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DEVELOPMENT AND EVALUATION OF METFORMIN LOADED SPANSULES

***Tanushi, Aparna Joshi, Kapil Kumar, Deepak Teotia, Ikram and Deepti Khairya**

Department of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Kashipur- 244713, Uttarakhand, India.

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***Corresponding Author**
Tanushi
Department of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Kashipur- 244713, Uttarakhand, India.

ABSTRACT

Spanules are the doses form having one API or more than one API in the form of granules, with a specific coating having a slow dissolving rate which alters the release pattern of the medicament in the Spanules ata different and predetermined time. Metformin is viewed as a enemy of hyperglycemic drugs as it brings down blood glucose fixation in type 2 diabetes without causing hypoglycemia. A through preformulation study has been performed on given sample in order to estimate the physiochemical properties like solubility, melting point to confirm authencity of sample and to conform that there are no significant barrier to the development of spansules. Evaluation parameters also have been studied to estimate the effect of spansules. An attempt was made to formulate and evaluate the Metformin spansules containing Metformin Hcl as a model drug. Prepared formulations were evaluated on different parameters like flow property, morphology, average weight, disintegration test and dissolution test. Study cocludes successful delivery of metformin by the means of spansules.

KEYWORDS: Metformin Hcl, spansules, evaluation.

INTRODUCTION

Spansules are the kind of capsules dosage form that contain one or more APIs in the form of granules which are coated with slow dissolving rate polymer resulting in delivery of drugs at different times. Spansules can be defined as combing both Span and capsule (Span capsule =Spansules). The dosages form which delivery medicine at different time spends.[1,2]

In Spansules, dissolution of the drug can be governed by microencapsulation. When the coating of the drug granules gets dissolved drug is released and now ready for dissolution. Drug release can be predetermined by varying the composition and changing the coating thickness. Spansules not be suitable to chew or broken because it may show to damage of coating layer. A Spansules contains many granules which are different from each other on the basis of coating of thickness and different in shape. These types of granules deliver a drug at a predetermined rate, first of all, the granules provide loading dose followed by drug release at different time span. These coated granules deliver drugs at 2 – 3 hours, 4-6 hours, and 6-9 hours.[3,4] Drug release is dependent on moisture permeation into the coating of particles which causes swelling of thickness material followed by rapture resulting in the drug release. Spansules are the best example of dissolution release systems.[5]

Metformin hydrochloride (N, N dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide class of oral antihyperglycemics. Metformin hydrochloride is a grayish clear powder that is dissolvable in water and is insoluble in CH3)2CO, ether, and chloroform. The pKa of Metformin is 12.4. The pH of a 1% watery blueprint of Metformin hydrochloride is 6.68.[6,7]

The purpose of current effort is to prepare and estimate slow dissolving spansules of Metformin, an anti- diabetic agent, using various excipients including polymer to achieve commercial availability, which has a great market potential.

The following are detailed and specific objectives lay down for the research.

- To minimize the adverse effects of the Metformin.
- To evade dose dumping by using slow dissolving spansules.
- To formulate Metformin slow dissolving spansules.
- To evaluate the post compression parameters for spansules including in-vitro evaluation.
- To increase the therapeutic efficacy of the Metformin.

MATERIALS AND METHODS

Metformin was obtained as a gift sample from Torrent research, Gujarat, India. HPMC, starch, talc, ethanol were obtained from CDH, Delhi, India. All used chemical ingredients were of analytical grade.

Preparation of Metformin spansules

The ingredients screened (#40 mesh), and mix for 3 min. then prepared starch mucilage(the starch mucilage is prepared by dissolving powdered starch in sufficient quantity of water and stirred until starch is dissolved) To the above screened mixture add starch mucilage drop wise and then all ingredients placed in mortar pestle and mixed well until wet dough is prepared. Wet dough passed through a sieve no. 12 to form granules. Place the wet granules in a hot air oven at 50°c.[8] Composition of various formulations –

Table 1: Composition of spansules.

Ingredients	Formulations					
	F1	F 2	F 3	F 4	F 5	F 6
Metformin	250	250	250	250	250	250
Lactose	70	70	73	75	75	73
Magnesium stearate	100	95	95	95	97	96
Talc	45	50	47	45	40	44
Acacia	12	10	10	15	13	13
Starch	23	25	25	20	25	24

Sub coating of spansules

The granules made waterproof by sub coating

Table 2: Sub Coating for Metformin spansules.

Ingredients	Quantity
Ethyl cellulose	2.0
Iso propyl alcohol	Quantity sufficient
Dichloromethane	Quantity sufficient

Coating of spansules

Solvent evaporation method

Solvent composition is alcohol/water (8:2) has been taken and mixed with HPMC which is not miscible with liquid medium. Then Drug particles dispersed in the coating solution with proper mixing to form uniform size Spansules. After that volatile solvent is evaporated with heating with stirring. Filling of spansules have been done with help of appropriate equipment.[9]

Evaluation of formulations

Flow properties

Angle of repose

To a proper level a channel connected and made powder/granules to go through the opening and afterward heap framed is estimated for its sweep (r), and level (h).[10]

Compressibility index

The compressibility list has been proposed as a circumlocutory extent of mass thickness, size and shape, surface district, so addends content and cohesiveness of materials since these can influence the saw compressibility document.[11]

Hausner ratio

The proportion of tapped thickness W/V50 to cushioned thickness (W/V0 g/ml) is known as the Hausner proportion.[12]

Moisture content / loss on drying

Definitively weighing exclusively 10 capsules and decided the normal of them , putting all the onto a spread paper with consistent weight, drying until arriving at steady weight, and computing weight reduction on drying of the container, in particular the dampness of the capsule, as per the decreased weight and the heaviness of the capsule prior to being dried.[13-16]

Uniformity of weight

10 capsules were independently weighed with electronic computerized balance (Citizen, CY-104) and the normal was determined and contrasted and the singular capsule loads. From this, %weight contrast was determined and afterward checked for IP details.

IP detail: Not multiple capsules are outside as far as possible.[17,18]

Disintegration test

Metformin capsules were exclusively positioned in each tube, and permitted to move in a disintegration medium at 37±2°c at 60rpm. Uncoated tablets not in excess of 15 min Enteric container: In Acidic media; will not crumbling 2 h and in soluble medium, cases will deteriorate inside 60 min. hard gelatin cases: Disintegration time will not be in excess of 30 min.[19,20]

Drug content

A sum of 10 capsules were gauged and ground. The amount of powder ≡ 75 mg was disintegrated in 100 ml of 0.1 N HCl. Then, at that point, the arrangement was sifted, weakened reasonably and examined utilizing an UV/noticeable spectrophotometer at 234 nm. Five capsules were weighed exclusively and powdered. The powder ≡10 mg was gauged and the medication was extricated in 0.1 N HCl, the medication not set in stone by estimating the absorbance at 243 nm after reasonable

weakening utilizing a Shimadzu UV-Vis twofold pillar spectrophotometer. 20 tablets gauged, ground up in a mortar. An identical to 100 mg was moved to a 50 mL volumetric flask, weakened by 20 mL of weakening arrangement. The volumetric flask was shaken truly, centrifuged at 3000 rpm for 5 min and afterward the stock arranged was weakened. An aliquot of the weakened arrangement was infused into a fluid chromatography with an indicator set at 234 nm. The reactions were contrasted with the norm with decide the amount in mg present in the example.[21]

In –vitro release study: Dissolution studies 100 mg Metformin HCl (MFH) was precisely gauged and broken down in phosphate support pH 6.8 (PB) and quantity rise up to 100 ml (solution1). 10 ml of arrangement 1 was weakened with PB to make 100ml (arrangement 2). Different volumes of arrangement 2 were taken in five different 25 ml volumetric carafes and volumes were made up with 1ml 0.1N HCl corrosive and adequate amount of PB to create five unique standard arrangements with convergences of 4, 8, 12, 16 and 20µg/ml. One of the standard arrangements was then examined. 234 nm frequencies were chosen for examination of Metformin HCl utilizing UV/Visible Spectrophotometer (SHIMAZDU, PHARMASPEC 1700, and Japan) to get λ max. The absorbance of Metformin HCl was viewed. Selected techniques linearity was seen in the fixation scope of 10-50 mg mL-1. In this strategy, the grouping of the not set in stone at 234 nm utilizing the separate absorptive worth. A Linear relationship was gotten between absorbance Vs fixation. Adjustment bend for Metformin HCl showed linearity in the focus range 10-50 mg mL−1. The linearity of the adjustment bend was approved by the worth of relationship coefficients (r2). Then, at that point, absorbances of all standard arrangements were estimated at noticed λ max.[21]

RESULTS AND DISCUSSION

The granules were tested for the flow properties viz., angle of repose, compressibility index, and Hauser's ratio and on the basis of them, formulation F4 have respectively excellent, good, excellent properties and formulation F4 found to be the best formulation compare to F1,F2,F3,F5,F6. Precisely weighing individually 10 capsule and have determined the average of them and results have shown in table no.XIV. Capsules have separately weighed with electronic digital balance as well as the average has calculated along with compared with the entity capsule weights. From this, %weight variation has deliberated. Average of formulation f1, f2, f3, f4, f5 and f6 have shown in table no. XV. After disintegration test, founded that Formulation f4 was completely disintegrated within 30 minutes. In –vitro drug release data have been performed meant for each formulation (f1, f2, f3, f4, f5 and f6) and consequences have exposed in table no. XVII.

Table 3: Evaluation parameters of formulations.

Formulations	**F1**		**F2**		**F3**		**F4**		**F5**		**F6**	
Angle of repose(°)	35	G	36	F	33	G	27	E	31	G	36	F
Compressibility index	18	F	17	F	16	F	12	G	18	F	20	F
Hausner ratio	1.15	G	1.12	G	1.17	G	1.10	E	1.15	G	1.16	G

Table 4: Moisture content / loss on drying.

S.no.	**Weight (mg)**											
	F 1		**F 2**		**F 3**		**F 4**		**F 5**		**F 6**	
	B	A	B	A	B	A	B	A	B	A	B	A
1	4.98	4.90	4.96	4.90	4.96	4.90	4.96	4.90	4.88	4.82	4.97	4.87
2	4.88	4.81	5.00	4.90	4.88	4.80	4.99	4.94	5.00	4.90	4.90	4.84
3	4.96	4.89	4.88	4.82	4.90	4.86	4.98	4.92	4.97	4.87	4.88	4.82
4	4.97	4.90	4.90	4.85	4.96	4.86	5.00	4.95	4.90	4.86	4.88	4.82
5	5.00	4.89	4.97	4.90	4.88	4.82	4.99	4.91	4.88	4.82	4.96	4.86
6	4.96	4.89	4.88	4.80	4.90	4.86	4.88	4.85	4.96	4.86	4.97	4.87
7	4.90	4.88	4.96	4.89	4.97	4.87	4.99	4.93	4.96	4.86	4.88	4.80
8	4.88	4.81	4.90	4.80	5.00	4.90	4.98	4.90	4.88	4.82	4.90	4.86
9	4.90	4.85	4.96	4.89	4.88	4.82.	4.99	4.90	4.97	4.86	5.00	4.90
10	4.96	4.89	4.97	4.88	4.96	4.86	4.97	4.91	4.90	4.82	4.96	4.87

Table 5: Uniformity of weight.

S.No.	**Weight (mg)**					
	F 1	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**
1	4.99	4.67	4.99	4.99	4.89	5.00
2	4.66	5.00	4.97	5.00	4.89	4.96
3	4.67	4.87	4.87	4.99	4.96	4.96

4	5.00	4.97	4.98	5.00	4.99	4.99
5	4.87	4.87	4.96	5.00	4.89	4.99
6	4.97	4.98	4.67	4.99	4.99	4.89
7	4.88	4.98	4.99	5.00	5.00	4.89
8	4.96	4.96	4.89	4.99	4.89	4.99
9	4.87	4.67	4.99	5.00	5.00	4.99
10	4.98	4.99	4.67	4.99	4.99	4.99
Average	4.88	4.89	4.89	4.99	4.94	4.96

Disintegration test

After disintegration test, founded that Formulation f4 was completely disintegrated within 30 minutes.

Table 6: *In –vitro* release study: Dissolution studies.

Time (hour)	Percentage release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0.5	6.9	5.7	8.7	9.7	12.3	55.8
1	10.4	12.7	11.6	15.7	14.4	89.5
2	16.5	18.2	16.7	30.0	32.0	94.4
3	22.2	22.5	19.9	38.6	46.6	96.7
4	28.9	26.2	23.3	44.4	54.6	97.5
5	30.4	29.9	27.6	50.1	61.8	98.3
6	34.4	33.6	30.0	62.0	72.8	99.2
8	38.6	38.9	35.5	74.2	82.6	100.0
10	41.1	40.5	39.2	81.0	86.3	
12	43.3	46.7	42.2	86.2	88.8	
14	48.7	52.3	50.0	88.2	91.6	
16	52.4	56.2	52.2	91.6	94.6	
20	55.6	61.8	59.1	94.3	100.0	
24	60.4	66.7	64.4	96.8		

CONCLUSION

The oral bioavailability is represented to be 50-60% with fairly short plasma end half-presence of about 2 h. This makes the interest being developed of sustain release formulation of Metformin. An attempt was made to formulate and evaluate the Metformin spansules containing Metformin HCl. Metformin received as a gift sample and thorough Preformulation study was performed on given sample in order to estimate the physicochemical properties like solubility, melting point etc. to conform the authencity of sample and confirm that there are no significant barriers to development of Metformin spansules. Metformin spansules formulation F4 was concluded as the best formulations among all 6 formulations based on different parameters like flow property, morphology, average weight, disintegration test and dissolution test ad stability studies. However there is need in-vivo study to justify the development of Metformin spansules.

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