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Puratchikody A
Department of Pharmaceutical Technology, Bharathidasan Institute of Technology, Tiruchirappalli, Anna University, Chennai, Tamilnadu, India.

Shanmugarathinam A
Department of Pharmaceutical Technology, Bharathidasan Institute of Technology, Tiruchirappalli, Anna University, Chennai, Tamilnadu, India.

Hari PG
Department of Pharmaceutical Technology, Bharathidasan Institute of Technology, Tiruchirappalli, Anna University, Chennai, Tamilnadu, India.

Faritha Begam N
Department of Pharmaceutical Technology, Bharathidasan Institute of Technology, Tiruchirappalli, Anna University, Chennai, Tamilnadu, India.

Sridhar G
Department of Pharmaceutical Technology, Bharathidasan Institute of Technology, Tiruchirappalli, Anna University, Chennai, Tamilnadu, India.

Correspondence:
Puratchikody A
Department of Pharmaceutical Technology, Bharathidasan Institute of Technology, Tiruchirappalli, Anna University, Chennai, Tamilnadu, India.

Formulation and development of sustained release metformin hydrochloride tablet

Puratchikody A, Shanmugarathinam A, Hari PG, Faritha Begam N, Sridhar G

Abstract
The objective of the work was to develop Metformin Hydrochloride sustained release tablet using Hypromellose (HPMC) as polymer by wet granulation method. Hypromellose 15 cps and 1 lakh cps were used by varying their proportion to develop sustained release tablets. All the batches were evaluated for thickness, weight variation, thickness, hardness, friability, percentage of drug content and *in vitro* release profiles. Formulation F5 was found to release drug at the regular interval up to 10 hr.

Keywords*:* Metformin Hydrochloride, Hypromellose, Diabetes Mellitus, Sustained Release, Tablet

1. Introduction
Diabetes mellitus, a global public health problem, a chronic disease and is now growing as an epidemic in both developed and developing countries. Diabetes mellitus, often simply called diabetes, a syndrome characterized by disordered metabolism and inappropriately high blood sugar (hyperglycemia).The World Health Organisation (WHO) recognizes the main forms of diabetes mellitus: Type 1 (insulin deficiency), Type 2 (insulin resistance) and gestational (occurring during pregnancy) which have similar signs, symptoms, and consequences [1].
According to IDF (International Diabetes Federation), 382 million people have diabetes and by 2035 this will rise to 592 million. It is estimated that 175 million people have undiagnosed Type 2 diabetes. Diabetes affects people in both urban and rural settings worldwide, with 64% of cases in urban areas and 36% in rural[2]. In human as well as financial terms, the burden of diabetes is enormous, provoking 5.1 million deaths and taking up some USD 548 billion dollars in health spending (11% of the total spent worldwide) in 2013 [2].
Metformin is the most popular oral antidiabetic drug from the biguanide class, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60 % with relatively short plasma half-life of 1.5 - 4.5 hour [3].
Hypromellose (HPMC), a semi synthetic derivative of cellulose, a swellable and hydrophilic polymer. It is widely used to prolong the drug release due to its rapid hydration, good compression and gelling characteristics along with its ease of use, availability and very low toxicity. It regulates the release of drug by controlling the swelling and cross linking. The main scope of this work was to enable the production of sustained release metformin hydrochloride tablets enabling improved patient compliance and better therapeutic effect [4].

2. Materials and Methods
Metformin HCl B.P as gift sample from Abhilash chemicals, T.N. Hypromellose (15 cps) from Ruitai Fine Chemicals, China. Hypromellose (100000 cps) from The Dow chemical company, U.S.A. Microcrystalline Cellulose and Magnesium stearate from Vijlak pharma, A.P. Sodium Carboxy Methyl Cellulose from reliance cellulose products, A.P.

3. Formulation of Sustained Release Tablets
Various batches of tablets were prepared by wet granulation technique (Table 1). Tablets were prepared by adding Sodium carboxy methyl cellulose as a binder. All the ingredients were thoroughly mixed and granules were prepared by wet granulation technique. The wet granules are dried in dryer at 60 – 70 ˚C. The granules are then passed through a sieve 16 mesh to get uniform granules. Required quantities of lubricant was weighed and passed through the sieve no. 60 mesh. Magnesium stearate, Hypromellose (1000000 cps) are mixed with prepared granules by using double cone blender for 15 minutes and then the granules are loaded in the hopper and compressed at 25 rpm [5].

Table 1: Composition of Metformin HCl Sustained Release Tablets

S. No.	Ingredients	Composition (%)				
		F1	F2	F3	F4	F5
01.	Metformin HCl	78.05	73.97	72.27	72.96	73.33
02.	Microcrystalline cellulose	5.53	10.42	10.22	8.60	6.33
03.	Sodium carboxymethyl cellulose	5.78	5.48	7.65	7.72	7.76
04.	Hypromellose (15 cps)	0.91	0.87	0.85	1.63	1.63
06.	Hypromellose (100000 cps)	9.18	8.70	8.50	8.58	10.44
07.	Magnesium stearate	0.55	0.52	0.51	0.51	0.51

4. Evaluation of Formulated Tablet [6]

4.1 Thickness, Hardness and Weight variation test

The tablet thickness was determined using vernier caliper. Hardness of tablets was measured by using pre-calibrated digital hardness tester. Twenty tablets were selected randomly and mean weight was calculated. The individual tablets were weighed and compared with average weight.

4.2 Friability test

This test was carried out on 20 randomly picked tablets from a batch using Roche friabilator. The friability index was a calculated.

$$\text{Percent Friablity} = \frac{(\text{Initial Weight} - \text{Final Weight})}{\text{Initial Weight}} \text{x } 100$$

4.3 *In vitro* drug release studies [8]

In vitro drug release of Metformin Hydrochloride was performed using USP type 1 (basket) apparatus. The studies were carried out in 900 ml of phosphate buffer of pH 6.8 for 10 hours at a temperature of 37 ± 0.5 °C at 100 rpm. Sample were withdrawn at predetermined time intervals and replaced with the same volume of dissolution media to maintain the constant volume. The samples were diluted to suitable concentration analyzed by using UV visible spectrophotometer.

4.4 Content Uniformity Test (Assay)

The Metformin HCl content in tablets was determined by this method. Twenty tablets in each batch were weighed and crushed. Powder equivalent 100 mg of Metformin HCl was dissolved in 70 ml of water. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 232nm.

5. Results and Discussion

In F1 and F2 formulation, the various problems were observed. Hence, the percentage release of drug was not estimated for F1 and F2. In F3 formulation, the evaluation parameters were acceptable. But the *In vitro* drug release of the tablet was not up to the specified limits. Hence, hypromellose 15 cps was increased in F4 formulation to overcome this problem. The release of the F4 formulation shows that, at the end of 5th hour about 94% of the drug was released. Then hypromellose 1 lakh cps was added for F5 formulation. The F5 formulation was release drug at the regular intervals of one hour up to 10th hour as shown in figure 1. The results were mentioned in Table 2.

Table 2: Results of Evaluation Studies

S. No.	Evaluation test	F1	F2	F3	F4	F5
1.	Weight Variation (%)	6.10	3.90	3.70	3.50	3.01
2.	Thickness (mm)	7.05	7.31	7.78	7.64	7.41
3.	Hardness (kg/cm^2)	3.00	2.00	6.00	8.00	9.00
4.	Friability (%)	1.12	2.21	0.53	0.39	0.18
5.	Drug content (%)	97.18	98.39	97.99	98.27	98.80

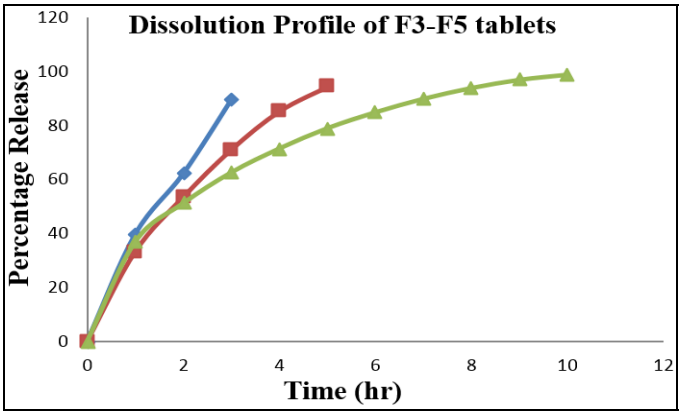

Fig 1: Cumulative Drug Release of Batch F3 – F5.

6. Conclusion

The aim of the work was to design the sustained drug delivery system in order to reduce frequency of dosing and to provide uniform drug delivery. The semi synthetic cellulose polymers have been becomes very important for controlling the drug release. The polymer of hypromellose of 15 cps and 1 lakh cps were used by varying their proportions. All the physical parameters of 5 batches were found to comply with the pharmacopoeial specifications whereas, the formulation F5 satisfactory *in vitro* release profile.

7. References

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