

Formulation and In-vitro Drug Release of Metformin HCL Extended Release Matrix Tablet

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Abstract: Purpose: To development and evaluation of oral metformin HCL extended release tablet using hydrophilic polymer and hydrophobic carrier, the formulation of metformin HCL tablet by melt granulation and direct compression technique.

Method: The metformin HCL formulation contain various hydrophobic carrier as well as hydrophilic polymer. The formulation procced by melt granulation method and direct compression method were evaluated. the in process quality control test as well as in- vitro release method were studied metformin HCL formulation tablet and the polymer, method of preparation and carrier directly influence on the metformin HCL release profile. **Result:** Physicochemical characterization of tablets were generally satisfactory. The polymer should be used be used in formulation directly effect on drug release profile. The metformin release rate was also depending on the formulation method, the cumulative drug release defined in the %CDR curve which indicate as release of metformin.

Conclusion: in the formulation hydrophobic carrier and hydrophilic polymer effect on the drug release. The polymer effectively controls initial drug release which is highly water soluble metformin HCL.

Keywords: Metformin HCL, extended release tablet, in-vitro drug release, Diabetic mellitus, cumulative drug release

1. Introduction

The metformin HCL extended release tablet should be used in diabetic mellitus. The diabetic mellitus is acute and chronic disease developed in various countries. The disorder is characterized by metabolism and high blood glucose level.

Diabetic mellitus classified as:

- Hyperglycemia: increasing blood glucose level in body
- Hypoglycemia: decreasing blood glucose level in body

The metformin HCL is most widely use oral anti-hyperglycemic agent. Metformin decrease hepatic glucose production, decrease intestinal absorption of glucose, and improve insulin sensitivity by increasing peripheral glucose uptake and utilization.it show incomplete absorption from gastrointestinal tract and bioavailability become 50 to 60%. The elimination half- life is approximately is 17.5hr. HPMC

become used in the formulation is synthetic derivative of

cellulose having swelling and hydrophilic property.it used to prolong drug release due to its rapid hydration, compression property.it give better therapeutic effect in the production of metformin HCL tablet which improving patient compliance.

2. Material and Method

The formulation of metformin HCL extended release tablet contain metformin HCL- 500mg, colloidal silicon dioxide- 0.55%, microcrystalline cellulose- 900mg, polyethylene oxide- 10%,20%,30% respectively, steric acid - 4%, 8%,12%.

A. Formulation of matrix tablet by melt granulation

The matric formulation procced by hot melt granulation technique. Steric acid melted in stainless steel vessel at 75°C. Then metformin HCL become sieved through an 850 μ screen and heated at 75°C. The melt granulation process was carried out by transfer the molten metformin hcl to a high shear mix granulator. Then add slowly molten steric acid. The speed of granulation was 100 rpm for impeller and 1500rpm for chopper with time 5min.

The produced granule of metformin HCL allow to cool in room temperature which sprayed on metal tray and then sieved through 850 μ aperture screen. The melt granule were mixed with polyethylene oxide and microcrystalline cellulose (pre-sieved through 600 μ screen), colloidal silicon dioxide (pre-sieved through 425 μ screen), magnesium stearate (pre-sieved through 425 μ screen), and the granule procced for compression of tablet.

B. Formulation of matrix tablet by direct compression technique

The metformin API and microcrystalline cellulose were sieved through 850 μ screen the blended for 5min manually, colloidal silicon dioxide sieved through 425 μ screen was added and blended for 3min. then magnesium stearate pre-sieved through a 425 μ screen was added and mix for 2min. the final mixing and blending was compressed into 19 x 9.7 mm oblong tablet in a stations cadmach compression machine.

C. Physicochemical characterization of tablets

- **Appearance:** General appearance of tablet, its identity, elegance is essential for consumer acceptance for to control lot to lot uniformity. To control general appearance of metformin tablet involve measurement of size, shape, colour, odour, taste etc.

Table 1
Appearance of metformin HCL tablet

S.no.	parameter	drug
1	Appearance	Crystalline powder
2	Colour	White
3	Odour	Odourless
4	Taste	tasetless

- **Thickness:** The thickness of tablet become inversely proportional to the hardness.so increase in tablet hardness – decrease the tablet thickness of tablet. Thickness of tablet is measured by Vernier caliper. Select randomly 5 tablet and thickness measured by Vernier caliper become NMT 5mm for metformin HCL tablet

- **Hardness:** Tablet required certain amount of strength of hardness and resistance to friability to withstand mechanical shock of handling in manufacturing, packaging and shipping.

Measurement: Select 5 tablet randomly for to detect hardness of the tablet.

Limit: as per IP- minimum 5kg/cm

Different hardness tester:

- Monsanto hardness tester
- Pfizer tester
- Schleuniger tester
- Erweka tester
- **Friability:** Friability is the determination of loss of weight of tablet due to removal of small fine particles from the surface of tablet. It can be measured by ROCHE FRIABILATOR. It consists of plastic chamber.
- **Measurement:** select 20 tablet randomly from the formulation and weight with balance. Tablet placed in chamber of ROCHE FRIABILATOR that rotated at 25rpm -100 revolution for 5 min. then tablet reweight again and detect.

The percent of weight can be calculated as:

$$\% \text{friability} = W1/W2 * 100$$

W1- initial weight of tablet, w2- final weight of tablet

The percent of weight loss can be calculated as:

$$\% \text{friability} = W1 - W2 / W2 * 100 \quad W1 - \text{initial weight of tablet, } w2 - \text{final weight of tablet}$$

Initial weight of tablet (W1) -911

Final weight of tablet (W2) – 908

$$\% \text{friability} = 911 - 908 / 911 * 100 = 0.329\%$$

Limit: the tablet are reweight compress tablet that loss less

than 0.5-1% of tablet weight arte acceptance

- **Weight variation:** Select 10 tablet randomly, the weight of the tablet weighed using electronic balance. Average weight of the 10 tablet measured. Then individually 10 alternate tablet weight measured. The weight variation proceed as following limit:

Table 2
Weight variation limit as per USP

S.No.	Avg. weight of tablet	Max % deviation allowed
1	130 or less	10%
2	130-324	7.5%
3	More than 324	5%

Table 3
Weight variation limit as per IP

S.No.	Avg. weight of tablet	Max % deviation allowed
1	84 or less	10%
2	84-250	7.5%
3	More than 250	5%

Total weight of 10 tablet= 9093.9mg

Avg. weight of tablet= 909.39mg

Table 4
Alternate weight of metformin HCL tablet

S. no. tablet	Weight of tablet (mg)
1	901.6
2	861.3
3	906
4	886.7
5	936.7
6	914.3
7	889.1
8	889.3
9	993.4
10	915.5

5% deviation occurs =

$$\begin{aligned} \text{Upper limit} &= \text{Avg. wt.} + 5\% \text{ deviation} \\ &= 909.39 + 5 \\ &= 914.39 \text{mg} \end{aligned}$$

$$\begin{aligned} \text{Lower limit} &= \text{Avg. wt.} - 5\% \text{ deviation} \\ &= 909.39 - 5 \\ &= 904.39 \text{mg} \end{aligned}$$

D. Evaluation of in-vitro drug release

In-vitro the drug release determination was proceed using USP TYPE 1 apparatus (basket apparatus) in 900mL of 0.1N HCL at 37± 5 °C for initial first 2 hour and then phosphate buffer Ph-6.8 for further next 3hour. The basket apparatus rotating at 100rpm through test proceed, then sample withdrawn per continuously 1 hour and at that time similarly replaced by fresh media with time interval. The withdrawn sample filtered with membrane filter and analyzed at 233nm for metformin HCL by using uv- spectrophotometer. The content of drug and cumulative drug release were derived from standard calibration curve of metformin HCL.

Dissolution apparatus: all the dissolution apparatus are enlist in table

Table 5
 Dissolution apparatus as per IP, USP, BP, EP

TYPE	I.P	U.S.P	B.P	E.P
TYPE 1	Paddle apparatus	Basket apparatus	Basket apparatus	Paddle apparatus
TYPE 2	Basket apparatus	Paddle apparatus	Paddle apparatus	Basket apparatus
TYPE 3		Reciprocating cylinder	Flow through cell	Flow through cell
TYPE 4		Flow through cell		
TYPE 5		Paddle over disk		
TYPE 6		Rotating cylinder		
TYPE 7		Reciprocating disk		

Dissolution study:

SSC of metformin HCL in 0.1N HCL: At λ_{max} -219nm

Table 6

Conc. $\mu\text{g/mL}$	Absorbance
3	0.192
6	0.325
9	0.48
12	0.65
15	0.756
18	0.932

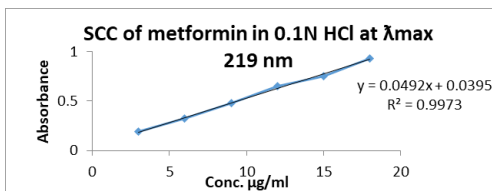


Fig. 1. SCC of metformin in 0.1N HCL

SSC of metformin HCL in PH6.8 phosphate buffer: At λ_{max} -223nm.

Table 7

Conc. $\mu\text{g/ml}$	Absorbance
2	0.222
4	0.356
6	0.561
8	0.749
10	0.911
12	1.062

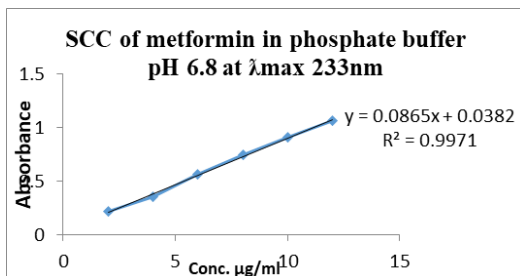


Fig. 2. SCC of metformin in phosphate buffer pH 6.8

%CDR- Cumulative drug release:

Table 8
 % cumulative drug release profile

Time(min)	Abs	Conc.	DF	Conc. $\mu\text{g/ml}$	Conc. mg/l	Conc. mg/5ml	Conc. mg/900ml	CDR	%CDR
0	0	0	0	0	0	0	0	0	0
60	0.221	3.683884	10	36.83884298	0.036839	0.184194215	33.15495868	0.066309917	6.630992
120	0.312	5.56405	10	55.64049587	0.05564	0.278202479	50.07644628	0.100152893	10.01529
180	0.592	6.236062	10	62.36061684	0.062361	0.311803084	56.12455516	0.11224911	11.22491
240	0.701	7.529063	10	75.29062871	0.075291	0.376453144	67.76156584	0.135523132	13.55231
300	0.835	9.118624	10	91.18623962	0.091186	0.455931198	82.06761566	0.164135231	16.41352
360	0.962	10.62515	10	106.2514828	0.106251	0.531257414	95.62633452	0.191252669	19.12527

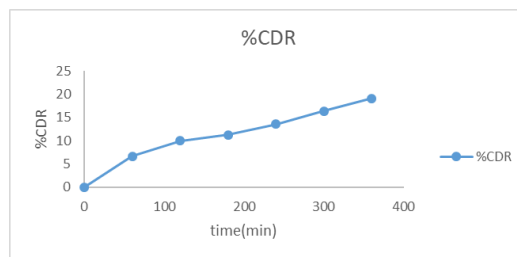


Fig. 3. %CDR

3. Discussion

The metformin HCL extended release tablet not only effect on the therapeutic efficacy with patient compliance but also increase in blood drug level and lower production of adverse effect. The content of formulation indicates amount of drug present in tablet and formulation showed satisfactory hardness, friability, thickness, and weight variation test.

The increase in conc. Of polyethylene dioxide range become decrease the release of drug rate. The metformin HCL is highly water soluble drug compounding in polyethylene oxide matrix result in faster polymer swelling rate, gel thickness and to prevent immediate release metformin HCL drug. The matrix compounding prevents the immediate disintegration of tablet due to water absorption and polymer swelling. Also when steric acid content matrix increase which effect on decrease in drug release due to effect of steric acid drug release over an extended period.

In-vitro drug release study the metformin HCL firstly 2hour drug release detected in 0.1N HCL and then continuously after 3-hour drug release detected in phosphate buffer PH-6.8. The releasement of drug in hcl was lowered as compare to phosphate buffer, but in phosphate buffer the drug releasement become continuously increased with time. The cumulative drug release of metformin hcl proceed on the basis of uv- spectrophotometer and the %CDR defined successfully as per the extending release tablet profile.

4. Conclusion

Hydrophobic carrier and hydrophilic polymer. The formulation of matrix tablet demonstrated that designed drug release using %cumulative drug release. The melt granulation technique is always better than direct compression granulation technique for controlling the release of highly water soluble metformin HCL drug. The release of drug depends on the matrix swelling and releasing with absorption of water. The

metformin Hcl drug completely combined with polymer matrix for to extending releasement, and the coating of polymer directly effect on the dissolution as well as disintegration of drug. The polymer coating increase the therapeutic efficacy of drug also with lowered adverse effect.

The % cumulative drug release defied the metformin HCL released in two different media and the curve represent the extending drug releasement profile.

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