04	71.8±0.12	58.37±0.15	52.31±0.16	53.46±0.06	48.6±0.01	44.7±0.18	42.5±0.16
9	16	72.32±0.01	75.92±0.03	80.48±0.15	63.76±0.13	61.22±0.18	61.65±0.03	54.9±0.03	49.8±0.12	47.8±0.13
10	18	78.28±0.03	83.45±0.04	88.26±0.14	72.17±0.17	70.91±0.13	71.06±0.08	59.6±0.05	53.2±0.15	52.4±0.19
11	20	85.51±0.02	88.67±0.05	97.5±0.13	80.23±0.12	75.48±0.12	74.56±0.04	65.8±0.04	59.7±0.19	57.5±0.15
12	22	90.35±0.03	93.11±0.02	-	83.72±0.15	80.86±0.15	78.33±0.05	69.2±0.07	64.7±0.17	63.9±0.17
13	24	93.25±0.02	98.44±0.03	-	88.51±0.13	85.71±0.18	82.63±0.02	75.3±0.05	70.8±0.12	67.2±0.13

Table No.5: Release Kinetic Data

S.No	Formulations	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyars peppas R^2	Hixso n R^2	Release Exponent n
1	F1	0.976	0.937	0.977	0.804	0.897	1.101
2	F2	0.973	0.843	0.98	0.79	0.673	1.1
3	F3	0.967	0.846	0.98	0.789	0.627	1.115
4	F4	0.979	0.951	0.974	0.817	0.925	1.1094
5	F5	0.984	0.95	0.959	0.839	0.929	1.102
6	F6	0.975	0.975	0.976	0.827	0.963	1.091
7	F7	0.986	0.982	0.969	0.86	0.973	1.089
8	F8	0.99	0.98	0.961	0.869	0.971	1.076
9	F9	0.988	0.987	0.961	0.885	0.982	1.086

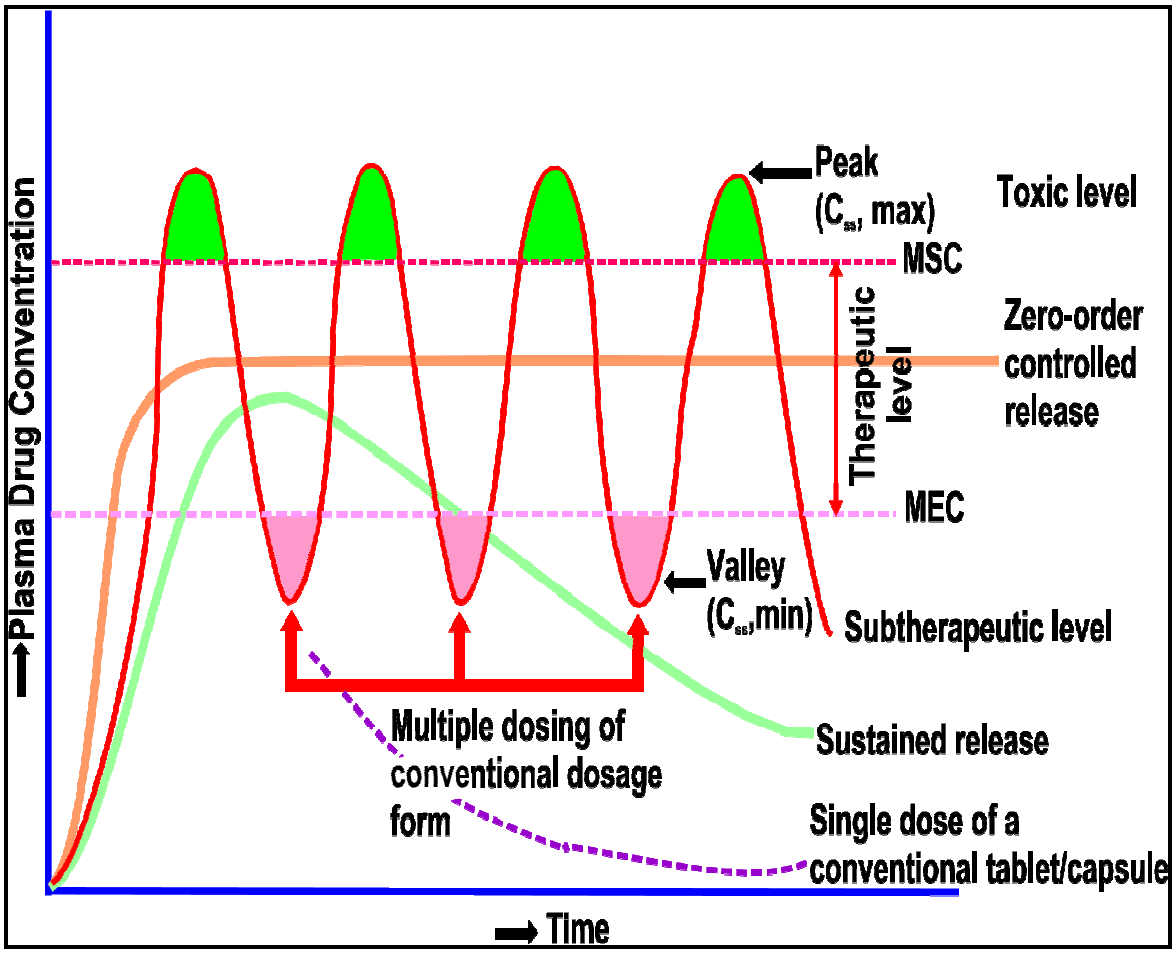

Figure No.1: A Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations

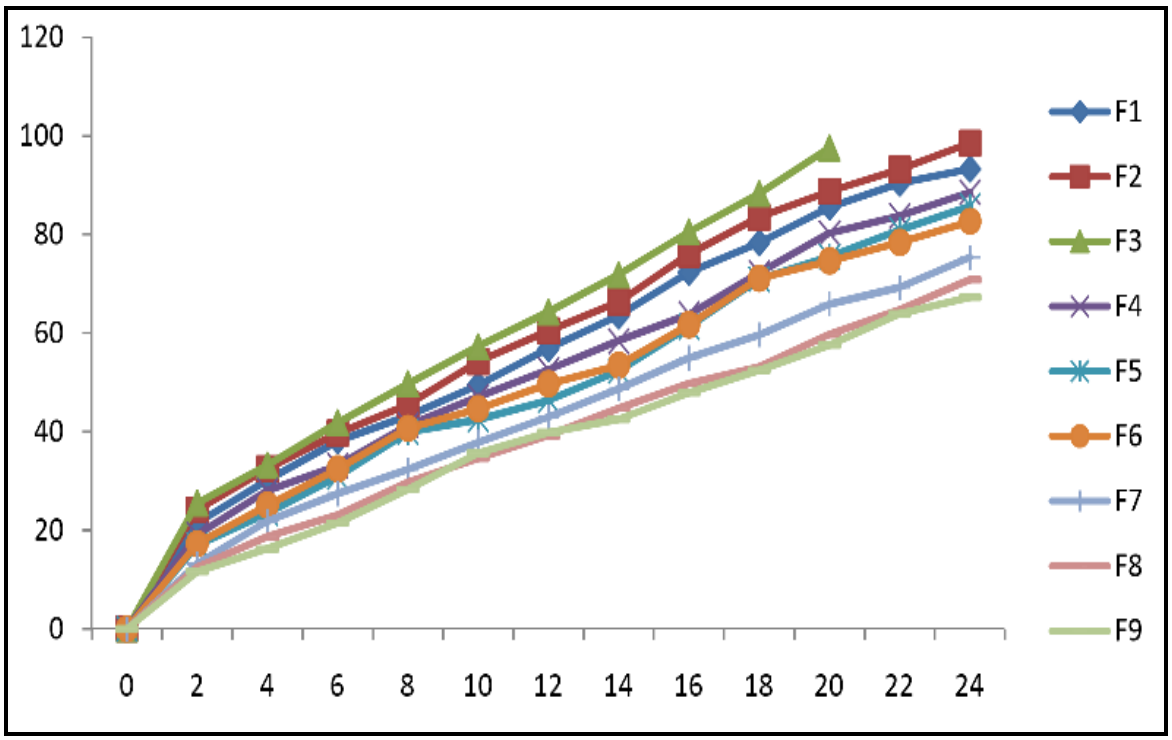

Figure No.2: Dissolution Graph of all 9 Formulations

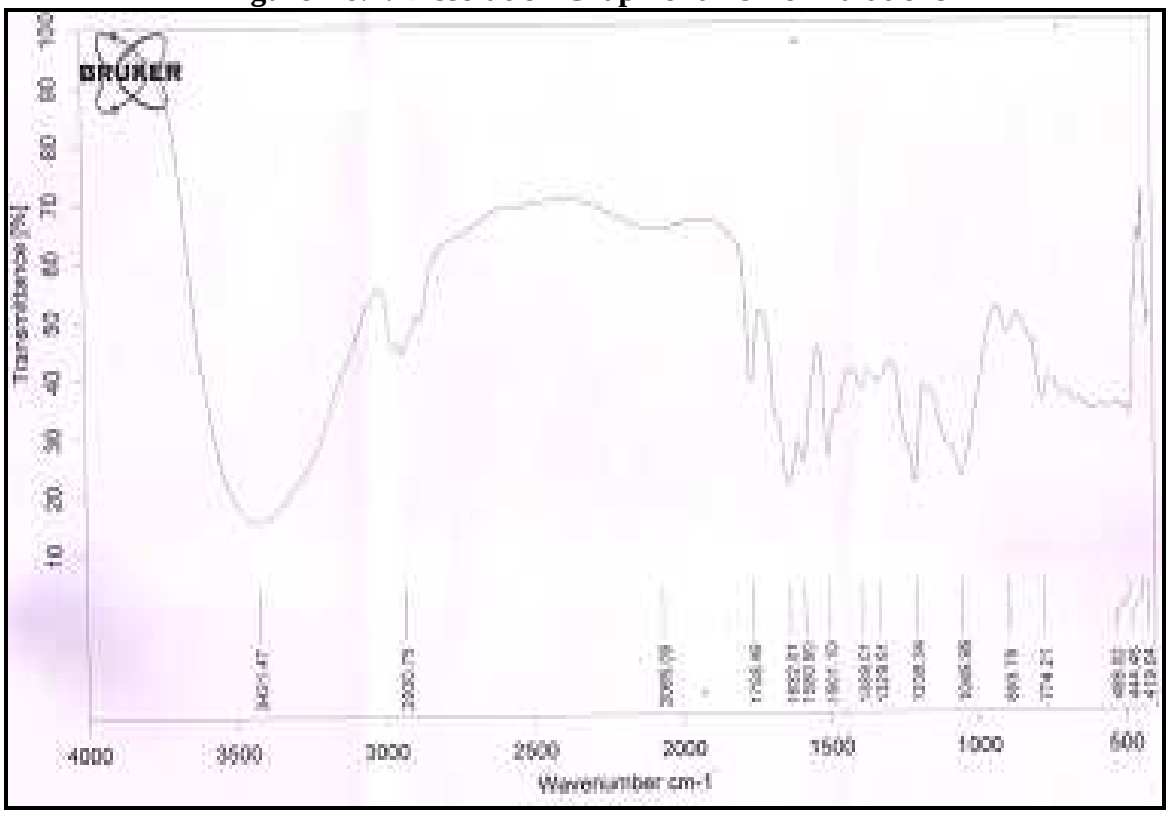

Figure No.3: FTIR Spectrum of Blend (Formulation)

CONCLUSION

- From the compatibility studies, it was concluded that HPMC, xanthan gum, and carbopol were compatible with Capecitabine and thus suitable.
- For the formulations of Capecitabine sustained release tablets.
- The physical properties like hardness, weight variation and friability of the batches complied with the pharmacopoeial specifications. The drug content all tablets was in range of 97- 99%.
- In vitro dissolution studies were performed for all the formulations, by using 0.1N HCL solution and 6.8 phosphate buffer at 37^0 C.
- From the invitro dissolution analysis it was found that the batches containing HPMC+ Xanthan gum showed better release than the batches with HPMC, HPMC+ carbopol.
- It was observed that the increasing concentration of polymers had a retarding effect on the drug release from the polymer matrices.
- From the dissolution profile modelling most of the formulations the R^2 value of Higuchi model is very near to 1 than the R^2 values of the other kinetic models.
- The release exponent n values of the best formulation were equal to 1.
- It is clear that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero order release kinetics. Therefore the most probable mechanism that the release patterns of the formulations followed was case II transport.
- Here the relaxation process of the macromolecules occurring upon water imbibition into the system is the rate controlling step. From the stability studies, it was concluded that there were no physical change in appearances and colour, the percentage of degradation with respect to drug content was observed 1-2%.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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