Current Trends in Biotechnology and Pharmacy
Vol. 15 (4) 416 - 425, October 2021, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2021.4.44

Design and Delivery Characteristics of Extended Release Dosage Form Using a Unique Combination of HPMC K100, Guar Gum and Chitosan as Release Retardant

Ganesh Lal, Meenakshi Bajpai*

Institute of Pharmaceutical Research, GLA University, Mathura, 281406 U.P., India
Corresponding author: meenakshi.bajpai@gla.ac.in

Abstract

The present work deals with extended release dosage form because conventional dosage forms have many limitations like patient noncompliance, chances of missing the dose because of frequent administration, peak-valley concentration profile, fluctuating blood levels, etc. Many patients are suffering from osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and like disease specially in elderly patient so that they need to extended release dosage form for their patient compliance. The objective of this research was to design and develop extended release (ER) dosage form by using a unique combination of HPMC K100, Guar gum, and Chitosan as release retardant. For fixing the desired range of variables (polymer concentration) required for the final formulation, a pre-optimization study was conducted with different concentration of polymers. As the concentration of polymers changed there was a direct effect on swelling index and drug release. Extended release of aceclofenac 200 mg tablet was prepared by dry compression method. The optimized ER tablet formulation had shown 99.7 % drug release in 54 hours and also follow the I.P specification. So the optimized formulation containing HPMC K100M at a concentration of 100 mg, and Guar gum used at a concentration of 50 mg, and chitosan is used at a concentration of 50 mg these concentration of polymer had shown the maximum retardation in the drug release.

Conclusion: It can be concluded that the formulation of ER matrix tablet of aceclofenac 200 mg was successfully formulated. The optimized ER tablet formulation had shown 99.7 % drug release in 54 hours.

Keywords: Extended Release, HPMC K100, Guar Gum, Chitosan, Aceclofenac, Arthritis, ankylosing spondylitis

Introduction

Oral route is most convenient route for the delivery of drug and it is preferably used. Most commonly used route is oral route. There are many work has been done on oral route drug delivery system and many types of dosage form has been developed and research is going on for best dosage form for oral route. From ancient time patients are always prefer oral route and easy to take, especially solid dosage form. As well as oral solid dosage forms are convenient dosage form in comparison to other dosage form. There are several oral solid dosage form available in the market. Followings are the orally administered solid dosage forms are conventional tablet, buccal tablet, tablet delivered through sublingual route, effervescent tablet, Lozenge, Pastilles, Dental cones, pills, Granules, Powder. Liquid dosage forms are Syrup, Chewable tablet, oral emulsion, oral suspension, elixir, linctuses oral drops, gargles, mouthwashes etc (1).

Tablet is the best oral dosage form. Delivery of drug in tablet dosage form via oral rout is very convenient and patient compliance (2). Tablet have property to deliver drug into the body on the principle of disintegration, dissolution and then absorption. Therefore, it takes some time to comes into the blood circulation (3). When tablet is compared with other liquid dosage form, oral liquid dosage forms have other disadvantages and limitation. Liquid dosage forms are much more expensive to ship and breakage or breakage during shipment is a more serious problem than tablet (4). Although when drug is administered through conventional tablet, the drug is released into systemic circulation and the drug concentration decline sudden in plasma drug concentration. plasma drug concentration goes down below MEC value that is loss of therapeutic action of drug. So that there is need to develop to attain the sustained release, usually next dose is given before reaching at point of MEC value and this process make high frequency of dosing (5).

By history the first work in the field of SR of dosage form had been done in 1938 and patented by Israel Lipowski (6).In this work there is a coted pallet for extended release of drug. As per specification ideally a drug candidate should have reached very fast at the site of action and maintained the therapeutic concentration level of drug for a longer period of time. Release of drug should be in optimized concentration to attained the remain constant for the desired time (7).The blood level of active constituent should be in the study state so that active constituent should be therapeutically active and non-toxic for an extended period of time. (8)Normally, pharmacokinetic parameter in human being is supposed to be controlled through chemical structure of medicine (9). One of the most stable and commonly used dosage form is tablet in sustained and controlled release dosage

form. Since after Nineteen century, tablet have been very popular and wide spread and still till now it is continued (10). Tablet dosage form is still remains continues and popular due to its advantageous affordedfor both to patient and to pharmaceutical industry (11). The tablet dosage form having advantages like accuracy of single dosage regimen, easy to handle, easy to administer, simplicity, economic in preparation, stability, convenient in packing, ease of transporting, dispensing and portability etc (12). The goal of designing of modified drug delivery device is to decrease frequency of dosing and to improve the potency of drug via achieving targeted delivery of drug and to reduce the amount of dose required to provide constant drug delivery (13).Reason behind selection of HPMC K100M, it is non ionized hydrophilic cellulose derivative containing methoxyl and hydroxypropyl group that support its hydration properties. Chan, Lai & Heng, et al. reported HPMC K100M having higher molecular weight due to which it results in more viscous gel and cause slower drug release from HPMC matrix tablet (14).HPMC K100M is used to control drug release from several pharmaceutical systems because of its non-toxic nature, easy compression (15).Swelling properties and accommodation to high level of drug. HPMC shows drug release processes better than the other product in case of sustained release dosage form. (16) Liver sidge GG et al., concluded that HPMC is more effective in sustaining the drug release when it is used with guar gum. Therefore, HPMC K100M could be considered as an excellent candidate to prepare ER tablet(17-18). Guar gum is a natural nonionic polysaccharide derived from seeds of cyamopsis tetragonolobus gumy substance (19). It is used as a binder. During the study it was fond that the Guar gum works best with the combination of Chitosan (20). Recently chitosan has been used in various research projects (21). (S Miyuki et al.,) have utilized chitosan with lactose in sustained release dosage form (22). The dosage form was compared with other SR product, chitosan has shown the better result, thus the mixture of chitosan, HPMC and lactose can form sustained release (23) preparation in acidic medium. Chitosan is naturally hydrolyzed derivative of chitin. Chitosan is non-toxic, biocompatible and biodegradable (24). Chitosan have cationic character which allow the establishment of hydrogen bonding with anionic mucin chains resulting in a good mucoadhesive property(25). Therefore, Chitosan has been considered as an excellent candidate to prepare ER tablet (26).

Due to narrow therapeutic window and short half-life of aceclofenac became an ideal drug candidate for extended release dosage form(27).Although first line drug gives relief from pain in Arthritis, and in other acute and chronic inflammatory disorders (28). Aceclofenac is derivative of Phenyl acetic acid derivative which is similar to diclofenac used as pain reliever (29-31). The aim of this research was to maximize the release of drug by using different combination of polymer so that it could reduce the limitation of conventional tablets as well as trying to maximize the release extension in controlled therapeutic manner.

Material and Methods

Materials

The study used the following substance: Aceclofenac, HPMC K100, Guar gum, Chitosan, Lactose, Magnesium stearate and talc were obtained from Yarrow chemical supplier. All other chemicals and solvents were of reagent grade.

Drug excipient compatibility studies via FTIR:

The excipients can affect the stability of drug. Sometime excipients cause the interaction with drug which affect the effectiveness and potency of drug. To know the compatibility of expient with drug, FTIR is liable method. Polymeric excipients are added in the formulation to modified the release along with dosage form and to protect from degradation. Ratio of drug and excipient were taken as 1:1 ratio and stores in glass vial at room temperature for 4 weeks. The sample was analyzed for compatibility study by using FTIR (32).

Formulation development

Design of composition of formulation:ER matrix

Table 1. Formulation table in term of %containing polymer for extended release tablets.

Name of ingredients (%)	Formulation batches													
	E-1	E-2	E-3	E-4	E-5	E-6	E-7	E-8	E-9	E-10 10	E-11	E-12	E-13 13	E-14
Aceclofenac	40	40	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K100M	20	-	-	20	-	20	15	20	15	20	15	20	15	20
Guar Gum	-	20	-	20	20	-	10	10	10	10	20	20	20	20
Chitosan	-	-	20	-	20	20	15	15	20	20	15	15	20	20
Lactose	37.6	37.6	37.6	17.6	17.6	17.6	17.6	12.6	12.6	7.6	7.6	2.6	2.6	-
Mag. stearate	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Talc	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6

tabled involve various excipient to produce desired therapeutic response and to fulfil the pre-decided hypothesis. It contains different polymer in different level of concentration to make such type of tablet which can make release extent. On the basis of various literature review, it was selected the appropriate polymer to achieve desired ER matrix tablet.

Polymer concentration optimization: To set the desired range of variables (polymer concentration) required for the final formulation, a pre-optimization study was conducted with different concentration of polymeric excipients. As the concentration of polymers changed there was a direct effect on swelling index and drug release. Tablets were prepared using concentration of polymers form low to high in each batch. HPMC K100M, Guar gum and Chitosan were used as polymers for retarding the drug release (Table 1). E- Extended release formulation; HPMC K100M- Hydroxypropylmethylcellulose; Mag. Stearate- Magnesium Stearate

Method of preparation:

Extended release of aceclofenac 200 mg tablet was prepared by dry compression method. Firstly, Aceclofenac drug, HPMC K100M, Guar gum, and Chitosan were accurately weighed according to formulation table. These four ingredients were blended uniformly in mortar pestle. Powder mixture was passed through sieve no. 40 to get uniform size. Then diluent lactose was added as a filler with specified amount in composition table. All the powder was mixed thoroughly and pass through sieve no. 44. All the pre-compression study was performed, Talc and magnesium stearate was added as lubricant and glidant before compression (33).

Characterization
Pre-compression study
Characterization of Powder blend:

Angle of Repose:5 g sample was accurately weighed and transferred into funnel which was fixed in holder stand 5cm above from the ground surface. Funnel was kept on stand at distance of 10 cm from surface of Flore, graph paper was placed under the hanging funnel. Heap's height of powder was measured. heap's circumference was drawn on graph paper with the help of pencil. Radius of heap was measured through scale. The angle of repose was estimated by using this formula. This procedure was done three times for each (34).

$$\theta = \tan^{-1} h/r$$

Where,

h = longitudinal height of pile

r = radius of pile

θ = angle of repose

Bulk density: Method specified in USP foe bulk density was calculated. Weighed amount of powder for tablet was taken in pre-weighted 50 ml graduated cylinder with 0.5ml markings. At least two time tapping the cylinder manually on slab surface, the bulk volume was measured (35).

Calculation of Bulk density (Db) was done by this formula,

$$(Db) = (M)/Vo$$

Where, M = mass of powder taken

Vo = unsettled apparent volume (Bulk volume) Determination were carried out in three replicates.

Tapped density: Method specified in USP foe tapped density was calculated. Weighed amount of powder for tablet was taken in pre-weighted 50 ml graduated cylinder of 0.5ml markings. Tapped volume marking was recorded after manually tapping after in increment of 500, 750 and 1250 taps of the cylinder two times on a flat slabsurface (36). The tapped density (Dt) was estimated by the formula,

$$Dt = Mass/Vb$$

Where, M = mass of powder taken

Vt = Tapped volume

Determination were carried out in three replicates.

Compressibility index: it was estimated by using thisequation (37).

$$\text{Compressibility index (CI)} = \{(D_t - D_b)/D_t\} \times 100$$

Where,

D_t = Tapped Density

D_b = Bulk Density

Hausner's ratio: This Hausner's ratio were obtained by calculation using following formula.

$$\text{Hausner's ratio} = Td / Bd$$

Where,

Td = tapped density.

Bd = bulk density.

Post compression study

Weight variation: Weight variation was determined by taking 20 tablet from each batch. These 20 tablets were taken and accurately weighed collectively and individually; the average weight of tablets were calculated (Table 2). Weight variation in terms of percentage was determined(38). formula used for calculation:

$$\% \text{ Deviation} = \frac{\text{Individual wt} - \text{Average wt}}{\text{Average weight}} \times 100$$

Thickness: Thickness of tablet was measured by using Vernier caliper. The tablet was held in the cavity of Vernier calipers. Three tablets were taken from each batch to check thickness of tablet in millimeter (39).

Hardness: Hardness of tablet was measured by using Monsanto tester of hardness. Tablet was held between the moving jaw and affixed and the scale was fixed at zero and the load was gradually increases until tablet become fractured. As tablet was fractured the reading was noted in Kg/cm2 (40).

Friability: Roche friabilator was used to determine the friability of tablet. 20 tablet was taken and preweighted then tablet was put in the circular box which is attached with fribilator and rpm was set at 25 rpm for 4 minute. Tablet was removed and dust was also removed then it was weighted, this weight was lower than initial weight. % friability was calculated using following formula (41).

% friability = {(initial wt - final wt) × 100 /initial weight}

Swelling index: Swelling behavior of formulation indicated that if formulation will not disintegrate for as much as longer time, it maximizes the retardation of drug .The swelling behavior of matrix tablets was determined in terms of % weight increased by the tablet. One tablet of each batch was kept in a beaker containing HCl buffer pH 1.2 at temperature 37° C. Tablets ware withdrawn from beaker after every 2 h up to 18 h. Wet tablets were kept on tissue paper for soaking access liquid. Then it was weighed. The swelling behavior of all formulations were studied. percentage weight gain of tablets were calculated by the formula(42). all the values of swelling index were observed and mentioned in table 4.

S.I = {(Mt – Mo) / Mo} x 100 (7)

Where,

S.I = swelling index,

Mt = weight of tablet at time t (h),

Mo = weig ht of tablet at zero time.

Uniformity of drug content: Drug content was determined by crushing 3 tablet and converted into powder form then powder was taken equivalent to 200mg of aceclofenac, dissolve in 100 ml of methanol in 100ml volumetric flax, sample was kept for 24 hours then it was filtered and 1ml of this liquid sample was taken and diluted with 100 ml of methanol and 1ml of this sample was again diluted with 10 ml of methanol in 10ml volumetric flax. Then the sample was taken for UV observation. The sample observation was taken in triplicate (43). Weight variation Thickness Hardness Friability Swelling index, drug content release profile and stability studies were done as per above.

Release study: *In-vitro* dissolution study was performed using six unit USP *II* dissolution apparatus at 50 rpm of 50 revolutions per minute at 37° c ± 0.5° c in Hcl buffer solution of pH 1.2. 5 ml sample was withdrawn at time interval of 30 minute, 1 h, 2 h, 4 h, 6 h, 8 h, 23 h, 25 h, 27 h, 29 h, 31 h, 48 h, 50 h, 52 h, 54 hours. Sample was filtered and kept in the test tube, 1ml pipette out of this sample and diluted with buffer solution of pH 1.2 in 10ml volumetric flax. Absorbance was taken by using UV visible spectrophotometer at lambda max of 204.34nm (44).

Release kinetics: The results of different kinetic model with correlation coefficient was found to be as- Kinetic drug release was performed to check which model was best fitted for drug release from ER matrix tablet of Aceclofenac. The release data was applied on various mathematical model.

a. *Zero order release model:*(45)

The data was applied on equation of zero order release kinetics.

Co – Ct = Ko t

Where,

Co = initial concentration of drug at time t.

Ct = amount of drug release at time t.

Ko = Zero order rate constant.

Thus model was gave release profile of Acelofenac 200 mg from ER matrix tablet. Evaluation was done by graphical representation. Graph was drawn between cumulative drug release Vs time.

Observation: Graph represented that the release of drug from system had not followed the principle of zero order release because the value of correlation coefficient (r2 = 0.933) slightly approaching (Fig.10)

First order release model:(46)

The data was applied on following equation of zero order release kinetics.

log C = log Co – (K1 t1/2) / 2.303

where,

Co = initial concentration of drug.

C = % drug remaining at time t.

K1 = first order rate constant in time-1.

Thus this model was applied in the release profile of Acelofenac 200 mg from ER matrix tablet. Evaluation was done by graphical representation. Graph was plotted between log cumulative % drug remaining Vs time.

Observation: the graph shows that the release of drug from system does not follow the principle of first order release because the value of correlation coefficient (r2 = 0.833) slightly approaching. (fig.11)

Higuchi kinetic release model: (47)

The release data was applied on the higuchi model of release kinetics:

Q = KH × t.05

Where,

Q = cumulative amount of release of drug at time t.

KH = Higuchi dissolution constant.

t1/2 = square root of time.

Thus, model was gave release profile of Acelofenac 200 mg from ER matrix tablet. Evaluation was done by graphical representation. Graph was drawn between cumulative % drug remaining Vs square root of time.

Observation: the graph shows that the release of drug from system follow the principle of Higuchi model of release kinetics because the value of correlation coefficient (r2 = 0.937) which is closest to the value of (r2 = 0.999) . So the drug release from system is followed with higuchi model. (fig. 12)

Korsmeyer-peppas model: (48)

The release data was applied on this following equation of Kprsmeyer-peppas model to know the release pattern.

log(Wt / W∞) = log Kkp + nlog t

where,

Wt = amount of drug release in time t.

W∞ = amount of drug release after time ∞.

N = drug release exponent.

Kkp = Korsmeyer release rate constant.

To study the kinetics of drug release, a graph is constructed between log cumulative % drug release log (Wt / W∞) Vs. log time.

Observation: the graph shows that the release of drug from system had not followed the principle of Korsmeyer-peppas model of release kinetic because the value of correlation coefficient (r2 = 0.5463) which is not fit. (fig. 13)

Result and Discussion

In this research work we designed extended release tablet of aceclofenac which In-Vitro release of drug was tried to maximize with therapeutic level by using three polymers at different concentration.

Compatibility study:

FTIR spectrum of drug and excipients were recorded respectively. The FTIR spectrum of Aceclofenac, HPMC K100M, Guar Gum and Chitosan were recorded individually then FTIR spectrum of drug and excipient powder blend were recorded respectively. Aceclofenac shows characteristic peak at 1712.68, 1771.47, 1589.53, 1055.90,2862.16, 1444.76, 773.47 suggesting the presence of COOH bending, C=O, NH bending, O-H bending, C-H stretching, C-C stretching respectively in Fig. 1. Individual FTIR spectrum of HPMC K100M shows characteristic peaks at 3470.09, 1934.86, 1461.08, 113.67, 1693.32, 1643.34, 2926.11 which indicating the presence of O-H stretching (alcohol), C-H stretching (alkane), =C-H bending, -C-O stretch (alcohol), -COOH, -CO-NH and CH in Fig. 3. FTIR of Chitosan shows characteristic peaks at 3478.79, 2924.86, 1656.56, 1571.05, 1423.12, 1377.18 that indicating the presence of O-H stretching, C-H stretching, –C=O, NH, -CH-OH and CH2OH respectively.Likewise, FTIR of Guar Gum shows characteristic peaks at 3446.61, 292.25, 1037.32, 1022.12 indicating the presence of O-H stretching, C-H stretching, CH2OH stretching CH2 twisting in. Compatibility study of drug and excipients, in which FTIR of Aceclofenac + HPMC K100M. Aceclofenac + Chitosan and Aceclofenac + Guar gum were recorded and determined by comparing FTIR spectrum of pure Aceclofenac and powder blend of Aceclofenac and excipients. characteristic peak at 1712.68, 1771.47, 1589.53, 1055.90,2862.16, 1444.76, 773.47 suggesting the presence of COOH bending, C=O, NH bending, O-H bending, C-H stretching, C-C stretching were observed in both, pure Aceclofenac and in powder blend of formulation Fig.2. It indicated that there is no chemical incompatibility between Aceclofenac and HPMC K100M, Chitosan, Guar gum.

Fourier transform infrared spectroscopy graphical result

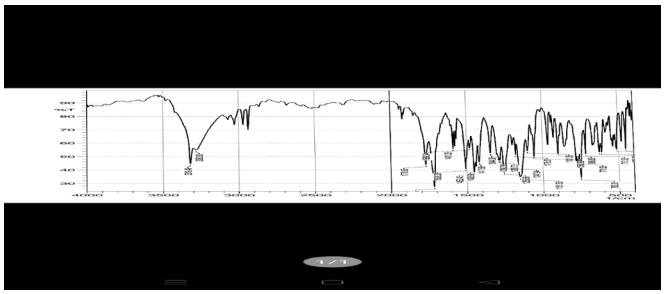

Fig. (1). FTIR of pure Aceclofenac drug

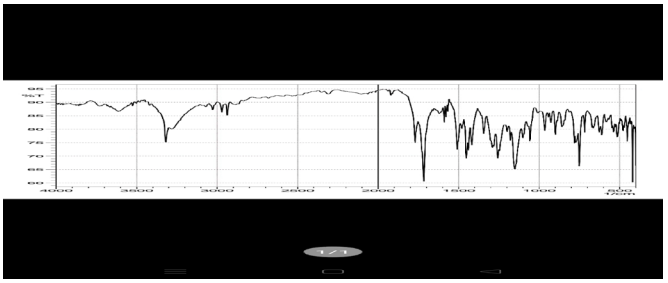

Fig. (2). FTIR of mixture blend of Aceclofenac + HPMC K100M + Chitosan + Guar gum

Current Trends in Biotechnology and Pharmacy
Vol. 15 (4) 416 - 425, October 2021, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2021.4.44

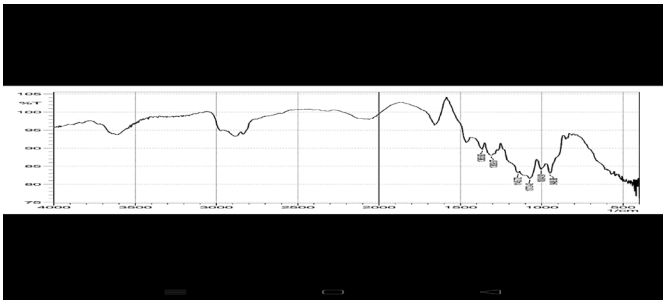

Fig. (3).FTIR of graph of HPMC K100M.

Pre-compression study

All pre-compression parameters were performed to check standard limit for compressing the tablets (49). Testing parameters for aceclofenac, mixed powder blend formed. The result of all the pre-compression parameters i.e. angle of repose, tapped density, bulk density, Carr's index, Hausner's ratio was found to be under the standard limit (Table 2.) which indicated that flow property of powder blendswere comply for further compression of tablet.

Table:2. Result of physical parameters of powder mixture.

formulations	Evaluation parameter				
	Angle of repose (0)	Bulk density (g/ml)	Tapped density (g/ml)	Com-pressibility index	Hausner's ratio
E-1	32.35	0.43	0.62	30.61	1.44
E-2	30.53	0.50	0.58	13.73	1.16
E-3	36.34	0.55	0.83	33.72	1.55
E-4	37.23	0.61	0.89	31.43	1.45
E-5	40.37	0.48	0.71	32.39	1.47
E-6	29.32	0.56	0.85	31.70	1.46
E-7	37.61	0.49	0.78	21.45	1.57
E-8	34.65	0.47	0.58	18.95	1.23
E-9	32.13	0.56	0.62	09.61	1.10
E-10	29.21	0.61	0.79	22.78	1.29
E-11	36.15	0.58	0.71	18.30	1.22
E-12	40.10	0.67	0.82	18.31	1.22
E-13	35.31	0.45	0.62	28.01	1.37
E-14	39.62	0.50	0.71	29.51	

Post compression study

All the post compression parameters i.e. hardness, thickness, weight variation, friability and drug content were analyzed from Table 3.Weight variation was found to be uniform in weight for all the batches. Hardness of formulation E-1 to E-6 were less because of single polymer excipient incorporated and formulation E-7 to E-14 had shown good and uniform hardness. Thickness of thickness of formulation E-1 to E-12 were found in uniform, E13 and E-14 found more thickness as compare to other formulations. Friability of formulation E-1 to E-11 were found little bit more than limit while friability of E-12 was found to be in limit i.e. not more than 1% as per IP reference. E-13 and F-14 also failed the limit of friability. The most important parameter i.e. Drug availability in all formulations were found to be within the range. The optimized formulation F-12 showed 99.30% drug content which was better than all other formulations (50).

Table3. Result of study of physical parameter of tablets.

formula-tions	Hardness (Kg/cm2)	Thickness (mm)	Weight variation (mg)	Friability (%)	Drug content (%)
F-1	2.4	3.43	530.21±0.6	1.32	97.50
F-2	1.9	3.51	490.31±0.5	2.15	98.80
F-3	2.5	3.47	512.25±0.4	2.12	91.00
F-4	3.0	3.46	525.34±0.7	1.52	93.60
F-5	3.2	3.31	518.16±0.6	1.62	96.50
F-6	3.5	3.48	520.26±0.4	1.10	95.40
F-7	5.1	3.11	566.42±0.5	2.65	91.60
F-8	6.2	3.14	540.67±0.6	1.12	99.39
F-9	6.3	5.13	552.83±0.7	0.91	94.36
F-10	5.4	3.11	560.63±0.5	1.10	98.31
F-11	6.2	3.12	545.53±0.4	1.13	97.32
F-12	5.8	3.13	570.42±0.6	0.98	99.30
F-13	6.2	5.19	654.93±0.7	1.56	111.62
F-14	5.9	5.12	680.83±0.5	3.67	90.02

Swelling Index

From the result it was confirmed for formulation E-1 to E-6 were not in good for extended release tablet. (Fig. 4). Swelling index were found to be only for 10 h after that these were became disintegrate because of only single retardant polymer was added to these formulations while formulation E-7 to E-14 had shown better swelling index up to 18 h and so on. Formulation E-7 to E14 were found to better swelling index due to incorporating three polymers in different concentration. (Fig.5).

In this table (-) showing- there were no more data found because tablets were becoming disintegrate after swelling maximum.

Figure: 4. Comparative swelling behavior of formulation E-1 to E-6. SI- Swelling Index; (ERF1 means E-1 i.e. formulation E-1 likewise others up to ERF6 means E6.)

Fig. 5. Comparative swelling behavior of formulation E-7 to E-14 (ERF7 means E-7 i.e. formulation E-14 likewise others up to ERF6 means E-14).

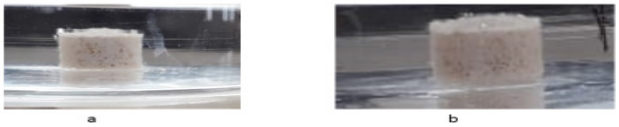

Fig. 6. Swelling characteristic of ER tablet. (a) tablets were poured in beaker containing solution and picture was taken after 2 h of experiment (b) it was taken after 6 h of experiment.

Table 4. Swelling index in terms of Percentage (%).

time in h	E-1	E-2	E-3	F4	E-5	E-6	E-7	E-8	E-9	E-10	E-11	E-12	E-13	E-14
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	40.32	36.92	45.3	41.38	35.15	39.62	29.31	15.61	17.32	21.65	19.4	20.31	13.43	10.31
4	69.21	48.51	55.61	54.45	46.32	48.31	36.25	19.43	21.41	26.45	21.32	21.42	18.52	15.41
6	78.32	82.31	61.35	68.38	62.42	58.95	44.25	26.25	28.51	35.51	29.41	31.48	23.61	23.51
8	89.21	89.24	79.12	74.35	79.35	61.32	53.28	29.42	38.41	42.48	35.82	38.82	29.51	26.51
10	95.32	-	-	82.41	87.35	-	61.45	43.35	48.36	62.48	45.31	58.19	38.71	36.52
12	-	-	-	-	-	-	78.62	48.42	52.13	65.61	51.22	61.65	43.45	41.42
14	-	-	-	-	-	-	81.51	58.45	58.45	71.42	63.42	68.45	51.61	48.5
16	-	-	-	-	-	-	85.82	61.71	62.92	76.42	69.31	72.42	59.39	54.3
18	-	-	-	-	-	-	73.1	72.42	80.35	85.32	73.42	76.51	68.68	68.5

In-Vitro Drug release analysis:

The formulation release study was done on the basis of parameter of prolonged release time of drug and as per I.P. specification. Drug should release 25-30% of drug at 1st part of whole time, at 2nd part of whole time it should release, not less than 50% of drug and it should release more than 80% of drug at 3rd part of time (51) Firstly, these three polymer HPMC K100M, Guar gum and Chitosan was taken individually and made batches of E-1, E-2, and E-3 and evaluation was performed. E-1, E-2, E-3 batch of formulation respectively shown 96.16 % drug release up to 8th hours, 99.48 % up to 8th hours and 98.39 % up to 6th hour this result did not fulfil the desired result of product (fig. 7). Then the concentration of polymer was selected and two polymers were taken and formulated as tablet the result was found to be 99.64 % drug release up to 24th hours, 94.25% drug release up to 23rd hours, and 98.73% drug release up to 23rd hours of batches E-4, E-5 and E-6 respectively (fig. 8). Yet this result was not satisfactory result. Then a full factorial design was selected to make all possible formulation at different level of concentration. So these three polymer was taken as three factor and two level of concentration has been taken to produce desired formulation. Therefore 23 full factorial design was selected and 8 formulations was found to make ER matrix tablet. Evaluation of this 8 batches were performed. Three formulations F-9, E-10, E12 was seen for better result (fig. 9). Although, E-9 was found to be 94.14 % drug release at 31st hours while desirable release was maximum hours. E-10 was found to be 99.28% up to 50th hour but it was also not fulfilling the desired release in comparison with E-12 which release was found to be 95.33% up to 54th hours that was prolonged release and release pattern was satisfied. Since the objective was to make ER tablet of aceclofenac which result should be maximum hour up to 72 hours. Hence E-12 formulation was found to be closest to the objective. The result was found to be as concentration of HPMC K100M increases and concentration of Guar gum, Chitosan keep at medium level, the release of drug shown up to maximum time of 54th hours. While concentration of HPMC K100M decreases and concentration of Chitosan increases, the release was reduced. Therefore, the optimized formulation was found to be E-12 which shows prolonged release and fulfil the criteria of I.P. specification of drug release for therapeutic effect. The result of E-12 batch indicated that it released the drug in a manner which is almost fulfil the hypothesis.

Fig. 7.Comparative graph of release profile of formulation E1-E3 with single polymer incorporated.

Fig. 8. Comparative release profile of formulation E4-E6. F-4= E4; F-5=E5; F-6=E6

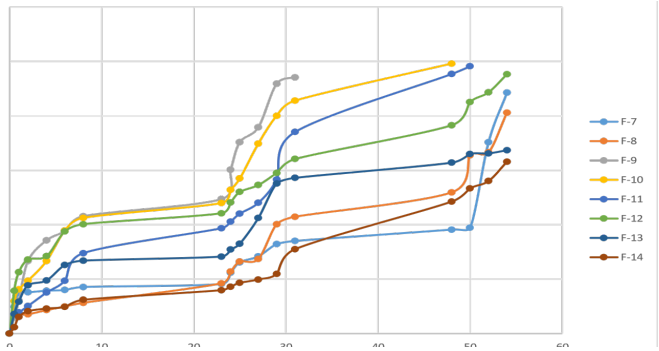

Fig. 9.Comparative release profile of formulation E7-E14. All ‘F’ were used at the place of ‘E’.

Release kinetic study:

From the release kinetics data, it is concluded that figure 11, 12, 13, 14 had showed the r2 value of coefficient of correlation of various kinetic models for optimized formulation E-12 aceclofenac 200 mg ER tablet. It was found that the best fitted model of release kinetic is higuchi model which was with highest correlation

coefficient value nearest to the 0.999 and greater than the first order kinetic and correspond to the zero order kinetic. Higuchi model of fitted formulation indicating that release from tablet is by diffusion model. Although, aceclofenac 200mg ER tablet is very close to zero order kinetic and Higuchi model (52).

Fig. 10. Zero order kinetic model of aceclofenac ER tablet of formulation E-12.

Fig. 11.First order kinetic model of aceclofenac ER tablet of E-12.

Fig. 12.Higuchi model kinetic release of aceclofenac ER tablet of E-12.

Fig. 13.Korsmeyer-peppas model kinetic release of aceclofenac ER tablet of E-12.

Conclusion

The formulation of ER matrix tablet of aceclofenac 200 mg was successfully formulated as release profile was found to be 99 % up to 54 hours that was desired.

The formulation of aceclofenac 200 mg ER tablet was successfully done by using polymer HPMC K100M, Guar gum, Chitosan, as a release retardant. The optimized ER tablet formulation had shown 99.7 % drug release in 54 hours and also follow the I.P specification. So the optimized formulation containing HPMC K100M at a concentration of 100 mg, and Guar gum used at a concentration of 50 mg, and chitosan is used at a concentration of 50 mg these concentration of polymer had shown the maximum retardation in the drug release. Different release kinetics were applied and best fit kinetics was found to be Higuchi model aceclofenac 200 mg ER tablet of optimized formulation E-12 showed diffusion release with correlation coefficient value of 0.937. Stability study of optimized formulation E-12 was performed for 60 days and was found to be stable.

Ethics Approval and Consent to Participate

Not Applicable.

Human and Animal Rights

There are no any animal and human were used in the study.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

References

(1). Lachman/ Lieberman's, the theory and practice of industrial pharmacy fourth edition 2014-page no. 311, 312.

(2). Chien YW. Oral drug delivery systems in novel drug delivery pharmaceutical technology. Marcel Dekker Inc. New York. 1992;139-52.

(2). Sherimeier S, Schmidt PC, Fast dispersible ibuprofen tablets. European Journal of Pharmaceutical Sciences,15, 2002, 295–305.

(3). Girish K Jani, Dhiren P Shah, Vipul D Prajapati et. al., (2009) gums and mucilages, AJPS, 4(5) 309-323.

(4). Tapaswi, & Dash, Tapaswi & Verma, Pankaj. Matrix Tablets: An Approach towards Oral Extentded Release Drug Delivery. International journal of Pharmaceutical research &review. 2013. 2.

(5). Ehrlich P. In collected papers of Paul Ehrlich. Immun Can Res 1902; 442.

(6). Al-Zoubi NM, AlKhatib HS, Obeidat WM. Evaluation of hydrophilic matrix tablets based on Carbopol(®) 971P and low-viscosity sodium alginate for pH-independent controlled drug release. Drug Dev Ind Pharm. 2011 Jul;37(7):798-808.

(7). Patil HG, Tiwari RV, Repka MA, Singh KK. Formulation and development of orodispersible sustained release tablet of domperidone. Drug Dev Ind Pharm. 2016;42(6):906-15.

(8). Girish JK, Dhiren SP, Vipul PD and Vineet JC. Gums and mucilages: versatile excipients for pharmaceutical formulations. Asian J Pharm Sci 2009; 4:309-323.

(9) Maggi L., Machiste E. O., Torre M. L., Conte U. Formulation of biphasic release tablets containing slightly soluble drugs. Eur. J. Pharm. Biopharm. 1999;48:37–42.

(10).Fukuda M., Nicholas A. P., McGinity J. W. Properties of sustained release hot-melt extruded tablets containing chitosan and xanthan gum. Int. J. Pharm. 2006;310:90–100.

(11). Wang K., Zhimin H. Alginate–konjac glucomannan–chitosan beads as controlled release matrix. Int. J. Pharm.2001;244:117–126.

(12). Negrin C. M., Delgado A., Llabres M., Evora C. In vivo–in vitro study of biodegradable methadone delivery systems. Biomaterials. 2001;22:563–570.

(13). Chan, Lai & Heng, P.W.S. & Wan, L.. (). Effect of cellulose derivatives on alginate microspheres prepared by emulsification. Journal of microencapsulation.2009, 14. 545-55.

(14). Hiremath, Praveen S, and Ranendra N Saha. "Controlled release hydrophilic matrix tablet formulations of isoniazid: design and in vitro studies." AAPS PharmSciTech vol. 9,4 2008, 1171-8.

(15). Velasco M., Ford J. L., Rowe P., Rajabi-Siahboomi A. R. Influence of drug:hydroxypropyl methylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC matrices. J. Control. Release. 1999;57:75–85.

(16). Varghas C. I., Ghaly E. S. Kinetic release of theophyline from hydrophilic swellable matrices. Drug Dev. Ind. Pharm. 1999;25:1045–1050.

(17). Alderman D. A. A review of cellulose ether in hydrophilic matrices for oral controlled release dosage forms. Int. J. Pharm. Technol. Prod. Manuf. 1984;5:1–9.

(18). Krishnaiah YS, Satyanarayana S, Prasad YV. Studies of guar gum compression-coated 5-aminosalicylic acid tablets for colon-specific drug delivery. Drug Develop. Ind. Pharm. 1999; 25: 651-7.

(19). Bhardwaj TR, Kanwar M, Lal R, Gupta A. Natural gums and modified naural gums as sustained-release carriers. Drug Develop. Ind. Pharm. 2000; 26: 1025-38.

(20). Sinha VR, Rachana K. Polysaccharides in colon specific drug delivery. Int. J.Pharm. 2001; 224: 19-38

(21). Sami AJ, Khalid M, Jamil T, Aftab S, Mangat SA, Shakoori AR, Iqbal S. Formulation of novel chitosan guargum based hydrogels for sustained drug release of paracetamol. Int J Biol Macromol. 2018 Mar;108:324-332.

(22). Inouye K, Machida Y, Nagai T. Sustained release tablets based on chitosan and carboxymethylcellulose sodium. Drug Des Deliv. 1987 May;1(4):297-305.

(23). Zhao D, Yu S, Sun B, Gao S, Guo S, Zhao K. Biomedical Applications of Chitosan and Its Derivative Nanoparticles. Polymers (Basel). 2018;10(4):462.

(24). Chua B.Y., Al Kobasi M., Zeng W., Mainwaring D., Jackson D.C. Chitoson microparticles and nanoparticles as biocompatible delivery vehicles for peptide and protein-based immunocontraceptive vaccines. Mol. Pharm. 2012;9:81–90.

(25). Kas H.S. Chitosan: Properties, preparation and application to microparticulate systems. J. Microencapsul. 1997;14:689–711.

(26). Kato Y., Onishi H., Machida Y. Application of chitin and chitosan derivatives in the pharmaceutical field. Curr. Pharm.Biotechnol. 2003;4:303–309.

(27). Shen J, Burgess DJ. Accelerated in-vitro release testing methods for extended-release parenteral dosage forms. J Pharm Pharmacol. 2012 Jul;64(7):986-96.

(28). K. Parfitt. Analgesics, anti-inflammatory and antipyretics. In J. E. F. Reynolds (ed.), Martindale: The Complete Drug Reference. 32nd ed, Massachusetts, 1999, pp. 1–12.

(29). Kay A. E., Alldred A. Rheumatoid arthritis and osteoarthritis. In: Walker R., Edwards C., editors. Clinical Pharmacy and Therapeutics. 3. London, UK: Churchill Livingstone; 2003. pp. 791–807.

(30). C. Moffet, M. D. Osselton, B. Widdop. Clarke's analysis of drugs and poisons. 3rd ed., Pharmaceutical Press, London, UK (2006).

(31). Roy, H., Brahma, C. K., Nandi, S., & Parida, K. R. Formulation and design of sustained release matrix tablets of metformin hydrochloride: Influence of hypromellose and polyacrylate polymers. International journal of applied & basic medical research,2013; 3(1), 55–63.

(32). Patel, P., Dave, A., Vasava, A., & Patel, P. Formulation and characterization of sustained release dosage form of moisture sensitive drug. International journal of pharmaceutical investigation, 2015; 5(2), 92–100.

(33). Shah, R. B., Tawakkul, M. A., & Khan, M. A. Comparative evaluation of flow for pharmaceutical powders and granules. AAPS PharmSciTech, 2008; 9(1), 250–258.

(34). Sousa e Silva JP, Splendor D, Gonçalves IM, Costa P, Sousa Lobo JM. Note on the measurement of bulk density and tapped density of powders according to the European Pharmacopeia. AAPS PharmSciTech. 2013;14(3):1098-1100.

(35). Aslani A, Beigi M. Design, Formulation, and Physicochemical Evaluation of Montelukast Orally Disintegrating Tablet. Int J Prev Med. 2016 Oct 26;7:120.

(36). Aslani A, Ghasemi A, Karbasizadeh Esfahani S. Design, Formulation and Physicochemical Evaluation of Dimenhydrinate Orally Disintegrating Tablets. Galen Med J. 2018 May 27;7:e936.

(37). Kamboj M, Goyal S, Rakha P, Arora G, Dureja H, Nagpal M. Formulation and evaluation of metformin oro-dispersible tablets. Acta Pol Pharm. 2011 Sep-Oct;68(5):717-23.

(38). Samie M, Bashir S, Abbas J, Khan S, Aman N, Jan H, Muhammad N. Design, Formulation and In Vitro Evaluation of Sustained-release Tablet Formulations of Levosulpiride. Turk J Pharm Sci.

2018 Dec;15(3):309-318.

(39). Sirisolla J, Ramanamurthy KV. Formulation and Evaluation of Cefixime Trihydrate Matrix Tablets Using HPMC, Sodium CMC, Ethyl Cellulose. Indian J Pharm Sci. 2015 May-Jun;77(3):321-7.

(40). Prajapati PH, Nakum VV, Patel CN. Formulation and evaluation of floating matrix tablet of stavudine. Int J Pharm Investig. 2012 Apr;2(2):83-9.

(41). Lakshmi P, Sridhar M, Shruthi B. Comparative evaluation of single and bilayered lamotrigine floating tablets. Int J Pharm Investig. 2013 Jul;3(3):157-62.

(42). Kadivar A, Kamalidehghan B, Javar HA, Davoudi ET, Zaharuddin ND, Sabeti B, Chung LY, Noordin MI. Formulation and in vitro, in vivo evaluation of effervescent floating sustained-release imatinib mesylate tablet. PLoS One. 2015 Jun 2;10(6):e0126874.

(43). Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and in vitro-in vivo evaluation in healthy human volunteers. Eur J Pharm Biopharm. 2010 Feb;74(2):332-9.

(44). Arza RA, Gonugunta CS, Veerareddy PR. Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin hydrochloride tablets. AAPS PharmSciTech. 2009;10(1):220-6.

(45). Xu G, Sunada H. Influence of formulation change on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. Chem Pharm Bull (Tokyo). **1995**;43:483–487.

(46). Bourne DWA. Pharmacokinetics. In: Banker GS, Rhodes CT, eds. Modern Pharmaceutics (4th ed). Marcel Dekker Inc. New York. 2002;67.

(47). Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. **1963**;52:1145–1149.

(48). Hixson AW, Crowell JH. Dependence of Reaction Velocity upon surface and Agitation. Ind Eng Chem. **1931**;23:923–931

(49). Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC) Adv Drug Deliv Rev. **2001**;48:139–157.

(50). Indian Pharmacopoeia; In. 6 ed: Indian Pharmacopoeia Commission; 1996; Vol 2 p, Appendix 7.1, A-80.

(51). Gunda RK; Manchineni PR. Statistical Design and Optimization of Sustained Release Formulations of Pravastatin. Turk J Pharm Sci.,**2020** Apr;17(2):221-227.