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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF ANTI DIABETIC DRUG BY MELT GRANULATION TECHNIQUE

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Abstract

The present work was carried out to design and evaluate sustained release tablet of highly soluble drug, a cellular acting anti-diabetic agent. The sustained release tablets were prepared by melt granulation technique using stearic acid and hydroxyl propyl methyl cellulose K200M as drug retardant polymers which controls the release of drug and is aimed to meet out the therapy for non-insulin dependent diabetes mellitus (NIDDM). Among the seven formulations, stearic acid alone was used as a drug release retarding agent in F_1. In the next three trials (F_2, F_3, F_4) hydroxyl propyl methyl cellulose K200M was taken with varying concentration as intra granular and extra granular and stearic acid as binder. In the next three trails (F_5 – F_7) stearic acid was added intra granular. It was observed for the extent to which the amount of hydrophilic polymer and concentration of hydrophobic carrier (stearic acid) influences the drug release. *In-vitro* release study results revealed that the drug release was retarded with the proportionate increase in polymer and stearic acid concentration. The present study indicated that, using a hydrophilic cellulose polymer and hydrophobic binder in an appropriate combination (intra and extra granular) in tablet could control the rate of drug release matching with that of the reference product.

Introduction

Oral dosage form is the most preferred route of administration of dosage due to its ease of administration, patient compliance. Among the oral dosage forms, tablets are more preferred due to its ease of administration, precise dosing, and increased stability **(**Convention Krowcyznski.L, 1987). Fluctuation of the drug concentration in the plasma and the tissues, undesirable toxicity and poor efficacy are the common problems observed while administering the drug as the conventional dosage form **(**Lachman et al, 1987). It is very important to maintain the concentration of the drug within the therapeutic window for effective treatment (Brahmankar et al, 1985). Conventional dosage form also suffers from the drawback of repetitive dosing and unpredictable absorption. These drawbacks lead to the new concept of Sustained release delivery system. Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects (Khan G. M. et al, 1995). In general the goal of sustained release dosage form is to maintain therapeutic blood or tissue level of the drug for extended period of time. This is generally accomplished by attempting to obtain "zero order" release from the dosage form. Sustained release systems generally do not attain this type of release and usually try to mimic zero order release by providing drug release in slow "first order" fashion i.e. concentration dependent (Bikiaris D et al, 2007).

2. Methodology

2.1. Materials:

Metformin was purchased from Harman Fine Chemicals Ltd, Aurangabad. Dicalcium phosphate anhydrous (DCP) from Rhodia Caers, Mumbai; Pregelatinized starch (PGS) and Stearic acid from The Dow Chemicals, Goa; HPMC from DKSH India Pvt LTD, Chennai; PVP K-90 from ISP Chemical Ltd, Ahmedabad; Colloidal anhydrous silica from Deggusa, France and Magnesium Stearate (MGS) were purchased from Amishi Drugs and Chemicals Ltd, Mumbai.

2.2 Method

Preformulation studies for color, melting point, particle size distribution and loss of drying were performed. Selection of suitable excipients or carrier for the formulation was done based on compatibility studies. Compatibility studies were carried out to check the interference between the drug (API) and other ingredients like Stearic Acid, PVP K-90, DCP, Aerosil, MGS and other excipients used for the study, using FTIR studies

2.2. A. Formulation of sustained release matrix tablet for anti-diabetic drug

The different batches of matrix tablets were formulated according to the composition given in the table 1.

2.2. B. Preparation of matrix tablet by melt granulation:

Procedure for preparation of granules (Jennifer Wang, et al, 2010; Gupta Surbhi, et al, 2012; Gavin M. Walker et al,2005) **:**

All the ingredients were accurately weighed (table 1).The API was passed through # 20 and other ingredients such as HPMC K200M, anhydrous DCP and PVP K 90 were passed through #20 and collected separately. The materials were loaded into Rapid mixer granulator (RMG), mixed for 10 min at low impeller speed to obtain granules. Melted stearic acid was added at low impeller speed and the blend was chopped for 15 sec. PVP K90 dissolved in water was added to the above obtained mixture at medium impeller speed for 5 min and chopped for 3 min. Addition of purified water and mixing was continued till proper consistency of wet mass was achieved. Granules were dried in fluidized bed drier at inlet temperature of 50°C to 55°C until LOD was in the limit range of 2-3% w/w. Dried granules were passed through #20 sieve and the retentions were milled through 2.0mm screen fitted to the Multimill and knives forward direction. Milled granules were passed through #20 sieves. Prelubrication of sized granules was done with Aerosil-200 (sifted through #40) and Hypromellose K200M for 5 minutes and lubricated with magnesium stearate (sifted through #60) for 3 minutes in Octagonal blender.

2.2. C. Evaluation of granules (K. Anand Kishore et al, 2012)**:**

The granules were evaluated for the angle of repose, bulk density, tapped density, hausner ratio, compressibility index (Carr's index) and friability, and compared with that of the powdered drug substance (table 2, table 3).

2.2. D. Preparation of tablets:

Lubricated blend was compressed with 20.6 x 8.5 mm capsule shaped punches with WM embossing on upper and lower sides.

2.2. D.1.Evaluation of tablets (Rakhi. B.Shah et al, 2008):

The tablets were evaluated for dimensions, hardness, friability, weight variation and *in vitro* drug release (table no.4).

2.2. E. Determination of drug content by HPLC:

The drug content of the tablets was determined with the following chromatographic conditions: Atlantis C 18; 25cm x 4.6 mm; 5µm column; ambient column temperature; Flow rate: 1.0 mL/min; Injection volume: 10 µl; Detector Wave length of 233 nm; Run Time: 10 min; Mobile phase: Buffer pH 5-Acetonitrile mixture.

2.2. F. *In Vitro* dissolution studies:

In vitro dissolution studies for the prepared tablets and the marketed product were performed in USP Type II (paddle) apparatus, with 900mL pH 6.8 phosphate buffers at an RPM of 100, 37.0 ± 0.5°C temperature. The samples were withdrawn at time intervals of 0.5, 1, 2, 3, 4, 5, 6, 8, 10 hours and analyzed for drug content by HPLC at 233nm (fig 1)(fig 2).

2.2. G. Assessment of similarity and dissimilarity factors (P. Costa, 2001 a, b)**:**
The dissolution profiles was compared by using two factors, f_1 (Dissimilarity factor) and f_2 (Similarity factor). FDA has set a public standard of f_2 value between50-100 indicate similarity of two dissolution profiles, and ensures equivalence of the performances of the two products. f_1 value should be ≥ 15 to indicate dissimilarity (table 5).

Dissimilarity factor (f_1):

$$f1 = \frac{\sum_{i=1}^{n}(Ri - Ti)}{\sum_{i=1}^{n} Ri} X100$$

Where R_i = percentage drug release of reference product at particular time.
T_i = percentage drug release of test product at particular time
Similarity factor (f_2):

$$f2 = 50\log\left[\frac{1}{\sqrt{1+\frac{\sum_{i=1}^{n}(Ri-Ti)^2}{N}}}\right]\times 100$$

Where N = Total number of time points.

2.2. H. Stability studies:
Stability is an important parameter evaluated for the formulations to assess the stability of the drug in the formulation at the probable storage conditions (table 6).

3 Results and Discussion

3.1. Preformulation studies:
Hausner ratio of <1.25 indicates a powder that is free flowing whereas >1.25 indicates poor flow ability. The smaller the Carr's Index the better the flow properties (5-15 indicates excellent, 12-16 good, 18-21 fair and > 23 poor flow) (Aulton, 2010). From the table 2, it is evident that the drug substance showed a poor flow property and hence the melt granulation technique was used to improve the flow of the powder.

From the table 3 it is evident that all the batches of the granules showed a Hausner ratio <1.25 and CI 18- 21 showing fair flow property while the batch F_7 has good flow property. This indicates that the granules showed an improved flow characteristic compared to the drug substance and are compressible. Angle of repose for all the formulations were $\leq 40^0$, indicating that the granules posses a reasonable potential to flow. All the physical parameters estimated for granules thus indicate that the flow characteristic of the granules was improved compared to that of the powder drug substance. All the formulations of the blend were taken for the preparation of tablets.
From the FTIR results the drug and excipients were found to be compatible, and suitable to develop the formulation. Based on the preformulation data HPMC K200M, PVP K90 and stearic acid were taken as drug release retardants for formulation of SR matrix tablets of a highly water soluble class III drug. The tablets were formulated by melt granulation technology.

3.2. Evaluation of tablets:
The weight variation tests were performed as per the procedure given in BP. The formulations found to show weight variation of <5% which was satisfactory. The thickness of the matrix tablets were found to be in the range of 6.9 to 7.2 mm which is in the limits of 7.13±0.3mm. The hardness of all batches ranged from 18.0-21.0 kp which is within the acceptable limit. The friability of all formulation ranged from (0.17 % to 0.19%) which was <1% as per IP indicating that the friability is within the specification limit.

3.3. *In vitro* release of the tablets:

The tablets of different batches were subjected to dissolution test. The sustained release tablets were formulated to release the drug up to 10 hrs by varying polymer (HPMC K200M) and Stearic acid concentration. Since the drug is hydrophilic it is customary to use a hydrophobic polymer to retard the drug release hence stearic acid was used.

In formulation F_1 only melt stearic acid (hydrophobic agent) was used as drug release retarding agent. From the dissolution studies it was observed that fast release of drug i.e. 99% of drug was released within 2 hr. This may be due to the fact that the core of the matrix tablet was not well bound with stearic acid. Also this suggests that the use

of stearic acid alone to retard the drug release is not suitable. Hence this necessitates the use of other polymers to affect the release.

In formulation F_2 2% HPMC K200M was used along with melt stearic acid. The drug release was retarded up to 5 hours, due to the retarding effect of HPMC K200M. Since this has got the viscosity of 80,000- 1, 20,000cps which gels and makes the drug to diffuse slowly through the matrix. But HPMC alone being hydrophilic allows the drug to diffuse fast hence stearic acid was used. In formulation F3, F4, 4.5% and 6.5% HPMC was used along with melt stearic acid, the drug release was retarded up to 8 hours. This shows that, as the polymer concentration is increased the release was retarded correspondingly.

The formulations were compared with the reference product (Marketed). The reference product showed an immediate release of around 21% in first 30 minutes and the remaining drug were released gradually extending upto 10 hours. At the end of the 10^{th} hour about 97% of the drug was released. Same release pattern was also expected from the present formulations. But the release pattern was not matched with the reference product and also with IP specifications. From formulation F4 to F7 1%, 2.5%, 4% stearic acid was added intra granularly, the drug release was retarded up to 10 hours and the release profile of F7 was almost matched with the reference product. The similarity factor was observed 81.16%. This could be due to the presence of stearic acid as intra granular material. As this concentration was increased there is no much effect on the release behavior but the results with the batch which are closer to the reference product were taken as the optimized batch.

In vitro release study data indicates that duration of release of drug is dependent on the percentage of selected polymer HPMC K200M and stearic acid used in the formulations and, an increase in the polymer concentration not only causes increase in the viscosity of the gel but also leads to formation of gel layer with a longer diffusion path and the stearic acid induces the hydrophobicity. This leads to a decrease in the diffusion of the drug and therefore a reduction in the drug release rate. Figure 2 shows almost a superimposed mirror image of the two formulations. Hence this product was taken as the optimized batch.

3.4 Similarity and dissimilarity factors

The f_2 factor is extensively used because the US FDA endorses it. In a number of recent guidance documents, the FDA has placed more emphasis on the meaningful comparison of dissolution profiles. Hence f2 factor was used as a tool to compare the dissolution profiles and f1 the difference factor. As per the US FDA the f2 values were achieved at 81.16% and the difference factor of about 3.1 which is closer to zero was achieved. This shows that the batch F7 which lies in the acceptable range and could be taken as the optimized batch.

From table 5, f_1 was found to be 3.1 which indicate that both the test product and the reference product do not vary much from each other. Similarly the f_2 was found to be 81.16 which indicate that the test and the reference products were similar. Thus it can be inferred that the dissolution profile of both the formulations is similar.

3.5 Stability studies:

From table 6, it is evident that the physical characteristics and dissolution profile of the matrix tablet has not changed during storage. Moreover the impurity profile was observed to be well within the specification limit of less than 0.2% for known impurity and 0.2% for unknown maximum single impurity and 1.5% for total impurity. Hence, the sustained release tablets were found to be stable at the specified storage conditions for a period of 3 months.

Table 1: Composition of different formulations of matrix tablet

* API = Active pharmaceutical ingredient, DCP = Dibasic calcium phosphate

S.NO	INGREDIENTS	F_1(mg)	F_2(mg)	F_3(mg)	F_4(mg)	F_5(mg)	F_6(mg)	F_7(mg)
Intra granular material								
1	API	850	850	850	850	850	850	850
2	PGS	40	40	40	40	40	40	40
3	HPMC	-----	10	20	30	30	30	30
4	DCP	20	95	70	45	30	15	
5	STEARIC ACID	----	----	----	----	15	30	45
Binders								
6	PVP K90	20	20	20	20	20	20	20
7	STEARIC ACID (MELT)	20	100	100	100	100	100	100
8	PURIFIED WATER	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Extra granular material								
9	HPMC K 200M	----	15	30	45	45	45	45
10	AEROSIL	10	10	10	10	10	10	10
11	MGS	10	10	10	10	10	10	10
	AVG WT(mg)	1150	1150	1150	1150	1150	1150	1150

Table 2: Flow property of drug substance

Parameters	Observation
Bulk density	0.34g/ml
Tapped density	0.59g/ml
Compressibility index	44.2
Hausner ratio	1.79

Table 3: Blend flow properties of different formulations

Sl. No	Formula Code	Bulk density	Tapped density	Hausner ratio	C.I	Angle of repose	LOD (%)
1	F_1	0.5	0.625	1.25	20	35±0.625	2.42
2	F_2	0.523	0.689	1.21	17.3	40±0.72	2.33
3	F_3	0.512	0.625	1.22	18	37±0.77	2.46
4	F_4	0.521	0.671	1.23	18.7	38±0.29	2.1
5	F_5	0.515	0.662	1.22	18	33±0.81	3.2
6	F_6	0.519	0.659	1.19	16	30±0.72	2.74
7	F_7	0.511	0.625	1.22	18	28±0.29	2.82

Table 4: Evaluation of physical parameters of tablets

Formula Code	Avg Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Drug content (%)
F_1	1148.2±2.8	7.19±0.05	18.5±0.458	0.174%	98.88±0.990
F_2	1150.35±2.	7.12±0.04	19.6±0.519	0.18%	99.81±1.206
F_3	1150.38±2.	7.18±0.07	20.3±0.435	0.15%	97.713±1.06
F_4	1151.06±3.	7.20±0.02	20.3±0.65	0.14%	100.45±2.45
F_5	1150.4±3.2	7.21±0.06	20.65±0.53	0.16%	99.69±0.687
F_6	1151.99±4.	7.09±0.09	19.9±50.5	0.19%	99.497±0.52
F_7	1150.46±3.	7.17±0.07	20.7±0.50	0.19%	101.81±1.55

n = 10, All the values are mentioned as mean ± SD

Table 5: Similarity and Dissimilarity Factor:

TIME (hr)	REFERENCE PRODUCT (R)	TEST PRODUCT (T)	(R – T)	$(R – T)^2$
0	0	0	0	0
0.5	21.1	23.6	2.5	6.25
1	33.4	35.5	2.1	4.41
2	47.8	49.3	1.5	2.25

3	56.8	59.6	2.8	7.84
4	68.2	71.7	3.5	12.25
5	78.3	84.5	1.2	1.44
6	87.4	88.7	1.3	1.69
7	93.7	95.8	2.1	4.41
10	97.2	98.5	1.3	1.69
f1	3.1			
f2	81.16			

Table 6: Stability study results of F_7:

Name of test		**LIMIT**	**Initial**	**1st month**	**2nd month**	**3rd month**
Description:	White		Complies	Complies	Complies	Complies
Hardness (kp)		18-22	18.4-21.7	18.5-21	18.9-20.8	18.2-21.4
Dissolution	Highly soluble drugs					
	1st hour	25.0- 50.0%	36.0±0.32	35.7±0.89	36.5±0.75	35.9±0.41
	3rd hour	45.0- 75.0%	60.3±0.15	58.4±0.91	62.1±0.84	59.8±0.48
	10 hour	NLT 85.0%	98.7±0.32	99.1±0.87	98.7±0.67	98.6±0.75
Loss on drying		NMT 0.5%	0.08%	0.9%	0.1%	0.12%
Assay	Highly soluble drugs	95-105%	98.2-99.8%	99.3-101.4%	98-102%	97-99.6%

Fig 1: *In vitro release* profile of the formulations

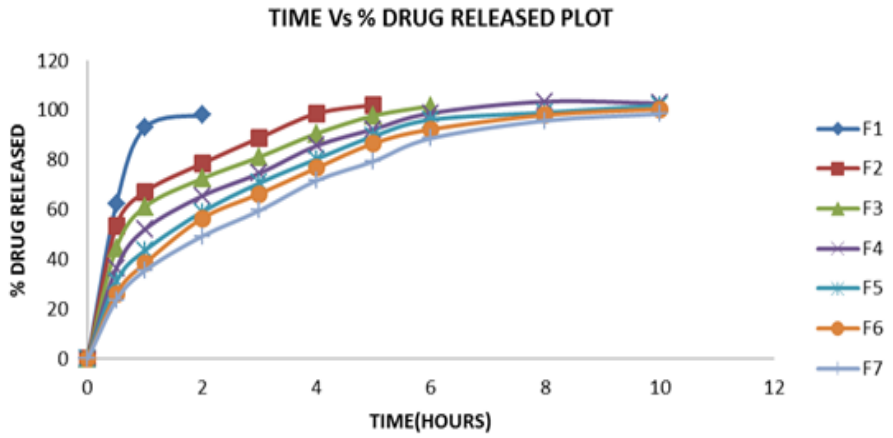
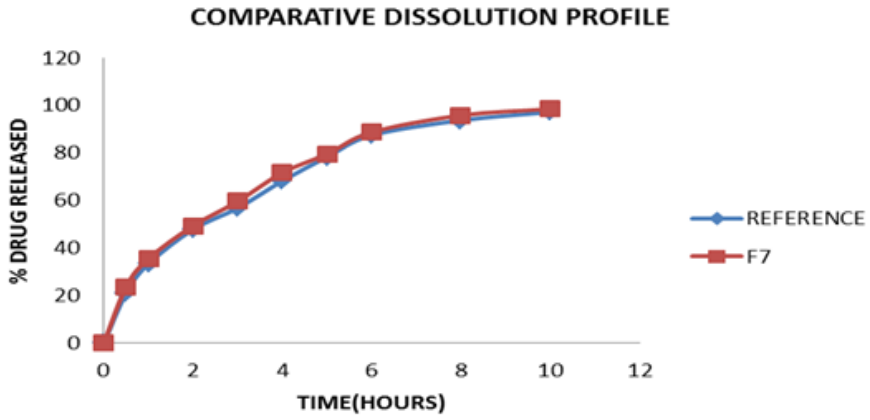


Fig 2: Comparative dissolution profile of F_7 and Reference product



4. Conclusion

From the above results, it can be concluded that all the formulations followed the sustained-release pattern of drug release. The present study indicated that the use of hydrophilic cellulose polymer and hydrophobic binder in an appropriate combination (intra and extra granular) in tablet could control the rate of drug release matching with that of the reference product. Success of the *in vitro* drug release studies recommends the product for further *in vivo* studies, which may improve patient compliance.

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